Received: 18 April 2018 | Revised: 16 October 2018 | Accepted: 17 October 2018

DOI: 10.1111/epi.14598

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Diagnostic and prognostic value of noninvasive long-term video-electroencephalographic monitoring in epilepsy surgery: A systematic review and meta-analysis from the E-PILEPSY consortium

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Summary

Objective: The European Union–funded E-PILEPSY network (now continuing within the European Reference Network for rare and complex epilepsies [Epi-CARE]) aims to harmonize and optimize presurgical diagnostic procedures by creating and implementing evidence-based guidelines across Europe. The present study evaluates the current evidence on the diagnostic accuracy of long-term video-electroencephalographic monitoring (LTM) in identifying the epileptogenic zone in epilepsy surgery candidates.

Methods: MEDLINE, Embase, CENTRAL, and ClinicalTrials.gov were searched for relevant articles. First, we used random-effects meta-analytical models to calculate pooled estimates of sensitivity and specificity with respect to postsurgical seizure freedom. In a second phase, we analyzed individual patient data in an exploratory fashion, assessing diagnostic accuracy within lesional and nonlesional temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (ETLE) patients. We also evaluated seizure freedom rate in the presence of "localizing" or "nonlocalizing" LTM within each group. The quality of evidence was assessed using the QUADAS-2 tool and the GRADE approach.

Results: Ninety-four studies were eligible. Forty-four were included in sensitivity meta-analysis and 34 in specificity meta-analysis. Pooled sensitivity was 0.70 (95% confidence interval [CI] = 0.60-0.80) and specificity was 0.40 (95% CI = 0.27-0.54). Subgroup analysis was based on individual data of 534 patients (41% men). In lesional TLE patients, sensitivity was 0.85 (95% CI = 0.81-0.89) and specificity was −0.19 (95% CI = 0.13-0.28). In lesional ETLE patients, a sensitivity of 0.47 (95% CI = 0.36-0.58) and specificity of 0.35 (95% CI = 0.21-0.53) were observed.

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Funding information
European Union grant agreement 20131203, in the framework of the Health Program

In lesional TLE, if LTM was localizing and concordant with resection site, the seizure freedom rate was 247 of 333 (74%), whereas in lesional ETLE it was 34 of 56 (61%). The quality of evidence was assigned as "very low."

Significance: Long-term video-electroencephalographic monitoring is associated with moderate sensitivity and low specificity in identification of the epileptogenic zone. Sensitivity is remarkably higher in lesional TLE compared to lesional ETLE. Substantial heterogeneity across the studies indicates the need for improved design and quality of reporting.

KEYWORDS
epilepsy surgery, seizure outcome, sensitivity, specificity, video-EEG

1 | INTRODUCTION

Epilepsy surgery has been proven to be a highly effective treatment in carefully selected patients with drug-resistant focal epilepsies[1–5] and is associated with a significant proportion of seizure-free patients, improved quality of life, and reduced health care and societal costs.[6–11] However, epilepsy surgery remains largely underutilized.[12]

In 2014, a European Union–funded pilot European Reference Network (E-PILEPSY; http://www.ucl.ac.uk/www.e-pilepsy.eu) of reference centers for refractory epilepsy and epilepsy surgery was established with the aim of harmonizing and optimizing presurgical diagnostic procedures by creating and implementing evidence-based guidelines and recommendations across Europe.

Video-electroencephalographic (EEG) long-term monitoring (LTM) is the centerpiece of the presurgical evaluation.[13–17] However, the diagnostic value of LTM in defining the particular brain region that has to be removed to make the patient seizure-free (ie, the epileptogenic zone [EZ]) is unclear. Here, we present a systematic review of the current evidence for sensitivity and specificity of LTM in defining the EZ.

Key Points

- The pooled sensitivity and specificity of LTM in identification of the EZ in presurgical evaluation of epilepsy were 70% and 40%, respectively
- In the subgroup of lesional TLE patients, sensitivity was higher (85%) compared to the sensitivity (47%) observed in the lesional ETLE group
- In lesional TLE patients, the rate of seizure freedom was 74% when LTM was "localizing" and concordant with the site of surgical resection
- A high risk of bias was observed in a considerable proportion of included studies; the quality of evidence was assigned as "very low"
- There is a clear need for improvement in planning, conducting, and reporting of studies on diagnostic utility of LTM

2 | MATERIALS AND METHODS

A protocol for this review was developed in consultation with the E-PILEPSY expert panel and published on PROSPERO (CRD42016041938).[18]

The review addressed the following research question: what is the diagnostic accuracy of noninvasive LTM in the presurgical evaluation of patients with pharmacoresistant epilepsy? The index test was LTM. The reference standard was seizure freedom (yes/no), based on data from at least 1 year of follow-up after surgery.

The results of this systematic review were reported in accordance with the PRISMA statement (Table S1).[19]

2.1 | Sources of information

The comprehensive search strategies (Appendix S1) were implemented in the bibliographic databases MEDLINE (PubMed), Embase, CENTRAL, and ClinicalTrials.gov. The searches were carried out in June 2015. The searches were limited to human studies; no other restrictions were imposed.

2.2 | Eligibility criteria

We included all studies, irrespective of their design and methodological quality if they (1) sought to assess the diagnostic accuracy of a presurgical noninvasive LTM or provided data sufficient for estimating sensitivity and specificity

of LTM, (2) included pharmacoresistant epilepsy patients (definition as stated in the article) who underwent epilepsy surgery (resective/palliative), and (3) reported postoperative seizure outcome at a minimum of 1 year of follow-up. Studies were excluded if they (1) were not published in English, (2) were narrative reviews, or (3) were published only in abstract form or as conference proceedings.

Patients had to fulfill the following criteria for inclusion in the subgroup analysis at the individual level: (1) underwent a presurgical noninvasive LTM, (2) had resective (complete resection) epilepsy surgery, (3) were followed up for at least 1 year after surgery, and (4) had detailed presentation of data on surgical intervention (eg, side, location). Patients were excluded if they had (1) a generalized epilepsy syndrome, (2) palliative epilepsy surgery, (3) incomplete resection due to proximity/overlap with eloquent brain area of a presumed EZ (as stated in the article), or (4) brain surgery not associated with epilepsy.

2.3 | Definitions

We applied the following definitions for the purpose of this review (the rationales behind these definitions are provided in Appendix S2):

- Long-term monitoring was defined as *localizing* when, based on ictal electroclinical findings, it pointed to a single focal brain area at a sublobar or lobar level, or to a contiguous brain region if more than one adjacent lobes were involved.
- The term *electroclinical findings* refers to lateralizing and localizing ictal EEG findings in combination with the seizure semiology being documented with the video-EEG recordings.
- Long-term monitoring was defined as *nonlocalizing* when, based on ictal electroclinical findings, it pointed to more than one separate brain area (ie, independent focus) or to the involvement of the entire brain, or was noninformative.
- Localizing LTM result was classified as true positive (TP) or false positive (FP) if, after resective surgery, the patient achieved or failed to achieve seizure freedom, respectively. Concordance between the site of LTM localization and the site of surgical resection was required.
- Localizing LTM was classified as concordant with the site of surgery if a brain area being localized by LTM coincided with the resected EZ at the sublobar or lobar level. Partial concordance at the sublobar level also qualified as a concordant result. However, if the resected EZ involved brain area that was not pointed out by LTM, it was considered discordant.
- Nonlocalizing LTM result was defined as true negative (TN) or false negative (FN) if, after resective surgery, the patient failed to achieve or achieved seizure freedom, respectively.
- Seizure freedom was defined as complete absence of seizures (Engel class IA or International League Against Epilepsy class Ia; if the study did not specify the subclass or the classification scale used, complete cessation of seizures had to be reported) at a minimum of 1 year of postoperative follow-up.
- Sensitivity was defined as the ability of a noninvasive LTM to correctly localize the EZ in patients with localization-related epilepsy who became seizure-free after resective surgery. In other words, sensitivity was the proportion of seizure-free patients who had localizing LTM results concordant with the site of surgical resection.
- Specificity was the proportion of patients with nonlocalizing LTM results who failed to achieve seizure freedom after resective surgery.

2.4 | Study selection

Titles and abstracts were screened initially, by pairs of 10 reviewers (T.K., G.Ku., J.H., G.Ka., M.L., J.D., A.R., C.N., F.E., F.B.). Full texts of selected articles were then evaluated for eligibility against predefined criteria. Any disagreements were resolved through discussion; a third reviewer was consulted when consensus could not be reached.

2.5 | Data collection

Two independent reviewers (T.K., G.Ku.) conducted the data extraction by using a Web-based, standardized, piloted data extraction form (Table S2). It was organized into six domains that contained 121 items. Disagreements were resolved through discussions. If consensus was not reached, the judgment was referred to a third reviewer (F.B.).

2.6 | Assessment of study quality

Two independent reviewers (T.K., G.Ku.) assessed the quality of individual studies in accordance with the QUADAS-2 tool,[20] with disagreements resolved by consensus or by consulting the third reviewer (F.B.). The items of a quality appraisal tool were adapted and piloted to ensure consistency of interpretation among the reviewers. Results were summarized and presented for studies that contributed to the individual level analysis only.

The quality of evidence across studies was assessed using the GRADE methodology.[21] Criteria suggested for downgrading the quality of evidence were modified when necessary. A list of all patient-important outcomes was generated and ranked according to their importance on a 1-9 scale. Quality appraisal was based on the consensus of two independent reviewers (T.K., F.B).

Summary of findings tables were generated for all patient-important outcomes that included a relevant number of patients.

2.7 | Synthesis of results

Data analysis was conducted in two phases.

2.7.1 | First phase: A study-level analysis

Studies that provided sufficient data to create 2 × 2 contingency tables were pooled in meta-analysis. In case the variance estimates were equal to 0 (ie, if sensitivity/specificity were 0 or 1), the rule "add two successes and two failures" proposed by Agresti and Caffo[22] was used. We set up two univariate random-effects meta-analytical models, with sensitivity and specificity as effect sizes, respectively. The rationale behind selecting this method is provided in Appendix S3.

2.7.2 | Second phase: Subgroup analysis at individual patient level

Individual patient data were collected from the original articles when available. There were two reasons for this decision that had evolved over the course of the review: (1) heterogeneity between studies or within study population (eg, patients with different epilepsy types or syndromes) and (2) evaluation of concordance between the site of LTM localization and the site of surgical resection was only possible at the individual level.

The analysis comprised two main steps. At first, we assessed the diagnostic accuracy of noninvasive LTM in different subgroups of patients. For this purpose, we classified the LTM findings for each patient as TP, TN, FP, or FN, as shown in Table 1.This classification had to be based on two variables: the result of a noninvasive LTM (index test) and the postoperative seizure outcome (reference standard). However, in our study reference, standard was determined by surgical intervention, and therefore surgery must have been considered when correlating the LTM result with the postoperative seizure outcome. Whenever localizing LTM was discordant with the site of surgery, the third variable (concordance with surgery) had to be incorporated into the analysis. This would make it impossible to use 2 × 2 table and hence to calculate the sensitivity and specificity. Furthermore, when LTM was localizing and discordant with the site of surgery and seizure remission was not achieved we were unable to classify such cases. Therefore, it was decided a priori to include in the 2 × 2 table only those cases where LTM was either localizing and concordant with the site of surgical resection, or was nonlocalizing. Hence, those cases where LTM was localizing but discordant with the site of surgical resection (13 cases for lesional temporal lobe epilepsy [TLE] and seven for lesional extratemporal lobe epilepsy [ETLE]) were excluded.

TABLE 1 A 2 × 2 contingency table illustrating correlation between the LTM results, site of surgery, and seizure outcome

LTM	Site of surgery	Seizure-free	Not seizure-free
Localizing[a] LTM	Concordant with the resection site[b]	TP	FP
Nonlocalizing[c] LTM	N/A	FN	TN

FN, false-negative; FP, false-positive; LTM, long-term video-electroencephalographic monitoring; N/A, not applicable; TN, true-negative; TP, true-positive.
[a]LTM findings localizing to a single focal brain area.
[b]Side and region of surgery is concordant with the LTM findings at the lobar/sublobar level.
[c]LTM findings pointing to more than one separate brain area or to the entire brain, or were noninformative.

Considering the abovementioned reasons, the following patient groups were included in the individual patient analysis:

- Patients with localizing LTM results who underwent surgery (concordant with the brain area pointed out by noninvasive LTM) and achieved seizure freedom.
- Patients with localizing LTM results who underwent surgery (concordant with the brain area pointed out by noninvasive LTM) but failed to enter surgical remission.
- Patients with nonlocalizing LTM results who underwent surgery and achieved seizure freedom.
- Patients with nonlocalizing LTM results who underwent surgery but failed to enter surgical remission.

Then, we calculated sensitivities and specificities for lesional TLE and lesional ETLE patients separately. Patients were allocated into the lesional or nonlesional epilepsy group on the bases of magnetic resonance imaging (MRI) and pathology findings. MRI-negative patients with a verifiable lesion on histology were attributed to the lesional group. Additionally, we assessed the impact of certain pathologies on LTM accuracy in a graphical way. For sensitivities, the number of TPs and FNs within each pathological category were displayed in a bar plot. Graphics for specificities were created analogously. To quantify the findings from this descriptive analysis, we additionally conducted simple logistic regression analyses for the data of lesional TLE and ETLE subgroups, for each specific pathology separately.

In the second part of the individual patient data analysis, we evaluated how postoperative seizure outcome may differ in the presence of localizing or nonlocalizing LTM

results. At first, for each subgroup, the LTM findings were classified as either localizing or nonlocalizing. The localizing LTMs were further categorized into concordant and discordant with respect to the site of surgical resection. We then calculated the number of seizure-free patients for each category and summarized the results in a tabular form. Finally, we compared the odds of being seizure-free between the patients with localizing and nonlocalizing LTM results. Patients with localizing LTM discordant with the resection site were excluded.

Statistical analyses were carried out using R version 3.3.2 (R Core Team 2016).[23]

3 | RESULTS

3.1 | Study selection

Ninety-four studies were included in the review. Of these 94 studies, only 48 were eligible for meta-analysis, and 40 for subgroup analysis (Table S3). The selection process using the PRISMA flow diagram is shown in Figure 1.

3.2 | Study characteristics

Ninety-four studies comprised 3541 patients. Eighty-eight of these studies were retrospective and six prospective, mainly consisting of case series and case reports. Study characteristics are summarized in Appendix S4 and Tables S4.1-S4.5.

3.3 | Synthesis of results

3.3.1 | Phase 1: The study-level meta-analysis

We had to exclude several studies (n = 46) for the following reasons: missing data (eg, studies in which neither TP nor FN values were available, and hence the sensitivity could not be calculated) and small "sample sizes" (eg, studies where the sum of the TP and FN values was equal to 0 or 1). Of the remaining 48 studies, we eventually included 44 studies (n = 1623 patients) in the sensitivity and 34 studies (n = 1391 patients) in the specificity meta-analysis, respectively.

The meta-analyses yielded a sensitivity estimate of 0.70 (95% confidence interval [CI] = 0.60-0.80) and a specificity estimate of 0.40 (95% CI = 0.27-0.54). Figures S1.1 and S1.2 show forest plots of sensitivity and specificity, respectively. In both forest plots, the between-study variability seems to be quite large, which is consistent with the highly significant results of the test for heterogeneity (sensitivity: $I^2 = 94.9\%$, 95% CI = 93.3-97.3, $P < 0.0001$; specificity: $I^2 = 92.6\%$, 95% CI = 86.6-95.1, $P < 0.0001$).

We incorporated moderator variables in the meta-analytical models to explain this variability at least to some extent. Among all variables included in the covariate analysis, significant impact on sensitivity was shown with increased proportion of patients with ETLE. Similar results were seen with larger proportion of patients with concordant MRI and LTM findings (Tables S5.1 and S5.2).

3.3.2 | Phase 2: Subgroup analysis

Individual patient data derived from 534 patients (156/384 [41%] men, 150/534 [28%] no data available) were pooled into one single dataset and analyzed in an exploratory fashion.

In the first step, the sensitivity and specificity estimates of the LTM were assessed. This was performed for the lesional TLE and lesional ETLE groups separately. In the nonlesional TLE and nonlesional ETLE groups, the sample size was too small to perform reliable statistical analysis (Table S6). In lesional TLE patients, the pooled sensitivity and specificity were 0.85 (95% CI = 0.81-0.89) and 0.19 (95% CI = 0.13-0.28), respectively, whereas in lesional ETLE patients, we found a pooled sensitivity of 0.47 (95% CI = 0.36-0.58) and specificity of 0.35 (95% CI = 0.21-0.53).

In both lesional TLE and ETLE patients, we further assessed the impact of certain etiologies (represented by pathological findings) on the LTM accuracy in a graphical way. The plots are depicted in Figures 2A, 2B, S2.1, and S2.2. Regarding the distribution of pathologies, we can see that in the lesional TLE group, hippocampal sclerosis is the most common (219/406, 54%) finding on pathology. The sensitivity and specificity of LTM with respect to hippocampal sclerosis were 0.88 (95% CI = 0.82-0.92) and 0.17 (95% CI = 0.09-0.29), respectively. Details are provided in Appendix S5 and Table S7.

In a second step, we assessed the rate of seizure freedom with respect to localizing and nonlocalizing LTM categories in each subgroup. The results showed that in the TLE group, the seizure freedom rate was 247 of 333 (74%) if LTM was localizing and concordant with the site of a resection. By contrast, in the nonlesional TLE group, the seizure freedom rate with localizing and concordant LTM was only four of 11 (36%; Table 2). We then compared the odds of seizure freedom between two groups of patients (LTM localizing and concordant with the resection site vs nonlocalizing LTM) to see how the odds of being seizure-free differ in the presence/absence of localizing LTM. The results showed that in the TLE group the odds of being seizure-free might be higher (odds ratio = 1.4, 95% CI = 0.8-2.5), when LTM is localizing and concordant with the resection site compared to a nonlocalizing LTM. By contrast, in the lesional ETLE group, the contrary is true, with

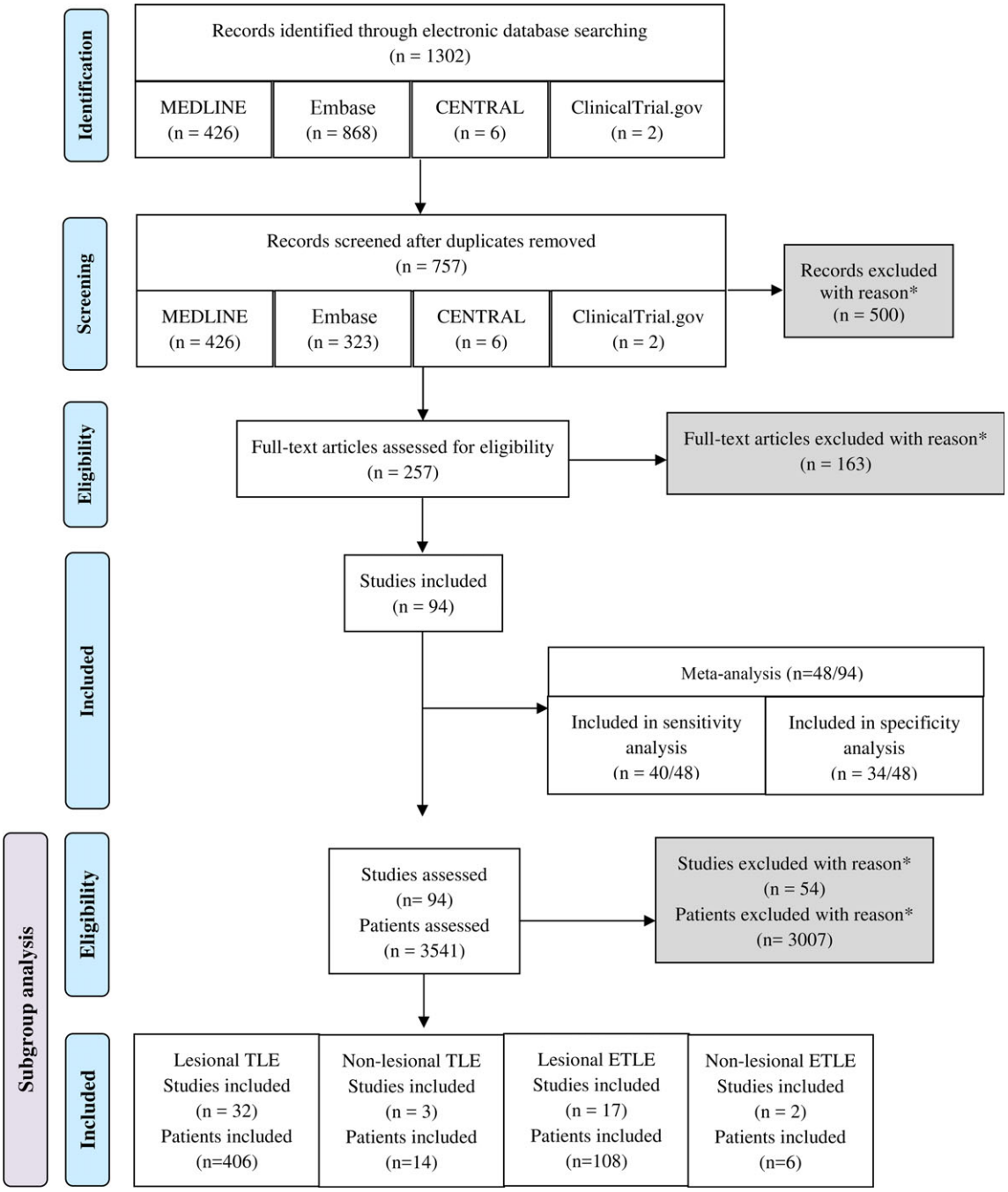

FIGURE 1 PRISMA flow diagram showing the selection process of the studies including in the review. *Reasons for excluding records or full-text articles were as follows. Title and abstracts screening stage: records were unrelated to the topic being reviewed (n = 498), abstracts were not available (n = 2). Full text screening stage: no data given to assess the "localization ability" of noninvasive long-term monitoring (LTM; n = 61), reference standard (postsurgical follow-up [FU]) < 1 year (n = 3), not available in English (n = 15), full texts not available (n = 7), abstract supplement (n = 75), data from single study was used in two papers (n = 1), no data given concerning epilepsy surgery (n = 1). Subgroup analysis: studies did not provide individual patient data required to populate 2 × 2 contingency table (n = 44, including 2731 patients; in addition, three more studies did not provide individual patient data for the subset of included patients [n = 109]; overall, individual patient data were not provided for 2840 patients), patients with generalized epilepsy syndrome (n = 17), patients with palliative surgery (n = 15), patients with incomplete resection (n = 18), patients in whom surgery was not performed (patient declined/lost to FU; n = 58), patients on ongoing evaluation/waiting list (n = 2/n = 1), lost to FU (n = 2), FU < 1 year (n = 14), insufficient data regarding noninvasive LTM (n = 35), no LTM performed (n = 2), surgery performed to treat acute symptomatic refractory status epilepticus (n = 1), bilateral surgery (n = 2). If there was more than one reason for exclusion for the same patient, we counted it only once (eg, if there was incomplete resection of the epileptogenic zone and FU < 1 year, only one of them was counted) in the above summary. For a more detailed description, see Table S2. ETLE, extratemporal lobe epilepsy; TLE, temporal lobe epilepsy

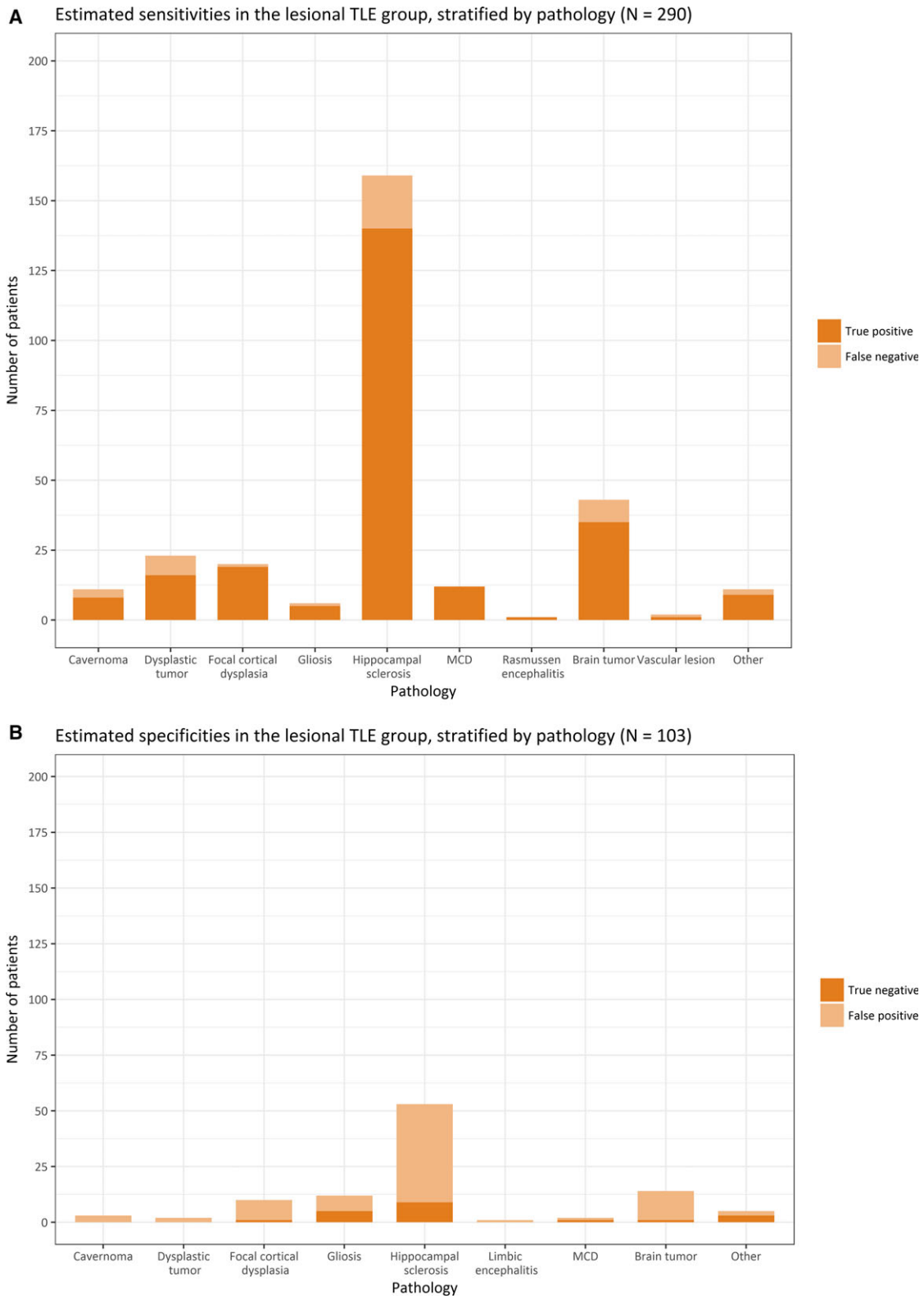

FIGURE 2 A, Sensitivity in the lesional temporal lobe epilepsy (TLE) group with respect to etiology represented by histopathological findings. B, Specificity in the lesional TLE group with respect to etiology represented by histopathological findings. MCD, malformation of cortical development

TABLE 2 Postoperative seizure freedom rates with respect to localizing and nonlocalizing LTM in different subgroups of patients

LTM	Site of surgical resection	Seizure-free patients, n (%)[a]	Non–seizure-free patients, n (%)[a]
Lesional TLE group			
Localizing[b] LTM	Concordant with resection site[c]	247 (74)	86 (26)
	Discordant with resection site	10 (83)	2 (17)
Nonlocalizing[d] LTM	N/A	41 (67)	20 (33)
Lesional ETLE group			
Localizing LTM	Concordant with resection site	34 (61)	22 (39)
	Discordant with resection site	2 (67)	1 (33)
Nonlocalizing LTM	N/A	38 (72)	11 (22)
Nonlesional TLE group			
Localizing LTM	Concordant with resection site	4 (36)	7 (64)
	Discordant with resection site	1 (33)	2 (67)
Nonlocalizing LTM	N/A	0 (0)	0 (0)
Nonlesional ETLE group			
Localizing LTM	Concordant with resection site	2 (50)	2 (50)
	Discordant with resection site	0 (0)	0 (0)
Nonlocalizing LTM	N/A	1 (50)	1 (50)

ETLE, extratemporal lobe epilepsy; LTM, long-term video-electroencephalographic monitoring; N/A, not applicable; TLE, temporal lobe epilepsy.
[a]Percentage was calculated per each category (eg, rate of seizure-free patients per "localizing LTM, concordant with resection site" category).
[b]LTM findings localizing to a single brain area.
[c]Side and region of surgery.
[d]LTM findings pointing to more than one separate brain area or to the involvement of an entire brain, or were noninformative.

TABLE 3 Odds ratios representing the odds of being seizure-free if the LTM is localizing[a] and concordant with the surgical resection compared to nonlocalizing[b] LTM

	Odds ratio[c]	95% CI lower	95% CI upper
Lesional TLE	1.41	0.79	2.53
Lesional ETLE	0.46	0.20	1.07
Nonlesional TLE	0.60	0.01	35.86
Nonlesional ETLE	1.00	0.06	17.51

CI, confidence interval; ETLE, extratemporal lobe epilepsy; LTM, long-term video-electroencephalographic monitoring; TLE, temporal lobe epilepsy.
[a]LTM findings localizing to a single brain area.
[b]LTM findings pointing to more than one separate brain area or to the entire brain, or were noninformative.
[c]The cutoff value is 1.

an odds ratio of 0.46 (95% CI = 0.2-1.0). Details are presented in Table 3.

3.4 | Risk of bias within studies

None of the 40 eligible studies was free from bias. Details on risk of bias and applicability assessments for each subgroup are presented in Appendix S6, Tables S8-S11, and Figures S3-S6.

3.5 | Risk of bias across studies

Postoperative seizure freedom and improved quality of life were selected as outcomes of critical importance. Sensitivity and specificity were categorized as important for decision making, and were rated as 6 and 4 on a 1-9 scale, respectively. Adverse events related to LTM were mainly classified as critical for decision making.

We defined baseline quality as high. The reasons for this decision are explained in Appendix S7. After applying the GRADE criteria, we eventually ended up with a very low quality of evidence. Rationales for our judgments were documented and made transparent (Appendix S7). Evidence tables and the summary of findings tables can be found in Tables S12-S21.2.

4 | DISCUSSION

This is the first systematic review and meta-analysis evaluating diagnostic accuracy of noninvasive LTM in the presurgical evaluation of epilepsy patients. As already mentioned in the Materials and Methods section, our approach was different from the conventional method of assessing the diagnostic accuracy of a test. This is mainly because the purpose of noninvasive LTM during presurgical

evaluation is to localize the EZ in patients with a previously established condition, and therefore it addresses the localization-related rather than the diagnostic question. Furthermore, in the case of a standard diagnostic test, dichotomization of test results into positive or negative depends on predefined cutoff values; however, this does not apply to LTM. This explains our choice to classify LTM findings into localizing and nonlocalizing. Another important issue to be considered was to precisely define the degree of overlap between the brain area being localized by LTM and the area resected during epilepsy surgery. In those cases where LTM pointed to a more extensive area than was surgically resected, we considered concordance as partial; however, we still classified them as concordant cases. After classifying results as TP, FN, TN, or FP, we attempted to translate these diagnostic accuracy measures into sensitivity and specificity. It must be emphasized that in the present review neither sensitivity nor specificity can be interpreted in a straightforward way. Specifically, sensitivity and specificity did not rely only on results of LTM (ie, it is not a pure indicator of diagnostic accuracy), but also on surgery itself. Hence, they reflect both diagnostic accuracy and prognosis. Furthermore, sensitivity and specificity of LTM can be influenced by the accuracy of other diagnostic modalities of presurgical workup, as they also contribute to the surgical decision and have an impact on postoperative seizure outcome. Considering that our study includes series from 1993 to 2017, the diagnostic technologies used in the presurgical workup might vary across included papers. However, available data do not allow exploration of the degree of heterogeneity between those technologies and their impact on the diagnostic accuracy of LTM.

Subgroup analysis demonstrated that the sensitivity is substantially higher in the lesional TLE group compared to the lesional ETLE group. This finding was also supported by moderator analyses that pointed to a significant impact on sensitivity with increasing proportion of patients with ETLE. These numbers reflect the clinical practice when LTM is usually nonlocalizing in frontal lobe epilepsy patients with hypermotor seizures (mainly such patients comprise the ETLE group). Moreover, our results indicate that the chance of being seizure-free is higher when LTM is localizing; however, substantial variability among studies indicates that definitive conclusions cannot be drawn. In summary, our findings are in line with the established scientific evidence showing that scalp EEG recordings are not sufficient in many instances, such as ETLE or nonlesional TLE, and further invasive investigations may be required.[24–26] Subgroup analysis demonstrated the low specificity of LTM in both the lesional TLE and ETLE groups. Low specificity was determined by a high proportion of FP cases. This would mean that LTM identified some presumed EZ, but the patient was not seizure-free after surgery. Partially, this means that LTM failed in correctly identifying the EZ. However, the fact that the patients could not achieve seizure freedom after surgery might also indicate failure of other diagnostic tests aside from LTM. We can only speculate that low specificity is determined by the proportion of "difficult" patients in whom the identification of the EZ is extremely challenging.

There are also some other determinants that may influence diagnostic test performance, including type and conduct of LTM, electrode placement systems employed, use of additional electrodes, duration of LTM, number of seizures recorded, provocative methods used to elicit seizures in epilepsy monitoring units (eg, withdrawal of antiepileptic drugs), and qualification of personnel reading the LTM recordings. Unfortunately, most studies (75/94, 80%) failed to report the relevant data. Hence, available evidence does not allow for any conclusions regarding the technical requirements and procedures of the LTM.

Another major challenge in evaluating the diagnostic accuracy of LTM is choosing the right reference standard. Although invasive LTM is considered a gold standard in the evaluation of patients for epilepsy surgery, not all candidates undergo investigations; hence, its applicability is limited. Another reference standard we sought to adopt for this review was a consensus decision made at the multidisciplinary epilepsy surgery conference. However, significant diversities observed in presurgical evaluation of patients across different epilepsy centers make this challenging.[27–29] Furthermore, studies either do not state explicitly, or do not report at all, the decision-making pathways used in assessment of eligibility for epilepsy surgery. Therefore, for the purpose of this review, we decided to choose postoperative seizure freedom as reference standard. It has been reported that the success of epilepsy surgery depends on the accurate localization of the EZ, which is defined as the minimum amount of brain tissue responsible for seizure generation, removal of which may lead to seizure freedom.[30] Therefore, the ability of LTM to correctly localize the EZ can be judged based on postoperative seizure outcome, where localizing LTM results are supported by achieving seizure freedom at a minimum of 1 year of postoperative follow-up. However, this reference standard also has some limitations that need to be addressed. Because the EZ is a hypothetical construct generated by results of different investigations, one can argue that the LTM alone is not sufficient to define the EZ (location and boundaries). Therefore, the diagnostic accuracy measures reported in our review should rather be considered as "diagnostic value of a multiple-investigations approach" including LTM. Furthermore, several factors influence postoperative seizure outcome. These include type of lesion, type of surgery performed, extent of surgical resection, professional

qualification of neurosurgeon, and setting where surgery was conducted. We attempted to minimize this influence by narrowing the target population for subgroup analysis down to the individual patient level. Particularly, we included only those patients who underwent resective surgery with a complete resection of a presumed EZ for pharmacoresistant focal epilepsy. By doing so, we created a scenario where achievement of postoperative seizure freedom was highly expected. If a patient failed to achieve seizure freedom, this could most likely be attributed to a limited diagnostic ability of LTM to correctly localize an EZ.

Several studies have looked at the postoperative seizure outcome with short (ie, 1-5 years) and long (ie, >5 years) of follow-up, respectively.[31–33] Of note, a systematic review by Tellez-Zenteno and colleagues[34] found that the long-term follow-up after epilepsy surgery is associated with less favorable seizure outcomes compared to outcomes observed relatively shortly after epilepsy surgery. In our study, three different postoperative evaluation scales were applied and the range of follow-up evaluation varied from 1.1 to 24.5 years, thus introducing an additional source of heterogeneity.

That LTM does not stand alone in presurgical evaluation of epilepsy but is part of a diagnostic hierarchy sometimes leads to discordant results between different investigations, and the decision for conducting surgery may be based on MRI results or other investigations rather than LTM. Therefore, it is essential to understand the independent contribution of each consecutive diagnostic modality to the decision-making process. Unfortunately, currently available scientific evidence does not allow for such an assessment.

5 | LIMITATIONS

The main limitations were associated with poor methodological quality and poor reporting of included studies leading to a large between-study variability/heterogeneity. We therefore analyzed the subgroups of patients at the individual patient level. However, due to the small number of studies, we could not assess the impact of several covariates simultaneously, but had to stay with separate univariate analyses. Moreover, a substantial number of studies, and hence also the respective patients were excluded due to unavailability of individual patient data. Especially in studies with moderately large samples, mainly aggregate data were reported. This could have introduced additional bias. Unfortunately, due to insufficient data, diagnostic accuracy could not be assessed in nonlesional TLE and ETLE groups at all. It is worth mentioning that in general original studies did not report data on the subset of patients who underwent noninvasive LTM but for some reason (eg, not a surgical candidate, refused to undergo surgery, lost to follow-up) did not undergo surgery. Although we acknowledge that these data could not be used for sensitivity and specificity analysis due to missing reference standard, it could still be useful for evaluating the extent to which the accuracy measures could have been underestimated/overestimated.

6 | CONCLUSIONS

Our systematic review found that the overall pooled estimates of sensitivity and specificity for noninvasive LTM in identification of EZ are moderate to low. In lesional TLE, sensitivity is relatively high, whereas specificity is considerably low. In lesional ETLE, both the sensitivity and specificity are moderate. Furthermore, the diagnostic accuracy in lesional TLE patients varies depending on etiology. However, due to limited, often incomplete, and very heterogeneous evidence, this aspect requires further investigation.

Our results also indicate that in lesional TLE patients, the chances of being seizure-free are larger when LTM is localizing and concordant with the site of surgical resection, compared to those patients in whom it is nonlocalizing. However, again, definitive conclusions cannot be made.

Considering the issues discussed above, it is obvious that the evaluation of diagnostic test performance on the basis of available scientific evidence has major limitations. The majority of the studies that we analyzed did not directly address the research question of our review. Therefore, the low quality of the evidence analyzed in the present study (as shown by QUADAS and GRADE results) leads to the conclusion that more focused studies are needed to reliably determine the role of LTM in epilepsy surgery. This is reflected in difficulties regarding interpretation and subsequent application of test accuracy measures in clinical practice. There is a clear need for improvement in planning, conducting, and reporting of studies on LTM. Moreover, prospective multicenter studies are necessary to evaluate the added value of different diagnostic modalities of presurgical workup, and to enable the standardization of this process. To this end, a national outcome registry with standardized recorded data from European epilepsy centers is essential. Despite the various substantial limitations, our study provides an important reference point for guiding further research and development in this area. Furthermore, we provide recommendations Appendix S7, Table S22 on reporting in future studies assessing the value of LTM in epilepsy surgery.

ACKNOWLEDGMENT

This publication arose from the project E-PILEPSY, which has received funding from the European Union (grant agreement 20131203) in the framework of the Health Program (2008-2013).

The data extraction form was created with SoSci Survey (Leiner, 2014) on www.soscisurvey.com.

DISCLOSURE OF CONFLICTS OF INTEREST

A.R. has received travel support and speaker honoraria from Eisai. C.N. has received travel support and speaker honoraria from Eisai. F.B. has received speaker honoraria from Eisai and Peer Voice, payment for consultancy from Eisai, and travel support from Eisai, ITALFARMACO, and UCB Pharma. G.Z. has received travel support from Eisai. J.H.C. has received remuneration to her department as a clinical investigator for Vitaflo, GW Pharma, and Zogenix. She has participated in advisory boards for UCB Pharma, Zogenix, GW Pharma, Nutricia, Takeda, and Eisai, and as a speaker for Shire, Nutricia, Zogenix, Nutricia, Biomarin, and GW Pharma, again for which remuneration was made to her department. She holds grants from the European Union, National Institute for Health and Research, Action Medical Research, Engineering and Physical Sciences Research Council, Epilepsy Research UK, Great Ormond Street Hospital Charity, and SPARKS. M.L. has received speaker honoraria from Eisai and Everpharma, and travel grants from Medtronic and UCB Pharma. The remaining authors have no conflicts of interest to report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kobulashvili T, Kuchukhidze G, Brigo F, et al. Diagnostic and prognostic value of noninvasive long-term video-electroencephalographic monitoring in epilepsy surgery: A systematic review and meta-analysis from the E-PILEPSY consortium. *Epilepsia*. 2018;59:2272–2283. https://doi.org/10.1111/epi.14598