

SURGERY FOR EPILEPSY

Assessing Evidence from

Observational Studies

Using Observational Studies in

Systematic Reviews

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BACKGROUND

- Surgery of epilepsy is a valuable option in patients in whom antiepileptic drugs have been shown to be ineffective and/or poorly tolerated
- Although up to 70-80% of cases with drug resistant epilepsy undergoing surgery are rendered seizure-free, the role of the indicators of the success of surgery is uncertain

ASSOCIATION OF PERIOPERATIVE FACTORS WITH OUTCOME OF EPILEPSY - I

- **Positive association**

- Prolonged FC
- EEG scalp: interictal AT localiz & unilat epileptiform abnorm
- EEG depth: ictal unilat sz onset & focal T localiz; long propag times
- MRI abnormalities
- MRI hippocampal sclerosis
- SPECT ictal hyperperfusion
- Qualitative PET T lobe abnorm
- IAT cogn impairm on resected lobe
- Extent of mesial resection

- **Negative association**

- Head trauma
- Preoperative convulsive sz
- EEG scalp: epileptiform abnorm 3 mos and 1 year after surgery
- MRI hippocampal sclerosis with developmental abnormalities
- Acute postop sz

McIntosh et al, *Epilepsia*
2001; 42: 1288-307

ASSOCIATION OF PERIOPERATIVE FACTORS WITH OUTCOME OF EPILEPSY - II

- **No association**

- Sex
- Age at onset
- Duration of epilepsy
- Age at surgery
- Preoperative aura
- Frequency of preop sz
- EEG depth vs scalp
- Tumor vs non-tumor or HS (MRI)
- Change of ECoG (pre- vs post-)
- Extent of lateral resection
- Length of follow-up

- **Inconclusive**

- Family hx of epilepsy
- Etiology (other than trauma)
- Simple and undef FC
- Type of preoperative sz
- Other EEG, ECoG, PET findings
- IQ measures
- HS and oth abnorm histopathology
- Tumor (type) vs non-tumor histop
- Type/timing acute postop sz
- Sz during 1st postop year

McIntosh et al, *Epilepsia*
2001; 42: 1288-307

REASONS FOR INCONCLUSIVE FINDINGS ABOUT RISK FACTORS

- Selection bias
- Small sample size
- Increased technologic, procedural, and diagnostic sophistication
- Varied measures of outcome and outcome analysis
- Univariate analysis of data

QUESTIONS INHERENT TO PROGNOSTIC STUDIES

- Which is (are) the outcome(s)?
- Which is the probability of occurrence of the outcome(s)?
- When the outcome is expected to occur?

VALIDITY OF THE SOURCES OF PROGNOSTIC STUDIES

- Representativeness of the study population
- Uniformity of inception cohort
- Length and completeness of follow-up
- “Blind” assessment of outcome measures
- Identification and assessment of relevant prognostic factors

SENSITIVITY ANALYSIS (example)

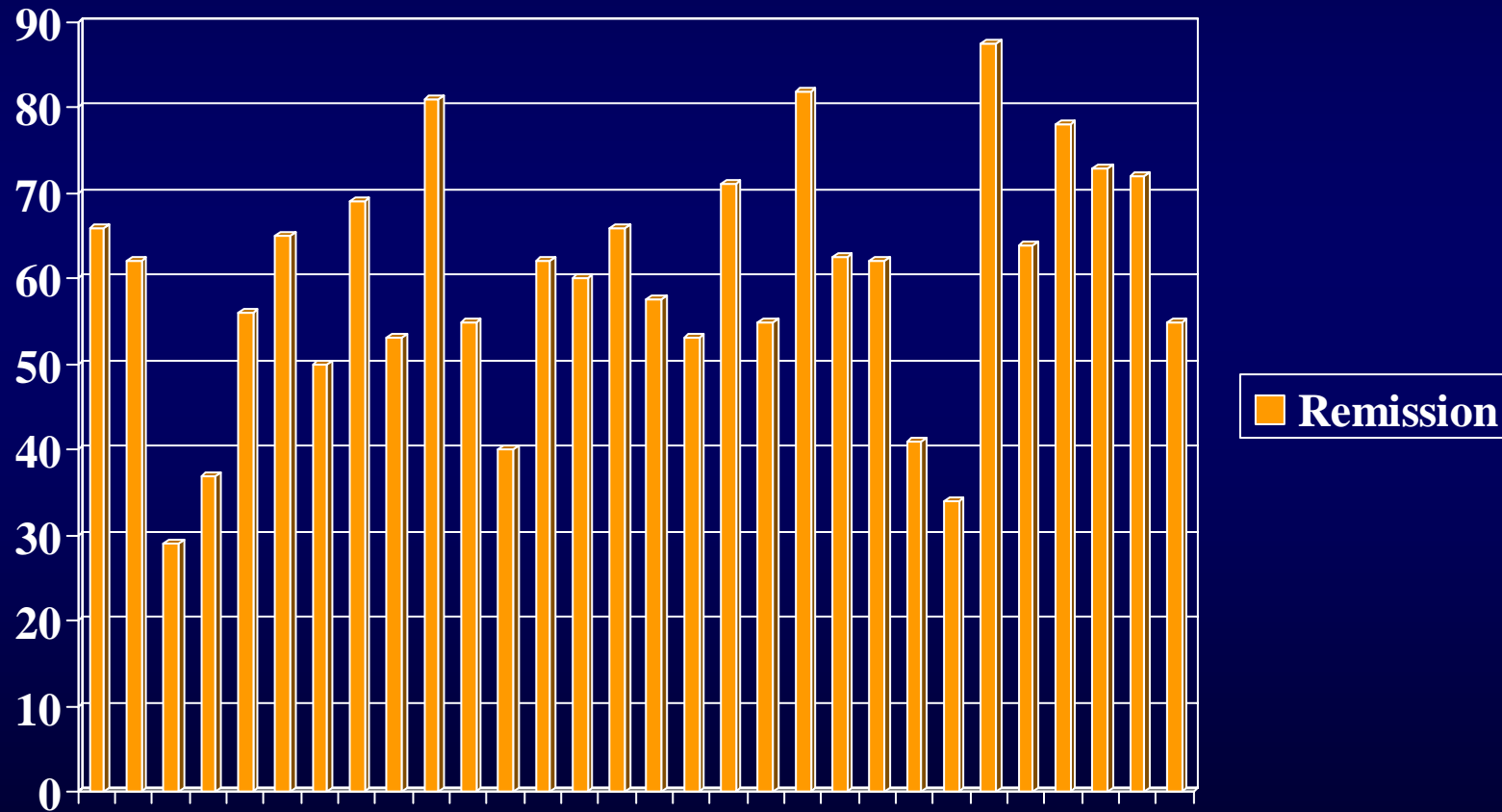
- Sample size 100, deceased 4, drop-outs 16: mortality $4/84 = 4.8\%$
- **Best scenario** (all drop-outs surviving): mortality $4/100 = 4\%$
- **Worst scenario** (all drop-outs dying): mortality $20/100 = 20\%$

CLASSIFICATION OF THE OUTCOME OF EPILEPSY

- **Class I** Free of disabling seizures (completely sz-free since surgery, non-disabling simple partial sz, some disabling sz after surgery but completely sz-free for 2+yr, and sz only after drug stop)
- **Class II** Almost sz-free (initially sz-free, then disabling sz, more than rare sz but now rare sz for 2+ yr, nocturnal sz only)
- **Class III** Worthwhile improvement (sz reduction or prolonged sz-free intervals up to half f-up (2+yr))
- **Class IV** No worthwhile improvement

Engel, Surgical Treatment of the Epilepsies, 1993

PERCENT OF SUCCESS AFTER SURGERY (Engel Class I = Remission)



PROBLEMS RELATED TO SEIZURE COUNTS

- Not all seizures are perceived or recalled by patient
- Seizures may not be witnessed
- Perception and description of seizures may be different
- Seizure occurrence may not be relevant for the patient
- Adverse treatment events may occur independently from seizure control

IDENTIFICATION AND ASSESSMENT OF PROGNOSTIC FACTORS

- Stratification
- Multivariate analysis
- Validation set

ASSESSMENT OF OUTCOME MEASURES

- Number (percent) of events at a given time point (eg 1 yr, 2 yr, etc.)
- Median “survival” (time at which 50% of events have occurred)
- Cumulative time-dependent number (percent) of events (survival analysis)

PRECISION OF PROGNOSTIC MEASURES

Point estimates with
confidence intervals

AIM OF THE STUDY

- To perform a meta-analysis of the results of published observational studies and assess the prognostic significance of selected variables outlining the characteristics of the clinical condition, the correlation between the epileptogenic and the functional lesion, and the extent of the surgical resection

SELECTION CRITERIA

- **Population:** children, adolescents and adults with temporal or extratemporal refractory epilepsy
- **Outcome measure:** seizure remission (Engel Class I)
- **Study pre-requisites** for inclusion:
 - Well-defined population (30+ patients)
 - Precise outline of study design
 - Illustration of type and extent of surgery
 - MRI performed in at least 90% of cases
 - Follow-up lasting one year or longer

DATA COLLECTION

- **Semi-structured form** containing:
 - **Methods of assessment** of eligible studies
 - **Demographic and clinical characteristics** of the sample
 - **Prognostic indicators**: neuromigrational defects, febrile seizures, tumors & other relevant CNS conditions, mesial temporal sclerosis, abnormal MRI, EEG/MRI concordance, intracranial monitoring, extent of resection
 - **Imaging and pathologic diagnosis**
 - **Surgery**: technique, side, site, complications
 - **Duration of follow-up**
 - **Outcome**: good (seizure remission) vs poor (other)

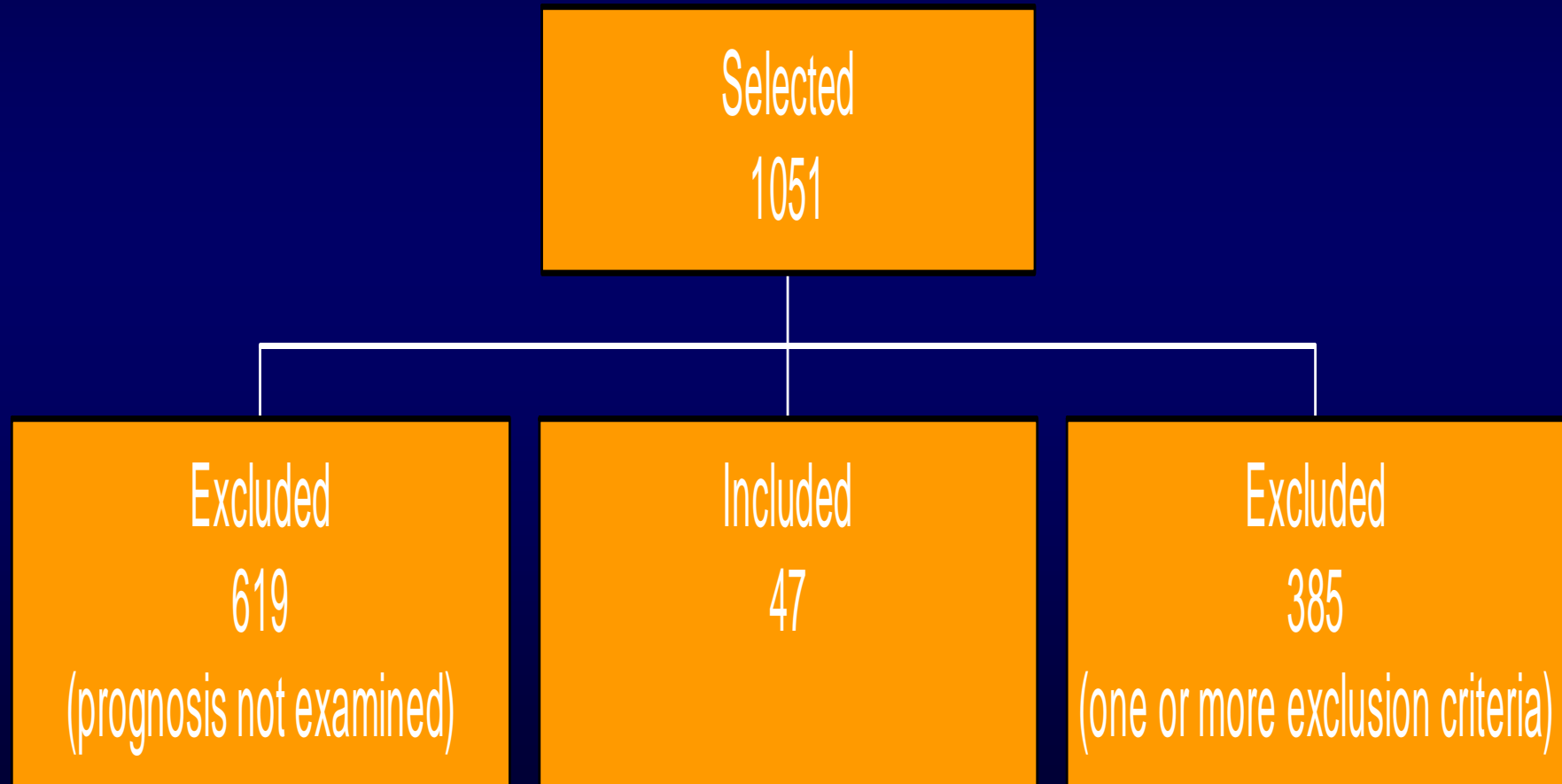
STRATEGY OF THE SYSTEMATIC REVIEW

- Medline search of studies on epilepsy surgery
- Articles examined by 4 pairs of international reviewers (each pair reviewing about one-fourth of total)
- Each article assessed for selection criteria and, if eligible, reviewed by both assessors
- Each pair had to reach a consensus on the eligibility of all articles; consensus was also required on each variable reported in the data collection form (by the two assessors or by a third reviewer who also checked for any discrepancy in the data recorded)

DATA ANALYSIS

- Each study's results were assessed for heterogeneity using the chi-square test
- For each prognostic indicator raw numbers were pooled into 2x2 contingency tables comparing that variable (present or absent) to the outcome of surgery (good vs poor)
- For each variable the chance of seizure remission (= good outcome) was calculated as an odds ratio (OR) with 95% confidence interval (CI)
- Data analysis was performed separately in the entire sample (all surgical sites) and in patients undergoing temporal lobectomy

PROCEDURE FOR SELECTION OF ARTICLES



CHARACTERISTICS OF EXAMINED STUDIES

- Total: 47
- Years of publication: 1991-2001
- Number of patients: 3511
- Follow-up (range): 4-216 months
- Percent sz-free: 35-80% (median 67%)
- Complications: <1% (deaths: <1%°)

GENERAL CHARACTERISTICS OF THE STUDIES - I

- **Study design**
 - Retrospective 35
 - Prospective 10
 - Combined 2
- **Participants**
 - < 50 20
 - 50-100 17
 - > 100 10
- **Age at surgery (min-max)** 0-86
- **Duration of epilepsy (min-max)** 0-81

GENERAL CHARACTERISTICS OF THE STUDIES - II

- Intervention

- Temporal	29
- Extratemporal	2
- Combined	16

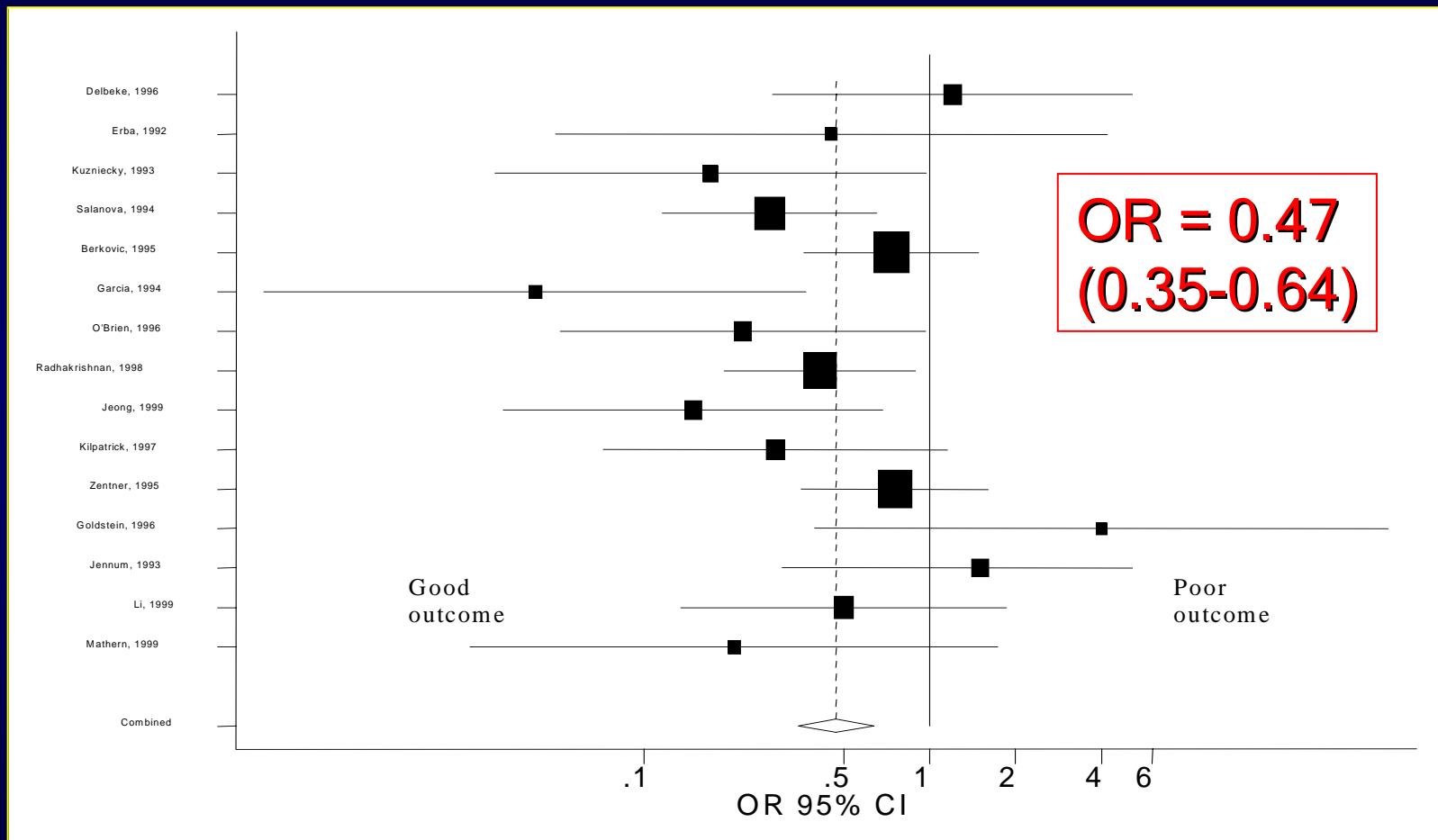
- Outcome measures

- Engel classification	22
- Seizure freedom >1yr	9
- Other	19

PROGNOSTIC INDICATORS (number of studies)

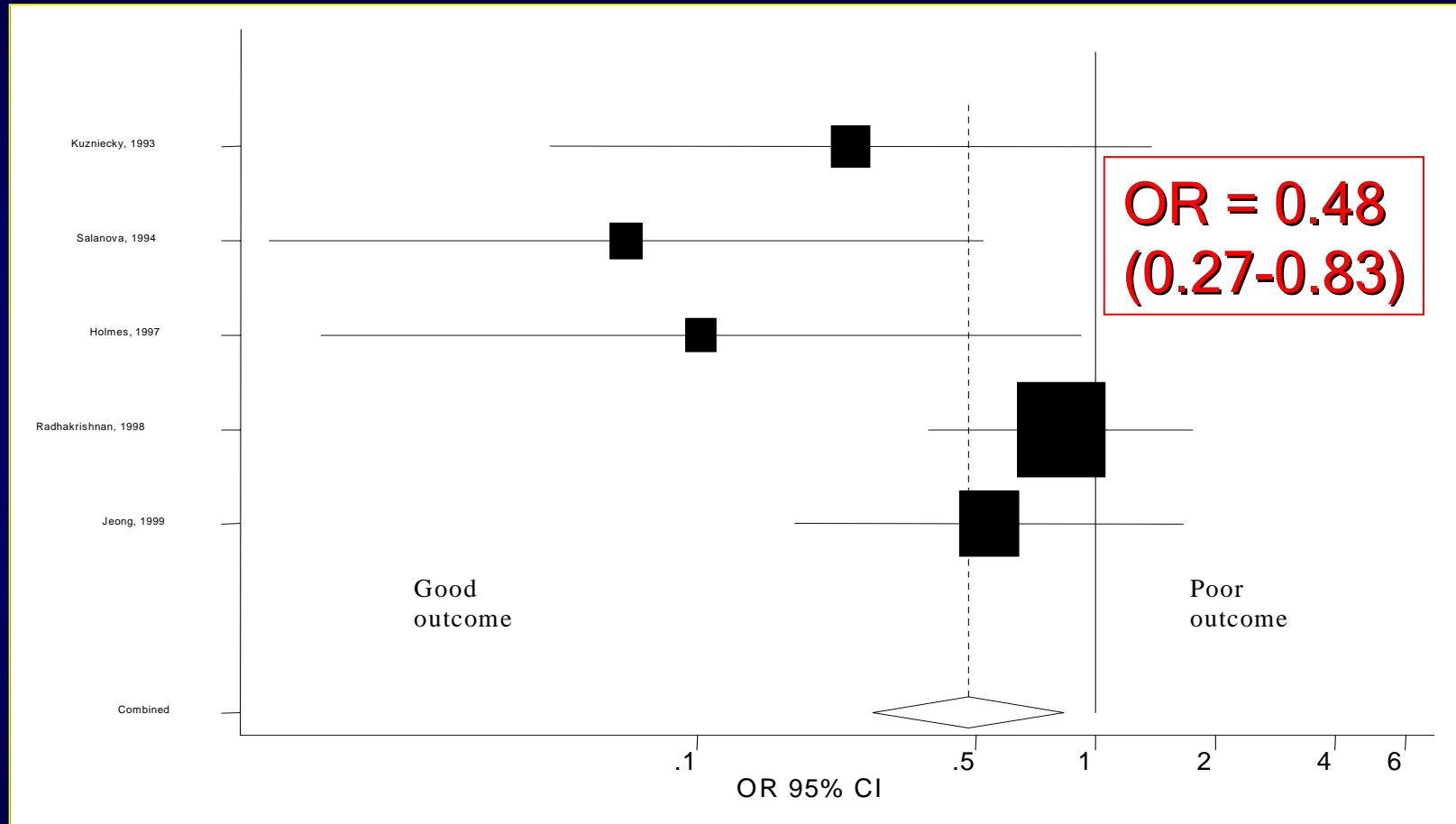
- MTS 19
- Tumors 15
- Abnormal MRI 12
- Extent resect 10
- Intracr monit 8
- EEG/MRI conc 7
- Febrile sz 6
- Neuromig def 6
- Side of resect 5
- Postop dischg 3
- Vascular dis 3
- CNS infect 2
- Interictal sz 2

MESIAL TEMPORAL SCLEROSIS



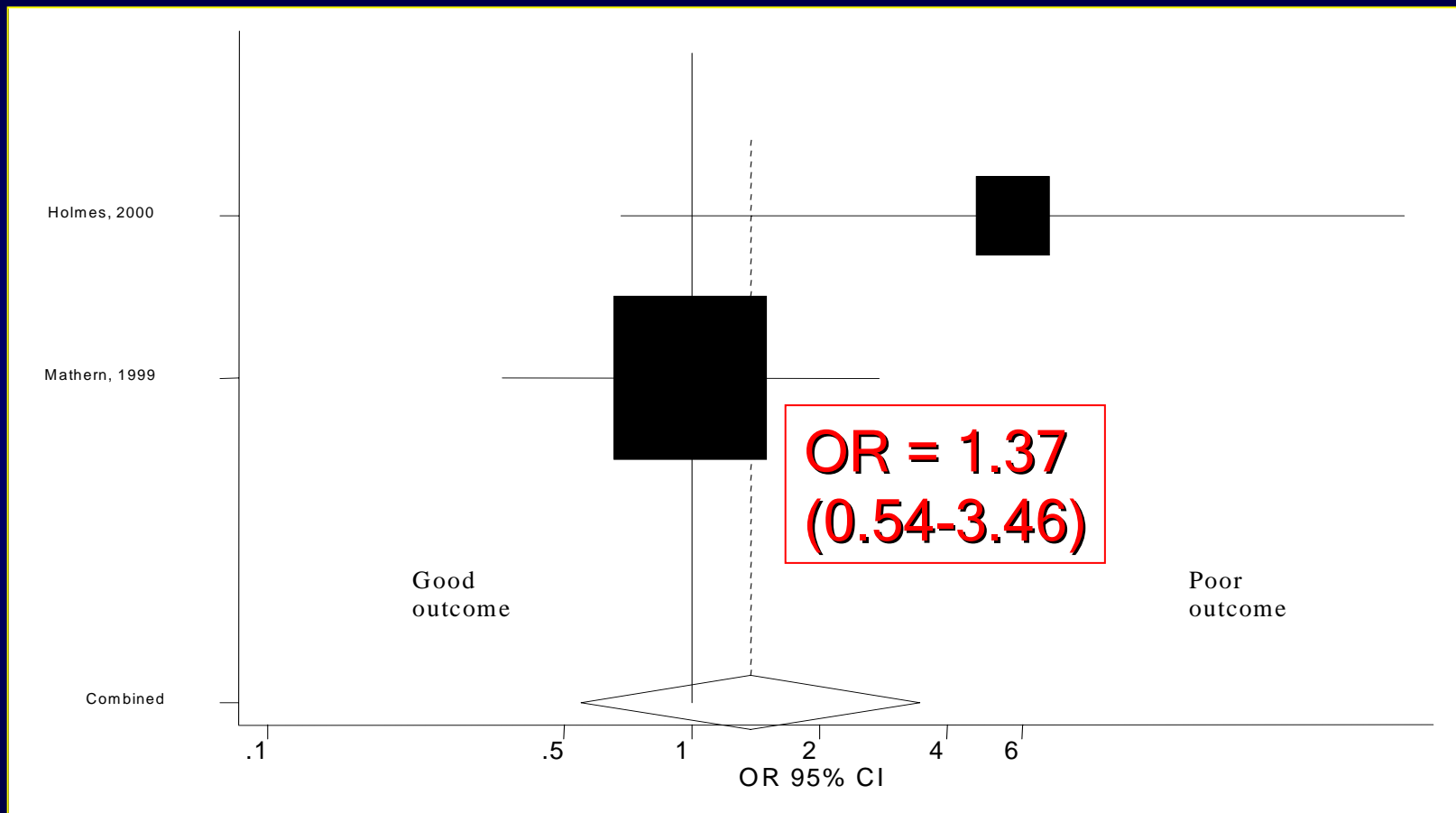
Average estimate (fixed effects) = 0.471 (95% C.I. 0.348 - 0.638)
Test for heterogeneity: $Q = 21.861$ on 14 degrees of freedom ($p = 0.082$)

FEBRILE SEIZURES



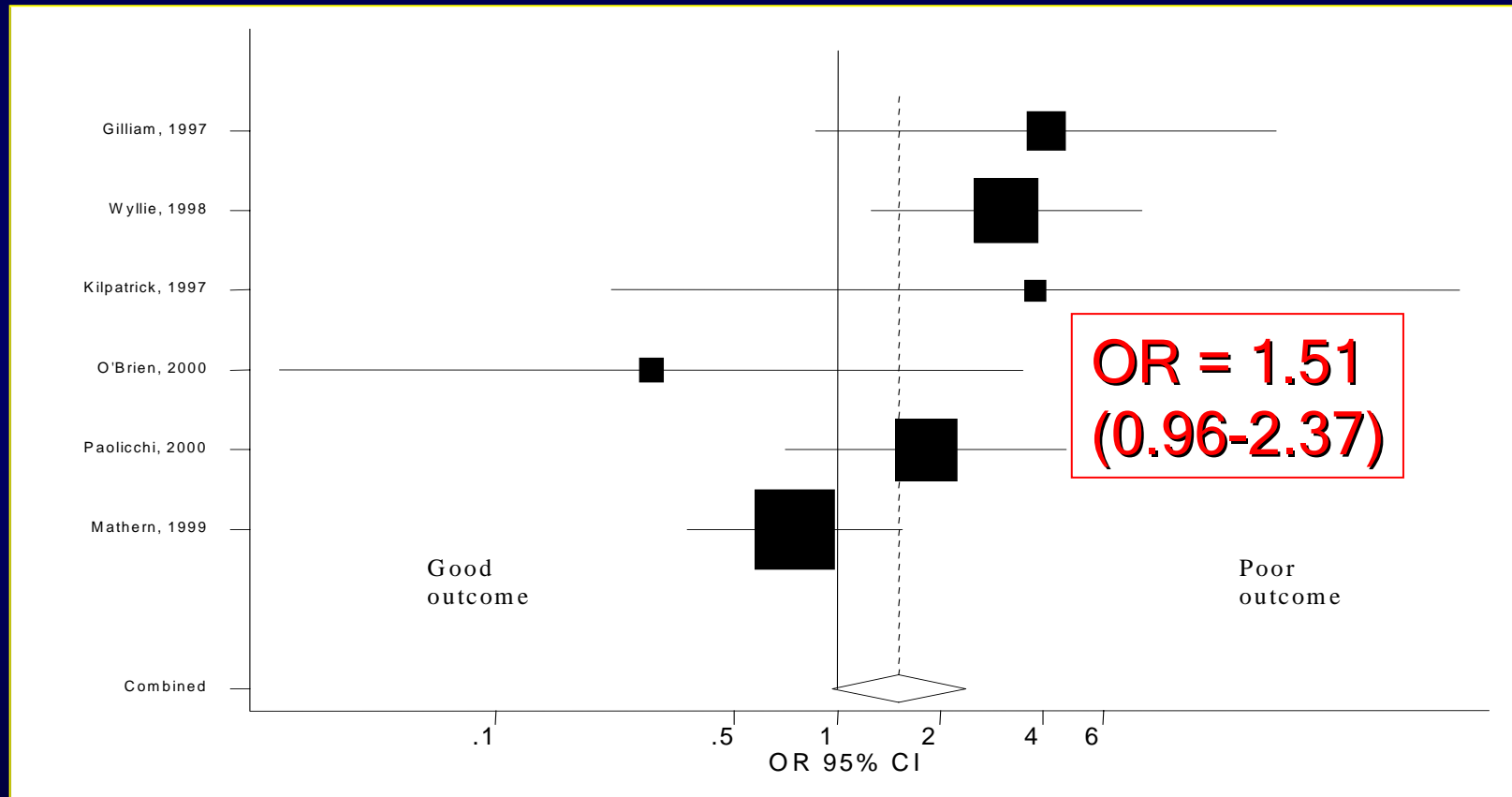
Average estimate (fixed effects) = 0.480 (95% C.I. 0.277 - 0.833)
Test for heterogeneity: $Q = 7.957$ on 4 degrees of freedom ($p = 0.093$)

CNS INFECTIONS



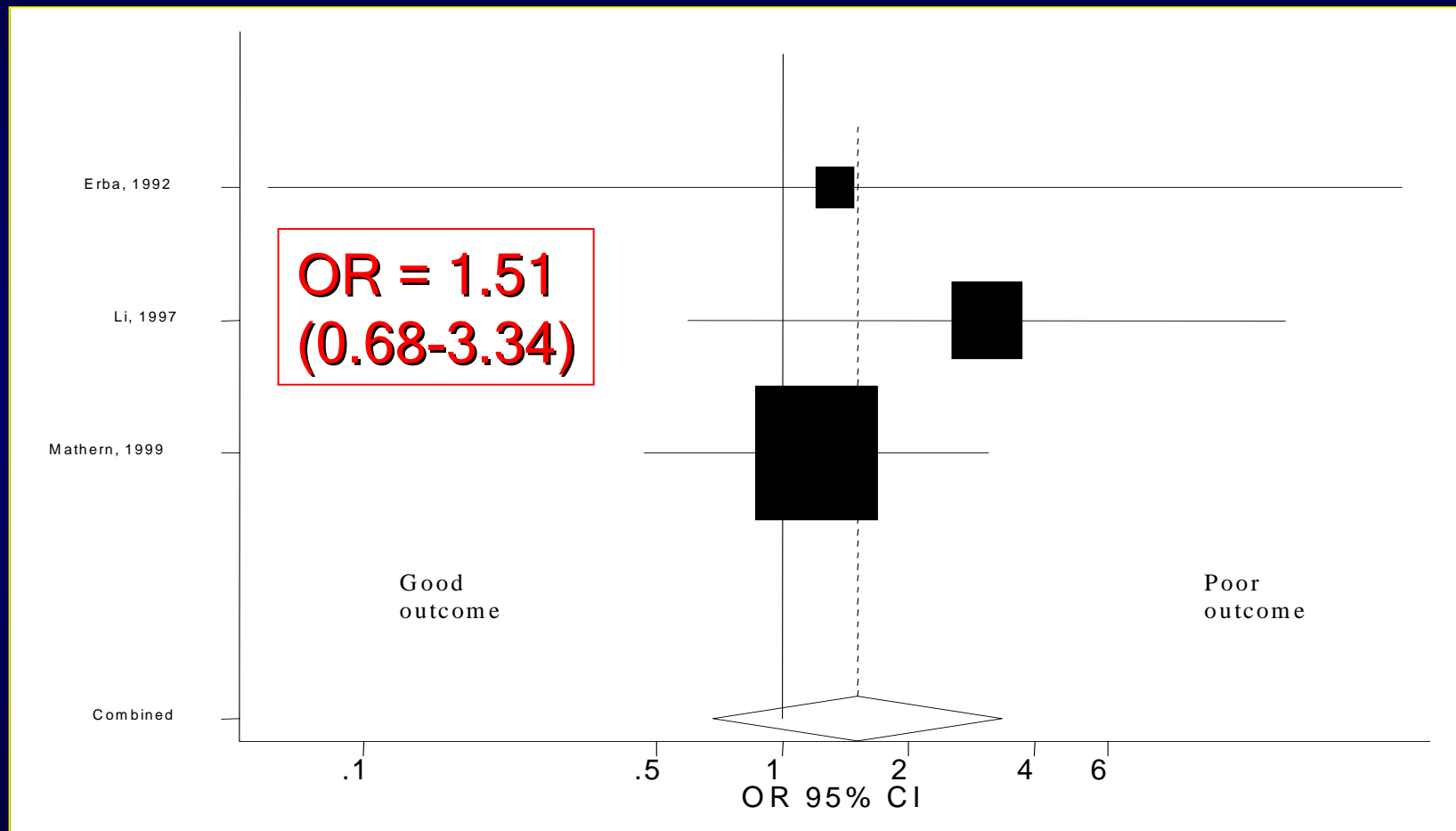
Average estimate (fixed effects)= 1.377 (95% C.I. 0.548 - 3.460)
Test for heterogeneity: $Q = 2.114$ on 1 degree of freedom ($p=0.146$)

NEUROMIGRATION DEFECTS



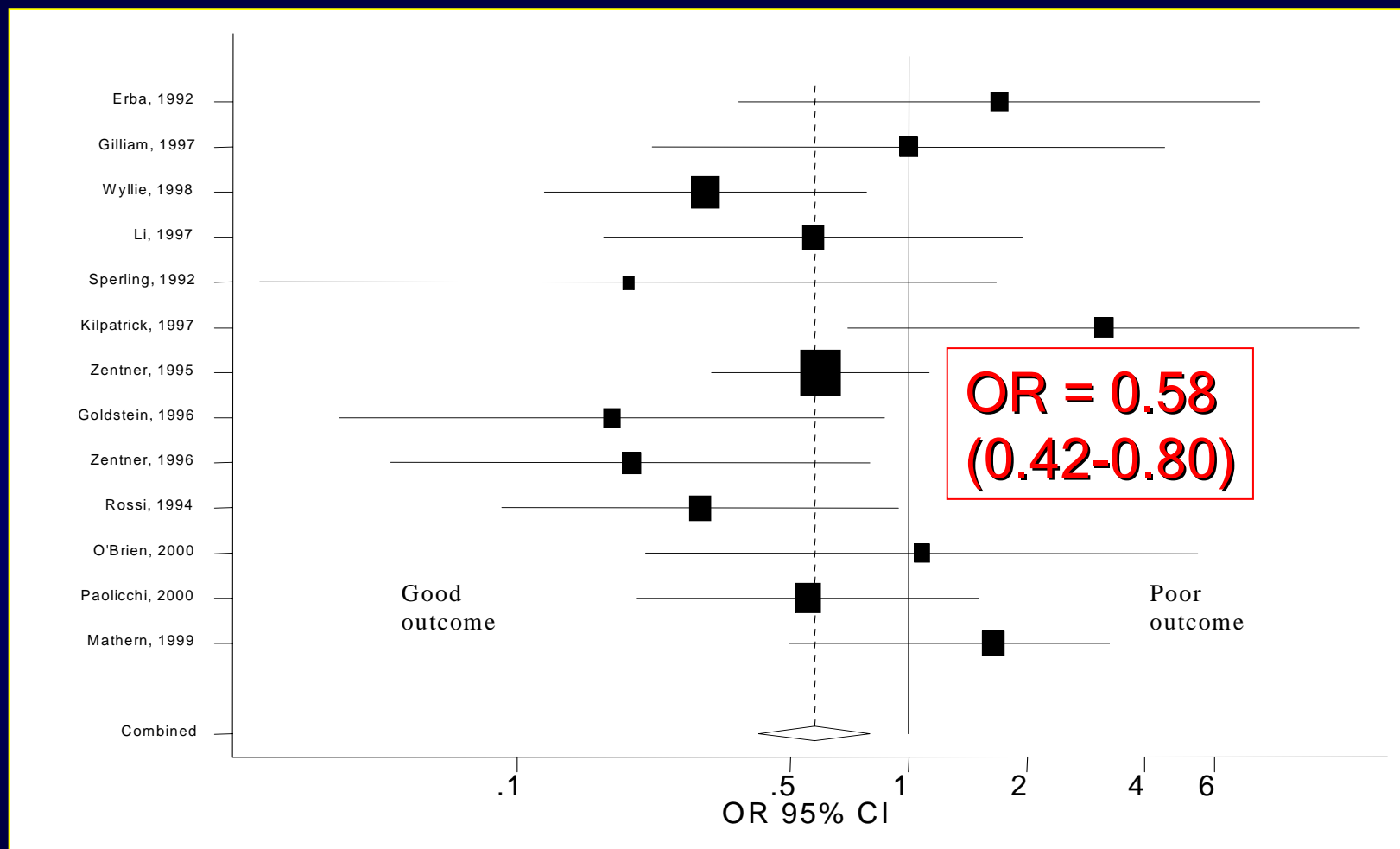
Average estimate (fixed effects) = 1.517 (95% C.I. 0.967 - 2.379)
Test for heterogeneity: $Q = 9.820$ on 5 degrees of freedom ($p=0.080$)

VASCULAR DISEASES



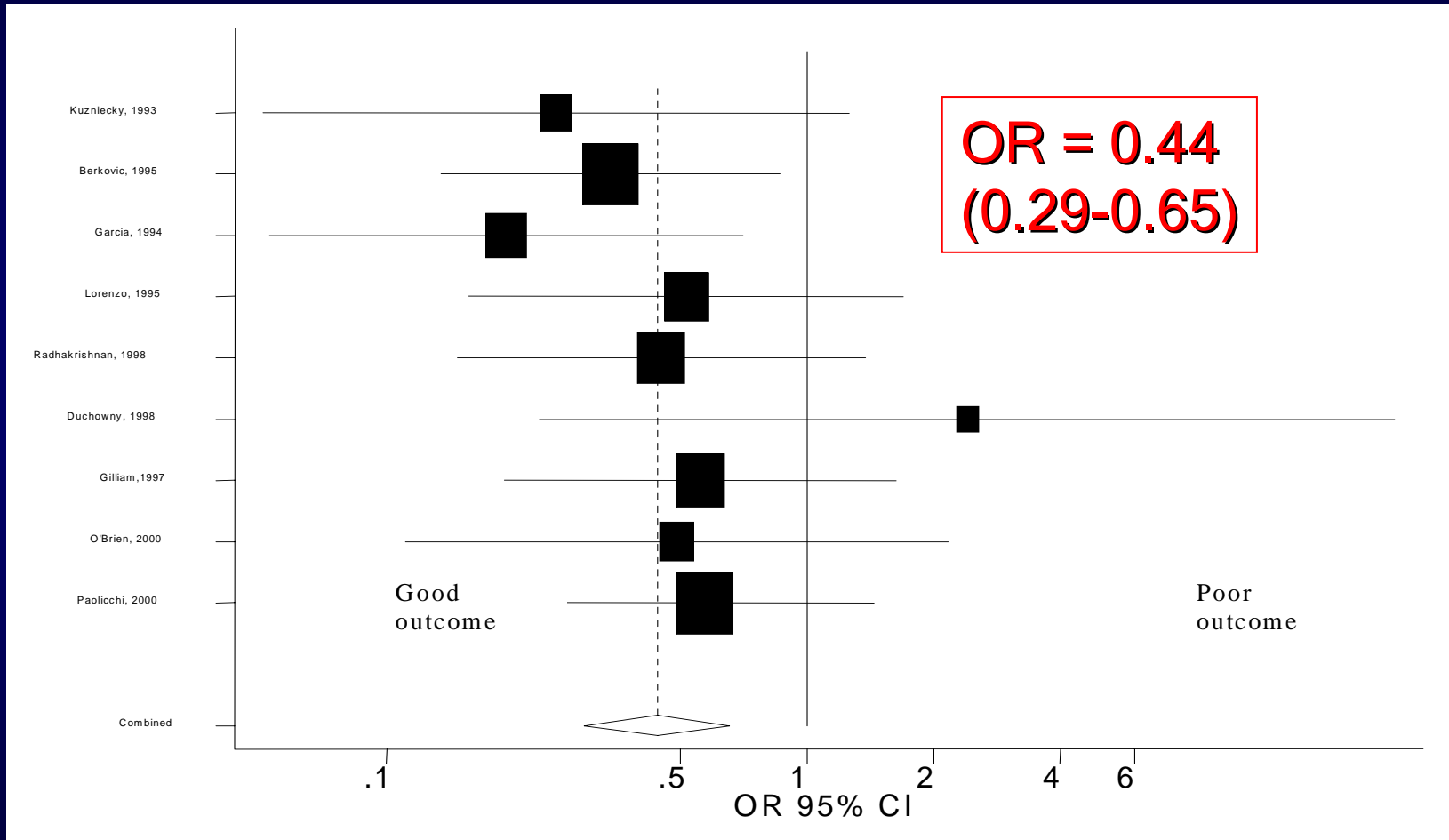
Average estimate (fixed effects) = 1.513 (95% C.I. 0.684 - 3.348)
Test for heterogeneity: $Q = 0.945$ on 2 degrees of freedom ($p=0.623$)

TUMORS



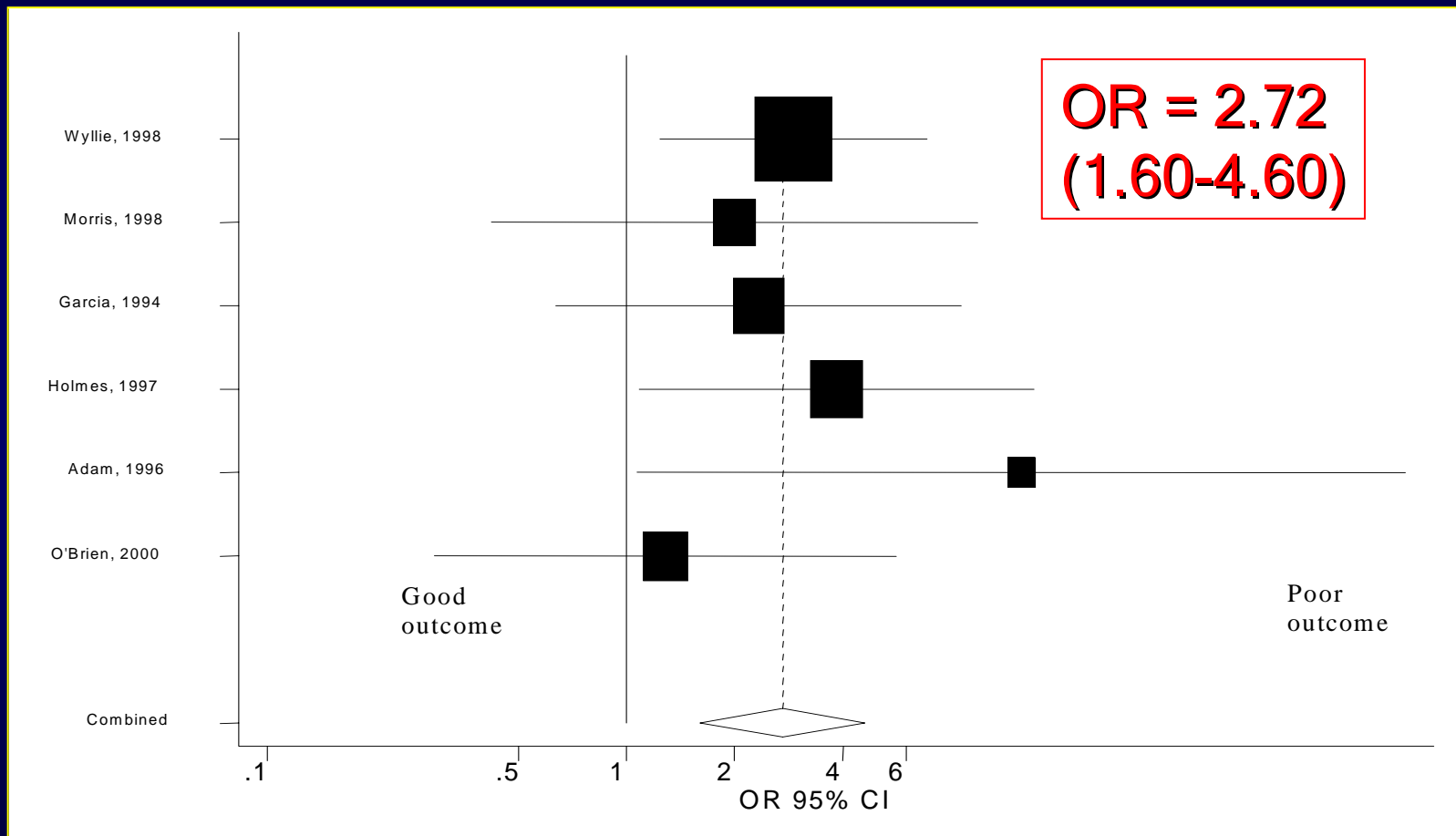
Average estimate (fixed effects) = 0.576 (95% C.I. 0.416 - 0.797)
 Test for heterogeneity: Q = 19.30 on 12 degrees of freedom (p=0.082)

ABNORMAL MRI



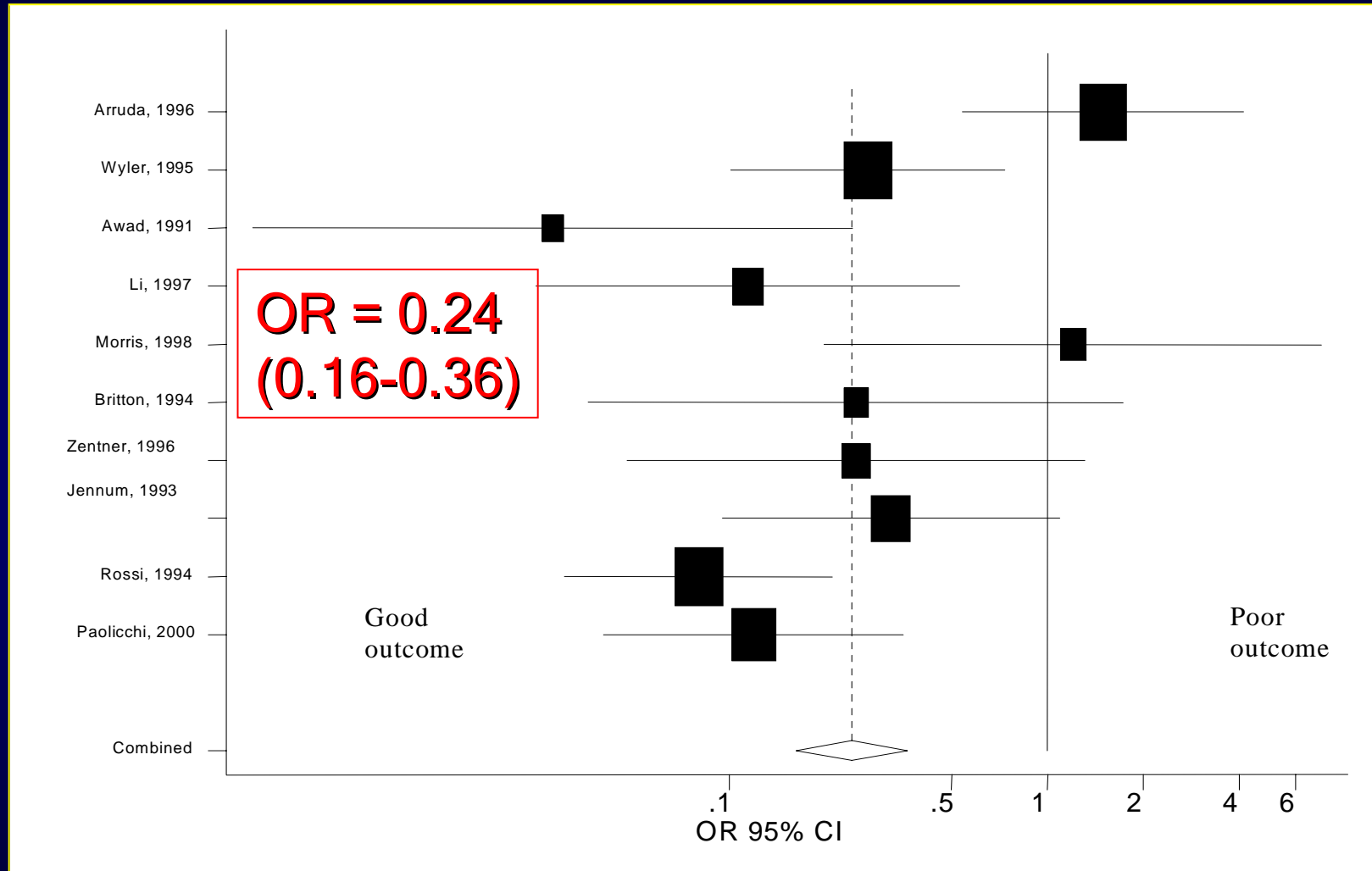
Average estimate (fixed effects) = 0.439 (95% C.I. 0.295 - 0.654)
Test for heterogeneity: $Q = 4.901$ on 8 degrees of freedom ($p=0.768$)

INTRACRANIAL MONITORING



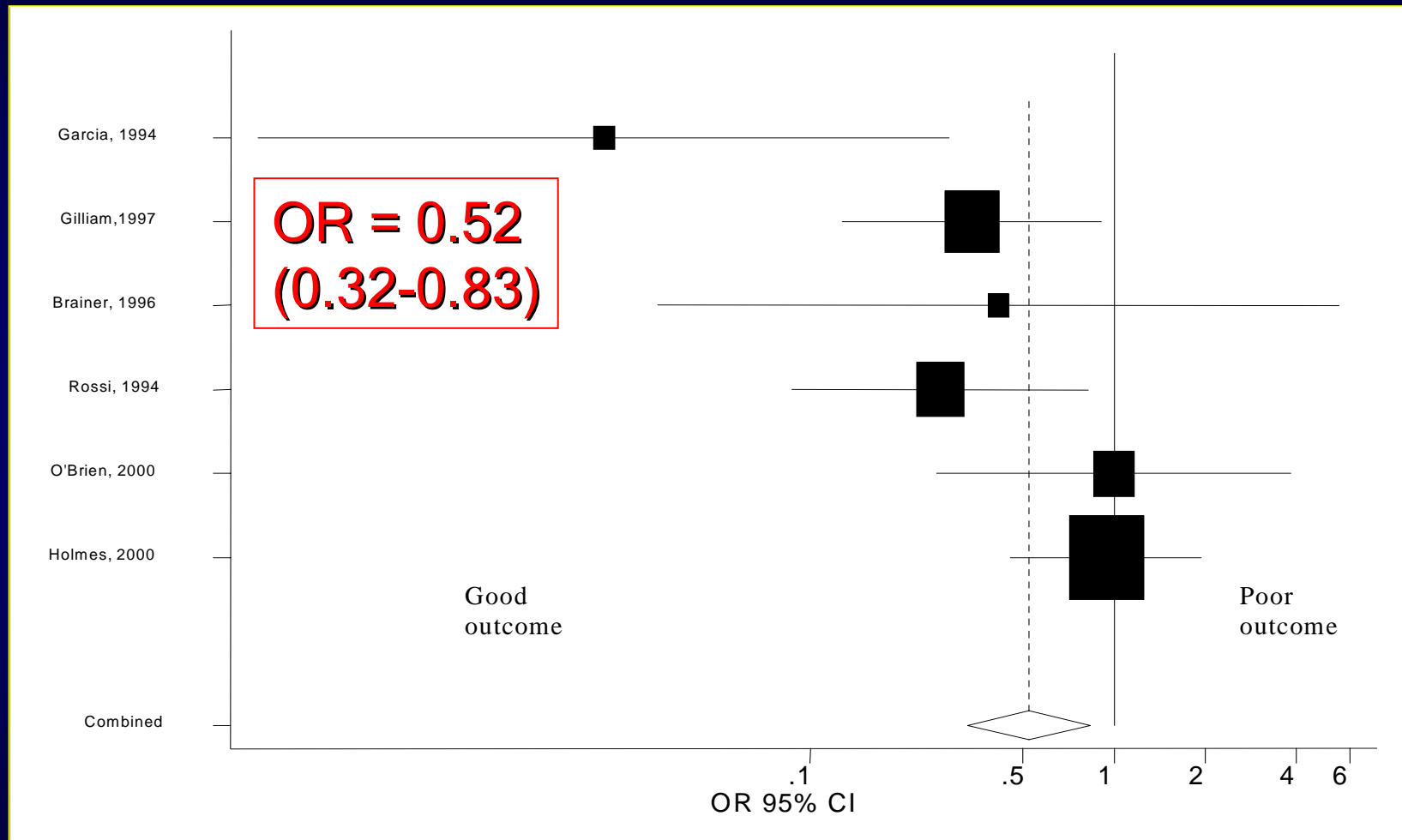
Average estimate (fixed effects) = 2.723 (95% C.I. 1.608 - 4.609)
Test for heterogeneity: $Q = 2.987$ on 5 degrees of freedom ($p=0.702$)

EXTENT OF RESECTION



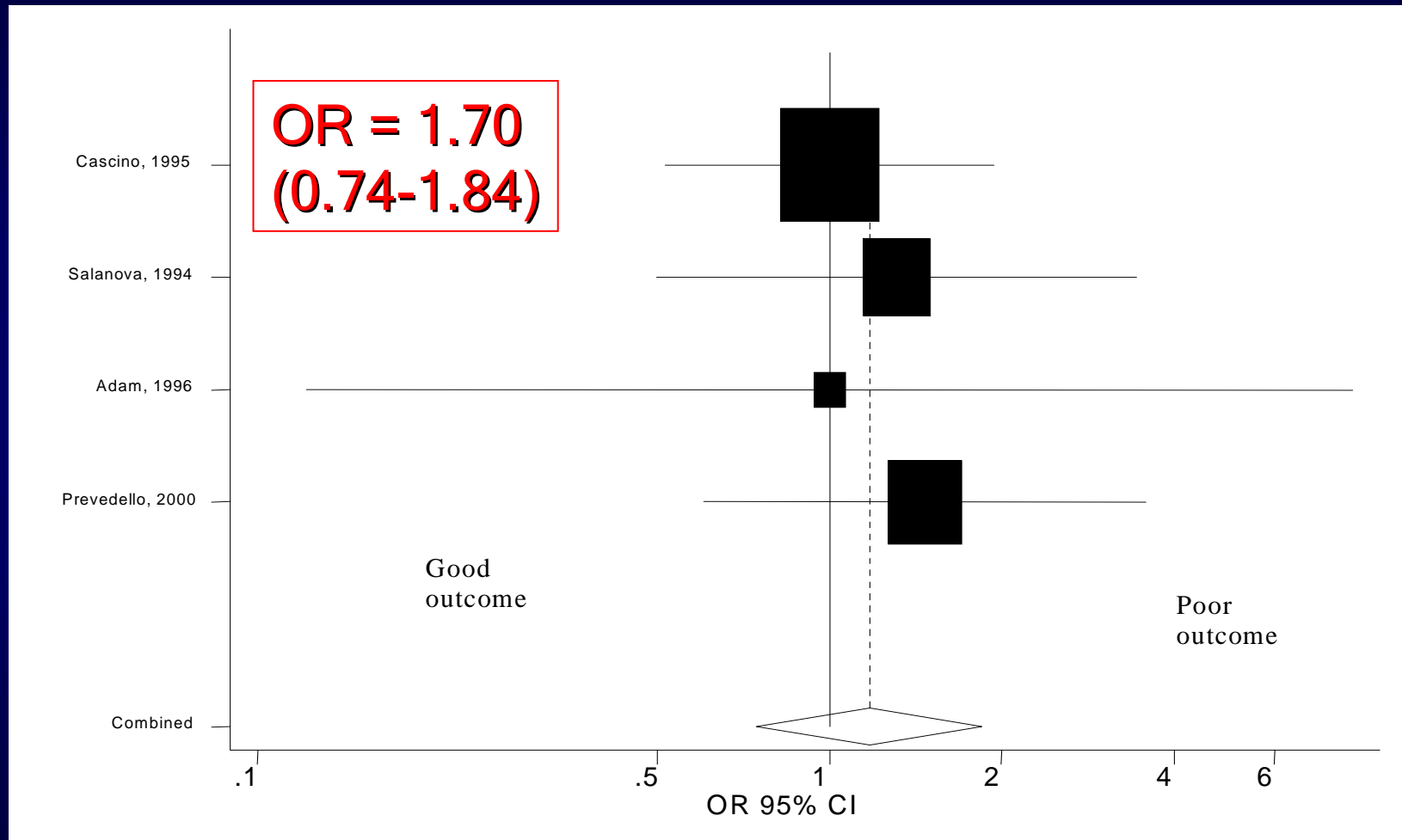
Average estimate (fixed effects) = 0.243 (95% C.I. 0.162 - 0.363)
Test for heterogeneity: Q = 26.942 on 9 degrees of freedom (p=0.001)

EEG/MRI CONCORDANCE



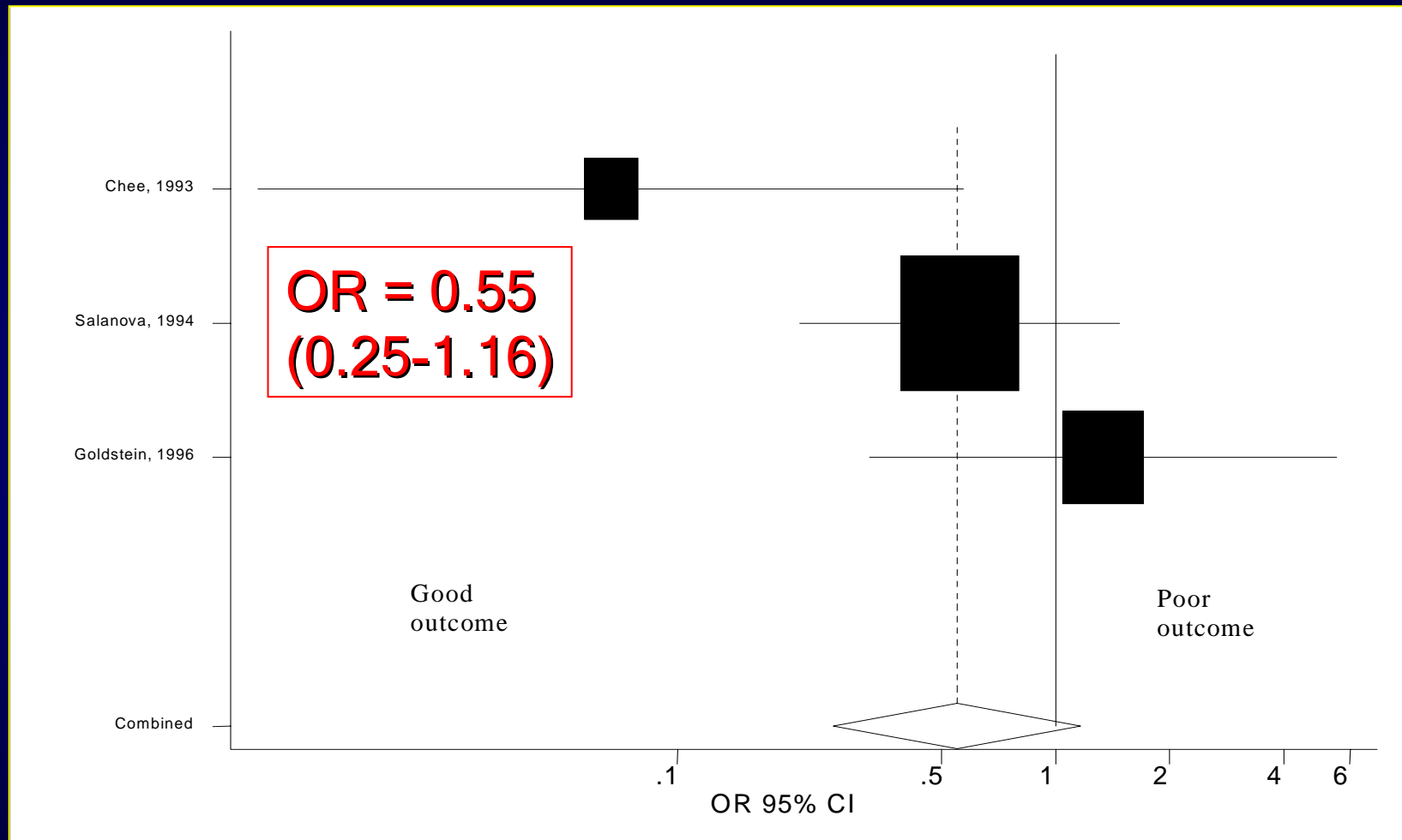
Average estimate (fixed effects) = 0.525 (95% C.I. 0.329 - 0.837)
Test for heterogeneity: $Q = 11.387$ on 5 degrees of freedom ($p=0.044$)

SIDE OF RESECTION



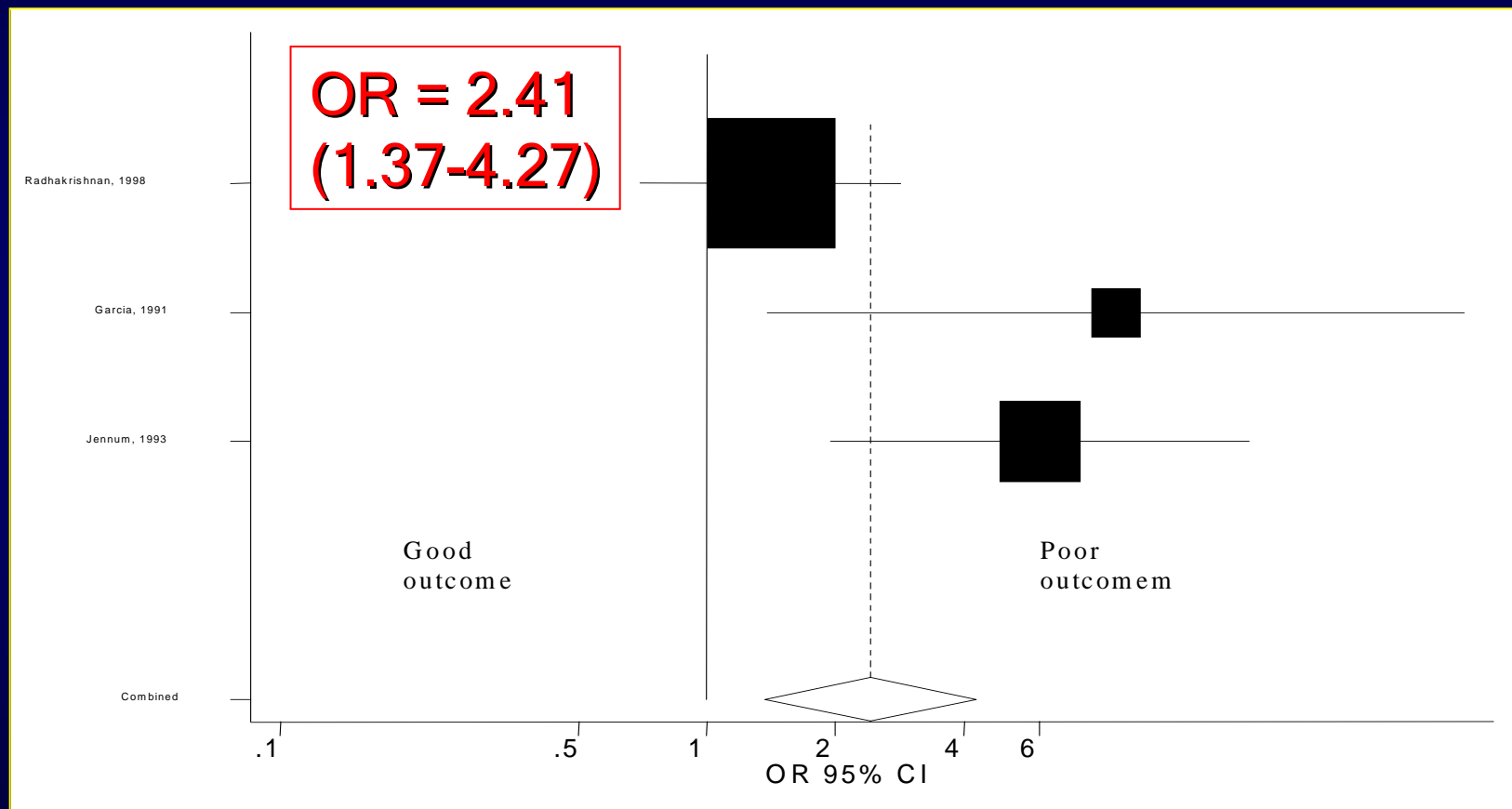
Average estimate (fixed effects) = 1.173 (95% C.I. 0.745 - 1.848)
Test for heterogeneity: $Q = 0.537$ on 3 degrees of freedom ($p=0.911$)

INTERICTAL SPIKES



Average estimate (fixed effects) = 0.548 (95% C.I. 0.258 - 1.164)
Test for heterogeneity: $Q = 5.197$ on 2 degrees of freedom ($p=0.074$)

POSTOPERATIVE DISCHARGES



Average estimate (fixed effects) = 2.419 (95% C.I. 1.369 - 4.273)
Test for heterogeneity: $Q = 6.684$ on 2 degrees of freedom ($p=0.035$)

CONCLUSIONS

- Extent of surgical resection, abnormal MRI, mesial temporal sclerosis, febrile seizures, EEG/MRI concordance, and tumor are in decreasing order the principal indicators of the success of surgery of epilepsy
- By contrast, intracranial monitoring and postoperative discharges tend to predict an unfavourable prognosis
- Although the heterogeneity of the eligible studies is low, the results of the meta-analysis may be affected by pooling studies with different case mix, variable methods, and unexamined or unknown confounding factors

STUDY LIMITATIONS

- The study results may be affected by pooling of data from heterogeneous reports (different patient series assessed with differing methods) or unexamined or unknown confounders
- Despite consistency of results, these data must be considered preliminary and cannot replace well-conducted prognostic studies (representative study populations, well-defined inception cohorts, satisfactory and complete follow-up, prospective design, and standard definition of prognostic factors)