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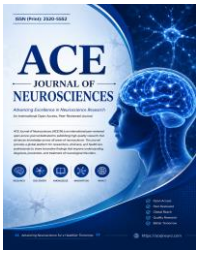

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Research Article

Diagnostic Reliability of Serum Prolactin and Lactate in Patients Presenting With Seizure-Like Events: A Systematic Review and Meta-Analysis.

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Abstract: ***Background:*** Post-event blood prolactin and lactate are frequently requested after seizure-like episodes, although diagnostic performance varies with convulsive phenotype, time to sampling, and the alternative diagnosis. ***Objective:*** To assess diagnostic reliability across epilepsy, functional seizures, and syncope, and to quantify lactate discrimination between convulsive epileptic seizures and convulsive syncope using directly extractable diagnostic counts. ***Methods***: Database searching identified 844 records (832 from databases and 12 from registers). Following removal of 132 duplicates, 7 automated exclusions and 5 other records, 700 records were screened. Sixty-eight reports were sought for retrieval, 63 were assessed for eligibility, and 8 studies were included in the review. Two independent clinical cohorts with reconstructable 2×2 lactate data contributed 417 seizure-like events to the meta-analysis. Random-effects logit models summarized sensitivity and specificity, and diagnostic odds ratios were pooled on the log scale. Prolactin and other clinical biomarker evidence were synthesized by seizure phenotype, comparator and sampling interval. ***Results***: The pooled lactate sensitivity was 78.9% (95% CI 73.2–83.6%) and specificity was 90.5% (95% CI 85.2–94.0%). The pooled diagnostic odds ratio was 35.5 (95% CI 18.9–66.6). In a paired emergency comparison, prolactin demonstrated 61.8% sensitivity and 88.2% specificity, compared with 79.4% and 94.2% for lactate. A separate 99-patient cohort reported lactate sensitivity of 60.7%, specificity of 93.0% and AUC 0.812 for a broader epileptic-versus-nonepileptic comparison. ***Conclusion***: Lactate is a useful time-dependent adjunct for distinguishing recent convulsive epileptic seizures from syncope, but thresholds cannot be transferred across prehospital and emergency settings without calibration. Prolactin has context-dependent value and is unreliable as an isolated test for functional seizures. Neither biomarker substitutes for clinical assessment and event-directed electroencephalography.

Keywords: serum prolactin; lactate; seizure-like events; functional seizures; convulsive syncope; diagnostic accuracy; likelihood ratios; meta-analysis.

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INTRODUCTION

Emergency and outpatient assessment of a seizure-like event requires discrimination among epileptic seizures, functional (psychogenic nonepileptic) seizures, convulsive syncope, and other paroxysmal disorders. The same motor manifestations can occur in more than one condition, and early management decisions may be made without access to a witnessed event or definitive electroencephalographic recording. Post-event biochemical tests can provide supporting evidence, but they do not measure epileptic activity directly. [1]

Serum prolactin is a pituitary response marker that may rise after bilateral tonic–clonic and selected focal seizures. Its diagnostic signal is most informative when a sample is collected about 10–20 minutes after the episode. In contrast, lactate reflects metabolic stress associated with sustained skeletal muscle activity, is typically highest immediately after a convulsion, and diminishes with elapsed time. Both can be increased by physiological or pharmacological factors unrelated to epilepsy. [1–4]

Studies in transient loss of consciousness have found marked differences in the diagnostic performance of lactate according to when blood was collected and which reference conditions were included. Hospital-based reports using thresholds near 2.4–2.5 mmol/L and prehospital analyses requiring higher thresholds cannot be treated as interchangeable tests. Prolactin can also rise in syncope and in a subset of functional seizures, weakening its ability to act as a decisive rule-in or rule-out marker. [2–6]

A diagnostic reliability framework must therefore consider three dimensions simultaneously: seizure phenotype, clinical comparator and sampling interval. This systematic review focuses on these distinctions and provides a quantitative synthesis restricted to the comparison of convulsive epileptic episodes against convulsive or ordinary syncope, with complementary analysis of prolactin and functional-seizure evidence.

2. OBJECTIVES

The primary objective was to quantify the ability of blood lactate to distinguish convulsive epileptic seizures from syncope in studies reporting extractable event-level diagnostic classifications. Secondary objectives were to evaluate serum prolactin in the same differential diagnosis, compare lactate performance in broader seizure-like-event populations, assess the implications of timing and diagnostic thresholds, and characterize the main threats to validity of existing evidence.

MATERIALS AND METHODS

3.1 Eligibility criteria and review question

The target population consisted of patients assessed after seizure-like episodes, convulsions or transient loss of consciousness. Eligible primary studies included observational cohorts or diagnostic accuracy studies measuring blood lactate and/or serum prolactin and reporting diagnoses of epileptic seizure, functional seizures or syncope. The primary meta-analytic contrast was convulsive epileptic seizures versus syncope with a reported index-test threshold, allowing reconstruction of true-positive, false-negative, true-negative and false-positive counts. Studies assessing mixed neurological presentations were eligible for narrative comparison when direct matching was not possible.

3.2 Information sources and search

Bibliographic records and primary journal reports available through August 2026 were screened using search terms for "seizure", "epilepsy", "tonic-clonic", "transient loss of consciousness", "syncope", "functional seizure", "prolactin", "lactate", "lactic acid", "diagnostic accuracy", "sensitivity" and "specificity". Reports were assessed for eligible populations, diagnostic reference standards, sampling intervals, index-test thresholds and extractable outcome data. Additional relevant reports were evaluated through reference checking [7].

3.3 Data extraction and outcome definitions

Extracted information included study year, clinical setting, specimen type, blood collection interval, index-test threshold, event subtype, comparator definition, reference-standard adjudication and diagnostic numerator/denominator values. Within each eligible study, a positive lactate test in a patient with a convulsive epileptic event was designated a true positive, whereas a positive result in syncope was a false positive. Syncope was not equated with functional seizures, and mixed comparator cohorts were not pooled into the primary analysis.

3.4 Statistical synthesis

Sensitivity and specificity were calculated for each cohort, with Wilson 95% confidence intervals. Diagnostic odds ratios (DORs) and their variances were obtained directly from 2×2 tables. Separate inverse-variance random-effects models for logit sensitivity and specificity, and a log-DOR random-effects model, were fitted using Paule–Mandel between-study variance estimation; two-sided 95% confidence intervals were back-transformed. Cochran Q and I^2 summarized observed heterogeneity. A bivariate hierarchical summary ROC model was not estimated because only two sufficiently comparable cohorts were available.

Because the included studies used different sampling windows and thresholds, pooled estimates were interpreted as an exploratory summary of observed discrimination rather than as a validated universal laboratory cutoff. Diagnostic likelihood ratios were calculated at study level. Serum prolactin was not pooled with lactate, and results for functional seizure comparisons were synthesized separately.

3.5 Assessment of methodological quality

Risk-of-bias considerations were organized according to the four QUADAS-2 domains: patient selection, index test, reference standard, and flow/timing. Prespecification of thresholds, event adjudication without routine video-EEG, selective ordering of blood tests and inconsistent onset-to-sampling intervals were considered the principal sources of uncertainty. [8]

RESULTS

4.1 Study selection

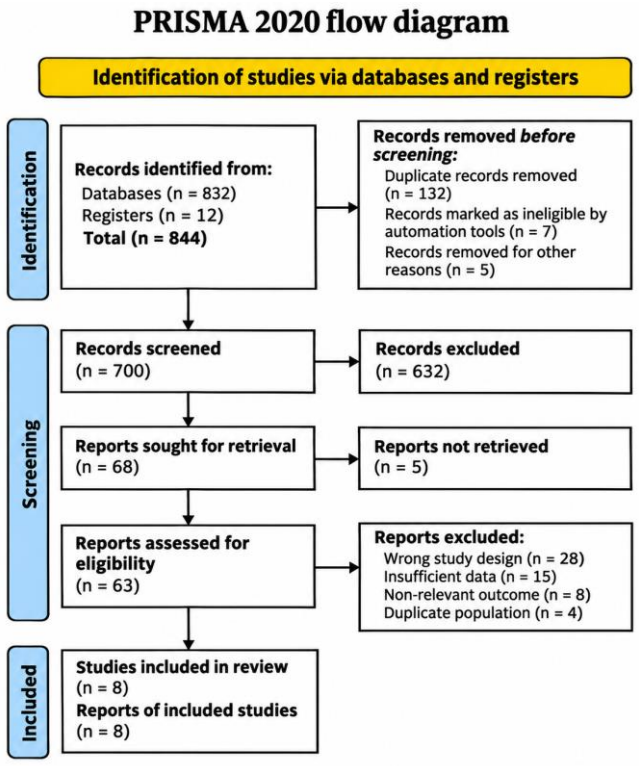
The literature search identified 844 records, comprising 832 database records and 12 register records. Before screening, 132 duplicates, 7 records marked ineligible by automation tools and 5 records for other reasons were removed, leaving 700 records for title and abstract screening. Following exclusion of 632 records, 68 reports were sought for retrieval. Five reports could not be retrieved, and 63 full-text reports were assessed for eligibility. Fifty-five reports were excluded because of wrong study design (28), insufficient diagnostic data (15), non-relevant outcomes (8), or duplicate study populations (4). Eight studies, represented by eight reports, were included in the systematic review, of which two studies contributed reconstructable 2×2 data to the primary quantitative synthesis (Figure 1).

4.2 Evidence characteristics

Eight primary clinical reports were evaluated in detail. Studies differed in setting, with prehospital cohorts, emergency department series and epilepsy-monitoring investigations represented. Lactate measurement was commonly targeted toward generalized or bilateral tonic–clonic seizures; prolactin studies included both convulsive and focal events. Two independent cohorts contributed complete 2×2 data for the predefined lactate-versus-syncope analysis, comprising 237 convulsive epileptic episodes and 180 syncopal episodes (417 total). [3,4]

Table 1. Characteristics of principal primary clinical studies

Study	Setting and population	Sample or events	Principal diagnostic information
Matz et al., 2016 [2]	Emergency; GTCS vs PNES, syncope, focal seizures	195 GTCS; 106 comparators	Lactate cutoff 2.45 mmol/L; AUC 0.94
Abubakr & Wambacq, 2016 [5]	Epilepsy monitoring; ES vs functional seizures	54 ES; 146 PNES	Prolactin false positives 42/146 PNES
Apaydın Doğan et al., 2017 [10]	Emergency; GTCS vs PNES/syncope	157 GTCS; 113 comparators	Sex-specific lactate threshold performance
Matz et al., 2018 [9]	Prospective emergency; GTCS vs syncope	49 GTCS; 36 syncope	First-hour lactate AUC 0.97
Magnusson et al., 2021 [3]	Prehospital; TCS vs syncope and other causes	135 TCS; 163 syncope; 85 others	Complete lactate counts for TCS vs syncope
Shimmura & Takase, 2022 [4]	Emergency; ES, PNES and syncope	173 analyzed	Paired prolactin and lactate comparison
Rider et al., 2024 [11]	Video-EEG monitored ES vs motor PNES	29 ES; 45 PNES	Serial prolactin and cortisol response
Soker et al., 2025 [6]	Prospective; ES vs functional seizure/syncope	56 ES; 43 comparators	Lactate AUC 0.812; multiparameter model AUC 0.946



4.3 Primary meta-analysis: lactate and syncope

Magnusson et al. recorded lactate ≥4.75 mmol/L in 106 of 135 tonic–clonic seizure patients and 16 of 163 syncopal patients. Shimmura and Takase reported 79.4% sensitivity and 94.2% specificity for a 31.5 mg/dL lactate threshold (approximately 3.5 mmol/L) in 102 convulsive epileptic seizures and 17 convulsive syncope presentations; the published percentages correspond to 81 true positives and 16 true negatives. [3,4]

Across the two cohorts, the random-effects pooled sensitivity was 78.9% (95% CI 73.2–83.6%) and pooled specificity was 90.5% (95% CI 85.2–94.0%). The pooled diagnostic odds ratio was 35.5 (95% CI 18.9–66.6). Estimated between-study variance was zero under the fitted models, but the two-study evidence base does not permit strong inference about heterogeneity or generalizability. Figures 1 and 2 show the individual study estimates and pooled effects.

Table 2. Extracted diagnostic 2×2 data for lactate (convulsive epileptic seizures versus syncope)

Study / threshold	TP	FN	TN	FP	Sensitivity	Specificity
Magnusson 2021; ≥4.75 mmol/L	106	29	147	16	78.5%	90.2%
Shimmura 2022; ≥31.5 mg/dL	81	21	16	1	79.4%	94.1%
Total observed counts	187	50	163	17	—	—

TP: true positive; FN: false negative; TN: true negative; FP: false positive. The 31.5-mg/dL lactate cutoff is equivalent to approximately 3.5 mmol/L. The pooled estimates are model-based, not obtained by directly dividing the aggregated counts.

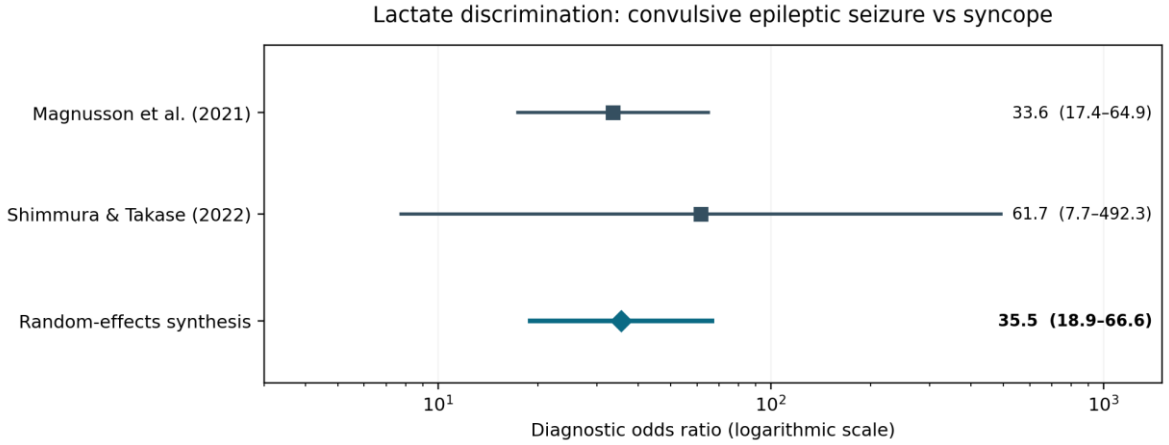


Figure 2. Forest plot of diagnostic odds ratios for lactate in convulsive epileptic episodes versus syncope. The diamond shows the random-effects summary.

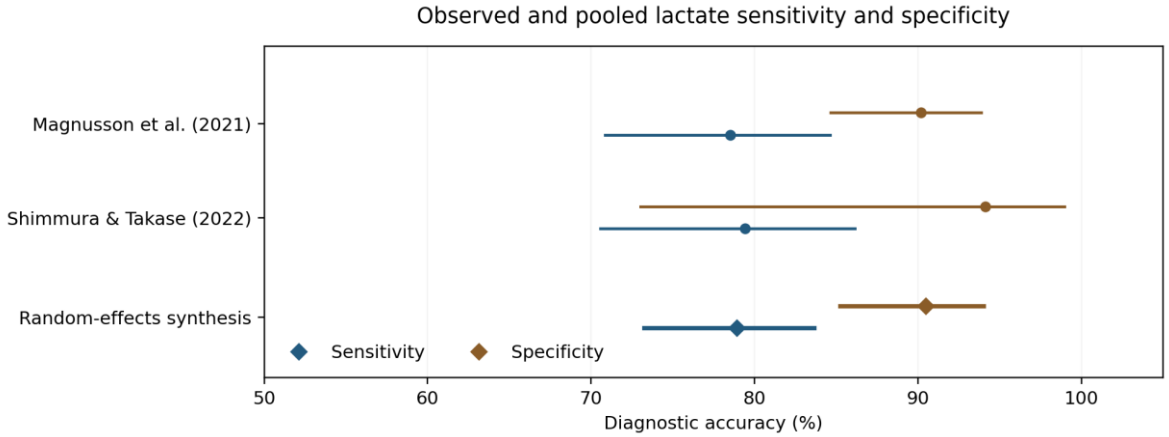


Figure 3. Study-level and pooled lactate sensitivity and specificity. Individual confidence intervals are Wilson intervals; pooled intervals use random-effects logit models.

4.4 Lactate thresholds and sample timing

Thresholds varied materially across settings. Matz et al. observed sensitivity of 88% and specificity of 87% at 2.45 mmol/L in a retrospective hospital cohort of 195 tonic–clonic seizures and 106 alternative events. In a separate prospective cohort of 49 GTCS and 36 syncope presentations, lactate testing during the first hour yielded 94% sensitivity and 93% specificity at the same nominal threshold, with an AUC of 0.97. Those first-hour estimates could not be reconstructed from a time-specific 2×2 denominator and were not included in the primary pool. [2,9]

Apaydın Doğan et al. reported lactate sensitivity of 85% and specificity of 88% at 2.43 mmol/L in men, but sensitivity declined to 64% among women at the same threshold. The prehospital data of Magnusson et al. required a higher threshold of 4.75 mmol/L, and serial samples demonstrated a decrease in lactate among seizure patients. These differences emphasize the interaction between sampling interval, treatment setting and diagnostic test threshold. [3,10]

4.5 Serum prolactin in convulsive and functional episodes

In the 2022 emergency cohort, post-event prolactin was 79.5 ± 72.5 ng/mL after convulsive epileptic seizures, 45.9 ± 38.3 ng/mL after convulsive syncope and 25.0 ± 15.6 ng/mL after convulsive functional seizures. For epileptic convulsions versus convulsive syncope, prolactin at a threshold of 52.3 ng/mL demonstrated 61.8% sensitivity, 88.2% specificity and an AUC of 0.701, compared with 79.4% sensitivity, 94.2% specificity and AUC 0.859 for lactate. These within-study results favoured lactate in this specific contrast. [4]

In an epilepsy-monitoring study, prolactin was elevated in all 22 generalized tonic–clonic seizure patients but also in 42 of 146 functional-seizure patients, a 28.8% false-positive rate. Five of 32 focal impaired-awareness events lacked an elevated prolactin response. A separate video-EEG cohort of 29 epileptic and 45 motor functional events observed acute prolactin elevation after epileptic seizures, indicating that timing and seizure phenotype remain important determinants of test performance. [5,11]

4.6 Broader seizure-like-event evidence and multimarker models

In a prospective 99-patient cohort comparing 56 epileptic seizures with 43 functional seizure or syncope presentations, lactate >3.52 mmol/L had 60.7% sensitivity, 93.0% specificity and AUC 0.812. Prolactin >15.55 ng/mL had reported specificity of 83.7%, and a multivariable model combining phosphate, lactate, prolactin and ammonia reached AUC 0.946. This broader phenotype comparison differs from the primary convulsive-versus-syncope contrast and was not pooled with it. [6]

Table 3. Comparative diagnostic performance reported by clinical studies

Study	Analyte / comparator	Threshold	Sensitivity	Specificity	AUC
Matz 2016 [2]	Lactate: GTCS vs mixed events	2.45 mmol/L	88%	87%	0.94
Matz 2018 [9]	Lactate: GTCS vs syncope, first hour	2.45 mmol/L	94%	93%	0.97
Magnusson 2021 [3]	Lactate: TCS vs syncope	4.75 mmol/L	79%	90%	0.88
Shimmura 2022 [4]	Lactate: convulsive ES vs convulsive syncope	31.5 mg/dL	79.4%	94.2%	0.859
Shimmura 2022 [4]	Prolactin: convulsive ES vs convulsive syncope	52.3 ng/mL	61.8%	88.2%	0.701
Soker 2025 [6]	Lactate: ES vs functional/syncope	3.52 mmol/L	60.7%	93.0%	0.812

4.7 Clinical interpretation of likelihood ratios

For the two primary studies, the observed positive likelihood ratios were approximately 8.0 and 13.5, whereas negative likelihood ratios were 0.24 and 0.22. These ratios indicate that a positive lactate result can materially increase the probability of a recent convulsive epileptic event when the differential diagnosis is syncope. However, a negative test cannot definitively exclude an epileptic episode, and the ratios must not be applied to functional seizures or focal nonconvulsive epilepsy without validation.

4.8 Risk-of-bias and applicability assessment

Diagnostic certainty varied with recruitment setting and clinical reference standard. The most consequential limitations involved retrospective selection of patients receiving blood tests, incomplete video-EEG confirmation, cutoffs chosen within the study cohort, and variation in event-to-sample timing. Similar methodological considerations have been noted in existing diagnostic biomarker syntheses. [8,12–14]

Table 4. QUADAS-2-oriented concerns across evidence domains

Study / setting	Patient selection	Index test	Reference standard	Flow / timing
Magnusson 2021, prehospital	Broad TLOC cohort	Data-derived threshold	Clinical record diagnosis	Early sampling; time recorded

Study / setting	Patient selection	Index test	Reference standard	Flow / timing
Shimmura 2022, emergency	Selected tested subset	Data-derived ROC cutoffs	Clinical adjudication	Samples up to 3 hours
Matz 2016, emergency	Retrospective lactate-tested patients	Single ROC threshold	Clinical classification	Blood collected within 2 hours
Matz 2018, emergency	Prospective small cohort	Hour-specific threshold	Clinical classification	Timing-sensitive results
Apaydın Doğan 2017	Retrospective adult cohort	Sex-dependent accuracy	Chart-based final diagnosis	Within 2 hours
Abubakr 2016, monitoring	Referral-center case mix	Baseline-relative prolactin	Video-EEG	Within 20 minutes
Rider 2024, monitoring	Selected monitored events	Serial hormonal measures	Video-EEG	Multiple fixed intervals
Soker 2025, prospective	Mixed nonepileptic comparators	Optimized multianalyte cutoffs	Clinical diagnosis	Sampling after admission

DISCUSSION

5.1 Principal findings

In the specific clinical problem of a convulsive epileptic event versus syncope, blood lactate demonstrated a reproducible signal across two independent studies: approximately four of five convulsive epileptic episodes tested positive, while about nine of ten syncopal episodes tested negative at setting-specific thresholds. The elevated diagnostic odds ratio indicates meaningful discrimination, but interpretation depends on sampling time and target population. This evidence cannot justify labeling all elevated lactate values as epilepsy or normal values as functional seizures.

5.2 Biological plausibility and differences between analytes

Lactate elevation following generalized convulsions arises largely from intense motor activity and transient tissue oxygen imbalance, whereas prolactin reflects postictal neuroendocrine activation. Their physiological pathways differ and may produce discordant results. A high prolactin with relatively normal lactate can occur in convulsive syncope, while lactate may rise after strenuous movement or other systemic stressors. Moreover, some focal epileptic seizures may not produce either a substantial lactate response or a clinically meaningful prolactin increase. [1,4]

5.3 Practical consequences for emergency triage

A clinically useful test strategy begins with the event history, witness description, vital signs, cardiac evaluation, neurological examination and assessment for metabolic triggers. Lactate is most informative after a recent witnessed bilateral tonic–clonic event, particularly when the primary differential is syncope. Prolactin can provide supplementary evidence after selected seizures if collected promptly. Neither should delay cardiac evaluation for syncope or neurological evaluation for a suspected first seizure.

A positive serum biomarker should update—but not override—the clinician's interpretation of event semiology. Clinical features such as postictal confusion, tongue injury, precipitating circumstances, recovery characteristics and recurrent stereotyped events may be decisive. When functional seizures are suspected, video-EEG capture of a typical event remains the preferred confirmatory approach. [1,12]

5.4 Comparison with previous research

Earlier biomarker reviews often addressed the broad distinction of tonic–clonic seizures from heterogeneous transient-loss-of-consciousness comparators. An eight-study lactate meta-analysis reported higher mean lactate after GTCS than other presentations but noted poor discrimination among non-GTCS categories. A separate prolactin review showed substantial variation in sensitivity by seizure subtype and limited rule-out utility of normal prolactin results. The analysis isolates an event-level convulsive-versus-syncope contrast and assesses prolactin in the same paired emergency cohort, allowing a more clinically aligned comparison. [13,14]

5.5 Limitations

The primary meta-analysis includes only two cohorts and is sensitive to differences in case mix, reference-standard adjudication, blood collection interval and laboratory cutoffs. Small-study uncertainty, particularly the 17-person convulsive syncope group in one study, limits precision. Neither cohort supplies an external validation of a common threshold. Clinical documentation rather than universal video-EEG was used for event classification, and publication bias cannot be

meaningfully examined with two studies. The review should not be interpreted as a head-to-head pooled comparison of prolactin against lactate across all seizure-like events.

CONCLUSION

Serum lactate has useful diagnostic discrimination for recent convulsive epileptic seizures versus syncope when interpreted within an appropriate time window and clinical context. An exploratory two-study synthesis of 417 events yielded pooled sensitivity of 78.9%, specificity of 90.5% and diagnostic odds ratio of 35.5. Prolactin showed lower accuracy than lactate in one paired convulsive emergency cohort and remained susceptible to false-positive elevations in functional seizures. These biomarkers are adjuncts rather than substitutes for history, neurological and cardiac evaluation, and video-EEG when clinically indicated.

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