

Burden of MBI-LCBI Among Central Line Associated Bloodstream Infections: A Systematic Review and Meta-Analysis

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Abstract

Background

Mucosal barrier injury–laboratory confirmed bloodstream infections (MBI-LCBI) represent an endogenous subset of central line–associated bloodstream infections (CLABSIs), particularly in immunocompromised patients. Misclassification may distort surveillance metrics and infection prevention strategies. This study aimed to estimate the proportion of MBI-LCBI among CLABSIs and explore sources of variability.

Methods

A PRISMA-compliant systematic review and meta-analysis (PROSPERO: CRD420261281159) was conducted using MEDLINE and EMBASE (2013–2026). Observational studies reporting MBI-LCBI (per 2013 NHSN criteria) among CLABSIs were included. Random-effects meta-analysis (REML) with logit transformation was performed. Heterogeneity, prediction intervals (PI), small-study effects, and subgroup analyses (pediatric and geographic) were evaluated.

Results

Twenty-seven studies ($n = 44,106$) were included. The exploratory pooled proportion of MBI-LCBI among CLABSIs was 40.3% (95% CI: 30.4%–51.1%), with extreme heterogeneity ($I^2=99.7\%$). The 95% PI ranged from 6.5% to 86.8%, indicating substantial variability across settings. Small-study effects were significant ($p = 0.0002$); excluding studies with < 200 participants reduced the estimate to 29.0% (95% CI: 18.2%–42.8%), with persistent heterogeneity. Pediatric estimates were comparable (38.8%), while geographic variation was not a significant moderator.

Conclusions

MBI-LCBI may represent a clinically important but highly variable proportion of CLABSIs. Given substantial heterogeneity and small-study effects, pooled estimates should be interpreted cautiously. Accurate differentiation of MBI-LCBI is essential for reliable surveillance, antimicrobial decision-making, and context-specific infection prevention strategies.

Highlights

1. MBI-LCBI burden highly variable; prediction interval 6.5%–86.8%
2. Endogenous gut translocation, not catheter, drives many CLABSIs

3. Guides empiric therapy toward enteric pathogens in high-risk hosts
4. Supports tailored care in neutropenic and transplant populations
5. Prevents misclassification, improving surveillance and stewardship

Introduction

Bloodstream infections (BSIs) remain a leading cause of hospital morbidity and mortality, contributing to an estimated 2.91 million deaths globally in 2019 (1). Historically, Central Line- Associated bloodstream infections (CLABSIs) have been predominantly attributed to exogenous contamination by skin commensals, such as coagulase-negative staphylococci and *Staphylococcus aureus*, during catheter insertion or maintenance (2).

However, emerging clinical and microbiological evidence highlights an endogenous pathway for these infections in high-risk populations (1-4). In patients with hematological malignancies, severe neutropenia, or those undergoing hematopoietic stem cell transplantation, CLABSIs frequently arise from the gastrointestinal tract. Systemic infections in these immunocompromised hosts often result directly from mucosal barrier injury (MBI) and bacterial translocation rather than external catheter contamination (2-4).

Distinguishing between exogenous CLABSIs and endogenous gut-derived infections is essential for accurate hospital surveillance and effective infection prevention. Endogenous CLABSIs involve a distinct microbial spectrum, including *Enterobacteriaceae*, *Enterococcus* spp., and *Candida* spp., necessitating specific preventive and empiric antimicrobial strategies. Misclassifying MBI-mediated infections as conventional CLABSIs causes disproportionately inflated rates, penalising facilities that care for highly vulnerable populations and confounding hospital quality metrics.

To address this surveillance challenge, the Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN) introduced the Mucosal Barrier Injury–Laboratory Confirmed Bloodstream Infection (MBI-LCBI) classification (5). This framework differentiates unavoidable translocation-based BSIs from potentially preventable, catheter-associated infections.

Despite its critical implications for hospital reporting, the global burden of MBI-LCBI remains incompletely defined. This systematic review and meta-analysis aims to quantify the proportion of MBI-LCBI among CLABSIs. Additionally, we perform subgroup analyses to evaluate this burden in pediatric populations, assess geographic variation, and identify key underlying comorbidities. By delineating this specific infection subset, we seek to inform refined surveillance metrics, improve the accuracy of CLABSI reporting, and guide targeted infection prevention strategies for high-risk patients.

Methods

Protocol and Registration: This systematic review and meta-analysis was conducted in accordance with PRISMA 2020 guidelines and Cochrane standards. The protocol was prospectively registered with PROSPERO on December 22, 2025 (CRD420261281159).

Search Strategy: We searched MEDLINE and EMBASE using a highly sensitive, PRISMA- compliant strategy for articles published between January 2013 and April 2026. Only English- language articles were included. Detailed search strings are provided in the supplementary material. **Study Selection:** We included observational studies (prospective and retrospective cohorts, surveillance studies, and case– control designs). Two reviewers (YR and AA) independently screened titles and abstracts, followed by a full-text assessment against predefined eligibility criteria.

Disagreements were resolved by a third reviewer (CJ).

Eligible studies enrolled adult or pediatric populations with indwelling vascular access devices and reported extractable data to calculate the proportion of mucosal barrier injury laboratory-confirmed bloodstream infections (MBI-LCBI)—defined by 2013 NHSN criteria, among total CLABSIs. We excluded studies reporting only secondary BSIs, lacking vascular access devices, or missing extractable MBI-LCBI data. Non-human studies and non-original reports (e.g., reviews, case reports) were also excluded. Figure 1 illustrates the PRISMA study selection flow.

Data Extraction: Two reviewers (YR and AA) independently extracted data using a standardized framework. Extracted variables included publication year, number of MBI-LCBI cases, total CLABSIs, age distribution, and underlying clinical conditions. The primary objective was to determine the proportion of MBI-LCBI among CLABSIs. Catheter-days were not incorporated, as the aim was to estimate the case proportion independent of catheter dwell time.

Risk of Bias Assessment: Risk of bias was independently assessed by two reviewers (YR and AA) using design-specific validated tools. The Newcastle–Ottawa Scale (NOS) (6) was used for cohort and case-control studies, the Joanna Briggs Institute (JBI) checklists (9) for cross-sectional and surveillance studies, and the ROBINS-I tool (7) for quasi-experimental designs. Discrepancies were resolved through consensus or consultation with a third reviewer (CJ). Studies were categorized as having a low, moderate, or high risk of bias based on tool-specific guidance.

Data Analysis: Statistical analyses were performed using R software (7) (version 4.3.1; R Foundation for Statistical Computing) utilizing the *meta* and *metafor* packages. The primary outcome, the proportion of MBI-LCBI among CLABSIs, was pooled using a random-effects model with restricted

maximum likelihood (REML) estimation. Proportions were logit-transformed to stabilize variance and back-transformed for presentation.

Given the anticipated clinical and methodological diversity across populations (e.g., varying neutropenia durations and transplant protocols), the pooled estimates were considered exploratory. Heterogeneity was quantified using the Cochran Q test and the I^2 statistic. Recognizing the extreme heterogeneity ($I^2 >$

95%), analyses prioritized the calculation of 95% prediction intervals (PIs) to estimate the expected range of true effects in future clinical settings.

To explore drivers of heterogeneity, pre-planned subgroup analyses evaluated patient age (pediatric vs. adult/mixed) and geographic location. A post-hoc univariate meta-regression assessing study sample size was conducted to evaluate potential small-study effects. Publication bias was assessed visually via funnel plot asymmetry and statistically using Egger's linear regression test.

To ensure the robustness of the primary findings and address overestimation driven by small-study effects, a sensitivity analysis was performed by excluding studies with fewer than 200 participants to calculate an adjusted estimate. A "leave-one-out" sensitivity analysis was also conducted. Finally, the association between study quality and the reported MBI-LCBI proportion was examined to ensure methodological limitations did not disproportionately skew findings. Statistical significance was defined as a two-tailed p -value < 0.05 .

Results

Study Selection and Characteristics: We identified 2,361 citations published between 2013 and 2026. Following the removal of duplicates and completion of title and abstract screening, 408 studies underwent full-text review. Twenty-seven studies were included in the final analysis, comprising 26 observational studies and one quasi-experimental quality improvement study. The total patient cohort across all included studies was 44,106.

Across all studies, mucosal barrier injury laboratory-confirmed bloodstream infections (MBI-LCBI) were defined using the 2013 National Healthcare Safety Network (NHSN) criteria. All patients possessed an indwelling vascular-access device. The studies represented a global distribution, with the largest volume of data originating from North America and Europe (specifically the Netherlands), supplemented by cohorts from Australia, South America (Brazil), and East Asia (China and Japan).

The majority of patients were admitted to high-acuity units, such as hematology-oncology and bone marrow transplant centers. Extractable pediatric-specific data accounted for 4,369 cases (Table 1; mixed cohorts lacking separate pediatric counts are denoted as "N/A"). All included reports were published in English.

Quality Assessment: Risk of bias assessment yielded 13 high-quality (low risk of bias) and 11 moderate-quality studies. Three studies were classified as low quality (high risk of bias): one quasi-experimental design assessed via the ROBINS-I tool (primarily due to non-randomization and unadjusted confounding) and two abstract-only reports. Among the moderate-quality observational studies, downgrades were mainly attributed to potential confounding and incomplete adjustment for key variables.

Primary Outcome: Proportion of MBI-LCBI among CLABSI. We used a random-effects model with restricted maximum likelihood (REML) estimation, the exploratory pooled proportion of MBI-LCBI among

total CLABSIs was 40.3% (95% CI: 30.4%–51.1%; logit-transformed estimate = -0.3916, SE = 0.2223). The crude (unweighted) proportion across studies was 17.13% (95% CI: 16.88%–17.38%). A forest plot illustrating individual study estimates is presented in Figure 2. A 95% prediction interval of 6.5% to 86.8% was calculated, indicating substantial variability in the expected true proportion across varying clinical settings.

Extreme between-study heterogeneity was observed: $I^2 = 99.73\%$, $\tau^2 = 1.2976$ (SE = 0.3737), $H^2 = 368.79$, and Cochran's Q = 4427.30 (df = 27, $p < 0.0001$).

Small-Study Effects and Meta-Regression: Visual inspection of the funnel plot (Figure 3) suggested asymmetry, which was statistically confirmed by Egger's regression test ($z = 3.68$, $p = 0.0002$). This indicates the presence of small-study effects, wherein smaller cohorts consistently reported higher MBI-LCBI proportions. A meta-regression utilizing log-transformed sample size as a moderator (Figure 4) demonstrated a significant inverse association between sample size and reported proportion ($\beta = -0.3062$, $p = 0.0017$), explaining 28.68% of the between-study heterogeneity ($R^2 = 28.68\%$).

Sensitivity Analysis: To address potential overestimation driven by small-study effects, a sensitivity analysis excluding studies with fewer than 200 participants was conducted. The adjusted pooled proportion was reduced to 28.96% (95% CI: 18.17%–42.80%). Following this exclusion, Egger's test was no longer significant ($z = 1.02$, $p = 0.3099$), indicating an attenuation of bias. However, extreme heterogeneity persisted ($I^2 > 99\%$), with a revised prediction interval of 4.4% to 78.3%.

TABLE 1: STUDY CHARACTERISTICS

Subgroup Analyses:

- a. *Pediatric Subgroup:* Six studies provided extractable pediatric-specific data. The pooled proportion of MBI-LCBI among CLABSIs in this subgroup was 38.8% (95% CI: 24.5%– 55.3%; logit = -0.4572, SE = 0.3419). Substantial heterogeneity remained present within the pediatric cohort ($I^2 = 93.49\%$; $\tau^2 = 0.6142$, SE = 0.4425; $H^2 = 15.36$; Q = 54.87, df = 5, $p < 0.0001$), resulting in a wide 95% prediction interval of 10.6% to 77.2%.
- b. *Geographic Subgroup:* Geographic variation was assessed across regions contributing multiple studies. The pooled MBI-LCBI proportion was 50.5% (95% CI: 33.2%–67.6%) for studies conducted in North America (k = 13) and 45.7% (95% CI: 23.3%–70.1%) for studies in Europe (k= 4). Studies with an unspecified geographic origin yielded an estimate of 54.9% (95% CI: 47.5%–62.1%). Meta-regression evaluating geographic region as a moderator found no significant association (QM = 6.37, $p = 0.38$), explaining only 0.19% of the observed heterogeneity, with significant residual variability persisting ($I^2 = 97.6\%$, $p < 0.001$).

Discussion

This systematic review and meta-analysis supports emerging evidence regarding the etiology of CLABSIs in high-risk patients. While they have traditionally been viewed as exogenous, preventable events linked to lapses in catheter insertion or maintenance, our findings highlight that a substantial proportion of MBI-LCBI among CLABSIs arises from the translocation of endogenous flora (9,11) (29,30).

Interpretation of Main Findings and Literature Comparison Although the initial pooled proportion was approximately 40%, small-study effects suggest overestimation; the adjusted estimate of approximately 29% likely provides a more reliable baseline for the proportion of MBI-LCBI among CLABSIs. This endogenous mechanism is biologically plausible in hematology–oncology populations, where intensive chemotherapy, gastrointestinal graft-versus-host disease, and prolonged neutropenia disrupt mucosal integrity (12,18) (30,32). Consequently, MBI-LCBI exhibits a distinct microbiological profile dominated by enteric Gram-negative bacilli, *Enterococcus* species, viridans group streptococci, and *Candida* species (11,12) (35).

Our findings align with large-scale surveillance data. The NHSN field test demonstrated that 36.5% of CLABSIs met MBI-LCBI criteria (14), with subsequent oncology-specific analyses reporting proportions near 45% (9). Pediatric oncology cohorts demonstrate a comparable burden (up to 44%) (28), while in hematopoietic stem cell transplant populations, early MBI-LCBI incidence approaches 13% (17,30).

Heterogeneity, Small-Study Effects, and Subgroup Insights Given the extreme heterogeneity ($I^2 \approx 99\%$), our pooled estimates must be considered exploratory. Such high variability indicates that a single summary statistic cannot precisely capture the true burden across all settings. Instead, the wide prediction interval (6.5%–86.8%) is more clinically informative, emphasizing that the proportion of MBI-LCBI is highly context-dependent. This variability likely stems from diverse patient populations (10,29) (30), evolving surveillance practices (9,32), and institutional differences in antimicrobial prophylaxis and catheter care protocols (26,31).

Furthermore, meta-regression revealed significant small-study effects, indicating that smaller cohorts frequently reported higher estimates. While excluding these studies reduced the pooled proportion to

~29%, the central finding, that MBI-LCBI represents a clinically significant, endogenous subset of CLABSIs, remains robust. Subgroup analyses confirmed this burden extends across age groups, including pediatric populations (~38-44%) (16,28), without geographic location emerging as a primary driver of variability.

Clinical and Surveillance Implications The recognition of MBI-LCBI has critical implications for hospital epidemiology and clinical management:

- **Infection Control and Surveillance:** Standard central line care bundles, designed to prevent exogenous contamination, have limited efficacy against MBI-LCBI (24,25). Failing to differentiate MBI-LCBI from conventional CLABSIs distorts metrics, falsely elevating reported infection rates by up to 45–50% in oncology units (13,14) (28). This misclassification disproportionately penalizes

facilities caring for highly vulnerable, immunocompromised populations and undermines the validity of hospital benchmarking.

- **Empiric Antimicrobial Therapy:** MBI-LCBI necessitates empiric coverage directed toward enteric pathogens rather than solely targeting Gram-positive skin flora, requiring careful antimicrobial stewardship to balance effective therapy with the avoidance of broad-spectrum overuse (11,12) (17).
- **Central Line Management:** Catheter removal is significantly less frequent in MBI-LCBI compared to conventional CLABSI (~15% vs ~54%) (27), supporting evidence that line salvage may often be safely pursued without compromising outcomes, thereby preserving vital vascular access (20,27).

Strengths, Limitations, and Future Directions This study provides a comprehensive, PRISMA- compliant synthesis utilizing robust statistical modeling. However, several limitations exist. The extreme heterogeneity limits the precision of the pooled estimates, and the reliance on observational data introduces potential confounding. As noted, small-study effects and publication bias likely led to initial overestimation. Misclassification bias due to variable institutional surveillance practices remains a factor. Finally, the inclusion of two abstract-only studies, while methodologically sound and non-disruptive in sensitivity analyses, warrants acknowledgment.

The substantial clinical and methodological variability underscores the urgent need for standardized MBI-LCBI reporting to improve the accuracy of surveillance metrics. Future research should prioritize prospective, multicenter studies incorporating detailed patient-level data, the validation of mucosal integrity biomarkers (e.g., citrulline) (12,33), and microbiome-targeted interventions to identify and protect high-risk patients.

Conclusion

In conclusion, this meta-analysis demonstrates that MBI-LCBI constitutes a substantial proportion of CLABSI, particularly in immunocompromised populations. This emphasizes that many of these infections are driven by endogenous mechanisms rather than exogenous contamination.

Distinguishing MBI-LCBI from conventional CLABSI is critical for accurate surveillance reporting, appropriate empiric antimicrobial therapy, and optimal catheter management. These findings highlight that not all CLABSI are uniformly preventable, supporting emerging evidence for refined hospital quality metrics and more nuanced, host-centred infection control approaches. Future prevention strategies must extend beyond traditional catheter care to incorporate the preservation of mucosal integrity, microbiome dynamics, and individualized patient risk assessment.

Declarations

-Ethics approval and consent to participate: N/A

-Consent to publish: Not applicable

-Availability of data and materials: MEDLINE and EMBASE

-Competing interests: NIL

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-Authors' contributions:

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Table

Table 1 is available in the Supplementary Files section.

Figures

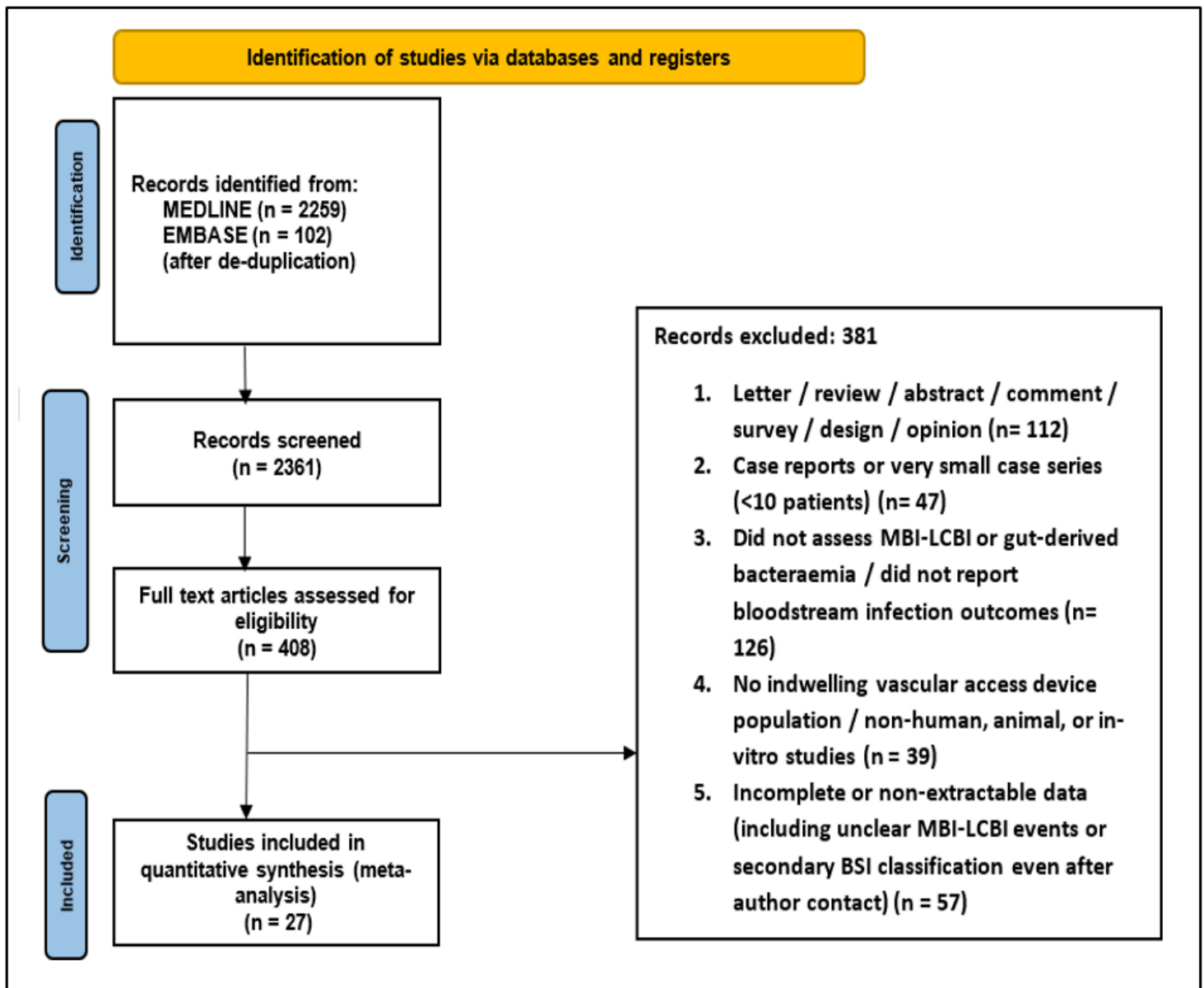


Figure 1

PRISMA 2020 Flow Diagram

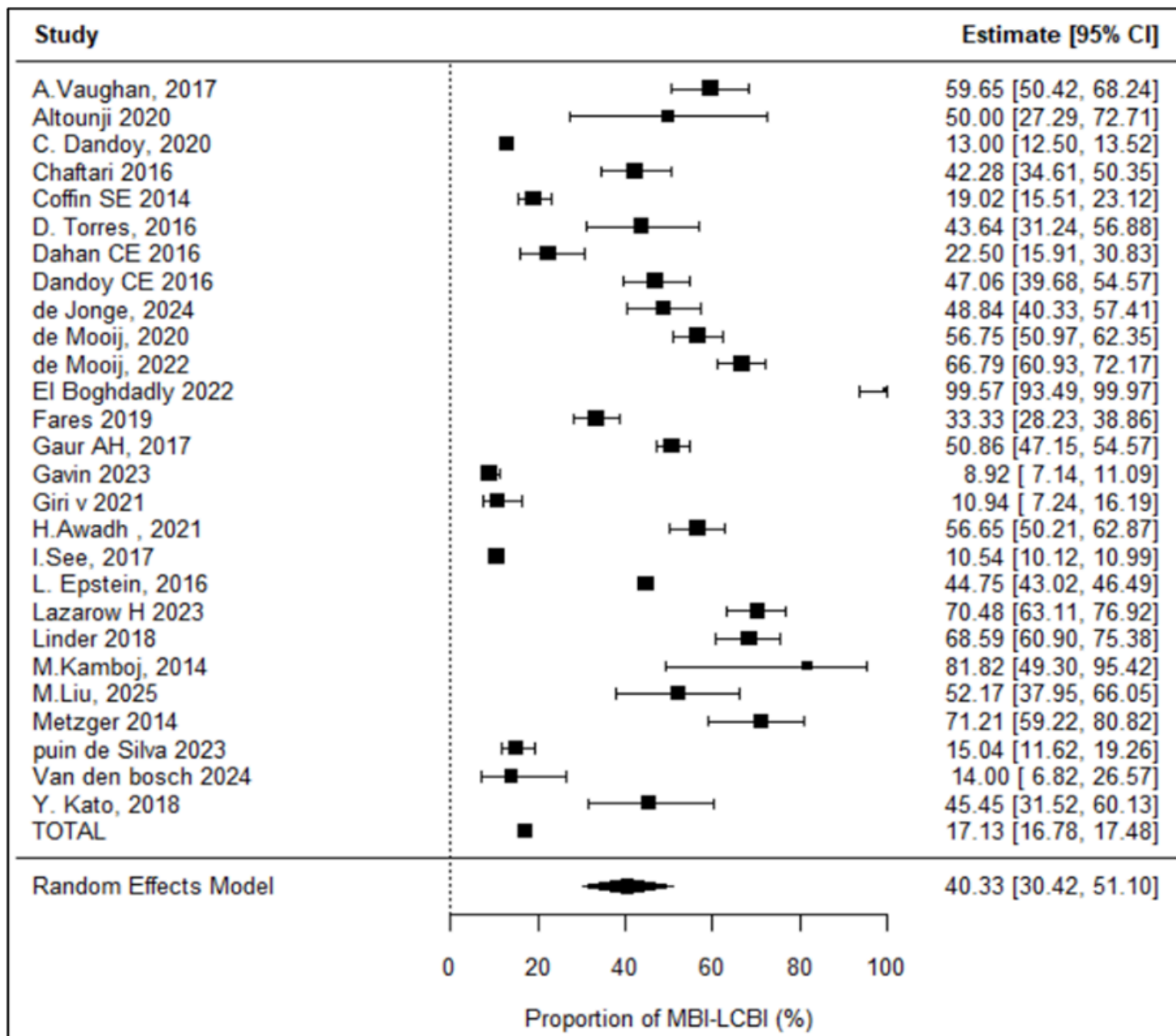


Figure 2

Forest plot of the pooled proportion of MBI-LCBI.

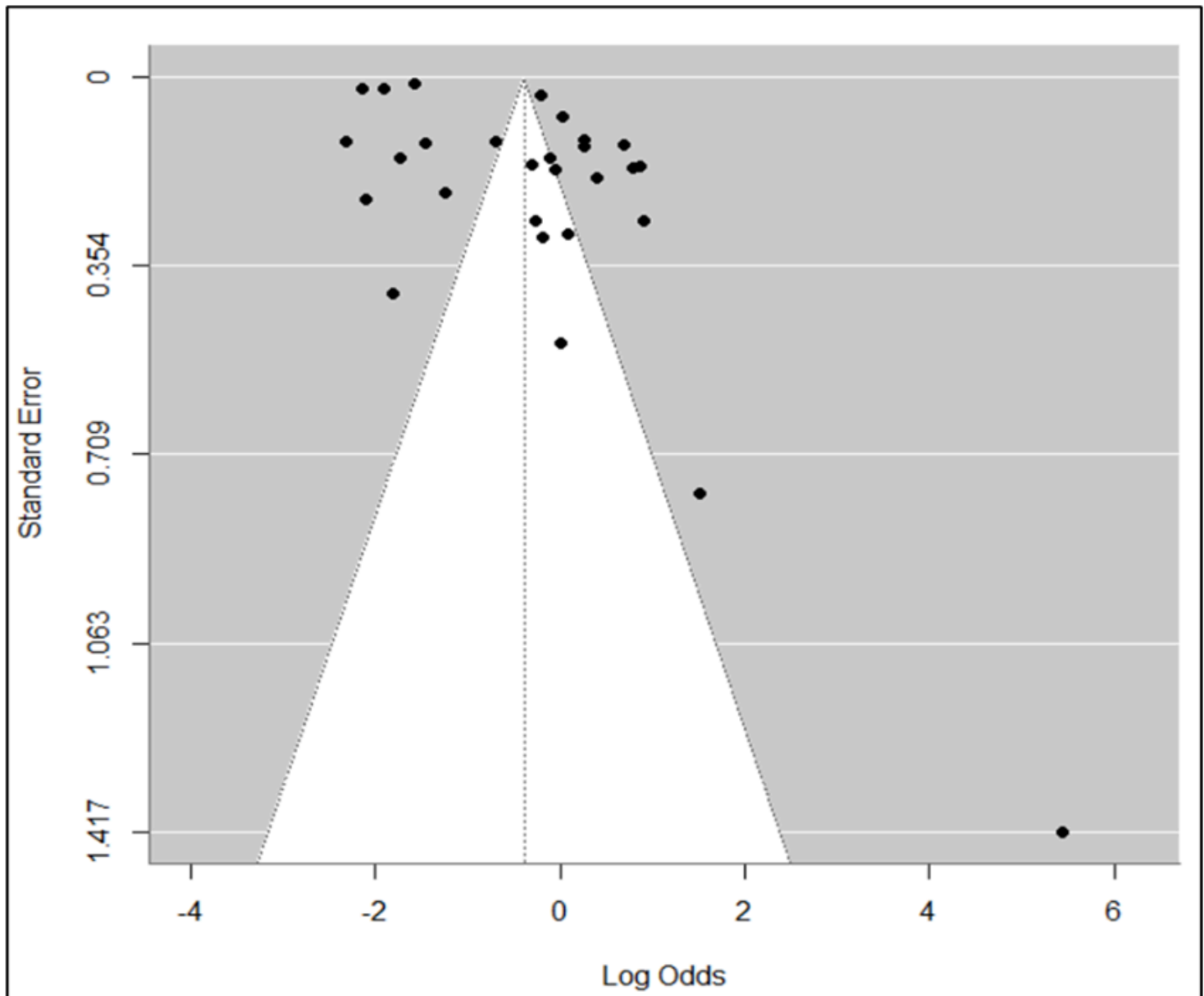


Figure 3

FUNNEL PLOT

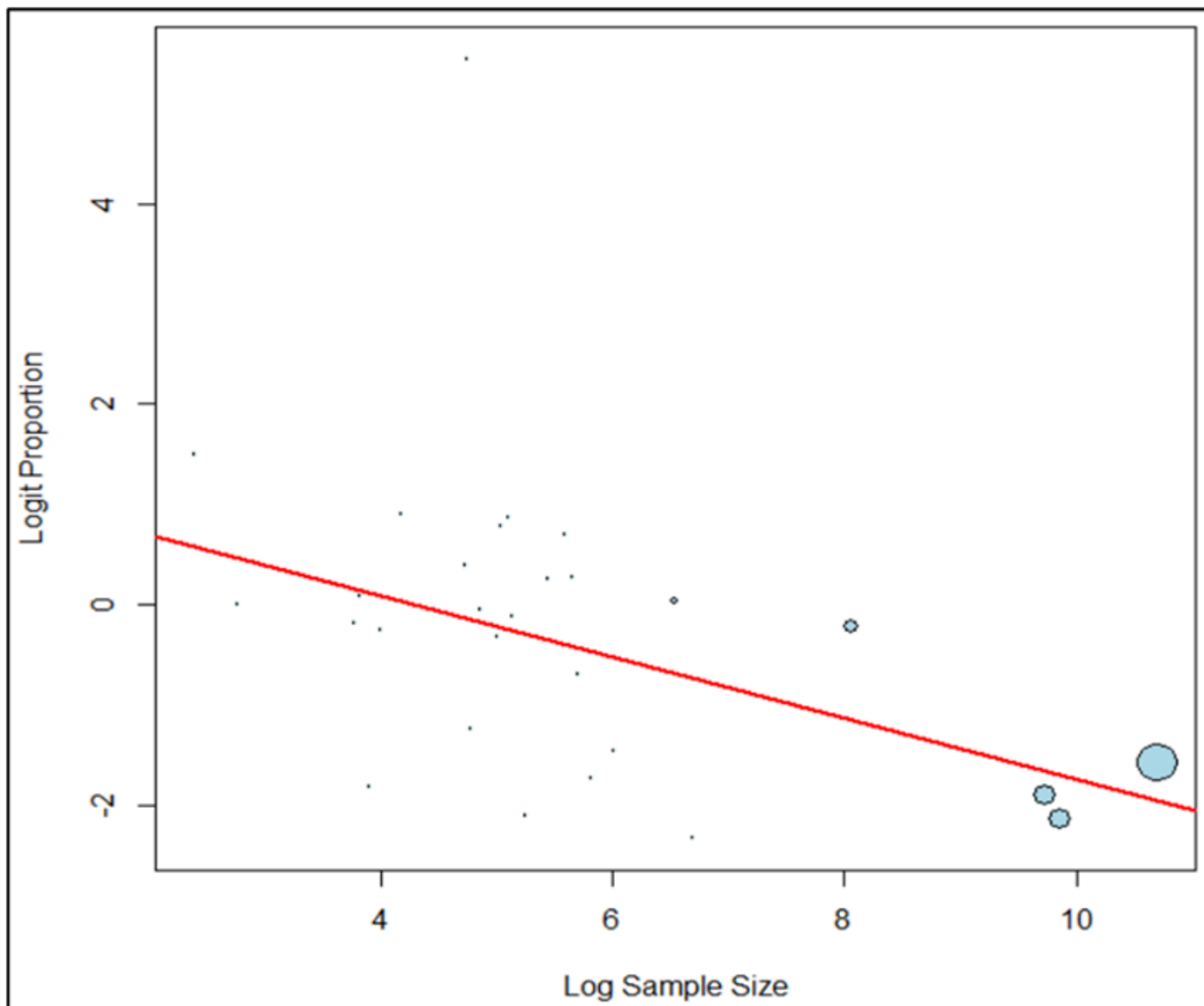


Figure 4

Meta-regression of MBI-LCBI proportion by study sample size.

Supplementary Files

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- [Searchstrategy.docx](#)
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