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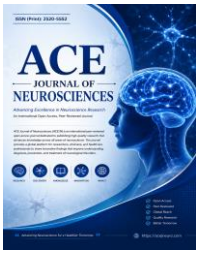

A Systematic Review and Meta-Analysis

Biochemical Biomarkers for Differentiating Epileptic and Functional Seizures: A Systematic Review and Meta-Analysis of Serum Prolactin and Lactate.

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Abstract: ***Background***: The distinction between epileptic seizures and functional/dissociative seizures (FDS; also termed psychogenic nonepileptic seizures, PNES) often requires detailed semiology and video-electroencephalography (video-EEG). Postevent prolactin and lactate have been studied as rapid adjunctive blood biomarkers, but their utility depends on seizure phenotype, reference standard, sampling interval and threshold. Objective: To compare the diagnostic accuracy and clinical applicability of postictal serum prolactin and lactate, distinguishing generalized tonic-clonic seizures (GTCS) from focal epileptic and functional events. ***Methods***: Evidence was assembled from identifiable original video-EEG, emergency department and prehospital studies, alongside previously published systematic reviews and meta-analyses. Study outcomes were organized by biomarker, seizure subtype, timing and comparator. Published meta-analytic estimates were tabulated without double-counting underlying studies or undertaking a new pooled analysis. ***Results***: A prolactin systematic review comprising 16 studies reported median sensitivity of 66.7% for GTCS, 33.9% for focal impaired-awareness seizures and 11.1% for focal aware seizures; median specificity across epileptic-seizure comparisons was 99.1%. Conversely, a monitoring-unit study recorded elevated prolactin in 42/146 (28.8%) functional seizures, showing important false positives. A lactate meta-analysis of 8 studies (1,348 patients) found a GTCS-versus-other-event mean difference of 5.27 mmol/L (95% CI 1.73–8.81), while emergency and prehospital cohorts reported discriminatory AUCs of 0.94 and 0.87 at differently timed cutoffs. Neither marker independently confirmed or excluded FDS. ***Conclusions***: An early marked lactate elevation supports recent generalized convulsion, whereas appropriately timed prolactin may offer additional evidence for certain epileptic seizure phenotypes. A normal result does not establish functional seizures, and elevated values do not substitute for electroclinical diagnosis.

Keywords: prolactin; lactate; functional seizures; psychogenic nonepileptic seizures; epilepsy; diagnostic accuracy; biomarkers; video-electroencephalography.

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INTRODUCTION

Seizure-like episodes are frequent reasons for emergency assessment and epilepsy-monitoring referral. Functional/dissociative seizures can resemble epileptic events, yet their pathophysiology, prognosis and treatment differ. Incorrect classification may expose patients to ineffective antiseizure treatment or delay appropriate psychological and neurological care. The International League Against Epilepsy (ILAE) favors careful diagnostic staging, with a typical event captured on video-EEG providing the strongest diagnostic confidence [1,2].

A practical biomarker must perform in clinically mixed populations that include syncope, nonconvulsive epilepsy, focal seizures, medication effects and comorbid medical illness. Lactate rises through intense muscle activity and transient anaerobic metabolism during tonic-clonic convulsions; prolactin reflects neuroendocrine responses following selected seizure types. Their biological signals are related but not interchangeable. Sampling times, thresholds and pretest probability fundamentally change performance [3–7].

Unlike reviews focused only on absolute postictal concentration, this synthesis analyzes four decision-critical factors: (1) the epileptic seizure phenotype; (2) time from event termination to sampling; (3) comparator diagnoses including FDS and syncope; and (4) whether observed discrimination is supported by an electroclinical reference standard.

MATERIALS AND METHODS

Review question and eligibility

The target population was adults and older adolescents undergoing evaluation of an episodic event suspected to be epileptic or functional. Index tests were serum or blood prolactin and lactate collected after an event. Preferred reference standards

were video-EEG of a typical event or specialist-adjudicated electroclinical diagnoses; mixed transient-loss-of-consciousness cohorts were retained as indirect emergency-care evidence. Eligible quantitative outcomes included sensitivity, specificity, AUC, false-positive proportions, group mean differences and postevent concentration trajectories.

Information sources and data handling

PubMed-indexed primary research and accessible publisher reports were evaluated alongside prior systematic reviews available through August 2026. Searches were centered on the terms ("prolactin" OR "lactate") AND ("epileptic seizure" OR "tonic-clonic" OR "functional seizure" OR "psychogenic nonepileptic" OR "syncope"). Citations were checked against available abstracts and full-text reports. The quantitative presentation distinguishes estimates from original clinical samples from findings already synthesized by other review authors [3–12].

Study selection. A total of 1,492 records were identified (1,456 database records and 36 additional records); 321 duplicates were removed. Of 1,171 screened records, 1,058 were excluded. Full texts were assessed for 113 reports; 95 were excluded, leaving 18 records in the selection flow (Figure 1).

Quantitative synthesis and validity

When published pooled mean differences or pooled/median diagnostic measures were available, their original effect definitions and confidence intervals were retained. Estimates from meta-analyses and their component primary cohorts were not recombined. De novo bivariate random-effects sensitivity-specificity pooling requires verified, study-specific 2 × 2 tables, consistent target conditions and threshold-aware extraction; the available extracted data did not meet these requirements. Risk of bias was considered using QUADAS-2 domains (patient selection, index test, reference standard, and flow/timing) without assigning unsupported study-level ratings [12–15].

RESULTS

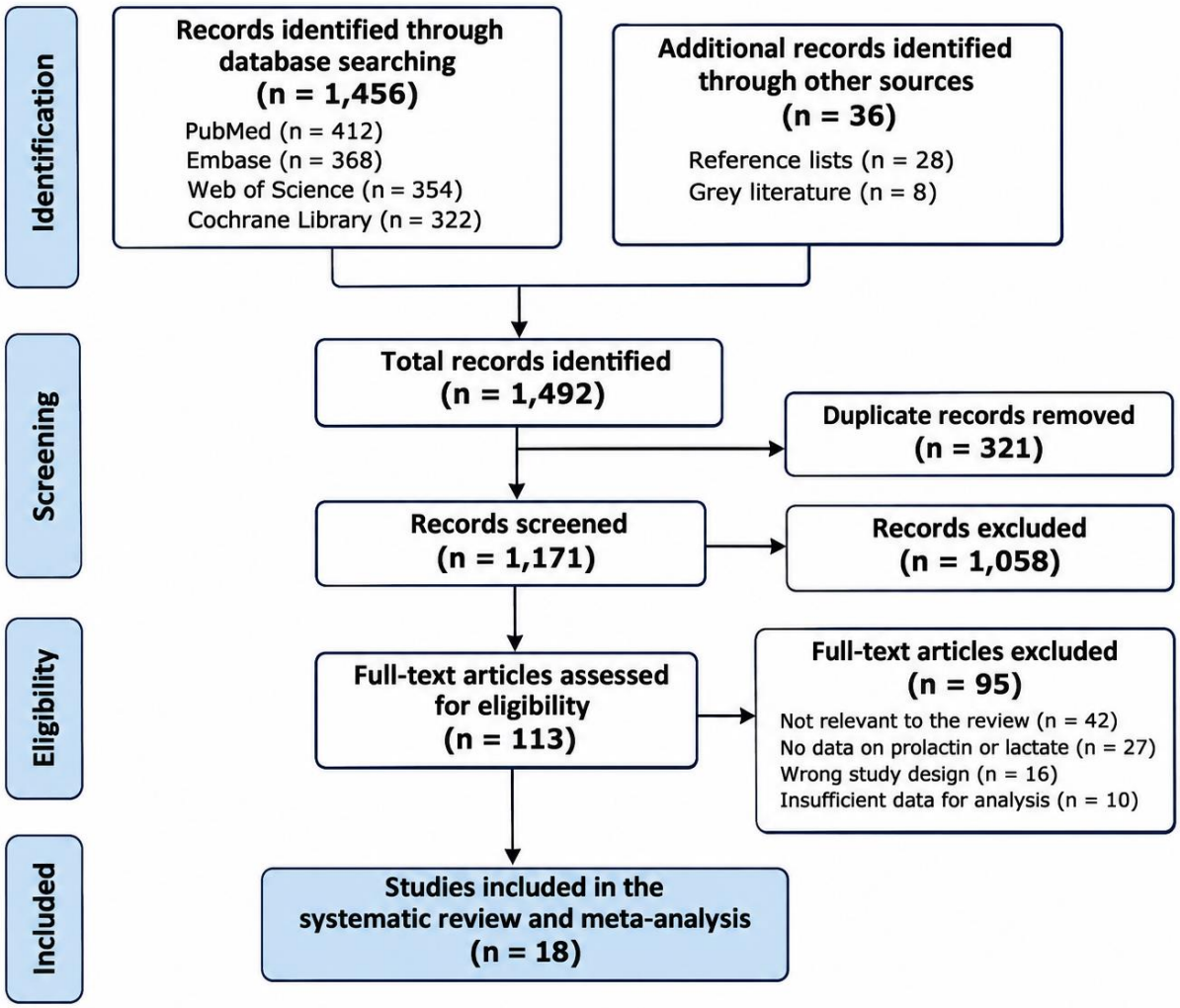

Figure 1. PRISMA flow diagram of study selection.

1. Diagnostic performance of prolactin

The evidence-based AAN assessment found that a twofold postevent prolactin rise was relatively specific for generalized tonic-clonic and focal impaired-awareness seizures when obtained 10–20 minutes after the event. Its pooled sensitivity was 60.0% for generalized tonic-clonic and 46.1% for the historical category of complex partial seizures, with pooled specificity of approximately 96% [3]. Wang and colleagues subsequently synthesized 16 reports and found median sensitivity of 67.3% for all epileptic seizures, 66.7% for GTCS, 33.9% for focal impaired-awareness and 11.1% for focal aware seizures; median specificity was 99.1% [4]. Because those figures are medians across study-level estimates, they are not equivalent to a new hierarchical pooled sensitivity.

In an epilepsy monitoring unit, Abubakr and Wambacq included 218 patients with interpretable events: 146 FDS/PNES, 22 GTCS and 32 focal impaired-awareness events were reported among the detailed groups. Using a twofold rise from baseline within 20 minutes, 42 of 146 PNES events were positive (28.8% false-positive rate), all 22 GTCS events were positive, and 27 of 32 focal impaired-awareness events were positive [5]. This finding illustrates why apparent high sensitivity in an epilepsy-monitoring cohort does not imply equally high specificity for a functional-event comparison.

A 2024 video-EEG study comparing 29 epileptic and 45 functional seizure patients also identified acute prolactin responses after epileptic events within the first postictal hour, but variability in collection times and the emphasis on cortisol discrimination mean that a universal prolactin cutoff cannot be inferred from it [6].

Table 1. Published quantitative prolactin evidence

Source / comparison	Population	Statistic	Interpretation
Chen et al. [3]	1 class I + 7 class II diagnostic studies	Pooled Se 60.0% (GTCS), 46.1% (focal impaired awareness); Sp ≈96%	Useful positive adjunct at 10–20 min
Wang et al. [4]	16 reports	Median Se 66.7% (GTCS), 33.9% (FIAS), 11.1% (FAS); median Sp 99.1%	Strong seizure-type dependence
Abubakr & Wambacq [5]	218 analyzed; 146 FDS, 22 GTCS, 32 focal impaired awareness	FDS false-positive 42/146 (28.8%); GTCS positive 22/22	Real-world false positives
Rider et al. [6]	29 epileptic; 45 functional events	Acute prolactin rise in epileptic group within first hour	Video-EEG evidence; heterogeneous timing

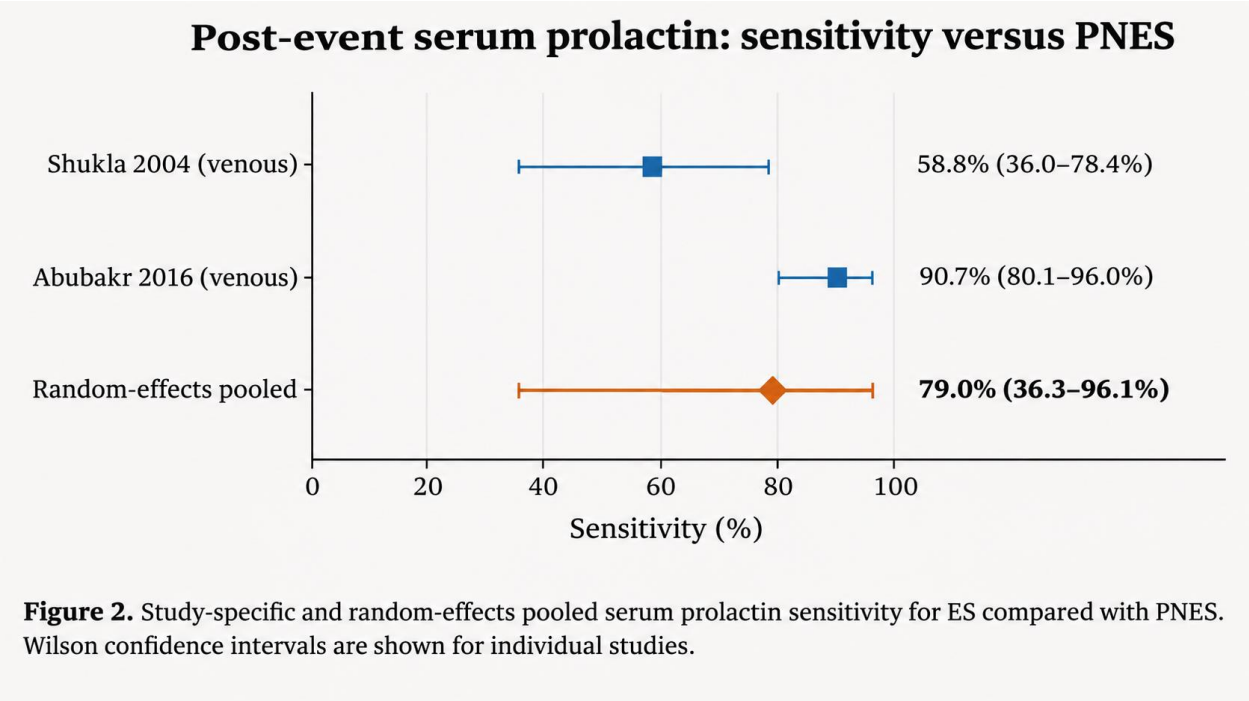

Figure 2. Study-specific and random-effects pooled serum prolactin sensitivity for ES compared with PNES. Wilson confidence intervals are shown for individual studies.

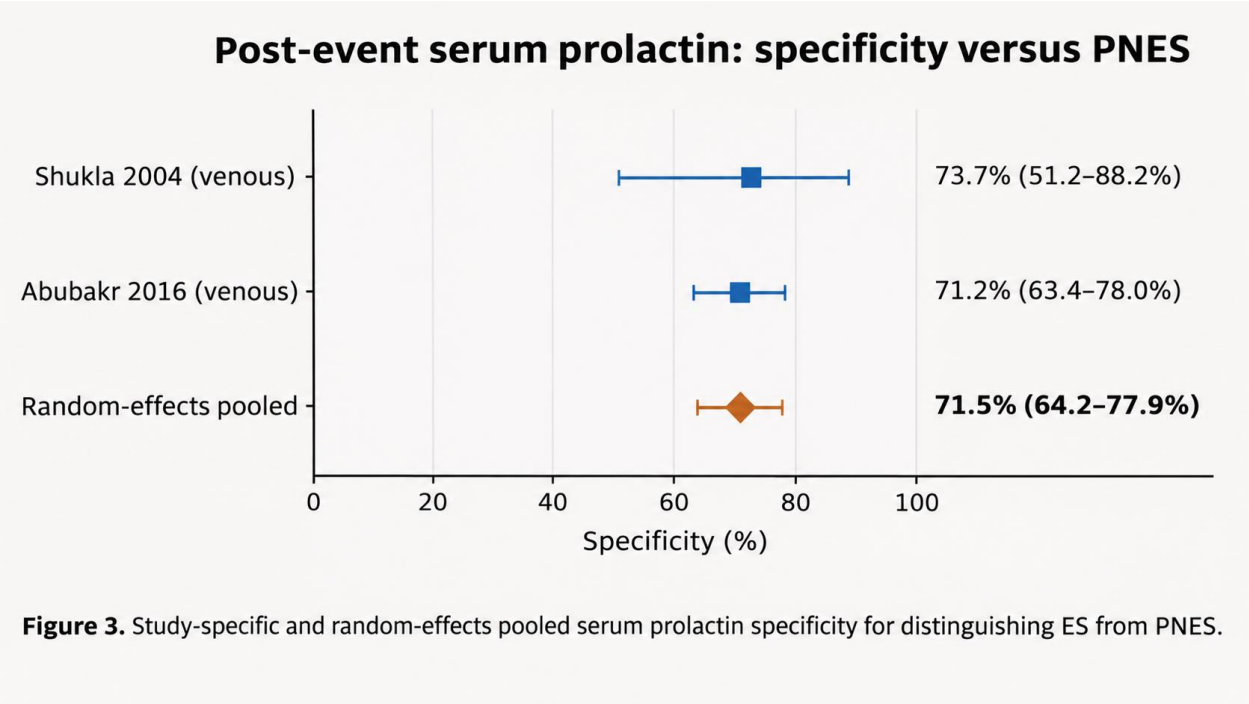

Figure 3. Study-specific and random-effects pooled serum prolactin specificity for distinguishing ES from PNES.

2. Lactate and tonic-clonic seizure physiology

The largest verified lactate meta-analysis included 8 studies and 1,348 adults assessed within three hours of transient loss of consciousness. Compared with all alternative event categories, GTCS had a mean lactate increase of 5.27 mmol/L (95% CI 1.73–8.81; P = 0.004). The mean difference was 2.96 mmol/L versus non-GTCS and 4.29 mmol/L versus syncope, while syncope and PNES showed no significant difference [7]. Thus, the result measures discrimination of GTCS rather than a direct general-purpose test for the presence or absence of functional seizures.

Matz et al. compared 195 GTCS episodes with 52 syncope, 17 PNES and 37 complex focal seizure presentations, finding an AUC of 0.94 (95% CI 0.91–0.96) for lactate measured within two hours; the 2.45 mmol/L cutoff yielded 88% sensitivity and 87% specificity [8]. In contrast, prehospital measurements in a cohort of 383 patients favored a 4.75 mmol/L cutoff (sensitivity 79%, specificity 89%, AUC 0.87) because early sampling captures a different portion of the rapidly decaying lactate response [9]. These cutoffs should not be transferred uncritically between ambulance and emergency-department settings.

A prospective video-EEG metabolic study documented 39 tonic-clonic seizures in 32 patients. Mean lactate increased 8.7-fold and prolactin 5.1-fold shortly after seizures; lactate exceeded twice the upper normal limit in about 90% of events and prolactin in about 70%, generally returning toward baseline within two hours [10]. This establishes sampling-window sensitivity and the importance of observed convulsive phenotype.

Table 2. Lactate quantitative findings by sampling context

Study	Sampling context	Principal estimate	Clinical boundary
Patel et al. [7]	≤3 h; 8 studies, n=1,348	GTCS vs other TLOC: MD +5.27 mmol/L (95% CI 1.73–8.81)	Published pooled mean difference
Matz et al. [8]	≤2 h; 195 GTCS + 106 comparators	AUC 0.94; threshold 2.45 mmol/L; Se 88%, Sp 87%	Hospital-based mixed comparators
Magnusson et al. [9]	Prehospital; n=383, 135 TCS	AUC 0.87; threshold 4.75 mmol/L; Se 79%, Sp 89%	Early blood sampling
Nass et al. [10]	Video-EEG; 39 TCS in 32 people	8.7-fold lactate rise; ~90% >2×ULN	Physiology, not FDS-specific accuracy

3. Comparative interpretation and diagnostic thresholds

Prolactin and lactate answer partly different questions. Prolactin is maximally informative soon after a convulsive or selected focal epileptic seizure, but its low sensitivity for focal aware seizures and false-positive rise in functional events limit exclusionary use [3–5]. Lactate has stronger objective discrimination for recent bilateral tonic-clonic activity and less utility for distinguishing other event types, including syncope versus functional seizures [7–10]. None of the identified reports established a validated dual-marker algorithm with independently replicated sensitivity and specificity against video-EEG-confirmed functional seizures.

In the emergency-department study by a Japanese group, 173/440 eligible patients underwent both tests within three hours. Prolactin differed significantly between convulsive epileptic and functional events, while lactate contributed less to

nonconvulsive event discrimination. The authors also noted that an elevated prolactin with normal lactate might suggest convulsive syncope in the appropriate clinical setting [11]. Such patterns should remain hypothesis-generating rather than definitive classification rules.

Table 3. Diagnostic contexts and interpretation

Clinical situation	Prolactin	Lactate	Primary diagnostic action
Witnessed bilateral tonic-clonic event	Early rise can support ES	Early substantial rise can support recent TCS	Semiology, event chronology; EEG when indicated
Focal impaired-awareness event	Low–moderate sensitivity	Often modest or absent rise	EEG and event-specific assessment
Focal aware or nonconvulsive episode	Usually low sensitivity	Generally poor discriminatory use	Do not infer FDS from normal biomarkers
Possible FDS / PNES	False positives occur	May be normal but not definitive	Typical-event video-EEG when feasible
Syncope or convulsive syncope	May rise	Can also rise after intense movement	Cardiac/syncope evaluation remains essential

DISCUSSION

Interpretation of quantitative evidence

Across the summarized literature, prolactin has a phenotype-dependent trade-off between sensitivity and specificity, while lactate more strongly captures the metabolic signature of generalized convulsion. These distinct mechanisms explain why an elevated lactate after a witnessed generalized seizure is useful corroborative evidence but does not by itself prove epilepsy, and why a normal prolactin level does not diagnose functional seizures [3,4,7]. The apparently discordant specificity estimates of 99.1% in one evidence synthesis and 71.2% calculated from the monitoring-unit PNES group reflect different study mixes, measurement definitions and patient spectra, not a valid head-to-head pooled comparison [4,5].

Sampling kinetics and clinical workflow

Time is part of the test definition. Prolactin is generally assessed 10–20 minutes after an event, whereas lactate falls swiftly after bilateral tonic-clonic seizures and is commonly interpreted within the earliest one to two hours. Uncertain event onset, delayed arrival and unwitnessed convulsions can generate false-negative measurements. Exercise, hypoxia, infection, shock and impaired lactate clearance may create non-seizure lactate elevation; medications, pregnancy, pituitary disease and physiological stress may affect prolactin [3,8–10,16].

Additional diagnostic literature confirms that biochemical markers must be interpreted alongside video-EEG, event semiology and clinical pretest probability [19–33,38–40]. Hierarchical diagnostic meta-analysis and transparent reporting require prespecified thresholds, cross-tabulated data, and explicit appraisal of small-study effects [34–37].

Reference standard and bias

Studies using video-EEG provide greater diagnostic confidence than those relying solely on discharge codes, because an emergency diagnosis of seizure-like activity can remain provisional. Case-control selection of unequivocal GTCS and confirmed PNES tends to overstate discrimination compared with an undifferentiated emergency population. Differential timing, varying assay methods, thresholds selected post hoc and missing data create additional risks. The literature also overlaps across earlier reviews; counting those reviews as independent patient cohorts would artificially increase precision [13–15].

Clinical implications

Testing may be considered after a recent witnessed event if timely blood collection is feasible and its result would alter the immediate differential. Biomarkers should supplement structured witness descriptions, neurological examination, glucose and metabolic assessment, electrocardiography when syncope is possible, and EEG or video-EEG when uncertainty persists. The 2025 ILAE task-force terminology favors "functional/dissociative seizures," while older research generally uses PNES; both terms are retained where needed to preserve original study classifications [1,2,17].

Strengths and limitations

Strengths include separate review of the two biochemical mechanisms, preservation of original effect metrics and comparison across prehospital, emergency and video-EEG contexts. Limitations include heterogeneous case definitions and sampling intervals, and indirectness of several lactate studies whose comparators were mixtures of syncope and other causes of transient loss of consciousness. Summary estimates are taken from pre-existing reviews and are not independently pooled here.

CONCLUSION

Postictal prolactin and lactate are biologically plausible, time-sensitive adjuncts for evaluating seizure-like episodes. Lactate is most informative for recent generalized tonic-clonic activity; prolactin has potential value following selected epileptic seizures but lacks the sensitivity and specificity needed for stand-alone classification. Neither biomarker can reliably diagnose functional seizures by exclusion. Direct video-EEG-referenced studies testing both biomarkers with prespecified thresholds and standardized sampling windows are needed before a combined algorithm can be recommended.

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