

Durable Survival Outcomes After Liver Transplantation for Colorectal Liver Metastases: A Systematic Review and Single-Arm Meta-analysis

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Abstract

Background:

Liver transplantation (LT) has emerged as a potential treatment option for selected patients with colorectal liver metastases (CRLM), but existing meta-analyses are limited by heterogeneous populations and mixed treatment modalities.

Methods:

A systematic review and single-arm meta-analysis were conducted in accordance with PRISMA guidelines. Studies reporting outcomes following LT for CRLM were included. Primary outcomes were overall survival (OS) and progression-free survival (PFS) at predefined time points. Secondary outcomes included adverse events. Pooled proportions were calculated using random-effects models with logit transformation and Hartung–Knapp adjustment. Heterogeneity was assessed using the I^2 statistic.

Results:

Pooled analysis demonstrated favorable survival outcomes following LT. The pooled 3-year OS was 69% (95% CI, 52–82%; $I^2 = 0.0\%$), and the pooled 5-year OS was 62% (95% CI, 36–83%; $I^2 = 14.6\%$). The pooled 3-year PFS was 33% (95% CI, 7–76%), with substantial heterogeneity ($I^2 = 62.8\%$). The pooled incidence of adverse events was 41% (95% CI, 25–60%; $I^2 = 0.0\%$). Sensitivity analyses confirmed the robustness of pooled estimates.

Conclusions:

In carefully selected patients with CRLM, LT is associated with durable long-term survival and an acceptable safety profile, supporting further prospective evaluation and refinement of selection criteria.

1. INTRODUCTION

Colorectal cancer (CRC) still remains a major global health burden and is currently the third most commonly diagnosed malignancy worldwide. According to the World Health Organization (WHO) and GLOBOCAN 2020 estimates, approximately 1.9 million new cases of colorectal cancer are diagnosed each year, accounting for almost 10% of all cancer diagnoses. CRC incidence and mortality are also projected to rise substantially over the coming decades (1, 2). CRC is also among the top 3 leading causes of cancer-related mortality worldwide, underscoring the dire need for effective treatment strategies for advanced disease (2).

The liver is the most frequent site of metastatic spread in colorectal cancer due to portal venous drainage. 20–30% of the patients present with synchronous liver metastases and up to 40–50% of the patients present with developing colorectal liver metastases (CRLM) during the course of their disease (3, 4). The development of CRLM is a very critical prognostic event, as untreated or unresectable metastatic disease is associated with poor long-term survival and limited curative options (5).

Current standard management for CRLM includes systemic chemotherapy and surgical liver resection when technically feasible. Advances in the systemic therapy have shown to improve median overall survival. However, durable and long-term survival remains uncommon in the absence of curative intervention (6). Hepatic resection offers the best chance of long-term survival, with reported 5-year survival rates ranging from 30% to 55%. The catch remains that only 10% to 20% of the patients are assessed to be eligible for resection due to tumor burden, unfavorable distribution, or extrahepatic disease (6, 7). Consequently, a large proportion of patients remain confined to palliative treatment strategies.

In this context, liver transplantation (LT) has emerged as a potential therapeutic option for highly selected patients with unresectable, liver-only CRLM. Early prospective studies demonstrated encouraging long-term survival following LT. The SECA-I trial reports a 5-year overall survival of approximately 60% despite high recurrence rates (8). Subsequent refinement in the SECA-II trial led to even more favorable outcomes, with reported 5-year overall survival of about 80–83% (9). These findings renewed interest in LT as a treatment strategy for CRLM.

Several systematic reviews and meta-analyses have attempted to synthesize the growing body of evidence on LT for CRLM. However, most previously published meta-analyses are limited due to their inclusion of highly heterogeneous populations. These analyses have frequently combined patients undergoing liver transplantation with those undergoing liver resection or other locoregional therapies, as well as mixed resectable and unresectable disease (10–12). Such methodological heterogeneity limits the interpretability of pooled survival estimates and obscures outcomes attributable specifically to liver transplantation.

To address this important gap, we conducted a systematic review and single-arm meta-analysis focusing exclusively on patients undergoing liver transplantation for colorectal liver metastases. By restricting the analysis to transplantation-only cohort and pooling time-specific survival and safety outcomes, this study aims to provide a more precise and clinically relevant assessment of survival durability and postoperative outcomes associated with LT in this highly selected population.

2. METHODOLOGY

2.1. Study Design:

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (13) to ensure transparency and reproducibility. The analysis focused on synthesizing evidence from observational studies and randomized controlled trials (RCTs) evaluating the safety and efficacy of liver transplant in patients with colorectal cancer liver metastases, with predefined outcomes including overall survival, progression-free survival, and adverse events.

2.2. Search Strategy and Databases:

A comprehensive literature search was performed from database inception through January 7th, 2026, across multiple electronic databases, including PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. The search strategy incorporated Medical Subject Headings (MeSH) terms and free-text keywords such as "liver transplant," "colorectal cancer with liver metastases," "liver metastases," "colorectal cancer," "orthotopic liver transplant." Boolean operators (AND, OR) were used to combine terms, with no language restrictions applied. Grey literature was searched via ClinicalTrials.gov, EU Clinical Trials Register, and conference proceedings. Reference lists of included studies and relevant reviews were hand-searched for additional trials.

2.3. Eligibility Criteria:

Studies were eligible if they met the Population, Intervention, Comparator, Outcome, Study design (PICOS) framework: (1) Population: adults (≥ 18 years) with colorectal cancer metastasizing to liver; (2) Intervention: Orthotopic Liver Transplant; (3) Comparator: None; (4) Outcomes: overall survival, progression free survival, adverse events; (5) Study design: phase III or IV RCTs with parallel-group design and non-randomized studies, observational designs. Exclusion criteria contained studies without predefined outcomes, studies without posted results or full texts, and studies with only partial liver resection.

2.4. Data Extraction and Outcomes:

Data were extracted independently by two reviewers using a standardized electronic form in Microsoft Excel, capturing study characteristics (author, year, design, sample size), participant demographics (age, sex, follow-up duration), intervention details, and outcome data (event counts). Discrepancies were reconciled by consensus, with corresponding authors contacted for missing data if necessary.

2.5. Quality and Certainty Assessment:

Risk of bias for observational studies was evaluated via Risk-of-Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tool (14), assessing domains including bias due to confounding, selection of participants, classification of interventions, missing data, measurement of outcomes, and selection of reported results. Each domain was rated as low risk, moderate risk, and serious risk of bias.

Publication bias was not assessed due to a small number of included studies.

2.6. Data Analysis and Synthesis

All statistical analyses were performed using R software (version 4.5.0) with the meta package. Given the absence of a consistent comparator arm across studies, a single-arm meta-analysis approach was employed. For time-to-event outcomes reported as survival proportions (overall survival and progression-free survival), pooled estimates were calculated at predefined time points (3-year and 5-year). Proportions were pooled using the logit transformation (PLOGIT) (15) to stabilize variances, with inverse-variance weighting. Random-effects models were applied using the Hartung–Knapp adjustment (16) to account for between-study variability. Fixed-effect models were additionally computed for completeness. Adverse events were pooled as proportions using the same analytical framework. For randomized trials, only data from the liver transplantation arm was included in the pooled analysis. Results are presented as pooled proportions with corresponding 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I^2 statistic, with values of approximately 25%, 50%, and 75% considered indicative of low, moderate, and high heterogeneity, respectively (17). In the presence of substantial heterogeneity, potential clinical and methodological sources were explored qualitatively. All pooled estimates were considered statistically significant when the 95% CI did not include the null value. Formal hypothesis testing and p-values were not emphasized, in accordance with best practices for single-arm meta-analyses. A leave-one-out sensitivity analysis was performed by removing the randomized study due to its methodological variability from other trials (18).

3. RESULTS

3.1. Baseline Characteristics of Included Studies

A total of 876 studies were yielded from the search strategy. After removal of 13 duplicates, 868 records were screened for their titles and abstracts. 25 studies were screened for their full texts, out of which 4 studies (9, 19–21) fit our inclusion criteria (Fig. 1). The study included 90 patients with a median age of 56.5 years. The male population accounted for 86.6% of the sample. A detailed breakdown of study characteristics is given in Table 1.

Table 1
Baseline Characteristics of Included Studies

Study	Study design	Country	Sample size (n)	Age, years (median)	Male sex, n (%)	Primary tumor resected, n (%)	Liver-only metastases, n (%)	Pre-transplant chemotherapy, n (%)	Chemotherapy response required	Tumor burden (median no. of metastases)
Hagness 2013 (SECA-I)	Prospective pilot study	Norway	21	55	13 (62%)	21 (100%)	21 (100%)	21 (100%)	No	8
Dueland 2019 (SECA-II)	Prospective cohort	Norway	15	56	10 (67%)	15 (100%)	15 (100%)	15 (100%)	Yes	5
Rajendran 2023	Prospective cohort	United Kingdom	50	58	34 (68%)	NR	50 (100%)	50 (100%)	No	NR
Adam 2024 (TransMet, LT arm)	Randomized controlled trial	Multicenter (Europe)	32	57	21 (66%)	32 (100%)	32 (100%)	32 (100%)	Yes	NR

3.2. Risk of Bias in Included Studies

All included studies were judged to be of moderate to serious overall risk of bias. Serious risk of bias due to confounding was detected in several studies due to their non-randomized and single-arm design. Because of highly selective eligibility criteria, a moderate risk of bias related to participant selection was detected across the studies. On the other hand, bias in intervention classification, deviations from intended interventions, missing data, and outcome measurement were persistently judged to be low. A moderate risk of selective reporting was detected in all studies, primarily because of the absence of preregistered protocols (Fig. 3).

3.3. Outcomes

3-Year Overall Survival

3-year overall survival following liver transplantation was consistently high across the included studies. Random-effects model yielded a 3-year overall survival (OS) of 69% (95% CI: 52%-82%) (Fig. 3). No between-study heterogeneity was observed ($I^2 = 0.0\%$) (Fig. 2.1), indicating a high degree of consistency in survival outcomes across cohorts despite differences in study design and patient selection. This suggests that the observed survival benefit is robust and reproducible across transplant centers.

Leave-one-out sensitivity analysis after removing Adam et al. displayed an increase in 3-year OS to 74% (95% CI: 36%-94%). This change is minor, but demonstrates that the pooled outcomes may be impacted due to heterogeneous study design (Supplementary Figure S1).

5-Year Overall Survival

Long-term survival remained favorable. The pooled 5-year overall survival with a random-effects model was 62% (95% CI: 36%-83%) (Fig. 2.2). Between-study heterogeneity was low ($I^2 = 14.6\%$), suggesting limited variability across studies. The persistence of survival benefit suggested that the survival benefit of liver transplantation may persist for a longer term in carefully selected patients.

Leave-one-out sensitivity analysis after removing Adam et al. displayed a decrease in 5-year OS to 52% (95% CI: 1%-99%). This change likely reflects the lack of standardized studies in the pooled analysis (Supplementary Figure S2).

3-Year Progression Free Survival

Pooled analysis of 3-year progression-free survival (PFS) demonstrated more variability across studies. The random-effects model yielded a pooled 3-year PFS of 33% (95% CI: 7%-76%) (Fig. 2.3). Substantial heterogeneity was detected between studies ($I^2 = 62.8\%$). This data suggests that post-transplant recurrence differences in patient and tumor characteristics may lead to variable progression-free survival in different patients.

Leave-one-out sensitivity analysis after removing Adam et al. did not change the pooled proportion for 3-year PFS [33% (95%CI: 1%-96%)], showing robustness of data across all study types (Supplementary Figure S3).

Adverse Events

The random-effects model for adverse events following liver transplantation yielded a pooled incidence of 41% (95% CI: 25% – 60%) (Fig. 2.4). No heterogeneity was observed ($I^2 = 0.0\%$), indicating consistent reporting of postoperative morbidity across studies.

Leave-one-out sensitivity analysis after removing Adam et al. displayed an increase in Adverse Events to 44% (95% CI: 15%-77%). This moderate change represents the robustness of data across study types. (Supplementary Figure S4).

4. DISCUSSION

This systematic review and single-arm meta-analysis suggested that liver transplantation is associated with favorable long-term survival in patients with colorectal cancer liver metastasis, demonstrating encouraging long-term survival. This highlights the importance of liver transplantation as a life-extending strategy in patients. However, the variable progression-free survival across the RCTs showed that disease recurrence remained widespread, highlighting the continual oncologic risk following transplantation. Secondary outcomes, which included post-transplant morbidity and mortality, quality of life measures, and selection/prognostic factors influencing outcomes, demonstrated that post-operative morbidity was common but manageable, while perioperative mortality remained low.

The included studies showed slightly heterogeneous but generally consistent results. Hagness et al.'s SECA-I pilot study showed promising survival rates, despite a high incidence of post-transplant recurrence, especially in the lungs (20). This study included broadly selected patients and established proof for transplantation, while simultaneously highlighting the importance of patient selection and tumor biology. In contrast, Dueland et al., in their SECA-II study, used stricter inclusion criteria, which included a favorable chemotherapy response and a lower tumor burden (9). This led to improved long-term survival with more homogenous outcomes. Rajendran et al. demonstrated results that were consistent with prior prospective studies, reaffirming the reproducibility of transplant outcomes, despite having a risk of recurrence (21). This study reported results from a larger, real-world cohort outside the SECA framework. Adam et al., in their TransMet trial, reported a significantly better survival rate in patients who underwent liver transplant and had chemotherapy, compared to patients who received chemotherapy alone (19). Taken together, these findings indicate that although early experience showed feasibility with high recurrence rates, liver transplantation is a viable and potentially life-extending option for carefully selected patients with colorectal cancer liver metastasis.

The scope and completeness of the evidence currently available are still restricted. Only a small number of trials qualified for inclusion, and many of those were non-randomized in nature and had modest sample sizes, highlighting the need for more RCTs on this topic. The majority of studies featured carefully chosen patients, who usually had liver-only disease, controlled primary tumors, and positive responses to systemic therapy, which may restrict generalizability to broader colorectal cancer populations. Furthermore, variation in inclusion criteria, transplant eligibility frameworks, and perioperative protocols further limits the application of these findings to routine clinical practice. Because of all of this, although the included trials provide valuable randomized data, they may not properly capture long-term risks or rare adverse effects in patients with colorectal cancer liver metastasis who undergo liver transplant.

The quality of the evidence was evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Some of the included studies were non-randomized or single-arm, so the overall risk of bias was judged to be moderate to serious across most categories. This is due to confounding and selection bias present in transplant oncology research, where patient eligibility is highly selective and randomized allocation is uncommon. The certainty of evidence was rated as low for most outcomes, mainly due to imprecision stemming from small sample sizes and differences in outcome definitions across studies, especially for progression-free survival and postoperative morbidity. Therefore, even though randomized evidence supporting liver transplant in these patients is available, several constraints limit the ability to draw definite conclusions about causality.

When interpreting these findings, several points related to the review process should be taken into account. A key strength of our analysis is the use of strict inclusion criteria, only including patients with an unresectable colorectal cancer liver metastasis, and excluding those who received liver resection alone. In order to support the robustness of our study, we also performed a sensitivity analysis, which showed consistent results that could potentially translate into clinical relevance. However, several limitations should also be acknowledged. The included studies had a single-arm design, which limits our ability to compare the outcomes to other treatments and interventions, making it difficult to make inferences on how effective liver transplantation is compared to other options. The reason for this single-arm design is the lack of comparative studies in the literature that include a homogeneous population. Additionally, the limited number of studies made it difficult to analyze small-study effects, hindering our ability to do a formal examination of publication bias or perform meaningful subgroup analyses to identify sources of heterogeneity. Moreover, even though the selection criteria were predetermined and study selection was systematic, we used only published data, which restricted our ability to account for unmeasured confounders, such as molecular tumor characteristics or variations in perioperative and systemic therapy protocols, which may have influenced results.

The results of this meta-analysis should be viewed in the context of already existing evidence reviewing liver transplantation in patients with colorectal cancer liver metastasis. An earlier meta-analysis by Varley et al. suggested promising survival outcomes with liver transplantation compared to existing chemotherapy data (22). However, this analysis had significant heterogeneity and confounding, and it included high-risk-of-bias study designs and data from small observational studies, including letters to the editor, further increasing heterogeneity. In contrast, our present analysis includes recent randomized data and applies a structured risk-of-bias assessment to better contextualize the results. A recent systematic review and meta-analysis by Dawood et al. also suggested encouraging long-term survival following transplantation in patients with non-resectable colorectal cancer liver metastasis, along with high rates of recurrence and heterogeneity (23). Similarly, Lee et al. suggested survival advantages compared to chemotherapy outcomes as well, while also mentioning the exploratory nature of liver transplantation and highlighting the lack of strong evidence to prove its effectiveness (24).

Stocco et al., in their narrative and cohort-based study, also reported improved survival outcomes in select patients with unresectable colorectal cancer liver metastasis, while highlighting difficulties associated with recurrence and long-term oncologic control (25). Recent expert reviews have also recognized liver transplant as a viable therapeutic option for patients with colorectal cancer liver metastasis, given that the patients meet specific inclusion criteria and the reporting of oncologic outcomes is standardized (26, 27). When considered collectively, the existing literature supports liver transplantation in selected patients and emphasizes the need for more randomized trials on this topic (28).

5. Conclusion

This systematic review and single-arm meta-analysis suggests that liver transplantation may offer meaningful long-term survival benefits in carefully selected patients with unresectable colorectal cancer liver metastasis, along with a consistent risk of disease recurrence. Well-designed randomized controlled trials are required in the future to define the role of liver transplantation in this population conclusively.

Declarations

Declaration of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions:

HWS screened for the literature, plan the analysis, and report the results, NS conceptualized the study and wrote the initial draft of the manuscript, MM screened the imported studies and wrote the initial draft of the manuscript, MH performed the analysis, MA wrote the initial draft of the manuscript, MO and TK extracted the data, MFI and AM performed the screening, RAK prepared the final draft of the manuscript and AHB conceptualized, supervised and reviewed the study.

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Figures

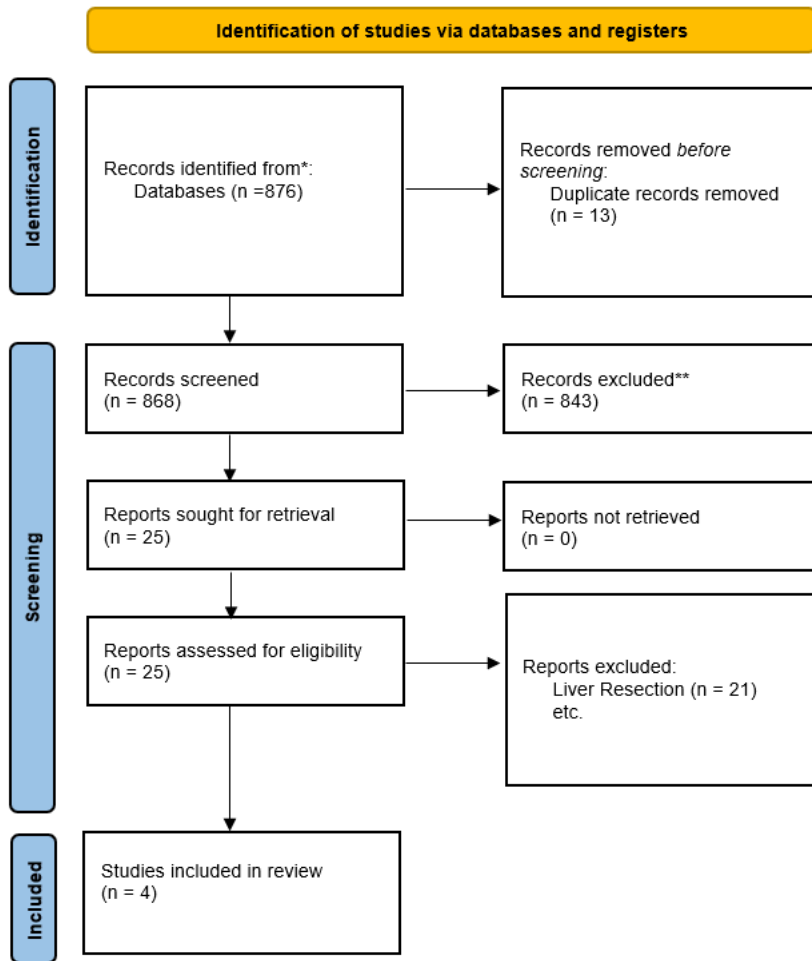


Figure 1

PRISMA Flowchart, A Summary of Inclusion Process

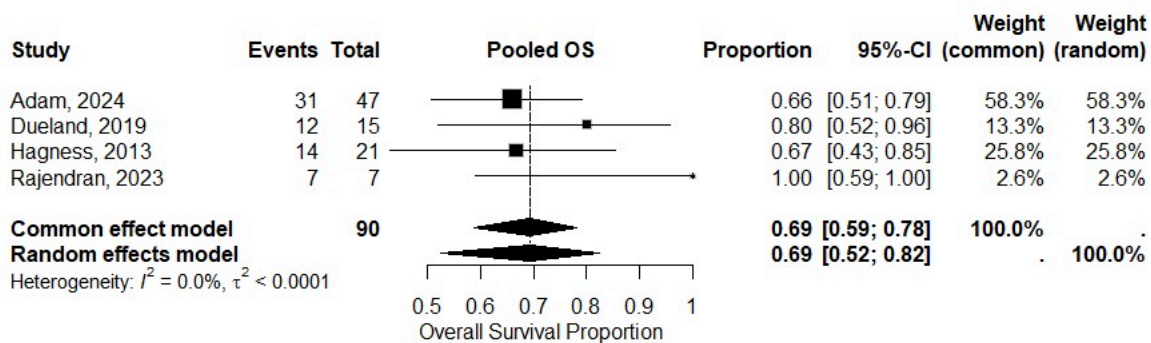


Figure 2

Figure 2.1: Forest Plot for 3-Year Overall Survival

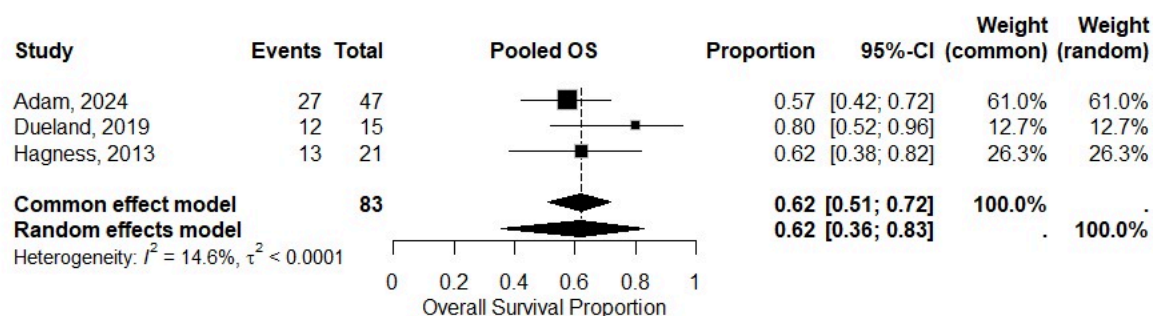


Figure 3

Figure 2.2: Forest Plot for 5-Year Overall Survival

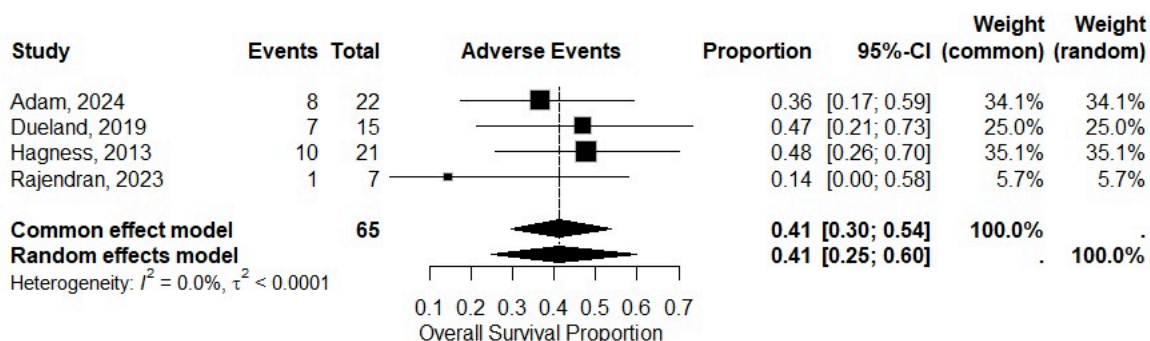


Figure 4

Figure 2.3: Forest Plot for 3-Year Progression-Free Survival

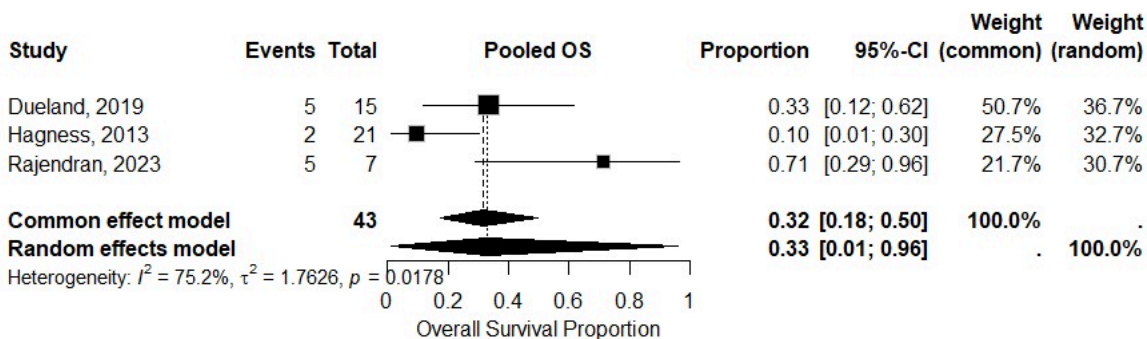


Figure 5

Figure 2.4: Forest Plot for Adverse Events

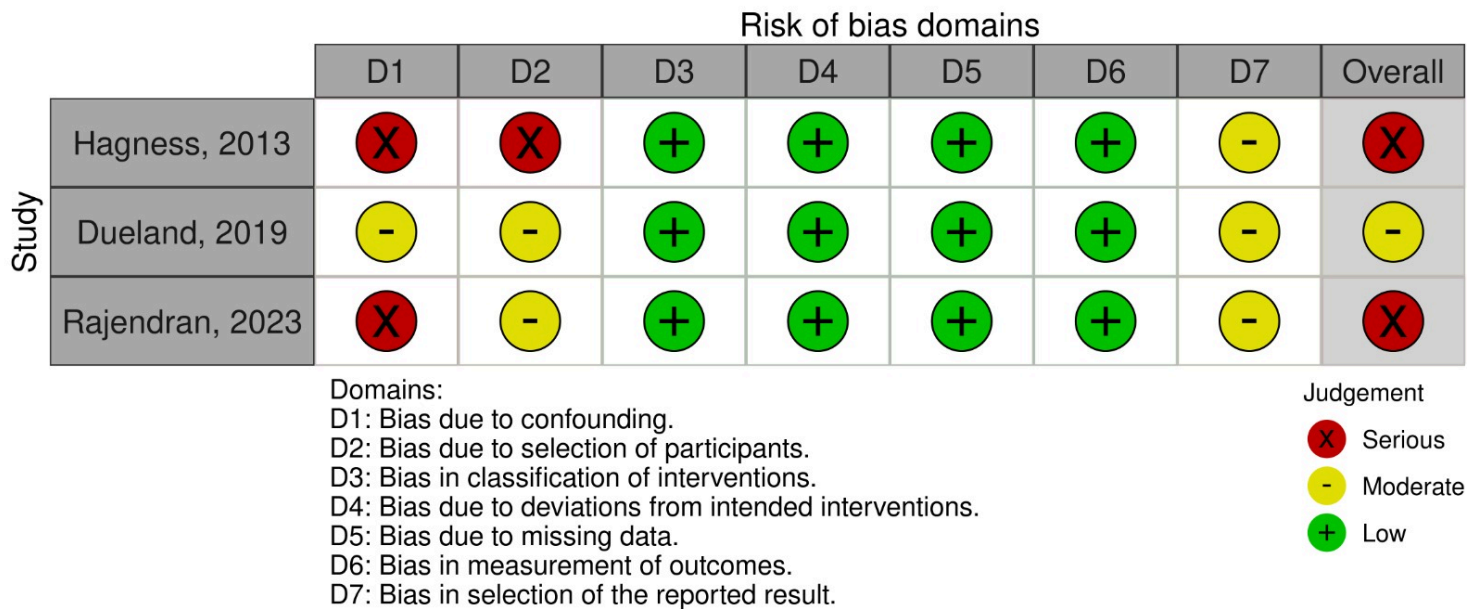


Figure 6

Figure 3: Risk of Bias Assessment (ROBINS-I)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary.docx](#)