

World Journal of *Gastroenterology*

World J Gastroenterol 2019 October 21; 25(39): 5897-6040



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World Journal of Gastroenterology

Volume 25 Number 39 October 21, 2019

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The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for WJG as 3.411 (5-year impact factor: 3.579), ranking WJG as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yu-Jie Ma*

Proofing Production Department Director: *Yun-Xiaojuan Wu*

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Subrata Ghosh, Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE

Ze-Mao Gong, Director

PUBLICATION DATE

October 21, 2019

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ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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Complete or partial split in associating liver partition and portal vein ligation for staged hepatectomy: A systematic review and meta-analysis

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Author contributions: Huang HC analyzed data, wrote the paper; Bian J performed research; Bai Y contributed analytic tools; Lu X performed research; Xu YY performed research; Sang XT performed research; Zhao HT designed research.

Conflict-of-interest statement: The authors deny any conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been adopted by liver surgeons in recent years. However, high morbidity and mortality rates have limited the promotion of this technique. Some recent studies have suggested that ALPPS with a partial split can effectively induce the growth of future liver remnant (FLR) similar to a complete split with better postoperative safety profiles. However, some others have suggested that ALPPS can induce more rapid and adequate FLR growth, but with the same postoperative morbidity and mortality rates as in partial split of the liver parenchyma in ALPPS (p-ALPPS).

AIM

To perform a systematic review and meta-analysis on ALPPS and p-ALPPS.

METHODS

A systematic literature search of PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov was performed for articles published until June 2019. Studies comparing the outcomes of p-ALPPS and ALPPS for a small FLR in consecutive patients were included. Our main endpoints were the morbidity, mortality, and FLR hypertrophy rates. We performed a subgroup analysis to evaluate patients with and without liver cirrhosis. We assessed pooled data using a random-effects model.

RESULTS

Four studies met the inclusion criteria. Four studies reported data on morbidity and mortality, and two studies reported the FLR hypertrophy rate and one study involved patients with cirrhosis. In the non-cirrhotic group, p-ALPPS-treated

Manuscript source: Unsolicited manuscript

Received: August 24, 2019

Peer-review started: August 24, 2019

First decision: September 10, 2019

Revised: September 17, 2019

Accepted: September 27, 2019

Article in press: September 27, 2019

Published online: October 21, 2019

P-Reviewer: Chandrakesan P, Shao L, Wittkopf N

S-Editor: Tang JZ

L-Editor: Ma JY

E-Editor: Ma YJ



patients had significantly lower morbidity and mortality rates than ALPPS-treated patients [odds ratio (OR) = 0.2; 95% confidence interval (CI): 0.07–0.57; $P = 0.003$ and OR = 0.16; 95% CI: 0.03–0.9; $P = 0.04$]. No significant difference in the FLR hypertrophy rate was observed between the two groups ($P > 0.05$). The total effects indicated no difference in the FLR hypertrophy rate or perioperative morbidity and mortality rates between the ALPPS and p-ALPPS groups. In contrast, ALPPS seemed to have a better outcome in the cirrhotic group.

CONCLUSION

The findings of our study suggest that p-ALPPS is safer than ALPPS in patients without cirrhosis and exhibits the same rate of FLR hypertrophy.

Key words: Liver, Cancer; Partial split; Staged hepatectomy; Systematic review; Meta-analysis

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Core tip: Several studies have reported the comparison of complete and partial associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). This meta-analysis, including all of these studies published to date, found that the partial ALPPS is safer than ALPPS in patients without cirrhosis and exhibits the same rate of future liver remnant hypertrophy. However, as the sample size is not large, more randomized controlled trials should be carried out.

Citation: Huang HC, Bian J, Bai Y, Lu X, Xu YY, Sang XT, Zhao HT. Complete or partial split in associating liver partition and portal vein ligation for staged hepatectomy: A systematic review and meta-analysis. *World J Gastroenterol* 2019; 25(39): 6016-6024

URL: <https://www.wjgnet.com/1007-9327/full/v25/i39/6016.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v25.i39.6016>

INTRODUCTION

In 2012, Schnitzbauer *et al*^[1] introduced a new surgical strategy termed associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for patients with an insufficient future liver remnant (FLR) after major hepatectomy. This technique involves ligation of the portal vein and a complete split of the liver parenchyma, which can considerably accelerate FLR hypertrophy and markedly reduce the time interval between stages. However, the surgery-related morbidity and mortality rates are high. A published analysis of the international ALPPS registry, which includes 202 patients, revealed an in-hospital mortality rate of 9% and a severe complication (grade $\geq 3b$)^[2] rate of 28%^[3]. Postoperative adverse events were evaluated according to the Clavien-Dindo classification of surgical complications^[2]. A major complication was defined as a grade $\geq 3a$ complication. The morbidity and mortality rates can reflect the safety of this surgical strategy, and the FLR hypertrophy rate can reflect the effectiveness. Recent evidence has demonstrated that a partial split (defined as 50%–80% of the complete transection surface) of the liver parenchyma in ALPPS (p-ALPPS) results in the same rate of FLR hypertrophy as a complete split but with lower postoperative morbidity and mortality rates^[4]. However, some evidence has also indicated that p-ALPPS does not have a comparable FLR hypertrophy rate and is associated with the same morbidity and mortality rates as in ALPPS^[5]. Therefore, we performed a systematic review and meta-analysis of split completeness and its impact on the FLR hypertrophy, morbidity, and mortality rates in patients with a small FLR.

MATERIALS AND METHODS

Search strategy and selection criteria

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement^[6] and was registered at the International Prospective Register of Systematic Reviews (number CRD42017057798). We performed a systematic search of PubMed, Embase, the

Cochrane Library, and Clinical Trials.gov for relevant studies performed until June 2019. We applied no language restrictions. The search terms used for PubMed were: ((ALPPS[All Fields] OR (associating[All Fields] AND ("liver"[MeSH Terms] OR "liver"[All Fields]) AND partition[All Fields] AND ("portal vein"[MeSH Terms] OR "portal"[All Fields] AND "vein"[All Fields]) OR "portal vein"[All Fields]) AND ("ligation"[MeSH Terms] OR "ligation"[All Fields]) AND staged[All Fields] AND ("hepatectomy"[MeSH Terms] OR "hepatectomy"[All Fields]))) OR partial-ALPPS[All Fields]) OR (staged[All Fields] AND ("hepatectomy"[MeSH Terms] OR "hepatectomy"[All Fields])). We considered all potentially eligible studies for review. The studies in the reference list were also assessed for eligibility.

Two authors performed the literature search and study inclusion independently. Inconsistent results were resolved by a group discussion including a third author. The inclusion criterion was direct comparison between p-ALPPS and ALPPS for patients with a small FLR.

Data extraction

Year of publication, number of patients treated, and dichotomous data from the two treatments, such as morbidity and mortality, were extracted from each included study. We also extracted the FLR hypertrophy rate from each study as continuous data.

Study quality assessment

The Newcastle-Ottawa scale was used to assess the quality of retrospective studies; if the study was scored > 6 , it was graded as I and when the score was ≤ 5 , it was graded as II^[7]. Funnel plots were used to evaluate the risk of publication bias.

Statistical analysis

We examined the effect of p-ALPPS *vs* ALPPS in patients with a small FLR and total patients in each study. Heterogeneity among the included studies was evaluated by I^2 statistic and Chi-square test^[8]. A random-effects model was applied when $P < 0.10$ or $I^2 > 50\%$ ^[9]. All statistical tests were two-sided, and a P value < 0.05 was considered significant. Publication bias was evaluated by funnel plots. Statistical analyses were performed using Review Manager 5.2 (The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Search results

We identified 398 studies, of which 4 (with data for 124 patients)^[4,5,10,11] were included in the meta-analysis (Figure 1).

Characteristics and quality assessment of included studies

The characteristics of the included studies are listed in Table 1. All four included studies were grade I according to the Newcastle-Ottawa scale^[7]. Patient information in the two treatment groups is presented in Table 2. Four studies reported data on morbidity and mortality, and two studies reported the FLR hypertrophy rate (Table 2).

Meta-analysis

Meta-analysis was performed in the p-ALPPS and ALPPS groups. In non-cirrhotic patients, as shown in Figure 2, a significant difference was found in the morbidity rate between the two groups [odds ratio (OR) = 0.2; 95% confidence interval (CI): 0.07–0.57; $P = 0.003$]. As shown in Figure 3, a significant difference was observed in the mortality rate between the two groups (OR = 0.16; 95%CI: 0.03–0.9; $P = 0.04$). The FLR hypertrophy rate was not significantly different between the two groups (OR = – 6.25; 95% CI: – 26.31–13.82; $P = 0.54$) (Figure 4).

The total effects indicated no difference in the FLR hypertrophy rate or perioperative morbidity and mortality rates between the two groups. However, the number of patients with cirrhosis was too small and only one study was involved. Therefore, the results should be interpreted with caution. Publication bias was evaluated by a funnel plot (Figure 5).

DISCUSSION

Our results show that compared with ALPPS, p-ALPPS can achieve lower surgery-

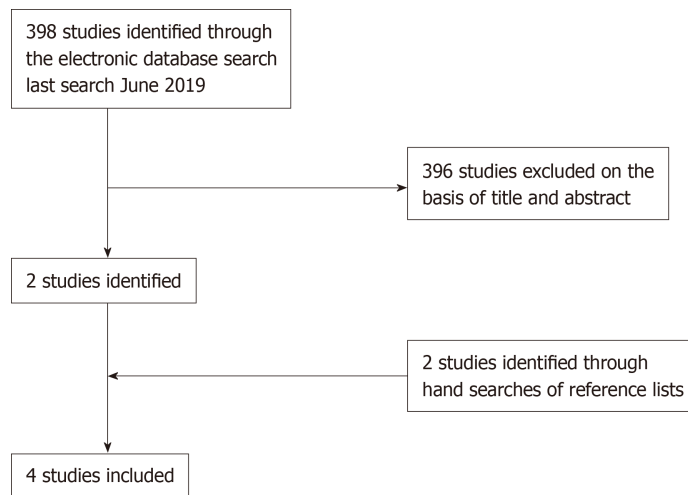


Figure 1 Flowchart for identifying eligible studies and study selection process.

related morbidity and mortality rates and exhibits the same FLR hypertrophy rate in non-cirrhotic patients. In cirrhotic patients, ALPPS seems to offer a better outcome with respect to FLR hypertrophy with no increase in morbidity or mortality. However, only one study focused on patients with cirrhosis. Therefore, the results should be interpreted with caution, and more studies are needed.

Before the introduction of ALPPS, some other strategies were applied to induce liver hypertrophy in patients with a small FLR. The most common methods were portal vein embolization (PVE) and portal vein ligation (PVL) for staged hepatectomy. PVE was first described in 1990 by Makuuchi *et al*^[12]. In this technique, embolism of the ipsilateral portal blood flow induces rapid proliferation of the FLR. PVL was primarily used in patients with colorectal cancer liver metastases and could reportedly trigger a similar or better regenerative response than PVE^[13,14]. PVE and PVL are now commonly applied in two-staged hepatectomy to improve the R0 resection rate^[15-17]. Although PVE or PVL can effectively stimulate the growth of FLR, the second step of surgery is not always successful^[18,19]. The main reasons include disease progression during the waiting period and insufficient liver hypertrophy. However, rapid and adequate FLR hypertrophy is the most prominent advantage of ALPPS. Although ALPPS is associated with greater FLR hypertrophy and a higher rate of completion of stage 2 than the two-staged hepatectomy, these advantages may be obtained at the cost of greater morbidity and mortality^[20,21].

These disadvantages triggered the development and improvement of the ALPPS procedure. Many techniques have been proposed to reduce the postoperative morbidity and mortality rates since the introduction of this new surgical strategy^[22-25]. These techniques include p-ALPPS, radiofrequency-assisted liver partition with portal vein ligation (RALPP), laparoscopic microwave ablation and portal vein ligation for staged hepatectomy, associating liver tourniquet and portal vein ligation for staged hepatectomy (ALTPS), and sequential ALTPS^[26].

Most of these techniques reduced the perioperative morbidity and mortality rates by avoiding a physical split of the liver parenchyma. RALPP uses radiofrequency ablation during the laparoscopic first stage to produce a line of avascular necrosis along the future line of transection^[27]. This technique ceases blood flow from the FLR to the diseased hemiliver while inducing FLR hypertrophy. The RALPP has better outcome of FLR hypertrophy than PVE and same outcome as by ALPPS, but has lower morbidity and mortality rates than ALPPS. Microwave ablation is used to treat hepatic tumors with electromagnetic microwaves to produce coagulative necrosis^[28]. ALTPS using a tourniquet to ensure parenchymal compression and cessation of blood flow across the future line of transection has been described in three studies^[29-31].

All of these modifications were developed to improve the safety of ALPPS. However, most of them are still in the initial stage with sporadic case reports and lack of comparison with ALPPS (with the exception of p-ALPPS, which has been addressed in many studies with some inconsistent results).

p-ALPPS is defined as ALPPS with a partial split of the liver parenchyma involving 50% to 80% of the complete transection surface. However, the exact amount of liver parenchyma that needs to be transected to trigger enough regeneration of the FLR remains unclear. Some authors have suggested extending the transection up to the middle hepatic vein^[10], which means more transection may be performed than

Table 1 Characteristics of the included studies

Authors	Country	Year of publication	Number of patients	NOS ^a	Liver cirrhosis
Alvarez <i>et al</i> ^[10]	Buenos Aires, Argentina	2015	30	I	N
Chan <i>et al</i> ^[5]	Hong Kong, China	2016	25	I	Y
Linecker <i>et al</i> ^[11]	Zurich, Switzerland	2017	45	I	N
Petrowsky <i>et al</i> ^[4]	Zurich, Switzerland	2015	24	I	N

^aNewcastle-Ottawa score: studies were graded I if the score was > 6 or II if the score was ≤ 5. NOS: Newcastle-Ottawa score.

actually needed. Other surgeons have suggested at least a 50% transection based on intraoperative estimation^[4]. In this case, however, the FLR hypertrophy rate may be too low. According to experimental and clinical data, p-ALPPS with a median partial transection of 61% can trigger FLR hypertrophy comparable with that of ALPPS with a complete split^[10,11]. Based on the studies evaluated in the current analysis, the waiting period before the second step and the completion rate of the second step were not significantly different between p-ALPPS and ALPPS. Additionally, there is no evidence indicating that p-ALPPS is associated with a higher rate of disease progression during the waiting period.

The mechanism of FLR hypertrophy in ALPPS or p-ALPPS remains unclear. This hypertrophy might be related to redistribution of the portal blood flow between the diseased segment/s and the FLR. A recent study indicated that accelerated regeneration in ALPPS was not solely related to parenchymal transection and discontinuation of the blood supply between the two parts of the liver, but was mostly due to an “inflammatory-like reaction” leading to enhanced hepatocyte growth. The interleukin-6 level in the plasma and the interleukin-6 and tumor necrosis factor- α levels in the liver tissue reportedly increase after the first step^[32], significantly facilitating the proliferation of the liver. In other words, the degree of liver parenchymal partitioning may not be the key factor in FLR hypertrophy. The similar FLR hypertrophy rate between ALPPS and p-ALPPS in the present study also seems to support these mechanisms. However, further studies are needed to determine whether there is a difference in inflammatory mediators between ALPPS and p-ALPPS.

This study has several limitations. Because of the small number of studies, especially studies involving patients with cirrhosis, this meta-analysis might have included an insufficient number of cases, leading to biased results. In addition, although a subgroup analysis was performed, the included studies may have still had publication bias as shown by the funnel plot. The retrospective nature of the studies contributes to this bias. Finally, further outcomes of this new technology should be followed up, but all included studies represent the latest research to date and thus lack long-term follow-up data.

Although our findings clearly support the use of p-ALPPS in non-cirrhotic patients with a small FLR, further studies are needed to fully evaluate the application of this treatment in practice.

Table 2 Outcomes of FLR hypertrophy rate, morbidity and mortality in each included study

Authors	FLR hypertrophy		Morbidity		Mortality	
	ALPPS	p-ALPPS	ALPPS	p-ALPPS	ALPPS	p-ALPPS
Alvarez <i>et al</i> ^[10]	107% (12.2)	90% (20.8)	8 (9)	8 (21)	1 (9)	1 (21)
Chan <i>et al</i> ^[5]	-	-	1 (13)	3 (12)	0 (13)	2 (12)
Linecker <i>et al</i> ^[11]	61% (15)	64.5% (12.1)	8 (22)	3 (23)	7 (22)	0 (23)
Petrowsky <i>et al</i> ^[4]	-	-	12 (18)	2 (6)	4 (18)	0 (6)

FLR: Future liver remnant; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; p-ALPPS: Partial split of the liver parenchyma in ALPPS.

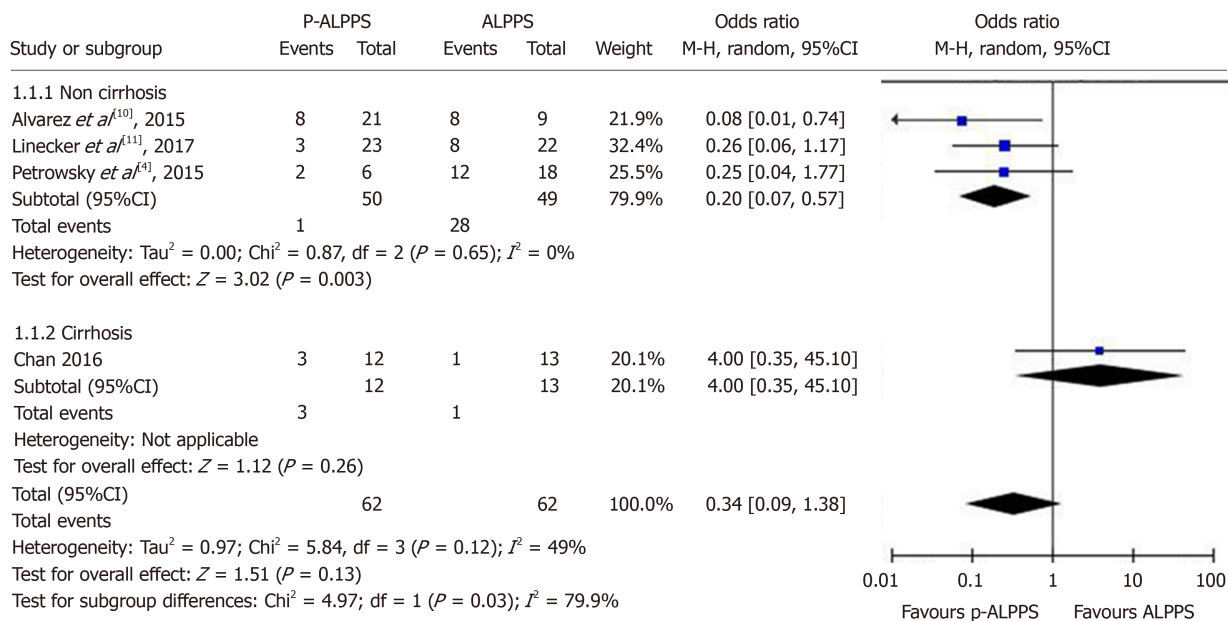


Figure 2 Meta-analysis and subgroup analysis of morbidity in p-ALPPS vs ALPPS (Dindo-Clavien classification $\geq 3a$). ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; p-ALPPS: Partial split of the liver parenchyma in associating liver partition and portal vein ligation for staged hepatectomy; CI: Confidence interval.

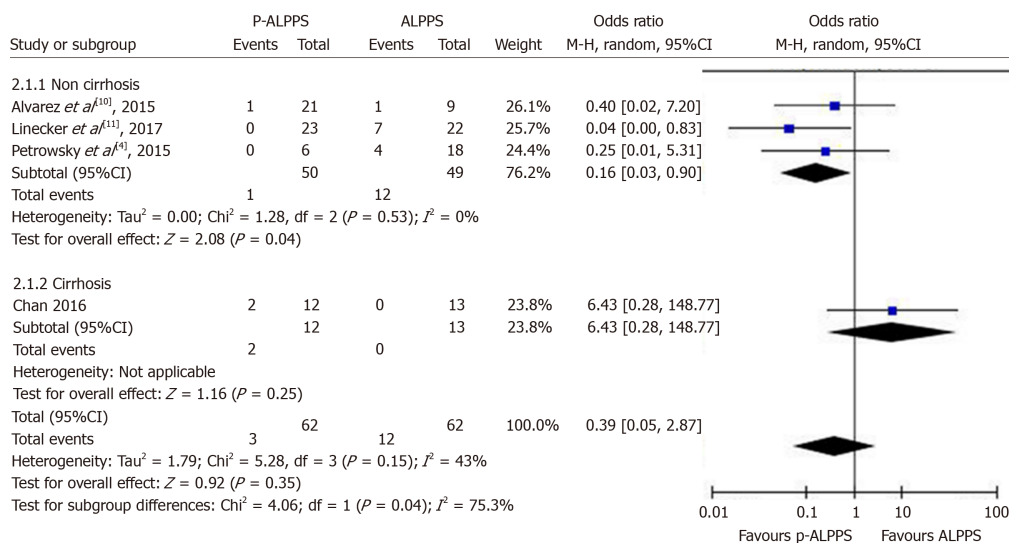


Figure 3 Meta-analysis and subgroup analysis of postoperative mortality in p-ALPPS vs ALPPS. ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; p-ALPPS: Partial split of the liver parenchyma in associating liver partition and portal vein ligation for staged hepatectomy; CI: Confidence interval.

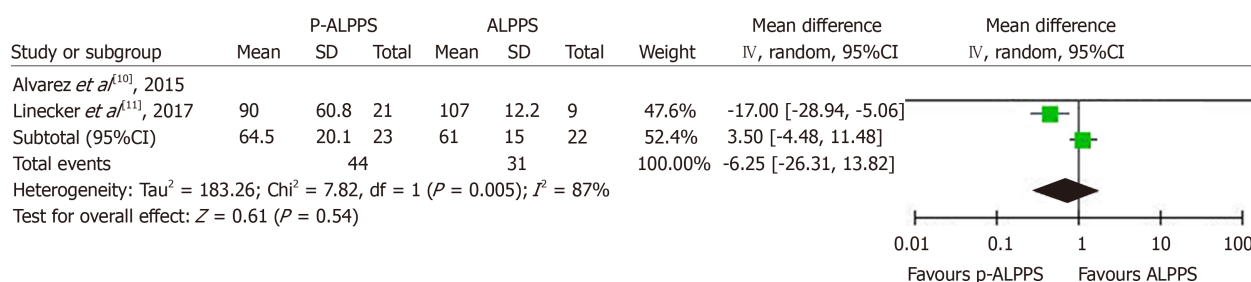


Figure 4 Meta-analysis of p-ALPPS vs ALPPS, and comparison of FLR hypertrophy in none-cirrhosis group. FLR: Future liver remnant; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; p-ALPPS: Partial split of the liver parenchyma in associating liver partition and portal vein ligation for staged hepatectomy; CI: Confidence interval.

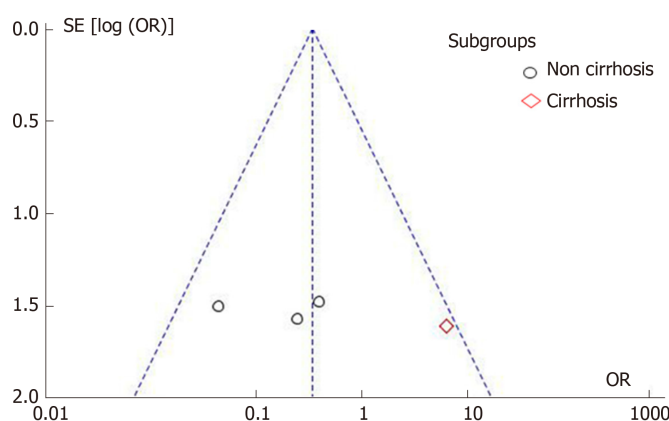


Figure 5 Funnel plot of publication bias. OR: Odds ratio.

ARTICLE HIGHLIGHTS

Research background

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been adopted by liver surgeons. However, ALPPS with a partial split has been proposed recent years. Conflicting results have been reported between the ALPPS and partial split of the liver parenchyma in ALPPS (p-ALPPS). This systematic review and meta-analysis evaluated the difference in the future liver remnant (FLR) hypertrophy rate, postoperative morbidity and mortality rates between the ALPPS and p-ALPPS.

Research motivation

The FLR hypertrophy rate and safety between ALPPS and p-ALPPS are controversial.

Research objectives

To compare the currently reported results between ALPPS and p-ALPPS to confirm which is better for patients.

Research methods

We systematically reviewed literatures on the ALPPS and p-ALPPS, and included relevant studies for meta-analysis.

Research results

The total effects indicated no difference in the FLR hypertrophy rate or perioperative morbidity and mortality rates between the ALPPS and p-ALPPS groups. However, p-ALPPS is safer than ALPPS in patients without cirrhosis and exhibits the same rate of FLR hypertrophy.

Research conclusions

In non-cirrhotic patients, p-ALPPS resulted in the same FLR hypertrophy rate compared with the ALPPS, and is safer than ALPPS.

Research perspectives

More studies to compare ALPPS with p-ALPPS in cirrhosis patients should be carried out.

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