

A systematic review and meta-analysis of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus traditional staged hepatectomy

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Abstract

It is still controversial whether associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) or traditional staged hepatectomy such as portal vein embolization (PVE) and 2-staged hepatectomy (TSH) is better. The aim of this study was to compare these 3 available strategies in extended hepatectomy.

Trials were identified by searching MEDLINE, PubMed, the Cochrane Library, and Embase and additional articles were identified by hand searching. Comparative clinical studies reporting volumetric changes, mortality, morbidity, and feasibility of the second stage about ALPPS versus PVE or ALPPS versus TSH were included.

Nine studies involving 557 patients met the inclusion criteria. Five studies reported on comparison of ALPPS and PVE, and the other 4 reported about ALPPS and TSH. In the comparison of ALPPS versus traditional staged hepatectomy (PVE and TSH), ALPPS was associated with a greater increase in the future liver remnant (FLR) (RR: 4.87; 95%CI, 3.41–6.33) and more frequent completion of stage 2 resection (RR: 1.32; 95%CI, 1.21–1.44). Compared with the traditional staged hepatectomy, ALPPS had a trend toward higher morbidity (RR: 1.19, 95%CI, 0.96–1.47) and mortality (RR: 2.11, 95%CI, 1.02–4.33) after stage 2 resection.

ALPPS is associated with greater future liver remnant hypertrophy and a higher rate of completion of stage 2, but this may be at the price of greater morbidity and mortality.

Abbreviations: ALPPS = associating liver partition and portal vein ligation for staged hepatectomy, FLR = future liver remnant, PLF = postoperative liver failure, PVE = portal vein embolization, PVL = portal vein ligation, TSH = 2-staged hepatectomy.

Keywords: ALPPS, complication, feasibility, PVE, TSH

1. Introduction

The safe removal of extensive tumor load in the liver has been one of the main focuses of laboratory and clinical research for hepatobiliary surgeons over the past 3 decades.^[1] The main reason for poor postoperative outcomes is inadequate volume of the future liver remnant (FLR), which leads to posthepatectomy liver failure.^[2] Several strategies have been developed over the past 3 decades to induce compensatory hypertrophy of the FLR, thereby increasing the chance of resectability and lowering the risk of postoperative complications.^[3–5] The first breakthrough is credited to Masatoshi Makuuchi, who in the 1980s, introduced

the concept of the portal vein embolization (PVE) of the right portal branch to induce hypertrophy of the left side of the liver, enabling a safer removal of large or multiple tumors, mostly located in the right hemiliver and segment IV.^[6] This technique was rapidly adopted by many to prevent liver failure after a variety of extensive right-sided hepatectomies.^[2,7] Today preoperative PVE is considered standard therapy for patients with an insufficient FLR before extended liver resection.^[8] However, insufficient hypertrophy of the FLR or disease progression after PVE may prevent curative liver resection in up to 20% of patients.^[9,10]

Two-stage hepatectomy was introduced in the year 2000 for patients with bilateral multinodular colorectal liver metastases.^[11] The liver grows in the interval between sequential resection, and the risk of postoperative liver failure (PLF) is presumably reduced due to the staged approach.^[12,13] Although 2-staged hepatectomy (TSH) is well established, failure to proceed to stage 2 is reported to be a problem in up to one-third of patients (8%–31% of cases depending on the series) and occurs due to tumor progression during the period of liver regeneration or due to insufficient FLR hypertrophy.^[12]

Recently, a novel technique of 2-stage liver resection was introduced, combining portal vein ligation (PVL) and transection of the liver between the FLR, and the deportalized part of the liver,^[4,14] which was associating liver partition with PVL for staged hepatectomy. ALPPS has been reported to induce hypertrophy of the FLR of up to 80% in a shorter time than PVL or PVE.^[14,15] However, this procedure has triggered serious concerns owing to the associated high morbidity and mortality rates of up to 40 and 15% respectively.^[16] The safety of ALPPS

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compared with traditional strategies to induce hypertrophy of the FLR, such as PVE and TSH, is still controversial.

The purpose of the present article was to assess the efficacy of the ALPPS and PVE/TSH strategies used to increase FLR volume before extended liver resection in patients with primary or secondary liver resections. The main endpoints were comparison of volumetric changes, feasibility of the second stage, as well as postoperative morbidity and mortality after ALPPS and PVE/TSH.

2. Methods

2.1. Trial selection

A comprehensive systematic search of the databases MEDLINE, PubMed, the Cochrane Library, and Embase was conducted using the following terms: “portal vein embolization,” “portal vein ligation,” “portal vein occlusion,” “hepatic vein embolization,” “hepatic vein occlusion,” “staged hepatectomy,” “staged liver resection,” “2-stage hepatectomy,” “TSH,” and “ALPPS,” “hepatectomy (liver resection or hepatic resection or surgery or transection or partition).” Two reviewers scanned the abstract of identified studies to determine eligibility. Full articles were then selected for further assessment if the abstract suggested the study was relevant. Only comparative studies including PVE/TSH and ALPPS were identified. The last electronic search was on October 28, 2018. There were no language or time restrictions. Additional articles were identified by hand searching. Corresponding authors of included publications were asked for missing information. If the e-mail address provided in the publication was no longer valid, the first author was contacted by e-mail. The results of our search and selection of studies are shown in Figure 1.

2.2. Outcome measures

Volumetric data for the FLR were collected before stage 1 and stage 2, including volume of FLR (mL), FLR (percent; calculated

as FLR/total liver volume \times 100) or standardized FLR% and volumetric changes after stage 1 (including absolute increase in volume and hypertrophy ratio of FLR). The feasibility rate of stage 2 was recorded, where feasibility was defined as completion of liver resection at stage 2. Investigated reasons for not proceeding to stage 2 included intrahepatic and extrahepatic tumor progression and failure of the FLR to hypertrophy.

The total number of patients with complications was determined. In comparative studies between ALPPS and other strategies, morbidity after ALPPS was analyzed including both stage 1 and 2, as complications occur during the same hospital stay and information for each patient summarized the whole admission. Where complications after stages 1 and 2 of ALPPS had been reported separately, the highest rate of complications was used for analysis. For the other strategies, only complications after stage 2 were considered for comparison with ALPPS. Mortality was reported as 90-day mortality. Mortality after stage 1 and stage 2 was analyzed together for each strategy.

2.3. Quality assessment

To assess the overall strength/quality of evidence for the various outcome parameters, a quality assessment was carried out in the style of the Oxford Centre for Evidence-based Medicine. Risk of bias in individual studies was assessed by means of the Newcastle–Ottawa quality assessment scale.

2.4. Statistics

Data were analyzed using the Comprehensive Meta-Analysis statistical software and were presented as proportions along with corresponding 95% confidence intervals (95% CIs), which were calculated by the Wilson score interval. To estimate pooled proportions we used random rather than fixed effects models in order to take into account the heterogeneity of the estimates.

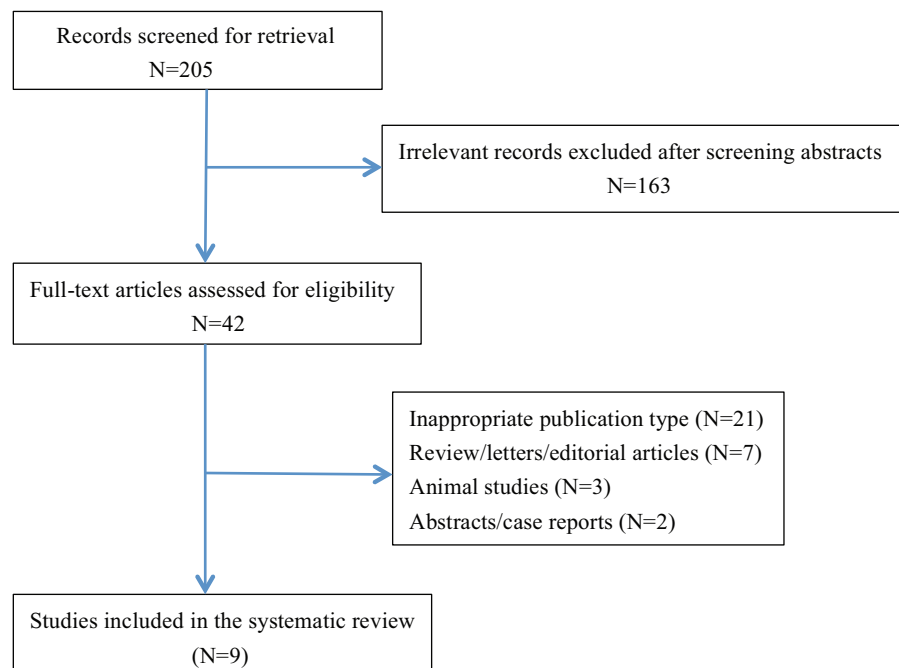


Figure 1. PRISMA diagram showing systematic search strategy.

Table 1
Characteristics of comparative studies.

Reference	Country	Year	Strategy	No. of patients	Increase of FLR per day (%/day)	Completed resection	Morbidity	Mortality
Knoefel et al	Germany	2009–2011	ALPPS/PVE	7/15	21% ± 10.00%/1.37% ± 1.23%	100%/80%	71.4%/60%	0/0
Croome et al	USA	2000–2013	ALPPS/PVE	15/53	10.8% ± 1.00%/0.9% ± 0.68%	100%/79.2%	NA/NA	0/3.8%
Schadde et al	Switzerland	2003–2012	ALPPS/PVE	48/83	9.92% ± 3.14%/0.67% ± 0.38%	83.3%/66.3%	13%/9%	15%/6%
Tanaka et al	Japan	1994–2014	ALPPS/TSH	11/54	5.23% ± 1.40%/1.89% ± 1.12%	100%/79.6%	45.5%/38.9%	9.1%/2.1%
Ratti et al	Italy	2008–2013	ALPPS/TSH	12/36	4.27% ± 4.32%/1.32% ± 0.81%	100%/94.4%	41.7%/17.6%	8.3%/2.8%
Adam et al	Japan	2010–2014	ALPPS/TSH	17/41	4.17% ± 0.96%/0.32% ± 0.15%	100%/63.4%	41.2%/39.0%	NA/NA
Daryl et al	Singapore	2007–2016	ALPPS/PVE	10/29	4.19% ± 1.34%/1.33% ± 0.33%	80%/58.6%	50%/35.3%	12.5%/0
Naokazu et al	Japan	2007–2016	ALPPS/PVE	2/27	2% ± 0.75%/0.42% ± 0.15%	NA/NA	NA/NA	0/0
Per et al	Sweden	2014–2016	ALPPS/TSH	48/49	6.18% ± 3.45%/0.84% ± 0.42%	91.7%/57.1%	68.2%/67.9%	8.3%/6.1%

ALPPS=associating liver partition and portal vein ligation for staged hepatectomy, FLR=future liver remnant, NA=not available, PVE=portal vein embolization, TSH=2-staged hepatectomy.

Statistical heterogeneity across studies was stated by using the Cochran's test, and quantified by I^2 (percentage of total variation across studies that is attributable to heterogeneity rather than chance); values were considered statistically significant when P was $<.1$. Subgroup analyses were performed to identify possible sources of heterogeneity. This meta-analysis is exempt from ethical approval as the analysis involves only already published and anonymized data.

3. Results

The strategies of the literature search and the selection of studies are summarized in Figure 1. Nine studies were included in the meta-analysis. Five studies comparing ALPPS with PVE and 4 studies comparing ALPPS with TSH met the inclusion criteria.^[17–25] Eight studies were retrospective and one was randomized controlled trial.^[2,3] The 9 studies involved 557 patients, of whom 207 were in the PVE group, 180 in the TSH group, and 170 in the ALPPS group. The characteristics of 9 studies included in this paper were summarized in Table 1. All of included studies were classified as evidence level 3 or 4, having a good quality score (Table 2). Pooled data were analyzed by combining the results of the 6 studies. A subgroup analysis was also performed to compare ALPPS with PVE^[17–19,24,25] and TSH,^[20–23] respectively.

3.1. Speed of future liver remnant hypertrophy before resection

The %age FLR increase was greater after ALPPS than PVE in 3 groups with 82 patients in the ALPPS group and 207 in the PVE group (RR: 6.30; 95%CI, 3.97–8.64). The same result was

obtained when comparing ALPPS with TSH (RR: 3.27; 95%CI, 1.63–4.91). Patients receiving the operation of ALPPS had better FLR increase rate compared with other strategies, such as PVE and TSH (RR: 4.87; 95%CI, 3.41–6.33). Heterogeneity among studies of ALPPS vs PVE, ALPPS vs TSH and ALPPS vs PVE/TSH was significant ($I^2=93.4%$, $94.4%$, $95.3%$, respectively). A random-effect model was used to estimate FLR increase rate between ALPPS, PVE, and TSH (Fig. 2).

3.2. Feasibility of second stage

The feasibility rates of stage 2 after ALPPS (82 patients) and PVE (207 patients) were 94% versus 63%, respectively (RR: 1.26; 95%CI, 1.11–1.43). The feasibility rates between ALPPS and TSH were 95% versus 72%, respectively (RR: 1.38; 95%CI, 1.21–1.44). The overall feasibility rates were 94% versus 69%, respectively (RR: 1.32; 95%CI, 1.21–1.44) (Fig. 3). Heterogeneity among studies of ALPPS versus PVE, ALPPS vs TSH and ALPPS vs PVE/TSH was moderate ($I^2=0$, $85.6%$, $60.8%$, respectively). A random-effect model was used to estimate feasibility rates between ALPPS, PVE, and TSH (Fig. 3).

3.3. Safety

Comparison of morbidity between the ALPPS and PVE groups was available in 3 studies^[17,19,24] with 65 patients in the ALPPS group and 127 patients in the PVE group. Complication rates were 25% after ALPPS and 21% after PVE (RR: 1.37, 95%CI, 0.84–2.21) (Fig. 4). There was no heterogeneity among included studies ($I^2=0$). Adjusted mortality rates were 10% after ALPPS and 5% after PVE in 3 studies (RR: 2.26, 95%CI, 0.88–5.80).

Table 2
Characteristics of comparative studies with evidence level and bias evaluation.

Reference	Country	Strategy	No. of patients	Evidence level	Quality score
Knoefel et al	Germany	ALPPS/PVE	7/15	4	7
Croome et al	USA	ALPPS/PVE	15/53	3b	9
Schadde et al	Switzerland	ALPPS/PVE	48/83	3a	9
Tanaka et al	Japan	ALPPS/TSH	11/54	3b	8
Ratti et al	Italy	ALPPS/TSH	12/36	3b	8
Adam et al	Japan	ALPPS/TSH	17/41	3b	8
Daryl K.A. Chia et al	Singapore	ALPPS/PVE	10/29	3a	9
Naokazu Chiba et al	Japan	ALPPS/PVE	2/27	3b	8
Per Sandstrom et al	Sweden	ALPPS/TSH	48/49	1b	9

ALPPS=associating liver partition and portal vein ligation for staged hepatectomy, PVE=portal vein embolization, TSH=2-staged hepatectomy.

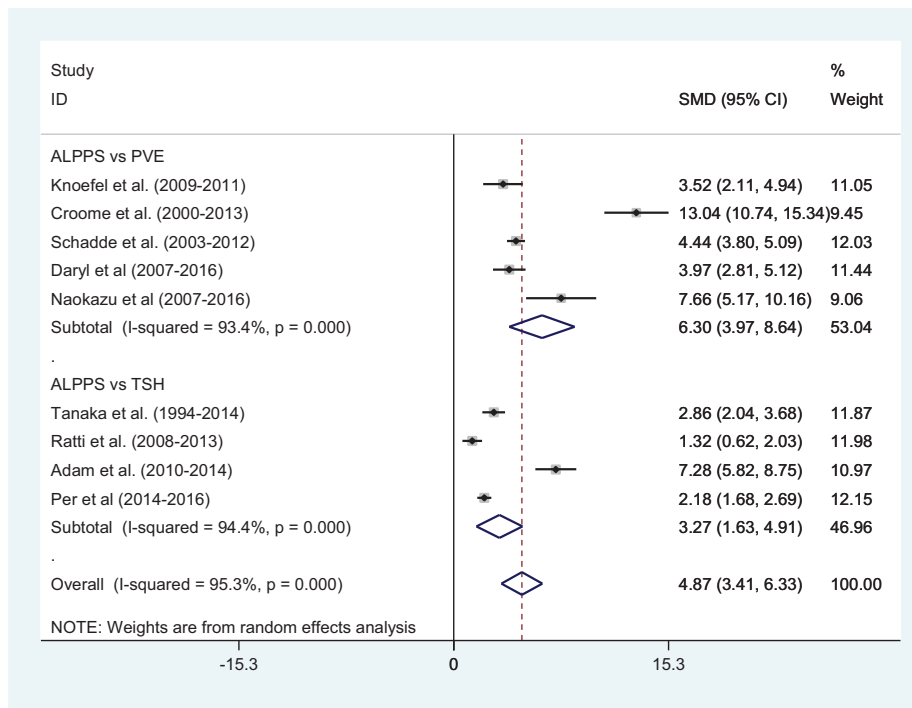


Figure 2. Comparison of FLR regeneration rate after first surgery between ALPPS and PVE/TSH. ALPPS=associating liver partition and portal vein ligation for staged hepatectomy, PVE=portal vein embolization, TSH=2-staged hepatectomy.

There was no heterogeneity among include studies ($I^2=0$) (Fig. 5).

Morbidity between ALPPS and TSH groups was available in 4 studies, with 42% after ALPPS and 33% after TSH (RR:

1.13, 95%CI, 0.89–1.44) (Fig. 4). The heterogeneity among include studies was very small ($I^2=1.9%$). Adjusted mortality rates were available in 3 studies,^[20,21,23] with 8.7% after ALPPS and 2.4% after TSH (RR: 1.89, 95%CI, 0.62–5.81).

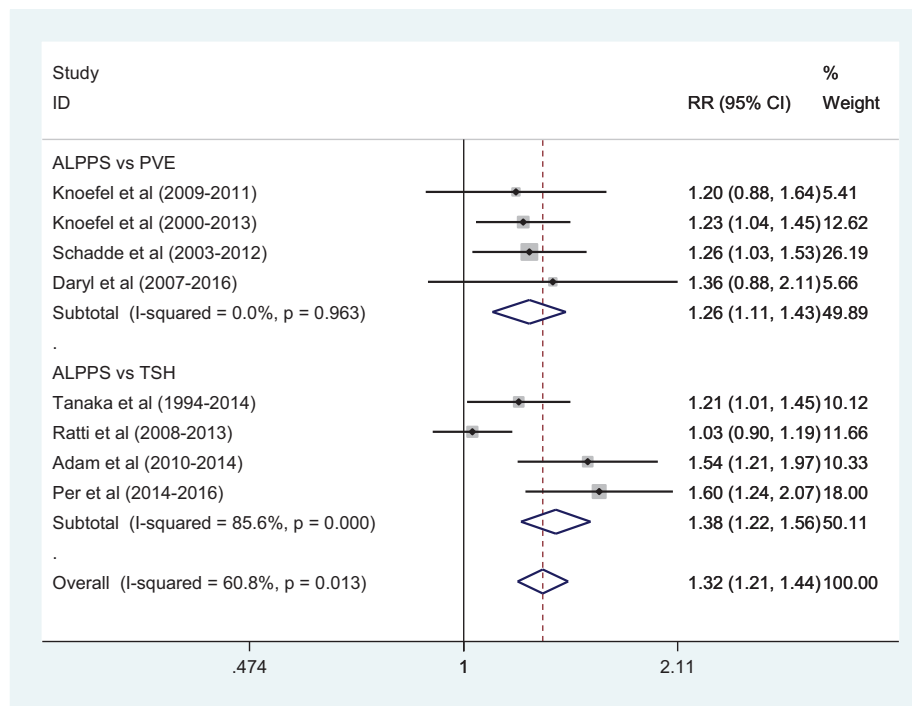


Figure 3. Comparison of resection rate after first surgery between ALPPS and PVE/TSH. ALPPS=associating liver partition and portal vein ligation for staged hepatectomy, PVE=portal vein embolization, TSH=2-staged hepatectomy.

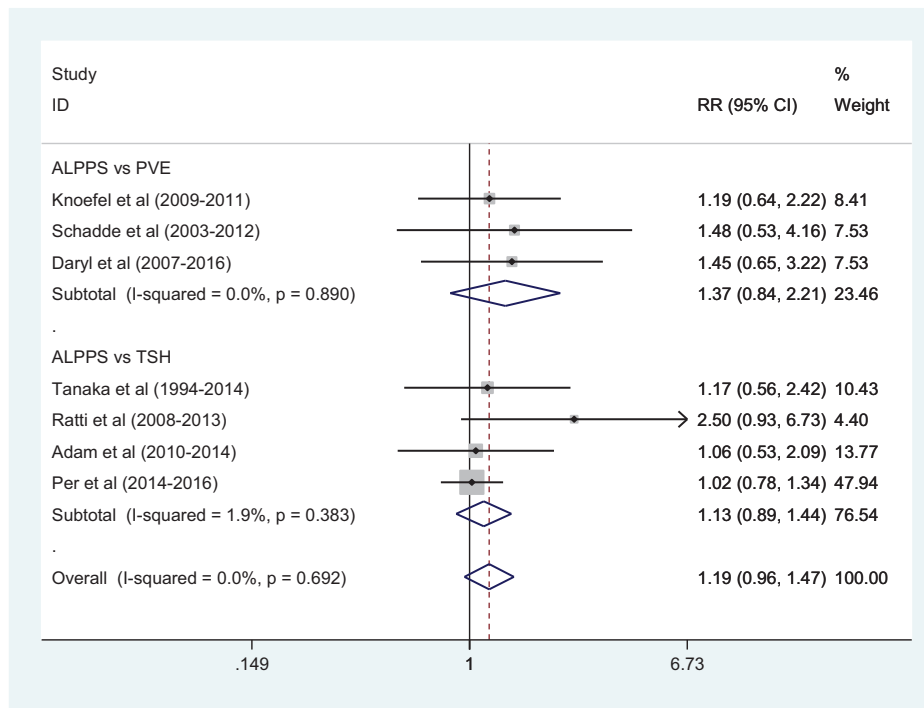


Figure 4. Comparison of morbidity rate after second surgery between ALPPS and PVE/TSH. ALPPS=associating liver partition and portal vein ligation for staged hepatectomy, PVE=portal vein embolization, TSH=2-staged hepatectomy.

There was no heterogeneity among include studies ($I^2=0$) (Fig. 5).

The overall morbidity between ALPPS and PVE/TSH groups was 29.7% and 26.1% (RR: 1.19, 95%CI, 0.96–1.47). There

was no heterogeneity among include studies ($I^2=0$). A fixed-effect model was used to estimate morbidity rates among ALPPS, PVE and TSH (Fig. 4). Adjusted mortality rates were 9.9% after ALPPS and 3.8% after PVE/TSH (RR: 2.11, 95%CI, 1.02–4.33).

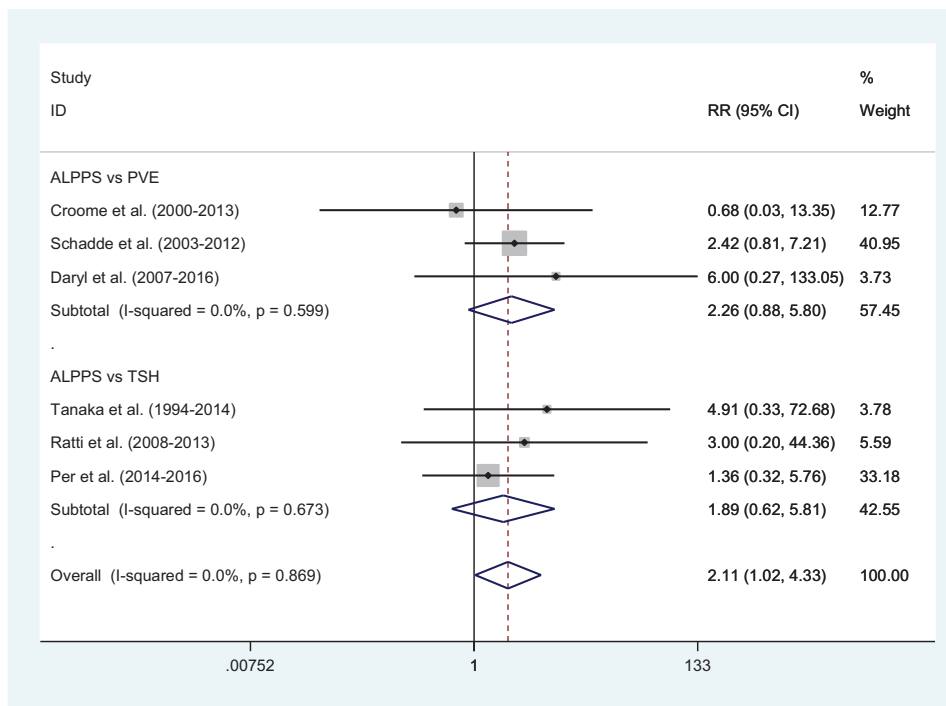


Figure 5. Comparison of mortality rate after second surgery between ALPPS and PVE/TSH. ALPPS=associating liver partition and portal vein ligation for staged hepatectomy, PVE=portal vein embolization, TSH=2-staged hepatectomy.

There was no heterogeneity among include studies ($I^2=0$). A fixed-effect model was used to estimate mortality rates among ALPPS, PVE, and TSH (Fig. 5).

4. Discussion

Since the original description by Schnitzbauer et al,^[4] the ALPPS technique has taken many routes, sparking both intense enthusiasm as well as skepticism alike among the surgery community. It is still unclear where the technique should fit within the surgeon's armament. The most important contribution of ALPPS is the rapid hypertrophy of liver parenchyma FLR and, therefore, the acceptance of a decrease in the estimated size of the FLR required to avoid posthepatectomy liver failure. ALPPS has enabled larger resections, and even the acceptance of a monosegmental FLR because of its expected hypertrophy to become a possibility.^[26,27] This increase in hypertrophy of the FLR raises the threshold for what is considered resectable, theoretically decreasing the proportion of patients who do not reach second stage.

Despite this enthusiasm, there is a lack of evidence to guide clinicians about the most appropriate role for ALPPS in liver surgery. To date, there is no Level 1 evidence that illustrates the benefit of ALPPS over PVE and 2-stage resections. Meaningful comparisons of clinical outcomes are difficult to make. To our knowledge, the only registered, randomized controlled trials recruiting currently are the Scandinavian multicenter Liver Growth Stimulation in Advanced Colorectal Liver Metastatic Disease (LIGRO) trial (ALPPS vs PVE) and the Regeneration of Liver: Portal Vein Embolization Versus Radiofrequency Assisted Ligation for Liver Hypertrophy (REBIRTH) trial from Imperial College London (RALPP vs PVE).

This systematic review and meta-analysis targeted available strategies aiming at increasing small FLR before extended liver resection in patients with primary or secondary liver malignancies. The main findings are that ALPPS induces a greater degree of hypertrophy of the FLR in a shorter time than PVE and TSH, that the likelihood of achieving a complete tumor-free resection is superior following ALPPS than after conventional 2-step procedures, and that there is a trend toward higher morbidity and mortality after ALPPS. The main reasons for not proceeding with the second step after PVE or TSH are intrahepatic or extrahepatic tumor progression.

This article has shown that ALPPS is associated with a trend toward higher morbidity and mortality compared with PVE and TSH. Different technical options in performing ALPPS (e.g., tourniquet, RFA, or microwave) were discussed including a lively debate about the use of partial versus complete transection of parenchyma during the first step to decrease morbidity and mortality rates. However, these variations are all at an early stage, without sufficient convincing data. The first analysis of the international ALPPS registry^[28] showed that better selection of patients and indications decreased mortality and morbidity rates. With signs of liver failure such as a Model of End stage Liver Disease score >10 after step 1, step 2 should be postponed. Patients >60 years are at higher risk of poor outcome, and this factor should be included in the evaluation for suitability to ALPPS. The main limitation of this meta-analysis is only 9 studies included in the study, which makes the power of conclusion quite weak. Whether the patients could get benefit from ALPPS is still controversial, thus more studies about ALPPS are needed to confirm this.

5. Conclusion

ALPPS is associated with greater future liver remnant hypertrophy and a higher rate of completion of stage 2, but this may be at the price of greater morbidity and mortality. As the level of evidence to support the superiority of ALPPS over others is low, a randomized trial should be conducted for better assessment of ALPPS compared with other available strategies.

Author contributions

Conceptualization: Kezhong Tang.

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Formal analysis: Yanmo Liu.

Funding acquisition: Yingxin Yang.

Investigation: Yingxin Yang.

Methodology: Shenglong Gu.

Project administration: Shenglong Gu, Kezhong Tang.

Resources: Kezhong Tang.

Writing – original draft: Kezhong Tang.

Writing – review & editing: Kezhong Tang.

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