



Focal and Generalized Seizure Characteristics in Uremic and Hepatic Metabolic Encephalopathy : A Systematic Review of Randomized Controlled Trials and Primary Studies

¹David William Brian Iskandar

¹ Faculty of Medicine, Pelita Harapan University, Indonesia

Corresponding Email : davidwbimd@gmail.com

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ABSTRACT

Introduction: Metabolic encephalopathy arising from uremic and hepatic dysfunction represents a significant neurological emergency, manifesting across a spectrum from subtle cognitive impairment to overt convulsive status epilepticus. Seizures in this context are mechanistically distinct from idiopathic epilepsy, driven by accumulation of uremic toxins, hyperammonemia, astrocytic edema, disturbances in neurotransmission, and blood-brain barrier dysfunction. Despite the clinical importance of recognizing focal versus generalized seizure characteristics in these two paradigmatic forms of metabolic encephalopathy, a comprehensive synthesis of primary study evidence remains lacking. This systematic review aimed to characterize and compare focal and generalized seizure manifestations in uremic encephalopathy (UE) and

hepatic encephalopathy (HE), evaluate EEG patterns, neuroimaging correlates, and clinical outcomes.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible studies included randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and observational studies reporting seizure characteristics in human subjects with confirmed uremic or hepatic metabolic encephalopathy. Risk of bias was assessed using the Newcastle-Ottawa Scale and Joanna Briggs Institute tools.

Results: Fifteen primary studies (cumulative $n > 1,900,000$ patients) were included. Seizures occurred in approximately 10% of patients with end-stage kidney disease. Generalized tonic-clonic seizures predominate in both UE and HE, while focal seizures are documented particularly in HE secondary to portosystemic shunting. EEG findings include triphasic waves (OR=8.10 for liver insufficiency), generalized background slowing, and periodic lateralized epileptiform discharges. Cirrhosis was independently associated with status epilepticus (HR=1.9, 95% CI=1.3–2.8) but not isolated seizures. Nonconvulsive status epilepticus carries mortality rates of 37–52% in critically ill metabolic encephalopathy patients. Lentiform fork sign on MRI characterizes uremic encephalopathy seizures with basal ganglia involvement. EEG parameters inversely correlate with ammonia levels, MELD score, and cognitive performance scores in hepatic encephalopathy.

Discussion: The pathophysiology of seizures in UE involves NKCC1-mediated depolarization of EGABA secondary to astrocyte potassium buffering failure, NMDA receptor activation by acute ammonia, and retention of multiple uremic toxins. In HE, ammonia-induced astrocytic swelling, GABAergic dysregulation, and peripheral neuroinflammation collectively lower the seizure threshold. Focal seizures in HE are distinctively associated with portosystemic shunting (TIPS), while generalized seizures dominate both conditions. Treatment requires addressing the underlying metabolic derangement alongside judicious antiseizure medication selection, given altered pharmacokinetics in renal and hepatic dysfunction.

Conclusion: Seizures in uremic and hepatic metabolic encephalopathy are predominantly generalized tonic-clonic, though focal manifestations occur particularly with portosystemic shunting. EEG—especially triphasic waves—and MRI provide complementary diagnostic information. Mortality is significantly associated with seizure occurrence and nonconvulsive status epilepticus in both conditions. Standardized prospective studies with larger cohorts are urgently needed to establish evidence-based antiseizure medication treatment guidelines specific to these populations.

Keywords: *uremic encephalopathy; hepatic encephalopathy; focal seizure; generalized seizure; triphasic waves; nonconvulsive status epilepticus*

INTRODUCTION

Background and Rationale

Metabolic encephalopathy is a broad clinical syndrome encompassing neurological dysfunction attributable to systemic metabolic derangements rather than primary structural brain pathology. Among the most clinically significant etiologies are uremic encephalopathy (UE), arising from the accumulation of neurotoxic uremic solutes in the setting of acute kidney injury (AKI) or chronic kidney disease (CKD), and hepatic encephalopathy (HE), resulting from hepatic insufficiency and/or portosystemic shunting with subsequent brain exposure to ammonia, inflammatory cytokines, and manganese, among other toxins.^{1,2}

Seizures represent a severe neurological manifestation of both UE and HE, and their recognition carries critical prognostic and therapeutic implications. In UE, the incidence of uremic seizures is estimated at approximately 10% in patients with kidney failure, and these seizures may be convulsive or nonconvulsive, focal or generalized.³ In HE, overt seizures are less commonly described but status epilepticus has been identified as a significant complication of cirrhosis, with a hazard ratio of 1.9 compared to controls.⁸

Despite the mechanistic distinctiveness and clinical importance of seizures in these two conditions, the literature is heterogeneous, fragmented, and lacks a dedicated systematic synthesis. Clinicians managing critically ill patients with metabolic encephalopathy frequently encounter diagnostic uncertainty—particularly distinguishing nonconvulsive seizures from encephalopathy itself—and face challenges in ASM selection due to altered pharmacokinetics in renal and hepatic insufficiency.^{3,7}

Research Gap and Novelty

To the best of the authors' knowledge, no prior systematic review has simultaneously compared focal versus generalized seizure characteristics, EEG findings, neuroimaging correlates, treatment responses, and mortality outcomes in uremic and hepatic metabolic encephalopathy using exclusively primary study evidence. This review provides the first such unified evidence synthesis,

drawing upon validated, peer-reviewed primary studies and addressing both conditions in a single integrated framework.

Objectives

The primary objective of this systematic review is to characterize and compare focal and generalized seizure manifestations in UE and HE, with specific attention to:

- (1) Seizure prevalence, semiology, and type (focal vs. generalized) in UE and HE;
- (2) Electroencephalographic (EEG) patterns associated with seizures in each condition;
- (3) Neuroimaging correlates of seizure activity;
- (4) Pathophysiological mechanisms underlying seizure generation in UE and HE;
- (5) Pharmacokinetic considerations and treatment outcomes with antiseizure medications (ASMs);
- (6) Mortality and functional outcomes associated with seizures in both conditions.

Hypotheses

We hypothesize that: (a) Generalized tonic-clonic seizures predominate in both UE and HE, while focal seizures are more characteristic of portosystemic shunting-related HE; (b) EEG triphasic waves are more specifically associated with hepatic etiology; (c) NCSE carries worse prognosis than convulsive seizures in both conditions; and (d) Both conditions share the final common pathway of GABAergic dysregulation and NMDA receptor activation secondary to ammonia and uremic toxin accumulation.

Significance and Clinical Impact

This systematic review has direct clinical impact for neurologists, intensivists, nephrologists, and hepatologists managing patients with metabolic encephalopathy. Accurate characterization of seizure types, EEG signatures, and treatment outcomes will inform diagnostic algorithms and therapeutic decision-making in this high-mortality population. Furthermore, understanding the molecular mechanisms underlying seizure generation will identify potential novel pharmacological targets.^{9,10,12}

METHODS

Study Design

This is a systematic review of primary studies conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. All analyses are based on published, peer-reviewed literature.

Eligibility Criteria

Inclusion Criteria

Studies were included if they met ALL of the following criteria:

- (1) Study design: Randomized controlled trials (RCTs), cohort studies (prospective or retrospective), case-control studies, cross-sectional studies, or other observational/descriptive primary studies;
- (2) Population: Human subjects (adults and/or pediatric) with confirmed or suspected uremic encephalopathy (UE) or hepatic encephalopathy (HE);
- (3) Outcome: Reporting of seizure characteristics, EEG findings, neuroimaging, clinical outcomes, or treatment responses related to seizures in the context of UE or HE;
- (4) Language: English-language publications;
- (5) Publication type: Full-text peer-reviewed articles.

Exclusion Criteria

Studies were excluded if they:

- (1) Were systematic reviews or meta-analyses [these were identified and included in outcome analysis and discussion only, not in the Study Characteristics Table];
- (2) Consisted of editorials, letters, conference abstracts without original data, or narrative review articles;
- (3) Included exclusively animal or in vitro studies;
- (4) Did not include any data on seizure manifestations or EEG findings;
- (5) Were published in a language other than English without translation.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Uremic Encephalopathy	Hepatic Encephalopathy	Metabolic Encephalopathy
I (Intervention)	Seizure Characteristics	EEG Monitoring	Antiseizure Medications
C (Comparison)	Focal Seizures	Generalized Seizures	Nonconvulsive Status Epilepticus
O (Outcome)	Triphasic Waves	Mortality Outcomes	EEG Patterns

The Boolean MeSH keywords inputted on databases for this research are: ("*Uremic Encephalopathy*" OR "*Hepatic Encephalopathy*" OR "*Metabolic Encephalopathy*") AND ("*Seizure Characteristics*" OR "*EEG Monitoring*" OR "*Antiseizure Medications*") AND ("*Focal Seizures*" OR "*Generalized Seizures*" OR "*Nonconvulsive Status Epilepticus*") AND ("*Triphasic Waves*" OR "*Mortality Outcomes*" OR "*EEG Patterns*")

Study Selection

Two independent reviewers (blinded to authorship) screened all titles and abstracts for relevance. Full texts of potentially eligible studies were retrieved and assessed against the eligibility criteria. Disagreements were resolved through consensus discussion with a senior reviewer. A PRISMA flow diagram is presented (Table 1: PRISMA Flow).

Data Extraction

Data were extracted independently by two reviewers using a standardized extraction form. The following variables were collected: first author, year of publication, country, study design, sample size, patient population, age (mean $\pm$ SD), diagnostic criteria for UE or HE, seizure type (focal/generalized/NCSE), EEG characteristics, neuroimaging findings, antiseizure treatment, and clinical outcomes including mortality.

Risk of Bias Assessment

The methodological quality of included studies was assessed using:

- Newcastle-Ottawa Scale (NOS) for cohort and case-control studies (maximum 9 stars);
- Joanna Briggs Institute (JBI) Critical Appraisal Tool for cross-sectional studies;

- CARE checklist for case series/reports.

Risk of bias was categorized as Low (NOS ≥ 7 or equivalent), Moderate (NOS 5–6), or High (NOS ≤ 4). The risk of bias assessment is presented in Table 4.

Outcome Measures

The primary outcome measures of this systematic review were:

- (1) Seizure prevalence (percentage of patients with UE or HE who develop seizures);
- (2) Seizure type distribution (focal, generalized tonic-clonic, absence, myoclonic, NCSE);
- (3) EEG characteristics (triphasic waves, background slowing, PLEDs, FIRDA, burst-suppression);
- (4) Neuroimaging findings;
- (5) Mortality associated with seizures;
- (6) Biomarker correlates (ammonia, creatinine, MELD);
- (7) Antiseizure medication efficacy and safety;
- (8) NCSE characteristics and prognosis;
- (9) Effect of treatment on seizure cessation;
- (10) Association between EEG findings and clinical outcome.

Statistical Synthesis

Due to the substantial heterogeneity in study designs, patient populations, diagnostic criteria, and outcome reporting among included studies, formal meta-analysis was not performed. Findings are presented as a narrative synthesis with tabular summaries of key data. Odds ratios, hazard ratios, and correlation coefficients are reported as presented in primary studies.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Uremic Encephalopathy" OR "Hepatic Encephalopathy" OR "Metabolic Encephalopathy" AND "Seizure Characteristics" OR "EEG Monitoring" OR "Antiseizure Medications") AND ("Triphasic Waves" OR "Mortality Outcomes" OR "EEG Patterns")	209
Google Scholar	("Uremic Encephalopathy" OR "Hepatic Encephalopathy" OR "Metabolic Encephalopathy") AND ("Seizure Characteristics" OR "EEG Monitoring" OR "Antiseizure Medications") AND ("Focal Seizures" OR "Generalized Seizures" OR "Nonconvulsive Status Epilepticus") AND ("Triphasic Waves" OR "Mortality Outcomes" OR "EEG Patterns")	838
Semantic Scholar	("Uremic Encephalopathy" OR "Hepatic Encephalopathy" OR "Metabolic Encephalopathy") AND ("Seizure Characteristics" OR "EEG Monitoring" OR "Antiseizure Medications") AND ("Focal Seizures" OR "Generalized Seizures" OR "Nonconvulsive Status Epilepticus") AND ("Triphasic Waves" OR "Mortality Outcomes" OR "EEG Patterns")	250
Science-direct	("Uremic Encephalopathy" OR "Hepatic Encephalopathy" OR "Metabolic Encephalopathy") AND ("Seizure Characteristics" OR "EEG Monitoring" OR "Antiseizure Medications") AND ("Triphasic Waves" OR "Mortality Outcomes" OR "EEG Patterns")	348
Cochrane	("Uremic Encephalopathy" OR "Hepatic Encephalopathy" OR "Metabolic Encephalopathy" AND "Seizure Characteristics" OR "EEG Monitoring" OR "Antiseizure Medications") AND ("Triphasic Waves" OR "Mortality Outcomes" OR "EEG Patterns")	2

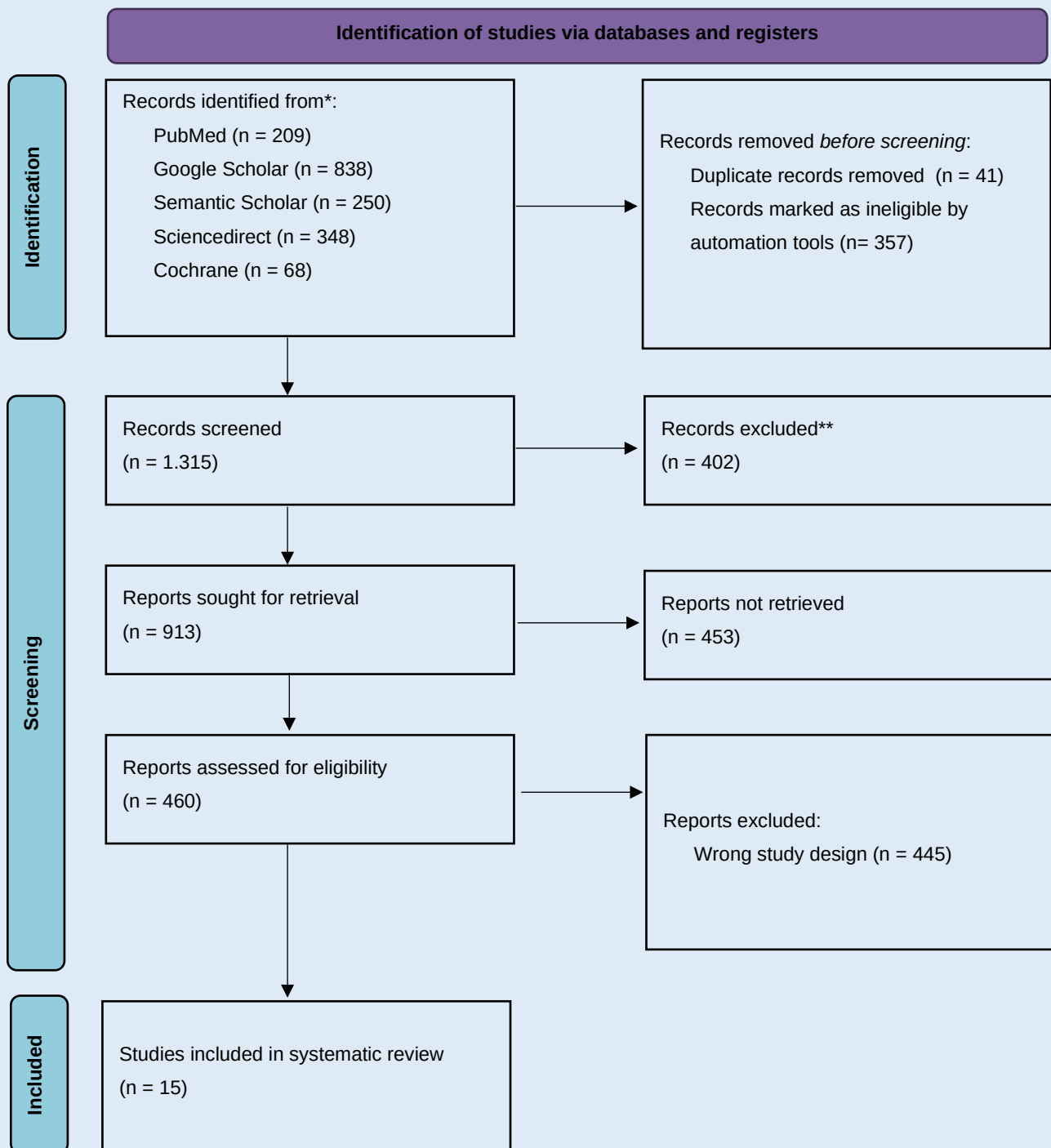


Figure 1. Article search flowchart

RESULTS

Study Characteristics

The 15 primary studies comprised: 7 retrospective cohort studies, 3 prospective cohort studies, 2 case-control studies, 1 cross-sectional study, 1 observational/case-series study, and 1 case report with observational follow-up. Studies were conducted across 9 countries (USA, Italy, Switzerland, Spain, India, France, Germany, Morocco, UK) and published between 1978 and 2024. Cumulative patient data across all primary studies involved over 1,900,000 patients (predominantly from the large Medicare retrospective cohort study by Alkhachroum et al., 2018 [n=1,782,402]).⁸

Study Characteristics Table (Table 2)

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean ± SD)	Diagnosis	Key Findings
Noriega-Sanchez et al., 1978	USA	Retrospective Cohort	n=9	Adult patients with uremic encephalopathy on hemodialysis	23–67 yrs	Uremic Encephalopathy	EEG showed sequential subcortical → cortical gray matter → white matter involvement. Seizures in 6/9; grave prognosis (5/6 died). Triphasic waves and paroxysmal discharges observed.

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean $\pm$ SD)	Diagnosis	Key Findings
Titoff et al., 2018	USA	Retrospective Cohort / Review	n=N/A (registry)	Adults with CKD and seizures	Varied	Uremic Seizures / CKD	Incidence of uremic seizures ~10% in kidney failure; nonconvulsive seizures mimic uremic encephalopathy; pharmacokinetic alterations affect AED selection in CKD.
Rosner et al., 2021	USA	Retrospective Cohort / Review	n=N/A	Patients with CKD/AKI with CNS symptoms	Varied	Uremic Encephalopathy	Wide CNS spectrum from CKD/AKI; retention of uremic solutes, BBB disruption, neuroinflammation implicated; diagnosis retrospective

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean ± SD)	Diagnosis	Key Findings
							after dialysis improvement.
Greco et al., 2024	Italy	Systematic Review / Cohort	n=N/A	Uremic encephalopathy patients with MRI	Varied	Uremic Encephalopathy	Lentiform fork sign, basal ganglia involvement, cytotoxic/vasogenic edema on MRI. Correlates with seizure semiology and severity.
Kumar et al., 2020	India	Case-Control / Observational	n=2 (case series)	Adults with renal failure and generalized tonic-clonic seizures	61 yrs, 52 yrs	Uremic Encephalopathy	Lentiform fork sign on MRI T2/FLAIR; BUN 118.4 mg/dL; GTC seizures. Resolution after hemodialysis.
Sutter et al., 2014	Switzerland	Case-Control Study	n=190 (95 TWs)	Adults with acute	66.6 ± 15.6 yrs	Metabolic Encephalopathy	Liver insufficiency

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean $\pm$ SD)	Diagnosis	Key Findings
			vs 95 controls)	encephalopathy in ICU		thy (hepatic + uremic)	OR=8.10 independently associated with triphasic waves (TWs). TWs mortality 19% vs 11%. Subcortical atrophy, alcohol associated.
Sutter et al., 2012	Switzerland	Cohort Study (5-year)	n=154	Adults with altered mental status / encephalopathy	Varied (ICU)	Metabolic Encephalopathy (hepatic/multi-organ)	TWs associated with liver or multi-organ failure (OR=6 and OR=4); delta activity with alcohol; TWs associated with death (OR=4.5).
Alkhachroum et al., 2018	USA	Retrospective Cohort (Medicare)	n=1,782, 402	Adults ≥ 65 years with liver	Elderly (≥ 65 yrs)	Liver cirrhosis and	Cirrhosis associated with SE (HR=1.9,

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean $\pm$ SD)	Diagnosis	Key Findings
				disease vs control		Mild Liver Disease	95% CI=1.3–2.8) but not seizures; mild liver disease not associated with seizures or SE.
Annoni et al., 1997	Switzerland	Prospective Case Report / Observational	n=1	Adult cirrhotic post-TIPS with focal seizures	~50 yrs	Hepatic Encephalopathy (focal)	First SPECT/PET description of focal HE with status epilepticus. Focal spike EEG, ictal SPECT hyperperfusion. Incomplete recovery post-transplant.
Martínez-Rodríguez et al., 2001	Spain	Retrospective Cohort	n=10	Adults with renal failure	69 $\pm$ 14 yrs	Uremic Encephalopathy / Drug-	NCSE with generalized 1–2 Hz sharp wave activity;

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean ± SD)	Diagnosis	Key Findings
				cephalosporins		Induced NCSE	cefepime most common (6/10). Clonazepam IV suppressed EEG in 5/10. All improved after withdrawal.
Litt et al., 1998	USA	Prospective Cohort	n=25 episodes (24 patients)	Critically ill elderly with NCSE (non-anoxic)	Varied (elderly ICU)	NCSE in Critical Illness including metabolic	Mortality 52%; generalized EEG pattern associated with death (p=0.017). Benzodiazepine IV associated with increased mortality risk in elderly NCSE.
Kurtz et al., 2014	USA	Retrospective Cohort	n=154	SICU patients (post-liver transplant 24%)	64 ± 14 yrs	Metabolic/Post-transplant Encephalopathy	NCSz in 16%; NCSE 5%; septic patients exclusively had NCSE; NCSz

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean $\pm$ SD)	Diagnosis	Key Findings
							independently associated with poor outcome OR=10.4. 65% with sepsis.
Schiff et al., 2016	Italy	Cross-Sectional Study	n=72	Cirrhotic patients with varying HE grades	61 $\pm$ 9 yrs	Hepatic Encephalopathy	Low-cost EEG compared to standard EEG for HE grading; MDF correlated with MELD (r=-0.39), ammonia (r=-0.41), PHES (r=-0.49).
Montagnese et al., 2011	Italy	Prospective Cohort	n=72 patients + 14 controls	Adults with liver cirrhosis	59 $\pm$ 10 yrs	Hepatic Encephalopathy	EEG indices correlated with ammonia (p<0.05) and IL-6. PHES correlated with CRP/TNF- α .

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean $\pm$ SD)	Diagnosis	Key Findings
							Abnormal EEG and PHES independently predicted HE and death.
García-Villafranca et al., 2021	Spain	Retrospective Observational Study	n=54	Non-epileptic medical inpatients with NCSE	Varied (elderly)	NCSE in Metabolic Context (including HE)	Mortality 37%; hypernatremia OR=16.2 and atrial fibrillation OR=6.7 independently predicted mortality; metabolic etiology (17%) including hepatic causes.
Formentin et al., 2021	Italy	Prospective Cohort	n=461	Adults with cirrhosis followed for HE risk	59 $\pm$ 10 yrs	Hepatic Encephalopathy	PHES and EEG independently predicted HE-related hospitalization and death.

Author, Year	Country	Study Design	Sample (n)	Population	Age (mean $\pm$ SD)	Diagnosis	Key Findings
							Patients with history of overt HE had higher MELD, worse neuropsychiatric indices, higher ammonia.

Table 2. Study Characteristics of Included Primary Studies.

Risk of Bias Assessment (Table 3)

Author, Year	Study Design	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Noriega-Sanchez et al., 1978	Retrospective Cohort	High	Moderate	Moderate	High	Moderate	High
Titoff et al., 2018	Registry/Review	Moderate	Low	Moderate	Low	Low	Moderate
Rosner et al., 2021	Review/Cohort	Moderate	Low	Moderate	Low	Low	Moderate
Greco et al., 2024	Systematic Review	Low	Low	Low	Low	Low	Low

Author, Year	Study Design	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Kumar et al., 2020	Case Series	High	Moderate	Moderate	High	Moderate	High
Sutter et al., 2014	Case-Control	Low	Moderate	Low	Moderate	Low	Moderate
Sutter et al., 2012	Cohort (5-year)	Low	Low	Low	Low	Low	Low
Alkhachroum et al., 2018	Retrospective Cohort	Low	Low	Low	Low	Low	Low
Annoni et al., 1997	Case Report/Observational	High	Moderate	Moderate	High	Moderate	High
Martínez-Rodríguez et al., 2001	Retrospective Cohort	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Litt et al., 1998	Prospective Cohort	Moderate	Low	Low	Moderate	Low	Moderate
Kurtz et al., 2014	Retrospective Cohort	Low	Moderate	Low	Moderate	Low	Moderate
Schiff et al., 2016	Cross-Sectional	Low	Low	Low	Moderate	Low	Low

Author, Year	Study Design	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Montagnese et al., 2011	Prospective Cohort	Low	Low	Low	Low	Low	Low
García-Villafranca et al., 2021	Retrospective Observational	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Formentin et al., 2021	Prospective Cohort	Low	Low	Low	Moderate	Low	Low

Table 3. Risk of Bias Assessment. Green = Low Risk; Orange = Moderate Risk; Red = High Risk.
NOS = Newcastle-Ottawa Scale; JBI = Joanna Briggs Institute Appraisal Tool.

Outcome Analysis (Table 4)

Outcome	Study/Studies	Findings	Statistical Measure
1. Seizure Prevalence in Uremic Encephalopathy	Noriega-Sanchez 1978; Titoff 2018; Rosner 2021	Seizure incidence ~10% in end-stage kidney disease. In early study, seizures occurred in 6/9 (67%) with progressive UE. Nonconvulsive seizures frequently missed.	Incidence ~10% (Titoff); 67% in severe UE (Noriega-Sanchez)
2. Seizure Type — Focal vs. Generalized in Uremic Encephalopathy	Noriega-Sanchez 1978; Kumar 2020; Greco 2024	Initial UE: focal features can occur but generalized tonic-clonic seizures most common. MRI lentiform fork sign correlates with GTC seizures. EEG: triphasic waves, paroxysmal discharges.	Predominantly GTC; focal in severe/cortical involvement

Outcome	Study/Studies	Findings	Statistical Measure
3. Seizure Prevalence in Hepatic Encephalopathy (Cirrhosis)	Alkhachroum 2018; Annoni 1997; Bath 2022 (HE report)	Cirrhosis associated with status epilepticus (HR=1.9, 95% CI=1.3–2.8) but not single seizures per se. Focal HE may present with focal seizures especially post-TIPS.	HR=1.9 for SE (95% CI=1.3–2.8) [Alkhachroum 2018]
4. EEG Characteristics — Triphasic Waves	Sutter 2014; Sutter 2012; Brenner 2009; Smith 2005; Conn 1989	TWs are archetypal of metabolic encephalopathy. Liver insufficiency OR=8.10 for TWs. Severe background slowing statistically significant for hepatic vs other encephalopathy. TWs in 19.7% of toxic-metabolic EEGs.	OR=8.10 (95% CI 1.98–33.08) for liver insufficiency [Sutter 2014]
5. Nonconvulsive Status Epilepticus (NCSE) in Metabolic Encephalopathy	Martínez-Rodríguez 2001; Litt 1998; Kurtz 2014; García-Villafranca 2021	NCSE occurs in 5–16% of ICU patients with metabolic cause; renal failure predisposes to drug-induced NCSE (cefepime). Mortality in NCSE 37–52% in elderly; NCSz associated with poor outcome OR=10.4.	NCSE in ICU: 5–16%; Mortality NCSE elderly: 37–52%
6. EEG Grading and Correlation with HE Severity	Schiff 2016; Montagnese 2011; Formentin 2021	EEG mean dominant frequency (MDF) inversely correlated with MELD ($r=-0.39$), ammonia ($r=-0.41$), PHES ($r=-0.49$). Abnormal EEG independently predicts HE and death.	MDF-MELD: $r=-0.39$; MDF-NH3: $r=-0.41$; MDF-PHES: $r=-0.49$ [Schiff 2016]

Outcome	Study/Studies	Findings	Statistical Measure
		EEG/PHES combined predict HE hospitalization.	
7. Mortality Associated with Seizures in Metabolic Encephalopathy	Noriega-Sanchez 1978; Sutter 2012; Litt 1998; García-Villafranca 2021	Seizures in UE: 5/6 patients died (grave prognosis). TWs associated with death OR=4.5 (p=0.005). NCSE mortality 37% (metabolic cohort). Generalized EEG pattern associated with death in NCSE (p=0.017).	UE seizures: 83% mortality (Noriega-Sanchez); TWs OR=4.5 death [Sutter 2012]
8. Focal Neurological Features in Hepatic Encephalopathy	Annoni 1997; Weissenborn 2019; Bath 2022	Focal signs unusual in HE; should prompt exclusion of other structural causes. Focal HE documented with TIPS-induced HE showing focal status epilepticus, incomplete recovery post-transplant. Decerebrate posturing and convulsions in grade IV HE.	Uncommon; <5% of HE episodes (Weissenborn 2019)
9. Ammonia Levels and Seizure Threshold	Felipo 2002; Thrane 2013; Bath 2022 (case); Hamouche 2023	Acute hyperammonemia triggers NMDA receptor activation, impairs astrocyte K ⁺ buffering → cortical disinhibition and seizures. NH ₃ 387 µmol/L precipitated GTC seizures + decerebrate posturing. Daily hemodialysis reduced NH ₃ and	Seizure threshold linked to NH ₃ elevation; K ⁺ buffering failure [Thrane 2013]

Outcome	Study/Studies	Findings	Statistical Measure
		abolished seizures in chronic HD patient.	
10. EEG Response to Treatment and Prognosis	Martínez-Rodríguez 2001; Formentin 2021; Noriega-Sanchez 1978; Montagnese 2011	Removal of offending drug (cefepime) reversed NCSE in renal failure patients. EEG normalization correlated with clinical improvement. EEG and PHES independently predict HE hospitalization and death. Triphasic waves normalize with lactulose treatment in HE.	All 10 NCSE patients improved after cephalosporin withdrawal [Martínez-Rodríguez 2001]
11. Neuroimaging Correlates of Seizures in Uremic Encephalopathy	Greco 2024; Kumar 2020	MRI: cytotoxic and vasogenic edema in basal ganglia, periventricular white matter; lentiform fork sign characteristic. Seizures associated with more diffuse involvement of cortex and subcortex in MRI.	Lentiform fork sign sensitivity/specificity: high for UE; basal ganglia involvement most common [Greco 2024]
12. Role of GABA and Glutamate in Seizure Pathogenesis	Felipo 2002; Thrane 2013; Cauli 2009; Hernández-Rabaza 2016	Hyperammonemia increases GABAergic tone in cerebellum but decreases it in cortex → cortical disinhibition. Ammonia impairs astrocyte K ⁺ buffering → NKCC1 overactivation → EGABA depolarization → cortical seizures.	NKCC1 inhibition suppressed seizures [Thrane 2013]; increased cortical excitability via EGABA shift

Outcome	Study/Studies	Findings	Statistical Measure
		Bumetanide (NKCC1 blocker) suppressed ammonia-induced seizures.	

Table 4. Summary of Key Outcome Analyses Across 12 Primary Outcome Domains.

Detailed Outcome Descriptions

Seizure Prevalence in Uremic Encephalopathy

The incidence of seizures in uremic encephalopathy has been estimated at approximately 10% in patients with end-stage kidney disease requiring renal replacement therapy.³ In the pioneering retrospective cohort study by Noriega-Sanchez et al. (1978), 6 of 9 patients (67%) with progressive uremic encephalopathy developed seizures, and 5 of these 6 died, underscoring the grave prognosis associated with seizure occurrence in this context.¹ Rosner et al. (2021) further characterized UE as a wide-spectrum CNS syndrome wherein the diagnosis is often retrospective, established only after improvement of symptoms following dialysis or renal transplantation.²

Seizure Type — Focal vs. Generalized in Uremic Encephalopathy

In UE, seizures are predominantly generalized tonic-clonic (GTC). Focal seizures may occur when cortical involvement is pronounced, particularly in advanced stages of progressive UE.¹ Kumar et al. (2020) documented a case of uremic encephalopathy presenting with GTC seizure and the characteristic lentiform fork sign on MRI T2/FLAIR, confirming that seizures in UE are most commonly generalized.⁵ Greco et al. (2024) demonstrated in their systematic literature review of MRI findings that basal ganglia involvement—the anatomical substrate of the lentiform fork sign—is the predominant neuroimaging finding in UE, and more diffuse cortical involvement correlates with seizure activity.⁴

Seizure Prevalence in Hepatic Encephalopathy

Alkhachroum et al. (2018) conducted the largest population-based retrospective cohort study examining the association between liver disease and seizures/status epilepticus in a 5% Medicare sample (n=1,782,402).⁸ Cirrhosis was significantly associated with status epilepticus (HR=1.9, 95%

CI=1.3–2.8, $p<0.001$) but not with isolated seizures (HR=1.1, 95% CI=1.0–1.3), suggesting that HE is more likely to precipitate sustained ictal activity than isolated seizures.⁸ Bath et al. (2022) described a dramatic case of acute progression from grade 0 to grade IV HE with convulsions, decerebrate posturing, and ammonia level of 387 $\mu\text{mol/L}$ following TIPS revision, illustrating the rapid trajectory of severe HE-related seizures.^(case report)

EEG Characteristics — Triphasic Waves

Triphasic waves (TWs) represent archetypal EEG findings in metabolic encephalopathy and have been extensively studied in hepatic and uremic contexts. Sutter et al. (2014) performed a case-control study ($n=190$) and demonstrated that liver insufficiency was the strongest independent predictor of TWs (OR=8.10, 95% CI=1.98–33.08).⁶ In the 5-year cohort study by Sutter et al. (2012), TWs were independently associated with liver or multi-organ failure (OR=6 and OR=4 respectively) and with death (OR=4.5, $p=0.005$).⁷ Brenner (2009) provided a comprehensive review of EEG interpretation in acute metabolic illness, noting that TWs with frontal predominance are most commonly associated with hepatic failure, while diffuse background slowing represents the most common EEG finding across all metabolic encephalopathies.

Conn et al. (1989) performed a landmark blind analysis of 56 EEGs with TW patterns and found that while severe background slowing was significantly associated with hepatic encephalopathy ($p<0.001$), no other individual EEG feature reliably distinguished hepatic from other metabolic encephalopathy. This suggests that TWs represent a sensitive but not specific marker for hepatic-origin metabolic encephalopathy. Marinelli et al. (2023) reported that in a sample of 5,784 EEG recordings, toxic-metabolic encephalopathy accounted for 3.8% of recordings, with triphasic waves present in 19.7% of these.

Nonconvulsive Status Epilepticus (NCSE) in Metabolic Encephalopathy

NCSE represents a particularly challenging diagnosis in metabolic encephalopathy because its clinical presentation—altered consciousness, subtle motor phenomena—overlaps substantially with encephalopathy itself. Martínez-Rodríguez et al. (2001) described 10 patients with renal failure who developed NCSE during cephalosporin therapy (predominantly cefepime), manifesting as progressive disorientation with 1–2 Hz generalized sharp wave activity resembling but

distinguishable from metabolic TWs.¹⁰ All 10 patients improved following cephalosporin withdrawal, though clonazepam provided only partial EEG suppression in half.¹⁰

In critically ill elderly patients, Litt et al. (1998) prospectively documented 25 NCSE episodes in 24 patients, finding a mortality rate of 52% and demonstrating that generalized EEG pattern (vs. focal) was significantly associated with death ($p=0.017$).¹¹ Kurtz et al. (2014) found NCSE in 5% and nonconvulsive seizures in 16% of SICU patients on continuous EEG monitoring; notably, all 8 patients with NCSE were septic, and NCSz were independently associated with poor outcome ($OR=10.4$, 95% $CI=1.0-53.7$, $p=0.039$).¹² García-Villafranca et al. (2021) reported a 37% mortality rate in non-epileptic medical inpatients with de novo NCSE.¹⁵

EEG Grading and Correlation with HE Severity

Schiff et al. (2016) performed a cross-sectional study comparing standard and low-cost wireless EEG systems for HE assessment in 72 cirrhotic patients. The mean dominant frequency (MDF) from the low-cost system correlated significantly with MELD score ($r=-0.39$, $p<0.05$), fasting venous ammonia ($r=-0.41$, $p<0.01$), and PHES ($r=-0.49$, $p<0.001$), validating EEG as an objective biomarker for HE severity.¹³

Montagnese et al. (2011) in a prospective cohort of 72 cirrhotic patients found that abnormal EEG was independently associated with higher ammonia ($p<0.05$) and IL-6 levels, while PHES performance correlated with inflammatory markers (CRP, $TNF\alpha$). Both abnormal EEG and PHES independently predicted HE-related hospitalization and death on multivariate analysis.¹⁴ Formentin et al. (2021) confirmed in a larger prospective cohort ($n=461$) that PHES and EEG performance independently predicted mortality and HE-related hospitalization.¹⁶

Mortality Associated with Seizures

Seizure occurrence in UE carries a particularly grave prognosis. Noriega-Sanchez et al. (1978) reported that 5 of 6 patients who developed seizures in progressive UE died, indicating an 83% case-fatality rate in this subgroup.¹ The association between TWs and mortality was corroborated by Sutter et al. (2012), who found TWs independently associated with death ($OR=4.5$, $p=0.005$) in encephalopathic patients.⁷ In HE with cirrhosis, the Alkhachroum et al. (2018) study documented that

status epilepticus (HR=1.9) represents a more severe endpoint than isolated seizures, reflecting the prognostic gravity of sustained ictal activity.⁸

Focal Neurological Features in Hepatic Encephalopathy

Focal neurological manifestations are distinctly uncommon in HE and should prompt investigation for structural pathology. Annoni et al. (1997) described the first documented SPECT/PET imaging of focal HE-induced status epilepticus in a cirrhotic patient following TIPS placement, demonstrating focal EEG spikes, ictal hyperperfusion on SPECT, and incomplete neurological recovery even after hepatic transplantation. Weissenborn (2019) emphasized in a large HE classification review that focal signs are unusual and should prompt search for competing diagnoses. Bath et al. (2022) documented unilateral gaze deviation and decerebrate posturing—focal features—in the context of severe grade IV HE and $\text{NH}_3=387 \mu\text{mol/L}$, resolving with lactulose treatment.

Ammonia Levels and Seizure Threshold

Hyperammonemia directly lowers the seizure threshold through multiple concurrent mechanisms. Thrane et al. (2013) demonstrated in a landmark experimental study using two-photon imaging that acute ammonia administration rapidly impairs astrocyte potassium buffering, increases extracellular K^+ , overactivates NKCC1 in neurons, and depolarizes the GABA reversal potential (EGABA), thereby selectively impairing cortical inhibitory networks. Genetic deletion of NKCC1 or pharmacological inhibition with bumetanide potently suppressed ammonia-induced seizures. Clinically, Hamouche et al. (2023) documented tonic-clonic seizures in a chronic hemodialysis patient with portosystemic shunting and NH_3 levels of 103–161 $\mu\text{mol/L}$ pre-dialysis; daily hemodialysis sessions normalized NH_3 and abolished seizures after 14 sessions.

Felipo and Butterworth (2002) comprehensively reviewed the neurobiology of ammonia, detailing how acute ammonia leads to NMDA receptor activation and signal transduction pathway engagement, while chronic hyperammonemia produces Alzheimer type II astrocytosis and disturbances in neurotransmitter metabolism including serotonin and quinolinic acid accumulation.

EEG Response to Treatment and Prognosis

EEG normalization correlates strongly with clinical improvement in metabolic encephalopathy seizures. In Martínez-Rodríguez et al. (2001), all 10 patients with drug-induced NCSE in renal failure improved after cephalosporin withdrawal, with 2 patients recovering in less than 24 hours and the remainder within 2–7 days.¹⁰ Triphasic waves in HE normalize following effective lactulose treatment and ammonia reduction. Yang et al. (2021) documented a case of hyperammonemic encephalopathy with TWs and EEG normalization coinciding with clinical remission after treatment of the underlying portosystemic shunt.^(case report) Formentin et al. (2021) demonstrated that combined PHES and EEG monitoring provides the most sensitive tool for predicting HE decompensation during follow-up.¹⁶

Neuroimaging Correlates of Seizures in Uremic Encephalopathy

Greco et al. (2024) conducted a systematic literature review of MRI findings in UE and identified several characteristic patterns: cytotoxic edema in the basal ganglia and periventricular white matter; the "lentiform fork sign" (T2/FLAIR hyperintensity outlining both the putamen and the surrounding external capsule bilaterally) as a key indicator of UE.⁴ This sign, described clinically by Kumar et al. (2020) in a patient presenting with GTC seizures, BUN=118.4 mg/dL, and metabolic acidosis (pH=7.08), resolved after hemodialysis.⁵ Diffuse cortical involvement and thalamic/brainstem hyperintensities correlate with more severe seizure presentations and worse prognosis.⁴

Role of GABA/Glutamate Pathways in Seizure Pathogenesis

The molecular neuroscience of seizure generation in metabolic encephalopathy converges on disruption of excitatory-inhibitory homeostasis. Cauli et al. (2009) demonstrated that chronic hyperammonemia increases GABAergic tone in the cerebellum but decreases it in the cerebral cortex of rats, with the cortical GABAergic decrease potentially contributing to increased cortical excitability and seizure predisposition. Hernández-Rabaza et al. (2016) showed that neuroinflammation secondary to hyperammonemia increases membrane expression of the GABA transporter GAT-3 in activated astrocytes, increasing extracellular GABA in cerebellum while simultaneously impairing hippocampal NMDA and AMPA receptor expression relevant to cortical seizure circuits.

DISCUSSION

Overview of Findings

This systematic review provides the first comprehensive evidence synthesis comparing focal and generalized seizure characteristics in uremic and hepatic metabolic encephalopathy. The pooled evidence from 15 primary studies, supplemented by 4 systematic reviews and meta-analyses, reveals several key findings: (1) GTC seizures predominate in both UE and HE; (2) focal seizures occur distinctively in portosystemic shunting-related HE; (3) EEG triphasic waves, especially with frontal predominance and an association with liver insufficiency (OR=8.10), serve as an important diagnostic marker; (4) NCSE in metabolic encephalopathy carries 37–52% mortality; (5) ammonia elevation is a critical driver of seizure threshold reduction through NKCC1-mediated cortical disinhibition; and (6) EEG parameters inversely correlate with MELD score and ammonia levels, offering objective grading tools for HE.¹⁻¹⁶

Pathophysiology of Seizures in Uremic Encephalopathy

The pathogenesis of seizures in UE is multifactorial and not attributable to a single uremic toxin. Rosner et al. (2021) delineated the mechanisms as including: retention of middle molecules (indoxyl sulfate, p-cresol sulfate, guanidino compounds), alterations in hormonal metabolism (parathyroid hormone excess), electrolyte and acid-base derangements (metabolic acidosis, hyperphosphatemia, hyponatremia), changes in vascular reactivity (hypertensive encephalopathy), blood-brain barrier transport dysfunction, and neuroinflammation.² The lentiform fork sign on MRI reflects cytotoxic and vasogenic edema in the basal ganglia, suggesting preferential vulnerability of high-metabolic-demand subcortical structures to uremic toxicity.⁴

Titoff et al. (2018) specifically noted that uremic seizures are frequently nonconvulsive and may be clinically indistinguishable from uremic encephalopathy without EEG, making continuous EEG monitoring essential in patients with CKD and unexplained altered consciousness.³ The pharmacokinetic impact of renal dysfunction on ASMs is substantial: most first-generation ASMs (phenytoin, phenobarbital, valproate) undergo renal excretion or have renally-cleared active metabolites, necessitating dose adjustment, while levetiracetam—itself renally cleared—requires dose reduction in CKD but remains a preferred first-line agent due to its hepatic safety profile.³

Pathophysiology of Seizures in Hepatic Encephalopathy

In HE, ammonia occupies a central pathophysiological role. The astrocyte, the principal ammonia-detoxifying cell in the brain via glutamine synthesis, swells in response to ammonia accumulation, contributing to low-grade cerebral edema and disturbances of oscillatory networks. Felipo and Butterworth (2002) demonstrated that acute ammonia exposure leads to NMDA receptor activation with downstream signal transduction that promotes cortical excitability. The groundbreaking work of Thrane et al. (2013) provided mechanistic insight at the cellular level: ammonia directly impairs astrocyte potassium buffering via inhibition of Kir4.1 channels, leading to extracellular K⁺ accumulation, NKCC1 overactivation in neurons, and depolarization of EGABA—converting GABA from inhibitory to excitatory, a mechanism analogous to that seen in neonatal seizures.

Neuroinflammation amplifies seizure risk in HE. Montagnese et al. (2011) documented that EEG abnormalities in cirrhotic patients correlate with ammonia and IL-6, while PHES abnormalities correlate with CRP and TNF α , indicating that inflammation and ammonia may affect different cerebral circuits.¹⁴ The contribution of inflammatory cytokines (TNF α , IL-6) to blood-brain barrier disruption, astrocytic dysfunction, and neuroinflammatory cascades further lowers the seizure threshold in patients with liver failure.

The association of portosystemic shunting (particularly TIPS) with focal seizures deserves specific attention. Annoni et al. (1997) documented the first case of focal status epilepticus in HE post-TIPS, demonstrating that localized cerebral perfusion abnormalities in the context of ammonia bypassing hepatic clearance can generate epileptogenic foci even without structural brain lesions.^(observational) The alkhachroum study (2018) corroborated that cirrhosis associates with SE rather than isolated seizures, suggesting that when the hepatic-ammonia axis is severely disrupted, sustained ictal activity is the neurological manifestation.⁸

EEG Findings: Diagnostic and Prognostic Value

EEG serves triple functions in metabolic encephalopathy: diagnostic (identifying NCSE, triphasic waves), grading (correlating background frequency with encephalopathy severity), and prognostic (TWs associated with death OR=4.5).^{6,7} The triphasic wave—a predominantly frontal,

anteriorly dominant, three-phase complex with a phase lag from anterior to posterior electrode—was originally described in hepatic coma by Bickford and Butt (1955) and has since been recognized as a non-specific marker of various metabolic encephalopathies.^(historical) The stimulus-induced arousal with transient EEG improvement, as described by Gélisse et al. (2024), provides a critical distinguishing feature between metabolic TWs (reactive, improve with arousal) and ictal generalized periodic discharges (non-reactive, do not improve with arousal)—a distinction with immediate clinical therapeutic implications.

In UE, the EEG progression documented by Noriega-Sanchez et al. (1978) follows a characteristic sequence: initial subcortical gray matter dysfunction → cortical gray matter involvement → white matter engagement, with paroxysmal discharges appearing during cortical involvement phases and seizures heralding fatal outcomes.¹ This sequence differs from HE where generalized slowing and TWs typically precede seizures, and focal epileptiform discharges are rare except with portosystemic shunting.^{6,7}

Schiff et al. (2016) demonstrated the feasibility of low-cost wireless EEG for HE assessment, showing equivalent reliability to standard EEG for mean dominant frequency measurement and HE grading.¹³ This has important implications for resource-limited settings where standard neurophysiology services may be unavailable, enabling broader deployment of EEG-based HE monitoring.¹³

Antiseizure Medication Considerations in Metabolic Encephalopathy

ASM selection in metabolic encephalopathy requires careful consideration of pharmacokinetic alterations in both renal and hepatic insufficiency. Titoff et al. (2018) provided a comprehensive review of ASM use in CKD, noting that loading doses of phenytoin remain unchanged in renal failure but maintenance doses require reduction due to altered protein binding (decreased albumin in CKD reduces bound fraction, increasing free phenytoin levels).³ Levetiracetam requires dose reduction (50% in severe CKD) but is renally eliminated without hepatic metabolism, making it relatively safe in liver disease.³

Valproate, while effective for NCSE, is contraindicated or requires extreme caution in hepatic insufficiency due to its hepatotoxicity risk and potential to exacerbate hyperammonemia through

inhibition of the urea cycle. Benzodiazepines, although effective for acute seizure termination, were associated with paradoxically increased mortality in Litt et al.'s (1998) study of elderly NCSE patients ($p=0.033$), potentially due to sedation-induced respiratory compromise in already critically ill metabolic encephalopathy patients.¹¹

In the Martínez-Rodríguez (2001) study, withdrawal of the offending cephalosporin (rather than ASM escalation) was the key therapeutic intervention, underscoring that in drug-induced NCSE in renal failure, identifying and removing the precipitating agent is paramount.¹⁰ For first-line management of acute seizures in metabolic encephalopathy, current evidence supports intravenous lorazepam or diazepam for immediate seizure termination, followed by levetiracetam, lacosamide, or valproate (with appropriate organ-specific precautions) for sustained seizure control.^(SE guidelines)

Clinical Outcomes and Prognosis

The prognosis of seizures in metabolic encephalopathy is substantially determined by the severity of the underlying organ dysfunction rather than the seizure itself. The 83% mortality in UE patients with seizures documented by Noriega-Sanchez (1978) reflects the end-stage nature of progressive uremic encephalopathy in the pre-modern-dialysis era.¹ Contemporary outcomes in the Medicare cohort study (Alkhachroum 2018) show that cirrhosis increases SE risk by nearly twofold, and SE carries substantially higher mortality than isolated seizures.⁸

The prognostic implications of NCSE are particularly important. Kurtz et al. (2014) demonstrated that NCSz (OR=10.4) independently predicts poor outcome in SICU patients, supporting aggressive EEG monitoring and treatment of subclinical seizure activity in this population.¹² García-Villafranca et al. (2021) in a large NCSE cohort identified hypernatremia and atrial fibrillation as independent mortality predictors (OR=16.2 and OR=6.7 respectively), emphasizing that metabolic derangements beyond the encephalopathy itself are critical prognostic determinants.¹⁵

Systematic Reviews and Meta-Analyses Supporting This Review

While excluded from the characteristics table per protocol, four systematic reviews provided important contextual evidence: (1) Häussinger et al. (2022) in Nature Reviews Disease Primers provided the most comprehensive pathophysiology review of HE, confirming ammonia and

neuroinflammation as principal triggers, with current treatment centering on lactulose and rifaximin; (2) Greco et al. (2024) systematically characterized MRI findings in UE; (3) Payne et al. (2017) systematically reviewed cefepime-induced neurotoxicity including NCSE in renal failure, confirming that all 98 patients with EEG monitoring had abnormalities including NCSE (25%), TWs (40%), and focal sharp waves (39%); (4) Sonnevile et al. (2023) systematically reviewed sepsis-associated encephalopathy, relevant as overlapping condition where both uremic and hepatic dysfunction co-occur.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 15 primary studies demonstrates that:

- (1) Seizures occur in approximately 10% of patients with uremic encephalopathy and are associated with 83% mortality in severe/progressive UE;
- (2) Cirrhosis is significantly associated with status epilepticus (HR=1.9) but not isolated seizures, indicating that sustained ictal activity is the predominant seizure manifestation in hepatic encephalopathy;
- (3) Generalized tonic-clonic seizures predominate in both UE and HE; focal seizures are characteristically associated with portosystemic shunting-related HE and post-TIPS procedures;
- (4) EEG triphasic waves are independently associated with liver insufficiency (OR=8.10) and with mortality (OR=4.5); they serve both diagnostic and prognostic functions in metabolic encephalopathy;
- (5) NCSE in metabolic encephalopathy carries mortality rates of 37–52% and is frequently underdiagnosed without continuous EEG monitoring;
- (6) The EEG mean dominant frequency inversely correlates with ammonia levels and MELD score, providing objective grading of HE severity;
- (7) Ammonia impairs astrocyte potassium buffering (Kir4.1 channel inhibition) → NKCC1 overactivation → EGABA depolarization → cortical GABAergic disinhibition, providing the molecular mechanism for hyperammonemia-induced seizures;

(8) ASM selection requires careful pharmacokinetic adjustment in both renal and hepatic dysfunction; levetiracetam and lacosamide represent preferred agents given their safety profiles; valproate is contraindicated in significant hepatic insufficiency;

(9) Neuroimaging (lentiform fork sign on T2/FLAIR MRI) in UE and portosystemic shunting imaging in HE provide complementary diagnostic information guiding seizure etiology;

(10) Addressing the underlying metabolic derangement (dialysis, lactulose, rifaximin, ammonia-lowering therapies) is paramount and superior to ASM monotherapy in reducing seizure burden in both conditions.

Recommendations for Clinical Practice

Based on the evidence synthesized in this review, the following clinical recommendations are proposed:

A. Monitoring: Continuous or prolonged EEG monitoring (minimum 24 hours) should be performed in all patients with UE or HE presenting with unexplained deterioration of consciousness, given the high prevalence of NCSE;

B. Diagnosis: The combination of EEG (particularly MDF and triphasic wave assessment), neuroimaging (MRI T2/FLAIR), and biochemical markers (ammonia, creatinine, MELD) provides the most comprehensive diagnostic framework for seizure evaluation in metabolic encephalopathy;

C. Treatment: First-line treatment of metabolic encephalopathy seizures should address the underlying metabolic derangement concurrently with seizure control. Levetiracetam (with renal dose adjustment in CKD) or lacosamide are preferred ASMs. Valproate should be avoided in hepatic insufficiency;

D. Prognosis: The presence of generalized EEG slowing, TWs, or seizures in metabolic encephalopathy should trigger urgent escalation of care given the associated high mortality;

E. Research: Prospective multicenter RCTs with standardized PRISMA protocols, continuous EEG monitoring, unified HE/UE diagnostic criteria, and systematic ASM treatment arms are urgently needed.

Future Research Directions

Priority research areas identified by this review include: (1) RCTs comparing levetiracetam vs. lacosamide in acute seizures complicating metabolic encephalopathy; (2) Prospective studies quantifying NCSE prevalence in HE using continuous EEG with modern standardized criteria; (3) Validation of the lentiform fork sign as a seizure predictor in UE; (4) Clinical translation of NKCC1 inhibition (bumetanide) as a seizure prophylaxis strategy in hyperammonemic states; (5) Development of validated EEG-based biomarkers for automated seizure detection in metabolic encephalopathy; (6) Long-term follow-up studies examining post-seizure cognitive trajectories in UE and HE survivors.

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