

Associating liver partition and portal vein ligation versus 2-stage hepatectomy

A meta-analysis

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Abstract

Background: The aim of this study was to conduct a meta-analysis comparing associating liver partition and portal vein ligation (ALPPS) with conventional 2-stage hepatectomy (TSH) in terms of clinical outcomes and to determine the feasibility and safety of ALPPS.

Methods: A comprehensive search strategy was adopted to search the PubMed, Embase, Cochrane Library, and China Biology Medicine disc databases for studies comparing ALPPS and TSH. The search was broadened by looking up the reference lists of the retrieved articles. A meta-analysis was performed using the statistical software RevMan (v 5.3; Cochrane Collaboration).

Results: A total of 7 studies involving 561 patients (ALPPS group, 136 patients; TSH group, 425 patients) were included in the present study, all of which were observational studies. Compared with TSH, ALPPS was associated with high completion rates of both stages [odds ratio (OR): 10.68, 95% confidence interval (95% CI): 3.26–34.97, $P < .0001$]. No significant differences were found in other outcomes such as complications of the first (OR: 4.04, 95% CI: 0.81–20.27, $P = .09$) and second surgical stage (OR: 1.59, 95% CI: 0.71–3.57, $P = .26$), liver failure (OR: 0.76, 95% CI: 0.29–1.98, $P = .58$) and the 90-day mortality rate (OR: 2.20, 95% CI: 1.00–4.84, $P = .05$).

Conclusion: ALPPS is associated with lower noncompletion rate and had similar perioperative outcomes relative to TSH. However, only retrospective observational studies were included in this meta-analysis, which may have limited the strength of the evidence. High-quality, large-scale studies are required to further evaluate the outcomes of ALPPS.

Abbreviations: ALPPS = associating liver partition and portal vein ligation for staged hepatectomy, CIs = confidence intervals, FLR = future liver remnant, NOS = Newcastle–Ottawa scale, NRCs = non-randomized comparative studies, OR = odds ratio, PVE = portal vein embolization, PVL = portal vein ligation, RCTs = randomized controlled trials, TSH = 2-stage hepatectomy.

Keywords: associating liver partition and portal vein ligation for staged hepatectomy, clinical outcomes, meta-analysis, two-stage hepatectomy

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1. Introduction

The key to the complete remission of liver tumors lies in R0 resection. However, in patients with large primary liver cancers or extensive hepatic metastases, the removal of the entire liver tumor burden to achieve R0 resection may lead to postoperative liver failure owing to insufficiency of the remnant liver.^[1] Hence, R0 resection must be performed with a prerequisite of adequate volume of the future liver remnant (FLR). Liver insufficiency can be avoided as long as the FLR is greater than 25% of the original liver volume in patients without an underlying hepatic disease (apart from the tumor). In patients with a chronic liver disease but without cirrhosis, the FLR should be more than 30%, while in patients with both chronic liver disease and cirrhosis, the FLR should be not less than 40%.^[1,2]

In the 1980s, Makuuchi et al.^[3] first described portal vein embolization (PVE). In this technique, typically, chemoembolization of the right portal branch is performed to induce hypertrophy of the left liver and reduce the incidence of postoperative liver failure. PVE before hepatectomy can increase the FLR by 20% to 46% within 2 to 8 weeks^[3–5] and the rate of R0 resection to 58% to 100%.^[6] Adam et al.^[7] proposed a 2-stage hepatectomy (TSH) procedure for the purpose of increasing the rate of R0 resection in patients with bilobar liver tumors. In addition, portal vein ligation (PVL) has been suggested as an improvement over PVE and has been shown to outperform PVE in terms of regenerative response.^[8,9] At present, it is believed that PVE and PVL are equally useful for TSH. Although TSH has greatly improved postoperative liver function in patients with large primary liver cancers or extensive hepatic metastases, as many as one-third of patients cannot undergo TSH as scheduled owing to rapid disease progression, insufficient liver regeneration, or comorbidities.^[10]

In 2012, Schnitzbauer et al.^[11] reported a novel form of TSH termed “associating liver partition and PVL for staged hepatectomy (ALPPS).” This procedure can increase the FLR volume by 74% in 9 days on average. Hence, it can greatly shorten the time between the two stages, and has been reported to help achieve a 100% rate of TSH.^[11] However, this procedure is also associated extremely high rates of postoperative complications and perioperative mortality, and has been the subject of fierce controversy ever since it was first proposed. In 2016, Eshmuminov et al.^[12] reported a meta-analysis that was aimed to compare the different strategies using ALPPS, PVE, or PVL in extended hepatectomy. And their results indicated that ALPPS is associated with greater FLR hypertrophy and a higher rate of completion of stage two, but this may be at the price of greater morbidity and mortality.^[12] But only 2 articles included in their meta-analysis involved the comparison between ALPPS and TSH. Herein, we conducted a different meta-analysis of studies comparing ALPPS with conventional TSH involving either PVE or PVL, to evaluate the potential applications of ALPPS in the field of hepatobiliary surgery.

2. Materials and methods

2.1. Search strategy

A comprehensive search strategy was adopted to search the PubMed, Embase, Cochrane Library, and China Biology Medicine disc databases for articles published between March 2012 and January 2017 (S-table 1, <http://links.lww.com/MD/C429>). The following search terms were used: “portal vein embolization,” “PVE,” “portal vein ligation,” “PVL,” “portal

vein occlusion,” “associating liver partition and portal vein ligation for staged hepatectomy,” “ALPPS,” “in situ liver transection with portal vein ligation,” “staged hepatectomy,” “staged liver resection,” and “liver resection.” The search was expanded by reading the references of the retrieved articles to identify eligible studies. Ethical approval was not necessary, because available data were collected from the previous published studies.

The inclusion criteria were as follows: original data from the included studies; primary studies consisting of well-designed randomized controlled trials (RCTs) or high-quality nonrandomized comparative studies (NRCs); studies with ALPPS, PVL, PVE, and other types of TSH as the procedures of interest; and studies written in English. Duplicate publications as well as studies with insufficient information or poor quality were excluded.

Data were extracted using a pre-designed data form. The data extracted were study characteristics: number, sex, and average age of patients included; and outcome measures: completion of both stages, complications of each stage, 90-day mortality, liver failure, FLR-regeneration rate, interval between stages, and total length of hospital stay. We contacted the authors of the relevant articles to fill in any gaps in the information reported.

2.2. Statistical analysis

The meta-analysis was performed using RevMan 5.3 software (Cochrane Collaboration). Heterogeneity was tested for results reported by multiple studies. A random-effects model was used for data pooling. Odds ratio (OR) was used for binary variables. All effect values were expressed in 95% confidence intervals (95% CIs). Funnel plots were used to detect publication bias. The presence of publication bias was then evaluated using the Begg test. Sensitivity analyses were conducted to determine the reliability of the results. The methodological quality of the included studies was assessed using the Newcastle–Ottawa scale (NOS).

3. Results

The database search yielded 296 studies for screening (Fig. 1). After removing duplicate studies and reading the titles and summaries of the retrieved articles, we were left with a total of 25 studies for further identification. After a full-text review, 18 articles were excluded. Two studies by Schadde et al.^[13,14] presented identical data from the same institution during practically the same study period; of these 2 studies, we included the study that provided more detailed data.^[14] Thus, a total of 7 studies^[14–20] were included in this meta-analysis.

The 7 included studies involved a total of 561 patients, with 136 patients in the ALPPS group and 425 patients in the TSH group. The general characteristics of these studies are summarized in Table 1. Two studies were from the United States, 3 from Europe (1 from Italy, 1 from France, and 1 from Switzerland), and the remaining 2 were from Japan. All the included studies were NRCs and the NOS scores ranged from 7 to 9.

3.1. Completion of both stages

Six of the 7 studies^[14–17,19,20] included in the meta-analysis reported data on the completion of both surgical stages. The heterogeneity among the studies was acceptable ($I^2=0\%$, $P=.57$). The risk of noncompletion was significantly higher in the TSH group than in the ALPPS group (OR: 10.68, 95% CI: 3.26–34.97, $P<.0001$; Fig. 2 A).

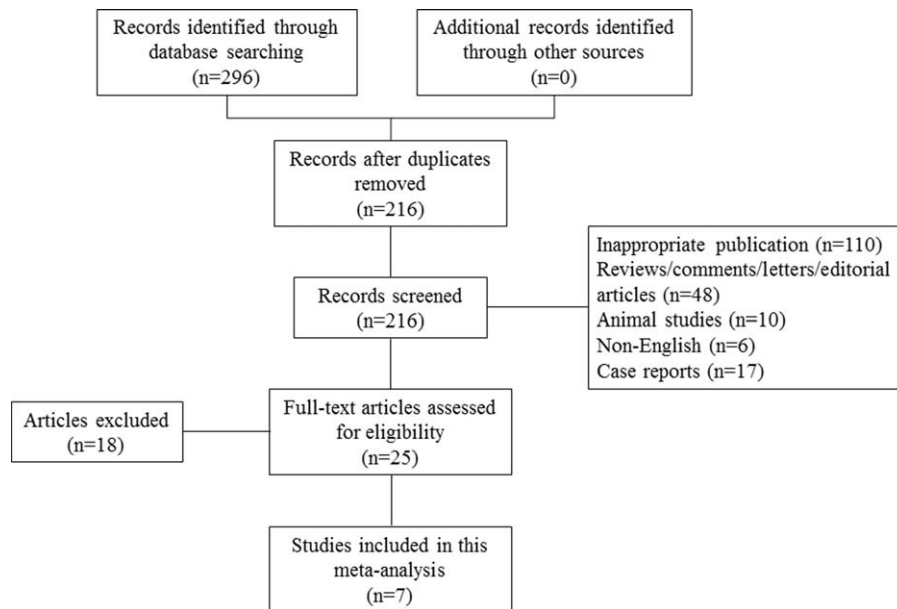


Figure 1. Search results and the selection procedure.

3.2. Complications

Four studies [14,17,19,20] reported complications associated with the first stage. Significant heterogeneity was detected ($I^2=78\%$, $P=.004$) among the studies, and therefore, the random-effects model was used for data pooling. The meta-analysis revealed no difference in the complication rates of the first stage between the 2 groups (OR: 4.04, 95% CI: 0.81–20.27, $P=.09$; Fig. 2 B).

Six studies [14,15,17–20] reported complications of the second stage. The heterogeneity among these studies was acceptable ($I^2=49\%$, $P=.08$), and so, the fixed-effects model was used for data pooling. We found no significant difference in the complication rate of the second surgical stage between the 2 groups (OR: 1.59, 95% CI: 0.71–3.57, $P=.26$; Fig. 2 C).

3.3. Liver failure

Data on liver failure were reported in 4 studies. [14,17,18,20] There was no difference in the incidence of liver failure between the ALPPS and TSH groups (OR: 0.76, 95% CI: 0.29–1.98, $P=.58$; Fig. 2 D). The heterogeneity among the studies was low ($I^2=0\%$, $P=.51$).

3.4. Mortality

All studies [14–20] reported the 90-day mortality, and the heterogeneity among the studies was low ($I^2=0\%$, $P=.83$). No significant difference in postoperative deaths was found between the ALPPS and TSH groups (OR: 2.20, 95% CI: 1.00–4.84, $P=.05$; Fig. 2 E).

Table 1
Characteristics of the studies included in this meta-analysis.

Study	Time	Country	Group	No. of patients	M/F	Mean age, y	Type of TSH	NOS score
Shindoh et al [14]	2013	USA	ALPPS	25	14/11	63 (32–75)	rPVE+IV	7
			TSH	144	106/38	58 (33–79)		
Kristopher et al [15]	2014	USA	ALPPS	15	11/4	55.9±12.1	PVE	7
			TSH	53	31/22	59.5±11.3		
Ratti et al [16]	2014	Italy	ALPPS	12	5/7	59 (51–79)	PVE/PVL	9
			TSH	36	19/17	59 (42–66)		
Schadde et al [13]	2014	Switzerland	ALPPS	48	29/19	57 (48.5–65)	PVE/PVL	9
			TSH	83	57/26	61 (54–69)		
Kenichi et al [17]	2015	Japan	ALPPS	8	4/4	68 (62–78)	PVE	9
			TSH	14	9/5	72 (35–81)		
Tanaka et al [18]	2015	Japan	ALPPS	11	7/4	68 (50–78)	PVE	9
			TSH	54	33/21	63 (35–76)		
Adam et al [19]	2016	France	ALPPS	17	12/5	58 (23–75)	PVL	9
			TSH	41	23/18	58 (32–75)		

ALPPS = associating liver partition and portal vein ligation for staged hepatectomy, F = female, M = male, NOS = Newcastle–Ottawa Scale, PVE = portal vein embolization, PVL = portal vein ligation, rPVE+IV = right plus segment IV portal vein embolization, TSH = 2-stage hepatectomy.

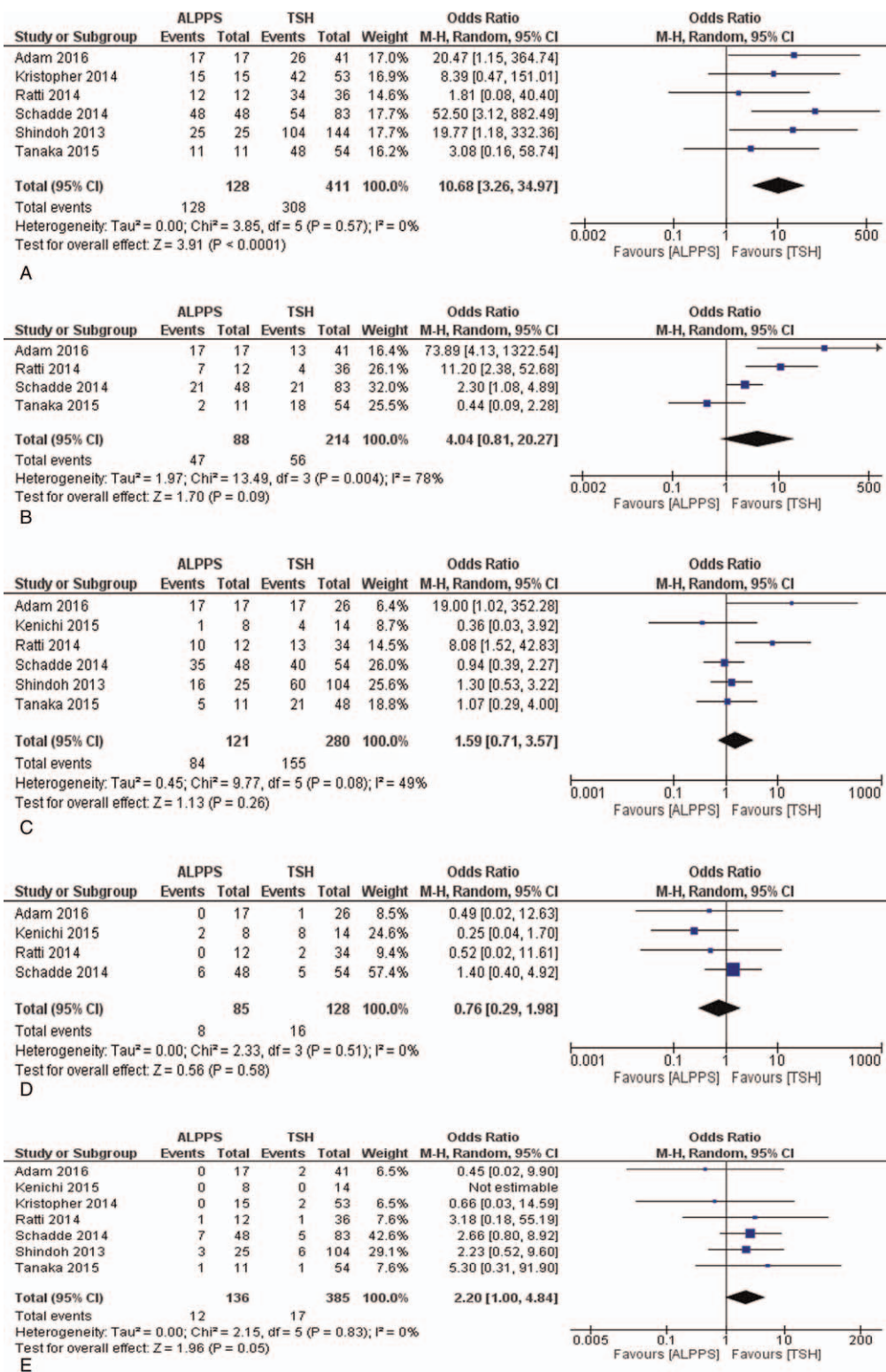


Figure 2. Forest plot diagram showing (A) completion of both stages, (B) complications associated with the first stage, (C) complications of the second stage, (D) liver failure, and (E) mortality.

3.5. FLR-regeneration rate

Although all the included studies [14–20] reported the FLR-regeneration rate, only 1 [16] was eligible for analysis. Therefore, no meta-analysis was done. Ratti et al [17], Schadde et al [14], and

Tanaka et al [19] reported that ALPPS was associated with a higher FLR-regeneration rate, while the remaining studies [15,16,20] reported no significant difference between the 2 methods (Table 2).

Table 2
Outcomes of FLR regeneration rate in this systematic review.

Study	FLR regeneration rate (%)		P
	ALPPS	TSH	
Shindoh et al [14]	62 (0.3–379)	74 (21–192)	NS
Kristopher et al [15]	36.1 ± 6.4	41.0 ± 15.3	NS
Ratti et al [16]	47 (38–133)	41 (29–79)	.024
Schadde et al [13]	41 (34–47)	35 (27–45)	<.001
Kenichi et al [17]	150 (130–190)	160 (120–270)	NS
Tanaka et al [18]	154 (133–194)	119 (66–168)	.005
Adam et al [19]	36 (26–49)	40 (25–55)	NS

ALPPS = associating liver partition and portal vein ligation for staged hepatectomy, NA = not available, NS = not significant, TSH = 2-stage hepatectomy.

3.6. Interval between stages

A total of 4 studies [15–17,20] reported on the interval between the two stages, but data from only 1 study [16] met the requirements for analysis. Therefore, no meta-analysis was done. Among the 4 studies, Ratti et al [17] and Adam et al [20] reported that ALPPS was associated with a shorter time interval. Only data without *P* values were provided by Shindoh et al [15] and Croome et al [16] (Table 3).

3.7. Total length of hospital-stay

Three studies [17–19] reported the total length of hospital stay, but all of the data were not available for meta-analysis; therefore, pooling of the data was not done. All 3 studies [17–19] reported that ALPPS was associated with a shorter overall length of hospital stay (Table 3).

3.8. Publication bias

Assessment of publication bias revealed no potential publication bias among the included studies (Begg test, *P* = .26).

4. Discussion

This meta-analysis showed that compared with TSH, ALPPS did not have any obvious deficiencies and had a higher completion rate. Since its inception, ALPPS has been a controversial procedure, with equally obvious advantages and disadvantages. Its biggest advantage is rapid FLR growth, but it is also accompanied by high rates of complications and mortality.

Due to the long waiting time between the 2 stages of conventional TSH, disease progression can occur during the

treatment period and is the main cause of treatment failure. Interval chemotherapy between the 2 stages was attempted to solve this problem, but the effect was not clear. In addition, prolonged chemotherapy can result in liver injury and further complications.^[21] We found that the rate of completion of both stages was significantly higher in the ALPPS group than in the TSH group (OR: 10.68, CI: 3.26–34.97, *P* < .0001), possibly because of the shorter interval between the 2 stages and the rapid FLR growth after the first stage. However, as the data for FLR-regeneration rate did not meet the criteria for meta-analysis, we could only conduct a systematic review of the FLR-regeneration rates reported in the selected studies. Three of the included studies [13,17,19] reported that the FLR-regeneration rate was higher for ALPPS than for TSH. Possible reasons for this difference are as follows: First, after liver transection and unilateral PVL, the liver blood flow changed; blood flow and liver regeneration are highly correlated, but the underlying mechanism is unclear.^[22] Second, cytokines and growth factors secreted after liver cell injury may stimulate liver regeneration.

Despite the high FLR-regeneration rate associated with ALPPS, a reported 77% of deaths after ALPPS are attributable to liver failure.^[23] The present meta-analysis, however, found no significant difference in the incidence of liver failure between the ALPPS and TSH groups (OR: 0.76, 95% CI: 0.29–1.98, *P* = .58). In addition, we found no difference between the ALPPS and TSH groups in terms of the rate of complications after either the first stage (OR: 4.04, 95% CI: 0.81–20.27, *P* = .09) or the second stage (OR: 1.59, 95% CI: 0.71–3.57, *P* = .26). The difference between our findings and those previously reported may stem from the separate comparisons of ALPPS with conventional TSH involving either PVE or PVL in earlier studies; in contrast, both PVE and PVL were included in the TSH group in our meta-analysis. TSH encompasses a variety of different methods, with varying overall complication rates. However, as the definition of TSH is not standardized, we believe that the present meta-analysis offers the most reliable results. Finally, although the 90-day mortality did not differ between the 2 groups in our meta-analysis (OR: 2.20, 95% CI: 1.00–4.84, *P* = .05), the oncological outcomes were not better with ALPPS than with TSH.^[20]

We assessed the methodological quality of the selected articles in accordance with established standards. Considering that ALPPS was first described in 2012 by Schnitzbauer et al,^[11] we limited the search to articles published after March 2012 in order to standardize the methods and quality of the selected literature. A high degree of heterogeneity ($I^2 = 78%$, *P* = .004) was found for the complication rate after the first stage; this finding may be attributable to the inclusion of different methods of conventional TSH involving either PVE or PVL in the control group. In

Table 3
Outcomes of time interval between stages and total length of hospital stay in this systematic review.

Study	Time interval between stages, d			Total length of hospital stay, d		
	ALPPS	TSH	P	ALPPS	TSH	P
Shindoh et al [14]	9 (5–28)	34 (12–385)	NA	NA	NA	NA
Kristopher et al [15]	7.8 ± 1.1	39.9 ± 14.2	NA	NA	NA	NA
Ratti et al [16]	11 (7–12)	31 (25–39)	.024	24 (16–42)	18 (14–38)	.05
Schadde et al [13]	NA	NA	NA	NA	NA	NA
Kenichi et al [17]	NA	NA	NA	12 (8–54)	27 (6–42)	.021
Tanaka et al [18]	NA	NA	NA	11 (8–54)	27 (8–124)	<.001
Adam et al [19]	12 (9–39)	103 (19–450)	<.001	NA	NA	NA

ALPPS = associating liver partition and portal vein ligation for staged hepatectomy, NA = not available, TSH = 2-stage hepatectomy.

addition, studies from different geographical areas may also differ greatly, leading to a high degree of heterogeneity.

This study has some limitations. First, we may have missed some articles due to a fact that we never searched the studies with Web of Science database. In addition, Goossen et al.^[24] recently defined a gold standard for literature search in surgical reviews and found that “Web of Science” has a value if there are no RCTs for a surgical topic; however, EMBASE was irrelevant. Second, the quality of present studies is not high according to our results. Therefore, our confidence in the presented evidence is low and therefore an RCT is urgently needed.

5. Conclusion

In our meta-analysis, ALPPS had similar perioperative outcomes relative to TSH, and is associated with lower noncompletion rate; however, long-term results are yet to be evaluated. Due to the lack of a unified and clear consensus on the definition and terminology of TSH, the selected literature in this meta-analysis may not be complete. Further high-quality, large-scale studies of ALPPS are required for a more comprehensive evaluation.

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