Meta-analysis Simplified

Breast Surgery & Surgical Oncology Fellows

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Basic Ideas of Meta-analysis

- Combining multiple, *similar* studies
- To increase sample size
- Increasing statistical power

Example

Mammography clinical trial from Sweden, 1995

- Not screened: 19,943 Deaths: 45
- Screened: 40,318 Deaths: 66
- Risk Ratio: 0.73 95% CI: 0.50 – 1.06

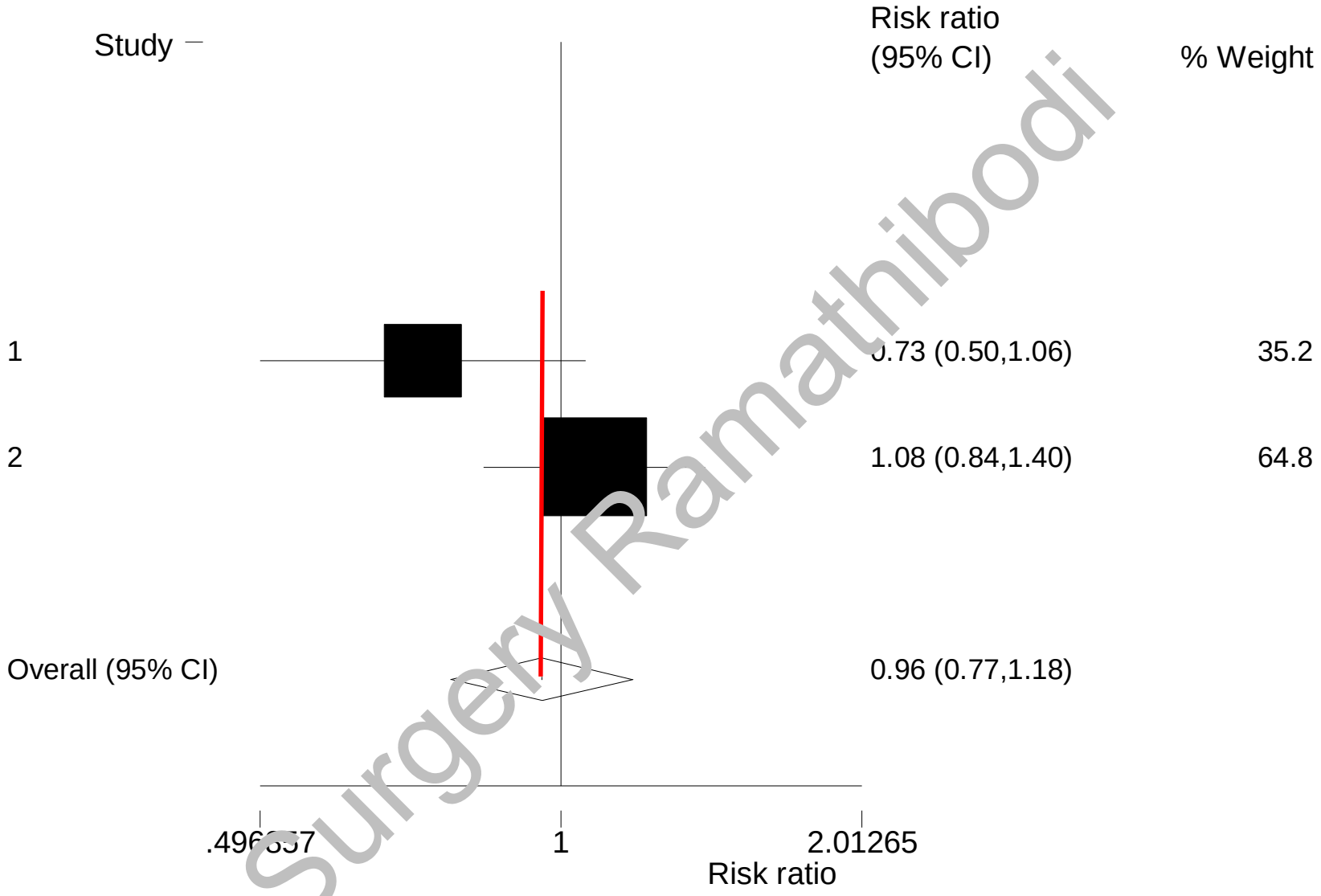
Lancet 2000; **355:** 129–34

Example

Mammography clinical trial from Canada, 1997

- Not screened: 44,910 Deaths: 111
- Screened: 44,925 Deaths: 120
- Risk Ratio: 1.08 95% CI: 0.84 – 1.40

Lancet 2000; **355:** 129–34



Systematic Review of Evidence

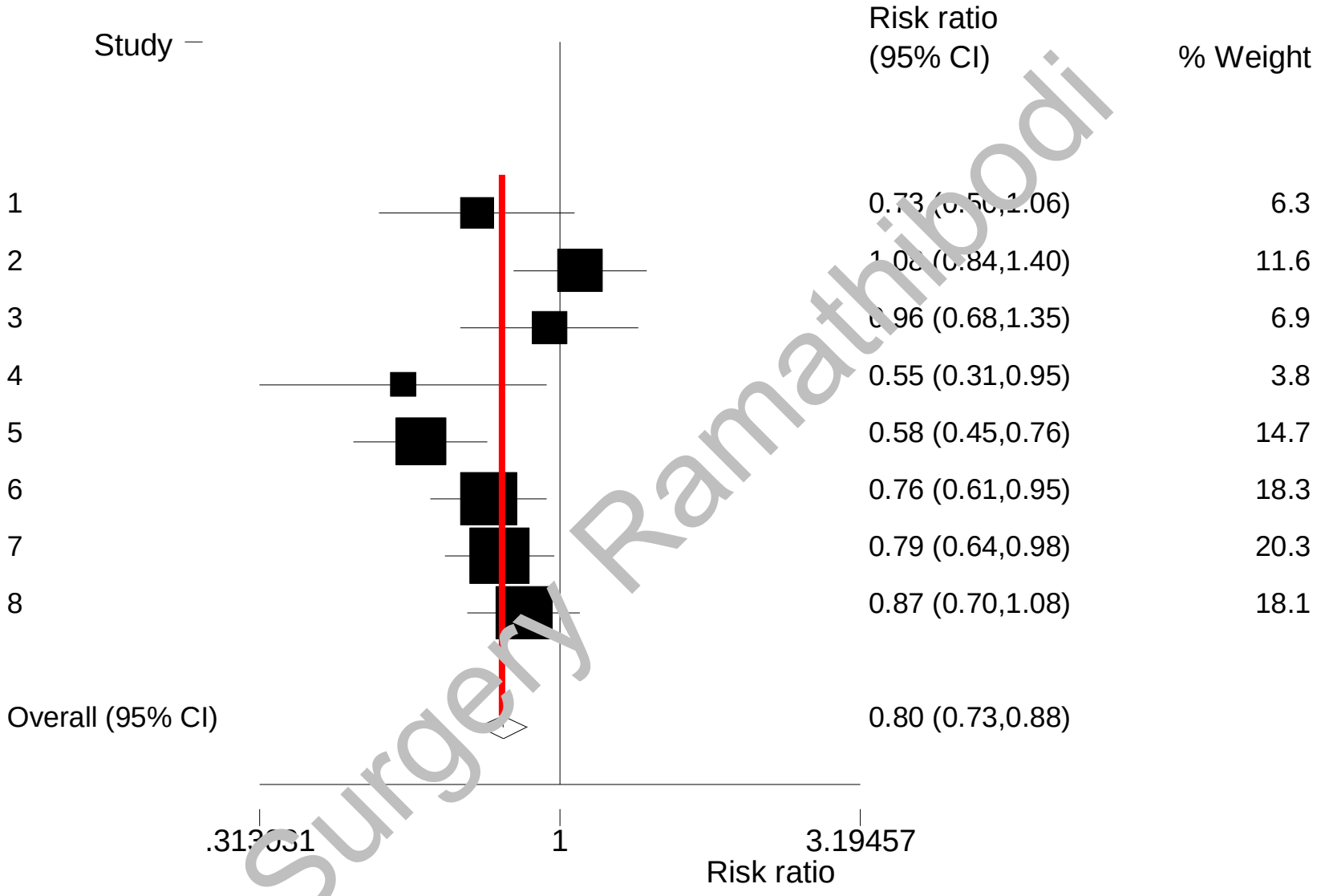
- Comprehensive
- Quality (higher validity)
- Objective (higher reliability)
- Observational in character

Meta-analysis of Evidence

- Similar methodology
- Same outcomes; sufficient numerical information
- Fixed-effect; random-effects

Summary of Evidence

- No meta-analysis
- With meta-analysis

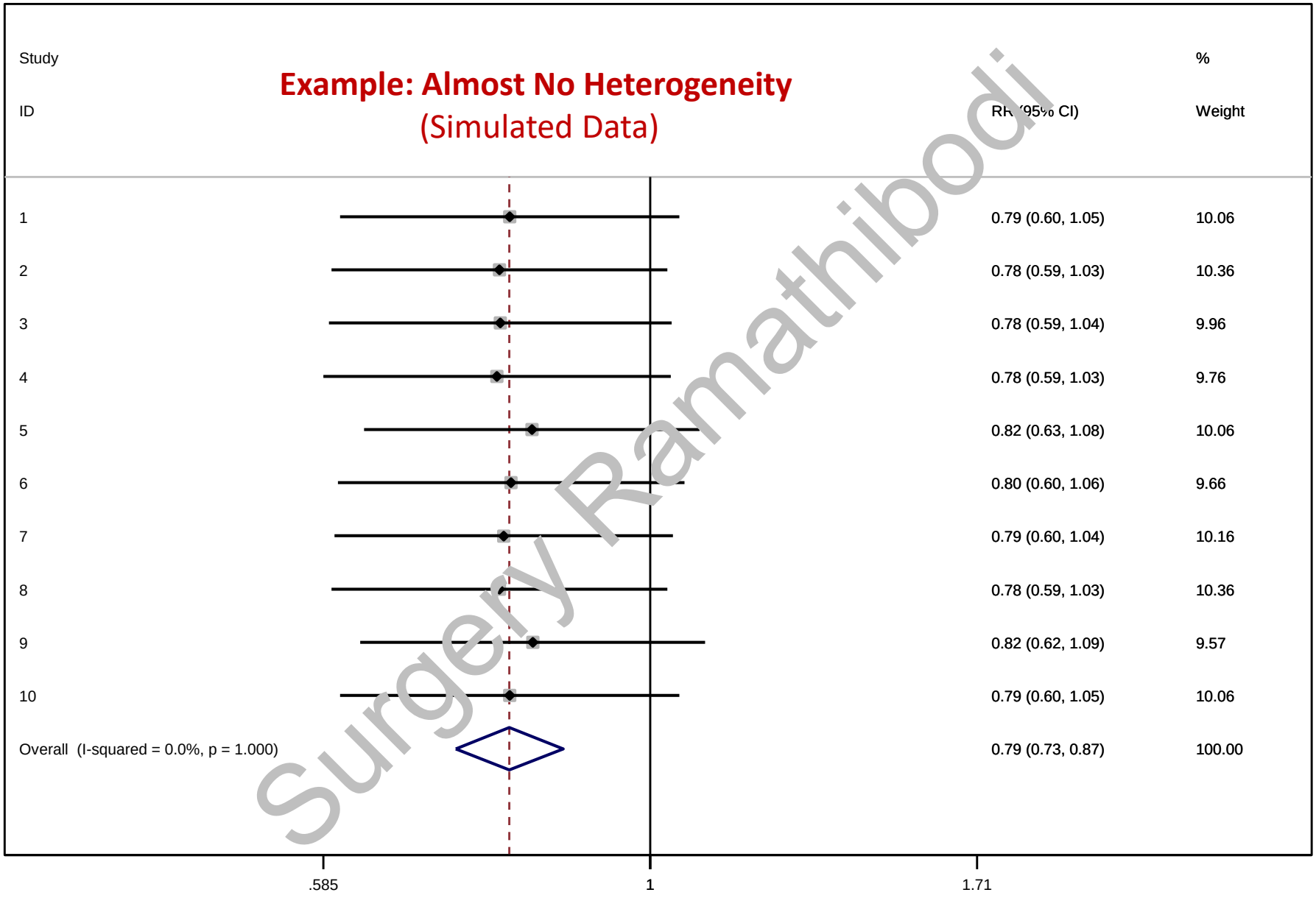


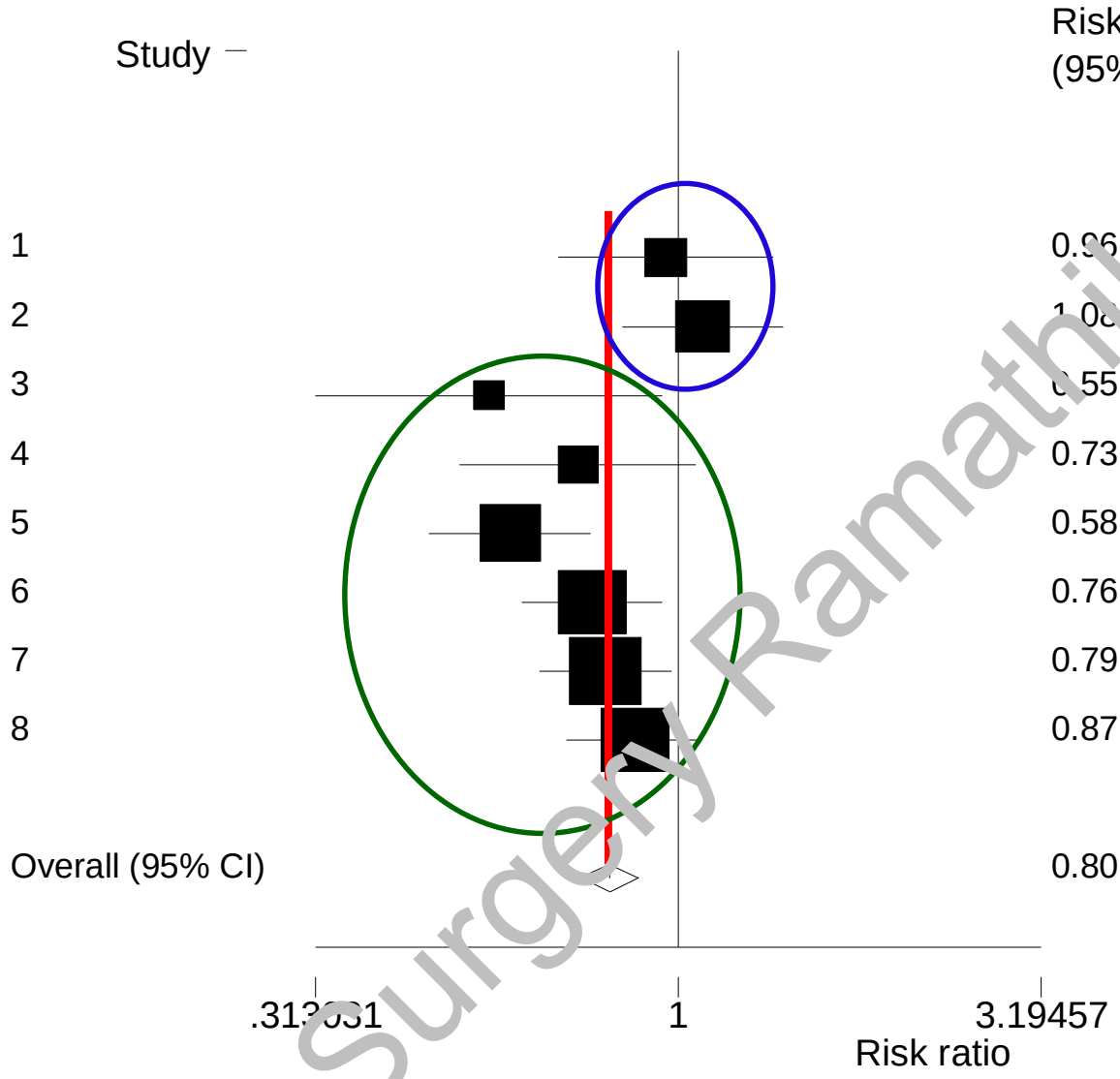
Lancet 2000; **355:** 129–34

Heterogeneity

- Content/methodological/clinical
- Statistical

Example: Almost No Heterogeneity
(Simulated Data)

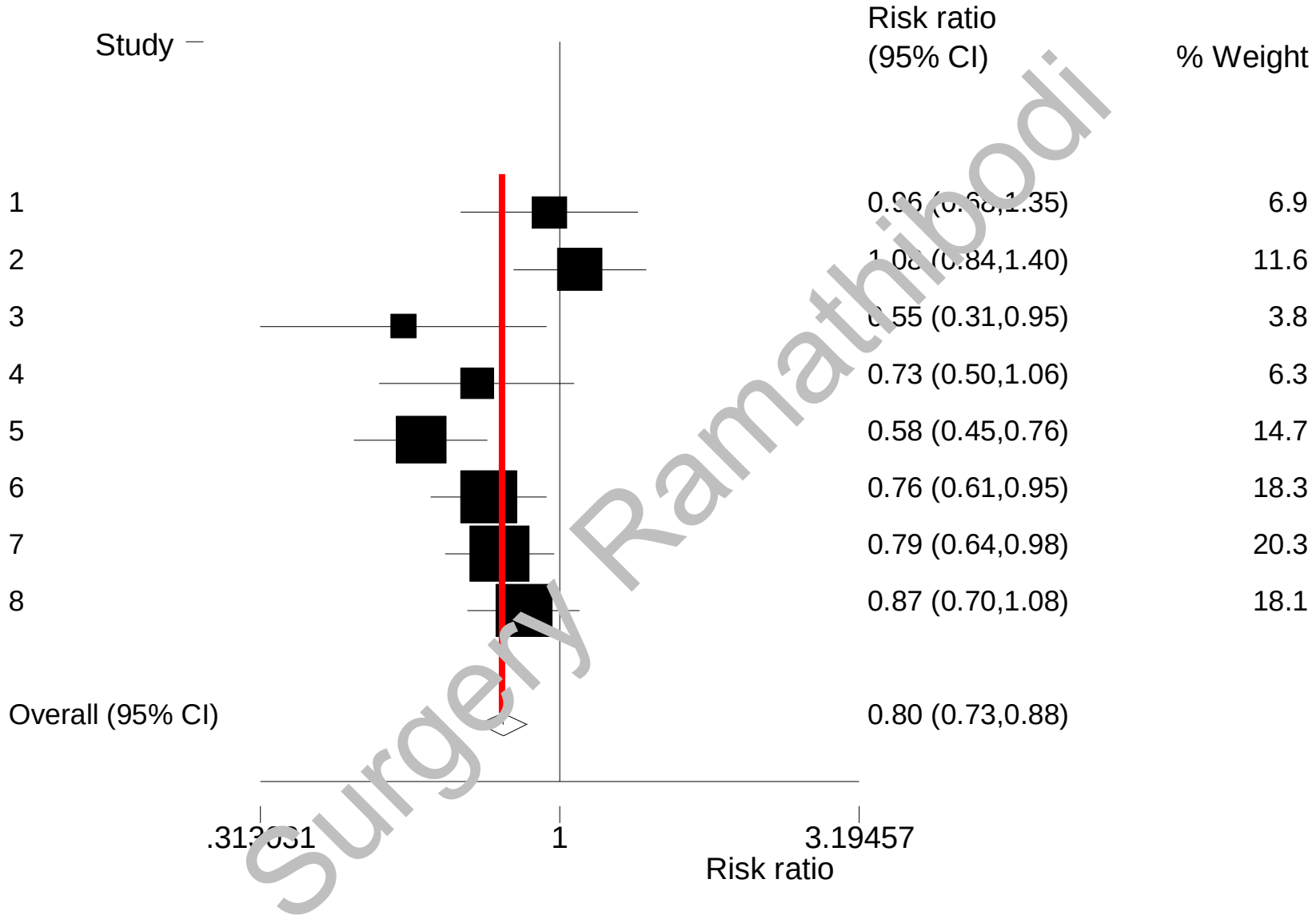




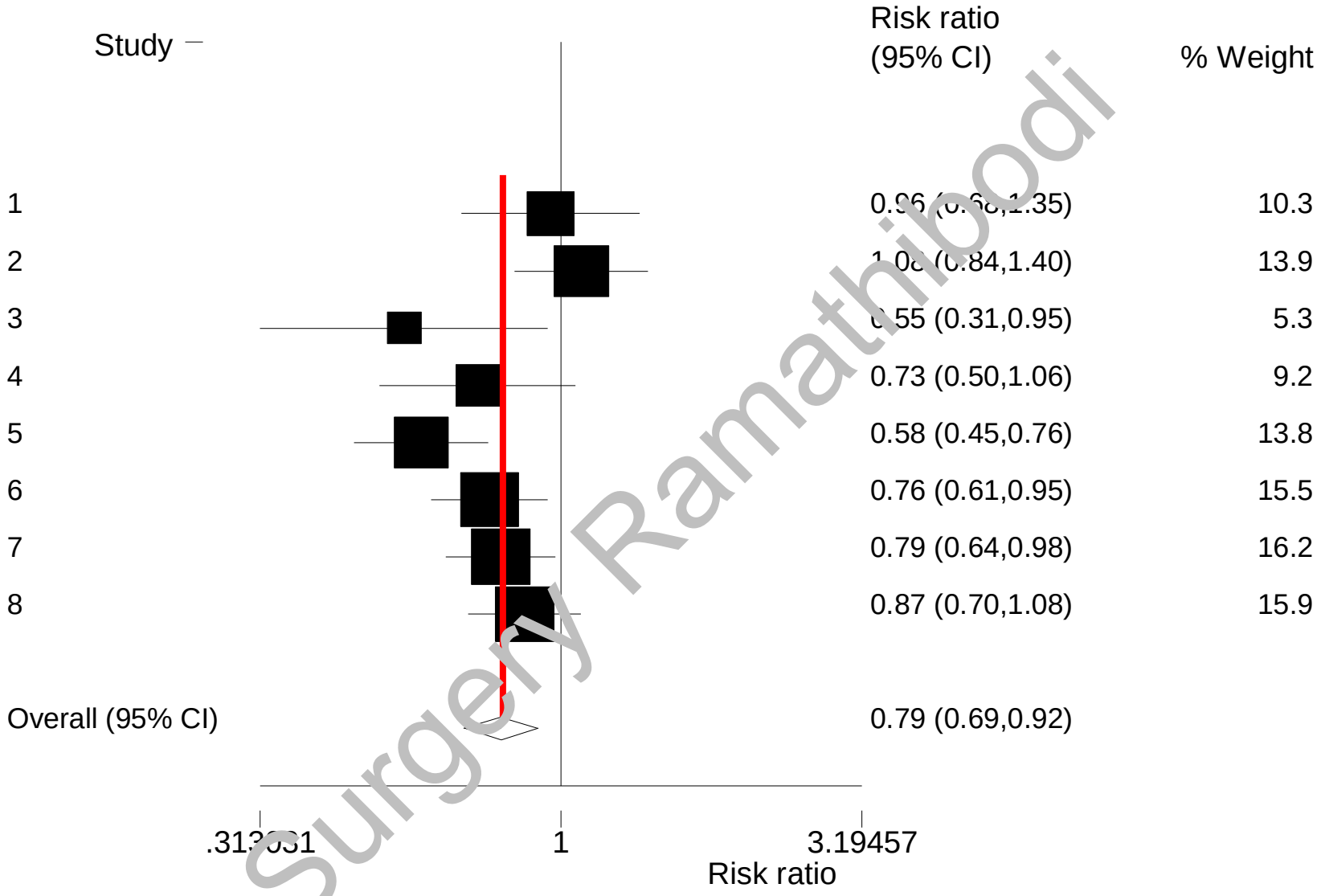
Heterogeneity/Homogeneity test p = 0.038

Variation *explained* by heterogeneity = 53%

$$I^2 = 100 \times \frac{Q - df}{Q}$$
$$= 100 \times \frac{14.87 - 7}{14.87}$$
$$= 53$$

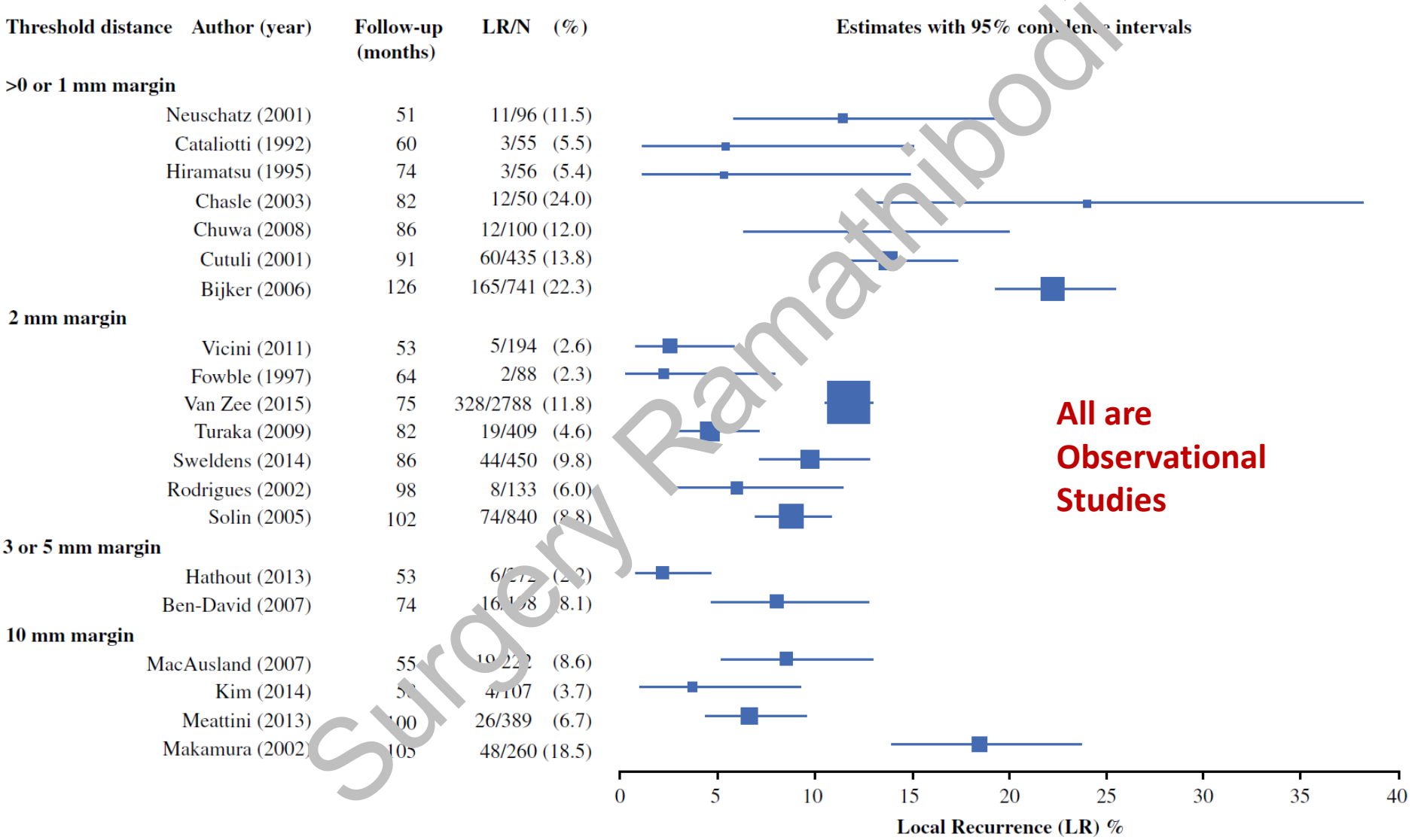


Fixed Effects (Samples from 1 Population)



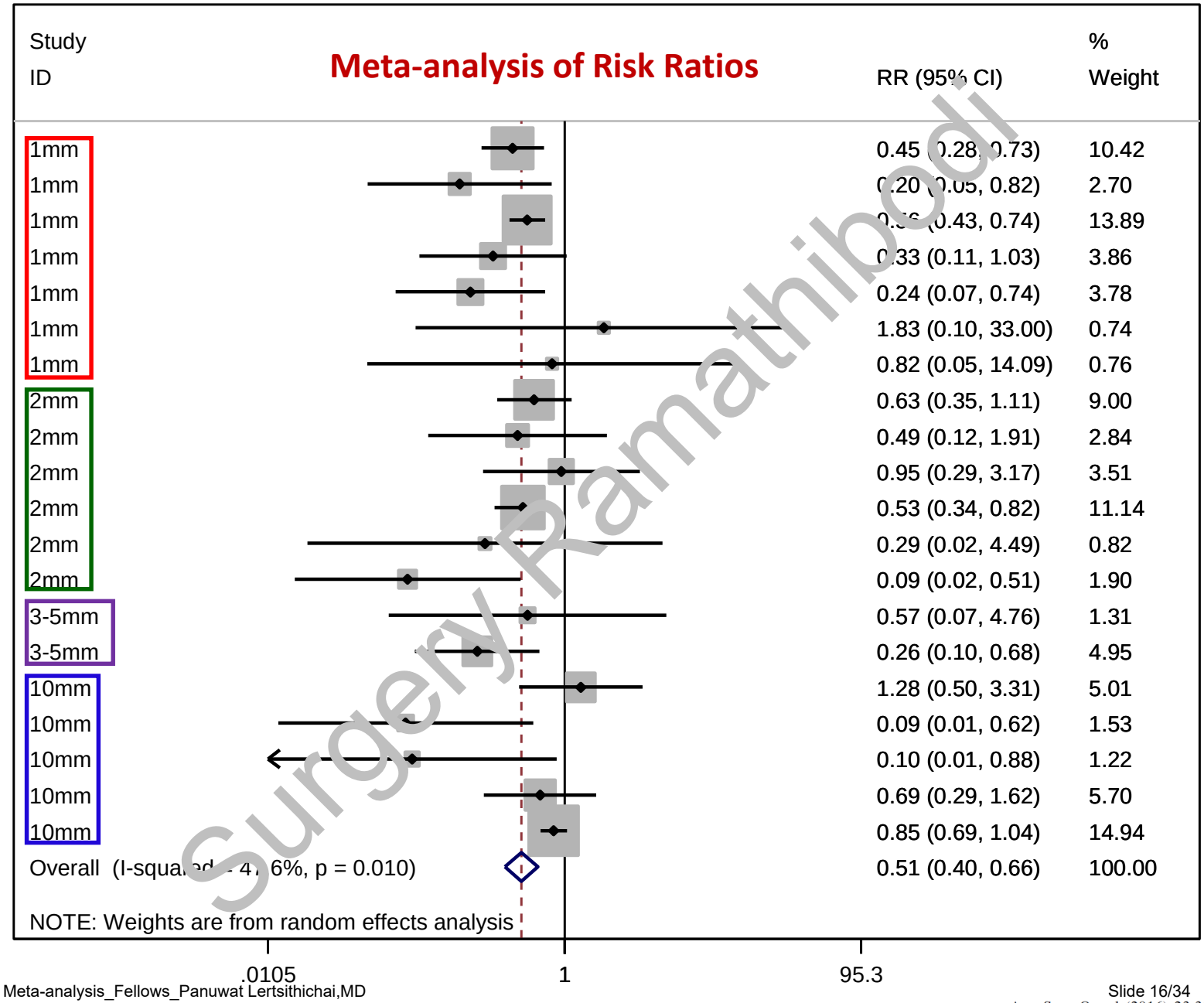
Random Effects (Samples from “Multiple” Populations)

Association between surgical margins and local recurrence in patients with DCIS



All are Observational Studies

Ann Surg Oncol (2016) 23:3811–3821



Ann Surg Oncol (2016) 23:3811–3821

Dealing with Heterogeneity

Content investigation ("Clinical")

- Investigate methodology, sample selection in detail

Statistical investigation

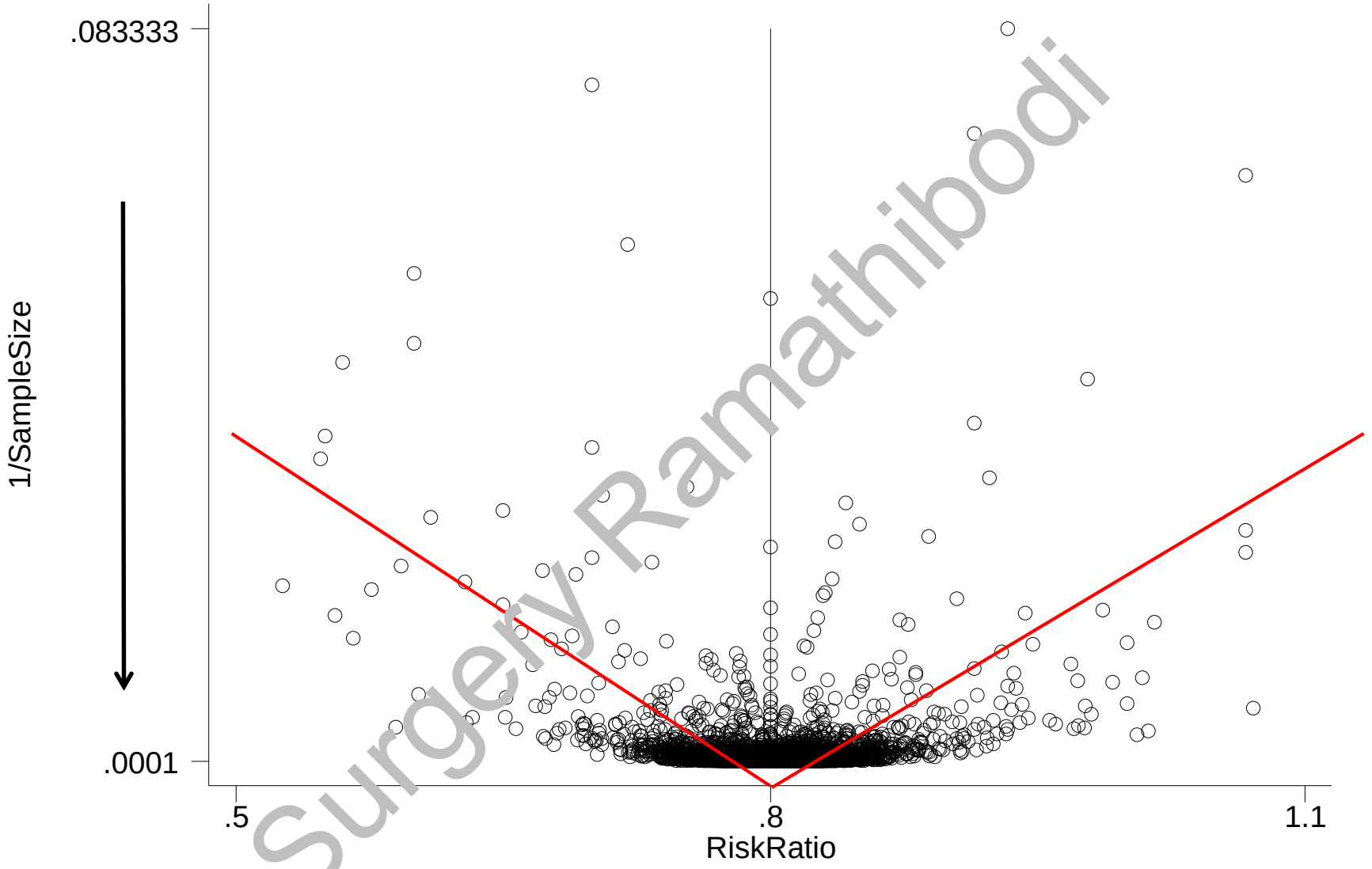
- Random-effects meta-analysis
- Do not combine all studies ?
- Subgroup analysis
- Meta-regression

Heterogeneity Table

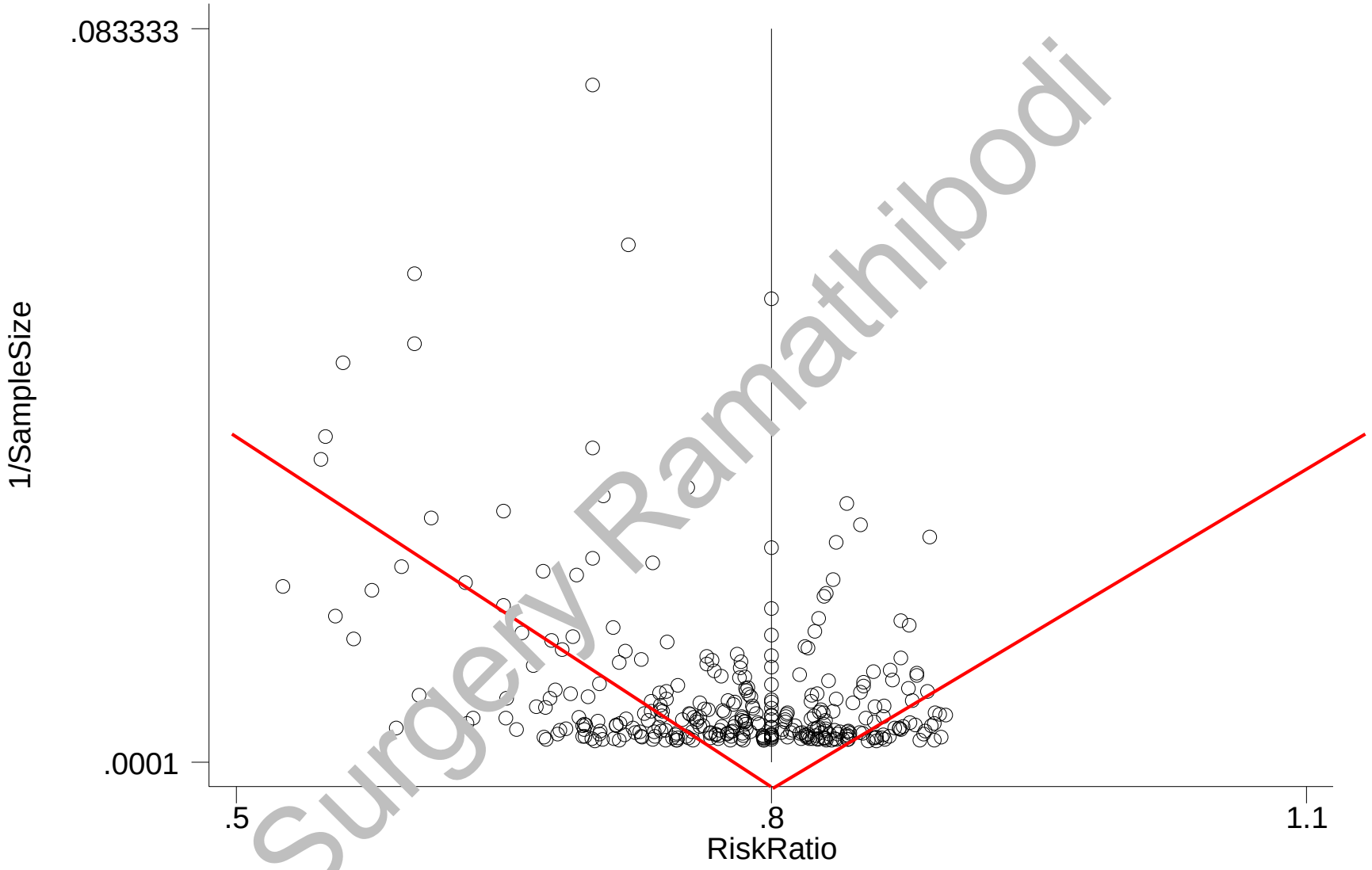
No Statistical Heterogeneity **No** Clinical Heterogeneity	Statistical Heterogeneity **No** Clinical Heterogeneity
No Statistical Heterogeneity Clinical Heterogeneity	Statistical Heterogeneity Clinical Heterogeneity

Biases

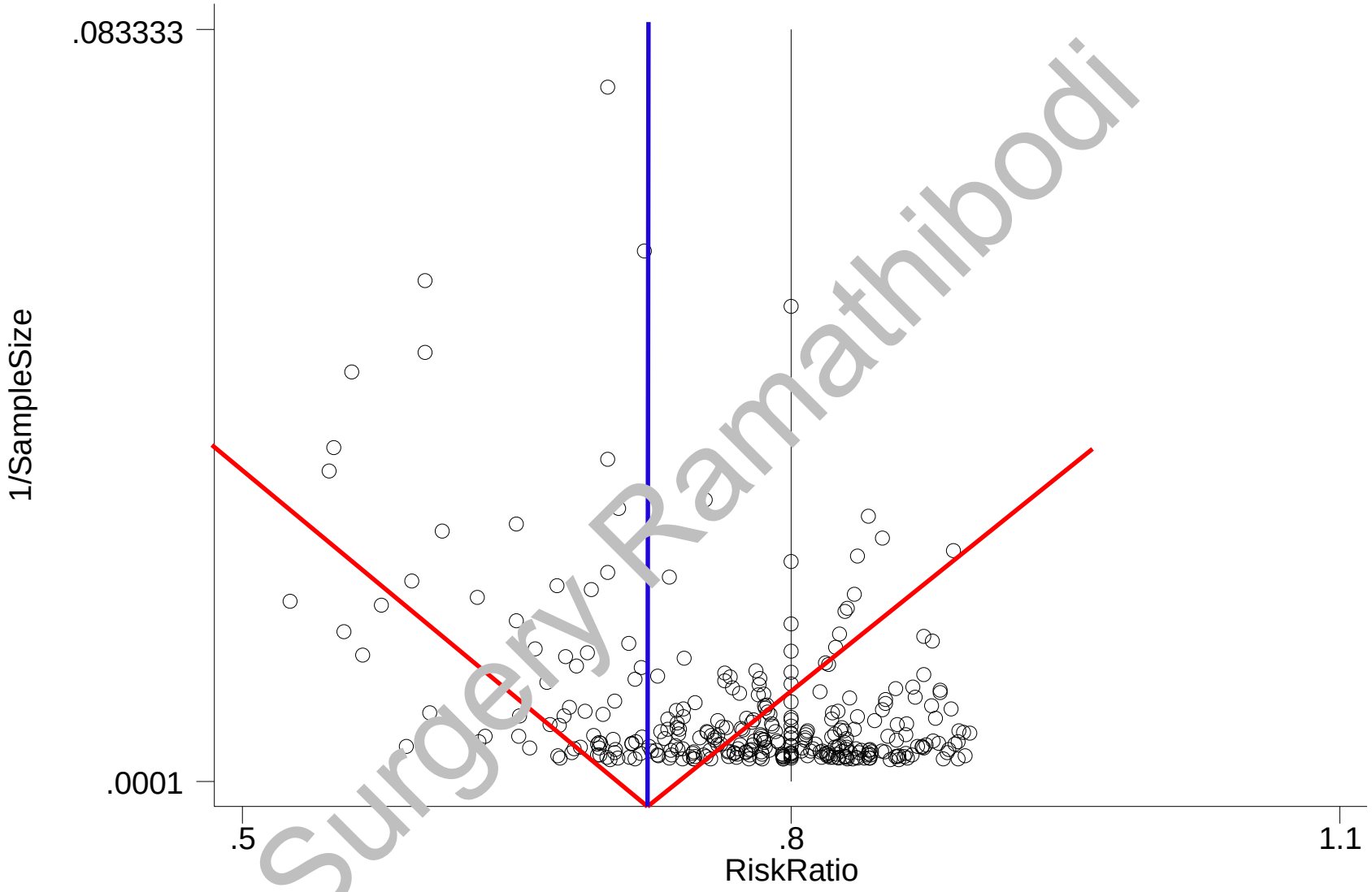
- Inherent bias in each study
- Publication bias



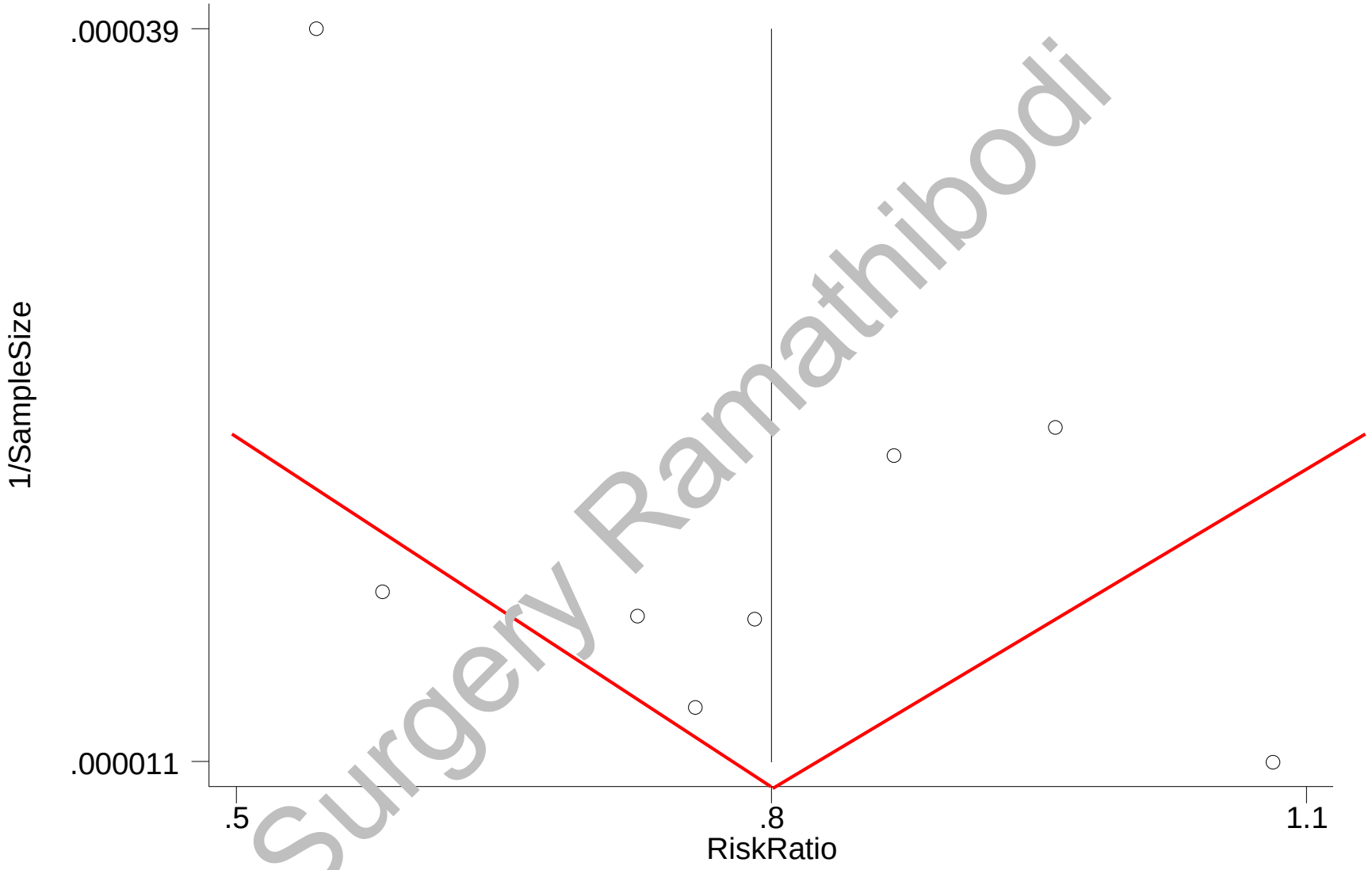
"Funnel Plot": **No** Asymmetry



"Funnel Plot": **With** Asymmetry



"Funnel Plot": **With** Asymmetry



"Funnel Plot": Actual Data

The prognosis of invasive micropapillary carcinoma compared with invasive ductal carcinoma in the breast: a meta-analysis

Yun Wu[1†], Ning Zhang[1†] and Qifeng Yang[1,2*]

Abstract

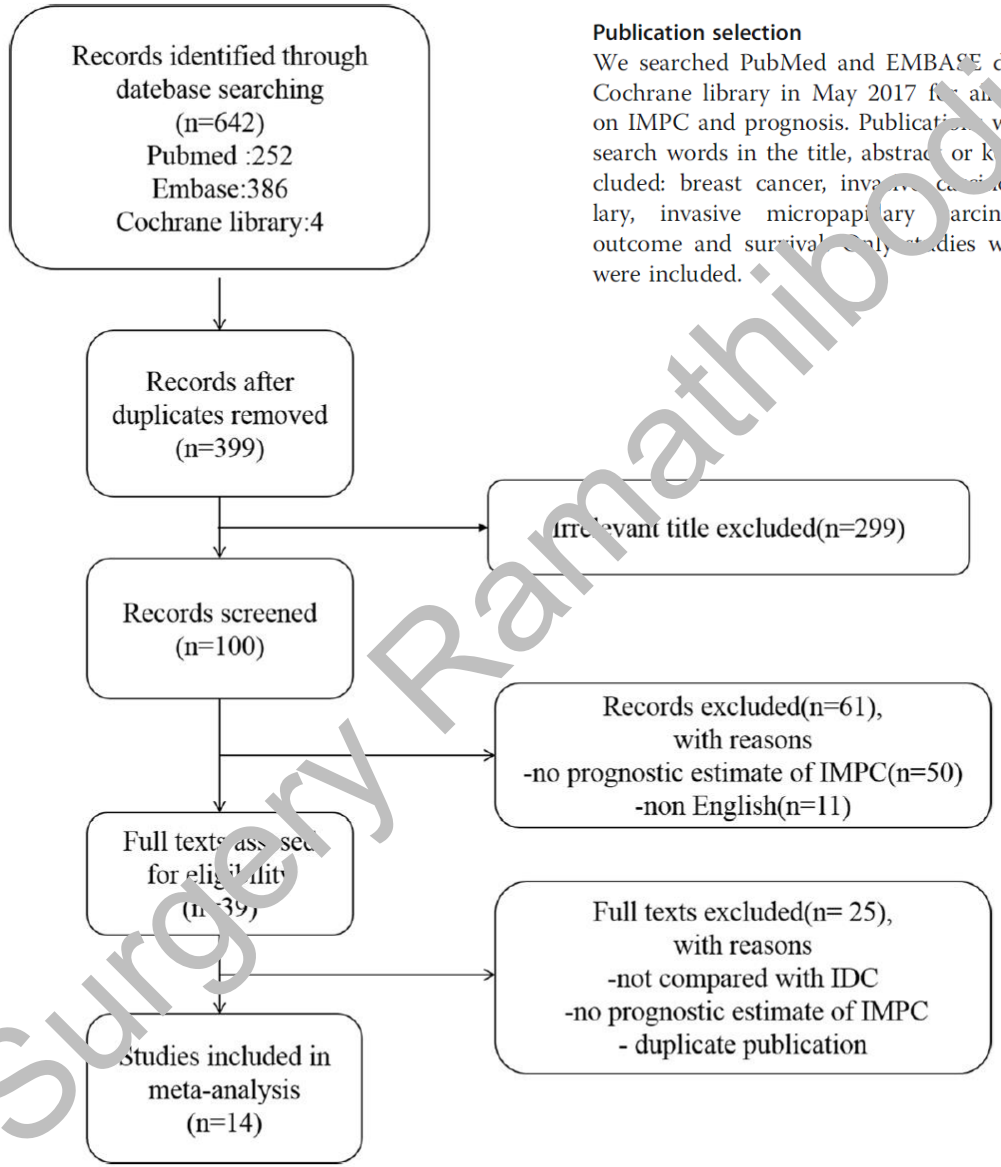
Background: Invasive micropapillary carcinoma (IMPC) of the breast is a rare variant of invasive ductal carcinoma (IDC). The prognosis of IMPC compared with that of IDC remains controversial; we conducted a meta-analysis to evaluate the prognostic difference between IMPC and IDC.

Methods: We searched the PubMed, Cochrane Library, and EMBASE databases for relevant studies comparing overall survival (OS), disease-specific survival (DSS), relapse-free survival (RFS), local-regional recurrence-free survival (LRRFS) or distant metastasis-free survival (DMFS) rates between IMPC and IDC. Fixed-effect and random-effect models were utilized based on the heterogeneity of the eligible studies. Heterogeneity was further evaluated by subgroup and sensitivity analyses.

Results: Fourteen studies with 1888 IMPC patients were included in the meta-analysis. The summarized odds ratio (OR) and 95% confidence interval (95% CI) was calculated to estimate the prognostic difference between IMPC and IDC. IMPC patients showed an unfavorable prognosis for RFS (OR; 2.04; 95% CI: 1.63–2.55) and LRRFS (OR: 2.82; 95% CI: 1.90–4.17) compared with IDC. However, no significant difference was observed in OS (OR: 0.93; 95% CI: 0.78–1.10), DSS (OR: 1.16; 95% CI: 0.95–1.40) and DMFS (OR: 0.95; 95% CI: 0.67–1.35) between IMPC and IDC. No obvious statistical heterogeneity was detected, except for DSS. Funnel plots and Egger's tests did not reveal publication bias, except for RFS.

Conclusions: This analysis showed that IMPC patients have a higher rate of loco-regional recurrence than IDC patients. However, OS, DSS and DMFS were not significantly different between IMPC and IDC. These results could help clinicians select therapeutic and follow-up strategies for IMPC patients.

Keywords: Invasive micropapillary carcinoma, IMPC, Breast cancer, Prognosis, Survival, Meta-analysis



Publication selection

We searched PubMed and EMBASE databases and the Cochrane library in May 2017 for all studies reporting on IMPC and prognosis. Publications with the following search words in the title, abstract or key words were included: breast cancer, invasive carcinoma, micropapillary, invasive micropapillary carcinoma, prognosis, outcome and survival. Only studies written in English were included.

Fig. 1 Flow diagram illustrating the selection of the included studies

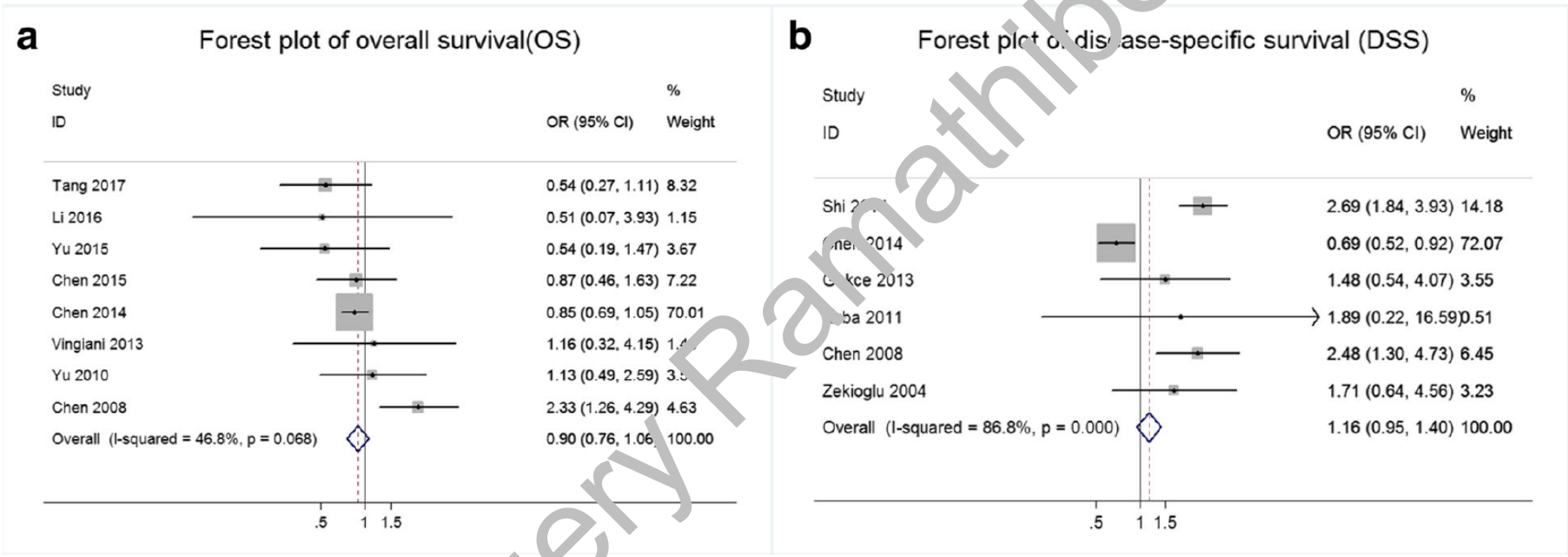
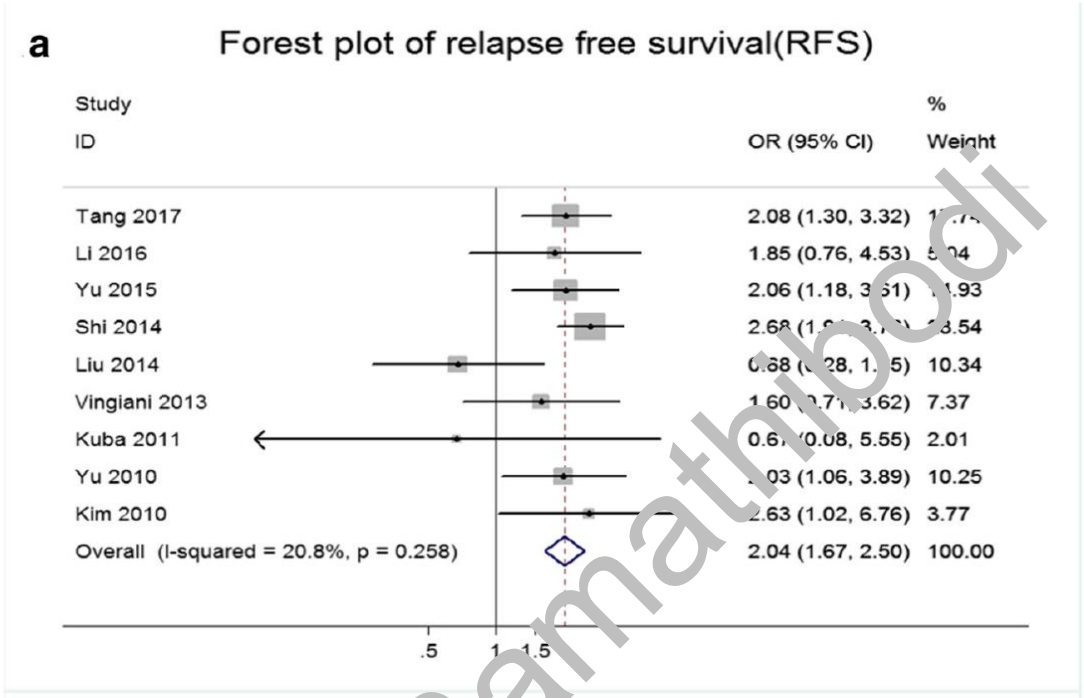
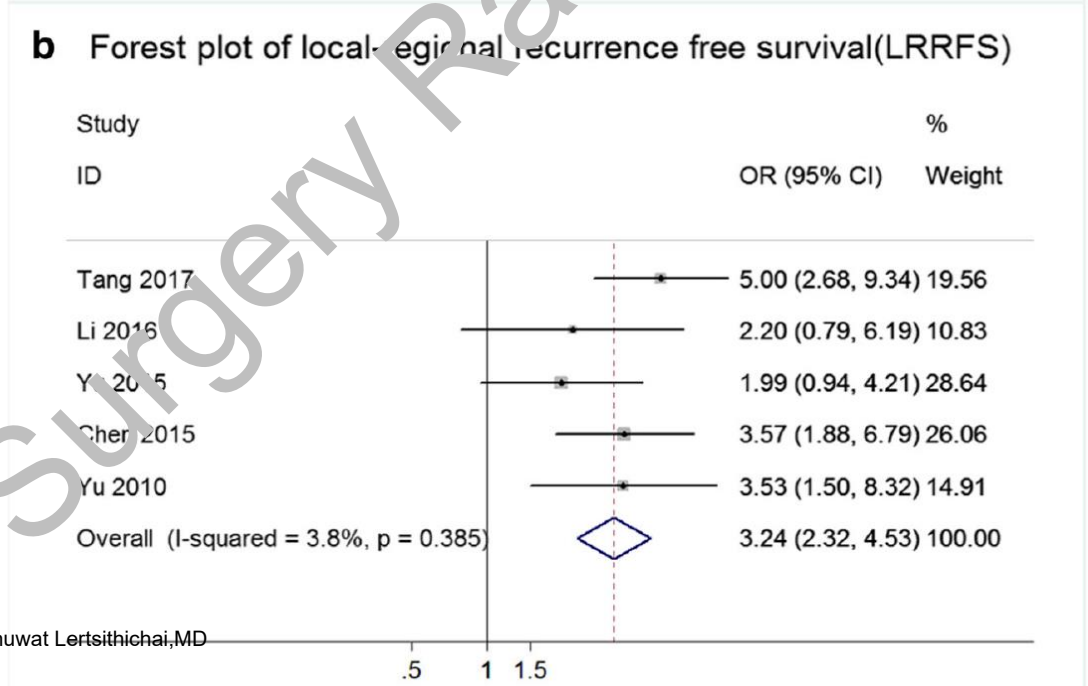
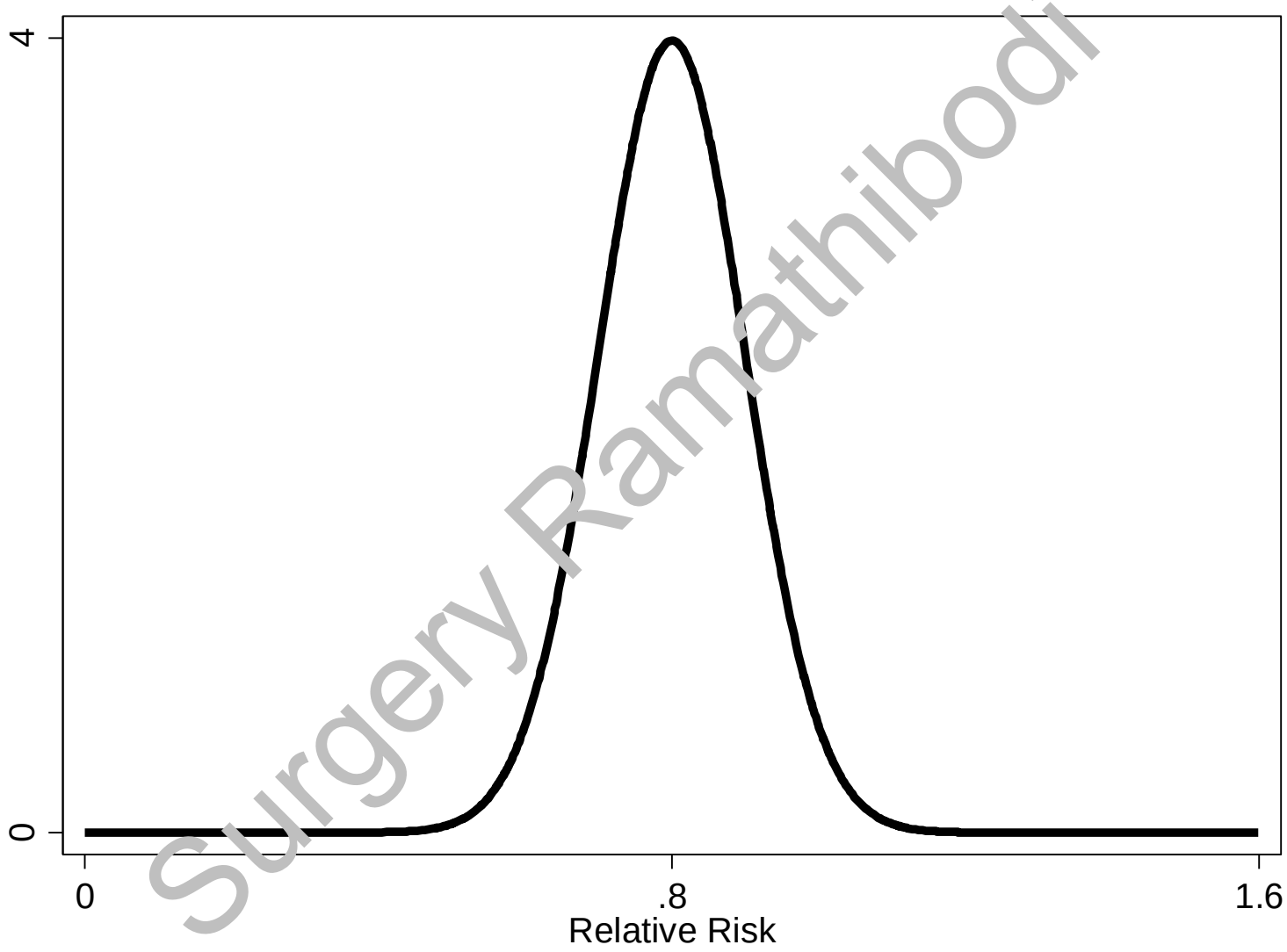


Fig. 2 Results of the survival analysis in IMPC compared with IDC. **a** Forest plot of the odds ratio (OR) for overall survival (OS) from eligible studies. **b** Forest plot of the odds ratio (OR) for disease-specific survival (DSS) from eligible studies



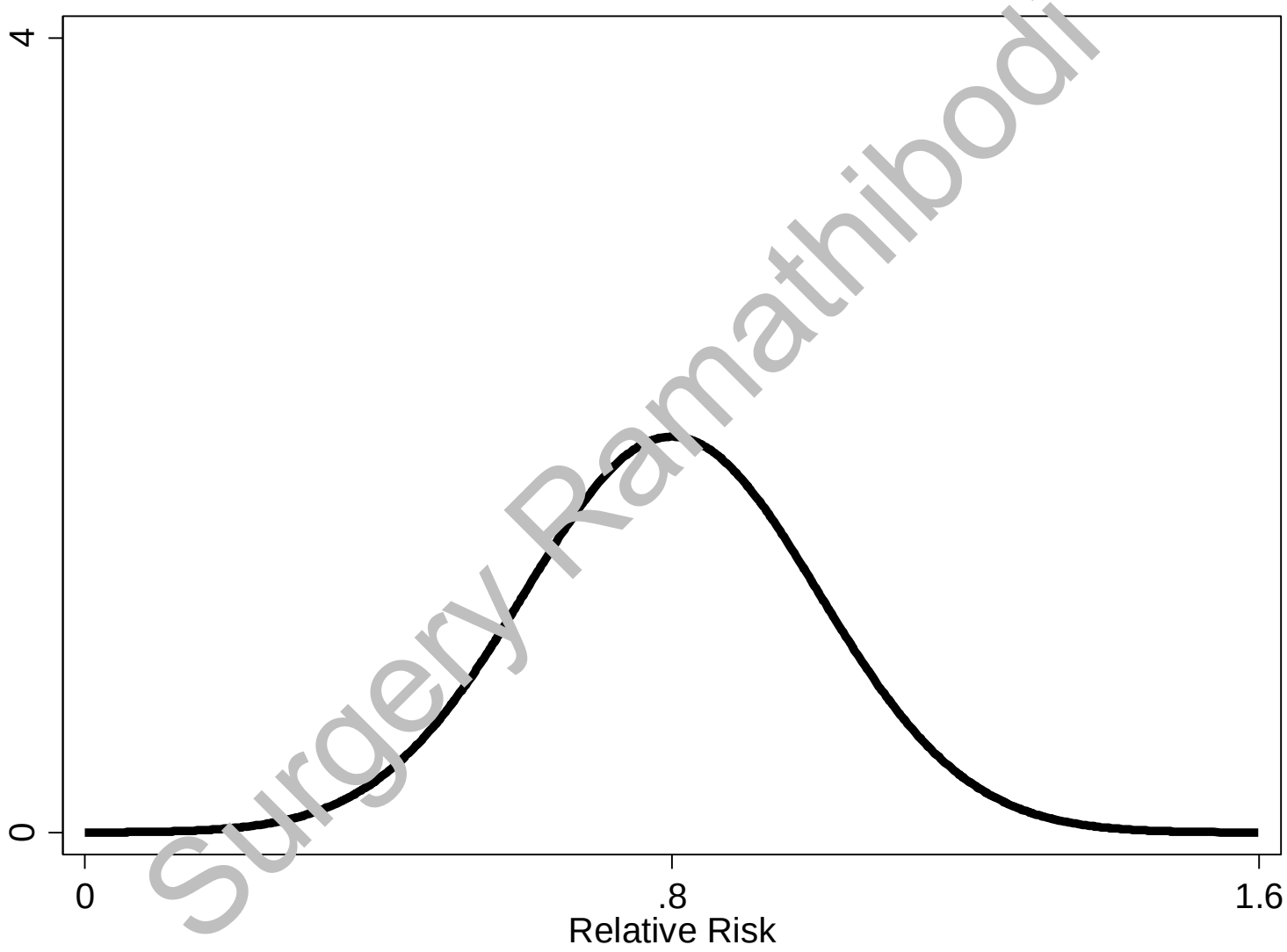


For any given sample size, a Fixed Effect Model assumes one population from which a theoretical sampling distribution can be constructed: e.g.



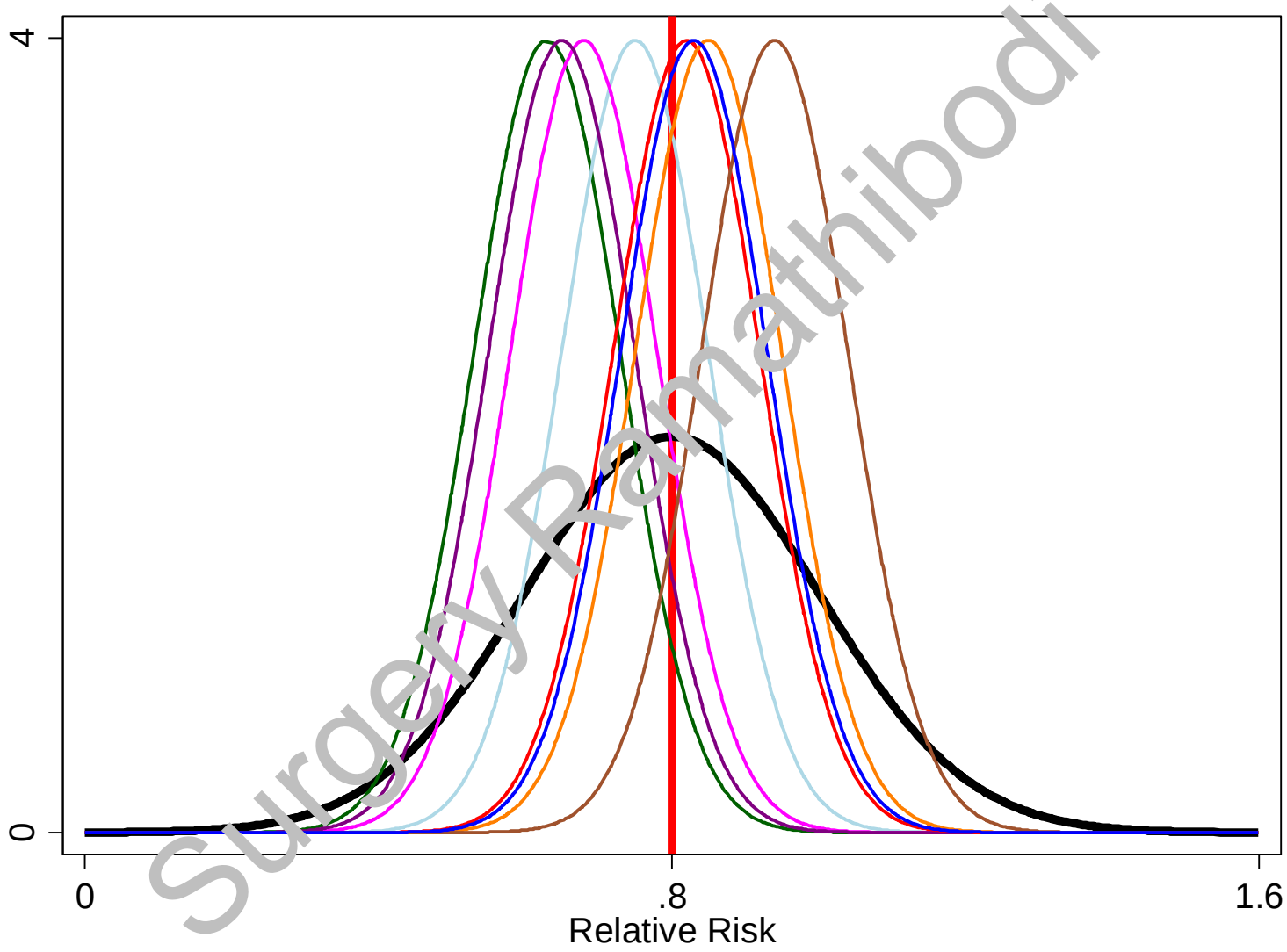
For *any given number of studies*, as subject-sample size increases, the variance approaches zero

For the **same** sample size & same number of studies, a Random Effects Model assumes one "superpopulation" from which a *wider* theoretical sampling distribution can be constructed:



For a *given number of studies*, as subject-sample size increases, the variance *does not* approach zero

This is because the Random Effects Model assumes multiple random **subpopulations,** each with the same variance as the Fixed Effect Model, in *combination*: e.g.



Fixed vs. Random Effects Models

- **Fixed effect** assumes data variation to have one component only: due to subject variation (any *apparent* between-study difference is due to sampling, *which approaches* 0 as *subject*-sample size increases)
- **Random effects** assume data variation to have (at least) two components: one due to subjects (within-study variation) and the other due to real between-study differences (between-study variation; *this does not approach* 0 as *subject*-sample size increases, *if* the number of studies is finite)

Simplified Theory

- No. of subjects, or subject-sample size, in study i, n_i
- Number of studies, m
- Total sample size, $N = \sum_i^m n_i$

- If all studies have the same subject-sample size, n
- Then total sample size would be, mn

Simplified Theory

- Fixed-effect

$$Y_i = \theta + e_i \;\; ; \text{for a study } i \in \{1, \ldots, m\}$$

- Random-effects

$$Y_i = \theta_i + e_i \; ; \text{where } \theta_i = \theta + u_i$$

- And where

$$e_i \sim N\left(0, \sigma_e^2\right); \; u_i \sim N\left(0, e_u^2\right); e \perp u$$

Thus, for simplicity, we assume all studies to have the same weight: subject-sample size is n for all i (iid e's)

Simplified Theory

- Summary statistic: $S = \sum_i Y_i / m$
- *Fixed-effect* variance

$$var(S) = \sigma^2 / nm$$

- *Random-effects* variance

$$var(S) = \left(\sigma^2 / n + \sigma_u^2\right) / m$$

Where $\sigma_e^2 \approx \sigma^2 / n$

Thus, as no. of studies $m \to \infty$, all variances approach 0

While as no. of subjects $n \to \infty$, only the fixed-effect variance approaches 0

And, so long as both n, m are finite, random effects variance will *always* be larger than that of the fixed effect