

Original Article

The efficacy of spleen-preserving distal pancreatectomy with or without splenic vessel preservation: a meta-analysis

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Abstract: Background: Spleen-preserving distal pancreatectomy can be performed with splenic vessel preservation (SPDP-SVP) or splenic vessel resection (SPDP-SVR). This meta-analysis aimed to evaluate the clinical outcomes of patients undergoing SPDP-SVP or SPDP-SVR. Method: A systematic literature search of PubMed, Embase, and the Cochrane Library was performed. The operative time, estimated blood loss, postoperative complications, pancreatic fistula (Grade B+C) rates, splenic infarction rates, gastric/perigastric varices rates and postoperative hospital stay were evaluated. RevMan 5.3 software was used to evaluate the differences between groups. Results: Nine studies involving 639 patients were included in this meta-analysis, of whom 402 underwent SPDP-SVP and 237 underwent SPDP-SVR. Patients who underwent SPDP-SVP had lower splenic infarction and gastric/perigastric varices rates. The operative time, estimated blood loss, postoperative complications, pancreatic fistula (Grade B+C) rates and postoperative hospital stays were comparable between these two groups. Conclusions: SPDP-SVP and SPDP-SVR are both safe, feasible procedures for the management of benign or low-grade malignant pancreatic body or tail tumors. However, SPDP-SVR is related to higher incidence rates of early splenic ischemia and gastric/perigastric varices.

Keywords: Distal pancreatectomy, spleen-preserving, splenic vessel, meta-analysis

Introduction

Distal pancreatectomy is indicated for benign or low-grade malignant lesions located in the body or tail of the pancreas. This approach can be accomplished with or without splenectomy [1]. Considering the close relationship of the splenic vessels to the pancreas and the risk for oncologic radicality as a consequence of preserving splenic artery during the surgery, distal pancreatic resection routinely involves splenectomy [2]. However, with the benefits of a lower risk of developing postoperative infection, intra-abdominal abscesses, lethal post-splenectomy sepsis, and malignancies after splenectomy, the popularity of spleen-preserving distal pancreatectomy has grown over recent years [3-6].

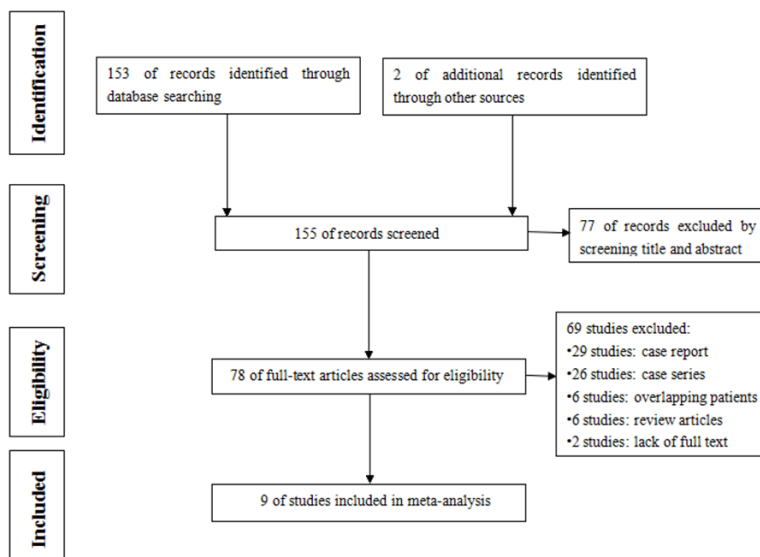
Salvaging the spleen during distal pancreatectomy can be achieved by conserving the splenic

artery and vein via careful ligation and excision of the small branches (SPDP-SVP) [7]. Warshaw et al. [8] introduced another method in which the splenic artery and vein are resected, leaving the short gastric and left gastroepiploic vessels to depend on the spleen for their blood supply (SPVP-SVR).

Generally, spleen-preserving distal pancreatectomy (SPDP) is the best choice to preserve the splenic vessels. However, SPDP-SVP is more challenging when applied to the meticulous separation between the pancreas and multiple small branches to the distal pancreas. A previous study dissecting the distal pancreas of ten cadavers demonstrated a mean of 7.6 branches of the splenic artery, as well as 22.1 tributaries of the splenic vein [9]. Moreover, Yoon et al. [10] have reported a risk of left-sided portal hypertension when the patency of the preserved splenic vein is not well maintained. The

Table 1. Newcastle-Ottawa Scale (NOS) assessment of the quality of the studies

References	Selection				Comparability	Outcome			Score
	1	2	3	4	5	6	7	8	
Matsushima [14]	*	*	*	*	*	*	*		7
Zhou [15]	*	*	*	*		*	*		6
Worhunsky [16]	*	*	*	*	**	*	*	*	9
Lv [17]	*	*	*	*	**	*	*	*	9
Adam [18]	*	*	*	*	**	*	*	*	9
Hwang [19]	*	*	*	*	**	*	*	*	9
Butturini [20]	*	*	*	*		*	*		6
Beane [21]	*	*	*	*	*	*	*	*	8
Baldwin [22]	*	*	*	*		*	*		6

**Figure 1.** Flow diagram of data extraction.

method involving the resection of the splenic vessels (SPDP-SVR) is easier and more feasible, especially for the patients with an unusually large tumor or an oppression of the splenic artery or vein by pancreatic lesions. However, this approach is related to a developing risk of morbidity, such as splenic infarction and gastric/perigastric varices [11, 12].

Until now, no randomized controlled trials on this topic have been reported, and the superiority of one approach over another is still untested. The aim of this meta-analysis was to provide better evidence supporting this problem.

Materials and methods

The Pubmed, Embase, and Cochrane Library electronic databases were searched for all

studies published as full papers that compared SPDP-SVP and SPDP-SVR up to March, 2015 using the following key words: distal pancreatectomy, spleen, vessel, preservation/conservation and Kimura technique. The publication language was limited to English, and relevant articles were also manually searched to identify other relevant studies.

Inclusion and exclusion criteria

The inclusion criteria were determined as follows: (1) studies comparing SPDP-SVP and SPDP-SVR for any indications; (2) SPDP-SVP or SPDP-SVR that was performed, regardless of the approach (open, laparoscopic or robotic-assisted); and (3) any type of comparative study.

The exclusion criteria used were as follows: (1) studies in which no interested indexes were provided or the indexes were impossible to calculate from the texts; (2) overlapping data; and (3) studies for which we could not obtain full texts.

Study quality

We used the Newcastle-Ottawa Quality Assessment Scale (NOS) for patient selection, comparability of patient groups and outcome assessments to determine the quality of each identified study [13]. All of the studies were graded as either level 1 (0 to 5) or level 2 (6 to 9) and NOS scores are presented in **Table 1**.

Data extraction

Two authors (Yu Tang, Sanhong Tang) independently extracted and appraised the data critically. The operative outcomes (operative time, estimated blood loss) and post-operative outcomes (postoperative complications, pancreatic fistula (Grade B+C) rates, splenic infarction rates, gastric/perigastric

SPDP-SVP versus SPDP-SVR

Table 2. Baseline characteristics of included studies

References	Study design	Approach	Number (N)	Age (y)	Sex (M/F)	BMI	ASA score	Lesion size (cm)	Operations (N)
Matsushima, 2014, Japan [13]	Retrospective	SPDP-SVP	7	70 (50-86)*	4/3	22.8 (17.2-25.5)*	NA	1.5 (1-4)*	Lap
		SPDP-SVR	17	49 (30-83)*	3/14	22.3 (18.2-35.8)*	NA	5 (1.3-12)*	Lap
Zhou, 2014, South Korea [14]	Retrospective	SPDP-SVP	206	49.9 ± 13.7	63/143	23.3 ± 3.2	NA	2.8 ± 1.5	Lap
		SPDP-SVR	40	46.6 ± 12.4	5/35	23.1 ± 2.5	NA	4.5 ± 2.6	Lap
Worhunsky, 2014, USA [15]	Retrospective	SPDP-SVP	19	56 ± 11	9/10	27.9 ± 3.9	2.4 ± 0.5	16 (5-105)*, #	Lap
		SPDP-SVR	31	54 ± 15	7/24	26.7 ± 3.8	2.3 ± 0.5	20 (5-100)*, #	Lap
Lv, 2013, China [16]	Retrospective	SPDP-SVP	12	37.5 ± 19.5	2/10	21.9 ± 4.4	NA	18.8 ± 27.5	Lap
		SPDP-SVR	8	42.8 ± 16.2	3/5	22.3 ± 2.3	NA	16.9 ± 22	Lap
Adam, 2013, France [17]	Retrospective	SPDP-SVP	55	52.9 ± 12.2	11/44	25.1 ± 4.6	2.1 ± 0.7	3.36 ± 1.97	Lap
		SPDP-SVR	85	56.9 ± 13.1	10/75	24.9 ± 5.1	1.9 ± 0.7	4.25 ± 2.99	Lap
Hwang, 2012, South Korea [18]	Retrospective	SPDP-SVP	17	43.7 ± 15.1	7/10	23.4 ± 3.2	NA	3.0 ± 1.2	Rob
		SPDP-SVR	4	36.8 ± 10.1	0/4	21.8 ± 2.8	NA	3.7 ± 2.1	Rob
Butturini, 2012, Italy [19]	Retrospective	SPDP-SVP	36	47.05 ± 17.51	7/29	NA	NA	25 (5-80)*, #	Lap
		SPDP-SVR	7	44.27 ± 17.23	1/6	NA	NA	25 (10-50)*, #	Lap
Beane, 2011, USA [20]	Retrospective	SPDP-SVP	45	53.4	10/35	NA	2.66	NA	3 Open, 21 Lap, 11 Rob
		SPDP-SVR	41	56.7	19/22	NA	2.78	NA	5 Open, 33 Lap, 3 Rob
Baldwin, 2011, USA [21]	Retrospective	SPDP-SVP	5	80 ± 7	NA	NA	NA	NA	Lap
		SPDP-SVR	4	82 ± 8	NA	NA	NA	NA	Lap

N = number; y = year; M = male; F = female; BMI = body mass index; ASA = American Society of Anesthesiologists score; *Lesion size measured by cm³; #data in the form of median (range).

SPDP-SVP versus SPDP-SVR

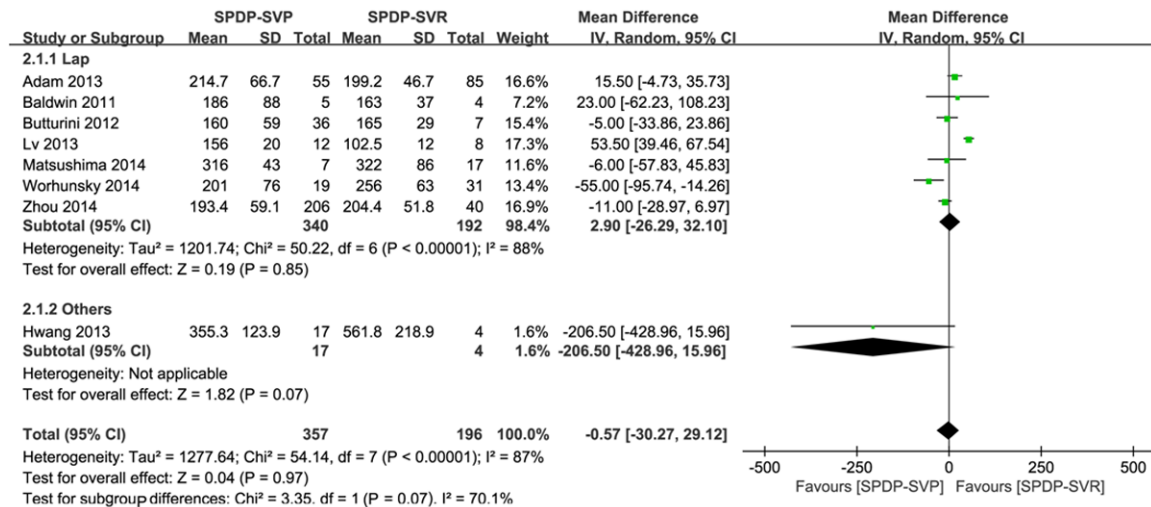


Figure 2. Forest plot of operative time. (Random-effect model).

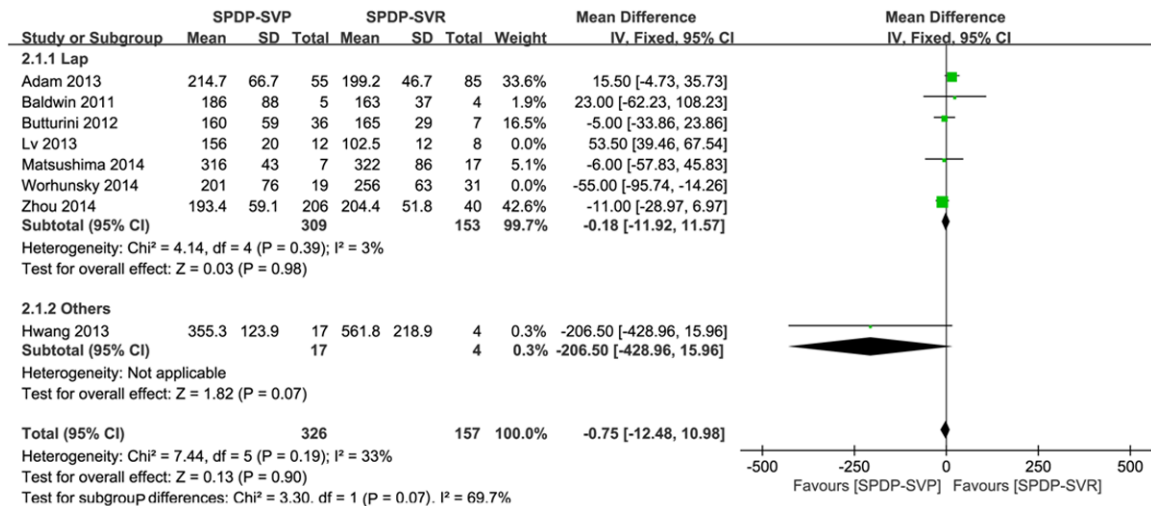


Figure 3. Forest plot of operative time, sensitivity analysis. (Fixed-effect model).

varices rates and postoperative hospital stay) were extracted to assess the clinical outcomes of these two procedures. In cases of any controversy, the disagreements were resolved by the senior author (Sanyuan Hu). We contacted the corresponding authors for missing data, but no more information was provided.

Statistical analysis

Review Manager (RevMan version 5.3) was used for statistical analysis. The weighted mean difference (WMD) for continuous outcomes and odds ratios (OR) for dichotomous outcomes with 95% confidence intervals (CI) is given. A P value < 0.05 was considered statisti-

cally significant when the differences in the outcomes were measured. Heterogeneity was detected by the Cochrane Q statistic along with the I^2 test, stipulating that $P < 0.10$ marked significant heterogeneity. Generally, a fixed-effect model was applied while a random-effect mode was used for comparison with statistically significant heterogeneity. Stata 12.0 software and the Begg's test were also used to evaluate publication bias based on postoperative complications.

Results

A total of 155 records were initially identified. Ultimately, nine retrospective, high-quality studies were included in the meta-analysis,

SPDP-SVP versus SPDP-SVR

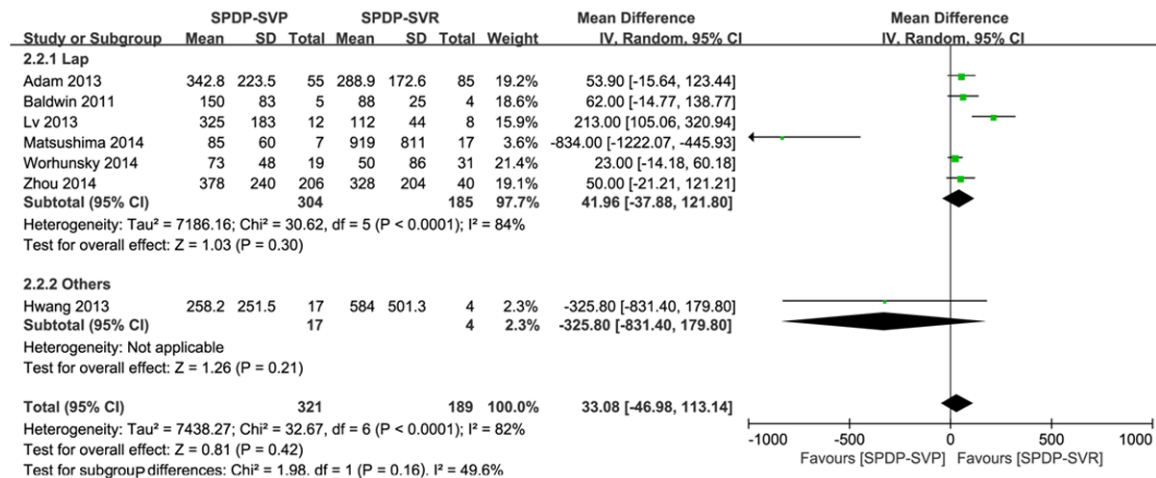


Figure 4. Forest plot of estimated blood loss. (Random-effect model).

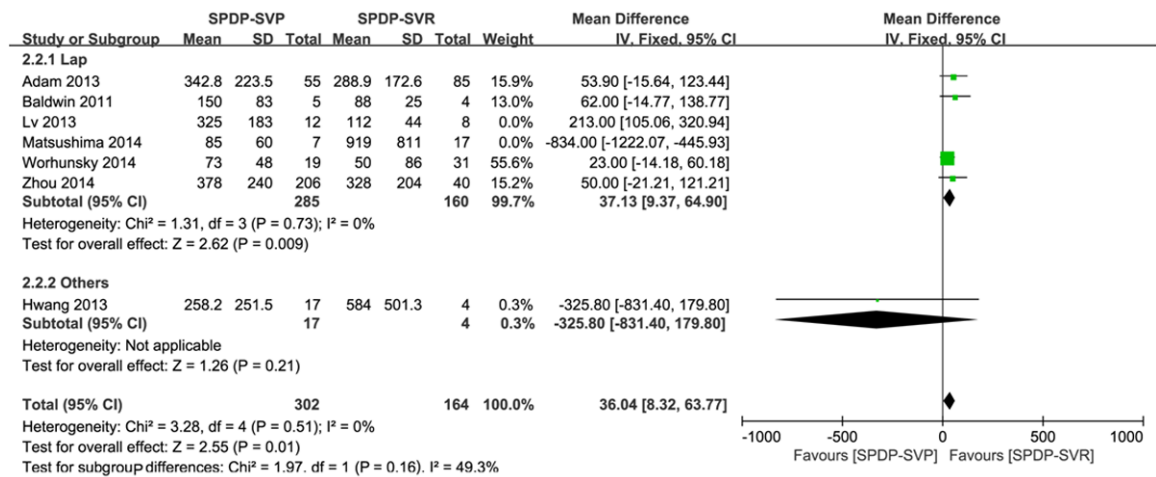


Figure 5. Forest plot of estimated blood loss, sensitivity analysis. (Fixed-effect model).

encompassing 639 patients: 402 in the SPDP-SVP group and 237 in the SPDP-SVR group (Figure 1). The characteristics of the included studies are presented in Table 2. All of the studies were retrospective studies that compared SPDP-SVP with SPDP-SVR through either consecutive or matched cases. Seven studies used a laparoscopic approach, where one approach each of robotic-assisted and mixed was included. Three studies were conducted in the USA, two in South Korea, one in China, one in Japan, one in France, and one in Italy.

Operative outcomes

Eight studies reported operative times and no significant difference was found when the ran-

dom-effect model was applied ($Z = 0.04$, $P = 0.97$; Figure 2) for there was a significant heterogeneity between these studies ($I^2 = 87\%$, P heterogeneity < 0.00001; Figure 2). Subgroup analysis of the laparoscopic approach revealed a similar result ($Z = 0.19$, $P = 0.85$; Figure 2), while heterogeneity was also significant ($I^2 = 88\%$, P heterogeneity < 0.00001; Figure 2). The studies by Worhunsky et al. [15] and LV et al. [16] could be responsible for the heterogeneity. When these two studies were excluded, the heterogeneity of total analysis and subgroup analysis of the laparoscopic approach both decreased ($I^2 = 33\%$, P heterogeneity = 0.19 and $I^2 = 3\%$, P heterogeneity = 0.39; Figure 3). No significant difference was found in

SPDP-SVP versus SPDP-SVR

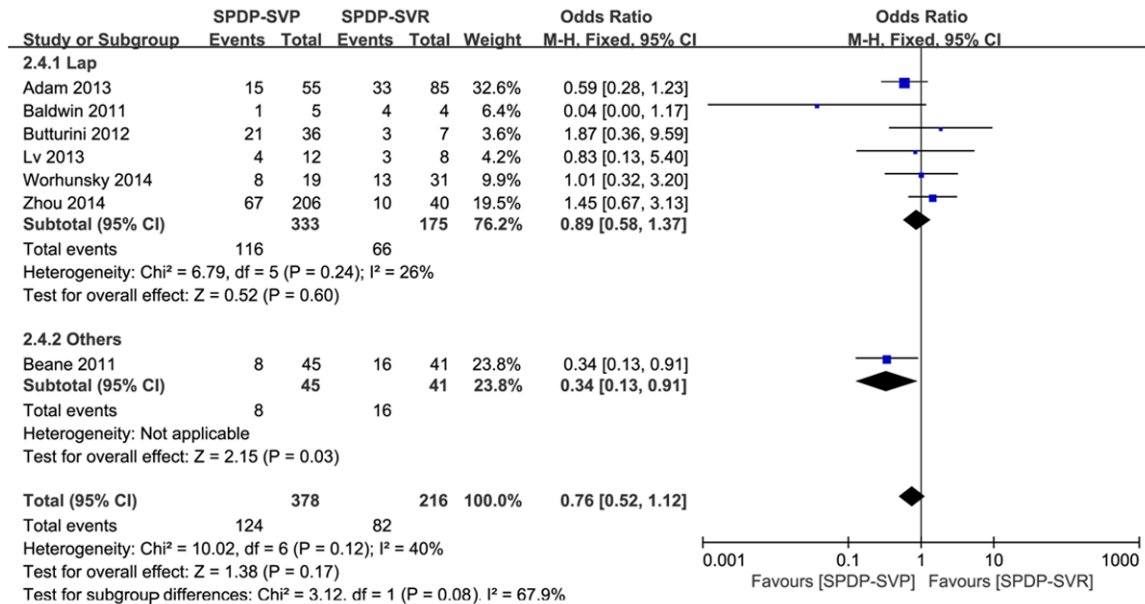


Figure 6. Forest plot f postoperative complications. (Fixed-effect model).

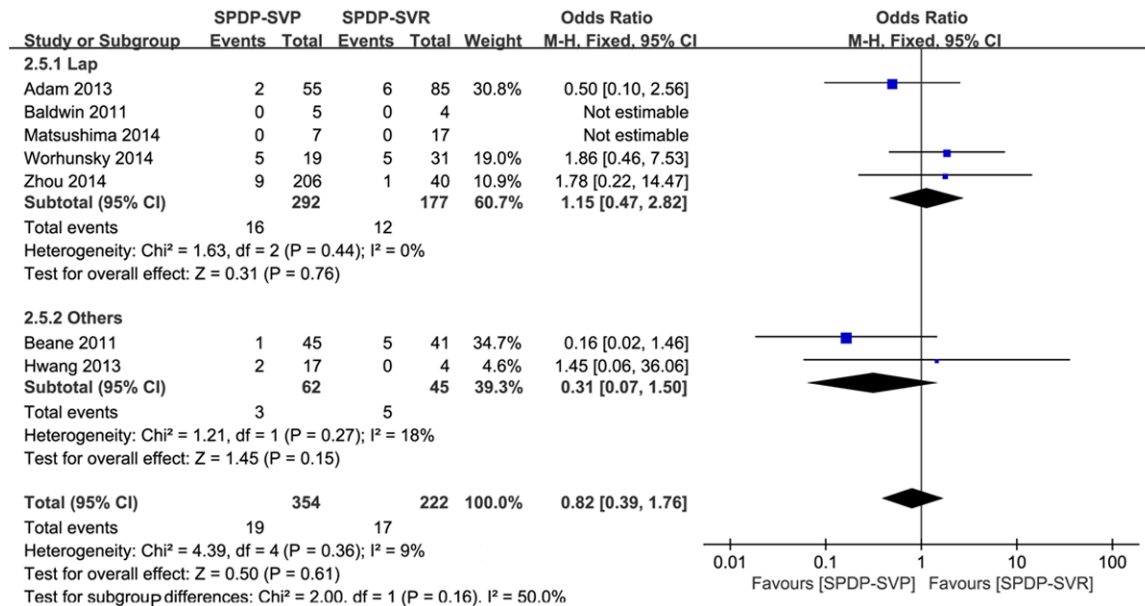


Figure 7. Forest plot of pancreatic fistula (Grade B+C). (Fixed-effect model).

total ($Z = 0.13$, $P = 0.90$; **Figure 3**) and subgroup ($Z = 0.03$, $P = 0.98$; **Figure 3**) analysis when the fixed-effect model was applied.

Seven reports compared the estimated blood loss between the two groups, with no significant difference when we used the random-effect model to compare these two groups ($Z = 0.81$, $P = 0.42$; $I^2 = 82\%$, P heterogeneity <

0.0001; **Figure 4**). The subgroup analysis also demonstrated similar statistical outcomes in the laparoscopic surgery group ($Z = 1.03$, $P = 0.30$; $I^2 = 84\%$, P heterogeneity < 0.0001; **Figure 4**). After sensitivity analysis, significant heterogeneity could be largely attributed to two studies [13, 16]. The heterogeneity decreased to $I^2 = 0\%$, P heterogeneity = 0.51 and $I^2 = 0\%$, P heterogeneity = 0.73 in total analysis and

SPDP-SVP versus SPDP-SVR

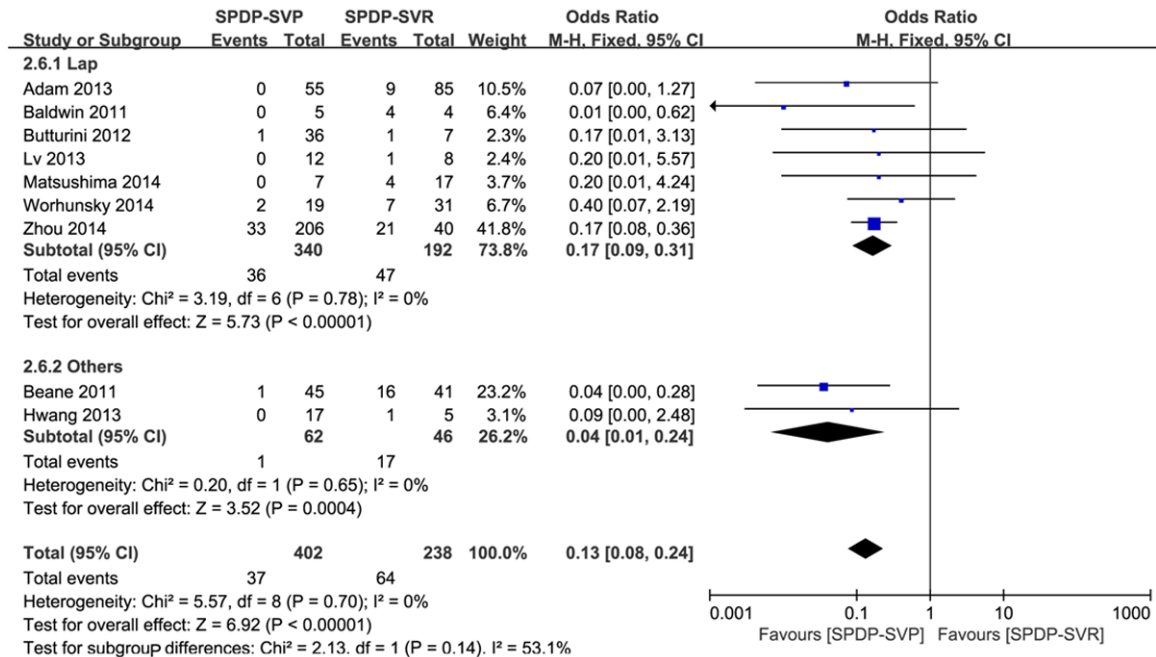


Figure 8. Forest plot of splenic infarction. (Fixed-effect model).

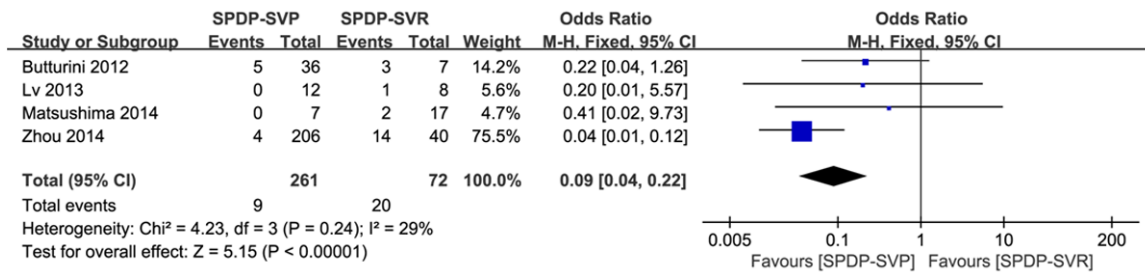


Figure 9. Forest plot of gastric/perigastric varices. (Fixed-effect model).

subgroup analysis of the laparoscopic approach respectively with less blood loss being evaluated in the SPDP-SVR group. (total analysis: $Z = 2.55$, $P = 0.01$; subgroup analysis of the laparoscopic approach: $Z = 2.62$, $P = 0.009$; **Figure 5**).

Post-operative outcomes

According to our analysis, there was no difference in the rates of post-operative complications between the two groups ($Z = 1.38$, $P = 0.17$; **Figure 6**). Subgroup analysis indicated that the post-operative complication rates were also comparable in the laparoscopic approach ($Z = 0.52$, $P = 0.60$; **Figure 6**). No significant difference existed according to the rates of pancreatic fistula (Grade B+C) between the SPDP

and DPS groups ($Z = 0.50$, $P = 0.61$; **Figure 7**). The rates of splenic infarction were significantly lower in the SPDP-SVP group than the SPDP-SVR group ($Z = 6.92$, $P \leq 0.00001$; **Figure 8**). Subgroup analysis also showed significantly lower rates of splenic infarction with SPDP-SVP for the laparoscopic approach ($Z = 5.73$, $P \leq 0.00001$; **Figure 8**). Four studies in the laparoscopic surgery group reported gastric/perigastric varices, and there was an evidence of statistically significant lower gastric/perigastric varices rates in the SPDP-SVP group ($Z = 5.15$, $P \leq 0.00001$; **Figure 9**).

Postoperative hospital stays were reported in eight studies. There was no statistically significant difference in the postoperative hospital stay between groups ($Z = 0.59$, $P = 0.56$; **Figure**

SPDP-SVP versus SPDP-SVR

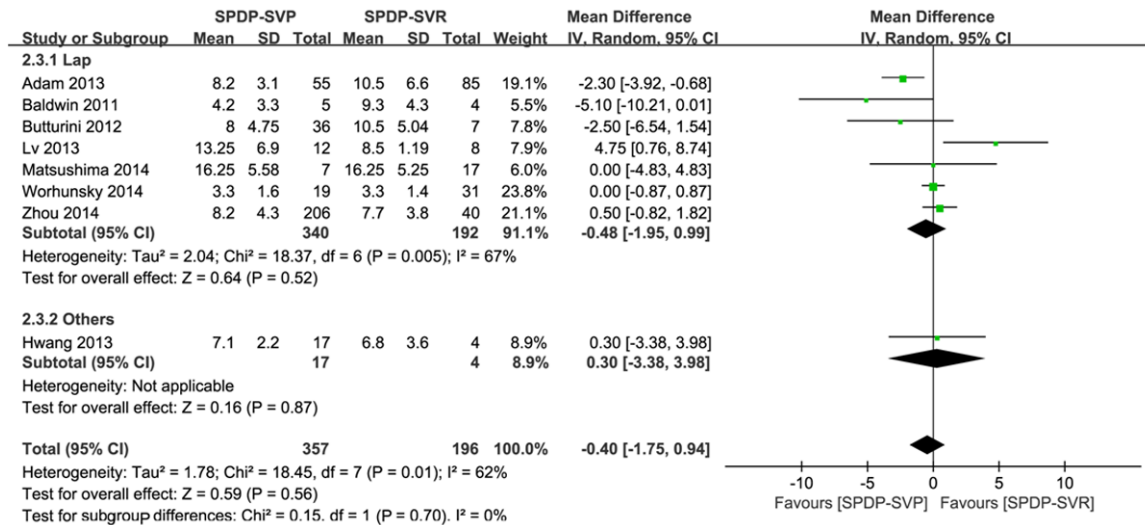


Figure 10. Forest plot of postoperative hospital stay. (Random-effect model).

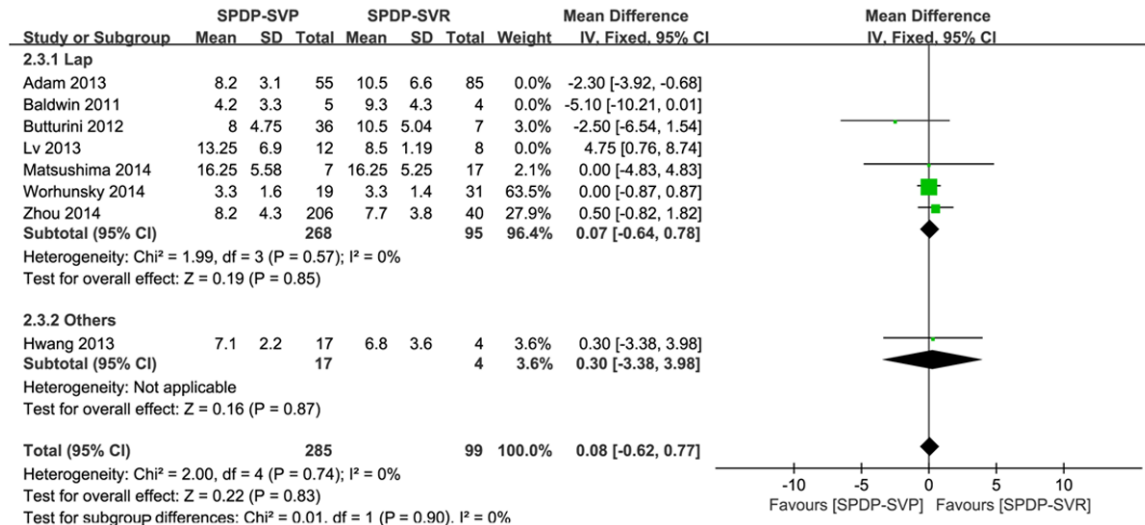


Figure 11. Forest plot of estimated blood loss, sensitivity analysis. (Fixed-effect Model).

10), with significant heterogeneity ($I^2 = 62\%$, P heterogeneity = 0.01; **Figure 10**). The studies reported by Adam et al. [17], Baldwin et al. [21] and Lv et al. [16] were responsible for the significant heterogeneity. When all were excluded, the difference remained unremarkable (**Figure 11**).

Publication bias

We used the Begg's test to evaluate the effect of publication bias based on post-operative complication rates and found no publication bias in the included studies ($P = 0.588$). The funnel plot is shown in **Figure 12**.

Discussion

The technique of distal pancreatectomy was first outlined by Mayo [23] in 1913. Traditionally, this procedure has been performed in combination with splenectomy. The lifetime risk of developing overwhelming post-splenectomy infection (OPSI) has been found to be 1 per 400-500 patient years, and the mortality due to OPSI has been estimated at approximately 1 per 800-1000 patient years [24]. Kristinsson et al. [25] have reported an increased incidence and mortality due to infections, thromboembolism, and cancer based on 8,149 splenectomized veterans with a follow-up of up to 27 years. Thus, splenic resection should be care-

SPDP-SVP versus SPDP-SVR

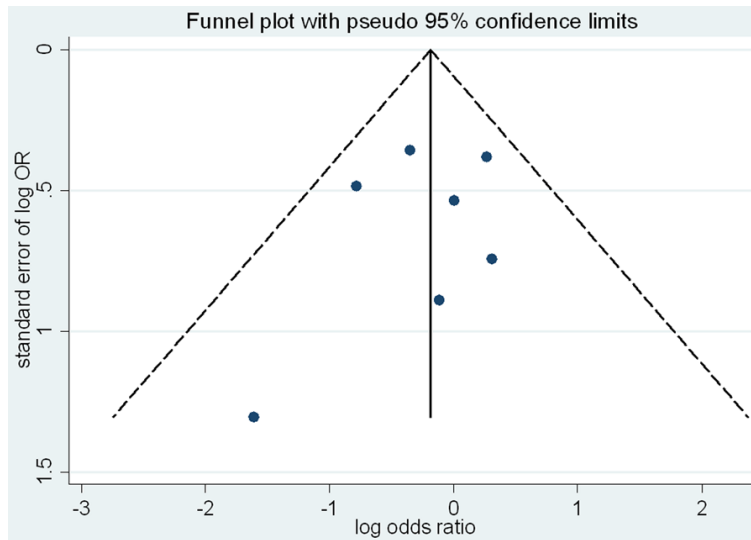


Figure 12. Publication bias based on post-operative complication rates.

fully assessed in view of the number of health disadvantages caused by splenectomy.

After resection of the splenic vessels, the perfusion of the spleen relies on short gastric and left gastroepiploic vessels, which undisputedly lead to hypoperfusion. A vessel-preserving procedure, however, can lead to a splenic infarct mainly due to splenic vein thrombosis. In our study, all the nine studies reported significantly higher splenic infarction rates in the SPDP-SVR groups ($Z = 6.92$, $P \leq 0.00001$). Severe post-operative splenic infarction was always related to a high risk of splenectomy reoperation. Therefore, it is important to estimate splenic perfusion during the operation of SPDP-SVR. Fernandez-Cruz et al. [26] reported on a patient undergoing SPDP-SPR who was rehospitalized for a splenectomy due to massive necrosis of spleen. A standard Doppler ultrasound or CT examination of the splenic supply is necessary to detect the process of infarction. However, transient splenic hypoperfusion caused by SPDP-SVR has also been mentioned [27], and Sato et al. [28] reported a case in which the splenic supply was cut in half after SPDP-SVR, although it had recovered to normal by day 10 as a result of the formation of collateral flow.

The development of gastric/perigastric varices after the ligation of the splenic vein is a major concern as a delayed complication as the consequence of increased venous pressure in the region of the short gastric and left gastroepiploic veins [29]. The pooled data showed statis-

tically higher gastric/perigastric varices rates in the SPDP-SVR groups ($Z = 5.15$, $P \leq 0.00001$). However, the occurrence of gastric/perigastric varices seemed not to be closely related to the gastric variceal bleeding [30]. A mean follow-up of 65 months for 38 patients undergoing a SPDP-SVR study was reported by Carrere et al. [31], who noted no gastric variceal bleeding in any patients. Ferrone et al. [32] also described 158 patients undergoing SPVP-SVR, 16 of 65 (25%) of whom appeared to develop gastric/perigastric varices after a median of 3.4 years follow-up;

however, none of the 158 patients showed evidence of gastrointestinal bleeding.

In this meta-analysis, the data revealed that the operative time ($Z = 0.04$, $P = 0.97$) and estimated blood loss ($Z = 0.81$, $P = 0.42$) were comparable between these two groups, although the delicate separation and dissection of the small branches of the splenic vessels during SPDP-SVP seemed to be time consuming. Bleeding from the splenic vessels was the main reason for intra-operative splenectomy [33] and also constituted a challenge for the performance of the laparoscopic approach.

As opposed to a previous systematic review of 23 studies [34], our meta-analysis found that SPDP-SVP can be accomplished without lengthening the post-operative hospital stay ($Z = 0.59$, $P = 0.56$). There was no statistically significant difference ($Z = 1.38$, $P = 0.17$) between the two groups regarding post-operative complication rates, although SPDP-SVR was related with a higher risk of developing splenic infarction. Based on our meta-analysis, we are able to conclude that both SPDP-SVP and SPDP-SVR are safe, reliable procedures in the treatment of patients who require distal pancreatectomy for a majority of the indicated complications (SPDP-SVP: 94.4%; SPDP-SVR: 82.1%). These findings are Grade I-II on the basis of the Clavien-Dindo classification [35], and the most common complications were pancreatic fistula, splenic infarction, splenic vascular obstruction, and fluid collection after SPDP.

Pancreatic fistula is one of the most serious complications after SPDP and can lead to a prolonged hospital stay and even mortality. Each pancreatic fistula can be classified as grade A, B or C [36]. No evidence of statistical significance was observed in the occurrence of any of the pancreatic fistula (Grade B+C) between the SPDP-SVP and SPDP-SVR groups ($Z = 0.50$, $P = 0.61$).

Attention should be paid to the heterogeneity and significant heterogeneity was mainly observed in the outcome variables of operation time, estimated blood loss and length of hospital stay. Clinical heterogeneity may arise from differences in the indications for distal pancreatectomy, patient demographics and operative techniques. Different points of learning curves and post-operative treatment discrepancies may also affect the overall outcomes for these two procedures. Methodological and statistical heterogeneity was also found to contribute to the total heterogeneity of the nine studies.

However, our study still has its limitations. All nine of the included studies were retrospective studies, and no randomized controlled trials were incorporated, resulting in less powerful conclusions than those of studies based on randomized controlled patients. Several of the studies had small sample sizes, and it was difficult for the characteristics of their patients to be absolutely matched. Furthermore, some of the data were not reported in the form of means and standard deviations and required transformation using a previously reported method [37]. Still, this method could have contributed to some inaccuracy in the results.

Conclusion

Our analysis confirms better clinical outcomes of SPDP-SVP compared with SPDP-SVR. However, all of the included trials were retrospective and non-randomized. Further clinical trials, especially high-quality, multicenter, randomized controlled trials, should be performed to ensure more persuasive conclusions.

Disclosure of conflict of interest

None.

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