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The Development and Management of Posttraumatic Epilepsy

Joshua Laing
BBiomedSci(hons), MBBS, FRACP

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Central Clinical School, Faculty of Medicine, Nursing and Health Sciences

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Abstract

Posttraumatic epilepsy (PTE) is a severe chronic condition characterised by spontaneous recurrent seizures, a sequelae of traumatic brain injury (TBI). Apart from prevention of TBI itself, there are no preventative strategies or current disease modifying treatments of PTE. Following TBI, there are several known clinical risk factors for the development of PTE, including early posttraumatic seizures (EPS). The significance of EPS and their contribution toward PTE is not well known. Further, there is an observable latency period prior to the development of PTE following TBI, called epileptogenesis. Therefore, PTE is an ideal model for investigating epileptogenesis and potential for preventative therapeutic interventions.

Chapter 1 evaluates the past 20 years of literature on the development and management of PTE, with focus on the heterogeneous clinical epidemiology of PTE across military and non-military cohorts and more recently investigated subsequent impact on morbidity and mortality. This literature search also shows a lack of knowledge of the importance of EPS and relationship to PTE as mentioned. Chapters 2 and 3 sought to evaluate some of these gaps using a high-powered large state-wide trauma registry. Chapter 2 showed that EPS have a unique risk factor profile, and significantly contribute to risk of mortality and morbidity when matched for injury severity and other factors. Chapter 3 investigates the clinical risk factors for PTE, showing good concordance of two statistical methods, and follow up poorer outcomes of mortality and morbidity secondary to PTE specifically.

Further research leveraged off a major NIH funded international multicentre study of biomarkers of epileptogenesis post TBI (EpiBios4Rx). The trial utilises continuous

electroencephalography (cEEG) which is standard of care in major North American centres, allowing for routine introduction of its use in Australia for the first time, and with experience may be further expanded. Chapter 4 includes an evaluation of cEEG practice across two large Australian adult tertiary hospitals, showing a conservative use with a high proportion of seizures detected in both ICU and wards outside a neuro-critical care unit setting. In Chapter 5, an Australian survey of clinical practice of cEEG and status epilepticus shows early adoption of cEEG and identifies significant barriers to expansion primarily personnel, equipment and funding. Chapter 6 is a position statement on cEEG use in Australia and New Zealand, a result of work from the cEEG Taskforce commissioned by the Epilepsy Society of Australia.

In summary, this research has contributed to key knowledge on risk factors of EPS and PTE, highlighting the importance of EPS and potential contribution to PTE, and poorer outcomes associated with both EPS and PTE. The role of cEEG in Australia is emerging and may be beneficial in selected patients. Further, the use of cEEG in evaluating those at risk of EPS represents an opportunity for possible intervention of epileptogenesis.

Publications During Enrolment

Laing J., Gabbe B., Chen Z., Perucca P., Kwan P., O'Brien T. *Risk Factors and Prognosis of Early Posttraumatic Seizures in Moderate-Severe Traumatic Brain Injury: A Population-Based Study. JAMA Neurol. 2022;79(4):334-341. doi:10.1001/jamaneurol.2021.5420*

Laing J., Lawn N., Perucca P., Kwan P., O'Brien T. *Continuous EEG use and Status Epilepticus Treatment in Australasia: a practice survey of Australian and New Zealand epileptologists.* BMJ Neurology Open, 2020;2(2):e000102. doi:10.1136/bmjno-2020-000102.

Thesis including Published Works Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes one original paper published in peer reviewed journals and one submitted publication. The core theme of the thesis is the development and management of posttraumatic epilepsy and the role of continuous EEG. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the department of neurosciences under the supervision of A/Prof Piero Perucca, Prof Patrick Kwan and Prof Terence O'Brien.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 2 and 5 my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status** *(published, in press, accepted or returned for revision, submitted)*	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student Y/N***
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Chapter 5	*Continuous EEG use and Status Epilepticus Treatment in Australasia: a practice survey of Australian and New Zealand epileptologists.*	*Published*	*80%. Concept and collecting data and writing first draft*	N. Lawn 5% P. Perucca 5% P. Kwan 5% T. O'Brien 5%	*No*

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Joshua Laing

Student signature: Date:

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Prof. Terence O'Brien

Main Supervisor signature: Date:

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Introduction

Posttraumatic epilepsy (PTE) is a serious sequela of traumatic brain injury (TBI), which has no preventative nor curative therapies. TBI is common and endemic around the world, and often results from motor vehicle accidents, falls and assaults. TBI is a significant risk factor for developing epilepsy, accounting for up to 20% of all cases of acquired epilepsy (1). The incidence of PTE is dependent on the rate of TBI, which has a world prevalence estimated at sixty-nine million people per year (2). PTE is defined in the literature as the occurrence of a seizure after the first week of injury, coinciding with the International League Against Epilepsy (ILAE) definition of epilepsy of one unprovoked seizure with a probability of subsequent seizures being over 60% (3). However, many patients with acute TBI are still in hospital and potentially the intensive care unit (ICU) after 7 days and be exposed to other risk factors for acute symptomatic seizures (4). Seizures during the early phase post TBI are called early posttraumatic seizures (EPS), and have difference mechanisms and subsequent risk of morbidity and mortality (4). As there are variable definitions of EPS and PTE in the literature, their relationship is unclear, although PTE may be considered following the acute phase TBI or admission. EPS is known to be a significant risk factor of PTE, with an important interaction yet to be sufficiently defined (5).

In this early phase of TBI when acute symptomatic seizures or EPS commonly occur, many seizures may appear clinically silent and go undetected, but may cause significant damage and contribute to immediate morbidity (5), and the subsequent development of PTE (5–9). Continuous electroencephalography (cEEG), the application of EEG in acutely unwell patients in hospital, can detect subclinical or electrographic seizures (ESz) in up to 50% of

critically ill patients with TBI (10). Intracranial depth electrode monitoring (iEEG) has also recently been shown to detect further subclinical seizure activity not seen on scalp EEG, by placing an electrode into the injured brain (11). ESz may alter brain metabolism and compound brain injury (12), although short and long term clinical outcomes as well as their effect on epileptogenesis are unclear. The optimal treatment of EPS beyond current guidelines for broad spectrum use of antiseizure prophylaxis for 7 days, including ESz detected by cEEG on recovery and development of PTE, is unknown. The use of cEEG in brain injured, unconscious, critically ill patients, is becoming increasingly widespread and advanced countries, in particular the United States (US), following the identification of an increased incidence of electrographic seizures in critically unwell inpatients (13). Not only has cEEG not been well adopted yet in other countries, the applicability and benefit of cEEG in specific cohorts such as TBI is not known and requires further investigation.

PTE is associated with significant disability (14–18), mortality (18–20), and treatment-resistant chronic epilepsy (21–24). Antiseizure prophylaxis has shown modest benefit in reducing clinically evident seizures in-hospital or EPS, but have shown no effect on the long-term development of PTE (25). PTE is an ideal model for the investigation of epileptogenesis, the process of the normal brain abnormally acquiring changes resulting in spontaneous and recurrent seizures, which may hold the key for novel disease modifying therapies in epilepsy. This concept is the focus of the National Institutes of Health (NIH)-funded, international, multicentre preclinical and clinical trial of anti-epileptogenic drug ‘EpiBios4RX’ (26). Clinical risk factors for the development of PTE have been reported, although specific risk factors and their contribution to PTE, are variable depending on cohorts and methods of analysis (27). There are no well-designed risk factor prediction or scoring systems validated for clinical use in PTE. Additional to clinical risk factors,

discovering diagnostic biomarkers for epileptogenesis hopes to better predict patients likely to develop epilepsy post-TBI, and allow future targeted disease modifying therapies to be more efficiently trialled. Moderate-severe TBI often requires intensive care management and given the early latency period until the development of PTE, represents an observable patient cohort to investigate with various modalities including serum, genetic, radiological and electrophysiological data. Current therapies for PTE are non-specific and merely symptomatic, commencing after epileptogenesis has already occurred, following a diagnosis of epilepsy. The prospect of more refined and focused clinical trials for patients predicted to develop PTE is essential with previous antiepileptogenic trial failure (28). Consolidating the clinical risk factors for PTE would aid in refining trial recruitment.

Literature Search Methods

A literature search was conducted using established databases MEDLINE, EMBASE and CINAHL, for recent articles on posttraumatic epilepsy. A subject search was performed for posttraumatic epilepsy, followed by a keyword search involving posttraumatic, seizur*, epilep*, and brain injur* to capture a wider range of articles. A generous recent capture of the literature of all articles from 2000 to 2020 were included, limited to human adult subjects. The decision to include only articles in the search from the last twenty years was made due to significant medical advances made over time, specifically in this patient group seizure prophylaxis, improved ICU care including neuro specific ICU, continuous EEG guided therapy, and improvements in neurorehabilitation. Only articles in English were included. Duplicates were removed. A total of 699 articles were found and their abstracts assessed for eligibility. Further manual removal of studies only referencing paediatric cohorts, animal studies, conference proceedings, and case reports. Title and abstract review were performed and any articles deemed irrelevant or not containing original research were

removed. When assessing ES or PTE incidence, studies were assessed for the appropriateness in this analysis, and studies were excluded based on no access to full text, or abstracts from conferences, or those deemed to have insufficient information to attribute incidence of ES or PTE.

Epidemiology of PTE

The incidence of PTE is dependent on the rate of TBI, which is prevalent around the world estimated at sixty-nine million people per year (2). Depending on the population, with some series of PTE from military cohorts, PTE may result in 1.3-32% of patients following TBI (Table 1). The largest cohort with over 2 million patients with TBI presenting to hospital or outpatients from a US registry study showed a 4% risk of PTE out to 9 years (9). Other cohorts of admitted patients with moderate to severe TBI have higher rates of PTE, with one large US registry study having a 5-year PTE incidence of 20.5% (29). Whilst there is heterogenous nature to PTE studies of specific cohorts and variable follow up, a recent meta-analysis showed a pooled prevalence of PTE following TBI was 15% (27). In a large population-based study in Denmark including over 1.6 million people, there were 78,572 people with TBI, 17,470 people who developed epilepsy with 1,017 having a preceding TBI (30). Therefore, the risk of developing epilepsy relative to no TBI was two times higher. Injury severity of mild, moderate and severe TBI result in an increased risk of PTE (30). As incident PTE is significantly associated with TBI severity, some patients may die prior to the development of PTE and are often excluded from analysis. The time to first seizure following TBI and diagnosis of PTE has been studied in various populations typically with most in the first year following injury, if not the first two years (Table 1). A high percentage 58-78% of patients that develop PTE occur within the first year post TBI (8,29,31), and 82-92% at the end of the second year (8,29), but the risk of PTE following TBI may persist for years (32,33).

The risk of further seizures after the first late seizure is as high as 86% at two years (34), meeting the threshold for diagnosis of epilepsy and recommendation of antiseizure medication (ASM) treatment (3).

As mentioned earlier, there is some variation in the literature regarding terminology of seizures that occur post TBI. Posttraumatic seizures have been classified as occurring within 24 hours (immediate), within the first week (early symptomatic), or late (remote symptomatic). 'Immediate' seizures have been associated with higher risk of PTE (5), but are not well defined and may include an antecedent seizure causing TBI, or even convulsive syncope and concussive convulsions which pose no risk to the development of epilepsy (24). The International League Against Epilepsy (ILAE) classifies acute symptomatic seizures as "occurring at the time of a systemic insult or in close temporal association with a documented brain insult" of which TBI is included as a cause (25). This recommendation also suggests use of the arbitrary cut off of 1 week, based on a cohort study of depressed TBI from 1973 (26). Within this paper, the practice of routine clinical prognostication at the 1-week mark is referenced, but makes no evaluation of the differences of acute seizures or EPS and the development of unprovoked seizures or PTE. Further, there is no evidence in the literature that 'late' (unprovoked) seizures or PTE should be defined at ≥1 week given any specified increase in risk of recurrence or aetiological differences at all. It is important however to define both EPS and subsequent PTE, as they are thought to reflect different mechanisms, rates of seizure recurrence, morbidity and mortality (29). Englander et al (41), closely followed patients from injury out to 2 years and reported that the high proportion of posttraumatic seizures occurring in the first month was likely multifactorial including acute provoking factors such as brain swelling, perioperative factors and metabolic factors. Hence EPS are not termed epilepsy due to acute provoking factors (40), however, their relationship

to epileptogenesis requires further evaluation as many patients with early seizures go on to develop PTE (5). Furthermore, as discussed earlier a potentially more accurate definition of EPS involving exposure to acute provoking factors for acute symptomatic seizures may be following the acute phase TBI illness or acute admission, which has been used in some studies. PTE would then be diagnosed and defined at any point following the acute admission.

TBI is a significant global public health problem, affecting predominantly young adults, many of whom will subsequently develop disabling seizures and loss of independence (29). Epilepsy alone is the most common neurological condition in young people causing significant disability, loss of independence, and risk of death, with up to a third of patients remaining drug resistant (35). The additional diagnosis of PTE on top of TBI is not well known, but has been associated with significantly compounded disability (14,16–18,36) and risk of mortality (18–20) (Table 2). The associated financial burden of PTE therefore is undoubtedly substantial. Previous small cohort studies show greater disability and self-reported satisfaction of life (15), more frequent medical attendances (18), less return to work (20), and higher levels of physical, cognitive and psychosocial long term impairment (16). Other studies show further neuropsychiatric problems such as personality disorders and behavioural disturbances (14) and increased risk of clinically significant anxiety (17). Furthermore, there is also an increased associated caregiver stress of looking after patients with PTE (37). A recent review of the paucity of evidence postulates a more wide reaching impact of PTE on the emotional, cognitive and psychosocial functioning (38). Whilst studies show short term mortality increases (18,19), patients with PTE have been reported to have a 1.75 times higher risk of death up to 15 years post-injury compared to matched TBI survivors who did not develop epilepsy (20). Causes of death were no different in that study,

however those with TBI are 60 times more likely to die from seizures compared to the general population (39).

Risk factors

The risk factors for PTE are largely governed by the severity of injury, however some studies may adjust for this to provide further insight into other potential epileptogenic risk factors. Concussive convulsions are non-epileptic phenomena of impact related cortical motor activity which does not increase risk of epilepsy (43,44), which may be seen as seizure-like episodes on sporting fields during high speed collisions. Concussions themselves, or mild TBI, are also typically not associated with the development of PTE (45), however there may be a weak association (46). Indeed increasing severity of TBI including focal neurological signs, loss of consciousness, and post traumatic amnesia, increases the risk of PTE (27,33). Other commonly reported injury severity related risk factors include penetrating injuries seen in military populations (6,7,41,47,48), parenchymal contusions (19,31,41), depressed skull fracture (7,30,31,41,49), subdural haematoma (14,41), secondary hydrocephalus (14), and associated surgical treatment interventions (7,8,14,29,41,47). Early seizures, discussed further, is also commonly cited as an independent risk factor for PTE (27). After review of the literature (Table 1), reported significant factors in multivariate analysis include age (8,47), Glasgow Coma Scale (GCS) (6,31,50), specific motor deficits (6,47), fall (47,50), gunshot (47), medical comorbidities (50), TBI severity (8,51), frontotemporal contusion (31,33), skull fracture (31), history of psychiatric disease (51), and alcohol related injury (51). Many of the reported studies vary significantly in both populations and methodology, making transferability of these risk factors difficult. When identifying those with PTE, various methods have been employed including using ICD codes, questionnaires, interviews and medical assessments. Reporting of injury specifics and other clinical risk factors is also

variable. Limitations within the datasets also include those not excluded with a prior diagnosis of epilepsy, early seizures and PTE not being separated, as well as variable length in follow up of subjects. A recent systematic review and meta-analysis in 2017 (27) attempted to address the heterogeneity. The most common risk factors being severe TBI (RR 8.37), early seizures (RR 5.14), intracranial haemorrhage (RR 2.65), contusion (RR 2.35), skull fracture (RR 2.27), history of alcohol abuse (RR 2.18), subdural haemorrhage (RR 2.00). GCS and associated amnesia, and focal neurological signs were also significant. Using a prediction model of risk factors on a small single cohort, one study attempted to predict those with seizures following TBI, with a modest result on a test population (52).

Table 1: Summary of Epidemiological Studies of Posttraumatic Epilepsy from 2000 to 2020.

Study	N	Population	Follow up (mean)	PTE incidence	Time to PTE	PTE Risk Factors
Aarabi (6)	489	Military penetrating TBI	39.4mths	32%	NA	GOS, initial GCS, motor deficit, mode of injury, transventricular injury, dysphasia, CNS infections, early seizures
Englander (41)	647	4 trauma centers US	24mths	14%	33.3% (22/66) of the late post-traumatic seizure occurred 8 days to 1-month postinjury, 63.6% (42/66) between 8 days to 6 months postinjury, 80.3% (53/66) between 8 days to 12 months postinjury, and 92.4% (61/66) between 8 days to 18 months postinjury.	Biparietal contusions (66%), dural penetration with bone and metal fragments (62.5%), multiple intracranial operations (36.5%), multiple subcortical contusions (33.4%), subdural hematoma with evacuation (27.8%), midline shift greater than 5mm (25.8%), or multiple or bilateral cortical contusions (25%). Initial GCS 3 to 8, 16.8%; GCS score of 9 to 12, 24.3%; and GCS score of 13 to 15, 8.0%
Temkin (7)	783	Sz prophylaxis study (high risk of PTE)	24mths	21%	Kaplin myer curve only	Evacuation of a subdural hematoma; surgery for an in-tracerebral hematoma; Glasgow Coma Scale in the severe range of 3 to 8; early seizures, especially delayed early seizures; time to following commands of a week or more; depressed skull fracture that was not surgically elevated; dural penetration by injury; at least one nonreactive pupil; and parietal lesions on CT scan

Mazzini (14)	143	Rehab Italy	>1yr	19%	Mean 12mths	Temporal SPECT hypoperfusion, degree of hydrocephalus, haematoma, neurosurgery
Safaz (47)	116	Military TBI Turkey	555 days median	13.8%	345 days	Age, open head injury, surgery, right sided neurological deficit, gun shot, falls
Andelic (53)	62	TBI Norway	10yrs	19%	NA	NA
Christensen (54)	78572	TBI Denmark (inc. children) Cross-section	Crossectional	1.3%	NA	Neuroimaging findings, clinical severity of TBI; onset time after skull fracture
Thapa (50)	520	Mild-mod TBI GCS>4 India	386 days median	2.7%	NA	Bundled with acute seizures and PTE
Ferguson (55)	1961	TBI US	3yrs	5.9%	NA	Severe TBI, early seizures, history of depression, three of more medical comorbidities
Englander (19)	508	TBI US	2yrs	14%	NA	Multiple cortical contusions
Bushnik (15)	182	TBI US, matched group 1:1	5yrs	NA – selected	NA	Prior arrest, incarceration
Zhao (8)	2826	TBI China military hospital	3-5yrs	5%	76% within first year, 92% within 2 years	Older age, greater severity of brain injury, abnormal neuroimaging, surgical treatment, and early-stage seizures
Yeh (49)	19336	TBI Taiwan	Not reported	1.9%	HR 38.2 within first year	Severity of TBI, skull fracture
Wang (31)	3093	TBI China	2yrs	9.8%	78% within first year	Frontal—temporal lobar contusion, Linear fracture and Severity of TBI measured by initial Glasgow Coma Scale (GCS)
Bhattacharyya (56)	320	Mild-mod TBI GCS>4 India	1yr	2.8%	NA	NA
Vaaramo (51)	739	TBI all ages Finland	10yrs	5.7%	NA	Alcohol-related index injury (adjusted HR 2.50, 95% CI 1.30 to 4.82, p=0.006), moderate-to-severe traumatic brain injury (TBI) as the index

						trauma (3.13, 1.46 to 6.71, p=0.003) and preceding psychiatric disease
Mahler (33)	422	TBI Sweden Cross section	NA	RR 2.7	RR 42.6 within first 6 mths	ICH, contusion
Pugh (57)	29297	TBI military US Cross sectional	NA	2.3%	NA	NA
Walker (48)	1171	TBI US	2yrs	13.4% (self reported)	NA	Penetrating head injury, LOS, age, sex, substance abuse, and race
Ritter (29)	796	TBI US	5yrs	20.5%	58% within 1st year, 82% at 2yrs	Surgery
DeGrauw (9)	2059870	TBI US (includes children)	9yrs	4.0%	25% within 1st year	Age, early seizure and TBI severity

Note: Underlined risk factors were significant on multivariable assessment.

Table 2: Studies Reporting Morbidity/Mortality Outcomes of PTE.

Study	N	Population	Follow up (mean)	Morbidity	Mortality
Mazzini (14)	143	Rehab Italy	>1yr	Personality disorders, disinhibited behavior, irritability, and agitated and aggressive behavior, worse overall 1yr functional outcomes (GOS, FMI)	
Englander (19)	508	TBI US	2yrs	NA	Significant 27% vs 10%. No diff in time to death, except were younger patients. No change in cause of death, risk of death in PTE was age and subdural.
Bushnik (15)	182	TBI US, matched group 1:1	5yrs	Use of dependent forms of transportation, higher Disability Rating Scale post rehab, lower Satisfaction With Life Scale scores	NA
Kolakowsky-Hayner (16)	25	PTE uncontrolled	5-13yrs	Physical, cognitive, psychosocial and reintegration issues	
Juengst (17)	867	TBI US	2yrs	3.34 times the odds of having clinically significant anxiety (GAD-7)	
Uski (20)[a]	714	TBI US, matched 1:2	15yrs	NA	Mortality was 1.75 times higher (p = 0.0001). There was no significant difference in causes of death
Lin (18)	2850	TBI Taiwan 1:1 matched	15yrs	Increased hospital stays and medical comorbities.	Mortality increased with aHR 2.31

a. Excluded deaths in first 3 months

Early Posttraumatic Seizures (EPS) in TBI

Seizures occurring during the acute phase of TBI within the first week or so, called EPS, are important due to compounding injury and subsequent risk of PTE. Some studies separate immediate seizures occurring in the first day, and early seizures being up till seven days after injury, however again there is minimal evidence to suggest that these two time points represent sufficiently different aetiologies of seizures and may also be grouped as acute

symptomatic seizures or EPS. The early phase of management in stabilising patients with TBI typically results in hospitalization and often intensive care unit (ICU) treatment. EPS are not uncommon following moderate to severe TBI in this cohort. Early seizures have also been associated with increased rates of in hospital complications including pneumonia, Acute Respiratory Distress Syndrome (ARDS), acute kidney injury and increased intracranial pressure (4). The causal relationship of these factors to EPS is unclear and requires further study. The incidence of early seizures varies depending on the population, however may be present in 0.4-10.5% of patients with TBI (4,8,9,29,41,50,56,58) (Table 3). Due to recent advancements in ICU care with continuous EEG monitoring, revealing a previously unknown large proportion of non-convulsive seizures, the incidence and management of early seizures is significantly changing (59). Most previous studies of EPS reporting largely clinically evident seizures, therefore represent the tip of the iceberg in relation to EPS in moderate-severe TBI. A large study of almost 1.5 million patients with TBI showed a low but important incidence 0.16% of generalized convulsive status epilepticus with the additional risk factors of age >35yrs, central nervous system infections, anoxic brain injury and ischaemic stroke (60). Early seizures are associated with subsequent risk of PTE (5), however the relationship is not completely understood and requires further evaluation. Risk factors for EPS are invariably not reported, with only few studies investigating separately from PTE. In those studies when adjusted for other risk factors for EPS, surgical evacuation (29), chronic alcohol abuse (2, 11), low Glasgow Coma Scale (GCS) (11), subdural haematoma (2), epidural haematoma (EDH) (11) and brain contusion (2) have been identified as predictors of EPS. Although again only in one small cohort, a prediction model for the identification of EPS included sex, craniotomy, contusion load and pre-injury cognitive parameters, had poor predictive performance (52).

Table 3: Epidemiology Studies Reporting Early Posttraumatic Seizures (ES) from 2000 to 2020.

Study	N	Population	Follow up (mean)	ES incidence	ES Risk Factors
Englander (41)	647	4 trauma centers US	24mths	3%	NA
Temkin (7)	196	Sz prophylaxis study – placebo group (high risk of PTE)	24mths	NA	Depressed skull fracture, subdural hematoma, intracerebral hematoma, penetrating head injury, Glasgow Coma Scale ≤ 10, epidural hematoma, cortical contusion, immediate seizures, linear fracture, posttraumatic amnesia >24, no or brief unconsciousness, age younger than 5 years.
Thapa (50)	520	Mild-mod TBI GCS>4 India	386 days median	2.1%	Bundled with acute seizures and PTE
Zhao (8)	2826	TBI China military hospital	3-5yrs	0.5%	NA
Bhattacharyya (56)	320	Mild-mod TBI GCS>4 India	1yr	4.4%	NA
Ritter (29)	796	TBI US	5yrs	10.5% (includes immediate)	Surgery
Majidi (4)	360863	TBI US National trauma databank	10days	0.4%	Age, race, moderate TBI, alcohol dependence, fall, subdural.
DeGrauw (9)	2059870	TBI US	9yrs	0.5%	NA
Liu (58)	144	TBI China	Unclear	15%	Injury site, injury type and injury degree

a. Manually excluded past medical history of epilepsy, patients also needed CT abnormalities in definition therefore were likely moderate-severe.

Anti-Seizure Prophylaxis in TBI

Current guidelines, from the Brain Trauma Foundation September 2016, provide a level IIA recommendation for the use of phenytoin, where safe, within the first 7 days to reduce early posttraumatic seizures and suggest that there is insufficient evidence for the use of levetiracetam over phenytoin at this stage (25). The recommendation for phenytoin comes from a randomised, double-blind, placebo-controlled trial of 404 patients in 1990 (61), that showed that phenytoin significantly reduced the incidence of seizures to 3.6% compared to placebo 14.2% at day 7, however the effect was non-sustained when continued beyond this time to two years. However, the safety profile, availability, and perceived equivalence in efficacy of levetiracetam has resulted in widespread use of levetiracetam over phenytoin in many centres admitting patients with moderate-severe TBI.

The largest study showing class III evidence for non-inferiority of levetiracetam and phenytoin for early posttraumatic seizures comes from a prospective observational study involving 1191 patients (62), that showed levetiracetam had a similar frequency of posttraumatic seizures 1.5% assessed clinically, compared to phenytoin. A more recent systematic review and meta-analysis of 11 pooled studies and 1614 patients for seizure prophylaxis in TBI showed that levetiracetam was not superior to phenytoin in regards to efficacy or safety (63). No ASMs have been shown to reduce the incidence of late posttraumatic seizures, and only prophylaxis for the first week is recommended (64). Some evidence may support a longer term benefit of levetiracetam on overall outcomes as measure by the Glasgow Outcome Scale (GOS-E) at 6 months (65). The requirement of cardiac and drug level monitoring makes phenytoin less desirable. Long term, if patients develop further seizures and treatment is to continue beyond the initial prophylactic period then the side effect profile of levetiracetam is more tolerable which has influenced practice

of levetiracetam being preferred (66). According to proceedings from an international critical care meeting in 2016, further improvements may also be made with increased dose of levetiracetam in critically unwell patients due to pharmacokinetics, up to 1.5g every 8 hours (67). Whilst levetiracetam has been well studied in this population, an important practice consideration of its use is the neuropsychiatric side effect profile which may exacerbate this cohort already vulnerable to mood related sequalae of TBI. More recently, another well tolerated alternative ASM lacosamide has been suggested in a small study to be possibly non-inferior to phenytoin for anti-seizure prophylaxis in TBI (68).

Clinical Epileptology of PTE

PTE is a heterogenous epilepsy, due to different TBI mechanisms and specific regional injuries, however there may be some common features including severity. There is a high rate of focal to bilateral tonic-clonic seizures, with 74% reported (69), and another study 43% with this seizure type (70). 75% of one Chinese military cohort with PTE were described as having severe seizures, but interestingly only 55% of the whole cohort were taking ASMs (8). Conversely in a US ex-military cohort, 88% of those with PTE were on ASMs (22). In the same study, left parietal focus for the seizures was most common as well as retained metal fragments increased risk of epilepsy. Brain volume loss was also associated with increased frequency of seizures. Penetrating injuries compared to blunt trauma were associated with high seizure frequency and seizures impairing consciousness, and were often frontal or parietal rather than temporal seizures (70). Whilst there may be a selection bias as a centre managing refractory epilepsy, in a cohort of war veterans the seizure frequency was high with those with blunt trauma having eight seizures per month and those with penetrating injuries fourteen per month. Eftekhar et al. found that seizures were persistent in over 85% of those with PTE at 16yrs follow up (24). As discussed above, the

impact of mild TBI on risk of epilepsy is unclear with conflicting studies, and in a surgical series mild TBI was overrepresented in refractory epilepsy compared to controls (23). It does seem that PTE is associated with severe tonic-clonic seizures and a high refractory rate, compared to others focal epilepsies.

Accurate diagnosis of seizures in the TBI population is difficult, both acutely in hospital and on follow up. Seizure like movements may often be seen during recovery in patients with TBI, and are often ascribed to epileptic seizures without consideration of mimics. Elective video-EEG monitoring (VEM), typically for a week, is used to accurately diagnosis and classify patients with paroxysmal neurological events. Hudak et al. (71) showed that in the TBI population, this is essential for accurate diagnosis especially when ASMs may worsen recovery and cognition in a fragile population of patients with TBI. In this study 88% of patients were able to have a confirmed diagnosis, 33% had psychogenic non-epileptic seizures (PNES). Around half of those with temporal lobe epilepsy had mesial temporal sclerosis. Another study showed a higher proportion of ex-military veterans with mild TBI during VEM have much higher rates of PNES (87%) than those with moderate-severe TBI (13%) (72). This diagnosis of PNES alone is important to establish not only as the management if different, but there is an associated mortality risk (73).

Management of PTE

The current management of PTE is largely symptomatic treatment of seizures with ASMs, which do not alter the disease course. ASM trials in TBI have been unsuccessful in suppressing seizures and preventing or altering the natural history of PTE. As mentioned above, the 2016 American Brain Trauma Foundation Guidelines for severe TBI support

prophylactic ASM upfront to all-patients, with some evidence of a modest effect on symptomatic seizure reduction (74). However, there still remains concerns and poor adherence to guidelines given the low rate of seizures published in many cohorts of <5% and that ASMs may hamper rehabilitation (66,75,76). Following this period there is no guidance for in which patients ASM treatment should continue, and there is no personalised clinical strategy for PTE specifically. The effect of current and specific ASMs on the subsequent development of PTE is likely minimal yet remains undefined, and a large proportion of patients go on to have severe seizures and drug-resistant epilepsy. As per those with drug-resistant epilepsy, patients with PTE should be considered for epilepsy surgery (77). Whilst those with temporal lobe epilepsy associated with MRI-detected hippocampal sclerosis generally have good outcomes, extratemporal PTE may also achieve excellent outcomes especially when encephalomalacia is present and also when guided by intracranial EEG (78). A neuropathological study following temporal lobectomies showed a consistent pattern of hilar hippocampal cell loss in patients with a history of TBI, implicating hippocampal onset temporal lobe epilepsy as a primary source of posttraumatic epilepsy (79). Additional surgical workup with advanced imaging and neurophysiological data may help to support better outcomes in more challenging cases (80). Many studies subcategorise PTE with generalized seizures, however these patients should be carefully assessed for surgically remediable focal epilepsy (81). Patients with penetrating wounds such as gunshot wounds should also be included (82). Alternative non-resective surgical options such as neurostimulation (e.g. vagal nerve stimulation, responsive neurostimulation) may also be beneficial (83) for patients not deemed to be surgical candidates.

The additional comorbid impact of PTE in addition to TBI is only partially known, requiring attention and management. Increased hospitalizations and comorbidities have been

associated with PTE requiring a holistic management approach (18). Other small studies have shown physical, cognitive, psychosocial and reintegration issues (16), as well as issues related to loss of independence (15). On study reported worsened mental health outcomes and levels of anxiety that are more than three times higher in those with PTE compared to TBI alone (17). Comorbid psychiatric disorders are high following TBI, including Post Traumatic Stress Disorder (PTSD) especially in military cohorts (84). As comorbid psychiatric conditions are prevalent in patients with PTE, concurrent assessment and management of these conditions is important when managing patients with PTE. TBI and epilepsy may also be overrepresented in prisons (85), but there may be behavioural considerations to explain this. Sleep dysfunction may be associated with TBI and PTE with insomnia being common which may complicate management (86). Interestingly, EEG abnormalities of sleep particularly reduction in REM sleep may be predictive of PTE (87). Whilst not tested, it would be reasonable to consider improvement in sleep may reduce posttraumatic seizures as a well-known provoking factor for seizures in general, however its potential antiepileptogenic effect on developing PTE is unknown. The management of survivors of TBI may be complex, due to concurrent neurobehavioral disorders and seizures, and both should be considered in relation to investigation and identification of those with PNES as well as appropriate ASM choice.

Epileptogenesis of PTE

Interventions against post-traumatic epileptogenesis, the development of epilepsy in individuals following TBI, may provide a preventative treatment for epilepsy. TBI presents an ideal model for investigation of anti-epileptogenic therapies as following TBI, as there is an intervenable period prior to the onset and development of epilepsy. Epileptogenesis represents a critical target in the investigation and understanding of the development of

epilepsy and potential for disease modifying therapeutic interventions. The identification of biomarkers in disease progression inform targets for intervention. The pathophysiological mechanisms by which TBI causes ongoing seizures and PTE is unknown, but recent evidence has implicated post traumatic inflammation resulting in neuronal changes that establish an epileptic network (88,89). Inflammatory and metabolic changes measurable through serum including low zinc (12,90), imaging of regional and network abnormalities via CT/MRI (27,91), electrical disruption using EEG (11,92), and genomic inflammatory polymorphisms (88), are biomarkers that may predict conversion from TBI and symptomatic seizures to an inherent susceptibility to PTE. Putative biomarkers of interictal activity such as periodic discharges, pathologic high-frequency oscillations (HFOs), repetitive HFOs and spikes (rHFOSs), and altered sleep spindles, have all been implicated in epileptogenesis requiring further investigation (92,93). Whilst the significance of subclinical seizures and treatment intensive requires further studies, utilisation of cEEG may identify the process of epileptogenesis in vivo and allow titration of therapeutic interventions in preventing PTE. Thorough evaluation of all biomarkers and clinical correlation may help identify patients at risk and allow for closer monitoring and intervention. Treatment trials targeting epileptogenesis have been unsuccessful to date, although biomarker identification may help to predict more suitable targets. An interesting finding from a large US database was the association of acetazolamide with a lower incidence of PTE, however the number of patients treated with acetazolamide was low and the observation requires further investigation (9). Further studies combining both clinical and novel biomarkers are essential in designing clinical trials of antiepileptogenic treatments. Successful candidate antiepileptogenic treatments may also be considered for other causes of epilepsy.

Continuous EEG in TBI

Continuous EEG (cEEG), the practice of acquiring prolonged EEG recordings in critically unwell inpatients, has become increasingly used and now recommended to detect previously undiagnosed and prevalent non-convulsive seizures and status epilepticus (13). Clinical recognition of epileptic seizures in acute TBI patients may be unreliable, and cEEG has been shown to significantly improve detection of convulsive and non-convulsive seizures following TBI (10). Without cEEG many of these seizures are clinically silent, which directly reflects the large disparity of the reported incidence of early seizures in populations with and without cEEG. In the US, cEEG has been shown to improve mortality at no further hospital cost (94,95), but this practice has yet widespread nor been established in Australia. Additional to cEEG, intracranial EEG (iEEG) via depth electrodes can potentially increase the diagnostic yield over surface EEG in TBI (11). Much work on the pathophysiological damage caused by non-convulsive seizures occurred from the observations of unexplained peaks in intracranial pressure (ICP), a biological marker used in TBI for many years. In a series of observations by Paul Vespa and his team at the University of California, Los Angeles (UCLA), the first being a study of thirteen patients with severe TBI, acute post traumatic symptomatic seizures were associated with severe metabolic crisis, measured as elevated lactate/pyruvate ratio measured by intracerebral microdialysis, which may represent ongoing brain damage due to seizures (96). A follow up study of twenty patients with moderate to severe TBI, showed correlations of seizures with both elevated lactate/pyruvate ratio and raised intracranial pressure (59). Further to these acute physiological data, pathological hippocampal atrophy on brain imaging was shown on the same side (ipsilateral) to the recorded non-convulsive seizures (97). Apart from overt seizures, periodic epileptic discharges may often be seen in the critically unwell population, and unsurprisingly these have also been shown to have negative associated physiology of local metabolic changes of elevated lactate (12). These observations have resulted in

increased use of multimodality monitoring, or multiple brain probes including intracranial EEG, forming a consensus statement (98). Using these bedside monitors to gain further insight into the brains physiology is not new given the use of intracranial pressure monitors for many years, however expands the repertoire of observations allowing for interventions that will hopefully result in neuroprotection from secondary brain injury. The optimal level of treatment of non-convulsive seizures has yet to be defined, nor has the effect of control of early seizures been investigated as an anti-epileptogenic treatment in its own right but lends itself well to the possibility. Using risk factors to identify patients at highest risk of early seizures in resource limited settings is ideal.

Conclusion

Whilst PTE may be largely governed by the prevalence of TBI which is difficult to control, PTE has been shown to significant impact morbidity and mortality of survivors of TBI. Further advances in understanding the associated risk factors of developing PTE may lead to important discoveries in addressing epileptogenesis. Recent discovery of a high proportion of early seizures detected by cEEG, has also provided for further investigation as to their importance in controlling against secondary brain injury and potentially epileptogenesis. Prediction of patients with EPS may help focus resources of cEEG using patient selection.

PhD Research Plan

Significant Gaps in Research Identified

- Refined clinical risk factors for early seizures and epilepsy following TBI are lacking
- The relationship of early seizures following TBI with subsequent risk of PTE is not fully understood, and may provide an insight into epileptogenesis
- The impact of EPS on short- and long-term outcomes following TBI is unknown
- Continuous EEG (cEEG) and guided treatment of early seizures represent an opportunity to identify those at risk of secondary injury and subsequent PTE
- There are no adult Australian cEEG reported series in the literature
- Ideal patient selection to utilize cEEG in patients with TBI is unknown.

Research Hypotheses Questions and Aims

Study 1 – Early Posttraumatic Seizures (EPS)

Questions:

- What clinical factors contribute to EPS?
- Can we predict those most likely to develop EPS?
- Do patients with EPS have a significantly higher morbidity and disability than patients who do not have EPS?

Aims:

- To investigate the demographic and clinical factors that increase the likelihood of EPS.
- To evaluate a prediction algorithm to identify patients most at risk of EPS.

- To determine whether the development of EPS impacts the short- and long-term outcomes of patients following moderate to severe TBI.

Study 2 – Cohort Study of the Development of Post Traumatic Epilepsy (PTE) in Victoria

Questions:

- What factors contribute to the development of PTE?
- Do patients with PTE have a significantly higher level of morbidity and disability than patients without PTE?
- Does non-brain injury related trauma contribute to the risk of developing PTE?
- Can we predict those most likely to develop PTE?

Aims:

- To investigate the demographic and clinical factors that increase the likelihood of PTE.
- To determine whether the development of PTE impacts the short- and long-term outcomes of patients following moderate to severe TBI.
- To evaluate a prediction algorithm to identify those most at risk of PTE.

Study 3 – Continuous EEG (cEEG) Practice Audit

Questions:

- What are the characteristics of patients undergoing cEEG monitoring?
- What risk factors are associated with seizures?
- What risk factors are associated with mortality?

Aims:

- To evaluate patients undergoing continuous EEG monitoring (cEEG) and analyse outcomes including mortality.

Study 4 – Australasian Practice Survey of Status Epilepticus and cEEG

Questions

- What are the current clinical practices and approaches to the use of cEEG in Australia?

Aims:

- To investigate current Australian practices and opinions of the use of cEEG and management of convulsive and non-convulsive status epilepticus
- Evaluate the barriers to cEEG use

Research Methods:

This PhD includes clinically targeted studies of development and management of EPS and PTE, and on in-hospital or acute seizures and use of cEEG in Australia. Firstly, using the Victorian State Trauma Registry (VSTR), which is a large comprehensive state-wide trauma database with 2 year outcomes that represents an unmined cohort for PTE, I examined risk factors for EPS (Chapter 2) and PTE (Chapter 3) cohorts separately, and their relationship to each other primarily using multivariable analyses. Given the size of the cohort, further statistical analysis to provide for a machine learning prediction model was evaluated. Morbidity and mortality analysis was performed for both cohorts with adjustment for confounders to enrich the results of patient outcomes.

Following these studies, the focus of subsequent chapters is centred around the practice of cEEG, which is relatively new and emerging in Australia, first implemented overseas in the

US in hospitalized patients post-TBI. I surveyed current clinical practice in Australia of the use of cEEG and subsequent management of status epilepticus (Chapter 4), and I undertook a clinical practice audit in 2 major metropolitan hospitals in Melbourne (Chapter 5). Finally, as a result of the work in chapters 4 and 5, I was invited to contribute as lead author in an Australian wide position statement (Chapter 6) on the use of cEEG in Australia for the Epilepsy Society of Australia (ESA).

REFERENCES

1. Agrawal A, Timothy J, Pandit L, Manju M. Post-traumatic epilepsy: An overview. Clin Neurol Neurosurg [Internet]. 2006 Jul [cited 2019 Jan 30];108(5):433–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16225987

2. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung Y-C, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg [Internet]. 2019 Apr 1 [cited 2020 Jan 28];130(4):1080–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29701556

3. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia [Internet]. 2014 Apr [cited 2020 Jan 22];55(4):475–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24730690

4. Majidi S, Makke Y, Ewida A, Sianati B, Qureshi AI, Koubeissi MZ, et al. Prevalence and Risk Factors for Early Seizure in Patients with Traumatic Brain Injury: Analysis from National Trauma Data Bank. Neurocrit Care [Internet]. 2017;27(1):90–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med13&NEWS=N&AN=28000125

5. Tubi MA, Lutkenhoff E, Blanco MB, Mcarthur D, Villablanca P, Ellingson B, et al. Early seizures and temporal lobe trauma predict post-traumatic epilepsy: A longitudinal study. Neurobiol Dis [Internet]. 2019 Mar [cited 2019 Jan 29];123(April 2018):115–21. Available from: https://doi.org/10.1016/j.nbd.2018.05.014

6. Aarabi B, Taghipour M, Haghnegahdar A, Farokhi M, Mobley L, Neurosurgery DO. Prognostic factors in the occurrence of posttraumatic epilepsy after penetrating head injury suffered during military service. Neurosurg Focus [Internet]. 2000;8(1):e1. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=44457508

7. Temkin NR. Risk factors for posttraumatic seizures in adults. Epilepsia [Internet]. 2003 [cited 2018 Mar 26];44 Suppl 1(SUPPL. 10):18–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14511390

8. Zhao Y, Wu H, Wang X, Li J, Zhang S, Y. Z, et al. Clinical epidemiology of posttraumatic epilepsy in a group of Chinese patients. Seizure [Internet]. 2012;21(5):322–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=51914976

9. DeGrauw X, Thurman D, Xu L, Kancherla V, DeGrauw T, X. D, et al. Epidemiology of traumatic brain injury-associated epilepsy and early use of anti-epilepsy drugs: An analysis of insurance claims data, 2004-2014. Epilepsy Res [Internet]. 2018;146:41–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medc&NEWS=N&AN=30071385

10. Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg [Internet]. 1999;91(5):750–60. Available from: http://thejns.org/doi/10.3171/jns.1999.91.5.0750

11. Waziri A, Claassen J, Morgan Stuart R, Arif H, Michael Schmidt J, Mayer SA, et al. Intracortical electroencephalography in acute brain injury. Ann Neurol. 2009;66(3):366–77.

12. Vespa P, Tubi M, Claassen J, Buitrago-Blanco M, McArthur D, Velazquez AG, et al. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. Ann Neurol [Internet]. 2016;79(4):579–90. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med12&NEWS=N&AN=26814699

13. Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus Statement

on Continuous EEG in Critically Ill Adults and Children , Part II : Personnel , Technical Specifications ,. 2015;32(2).

14. Mazzini L, Cossa FM, Angelino E, Campini R, Pastore I, Monaco F, et al. Posttraumatic epilepsy: neuroradiologic and neuropsychological assessment of long-term outcome. Epilepsia [Internet]. 2003;44(4):569–74. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=37057502

15. Bushnik T, Englander J, Wright J, Kolakowsky-Hayner SA. Traumatic brain injury with and without late posttraumatic seizures: what are the impacts in the post-acute phase: a NIDRR Traumatic Brain Injury Model Systems study. J Head Trauma Rehabil [Internet]. 2012;27(6):E36-44. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=23131969

16. Kolakowsky-Hayner SA, Wright J, Englander J, Duong T, Ladley-O'Brien S, S.A. K-H, et al. Impact of late post-traumatic seizures on physical health and functioning for individuals with brain injury within the community. Brain Inj [Internet]. 2013;27(5):578–86. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS=N&AN=368731399

17. Juengst SB, Wagner AK, Ritter AC, Szaflarski JP, Walker WC, Zafonte RD, et al. Post-traumatic epilepsy associations with mental health outcomes in the first two years after moderate to severe TBI: A TBI Model Systems analysis. Epilepsy Behav [Internet]. 2017;73:240–6. Available from: http://www.elsevier.com/inca/publications/store/6/2/2/8/2/2/index.htt

18. Lin W-JJ, Harnod T, Lin C-LL, Kao C-HH. Mortality Risk and Risk Factors in Patients with Posttraumatic Epilepsy: A Population-Based Cohort Study. Int J Environ Res Public Health [Internet]. 2019;16(4):589. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=30781634

19. Englander J, Bushnik T, Wright JM, Jamison L, Duong TT, J. E, et al. Mortality in late post-traumatic seizures. J Neurotrauma [Internet]. 2009;26(9):1471–7. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=355680267

20. Uski J, Lamusuo S, Teperi S, Löyttyniemi E, Tenovuo O, Loyttyniemi E, et al. Mortality after traumatic brain injury and the effect of posttraumatic epilepsy. Neurology [Internet]. 2018;91(9):e878–83. Available from: http://www.neurology.org

21. Wang, HC, Chang, WN, Chang, HW, et al. Factors predictive of outcome in posttraumatic seizures. J Trauma - Inj Infect Crit Care [Internet]. 2008 Apr;64(4):883–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=18404052

22. Raymont V, Salazar AM, Lipsky R, Goldman D, Tasick G, Grafman J, et al. Correlates of posttraumatic epilepsy 35 years following combat brain injury. Neurology [Internet]. 2010;75(3):224–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=359248605

23. Jabbari B, Prokhorenko O, Khajavi K, Mena H. Intractable epilepsy and mild brain injury: Incidence, pathology and surgical outcome. Brain Inj [Internet]. 2002 Jun;16(6):463–7. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=106794940&site=ehost-live

24. Eftekhar B, Sahraian MA, Nouralishahi B, Khaji A, Vahabi Z, Ghodsi M, et al. Prognostic factors in the persistence of posttraumatic epilepsy after penetrating head injuries sustained in war: Clinical article. J Neurosurg [Internet]. 2009;110(2):319–26. Available from: http://thejns.org/doi/pdf/10.3171/2008.4.17519

25. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery [Internet]. 2016 Sep 1

[cited 2018 Mar 26];80(1):1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27654000

26. Vespa PM, Shrestha V, Abend N, Agoston D, Au A, Bell MJ, et al. The epilepsy bioinformatics study for anti-epileptogenic therapy (EpiBioS4Rx) clinical biomarker: Study design and protocol. Neurobiol Dis [Internet]. 2019;123:110–4. Available from: http://www.elsevier.com/inca/publications/store/6/2/2/9/2/3/index.htt

27. Xu T, Yu X, Ou S, Liu X, Yuan J, Huang H, et al. Risk factors for posttraumatic epilepsy: A systematic review and meta-analysis. Epilepsy Behav [Internet]. 2017 Feb [cited 2017 May 30];67:1–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28076834

28. Pitkänen A, Immonen R. Epilepsy related to traumatic brain injury. Neurotherapeutics [Internet]. 2014 Apr;11(2):286–96. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=103819614&site=ehost-live

29. Ritter AC, Wagner AK, Fabio A, Pugh MJ, Walker WC, Szaflarski JP, et al. Incidence and risk factors of posttraumatic seizures following traumatic brain injury: A Traumatic Brain Injury Model Systems Study. Epilepsia [Internet]. 2016 Dec [cited 2017 May 30];57(12):1968–77. Available from: http://www3.interscience.wiley.com/journal/117957420/issueyear?year=2009

30. Christensen, J, Pedersen, M, Pedersen, C, Sidenius, P, Olsen, J, Vestergaard, M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. Lancet [Internet]. 2009;373(9669):1105–10. Available from: http://www.journals.elsevier.com/the-lancet/

31. Wang H, Xin T, Sun X, Wang S, Guo H, Holton-Burke C, et al. Post-traumatic seizures-A prospective, multicenter, large case study after head injury in China. Epilepsy Res [Internet]. 2013;107(3):272–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med9&NEWS=N&AN=24239245

32. Chen W, Li M De, Wang GF, Yang XF, Liu L, Meng FG. Risk of post-traumatic epilepsy after severe head injury in patients with at least one seizure. Neuropsychiatr Dis Treat [Internet]. 2017;13:2301–6. Available from: https://www.dovepress.com/getfile.php?fileID=38180

33. Mahler B, Carlsson S, Andersson T, Adelöw C, Ahlbom A, Tomson T. Unprovoked seizures after traumatic brain injury: A population-based case-control study. Epilepsia. 2015;56(9):1438–44.

34. AM H, NR T, SS D, Haltiner AM, Temkin NR, Dikmen SS. Risk of seizure recurrence after the first late posttraumatic seizure. Arch Phys Med Rehabil [Internet]. 1997 Aug;78(8):835–40. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=107240211&site=ehost-live

35. McCrory PR, Bladin PF, Berkovic SF. Retrospective study of concussive convulsions in elite Australian rules and rugby league footballers: phenomenology, aetiology, and outcome. BMJ [Internet]. 1997 Jan 18 [cited 2017 May 30];314(7075):171–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9022428

36. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia [Internet]. 2010 Apr 1 [cited 2020 Feb 4];51(4):671–5. Available from: http://doi.wiley.com/10.1111/j.1528-1167.2009.02285.x

37. Jennett B, Teather D, Bennie S. Epilepsy After Head Injury. Lancet [Internet]. 1973 Sep;302(7830):652–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673673924884

38. Englander J, Bushnik T, Duong TT, Cifu DX, Zafonte R, Wright J, et al. Analyzing risk factors for late posttraumatic seizures: A prospective, multicenter investigation. Arch Phys Med Rehabil [Internet]. 2003;84(3 SUPPL. 1):365–73. Available from:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12638104

39. Kwan P, Schachter SC, Brodie MJ. Drug-Resistant Epilepsy. N Engl J Med [Internet]. 2011 Sep 8 [cited 2017 May 30];365(10):919–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21899452

40. Bushnik T, Englander J, Duong T. Medical and social issues related to posttraumatic seizures in persons with traumatic brain injury. J Head Trauma Rehabil [Internet]. 2004 Jul;19(4):296–304. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=106556600&site=ehost-live

41. Jabbarinejad R, Cohen-Zimerman S, Wagner AK, Grafman J. Determinants of caregiver burden in male patients with epilepsy following penetrating traumatic brain injury. Epilepsy Behav [Internet]. 2021 Mar;116:107768. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1525505021000020

42. Semple BD, Zamani A, Rayner G, Shultz SR, Jones NC. Affective, neurocognitive and psychosocial disorders associated with traumatic brain injury and post-traumatic epilepsy. Neurobiology of Disease [Internet]. 2018;0–1. Available from: https://doi.org/10.1016/j.nbd.2018.07.018

43. CL H-F. Mortality and life expectancy after traumatic brain injury rehabilitation. [Internet]. Mortality & Life Expectancy After Traumatic Brain Injury Rehabilitation. University of Colorado Health Sciences Center; 2003. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=109843473&site=ehost-live

44. Tenyi D, Gyimesi C, Horvath R, Kovacs N, Abraham H, Darnai G, et al. Concussive convulsions: A YouTube video analysis. Epilepsia [Internet]. 2016;57(8):1310–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med12&NEWS=N&AN=27334642

45. Wennberg R, Hiploylee C, Tai P, Tator CH, R. W, C. H, et al. Is Concussion a Risk Factor for Epilepsy? Can J Neurol Sci [Internet]. 2018;45(3):275–82. Available from: http://journals.cambridge.org/action/displayBackIssues?jid=CJN

46. Webb TS, Whitehead CR, Wells TS, Gore RK, Otte CN. Neurologically-related sequelae associated with mild traumatic brain injury. Brain Inj [Internet]. 2015 Apr;29(4):430–7. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=103788445&site=ehost-live

47. Safaz I, Alaca R, Yasar E, Tok F, Yilmaz B, I. S, et al. Medical complications, physical function and communication skills in patients with traumatic brain injury: A single centre 5-year experience. Brain Inj [Internet]. 2008;22(10):733–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=352378572

48. Walker WC, Ketchum JS, Marwitz JH, Kolakowsky-Hayner SA, McClish DK, Bushnik T, et al. Global Outcome and Late Seizures After Penetrating Versus Closed Traumatic Brain Injury: A NIDRR TBI Model Systems Study. J Head Trauma Rehabil [Internet]. 2015 Jul;30(4):231–40. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=109626612&site=ehost-live

49. Yeh C-C, Chen T-L, Hu C-J, Chiu W-T, Liao C-C. Risk of epilepsy after traumatic brain injury: a retrospective population-based cohort study. J Neurol Neurosurg Psychiatry [Internet]. 2013 Apr;84(4):441–5. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=104247448&site=ehost-live

50. Thapa A, Chandra SP, Sinha S, Sreenivas V, Sharma BS, Tripathi M. Post-traumatic seizures-A prospective study from a tertiary level trauma center in a developing country. Seizure [Internet]. 2010;19(4):211–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=50812746

51. Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M. Predictors of new-onset seizures: A 10-year follow-

up of head trauma subjects with and without traumatic brain injury. J Neurol Neurosurg Psychiatry [Internet]. 2014 Jun;85(6):598–602. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=103942457&site=ehost-live

52. Ritter AC, Wagner AK, Szaflarski JP, Brooks MM, Zafonte RD, Pugh MJ V, et al. Prognostic models for predicting posttraumatic seizures during acute hospitalization, and at 1 and 2 years following traumatic brain injury. Epilepsia [Internet]. 2016;57(9):1503–14. Available from: http://www3.interscience.wiley.com/journal/117957420/issueyear?year=2009

53. Andelic N, Hammergren N, Bautz-Holter E, Sveen U, Brunborg C, Roe C. Functional outcome and health-related quality of life 10 years after moderate-to-severe traumatic brain injury. Acta Neurol Scand [Internet]. 2009;120(1):16–23. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=18976326

54. Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M, et al. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. Lancet [Internet]. 2009 Mar 28;373(9669):1105–10. Available from: http://dx.doi.org/10.1016/S0140-6736(09)60214-2

55. Ferguson PL, Smith GM, Wannamaker BB, Thurman DJ, Pickelsimer EE, Selassie AW, et al. A population-based study of risk of epilepsy after hospitalization for traumatic brain injury. Epilepsia [Internet]. 2010;51(5):891–8. Available from: http://www3.interscience.wiley.com/cgi-bin/fulltext/122655977/PDFSTART

56. Bhattacharyya K, Mandal N, Paul UK uma., Bhattacharyya AK uma., Sinharay K, Gantait K. Post-traumatic seizure: a multicentric epidemiological study. J Indian Med Assoc [Internet]. 2014;112(2):93–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med10&NEWS=N&AN=25935962

57. Pugh MJ V., Orman JA, Jaramillo CA, Salinsky MC, Eapen BC, Towne AR, et al. The prevalence of epilepsy and association with traumatic brain injury in veterans of the Afghanistan and Iraq wars. J Head Trauma Rehabil [Internet]. 2015 Jan;30(1):29–37. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=103878770&site=ehost-live

58. Liu Z, Chen Q, Chen Z, Wang J, Tian D, Wang L, et al. Clinical analysis on risk factors and prognosis of early post-traumatic epilepsy. Arq Neuropsiquiatr [Internet]. 2019;77(6):375–80. Available from: http://www.scielo.br/pdf/anp/v77n6/0004-282X-anp-77-6-0375.pdf

59. Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med [Internet]. 2007;35(12):2830–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=350175782

60. Dhakar MB, Sivakumar S, Bhattacharya P, Shah A, Basha MM. A retrospective cross-sectional study of the prevalence of generalized convulsive status epilepticus in traumatic brain injury: United States 2002-2010. Seizure [Internet]. 2015 Nov;32:16–22. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=111569661&site=ehost-live

61. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A Randomized, Double-Blind Study of Phenytoin for the Prevention of Post-Traumatic Seizures. N Engl J Med [Internet]. 1990;323(8):497–502. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJM199008233230801

62. Inaba, K, Menaker, J, Branco, B et al. A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. J Trauma Acute Care Surg [Internet]. 2013 Mar [cited 2017 May 30];74(3):766–73. Available from:

http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=01586154-201303000-00008

63. Yang Y, Zheng F, Xu X, Wang X. Levetiracetam Versus Phenytoin for Seizure Prophylaxis Following Traumatic Brain Injury: A Systematic Review and Meta-Analysis. CNS Drugs [Internet]. 2016 Aug 9 [cited 2018 Mar 26];30(8):677–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27395404

64. Chang BS, Lowenstein DH, Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology [Internet]. 2003 Jan 14 [cited 2018 Mar 26];60(1):10–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12525711

65. Bakr A, Belli A. A systematic review of levetiracetam versus phenytoin in the prevention of late post-traumatic seizures and survey of UK neurosurgical prescribing practice of antiepileptic medication in acute traumatic brain injury. Br J Neurosurg [Internet]. 2018;32(3):237–44. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medc1&NEWS=N&AN=29688078

66. Candy N, Tsimiklis C, Poonnoose S, Trivedi R. The use of antiepileptic medication in early post traumatic seizure prophylaxis at a single institution. J Clin Neurosci [Internet]. 2019;69:198–205. Available from: http://www.elsevier.com/inca/publications/store/6/2/3/0/5/6/index.htt

67. Bateman RM, Sharpe MD, Jagger JE, Ellis CG, Solé-Violán J, López-Rodríguez M, et al. 36th International Symposium on Intensive Care and Emergency Medicine. Crit Care [Internet]. 2016 Apr 20;20(S2):94. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=72279134

68. Kwon SJ, Barletta JF, Hall ST, Mangram AJ, Dzandu JK, Abdulhamid M, et al. Lacosamide versus phenytoin for the prevention of early post traumatic seizures. J Crit Care [Internet]. 2019;50:50–3. Available from: http://www.elsevier.com/inca/publications/store/6/2/3/1/4/3/index.htt

69. Ogunrin OA, Adeyekun AA, O.A. O, Ogunrin OA, Adeyekun AA. Profile of post-traumatic epilepsy in Benin City, Nigeria. West Afr J Med [Internet]. 2010;29(3):153–7. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medc&NEWS=N&AN=20665457

70. Kazemi, H, Hashemi-Fesharaki, S, Razaghi, S et al. Intractable epilepsy and craniocerebral trauma: Analysis of 163 patients with blunt and penetrating head injuries sustained in war. Injury [Internet]. 2012;43(12):2132–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=22763317

71. Hudak AM, Trivedi K, Harper CR, Booker K, Caesar RR, Agostini M, et al. Evaluation of seizure-like episodes in survivors of moderate and severe traumatic brain injury. J Head Trauma Rehabil [Internet]. 2004 Jul;19(4):290–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=38938194

72. Salinsky M, Storzbach D, Goy E, Evrard C. Traumatic brain injury and psychogenic seizures in veterans. J Head Trauma Rehabil [Internet]. 2015 Jan;30(1):E65–70. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=103878775&site=ehost-live

73. Nightscales R, McCartney L, Auvrez C, Tao G, Barnard S, Malpas CB, et al. Mortality in patients with psychogenic nonepileptic seizures. Neurology [Internet]. 2020 Aug 11;95(6):e643–52. Available from: http://www.neurology.org/lookup/doi/10.1212/WNL.0000000000009855

74. Temkin NR. Preventing and treating posttraumatic seizures: The human experience. In: Epilepsia. 2009.

75. Kancharla TR, Ravula V, Mohan R, Nagesh A. Comparing the Efficacy of Phenytoin, Levetiracetam

and Sodium Valproate in Prevention of Post-Traumatic Seizures in Brain Injury. Int Res J Pharm [Internet]. 2019;10(4):156–60. Available from: http://www.irjponline.com

76. Mee H, Kolias AG, Chari A, Ercole A, Lecky F, Turner C, et al. Pharmacological management of post-traumatic seizures in adults: current practice patterns in the UK and the Republic of Ireland. Acta Neurochir (Wien) [Internet]. 2019;161(3):457–64. Available from: lhttp://www.springer.com/medicine/surgery/journal/701

77. Zimmermann LL, Martin RM, Girgis F. Treatment options for posttraumatic epilepsy. Curr Opin Neurol [Internet]. 2017 Dec;30(6):580–6. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=126212812&site=ehost-live

78. Hakimian S, Kershenovich A, Miller JW, Ojemann JG, Hebb AO, D'Ambrosio R, et al. Long-term outcome of extratemporal resection in posttraumatic epilepsy. Neurosurg Focus [Internet]. 2012 Mar [cited 2019 Jan 29];32(3):E10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22380851

79. Swartz BE, Houser CR, Tomiyasu U, Walsh GO, DeSalles A, Rich JR, et al. Hippocampal cell loss in posttraumatic human epilepsy. Epilepsia [Internet]. 2006;47(8):1373–82. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=44200419

80. Storti SF, Formaggio E, Franchini E, Bongiovanni LG, Cerini R, Fiaschi A, et al. A multimodal imaging approach to the evaluation of post-traumatic epilepsy. Magn Reson Mater Physics, Biol Med [Internet]. 2012;25(5):345–60. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=22592963

81. Gupta PK, Sayed N, Ding K, Agostini MA, Van Ness PC, Yablon S, et al. Subtypes of Post-Traumatic Epilepsy: Clinical, Electrophysiological, and Imaging Features. J Neurotrauma [Internet]. 2014;31(16):1439–43. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed15&NEWS=N&AN=373780717

82. Esquenazi Y, Kalamangalam GP, Hope OA, Krish SN, Slater J, Tandon N. Surgical Resection for Epilepsy Following Cerebral Gunshot Wounds. World Neurosurg [Internet]. 2016;95:276–84. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med12&NEWS=N&AN=27546337

83. Hitti FL, Piazza M, Sinha S, Kvint S, Hudgins E, Baltuch G, et al. Surgical Outcomes in Post-Traumatic Epilepsy: A Single Institutional Experience. Oper Neurosurg [Internet]. 2019;18(1):12–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexb&NEWS=N&AN=627166476

84. Rehman R, Kelly PR, Husain AM, Tran TT. Characteristics of veterans diagnosed with seizures within veterans health administration. J Rehabil Res Dev [Internet]. 2015 Aug;52(7):751–62. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=111491880&site=ehost-live

85. Durand E, Watier L, Fix M, Weiss JJ, Chevignard M, Pradat-Diehl P. Prevalence of traumatic brain injury and epilepsy among prisoners in France: Results of the Fleury TBI study. Brain Inj [Internet]. 2016;30(4):363–72. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med12&NEWS=N&AN=26963289

86. Lopez MR, Cheng JY, Kanner AM, Carvalho DZ, Diamond JA, Wallace DM. Insomnia symptoms in South Florida military veterans with epilepsy. Epilepsy Behav [Internet]. 2013;27(1):159–64. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS=N&AN=368452635

87. Busek P, Faber J. The influence of traumatic brain lesion on sleep architecture. Sborník lékarský [Internet]. 2000;101(3):233–9. Available from:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=33444500

88. Cotter D, Kelso A, Neligan A. Genetic biomarkers of posttraumatic epilepsy: A systematic review. Seizure [Internet]. 2017 Mar [cited 2017 May 30];46:53–8. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=122088002&site=ehost-live

89. Hunt RF, Boychuk JA, Smith BN. Neural circuit mechanisms of post–traumatic epilepsy. Front Cell Neurosci [Internet]. 2013;7(June):1–14. Available from: http://journal.frontiersin.org/article/10.3389/fncel.2013.00089/abstract

90. Saghazadeh A, Mahmoudi M, Meysamie A, Gharedaghi M, Zamponi GW, Rezaei N. Possible role of trace elements in epilepsy and febrile seizures: a meta-analysis. Nutr Rev [Internet]. 2015 Nov [cited 2017 May 30];73(11):760–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26433016

91. Immonen R, Kharatishvili I, Gröhn O, Pitkänen A, Grö Hn O, Pitkä Nen A. MRI Biomarkers for Post-Traumatic Epileptogenesis. J Neurotrauma [Internet]. 2013 Jul 15 [cited 2017 May 30];30(14):1305–9. Available from: www.liebertpub.com/neu

92. Bragin A, Li L, Almajano J, Alvarado-Rojas C, Reid AY, Staba RJ, et al. Pathologic electrographic changes after experimental traumatic brain injury. Filizola M, editor. Epilepsia [Internet]. 2016 May;57(5):735–45. Available from: http://link.springer.com/10.1007/978-1-4939-2914-6

93. Perucca P, Smith G, Santana-Gomez C, Bragin A SR. Electrophysiological biomarkers of epileptogenicity after traumatic brain injury. Neurobiol Dis. 2018;In Press,.

94. Ney JP, Goes DN Van Der, Nuwer MR, Nelson L, Eccher MA, Van Der Goes DN, et al. Continuous and routine eeg in intensive care. Neurology [Internet]. 2013 [cited 2018 Apr 23];81(23):2002–8. Available from: www.neurology.org

95. Hill CE, Blank LJ, Thibault D, Davis KA, Dahodwala N, Litt B, et al. Continuous EEG is associated with favorable hospitalization outcomes for critically ill patients. Neurology. 2019;92(1):E9–18.

96. Vespa P, Martin NA, Nenov V, Glenn T, Bergsneider M, Kelly D, et al. Delayed increase in extracellular glycerol with post-traumatic electrographic epileptic activity: Support for the theory that seizures induce secondary injury. Acta Neurochir Suppl [Internet]. 2002;81(81):355–7. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=35531678

97. Vespa PM, McArthur DL, Xu Y, Eliseo M, Etchepare M, Dinov I, et al. Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. Neurology [Internet]. 2010;75(9):792–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=20805525

98. Le Roux P, Menon DK, Citerio G, Vespa P, Bader MK, Brophy GM, et al. Consensus Summary Statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: A statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive C. Neurocrit Care. 2014;21(2):1–26.

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Risk Factors and Prognosis of Early Posttraumatic Seizures in Moderate-Severe Traumatic Brain Injury: A Population-Based Study

Joshua Laing, Belinda Gabbe, Zhibin Chen, Piero Perucca, Patrick Kwan, Terence J. O'Brien

KEY POINTS

Questions:

What are the risk factors, and what is the impact of early posttraumatic seizures (EPS) following moderate to severe traumatic brain injury (TBI)?

Findings:

Risk factors for EPS may be identified via multivariable analysis and prediction algorithm. TBI severity, prior medical comorbidities, and presence of subdural haematoma or subarachnoid haemorrhage are most important. EPS are associated with poor outcomes including mortality after adjustment for confounders.

Meaning:

EPS are important following moderate to severe TBI and may be predicted via identified clinical risk factors.

ABSTRACT

Importance:

Early posttraumatic seizures (EPS) may occur following traumatic brain injury (TBI), associated with poorer outcomes and development of posttraumatic epilepsy (PTE).

Objective:

To evaluate risk factors for EPS, associated morbidity and mortality, and contribution to PTE.

Design:

Australian registry-based cohort study of adults (age ≥18 years) with moderate to severe TBI from January 2005 to December 2019, with 2-year follow up.

Setting:

Victorian (population 6.5 million) statewide trauma registry.

Participants:

15,152 patients with moderate-to-severe TBI identified via Abbreviated Injury Scale (AIS) head score were included in the registry conducted on an opt-out basis (<0.5%).

Main outcomes:

EPS was identified via ICD-10-AM codes recorded following the acute admission. Outcome measures also included in-hospital metrics, 2-year outcomes including PTE, and post-discharge mortality. Adaptive least absolute shrinkage and selection operator (LASSO) regression was used to build a prediction model for risk factors of EPS .

Results:

Among the 15,152 participants (10,457 [69%] male, median age [Interquartile range, IQR]: 60 [35-79]), 416 (2.7%) were identified with EPS, including 27 (0.2%) with status epilepticus. Significant risk factors on multivariable analysis for developing EPS were younger age, higher Charlson Comorbidity Index, TBI sustained from a low fall, subdural hemorrhage, subarachnoid hemorrhage, higher Injury Severity Score, and greater head injury severity, measured using the AIS and Glasgow Coma Score. Following adjustment for confounders, EPS was associated with increased ICU admission and length of stay (LoS), ventilation and

duration, hospital LoS, discharge to inpatient rehabilitation rather than home, but not in-hospital mortality. Outcomes in TBI admission survivors at 24-months, including mortality (relative risk [RR]=2.14, 95% CI: 1.32-3.46, p=0.002), development of PTE (RR=2.91, 95% CI: 2.22-3.81, p<0.001), and use of antiseizure medications (RR=2.44, 95% CI: 1.98-3.02, p<0.001), were poorer for cases with EPS after adjustment for confounders. The prediction model for EPS had an area under the receiver operating characteristics curve of 0.72 (95% CI: 0.66-0.79), sensitivity of 66% and specificity of 73% in the validation set.

Discussion:

We identified important risk factors for EPS following moderate-to-severe TBI. EPS were associated with longer ICU and hospital admissions, ICU ventilation, and poorer 24-month outcomes including mortality and development of PTE.

INTRODUCTION

Early posttraumatic seizures (EPS) occur during the acute phase following a traumatic brain injury (TBI). The incidence of EPS varies, depending on the population and EPS definition, from 0.4 to 10.5% (1–8). EPS have been associated with greater morbidity and mortality (6,9).

The role of EPS in the subsequent development of recurrent unprovoked seizures, or posttraumatic epilepsy (PTE), is not well understood. EPS may increase the risk of PTE (10). Whether treatment of EPS exerts an anti-epileptogenic effect on developing PTE is largely unknown. Anti-seizure prophylaxis is recommended for the first 7 days following TBI, but has no known longer term benefits in preventing PTE (11). Once the first late unprovoked posttraumatic seizure occurs, the prevalence of seizures is as high as 86% at two years (12). Suppression of EPS may reduce the risk of PTE, which accounts for 20% of acquired, and 5% of all, epilepsies (13). Prediction of patients at higher risk of EPS may allow a precision medicine approach to diagnosis and would inform clinical trials of potential anti-epileptogenic therapies.

Studies evaluating risk factors for the development of EPS are relatively few. Older age (6), TBI severity (6,11), medical comorbidities, subdural haemorrhage (SDH) (2,6), epidural haematoma (ED) (11), brain contusion (2), and chronic alcohol abuse (2,11), and other in-hospital complications (6) have been identified as risk factors for EPS. Only one study developed a model of predicting EPS but had poor predictive performance (14).

Using an Australian population-based trauma registry, the aims of this study were to: (i) identify risk factors for EPS, (ii) assess the association between EPS and short-term and long-term morbidity, including PTE, and mortality, and (iii) develop a risk assessment prediction model for EPS.

METHODS

Study Design

This was a registry-based cohort study. Adult patients (≥ 18 years), with a date of injury from January 2005 to December 2019, registered on the Victorian State Trauma Registry (VSTR), with a moderate to severe TBI were included. Patients with a pre-existing diagnosis of epilepsy were excluded from the study.

Data Collection

Moderate to severe TBI was defined as an Abbreviated Injury Scale (AIS) head severity score of 3-6, indicating moderate to severe intracranial injury or skull fracture (15). The AIS is an anatomical injury severity scoring system, with established correlation with TBI outcomes (15). Anonymized data for these cases were extracted. Data extracted included demographics, admission information, injury event details, operations and procedures, ICD-10-AM diagnosis and comorbidities, and discharge information including in-hospital mortality.

International Statistical Classification of Diseases and Related Health Problems 10th Revision–Australian Modification (ICD-10-AM) codes (R56.8 – unspecified convulsions, G41 – status epilepticus, G40 – acute symptomatic seizures) were used to identify EPS as new onset seizures during the acute admission, excluding pre-existing seizures and epilepsy, as per previous studies (6,7). Non-convulsive seizures or electrographic were not independently identified. Trained registry coders complete the ICD-10-AM coding once the admission is complete and are regularly audited. Isolated TBI was defined as the absence of an any other AIS body region with a severity score >1. The Injury Severity Score (ISS) is derived from the AIS to provide an overall severity score (15). The initial Glasgow Coma Scale (GCS) score was used as a further measure of TBI severity. Other initial vital sign observations were recorded. The Charlson Comorbidity Index (CCI), and indicators for pre-existing mental health, drug and alcohol conditions, were mapped from the ICD-10-AM codes (16,17). The Accessibility and Remoteness Index of Australia (ARIA), a measure used for relation to

accessible services including healthcare, and the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) to social status, were determined by residential postcode.

All cases on the VSTR are routinely followed-up by standardized, structured telephone interview at 6, 12 and 24 months post-injury and the Glasgow Outcome Scale-Extended (GOS-E) collected. Consistent with other studies, diagnosis of PTE was determined by patient responses to the GOS-E question "Since the injury, has the patient had any epileptic fits?" (18). Post-discharge mortality was determined by data linkage with the Victorian Registry of Births, Deaths and Marriages (BDM) to July 2019.

Statistical Analysis

Frequencies and percentages for categorical variables, and median and interquartile ranges (IQR) for non-normally distributed continuous variables, were used to summarize the data. Incidence of EPS was calculated as the ratio of EPS to TBI in each year of the study. Poisson regression with adjustment for age and sex was used to measure the change in the incidence of EPS over the study period. Univariable associations between individual variables and development of EPS were assessed using chi-square statistics for categorical variables and Mann-Whitney U-tests for non-normally distributed continuous variables. Factors with a p-value <0.2 were included in the multivariable Poisson regression model with robust variance to measure their association with EPS. Adjusted risk ratios, and the corresponding 95% confidence intervals, were reported. Multivariable multinomial logistic regression was performed to assess the association between EPS and GOS-E outcomes in survivors at 24-months. Little's test of missing completely at random (19) was used to test the missingness of the follow-up outcomes (GOS-E and PTE) at each time point. To assess the association between EPS and long-term mortality in survivors, univariable log-rank test for categorical variables and Wald test in Cox regression for continuous variables were first performed to screen potential risk factors for long-term mortality. EPS and covariates with univariable p-values <0.2 were included in the multivariable Cox regression model. Statistical significance level was set at $p<0.05$. Holm-Bonferroni method was used to correct for post-hoc pairwise comparisons in categorical variables with more than 2 groups.

Prediction model

Adaptive least absolute shrinkage and selection operator (LASSO) regression (20) was used to develop a prediction model for EPS. Adaptive LASSO is a multistep version of the conventional cross-validation based LASSO where adaptive weights are further applied for penalizing different coefficients. Covariates whose estimated coefficients are zero were excluded. Per conventional partition protocol, we randomly selected 80% of patients in the cohort as the training set and the remaining 20% as the test set. The ability of the model to predict EPS was evaluated with a series of metrics including area under the receiver operating characteristics (ROC) curve, accuracy, sensitivity, and specificity. All statistical tests and adaptive LASSO regression were performed using Stata version 16 (StataCorp, College Station, TX).

RESULTS

Incidence of EPS

A total of 15,152 patients met the criteria for inclusion (median length of stay [LoS]: 7.0 days, [IQR]: 3.6-13.8); 416 (2.7%) had EPS (median LoS: 17.0 days, IQR: 9.4-28.6) (eTable 1). EPS incidence decreased each year (incidence rate ratio: 0.94; 95% confidence interval [CI]: 0.92-0.96, p<0.001). Of patients with EPS, 6.5% experienced status epilepticus (0.2% of all cases).

Demographics and Pre-existing Illness

Patients experiencing EPS were older than patients who did not experience EPS (median [IQR]: 69 [44-81] vs. 60 [35-79] years). There was no association between sex, service accessibility and rurality (ARIA), pre-existing mental health conditions and drug misuse, and socioeconomic status, and EPS (eTable 2). Compared to patients without EPS, a higher CCI and pre-existing alcohol misuse were associated with EPS (eTable 2).

Injury and Neurosurgical Characteristics

A higher proportion of patients with EPS sustained their injury in a low fall (from standing height or <1m) than patients without EPS (eTable 3). The prevalence of isolated TBI, SDH, subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), EDH and base of skull fracture (BOSF) was higher in patients with EPS, , than patients without EPS. Greater severity of head injury (AIS or GCS), and injury overall (ISS) was associated with EPS. Any neurosurgical intervention was associated with a higher proportion of EPS compared to patients without EPS.

Hospital Services and Vital Characteristics

A higher proportion of patients who developed EPS were admitted to major trauma services and took longer to arrive at hospital (eTable 4). Median pulse rate, respiratory rate did not differ by EPS group; median blood pressure was higher (140 vs 147mmHg) in patients who developed EPS.

Hospital Morbidity and Mortality

Compared to patients without EPS, a higher proportion of patients with EPS were admitted to ICU (eTable 5), spent longer in ICU (median 5 vs 8 days) and were more often ventilated and for longer (median 4 vs 6 days), spent longer in hospital (median 7 vs 17 days) and a higher proportion were discharged to rehabilitation.

Outcomes at 24 months Follow Up

At 24 months post-injury, 75% of patients eligible for 24-month follow-up had a completed GOS-E. A higher proportion of patients who developed EPS were severely disabled or deceased, compared to patients who did not develop EPS (eTable 6). The PTE question was complete in 1,665 (15%) patients. Higher proportions of patients with EPS had developed PTE (78% [35/45] vs 19% [314/1620], p<0.001) or on anti-seizure medication (ASM) (68% [46/68] vs. 19% [543/2878], p<0.001) by 24 months post-injury.

Long Term Mortality

Long term mortality rate was 14% (n=1,658) in the group without EPS group and 24% (n=76) in the EPS group (P<0.001).

Multivariable Analysis

The variables included in the multivariable analysis are shown in Table 1. Age showed a negligible (RR=0.99) association with EPS. Increasing comorbidity severity was associated with 1.76 (CCI=1) and 3.87 (CCI=2) times the risk of EPS when compared to patients without a CCI condition. Alcohol misuse and trauma type were not associated with EPS. Patients injured from low falls had 1.63 times the risk of EPS compared to patients injured in motor vehicle crashes. Presence of a SDH increased EPS risk by 77%, and SAH by 40%. Patients with an AIS head severity of 5-6 had more than 3 times the risk of EPS compared to patients with AIS 3, and patients with a GCS of 3-8 had 1.47 times the risk of EPS compared to patients with mild head injury. The ISS showed an associated modest smaller risk of EPS.

After adjustment for potential confounders, EPS was associated with in-hospital (Table 2) and longer-term (Table 3), outcomes (Table 3). Patients who developed EPS in hospital had an increased risk of ICU admission, ventilation, and spending longer in ICU ventilated, and longer in hospital, compared to patients who did not develop EPS. Patients with EPS also experienced a higher risk of discharge to inpatient rehabilitation EPS was not associated with in-hospital mortality after adjustment for potential confounders (p=0.67).

Following adjustment for potential confounders, EPS increased the risk of being severely disabled (RR=2.10), in a vegetative state (RR=3.97), and deceased (RR=2.14) at follow-up (Table 3). Patients with EPS had a higher risk of developing PTE (RR=2.91) and being on ASMs (RR=2.44) in the first 24 months after injury. Risk of long-term mortality was similar in patients with EPS and patients without EPS (hazard ratio [HR]=1.22, 95% CI: 0.95-1.55, p=0.12). The median follow-up time for the linkage in patients who survived the TBI was 5.5 years (IQR: 1.9-9.6).

Prediction Modelling Analysis

Using a risk factor prediction algorithm via LASSO regression, EPS were associated with trauma type (isolated TBI over multi-trauma), lower social status (IRSAD), higher medical comorbidity scores, cause of injury including low falls, injury specifics of SDH, SAH, injury severity indicators of AIS head, ISS and GCS. Pre-existing CCI of 2+ (penalized coefficient 0.303), SDH (0.333) and AIS head severity of 5-6 (0.333) were the three highest contributors towards prediction of EPS, with lower pre-existing CCI of 0 having the strongest negative predictor (-0.270) of EPS in the model (Table 4).

The adaptive LASSO regression prediction model for EPS demonstrated an overall performance of area under the ROC curve of 0.72 (95% CI: 0.66-0.79) in the validation set (Figure 1), with a maximum value of Youden's index of 0.39 at total penalized coefficient value of 1.05 (sensitivity=66% and specificity=73%).

DISCUSSION

In this population-based study of >15,000 patients with moderate to severe TBI, we identified clinically relevant risk factors for the development of EPS, and demonstrated a higher risk of morbidity, mortality, and subsequent PTE, in patients with EPS.

The observed prevalence of EPS (2.7%) was consistent with previous studies, although EPS has been variably defined. Some studies separated 'immediate' seizures within 24 hours and 'early' seizures up to 7 days of the TBI. 'Immediate' seizures have been associated with higher risk of PTE (5), but are not well defined and may include an antecedent seizure causing TBI. The International League Against Epilepsy (ILAE) classifies acute symptomatic seizures as "occurring at the time of a systemic insult or in close temporal association with a documented brain insult" of which TBI is included (21). This also suggests use of the arbitrary cut off of 1 week, based on a cohort study of depressed TBI from 1973 (22). There is no evidence that 'late' (unprovoked) seizures or PTE should be defined at ≥1 week given any specified increase in risk of recurrence or aetiological differences.

We observed a prevalence of PTE in patients who had experienced EPS of 11% at 2 years (3% in patients without EPS), with ICU and hospital average length of stay being 10.4 days and 24.5 days respectively for patients with EPS (compared with 7.7 days and 11.0 days respectively for those without EPS). Englander et al (1), closely followed patients from injury to 2 years and reported a high proportion of posttraumatic seizures occurring in the first month was likely multifactorial including acute provoking factors such as brain swelling, perioperative and metabolic factors. Considering the associated complications of mechanical ventilation and other in-hospital sequala moderate-severe TBI (6), any seizure occurring during the acute hospital stay may represent a provoked acute posttraumatic seizure, and therefore termed EPS. Accordingly, the role and duration of antiseizure prophylaxis requires further investigation (23).

Most studies examining EPS were conducted prior to the widespread use of cEEG technology in ICU patients post-TBI. The rate of status epilepticus of 0.2% in this study comparable to previous studies (24), likely exclusively represents convulsive status epilepticus, as the incidence of non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) detected by cEEG in patients post-severe TBI is much higher (25). Whilst long-term outcomes of NCS/NCSE in TBI may be unclear, they are associated with neurophysiological metabolic damage causing secondary injury (26,27), and structural hippocampal atrophy (28). Clinically overt seizures therefore represent "the tip of the iceberg" in relation to all EPS and the incidence rate found in this study is likely a marked underestimate. The use of cEEG may not be beneficial for patients at low risk of acute seizures (29), therefore patient selection for cEEG in TBI using risk factors appears important.

Several risk factors have been identified for EPS following moderate-severe TBI. Pre-injury patient factors such as a history of alcohol misuse and medical comorbidities, previously associated with EPS (6,9,30), may interact with TBI and decompensation during acute admission contributing to EPS separately. TBI severity, measured by surrogate initial GCS or more accurately via composite severity scores such as AIS, confer a worse acute neurological insult provoking EPS (15). This correlates with acute blood products causing irritation of the brain, such as SAH and SDH which are known to independently cause acute seizures. Neurosurgical procedures may also inadvertently cause cerebral irritation and oedema, and were associated with EPS in this as well as in another study (14). The mechanism of injury seems less important and potentially difficult to interpret; although here low falls correlated with EPS in multivariable analysis raising the possibility that an unwitnessed seizure caused the fall. In-hospital complications such as sepsis and metabolic derangements, not evaluated in this study, may contribute to EPS risk although are difficult to predict and attribute causality on a group level. Most variables identified by the prediction algorithm are concordant with the multivariable analysis in this study, including medical comorbidities, low falls, SDH, SAH, and injury severity measures (AIS head, ISS and GCS). Identifying patients at high risk of EPS may assist clinical management and focus evaluation with cEEG, and potentially aid in clinical trial protocol development including antiepileptogenic therapies.

EPS was associated with risk of worsened morbidity and mortality, adjusted for injury severity and other factors in this cohort. As per previous studies, EPS was associated with a longer hospital stay (6), but also ICU admission, ventilation and its duration, and discharge to rehabilitation rather than home. In-hospital mortality was increased in the EPS group but not when adjusted for EPS risk factors including injury severity; yet, patients with EPS had an increased risk of poorer outcomes including mortality at 24 months as measured by the study follow up GOS-E. The instantaneous risk of mortality as assessed by hazard ratio using linkage to the death index (median follow-up 5.5yrs) was non-significant, although the confidence interval only marginally crossed the threshold of non-significance (95% CI: 0.95-1.55, p=0.12).

The association of EPS with an increased risk of developing PTE has been consistently reported (10), however the causal link or epileptogenic process remains unclear. In this study of moderate to severe TBI inclusive of all seizures during the acute admission, just 11% of those with EPS developed PTE, although this was significantly greater that the 3% incidence in patients without EPS. Many risk factors of EPS are similar for PTE, and some studies do not separate these in their analysis. As mentioned earlier, blurring of timeframes for the definitions of EPS and PTE likely contributes to conflicting data in the literature. PTE is associated with significant disability, mortality, and treatment-resistant chronic epilepsy, with the latent phase of PTE or epileptogenesis being the target for novel biomarkers and potential anti-epileptogenic treatments of the international multicenter study EpiBioS4Rx in TBI (31). Even though EPS are associated with an increased risk for developing PTE, the overall risk is not high enough for the recommendation of lifelong ASM therapy. The effect of identification of EPS and its suppression with ASMs on the development of PTE warrants investigation.

This study is an observational study based on registry coded diagnoses, whilst well managed and regularly audited, is a limitation to causality. Whilst there is some missing data, there was a high rate of follow up and the mortality data is strengthened by linkage analysis. Identification of moderate to severe TBI by AIS head

is novel in the literature, considered more accurate than other measures correlating well with overall TBI outcomes (15). Association of EPS with other in-hospital risk factors of acute symptomatic seizures such as systemic infections etc, as assessed in one study (6), was not evaluated due to difficultly in implying causality to EPS. The diagnosis of PTE was performed via self-report questionnaire, rather than epileptologist diagnosed PTE, the later being difficult to implement on a large population level. Given the open questioning in the GOS-E on PTE, patients may have included EPS in their responses to seizures post injury. Despite these limitations, this study remains significant in its cohort size of EPS, multivariable analysis of risk factors for EPS including a novel prediction model, and outcomes with matched cohorts based on risk factors of EPS identified in multivariable analysis.

CONCLUSION

This large cohort study of moderate-severe TBI identified several clinical risk factors that may be used to predict EPS, showing good concordance with a novel machine learning approach, specifically prior medical comorbidities, SAH and SDH, and injury severity. EPS are associated with significant in-hospital morbidity and poorer outcomes, and subsequent risk of mortality at 24 months on follow up GOS-E. Identification of patients at high risk of developing EPS may allow a precision medicine diagnostic approach, focusing management strategies and targeting clinical trials of antiepileptogenic therapies.

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Ethics

All data was supplied by the Victorian State Trauma Outcomes Registry and Monitoring Group (VSTORM), following local ethics approval (MUHREC Project ID 18104). The VSTR has ethical approval from the Victorian Department of Health and Human Services HREC (DHHREC 11/14) and the Monash University HREC (CF13/3040–2001000165).

Disclosures

JL's institution has received honoraria from UCB Pharma, outside the submitted work. PP has received speaker honoraria or consultancy fees to his institution from Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus, and UCB Pharma, outside the submitted work. He is an Associate Editor for Epilepsia Open. ZC's institution has received consultancy fees and/or research grants from Arvelle Therapeutics and UCB Pharma, outside the submitted work. PK's institution has received research grants from Biscayne Pharmaceuticals, Eisai, GW Pharmaceuticals, LivaNova, Novartis, UCB Pharma, and Zynerba outside the submitted work; he has received speaker fees from Eisai, LivaNova, and UCB Pharma, outside the submitted work. TO's institution has received research funding and consultancy fees from UCB, Eisai, LivaNova, Supernus, Praxis Pharmaceuticals, ES Therapeutics and Biogen, outside the submitted work.

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REFERENCES

1. Englander J, Bushnik T, Duong TT, et al. Analyzing risk factors for late posttraumatic seizures: A prospective, multicenter investigation. *Arch Phys Med Rehabil*. 2003;84(3 SUPPL. 1):365–73.
2. Thapa A, Chandra SP, Sinha S, Sreenivas V, Sharma BS, Tripathi M. Post-traumatic seizures-A prospective study from a tertiary level trauma center in a developing country. *Seizure*. 2010;19(4):211–6.
3. Zhao Y, Wu H, Wang X, Li J, Zhang S. Clinical epidemiology of posttraumatic epilepsy in a group of Chinese patients. *Seizure*. 2012;21(5):322–6.
4. Bhattacharyya K, Mandal N, Paul UK, Bhattacharyya AK, Sinharay K, Gantait K. Post-traumatic seizure: a multicentric epidemiological study. *J Indian Med Assoc.* 2014;112(2):93–5.
5. Ritter AC, Wagner AK, Fabio A, et al. Incidence and risk factors of posttraumatic seizures following traumatic brain injury: A Traumatic Brain Injury Model Systems Study. *Epilepsia*. 2016 Dec [cited 2017 May 30];57(12):1968–77.
6. Majidi S, Makke Y, Ewida A, et al. Prevalence and Risk Factors for Early Seizure in Patients with Traumatic Brain Injury: Analysis from National Trauma Data Bank. *Neurocrit Care*. 2017;27(1):90–5.
7. DeGrauw X, Thurman D, Xu L, et al. Epidemiology of traumatic brain injury-associated epilepsy and early use of anti-epilepsy drugs: An analysis of insurance claims data, 2004-2014. *Epilepsy Res*. 2018;146:41–9.
8. Liu Z, Chen Q, Chen Z, et al. Clinical analysis on risk factors and prognosis of early post-traumatic epilepsy. *Arq Neuropsiquiatr*. 2019;77(6):375–80.
9. Wiedemayer H, Triesch K, Schafer H, Stolke D. Early seizures following non-penetrating traumatic brain injury in adults: Risk factors and clinical significance. *Brain Inj*. 2002;16(4):323–30.
10. Tubi MA, Lutkenhoff E, Blanco MB, et al. Early seizures and temporal lobe trauma predict post-traumatic epilepsy: A longitudinal study. *Neurobiol Dis*. 2019 Mar;123:115-121.
11. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury (4th Edition). 2016 Sept. https://braintrauma.org/uploads/03/12/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf. Accessed September 2, 2021
12. Haltiner AM, Temkin NR, Dikmen SS. Risk of seizure recurrence after the first late posttraumatic seizure. *Arch Phys Med Rehabil*. 1997 Aug;78(8):835–40.
13. Agrawal A, Timothy J, Pandit L, Manju M. Post-traumatic epilepsy: An overview. *Clin Neurol Neurosurg*. 2006 Jul;108(5):433–9.
14. Ritter AC, Wagner AK, Szaflarski JP, et al. Prognostic models for predicting posttraumatic seizures during acute hospitalization, and at 1 and 2 years following traumatic brain injury. *Epilepsia*. 2016;57(9):1503–14.
15. Foreman BP, Caesar RR, Parks J, et al. Usefulness of the Abbreviated Injury Score and the Injury Severity Score in Comparison to the Glasgow Coma Scale in Predicting Outcome After Traumatic Brain Injury. *J Trauma Inj Infect Crit Care*. 2007 Apr;62(4):946–50.
16. Gabbe BJ, Magtengaard K, Hannaford AP, Cameron PA. Is the Charlson Comorbidity Index useful for predicting trauma outcomes? *Acad Emerg Med*. 2005 Apr 1;12(4):318–21.
17. Nguyen TQ, Simpson PM, Braaf SC, Cameron PA, Judson R, Gabbe BJ. Comparison of the performance of mental health, drug and alcohol comorbidities based on ICD-10-AM and medical records for predicting 12-month outcomes in trauma patients. *BMC Health Serv Res*. 2018 Dec 5;18(1):408.
18. Wilson JTL, Pettigrew LEL, Teasdale GM. Structured Interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for Their Use. *J Neurotrauma*. 1998 Aug;15(8):573–85.
19. Little RJA. A Test of Missing Completely at Random for Multivariate Data with Missing Values. *J Am Stat Assoc*. 1988 Dec;83(404):1198.
20. Zou H. The Adaptive Lasso and Its Oracle Properties. *J Am Stat Assoc*. 2006 Dec 1;101(476):1418–29.

21. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia*. 2010 Apr 1;51(4):671–5.
22. Jennett B, Teather D, Bennie S. Epilepsy After Head Injury. *Lancet*. 1973 Sep;302(7830):652–3.
23. Chang BS, Lowenstein DH, Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2003 Jan 14;60(1):10–6.
24. Dhakar MB, Sivakumar S, Bhattacharya P, Shah A, Basha MM. A retrospective cross-sectional study of the prevalence of generalized convulsive status epilepticus in traumatic brain injury: United States 2002-2010. *Seizure*. 2015 Nov;32:16–22.
25. Vespa, P, Nenov, V, Nuwer M. Continuous EEG monitoring in the intensive care unit. *J Clin Neurophysiol*. 1999;16(1):1–13.
26. Vespa PM, Miller C, McArthur D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. *Crit Care Med*. 2007;35(12):2830–6.
27. Witsch J, Frey HP, Schmidt JM, et al. Electroencephalographic periodic discharges and frequency-dependent brain tissue hypoxia in acute brain injury. *JAMA Neurol*. 2017 Mar 1;74(3):301–9.
28. Vespa PM, McArthur DL, Xu Y, et al. Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. *Neurology*. 2010;75(9):792–8.
29. Rossetti AO, Schindler K, Sutter R, et al. Continuous vs Routine Electroencephalogram in Critically Ill Adults With Altered Consciousness and No Recent Seizure. *JAMA Neurol*. 2020 Jul 27;1–8.
30. Parmontree P, Tunthanathip T, Doungngern T, Rojpitbulstit M, Kulviwat W. Predictive Risk Factors for Early Seizures in Traumatic Brain Injury. *J Neurosci Rural Pract*. 2019;10(4):582–7.
31. Vespa PM, Shrestha V, Abend N, et al. The epilepsy bioinformatics study for anti-epileptogenic therapy (EpiBioS4Rx) clinical biomarker: Study design and protocol. *Neurobiol Dis*. 2019;123:110–4.

TABLES AND FIGURES

Table 1. Multivariable analysis of demographics, pre-existing conditions and injury characteristics associated with EPS development

Variable	Adjusted Risk Ratio	(95% CI)	*p*-value
Age	0.99	(0.99-1.00)	**0.045**
IRSAD quintile - 1st quintile (most disadvantaged) as reference			0.23
2nd	1.31	(0.93-1.85)	0.12
3rd	0.98	(0.69-1.40)	0.93
4th	0.96	(0.68-1.35)	0.81
5th - least disadvantaged	1.19	(0.87-1.63)	0.29
Pre-existing Charlson comorbidity index - 0 as reference			**<0.001**
1	1.76	(1.34-2.33)	**<0.001**
2+	3.87	(2.95-5.09)	**<0.001**
History of alcohol misuse	1.06	(0.78-1.43)	0.72
Trauma type - isolated TBI as reference			
Multi-trauma	0.95	(0.74-1.22)	0.69
Cause of injury - motor vehicle accident as reference			0.38
Motorcycle	0.88	(0.42-1.84)	0.73
Bicycle	1.51	(0.74-3.11)	0.26
Pedestrian	1.38	(0.79-2.42)	0.26
Low fall	1.63	(1.03-2.56)	**0.035**
High fall	1.33	(0.79-2.23)	0.29
Others	1.46	(0.90-2.38)	0.12
Subdural hematoma	1.77	(1.32-2.37)	**<0.001**
Subarachnoid haemorrhage	1.40	(1.13-1.74)	**0.002**
Intraventricular haemorrhage	1.11	(0.68-1.81)	0.67
Epidural haematoma	0.83	(0.59-1.18)	0.31
Base of skull fracture	0.82	(0.63-1.06)	0.13
Vault fractures	0.89	(0.67-1.19)	0.44
AIS head - 3 as reference			**<0.001**
4	1.45	(1.01-2.07)	**0.042**
5-6	3.02	(1.88-4.84)	**<0.001**
Injury Severity Score	0.98	(0.96-1.00)	**0.037**
Glasgow Coma Scale score- mild head injury as reference			**0.007**
Moderate	1.21	(0.88-1.65)	0.241
Severe	1.47	(1.15-1.87)	**0.002**

AIS, abbreviated injury scale; CI, confidence interval; IRSAD, index of relative socio-economic advantage and disadvantage; TBI, traumatic brain injury.
Factors were included into multivariable analysis with a cut off p=0.2

Table 2. Multivariable analyses of associations between early posttraumatic seizure and hospital outcomes

Hospital Outcome	EPS vs No EPS*		
	Incidence Rate Ratio/Risk Ratio	(95% CI)	*p*-value
ICU admission	1.43	(1.31-1.57)	**<0.001**
ICU ventilated	1.12	(1.07-1.17)	**<0.001**
ICU length of stay - days	1.38	(1.25-1.52)	**<0.001**
ICU ventilated length of stay - days	1.33	(1.19-1.49)	**<0.001**
Hospital length of stay - days	1.89	(1.70-2.10)	**<0.001**
Discharge to home	0.42	(0.31-0.56)	**<0.001**
Discharge to rehabilitation	1.44	(1.30-1.58)	**<0.001**
In-hospital mortality	1.04	(0.86-1.27)	0.67

AIS, abbreviated injury scale; EPS, early posttraumatic seizure; IRSAD, index of relative socio-economic advantage and disadvantage.
*Main predictor is EPS, which is adjusted for age, IRSAD quintile, pre-existing Charlson comorbidity index, history of alcohol abuse, trauma type, cause of injury, subdural hematoma, subarachnoid haemorrhage, intraventricular haemorrhage, epidural haematoma, base of skull fracture, vault fractures, categorized AIS head score, injury severity score and categorized Glasgow coma scale.

Table 3. Multivariable analyses of associations between early posttraumatic seizure and follow-up outcomes among patients survived the initial admission

Follow-up Outcomes	EPS vs No EPS*		
	Relative Risk Ratio/Risk Ratio/Hazard Ratio	(95% CI)	*p*-value
Glasgow outcome scale at 24-month - good recovery as base outcome			
Moderate disability	1.24	(0.78-1.97)	0.37
Severe disability	2.10	(1.35-3.28)	**0.001**
Vegetative state	3.97	(1.03-15.3)	**0.046**
Dead	2.14	(1.32-3.46)	**0.002**
Posttraumatic epilepsy within 24 months	2.91	(2.22-3.81)	**<0.001**
Use of ASM within 24 months	2.44	(1.98-3.02)	**<0.001**

AIS, abbreviated injury scale; CI, confidence interval; EPS, early posttraumatic seizure; ICU, intensive care unit; IRSAD, index of relative socio-economic advantage and disadvantage.
*Main predictor is EPS, which is a adjusted for age, IRSAD quintile, pre-existing Charlson comorbidity index, history of alcohol abuse, trauma type, cause of injury, subdural hematoma, subarachnoid haemorrhage, intraventricular haemorrhage, epidural haematoma, base of skull fracture, vault fractures, categorized AIS head score, injury severity score and categorized Glasgow coma scale.

Table 4. Variables with non-zero penalized coefficient in the adaptive least absolute shrinkage and selection operator regression

Variable	Penalized Coefficient
IRSAD quintile	
1st quintile (most disadvantaged)	0
2nd	0.036
3rd	0
4th	-0.059
5th - least disadvantaged	0
Cause of injury - low-fall	0.0406
Pre-existing Charlson comorbidity index	
0	-0.270
1	0
2+	0.303
Trauma type - isolated TBI	0.081
Subdural hematoma	0.333
Subarachnoid haemorrhage	0.165
AIS head	
3	-0.104
4	0.000
5-6	0.333
Injury severity score	-0.163
Glasgow coma scale category	
Mild	-0.115
Moderate	0
Severe	0

AIS, abbreviated injury scale; TBI, traumatic brain injury.

Online Only Supplementary Materials

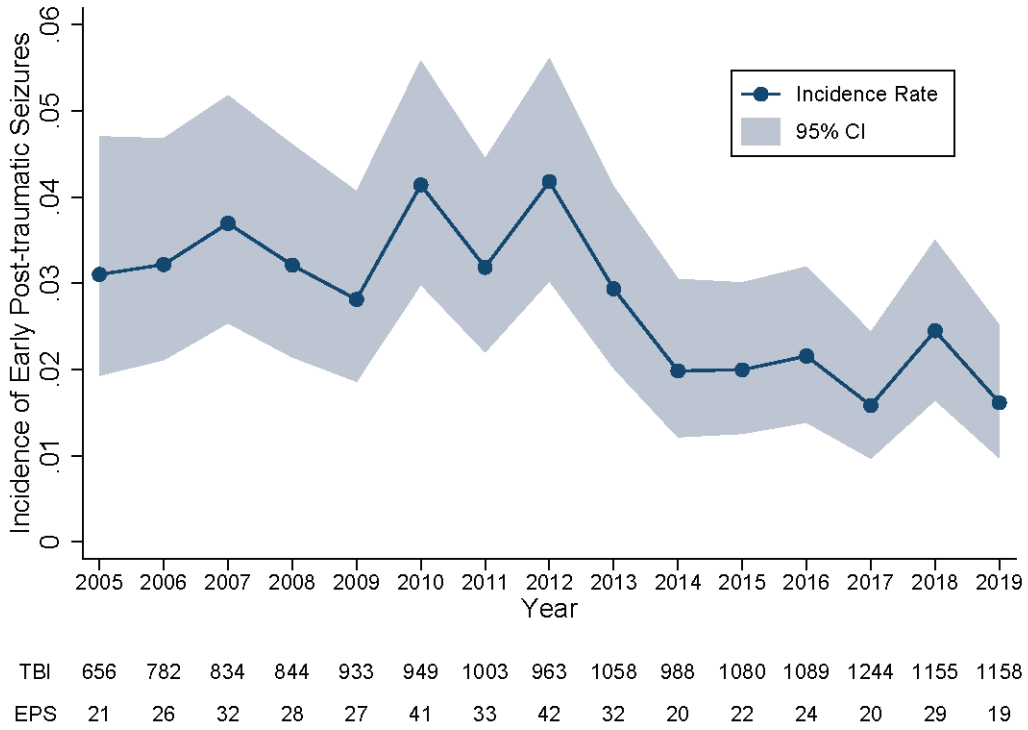
Data Collection

All data was supplied by the Victorian State Trauma Outcomes Registry and Monitoring Group (VSTORM), following local ethics approval (MUHREC Project ID 18104). The VSTR is a population-based trauma registry collecting data about hospitalized patients with major trauma from all 138 trauma receiving health services within the state of Victoria, Australia (population 6.5 million people) (1). Patients are included using an opt-out process, where all eligible patients are included and provided with a letter and brochure detailing their inclusion, the purpose of the registry, and how to opt-out if they wish to do so. Verbal consent for telephone interviews are obtained at follow up. The registry has ethics approval from the Department of Health and Human Services Human Research Ethics Committee (HREC), Monash University HREC, and participating trauma-receiving hospitals. Existing registry data were used and patients were not contacted as part of this study.

eTable 1. Prevalence of EPS

Category	N=15,152 (%)	
No EPS	14,736	(97.3)
All EPS	416	(2.7)
- **Seizure**	389	(2.6)
- **Status epilepticus**	27	(0.2)

eFigure 1: Incidence of Early Posttraumatic Seizures by Year from 2005-2019



eTable 2. Demographics and pre-existing illness

Variable	No EPS N=14,736		EPS N=416		*p*-value	Corrected *p*-value^
Age - yrs					**<0.001**	
Median (IQR)	60	(35-79)	69	(44-81)		
Sex (%)					0.82	
Male	10,172	(97.3)	285	(2.7)		
Female	4,564	(97.2)	131	(2.8)		
ARIA (%)					0.36	
Urban	13574	(97.3)	382	(2.7)		
Rural	681	(97.8)	15	(2.2)		
Missing	481	(96.2)	19	(3.8)		
IRSAD quintile (%)					0.16	
1st - most disadvantaged	2,248	(97.4)	60	(2.6)		
2nd	2,119	(96.8)	71	(3.2)		
3rd	2,783	(97.7)	66	(2.3)		
4th	3,166	(97.6)	78	(2.4)		
5th - least disadvantaged	3,951	(97.0)	122	(3.0)		
Missing	469	(96.1)	19	(3.9)		
Charlson Comorbidity Index weight (%)					**<0.001**	
0	7,146	(98.6)	103	(1.4)	**<0.001**	**<0.001**
1	5,415	(97.2)	156	(2.8)	0.753	0.753

2+	2,175	(93.3)	157	(6.7)	**<0.001**	**<0.001**
History of alcohol misuse (%)					**0.020**	
No	13,019	(97.4)	352	(2.6)		
Yes	1,717	(96.4)	64	(3.6)		
History of drug misuse (%)					0.54	
No	14,423	(97.2)	409	(2.8)		
Yes	313	(97.8)	7	(2.2)		
History of mental health conditions (%)					0.71	
No	11,830	(97.2)	337	(2.8)		
Yes	2,906	(97.4)	79	(2.6)		

ARIA, accessibility and remoteness index of Australia; EPS, early posttraumatic seizure; IQR, interquartile range; IRSAD, index of relative socio-economic advantage and disadvantage.

^*p*-values from pairwise comparisons were corrected for multiple comparisons using Holm-Bonferroni method.
All p values for categories compared to those not in that category.

eTable 3. Injury and neurosurgery characteristics

Variable	No EPS N=14,736		EPS N=416		*p*-value	Corrected *p*-value^
Nature of injury (%)					**<0.001**	
Isolated TBI	6,228	(96.4)	234	(3.6)		
Multi-trauma	8,508	(97.9)	182	(2.1)		
Cause of injury (%)					**<0.001**	
Motor vehicle incident	2,165	(98.6)	31	(1.4)	**<0.001**	**<0.001**
Motorcycle	820	(98.3)	14	(1.7)	0.05	0.26
Bicycle	568	(98.1)	11	(1.9)	0.20	0.61
Pedestrian	1,081	(97.7)	25	(2.3)	0.31	0.61
Low fall <1m	6,078	(96.2)	237	(3.8)	**<0.001**	**<0.001**
High fall	1,639	(97.8)	37	(2.2)	0.15	0.61
Others	2,385	(97.5)	61	(2.5)	0.41	0.41
Nature of Head Injury (%)						
Subdural hematoma	9,018	(96.4)	340	(3.6)	**<0.001**	**<0.001**
Contusion	4,495	(97.1)	135	(2.9)	0.40	0.79
Subarachnoid haemorrhage	5,553	(96.6)	193	(3.4)	**<0.001**	**0.002**
Intraventricular haemorrhage	503	(95.8)	22	(4.2)	**0.039**	0.20
Epidural haematoma	2,132	(97.9)	45	(2.1)	**0.036**	0.22
Intracerebral haemorrhage	1,913	(97.0)	60	(3.0)	0.39	1.00
Diffuse axonal injury	700	(96.8)	23	(3.2)	0.46	0.46
Base of skull fracture	4,809	(97.9)	104	(2.1)	**0.001**	**0.007**
Vault fractures	2,641	(97.7)	62	(2.3)	0.11	0.45

AIS head					**<0.001**	
3	4,972	(98.8)	60	(1.2)		
4	5,402	(97.6)	134	(2.4)		
5-6	4,362	(95.2)	222	(4.8)		
Injury Severity Score (ISS)					**<0.001**	
Median (IQR)	21.0	(16-26)	25.0	(17-26)		
Glasgow coma scale - head injury severity (%)					**<0.001**	
Mild (13-15)	9,948	(97.7)	237	(2.3)	**<0.001**	**<0.001**
Moderate (9-12)	1,202	(96.1)	49	(3.9)	**0.008**	**0.023**
Severe (≤8)	2,808	(96.3)	107	(3.7)	**<0.001**	**0.001**
Missing	778	(97.1)	23	(2.9)		
Any neurosurgery (%)	2,084	(94.5)	121	(5.5)	**<0.001**	
Craniotomy	459	(93.1)	34	(6.9)	**<0.001**	**<0.001**
Burr hole	192	(91.4)	18	(8.6)	**<0.001**	**<0.001**
EVD/ICP	1,686	(94.5)	98	(5.5)	**<0.001**	**<0.001**

AIS, abbreviated injury scale; EPS, early posttraumatic seizure; EVD, external ventricular drain; ICP, intracranial pressure; IQR, interquartile range; TBI, traumatic brain injury.

^*p*-values from pairwise comparisons were corrected for multiple comparisons using Holm-Bonferroni method.
All p values for categories compared to those not in that category.

eTable 4. Health services and vital characteristics

Variable	**No EPS N=14,736**		**EPS N=416**		***p*-value**
Outcome hospital (%)					**<0.001**
Major	12,082	(82)	375	(90)	
Others	2,654	(18)	41	(10)	
Time to primary centre - hrs	n=14,384		n=403		**0.003**
Median (IQR)	1.62	(1.08-3.80)	1.77	(1.13-14.5)	
Time to head CT - hrs	n=12,865		n=358		0.74
Median (IQR)	3.58	(2.33-8.50)	3.58	(2.10-17.3)	
Heart rate - beats/min	n=14,249		n=401		0.71
Median (IQR)	85	(72-100)	85	(73-100)	
Blood pressure - mmHg	n=14,220		n=400		**<0.001**
Median (IQR)	140	(125-160)	147	(130-166)	
Hypotension - bp≤90 mmHg (%)					0.14
No	13,743	(93)	392	(94)	
Yes	477	(3)	8	(2)	
Missing	516	(4)	16	(4)	

Respiratory rate - breaths/min	n=12,939		n=359		0.75
Median (IQR)	18	(16-20)	18	(16-20)	

bp, blood pressure; CT, computed tomography; EPS, early posttraumatic seizure; IQR, interquartile range.

eTable 5. Hospital morbidity and mortality

Variable	No EPS N=14,736		EPS N=416		*p*-value	Corrected *p*-value^
ICU admission					**<0.001**	
No	9,324	(63)	154	(37)		
Yes	5,412	(37)	262	(63)		
ICU ventilated	n=5,412		n=262		**<0.001**	
No	1,129	(21)	32	(12)		
Yes	4,283	(79)	230	(88)		
ICU length of stay - days	n=5,394		n=262		**<0.001**	
Median (IQR)	5	(2-11)	8	(4-14)		
ICU ventilated length of stay - days	n=4,281		n=230		**<0.001**	
Median (IQR)	4	(1-9)	6	(2-12)		
Hospital length of stay - days	n=14,394		n=403		**<0.001**	
Median (IQR)	7	(4-13)	17	(9-29)		
In-Hospital Mortality*					**<0.001**	**<0.001**
No	12,416	(84)	323	(78)		
Yes	2,320	(16)	93	(22)		
Discharge destination					**<0.001**	
Home	5,514	(37)	36	(9)	**<0.001**	**<0.001**
Rehabilitation	5,529	(38)	232	(56)	**<0.001**	**<0.001**
Others	1,372	(9)	55	(13)	**<0.001**	**<0.001**
Missing	1	(0.01)	0	(0)		

EPS, early posttraumatic seizure; ICU, intensive care unit; IQR, interquartile range.

^*p*-values from pairwise comparisons were corrected for multiple comparisons using Holm-Bonferroni method.

*1 result missing for EPS group.

eTable 6. Follow-up outcomes among patients survived the initial TBI admission and due for 24-month follow-up

Variable	No EPS n=11,071		EPS n=311		*p*-value^
Glasgow outcome scale at 24 months post-injury					**<0.001**
Good recovery	2,686	(24)	40	(13)	
Moderate disability	2,384	(22)	45	(14)	
Severe disability	1,765	(16)	80	(25)	
Vegetative state	21	(0.2)	3	(1)	
Deceased	1,462	(13)	68	(22)	

Unable to determine/missing	2,753	(25)	75	(24)	
PTE by 24 months post-injury					**<0.001**
No	1,306	(12)	10	(3)	
Yes	314	(3)	35	(11)	
Incomplete#	492	(4)	18	(4)	
Missing	8,959	(81)	260	(81)	
Use of ASM within 24 months					**<0.001**
No	2,335	(21)	22	(7)	
Yes	543	(5)	46	(15)	
Incomplete#	1,287	(12)	23	(7)	
Missing	6,906	(62)	220	(71)	

ASM, antiseizure medication; EPS, early posttraumatic seizure; IQR, interquartile range.

^p-value from complete case analysis, i.e. excluded missing or incomplete data.

#Patients did not report development of posttraumatic epilepsy or use of ASM at 6- and/or 12-month follow-up, but missing 24-month follow-up.

REFERENCES

1. Cameron PA, Finch CF, Gabbe BJ, Collins LJ, Smith KL, McNeil JJ. Developing Australia's first statewide trauma registry: what are the lessons? *ANZ J Surg*. 2004 Jun 8;74(6):424–8.

Clinical Risk Factor Identification and the Impact of Posttraumatic Epilepsy on Moderate to Severe TBI Survivors

Joshua Laing, Belinda Gabbe, Zhibin Chen, Piero Perucca, Patrick Kwan, Terence O'Brien

Note: This study is intended for first author publication and the authors mentioned above secondarily contributed to this work.

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of acquired epilepsy, referred to as "posttraumatic epilepsy (PTE)". PTE has been estimated to represents up to 20% of cases with acquired epilepsy, and 5% of all epilepsies (1). The diagnosis of PTE is made when, following the acute TBI phase, the first recurrent spontaneous seizure occurs. PTE causes significant disability, loss of independence, and risk of death, with up to a third of patients being drug resistant (2). Unlike most epilepsies, PTE has an identifiable and observable "latent phase" between the epileptogenic insult (i.e. the TBI) and the manifestation of the PTE, which provides a potential window of opportunity for anti-epileptogenic interventions. However there are currently no clinically proven anti-epileptogenic disease modifying therapies to prevent PTE or mitigate its severity (3). The 2016 American Brain Trauma Foundation Guidelines for severe TBI support the short-term use of prophylactic antiseizure medication in patients presenting with moderate to severe TBI, as it can reduce the risk of early posttraumatic seizures (EPS) but does not impact on subsequent development of PTE (4).

The incidence of PTE is dependent on the rate of TBI, which is prevalent around the world, estimated to afflict sixty-nine million people per year (5). Over the last 20 years, studies have reported that between 1.3-32% of patients with TBI develop PTE (6–26). A pooled prevalence of 15% of patients following a moderate-severe TBI developing PTE was reported in a recent systematic review (27). Whilst the incidence of PTE correlates with TBI severity (27), many patients with severe TBI may die prior to the development of PTE and are often excluded from analysis. The additional diagnosis of PTE in TBI survivors significantly compounds disability (8,20,28–30) and risk of mortality (26,30,31). Patients with PTE have a 1.75 times higher risk of death up to 15 years post-TBI compared to

matched TBI survivors (31). As TBI often affects predominantly young adults, many of those that develop incapacitating seizures and PTE often experience a significant loss of independence and work options (17). The associated financial burden of PTE alone therefore is substantial.

Broadly categorized by the International League Against Epilepsy (ILAE) into acute symptomatic seizures, early posttraumatic seizures (EPS) may occur due to an identifiable provoking factor such as acute phase TBI (32). The literature often extends EPS to 7 days post TBI, however many patients with moderate-severe TBI are still in ICU or hospital, and exposed to various other causes of acute symptomatic seizures beyond this juncture (33). As EPS may be precipitated by the acute effects of TBI, EPS is not termed epilepsy (32). EPS are thought to reflect different underlying mechanisms, with separate rates of seizure recurrence, morbidity and mortality (33). The relationship between EPS and epileptogenesis, or neurobiological mechanisms underlying the development of epilepsy, requires further evaluation as EPS is a known significant risk factor for PTE (34).

Late seizures post the acute phase of TBI are considered PTE as they are associated with considerable recurrent seizure risk (26). The time to first seizure or diagnosis of PTE following TBI has been studied in various populations typically with most in the first year following injury, if not the first two years (7). The risk of further seizures after the first late seizure is as high as 86% at two years (35) but may persist for years (36,37). Drug-resistant PTE was found in 20% of people with PTE, and tonic-clonic seizures are typically the predominant seizure type (38). Survivors of TBI are up to 60 times more likely to die from seizures than the general population (39). Further confirmation of the effect of PTE on overall morbidity and mortality is needed.

The major risk factor for the development of PTE is the severity of injury. Concussions themselves, or mild TBI, is also typically not associated with the development of PTE, however there may be some weak association (40,41). Moderate to severe TBI with focal neurological signs, loss of consciousness, and post traumatic amnesia, significantly increases the risk of PTE (27,37). Other commonly reported injury severity related risk factors include penetrating injuries seen in military populations (6,7,16,18,21), parenchymal contusions (7,26,42), depressed skull fracture (7,10,18,42,43), subdural haematoma (7,20), secondary hydrocephalus (20), and associated surgical treatment interventions (7,9,17,18,20,21). Family history of epilepsy has also been reported as a risk factor for PTE (23). EPS, as mentioned above, are also commonly reported as an independent risk factor for PTE, but this is not well understood as many patients with EPS do not develop PTE (27). Reported significant factors for PTE in multivariable analyses include age (9,21), GCS (6,24,42), specific motor deficits (6,21), fall (21,24), gunshot (21), medical comorbidities (24), TBI severity (9,13), frontotemporal contusion (37,42), skull fracture (42), history of psychiatric disease (13), and alcohol related injury (13). Many of the reported studies vary significantly in both populations and methodology, making generalizability of these risk factors difficult. When identifying those with PTE, various methods have been employed including using ICD codes, questionnaires, interviews and medical assessments. Reporting of injury specifics and other clinical risk factors is also variable. Limitations within current studies also include lack of exclusion of patients with a prior diagnosis of epilepsy, early seizures and PTE not being separated, as well as variable length in follow up of subjects. A recent systematic review and meta-analysis in 2017 (27) attempted to address the heterogeneity in reported studies of PTE. The most common risk factors being severe TBI, early seizures, intracranial haemorrhage, contusion, skull fracture, history of alcohol abuse, subdural haemorrhage. GCS and associated amnesia, and focal neurological signs were

also significant. Using a prediction model of risk factors, one study attempted to predict those with seizures following TBI, with a modest result on a small test population (44).

This current study aimed to utilize a large population based TBI registry to advance knowledge regarding the risk factors for PTE following TBI. A novel prediction algorithm was derived to identify patients at high risk for developing PTE, which highlight important clinical risk factors that may be used in future scoring systems. Furthermore, the study aimed to investigate the overall morbidity and mortality of PTE, specifically to determine the additional impact of PTE over that of TBI itself.

METHODS

Study Design

This was a registry-based cohort study of adults (aged 18 years and over) with moderate to severe TBI.

Participants

All patients suffering moderate to severe TBI in the Australian state of Victoria during January 2005-December 2019 were identified by utilizing the Victorian State Trauma Registry (VSTR). For the purposes of this study, patients with moderate to severe TBI were identified by an Abbreviated Injury Scale (AIS) head score of 3-6 (45). The identification of patients that developed PTE was determined via response to questions, as part of structured interviews evaluating overall functional outcomes with 2-year follow up. Patients with a pre-existing diagnosis of epilepsy identified by International Statistical Classification of Diseases and Related Health Problems 10th Revision–Australian Modification (ICD-10-AM) codes were excluded from the study.

Data Collection

All data were supplied by the Victorian State Trauma Outcomes Registry and Monitoring Group (VSTORM), following ethics local ethics approval (MUHREC Project ID 18104). Information was retrieved from the VSTR, which prospectively collects data from all hospitalized patients with major trauma in the state of Victoria, Australia (46). Patients are included on the VSTR using an opt-out consent process, and none needed to be contacted directly as part of this study. Anonymized, patient-level data were extracted for eligible patients and included demographics, admission information, injury diagnoses, coded injury

event details, severity scores, operations and procedures, ICD-10-AM diagnosis and comorbidities, and discharge information including in-hospital mortality. Regularly audited, trained registry coders collect all information following admission to complete ICD-10-AM coding.

Utilizing the ICD-10-AM codes, the Charlson Comorbidity Index (CCI), and indicators for pre-existing mental health, drug and alcohol conditions, were derived (47,48). Residential postcodes were used to define the Accessibility and Remoteness Index of Australia (ARIA), a measure used for relation to accessible services including healthcare, and the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) to social status. Nature of injury was grouped into isolated TBI and multi-trauma, which was defined as an AIS severity score >1 in any other AIS body region. The Injury Severity Score (ISS) is derived from the AIS to provide an overall severity score (45). Trauma outcome hospital was categorized into the major trauma services including the designated state-wide trauma hospitals, and others.

Subsequent diagnosis of PTE was determined by structured interview question of the Extended Glasgow Outcome Scale (GOS-E);“Since the injury, has the patient had any epileptic fits?” at 6, 12, and 24 mths (49). For patients with a date of injury prior to March 12 2018, these were only asked if the patient scored a good recovery or higher on the GOS-E. For patients with a subsequent date of injury, the questions were asked for all patients. Proxy interviews with a close other (e.g. family member or carer) were used where direct interview of the patient was not possible.

Overall outcomes were measured using the Glasgow Outcome Scale-Extended (GOS-E) structured questionnaire at 6, 12 and 24 months post-injury. The European Quality of Life

Five Dimensions (EQ-5D-3L) is a validated quality of life measure used in patients with TBI (48). The registry is routinely linked with the Victorian Registry of Births, Deaths and Marriages (BDM) to identify post-discharge deaths and deaths up until July 2019 were included in this study.

Statistical Analysis

We used descriptive statistics using percentages for categorical variables and interquartile ranges for non-normally distributed variables. Univariable associations between factors and development of PTE were assessed using Chi-square statistics for categorical variables and Mann-Whitney U-tests for non-normally distributed continuous variables. Factors with a p-value ≤0.2 were included in the multivariable Poisson regression model with robust variance to measure their effect on development of PTE. A similar approach was used for including covariates associated with mortality rate in the multivariable Cox regression to assess the difference in mortality rate between patients who developed PTE within 2 years of TBI and patients who did not.

Adjusted risk ratios, hazard ratio and the corresponding 95% confidence intervals, were reported. Statistical significance level was set at $p<0.05$. Holm-Bonferroni method was used to correct for post-hoc pairwise comparisons in categorical variables with more than 2 groups.

Prediction model

Adaptive least absolute shrinkage and selection operator (LASSO) regression (50) was used to develop a prediction model for PTE. Adaptive LASSO is a multistep version of the conventional cross-validation based LASSO where adaptive weights are further applied for

penalizing different coefficients. Covariates whose estimated coefficients are zero were excluded. Per conventional partition protocol we randomly selected 80% of patients in the cohort as the training set and the remaining 20% as the test set. The ability of the model to predict PTE was evaluated with a series of metrics including area under the receiver operating characteristics curve (AUC), accuracy, sensitivity and specificity.

All statistical tests and prediction model building were performed by using Stata version 16 (StataCorp, College Station, TX).

RESULTS

Overall, 1,665 patients with moderate to severe TBI were included in the study with a PTE prevalence at 24-months of 21.0% (n=349).

Demographics and Pre-Existing Illness

Compared to patients who did not develop PTE, those with PTE were younger (median age 50 vs 57 years) and had a higher representation of males (Table 1). Access to services and rurality, and social class, did not differ between the two groups. A higher number of medical comorbidities were associated with development of PTE (21% v 13%). Early posttraumatic seizures occurred more frequently among patients who developed PTE (10% vs 1%). A history of alcohol (17% vs 8%) but not drug misuse was more common in the PTE group. A higher proportion of patients with PTE had prior mental health conditions (29% vs 16%).

Table 1. Demographics and pre-existing conditions

Variable	No PTE N=1,316		PTE N=349		*p*-value	Corrected *p*-value^
Age - yrs					**<0.001**	
Mean (SD)	57	(22)	50	(22)		
Sex (%)					**0.002**	
Male	911	(69)	271	(78)		
Female	405	(31)	78	(22)		
ARIA (%)					0.30	
Urban	1,216	(92)	312	(89)		
Rural	66	(5)	22	(6)		
Missing	34	(3)	15	(4)		
IRSAD quintile (%)					0.88	
1st - most disadvantaged	196	(15)	58	(17)		
2nd	191	(15)	46	(13)		
3rd	247	(19)	62	(18)		
4th	295	(22)	80	(23)		
5th - least disadvantaged	353	(27)	89	(26)		
Missing	34	(3)	14	(4)		

Pre-existing Charlson comorbidity index (%)					**<0.001**	
0	621	(47)	124	(36)	**<0.001**	**<0.001**
1	523	(40)	153	(44)	0.17	0.17
2+	172	(13)	72	(21)	**<0.001**	**<0.001**
Early posttraumatic seizure (%)					**<0.001**	
No	1,306	(99)	314	(90)		
Yes	10	(1)	35	(10)		
History of alcohol misuse (%)					**<0.001**	
No	1,208	(92)	289	(83)		
Yes	108	(8)	60	(17)		
History of drug misuse (%)					0.18	
No	1,293	(98)	339	(97)		
Yes	23	(2)	10	(3)		
History of mental health conditions (%)					**<0.001**	
No	1,100	(84)	249	(71)		
Yes	216	(16)	100	(29)		

ARIA, accessibility and remoteness index of Australia; IQR, interquartile range; IRSAD, index of relative socio-economic advantage and disadvantage; PTE, posttraumatic epilepsy; SD, standard deviation.

^*p*-values from pairwise comparisons were corrected for multiple comparisons using Holm-Bonferroni method.

Injury and Neurosurgical Characteristics

A higher proportion of patients with isolated TBI rather than multi-trauma developed PTE (Table 2). Regarding cause of injury, there were no between-group differences except for high falls being less prevalent among patients with PTE, whereas other causes of TBI being more prevalent among patients with PTE. SDH (70% vs 61%), SAH (52% vs 39%) and ICH (16% vs 6%) were all associated with development of PTE. Contusions when statistically corrected was not associated with PTE. Injury severity indicators of AIS head, ISS and GCS were all associated with the development of PTE. Any form of neurosurgery also resulted in a larger proportion of PTE (22% vs 10%).

Table 2. Injury and neurosurgery characteristics

Variable	**No PTE N=1,316**	**PTE N=349**	***p*-value**	**Corrected *p*-value^**

Trauma type (%)					**0.009**	
Isolated TBI	498	(38)	159	(46)		
Multi-trauma	818	(62)	190	(54)		
Cause of injury (%)					**0.041**	
Motor vehicle accident	169	(13)	46	(13)	0.87	0.87
Motorcycle	98	(7)	17	(5)	0.092	0.46
Bicycle	63	(5)	14	(4)	0.54	1.00
Pedestrian	106	(8)	27	(8)	0.85	1.00
Low fall	503	(38)	142	(41)	0.40	1.00
High fall	181	(14)	32	(9)	**0.023**	0.14
Others	196	(15)	71	(20)	**0.014**	0.10
Injury specifics (%)						
Subdural hematoma	801	(61)	243	(70)	**0.003**	**0.018**
Contusion	411	(31)	135	(39)	**0.008**	0.050
Subarachnoid haemorrhage	515	(39)	181	(52)	**<0.001**	**<0.001**
Intraventricular haemorrhage	47	(4)	16	(5)	0.38	1.00
Epidural haematoma	170	(13)	59	(17)	0.055	0.27
Intracerebral haemorrhage	114	(9)	55	(16)	**<0.001**	**<0.001**
Diffuse axonal injury	61	(5)	20	(6)	0.40	1.00
Base of skull fracture	467	(35)	118	(34)	0.56	0.56
Vault fractures	224	(17)	66	(19)	0.41	0.82
AIS head					**<0.001**	
3	532	(40)	84	(24)		
4	512	(39)	142	(41)		
5-6	272	(21)	123	(35)		
Injury severity score (ISS)					**0.002**	
Median (IQR)	20	(16-26)	22	(17-26)		
Glasgow coma scale - head injury severity (%)					**<0.001**	
Mild (13-15)	1,034	(79)	213	(61)	**<0.001**	**<0.001**
Moderate (9-12)	74	(6)	34	(10)	**0.006**	**0.006**
Severe (≤8)	124	(9)	83	(24)	**<0.001**	**<0.001**
Missing	84	(6)	19	(5)		
Any neurosurgery (%)	128	(10)	77	(22)	**<0.001**	
Craniotomy	21	(2)	28	(8)	**<0.001**	**<0.001**
Burr hole	13	(1)	6	(2)	**0.001**	**0.001**
EVD/ICP	99	(8)	55	(16)	**<0.001**	**<0.001**

AIS, abbreviated injury scale; EVD, external ventricular drain; ICP, intracranial pressure; IQR, interquartile range; PTE, posttraumatic epilepsy; SD, standard deviation; TBI, traumatic brain injury.

^*p*-values from pairwise comparisons were corrected for multiple comparisons using Holm-Bonferroni method.

Multivariate Analysis of Risk Factors for PTE

Following multivariable analysis, younger age was associated with a modest increased risk of PTE (RR 0.99) (Table 3). There was no difference in the risk of PTE between the sexes. A higher medical comorbidity score (CCI2+) showed an increase in PTE (RR 1.33), whilst EPS was associated with a three-fold increased risk of developing PTE (RR 3.00). There was a higher risk of PTE with a history of alcohol (RR 1.33) but not drug misuse. PTE was also more common in those with a mental health condition history (RR 1.51). Motor vehicle accident as a cause of injury was significant when compared to other causes of injury, although trauma type was non-significant following adjustment on multivariate analysis. ICH (RR 1.30), but not SAH or EDH, were associated with an independent increased risk of PTE. TBI severity indicators of AIS head and severe GCS were significant for PTE risk, but not global injury score ISS. Neurosurgical intervention was not statistically significant in multivariable analysis, however there was a trend towards an association.

Table 3. Multivariable analysis of demographics, pre-existing conditions and injury characteristics associated with posttraumatic epilepsy at 24-months.

Variable		Risk Ratio	(95% CI)	*p*-value
Age		0.99	(0.98-0.99)	**<0.001**
Sex - male as reference				
	Female	0.84	(0.66-1.07)	0.16
Pre-existing Charlson comorbidity index - 0 as reference				**0.024**
	1	0.95	(0.74-1.22)	0.70
	2+	1.33	(1.01-1.77)	**0.045**
Early posttraumatic seizure		3.00	(2.31-3.88)	**<0.001**
History of alcohol misuse		1.33	(1.02-1.73)	**0.034**
History of drug misuse		1.19	(0.72-1.99)	0.50
History of mental health conditions		1.51	(1.21-1.89)	**<0.001**
Trauma type - isolated TBI as reference				
	Polytrauma	1.04	(0.83-1.31)	0.72
Cause of injury - motor vehicle accident as reference				**0.043**
	Motorcycle	0.63	(0.40-1.01)	0.055
	Bicycle	0.74	(0.44-1.25)	0.27
	Pedestrian	0.90	(0.59-1.36)	0.60
	Low fall	1.19	(0.82-1.72)	0.36
	High fall	0.71	(0.47-1.07)	0.10

	Others	1.03	(0.72-1.47)	0.88
Subdural hematoma		1.23	(0.97-1.55)	0.088
Contusion		0.97	(0.79-1.19)	0.75
Subarachnoid haemorrhage		1.21	(0.98-1.48)	0.073
Epidural haematoma		1.07	(0.81-1.40)	0.63
Intracerebral haemorrhage		1.30	(1.01-1.67)	**0.041**
AIS head - 3 as reference				0.055
	4	1.35	(1.02-1.78)	**0.035**
	5-6	1.55	(1.07-2.24)	**0.020**
Injury severity score		0.99	(0.98-1.01)	0.31
Glasgow coma scale - mild head injury as reference				0.066
	Moderate	1.06	(0.77-1.45)	0.73
	Severe	1.37	(1.05-1.80)	**0.022**
Any neurosurgery – no as reference				0.21
	Yes	1.31	(0.97-1.77)	0.082
	Other	1.09	(0.87-1.38)	0.45

AIS, abbreviated injury scale; CI, confidence interval; TBI, traumatic brain injury.

Prediction Model

On adaptive LASSO regression, there were several identified risk factors for PTE including EPS, younger age, male sex, medical comorbidities (CCI2+), alcohol and cannabinoid misuse, mental health conditions (including mood disorders), causes of injury (motorcycle, bicycle, low and high falls), SDH, SAH, ICH, base of skull fracture, AIS head, initial GCS, and neurosurgical intervention, with good overall performance on the test set (area under the receiver operating curve (ROC) = 0.7364) (Table 4, Figure 1). The sensitivity and specificity of the model are 59% and 80%, respectively, at the optimal cut-off of -0.22 with an overall accuracy of 76%.

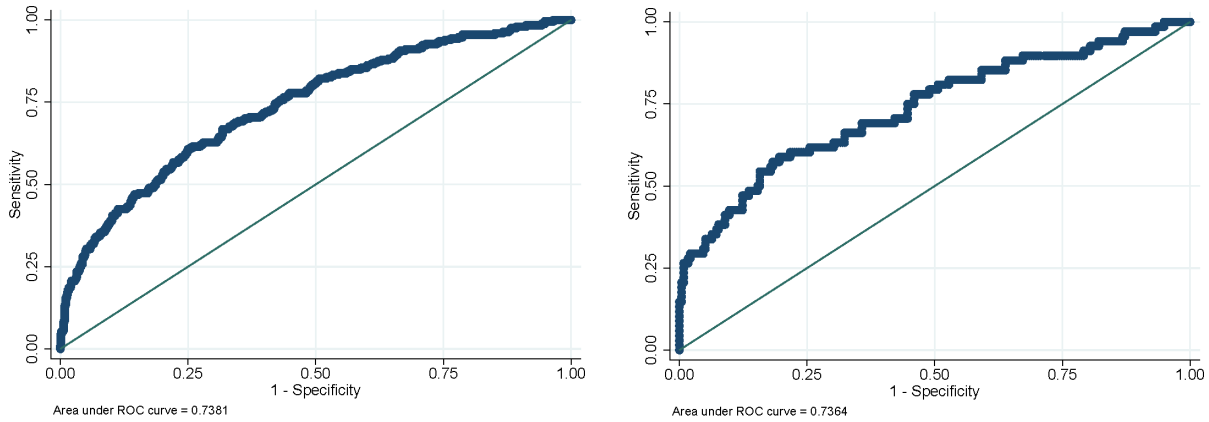
Table 4. Variables with non-zero penalized coefficient in the adaptive least absolute shrinkage and selection operator regression

Variable	Penalized Coefficient
Early posttraumatic seizure	0.360
Age	-0.352
Sex - male	0.087
Cause of injury	

	Motorcycle	-0.107
	Bicycle	-0.115
	Low-fall	0.022
	High-fall	-0.154
Pre-existing Charlson comorbidity index		
	2+	0.140
History of alcohol misuse		0.101
History of cannabinoids misuse		0.107
History of mental health conditions		0.212
Trauma type - isolated TBI		0.037
Subdural hematoma		0.164
Subarachnoid haemorrhage		0.179
Intracerebral haemorrhage		0.102
Base of skull fracture		-0.172
AIS head		
	3	-0.109
Glasgow coma scale category		
	Severe	0.173
Any neurosurgery		
	Yes	0.125

TBI, traumatic brain injury.

Figure 1. LASSO Regression Model Performance in Test and Validation sets, measured in area under the ROC curve.



Morbidity Measured by EQ-5D and GOS-E

Overall health related quality of life as measured by the point estimate difference of total patient reported scores on the ED-5D-3L at 24 months was 0.08 less for patients with PTE (0.68 vs 0.76, P=0.004, 95% CI: -0.13 to -0.02), when adjusted for confounders of risk

factors for EQ-5D outcomes (Table 5). Individual dimension scores were similar, except for the activity domain which showed a significant reporting of some or severe problems for patients with PTE (ARR 1.26, P=0.032, 95% CI 1.02 to 1.55).

Table 5. Number of patients reported some/severe problems in each of the EQ-5D-3L dimensions at 24 months - results of multivariable analyses

Dimensions - n (%)	PTE vs No PTE						
	PTE (n=120)		No PTE (n=823)		Adjusted relative risk^ (95% CI)		*p*-value
Mobility	43	(0.36)	298	(0.36)	1.14	(0.89-1.45)	0.29
Selfcare	31	(0.26)	183	(0.22)	1.26	(0.92-1.73)	0.15
Activity	59	(0.49)	339	(0.41)	1.26	(1.02-1.55)	**0.032**
Pain/Discomfort	53	(0.44)	371	(0.45)	1.06	(0.85-1.32)	0.61
Anxiety/Depression	57	(0.48)	313	(0.38)	1.14	(0.92-1.42)	0.24

^ Adjusted for following covariates that had p-value<0.2 in univariable analysis: age, sex, IRSAD quintile, pre-existing Charlson comorbidity index, history of mental health conditions, trauma type, cause of injury, contusion, subarachnoid haemorrhage, epidural haematoma, diffuse axonal injury, base of skull fracture, vault fractures, injury severity score and categorized Glasgow coma scale.
PTE, posttraumatic epilepsy

Twenty-four-month morbidity as per the GOS-E showed a significant increased risk of poorer outcomes in patients with PTE, with a 2.17 increased risk of moderate disability, and 3.68 increased risk of severe disability (or vegetative state) compared to a good recovery when adjusted for confounders of PTE (Table 6).

Table 6. Multivariable analysis of associations between posttraumatic epilepsy and follow-up Glasgow outcome scale measured at 24 months among patients survived for at least 24 months after the initial traumatic brain injury

Variable	PTE vs No PTE (n = 209 vs 1,199)		
	Relative Risk Ratio^	(95% CI)	*p*-value
Glasgow outcome scale - good recovery as the reference			
Moderate disability	2.17	(1.44-3.29)	**<0.001**
Severe disability or Vegetative state*	3.68	(2.32-5.84)	**<0.001**

^ Adjusted for following covariates that had p-value<0.2 in univariable analysis: age, sex, IRSAD quintile, pre-existing Charlson comorbidity index, history of mental health conditions, trauma type, cause of injury, contusion, subarachnoid haemorrhage, epidural haematoma, diffuse axonal injury, base of skull fracture, vault fractures, injury severity score and categorized Glasgow coma scale.
*Vegetative state was combined with Severe disability as only 1 patient (No PTE) reported vegetative state.

CI, confidence interval; IRSAD, index of relative socio-economic advantage and disadvantage; PTE, posttraumatic epilepsy

Long Term Mortality

When adjusted for confounders of mortality, the overall mortality via linkage analysis with median follow up following PTE at 0.82 years (IQR: 0.39-1.31) showed a 3.2-fold (P=0.03, 95% CI 1.11-9.15) increased risk of death in patients with PTE compared to those who did not develop PTE.

DISCUSSION

This study, utilizing a comprehensive state-wide trauma registry (VSTR), demonstrated a PTE prevalence of 21.0% after moderate to severe TBI, and identifiable clinical risk factors for PTE via standard multivariable analysis. It also developed a novel prediction algorithm based on readily available clinical features that could be useful in clinical practice and trials to identify patients at high risk of developing PTE after a TBI. Furthermore, the study demonstrated that when statistically adjusted for confounders, PTE was independently associated with an increase in morbidity and mortality. Advancing on previous studies of PTE, we used the anatomically based AIS head score to identify moderate to severe TBI which is highly correlated with subsequent outcomes compared to clinical parameters such as presence of amnesia, GCS and overall injury scores (45). It is noteworthy the prevalence of PTE of 21.0% in this study following moderate to severe TBI is higher than the previously reported pooled analysis of TBI including minor TBI of 15% (27).

The identification of clinical risk factors not only help to predict patients at high risk of PTE, but also provides an insight into epileptogenesis. Various studies in the literature report a range of risk factors for PTE, mostly via univariable and so with subsequent multivariable analysis, with few studies evaluating prediction models. Our study confirms many of the previously reported risk factors in this cohort, including premorbid medical comorbidities, history of mental illness and alcohol misuse. Medical comorbidities may theoretically interact with TBI to exacerbate neuroinflammation in the epileptogenesis of PTE (51). Pre-existing mental illnesses have been believed to have a bidirectional relationship with the development of epilepsy (51). Age may have a more complex relationship with neuroinflammation and understanding PTE risk (52), as lower age was associated with PTE in this study. Alcohol misuse has consistently been reported as a risk factor for PTE, which

may be due to its association with alcohol related seizures, injuries, and poor medical attendance (53). Injury severity has a well-known relationship with the development of PTE, analogous to a dose-dependent response, and repeated TBI has also been associated with PTE (54). The present study demonstrates the risk of PTE from increasing AIS head score, as well as GCS. ISS was not significant, as this is closely linked and confounded by the AIS head score. Polytrauma was non-significant in this study also likely similarly to the confounding in ISS, however its relationship to PTE requires further study as polytrauma may have theoretical links to systemic inflammation that may contribute to PTE (55). In this study, intracranial haemorrhage was associated with an increased risk of PTE, and SAH and SDH showed a non-significant trend towards risk of PTE. Intracranial blood from any of these mechanisms appears to contribute to PTE risk, and may in part be explained by alteration in the blood brain barrier and neuroinflammatory cascades (56). Neurosurgical intervention in TBI, which may also contribute to these mechanisms often correlates with injury severity, however not in our study. Further neuroimaging biomarkers of subcortical volume loss and cortical thinning may contribute to PTE risk (57). Further paraclinical biomarkers of PTE including imaging and molecular may complement the clinical determinants of PTE (58).

The relationship and contribution of EPS to PTE is complex, and there is little evidence of comparing the common risk factors of EPS to PTE. After adjusting for confounders, EPS was the most significant factor for PTE identified in this study, increasing the risk of PTE over 3 times. The reason for the strong association between EPS and the later development of PTE is uncertain. It is possible that they are both associated with common risk factors, such as younger age, higher medical comorbidities CCI score, SDH and SAH, and head injury severity measured by the AIS head score and GCS. It is also possible that the EPS

have a kindling effect on the brain to promote post-traumatic epileptogenesis and ultimately PTE. Early EEG biomarkers post-TBI, some similar to those found in epileptogenic tissue identified via studies in epilepsy surgery such as high frequency oscillations, may suggest that EPS reflect an enduring electrical predisposition to the development of seizures and PTE (59). Standardized treatment protocols of seizure prophylaxis, as per the Brain Trauma Foundation exist for treatment of moderate to severe TBI for the first 7 days of acute inpatient care only. The rapid rise in use of cEEG in the critically ill including TBI, has recognized a much higher proportion of patients with subclinical or electrographic seizures (47). Whilst there is ongoing debate regarding the contribution to morbidity and mortality of cEEG detected seizures in these populations, treatment guidelines are also lacking. To date there are no studies evaluating the use of cEEG in TBI vs no cEEG on outcomes, however the practice is being widely employed in Northern America. Given that our study was carried out in Australia at a time when cEEG was rarely used in practice, the effect of EPS on PTE would be relatively unaffected by the detection of NCS/NCSE on cEEG and its management. The effect of early identification and management of EPS on the development of PTE is unknown, but may represent an antiepileptogenic strategy.

Discovering clinical biomarkers for epileptogenesis will better predict patients likely to develop PTE, and allow future targeted disease modifying therapies to be more efficiently trialled. There is currently no individualized approach, or management strategies, in assessing those at high risk for the development of PTE. In our study, risk factors were determined via a novel prediction model using LASSO regression, some which correlated with the multivariable evaluation including younger age, medical comorbidities, EPS, history of alcohol misuse, preexisting psychiatric illness, cause of injury via MVA, ICH and injury severity (AIS head and GCS). Few studies have investigated prediction algorithms

identifying clinical risk factors for modelling PTE. Ritter et al (44) used a similar but smaller database, identifying TBI severity by GCS and other early clinical signs as opposed to a composite score such as AIS head score, and identified factors including pre-existing mental health conditions, incarceration, posttraumatic amnesia, SDH, contusion, neurosurgical interventions of craniotomy and craniectomy, and seizure during acute hospitalization. The study showed reasonable performance of their prediction algorithm via a backward step variable selection, which suffers from internal bias via multicollinearity, whereas LASSO regression applies a tuning parameter to penalize all variables and cross validation to avoid internal validation bias. A more recent study (60) including a nomogram, also used a forward stepwise algorithm suffering from the same biases. The independent factors identified in this model were male sex, loss of consciousness, TBI severity measured by GCS, SDH, contusion site, EPS, and neurosurgical intervention. Importantly, as previous discussed the differences in EPS and PTE are important to separate in assessing risk of PTE, and in our study unlike others EPS includes all in-hospital seizures and PTE taken at the 2 year mark which should adequately eliminate confounders of the blurred margin of when EPS becomes PTE. Using prediction modelling and validating them on additional cohorts, may provide for a robust clinical tool to identify patients at high risk of PTE. This could extend to closer follow up clinical care including EEG assessment prior to clinic following discharge from hospital. As discussed earlier, seizure prophylaxis recommendations require an updated revision as they are largely ineffective in preventing PTE and are not selective. Furthermore, accurate risk prediction models of PTE may assist in informing precision medicine approaches in clinical trials of antiepileptogenic treatments.

The added morbidity of PTE on TBI survivors is not well known, although several studies have reported an increase in mortality. In this study, health related quality of life measured

by the EQ-5D was significantly lower for patients with PTE as well as overall GOS-E disability related outcomes. Previous small cohort studies show greater disability and self-reported satisfaction of life (61), more frequent medical attendances (30), less return to work (31), and higher levels of physical, cognitive and psychosocial long term impairment (28). Other studies show compounded neuropsychiatric problems such as personality disorders and behavioral disturbances (20) and increased risk of clinically significant anxiety (29), as well as increased associated caregiver stress (62). A recent review of the paucity of evidence postulates a more wide reaching impact of PTE on the emotional, cognitive and psychosocial functioning (63). Whilst studies show short term mortality increases (26,30), patients with PTE have been reported to have a 1.75 times higher risk of death out to 15 years post-injury compared to matched TBI survivors who did not develop epilepsy (31). Causes of death were no different in that study, however those with TBI are 60 times more likely to die from seizures compared to the general population (39). Our study demonstrated and even greater mortality impact of PTE, being associated with a risk that was 3.2 times higher than patients matched for other risk factors post-TBI.

This study has some limitations. Although the diagnosis of PTE was made on interview questioning by trained registry staff, in clinical practice it requires medical assessment and consultation with a neurologist or epileptologist, which is difficult to assess in large cohorts. There is also a short delay from diagnosis of PTE to the overall outcomes at 2 years. Whilst this study identified clinical risk factors for the development of PTE, and developed a novel prediction algorithm based on this. Future studies could incorporate biological biomarkers for which there is emerging evidence for their value for the prediction of PTE (64). The NIH funded Centre without Walls EpiBios4rx study was designed to identify biomarkers to

facilitate the identification of patients at high risk of developing PTE to target for antiepileptogenic drug trials post moderate-severe TBI (65).

CONCLUSION

This study identified independent clinical risk factors for the development of PTE following a moderate to severe TBI: younger age, higher CCI score, history of alcohol abuse, mental illness, EPS, intracerebral haemorrhage, and TBI severity (GCS and AIS head). Furthermore, we developed a novel prediction algorithm for PTE based on that could be used clinical and in trials to identify those at highest risk, and target interventions. Multicentre studies to validate a potential scoring system via predication analysis are needed, which can then be applied in future clinical trials of antiepileptogenic strategies. Our study also demonstrated the significant added impact that the development of PTE has on morbidity and mortality on top of that of TBI itself, and therefore the importance of identifying these patients early and implementing strategies for improving the management and ultimately prevention.

Ethics

All data was supplied by the Victorian State Trauma Outcomes Registry and Monitoring Group (VSTORM), following local ethics approval (MUHREC Project ID 18104). The VSTR has ethical approval from the Victorian Department of Health and Human Services HREC (DHHREC 11/14) and the Monash University HREC (CF13/3040–2001000165).

REFERENCES

1. Agrawal A, Timothy J, Pandit L, Manju M. Post-traumatic epilepsy: An overview. Clin Neurol Neurosurg [Internet]. 2006 Jul [cited 2019 Jan 30];108(5):433–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16225987

2. Kwan P, Schachter SC, Brodie MJ. Drug-Resistant Epilepsy. N Engl J Med [Internet]. 2011 Sep 8 [cited 2017 May 30];365(10):919–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21899452

3. Saletti PG, Ali I, Casillas-Espinosa PM, Semple BD, Lisgaras CP, Moshé SL, et al. In search of antiepileptogenic treatments for post-traumatic epilepsy. Neurobiol Dis [Internet]. 2019;123(May 2018):86–99. Available from: https://doi.org/10.1016/j.nbd.2018.06.017

4. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery [Internet]. 2016 Sep 1 [cited 2018 Mar 26];80(1):1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27654000

5. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung Y-C, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg [Internet]. 2019 Apr 1 [cited 2020 Jan 28];130(4):1080–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29701556

6. Aarabi B, Taghipour M, Haghnegahdar A, Farokhi M, Mobley L, Neurosurgery DO. Prognostic factors in the occurrence of posttraumatic epilepsy after penetrating head injury suffered during military service. Neurosurg Focus [Internet]. 2000;8(1):e1. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=44457508

7. Englander J, Bushnik T, Duong TT, Cifu DX, Zafonte R, Wright J, et al. Analyzing risk factors for late posttraumatic seizures: A prospective, multicenter investigation. Arch Phys Med Rehabil [Internet]. 2003;84(3 SUPPL. 1):365–73. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12638104

8. Bushnik T, Englander J, Duong T. Medical and social issues related to posttraumatic seizures in persons with traumatic brain injury. J Head Trauma Rehabil [Internet]. 2004 Jul;19(4):296–304. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=106556600&site=ehost-live

9. Zhao Y, Wu H, Wang X, Li J, Zhang S, Y. Z, et al. Clinical epidemiology of posttraumatic epilepsy in a group of Chinese patients. Seizure [Internet]. 2012;21(5):322–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=51914976

10. Yeh C-C, Chen T-L, Hu C-J, Chiu W-T, Liao C-C. Risk of epilepsy after traumatic brain injury: a retrospective population-based cohort study. J Neurol Neurosurg Psychiatry [Internet]. 2013 Apr;84(4):441–5. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=104247448&site=ehost-live

11. H.-C. W, W.-N. C, H.-W. C, J.-T. H, T.-M. Y, W.-C. L, et al. Factors predictive of outcome in posttraumatic seizures. J Trauma - Inj Infect Crit Care [Internet]. 2008 Apr;64(4):883–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=18404052

12. Bhattacharyya K, Mandal N, Paul UK uma., Bhattacharyya AK uma., Sinharay K, Gantait K. Post-traumatic seizure: a multicentric epidemiological study. J Indian Med Assoc [Internet]. 2014;112(2):93–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med10&NEWS=N&AN=25935962

13. Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M. Predictors of new-onset seizures: A 10-year follow-

up of head trauma subjects with and without traumatic brain injury. J Neurol Neurosurg Psychiatry [Internet]. 2014 Jun;85(6):598–602. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=103942457&site=ehost-live

14. Mahler B, Carlsson S, Andersson T, Tomson T. Risk for injuries and accidents in epilepsy: A prospective population-based cohort study. Neurology [Internet]. 2018 Feb 27;90(9):e779–89. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=128347241&site=ehost-live

15. Pugh MJ V., Orman JA, Jaramillo CA, Salinsky MC, Eapen BC, Towne AR, et al. The prevalence of epilepsy and association with traumatic brain injury in veterans of the Afghanistan and Iraq wars. J Head Trauma Rehabil [Internet]. 2015 Jan;30(1):29–37. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=103878770&site=ehost-live

16. Walker WC, Ketchum JS, Marwitz JH, Kolakowsky-Hayner SA, McClish DK, Bushnik T, et al. Global Outcome and Late Seizures After Penetrating Versus Closed Traumatic Brain Injury: A NIDRR TBI Model Systems Study. J Head Trauma Rehabil [Internet]. 2015 Jul;30(4):231–40. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=109626612&site=ehost-live

17. Ritter AC, Wagner AK, Fabio A, Pugh MJ, Walker WC, Szaflarski JP, et al. Incidence and risk factors of posttraumatic seizures following traumatic brain injury: A Traumatic Brain Injury Model Systems Study. Epilepsia [Internet]. 2016 Dec [cited 2017 May 30];57(12):1968–77. Available from: http://www3.interscience.wiley.com/journal/117957420/issueyear?year=2009

18. Temkin NR. Risk factors for posttraumatic seizures in adults. Epilepsia [Internet]. 2003 [cited 2018 Mar 26];44 Suppl 1(SUPPL. 10):18–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14511390

19. DeGrauw X, Thurman D, Xu L, Kancherla V, DeGrauw T, X. D, et al. Epidemiology of traumatic brain injury-associated epilepsy and early use of anti-epilepsy drugs: An analysis of insurance claims data, 2004-2014. Epilepsy Res [Internet]. 2018;146:41–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medc&NEWS=N&AN=30071385

20. Mazzini L, Cossa FM, Angelino E, Campini R, Pastore I, Monaco F, et al. Posttraumatic epilepsy: neuroradiologic and neuropsychological assessment of long-term outcome. Epilepsia [Internet]. 2003;44(4):569–74. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=37057502

21. Safaz I, Alaca R, Yasar E, Tok F, Yilmaz B, I. S, et al. Medical complications, physical function and communication skills in patients with traumatic brain injury: A single centre 5-year experience. Brain Inj [Internet]. 2008;22(10):733–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=352378572

22. Andelic N, Hammergren N, Bautz-Holter E, Sveen U, Brunborg C, Roe C. Functional outcome and health-related quality of life 10 years after moderate-to-severe traumatic brain injury. Acta Neurol Scand [Internet]. 2009;120(1):16–23. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=18976326

23. Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M, et al. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. Lancet [Internet]. 2009 Mar 28;373(9669):1105–10. Available from: http://dx.doi.org/10.1016/S0140-6736(09)60214-2

24. Thapa A, Chandra SP, Sinha S, Sreenivas V, Sharma BS, Tripathi M. Post-traumatic seizures-A prospective study from a tertiary level trauma center in a developing country. Seizure [Internet]. 2010;19(4):211–6. Available from:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=50812746

25. Ferguson PL, Smith GM, Wannamaker BB, Thurman DJ, Pickelsimer EE, Selassie AW, et al. A population-based study of risk of epilepsy after hospitalization for traumatic brain injury. Epilepsia [Internet]. 2010;51(5):891–8. Available from: http://www3.interscience.wiley.com/cgi-bin/fulltext/122655977/PDFSTART

26. Englander J, Bushnik T, Wright JM, Jamison L, Duong TT, J. E, et al. Mortality in late post-traumatic seizures. J Neurotrauma [Internet]. 2009;26(9):1471–7. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=355680267

27. Xu T, Yu X, Ou S, Liu X, Yuan J, Huang H, et al. Risk factors for posttraumatic epilepsy: A systematic review and meta-analysis. Epilepsy Behav [Internet]. 2017 Feb [cited 2017 May 30];67:1–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28076834

28. Kolakowsky-Hayner SA, Wright J, Englander J, Duong T, Ladley-O'Brien S, S.A. K-H, et al. Impact of late post-traumatic seizures on physical health and functioning for individuals with brain injury within the community. Brain Inj [Internet]. 2013;27(5):578–86. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS=N&AN=368731399

29. Juengst SB, Wagner AK, Ritter AC, Szaflarski JP, Walker WC, Zafonte RD, et al. Post-traumatic epilepsy associations with mental health outcomes in the first two years after moderate to severe TBI: A TBI Model Systems analysis. Epilepsy Behav [Internet]. 2017;73:240–6. Available from: http://www.elsevier.com/inca/publications/store/6/2/2/8/2/2/index.htt

30. Lin W-JJ, Harnod T, Lin C-LL, Kao C-HH, W.-J. L, T. H, et al. Mortality Risk and Risk Factors in Patients with Posttraumatic Epilepsy: A Population-Based Cohort Study. Int J Environ Res Public Health [Internet]. 2019;16(4):589. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=30781634

31. Uski J, Lamusuo S, Teperi S, Löyttyniemi E, Tenovuo O, Loyttyniemi E, et al. Mortality after traumatic brain injury and the effect of posttraumatic epilepsy. Neurology [Internet]. 2018;91(9):e878–83. Available from: http://www.neurology.org

32. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia [Internet]. 2010 Apr 1 [cited 2020 Feb 4];51(4):671–5. Available from: http://doi.wiley.com/10.1111/j.1528-1167.2009.02285.x

33. Majidi S, Makke Y, Ewida A, Sianati B, Qureshi AI, Koubeissi MZ, et al. Prevalence and Risk Factors for Early Seizure in Patients with Traumatic Brain Injury: Analysis from National Trauma Data Bank. Neurocrit Care [Internet]. 2017;27(1):90–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med13&NEWS=N&AN=28000125

34. Tubi MA, Lutkenhoff E, Blanco MB, Mcarthur D, Villablanca P, Ellingson B, et al. Early seizures and temporal lobe trauma predict post-traumatic epilepsy: A longitudinal study. Neurobiol Dis [Internet]. 2019 Mar [cited 2019 Jan 29];123(April 2018):115–21. Available from: https://doi.org/10.1016/j.nbd.2018.05.014

35. AM H, NR T, SS D, Haltiner AM, Temkin NR, Dikmen SS. Risk of seizure recurrence after the first late posttraumatic seizure. Arch Phys Med Rehabil [Internet]. 1997 Aug;78(8):835–40. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=107240211&site=ehost-live

36. Chen W, Li M De, Wang GF, Yang XF, Liu L, Meng FG. Risk of post-traumatic epilepsy after severe head injury in patients with at least one seizure. Neuropsychiatr Dis Treat [Internet]. 2017;13:2301–6. Available from: https://www.dovepress.com/getfile.php?fileID=38180

37. Mahler B, Carlsson S, Andersson T, Adelöw C, Ahlbom A, Tomson T. Unprovoked seizures after

traumatic brain injury: A population-based case-control study. Epilepsia. 2015;56(9):1438–44.

38. Yu T, Liu X, Sun L, Wu J, Wang Q. Clinical characteristics of post-traumatic epilepsy and the factors affecting the latency of PTE. BMC Neurol [Internet]. 2021 Dec 5;21(1):301. Available from: https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-021-02273-x

39. CL H-F. Mortality and life expectancy after traumatic brain injury rehabilitation. [Internet]. Mortality & Life Expectancy After Traumatic Brain Injury Rehabilitation. University of Colorado Health Sciences Center; 2003. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=109843473&site=ehost-live

40. Tenyi D, Gyimesi C, Horvath R, Kovacs N, Abraham H, Darnai G, et al. Concussive convulsions: A YouTube video analysis. Epilepsia [Internet]. 2016;57(8):1310–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med12&NEWS=N&AN=27334642

41. McCrory PR, Bladin PF, Berkovic SF. Retrospective study of concussive convulsions in elite Australian rules and rugby league footballers: phenomenology, aetiology, and outcome. BMJ [Internet]. 1997 Jan 18 [cited 2017 May 30];314(7075):171–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9022428

42. Wang H, Xin T, Sun X, Wang S, Guo H, Holton-Burke C, et al. Post-traumatic seizures-A prospective, multicenter, large case study after head injury in China. Epilepsy Res [Internet]. 2013;107(3):272–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med9&NEWS=N&AN=24239245

43. J. C, M.G. P, C.B. P, P. S, J. O. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. Lancet [Internet]. 2009;373(9669):1105–10. Available from: http://www.journals.elsevier.com/the-lancet/

44. Ritter AC, Wagner AK, Szaflarski JP, Brooks MM, Zafonte RD, Pugh MJ V, et al. Prognostic models for predicting posttraumatic seizures during acute hospitalization, and at 1 and 2 years following traumatic brain injury. Epilepsia [Internet]. 2016;57(9):1503–14. Available from: http://www3.interscience.wiley.com/journal/117957420/issueyear?year=2009

45. Foreman BP, Caesar RR, Parks J, Madden C, Gentilello LM, Shafi S, et al. Usefulness of the Abbreviated Injury Score and the Injury Severity Score in Comparison to the Glasgow Coma Scale in Predicting Outcome After Traumatic Brain Injury. J Trauma Inj Infect Crit Care [Internet]. 2007 Apr;62(4):946–50. Available from: https://journals.lww.com/00005373-200704000-00021

46. Cameron PA, Finch CF, Gabbe BJ, Collins LJ, Smith KL, McNeil JJ. Developing Australia's first statewide trauma registry: What are the lessons? Vol. 74, ANZ Journal of Surgery. 2004.

47. Gabbe BJ, Magtengaard K, Hannaford AP, Cameron PA. Is the Charlson Comorbidity Index useful for predicting trauma outcomes? Acad Emerg Med [Internet]. 2005 Apr 1;12(4):318–21. Available from: http://doi.wiley.com/10.1197/j.aem.2004.12.002

48. Nguyen TQ, Simpson PM, Braaf SC, Cameron PA, Judson R, Gabbe BJ. Comparison of the performance of mental health, drug and alcohol comorbidities based on ICD-10-AM and medical records for predicting 12-month outcomes in trauma patients. BMC Health Serv Res [Internet]. 2018 Dec 5;18(1):408. Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-018-3248-x

49. WILSON JTL, PETTIGREW LEL, TEASDALE GM. Structured Interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for Their Use. J Neurotrauma [Internet]. 1998 Aug;15(8):573–85. Available from: http://www.liebertpub.com/doi/10.1089/neu.1998.15.573

50. Zou H. The Adaptive Lasso and Its Oracle Properties. J Am Stat Assoc [Internet]. 2006 Dec

1;101(476):1418–29. Available from: https://www.tandfonline.com/doi/full/10.1198/016214506000000735

51. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol [Internet]. 2016 Jan;15(1):106–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1474442215002252

52. Webster KM, Sun M, Crack P, O'Brien TJ, Shultz SR, Semple BD, et al. Inflammation in epileptogenesis after traumatic brain injury. J Neuroinflammation [Internet]. 2017 Jan 13;14:1–17. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=120778993&site=ehost-live

53. Hamerle M, Ghaeni L, Kowski A, Weissinger F, Holtkamp M. Alcohol Use and Alcohol-Related Seizures in Patients With Epilepsy. Front Neurol [Internet]. 2018 Jun 5;9. Available from: https://www.frontiersin.org/article/10.3389/fneur.2018.00401/full

54. Lolk K, Dreier JW, Christensen J. Repeated traumatic brain injury and risk of epilepsy: a Danish nationwide cohort study. Brain [Internet]. 2021 Apr 12;144(3):875–84. Available from: https://academic.oup.com/brain/article/144/3/875/6095703

55. Corps KN, Roth TL, McGavern DB. Inflammation and Neuroprotection in Traumatic Brain Injury. JAMA Neurol [Internet]. 2015 Mar 1;72(3):355. Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/jamaneurol.2014.3558

56. Garner R, La Rocca M, Vespa P, Jones N, Monti MM, Toga AW, et al. Imaging biomarkers of posttraumatic epileptogenesis. Epilepsia [Internet]. 2019 Nov 8;60(11):2151–62. Available from: https://onlinelibrary.wiley.com/doi/10.1111/epi.16357

57. Lutkenhoff ES, Shrestha V, Ruiz Tejeda J, Real C, McArthur DL, Duncan D, et al. Early brain biomarkers of post-traumatic seizures: initial report of the multicentre epilepsy bioinformatics study for antiepileptogenic therapy (EpiBioS4Rx) prospective study. J Neurol Neurosurg Psychiatry [Internet]. 2020 Nov;91(11):1154–7. Available from: https://jnnp.bmj.com/lookup/doi/10.1136/jnnp-2020-322780

58. Pitkänen A, Paananen T, Kyyriäinen J, Das Gupta S, Heiskanen M, Vuokila N, et al. Biomarkers for posttraumatic epilepsy. Epilepsy Behav [Internet]. 2021 Aug;121:107080. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1525505020302596

59. Perucca P, Smith G, Santana-Gomez C, Bragin A, Staba R, Perucca P, Smith G, Santana-Gomez C, Bragin A SR, et al. Electrophysiological biomarkers of epileptogenicity after traumatic brain injury. Neurobiol Dis [Internet]. 2019 Jun [cited 2018 Jun 10];123(April 2018):69–74. Available from: https://doi.org/10.1016/j.nbd.2018.06.002

60. Wang X, Zhong J, Lei T, Wang H, Zhu L, Chu S, et al. Development and external validation of a predictive nomogram model of posttraumatic epilepsy: A retrospective analysis. Seizure [Internet]. 2021 May;88:36–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1059131121000996

61. Bushnik T, Englander J, Wright J, Kolakowsky-Hayner SA. Traumatic brain injury with and without late posttraumatic seizures: what are the impacts in the post-acute phase: a NIDRR Traumatic Brain Injury Model Systems study. J Head Trauma Rehabil [Internet]. 2012;27(6):E36-44. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=23131969

62. Jabbarinejad R, Cohen-Zimerman S, Wagner AK, Grafman J. Determinants of caregiver burden in male patients with epilepsy following penetrating traumatic brain injury. Epilepsy Behav [Internet]. 2021 Mar;116:107768. Available from:

https://linkinghub.elsevier.com/retrieve/pii/S1525505021000020

63. Semple BD, Zamani A, Rayner G, Shultz SR, Jones NC. Affective, neurocognitive and psychosocial disorders associated with traumatic brain injury and post-traumatic epilepsy. Neurobiology of Disease [Internet]. 2018;0–1. Available from: https://doi.org/10.1016/j.nbd.2018.07.018

64. Sharma S, Tiarks G, Haight J, Bassuk AG. Neuropathophysiological Mechanisms and Treatment Strategies for Post-traumatic Epilepsy. Front Mol Neurosci [Internet]. 2021 Feb 23;14. Available from: https://www.frontiersin.org/articles/10.3389/fnmol.2021.612073/full

65. Vespa PM, Shrestha V, Abend N, Agoston D, Au A, Bell MJ, et al. The epilepsy bioinformatics study for anti-epileptogenic therapy (EpiBioS4Rx) clinical biomarker: Study design and protocol. Neurobiol Dis [Internet]. 2019;123:110–4. Available from: http://www.elsevier.com/inca/publications/store/6/2/2/9/2/3/index.htt

Use of Continuous EEG outside of the Dedicated NeuroICU Setting

Joshua Laing, Georgia Grant, Elise White, Cecilia Harb, Max Cowey, Zhibin Chen, Piero Perucca, Patrick Kwan, Terence O'Brien.

Note: This study is intended for first author publication and the authors mentioned above secondarily contributed to this work.

ABSTRACT

Introduction

The use of Continuous EEG (cEEG) to evaluate for subclinical seizures and encephalopathic states in unwell inpatients was first evaluated in neuro-intensive Care Unit (Neuro-ICU), with high rates of seizure detection. In non-Neuro-ICU based settings, cEEG services are run by neurology departments and in collaboration with ICUs. The differences in patient cohorts and outcomes between cEEG in the ICU and ward settings is unknown.

Methods

We conducted a retrospective cohort study of adults (18 or above) non-electively admitted adult (18 or above) inpatients undergoing cEEG of longer than 6hrs duration in a non-Neuro-ICU setting. Demographic, clinical, cEEG specifics, and outcomes including mortality were evaluated, comparing cEEG in ward and general ICU cohorts.

Results

245 individual studies from 231 patients (125 [51%] male, average age 50.4) with a median cEEG session duration 44 hours (IQR 22.5-92.5 hours) were recorded, with 111 (45%) being commenced in the ICU and 134 (55%) on the ward. Compared to ward, patient studies performed in the ICU were older (53.1years), more often male (60%), investigating unexplained altered conscious state (94%), had lower proportions of patients with a history or epilepsy (27%) and prior clinical seizure (63%), had abnormal neuroimaging (63%), and longer in duration (median 63 vs 39 hours). Seizures were common in the whole cohort present in 50%, higher in the ICU cohort 60%, with a high proportion of status epilepticus 76% of total seizures. 81% had a documented management change following cEEG across

the cohort, with an increase in ASM being most common (58%). Patients in ICU had poorer outcomes in relation to discharge destination and in-hospital mortality, with 30% of patient studies associated with in-hospital mortality. Risk factors for seizures on multivariable analysis included age (P=0.03, RR 1.0), unexplained altered conscious state (P<0.0001, RR 4.2), and prior clinical seizure (P=0.03, RR 1.6). Risk factors for mortality on multivariable analysis were older age (P=0.005, RR 1.1) and inversely associated with prior clinical seizure (P= 0.007, RR 0.2), with a trend towards mortality with location in ICU and seizures.

Conclusion

This cohort study highlights a conservative use of cEEG in a non-Neuro-ICU setting, with a high rate of seizure detection and cEEG guided management changes. Whilst performed by the same neurology department run service, there are significant differences in patient cohorts of cEEG studies commenced in the ward or ICU. Consideration of clinical risk factors associated with seizures and mortality is important, and further outcome studies are essential to further delineate the role of cEEG in these cohorts.

BACKGROUND

There is increasing use of continuous electroencephalography (cEEG) in Australia, and around the globe, supported by the growing evidence of frequent subclinical seizures detected in critically unwell patients – in particular those with a brain injury, cerebral haemorrhage or status epilepticus (1–9). cEEG typically lasts hours to days, whereas routine EEG (rEEG) is usually 20-60mins duration and may be used for screening purposes. Whilst EEG is a broad neurophysiological tool to measure brain activity, cEEG is primarily used to detect and characterise seizures and encephalopathic states in critically unwell patients. In large US cross sectional studies, use of cEEG has been associated with improved mortality in unselected ICU inpatients (10,11). Seizures identified by cEEG in critically unwell patients are largely non-convulsive, electrographic seizures (ESz) or often electrographic status epilepticus (ESE), and are unable to be detected clinically in unconscious patients (12). ESz/ESE have been associated with increased morbidity (4,13–15) and mortality (4,5,14–16), additional to the underlying aetiology. The diagnosis of ESz/ESE is complex, requiring cEEG trained and experienced specialist supervision and oversight. Recently updated cEEG terminology guidelines from the American Clinical Neurophysiology Society further clarify the criteria for the diagnosis of ESz/ESE, and for the first time provide a definition of the ictal-interictal continuum (17). This update largely expands on the Salzburg diagnostic criteria for ESE (18). These updates follow on from the 2015 American Clinical Neurophysiology Society consensus statement for the use of cEEG, with recommendations for the indications and practical use of critical care cEEG use and its technical setup (19,20). Whilst the updated cEEG terminology combined with the previous consensus statements for the use of cEEG aim to establish the role of cEEG, there are still large gaps in our understanding of the significance of specific cEEG patterns, and evidence-based treatment guidelines are yet to be established.

Most of the cEEG literature has been from North America where dedicated neuro-ICU units are common. However, most hospital settings in Australia and elsewhere in the world do not have dedicated neuro-ICUs, and the relevance of the North American experience to these settings is uncertain (21,22). How cEEG should be optimally used in these non-NeuroICU hospitals requires specific attention. EEG services for inpatients are typically provided by neurology and/or epilepsy units, which often involves collaboration with ICU teams when EEG studies are conducted in the ICU. Whilst it has been shown that rapid upskilling of non-neuro intensive care staff is possible (23), this gap remains significant in the delivery of quality cEEG services in a very complex and evolving field. There are also significant logistical and funding considerations to providing cEEG services in non-neuro ICU hospital settings (24), and equity of access outside of major metropolitan hospitals in developed countries is a concern.

In clinical practice for neurology/epilepsy units conducting cEEG services throughout the hospital there are other non-ICU patient cohorts to consider. The American Clinical Neurophysiology Society consensus statements of cEEG are restricted to critically ill patients , as are many papers reporting cEEG cohorts. Inpatient EEG referrals can be dichotomised and broadly split into two categories, unexplained altered conscious state and paroxysmal clinical events for investigation both being suspicious for seizures, excluding referrals for neuroprognostication. Patient selection via clinical risk is essential to the appropriate and cost beneficial use of cEEG, and different sensitivity and specificity thresholds of service can be modelled given available resources (25). Whilst performing cEEG for all patients in the ICU as another form of bedside monitoring that can provide real time neurophysiological information, however unlike other modalities such as ECG,

oxygenation, etc. cEEG is difficult to interpret clinically by ICU nurses and doctors (26). Current evidence does not support a benefit of cEEG in low risk critically ill patients with altered conscious state as per a recent controlled trial of cEEG vs routine EEG (27), therefore using cEEG as a screening tool for all critically unwell patients is not only logistically and financial cumbersome, but clinically unwarranted. Given the paucity of evidence of the role of cEEG in management approaches, there is a possibility that its use may lead to treatment related harms. We know that using cEEG changes management including ASM changes for the majority of monitored patients (28), especially those with status epilepticus (29). Evidence from the paediatric literature suggests improved outcomes and cost effectiveness of 24-48hr EEG to manage NCSE (30), however this has not been replicated in adults. Recent pragmatic approaches to patient selection have been evaluated with the HELPS2B score that combines clinical risk factors of prior seizure and high risk EEG features (31), but further work is required. There is a paucity of studies evaluating the use of cEEG provided by non-neuro ICU epilepsy departments both in the ICU and the general ward settings, which represents the setting for the majority for the hospital EEG services around the world that perform cEEG on selected patients. The aim of this study was to review the clinical practice of cEEG in a non-NeuroICU setting across two major trauma receiving metropolitan hospitals, evaluating studies conducted in both ICU and ward inpatients comparing the cohorts, and investigating clinical risk factors for seizures, management changes, and outcomes including mortality.

METHODS

Study design and Patients

We report a retrospective cohort study of consecutive adult patients (18 years or above) undergoing non-electively inpatient cEEG longer than 6hrs during their acute admission from January 2018 to June 2020, both in ICU and non-ICU wards. Patients were recruited from two large specialist adult hospitals: The Alfred (Hospital 1) and The Royal Melbourne Hospitals (Hospital 2), two of the largest critical care hospitals in Melbourne, Australia, and home to the two state-designated trauma centres. Elective admissions to the video monitoring epilepsy units were excluded.

All cEEG studies were acquired using the standard international 10:20 montage system, with the exception of in patients where physical barriers (e.g. bandages from craniotomies) precluded some electrode placements. All cEEG studies were performed, reviewed and reported by the Epilepsy Units at each hospital, supervised by a fellowship-trained Australian and New Zealand Association of Neurologist (ANZAN) Level 3 accredited consultant epileptologist/EEG reader. Each study underwent at least twice daily review with daily reporting by an epilepsy fellow, supported by the rostered on-duty consultant epileptologist. All studies were reviewed at the multidisciplinary weekly epilepsy case conference attended by multiple ANZAN Level 3 accredited consultant epileptologist/EEG readers, and a consensus interpretation finalised. Other relevant inpatient records including neuroimaging findings and other investigation results are also reviewed.

Data collection

Demographic and clinical information regarding their admission was collected. History of epilepsy and prior clinical seizure was determined from inpatient medical notes, and neuroimaging results via imaging reports. Indications for cEEG were variably requested, however they were reviewed and grouped into two specific clinical indications of investigation of altered conscious state and paroxysmal clinical events suspicious for seizures. Location of initial cEEG was categorised as being in the ICU or ward. cEEG reports were reviewed for characteristics including focal slowing, interictal discharges, seizures, and proportion of those with status epilepticus both convulsive and non-convulsive. Discharge disposition including in-hospital mortality was also assessed, as well as mortality documented in the medical records at 12 months post cEEG. Management changes made because of the cEEG were determined by review of cEEG report and medical record review.

Statistical analysis

Descriptive statistics of the patient group was made with proportional analysis represented as percentages, and comparative analysis was performed using Fisher Exact tests, with reported risk ratios following univariate and multivariate analysis. All clinical risk factor variables were only available for multivariable analysis for half of the total cohort, for Hospital 1.

Ethics

Data from the Royal Melbourne Hospital in Melbourne was retrieved under the epilepsy quality assurance program (Melbourne Health ethics No: QA2012044), and under the Alfred Epilepsy Registry (Alfred Health Ethics Project No: 282/19).

RESULTS

Patient Characteristics

231 consecutive patients were identified to have undergone emergent cEEG recording during the study period across the two hospitals, with a total of 245 cEEG studies (Table 1). The median duration of the recordings was 44 hours (IQR 22.5-92.5 hours). Just under half of the patients underwent cEEG in the ICU (45%), and the remainder on wards (55%). The average age of the cohort was 50.4 years, and roughly half were females (49%) and males (51%). The indication for cEEG was unexplained altered conscious state in 66% and paroxysmal events in 34%. Regarding risk factors for cEEG seizures, 45% had a history of epilepsy, 72% had a prior clinical seizure, and 53% had abnormal neuroimaging. Within the ICU cohort, there is a much larger proportion of patients being evaluated with unexplained altered conscious state rather than paroxysmal clinical events. Associated with this was a lower proportion of patients with other risk factors of history of epilepsy, prior clinical seizure, but more had abnormal neuroimaging.

Table 1: Patient Characteristics Undergoing cEEG

Variable	Total N = 245	Ward (N=134)	ICU (N =111)
Median cEEG duration hrs (IQR)	44 (22.5-92.5)	39 (22-72.8)	63 (24-115)
Location (%) - ICU - Ward	 111 (45%) 134 (55%)	-	-
Age (ave yrs)	50.4	48.1	53.1
Sex (%) - Male - Female	 125 (51%) 120 (49%)	 58 (43%) 76 (57%)	 67 (60%) 44 (40%)
Indication (%) - Unexplained altered conscious state - Paroxysmal clinical events	 162 (66%) 83 (34%)	 58 (43%) 76 (57%)	 104 (94%) 7 (6%)

History of Epilepsy* (%)	53 (45%)	39 (59%)	14 (27%)
Prior Clinical Seizure* (%)	84 (72%)	52 (79%)	32 (63%)
Neuroimaging* (%) - Normal - Abnormal	 55 (47%) 62 (53%)	 36 (55%) 30 (45%)	 19 (37%) 32 (63%)

*Available at only 1 hospital, N = 117.

Characteristics of cEEG

Over half of the cEEG studies detected epileptiform discharges (56%), and 44% had focal slowing (Table 2). Half of all cEEG studies revealed seizures (n=123), with 93 (40% of total, and 76% of patients with seizures) of all being diagnosed with status epilepticus. Epileptiform abnormalities including interictal discharges and seizures were more common in patients studied in ICU compared to those in the ward, and more were diagnosed with status epilepticus with almost all the patients recognised with seizures in the ICU being diagnosed with SE (64/67, 96%).

Table 2: cEEG Characteristics

Variable	Total cohort N = 245	Ward N=134	ICU only N = 111
Focal slowing* (%)	107 (44%)	61 (46%)	46 (41%)
Interictal epileptiform abnormalities (%)	138 (56%)	62 (46%)	76 (68%)
Seizures (%)	123 (50%)	56 (42%)	67 (60%)
Status epilepticus (%)	93 (40%)	29 (22%)	64 (58%)

*Missing data, N=4.

Outcomes following cEEG Studies

There were a large proportion (81%) of patients in whom there was a management change as a result of the cEEG study (Table 3). This included not only increases in ASMs and

anaesthetics doses, but also a not insignificant number of cEEG studies that resulted in a decrease in ASMs (14%) and patients diagnosed with PNES receiving in-hospital neuropsychiatric interventions (9%). Some patients received immunotherapy (4%) as part of their management of ongoing seizures, and 1 required a pacing wire for a discovered cardiac rhythm abnormality. 19% of studies resulted in no obvious clinical management change. Management changes were similar between the ward and ICU cohorts.

Almost half of the patients undergoing cEEG were ultimately discharged home, and almost a quarter discharged to subacute services predominantly inpatient rehabilitation. Some of the patients were discharged to another hospital, usually a regional hospital, and some required reconnection of cEEG during their hospital stay. 15% died in hospital, and an increase to 21% had died by 12 months following their cEEG study.

Table 3: Outcomes following cEEG Studies

Variable	Total cohort N = 245	Ward only N=134	ICU only N=111
Management Changes (%)*	196 (81%)	104 (78%)	92 (83%)
• Increased/started AEDs	141 (58%)	67 (50%)	74 (67%)
• Decreased/stopped AEDs	34 (14%)	20 (15%)	14 (13%)
• Neuropsychiatric intervention for PNES	21 (9%)	19 (14%)	2 (2%)
• Immunotherapy	9 (4%)	7 (5%)	2 (2%)
• Pacing wire	1 (<1%)	1 (1%)	0 (0%)
• No change	46 (19%)	25 (19%)	21 (19%)
Discharge Destination (%)			
- Home	116/245 (47%)	90 (67%)	26 (23%)
- Subacute	55/245 (22%)	24 (18%)	31 (28%)
- Other hospital	22/245 (9%)	8 (6%)	14 (13%)
- Study reconnected	14/245 (6%)	5 (4%)	9 (8%)
Mortality (%)			
- In hospital	37 (16%)	6 (5%)	31 (30%)
- At 12 months	51 (22%)	15 (12%)	35 (34%)

*Some missing data
Note: Mortality was assessed per patient, rather than per cEEG study

Risk Factors for Seizures

In the total cohort, seizures were recorded during cEEG in 123 patients (Table 4). On univariable analysis, there were a higher proportion of patients with cEEG recorded seizures that were located in the ICU (RR 1.4, P=0.004, 95% CI 1.1.-1.9), were being investigated for ACS (RR 3.2, P=0.0001, 95% CI 2.1-5.0), and had concurrent cEEG features of focal slowing (RR 1.3, P=0.02, 95% CI 1.0-1.7) and interictal discharges (RR 5.2, P=0.0001, 95% CI 3.2-8.2). Other variables of sex, prior clinical seizure, abnormal imaging, and history of epilepsy were not significant.

Table 4: Univariable analysis of whole cohort of Risk Factors for Seizures

Variable	Total N=245	Seizure N=123	No Seizure N=122	P value	Risk Ratio (95%CI)
Age – Ave (SD)	X	X	X	X	X
Sex (%) • Male • Female	 125 (51%) 120 (49%)	 63 (51%) 60 (49%)	 62 (51%) 60 (49%)	0.53	1.0 (0.8-1.3)
Indication (%) • ACS • PE	162 (66%) 83 (34%)	106 (86%) 17 (14%)	56 (46%) 66 (54%)	**0.0001**	**3.2 (2.1-5.0)**
Location in ICU (%)	111 (45%)	67 (54%)	44 (36%)	**0.004**	**1.4 (1.1-1.9)**
History of epilepsy* (%)	53 (45%)	22 (39%)	31 (51%)	0.21	0.8 (0.5-1.2)
Prior clinical seizure* (%)	84 (72%)	44 (79%)	40 (66%)	0.12	1.4 (0.9-2.4)
Abnormal neuroimaging* (%)	62 (53%)	31 (55%)	31 (51%)	0.62	1.1 (0.8-1.6)
Interictal discharges (%)	138 (56%)	107 (87%)	31 (25%)	**0.0001**	**5.2 (3.2-8.2)**
Focal slowing# (%)	107 (44%)	63 (52%)	44 (37%)	**0.02**	**1.3 (1.0-1.7)**

*Data only from 1 hospital
#Missing data (n=4, 1sz)

On multivariable assessment using the hospital 1 cohort with complete data for all the variables, there were three significant variables identified (Table 5). ACS was associated with a 4.2 times risk of seizures compared to PE. Prior clinical seizures although non-significant on univariable analysis, showed a 1.6 times increased risk of seizures compared to patients with no prior seizure. Increased age showed a marginally statistically significant result, however non-clinically relevant. Patients being situated in the ICU had no independent predictive value of seizure detection on cEEG.

Table 5: Multivariable Analysis of Seizure Risk in Hospital 1 Cohort

Variable	Total N=117	Seizures N=56	Univariate P value	Multivariate P value	Risk Ratio (95%CI)
Age – Ave (SD)		56 (19)	**0.003**	**0.03**	**1.0 (1.0-1.0)**
Sex (%) • Male • Female	 62 (53%) 55 (47%)	 29 (52%) 27 (48%)	0.80		
Indication (%) • ACS • PE	78 (67%) 39 (33%)	50 (89%) 6 (11%)	**0.0001**	**0.0001**	**4.2 (2.0-9.0)**
Location in ICU (%)	51 (44%)	28 (50%)	0.18	0.47	0.9 (0.6-1.2)
History of epilepsy (%)	53 (45%)	22 (39%)	0.21		
Prior clinical seizure (%)	84 (72%)	44 (79%)	0.12	**0.03**	**1.6 (1.0-2.5)**
Abnormal neuroimaging (%)	62 (53%)	31 (55%)	0.62		

*Variable were selected for multivariable analysis if P<0.2.

Clinical Risk Factors for In-Hospital Mortality

A total of 37 patients died in-hospital following their cEEG (Table 6). More patients who died were investigated for unexplained altered conscious state rather than paroxysmal clinical events (RR 9.0, P=0.0001, 95% CI 2.2-36.4). Location in ICU was associated with mortality (RR 6.2, P=0.0001, 95% CI 2.7-14.4). Status epilepticus (RR 5.1, P=0.0001, 95% CI 2.5-

10.3), as well as all seizures (RR 3.6, P=0.001, 95% CI 1.7-7.5) and interictal discharges (RR 2.1, P=0.03, 95% CI 1.1-4.1) were all also associated with mortality. Abnormal neuroimaging (RR 3.3, P=0.04, 95% CI 1.0-11.1) was more often seen in patients whom died, whilst prior clinical seizure (RR 0.3, P=0.01, 95% CI 0.1-0.8) had a negative association with mortality. Mortality was also more common in patients that had ASM commenced or increased (RR 2.2, P=0.04, 95% CI 1.0-3.9).

Table 6: Univariable Analysis of Clinical Risk Factors on Mortality Risk in Whole Cohort

Variable	Total cohort N=245 (%)	Mortality N=37 (%)	P value	Risk Ratio (95%CI)
Age – Ave (SD)				
Sex (%) • Male • Female	125 (51%) 120 (49%)	15 (41%) 22 (59%)	0.17	0.7 (0.4-1.2)
Indication (%) • ACS • PE	162 (66%) 83 (35%)	35 (22%) 2 (2%)	**0.0001**	**9.0 (2.2-36.4)**
Location in ICU (%)	111 (45%)	31 (28%)	**0.0001**	**6.2 (2.7-14.4)**
History of Epilepsy* (%)	53 (45%)	3 (21%)	0.06	0.3 (0.1-1.1)
Prior Clinical Seizure* (%)	84 (72%)	6 (43%)	**0.01**	**0.3 (0.1-0.8)**
Abnormal neuroimaging* (%)	62 (53%)	11 (79%)	**0.04**	**3.3 (1.0-11.1)**
Focal slowing# (%)	107 (44%)	15 (39%)	0.72	0.9 (0.5-1.6)
Interictal discharges (%)	138 (58%)	27 (73%)	**0.03**	**2.1 (1.1-4.1)**
Seizures (%)	123 (50%)	29 (78%)	**0.001**	**3.6 (1.7-7.5)**
Status epilepticus (CSE/NCSE) (%)	93 (38%)	28 (76%)	**0.0001**	**5.1 (2.5-10.3)**

AEDs started/increased (%)	141 (58%)	27 (73%)	**0.04**	**2.0 (1.0-3.9)**

* Data only from 1 hospital
#Missing data, N=4, 1 mortality.

Multivariable assessment of clinical risk factors in Hospital 1 cohort was performed (Table 7). Initial evaluation on this smaller cohort in univariable analysis showed significance of age, ACS, location in the ICU, prior clinical seizure, abnormal neuroimaging and status epilepticus. Following multivariable analysis, increased age showed a small increased risk (RR 1.1, P=0.005, 95% CI 1.1-1.1) of mortality. Prior clinical seizure showed a reduced risk of mortality (RR 1.1, P=0.005, 95% CI 1.1-1.1) on this multivariable analysis. Status epilepticus was not included in the assessment due to the collinearity with seizures.

Table 7: Multivariable Analysis of Clinical Risk Factors on Mortality Risk in Hospital 1 Cohort

Variable	Total N= 117 (%)	Mortality N=14 (%)	Univariate P value	Multivariate P value	Risk Ratio (95%CI)
Age – Ave (SD)		69 (14)	**0.003**	**0.005**	**1.1 (1.1-1.1)**
Sex (%) • Male • Female	61 (53%) 55 (47%)	8 (57%) 6 (43%)	0.716		
Indication (%) • ACS • PE FI	77 (66%) 39 (34%)	13 (93%) 1 (7%)	**0.025**	0.69	1.4 (0.2-9.1)
Location in ICU (%)	50 (43%)	12 (86%)	**0.001**	0.06	5.1 (0.9-28.0)
History of epilepsy (%)	52 (45%)	3 (21%)	0.060	0.64	1.4 (0.3-6.5)
Prior clinical seizure (%)	83 (72%)	6 (43%)	**0.01**	**0.007**	**0.2 (0.1-0.7)**
Abnormal neuroimaging (%)	61 (53%)	11 (79%)	**0.04**	0.74	0.8 (0.2-2.8)
Focal slowing (%)	50 (43%)	8 (57%)	0.258		

Interictal discharges (%)	64 (55%)	10 (71%)	0.19	0.39	0.6 (0.2-1.7)
Seizures (%)	55 (47%)	10 (71%)	0.055	0.08	2.6 (0.9-7.6)
Status epilepticus* (%)	42 (36%)	10 (71%)	**0.003**		

*Status epilepticus was not assessed in the multivariate model due to collinearity with seizures.
Variable were selected for multivariable analysis if P<0.2.

DISCUSSION

This study evaluated a cohort of 245 consecutive cEEG studies in 231 patients across two hospitals performed on the ward and ICU, in a non-neuro ICU setting. The inclusion of cEEGs acquired on patients on the ward differentiates this series from most previous reports of cEEG, but reflects the experience of the majority of centres where performing cEEG on these less critically unwell patients is an important component to the service they offer. Of the patients undergoing cEEG in the ICU (N=111) in this cohort, compared to those in the ward, there were some key differences. More patients in the ICU were assessed for unexplained altered conscious state rather than paroxysmal clinical events, and when seizures were detected on cEEG the majority were diagnosed with SE. Most seizures detected on cEEG in the ICU in this cohort were classified as SE (96%), which is higher than in previously reported cEEG cohorts in the ICU, and suggests a more conservative use of cEEG in the ICU in our centres. Prior clinical seizures and history of epilepsy were more common in ward patients, compared to ICU, presumably an important risk factor more often needed when assessing paroxysmal events with a higher threshold to require cEEG.

Whilst there are recommendations for the use of cEEG in specific patient groups that may benefit from cEEG (20), these are limited to critically ill patients and therefore there is no guidance on urgent cEEG use including ward-based patients. In fact, there are no evidence-based guidelines or recommendations for the use of inpatient urgent rEEG, yet rEEG is used widely around the world to address various inpatient clinical indications. Whilst neuroprognostication is a common inpatient rEEG referral which would not usually lead to cEEG, limited studies suggest emergent use of inpatient rEEG most frequently assesses for ES and ESE with good overall utility and high abnormality rate (32,33). Cost benefit of urgent inpatient rEEG has been poorly studied, and costs aren’t always remunerated to

neurophysiology units. There are many neurophysiology units that have conducted cEEG as such conservatively for some time, that may have been increased recently following a new appreciation for the proportion of critically ill patients with ESE detected on cEEG and an improved understanding of cEEG defined patterns. There are not many similar published series, but one study investigating the management changes from using cEEG reported 300 studies, 189 of those in the ICU (28). Our study showed that in 72% of patients there was ASM changes post cEEG, which is much higher than previously reported 52% (28).

Following early work demonstrating a high prevalence of seizures detected in ICU patients, predominantly ES and ESE, patient selection has become increasingly important. Previous studies using cEEG for seizure detection in critically ill patients suggested up to 24 and 48 hrs were required to pick up 93% of seizures (34). In the context of limited resources, a higher specificity and accepting a lower sensitivity may require a much smaller feasible number of patients to undergo cEEG (25). Aetiology specific considerations exist with ES and ESE common following convulsive SE, and other acute neurological insults including TBI, SAH, stroke, CNS infections, and sepsis-associated encephalopathy (20). A high rate of epileptiform abnormalities present in the first 30mins of EEG recording was found to be predictive of subsequent seizure detection on cEEG (3). After two significant risk factors of coma (OR 1.8) and history of clinical seizures (OR 3.0) were determined as primary risks of cEEG detected seizures, a time dependent risk algorithm was determined showing a reduced time to screen patients dependent on risk profile and initial EEG factors (35). The definition of coma in this study was defined as lack of purposeful response including to noxious stimuli (35), which may be difficult to assess reliably and apply to non-ICU patients although responsiveness is known to be impaired in seizures but may be assessed systematically (36). History of clinical seizures also referred to patients both with a history

of epilepsy or clinical suspicion of seizures, which are clinically distinct given the higher diagnostic certainly of the former. rEEG parameters on 1hr screening EEG were included into the risk evaluation of seizures, with the 2HELPS2B study identifying factors of prior seizure, independent discharges, frequency of >2Hz, lateralised periodic discharges or delta activity, brief ictal rhythmic discharge, and plus features, incorporated into a scoring system (37) with subsequent validation study (31). Although this study did not specify if patients were in ICU, apart from the acute neurological condition and a proportion of patients with prior seizures, the indications for cEEG was not clear. A follow up study demonstrated good performance of the 2HELPS2B score combined with prior clinical seizure specifically in patients with TBI and no history of epilepsy (38). Like the 2HELPS2B score that investigated risk of ES and provided an algorithm to detect ES over time, the TERSE study used the clinical risk factors of coma and combined risk of history of epilepsy or clinical seizure. Unlike the 2HELPS2B study, clinical risk factors determined the initial EEG duration which was then subsequently refined in a second step following pre-defined EEG epoch rick factor review with epileptiform abnormalities to determine final cEEG duration required to detect 95% of ES (39). This was a retrospective study which also showed a significant reduction in total cEEG time required compared to what was performed in this cohort. Again, coma here was defined similarly to the 2HELPS2B study but clarified the use of the motor component of GCS <5. Whilst our study did not specifically assess this, the referral indication of ACS as well as prior clinical seizure were identified as clinical risk factors for seizures on multivariable analysis consistent with the current literature. Post-hypoxic brain injury as a primary aetiology is usually excluded from these studies due to overall prognostic differences, and although there may appear benefit of cEEG this is not clear over rEEG (20).

Whilst the excitement around the widespread detection of ES in critically unwell patients exists even with improvements in efficiency patient selection, the outcomes of associated management of ES and ESE requires further evaluation hence the conservative approach to cEEG of our group. A large cross sectional study of over 40,000 inpatients in the US found that cEEG was associated with improved mortality over rEEG, in mechanically ventilated ICU inpatients (11). A follow up US ICU study in 2019 showed a mortality benefit in 22,728 cEEG monitored patients matched in a cohort of over 7millon patients (10), with longer length of stay and hospital costs. As mentioned above, there are some limited observational studies showing morbidity (4,13–15) and mortality (4,5,14–16) in patients with cEEG detected ES and ESE. Several neurophysiological studies have demonstrated the pathophysiological (2,40) and anatomical (41) damage of ES and ESE. The recent prospective randomised controlled trial of rEEG vs cEEG for low risk patients without prior clinical seizure showed no difference in outcomes between the two strategies (27). A limitation of this study was the inclusion of patients with post-hypoxic brain injury, and post-hoc analysis excluding these patients suggested benefit from cEEG. The diagnosis of PNES can be difficult and is an issue even in well-constructed RCTs, as was seen in the ESETT trial of antiseizure medication for established status epilepticus (42). Whilst there may not be a high immediate mortality, PNES is associated with increased long term mortality and early identification and appropriate management is essential (43), therefore making emergent cEEG important. The benefit of cEEG in patients with severe COVID is still unclear, despite epileptiform findings in some (44). Treatment guidelines for patient undergoing cEEG are urgently lacking, and although may be technically complex (45) to evaluate is often the topic of international debate (46).

The practice of cEEG is time consuming, and labour and resourse intense, with lack of funding, equipment and expertise being the most common barriers to performing cEEG (24). Apart from honing cEEG toward risk factor identification in making cEEG more efficient, rather than using cEEG as a monitoring tool for unselected patient groups, there are additional tools to improve efficiency. Typically, cEEG uses the 10:20 international electrode system involving 21 electrodes, however limited electrode montages in these cohorts may be acceptable especially as the special resolution and precision of seizure localisation is not essential. Although some studies have investigated limited montages (47) including those with rapid application and cost beneficial for inpatient evaluation (48), and easy access wireless headsets have also been shown to be feasible, able to be applied by any staff (49), these have not been evaluated systematically in large studies. Furthermore, quantitative EEG (QEEG) providing a user-friendly visual analysis of compressed EEG may be accurate in detecting seizures and reducing reading time (50). Although this is not yet widely adopted, recent investigation shows good inter-rater agreement with standardised nomenclature (51). cEEG is often restricted to specialised centres, and although centralised tele-cEEG services has been pursued to support hospitals without capacity for cEEG (52), there remains an equity issue in accessing cEEG. Combined, these strategies as well as good and appropriate patient selection may reduce the economic and access considerations of cEEG.

This study has several limitations, due to the data being retrospectively collected as a quality audit of practice of cEEG. A screening EEG was not captured during our analysis, although many of the clinical decisions made would have likely involved considering the early EEG changes. Only limited cEEG patterns were reported from cEEG reports, as the use of ACNS ICU cEEG terminology (17) has not yet been become standard clinical practice. A purpose designed comprehensive prospective database is planned to address these issues, with

further clinical information to enrich subsequent analysis and identify specific patient groups such as PNES and post-hypoxic brain injury, as well as outcome data in a field that often fails to assess the overall impact of cEEG.

Conclusion

This cohort study across two Australian hospitals highlights a conservative use of cEEG in the non-neuro ICU setting detecting seizures in 50% of those undergoing cEEG, most of which were diagnosed with ESE. cEEG extends beyond the ICU and may include patients from the ward, with some key differences between the groups. Risk factors of prior clinical seizure and being referred for ACS were predictive of detecting seizures on the cEEG, which is consistent with the literature. 81% of patients had management changes because of cEEG, and despite the lack of good outcome and treatment guidelines we must identify patients that may benefit from cEEG. Larger more comprehensive cohorts are required to assess the further identification of patients with ES on cEEG, and importantly treatment related outcomes.

REFERENCES:

1. Claassen J, Albers D, Schmidt JM, De Marchis GM, Pugin D, Falo CM, et al. Nonconvulsive seizures in subarachnoid hemorrhage link inflammation and outcome. Ann Neurol [Internet]. 2014 May [cited 2020 Jun 9];75(5):771–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24771589
2. Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med [Internet]. 2007;35(12):2830–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=350175782
3. Westover MB, Shafi MM, Bianchi MT, Moura LMVR, O'Rourke D, Rosenthal ES, et al. The probability of seizures during EEG monitoring in critically ill adults. Clin Neurophysiol [Internet]. 2015;126(3):463–71. Available from: http://dx.doi.org/10.1016/j.clinph.2014.05.037
4. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. Crit Care Med. 2009;37(6):2051–6.
5. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: An investigation of variables associated with mortality. Neurology [Internet]. 1996;47(1):83–9. Available from: http://www.neurology.org/cgi/doi/10.1212/WNL.47.1.83
6. Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg [Internet]. 1999;91(5):750–60. Available from: http://thejns.org/doi/10.3171/jns.1999.91.5.0750
7. Kubota Y, Nakamoto H, Egawa S, Kawamata T. Continuous EEG monitoring in ICU. J Intensive Care. 2018;6(1):1–8.
8. Newey CR, Kinzy TG, Punia V, Hantus S. Continuous electroencephalography in the critically ill: Clinical and continuous electroencephalography markers for targeted monitoring. J Clin Neurophysiol. 2018;35(4):325–31.
9. Freund B, Probasco JC, Ritzl EK. Seizure incidence in the acute postneurosurgical period diagnosed using continuous electroencephalography. J Neurosurg. 2019;130(4):1203–9.
10. Hill CE, Blank LJ, Thibault D, Davis KA, Dahodwala N, Litt B, et al. Continuous EEG is associated with favorable hospitalization outcomes for critically ill patients. Neurology. 2019;92(1):E9–18.
11. Ney JP, Goes DN Van Der, Nuwer MR, Nelson L, Eccher MA, Van Der Goes DN, et al. Continuous and routine eeg in intensive care. Neurology [Internet]. 2013 [cited 2018 Apr 23];81(23):2002–8. Available from: www.neurology.org
12. Hirsch LJ. Continuous EEG Monitoring in the Intensive Care Unit. Jounral Clin Neurophysiol [Internet]. 2004 Sep 3;21:332–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15592007
13. De Marchis GM, Pugin D, Meyers E, Velasquez A, Suwatcharangkoon S, Park S, et al. Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome. Neurology. 2016;86(3):253–60.
14. Kurtz P, Gaspard N, Wahl AS, Bauer RM, Hirsch LJ, Wunsch H, et al. Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med. 2014;40(2):228–34.
15. Claassen J, Jetté N, Chum F, Green R, Schmidt M, Choi H, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. Neurology [Internet]. 2007 Sep 25 [cited 2020 Jun 9];69(13):1356–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17893296
16. Waterhouse EJ, Vaughan JK, Barnes TY, Boggs JG, Towne AR, Kopec-Garnett L, et al. Synergistic effect of status epilepticus and ischemic brain injury on mortality. Epilepsy Res [Internet]. 1998 Feb [cited 2020 Jul 22];29(3):175–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9551779
17. Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. J Clin Neurophysiol. 2021;38(1):1–29.
18. Leitinger M, Trinka E, Gardella E, Rohracher A, Kalss G, Qerama E, et al. Diagnostic accuracy of the

Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol [Internet]. 2016 Sep 1 [cited 2020 May 6];15(10):1054–62. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1474442216301375
19. Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus Statement on Continuous EEG in Critically Ill Adults and Children , Part II : Personnel , Technical Specifications ,. 2015;32(2).
20. Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I. J Clin Neurophysiol [Internet]. 2015;32(2):87–95. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004691-201504000-00001
21. Kramer AH, Couillard P. Neurocritical Care: A Growing International Collaborative. Neurocrit Care [Internet]. 2020 Feb;32(1):80–3. Available from: http://link.springer.com/10.1007/s12028-019-00858-6
22. Ward MJ, Shutter LA, Branas CC, Adeoye O, Albright KC, Carr BG. Geographic access to US Neurocritical Care Units registered with the Neurocritical Care Society. Neurocrit Care [Internet]. 2012 Apr [cited 2020 Jun 3];16(2):232–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22045246
23. Seiler L, Fields J, Peach E, Zwerin S, Savage C. The effectiveness of a staff education program on the use of continuous EEG with patients in neuroscience intensive care units. J Neurosci Nurs [Internet]. 2012 Apr [cited 2020 Jun 1];44(2):E1-5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22367276
24. Laing J, Lawn N, Perucca P, Kwan P, O'Brien TJ. Continuous EEG use and status epilepticus treatment in Australasia: a practice survey of Australian and New Zealand epileptologists. BMJ Neurol Open. 2020;2(2):e000102.
25. Yang A, Arndt DH, Berg RA, Carpenter JL, Chapman KE, Dlugos DJ, et al. Development and validation of a seizure prediction model in critically ill children. Seizure. 2015;25:104–11.
26. Kurtz P, Hanafy KA, Claassen J. Continuous EEG monitoring: is it ready for prime time? Curr Opin Crit Care [Internet]. 2009 Apr;15(2):99–109. Available from: http://journals.lww.com/00075198-200904000-00006
27. Rossetti AO, Schindler K, Sutter R, Rüegg S, Zubler F, Novy J, et al. Continuous vs Routine Electroencephalogram in Critically Ill Adults With Altered Consciousness and No Recent Seizure. JAMA Neurol [Internet]. 2020 Jul 27;1–8. Available from: https://jamanetwork.com/journals/jamaneurology/fullarticle/2768699
28. Kilbride RD, Costello DJ, Chiappa KH. How Seizure Detection by Continuous Electroencephalographic Monitoring Affects the Prescribing of Antiepileptic Medications. Arch Neurol [Internet]. 2009 Jun 1;66(6). Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/archneurol.2009.100
29. Holm-Yildiz S, Richter Hansen J, Thonon V, Beniczky S, Fabricius M, Sidaros A, et al. Does continuous electroencephalography influence therapeutic decisions in neurocritical care? Acta Neurol Scand [Internet]. 2021 Mar 11;143(3):290–7. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ane.13364
30. Abend NS, Topjian AA, Williams S. Could EEG Monitoring in Critically Ill Children Be a Cost-effective Neuroprotective Strategy? 2015 Dec [cited 2020 Jun 1];32(6). Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004691-201512000-00009
31. Struck AF, Fesharaki MT, Schmitt SE, Ruiz AR, Swisher CB, Subramaniam T, et al. Assessment of the Validity of the 2HELPS2B Score for Inpatient Seizure Risk Prediction. JAMA Neurol [Internet]. 2020;53705:1–8. Available from: https://jamanetwork.com/journals/jamaneurology/fullarticle/2758318
32. Praline J, Grujic J, Corcia P, Lucas B, Hommet C, Autret A, et al. Emergent EEG in clinical practice. Clin Neurophysiol [Internet]. 2007 Oct;118(10):2149–55. Available from:

https://linkinghub.elsevier.com/retrieve/pii/S1388245707003653
33. Firosh Khan S, Ashalatha R, Thomas SV, Sarma PS. Emergent EEG is helpful in neurology critical care practice. Clin Neurophysiol [Internet]. 2005 Oct;116(10):2454–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1388245705002701
34. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology [Internet]. 2004 [cited 2018 Jul 2];62:1743–8. Available from: http://n.neurology.org/content/neurology/62/10/1743.full.pdf
35. Struck AF, Osman G, Rampal N, Biswal S, Legros B, Hirsch LJ, et al. Time-dependent risk of seizures in critically ill patients on continuous electroencephalogram. Ann Neurol. 2017;82(2):177–85.
36. Yang L, Shklyar I, Lee HW, Ezeani CC, Anaya J, Balakirsky S, et al. Impaired consciousness in epilepsy investigated by a prospective responsiveness in epilepsy scale (RES). Epilepsia [Internet]. 2012 Mar;53(3):437–47. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2011.03341.x
37. Struck AF, Ustun B, Ruiz AR, Lee JW, LaRoche SM, Hirsch LJ, et al. Association of an electroencephalography-based risk score with seizure probability in hospitalized patients. JAMA Neurol. 2017;74(12):1419–24.
38. Moffet EW, Subramaniam T, Hirsch LJ, Gilmore EJ, Lee JW, Rodriguez-Ruiz AA, et al. Validation of the 2HELPS2B Seizure Risk Score in Acute Brain Injury Patients. Neurocrit Care [Internet]. 2020 Dec 27;33(3):701–7. Available from: http://link.springer.com/10.1007/s12028-020-00939-x
39. Cissé FA, Osman GM, Legros B, Depondt C, Hirsch LJ, Struck AF, et al. Validation of an algorithm of time-dependent electro-clinical risk stratification for electrographic seizures (TERSE) in critically ill patients. Clin Neurophysiol [Internet]. 2020 Aug [cited 2020 Jul 22];131(8):1956–61. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1388245720303680
40. Witsch J, Frey HP, Schmidt JM, Velazquez A, Falo CM, Reznik M, et al. Electroencephalographic periodic discharges and frequency-dependent brain tissue hypoxia in acute brain injury. JAMA Neurol. 2017 Mar 1;74(3):301–9.
41. Vespa PM, McArthur DL, Xu Y, Eliseo M, Etchepare M, Dinov I, et al. Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy. Neurology [Internet]. 2010;75(9):792–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=20805525
42. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019;381(22):2103–13.
43. Nightscales R, McCartney L, Auvrez C, Tao G, Barnard S, Malpas CB, et al. Mortality in patients with psychogenic nonepileptic seizures. Neurology [Internet]. 2020 Aug 11;95(6):e643–52. Available from: http://www.neurology.org/lookup/doi/10.1212/WNL.0000000000009855
44. Louis S, Dhawan A, Newey C, Nair D, Jehi L, Hantus S, et al. Continuous electroencephalography characteristics and acute symptomatic seizures in COVID-19 patients. Clin Neurophysiol [Internet]. 2020 Nov;131(11):2651–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1388245720304430
45. Ferguson M, Bianchi MT, Sutter R, Rosenthal ES, Cash SS, Kaplan PW, et al. Calculating the Risk Benefit Equation for Aggressive Treatment of Non-convulsive Status Epilepticus. Neurocrit Care [Internet]. 2013 Apr 11;18(2):216–27. Available from: http://link.springer.com/10.1007/s12028-012-9785-y
46. Rossetti AO, Hirsch LJ, Drislane FW. Nonconvulsive seizures and nonconvulsive status epilepticus in the neuro ICU should or should not be treated aggressively: A debate. Clin Neurophysiol Pract [Internet]. 2019;4:170–7. Available from: https://doi.org/10.1016/j.cnp.2019.07.001
47. Ma BB, Johnson EL, Ritzl EK. Sensitivity of a Reduced EEG Montage for Seizure Detection in the Neurocritical Care Setting. J Clin Neurophysiol [Internet]. 2018 May;35(3):256–62. Available from: http://journals.lww.com/00004691-201805000-00012
48. Ney JP, Gururangan K, Parvizi J. Modeling the economic value of Ceribell Rapid Response EEG in the inpatient hospital setting. J Med Econ [Internet]. 2021 Jan 1;24(1):318–27. Available from: https://www.tandfonline.com/doi/full/10.1080/13696998.2021.1887877

49. Caricato A, Della Marca G, Ioannoni E, Silva S, Benzi Markushi T, Stival E, et al. Continuous EEG monitoring by a new simplified wireless headset in intensive care unit. BMC Anesthesiol [Internet]. 2020 Dec 7;20(1):298. Available from: https://bmcanesthesiol.biomedcentral.com/articles/10.1186/s12871-020-01213-5
50. Haider HA, Esteller R, Hahn CD, Westover MB, Halford JJ, Lee JW, et al. Sensitivity of quantitative EEG for seizure identification in the intensive care unit. Neurology. 2016;87(9):935–44.
51. Zafar SF, Amorim E, Williamsom CA, Jing J, Gilmore EJ, Haider HA, et al. A standardized nomenclature for spectrogram EEG patterns: Inter-rater agreement and correspondence with common intensive care unit EEG patterns. Clin Neurophysiol [Internet]. 2020 Sep;131(9):2298–306. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1388245720303692
52. Limotai C, Ingsathit A, Thadanipon K, Pattanaprateep O, Pattanateepapon A, Phanthumchinda K, et al. Efficacy and economic evaluation of delivery of care with tele-continuous EEG in critically ill patients: a multicentre, randomised controlled trial (Tele-cRCT) study protocol. BMJ Open [Internet]. 2020 Mar 4;10(3):e033195. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2019-033195

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Continuous EEG use and status epilepticus treatment in Australasia: a practice survey of Australian and New Zealand epileptologists

Joshua Laing,[1,2] Nicholas Lawn,[3] Piero Perucca,[4,5] Patrick Kwan,[1,2] Terence J O'Brien[1,2]

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[1]Neuroscience, Monash University, Melbourne, Victoria, Australia
[2]Epilepsy Unit, Alfred Health, Melbourne, Victoria, Australia
[3]WA Adult Epilepsy Service, Western Australia Health Networks, Perth, Western Australia, Australia
[4]Alfred Health, Monash University, Melbourne, Victoria, Australia
[5]Departments of Medicine and Neurology, The Royal Melbourne Hospital, Parkville, Victoria, Australia

Correspondence to
Dr Joshua Laing;
joshua.laing@monash.edu

ABSTRACT

Objective Continuous electroencephalography (cEEG) is increasingly used to detect non-convulsive seizures in critically ill patients but is not widely practised in Australasia. Use of cEEG is also influencing the management of status epilepticus (SE), which is rapidly evolving. We aimed to survey Australian and New Zealand cEEG use and current treatment of SE

Methods A web-based survey was distributed to Epilepsy Society of Australia (ESA) members, between October and November 2019. Adult and paediatric neurologists/epileptologists with ESA membership involved in clinical epilepsy care and cEEG interpretation were invited to participate.

Results Thirty-five paediatric/adult epileptologists completed the survey, 51% with over 10 years of consultant experience. cEEG was always available for only 31% of respondents, with the majority having no or only ad hoc access to cEEG. Lack of funding (74%) and personnel (71%) were the most common barriers to performing cEEG. Although experience with SE was common, responses varied regarding treatment approaches for both convulsive and non-convulsive SE. Escalation to anaesthetic treatment of convulsive SE tended to occur later than international guideline recommendations. There was general agreement that formal training in cEEG and national guidelines for SE/cEEG were needed.

Conclusions cEEG availability remains limited in Australia, with lack of funding and resourcing being key commonly identified barriers. Current opinions on the use of cEEG and treatment of SE vary reflecting the complexity of management and a rapidly evolving field. An Australian-based guideline for the management of SE, including the role of cEEG is recommended.

INTRODUCTION

Assessment and management of status epilepticus (SE) and urgent electroencephalography (EEG) review is an essential component of emergency neurology and epileptology. Use of continuous EEG (cEEG) to guide diagnosis and management of SE and non-convulsive seizures is increasing worldwide.[1] The identification of seizures, which are predominantly non-convulsive (or subclinical), in a substantial proportion of critically ill patients, and the recognition of the contribution of these seizures to morbidity and mortality has attracted significant attention over the last decade.[2] cEEG is defined as a prolonged recording and allows non-invasive real-time measurement of brain electrophysiological activity in critically ill patients in whom clinical assessment is unreliable, typically in the intensive care unit (ICU). However, cEEG is highly labour and resource intense, and requires specialised expertise and training of medical, EEG neuroscientist and nursing staff. Two pivotal large database studies, 1 of 41 000 unselected ventilated adult patients in the ICU and the other involving over 7 million ICU patients of whom 22 700 had cEEG, showed that the use of cEEG was associated with a significantly improved mortality compared with just using routine EEG in age-matched and illness-matched patients.[1 3] However, a prospective European study of 364 patients with altered consciousness randomised to cEEG or repeated routine EEG, showed no between-group differences in mortality at 6 months; notably, this study excluded patients who experienced a seizure within 36 hours of the EEG, and included a high proportion of patients with hypoxic ischaemic encephalopathy, a group that rarely requires cEEG.[4]

The mortality risk of SE is substantial, and becomes even higher once medically refractory, beyond the effect of the underlying aetiology. A recent review showed poor long-term outcomes after SE, with mortality rates reaching 20% for children and 55% in adults.[5] The most recent definition of SE from the International League Against Epilepsy provides a time 't1' for when seizures are prolonged where normal mechanisms

that serve to terminate seizures fail, and a time 't2' in which long-term consequences are likely to occur.[6] Akin to hyperacute stroke treatment, the concept of 'time is brain' is increasingly used for SE to stress the importance of urgent cessation of seizures and the avoidance of subsequent morbidity and mortality associated with ongoing seizures. The use of cEEG use for the assessment and management of convulsive SE (CSE) and non-convulsive SE (NCSE), excluding seizure mimics where unnecessary and dangerous escalation of care including intubation may occur, has also been recommended in specific settings[7 8] and should be included in guidelines for SE The overall cost–benefit of cEEG guided management of SE, taking into account improvements in morbidity and mortality, is unknown.[9]

Various international guidelines exist for the assessment and management of SE, but are lacking in the Australian context.[10] A recent systematic review from Australian authors concluded that there are often deviations from published within hospital guidelines of SE, and that non-adherence to these guidelines is associated with worse outcomes.[11] Significantly improved outcomes in seizure cessation, necessity for ICU admission and length of stay, have been demonstrated with adherence to treatment protocols.[12] While neurologists and epileptologists may not always be involved in the initial management of CSE, their input is invariably needed in NCSE; thus, their involvement in the development of treatment guidelines and use of cEEG is required.

The current Australian landscape of cEEG and treatment of SE is unknown, on both an individual health service and state levels. This study sought to capture current clinical practices in Australia and to assess opinions of practising clinicians in the Australian epilepsy community.

METHODS

Design

A web-based survey of cEEG use and management of SE was distributed via electronic mailing lists.

Population

Clinicians who are members of the Epilepsy Society of Australia (ESA), which includes some practising in New Zealand, were invited to complete the survey between October and November 2019. Participation was strictly voluntary, and all responses were anonymous. A decision to commence the survey indicated consent to use any data provided for the purposes described.

Questions

Survey questions were designed by the investigators, aiming to capture information on respondent demographics and level of experience, fellowship training in epilepsy, college affiliation, participants' availability and use of urgent and cEEG, and experience in managing CSE and NCSE (see online supplemental material).

Data analysis

Descriptive analysis was undertaken and compared with available guidelines.

RESULTS

A total of 43 responses were obtained between October and November 2019. Of these, 7 incomplete responses, defined as less than half the questions completed, and one respondent who was exclusively ICU trained were excluded. Therefore, 35 responses were included in the analysis. One respondent did not complete the cEEG questions and another did not complete SE management questions.

Demographics and expertise of respondents

Characteristics of respondents are shown in table 1. Most were males. The sample comprised adult (66%) and paediatric (31%) neurologists/epileptologists from all Australian states (n=33) and New Zealand (n=2). Expertise displayed a bimodal distribution of both early career (n=9, 30%) but predominantly experienced physicians (n=18, 60%), of whom eighteen self-identified as epileptologists. Membership across the Royal Australasian College of Physicians, Australian and New Zealand Association of Neurologists (ANZAN) and ESA was almost universal. Level 3 ANZAN EEG board certification was common (54%), with most having done at least 1 year of epilepsy fellowship. Ninety-four per cent were involved in reporting cEEG.

Self-reported confidence was high in the diagnosis of NCSE, as well as the management of NCSE and CSE. The majority of respondents felt that there should be formal teaching in cEEG (n=33, 94%), and most agreed that Australian cEEG guidelines should be developed (n=26, 74%). Individual comments regarding cEEG training centred on importance of recognition of clinically significant EEG patterns, cEEG training being taught alongside traditional EEG training, and provision for critical care EEG fellowships.

Facilities, equipment and personnel

All respondents had access to an ICU, but less than half to a neurohigh-dependency unit (n=15, 43%; table 2). cEEG was only available on an ad hoc basis for just over half (n=19, 54%), always available to some (n=11, 31%), with routine EEG only available in a smaller group (n=5, 14%). There were similarly split proportions of neuroscientist coverage to set up the cEEG with 24 hours on-call availability for 9 (26%), 7 days in-hours only for 11 (31%) and 5 days a week for 15 (43%). Rostered on-call 24 hours epileptologist coverage was available for 26%; 20% reported unrostered and unpaid 24 hours cover and the remainder provided epileptology or neurology cover for EEG within standard hours or less. Twenty-eight respondents had remote access to EEG (n=28, 80%), with 57% having access to live real-time recordings. Review of EEG was largely performed on an ad hoc basis (n=21,

Table 1 Characteristics of respondents

	Responses (%) N=35
Gender	
Male	25 (71)
Female	10 (29)
Population managed	
Paediatrics	11 (31)
Adults	23 (66)
Paediatrics and adults	1 (3)
Hospital type	
Tertiary/metropolitan	35 (100)
State/region	
Victoria	15 (43)
Queensland	7 (20)
New South Wales	6 (17)
Western Australia	3 (9)
New Zealand	2 (6)
South Australia	1 (3)
Tasmania	1 (3)
Position	
Consultant epileptologists	18 (51)
Consultant neurologists	12 (34)
Epilepsy fellows	3 (9)
Advanced trainee in neurology	2 (6)
Consultant experience*	
1–5 years	9 (30)
6–10 years	3 (10)
>10 years	18 (60)
College membership	
ESA	32 (91)
RACP	31 (89)
ANZAN	29 (83)
ANZAN EEG Board Certification	
None	11 (31)
Level 1	0 (0)
Level 2	5 (14)
Level 3	19 (54)
Epilepsy fellowship	
None	7 (20)
1 year	10 (29)
2+ years	18 (51)
Do you report cEEG?	
Yes	33 (94)
No	2 (6)
Confidence in diagnosis of NCSE	
Confident	30 (86)
Somewhat confident	3 (9)
Neutral	2 (6)
Somewhat not confident	0 (0)
Not confident	0 (0)
Confidence in management of NCSE	
Confident	30 (86)
Somewhat confident	4 (6)
Neutral	1 (3)
Somewhat not confident	0 (0)
Not confident	0 (0)
Confidence in management of CSE	
Confident	29 (83)
Somewhat confident	5 (14)
Neutral	1 (3)
Somewhat not confident	0 (0)
Not confident	0 (0)
Opinion that should have formal cEEG training	
Yes	33 (94)
No	2 (6)
Implementation of Australian cEEG guidelines	
Strongly agree	13 (37)
Agree	13 (37)
Neutral	6 (17)
Disagree	3 (9)
Strongly disagree	0 (0)

*N=30.
ANZAN, Australian and New Zealand Association of Neurologists; cEEG, continuous EEG; CSE, convulsive status epilepticus; EEG, electroencephalography; ESA, Epilepsy Society of Australia; NCSE, non-convulsive status epilepticus; RACP, Royal Australasian College of Physicians.

60%), with only few utilising quantitative EEG (QEEG) (n=4, 11%). Lack of funding (n=26, 74%) and personnel (n=25, 71%) were the most consistently reported barriers to the practice of cEEG, with lack of physical resources (n=12, 34%) also identified as an important barrier. Five respondents felt there was a lack of evidence for cEEG (n=5, 14%).

Initial management of SE

The most common initial treatment of SE was intravenous midazolam (n=25, 73%), see figure 1. Clonazepam was the second choice for first-line therapy. Second-line therapy was split evenly between levetiracetam (n=17, 50%) and phenytoin (n=16, 47%), with one response for valproate. Interestingly, for third line therapy levetiracetam and phenytoin were the most common (29% each) reflecting movement from each of the groups for

Table 2 Facilities, equipment and personnel

Variable	Responses (%), n=35
Neuro-HDU	
Yes	15 (43)
No	20 (57)
ICU	
Yes	35 (100)
cEEG (1–24 hour+) availability	
Yes always	11 (31)
Yes but ad hoc	19 (54)
No only routine EEG	5 (14)
cEEG recordings per month	
None	7 (20)
1–2	10 (29)
3–10	11 (31)
>10	7 (20)
Neuroscientist coverage	
24/7	9 (26)
7 days in hours only	11 (31)
5 days week	15 (43)
Epileptologist coverage	
24/7	10 (29)
24/7 unrostered	7 (20)
Standard hours or less	12 (34)
Staff neurologists	6 (17)
Remote EEG capacity	
Yes and live	20 (57)
Yes but non-live	8 (23)
No	7 (20)
Frequency of EEG review	
Ad hoc	21 (60)
Twice daily	6 (17)
Once daily	2 (6)
Retrospective post completion	2 (6)
Other/none	4 (11)
Use of quantitative EEG	
Yes	4 (11)
No	31 (89)
Barriers to cEEG (multiple choices available)	
Lack of funding	26 (74)
Lack of physical resources	12 (34)
Lack of personnel	25 (71)
Lack of knowledge to run cEEG service	3 (9)
Perceived lack of evidence	5 (14)
Other: need to expand, need more reporting	2 (6)

cEEG, continuous EEG; EEG, electroencephalography; HDU, high-dependency unit; ICU, intensive care unit.

second line to the alternate medication. Only 18% of respondents indicated that they would use anaesthetic induction if there were ongoing seizures after administration of a benzodiazepine and the second line agent. Although specific dosing information was asked for each of the lines of therapy, responses were highly variable and therefore not reported here.

Subsequent management of SE

Sixty-five per cent of respondents indicated they would advise administration of an anaesthetic following failure of the second antiepileptic drug (AED), with 65% applying this approach for CSE and 50% for NCSE (see online supplemental material). Only 26% of respondents would advise treatment with an anaesthetic and intubation following first AED and second line failure for CSE. Nine per cent would never advise the use of an anaesthetic for NCSE. There were varied comments regarding anaesthetic induction for NCSE, with most suggesting that repeated trials of other AEDs may be required and that the approach should be tailored to the clinical situation. Propofol (n=24, 73%) followed closely by midazolam (n=21, 64%) were the most commonly reported anaesthetics recommended. Barbiturates were less commonly preferred. ICU management including intubation was accepted as maximal therapy in nearly half of respondents for NCSE (n=16, 48%). In the setting of a poor recovery following offset of an overt seizure and when suspecting NCSE, most would recommend an EEG within an hour (n=30, 88%) and some after 10 min (n=5, 15%). There was a wide range of responses regarding the required EEG duration when assessing for non-convulsive seizures, with thirty-eight percent suggesting a 24-hour recording and 24% a 1-hour recording only. Treatment targets for refractory SE also varied, with some suggesting a target of electrographic seizure cessation (n=10, 30%) and others would aim for a 24-hour or greater period of burst suppression (n=9, 27%). Seizure cessation defined via cEEG was preferred for NCSE by 48% of respondents. Seventy-eight per cent of respondents were in favour of national guidelines for SE

DISCUSSION

Use of cEEG

This study surveyed practices of experienced paediatric and adult epileptologists from Australia and New Zealand, who are at the forefront of decision making in the management of SE and use of cEEG. The findings are comparable to other similarly themed international surveys.[13] Substantial barriers to cEEG were identified, with un-rostered, unfunded and resource-limited work leading to a restricted ability to offer cEEG services to a wider patient group. Epilepsy services and cEEG are also typically limited to major metropolitan hospitals. Lack of physical resourcing of EEG machines and remote access to live recordings, limited personnel availability including

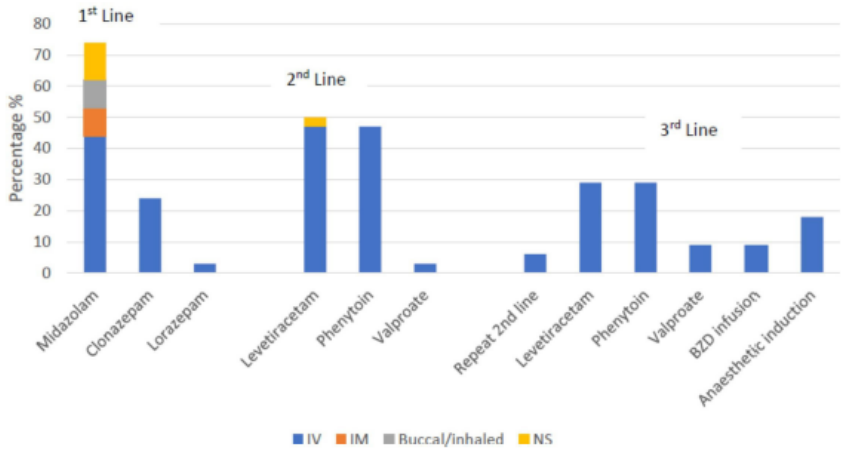

Figure 1 Initial management of SE. BZD, benzodiazepine; NS, not specified.

scientist coverage, and physician time to report the studies are also significant issues.

The identification of non-convulsive seizures requires the use of cEEG. The accurate diagnosis of non-convulsive seizures and NCSE is challenging, requiring experienced cEEG trained personnel, and is context specific with some clinical situations having a high pretest probability of identifying non-convulsive seizures. Therefore, specificity may be preferable to sensitivity when determining whom to test, especially when establishing a cEEG service. Although published recommendations may include a range of potential indications for cEEG,[7 14] this must be balanced on the available resources and equity for patients. Careful attention to patient selection and screening EEG duration are important practical considerations, that may improve pretest probability. Epileptiform abnormalities seen in the first 30 min of a recording may help predict sensitivity of detecting seizures,[15 16] representing a practical step in algorithm flow of EEG assessment. A recent study developed a scoring system, the 2HELPS2B score, to predict seizures in this patient group to help triage cEEG services.[17]

Real-time cEEG 'monitoring', rather than retrospective cEEG 'review', requires a dynamic setup including remote and live review capacity and at least twice daily review and reporting.[7] A minimum set of technical requirements are needed to adequately and safety perform cEEG.[8] In centres without a dedicated neurology specific ICU, the provision of cEEG is the responsibility of the neurology department. Close communication with ICU staff regarding the EEG results and suggested management changes is imperative which should be supervised by cEEG trained epileptologists. QEEG is an emerging EEG trend analysis software with the ability for rapid EEG review and reasonably accurate automated seizure detection.[18] QEEG is an underused tool that may significantly reduce the workload associated with 24-hour raw EEG review using a compressed timescale, and trend guided analysis alongside referencing with the raw EEG. Other avenues of allowing a more rapid and user-friendly EEG assessment are adaptation of standard EEG montages with a reduction in electrodes. The balance of lower resolution and maintenance of seizure detection accuracy is essential, and there are some devices already in development.

Management of SE

The management of SE is a time critical emergency with outcomes improved by early cessation of seizures, necessitating a clear understanding of principles to guide evidence-based rapid algorithmic care. There are no unified Australian guidelines or consensus within the national context, although some specific hospital guidelines exist. International guidelines from Europe,[19] UK[20] and USA[21] are variable and may not be appropriate for use in Australia given the different availability of drugs in our country. There is no consensus in the literature regarding choice of the first-line benzodiazepine with diazepam, lorazepam and clonazepam appearing in the different guidelines; despite its widespread use, intravenous midazolam has never been adequately tested but may be safely given in the prehospital setting via intramuscular, intrabuccal or intranasal routes. Clonazepam is often used in epilepsy monitoring units to terminate prolonged seizures and has been used in one prehospital trial of early SE,[22] but is not commonly used in Australian emergency departments. Inadequate dosing and overuse of benzodiazepines leading to respiratory failure and intubation, and a delay to second-line therapy have previously been highlighted.[11]

Second-line treatment of established SE was essentially evenly split evenly between phenytoin and levetiracetam in this survey, which reflects the current literature, with the trend towards the newer and easier to us levetiracetam, which has been recently shown to be non-inferior to phenytoin in both children and adults.[23–25] Levetiracetam treatment failure in the past may have been attributable to significant underdosing. Valproate remains an

equally efficacious alternative,[23] but was not a preferred choice in our survey.

Provided that adequate dosing of an AED as second-line therapy is achieved, adding a further alternative AED may delay anaesthetic induction and intubation as recommended for refractory convulsive SE in international guidelines.[21] Anaesthetic preference varied in this survey, although propofol and midazolam remain most popular, reflecting the literature and the widespread experience with these drugs. Treatment of NCSE diverges at this point from recent recommendations suggesting that aggressive management via ICU treatment may lead to poorer outcomes. The use of cEEG is pivotal here, first in establishing the diagnosis of SE, but also in evaluating treatment response. Urgent EEG assessment of an unresponsive patient with suspected non-convulsive seizures or SE is recommended. Treatment aggressiveness of non-convulsive seizures and NCSE is often the topic of debate at international conferences,[26] although recent evidence from dynamic neurophysiological changes and outcome studies are supporting the role of suppression of seizures for a neuroprotective benefit.[9] Treatment targets vary from seizure suppression to burst suppression, although in some cases in order to achieve the first aim burst suppression may be required. These complex decisions often arise on a case-by-case basis, considering concurrent active medical issues and the state of the patient. Various treatments exist in super-refractory SE with limited evidence due to the lack of controlled studies or even large-scale cohort studies. Recognition of the association of autoimmune encephalitis underlying a large proportion of new-onset refractory SE is essential, as immunotherapy may be indicated and can significantly improve outcomes.[27]

Limitations

Participant numbers, or responder rate, in this survey was relatively low which is comparable to other physician web-based surveys. The number of subspecialist epileptologists in Australia is not known. At the time of the survey, there were 188 ESA members whom were specified as clinicians in neurology. Therefore, a 19% (35/188) responder rate overall, including a 28% (30/108) responder rate specifically for consultant neurologists/epileptologists was deemed reasonable. Considering the spread of respondents from different states, this is also reflective of the few hospitals with specialist epilepsy services within Australia that have the capacity for cEEG and lead the management of SE.

Conclusion

This study shows characterisation of adoption of cEEG in Australia, and the current practices in managing SE, identifying key barriers to further implementation of cEEG and a variable approach to SE Given the experienced subspecialist epileptologists surveyed in this study, there is likely further substantial variation in SE management in non-speciality centres. Ongoing engagement with the Australian epilepsy and critical care communities will aid in understanding gaps in the use of cEEG and in the treatment of SE, ultimately leading to the development of appropriate Australian guidelines.

Contributors JL designed the study with assistance from NL, PP, PK and TJO. JL conducted the recruitment, data collection and analysis. All authors critically revised the manuscript and contributed to the final submission and review process.

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REFERENCES

1 Hill CE, Blank LJ, Thibault D, *et al*. Continuous EEG is associated with favorable hospitalization outcomes for critically ill patients. *Neurology* 2019;92:e9–18.
2 Kubota Y, Nakamoto H, Egawa S, *et al*. Continuous EEG monitoring in ICU. *J Intensive Care* 2018;6:1–8.
3 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;81:2002–8.
4 Rossetti AO, Schindler K, Sutter R, *et al*. Continuous vs routine electroencephalogram in critically ill adults with altered consciousness and no recent seizure. *JAMA Neurol* 2020;77:1225–8.
5 Sculier C, Gaínza-Lein M, Sánchez Fernández I, Fernández S I, *et al*. Long-term outcomes of status epilepticus: a critical assessment. *Epilepsia* 2018;59:155–69.
6 Trinka E, Cock H, Hesdorffer D, *et al*. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015;56:1515–23.
7 Herman ST, Abend NS, Bleck TP, *et al*. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. *J Clin Neurophysiol* 2015;32:87–95.
8 Herman ST, Abend NS, Bleck TP, *et al*. 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.
9 Abend NS, Topjian AA, Williams S. Could EEG monitoring in critically ill children be a cost-effective neuroprotective strategy? *J Clin Neurophysiol* 2015;32:486–94.
10 Jones CL, Koios J. Algorithm for the treatment of status epilepticus: an Australian perspective. *Intern Med J* 2016;46:500–3.
11 Uppal P, Cardamone M, Lawson JA. Outcomes of deviation from treatment guidelines in status epilepticus: a systematic review. *Seizure* 2018;58:147–53.
12 Aranda A, Foucart G, Ducassé JL, *et al*. Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. *Epilepsia* 2010;51:2159–67.

13 Gavvala J, Abend N, LaRoche S, *et al*. Continuous EEG monitoring: a survey of neurophysiologists and neurointensivists. *Epilepsia* 2014;55:1864–71.
14 Claassen J, Taccone FS, Horn P, *et al*. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. *Intensive Care Med* 2013;39:1337–51.
15 Koren J, Herta J, Draschtak S, *et al*. Early epileptiform discharges and clinical signs predict nonconvulsive status epilepticus on continuous EEG. *Neurocrit Care* 2018;29:388–95.
16 Shafi MM, Westover MB, Cole AJ, *et al*. Absence of early epileptiform abnormalities predicts lack of seizures on continuous EEG. *Neurology* 2012;79:1796–801.
17 Struck AF, Ustun B, Ruiz AR, *et al*. Association of an electroencephalography-based risk score with seizure probability in hospitalized patients. *JAMA Neurol* 2017;74:1419–24.
18 Haider HA, Esteller R, Hahn CD, *et al*. Sensitivity of quantitative EEG for seizure identification in the intensive care unit. *Neurology* 2016;87:935–44.
19 Meierkord H, Boon P, Engelsen B, *et al*. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010;17:348–55.
20 National Institute for Health and Care Excellence. *Treating prolonged or repeated seizures and status epilepticus*. London, 2018: 1–13. https://pathways.nice.org.uk/pathways/epilepsy/treating-prolonged-or-repeated-seizures-and-status-epilepticus.pdf
21 Glauser T, Shinnar S, Gloss D, *et al*. Evidence-Based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr* 2016;16:48–61.
22 Navarro V, Dagron C, Elie C, *et al*. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. *Lancet Neurol* 2016;15:47–55.
23 Kapur J, Elm J, Chamberlain JM, *et al*. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med* 2019;381:2103–13.
24 Lyttle MD, Rainford NEA, Gamble C, *et al*. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (eclipse): a multicentre, open-label, randomised trial. *Lancet* 2019;393:2125–34.
25 Dalziel SR, Borland ML, Furyk J, *et al*. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. *Lancet* 2019;393:2135–45.
26 Rossetti AO, Hirsch LJ, Drislane FW. Nonconvulsive seizures and nonconvulsive status epilepticus in the neuro ICU should or should not be treated aggressively: a debate. *Clin Neurophysiol Pract* 2019;4:170–7.
27 Khawaja AM, DeWolfe JL, Miller DW, *et al*. New-onset refractory status epilepticus (NORSE)--The potential role for immunotherapy. *Epilepsy Behav* 2015;47:17–23.

This Chapter including the ESA cEEG position paper was produced following consultation of a working group of paediatric and adult epileptologists from around the country with experience and interest in cEEG. Simon Harvey was appointed as chair for the group. The authors of the paper, myself, Simon Harvey, Michaela Waak, Nicholas Lawn, Lakshmi and Nagarajan met regularly to discuss the content of the position paper, with sections completed by individual/combined authors. I was the lead author for the writing of the paper, but all authors contributed in the conception of the position paper via workshopping ideas in regular conference calls. Following compilation of individual sections, further meetings were held to edit sections, and further editing was done by all via email. The paper was submitted to the ESA executive for feedback and review.

Epilepsy Society of Australia

Position Statement:

Continuous Electroencephalography Monitoring in the Intensive Care Unit

29/10/2021

ESA Continuous EEG Taskforce

Joshua Laing, Alfred Hospital, Melbourne

Michaela Waak, Queensland Children's Hospital, Brisbane

Lakshmi Nagarajan, Perth Children's Hospital, Perth

Nicholas Lawn, WA Adult Epilepsy Service, Perth

A. Simon Harvey (Chair), Royal Children's Hospital, Melbourne

Contents

Executive Summary

Seizures, predominantly subclinical or electrographic-only seizures, occur in some ICU patients with depressed conscious state; electrographic status epilepticus is present in a proportion of these patients. The prevalence of seizures in ICU patients with depressed conscious state depends on age (neonates > children > adults), the presence of prior clinical seizures (acute symptomatic or epilepsy), and aetiology (highest risk in patients with stroke, encephalitis, traumatic brain injury, hypoxic-ischaemic encephalopathy, neonatal encephalopathies, and intracerebral haemorrhage). Reported prevalence rates for electrographic seizures and status epilepticus are 10-30% and 5% respectively in at risk patients in ICU. These seizures are often not obvious clinically and may only be detected on EEG recordings.

There is some evidence, particularly in neonates and children, indicating status epilepticus and high seizure burden (electroclinical and electrographic only) have adverse effects on outcome, over and above that of the underlying condition. However, there is a paucity of evidence that detection and treatment of such seizures improves health or economic outcomes.

Routine EEG is widely available and effective for the diagnosis of many seizure-related issues in the ICU e.g., detection of frequent seizures or status epilepticus, clarification of frequent clinical or amplitude-integrated EEG phenomena. Additionally, routine EEG may show background abnormalities, interictal epileptiform discharges or rhythmic/periodic patterns indicating a high likelihood of subsequent electrographic seizures. Continuous EEG monitoring (cEEG), that is video-EEG recordings of at least 3 hours and typically greater than 12 hours duration, allows detection of infrequent or variable frequency seizures and periods of status epilepticus, determination of seizure burden, and assessment of the response to treatment of seizures.

Numerous cohort studies of cEEG in different ICU settings report potential negative outcomes of uncontrolled seizures and status epilepticus, but few adequately assess the clinical and economic impact of the *practice of cEEG* in ICU. Studies in adult ICU patients comparing cEEG with routine EEG have been conflicting, with two large registry studies reporting reduced mortality associated with cEEG, but one randomised study reporting no benefit of cEEG on mortality in patients without prior clinical seizures. Health economic modelling of data from neonatal and paediatric ICUs suggest 24 hours of cEEG monitoring would be cost-effective if electrographic status epilepticus identification and treatment improved patient outcomes by as little as 3%. Additional potential benefits of cEEG include evaluation of therapeutic interventions, prevention of inappropriate use of anti-seizure medication, and prognostication of outcome.

Neurological consultation, with or without routine EEG and neuroimaging, remains the gold standard of initial seizure assessment in ICU. Routine EEG in ICU, where indicated, should be performed with video and a view to continuing as cEEG in appropriately selected patients. cEEG in ICU should be considered in patients with clinical or routine EEG risk factors for seizures, and patients in whom routine EEG fails to clarify the clinical question. International guidelines provide recommendations for patient selection for cEEG. Routine cEEG in unselected patients in the ICU is not recommended.

cEEG should only be undertaken by appropriately trained and experienced neurophysiology scientists and neurologists, the latter typically being epileptologists with ICU EEG experience. The resources and funding required to implement and maintain a robust cEEG service in ICU are substantial. Although video-EEG monitoring capabilities exist at most tertiary hospitals, this is notionally for epilepsy care in epilepsy monitoring units, not cEEG in ICUs. Furthermore, remuneration for video-EEG monitoring is poor and insufficient for many hospitals to establish or maintain a service. A case should be made by neurologists and intensivists to hospitals and health departments for funding of targeted cEEG of appropriate duration in high-risk ICU patients. Advocacy by professional societies would help promote awareness of the value of targeted cEEG in ICU. One important, presently unmet need for cEEG is for neonates and infants in ICUs, where on-site neurological and neurophysiological service provision is often limited, and management is often undertaken by intensivists using amplitude-integrated EEG and cerebral function monitors.

High-quality clinical research (multi-centre, age-specific, prospective, randomised, pragmatic, including health economic evaluations) is required to better define the appropriate patient groups for cEEG, the ideal duration of monitoring, and the outcomes of detection and treatment of cEEG-based seizures. Until that time, and until adequate resourcing and funding is provided, neurologists and intensivists will need to rely upon targeted use of existing clinical and EEG services.

Glossary of Terminology, Acronyms, Synonyms and Definitions

Terminology (Synonym)	Acronym	Definition
American Clinical Neurophysiology Society	ACNS	Professional organisation in the United States devoted to the establishment and maintenance of standards of professional excellence in clinical neurophysiology.
Amplitude-integrated EEG	aEEG	Compressed (amplitude is logarithmic and time is linear) recording of EEG using 2 or several channels, typically of greater than 12 hours duration and in ICU settings, with the aim of detecting background changes indicative of encephalopathy or suggestive of seizures.
Anti-seizure medication (anti-epileptic drug)	ASM (AED)	A medication given by oral or parenteral routes, in single or regular doses, to treat or prevent seizures.
Continuous EEG monitoring	cEEG	≥16 channels (≥ 8 in neonates) of EEG recording with simultaneous video recording, typically of greater than 12 hours duration and in ICU settings, with the aim of detecting and monitoring seizures, including electrographic-only seizures.
EEG background		The predominant EEG activity, in ICU EEG recordings typically categorized as: normal or sedated sleep; slow and disorganized; discontinuous or burst suppression; or attenuated and featureless (1,2,9,96).
Electroclinical seizure (clinical seizure, convulsive seizure)	ECSz (CS)	A seizure with clinical manifestations and time-locked to an EEG pattern (note: EEG pattern does not need to fulfil electrographic seizure criteria) OR an electrographic seizure and subsequent clinical improvement attributable to suppression of seizures with an ASM (3,4).
Electroclinical status epilepticus (clinical or convulsive status epilepticus)	ECSE (CSE)	An uninterrupted electrographic seizure lasting 10 minutes or longer OR recurrent seizures totalling 12 minutes in any 1-hour period (hourly seizure burden ≥ 20%) with clinical manifestations OR ≥ 5 min of a convulsive (i.e. with bilateral tonic-clonic motor activity) seizure (3-5).
Electrographic seizure (EEG seizure)	ESz	An abnormal paroxysmal electrographic event that differs from the background activity, lasts longer than 10 seconds (briefer if associated with clinical change), has a plausible electrographic field, typically has a frequency of > 2.5 Hz, and evolves in frequency, morphology, or spatial distribution (except for neonatal seizures which may not evolve). Electrographic seizures may be electroclinical, subtle clinical or electrographic-only (5,6).
Electrographic status epilepticus	ESE	(i) An uninterrupted electrographic seizure lasting 10 minutes or longer OR recurrent seizures totalling 12 minutes in any 1-hour period (hourly seizure burden ≥ 20%), with or without clinical manifestations (3,5), OR (ii) An uninterrupted electrographic seizure lasting longer than 5 min, with or without clinical manifestations, OR recurrent electrographic seizure activity without return to baseline between seizures (4).

Electrographic-only seizure (subclinical seizure, non-convulsive seizure)	EOSz (SCS, NCS)	An electrographic seizure that occurs without any clinical manifestations (3-6).
Electrographic-only status epilepticus (subclinical status epilepticus, non-convulsive status epilepticus)	EOSE (SCSE, NCSE)	Frequent seizures or continuous ictal activity: (A) in patients without known epileptic encephalopathy: focal or generalized spikes, sharp waves, or sharp-and-slow complexes at frequencies >2.5 Hz OR focal or generalized spikes, sharp waves, or sharp-and-slow complexes at frequencies ≤2.5 Hz or rhythmic activity >0.5 Hz and one of the following: (i) electrographic AND clinical improvement after an IV trial of an ASM, (ii) subtle clinical ictal phenomena during the EEG pattern, or (iii) typical spatiotemporal evolution of voltage, frequency or location; (B) in patients with chronic epilepsy and an epileptic encephalopathy/syndrome: frequent or continuous generalized spike-wave discharges, with significant changes in intensity or frequency (usually faster) compared with baseline EEG (7-12).
Extracorporeal membrane oxygenation	ECMO	Technology to deliver extracorporeal life support.
Hypoxic-ischemic encephalopathy	HIE	Brain injury acquired by limited oxygen delivery to the brain by hypoxemia or decreased cerebral blood flow.
Ictal-Interictal Continuum	IIC	An EEG pattern that does not qualify as an electrographic seizure or electrographic status epilepticus, but there is a reasonable chance that it may be contributing to coma, causing other clinical symptoms, and/or contributing to neuronal injury. Patterns including PD, SW, RDA, BIRDA can be considered on the IIC (5).
Neonatal intensive care unit	NICU	ICU for neonates, typically in paediatric and maternity hospitals.
Paediatric intensive care unit	PICU	ICU for neonates, children, and adolescents, typically in paediatric hospitals.
Quantitative EEG	qEEG	Mathematical analysis and/or display of data extracted from the digitised EEG, often displayed in coloured, graphical format of variable epochs on a bedside monitor in ICU (13).
Routine EEG	rEEG (EEG)	≥ 16 channels (≥ 8 in neonates) of EEG recording, 20-60 minutes duration, typically with simultaneous video recording, with the aim of detecting abnormalities of EEG background, interictal epileptiform discharges, and status epilepticus. In ICU settings, routine EEG is considered a screening tool.
Sporadic (interictal) epileptiform discharges	SEDs (IEDs)	Non-rhythmic and non-periodic (intermittent) interictal EEG phenomena that are intermixed with the background and are associated with seizures e.g. spikes, polyspikes, sharp waves (5).
Subarachnoid haemorrhage	SAH	Bleeding in the subarachnoid space, often related to vascular malformations or aneurysmal rupture.

Total seizure burden		The total amount of time occupied by electrographic seizures during cEEG (14).
Traumatic brain injury	TBI	Acquired brain injury that occurs by sudden trauma.
Video-EEG monitoring	vEEG (VEM)	≥16 channels (≥ 8 in neonates) of EEG recording with simultaneous video recording, typically greater than 3 hours duration and in ward or ambulatory settings, with the aim of recording seizures and other episodic phenomena. In ICU, vEEG is generally referred to as cEEG.

1. Introduction

Patients in the ICU with non-pharmacologically depressed conscious state, particularly those with acute neurological disorders and brain injuries, are at risk of seizures, often without overt clinical manifestations. Electrographic or EEG seizures (ESz), including electroclinical (ECSz) and electrographic-only (subclinical) seizures (EOSz), are particularly prevalent in ICU patients with prior clinical seizures, infective and autoimmune encephalitis, stroke, traumatic brain injury (TBI), hypoxic-ischaemic encephalopathy (HIE) and extracorporeal membrane oxygenation (ECMO) therapy. Seizures may have an adverse impact on neurological outcome, over and above that of the underlying neurological disorder, and prompt consideration of treatment with anti-seizure medication (ASM). In some patients, electrographic status epilepticus (ESE) is the sole cause of altered consciousness and prompt treatment with ASM reverses the coma. Conversely, episodic non-epileptic movements and autonomic changes in ICU patients are commonly misinterpreted and unnecessarily treated as seizures, prolonging ICU stay and impacting adversely on outcome (15-25).

EEG with video is essential for accurate diagnosis of seizures, ESE and non-epileptic phenomena in the ICU, with recordings of relatively brief duration (0.5-3 hours) often sufficient. Longer duration, continuous EEG monitoring (cEEG) may help detect those patients with infrequent ESz and intermittent ESE, determine seizure burden, monitor progress, and allow assessment of response to therapy in ICU patients (26). Other potential indications for cEEG include monitoring for vasospasm in subarachnoid haemorrhage (SAH) and monitoring of pharmacological burst-suppression during management of raised intracranial pressure (15-27).

Unlike in North America and Europe, cEEG is not utilised routinely in Australian ICUs (15). The availability of inpatient EEG services varies around the country, particularly between city versus rural and paediatric versus adult hospitals. The main impediments to cEEG are that it is a resource and time intensive investigation, well-trained staff to perform and interpret cEEG in a timely fashion are few, the clinical significance of some cEEG findings remains uncertain, the cost-effectiveness of cEEG and treatment of EOSz remains to be demonstrated, and financial reimbursement in Australia is lacking.

This position statement attempts to: (i) summarise the evidence for, practicalities of, and controversies in cEEG for detection of ESz and ESE in ICU patients with depressed conscious state, this practice being an extension (i.e. longer duration recording and expanded patient group) of currently available EEG services in Australia, and (ii) provide recommendations for clinical practice, research, and reimbursement of cEEG in the ICU.

The Epilepsy Society of Australia (ESA) tasked this working group to review the literature, survey current practices and establish consensus recommendations for the use of cEEG in Australian ICUs. For the purposes of this statement, we consider cEEG to be 8 or more (usually standard 10-20 system in adults and children) channels of scalp EEG recording in ICU patients for greater than 12 hours duration, with simultaneous video recording, being reviewed either continuously or intermittently. Literature searches were conducted with the goal of identifying relevant clinical studies and international practice guidelines on cEEG in ICU. Studies reporting on shorter duration EEG in the ICU, and animal research, were not reviewed. The terminology and acronyms used in this document are those recommended by the American Clinical Neurophysiology Society (ACNS) (5).

2. Evidence for value of continuous EEG monitoring in ICU

2a. Continuous EEG monitoring in the neonatal ICU (NICU)

Seizure burden in neurologically sick neonates is higher than at any other time in life, with neonatal seizures occurring in 1-4/1000 live births (28-30). Evidence suggests that seizures contribute to secondary brain injury in neonates, especially in neonates with HIE (31-38). Delay in recognition and treatment of seizures is associated with poorer response to treatment and outcomes (39,40).

Neonatal seizures are challenging to manage as many paroxysmal phenomena mimic seizures, seizures have variable clinical features, and most neonatal seizures are EOSz, especially once ASM is commenced and in neonates with HIE (41-47). Experienced neonatologists and neurologists are unreliable at distinguishing between seizures and non-epileptic movements at the bedside (41,48). Studies indicate that 20-46% of neonates receiving ASM for clinical or amplitude-integrated EEG (aEEG) detected seizures do not have ESz on cEEG monitoring, exposing them to the risk of adverse neurodevelopmental effects of ASM (48-54). Conversely, under-recognition and under-treatment of neonatal seizures, including electrographic-only status epilepticus (EOSE), is associated with worse neurodevelopmental outcomes (31,32,39,55-63).

aEEG is used frequently in NICUs, aEEG background being a useful indicator of neurological prognosis, especially in term and near-term infants. However, aEEG has low sensitivity and specificity for detection of ESz, especially ESz of low amplitude, brief duration and occurring away from the aEEG leads; differences in clinical presentations and methodology of aEEG (number of channels, raw EEG visible vs not visible) might influence this (64-68). vEEG remains the gold standard for diagnosis of seizures in neonates (69-72).

cEEG monitoring is widely used in NICUs in North America (24,73). cEEG studies in NICU report seizures in 20-60% of high-risk neonates (80-90% EOSz) and status epilepticus in up to 40% (55,70,71). High risk groups include neonates with HIE, metabolic/genetic disorders, stroke, meningitis, and neonates on ECMO (21,55).

cEEG has been shown to impact on clinical care in up to 75% neonates, including the early detection of seizures and encephalopathy, and diminishing use of ASM (23,62,63,74). Both under-recognition and over-estimation of seizures occur when cEEG is unavailable in NICU, with under treatment and over treatment contributing to adverse neurodevelopmental outcomes (52,54, 70,75-77). Studies suggest improved long-term outcomes and cost effectiveness for neonates with HIE or status epilepticus when managed with cEEG (38,78-83).

2b. Continuous EEG monitoring in the paediatric ICU (PICU)

cEEG detected seizures occur in up to 30-40% of children in PICU with unexplained coma and risk factors (20,23,55,84-95). Risk factors include age < 2 years, prior clinical seizures, HIE, stroke, head injury, encephalitis, ECMO, cardiac surgery and rEEG showing discontinuous background activity and epileptiform discharges (4,14,96-106).

Continuous EEG is widely used in North American and European PICUs, with some variation in indications (88). The role of cEEG in PICU patients with refractory status

epilepticus is well established (4,55,107-112), there being moderate supporting evidence for cEEG to detect seizures in patients with unexplained, persistently depressed or fluctuating consciousness, and patients with acute cerebral injury. Other indications include patients under pharmacological paralysis and patients with paroxysmal events suspected to be seizures by PICU staff, though evidence supporting these practices is weaker (100,101,104,112-114).

Several cohort studies of children in PICU have shown an association between prolonged ESz and ESE with increased mortality and poor neurologic outcome, when corrected for other risk factors including aetiology (86,87,94-110). Seizure burden and the presence of ESE are associated with worse outcomes (14,115). Delays in management of ESE result in decreased medication effectiveness and decreased likelihood of seizure termination in children (92). Improved detection and treatment of ESz, guided by cEEG monitoring, have been shown to improve patient outcomes, including mortality, length of stay and short-term neurologic outcomes in children admitted to PICU with altered level of consciousness due to all causes (14,91,106,107,111). Impact on longer-term outcomes, including likelihood of later epilepsy and neurocognitive outcomes, is being explored (112,115).

The impact of cEEG on resource utilisation depends on selection of patients for cEEG monitoring (116). Health economic modelling suggests cost effectiveness of cEEG of 24-48 hours duration if identification and management of ESE improve patient outcomes, measured as quality adjusted life years, by as little as 3-7% (117). International studies suggest that monitoring high-risk patient groups could be cost-effective (116,117).

2c. Continuous EEG monitoring in the adult ICU

ESz and ESE are detected on cEEG in 10-30% of adults with critical illness in ICU, particularly following electroclinical or convulsive status epilepticus (ECSE) and those with TBI, cerebral infection, intracranial haemorrhage, and other acute neurological insults (118-131,131a).

Clinical predictors most consistently associated with ESz in adults are the presence of persistent coma and prior clinical seizures (118,132). Additionally, the presence of epileptiform abnormalities and periodic or rhythmic patterns on rEEG are associated with a 2-3-fold increase in the likelihood of detecting ESz on cEEG (120,133,134). A simple algorithm which combines clinical and initial EEG features ("2HELPS2B" score) has been validated to identify patients most likely to have ESz, this potentially being useful to guide clinical practice and rational use of cEEG (135,136) (https://reference.medscape.com/calculator/700/2helps2b-score).

There is mounting evidence that ESz have harmful secondary effects on cerebral physiology. Inflammation, elevated neuron-specific enolase, low brain oxygen, high lactate and increased intracranial pressure are more commonly identified in adults with acute brain insults such as TBI who have ESz compared to matched patients without seizures (119,137-141). Supporting this are case series showing increased mortality and morbidity in adults with ESz, and particularly ESE, compared to matched cohorts without seizures (121,123,137,142-145). Furthermore, two large registry studies of critically ill adults admitted to ICU reported those undergoing cEEG compared with only rEEG had a lower mortality rate (146). However, the evidence that cEEG-identified ESz and ESE confer a worse prognosis independent of the underlying aetiology is conflicting (144-150). A recent study of critically ill patients with impaired consciousness, without recent prior seizure, randomised to cEEG

or rEEG found no difference in mortality or morbidity (151). Therefore, it is unlikely that all unconscious patients will benefit from cEEG and patient selection via risk factor stratification is essential.

3. Controversies, uncertainties, and gaps in evidence with continuous EEG monitoring

Whilst there is no debate that ESz are present in a proportion of critically ill patients in the ICU, well-designed, large-scale, prospective trials to evaluate the impact on morbidity and mortality of detecting and treating these ESz are few. Additionally, cEEG studies typically include findings that could be determined and actioned from short duration rEEG.

Many of the observational studies of cEEG showing poorer outcomes for patients with recorded seizures have failed to differentiate the impact of seizures from the impact of the underlying condition and the effects of ASM and anaesthesia.

The goals of treatment (e.g., abolition of all seizures vs reduction of seizure burden) and whether infrequent brief seizures need to be treated are areas of ongoing investigation. Treatment impact may differ based on seizure aetiology, duration, and management approach (94,97). Given the loss of equipoise in prospective studies in not treating cEEG identified ESz and ESE, novel study designs have been suggested. Further focus on treatment of specific, as well as potentially uncertain cEEG patterns, as well as a minimal data-set and defined outcome sets are needed.

Inter-rater reliability and training issues regarding the interpretation of cEEG patterns have only been partially addressed by the introduction of internationally agreed and standardised ICU EEG terminology (5). Furthermore, there remains no clear international consensus on the definition of ESz and ESE, although the Salzberg criteria address this (9). Recent improvements and clarification of cEEG patterns and definitions of ESz, ESE and the ictal-interictal continuum were published by the ACNS (5).

Cost-benefit analysis of cEEG has not been adequately investigated. Cost assessment needs to include (in addition to the costs of cEEG) the treatments that cEEG findings often lead to, and benefit analysis needs to include (in addition to identification of seizures) ICU length of stay and long-term patient outcomes. The impact of the underlying neurological condition or injury on long-term outcome in patients often confounds interpretation of potential benefits.

Whilst consensus statements suggest indications for patient selection and ideal cEEG monitoring set up, there are no recommendations for resource poor settings.

The Critical Care EEG Monitoring Research Consortium is a large international collaboration of experts in cEEG committed to addressing uncertainties in these areas. Studies scaled to include mid- and long-term functional outcomes and health-economic data are needed. Quaternary centres in Australasia could commit to contribute to the evidence base.

4. Guidelines and recommendations for continuous EEG monitoring

Whilst there are no universally accepted international guidelines or consensus for the use of cEEG, there are the Consensus Summary Statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care (18,19) and

several country-specific consensus statements with evidence-based recommendations. The ACNS has produced standardised, critical care EEG terminology, with a recent update (5,152), as well as consensus statements on the practice and technical standards for cEEG in neonates (21, 23), children (20,153) and adults (20,153). Guidelines and consensus statements have also been published by several other neurocritical care societies (16, 17,21-24).

The ICU patient subgroups and clinical problems recommended or suggested by the ACNS for cEEG are as follows (20):
- Diagnosis of ESz, ESE and paroxysmal events (recommended)
- Assessment of efficacy of therapy for seizures and status epilepticus (recommended)
- Identification of cerebral ischaemia (suggested)
- Monitoring of sedation and high dose intravenous anaesthetic therapy (suggested)
- Assessment of severity of encephalopathy and prognostication (not yet suggested)

The ICU patient subgroups and clinical problems recommended by the European Academy of Neurology for cEEG are as follows, with level of evidence in parentheses (25):
- Not waking 60 minutes post convulsive status epilepticus (Grade 1C)
- Refractory status epilepticus (Grade 1C)
- TBI, SAH, intracerebral haemorrhage, encephalitis with unexplained altered consciousness (Grade 1C)
- Cardiac arrest with persistent coma (Grade 1C)
- Unexplained altered consciousness without primary brain injury (Grade 1B)
- Severe TBI with high-risk features e.g. large contusion (Grade 2C)
- Acute ischaemic stroke with unexplained altered consciousness (Grade 2D)
- Other non-seizure indications e.g. SAH associated cerebral ischaemia, prognostication in all ICU patients with unexplained coma, prognostication in cardiac arrest with persistent coma, prognostication in encephalitis with unexplained coma (Grade 2C)

The ICU patient subgroups and clinical problems recommended by the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care for cEEG are as follows (18):
- All patients with TBI and unexplained and persistent altered consciousness (strong recommendation, low quality of evidence)
- ECSE with no return to functional baseline within 60 min after ASM and patients with refractory ESE (strong recommendation, low quality of evidence)
- During therapeutic hypothermia and within 24 hours of rewarming to exclude EOSz in all comatose patients after cardiac arrest (strong recommendation, low quality of evidence)
- Comatose ICU patients without an acute primary brain condition and with unexplained impairment of mental status or unexplained neurological deficits to exclude EOSz, particularly in those with severe sepsis or renal/hepatic failure (weak recommendation, low quality of evidence)

These publications acknowledge insufficient high-quality evidence to support many of the recommendations and are therefore written as consensus statements rather than guidelines. They describe an ideal system that may help guide cEEG program development but may be difficult to completely put into practice.

5. Challenges with implementation of continuous EEG monitoring in Australian ICUs

Considerable challenges exist to providing cEEG monitoring services in Australia in a coordinated and equitable manner, both at single centres and nationwide. As such, uptake of cEEG in Australian ICUs has been limited (15,70,100).

cEEG would typically be provided by the EEG department of a major teaching hospital, potentially as an extension of their vEEG monitoring service for patients with epilepsy. cEEG would be impossible in small, maternity, private and rural hospitals without partnerships with a major neurological centre, access to neurophysiology personnel and equipment, and a high-bandwidth telemedicine platform. More likely, patients in peripheral ICUs and high dependency units would be transferred to major centres for cEEG monitoring.

The additional equipment, staff and time required for most well-resourced neurology departments to provide cEEG as a new Neurology/ICU service would include:
- one or more portable, digital vEEG recording units
- neurophysiology scientists with experience in cEEG, the ICU environment and ICU EEG patterns
- neurologists with expertise in EEG patterns related to coma, cerebral injury and disease, anaesthetic drugs, and seizures, and the use of specialised EEG analysis tools
- afterhours availability of neurophysiology scientists (to commence, maintain, troubleshoot, and cease cEEG recordings) and neurologists (to interpret cEEG) to assist ICU staff in patient management
- network connectivity with the neurology department's EEG server and archive storage
- remote access from neurology clinics/offices in the hospital and from home to live and archived ICU EEG recordings
- funded time for neurophysiology scientists and neurologists to review, report and archive cEEG studies in a timely fashion each day (given that continuous, live cEEG review would be impractical at most centres)
- online analysis software with compressed EEG display, trend analysis and seizure detection capabilities
- cEEG training and continuing education programs across neurology, neurophysiology and ICU teams.

Paramount to successful implementation of cEEG is a good working relationship between medical, nursing, and technical staff in the neurology, ICU and medical imaging departments, and the development of appropriate clinical standards and protocols. Additionally, specific training would be necessary for ICU nurses, staff neurologists and intensivists, rotating neurology and ICU trainees, and neurophysiology scientists, in cEEG technology, the capabilities and caveats of cEEG, and the management of cEEG detected seizures. An appropriately credentialed neurologist/neurophysiologist with experience in cEEG and ICU medicine would ideally oversee, supervise, and coordinate the service, collaborate in national and international research, and conduct periodic audits.

Lack of funding/reimbursement is a major challenge for implementation of cEEG in Australia. Inpatient EEG services are poorly reimbursed in general, and some EEG services are not recognised by funding bodies e.g., intracranial EEG monitoring. For public inpatients, reimbursement is typically by activity-based funding to hospitals according to patient diagnoses. A minority of patients in ICUs of major teaching hospitals are privately insured or compensable, and even then, reimbursement is meagre. For example, the Medicare items 11003/4/5 used for prolonged EEG monitoring attract a scheduled fee of only $330/day. Such reimbursement would barely cover the salary of a neurophysiology scientist

performing cEEG, let alone the equipment, consumables, and neurologist time. While case-mix funding for ICU patients is significantly greater than for typical ward patients, based on their complexity, complications, comorbidities and protracted LOS, this funding is not directly shared with ancillary departments providing care in the ICU, such as neurology. Furthermore, it would be inadequate to support the interdisciplinary, neurocritical care team required for implementation of this new service.

Providing cEEG without the appropriate resources, training and reimbursement risks poor clinical outcomes for patients, cost overruns for neurology departments, staff burnout and diversion of care away from established EEG services e.g., epilepsy diagnosis, epilepsy surgery. Attempts to convince hospital administrators and health funding bodies to support cEEG would require detailed "new technology" submissions from neurology and ICU departments for block funding, with submissions supported by robust clinical and health economic evidence of improved patient outcomes and cost-benefits.

6. Conclusions and Recommendations

ESz, predominantly EOSz, occur in some ICU patients with depressed conscious state; ESE is present in a proportion of these patients. The prevalence of ESz in ICU patients with depressed conscious state depends on age (neonates > children > adults), the presence of prior clinical seizures (acute symptomatic or epilepsy), and aetiology (highest risk in patients with stroke, encephalitis, TBI, HIE, neonatal encephalopathies, and intracerebral haemorrhage). Reported prevalence rates for ESz and ESE are 10-30% and 5% respectively in at risk patients in ICU. These seizures are often not obvious clinically and may only be detected on EEG recordings.

There is some evidence, particularly in neonates and children, indicating ESE and high seizure burden (ECSz and EOSz) have adverse effects on outcome, over and above that of the underlying condition. However, there is a paucity of evidence that detection and treatment of such seizures improves health or economic outcomes.

Routine EEG is widely available and effective for the diagnosis of many seizure-related issues in the ICU e.g., detection of frequent ESz or ESE, clarification of frequent clinical or aEEG phenomena. Additionally, rEEG may show background abnormalities, interictal epileptiform discharges or rhythmic/periodic patterns indicating a high likelihood of subsequent ESz. Continuous EEG monitoring (cEEG), that is vEEG recordings of at least 3 hours and typically greater than 12 hours duration, allows detection of infrequent or variable frequency ESz and periods of ESE, determination of seizure burden, and assessment of the response to treatment of seizures.

Numerous cohort studies of cEEG in different ICU settings report potential negative outcomes of uncontrolled ESz and ESE, but few adequately assess the clinical and economic impact of the *practice of cEEG* in ICU. Studies in adult ICU patients comparing cEEG with rEEG have been conflicting, with two large registry studies reporting reduced mortality associated with cEEG, but one randomised study reporting no benefit of cEEG on mortality in patients without prior ECSz. Health economic modelling of data from neonatal and paediatric ICUs suggest 24 hours of cEEG monitoring would be cost-effective if ESE identification and treatment improved patient outcomes by as little as 3%. Additional potential benefits of cEEG include evaluation of therapeutic interventions, prevention of inappropriate use of ASM, and prognostication of outcome.

Neurological consultation, with or without rEEG and neuroimaging, remains the gold standard of initial seizure assessment in ICU. Routine EEG in ICU, where indicated, should be performed with video and a view to continuing as cEEG in appropriately selected patients. cEEG in ICU should be considered in patients with clinical or rEEG risk factors for seizures, and patients in whom routine EEG fails to clarify the clinical question. International guidelines provide recommendations for patient selection for cEEG. Routine cEEG in unselected patients in the ICU is not recommended.

cEEG should only be undertaken by appropriately trained and experienced neurophysiology scientists and neurologists, the latter typically being epileptologists with ICU EEG experience. The resources and funding required to implement and maintain a robust cEEG service in ICU are substantial. Although vEEG monitoring capabilities exist at most tertiary hospitals, this is notionally for epilepsy care in epilepsy monitoring units, not cEEG in ICUs. Furthermore, remuneration for vEEG monitoring is poor and insufficient for many hospitals to establish or maintain a service. A case should be made by neurologists and intensivists to hospitals and health departments for funding of targeted cEEG of appropriate duration in high-risk ICU patients. Advocacy by professional societies would help promote awareness of the value of targeted cEEG in ICU. One important, presently unmet need for cEEG is for neonates and infants in ICUs, where on-site neurological and neurophysiological service provision is often limited, and management is often undertaken by neonatologists and intensivists using aEEG and cerebral function monitors.

High-quality clinical research (multi-centre, age-specific, prospective, randomised, pragmatic, including health economic evaluations) is required to better define the appropriate patient groups for cEEG, the ideal duration of monitoring, and the outcomes of detection and treatment of cEEG-based seizures. Until that time, and until adequate resourcing and funding is provided, neurologists and intensivists will need to rely upon targeted use of existing clinical and EEG services.

References (Australian and New Zealand studies bolded)

1. Nielsen N, Stammet P, van Rootselaar A-F, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology. 2016;86(16):1482-1490. doi:10.1212/wnl.0000000000002462
2. Mandel R, Martinot A, Delepoulle F, et al. Prediction of outcome after hypoxic-ischemic encephalopathy: A prospective clinical and electrophysiologic study. J Pediatr. 2002;141(1):45-50. doi:10.1067/mpd.2002.125005
3. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015; 56:1515.
4. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23.
5. Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J Clin Neurophysiol*. 2021;38(1):1-29. doi:10.1097/WNP.0000000000000806
6. Gaspard N, Hirsch LJ, LaRoche SM, Hahn CD, Brandon M. Interrater agreement for Critical Care EEG Terminology. Epilepsia. 2014;55(9):1366-1373. doi:10.1111/epi.12653
7. Jirsch J, Hirsch LJ, et al (2021). Nonconvulsive status epilepticus: Classification, clinical features, and diagnosis. UpToDate. Retrieved 18 May 2021 from Nonconvulsive status epilepticus: Classification, clinical features, and diagnosis – UpToDate
8. Sutter R, Kaplan PW. Electroencephalographic criteria for nonconvulsive status epilepticus: synopsis and comprehensive survey. Epilepsia 2012; 53 Suppl 3:1.
9. Leitinger M, Beniczky S, Rohracher A, et al. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus - approach to clinical application. Epilepsy Behav. 2015;49:158-163. doi:10.1016/j.yebeh.2015.05.007
10. Leitinger M, Trinka E, Gardella E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. Lancet Neurol 2016; 15:1054
11. Husain AM. Clarity in EEG diagnosis of non-convulsive status epilepticus. Lancet Neurol. 2016;15(10):1001-1003. doi:10.1016/S1474-4422(16)30172-7
12. Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013; 54 Suppl 6:28.
13. Massey SL, Topjian AA. PICU Bedside Quantitative Electroencephalography: Ready for "real-Time." Pediatr Crit Care Med. 2020;21(6):592-593. doi:10.1097/PCC.0000000000002283
14. Payne ET, Zhao XY, Frndova H, McBain K, Sharma R, Hutchison JS, et al. Seizure burden is independently associated with short term outcome in critically ill children. Brain. 2014;137(5):1429–38. doi:10.1093/brain/awu042
15. **Laing J, Lawn N, Perucca P, Kwan P, O'Brien TJ. Continuous EEG use and status epilepticus treatment in Australasia: a practice survey of Australian and New Zealand epileptologists. BMJ Neurol Open. 2020;2(2):e000102. doi:10.1136/bmjno-2020-000102**
16. Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M. Recommendations on the use of EEG monitoring in critically ill patients: Consensus statement from the neurointensive care section of the ESICM. Intensive Care Med. 2013;39(8):1337–51.
17. Recommendations for Electroencephalography Monitoring in Neurocritical Care Units. Chin Med J (Engl). 2017 Aug;130(15):1851–5.
18. Le Roux P, Menon DK, Citerio G, Vespa P, Bader MK, Brophy GM, et al. Consensus Summary Statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: A statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive C. Neurocrit Care. 2014;21(2):1–26.
19. Le Roux P, Menon DK, Citerio G, et al. The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: Evidentiary Tables: A Statement for Healthcare Professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicin. Neurocrit Care. 2014;21(2):297-361. doi:10.1007/s12028-014-0081-x
20. Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I. J Clin Neurophysiol. 2015;32(2):87–95.

21. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. J Clin Neurophysiol. 2011 Dec;28(6):611–7.
22. Dilena R, Raviglione F, Cantalupo G, et al. Consensus protocol for EEG and amplitude-integrated EEG assessment and monitoring in neonates. Clin Neurophysiol. 2021;132(4):886-903. doi:10.1016/j.clinph.2021.01.012
23. Ra S, Chang T, Tsuchida T, Ms S, Jj R, Ns A, et al. The American Clinical Neurophysiology Society ' s Guideline on Continuous EEG Monitoring in Neonates. ACNS Guideline. 2012;28(6):1–17. Available from: https://www.acns.org/practice/guidelines
24. Buttle SG, Sell E, Webster R, Varin M, Lemyre B, Hahn C, et al. Continuous Electroencephalography Monitoring for Critically Ill Neonates: A Canadian Perspective. Can J Neurol Sci / J Can des Sci Neurol . 2019 Jul 29;46(04):394–402. Available from: https://www.cambridge.org/core/product/identifier/S0317167119000362/type/journal_article
25. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol. 2010;17(3):348-355. doi:10.1111/j.1468-1331.2009.02917.x
26. Gilmore EJ. Continuous Electroencephalogram—Necessity or Luxury? *JAMA Neurol*. 2020.
27. Claassen J, Hirsch LJ, Kreiter KT, et al. Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor-grade subarachnoid hemorrhage. Clin Neurophysiol 2004;115:2699–2710.
28. Saliba R, Annegers JF WD. Incidence of neonatal seizures in Harris County, Texas, 1992-1994. Am J Epidemiol. 1999;(150):763–9.
29. Chapman K, Raol Y AB-K. Controversies and challenges in translating new therapies from the lab to the isolette. Eur J Neurosci. 2012;(35):1857–65.
30. Tsuchida TN. American clinical neurophysiology society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee. J Clin Neurophysiol. 2013;30(2):161–73.
31. Glass HC, Glidden D JR. Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury. J Pediatr. 2009;155:318–23.
32. van Rooij LGM, Toet MC, van Huffelen AC, Groenendaal F, Laan W, Zecic A, et al. Effect of Treatment of Subclinical Neonatal Seizures Detected With aEEG: Randomized, Controlled Trial. Pediatrics. 2010 Feb 1;125(2):e358–66. Available from: http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2009-0136
33. Wietstock SO, Bonifacio SL, McCulloch CE, Kuzniewicz MW, Glass HC. Neonatal neurocritical care service is associated with decreased administration of seizure medication. J Child Neurol. 2015;30(9):1135–41.
34. Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. Nat Rev Neurol 2009 Jul;5(7):380–91. Available from: http://www.nature.com/articles/nrneurol.2009.80
35. Shah DK, Wusthoff CJ CP. Electrographic seizures are associated with brain injury in newborns undergoing therapeutic hypothermia. Arch Dis Child - Fetal Neonatal Ed. 2014;99:F219–24.
36. Dunne JM, Wertheim D, Clarke P, Kapellou O, Chisholm P, Boardman JP, et al. Automated electroencephalographic discontinuity in cooled newborns predicts cerebral MRI and neurodevelopmental outcome. Arch Dis Child Fetal Neonatal Ed. 2017 Jan 1;102(1):F58–64.
37. Srinivasakumar P, Zempel J, Trivedi S, Wallendorf M, Rao R, Smith B, et al. Treating EEG seizures in hypoxic ischemic encephalopathy: A randomized controlled trial. Pediatrics. 2015;136(5):e1302–9.
38. van Rooij LGM, de Vries LS van HA. Additional value of two-channel amplitude integrated EEG recording in full-term infants with unilateral brain injury. Arch Dis Child - Fetal Neonatal Ed. 2010;95:F160–8.
39. Toet MC, Groenendaal F OD. Postneonatal epilepsy following amplitude-integrated EEG-detected neonatal seizures. Pediatr Neurol. 2005;32:241–7.
40. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, et al. Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. Pediatrics. 2020 Jun;145(6):e20193182. Available from: http://pediatrics.aappublications.org/lookup/doi/10.1542/peds.2019-3182

41. Boylan GB, Stevenson NJ, Vanhatalo S. Monitoring neonatal seizures. Vol. 18, Seminars in Fetal and Neonatal Medicine. 2013. p. 202–8.
42. Pressler RM, Cilio MR, Mizrahi EM, et al. The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. Epilepsia. 2021;62(3):615-628. doi:10.1111/epi.16815
43. Rennie JM, De Vries LS, Blennow M, Foran A, Shah DK, Livingstone V, et al. Characterisation of neonatal seizures and their treatment using continuous EEG monitoring: A multicentre experience. Arch Dis Child Fetal Neonatal Ed. 2019;104(5):F493–501.
44. Clancy RR, Legido A LD. Occult neonatal seizures. Epilepsia. 1988;29:256–61.
45. Nagarajan L. Classification of Clinical Semiology in Epileptic Seizures in Neonates. Eur J Paediatr Neurol. 2012;16(2):118–25.
46. Scher MS, Alvin J, Gaus L, Minnigh B PM. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. Pediatr Neurol. 2003;28:277–80.
47. Biagioni E, Ferrari F, Boldrini A, Roversi MF CG. Electroclinical correlation in neonatal seizures. Eur J Paediatr Neurol. 1998;2:117–25.
48. Bye AM FD. Spatial and temporal characteristics of neonatal seizures. Epilepsia. 1995;36:1009–16.
49. Nagarajan L. Ictal electroencephalograms in neonatal seizures: characteristics and associations. Pediatr Neurol. 2011;45(1):11–6.
50. Nagarajan L. Brief electroencephalography rhythmic discharges (BERDs) in the neonate with seizures: their significance and prognostic implications. J Child Neurol. 2011;26(12):1529–33.
51. Forcelli PA, Janssen MJ, Vicini S, Gale K. Neonatal exposure to ASMs disrupts striatal synaptic development. Ann Neurol. 2012;72(3):363–72.
52. Maitre NL, Smolinsky C, Slaughter JC, Stark AR. Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. J Perinatol. 2013;33(11):841–6. Available from: http://www.nature.com/doifinder/10.1038/jp.2013.116
53. Bittigau P, Sifringer M, Ikonomidou C. ASMs and Apoptosis in the Developing Brain. 2003;114:103–14. Ann N Y Acad Sci
54. Fitzgerald MP, Kessler SK, Abend NS. Early discontinuation of antiseizure medications in neonates with hypoxic-ischemic encephalopathy. Epilepsia. 2017;1–7. Available from: http://doi.wiley.com/10.1111/epi.13745
55. Abend NS, Wusthoff CJ, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. Lancet Neurol. 2013;12(12):1170–9. Available from: http://dx.doi.org/10.1016/S1474-4422(13)70246-1
56. Kang S SK. Neonatal Seizures: Impact on Neurodevelopmental Outcomes. Front Pediatr. 2015;3:101.
57. van Rooij LG, de Vries LS HS. Neurodevelopmental outcome in term infants with status epilepticus detected with amplitude-integrated electroencephalography. Pediatrics. 2007;120:e354–63.
58. Iyer KK, Roberts JA, Hellström-Westas L, Wikström S, Pupp IH, Ley D, et al. Early detection of preterm intraventricular hemorrhage from clinical electroencephalography. Crit Care Med. 2015;43(10):2219–27.
59. Fitzgerald MP, Massey SL, Fung FW, Kessler SK, Abend NS. High electroencephalographic seizure exposure is associated with unfavorable outcomes in neonates with hypoxic-ischemic encephalopathy. Seizure. 2018;61(August):221–6. Available from: https://doi.org/10.1016/j.seizure.2018.09.003
60. Pisani F, Facini C, Pelosi A, Mazzotta S, Spagnoli C, Pavlidis E. Neonatal seizures in preterm newborns: A predictive model for outcome. Eur J Paediatr Neurol. 2016 Mar;20(2):243–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1090379815002184
61. Mcbride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. 2000; Neurology. 2000 Aug 22;55(4):506-13. doi: 10.1212/wnl.55.4.506.
62. Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP CS. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. Arch Dis Child Fetal Neonatal Ed. 2008;93:F187–91.

63. Uria-Avellanal C, Marlow N, Rennie JM. Outcome following neonatal seizures. Semin Fetal Neonatal Med. 2013 Aug;18(4):224–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1744165X13000036
64. Rakshasbhuvankar, A. et al. Amplitude Integrated Electroencephalography Compared With Conventional Video EEG for Neonatal Seizure Detection: A Diagnostic Accuracy Study. J Child Neurol. 2017;32(9):815–22.
65. Buttle SG, Lemyre B, Sell E, Redpath S, Bulusu S, Webster RJ, et al. Combined Conventional and Amplitude-Integrated EEG Monitoring in Neonates: A Prospective Study. J Child Neurol. 2019;088307381982925. Available from: http://journals.sagepub.com/doi/10.1177/0883073819829256
66. Rakshasbhuvankar, A. et al. Inter-rater reliability of amplitude-integrated EEG for the detection of neonatal seizures. Early Hum Dev. 2020;143:105011.
67. Lawrence R, Mathur A, Nguyen The Tich S, Zempel J IT. A pilot study of continuous limited-channel aEEG in term infants with encephalopathy. J Pediatr. 2009;154:835–41.e1.
68. Rakshasbhuvankar A, Paul S, Nagarajan L, Ghosh S, Rao S. Amplitude-integrated EEG for detection of neonatal seizures: A systematic review. Seizure. 2015;33:90–8. Available from: http://dx.doi.org/10.1016/j.seizure.2015.09.014
69. Nagarajan, L & Ghosh G. The Role of the Video EEG in Neonates with Seizures. In Neonatal Seizures Current Management and future challenges. MacKeith Press London. 2016;12–29.
70. Sharpe C, Davis SL, Reiner GE, Lee LI, Gold JJ, Nespeca M, et al. Assessing the Feasibility of Providing a Real-Time Response to Seizures Detected With Continuous Long-Term Neonatal Electroencephalography Monitoring. J Clin Neurophysiol. 2019 Jan;36(1):9–13. Available from: http://journals.lww.com/00004691-201901000-00002
71. Fitzgerald MP. Expanding Access to Continuous EEG Monitoring in Neonatal Intensive Care Units. J Clin Neurophysiol. 2020;
72. MacDonald-Laurs E, Sharpe C, Nespeca M, et al. Does the first hour of continuous electroencephalography predict neonatal seizures? Arch Dis Child Fetal Neonatal Ed. 2021;106(2):162-167. doi:10.1136/archdischild-2020-318985
73. Boylan G, Burgoyne L, Moore C, O'Flaherty B, Rennie J. An international survey of EEG use in the neonatal intensive care unit. Acta Paediatr. 2010 Mar 26;99(8):1150–5. Available from: http://doi.wiley.com/10.1111/j.1651-2227.2010.01809.x
74. Shellhaas R BA. Impact of amplitude-integrated EEG on the clinical care for neonates with seizures. Pediatr Neurol. 2012;46(1):32–5.
75. Rakshasbhuvankar A, Rao S, Ghosh S, Nathan EA, Nagarajan L. Why do neonates receive antiseizure medications? J Matern Neonatal Med. 2020;0(0):1-5. doi:10.1080/14767058.2020.1819976
76. Pisani F, Fusco C, Nagarajan L, Spagnoli C. Acute symptomatic neonatal seizures, brain injury, and long-term outcome: The role of neuroprotective strategies. Expert Rev Neurother. 2021;21(2):189-203. doi:10.1080/14737175.2021.1848547
77. Bittigau, P., Sifringer, M., & Ikonomidou C. ASMs and Apoptosis in the Developing Brain. Brain. 2003;114:103–114.
78. Kharoshankaya L, Stevenson NJ, Livingstone V, Murray DM, Murphy BP AC. Seizure burden and neurodevelopmental outcome in neonates with hypoxic-ischemic encephalopathy. Dev Med Child Neurol. 2016;58(12):1242–8.
79. Bashir RA, Espinoza L, Vayalthrikkovil S, Buchhalter J, Irvine L, Bello-Espinosa L, et al. Implementation of a Neurocritical Care Program: Improved Seizure Detection and Decreased Antiseizure Medication at Discharge in Neonates With Hypoxic-Ischemic Encephalopathy. Pediatr Neurol. 2016 Nov;64:38–43. Available from: https://linkinghub.elsevier.com/retrieve/pii/S088789941630306X
80. Harris ML, Malloy KM, Lawson SN, Rose RS, Buss WF, Mietzsch U. Standardized Treatment of Neonatal Status Epilepticus Improves Outcome. J Child Neurol. 2016 Dec 29;31(14):1546–54. Available from: http://journals.sagepub.com/doi/10.1177/0883073816664670
81. Hellstrom-Westas L, Blennow G, Lindroth M, Rosen I, Svenningsen NW. Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period. Arch Dis Child - Fetal Neonatal Ed . 1995 Mar 1;72(2):F97–101. Available from:

https://fn.bmj.com/lookup/doi/10.1136/fn.72.2.F97
82. Gray J, Geva A, Zheng Z, Zupancic JAF. CoolSim: Using Industrial Modeling Techniques to Examine the Impact of Selective Head Cooling in a Model of Perinatal Regionalization. Pediatrics. 2008 Jan 1;121(1):28–36. Available from: http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2007-0633
83. Massaro AN, Murthy K, Zaniletti I, Cook N, DiGeronimo R, Dizon MLV, et al. Intercenter Cost Variation for Perinatal Hypoxic-Ischemic Encephalopathy in the Era of Therapeutic Hypothermia. J Pediatr. 2016 Jun;173:76-83.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022347616001979
84. Fung FW, Fan J, Vala L, et al. EEG monitoring duration to identify electroencephalographic seizures in critically ill children. Neurology. July 2020:10.1212/WNL.0000000000010421. doi:10.1212/WNL.0000000000010421
85. Vlachy J, Jo M, Li Q, Ayer T, Keskinocak P, Swann J, et al. Risk factors for seizures among young children monitored with continuous electroencephalography in intensive care unit: A retrospective study. Front Pediatr. 2018;6(October):1–7.
86. Abend NS, Topjian AA, Gutierrez-Colina AM, Donnelly M, Clancy RR, Dlugos DJ. Impact of continuous EEG monitoring on clinical management in critically ill children. Neurocrit Care. 2011;15(1):70–5.
87. Kirkham FJ, Wade AM, Boyd SG, Tasker RC, Neville BGR, Newton CRJC. Seizures in 204 comatose children : incidence and outcome. 2012;853–62.
88. Gaínza-Lein M, Sánchez Fernández I, Loddenkemper T. Use of EEG in critically ill children and neonates in the United States of America. J Neurol. 2017; Available from: http://link.springer.com/10.1007/s00415-017-8510-3
89. Abend NS, Gutierrez-Colina AM, Topjian AA, Zhao H, Guo R, Donnelly M, et al. Nonconvulsive seizures are common in critically ill children. Neurology. 2011;76(12):1071–7.
90. Abend NS, Dlugos DJ, Clancy RR. A Review of Long-term EEG Monitoring in Critically Ill Children With Hypoxic–Ischemic Encephalopathy, Congenital Heart Disease, ECMO, and Stroke. J Clin Neurophysiol . 2013 Apr;30(2):134–42. Available from: http://journals.lww.com/00004691-201304000-00006
91. Kirkham FJ, Wade AM, McElduff F, Boyd SG, Tasker RC, Edwards M, et al. Seizures in 204 comatose children: Incidence and outcome. Intensive Care Med. 2012;38(5):853–62.
92. Williams RP, Banwell B, Berg RA, Dlugos DJ, Donnelly M, Ichord R, et al. Impact of an ICU EEG monitoring pathway on timeliness of therapeutic intervention and electrographic seizure termination. Epilepsia. 2016;57(5):786–95.
93. Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. J Clin Neurophysiol 2005;22(2):79–91.
94. Sánchez SM, Arndt DH, Carpenter JL, Chapman KE, Cornett KM, Dlugos DJ, et al. Electroencephalography monitoring in critically ill children: Current practice and implications for future study design. Epilepsia. 2013 Aug;54(8):1419–27. Available from: http://doi.wiley.com/10.1111/epi.12261
95. Sanchez SM, Carpenter J, Chapman KE, Dlugos DJ, Gallentine WB, Giza CC, et al. Pediatric ICU EEG Monitoring. J Clin Neurophysiol. 2013;30(2):156–60.
96. Ramantani G, Schmitt B, Plecko B, Pressler RM, Wohlrab G, Klebermass-Schrehof K, et al. Neonatal Seizures—Are We there Yet? Neuropediatrics. 2019 Oct 24;50(05):280–93. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0039-1693149
97. Abend NS, Arndt DH, Carpenter JL, Chapman KE, Cornett KM, Gallentine WB, et al. Electrographic seizures in pediatric ICU patients: Cohort study of risk factors and mortality. Neurology. 2013;81(4):383–91.
98. Yang A, Arndt DH, Berg RA, Carpenter JL, Chapman KE, Dlugos DJ, et al. Development and validation of a seizure prediction model in critically ill children. Seizure. 2015 Feb;25(1):104–11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf
99. Fung FW, Jacobwitz M, Parikh DS, et al. Development of a model to predict electroencephalographic seizures in critically ill children. Epilepsia. 2020;61(3):498-508. doi:10.1111/epi.16448

100. Shahwan A, Bailey C, Shekerdemian L, Harvey AS. The prevalence of seizures in comatose children in the pediatric intensive care unit: A prospective video-EEG study. 2010;51(7):1198–204.
101. Gutierrez-Colina AM, Topjian AA, Dlugos DJ, Abend NS. Electroencephalogram Monitoring in Critically Ill Children: Indications and Strategies. Pediatr Neurol. 2012 Mar;46(3):158–61. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0887899411005467
102. Sánchez Fernández I, Sansevere AJ, Gaínza-Lein M, Buraniqi E, Tasker RC, Loddenkemper T. Time to continuous electroencephalogram in repeated admissions to the pediatric intensive care unit. Seizure. 2018;54(2018):19–26. Available from: http://dx.doi.org/10.1016/j.seizure.2017.11.013
103. Wilson CA. Continuous electroencephalogram detection of non-convulsive seizures in the pediatric intensive care unit: review of the utility and impact on management and outcomes. Transl Pediatr. 2015;4(4):283–9.
104. Schreiber JM, Zelleke T, Gaillard WD, Kaulas H, Dean N, Carpenter JL. Continuous video EEG for patients with acute encephalopathy in a pediatric intensive care unit. Neurocrit Care. 2012;17(1):31–8.
105. McCoy B, Sharma R, Ochi A, Go C, Otsubo H, Hutchison JS, et al. Predictors of nonconvulsive seizures among critically ill children. Epilepsia. 2011;52(11):1973–8.
106. Gwer S, Idro R, Fegan G, Chengo E, Garrashi H, White S, et al. Continuous EEG monitoring in Kenyan children with non-traumatic coma. Arch Dis Child. 2012;97(4):343–9.
107. Topjian AA, Gutierrez-Colina AM, Sanchez SM, Berg RA, Friess SH, Dlugos DJ, et al. Electrographic status epilepticus is associated with mortality and worse short-term outcome in critically III children. Crit Care Med. 2013;41(1):215–23.
108. Greiner HM, Holland K, Leach JL, Horn PS, Hershey a. D, Rose DF. Nonconvulsive Status Epilepticus: The Encephalopathic Pediatric Patient. Pediatrics. 2012;129:e748–55.
109. Jette N, Claassen J, Emerson RG, Hirsch LJ. Frequency and predictors of nonconvulsive seizures during continuous electroencephalographic monitoring in critically ill children. Arch Neurol. 2006;63(12):1750–5.
110. Pinchefsky EF, Hahn CD. Outcomes following electrographic seizures and electrographic status epilepticus in the pediatric and neonatal ICUs. Curr Opin Neurol. 2017;30(2):156–64.
111. Abend NS, Wagenman KL, Blake TP, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and neurobehavioral outcomes in critically ill children. Epilepsy Behav. 2015 Aug;49(1):238–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1525505015001183
112. Lalgudi Ganesan S, Hahn CD. Electrographic seizure burden and outcomes following pediatric status epilepticus. Epilepsy Behav. 2019;101:106409. doi:10.1016/j.yebeh.2019.07.010
113. Sanchez Fernandez I, Abend NS, Agadi S, An S, Arya R, Brenton JN, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology. 2015;84(23):2304–11.
114. Abend NS, Chapman KE, Gallentine WB, Goldstein J, Hyslop AE, Loddenkemper T, et al. Electroencephalographic monitoring in the pediatric intensive care unit. Curr Neurol Neurosci Rep. 2013;13(3):330.
115. Abend NS, Arndt DH, Carpenter JL, Chapman KE, Cornett KM, Gallentine WB, et al. Electrographic seizures in pediatric ICU patients: Cohort study of risk factors and mortality. Neurology. 2013;81(4):383–91.
116. Abend NS, Topjian AA, Williams S. How much does it cost to identify a critically ill child experiencing electrographic seizures? J Clin Neurophysiol. 2015;32(3):257–64.
117. Abend NS, Topjian A a, Williams S. Could EEG monitoring in critically ill children be a cost-effective neuroprotective strategy? J Clin Neurophysiol. 2015;32(6):486–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26057408
118. Claassen J, Albers D, Schmidt JM, De Marchis GM, Pugin D, Falo CM, et al. Nonconvulsive seizures in subarachnoid hemorrhage link inflammation and outcome. Ann Neurol. 2014 May; 75(5):771–81.
119. Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med. 2007;35(12):2830–6.
120. Westover MB, Shafi MM, Bianchi MT, Moura LMVR, O'Rourke D, Rosenthal ES, et al. The

probability of seizures during EEG monitoring in critically ill adults. Clin Neurophysiol. 2015;126(3):463–71.
121. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. Crit Care Med. 2009;37(6):2051–6.
122. Ney JP, Van Der Goes DN, Nuwer MR, Nelson L, Eccher MA. Continuous and routine eeg in intensive care. Neurology. 2013;81(23):2002–8.
123. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: An investigation of variables associated with mortality. Neurology. 1996;47(1):83–9.
124. Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg. 1999;91(5):750–60.
125. Kubota Y, Nakamoto H, Egawa S, Kawamata T. Continuous EEG monitoring in ICU. J Intensive Care. 2018;6(1):1–8.
126. Newey CR, Kinzy TG, Punia V, Hantus S. Continuous electroencephalography in the critically ill: Clinical and continuous electroencephalography markers for targeted monitoring. J Clin Neurophysiol. 2018;35(4):325–31.
127. Hill CE, Blank LJ, Thibault D, Davis KA, Dahodwala N, Litt B, et al. Continuous EEG is associated with favorable hospitalization outcomes for critically ill patients. Neurology. 2019;92(1):E9–18.
128. Freund B, Probasco JC, Ritzl EK. Seizure incidence in the acute postneurosurgical period diagnosed using continuous electroencephalography. J Neurosurg. 2019;130(4):1203–9.
129. Towne AR, Waterhouse EJ, Boggs JG, Garnett LK, Brown AJ, Eeg R, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000;54:340–5.
130. Alvarez V, Rodriguez Ruiz A, LaRoche S et al. The use and yield of continuous EEG in critically ill patients: A comparative study of three centers. Clinical Neurophysiology 2017;128: 570-8
131. Limotai C, Ingsathit A, Thadanipon K et al. How and whom to monitor for seizures in an ICU: A systematic review and meta-analysis. Crit Care Med 2019;47:e366-e373

131a. DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia. 1998;39(8):833-840. It is the classic study pouting this issue on the map.

132. Struck AF, Osman G, Rampal N et al. Time-dependent risk of seizures in critically ill patients on continuous electroencephalogram. Ann Neurol 2017;82:177–185
133. Shafi MM,Westover MB, Cole AJ et al. Absence of early epileptiform abnormalities predicts lack of seizures on continuous EEG. Neurology. 2012;79:1796-1801.
134. Rodrigues Ruiz A, Vlachy J, Lee JW et al. Association of periodic and rhythmic electroencephalographic patterns with seizures in critically ill patients. JAMA Neurol. 2017;74:181-188
135. Struck AF, Ustun B, Ruiz AR, et al. Association of an electroencephalography-based risk score with seizure probability in hospitalized patients. JAMA Neurol. 2017;74:1419-1424
136. Struck AF, Tabaeizadeh M, Schmitt SE, et al. Assessment of the validity of the 2HELPS2B score for inpatient seizure risk prediction. JAMA Neurol. 2020;77:500-507.doi: 10.1001/jamaneurol.2019.4656
137. De Marchis GM, Pugin D, Meyers E, Velasquez A, Suwatcharangkoon S, Park S, et al. Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome. Neurology. 2016;86(3):253–60
138. Vespa P, Tubi M, Claassen J, Buitrago-Blanco M, McArthur D, Velazquez AG, et al. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. Ann Neurol. 2016;79(4):579–90
139. Vespa P, Martin NA, Nenov V, Glenn T, Bergsneider M, Kelly D, et al. Delayed increase in extracellular glycerol with post-traumatic electrographic epileptic activity: Support for the theory that seizures induce secondary injury. Acta Neurochir Suppl . 2002;81(81):355–7.
140. Claassen J, Perotte A, Albers D, Kleinberg S, Schmidt JM, Tu B, et al. Nonconvulsive seizures

after subarachnoid hemorrhage: Multimodal detection and outcomes. Ann Neurol. 2013 Jul 1;74(1):53–64.
141. Witsch J, Frey HP, Schmidt JM et al. Electroencephalographic periodic discharges and frequency-dependent brain tissue hypoxia in acute brain injury. JAMA Neurol. 2017; 74, 301–309.
142. Kurtz P, Gaspard N, Wahl AS, Bauer RM, Hirsch LJ, Wunsch H, et al. Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med. 2014;40(2):228–34.
143. Waterhouse EJ, Vaughan JK, Barnes TY, Boggs JG, Towne AR, Kopec-Garnett L, et al. Synergistic effect of status epilepticus and ischemic brain injury on mortality. Epilepsy Res. 1998 Feb;29(3):175–83.
144. Claassen J, Jetté N, Chum F, Green R, Schmidt M, Choi H, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. Neurology. 2007 Sep 25;69(13):1356–65. Available from: ttp://www.ncbi.nlm.nih.gov/pubmed/17893296
145. Sculier C, Gaínza-Lein M, Sánchez Fernández I, Loddenkemper T. Long-term outcomes of status epilepticus: A critical assessment. Epilepsia. 2018;59:155–69.
146. John P. Ney, David N. van der Goes, Marc R. Nuwer, Lonnie Nelson, Matthew A. Eccher Continuous and routine EEG in intensive care Utilization and outcomes, United States 2005-2009 Neurology 2013 DOI: https://doi.org/10.1212/01.wnl.0000436948.93399.2a
147. Khawaja AM, Wang G, Cutter GR, Szaflarski JP. Continuous electroencephalography (cEEG) monitoring and outcomes of critically ill patients. Med Sci Monit. 2017;23:649-658.
148. Alvarez V, Drislane FW, Westover MB, Dworetzky BA, Lee JW. Characteristics and role in outcome prediction of continuous EEG after status epilepticus: A prospective observational cohort. Epilepsia. 2015 Jun; 56: 933–941.
149. Crepeau AZ, Fugate J, Mandrekar J et al. Value analysis of continuous EEG in patients during therapeutic hypothermia after cardiac arrest. Resuscitation 2014 Jun;85:785-9. doi: 10.1016/j.resuscitation.2014.01.019. Epub 2014 Feb 21
150. Rosetti, AO, Hirsch LJ, Drislane FW. Nonconvulsive seizures and nonconvulsive status epilepticus in the neuro ICU should or should not be treated aggressively: A debate. Clinical Neurophysiology Practice2019;4:170–177.
151. Rossetti AO, Schindler K, Sutter R et al. Continuous vs routine electroencephalogram in critically ill adults with altered consciousness and no recent seizure: A multicenter randomized clinical trial. JAMA Neurol. doi:10.1001/jamaneurol.2020.2264
152. Hirsch LJ, Laroche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American clinical neurophysiology society's standardized critical care EEG terminology: 2012 version. J Clin Neurophysiol. 2013;30(1):1–27.
153. Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus Statement on Continuous EEG in Critically Ill Adults and Children , Part II : Personnel , Technical Specifications ,. 2015;32(2).

Discussion, Limitations, Future Research Directions and Conclusions

In this thesis I studied the development of epilepsy in patients who had suffered a moderate to severe traumatic brain injury (TBI), i.e. posttraumatic epilepsy (PTE) and epileptogenesis. This included investigating the detection and impacts of early posttraumatic seizures (EPS), including their relationship to the later development of PTE. This included developing a predictive tool for the development of PTE following a moderate to severe TBI that has potential to be used in clinical practice. Relevant to this, I also investigated the practice of detecting subclinical EPS with cEEG, a novel use of EEG in critically ill inpatients pioneered in the US, which is increasing being adopted in specialty hospitals in Australian. A potentially underutilised diagnosis and management strategy, whether cEEG guided detection and suppression of EPS may have an anti-epileptogenic effect yet to be examined. I lead the drafting of a position statement for the use cEEG in practice in Australia, as part of an expert group convened under the governance of the Epilepsy Society of Australia, consulting with other relevant professional societies including the Australian and New Zealand Association of Neurologists (ANZAN), and Australian critical care communities.

From the Chapter 1 review of the literature from 2000-2020, it is evident that a range of risk factors for PTE have been identified in studies across heterogenous populations; however, there was a disconnect with clinical practice, with no validated formalised risk assessment clinical tool in use in practice. Only few prior attempts had been made to evaluate prediction models on small datasets (1,2). Although various epidemiological studies have identified risk factors for PTE there has not been prediction models on large cohorts, and the impact of

PTE as a sequela of TBI was not fully understood. Epilepsy alone is known to cause significant disability, loss of independence, and risk of death, with up to a third of patients remaining drug resistant (25), however this has not been well demonstrated in the context of TBI. Furthermore, it was apparent that much focus has been on PTE and its risk factors with several studies in this area, with little attention and studies evaluating the mechanisms of occurrence via risk factor analysis of EPS.

In Chapter 2, using the comprehensive state-wide Neurotrauma Registry, I found that there were several important identifiable risk factors for the development EPS in the first week in patients who had suffered a moderate to severe TBI. Firstly, in this cohort, 2.7% developed EPS consistent with other studies (3). Using multivariate analysis that relies on the subsequent dependent analysis of each risk factor, the factors identified as statistically significant were pre-existing medical comorbidities as measured by the Charlson Comorbidity Index, low falls from standing height or <1m, subdural hematoma and subarachnoid haemorrhage, and worse injury severity indices of Abbreviated Injury Score head subdomain and Glasgow Coma Scale. Age and Injury Severity Score had a positive but negligible association. Complementing the multivariate analysis, I employed a novel machine learning prediction algorithm with independent analysis via least absolute shrinkage and selection operator (LASSO) regression of risk factors for EPS, there was concordance with low falls (albeit weak association), pre-existing medical comorbidities, subdural hematoma and subarachnoid haemorrhage, and worse injury severity index of Abbreviated Injury Score head subdomain but not Glasgow Coma Scale. There was also a weak association of a measure of socio-economic status Index of Relative Socio-economic Advantage and Disadvantage, as well as isolated TBI compared to multi-trauma. Taken together, the most significant and important risk factors common to both analyses were TBI

severity, prior medical comorbidities, and presence of subdural haematoma or subarachnoid haemorrhage. For follow up analysis of outcomes, when confounders were taken into consideration identified by EPS risk factor analysis, the outcomes of patients with EPS were poorer compared to patients with TBI and no EPS as measured by the Glascow Outcome Scale which is widely used in studies of neurological outcomes. I also showed the clinical importance of EPS, being associated with longer ICU and hospital stays, well beyond 7 days (10 and 24.5 days respectively), which was the time point commonly referred to as the transition of provoked EPS to unprovoked PTE although there is no evidence of aetiological differences here. This study therefore, at least in patients with moderate to severe TBI, suggests that EPS should potentially be defined differently to include the acute post-TBI admission due to ongoing in-hospital acute provoking factors, seen in other studies (4,5). Regarding the association of EPS on mortality in my study, in-hospital mortality was non-significant but may have been due to proximity to followed EPS, although the effect of EPS on mortality was statistically significant at the 24-month mark, which is a novel finding of this thesis, with the paper reporting this now accepted for publication in the leading Neurological journal, *JAMA Neurology*. Longer term follow-up mortality as measured by hazard ratio or instantaneous risk of death was non-significant, which may reflect inadequate power due to inconsistencies in the length of follow-up of patients in the cohort beyond 24 months. As expected per previous studies, EPS contributed to PTE risk and ASM use. The link between EPS and PTE remains an ongoing area of evaluation. Overall, this study was highly novel highlighting the importance and impact of EPS independent of confounders, and the concordance of prediction of risk factors for EPS using two statistical methods. As previously mentioned this study also has potential to contribute to an EPS definition change from occurring within 7 days of TBI to encompassing the whole acute admission.

Chapter 3 investigated risk factors for the development of PTE at 2 years in patients who had suffered a moderate to severe TBI, and evaluated the impact on morbidity and mortality, using the comprehensive Victorian State Trauma Registry. Multivariable analysis was used to identify risk factors for PTE including pre-existing medical comorbidities, history of alcohol misuse and prior mental health conditions, motor vehicle accident as mechanism of injury, intracerebral haemorrhage, and injury severity indices of Abbreviated Injury Score head subdomain and Glasgow Coma Scale were significant. Most noteworthy was the associated risk of EPS on PTE, with a risk ratio of 3.00 of developing PTE at 2 years post TBI. Age showed a negligible associated risk on PTE. Using the LASSO prediction model, EPS was highly significant along with other concordant risk factors of pre-existing medical comorbidities, history of alcohol misuse and prior mental health conditions, intracerebral haemorrhage, and injury severity indices of Abbreviated Injury Score head subdomain and Glasgow Coma Scale. Further factors were identified using the prediction model including age, male sex, cannabinoid misuse, isolated TBI compared with multi-trauma, subdural hematoma and subarachnoid haemorrhage, neurosurgical intervention, and some other weaker associations with causes of injury and base of skull fracture. The differences between the identification of risk factors between the analysis methods is interesting, especially when little prior attempts were made in modelling risk factors in PTE. In this study, health related quality of life measured by the EQ-5D was significantly lower for patients with PTE as well as overall GOS-E disability related outcomes after adjusting for confounders. The study also demonstrated a mortality risk that was 3.2 times higher than patients matched for other risk factors post-TBI.

An unpublished observation of the intersection of Chapters 2 and 3 when assessing risk factors of EPS and PTE, is the risk factors identified that were common to both EPS and

PTE. This observation may assist in highlighting mechanisms of epileptogenesis, of those patients whom have EPS and develop PTE. Factors common to both may therefore improve signal to noise in relation to the identification of pro-epileptogenic factors linking EPS to PTE, rather than investigating risk factors for PTE independently.

Continuous EEG (cEEG) use was pioneered in the US more than a decade ago using moderate to severe TBI as the model patient cohort (6), and recent years has become increasingly used in specialist Australian hospitals. In Chapter 4 I investigated the use of cEEG in the two largest trauma receiving centres in Melbourne, who have been “early adopters” of cEEG in Australia. Whilst there are fundamental differences in the way that cEEG is used in the US, which is at least partly driven by the well-funded private hospitals with available resources and dedicated neurointensive care units, cEEG is conservatively used in Australia as more of an extension of inpatient hospital EEG services rather than a standalone neurocritical care service. I identified a gap of cEEG use in Australia early in my PhD research, and decided to prospectively recruit all patients undergoing cEEG throughout the duration of my PhD candidature 2018-2020 and to analyse the cohort and outcomes. My audit of cEEG practice across two major trauma receiving metropolitan hospitals in Melbourne included 245 cEEG studies, with around half in the ICU and the other half on the ward. Most published studies restrict cohort studies of cEEG to the ICU, primarily due to the organisation of specialised neurointensive care units in the US. There were some key differences between the ICU and ward cohorts as expected, with ICU patients being more often referred for evaluation of unexplained altered conscious state, having higher rates of seizures detected on cEEG, and having worse overall outcomes.

In Chapter 5, I examined the practice of cEEG use and the associated management of status epilepticus in Australia via a voluntary survey of paediatric and adult epileptologists. Previous surveys in the US and other countries have been performed showing a substantial varied practice (7,8). The survey targeted Australian and New Zealand epileptologists via contact through the Epilepsy Society of Australia. There were thirty-five paediatric/adult epileptologists who completed the survey, with 51% with over 10 years of consultant experience. Self-reported confidence was high (~85%) for the diagnosis and management of both non-convulsive and convulsive status epilepticus. The majority agreed that there should be formal training in cEEG (94%), and agreed that a national cEEG guideline should be implemented (74%). The practice of cEEG varied amongst the responses, with cEEG available for most but largely on an ad-hoc basis. Availability of neuroscientists to perform the studies and supervising epileptologists was variable. Only half of the respondents had remote and live review capacity. Taken together, the model of care across most responses best fits with a transitional or remote off-site staffing model of delayed review compared to an in-house live model of cEEG monitoring. There are several barriers to reaching a live model, predominantly staffing, with the most significant barriers reported by respondents as lack of funding, personnel, and physical resources (9).

Following focus of cEEG at the annual Epilepsy Society of Australia scientific meeting in 2019, including early data I presented from Chapter 4 and promotion of the cEEG survey reported in Chapter 5, I was invited to join a Task Force for cEEG in Australia commissioned by the Epilepsy Society of Australia Executive Committee. The taskforce included neurologists from around Australia covering neonatology, paediatrics and adults with expertise in cEEG. Regular meetings over 18mths took place via teleconference firstly to discuss various issues of cEEG including available and current evidence, and also the

practicalities and barriers to implementing cEEG in Australia. In Chapter 6, this work is presented as a position paper summarising the current evidence for cEEG in children and adults as well as the place of cEEG within the Australian landscape of EEG services and the Australian public hospital system. The position statement will also be used to liaise with Australian critical care groups of the intensive care and emergency communities. Following this, determining the role of cEEG in Australia and requesting associated funding will be necessary to improving cEEG access and services for eligible patients. Chapters 4-6 represent a direct translational series of research influencing current medical practice of the use of cEEG in Australia.

Strengths and Limitations

There are several limitations of the study methodologies that I used in the research projects reported in my PhD thesis. Firstly, the two epidemiological studies of EPS and PTE used a large prospective population-based trauma registry (i.e. the Victorian State Trauma Registry) that while powerful in identifying associations, is limited in his ability to determine direct causality for outcomes. Also, although the Registry is well curated, the information available was limited by what was collected in the Registry. The definition of EPS used ICD-10AM codes and PTE defined by patient or proxy reported event of seizures, whilst the diagnosis of seizures and epilepsy may be complex and best determined by an epileptologist although this is difficult to undertake on a large dataset. Further to the PTE cohort, unfortunately the Registry only had data for identifying PTE in a smaller cohort compared to the larger 10-year series in EPS, due to the PTE questions being more newly added to the registry. Due to the large patient numbers within the cohorts and rich follow up data however, this improves the statistical power of examining associations and outcomes with significant and novel outcomes for EPS and PTE reported in these studies.

The cEEG cohort series began as an audit of practice rather than a dedicated research study, and although there were some key risk factors identified in prior literature to direct sensitivity of recording seizures, there lacks a richness in the data collected, particularly in relation to EEG characteristics and other clinical parameters. The cEEG survey study had a low responder rate of 19% (35/188) clinicians and 28% (30/108) consultant clinicians identified by the Epilepsy Society of Australia member list, although the overall number of qualified epileptologists in Australia is actually unknown. Overall, the cohort was diverse with a high proportion of experienced clinicians, and given the concentration of specialised epilepsy and EEG services to major metropolitan hospitals that the cohort likely represented a large percentage of clinicians in Australia involved in cEEG.

Future Directions

There are several avenues of potential novel and important future investigation highlighted throughout this PhD. In relation to the study investigating EPS, firstly the definition of EPS is highlighted as potentially contentious in this study. In most epidemiological papers on EPS, the definition is occurring within the first 7 days. This definition has been carried over from a study from 1973 (10), where treating clinicians would routinely make predictions of the development of PTE at this arbitrary time point. The essence of the definition of EPS however aligns within the definition of acute symptomatic seizures as determined by the International League Against Epilepsy as “occurring at the time of a systemic insult or in close temporal association with a documented brain insult” (11). This more pathobiological definition fits more closely with the definition of EPS used in my study and suggested by others (4,5), with all seizures occurring during the acute phase TBI illness admission being included as EPS. For some patients this may be less than 7 days, but for moderate to severe

TBI this may be up to ~25 days as per the median hospital length of stay in the study in Chapter 2. A move toward a pathobiological definition of EPS and PTE is important both for clinical interpretation of when epilepsy or PTE can be more accurately diagnosed, but also in the understanding of the differences and relationship between EPS and PTE. Chapter 2 also specifically highlights the independent impact of EPS on TBI including increased mortality, and its prediction may importantly focus clinical attention and also cEEG resources to further identify electrographic or non-convulsive EPS. Further, current antiseizure prophylaxis recommendations require reappraisal not only as they outline use over 7 days according to the previously mentioned inadequate definition, but are also unchanged since the advent of cEEG identified seizures which have no associated treatment recommendations. Interestingly, early identification and treatment of EPS and cEEG identified electrographic EPS could represent an antiepileptogenic strategy in reducing the subsequent progression and diagnosis of PTE. Such a prospective study would tie in all elements of this PhD work!

Regarding better research into improved identification in clinical practice of patients at risk of PTE, Chapter 3 demonstrated two separate statistical analysis of risk factors for PTE, which could further be incorporated to develop a clinical risk tool and therefore potentially improve closer management of patients at risk of PTE for example with clinical surveillance and repeat EEG testing. A recent study with a small cohort of 235 patients with PTE produced a nomogram scoring system for PTE risk, with key factors of loss of consciousness following acute TBI, male sex, subdural hamaetoma, EPS, injury severity, contusion and site, and surgical treatments, with reasonably good performance (receiver operating curve, AUC of 0.859) (1). Many of these factors were similar to those identified in Chapter 3. Further complimentary biomarkers of epileptogenesis in identifying patients at risk of PTE is the

focus of the ongoing Epibios4rx study (12), which includes EEG and MRI biomarkers including visualising epileptogenic networks (13).

As mentioned above, Chapters 4-6 highlighted a direct transitional research impact of improving and expanding cEEG services in Australia. Several barriers were identified to further expansion and subsequent future directions in applying cEEG more widely therefore rely on directing cEEG more efficiently, which may include the implementation of QEEG (14), streamlined cEEG montages and devices which were used successfully during the COVID pandemic (15), and semi-automated seizure detection in the critical care population. Cost benefit evaluation may be required to attract further funding for cEEG in Australia, which has been successfully shown in some populations including children (16). Following the cEEG cohort study in Chapter 4, a follow up larger registry targeting both risk factors for seizures to improve patient selection but focussing on treatment outcomes would improve local use of cEEG in Australia, but also contribute to international knowledge of treatment outcomes and inform treatment guidelines which are significantly lacking.

Conclusion

This PhD investigated various novel elements of seizures post-TBI, both EPS and PTE, and identified key advances in the understanding of this interaction. Specifically, this research has highlighted the uniqueness and importance of EPS and investigated the use of cEEG in this context and resulted in direct translation of outlining cEEG services in Australia via the ESA taskforce position paper. The use of cEEG guided investigation and management of patients predicted at high risk of EPS, and their outcomes remains an appealing opportunity for evaluating anti-epileptogenic strategies in reducing the impact of PTE.

REFERENCES

1. Wang X, Zhong J, Lei T, Wang H, Zhu L, Chu S, et al. Development and external validation of a predictive nomogram model of posttraumatic epilepsy: A retrospective analysis. Seizure [Internet]. 2021 May;88:36–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1059131121000996
2. Ritter AC, Wagner AK, Szaflarski JP, Brooks MM, Zafonte RD, Pugh MJ V, et al. Prognostic models for predicting posttraumatic seizures during acute hospitalization, and at 1 and 2 years following traumatic brain injury. Epilepsia [Internet]. 2016;57(9):1503–14. Available from: http://www3.interscience.wiley.com/journal/117957420/issueyear?year=2009
3. Xu T, Yu X, Ou S, Liu X, Yuan J, Huang H, et al. Risk factors for posttraumatic epilepsy: A systematic review and meta-analysis. Epilepsy Behav [Internet]. 2017 Feb [cited 2017 May 30];67:1–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28076834
4. Englander J, Bushnik T, Duong TT, Cifu DX, Zafonte R, Wright J, et al. Analyzing risk factors for late posttraumatic seizures: A prospective, multicenter investigation. Arch Phys Med Rehabil [Internet]. 2003;84(3 SUPPL. 1):365–73. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12638104
5. Majidi S, Makke Y, Ewida A, Sianati B, Qureshi AI, Koubeissi MZ, et al. Prevalence and Risk Factors for Early Seizure in Patients with Traumatic Brain Injury: Analysis from National Trauma Data Bank. Neurocrit Care [Internet]. 2017;27(1):90–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med13&NEWS=N&AN=28000125
6. Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg [Internet]. 1999;91(5):750–60. Available from: http://thejns.org/doi/10.3171/jns.1999.91.5.0750
7. Gavvala J, Abend N, LaRoche S, Hahn C, Herman ST, Claassen J, et al. Continuous EEG monitoring: A survey of neurophysiologists and neurointensivists. Epilepsia. 2014;55(11):1864–71.
8. Koffman L, Rincon F, Gomes J, Singh S, He Y, Ritzl E, et al. Continuous Electroencephalographic Monitoring in the Intensive Care Unit: A Cross-Sectional Study. J Intensive Care Med [Internet]. 2020 Nov 13;35(11):1235–40. Available from: http://journals.sagepub.com/doi/10.1177/0885066619849889
9. Laing J, Lawn N, Perucca P, Kwan P, O'Brien TJ. Continuous EEG use and status epilepticus treatment in Australasia: a practice survey of Australian and New Zealand epileptologists. BMJ Neurol Open. 2020;2(2):e000102.
10. Jennett B, Teather D, Bennie S. Epilepsy After Head Injury. Lancet [Internet]. 1973 Sep;302(7830):652–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673673924884
11. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia [Internet]. 2010 Apr 1 [cited 2020 Feb 4];51(4):671–5. Available from: http://doi.wiley.com/10.1111/j.1528-1167.2009.02285.x
12. Vespa PM, Shrestha V, Abend N, Agoston D, Au A, Bell MJ, et al. The epilepsy bioinformatics study for anti-epileptogenic therapy (EpiBioS4Rx) clinical biomarker: Study design and protocol. Neurobiol Dis [Internet]. 2019;123:110–4. Available from: http://www.elsevier.com/inca/publications/store/6/2/2/9/2/3/index.htt
13. La Rocca M, Garner R, Amoroso N, Lutkenhoff ES, Monti MM, Vespa P, et al. Multiplex Networks to Characterize Seizure Development in Traumatic Brain Injury Patients. Front Neurosci [Internet]. 2020 Nov 30;14. Available from: https://www.frontiersin.org/articles/10.3389/fnins.2020.591662/full
14. Haider HA, Esteller R, Hahn CD, Westover MB, Halford JJ, Lee JW, et al. Sensitivity of quantitative EEG for seizure identification in the intensive care unit. Neurology.

2016;87(9):935–44.
15. LaMonte MP. Ceribell EEG shortens seizure diagnosis and workforce time and is useful for COVID isolation. Epilepsia Open [Internet]. 2021 Jun 27;6(2):331–8. Available from: https://onlinelibrary.wiley.com/doi/10.1002/epi4.12474
16. Abend NS, Topjian AA, Williams S. Could EEG Monitoring in Critically Ill Children Be a Cost-effective Neuroprotective Strategy? 2015 Dec [cited 2020 Jun 1];32(6). Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004691-201512000-00009