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Review

A Systematic Review of Minimally Invasive *Versus* Open Radical Antegrade Modular Pancreatosplenectomy for Pancreatic Cancer

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Abstract. *Background/Aim: The aim of this study was to investigate surgical and oncological outcomes of minimally invasive (MI) and open radical antegrade modular pancreatosplenectomy (RAMPS) for the treatment of left-sided pancreatic cancer. Materials and Methods: A systematic literature search and meta-analyses were performed focusing on short-term surgical oncology of MI- and open-RAMPS. Results: A total of seven studies with 423 patients were included in this review. The equivalent short-term and long-term outcomes of the groups were confirmed. The results of meta-analyses found no significant difference in R0 resection rates (OR=1.78, 95%CI=0.76-4.15, p=0.18), although MI-RAMPS was associated with a smaller number of dissected lymph nodes (MD=–3.14, 95%CI=–4.75 - –1.53, p<0.001) and lymph node metastases (OR=0.55, 95%CI=0.31-0.97, p=0.04). Conclusion: MI-RAMPS could provide surgically and oncologically feasible outcomes for well-selected left-sided pancreatic cancer as compared to open-RAMPS. However, further high-level evidence should be needed to confirm survival benefits following MI-RAMPS.*

Radical antegrade modular pancreatosplenectomy (RAMPS) is a standardized technique for left-sided pancreatic cancer (1). The feasibility of applying RAMPS to patients with pancreatic cancer has been demonstrated (2-4). In contrast, the evidence of minimally invasive distal pancreatectomy for pancreatic cancer is still lacking despite recent rapid development of minimally invasive pancreas resection (5). This is because that there are several critical issues still under debate with respect to surgical and oncological feasibility of minimally invasive RAMPS (MI-RAMPS) over open RAMPS (open-RAMPS) (6). To date, surgical and oncological feasibility of MI-RAMPS compared to open-RAMPS have not yet been systemically examined in patients with pancreatic cancer.

The aim of this study was to investigate surgical and oncological outcomes of MI-RAMPS in comparison with those of open-RAMPS. Furthermore, meta-analysis was performed focusing on short-term surgical oncology of MI- and open-RAMPS for pancreatic cancer.

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Key Words: Distal pancreatectomy, laparoscopic, pancreatic cancer, radical antegrade modular pancreatosplenectomy, robotic, review.

Materials and Methods

Search methodology. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (7). A systematic search of Pubmed Central, Web of Science, and Cochrane CENTRAL was performed on August 7th, 2021, radical antegrade modular pancreatosplenectomy as a key word phrase.

Reports in the English language that compared outcomes of MI- and open-RAMPS for pancreatic cancer were included. Reports without abstracts, conference abstracts, and reviews were excluded.

Following the removal of duplicate records, all abstracts were screened independently by two investigators. Next, full-text manuscripts were assessed for eligibility. Extracted data were as follows: year and country of study publication, study design, surgical approach (MI- or open-RAMPS), operative outcomes (operative time and blood loss), pathological outcomes (tumor size, number of dissected lymph nodes and lymph node metastasis, and R0 resection rates), short-term outcomes [postoperative complications, postoperative pancreatic fistula (POPF), and postoperative length of stays], and long-term outcomes (survival and recurrence).

Investigators evaluated the methodologic quality of the studies included in the meta-analysis according to the Newcastle-Ottawa quality assessment scale for cohort studies (8). Studies with a total score of ≤5, 6-7, and ≥8 were considered to be of low quality, moderate quality, and high quality, respectively (9).

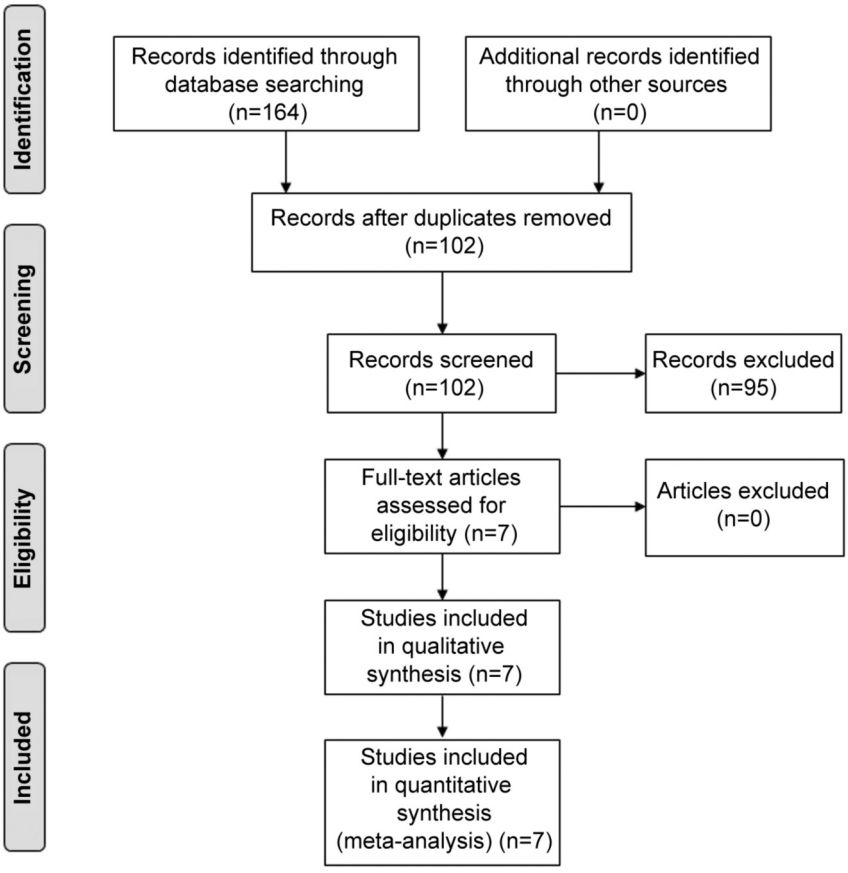

Figure 1. *PRISMA 2009 flow diagram*.

Statistical analysis. Outcomes were demonstrated as they were presented in original articles in accordance with the defined variables. A meta-analysis was conducted with the use of Review Manager, version 5.3 (the Cochrane Collaboration, 2014). The pooled odds ratio (OR) with corresponding 95% confidence interval (95%CI) for dichotomous variables was calculated with the Mantel-Haenszel method. The mean difference (MD) for continuous variables was calculated with the inverse variance method. Heterogeneity among studies was analyzed by calculating the I^2 values and the Chi-square test. A fixed-effects model was used, however, a random-effects model was used in cases with I^2 values of 40% or more. Potential publication bias for outcomes was evaluated with visual inspection of the Funnel plots.

Results

Study characteristics. The PRISMA flow chart in this study is demonstrated in Figure 1. Following removal of duplicate articles and screening full-text articles for eligibility, a total of seven studies (10-16) matched the inclusion criteria. Overall, seven studies with 423 patients were included in the meta-analysis.

A summary of the included studies is demonstrated in Table I. All included studies were single-center retrospective series from Korea (n=1), China (n=3), Japan (n=2), and Italy (n=1). Out of 423 patients, there were 145 undergoing MI-RAMPS and 278 with open-RAMPS. With regards to indication of MI-RAMPS for pancreatic cancer, the Yonsei criteria were commonly introduced for selecting patients (10, 12). In general, tumors involving major vessels, such as the portal vein and celiac trunk, should be excluded from the indication for MI-RAMPS. However, Rosso *et al*. (13) reported the feasibility of MI-RAMPS with vascular resection. The methodologic quality of the studies included was evaluated to be of low quality for three studies (13, 15, 16), and moderate quality for four studies (10-12, 14).

Operative and pathological outcomes in the included studies are summarized in Table II. The average operative time was approximately 324 minutes for MI-RAMPS, and 293 minutes for open-RAMPS. The estimated blood loss was approximately 271 ml for MI-RAMPS and 447 ml for open-RAMPS. Out of all pathological outcomes, all of the included studies reported R0 resection rates of 95.2% for the MI-RAMPS group and 88.8% for the open-RAMPS group.

The results of postoperative short- and long-term outcomes between the MI- and open-RAMPS groups are depicted in Table III. The MI-RAMPS group had an overall

Table I. *Published studies reporting on outcomes of minimally invasive versus open radical antegrade modular pancreatosplenectomy for pancreatic cancer.*

Study (Year)	Country	Study design	No. of patients	Details of MIS	Indication of MIS for pancreatic cancer	Quality†
Lee *et al*. (2014) (10)	Korea	Retrospective, single center	MIS (n=12) Open (n=78)	Laparoscopic or robotic	Yonsei criteria: 1) Tumor confirmed to the pancreas 2) Intact fascia layer between the distal pancreas and the left adrenal gland and kidney 3) Tumor located at least 1-2 cm away from the celiac axis	7
Zhang *et al*. (2017) (11)	China	Retrospective, single center	MIS (n=22) Open (n=76)	Laparoscopic	N.A.	6
Kawabata *et al*. (2020) (12)	Japan	Retrospective, single center	MIS (n=30) Open (n=33)	Laparoscopic	Yonsei criteria	7
Rosso *et al*. (2020) (13)	Italy	Retrospective, single center	MIS (n=17) Open (n=6)	Laparoscopic	Critical points for vascular resection: 1) the length of venous involvement 2) the presence of splenic artery and celiac trunk involvement 3) the need to preserve the pancreatic-duodenal veins Exclusion criteria: 1) simultaneous venous and arterial invasion 2) portal vein stricture with portal hypertension	5
Zhang *et al*. (2020) (14)	China	Retrospective, single center	MIS (n=25) Open (n=23)	Laparoscopic	N.A.	6
Huang *et al*. (2021) (15)	China	Retrospective, single center	MIS (n=20) Open (n=31)	Laparoscopic	N.A.	5
Hirashita *et al*. (2021) (16)	Japan	Retrospective, single center	MIS (n=19) Open (n=31)	Laparoscopic	Exclusion criteria: Major vessel invasions, including the portal vein, superior mesenteric artery, and celiac artery.	5

†A total score of 9 evaluated by the Newcastle–Ottawa quality assessment scale for cohort studies (8). MIS: Minimally invasive surgery; N.A.: not available.

complication rate of 24%, and a POPF rate (grade B/C) of 14%. The rates of overall complications and POPF were 32% and 13.3%, respectively, in the open-RAMPS group. No mortality following MI-RAMPS was reported.

Regarding long-term outcomes following MI- and open-RAMPS, only one study [Lee *et al*. (10)] reported a 5-year overall survival showing a significantly longer survival in MI-RAMPS compared to open-RAMPS (55.6% *versus* 30.0%, p=0.02). However, other studies demonstrated no significant differences in overall survival as well as recurrence-free survival between the groups. Zhang *et al*. (11) showed a mean overall survival of 29.6 months for the MI-RAMPS group and 27.6 months for the open-RAMPS group (p=0.34). A study by Kawabata *et al*. (12) found no significant differences in overall (p=0.82) and recurrence-free (p=0.31) survival between the groups. Another study [Zhang *et al*. (14)] presented a median overall and disease-free survival of 24.5 and 18.1 months, respectively, for MI-RAMPS, with no significant differences compared to open-RAMPS. In a study by Huang *et al*. (15), the survival rates at 1 year and 2 years were not statistically different between the MI- and open-RAMPS groups (67.0% *versus* 78.0% and 50.2% *versus* 39.3%; p=0.41). Hirashita *et al*. (16) showed no significant differences in overall (p=0.40) and recurrence-free (p=0.08) survival between the groups.

Meta-analysis of MI- versus open-RAMPS.

Operative outcomes. Meta-analyses including five studies demonstrated significantly longer operative time (MD=30.0, 95%CI=7.58-52.4, p=0.009, I^2=44%, n=337), but less estimated blood loss (MD=–163, 95%CI=–293-–33.4, p=0.01, I^2=77%, n=337) with MI-RAMPS compared to open-RAMPS (Figure 2A and B).

Pathological outcomes. Meta-analyses found significant associations between MI- and open-RAMPS in terms of tumor size (MD=–0.62, 95%CI=–1.01 - –0.23, p=0.002, I^2=0%, n=337), number of dissected lymph nodes (MD=–3.14, 95%CI=–4.75 - –1.53, p<0.001, I^2=0%, n=337), and lymph node metastasis (OR=0.55, 95%CI=0.31-0.97, p=0.04, I^2=0%, n=312) (Figure 2C, D and E). In contrast, no significant difference was found in the R0 resection rates between the groups (OR=1.78, 95%CI=0.76-4.15, p=0.18, I^2=0%, n=423), as shown in Figure 2F. The results were homogeneous for pathological outcomes.

Table II. *Operative and pathological outcomes of minimally invasive versus open radical antegrade modular pancreatosplenectomy for pancreatic cancer.*

Study	Procedure	Operative time (min)	Blood loss (ml)	Tumor size (cm)	Dissected LN	LN metastasis (%)	R0 resection (%)
Lee *et al*. (10)	MIS (n=12)	324.3 (154.2)	445.8 (346.1)	2.8 (1.3)	10.5 (7.1)	3 (25)	12 (100)
	Open (n=78)	270.1 (140.4)	669.5 (776.1)	3.5 (1.9)	13.8 (11.1)	37 (47.4)	67 (85.9)
Zhang *et al*. (11)	MIS (n=22)	188 (39)	210 (130)	3.6 (1.3)	11.2 (4.6)	8 (36)	20 (91)
	Open (n=76)	160 (35)	240 (120)	4.4 (1.4)	14.4 (5.5)	31 (41)	66 (87)
Kawabata *et al*. (12)	MIS (n=30)	389 (280-576)	18 (0-180)	2.3 (0.4-8.3)	18 (5-51)	N.A.	29 (96.7)
	Open (n=33)	382 (256-674)	215 (30-1,030)	2.0 (0.4-4.1)	25 (7-80)		30 (90.9)
Rosso *et al*. (13)	MIS (n=17)	395-412	N.A.	N.A.	30-35	15 (88)	17 (100)
	Open (n=6)	450			37	6 (100)	6 (100)
Zhang *et al*. (14)	MIS (n=25)	212.2 (66.3)	402 (258.8)	3.7 (1.7)	15.8 (6.7)	N.A.	23 (92)
	Open (n=23)	203.1 (39.7)	506.5 (418.4)	4.4 (2.0)	18.2 (8.0)		21 (91)
Huang *et al*. (15)	MIS (n=20)	273.8 (90.3)	252.5 (198.3)	4.2 (1.9)	9.6 (6.4)	6 (30)	20 (100)
	Open (n=31)	264.3 (77.1)	472.6 (428)	4.2 (1.6)	12.8 (5.8)	12 (39)	30 (97)
Hirashita *et al*. (16)	MIS (n=19)	397 (78)	299 (237)	2.8 (2.3)	14 (17)	5 (26)	17 (89)
	Open (n=31)	319 (80)	576 (78)	3.4 (1.8)	19 (18)	16 (52)	27 (97)

Values are indicated as mean (standard deviation), or median (range). LN: Lymph node; MIS: minimally invasive surgery; N.A.: not available.

Table III. *Postoperative short- and long-term outcomes of minimally invasive versus open radical antegrade modular pancreatosplenectomy for pancreatic cancer.*

Study	Procedure	Complication (%)	POPF (%)	Mortality (%)	LOS (days)	Survival (MIS *vs*. open)
Lee *et al*. (10)	MIS (n=12)	Overall: 3 (25)	Grade B/C: 0 (0)	0 (0)	12.3 (6.8)	5-year OS (%):
	Open (n=78)	29 (37.2)	8 (10.3)	2 (2.6)	22.4 (21.6)	55.6 *vs*. 30.0 (p=0.024)
Zhang *et al*. (11)	MIS (n=22)	N.A.	Grade B/C: 2 (9.1)	0 (0)	N.A.	Mean OS (months):
	Open (n=76)		7 (9.2)	0 (0)		29.6 (3.7) *vs*.
						27.6 (2.1) (p=0.34)
Kawabata *et al*. (12)	MIS (n=30)	Overall: 4 (13.3)	Grade B/C: 1 (3.3)	0 (0)	14 (8-67)	2-year OS (%):
	Open (n=33)	6 (18.2)	2 (6.1)	0 (0)	16 (8-96)	90.9 *vs*. 78.9 (p=0.82)
						2-year RFS (%):
						92.9 *vs*. 62.5 (p=0.31)
Rosso *et al*. (13)	MIS (n=17)	Overall: 9 (52.9)	Overall: 3 (17.6)	0 (0)	N.A.	N.A.
	Open (n=6)	3 (50)	2 (14.7)	0 (0)		
Zhang *et al*. (14)	MIS (n=25)	Overall: 4 (16)	Overall: 2 (8)	0 (0)	11.7 (5.2)	Median OS (months):
	Open (n=23)	3 (13)	0 (0)	0 (0)	12.9 (5.0)	24.5 *vs*. 28.7 (p=0.63)
						Median DFS:
						18.1 *vs*. 20.0 (p=0.99)
Huang *et al*. (15)	MIS (n=20)	Overall: 5 (25)	Grade B/C: 9 (45)	0 (0)	19 (9.9)	2-year OS (%):
	Open (n=31)	13 (41.9)	10 (32.3)	0 (0)	19.6 (16.8)	50.2 *vs*. 38.3 (p=0.41)
Hirashita *et al*. (16)	MIS (n=19)	N.A.	Grade B/C: 2 (11)	0 (0)	21.5 (10.5)	OS: N.S. (p=0.40)
	Open (n=31)		6 (19)	0 (0)	29.4 (23.3)	RFS: N.S. (p=0.08)

Values are indicated as mean (standard deviation), or median (range). POPF: Postoperative pancreatic fistula; LOS: length of stay; MIS: minimally invasive surgery; OS: overall survival; RFS: relapse/recurrence-free survival; DFS: disease-free survival; N.A.: not available; N.S.: not statistically different.

Short-term outcomes. Meta-analyses indicated no significant differences in MI- and open-RAMPS regarding the overall complication rate (OR=0.69, 95%CI=0.36-1.30, p=0.25, I^2=0%, n=275; Figure 3A), POPF (grade B and C) (OR=0.91, 95%CI=0.44-1.88, p=0.79, I^2=0%, n=352; Figure 3B), and the postoperative length of hospital stay (MD=–1.94, 95%CI=–4.48-0.59, p=0.13, I^2=11%, n=239; Figure 3C). No significant heterogeneity was found across the studies included.

Publication bias. Funnel plots demonstrated no obvious asymmetry regarding the number of dissected lymph nodes and lymph node metastases, and R0 resection, as shown in Figure 4.

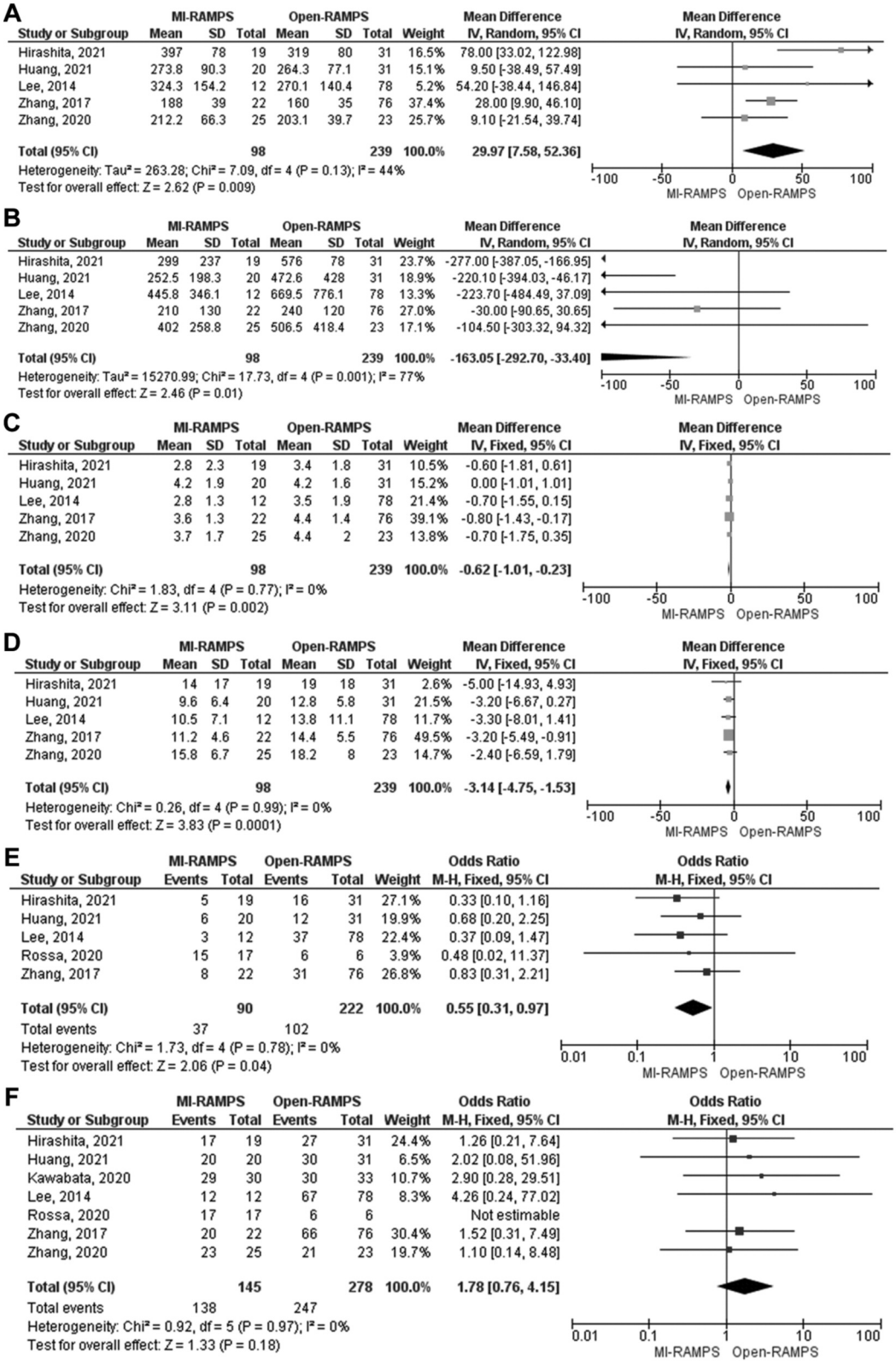

Figure 2. *The results of the meta-analysis demonstrating operative and pathological outcomes in terms of minimally invasive- versus open-radical antegrade modular pancreatosplenectomy. (A) Operative time; (B) blood loss; (C) tumor size; (D) number of dissected lymph nodes; (E) number of lymph node metastases; and (F) R0 resection.*

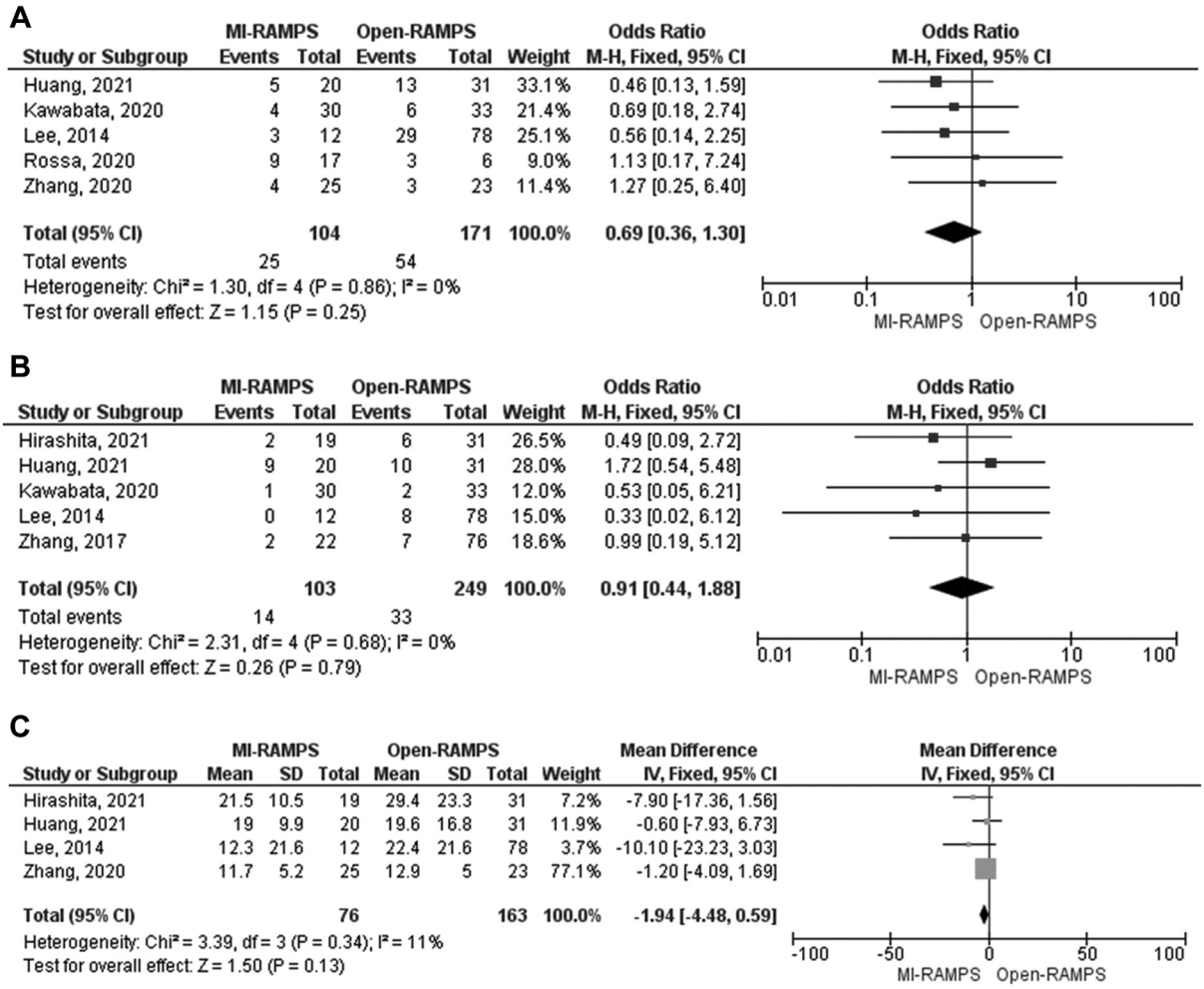

Figure 3. *The results of the meta-analysis demonstrating short-term outcomes in terms of minimally invasive- versus open-radical antegrade modular pancreatosplenectomy. (A) Overall complications; (B) postoperative pancreatic fistula; and (C) postoperative length of hospital stay.*

Discussion

The present study summarized the current evidence on MI- and open-RAMPS in patients with pancreatic cancer. To the best of our knowledge, this is the first study to investigate surgical and oncological outcomes following MI-RAMPS in comparison with those following open-RAMPS. The results of meta-analyses found favorable surgical and oncological outcomes following MI-RAMPS for well-selected left-sided pancreatic cancer.

RAMPS enables early vascular control, improved visualization of the proper posterior dissection line, and higher lymph node dissection and negative tangential margin rates (17). Furthermore, meta-analyses have shown that RAMPS is associated with higher R0 resection rates and a greater number of dissected lymph nodes as compared to the standard distal pancreatectomy (2-4). However, high-level evidence to support a survival benefit following RAMPS is still lacking. With respect to MI-RAMPS, a recent systematic review, including eight studies with 92 cases, demonstrated technical feasibility and oncologically acceptable outcomes for the treatment of pancreatic cancer (6). To date, however, there are no published meta-analyses that compare surgical and oncological outcomes of MI- and open-RAMPS.

The results of this meta-analysis indicated that the MI-RAMPS group had a significantly smaller number of dissected lymph nodes and lymph node metastases. However, no statistically significant difference was found in terms of R0 resection rates. In addition, comparable postoperative short-term outcomes were confirmed between the groups. Regarding long-term outcomes following MI- and open-RAMPS, equivalent overall and recurrence-free survival have been reported. Among several oncological factors, R0 resection rate is known as an important factor that should be achieved to improve survival following surgery for pancreatic cancer (18, 19). It is also

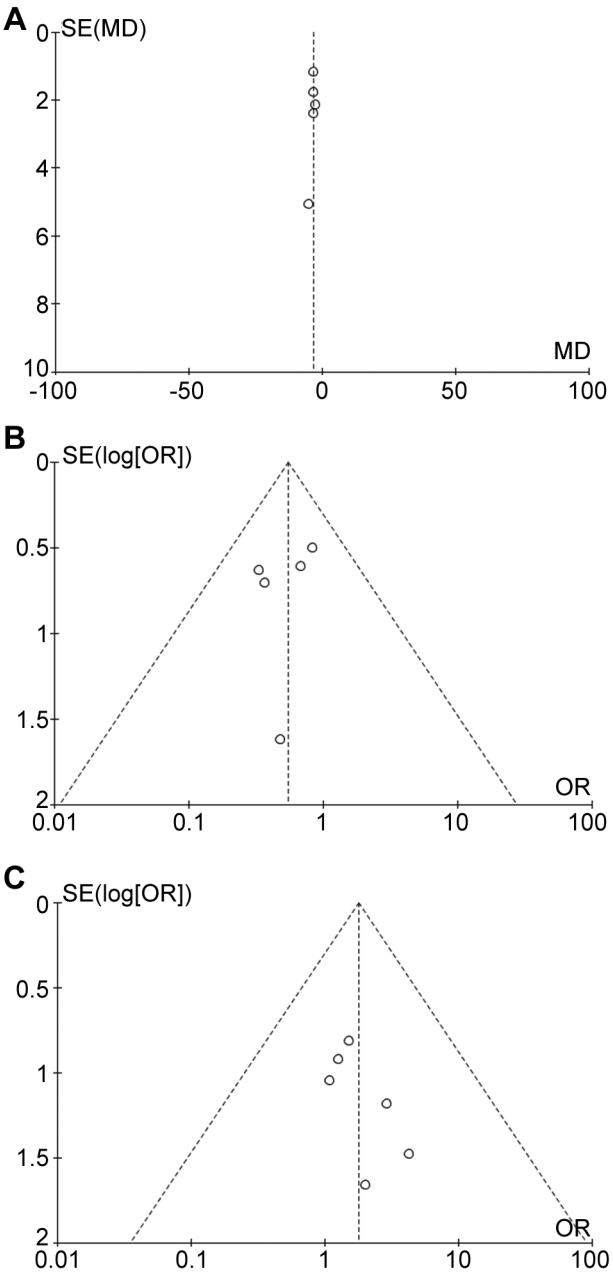

Figure 4. *Funnel plots demonstrating pathological outcomes in terms of minimally invasive- versus open-radical antegrade modular pancreatosplenectomy. (A) number of dissected lymph nodes; (B) number of lymph node metastases; and (C) R0 resection.*

important to understand the risk factors for postoperative long-term outcomes after curative resection in determining the indication of MI- and open-RAMPS (20, 21).

Several limitations are associated with the present study. Firstly, all the included studies were retrospective series with relatively small sample sizes. The number of included studies in the meta-analysis was also small. The results could be affected by a publication bias. Secondly, meta-analyses were performed focusing on short-term surgical oncology outcomes in pancreatic cancer, but not for long-term outcomes due to limited data. Therefore, further studies should be conducted to investigate survival benefits following MI- and open-RAMPS for pancreatic cancer. Thirdly, various surgical techniques for MI-RAMPS were reported (6). Moreover, evidence on robotic RAMPS for pancreatic cancer is still lacking. Robotic surgery with improved three-dimensional visualization and flexible manipulation should overcome technical difficulties of the medial approach in laparoscopic RAMPS (22, 23).

Conclusion

The present study suggests that MI-RAMPS could provide surgically and oncologically feasible outcomes for well-selected left-sided pancreatic cancer as compared to open-RAMPS. Further investigations are needed to confirm survival benefits following MI-RAMPS. Last but not least, well-designed studies with larger sample sizes should be performed to prove the significance of MI-RAMPS.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

K.T. contributed to the study conception and design, the acquisition of data, the development of the protocol, and the drafting of the manuscript. Y.U. and R.Y. contributed to the analysis and interpretation of the results and the revision of the final draft. T.Y. and T.F. contributed to the development of the protocol and the critical revision of the final draft. All Authors have approved the final version.

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