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Prognostic Value of Electroencephalography in Critically Ill Adult Patients with Traumatic Brain Injury: A Systematic Review

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Abstract

Prognostication after moderate-to-severe traumatic brain injury (TBI) remains challenging in the intensive care unit (ICU) despite the existence of well-validated online prognostication tools. Changes in brain activity related to TBI can be measured using electroencephalography (EEG), making it a potentially interesting diagnostic tool to refine prognostication. The primary objective of this systematic review was to evaluate the literature concerning the prognostic value of EEG among patients with TBI in the ICU. Five databases were searched from inception until August 13, 2024. The search identified 1492 unique records. Eventually, 27 manuscripts met the inclusion criteria (>18 years old, Glasgow Coma Scale ≤12, EEG performed in the ICU). The QUIPS (QUality In Prognostic Studies) and PROBAST (Prediction model Risk Of Bias ASsessment Tool) tools were used to assess the study quality and bias. Due to high heterogeneity in EEG feature and outcome definitions and a lack of correction for confounding factors, all studies had a moderate-to-high risk of bias. Nonetheless, specific EEG features (identified through visual and quantitative EEG, EEG reactivity, and machine learning techniques) were found to be predictive of neurological outcomes up to 1.5 years after TBI. While epileptiform discharges and seizures were not consistently associated with outcomes, a higher alpha variability, a more continuous EEG, present EEG reactivity, and present EEG sleep features were predictive of better outcomes. The combination of EEG features with clinical parameters demonstrated improved predictive performance compared with models using standard clinical parameters alone. Still, the EEG features described and their potential additional value in outcome prediction after TBI merit further investigation.

Keywords: EEG; intensive care unit; prognosis; review; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability, with an estimated worldwide incidence of 50–60 million new cases a year.[1] Patients with moderate-to-severe TBI—classified as a Glasgow Coma Scale (GCS) ≤12, approximately 10% of all cases—present with a disorder of consciousness (DoC), which often requires endotracheal intubation and admission to the intensive care unit (ICU). These patients have an estimated 30% risk of death, and survivors of the disease are often left with severe disabilities that result in a significant socioeconomic burden.[2–5] Currently, most patients with severe TBI die from withdrawal of life support.[6] Predicting outcomes in patients with a DoC, especially in the acute phase after TBI, is significantly limited by a scarcity of reliable prognostic factors and the generally low quality of existing studies.[7,8] An accurate and timely prognosis of outcome after moderate-to-severe TBI is of great importance to provide reliable expectations for the patient's relatives while the patient is in the ICU and often has a DoC. Furthermore, an accurate prognosis can inform clinical management decisions, including considerations about limitations of care or even early withdrawal of life support, or—vice versa—

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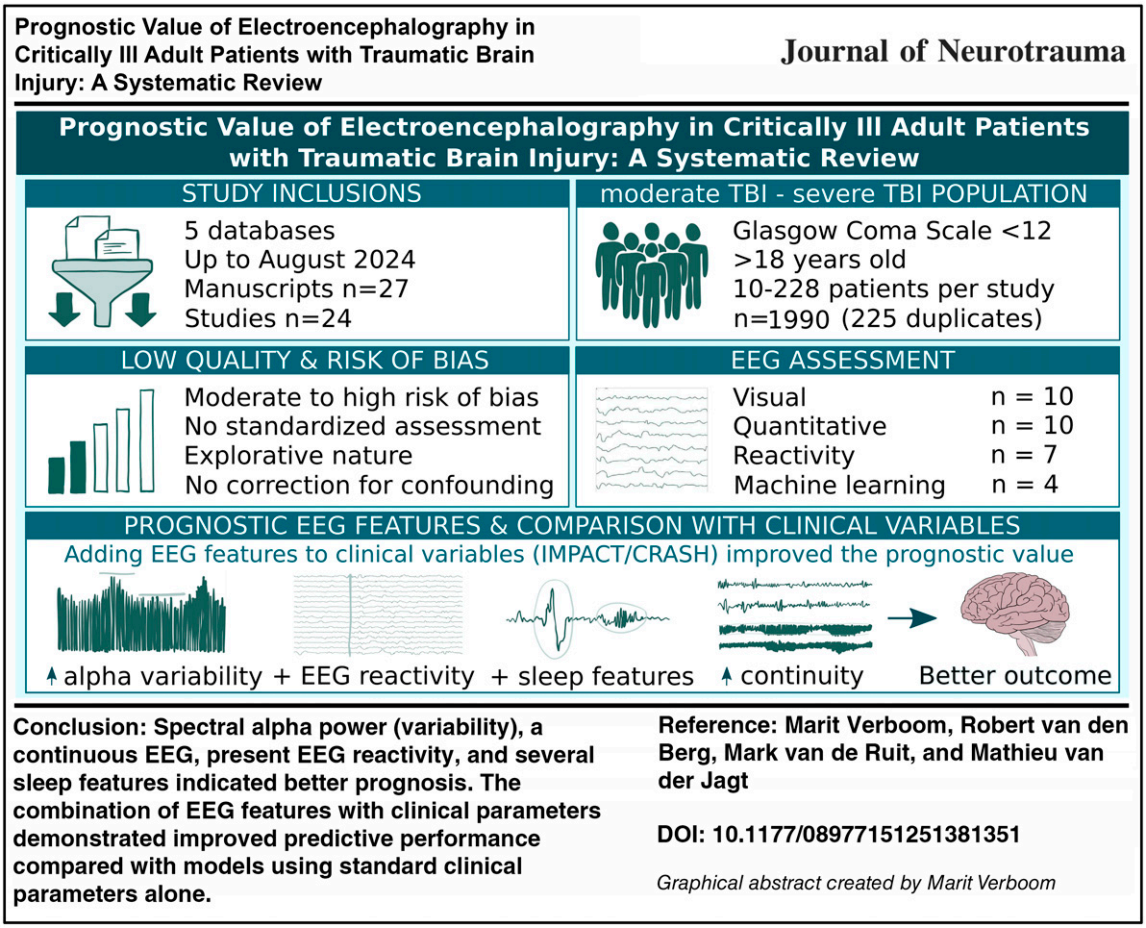

continued life support. Therefore, accurate tools for individual prognostication after TBI are desired, especially during the acute phase in the first days after admission.[9]

Two well-known and well-validated models for the prognosis after TBI are the Corticoid Randomisation After Significant Head Injury (CRASH) and the International Analysis of Clinical Trials (IMPACT), which include patient characteristics at the time of ICU admission.[10,11] Despite these models showing good discrimination between favorable and unfavorable long-term outcomes, their performance has yet to meet the standards required for implementation in clinical practice.[12] Hence, there still is a need to identify more accurate prognostic biomarkers, including biomarkers with information extending beyond ICU admission, that could further improve early prognostication after TBI.

Electroencephalography (EEG) is a potential biomarker that has gained interest in TBI research regarding, for example, ischemia detection, changes in intracranial pressure, recovery of consciousness, and prognostication.[13] EEG is an increasingly used modality in ICUs because it is easily applicable at the bedside, noninvasive, and has low costs compared with other monitoring modalities.[14] TBI-related electrophysiological changes, potentially caused by both neuronal damage and/or alterations to surviving brain circuits after TBI, can be measured using EEG.[15] However, the predictive value of the electrophysiological changes measured using EEG is not well established, especially in the case of prognostication after TBI.

Two prior reviews have addressed the potential of EEG as a prognostic tool in disorders of consciousness following TBI.[16,17] However, these reviews were limited by a narrow focus on specific EEG types, particularly resting-state EEG and machine learning techniques, and lacked the ability to capture the full potential of EEG. Additionally, in the study by Noor et al. (2020), the inclusion of patients with mild, moderate, and severe TBI complicated the interpretation of the results for use in the ICU. Furthermore, neither review addressed the timing of EEG recordings, while electrophysiological changes can occur over different phases after TBI.[18] Lastly, given the recent surge in interest and advancements in EEG analysis and prediction models, an updated and comprehensive review is needed to provide the latest insights.

The primary objective of this systematic review was to evaluate the existing literature concerning the prognostic value of EEG measures in acute phases among patients with TBI admitted to the ICU. Emphasizing a broad perspective on EEG monitoring approaches, we aim to provide a comprehensive overview of prognostic evidence in this critical timeframe.

Methods

This systematic review was conducted and reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Methods Prognosis.[19,20] The review protocol was registered within the International Prospective Register of Systematic Reviews (PROSPERO CRD42023402396).

Search strategy

We searched five databases (Medline ALL, Embase, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar) from inception until August 13, 2024. The review question was formulated according to the PICOTS format (Table 1).[21] Keywords for the search included "Electroencephalography," "Traumatic Brain Injury," "Prognosis," and "Intensive Care Unit." All searches were limited to articles in the English language, and an additional filter was used to hide conference abstracts. Search queries were designed in collaboration with an experienced medical information specialist from the Erasmus Medical Center, Rotterdam, the Netherlands. An elaborate description of the search strategy can be found in Supplementary Data S1.

Selection criteria

Studies were eligible for inclusion if (1) the article evaluated one or more EEG features for any outcome prediction in patients with moderate-to-severe TBI; (2) the study population suffered from TBI and was admitted to the ICU, or included a subgroup analysis focusing on patients with TBI admitted to the ICU; and (3) EEG recordings were performed while the patients remained in the ICU. Articles were excluded if (1) full text was not available; (2) the article was a review, conference abstract, or letter to the editor; (3) the majority of the study population was <18 years old; (4) the study population was nonhuman; and/or (5) no separate results were reported for the TBI population and/or EEG measures. We did not exclude papers based on how the authors handled and/or reported epileptiform activity observed on the EEG.

Screening and selection process

All titles and abstracts were screened by two researchers (M.V. and R.v.d.B.) using the collaborative review application Rayyan.[22] Articles that seemed eligible based on title and abstract, and those that required further reading, were screened for eligibility based on full texts. In case of doubt, consensus was sought through discussion between both reviewers (M.V. and R.v.d.B.).

Table 1. PICOTS of Interest Used for the Formulation of the Research Question for the Search Strategy of This Systematic Review

Population	*Patients with moderate-to-severe TBI (GCS <12)*
Index	Prognostic factors and prognostic models based on EEG
Comparator	Not applicable
Outcomes	All reported neurological outcome measures
Timing	(1) Prediction: during coma in the ICU (2) Follow-up: no timeframe
Setting	Evaluate the potential prognostic value of EEG in patients with TBI admitted to ICU

Developed according to "A Guide to Systematic Review and Meta-Analysis of Prediction Model Performance".

TBI, traumatic brain injury; GCS, Glasgow Coma Scale; EEG, electroencephalography; ICU, intensive care unit.

Study quality and risk of bias

Different types of prognostic studies can be distinguished, which require different types of bias analyses. Prognostic factor studies aim to identify one or more predictive variables, whereas prognostic model studies aim to identify a combination of factors in a multivariable model that can predict a certain outcome.[20] The QUality In Prognostic Studies (QUIPS) tool was used for the evaluation of studies on prognostic factors.[23] Risk of bias and applicability of the included studies on prognostic models were assessed using the PROBAST (Prediction model Risk Of Bias ASsessment Tool).[24]

Data extraction and analyses

Data extraction was performed following the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prognostic Studies (CHARMS-PF).[25] For all included studies, we extracted the following characteristics: type of prognostic study (retrospective or prospective), number of included patients, inclusion criteria, type of prognostic study (prognostic factor or prognostic model), primary outcome measure, and time to follow-up for outcome prediction. The following factors were extracted regarding the EEG recordings: EEG evaluation or use (visual, quantitative, or reactive), time from TBI to first EEG recording, duration of EEG recording, EEG features studied, and methods used to extract EEG features. The different EEG features were divided into (1) resting-state EEG features, consisting of epileptiform activity, power spectral analysis, continuity of the EEG, sleep features, complexity, and connectivity domains; and (2) EEG reactivity. For prognostic model studies, the type of model and methods of model development were extracted. As a primary outcome, results on the relationship between the studied EEG features and the neurological outcome were collected from

all studies. Additionally, the comparison between the prognostic value of EEG features versus clinical parameters was extracted when this analysis was performed.

Results and significance levels from the included studies are described using a narrative approach and are presented as reported in the original manuscripts. We considered analyzing associations between EEG features and neurological outcome with random-effects models when several studies reported homogeneous inclusion criteria, methods, and results. However, due to the heterogeneity in studied EEG features, neurological outcome measures, and reported statistical measures across included studies, no meta-analyses were conducted.

Results

Study selection

The search strategy yielded 2036 records. After deduplication, a total of 1492 titles and abstracts were screened, of which 1275 records were excluded as they did not meet our inclusion criteria. Ten records could not be retrieved. Thus, 144 studies were selected for full-text assessment. Eventually, 27 full-text articles from 24 different studies that fulfilled the inclusion criteria for further analysis were included (Fig. 1).

Study quality and risk of bias

All included studies had a moderate-to-high risk of bias (Fig. 2). Using the QUIPS tool, all studies had moderate or high risk of bias in at least 1 of the 6 domains (Fig. 2A and Supplementary Data S2). A moderate or high risk of bias in the domain of factor measurement was usually caused by a lack of clear definition of the EEG feature studied or because the definition was not according to the American Clinical Neurophysiology Society (ACNS) criteria.[26] All studies had a moderate-to-high risk of bias in the confounding domain, mainly due to a lack of correction for sedatives used. Only four studies used a multivariable model to predict outcome after TBI and were assessed using the PROBAST tool. These studies all scored a high risk of bias in at least one domain (Fig. 2B and Supplementary Data S2).

Study characteristics

Twenty-one studies included only adult participants, whereas six studies also included a small subset of

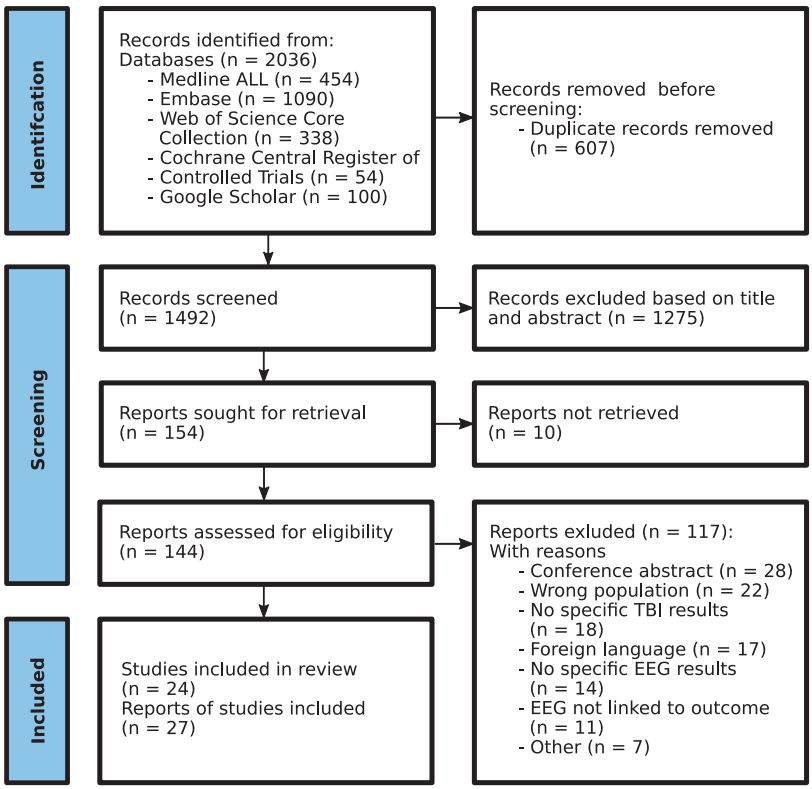

FIG. 1. PRISMA 2020 flow diagram of the study selection process. Twenty-four different TBI populations were studied, with 27 manuscripts published. "Wrong population" includes all studies that did not focus on patients with moderate-to-severe TBI who were >18 years of age or older, and admitted to the ICU. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; EEG, electroencephalography; TBI, traumatic brain injury; ICU, intensive care unit.

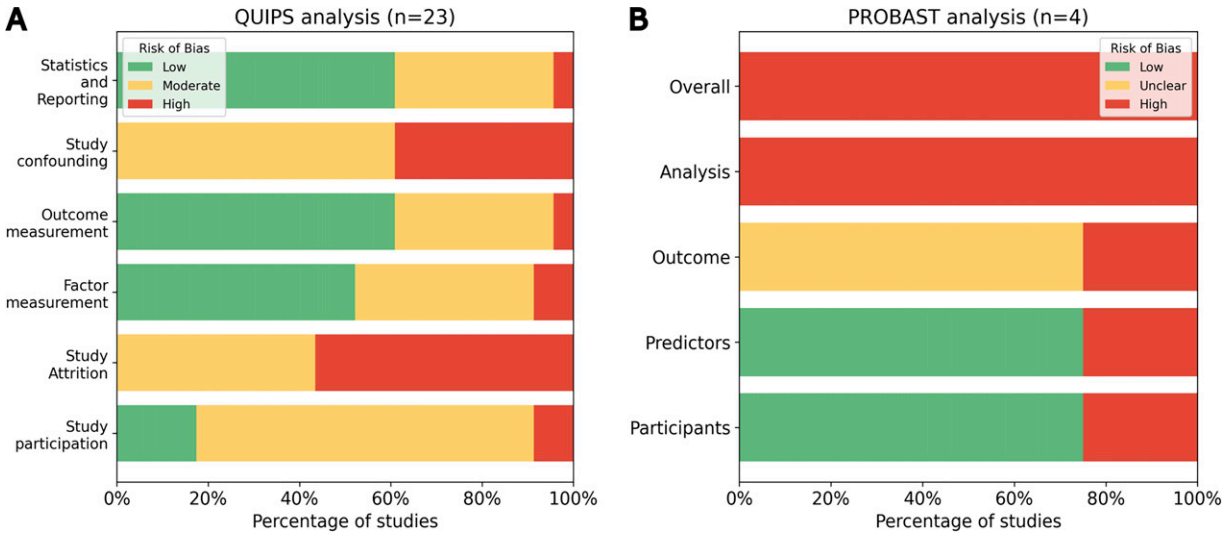

FIG. 2. Summary of risk of bias analyses performed. **(A)** QUIPS (QUality In Prognostic Studies) analysis to assess the risk of bias of all included prognostic factor studies ($n = 23$), based on six different domains. **(B)** PROBAST (Prediction model Risk Of Bias ASsessment Tool) analysis to assess the risk of bias of all included prognostic model studies ($n = 4$), based on five different domains.

participants under the age of 18 years. Approximately half of the studies ($n = 12$) included patients with moderate-to-severe TBI, while the remaining studies ($n = 15$) focused exclusively on patients with severe TBI (GCS ≤8). The number of patients included ranged from 10 to 228. Sample size calculations were not performed for any of the studies. Exclusion criteria used in the included studies were generally aimed at excluding patients with pre-existing brain disorders. Among the studies included in our systematic review, we observed various approaches regarding epileptiform EEG activity. Some studies excluded patients with seizures or epileptiform activity on their EEGs ($n = 4$), while others specifically examined this epileptiform activity as a potential prognostic factor ($n = 6$). Some studies applied additional exclusion criteria, such as overwhelming concurrent hepatic or metabolic encephalopathy ($n = 3$), burst suppression ($n = 3$), or high-dose sedation ($n = 2$). Full details on inclusion and exclusion criteria and additional study characteristics are provided in Table 2.

Outcome measures

Neurological outcomes were assessed using a variety of measures (Supplementary Data S3). The most frequently used outcome measures were the Glasgow Outcome Scale (GOS, $n = 10$) and its extended version (GOSe, $n = 11$). Other outcome measures were the Cerebral Performance Category ($n = 2$), the modified Ranking Score (mRS, $n = 1$), the Rapid Disability Rating Scale ($n = 1$), the Repeatable Battery for the Assessment of Neuropsychological Status ($n = 1$), and consciousness level ($n = 2$). The dichotomization of favorable and unfavorable outcomes varied between studies. Time to follow-up also differed, ranging from the moment of discharge from the ICU to 18 months after the initial TBI (discharge: $n = 6$; <3 months: $n = 7$; 6 months: $n = 11$; ≥1 year: $n = 7$).

Prognostic value of EEG

The prognostic value of EEG for the neurological outcome after TBI was studied for a variety of different EEG features. Seventeen studies focused on specific EEG features to predict outcome based on resting-state EEG (visually assessed [$n = 9$], quantitatively assessed [$n = 10$]), as summarized in Table 3. Additionally, seven studies performed EEG reactivity analysis (Table 4). Four studies developed a prognostic machine learning model (Table 5). Finally, five studies directly compared the prognostic value of EEG features to that of established clinical predictors, such as age, GCS, and CT findings (Table 6). Across the studies that assessed the same EEG features (e.g., epileptiform activity), there was variability in how these measures were defined. For example, some authors did not adhere to the ACNS criteria for epileptiform activity. The precise definitions employed by each study are summarized in Supplementary Data S4.

Resting-state EEG features

The reporting on electrographic epileptiform activity following TBI was inconsistent, with only 6 out of 28 studies reporting its prognostic value.[32,39,40,43,44,46] Mixed associations between epileptiform activity on the EEG and neurological outcome were observed. Some studies

Table 2. Study Characteristics of All Included Studies

Author	Year	Study design	n (% female)	Age (years)	Population	Inclusion	Time to EEG	EEG duration	EEG analysis type	Time to follow-up	Outcome measure	Dichotomization (bad, good)	EEG predictive of outcome
Amantini et al.[27]	2005	Retrospective	60 (–)	17–72	sTBI	GCS ≤7, coma >7 days, lack of pre-existing brain disease.	48–72 h and 1 week	>30 min	Reactivity	At least 1 year	GOS	1–3, 4–5	Yes
Alkhachroum et al.[28]	2024	Retrospective	113 (22)	40.4 (good) vs. 50.1 (good)	sTBI	Comatose patients admitted to the ICU, EEG during hospital stay, >18 years old.	6 days (IQR: 1–12 days)	10 min	Quantitative and machine learning	Discharge	Recovery of consciousness	Not dichotomized	Yes
Beridze et al.[29]	2010	Prospective	53 (26)	25–55	sTBI	No inclusions; exclusion criteria comprised the extra- and intra-axial damages needing the neurosurgical intervention due to hemorrhage.	5 days	—	Visual	1 month	death, vegetative state, recovery	—	Yes
Cleri et al.[30]	2023	Retrospective	195 (25)	48.83 (SD: 20.02)	sTBI	All patients with sTBI who underwent EEG monitoring within 30 days after injury. Exclusion: not intubated.	Within 30 days	—	Visual	Discharge and 6 months	GOSe	1–4, 5–8	Yes
Edlow et al.[31]	2017	Prospective	15 (27)	18–51	sTBI	18–65 years old, GCS 3–8 with no eye opening for at least 24 h. Exclusion: life expectancy <6 months, prior severe brain injury or neurodegenerative disease, penetrating TBI with intracranial metal precluding MRI, no fluency in English prior to injury.	2–23 days	During protocol	Reactivity	6 months	GOSe	Not dichotomized	No
Foreman et al.[32]	2022	Retrospective	89 (–)	—	modTBI and sTBI	18–70 years old with nonpenetrating TBI, GCS 4–12, and hemodynamic stability. Exclusion: spinal cord injury, significant bodily co-injuries, prior brain injury requiring hospitalization, severe comorbidities, weight >150 kg, fluid resuscitation greater than 6 L prior to randomization, and those at risk for QT prolongation.	13.6 ± 10.4 h after injury	≥72 h	Visual	3 months	RBANS	Not dichotomized	Yes
Frohlich et al.[33]	2022	Prospective	34 (18)	40 ± 17	modTBI and sTBI	GCS ≤8, or GCS 9–14 with CT intracranial bleeding. Exclusion: GCS >14, history of neurological disease or TBI, and brain death.	During ICU stay	15–320 h	Quantitative	6 months	GOSe	1–4, 5–8	No
Frohlich et al.[34]	2021	Prospective	32 (16)	41 ± 17	modTBI and sTBI	GCS ≤8, or GCS 9–14 with CT intracranial bleeding. Exclusion: GCS >14, history of neurological disease or TBI, and brain death.	During ICU stay	Multiday	Quantitative	Discharge and 6 months	GOSe	1–4, 5–8	Yes
Gutling et al.[35]	1995	Prospective	50 (–)	30	sTBI	Age 14–55, no intoxications, no history of psychiatric or cerebral damage. Pretraumatic knowledge of German and a domicile within 100 km.	48–72 h	During protocol	Reactivity	1.5 years	GOS	1–3, 4–5	Yes

(*continued*)

Table 2. (Continued)

Author	Year	Study design	n (% female)	Age (years)	Population	Inclusion	Time to EEG	EEG duration	EEG analysis type	Time to follow-up	Outcome measure	Dichotomization (bad, good)	EEG predictive of outcome
Haveman et al.[36]—prior to Tewarie et al.[37]	2019	Prospective	57 (23)	>18	modTBI and sTBI	>18 years old, GCS ≤12, expected at least 24 h at ICU. Exclusion: severe circulatory failure, earlier TBI/CVA without full recovery, progressive brain illness, limited life expectancy <6 months prior to trauma.	As soon as possible	Up to 7 days	Quantitative and machine learning	1 year	GOSe	1–2, 3–8	Yes
Hebb et al.[38]	2007	Prospective	38 (–)	—	modTBI and sTBI	GCS ≤13, age 16–85 years, and abnormal head CT. Exclusion: brain death or GCS ≥14 within 8 h of admission, BS therapy with propofol or pentobarbital, pre-existing neurological disorders, and overwhelming concurrent hepatic or metabolic encephalopathy.	At admission to the ICU	7 days	Visual	6 months	GOS	1–3, 4–5	Yes
Lee et al.[39]	2019	Retrospective	152 (12)	34.5 ± 18	modTBI and sTBI	18–70 years old with nonpenetrating TBI, GCS 4–12 and hemodynamic stability. Exclusion: spinal cord injury, significant bodily co-injuries, prior brain injury requiring hospitalization, severe comorbidities, weight >150 kg, fluid resuscitation greater than 6 L prior to randomization, and those at-risk for QT prolongation.	24–48 h after ICU admission	≥72 h	Visual	3 months	GOSe	1–4, 5–8	Yes
Müller et al.[40]	2020	Prospective	44 (27)	63 (IQR: 40–73)	modTBI and sTBI	>18 years old, GCS ≤11 or FOUR ≤12, ICU, EEG requested due to medical reasons. Exclusion: clinical or EEG signs of seizures in the 36 h or status epilepticus in the 96 h preceding randomization in the CERTA study.	71 h (IQR: 43–112)	Standard EEG	Visual and machine learning	6 months	CPC	1–2, 3–5	Yes
O'Donnel et al.[41]	2021	Prospective	18 (17)	20–86	modTBI and sTBI	GCS *M* < 6, ≥18 years old. Exclusion: moribund, history of m/sTBI or neurological disorder, non-English speakers, CT evidence of brainstem-only lesion (locked-in), focal lateral temporal lobe lesions (language deficit), hearing impairments.	3–24 days	5–10 min	Quantitative	3 and 6 months	GOSe	Not dichotomized	Yes
Portnova et al.[42]	2020	Prospective	10 (20)	18–51	sTBI	Exclusion: history of psychiatric or neurological disorders, presence of seizure or epileptiform activity on EEG.	4 days to 2 months and 25 days	During protocol	Reactivity and quantitative	–	GOSe	Not dichotomized	Yes
Rae-Grant et al.[43]	1996	Prospective	69 (30)	15–82	modTBI and sTBI	GCS ≤8, >15 years old, comatose for >48 h after admission, closed head injury. Exclusion: brain dead	5–7 days after injury	≥30 min	Visual	Day 0, 7 and discharge	GOS and DRS	Not dichotomized	Yes

(*continued*)

Table 2. (Continued)

Author	Year	Study design	n (% female)	Age (years)	Population	Inclusion	Time to EEG	EEG duration	EEG analysis type	Time to follow-up	Outcome measure	Dichotomization (bad, good)	EEG predictive of outcome
Sandsmark et al.[44]	2016	Retrospective	64 (17)	15–97	modTBI and sTBI	> 18 years old, imaging findings of TBI, GCS requiring ICU admission, and underwent ≥24 h EEG monitoring within 14 days after injury.	Within 14 days after surgery	≥24 h	Visual	Discharge	mRS	≥4, <4	Yes
Sokoliuk et al.[45]	2021	Prospective	17 (18)	26–86	sTBI	GCS M < 6, >18 years. Exclusion: moribund, history of moderate/severe TBI or neurological disorder, non-English speakers, CT evidence of brainstem-only lesion or focal left lateral temporal lobe lesions, known hearing impairments.	3–19 days	During protocol	Reactivity	3 and 6 months	GOSe	Not dichotomized	Yes
Tewarie et al.[37]	2023	Prospective	104 (28)	Bad: 59 (IQR: 46–70), good: 43 (IQR: 13–47)	modTBI and sTBI	>18 years old, GCS ≤12, expected at least 24 h at ICU. Exclusion: severe circulatory failure, earlier TBI/CVA without full recovery, progressive brain illness, limited life expectancy <6 months prior to trauma.	At admission to the ICU	Up to 7 days	Quantitative and machine learning	1 year	GOSe	1–3, 4–8	Yes
Tao et al.[46]	2023	Retrospective	33 (–)	—	sTBI	GCS ≤7 with E = 1, V ≤2, and M ≤4; EEG within 4 weeks after admission, including at least four frontoparietal channels, and a duration of at least 30 min, at least 24 h after last sedatives. Exclusion: brain dead or regainment of consciousness during EEG monitoring.	Within 4 weeks	—	Quantitative	60 days	GOS	1–2, 3–5	Yes
Theilen et al.[47]	2000	Prospective	32 (–)	18–75	sTBI	GCS ≤8 first 6 h after closed head trauma. Excl: raw EEG showed electrocerebral inactivity or a burst-suppression pattern initially or during the first 2 days of treatment, metabolic disorders, sepsis, barbiturate, propofol, of gamma-hydroxybutyrate usage	<12 h	24–96 h	Quantitative	6 months	GOS and RDRS	1–3, 4–5 and ≥15, <15	Yes
Tolonen et al.[48]	2018	Prospective	28 (21)	Bad: 52.5 ± 17.6, good: 36.9 ± 19.9	sTBI	Exclusion: <18 years old, severely injured scalp, consciousness before EEG monitoring, perforating, or penetrating mechanism of TBI, inability to live independently due to pre-injury brain disease or other medical cause.	2–5 days	72 h	Quantitative	6 and 12 months	GOS	1–3, 4–5	Yes
Valente et al.[49]	2002	Prospective	24 (21)	16–74	sTBI	Exclusion: GCS >9 at admission, seizures or clinical/EEG signs of brain death	7–14 days	24 h	Visual	1–3 years	GOS	1–3, 4–5	Yes

(*continued*)

Table 2. (Continued)

Author	Year	Study design	n (% female)	Age (years)	Population	Inclusion	Time to EEG	EEG duration	EEG analysis type	Time to follow-up	Outcome measure	Dichotomization (bad, good)	EEG predictive of outcome
Vespa et al.[50]	2002	Prospective	89 (19)	39 ± 18.2	modTBI and sTBI	GCS scores <14, age 16–80, abnormal findings on the admission CT scan. Exclusion: brain death or GCS >14 within 8 h after admission, pentobarbital- or propofol-induced burst suppression, pre-existing neurological disorder, and overwhelming concurrent hepatic or metabolic encephalopathy.	9.6 ± 5.4 h after ICU admission	7 days	Visual	Discharge	GOS	1–2, 4–5	Yes
Wang et al.[51]	2022	Prospective	56 (36)	54.8 ± 11.9	sTBI	>18 years old, GCS ≤8, TBI within 14 days prior, >35°C. Exclusion: history of neurological disorder, EEG recorded during sedation >2 mg/h midazolam or >1.2 mg/kg/h propofol, burst suppression.	Within 14 days	8–12 h	Reactivity and quantitative	3 months	GOS	1–2, 3–5	Yes
You et al.[52]	2018	Prospective	65 (–)	—	sTBI	>18 years old, GCS ≤8, acute brain injury (including TBI). Exclusion: pre-existing neurological disorders, overwhelming concurrent hepatic or metabolic encephalopathy, co-existing systemic disease, reduced life expectancy, brain death.	7 days	6–12 h	Quantitative	6 months	CPC	3–5, 1–2	Yes
Zhang et al.[53]	2022	Retrospective	228 (41)	Median 40 (IQR: 33–47)	sTBI	GCS ≤8, coma after 7 days, RMNS therapy, >18 years old. Hematomas, SAH, or DAI on CT. Stable vital signs. Exclusion: severe heart arrhythmias or pacemaker, epilepsy, pregnancy, decreased life expectancy, and co-occurring systemic disorders.	Within 1 week	3 days	Reactivity	12 months	GOSe	1–2, 3–8	Yes

sTBI, severe traumatic brain injury; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; EEG, electroencephalography; GOSe, Glasgow Outcome Scale extended; modTBI, moderate traumatic brain injury; RBANS, The Repeatable Battery for the Assessment of Neuropsychological Status; ICU, intensive care unit; CVA, cerebrovascular accident; BS, burst suppression; IQR, inter quartile range; FOUR, Full Outline of UnResponsiveness; CERTA, continuous versus routine EEG in patients after cardiac arrest: Analysis of a randomized controlled trial; CPC, Cerebral Performance Category; DRS, Disability Rating Scale; mRS, modified Ranking Scale; RDRS, Rapid Disability Rating Scale; RMNS, Right Median Nerve Stimulation; SAH, subarachnoid hemorrhage; DAI, diffuse axonal injury.

Table 3. Summary of All Studies Using Resting-State Electroencephalography (EEG) Analysis

EEG feature	*Author*	*Feature definition*	*Time to EEG*	*Outcome measures*	*Outcome timing*	*Analysis*	*Statistical methods*	*Main findings*
Epileptiform activity	Foreman et al. (2022)[32]	IIC pattern (present/absent), IIC burden (Hz/h),	13.6 ± 10.4 h after injury	RBANS	3 months	Visual	Univariate and multivariate logistic regression	Univariate: no significant differences. IIC burden higher in below-median cognitive outcome (0.73 above median vs. 0.03 below median, $p = 0.002$). Multivariate: log transform IIC burden independently associated with RBANS (OR: 0.74, $p = 0.06$).
	Lee et al. (2019)[39]	Ictal-Interictal Continuum (IIC) categories for poor outcome	24–48 h after ICU admission	GOSe	3 months	Visual	Multivariate logistic regression	There was no association between the presence of moderate-to-severe IIC categories, including electrographical seizures, and functional and dichotomized outcomes.
	Sandsmark et al. (2016)[44]	Status epilepticus, seizures for poor outcome	Within 14 days after surgery	mRS	Discharge	Visual	Logistic regression and multivariate analysis	Status epilepticus and seizures were significantly associated with death or discharge to a skilled nursing facility. Epileptic features were not significantly associated with mRS at discharge.
Power spectral analysis: total power	Tolonen et al. (2018)[48]	59 qEEG features in groups: absolute power, relative power, asymmetry, variability, other (i.e., mean dominant frequency, SEF95, spectral entropy)	2–5 days	GOS	6–12 months	Quantitative	ROC	Total power (AUC: 0.82, $p = 0.01$) for the prediction of a good outcome.
Power spectral analysis: delta power	Beridze et al. (2010)[29]	Dominating background pattern: delta, frequency not specified.	5 days	Death, persistent vegetative state	1 month	Visual	Spearman's rank correlation and linear regression	Delta EEG pattern correlated with death and persistent vegetative state (rho: +0.57, $p < 0.05$).
	Lee et al. (2019)[39]	Delta activity for poor outcome	24–48 h after ICU admission	GOSe	3 months	Visual	Multivariate logistic regression	Presence of delta activity (OR: 2.82, $p < 0.008$).
	Frohlich et al. (2022)[33]	ABCD types (based on PSD) Presence of alpha/theta peaks in PSD	During ICU stay	GOSe	6 months	Quantitative	Multiple linear regression	No features correlated with outcome ($t = 0.92$, $p = 0.37$; $t = 0.65$, $p = 0.52$).
Power spectral analysis: theta power	Beridze et al. (2010)[29]	Dominating background pattern: theta, frequency not specified	5 days	Death, persistent vegetative state	1 month	Visual	Spearman's rank correlation and linear regression	No correlation with death and persistent vegetative or survival.
	Lee et al. (2019)[39]	Theta within 72 h for good outcome	24–48 h after ICU admission	GOSe	3 months	Visual	Multivariate logistic regression	Present PDR, N2 transients, theta, or alpha activity within 72 h were associated with a better GOSe score (sensitivity: 0.28, specificity: 0.96, ppv: 0.86).
	Frohlich et al. (2022)[33]	ABCD types (based on PSD) Presence of alpha/theta peaks in PSD	During ICU stay	GOSe	6 months	Quantitative	Multiple linear regression	No features correlated with outcome ($t = 0.92$, $p = 0.37$; $t = 0.65$, $p = 0.52$).
Power spectral analysis: theta power variability	Tolonen et al. (2018)[48]	59 qEEG features in groups: absolute power, relative power, asymmetry, variability, other (i.e., mean dominant frequency, SEF95, spectral entropy)	2–5 days	GOS	6–12 months	Quantitative	ROC	Relative fast theta power variability (AUC: 0.84, $p < 0.00$) for the prediction of a good outcome.

(*continued*)

Table 3. (Continued)

EEG feature	Author	Feature definition	Time to EEG	Outcome measures	Outcome timing	Analysis	Statistical methods	Main findings
Power spectral analysis: alpha power	Beridze et al. (2010)[29]	Dominating background pattern: alpha, frequency not specified	5 days	Death, persistent vegetative state	1 month	Visual	Spearman's rank correlation and linear regression	No correlation with death and persistent vegetative or survival.
	Cleri et al. (2023)[30]	PDR (alpha 8–13 Hz at posterior channels)	Within 30 days	Survival, command following, GOSe	In hospital, in hospital, discharge and 6 months	Visual	Linear regression	Present PDR on EEG correlated with survival in-hospital (OR: 3.32, $p = 0.014$; 84.5% present vs. 63.9% absent, $p = 0.007$), recovery to command following (76.5% present vs. 53.5% absent, $p = 0.004$), and higher GOSe score at hospital discharge (3.31 present vs. 3.77 absent, $p = 0.014$), but not at 6 months (OR: 2.75, $p = 0.326$).
	Foreman et al. (2022)[32]	PDR	13.6 ± 10.4 h after injury	RBANS	3 months	Visual	Univariate and multivariate logistic regression	Univariate: no significant differences. Multivariate: PDR not related to cognitive outcome.
	Lee et al. (2019)[39]	PDR+, alpha background within 72 h for good outcome	24–48 h after ICU admission	GOSe	3 months	Visual	Multivariate logistic regression	Present PDR, N2 transients, theta or alpha activity within 72 h were associated with a better GOSe score (sensitivity: 0.28, specificity: 0.96, ppv: 0.86).
	Frohlich et al. (2022)[33]	ABCD types (based on PSD) Presence of alpha/theta peaks in PSD	During ICU stay	GOSe	6 months	Quantitative	Multiple linear regression	No features correlated with outcome ($t = 0.92$, $p = 0.37$; $t = 0.65$, $p = 0.52$).
	Tolonen et al. (2018)[48]	59 qEEG features in groups: absolute power, relative power, asymmetry, variability, other (i.e., mean dominant frequency, SEF95, spectral entropy)	2–5 days	GOS	6–12 months	Quantitative	ROC	Median alpha power (AUC: 0.87, $p < 0.01$) for the prediction of a good outcome.
Power spectral analysis: alpha power variability	Hebb et al. (2007)[38]	PAV (mean PAV first 3 days) PAV (mean PAV first 3 days, threshold <0.2 for bad outcome)	At admission to the ICU	GOS	6 months	Visual and quantitative	Spearman's rank correlation and ROC	3-day PAV correlated with GOS (OR: 0.47, $p = 0.003$; 0.15 ± 0.015 vs. 0.20 ± 0.007, $p = 0.009$). Using a cut-off of PAV <0.20, poor outcome was classified with a sensitivity of 0.87.
	Vespa et al. (2002)[50]	PAV (PAV <0.1 for bad outcome) PAV (PAV >0.15 for good outcome)	9.6 ± 5.4 h after ICU admission	GOS	Discharge	Visual and quantitative	Linear regression	PAV <0.1 predicted poor outcome on GOS scale (sensitivity: 0.93, specificity: 0.63, ppv: 0.86), and PAV >0.15 predicted good outcome on GOS scale (sensitivity: 0.63, specificity: 0.62, ppv: 0.63).
	O'Donnell et al. (2021)[41]	RAV	3–24 days	GOSe	3 and 6 months	Quantitative	Multivariate linear regression	Relative alpha power associated with GOSe at 3 months after injury (adjusted R^2: 0.50, $p = 0.039$), which increased the model performance in addition to GCS score, but not for GOSe at 6 months.

(*continued*)

Table 3. (Continued)

EEG feature	Author	Feature definition	Time to EEG	Outcome measures	Outcome timing	Analysis	Statistical methods	Main findings
	Tolonen et al. (2018)[48]	59 qEEG features in groups: absolute power, relative power, asymmetry, variability, other (i.e., mean dominant frequency, SEF95, spectral entropy)	2–5 days	GOS	6–12 months	Quantitative	ROC	Relative alpha power variability (AUC: 0.82, $p < 0.01$) for the prediction of a good outcome.
	Wang et al. (2022)[51]	RAV	Within 14 days	GOS	3 months	Quantitative	ROC, logistic regression	RAV and EEG reactivity ([Table 4]) predictive of poor outcome (AUC: 0.84, sensitivity: 0.83, specificity: 0.84, ppv: 0.80, accuracy: 0.84; OR: 19.48, $p < 0.001$).
Power spectral analysis: beta power	Beridze et al. (2010)[29]	Dominating background pattern: beta, frequency not specified	5 days	Death, persistent vegetative state	1 month	Visual	Spearman's rank correlation and linear regression	No correlation with death and persistent vegetative or survival.
	Frohlich et al. (2022)[33]	ABCD types (based on PSD)	During ICU stay	GOSe	6 months	Quantitative	Multiple linear regression	No features correlated with outcome ($t = 0.92$, $p = 0.37$; $t = 0.65$, $p = 0.52$).
	Tolonen et al. (2018)[48]	59 qEEG features in groups: absolute power, relative power, asymmetry, variability, other (i.e., mean dominant frequency, SEF95, spectral entropy)	2–5 days	GOS	6–12 months	Quantitative	ROC	Slow beta power (AUC: 0.84, $p < 0.00$) for the prediction of a good outcome.
Sleep features	Foreman et al. (2022)[32]	Sleep transients	13.6 ± 10.4 h after injury	RBANS	3 months	Visual	Univariate and multivariate logistic regression	Univariate: no significant differences. Multivariate: sleep transients not related to cognitive outcome.
	Lee et al. (2019)[39]	N2 transients, for good outcome Absence of N2 sleep transients for poor outcome	24–48 h after ICU admission	GOSe	3 months	Visual	Multivariate logistic regression	Present PDR, N2 transients, theta or alpha activity within 72 h were associated with a better GOSe score (sensitivity: 0.28, specificity: 0.96, ppv: 0.86). Absence of N2 transient or PDR, presence of delta activity, and a discontinuous background were associated with poor outcome (OR: 3.69, $p = 0.001$; OR: 3.38, $p = 0.013$; OR: 2.82, $p < 0.008$, OR: 5.33; $p < 0.001$).
	Sandsmark et al. (2016)[44]	Vertex waves, sleep spindles, K-complexes for good outcome	Within 14 days after surgery	mRS	Discharge	Visual	Logistic regression and multivariate analysis	Present sleep features were associated with mRS >4 (OR: 5.98 ± 0.21).
	Valente et al. (2002)[49]	Sleep pattern organization complexity (low voltage delta, absence of sleep elements in the presence of recurrent abnormal spontaneous arousal activity, presence of K-complexes and/or spindles, well-structured NREM or REM	7–14 days	GOS	12–34 months	Visual	Multiple regression analysis	The presence of well-structured sleep patterns (NREM or REM) on EEG recordings was associated with a good outcome on the GOS scale (sensitivity: 1.00, specificity: 0.83, ppv: 0.86, OR: 10.78).

(*continued*)

Table 3. (Continued)

EEG feature	*Author*	*Feature definition*	*Time to EEG*	*Outcome measures*	*Outcome timing*	*Analysis*	*Statistical methods*	*Main findings*
EEG continuity	Frohlich et al. (2021)[34]	SIBSR (suppression defined as <1 μV)	During ICU stay	GOSe	6 months	Quantitative	Multi-model interference	Maximum SIBSR was associated with GOSe at 6 months (OR: 3.38E + 10, $p = 0.022$).
	Theilen et al. (2000)[47]	ESR >20% for poor outcome	<12 h	GOS and RDRS	6 months	Quantitative	Pearson's correlation, logistic regression	ESR >20% was predictive of poor outcome (sensitivity: 0.91, specificity: 0.91, ppv: 0.86) ESR was significantly different between good and bad outcome at 6 months (10.0% vs. 51.7%, $p < 0.001$).
	You et al. (2018)[52]	aEEG background pattern (quantitatively dichotomized in favorable and intermediate + unfavorable)	7 days	CPC	6 months	Quantitative	ROC	A favorable aEEG pattern was predictive of good outcome (ppv: 0.83, npv: 0.94). All patients with unfavorable aEEG did not survive (ppv: 1.00, npv: 0.75).
	Zhang et al. (2022)[53]	aEEG background pattern (favorable and intermediate) for good outcome	Within 1 week	GOSe	12 months	Quantitative	Cox hazards regression	A continuous and discontinuous aEEG were related to a good GOSe score ($t = 0.35$, $p < 0.001$).
Dichotomous rating scale	Rae-Grant et al. (1996)[43]	Dichotomous EEG rating scale (0–21) based on absence/presence of: background activity, symmetry, reactivity, variability, and additional parameters (burst suppression, epileptiform activity)	5–7 days after injury	GOSe and DRS	6 months	Visual	Chi-squared analysis and likelihood ratio	EEG score was independently associated with GOSe (rho: 0.54, $p = 0.0001$).
EEG complexity and connectivity	Tao et al. (2023)[46]	PLI (F3, P4)	Within 4 weeks	GOS	60 days	Quantitative	*t*-test	PLI was higher for a good outcome than a bad outcome (0.88 vs. 0.71, $p = 0.048$). Other features not significantly different.

Studied EEG features without reported outcomes in manuscripts were excluded from this table.

IIC, Icta-Interictal Continuum; RBANS, The Repeatable Battery for the Assessment of Neuropsychological Status; GOS(e), Glasgow Outcome Scale (extended); mRS, modified Ranking Scale; ROC, receiver operating characteristics; AUC, area under the curve; PSD, power spectral density; ppv, positive predictive value; PDR, posterior dominant rhythm; OR, odds ratio; PAV, percent alpha variability; RAV, relative alpha variability; GCS, Glasgow Coma Scale; N2, stage 2 of non-rapid eye movement (NREM) sleep characterized by sleep spindles and K-complexes; NREM, non-Rapid Eye Movement; REM, Rapid Eye Movement; SIBSR, Sedation Induced Burst Suppression Ratio; ESR, EEG silence ratio; RDRS, Rapid Disability Rating Scale; CPC, Cerebral Performance Category; DRS, Disability Rating Scale; PLI, phase lag index.

Table 4. Summary of All Studies Using Electroencephalography (EEG) Reactivity Analysis

Author	*Outcome measures*	*Timing*	*Time to EEG*	*EEG features and type of stimulation*	*Statistical methods*	*Main findings*
Amantini et al. (2005)[27]	GOS	>1 year	48–72 h and 1 week	Shouting patient name, pain stimulus, passively opening/closing eyes; present: reactivity in amplitude and/or frequency	Logistic regression	Present EEG reactivity was associated with a good neurological outcome (sensitivity: 0.79, specificity: 0.55, ppv: 0.64, npv: 0.75). In a multivariate analysis, there was no additional prognostic value of EEG reactivity compared with somatosensory evoked potentials.
Edlow et al. (2017)[31]	GOSe	6 months	2–23 days	EEG reactivity after language, music, and motor-imagery stimuli	Two-sided Mann–Whitney tests	GOSe scores 6 months after TBI were not associated with EEG responses to language (U: 18.5, $p = 0.37$), music (U: 23.5, $p = 0.63$), or motor imagery (U: 13.0, $p = 0.81$).
Gutling et al. (1995)[35]	GOS	18 months	48–72 h	EEG reactivity (loud click and pain [nasal septum])	Discriminative analysis	Present EEG reactivity predicted a good outcome (sensitivity: 0.92, specificity: 0.93, ppv: 0.97, npv: 0.81, accuracy: 0.92). Adding somatosensory evoked potentials resulted in 98% accuracy.
Portnova et al. (2020)[42]	GOSe	N/A	4 days to 2 months and 25 days	PSD theta (4–6 Hz), alpha (11–13 Hz), and beta (17–20 Hz) after tactile stimulation	Spearman's correlation	A decrease in theta power after tactile stimulation was associated with a better outcome (rho: 0.28, $p = 0.02$).
Sokoliuk et al. (2021)[45]	GOSe	3 and 6 months	3–19 days	EEG reactivity to words, phrases, and sentences by the inter-trial phase coherence	Spearman correlation	Higher level comprehension (e.g., reaction to phrases and sentences) was associated with GOSe score at 3 and 6 months after TBI (rho: 0.64, $p = 0.006$; rho: 0.75, $p = 0.001$), whereas lower level comprehension (e.g., EEG reactivity to words) did not correlate with outcome.
Wang et al. (2022)[51]	GOS	3 months	Within 14 days	Nail bed pressure and clapping, calling out the patient's name. Present: any change visible with the naked eye	ROC, logistic regression	Visually observed reactivity on EEG after several stimuli was predictive of poor outcome based on GOS at 3 months after TBI (AUC: 0.73, sensitivity: 0.75, specificity: 0.72, ppv: 0.67, npv: 0.79, accuracy: 0.73).
Zhang et al. (2022)[53]	GOSe	12 months	Within 1 week	Painful (pinching the nipple or limbs), visual (opening eyes under light), and auditory (patient's name); reactivity in amplitude and/or frequency (present/absent/SIRPIDS)	multivariate regression models	SIRPIDS were associated with a good neurological outcome at 12 months after TBI, compared with no EEG reactivity (HR: 1.76, $p = 0.008$).

GOS(e), Glasgow Outcome Scale (extended); ppv, positive predictive value; npv, negative predictive value; TBI, traumatic brain injury; PSD, power spectral density; AUC, area under the curve; SIRPIDS, Stimulus Induced Rhythmic Periodic or Ictal Discharges.

Table 5. Summary of All Studies Using Prognostic Machine Learning Models Based on Electroencephalography (EEG) Features

Author	*Outcome measures*	*Timing*	*Time to EEG*	*EEG features*	*Model type*	*Model development and validation*	*Top EEG features*	*Main findings*
Alkhachroum et al. (2024)[28]	GOSe—prediction of favorable outcome	Discharge	6 days (IQR: 1–12 days)	44 qEEG features (based on PSD, PE, wSMI, Kolmogorov complexity)	SVM	Support vector machine—10-fold cross-validation—no external validation	Kolmogorov complexity, normalized beta power, beta variability, delta power	Patients who recovered had higher Kolmogorov complexity, higher normalized beta power and variability, and lower delta power. The model performed better than a model based on clinical parameters (AUC: 0.69)
Müller et al. (2020)[40]	CPC—prediction of favorable outcome	6 months	71 h (IQR: 43–112 h)	Continuity, amplitude, frequency, reactivity, symmetry, N2 sleep transients, sporadic epileptiform discharges, rhythmic or periodic patterns (visually assessed)	RF classifier, fivefold CV	Random forest classifier, -fivefold cross-validation—no external validation	Reactivity, amplitude, continuity	Using visual EEG features, the RF model could predict favorable outcome after TBI (AUC: 0.79, sensitivity: 0.85, specificity: 0.61, ppv: 0.57, npv: 0.87, accuracy: 0.703).
Tewarie et al. (2023)[37]	GOSe—prediction of unfavorable outcome	12 months	At admission to the ICU	16 qEEG features (BSI, alpha variability, relative alpha power, absolute beta power, aperiodic exponent, coherence, absolute delta power, Shannon entropy, total power, regularity, aperiodic offset, relative delta power, absolute theta, absolute alpha, Hurst ampl. delta, relative beta)	RF classifier, fivefold CV	Random forest classifier—fivefold cross-validation—no external validation	BSI, alpha variability, relative alpha power, absolute beta power, aperiodic exponent	The best model included qEEG features at 72 h after injury (AUC: 0.82, sensitivity: 0.74, specificity: 0.83).
Haveman et al. (2019)[36]—prior to Tewarie et al. (2023)[37]	GOSe—prediction of unfavorable outcome	12 months	As soon as possible	qEEG features (spectral parameters, variability, amplitude, coherence, entropy, regularity, SEF90)	RF classifier, LOO CV	Random forest classifier—leave-one-out cross-validation—naïve validation cohort	Minimal amplitude, SEF90, relative alpha, beta variability, and theta variability	The developed RF model was able to predict poor outcome after TBI (Development AUC: 0.88, sensitivity: 0.92, specificity: 0.77; Validation AUC: 0.75, sensitivity: 0.83, specificity: 0.88).

Reported results are based on the validation method as described in "model development and validation."

GOS(e), Glasgow Outcome Scale (extended); qEEG, quantitative electroencephalography; PSD, power spectral density; PE, permutation entropy; wSMI, weighted symbolic mutual information; AUC, area under the curve; ppv, positive predictive value; npv, negative predictive value; BSI, brain symmetry index; SEF90, spectral edge frequency at 90%.

Table 6. Summary of All Studies Comparing the Prognostic Value of Electroencephalography (EEG) Features to Clinical Variables or a Combination of EEG Features and Clinical Variables

Author	*Outcome measures*	*Time to EEG*	*Timing*	*EEG features*	*Clinical variables*	*EEG/clinical/EEG + clinical*	*Comparison*
Alkhachroum et al. (2024)[28]	GOSe—prediction of favorable outcome	6 days (IQR: 1–12 days)	Discharge	44 qEEG features (based on PSD, PE, wSMI, Kolmogorov complexity)	Age, sex, race, ethnicity, mechanism of injury, type of injury, GCS on admission, pupil reactivity, surgical treatments, seizures, and sedative levels	Clinical: AUC: 0.66, 95% CI: 0.66–0.67 EEG + clinical: AUC: 0.69, 95% CI: 0.68–0.70	EEG + clinical vs. clinical: $p < 0.001$ EEG + clinical vs. EEG : $p > 0.05$ EEG vs. clinical: $p < 0.001$
Tewarie et al. (2023)[37]	GOSe—prediction of unfavorable outcome	At admission to the ICU	12 months	16 qEEG features (BSI, alpha variability, relative alpha power, absolute beta power, aperiodic exponent, coherence, absolute delta power, Shannon entropy, total power, regularity, aperiodic offset, relative delta power, absolute theta, absolute alpha, Hurst ampl. delta, relative beta)	IMPACT variables (age, glucose, hemoglobin, CT classification, pupils, tSAH on CT, hypotension, epidural mass on CT, motor score, hypoxia)	EEG: AUC: 0.82, 95% CI: 0.69–0.92 Clinical: AUC: 0.81, 95% CI: 0.62–0.93 EEG + clinical: AUC: 0.89, 95% CI: 0.72–0.99	EEG + clinical vs. clinical: $p < 0.001$
Haveman et al. (2019)[36]—prior to Tewarie et al. (2023)[37]	GOSe—prediction of unfavorable outcome	As soon as possible	12 months	qEEG features (spectral parameters, variability, amplitude, coherence, entropy, regularity, SEF90)	IMPACT variables (age, glucose, hemoglobin, CT classification, pupils, tSAH on CT, hypotension, epidural mass on CT, motor score, hypoxia)	EEG: AUC: 0.88, 95% CI: 0.83–0.91 Clinical: AUC: 0.74, 95% CI: 0.66–0.79 EEG + clinical: AUC: 0.94, 95% CI: 0.89–0.96	N/A
O'Donnel et al. (2021)[41]	GOSe	3–24 days	3 and 6 months	Relative alpha power	GCS at time of EEG	EEG: N/A Clinical: adjusted R^2: 0.150 at 3 months, 0.305 at 6 months EEG + clinical: adjusted R^2: 0.502 at 3 months, N/A at 6 months	N/A
Vespa et al. (2002)[50]	GOS	9.6 ± 5.4 h after ICU admission	Discharge	Percent alpha variability (mean of first 3 days)	Pupillary response to light, CT scan lesion score, GCS score, age, early hypotension and/or hypoxemia	EEG: AUC: 0.72 Clinical: AUC: 0.76 EEG + clinical: AUC: 0.83	N/A

GOS(e), Glasgow Outcome Scale (extended); qEEG, quantitative electroencephalography; PSD, power spectral density; PE, permutation entropy; wSMI, weighted symbolic mutual information; GCS, Glasgow Coma Scale; AUC, area under the curve; BSI, brain symmetry index; tSAH, traumatic subarachnoid hemorrhage; SEF90, spectral edge frequency at 90%.

showed that seizures and abnormal periodic or rhythmic patterns were linked with worse cognition,[32] increased mortality, or discharge to skilled nursing facilities.[44] However, other studies found no significant differences between seizure and non-seizure groups based on dichotomized outcome measures like the GOSe[39] or mRS.[31] Furthermore, one study reported that there was no association between epileptiform activity and neurological outcome in a study cohort including TBI, hemorrhagic stroke, ischemic stroke, and post-cardiac arrest, but did not report on this for the TBI subgroup only.[46] Finally, two studies included EEG features describing epileptiform activity in their analyses but did not report individual results of the association between these features and outcome.[40,43]

Power spectral analysis, also known as frequency domain analysis, is a method to quantify the distribution of frequencies that are present in the EEG signal. This type of analysis was performed in several studies and was in most cases defined as frequency bands: delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (>12 Hz). A strong association between EEG frequencies and neurological outcome was found for the alpha frequency band. In four studies, the absence/presence of a (posterior) alpha rhythm was associated with an unfavorable/favorable neurological outcome, respectively,[30,39,41,48] although one study could not reproduce this finding.[33] Additionally, a higher variability of this alpha rhythm was associated with a better neurological outcome in four studies.[38,48,50,51] Predominant delta activity was associated with unfavorable neurological outcome in two studies.[29,39] A final frequency feature associated with favorable outcome was the variability of the power in the theta frequency band.[48]

The continuity of the EEG was frequently studied as well.[34,47,52,53] Highly significant relationships between the EEG silence ratio (ESR), defined as periods of >240 ms during which the EEG voltage does not exceed 5 μV, and an unfavorable neurological outcome were found.[47] Additionally, >10% suppression within the first 72 h of EEG recording was associated with a poor neurological outcome.[39] Moreover, two studies analyzed EEG continuity using amplitude-integrated EEG (aEEG).[52,53]

In both studies, aEEG patterns were first visually categorized into five distinct groups and then grouped into two broader categories for analysis: (1) continuous or discontinuous patterns, defined as aEEG with alternating amplitudes consistently above 5 μV; and (2) suppressed patterns, which included burst suppression (alternating amplitudes with periods <5 μV), low-voltage, and isoelectric backgrounds. Both studies found that patients with continuous or discontinuous EEG patterns (category 1) had more favorable outcomes after TBI compared with those with suppressed patterns (category 2).[52,53]

Four studies on sleep EEG were performed. These studies showed that a well-structured sleep pattern and the presence of sleep features, especially sleep spindles, were independently associated with a favorable outcome after TBI.[32,39,44,49]

In addition to features based on frequency, continuity, and sleep, features from more complex domains (complexity and connectivity domains) were investigated in a limited number of studies. One study showed a relationship between a lower spectral entropy (a less complex EEG signal) and unfavorable neurological outcome.[48] A second study showed a higher phase lag index (connectivity) between the left frontal and right parietal electrodes in patients with a favorable neurological outcome.[46] However, a third study added features from these domains to their analyses but found no association with neurological outcome after TBI.[41]

EEG reactivity

EEG reactivity refers to changes in EEG background activity in response to an external stimulation, either observed through visual assessment of the EEG or power spectral analyses. Seven studies evaluated the use of EEG reactivity in TBI, using various types of external stimulation.[27,31,35,40,42,45,51,53] Variations included shouting the patient's name, various words and/or sentences, clapping, and pain stimuli (Table 4). Six out of seven studies showed that EEG reactivity in response to auditory, tactile, and/or pain stimuli was associated with favorable neurological outcome after TBI.

Prognostic machine learning models

Three different machine learning models were developed (Table 5). One of these was able to predict an unfavorable outcome after TBI with an area under the curve (AUC) of 0.82 for EEG alone.[36,37] The most important EEG features of the model included the brain symmetry index, alpha variability, and relative alpha power. A second model predicted a favorable outcome with an AUC of 0.72. The most important features of this model were rhythmic or periodic patterns in the EEG, followed by background symmetry, EEG reactivity, and continuity.[40] The last model, based on resting-state EEG, predicted recovery of consciousness with an AUC of 0.69. A more complex EEG signal with varying frequencies and amplitudes was associated with a higher level of consciousness.

Comparison with clinical parameters

The added value of EEG compared with clinical parameters was evaluated in five studies (Table 6). All studies consistently showed a better performance or added value of EEG features compared with clinical parameters like age, sex, GCS on admission, and other variables from the CRASH and IMPACT models. The average

improvement in model performance of clinical variables versus EEG and clinical parameters was 9.5% (standard deviation 7.3%) on the AUC.[28,36,37,50] In the remaining studies, the prognostic value of EEG features was also examined in relation to patient outcomes, but no direct comparisons were made with the prognostic performance of established clinical parameters. This makes it impossible to establish the independent or additional prognostic value of these EEG features beyond currently used clinical predictors.

Discussion

In this systematic review, we explored the prognostic value of EEG in critically ill patients with TBI based on 27 studies. We identified four groups of prognostic EEG features that stood out: alpha power and variability, EEG reactivity, EEG continuity, and EEG features related to sleep. Furthermore, five studies compared the prognostic value of EEG with clinical parameters, demonstrating that the addition of EEG to clinical parameters yielded better results.[28,36,37,40,41,50]

Several studies reported an association between (relative) alpha power and outcome, where a more prominent alpha rhythm was associated with a better outcome. One aspect of the alpha rhythm often studied is its variability over a longer period.[30,39,41,48] Low alpha variability has previously been associated with unfavorable outcome after coma,[54] although consensus is lacking.[55] All studies included in this review demonstrated a significant correlation between lower alpha variability values and unfavorable outcomes after TBI.[38,48,50,51] One hypothesis on the origin of alpha oscillations is that they are generated by the synchronous firing of thalamic neurons. In this theory, alpha activity and variability are a sign of intact thalamo-cortical loops essential in consciousness,[56,57] meaning that patients with higher variability in alpha activity are more likely to recover. This was indeed shown in all included studies investigating this EEG feature.

The presence of EEG reactivity had a high sensitivity but rather low specificity for the prediction of a favorable neurological outcome. EEG reactivity is suggested to reflect the intactness of cortical and subcortical structures, which are often damaged as a result of TBI.[58,59] In the included studies, patients with a disordered consciousness and present EEG reactivity often regained consciousness, which is also reported for other etiologies.[60] To be able to reproduce these results, standardization of the type of stimulus and the interpretation method is required.

The degree of continuity of the EEG was an important prognostic factor. A less continuous EEG pattern is generally associated with less favorable neurological outcomes.[47,51,52] However, the introduction of sedatives that induce a discontinuous burst-suppression pattern may bias this assessment, complicating the interpretation of the patient's neurological status. Careful consideration of sedative use is therefore essential when assessing this EEG feature.

Lastly, the presence of sleep features (sleep spindles, K-complexes, and slow-wave sleep) on the EEG was associated with a good neurological outcome.[32,39,44,49] However, their absence was not consistently associated with a poor outcome.

In current clinical TBI management, the EEG is often used for the detection and/or exclusion of epilepsy. However, epileptiform activity on the EEG itself was often not studied as a prognostic feature. Among the seven studies that explored the relationship between epileptiform activity and outcome, only two showed that the presence of epileptiform activity on the EEG was predictive of poor neurological outcomes.[32,44] Interpretation of these results is complicated by confounding factors such as the treatment of potential epileptiform activity observed on EEG. The absence of physician blinding in these studies often led to seizure treatment, thereby hindering robust evaluation of its prognostic value. An additional limitation to establishing electrographic seizures as a prognostic feature for outcome is that most studies did not clearly distinguish between early post-traumatic seizures (within 7 days post-injury) and late post-traumatic seizures (after 7 days). Early clinical seizures are associated with a poor outcome,[61] even though treatment does not seem to affect the clinical course.[62] However, the prognostic value of electrographic seizures and epileptiform activity on the EEG without clinical correlate remains uncertain. Further research is necessary to determine whether seizure monitoring in patients with TBI leads to measurable clinical benefits, as the prognostic value of this approach remains speculative even in more thoroughly studied populations like postanoxic encephalopathy.[63]

The timing of EEG recordings varied widely. Pathophysiological changes after TBI, possibly indicating the severity of injury and outcome, occur over varying time periods.[64] Therefore, changes in the EEG may occur over time, and trends of feature values reflecting these changes may be of additional value in outcome prediction. Although in postanoxic encephalopathy early EEG (within 24 h after cardiac arrest) is known to be the most sensitive, this might not be the case for TBI. Indeed, several included studies showed that EEG at 72 h after TBI had the highest prognostic value.[36,37,39]

Review strengths and limitations

This study has several strengths. We used standardized frameworks like the PRISMA statement, the CHARMS-PF checklist, a mobile app (Rayyan), and a quality and risk of bias analysis, which allowed for structured and reproducible

screening and accurate and contextual interpretation of the results. Furthermore, we were the first to systematically review all existing literature on EEG prognosis after moderate-to-severe TBI and compare the prognostic value of EEG to that of clinical parameters in the CRASH and IMPACT models. Previous reviews have typically focused on specific aspects, such as resting-state EEG, or focused on patients ranging from mild to severe TBI, complicating the clinical applicability.[16,17] We have demonstrated that other aspects such as EEG reactivity also hold significant prognostic value and that EEG has added value compared with clinical parameters alone.

The lack of a quantitative analysis of the results, that is, a meta-analysis, could be considered a limitation. However, it is recommended to only perform this type of analysis when multiple studies are available on the same prognostic factor with the same outcome measure, or when at least 5 external validation studies on a prognostic model are performed.[20] Neither was the case in this review, and due to unreported results in several included studies, a meta-analysis could be strongly influenced by publication bias.

The risk of bias analysis revealed that all studies had at least moderate bias, primarily due to a lack of correction for confounding factors such as age, blood pressure, consciousness level, and sedative use during EEG recordings, which are all associated with TBI outcomes.[65–67] Additionally, self-fulfilling prophecy bias often influences prognostic studies, particularly in ICU settings where physicians may be influenced by EEG results when making life-sustaining treatment decisions.[68] Furthermore, many studies lacked statistical validation, focusing on correlations between EEG features and outcomes without providing key metrics like sensitivity, specificity, or AUC, limiting insight into the clinical relevance of identified prognostic EEG features.[69] Lastly, none of the included studies reported a sample size calculation, making it difficult to assess whether nonsignificant findings were due to a true lack of association or insufficient statistical power. As a result, studies reporting negative results may have lacked the ability to detect meaningful differences in outcome based on EEG features due to sample size limitations.

Clinical implications and future research

This review identified several prognostic EEG features that could have added value to the current prognostic CRASH and IMPACT models. Future research should focus on the combination of EEG features, clinical parameters, and other neuro-monitoring modalities, possibly using artificial intelligence, to provide optimal prognostication for critically ill patients with TBI. Such models would preferably be developed in multicenter studies to ensure a large enough sample size for reliable predictions and the opportunity for validation of the results. Additionally, the identified EEG features, and especially their course over time, could possibly be used to identify patients that would benefit from certain diagnostic work-up or treatments after TBI.

To improve the accuracy of TBI outcome predictions, standardization of definitions and outcome measures is essential.[7] Varying cutoffs affect the prognostic value of EEG. Adopting consistent measures and developing models predicting specific scores instead of dichotomized ones improves comparability and accounts for cultural and subjective variations.[70] Additionally, the use of standardized EEG terminology such as proposed by the ACNS and the adoption of Common Data Elements for EEG in TBI research are strongly recommended to facilitate comparability across studies.[26,71]

EEG recordings of critically ill patients with TBI could be used for other purposes besides traditional seizure detection and potential prognostication alone. The reviewed studies showed correlations with GCS,[29,33,41] size of brain injury,[29] mesocircuit recovery,[33] the presence of multiple subcortical lesions,[38] and the general clinical picture of patients with TBI.[41] Additionally, it was suggested that the EEG could be used to monitor increased intracranial pressure, which is a common complication after TBI.[72] Furthermore, EEG could play a vital role in clinical management of patients with TBI by detection of secondary brain injury, for example, due to hemorrhage, vasospasms, and ischemia, allowing for timely interventions.[13] Future studies could thus expand their focus to the general application of EEG in critically ill patients with TBI.

Conclusion

In this systematic review, we assessed the prognostic value of several EEG features in critically ill patients with TBI that have not previously been reported in a systematic manner. We found that spectral alpha power (variability), a continuous EEG, present EEG reactivity, and several sleep features indicated better prognosis. The combination of EEG features with clinical parameters demonstrated improved predictive performance compared with models using standard clinical parameters alone. However, implementation is hindered by high heterogeneity in feature and outcome definition, the explorative nature of most of the included studies, and the high risk of bias in most studies. Standardization of EEG recording and analysis methods, along with larger multicenter studies, could facilitate better integration of EEG into multimodality neuro-prognostication. These findings argue for the potential added value both in prognosis, diagnosis, and management of TBI and substantiate the basis for further clinical EEG studies.

Transparency, Rigor, and Reproducibility Statement

This systematic review was preregistered with the international prospective register of systematic reviews (PROSPERO CRD42023402396, https://www.crd.york.ac.uk/prospero/). The search strategy was designed in collaboration with a Medical Information specialist from the Erasmus Medical Center, Rotterdam, the Netherlands. Screening of titles and abstracts was performed using an online collaborative screening tool called Rayyan. Two authors were blinded to the assessment of the other author until completion of the screening process based on title and abstract, and disagreements were resolved through discussion. To ensure reproducibility, this systematic review was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Methods Prognosis. Data were extracted using the Checklist for Critical Appraisal and Data Extraction for Systematic Review of Prognostic Studies (CHARMS-PF). The quality of all included studies was assessed using the QUIPS and PROBAST tools. Additional data from this systematic review will be made available upon request from qualified researchers.

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Authors' Contributions

M.V.: Conceptualization, methodology, validation, formal analysis, investigation, writing—original draft. R.v.d.B.: Conceptualization, methodology, investigation, writing—review and editing. M.R.: Conceptualization, methodology, writing—review and editing. M.v.d.J.: Conceptualization, methodology, writing—review and editing. All authors approved the final version of this article.

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Supplementary Material

Supplementary Data S1
Supplementary Data S2
Supplementary Data S3
Supplementary Data S4

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