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SYSTEMATIC REVIEW

The efficacy of radical antegrade modular pancreatosplenectomy: A systematic review and meta-analysis

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Abstract

Background/Purpose: Previous systematic reviews have shown that radical antegrade modular pancreatosplenectomy (RAMPS) had favorable outcomes including prognosis. However, recent large studies have shown opposite results, thus necessitating clarification of RAMPS efficacy. We aimed to update existing evidence on the clinical outcomes of RAMPS for left-sided pancreatic cancer by comparing them to those of the conventional approach.

Methods: Electronic databases and registries were searched until August 2021 to perform random-effect meta-analysis. Methodological quality was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation approach. The protocol was registered at protocols.io (https://doi.org/10.17504/protocols.io.bxhfpj3n).

Results: Thirteen cohort studies (1641 patients) and four ongoing randomized controlled trials (RCTs) were identified. RAMPS increased disease-free survival (hazard ratio [HR] 0.62, 95% confidence interval [CI] = 0.42-0.91), but it had little effect on overall survival (HR 0.92, 95% CI = 0.79-1.09) and recurrence-free survival (HR 0.72, 95% CI = 0.37-1.38) with low certainty of evidence.

Conclusion: The meta-analysis of recent studies suggests that RAMPS may have little effect on clinical outcomes. These findings highlight the necessity of further studies, including RCTs to determine the efficacy and subsequent indication of RAMPS in clinical cases.

KEYWORDS

meta-analysis, mortality, pancreatic neoplasms, prognosis, systematic review

1 | INTRODUCTION

Pancreatic cancer is an aggressive cancer with a median survival of 3-6 months and a 5-year survival rate of <6%.[1] Early diagnosis of left-sided pancreatic cancer is rare because of the lack of early symptoms. Moreover, the pancreatic body and tail cancers have a poor prognosis compared to head pancreatic cancer.[2] Conventionally, distal pancreatectomy (DP) and splenectomy have been performed to treat pancreatic cancer of the body and tail in a left-to-right retrograde fashion, in which mobilization of the spleen and pancreas is followed by vascular control and division of the pancreas. DP has also been associated with high positive margin rates, low retrieved lymph node counts, and poor overall survival.[3] In 2003, a new DP approach called "radical advanced modular pancreatectomy and splenectomy (RAMPS)" was developed.[4] In RAMPS, the retroperitoneal incision either continues medially to the left, exposing the left renal vein and removing the Gerota fascia from the left kidney, or continues until posterior to the diaphragm using the retroperitoneal muscle as the posterior margin.[5] The rationale for performing RAMPS is achievement of a negative deep margin with complete regional lymph node dissection.

Previous systematic reviews have shown that RAMPS was associated with favorable postoperative outcomes and overall survival.[6–9] However, these reviews[6–9] included only single-center or small-sample studies. According to the Cochrane handbook,[10] these studies were also methodologically incorrect because meta-analysis was performed using fixed-effects models and registry trial databases were not searched. Further, in recent large cohort studies, RAMPS was not associated with an improvement in overall survival (OS).[11,12]

An updated systematic review and meta-analysis with appropriate methodology would benefit both surgeons and patients because it may reduce ambiguity by providing a better understanding of the current evidence for RAMPS efficacy in patients with distal pancreatic cancer. Therefore, the aim of the present study was to compare the prognosis and surgical outcomes of patients with left-sided pancreatic cancer who underwent RAMPS with those of patients who underwent conventional DP.

2 | METHODS

2.1 | Protocol

This study was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) -2020 (Appendix S1).[13] The study protocol was registered at protocols.io (10.17504/protocols.io.bxhfpj3n).

2.2 | Inclusion criteria of the articles for the review

We included randomized controlled trials (RCTs) and non-RCTs that compared RAMPS with conventional approaches for treating patients with left-sided pancreatic cancer. We did not apply language or country restrictions. We included several article categories, such as published and unpublished articles, and conference abstracts. However, reviews, letters, and case reports were excluded. We did not exclude studies based on the observation period or publication year. The inclusion criteria for study participants were adults aged >18 years who were scheduled to receive DP. Patients who did not provide consent were excluded. The primary outcomes were OS, recurrence-free survival (RFS), and disease-free survival (DFS). The secondary outcomes were R0 resection, number of retrieved lymph nodes, postoperative complications, postoperative pancreatic fistula (POPF), length of hospitalization (LOH) (day), blood loss (mL), and operative time (min). POPF was defined using the definition proposed by the International Study Group on Pancreatic Fistula and classified into three grades—biochemical and grades B and C,[14] where grades B or C were considered clinical pancreatic fistulas.

2.3 | Search method

The following electronic databases and trial registry databases were searched: MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (Cochrane Library), EMBASE (Dialog), the World Health Organization International Clinical Trials Platform Search Portal (ICTRP), and ClinicalTrials.gov (Appendix S2). The reference lists of eligible studies were checked, including those of international guidelines[15–17] and articles citing eligible studies. Authors of original studies were asked for unpublished or additional data, if required.

2.4 | Data collection and analysis

Two independent reviewers (JW and KR) independently performed the screening and data extraction procedures. The risk of bias was evaluated using the Newcastle–Ottawa Quality Rating Scale (NOS).[18] Study quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[19]

Disagreements between the two reviewers were resolved by discussion or a third reviewer acting as an arbiter (KK) when discussion failed.

The hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled for OS, RFS, and DFS. Clinically considerable (eg, age, TNM, R1, and chemoradiotherapy) or significant variables were included in multivariable analysis. When RAMPS was not found to be a statistically significant variable in univariable analysis, the results of the univariable analysis were adopted.[10] The relative risk ratios (RRs) and 95% CIs were pooled for the following binary variables: postoperative complications, POPF, and R0 resection. The mean differences (MD) and 95% CIs were pooled for the following continuous variables: number of retrieved lymph nodes, LOH (day), blood loss (mL), and operative time (min). Meta-analysis was performed using Review Manager software (RevMan 5.4.2) to generate a random-effects model.[10] For continuous data, missing data were not imputed based on the recommendation of the Cochrane handbook.[10] When propensity score matching was performed, the data were adjusted using this method.[20] Missing data were collected from the original authors.

Statistical heterogeneity was evaluated by visual inspection of the forest plots and the I^2 statistic (0%-40%: might not be important; 30%-60%: may represent moderate heterogeneity; 50%-90%: may represent substantial heterogeneity; 75%-100%: considerable heterogeneity).[10] When there was substantial heterogeneity ($I^2 > 50\%$), the reason for the heterogeneity was assessed in subgroup analyses of countries (Asia versus Western countries).[21]

Additionally, we searched the clinical trial registry system (ClinicalTrials.gov and ICTRP). We did not conduct the funnel plot because we did not find <10 trials for each outcome according to the Cochrane handbook.[10]

A summary of the findings table was created for the following outcomes based on the Cochrane handbook[10]: OS, RFS, DFS, R0 resection, number of retrieved lymph nodes, and postoperative complications.

2.5 | Additional analysis

The following sensitivity analyses were performed to assess whether the results of the review were robust to the decisions made during the review process: exclusion of studies using imputed statistics, only patients who completed the study with complete data, or only patients who had pancreatic adenocarcinoma. Additionally, as a post-hoc sensitivity analysis, the HRs and 95% CIs were pooled for OS, RFS, and DFS for studies excluding conference articles.

3 | RESULTS

Figure 1 illustrates the literature search process. After the duplicates were removed using the Mendeley Desktop Software (www.mendeley.com, version 1.19.4, Mendeley Ltd.), a total of 177 studies were searched until August 19, 2021. After screening, 133 studies were excluded because they did not focus on the comparison between RAMPS and conventional approaches and 19 studies met the inclusion criteria. Three studies were excluded because no outcomes were available after contacting the authors.[22–24] An additional study was identified through citation search.[25] There were no protocols without unpublished results. Seventeen studies were identified in qualitative synthesis, including four ongoing RCTs (NCT03679169, NCT04253847, NCT04600063 and ChiCTR2000036489) and 13 cohort studies. Finally, 13 studies (1641 patients) were included in meta-analysis.[11,12,25–35]

Table 1 and Appendix Figure S3 summarize the characteristics of the included studies.[11,12,25–35] Among the 13 studies, 10 were published in Asia (five in Korea, four in China, and one in Japan), and three were published in Western countries (two in the USA, and one in Italy). Two studies included tumors that did not have adenocarcinoma.[29,31] Study quality was assessed using the NOS, with a median score of 6 and a range of 3-8 (Appendix Figure S4).

Table 2 summarizes the findings using the GRADE approach.

3.1 | Primary outcomes

Radical antegrade modular pancreatosplenectomy had little effect on OS (HR 0.92, 95% CI = 0.79-1.09; $I^2 = 5\%$) and RFS (HR 0.72, 95% CI = 0.37-1.38; $I^2 = 73\%$). RAMPS increased DFS (HR 0.59, 95% CI = 0.41-0.86; $I^2 = 40\%$) (Figure 2). The certainty of the evidence was low.

3.2 | Secondary outcomes

Radical antegrade modular pancreatosplenectomy increased the number of retrieved lymph nodes (MD 4.06, 95% CI = 2.37-5.76; $I^2 = 86\%$) and decreased blood loss (MD −157.69, 95% CI = −221.96 to 93.42; $I^2 = 69\%$), but did not increase R0 resection (RR 1.06, 95% CI = 0.98-1.15; $I^2 = 58\%$). Moreover, RAMPS had little effect on postoperative complications (RR 0.85, 95% CI = 0.51-1.41; $I^2 = 77\%$), POPF (RR 1.15, 95% CI = 0.81-1.65; $I^2 = 0\%$), LOH (MD −2.42, 95% CI = −6.26 to 1.41; $I^2 = 93\%$), and

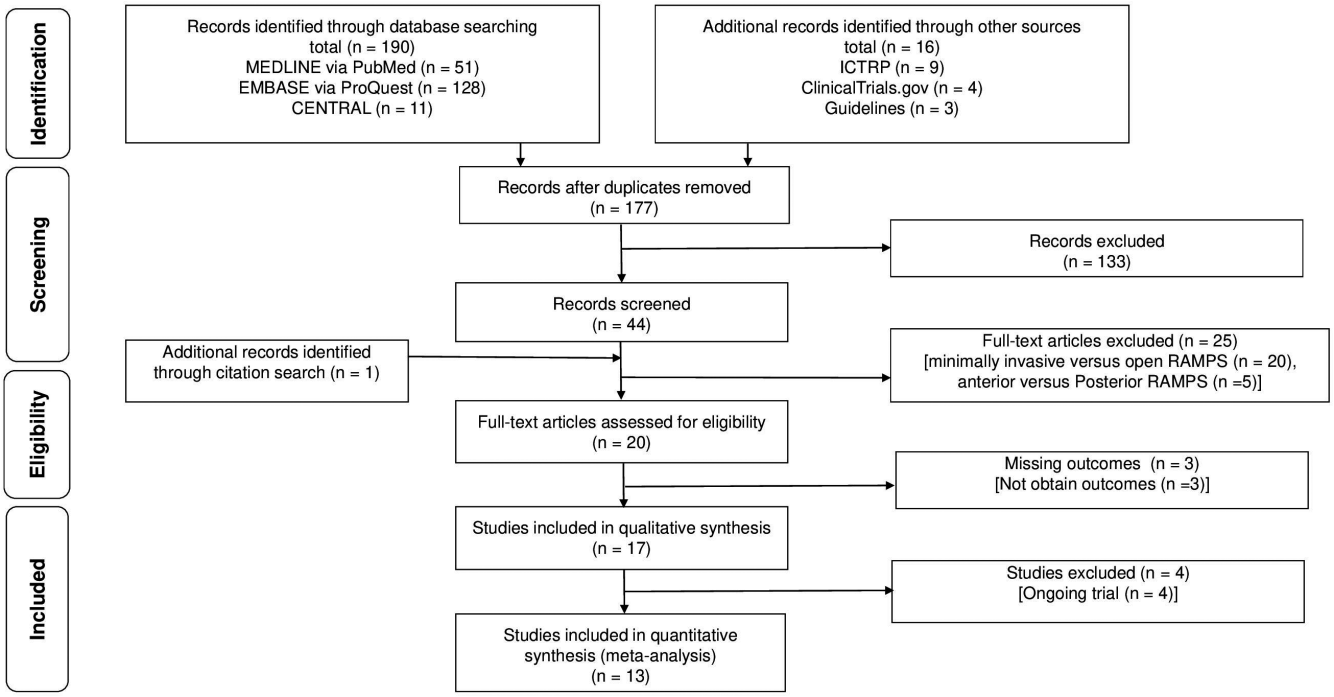


FIGURE 1 Flow of the literature search process

TABLE 1 The characteristics of the include studies

Authors [ref no.]	Year	Country	Study type	Propensity score matching	RAMPS no.	Control no.	Center	Age, year	Male, %	Stage	NOS
You[26]	2010	Korea	P	No	11	50	Single	61	64	NR	4
Latorre [27]	2013	Italy	R	No	8	17	Single	61	64	NR	6
Park[28]	2014	Korea	R	No	38	54	Single	63	63	I-IV	4
Trottman [29]	2014	USA	P	No	6	20	Single	NR	NR	NR	3
Abe[30]	2016	Japan	R	No	53	40	Single	69	65	I-III	7
Kim EY[31]	2016	Korea	R	No	30	19	Single	64	40	I-II	6
Xu[25]	2016	China	R	No	21	78	Single	62	52	I-IV	4
Huo [32]	2019	China	R	No	11	16	Single	64	48	I-IV	4
Kim NH[33]	2019	Korea	R	Yes	139	71	Multi	NR	NR	NR	7
Sham[11]	2020	USA	R	No	253	193	Multi	65	60	NR	5
Yin[34]	2020	China	R	Yes	101	203	Single	64	NR	NR	6
Dai[35]	2021	China	R	No	46	57	Single	62	50	I-III	8
Kim HS[12]	2021	Korea	R	Yes	53	53	Multi	66	45	I-III	8

Abbreviations: NOS, the Newcastle-Ottawa Quality Rating Scale; NR, not reported; P, prospective cohort study; R, retrospective cohort study.

operative time (MD 10.07, 95% CI = −40.47 to 60.61; I^2 = 98%) (Figure 3).

3.3 | Additional analysis

In subgroup analyses of countries (Appendix Figure S1 and S2), RAMPS increased R0 resection in Asia (RR 1.10, 95% CI = 1.04-1.17; I^2 = 3%), but not in Western countries (RR 0.95, 95% CI = 0.90-1.00; I^2 = 0%) (test for subgroup differences: P = .0003). Similarly, the number of lymph nodes retrieved by RAMPS in Asia (MD 4.51, 95% CI = 2.42 to 6.61; I^2 = 77%) was higher than that in Western countries (MD 2.03, 95% CI = 1.34 to 2.71; I^2 = 0%) (test for subgroup differences: P = .03). The sensitivity analyses of patients restricted to pancreatic adenocarcinoma showed similar trends of the results of whole patients (Appendix Figures S3 and S4). The other prespecified sensitivity

TABLE 2 Summary of findings

The efficacy of radical antegrade modular pancreatosplenectomy (RAMPS)				
Patient or population: adults, setting: pancreatosplenectomy, intervention: RAMPS, Comparison: Control				
Outcomes	**Relative effect (95% CI)***	**Patient number (Studies)**	**Certainty of the Evidence (GRADE)**	**Comments**
OS	HR 0.92 (0.79 to 1.09)	1119 (9 cohort studies)	Low[a,b]	RAMPS resulted in little difference in OS
RFS	HR 0.72 (0.37 to 1.38)	711 (4 cohort studies)	Low [a,b]	RAMPS resulted in little difference in RFS
DFS	HR 0.59 (0.41 to 0.86)	792 (6 cohort studies)	Low [a,b]	RAMPS increased DFS
R0 resection	RR 1.06 (0.98 to 1.15)	1198 (10 cohort studies)	Low [a,c]	RAMPS did not increase R0 resection
Retrieved lymph nodes	MD 4.06 (2.37 to 5.76)	1468 (10 cohort studies)	Low [a,c]	RAMPS increased number of retrieved lymph nodes
Postoperative complications	RR 0.85 (0.51 to 1.41)	911 (7 cohort studies)	Low[b,c]	RAMPS did not decrease postoperative complications

CI, confidence interval; HR, hazard ratio; MD, mean difference; MD, mean difference; RR, risk ratio.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence; High certainty: We are very confident that the true effect lies close to that of the estimated effect. Moderate certainty: We are moderately confident in the estimated effect. The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the estimated effect is limited: The true effect may be substantially different from the estimated effect. Very low certainty: We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect.

[a]Downgraded because of inconsistency due to statistical analysis and reporting.

[b]Downgraded because of imprecision due to the small sample size.

[c]Downgraded because of inconsistency due to substantial heterogeneity.

analyses could not be performed because there were no studies using imputed statistics and no studies contained incomplete data. In post-hoc sensitivity analyses excluding abstract conferences, RAMPS had little effect on OS (HR 0.90, 95% CI = 0.76-1.06; $I^2 = 0\%$) and RFS (HR 0.73, 95% CI = 0.33-1.62; $I^2 = 81\%$), which were consistent with the original results of all studies including the abstract conferences.

4 | DISCUSSION

The present systematic review and meta-analysis demonstrated that although RAMPS may increase DFS, it has little effect on OS and RFS. In addition, RAMPS may increase the number of retrieved lymph nodes, but it may not increase R0 resection. However, in subgroup analyses, RAMPS increased R0 resection in Asia. The present systematic review used updated information and modified the findings from previous systematic reviews, which showed that RAMPS improved prognosis.

Our review was rigorously performed according to a predefined protocol using the PRISMA statement and the GRADE approach. Previous systematic reviews[6–9] have used the incorrect methodology of meta-analysis because the meta-analysis was performed using fixed-effects models.[10] In addition, RFS and DFS results were mixed in the meta-analysis, unpublished studies, such as conference abstract and trial registry databases, were not included, and patients who did not have pancreatic adenocarcinoma were included. Because of the clinical differences in RAMPS among regions with R0 resections in the present systematic review,[6–9] a meta-analysis comparing RAMPS with the conventional approach would be better using a random-effects model rather than a fixed-effects model.[36] Although previous systematic reviews excluded conference abstracts, the present review added seven studies through an update search[11,12,32,34,35] and included conference abstracts.[26,33] In addition, we confirmed that the results were consistent with the original results through sensitivity analysis of only patients with pancreatic adenocarcinoma. In the present review, RFS and DFS were evaluated as separate outcomes. Further reviews are needed to follow a rigorous methodology based on the Cochrane Handbook.[10]

RAMPS increased the number of retrieved lymph nodes but had little effect on OS because postoperative adjuvant chemotherapy can increase survival.[37–39] In three studies included in multivariable analysis,[11,28,35] RAMPS increased OS compared with the conventional

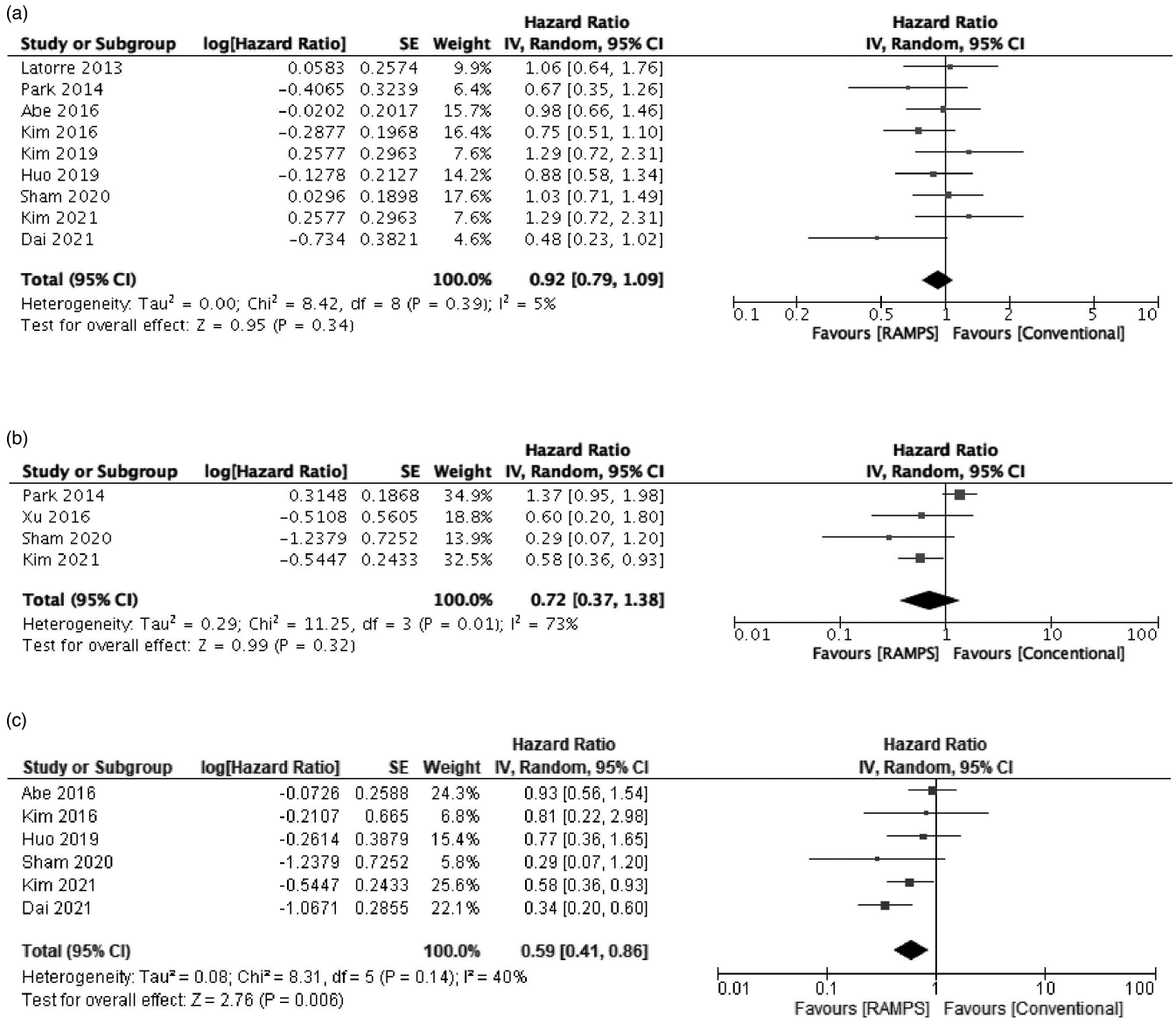


FIGURE 2 Forest plot of (A) overall survival, (B) recurrence-free survival, and (C) disease-free survival

approach in univariable analyses, but no difference was observed in survival between the two groups in multivariable analysis. This difference can be attributed to the different proportions of patients receiving chemotherapy between the two groups. Data regarding the specific drug, dose, and duration data, is required to estimate the relative effectiveness of chemotherapy between the two surgical approaches.

In the present review, RAMPS increased DFS, which may be due to the different years of surgery. Discrepancies between historical and concurrent controls may have increased the bias related to the assessment of control response and therefore related to the assessment of RAMPS efficacy. These discrepancies could be caused by improvements in clinical care from those practiced at the time of a previous study.[40] Recent multicenter studies have eliminated these discrepancies by using propensity score matching methods,[12] but only few high-quality studies are available. Therefore, further studies adjusted for the year of surgery are required.

This meta-analysis showed that RAMPS decreased blood loss, which is consistent with the findings of previous meta-analyses.[7–9] RAMPS is a no-touch isolation approach to control major blood vessels such as the splenic, renal, and adrenal vessels by early separation of the pancreatic neck from the pancreas to the spleen.[41] This technique may reduce the volume of blood loss.

Deep dissection with complete lymphadenectomy may be more easily performed in RAMPS.[42] However, number of retrieved lymph nodes and R0 resection rates differed by region. It may be due to differences in clinical guidelines between Eastern and Western countries.[15–17,43]

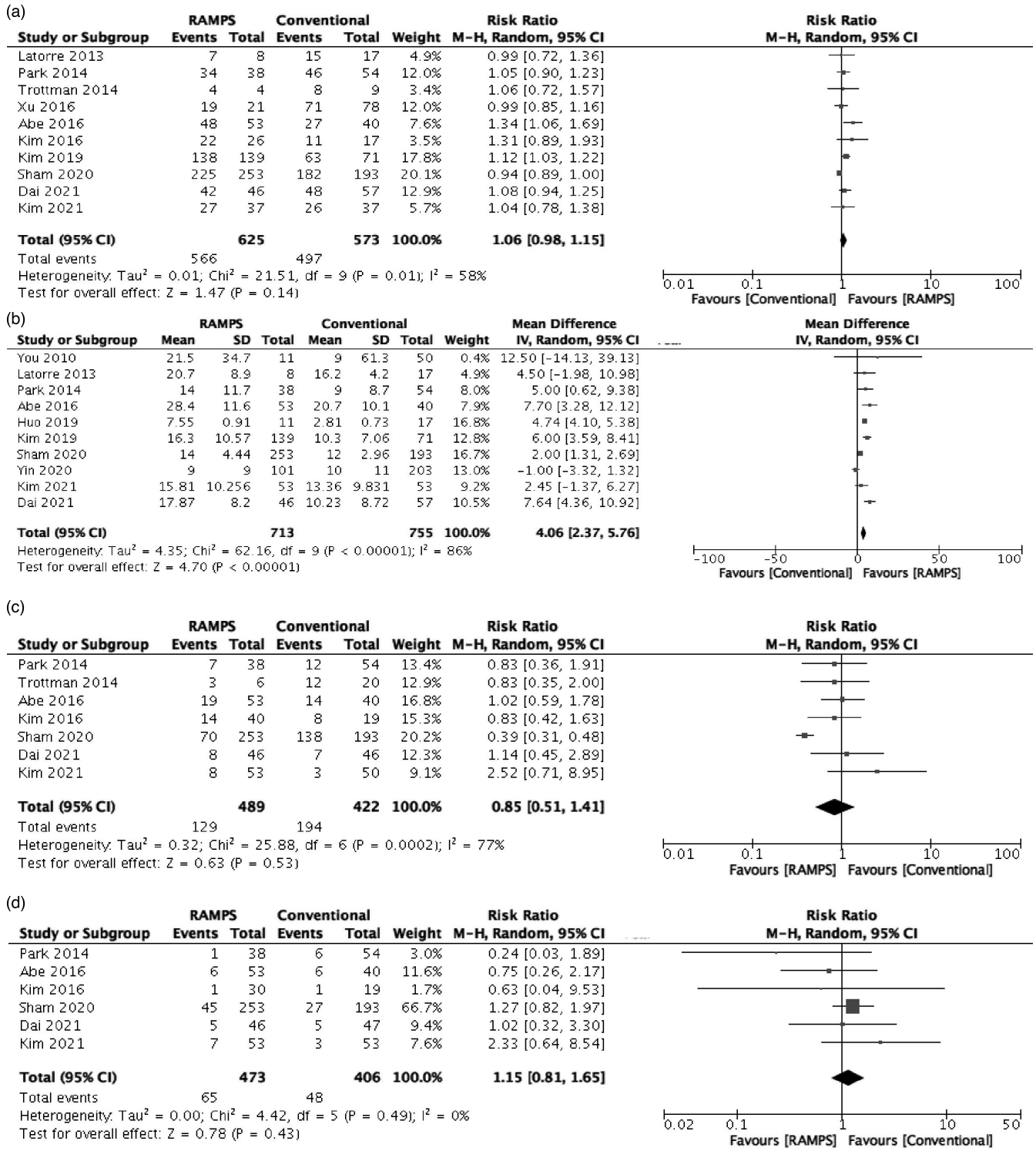
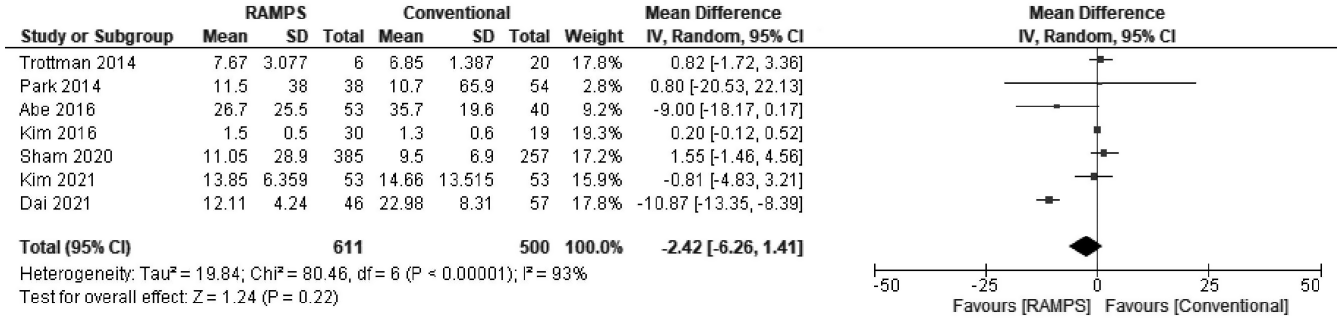


FIGURE 3 Forest plot of (A) R0 resection, (B) number of retrieved lymph nodes, (C) postoperative complications, (D) postoperative pancreatic fistula, (E) length of hospitalization, (F) blood loss, and (G) operative time

In the present review, the certainty of the evidence was low, mainly due to a lack of adjustment for confounding factors, such as pathological stage and systemic therapy. Adjuvant chemotherapy can significantly improve patient survival.[37–39] Information on the association between RAMPS and clinical outcomes after adjustment for confounding factors may help clarify the impact of RAMPS on clinical outcomes. Four ongoing RCTs (NCT03679169, NCT04253847, NCT04600063 and ChiCTR2000036489) were identified through a search of trial registries and the results of these RCTs are awaited.

(e)



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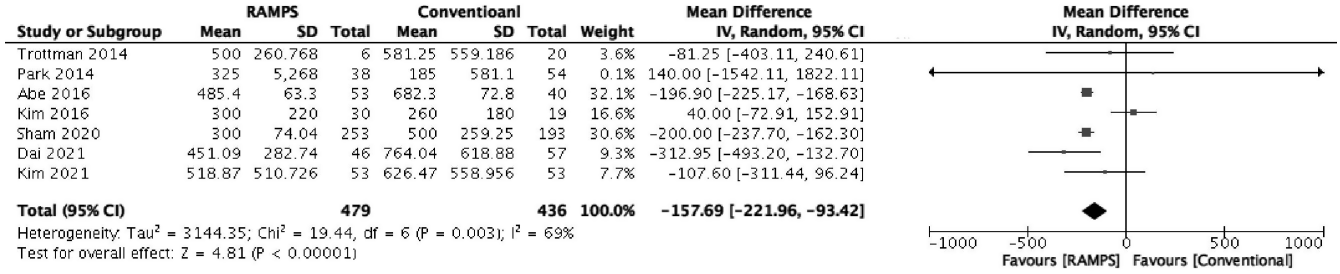

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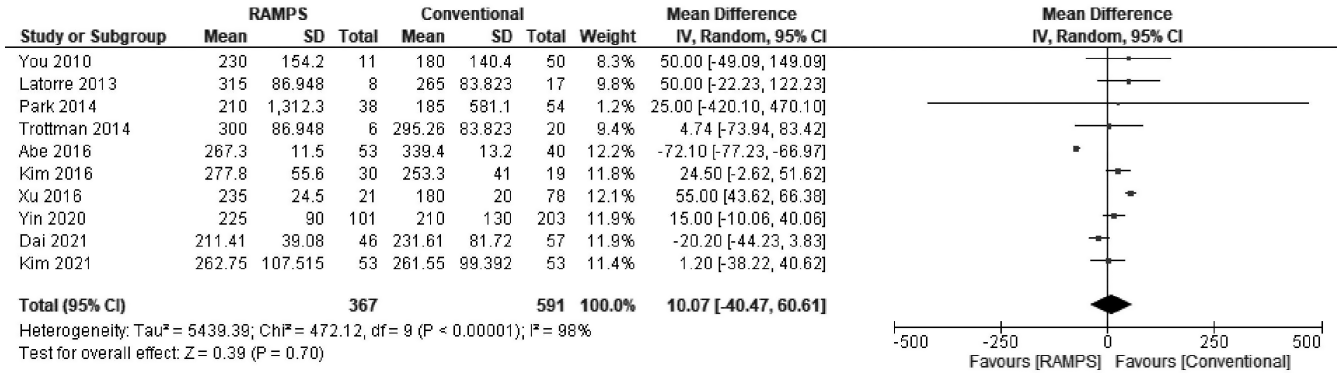

FIGURE 3 (Continued)

This review has several limitations. First, the certainty of the evidence was low because we included only non-RCTs. Second, postoperative adjuvant chemotherapy can significantly improve survival[40,41,43] and should be adjusted between the two groups. Future studies with adjustment for confounding factors are warranted to determine the impact of RAMPS on clinical outcomes.

5 | CONCLUSION

The present review provides updated evidence that suggests RAMPS has little effect on the prognosis of patients with left-sided pancreatic cancer. The technical approach to pancreatosplenectomy should be selected based on the surgeon's experience and comfort, with the understanding that long-term oncologic outcomes are influenced by disease biology and systemic therapy. Further studies, including RCTs, are needed to establish the efficacy of RAMPS.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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