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Minimally invasive versus open hepatectomy for the resection of colorectal liver metastases: a systematic review and meta-analysis

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Abstract

Background While surgical resection has a demonstrated utility for patients with colorectal liver metastases (CRLM), it is unclear whether minimally invasive surgery (MIS) or an open approach should be used. This review sought to assess the efficacy and safety of MIS versus open hepatectomy for isolated, resectable CRLM when performed separately from (Key Question (KQ) 1) or simultaneously with (KQ2) the resection of the primary tumor.

Methods PubMed, Embase, Google Scholar, Cochrane CENTRAL, International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov databases were searched to identify both randomized controlled trials (RCTs) and non-randomized comparative studies published during January 2000—September 2020. Two independent reviewers screened literature for eligibility, extracted data from included studies, and assessed internal validity using the Cochrane Risk of Bias 2.0 Tool and the Newcastle–Ottawa Scale. A random-effects meta-analysis was performed using risk ratios (RR) and mean differences (MD).

Results From 2304 publications, 35 studies were included for meta-analysis. For staged resections, three RCTs and 20 observational studies were included. Data from RCTs indicated MIS having similar disease-free survival (DFS) at 1-year (RR 1.03, 95%CI 0.70–1.50), overall survival (OS) at 5-years (RR 1.04, 95%CI 0.84–1.28), fewer complications of Clavien-Dindo Grade III (RR 0.62, 95%CI 0.38–1.00), and shorter hospital length of stay (LOS) (MD -6.6 days, 95%CI -10.2, -3.0). For simultaneous resections, 12 observational studies were included. There was no evidence of a difference between MIS and the open group for DFS-1-year, OS-5-year, complications, R0 resections, blood transfusions, along with lower blood loss (MD -177.35 mL, 95%CI -273.17, -81.53) and shorter LOS (MD -3.0 days, 95%CI -3.82, -2.17).

Conclusions Current evidence regarding the optimal approach for CRLM resection demonstrates similar oncologic outcomes between MIS and open techniques, however MIS hepatectomy had a shorter LOS, lower blood loss and complication rate, for both staged and simultaneous resections.

Keywords Laparoscopic hepatectomy · Laparoscopic surgery · Minimally invasive surgery · Metastasectomy · Liver tumor · Colorectal cancer

Colorectal cancer (CRC) impacts millions of individuals globally, and currently ranks among the three most common cancers both by incidence and mortality worldwide [1]. In the United States (US), colorectal cancer was the cause of death in over 50,000 individuals in 2020 [2, 3]. Current US trends indicate that long-term declines in CRC mortality have slowed down significantly over the past few years. Colorectal liver metastases (CRLM) develop in nearly 50% of patients over the course of their disease, as it is the most common solid organ involved in CRC metastases [4]. Despite oncological advances, surgical resection currently remains the only potentially curative treatment for CRLM. While hepatectomy in select individuals has consistently

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been associated with improved survival, the 5-year survival rate post-hepatectomy remains between 40–57% [5–7]. Perioperative advances have drastically improved the risk profile of liver surgery, with mortality decreasing from 24% in 1970 [8] to < 2% currently [8–10].

Surgical resection of liver tumors may be carried out through either conventional open or minimally invasive surgical (MIS) approaches, including laparoscopic or robotic techniques. While MIS approaches have lower perioperative morbidity and mortality [5], it is unclear whether they are oncologically similar in the long-term to the open approach. Therefore, the objective of this study was to compare the efficacy/effectiveness and safety of MIS versus open hepatectomy for resectable CRLM through a systematic review meta-analysis of the literature.

Methods

Members of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Guidelines Committee and content expert representatives from the Americas Hepato-Pancreato-Biliary Association (AHPBA), who had received formal training in systematic review methodology [11], carried out the following systematic review and meta-analysis and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [12]. Using the Population, Intervention, Comparator, Outcomes (PICO) format, the working group created four key questions (KQs), two pertaining to colon cancer metastases and two pertaining to rectal cancer metastases (see Appendix 1). Based on the available literature, these were later condensed into two KQs (colorectal).

Key Question 1 (KQ1)

Should MIS versus open hepatectomy be used for resection of resectable colorectal liver metastases when performed *separately* from resection of primary cancer?

Key Question 2 (KQ2)

Should MIS versus open hepatectomy be used for resection of synchronous, resectable colorectal liver metastases when performed *simultaneously* with resection of primary cancer?

Studies that only reported mixed data from simultaneous and staged procedures were excluded by the SAGES Guidelines Committee after data extraction, as those studies did not fit the screening criteria of the two KQs; however, their data have been reported in Appendix 2 and 3.

Types of studies

We included peer-reviewed randomized controlled trials and non-randomized comparative studies, published in English. We excluded case reports, studies with a total sample size of < 5 patients total, correspondence, lay press articles, narrative and systematic reviews, single-arm studies, records published in non-English languages, and studies with published abstracts only. In addition, we included studies published between January 2000-September 2020, to ensure that the data was reflective of clinical outcomes corresponding to the use of modern chemotherapy.

Types of participants

Studies with adult patients (aged 18 years or older) with colorectal cancer and resectable colorectal liver metastases (CRLM) were included for which they were undergoing surgery. Studies with repeat hepatectomy were also included. The decision to undergo liver resection was already made for all study participants. The decision of who should get a liver resection was beyond the scope of this review.

Types of interventions

All studies comparing open and MIS approaches were included. MIS was defined as laparoscopic, laparoscopic hand-assisted, robotic, and hybrid approaches. In addition, studies that had combined chemoembolization, radiofrequency ablation with surgery, or had utilized neoadjuvant chemotherapy were included. Only those studies that provided data for only staged or simultaneous procedures were included for the final results.

Types of outcome measures

Outcomes were defined a priori. Outcomes of interest were (1) overall survival, (2) disease-free survival, (3) perioperative complications of Clavien-Dindo grade ≥ 3, and (4) length of hospital stay. Our secondary outcomes were (1) achievement of R0 resection, (2) estimated blood loss, and (3) blood transfusion. Of note, mortality was defined as the inverse of overall survival.

Search strategy

With the assistance of a medical librarian, we developed a clinically guided search strategy (Appendix 1). PubMed, Embase, Cochrane CENTRAL, ClinicalTrials.Gov, International Clinical Trials Registry Platform (ICTRP), and Google Scholar were queried. We restricted the search to in-human studies between January 2000 to September 2020. We combined search results in EndNote (Clarivate Analytics, London, UK) and exported them to Covidence (Veritas Health Innovation, Melbourne, Australia), with both programs used for duplicate removal. Finally, we hand-searched the reference lists of included studies, especially any pertinent meta-analyses. For included RCTs, we searched databases to extract updated results from follow-up publications.

Selection of studies

Before the beginning of study selection, reviewers' screening thresholds were calibrated, for which everyone reviewed 100 randomly selected abstracts on Abstrackr (Brown University, Providence, Rhode Island, US), and disagreements were resolved on a conference call. After reviewer calibration, study selection was carried out in Covidence (Veritas Health Innovation, Melbourne, Australia). Each record was first screened by the title and abstract, and then by the full text. Two independent reviewers screened each abstract and full text. Disagreements were resolved by consensus between the two reviewers, and if reconciliation could not be reached, then consultation with a third reviewer was utilized. During the full text screening phase, the reasons for exclusion were recorded. The entire process was captured in a PRISMA flow diagram.

Data extraction and management

Two reviewers extracted data from each included study through a standardized data extraction form that the working group had built and imported into Covidence. Data were captured regarding study characteristics, demographic details of study participants, surgical technique, and *a priori* outcomes. Disagreements in data extraction were resolved through consensus between the two reviewers. We did not contact study authors for missing data. Before analysis, consensus data were exported from Covidence and manually rechecked by three reviewers (AO, ACA, and AC).

Assessment of internal validity

Two reviewers assessed the quality of each study independently. For randomized controlled trials (RCTs), we used the Cochrane Risk of Bias 2.0 Tool [13]. For non-randomized comparative studies, we used a modified Newcastle–Ottawa Scale (NOS), with its full version given in Appendix 1. Consensus in RoB assessment was achieved through discussion between the two reviewers, and if not achieved, then through consultation with a third reviewer. A final RoB assessment was generated for each included study. Traffic light plots for visualization of RoB assessments were generated through the Risk-of-bias VISualization (robvis) tool [14].

Data analysis and interpretation

Meta-analysis was performed in RevMan Version 5.4 (Nordic Cochrane Centre, Copenhagen, Denmark) using a random-effects model. Dichotomous data are presented as Mantel–Haenszel risk ratios (RRs) and continuous data as inverse-variance-weighted mean differences, with corresponding 95% confidence intervals. Separate meta-analyses were completed for KQ1 and KQ2. Since several studies did not report outcomes separately from patients undergoing staged and simultaneous procedures, a third set of meta-analyses for studies with this mixed patient population was completed and included in Appendix 2 and 3.

We followed Gagnier et al.'s recommendations for assessing clinical heterogeneity in systematic reviews and evaluated statistical heterogeneity using the I^2 and χ^2 statistics [15]. According to best practice, we constructed a funnel plot for outcomes where ten or more studies were included in the meta-analysis to detect risk of publication bias [16].

Results

A total of 2304 publications were identified for screening from database searching and hand-searching. After duplicate removal, 1055 records were screened by their title and abstract. 224 studies had their full texts screened and 54 records were initially included. After data extraction, 14 records were further excluded, given that they provided mixed data of staged (KQ1) and simultaneous (KQ2) resections. Due to overlapping patient data from five records, four manuscripts had to be excluded from KQ1, while the study with the largest number of study participants was included [17]. Finally, 36 records, pertaining to 35 studies, were found eligible for inclusion in the meta-analysis [17–52]. The PRISMA flow diagram of the systematic review is given in Fig. 1, with the list of excluded studies is provided in Appendix 4. The characteristics of the included studies are shown in Table 1.

Key question 1: MIS versus open hepatectomy for CRLM, when performed separately from resection of the primary tumor

A total of 23 studies (24 records) met the inclusion criteria for KQ1, composed of 20 observational studies [17, 22–40], and three RCTs [18–21], with one of the RCTs having two

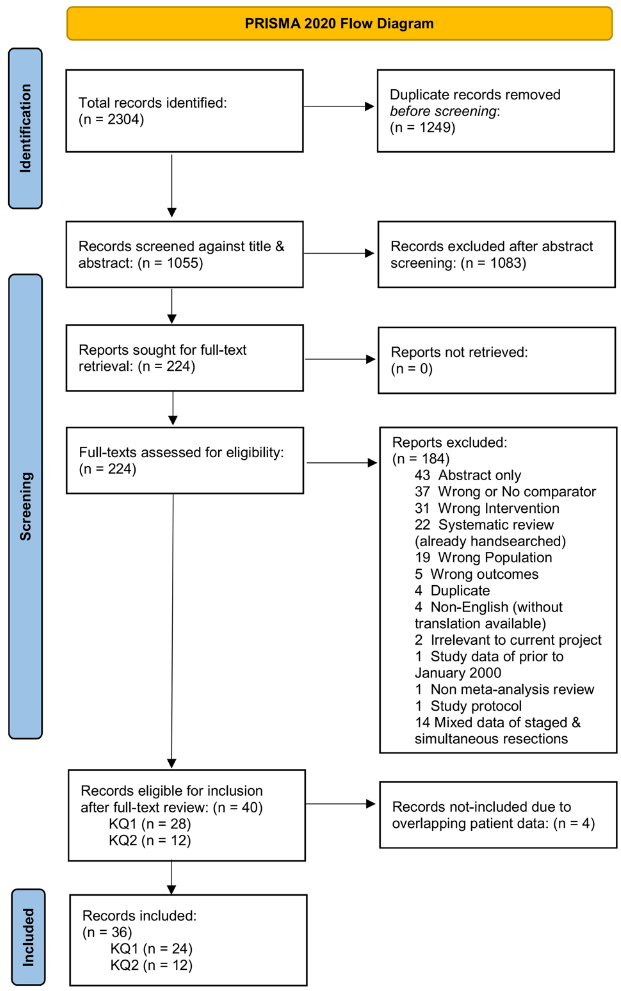


Fig. 1 PRISMA Flow Diagram for the systematic review

linked records [19, 20]. Funnel plots for the outcomes have been provided in Appendix 5.

Internal validity

The RoB across evidence varied for both randomized (Fig. 2a) and non-randomized studies (Fig. 2b). RCTs published by Fretland et al. and Robles-Campos et al. had an overall low risk of bias [19–21]. However, the RCT published by Kasai and colleagues was rated as having an unclear risk of bias due to reviewers' concerns over the randomization process. After randomization, the open group had tumors of larger size, which might have biased results in favor of MIS [18]. Of the twenty observational studies, six had a low quality (30%), three had moderate quality (15%) and the rest had a high quality (55%). One observational study, Lewin et al., which did perform appropriate matching to reduce confounding had to be downgraded to high risk of bias, due to non-reporting of the sample size of matched therefore contributing unmatched data for meta-analysis [35].

Perioperative complications

All three RCTs and 17 observational studies contributed data for perioperative complications of Clavien-Dindo Grade ≥ 3. With regards to evidence from RCTs, pooled data from 245 MIS patients and 261 open patients demonstrated a lower risk of complications with MIS hepatectomy (RR 0.62, 95% CI 0.38 to 1.00, I^2 0%, Fig. 3). Observational data from 916 MIS and 1378 open patients demonstrated a statistically significant decrease in complications with MIS (RR 0.53, 95% CI 0.38 to 0.74, I^2 0%, Fig. 3).

Hospital length of stay

RCTs' pooled data from 245 MIS and 261 open group patients demonstrated a lower hospital length of stay after MIS hepatectomy (mean difference (MD) 6.61 fewer days, 95%CI 10.19 fewer to 3.03 fewer, I^2 0%, Fig. 4). Observational data were concordant; however, with moderate heterogeneity, from pooled data of 869 MIS and 1077 open patients (MD 2.67 fewer days, 95% CI 3.27 fewer to 2.07 fewer, I^2 53%, Fig. 4).

Estimated blood loss

Three RCTs reported a lower estimated blood loss (EBL) in MIS than open (MD -251.61 mL, 95% CI -555.45 mL to + 52.23 mL, I^2 85%, Fig. 5). While this difference was statistically non-significant, it was in line with the results of observational studies, which reported significantly less EBL with MIS hepatectomy (MD -178.80 mL, 95% CI -234.50 mL to -123.11 mL, I^2 92%, Fig. 5). There was significant heterogeneity across both RCTs and observational studies, which could not be explained by study design, included participants, or quality assessment and most likely reflects the subjective reporting of EBL.

R0 resection

No significant difference was detected between the proportion of patients who received an R0 resection in MIS versus the open group. Only a single included RCT reported on R0 resection. Robles-Campos et al. reported an R0

Table 1 Summary of included studies, including the type of study and country of origin

Reference, Year	Type of Study	Country	N* of MIS	N* of Open
KQ1: Key Question 1 (KQ1): Should MIS versus open hepatectomy be used for resection of resectable CRLM when performed separately from resection of primary cancer?				
Kasai et al., 2018 [18]	RCT	Belgium	20	20
Fretland et al., 2018 Aghayan et al., 2021 [19, 20] *[OSLO-COMET trial]*	RCT	Norway	129	144
Robles-Campos et al., 2019 [21] *[LapOpHuva trial]*	RCT	Spain	96	97
Mala et al., 2002 [22]	Observational	Norway	13	14
Guerron et al., 2013 [23]	Observational	USA	40	40
Inoue et al., 2013 [24]	Observational	Japan	23	24
AnneDoughtie et al., 2013 [25]	Observational	USA	8	76
Cheung et al., 2013 [26]	Observational	Hong Kong	20	40
Qiu et al., 2013 [27]	Observational	China	30	30
Hirokawa et al., 2013 [28]	Observational	Japan	46	78
Qiu et al., 2014 [29]	Observational	China	24	25
Vavra et al., 2015 [30]	Observational	Czech Republic	25	41
De'Angelis et al., 2015 [31]	Observational	France	52	52
Hasegawa et al., 2015 [32]	Observational	Japan	102	69
Nachmany et al., 2015 [33]	Observational	Israel	42	132
Cipriani et al., 2016 [17]	Observational	Multi-center	133	133
Karagkounis et al., 2016 [34]	Observational	USA	65	65
Lewin et al., 2016 [35]	Observational	Australia	146	138
Untereiner et al., 2016 [36]	Observational	France	18	18
Zeng et al., 2016 [37]	Observational	China	79	79
Hallet et al., 2017 [38]	Observational	France	27	81
Ratti et al., 2018 [39]	Observational	Italy	104	412
Efanov et al., 2020 [40]	Observational	Russia	20	20
Key Question 2 (KQ2): Should MIS versus open hepatectomy be used for resection of synchronous, resectable CRLM when performed simultaneously with resection of primary cancer?				
Chen et al., 2011 [41]	Observational	China	23	18
Huh et al., 2011 [42]	Observational	South Korea	20	20
Hu et al., 2012 [43]	Observational	China	13	13
Takasu et al., 2014 [44]	Observational	Japan	7	7
Jung et al., 2014 [45]	Observational	South Korea	24	24
Ratti et al., 2016 [46]	Observational	Italy	25	50
Ivanecz et al., 2018 [47]	Observational	Slovenia	10	10
Goumard et al., 2018 [48]	Observational	USA	43	121
Xu et al., 2018 [49]	Observational	China	20	20
Chen et al., 2019 [50]	Observational	Taiwan	15	15
Shin et al., 2019 [51]	Observational	South Korea	109	109
Kawakatsu et al., 2020 [52]	Observational	Japan	37	104

*Sample size (N) mentioned refers to the sample size used in the meta-analysis, which for RCTs refers to the number at randomization. For some observational studies whose propensity score (PS) matched data was used, N refers to the number of individuals after PS matching, while for some others N refers to non-PS-matched data; RCT, Randomized Controlled Trial

resection in 95.8% of MIS versus 88.7% of open patients (RR 1.08 in favor of the MIS, 95% CI 1.00–1.17, Fig. 6) [21]. A total of 17 observational studies reported nearly similar rates of R0 resection, from 913 MIS and 1429 open patients (RR 1.01, 95% CI 0.99–1.02, Fig. 6). Most studies had an R0 resection rate of over 90%, with those reporting outcomes below this threshold possibly due to long follow-up periods, for example, 13 years in the work of De'Angelis et al. [31].

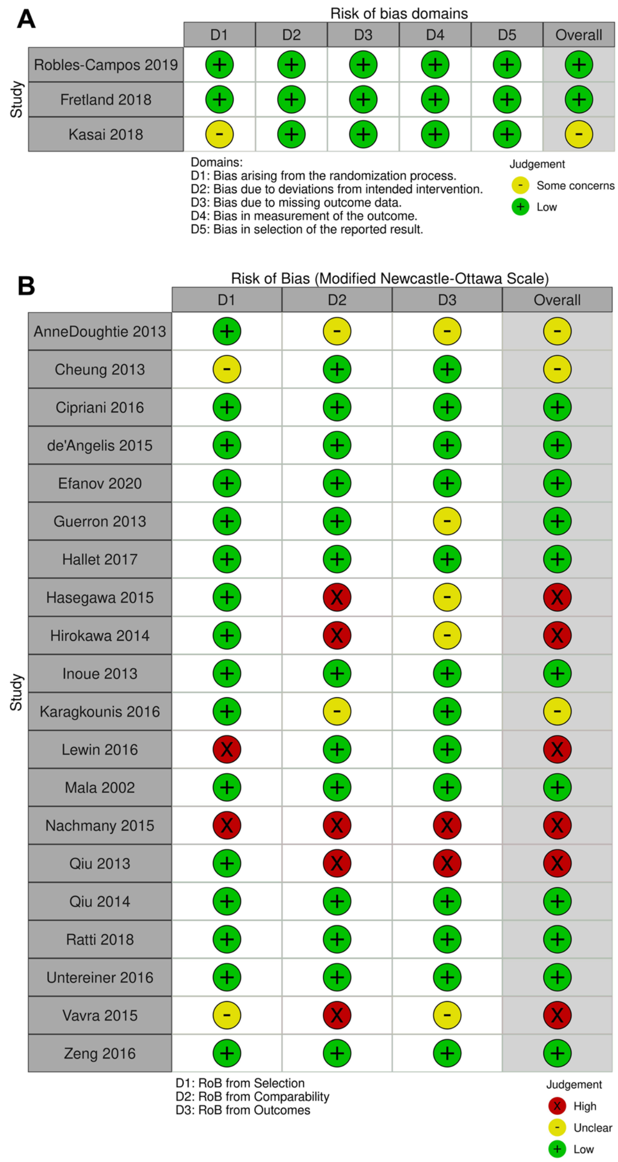


Fig. 2 Risk of Bias (RoB) for included studies (a) for the randomized controlled studies included under Key Question 1, as assessed by the Cochrane ROB 2.0 Scale. **(b)** non-randomized studies included under Key Question 1, as assessed by a modified version of the Newcastle Ottawa Scale

Blood transfusion

Blood transfusion was defined, for this study, as the number of patients requiring a transfusion during their hospitalization. Two RCTs, with a total of 225 MIS and 241 open approach patients, reported a lower, although not significant, need for transfusion with MIS hepatectomy (RR 0.81, 95% CI 0.45 to 1.49, I^2 0%, Fig. 7) [19, 21]. Twelve observational studies, with data from 544 MIS and 1024 open approach patients, reported a significantly lower need for transfusion after MIS hepatectomy (RR 0.54, 95% CI 0.39 to 0.75, I^2 0%, Fig. 7).

Disease-free survival (DFS)

DFS at 1-year

Data from two RCTs, having a total of 116 MIS and 117 open approach patients demonstrated similar DFS at 1-year between MIS and open hepatectomy (RR 1.03, 95% CI 0.70 to 1.50, I^2 56%, Fig. 8a) [18, 21]. Similarly, pooled data from six observational studies, with a total of 189 MIS and 296 open approach patients, also indicated similar DFS at one year (RR of 1.05, 95% CI 0.91 to 1.21 I^2 0%, Fig. 8a).

DFS at 3-years

DFS at 3-years was available from all three included RCTs, with 142 MIS and 155 open approach individuals, and again was similar between MIS and open hepatectomy (RR 1.08, 95% CI 0.77 to 1.51, I^2 0%, Fig. 8b). However, DFS at 3-years was available only from 1 observational study, with a total sample size of 49 patients, and was not able to show a significant difference between MIS and open hepatectomy (RR 1.04, 95% CI 0.47 to 2.33, I^2 0%, Fig. 8b).

DFS at 5-years

Pooled data regarding DFS at 5-years was available from all three RCTs, with 121 MIS and 123 open approach patients, and was unable to show a significant difference in DFS between MIS and open hepatectomy (RR 1.02, 95% CI 0.65 to 1.60, I^2 0%, Fig. 8c). Only two observational studies contributed data to this outcome, and did not show a significant difference between the two interventions (RR 1.10, 95% CI 0.79 to 1.53, I^2 0%, Fig. 8c).

Overall survival (OS)

OS at 1-year

As a binary outcome, overall survival at 1-year was found to similar between MIS and open hepatectomy from both randomized and non-randomized evidence. All three of the included RCTs, with 249 MIS and 264 open approach patients, had a pooled risk ratio of 1.01 (95% CI 0.96 to 1.06, I^2 0%, Fig. 9a). Similarly, the nine observational studies, with 366 MIS and 420 open approach patients, demonstrated a RR of 1.01 (95% CI 0.98 to 1.05, I^2 0%, Fig. 9a). The forest plot for mortality at 1-year has been provided in the Appendix 6.

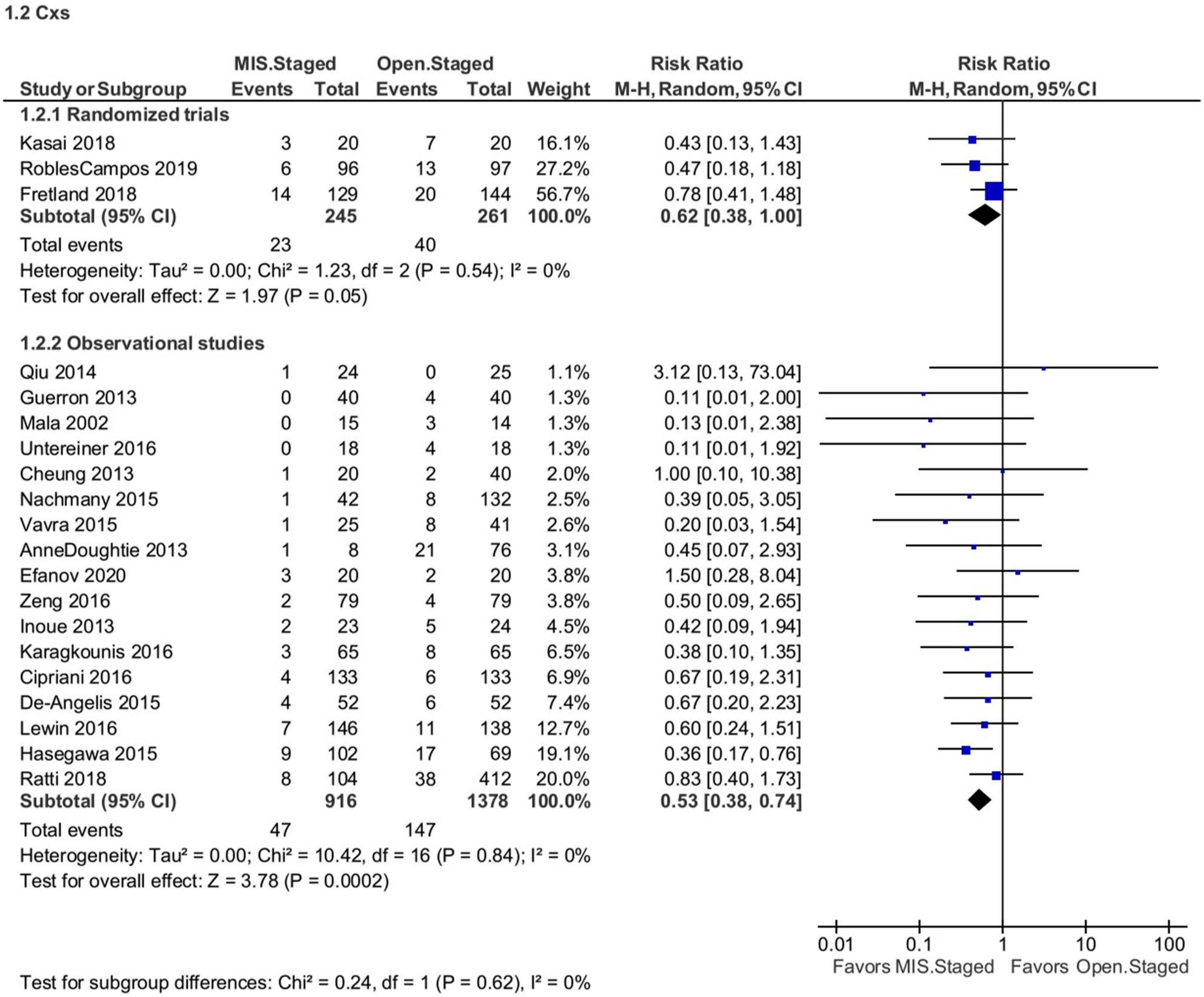


Fig. 3 Forest plot of perioperative complications of Clavien-Dindo Grade ≥ 3 for staged resections of CRLM

OS at 3-years

Overall survival at 3-years was also found to be similar between the two groups. Data from three RCTs, having 199 MIS and 217 open approach patients, indicated a risk ratio of 1.07 (95% CI 0.86 to 1.34; Fig. 9b), however, substantial heterogeneity was present (I^2 61%, Fig. 9b). Meanwhile, pooled data from three observational studies, having 131 MIS and 222 open group patients, indicated a risk ratio of 0.95 (95% CI 0.82 to 1.10), with minimal heterogeneity (I^2 0%, Fig. 9b) [29, 33, 34]. Forest plot for mortality at three years is provided in Appendix 6.

OS at 5-years

Pooled data from all three RCTs suggested similar OS for the two approaches for OS at 5-years. The RCTs cumulatively contributed 152 MIS and 162 open group patients and indicated a risk ratio of 1.04 (95% CI 0.84 to 1.28, Fig. 9c), with minimal heterogeneity ($I^2 = 0\%$). Similarly, data from four observational studies, having pooled results for 290 MIS and 251 open group individuals, indicated a risk ratio of 1.01 (95% CI 0.82 to 1.25; Fig. 9c), although moderate heterogeneity was present (I^2 37%, Fig. 9c).

Key question 2: minimally invasive versus open hepatectomy for CRLM, when performed simultaneously with resection of the primary tumor

A total of 12 observational studies, and no RCTs, were found eligible for inclusion [41–52]. Funnel plots for KQ2 are provided in Appendix 5.

1.10 LOS

Study or Subgroup	MIS.Staged Mean	MIS.Staged SD	MIS.Staged Total	Open.Staged Mean	Open.Staged SD	Open.Staged Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 Randomized trials								
RoblesCampos 2019	4	46.36	96	6	42.86	97	8.1%	-2.00 [-14.60, 10.60]
Fretland 2018	2.2	46.36	129	4	42.86	144	11.3%	-1.80 [-12.43, 8.83]
Kasai 2018	6.25	3.25	20	14	8.5	20	80.6%	-7.75 [-11.74, -3.76]
Subtotal (95% CI)			**245**			**261**	**100.0%**	**-6.61 [-10.19, -3.03]**
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 2 (P = 0.45); I² = 0%								
Test for overall effect: Z = 3.62 (P = 0.0003)								
1.10.2 Observational studies								
Hasegawa 2015	9	42	102	16	34.75	69	0.3%	-7.00 [-18.56, 4.56]
AnneDoughtie 2013	3.5	13.25	8	7	24.67	76	0.3%	-3.50 [-14.23, 7.23]
Cheung 2013	17	13.25	20	7	23.5	40	0.4%	10.00 [0.69, 19.31]
Inoue 2013	10.8	11.2	23	13.9	10.3	24	0.9%	-3.10 [-9.26, 3.06]
Lewin 2016	5	13.25	146	8	24.67	138	1.5%	-3.00 [-7.64, 1.64]
Cipriani 2016	4	9.33	133	7	24.67	133	1.6%	-3.00 [-7.48, 1.48]
Hallet 2017	9	2.5	27	12	18.37	81	1.9%	-3.00 [-7.11, 1.11]
Untereiner 2016	6.28	0.63	18	7.5	6.49	18	3.2%	-1.22 [-4.23, 1.79]
Mala 2002	3.75	1.45	15	11.25	5.43	14	3.3%	-7.50 [-10.44, -4.56]
Efanov 2020	12.75	5.25	20	11.75	3.25	20	3.8%	1.00 [-1.71, 3.71]
Vavra 2015	8.4	2	25	10.5	5.8	41	6.1%	-2.10 [-4.04, -0.16]
De-Angelis 2015	6	2.75	52	9	5	52	7.9%	-3.00 [-4.55, -1.45]
Qiu 2014	7.4	1.7	24	10.4	2.8	25	9.5%	-3.00 [-4.29, -1.71]
Nachmany 2015	6.7	2.7	42	8.4	5.6	132	9.7%	-1.70 [-2.96, -0.44]
Qiu 2013	7.5	1.5	30	11.5	3	30	10.1%	-4.00 [-5.20, -2.80]
Zeng 2016	10	2.83	79	13	3.67	79	11.4%	-3.00 [-4.02, -1.98]
Karagkounis 2016	4	4.11	65	6	0.5	65	11.5%	-2.00 [-3.01, -0.99]
Guerron 2013	3.7	0.5	40	6.5	0.5	40	16.6%	-2.80 [-3.02, -2.58]
Subtotal (95% CI)			**869**			**1077**	**100.0%**	**-2.67 [-3.27, -2.07]**
Heterogeneity: Tau² = 0.55; Chi² = 36.22, df = 17 (P = 0.004); I² = 53%								
Test for overall effect: Z = 8.75 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.52, df = 1 (P = 0.03), I² = 77.9%								

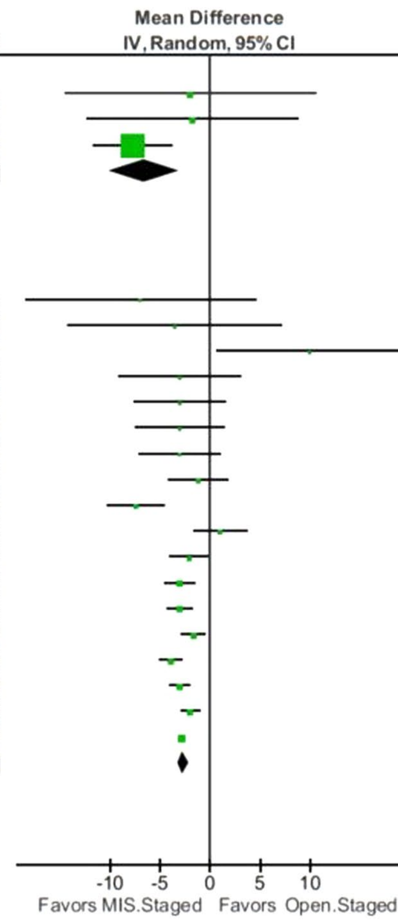


Fig. 4 Forest plot of hospital length of stay (LOS) for staged resections

Internal validity

Six studies (50%) were of high quality, while four (33%) had a moderate quality, and two others (16%) were assessed to be of low quality (Fig. 10). For outcomes like estimated blood loss and length of stay, where more than ten studies had contributed patient data, funnel plots were created (Appendix 5). One observational study, performed by Goumard et al., which had performed appropriate matching to reduce confounding had to be downgraded to high risk of bias, due to non-reporting of the sample size of matched cohorts with subsequent use of unmatched data for meta-analysis [48].

Perioperative complications of clavien-dindo grade ≥ 3

Nine observational studies, with 199 MIS and 369 open group patients, demonstrated a decreased risk of complications after MIS hepatectomy, although this was not statistically significant (RR 0.68, 95% CI 0.68 to 1.12, I^2 0%, Fig. 11).

Hospital length of stay

Data from 11 studies, with 331 MIS and 496 open patients, demonstrated a significant decrease in hospital (LOS) with MIS hepatectomy (MD -3 days, 95% CI -3.82 to -2.17), although moderate heterogeneity was present (I^2 48%, Fig. 12).

Estimated blood loss

Pooled data from ten studies, with 222 MIS patients and 387 open, showed significantly less EBL with MIS hepatectomy (MD -177.35 mL, 95% CI -273.17 mL to

1.9 EBL

Study or Subgroup	MIS.Staged Mean	MIS.Staged SD	MIS.Staged Total	Open.Staged Mean	Open.Staged SD	Open.Staged Total	Weight	Mean Difference IV, Random, 95% CI
1.9.1 Randomized trials								
RoblesCampos 2019	100	976.82	96	200	1,115.5	97	29.0%	-100.00 [-395.74, 195.74]
Kasai 2018	150	125	20	712.5	500	20	32.8%	-562.50 [-788.37, -336.63]
Fretland 2018	200	437.5	129	300	450	144	38.2%	-100.00 [-205.37, 5.37]
Subtotal (95% CI)			**245**			**261**	**100.0%**	**-251.61 [-555.45, 52.23]**
Heterogeneity: Tau² = 60032.52; Chi² = 13.50, df = 2 (P = 0.001); I² = 85%								
Test for overall effect: Z = 1.62 (P = 0.10)								
1.9.2 Observational studies								
Mala 2002	1,150	976.82	15	1,200	1,115.5	14	0.5%	-50.00 [-815.37, 715.37]
AnneDoughtie 2013	225	976.82	8	400	1,115.5	76	0.6%	-175.00 [-896.86, 546.86]
Efanov 2020	998	825	20	649.5	445	20	1.5%	348.50 [-62.31, 759.31]
Lewin 2016	200	976.82	146	600	1,115.5	138	3.3%	-400.00 [-644.43, -155.57]
Hasegawa 2015	127	486.17	102	620	693.25	69	4.4%	-493.00 [-681.83, -304.17]
Cheung 2013	427.5	322.5	20	310	350	40	4.6%	117.50 [-60.66, 295.66]
Inoue 2013	99	207	23	397	381	24	4.7%	-298.00 [-472.33, -123.67]
Cipriani 2016	200	465	133	500	741.67	133	5.4%	-300.00 [-448.77, -151.23]
Qiu 2014	210	170	24	380	265	25	6.1%	-170.00 [-294.16, -45.84]
Vavra 2015	132.3	218	25	149.5	277.5	41	6.2%	-17.20 [-137.69, 103.29]
Nachmany 2015	251	305	42	422.7	410	132	6.4%	-171.70 [-287.46, -55.94]
Qiu 2013	215	170	30	285	260	30	6.5%	-70.00 [-181.16, 41.16]
De-Angelis 2015	200	125	52	300	312.5	52	7.1%	-100.00 [-191.48, -8.52]
Guerron 2013	376	122	40	753	120	40	8.2%	-377.00 [-430.03, -323.97]
Karagkounis 2016	200	112.5	65	400	118.75	65	8.4%	-200.00 [-239.77, -160.23]
Ratti 2018	350	150	104	600	183.33	412	8.5%	-250.00 [-283.83, -216.17]
Untereiner 2016	56.75	26.75	18	186.75	63.25	18	8.6%	-130.00 [-161.73, -98.27]
Zeng 2016	250	43.33	79	351	8.33	79	8.8%	-101.00 [-110.73, -91.27]
Subtotal (95% CI)			**946**			**1408**	**100.0%**	**-178.80 [-234.50, -123.11]**
Heterogeneity: Tau² = 9146.68; Chi² = 222.56, df = 17 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 6.29 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.64), I² = 0%								

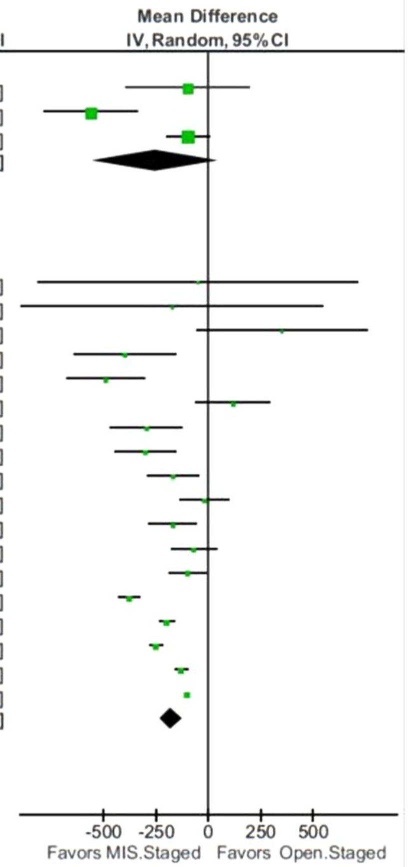


Fig. 5 Forest plot of estimated blood loss (EBL) for staged resections

-81.53 mL, Fig. 13). While considerable heterogeneity was present (I^2 92%), the majority of included studies favored MIS. However, several of the studies with the highest weights in the meta-analysis had an unclear or high risk of bias.

R0 resection

Across seven studies, there was similar R0 liver resection rate between MIS (N = 268) and open (N = 438) hepatectomy (RR of 1.02, 95% CI 0.98 to 1.02, I^2 34%, Fig. 14).

Blood transfusion

Five studies found a slight decrease in transfusion requirements after MIS hepatectomy (N = 177) compared to open (N = 202), however, this was not statistically significant (RR 0.92, 95% CI 0.58 to 1.45, I^2 0%, Fig. 15).

Disease-free survival (DFS)

DFS at 1-year

Only two studies, with 25 patients total in each cohort, contributed to this outcome. There was no difference in the pooled effects (RR 0.98, 95% CI 0.54 to 1.78, I^2 34%, Fig. 16a); however, the studies had effect estimates on the opposite sides of the threshold, indicating contradictory findings. While one of these had a high risk of bias, the other had a low risk [47, 50].

DFS at 3-years

Disease-free survival at 3-year data was available from four studies, which contributed a total of 144 MIS and 144 open approach patients. Similar results between the two groups were suggested by the non-significant pooled risk ratio of 1.02 (95% CI 0.83 to 1.25, I^2 0%, Fig. 16b).

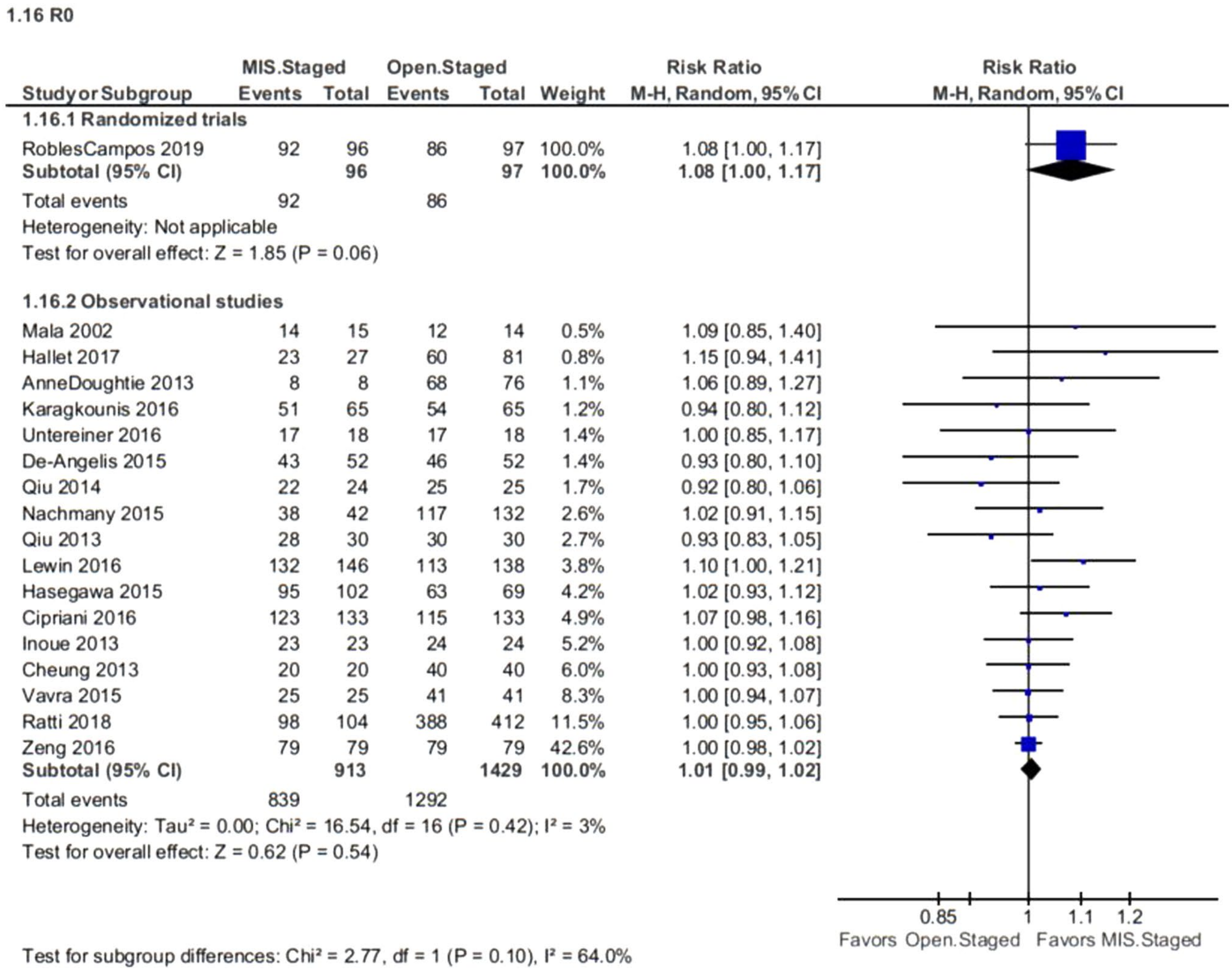


Fig. 6 Forest plot of the frequency of R0 liver resections for staged hepatectomy

DFS at 5-years

No included studies reported on disease-free survival at 5-years.

Overall survival (OS)

OS at 1-year

Across five observational studies, which represented a total of 68 MIS and 63 open approach patients, OS was similar at 1-year between MIS and open hepatectomy (RR 1.03, 95% CI 0.93 to 1.15, I^2 0%, Fig. 17a). Forest plots for mortality at one year are provided in Appendix 6.

OS at 3-years

Six studies contributed data towards overall survival at 3-years, having a total of 192 MIS and 188 open approach patients, with no difference found between the two interventions (RR 0.94, 95% CI 0.83 to 1.07, I^2 0%, Fig. 17b). Forest plot for mortality at three years has been provided in Appendix 6.

OS at 5-years

Three observational studies contributed data towards overall survival at 5 years, having a total of 43 MIS and 38 open approach patients. There was a slight increase in 5-year OS with MIS hepatectomy, however, this was not statistically significant (RR 1.26, 95% CI 0.59 to 2.70, I^2 0%, Fig. 17c).

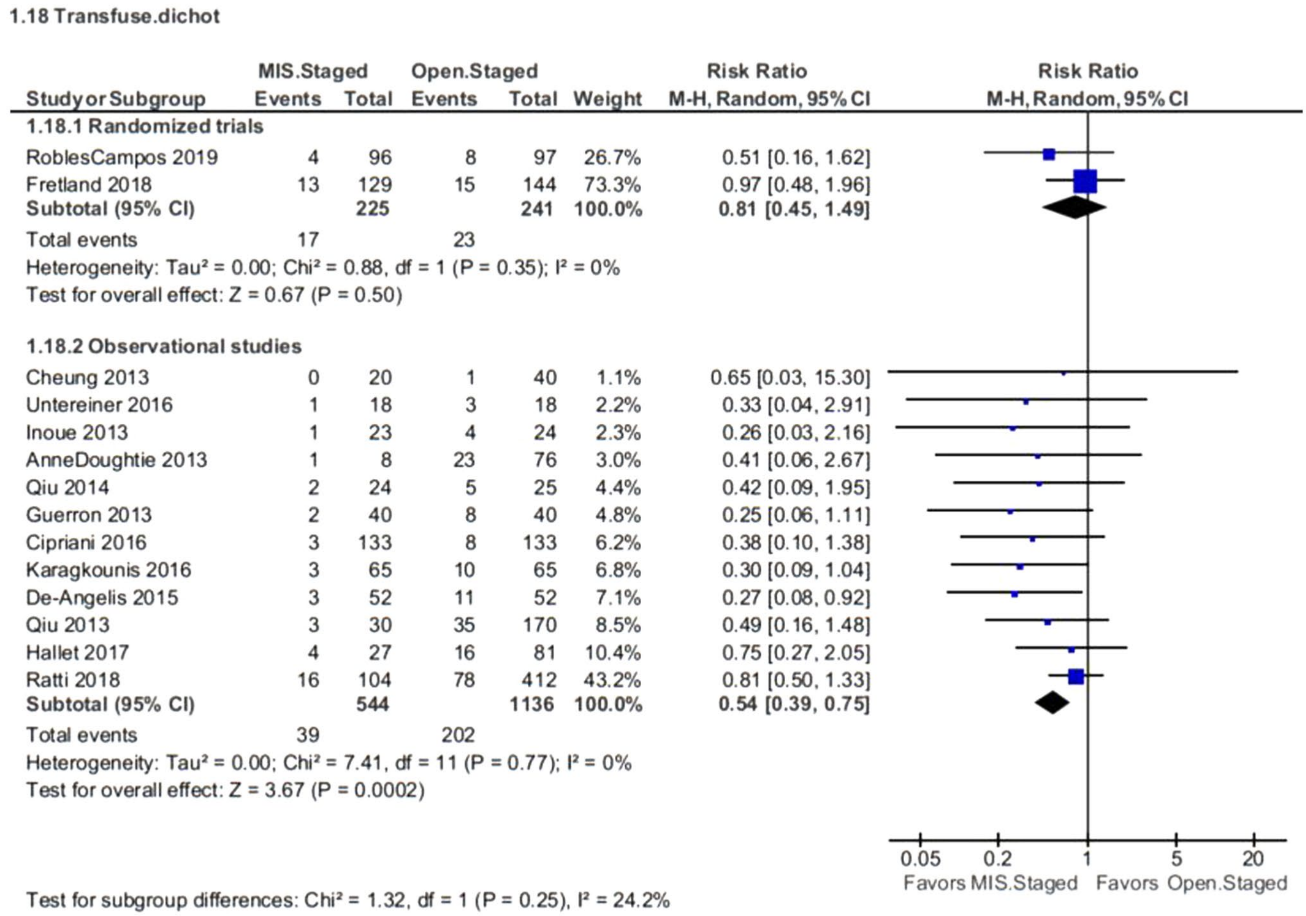


Fig. 7 Forest plot of the frequency of blood transfusion for staged resections

Notably, of the three included studies, one had a high risk of bias [41], while the other had an unclear risk [43]. The forest plot for mortality at five years is provided in Appendix 6.

Discussion

This systematic review finds that, for resectable CRLM, a better safety profile and similar oncological outcomes exist for minimally invasive surgery (MIS) compared to open hepatectomy for both staged and simultaneous resections. For staged resections (KQ1), pooled data from three well-conducted RCTs indicated that MIS had similar disease-free survival (DFS) and long-term overall survival (OS) compared to an open approach. Supported by evidence from observational data, MIS was demonstrated to have fewer severe perioperative complications, lower EBL, lower hospital LOS, fewer patients undergoing blood transfusion, while not compromising R0 resection. Further, simultaneous MIS hepatectomy, when combined with primary tumor resection (KQ2), also had significantly lower EBL and lower hospital LOS, compared to the open approach. Although many of the outcomes may have been underpowered to detect a statistically significant difference, MIS was found to have similar pooled effect estimates as the open group for DFS, OS, perioperative complications, R0 resections, and blood transfusion.

The findings of this meta-analysis are consistent with most of the prior systematic reviews on the subject [53–68]. Several systematic reviews, including both recently published ones [58–64], and older works [65–68], comparing MIS and open hepatectomy for resectable CRLM, have found MIS approach having superior perioperative outcomes along with similar oncological outcomes. However, unlike our current review, some included single-arm studies resulting in increased data inclusion but without the ability for direct comparison of the interventions [55, 56]. Others had less comprehensive search strategies than this present review, resulting in fewer included studies. Taillieau et al., in a systematic review published in 2021 on the outcomes of laparoscopic CRLM resection, found 14 eligible studies and demonstrated similar results as ours [54].

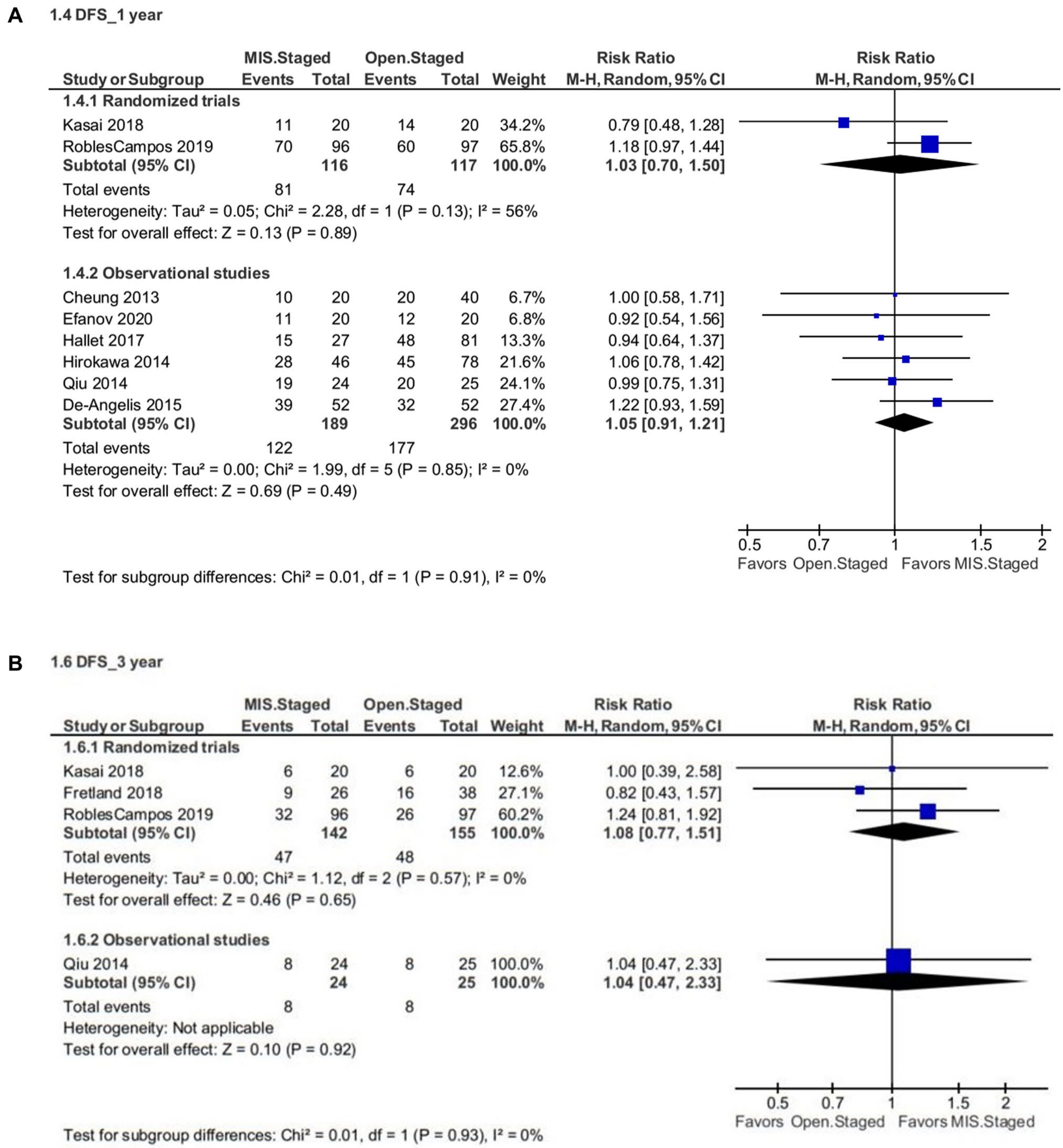


Fig. 8 Forest plot of the proportion of patients having disease-free survival for staged resections: **A** 1-year; **B** 3-years; **C** 5-years

The findings of this systematic review achieve greater relevance to clinical practice globally given the expanding accessibility of laparoscopic techniques worldwide, along with rising skill acquisition amongst surgeons worldwide. Chua et al., in a recent systematic review, demonstrated that for surmounting learning curves in MIS hepatectomy, a median of 25 and 50 procedures was required for robotic and laparoscopic resections, respectively [69]. Furthermore, the number of cases needed to pass this curve has decreased from 48.3 in 1995 to 23.8 in 2015, indicating increasing ease of attaining competency in MIS skills generally and MIS hepatectomy specifically.

Prior reviews have also utilized methodologies and investigated questions beyond the scope of the current review.

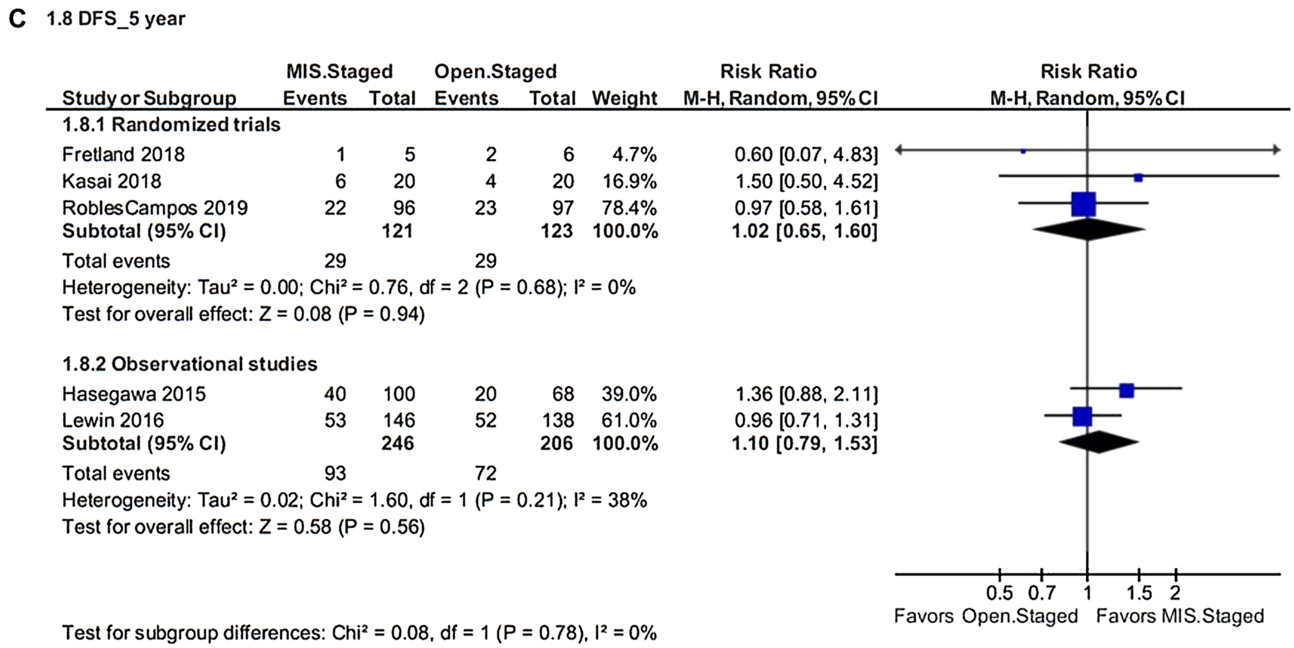


Fig. 8 (continued)

In particular, individual patient data (IPD) meta-analyses, which have been termed the 'gold standard' of systematic reviews [70, 71], have also been conducted [59, 60]. In 2020, Syn and colleagues published an IPD meta-analysis on laparoscopic versus open resections for CRLM. They utilized IPD from two RCTs and 13 propensity score-matched observational studies and demonstrated a significantly lower hazard of death for laparoscopic resections (hazard ratio 0.853) [59]. They also reported that at 10-year follow-up, the restricted mean survival time was significantly longer for the MIS arm, being 12% more. Furthermore, patients aged ≥ 65 undergoing MIS hepatectomy had a 6% higher 3-year life expectancy. Additionally, in 2018, Kasai et al. had published an IPD meta-analysis of MIS versus open major hepatectomy for all indications and had reported similar perioperative outcomes between the two groups [60]. Meanwhile, Haney et al. had conducted a systematic review of RCTs only comparing laparoscopic versus open liver resections for both benign and malignant indications. Thirteen included studies reported similar findings as the current review in favor of the laparoscopic group [72].

As robotic hepatectomy grows in prevalence, it is appropriate to evaluate these outcomes as well. Rocca et al. described the role of robotic surgery for resectable CRLM and, based on nine single-arm studies, found a 3-year DFS of 55.25%, 3-year OS of 37%, mean blood loss of 309.4 mL, mean length of stay of 7.98 days, and a Clavien-Dindo Grade III-IV complication rate of 8.4% [61]. Meanwhile, Machairas et al. systematically reviewed the landscape of robotic simultaneous resections for CRLM and primary tumor, and found similar perioperative outcomes from a very small, pooled sample, while data were sparse on long-term outcomes [60]. Furthermore, Merali et al. authored a systematic review in 2021 comparing robotic versus laparoscopic hepatectomy for CRLM. Data from 1340 patients reported that robotic approaches did not lead to significantly better outcomes except EBL while increasing operative time and perioperative complications [73].

Limitations

Our systematic review had several limitations. Several of the outcomes had significant heterogeneity in the pooled data, even in results that consistently favored one intervention over the other in certain outcomes. We attributed this heterogeneity to the inclusion of non-randomized studies, where effect size was varying and to varying populations in different studies. Further, several of the included studies had a high or unclear risk of bias, a common problem encountered when performing the meta-analysis of data from non-randomized studies. This may have impacted our findings in certain meta-analyses. For instance, for DFS at 1-year after simultaneous resections, conflicting findings were present in the two included studies. This may have been due to the difference in patient selection between the two, contributing to an increased risk of bias. Ivanecz et al. was a well-performed propensity score-matched study [47], whereas Chen et al. (2019) did not utilize balanced cohorts through any matching method [50].

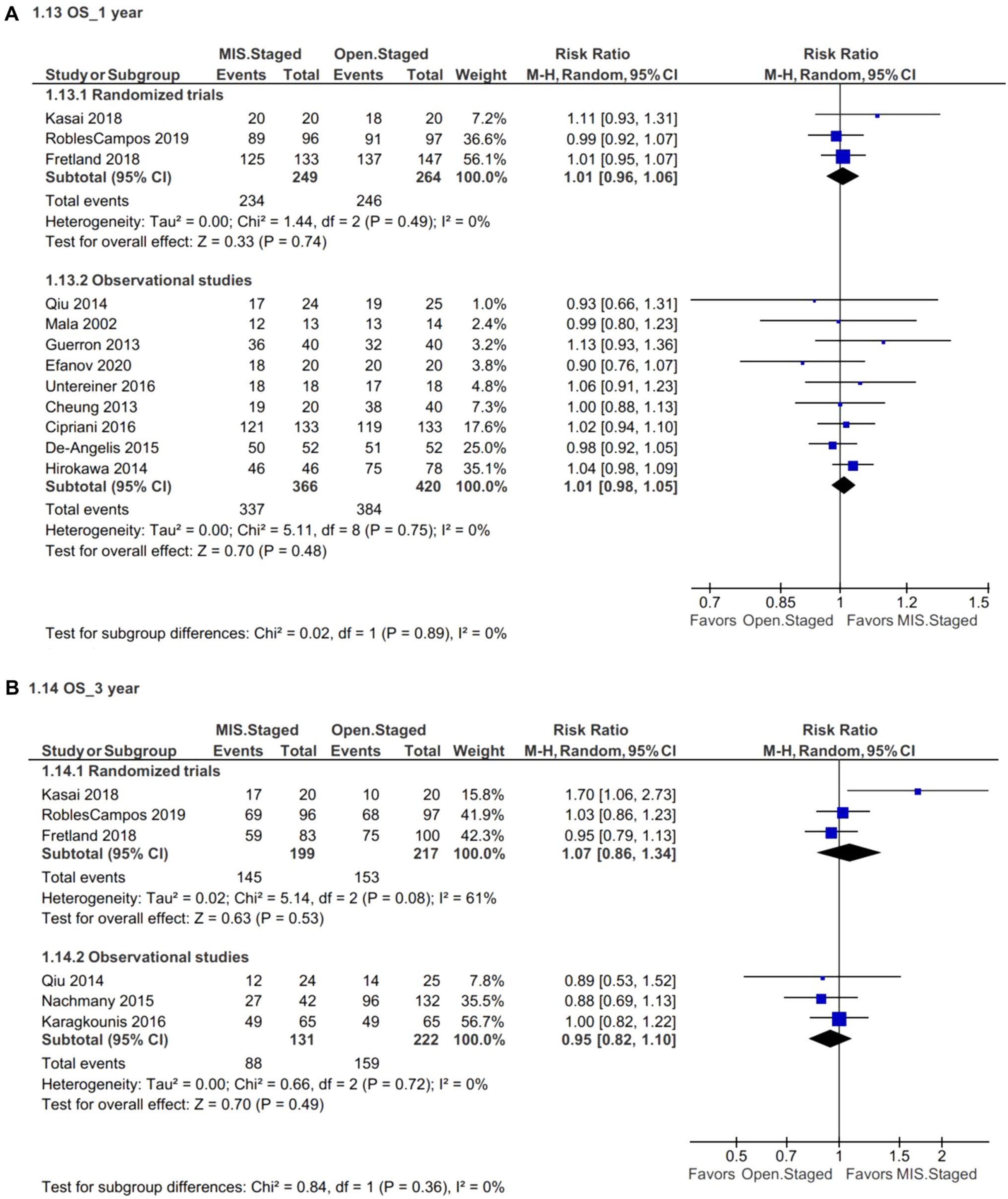


Fig. 9 Forest plot of the proportion of overall survival for staged resections; **A** 1-year; **B** 3-years; **C** 5-years

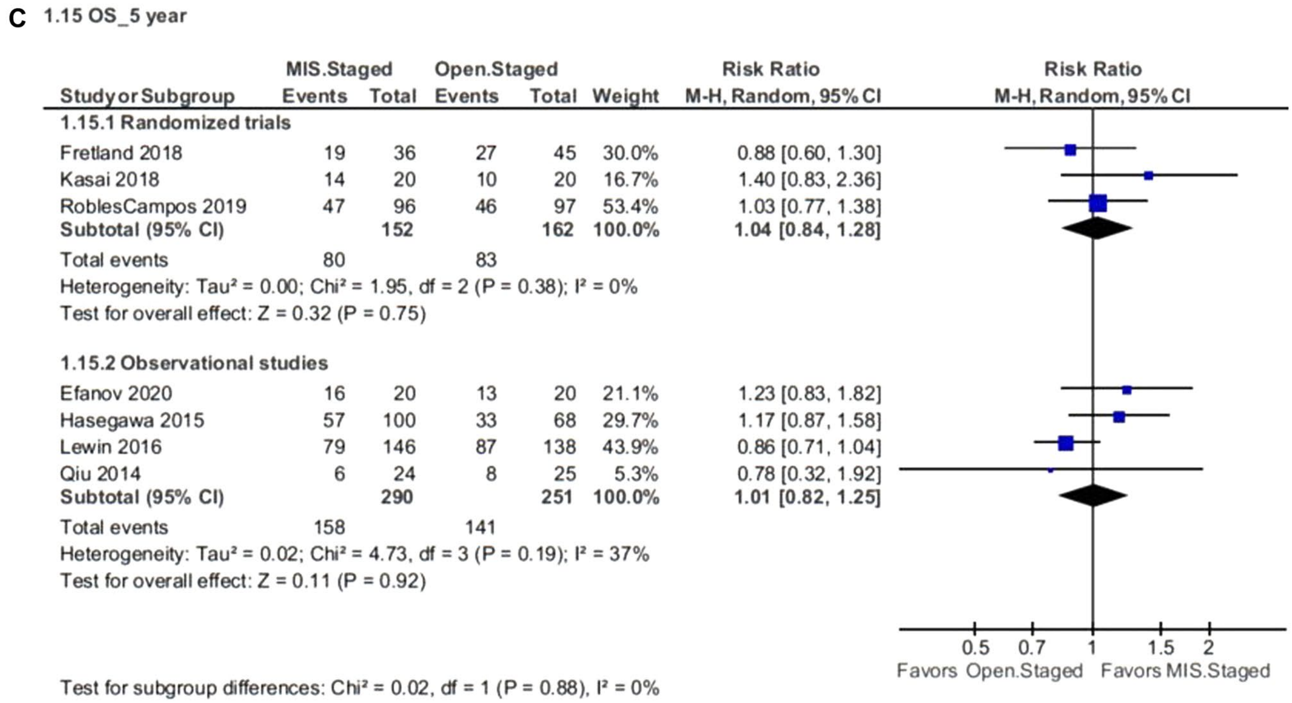


Fig. 9 (continued)

We did not approach authors for missing data, especially the long-term oncological data. Therefore, we had considerable missing data from multiple studies for several outcomes. Of the three RCTs included in KQ1 (staged), only two provided the number at risk for OS and DFS at 3 yr. At 3-year follow-up, Robles-Campos et al. had 42 patients in the open cohort and 52 patients in the MIS cohort who were at risk for OS and only 18 patients and 23 patients, respectively, at risk for DFS. Similarly, in the OSLO-COMET trial at 3 years, OS had 100 patients in the open group and 83 in the MIS group and DFS had 38 patients and 26 patients, respectively. The number at risk was not reported in Kasai et al. Due to loss of follow-up and progression of disease, the smaller sample sizes are likely underpowered introduce some fragility into the weight of these outcomes. In addition, we did not search for articles published in non-English languages. Our pre-specified outcomes did not include any patient-reported outcomes such as quality of life and time to return to daily activity post-procedure. Fourth, we had to exclude four studies that fit our eligibility criteria due to their likely overlapping data sets with other publications to prevent dual counting of patients in meta-analysis. Finally, this was not an IPD meta-analysis, and we had to rely on reported summary statistics. Due to this, we did not have granular data available from studies and could not answer several major questions, including the safety and efficacy of MIS in specifically 'liver first' resection for synchronous, resectable CRLM and the impact of site of the primary tumor (colon versus rectum).

Future research recommendations

In this review, several studies presented the results of colon cancer metastases and rectal cancer metastases in a combined fashion for most of the outcomes. We recommend that future studies report the outcomes of these two diseases separately. In addition, while there were three RCTs pertaining to staged resection (KQ1), no RCTs were available for the simultaneous resection (KQ2), resulting in a lack of high-level evidence to evaluate the efficacy and safety of MIS over an open approach in simultaneous resections. Well-planned RCTs are urgently needed to help answer these questions.

Given the increasing ease of multicentric research, the establishment of surgical research networks, and the rise of collaborative authorship that helps local investigators become involved, we, therefore, endorse the use of more high-quality multicentric studies with adequate follow-up periods. Such studies would help assess the feasibility of adopting MIS hepatectomy worldwide. Future observational studies should attempt to utilize statistical matching methods as extensively as possible to remove known confounders in order to delineate the impact of newer approaches, especially robotic procedures. High-quality comparative data are also needed regarding the

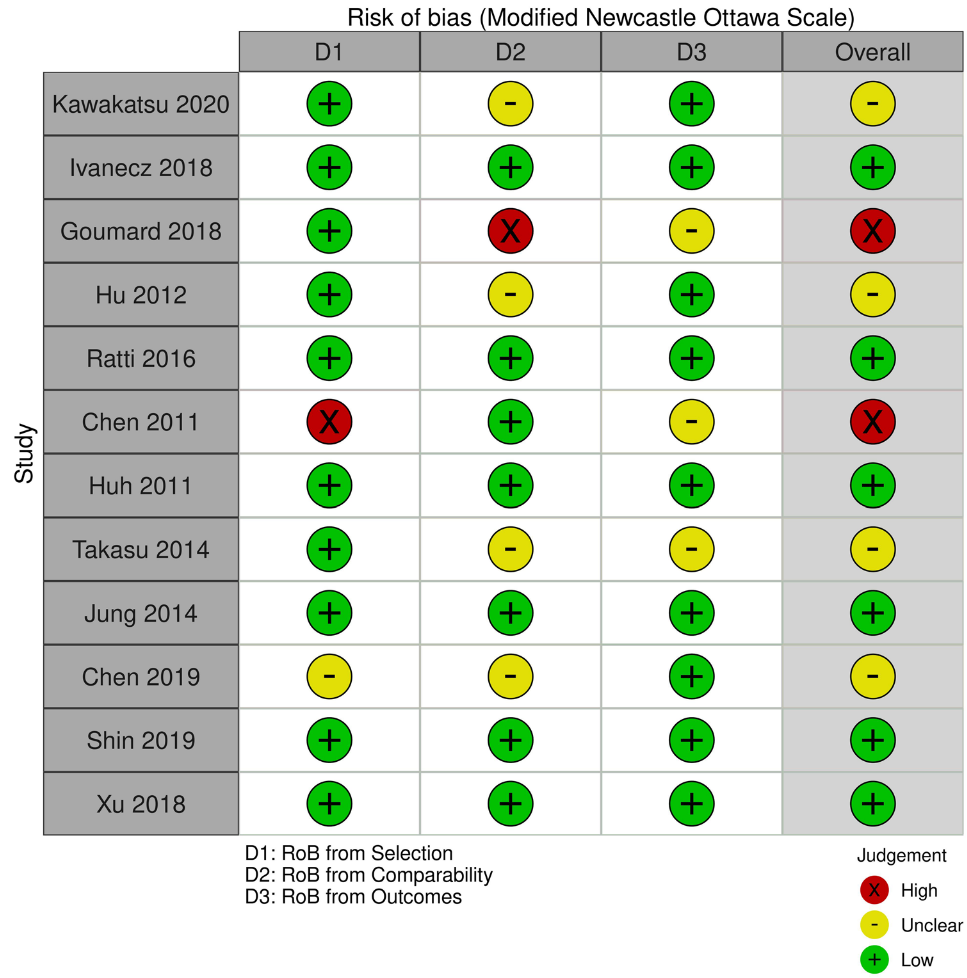


Fig. 10 Traffic light figure for quality assessment of the studies included under Key Question 2, as assessed by a modified version of the Newcastle Ottawa Scale

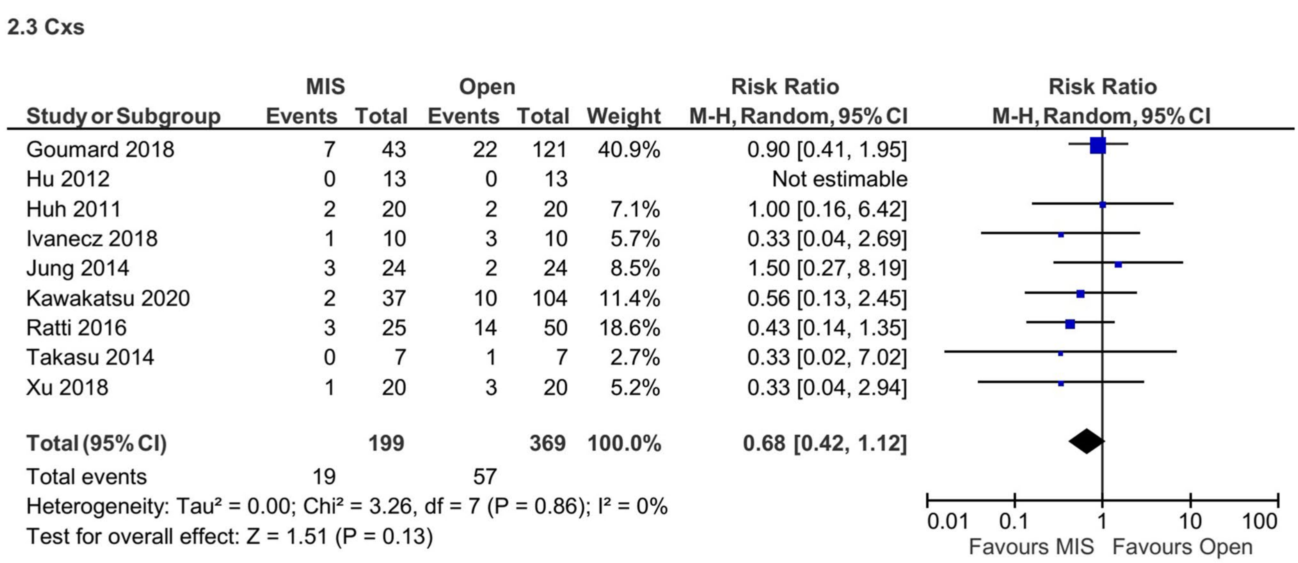


Fig. 11 Forest plot of perioperative complications of Clavien-Dindo Grade ≥ 3 for simultaneous resections

2.6 LOS

Study or Subgroup	MIS Mean	MIS SD	MIS Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI
Chen 2011	12	1.5	23	16	2.5	18	15.1%	-4.00 [-5.31, -2.69]
Goumard 2018	4	2.88	43	6	4.83	121	15.9%	-2.00 [-3.22, -0.78]
Hu 2012	8.5	1.9	13	11.2	1.8	13	14.1%	-2.70 [-4.12, -1.28]
Huh 2011	14.25	5.75	20	14.75	6	20	4.3%	-0.50 [-4.14, 3.14]
Ivanecz 2018	9	1.29	10	11.5	18.55	10	0.5%	-2.50 [-14.02, 9.02]
Jung 2014	11	4.5	24	13	3.75	24	8.2%	-2.00 [-4.34, 0.34]
Kawakatsu 2020	15	15.75	37	15	10.5	104	2.1%	0.00 [-5.46, 5.46]
Ratti 2016	9.75	3.76	25	16.5	8.1	50	6.8%	-6.75 [-9.44, -4.06]
Shin 2019	12	6	109	15	6	109	12.8%	-3.00 [-4.59, -1.41]
Takasu 2014	16.2	6.1	7	36.1	24.9	7	0.2%	-19.90 [-38.89, -0.91]
Xu 2018	9.5	0.875	20	12.56	1.56	20	20.0%	-3.06 [-3.84, -2.28]
Total (95% CI)			**331**			**496**	**100.0%**	**-3.00 [-3.82, -2.17]**

Heterogeneity: Tau² = 0.73; Chi² = 19.24, df = 10 (P = 0.04); I² = 48%
Test for overall effect: Z = 7.10 (P < 0.00001)

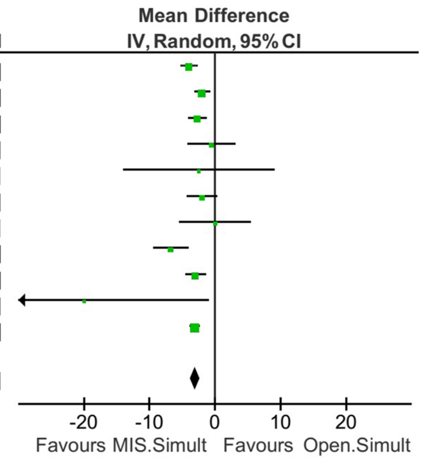


Fig. 12 Forest plot of length of stay (LOS) for simultaneous resections

2.5 EBL

Study or Subgroup	MIS Mean	MIS SD	MIS Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI
Chen 2011	275	96	23	590	85	18	10.9%	-315.00 [-370.51, -259.49]
Goumard 2018	100	198.75	43	200	158.33	121	10.8%	-100.00 [-165.76, -34.24]
Hu 2012	258	111	13	273	95	13	10.5%	-15.00 [-94.42, 64.42]
Huh 2011	442.5	207.5	20	575	275	20	8.8%	-132.50 [-283.48, 18.48]
Ivanecz 2018	105	121	10	160	46.55	10	10.5%	-55.00 [-135.35, 25.35]
Jung 2014	400	212.5	24	350	200	24	9.7%	50.00 [-66.75, 166.75]
Kawakatsu 2020	200	173.75	37	708.75	418.75	104	10.1%	-508.75 [-606.79, -410.71]
Ratti 2016	450	259.8	25	675	317.55	50	9.3%	-225.00 [-359.61, -90.39]
Takasu 2014	152	128	7	496	191	7	8.3%	-344.00 [-514.33, -173.67]
Xu 2018	181.25	43.75	20	334.38	103.13	20	11.0%	-153.13 [-202.23, -104.03]
Total (95% CI)			**222**			**387**	**100.0%**	**-177.35 [-273.17, -81.53]**

Heterogeneity: Tau² = 21085.45; Chi² = 117.76, df = 9 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.63 (P = 0.0003)

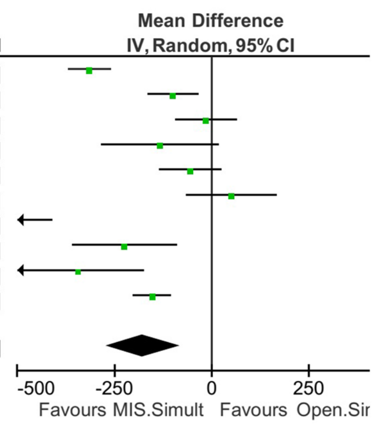


Fig. 13 Forest plot of estimated blood loss (EBL) for simultaneous resections

2.1 R0 Resection

Study or Subgroup	MIS.Simult Events	MIS.Simult Total	Open.Simult Events	Open.Simult Total	Weight	Risk Ratio M-H, Random, 95% CI
Goumard 2018	35	43	99	121	3.8%	0.99 [0.84, 1.17]
Huh 2011	20	20	20	20	10.1%	1.00 [0.91, 1.10]
Ivanecz 2018	10	10	10	10	3.2%	1.00 [0.83, 1.20]
Jung 2014	24	24	24	24	13.1%	1.00 [0.92, 1.08]
Kawakatsu 2020	37	37	93	104	13.8%	1.11 [1.03, 1.20]
Ratti 2016	25	25	49	50	15.0%	1.01 [0.94, 1.09]
Shin 2019	109	109	109	109	40.8%	1.00 [0.98, 1.02]
Total (95% CI)		**268**		**438**	**100.0%**	**1.02 [0.98, 1.05]**
Total events	260		404			

Heterogeneity: Tau² = 0.00; Chi² = 9.13, df = 6 (P = 0.17); I² = 34%
Test for overall effect: Z = 0.90 (P = 0.37)

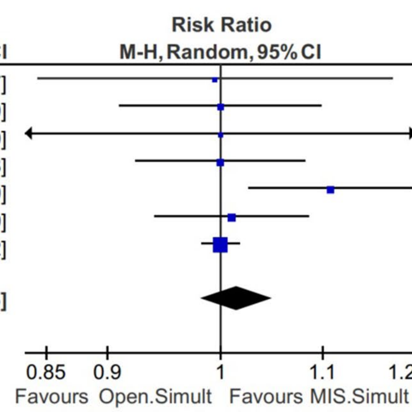


Fig. 14 Forest plot of R0 liver resections for simultaneous procedures

2.2 Transfuse_dichot

Study or Subgroup	MIS Events	MIS Total	Open Events	Open Total	Weight	Risk Ratio M-H, Random, 95% CI
Hu 2012	2	13	3	13	8.1%	0.67 [0.13, 3.35]
Ivanecz 2018	3	10	3	10	11.8%	1.00 [0.26, 3.81]
Ratti 2016	4	25	12	50	20.2%	0.67 [0.24, 1.86]
Shin 2019	15	109	13	109	44.1%	1.15 [0.58, 2.31]
Xu 2018	4	20	5	20	15.8%	0.80 [0.25, 2.55]
Total (95% CI)		**177**		**202**	**100.0%**	**0.92 [0.58, 1.45]**
Total events	28		36			

Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 4 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

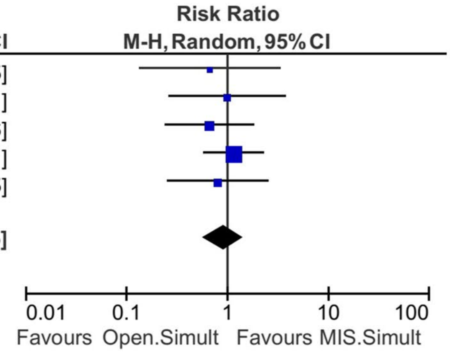
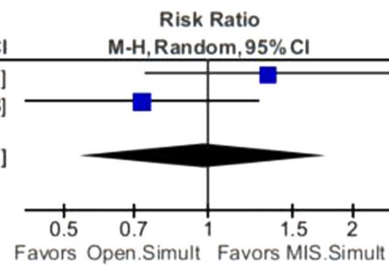


Fig. 15 Forest plot of the frequency of blood transfusion for simultaneous procedures

A **2.4 DFS_1 year**

Study or Subgroup	MIS.Simult Events	MIS.Simult Total	Open.Simult Events	Open.Simult Total	Weight	Risk Ratio M-H, Random, 95% CI
Ivanecz 2018	8	10	6	10	48.8%	1.33 [0.74, 2.41]
Chen 2019	8	15	11	15	51.2%	0.73 [0.41, 1.28]
Total (95% CI)		**25**		**25**	**100.0%**	**0.98 [0.54, 1.78]**
Total events	16		17			

Heterogeneity: Tau² = 0.10; Chi² = 2.13, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 0.07 (P = 0.94)



B **2.6 DFS_3 year**

Study or Subgroup	MIS.Simult Events	MIS.Simult Total	Open.Simult Events	Open.Simult Total	Weight	Risk Ratio M-H, Random, 95% CI
Takasu 2014	3	7	6	7	5.2%	0.50 [0.20, 1.24]
Xu 2018	6	18	7	18	5.6%	0.86 [0.36, 2.05]
Ivanecz 2018	6	10	6	10	8.3%	1.00 [0.49, 2.05]
Shin 2019	65	109	60	109	80.9%	1.08 [0.86, 1.36]
Total (95% CI)		**144**		**144**	**100.0%**	**1.02 [0.83, 1.25]**
Total events	80		79			

Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)

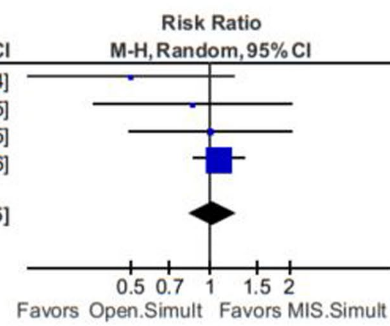


Fig. 16 Forest plot of disease-free survival for simultaneous procedures; **a)** 1-year; **b)** 3-years

utility of laparoscopic versus robotic hepatectomies for resectable CRLM. Finally, the decision of which patients should undergo staged vs. simultaneous liver resection was beyond the scope of this review, however, it is an area that is worthy of further study. Once evidence has accumulated in this area, a follow-up systematic review will need to be performed to help inform this decision.

Conclusion

Current available evidence regarding the optimal surgical approach for the treatment of resectable colorectal liver metastases (CRLM) favors minimally invasive surgery (MIS) over an open technique, for both staged and simultaneous approaches. This review demonstrated that MIS has similar oncological outcomes and improved safety profile, compared to an open approach. Given the significant

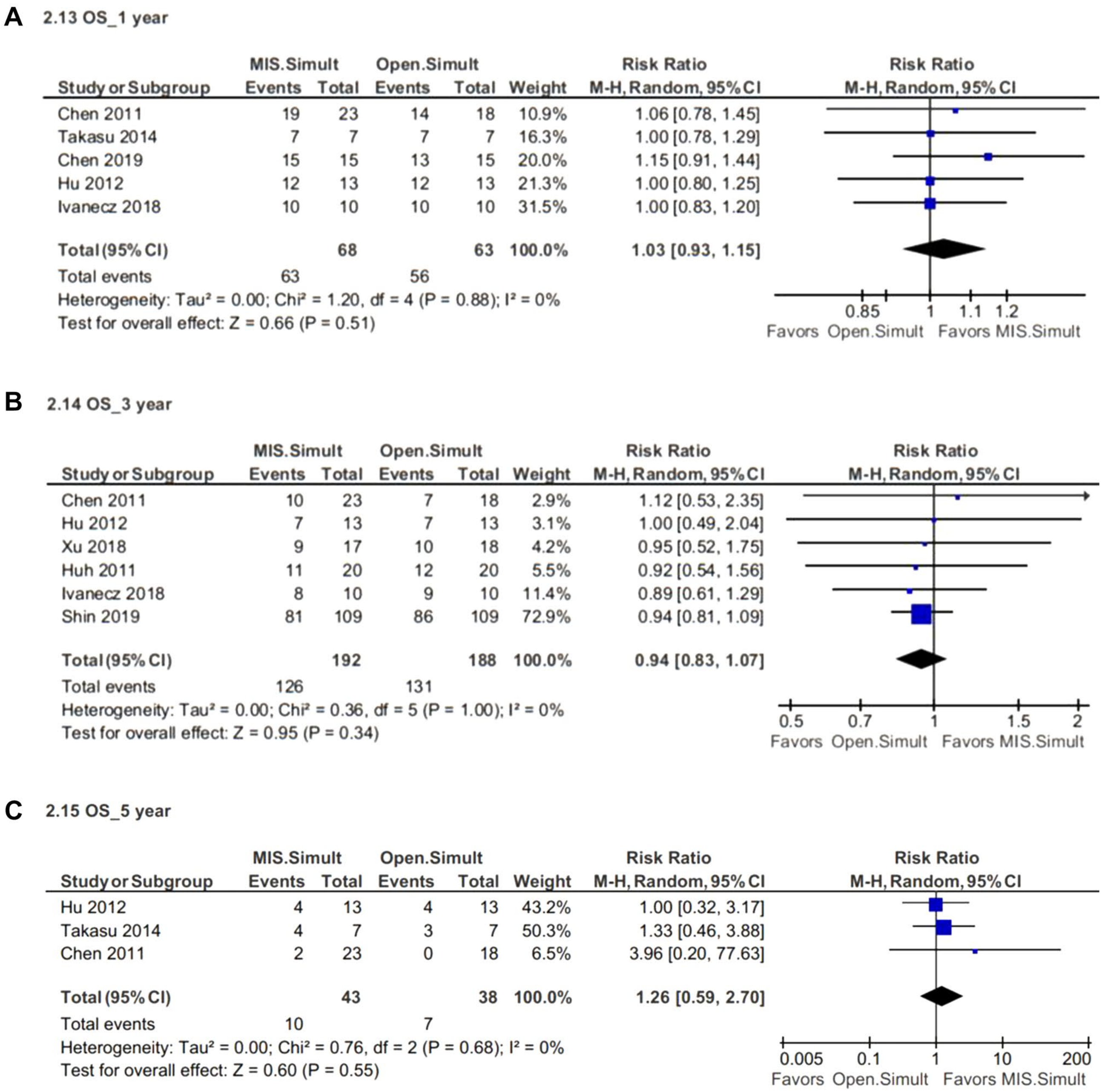


Fig. 17 Forest plot of overall survival for simultaneous resections: **A** 1-year; **B** 3-years; **C** 5-years

imprecision in pooled outcomes and the learning curve associated with MIS, high-quality randomized controlled trials and multicentric observational studies are needed to further delineate the oncological efficacy and the wider applicability of this intervention. These findings will inform the SAGES/AHPBA Guidelines on the utility of MIS hepatectomy for CRLM.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00464-022-09612-0.

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Declarations

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