The comparison of associating liver partition and portal vein ligation for staged hepatectomy versus portal vein embolization in postoperative outcomes and complications for the treatment of liver cancer with insufficient future liver remnant: a Meta analysis and systematic review

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Research article

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Abstract

Background: This study evaluated the feasibility, safety and effectiveness in patients treated with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and portal vein embolization (PVE) for the treatment of liver malignant tumors with insufficient future liver remnant (FIR). Method: We performed a computer search on the PubMed databases to retrieve the RCT or clinical trials comparing ALPPS and PVE published from January 2010 to January 2020. The quality of the included trials was assessed according to the inclusion and exclusion criteria by two researchers independently. The RevMan 5.3 and STATA 12.0 software were used to extract and analyze the data. Result: A total of 11 retroprospective clinical trial articles comprising 867 patients were included in the study. The number of patients who underwent ALPPS were 247 and 620 for PVE. There were significant differences (P <0.05) in the second stage hepatectomy（OR=11.25, 95%CI: 5.64~22.43, Z=6.87, P＜0.001）, the sufficient FLR growth（MD=46.85, 95% CI:4~89.70, Z=2.41, P=0.03）, the time to stage II operation (MD=-22.85, 95% CI:-33.87~-11.84, Z=4.07, P＜0.001) and rate of R0 resection（OR=2.29, 95%CI: 1.07~4.90, Z=2.13, P=0.03） between the two groups. However, no significant differences were observed between ALPPS and PVE in terms of mortality within 90 days of perioperative period, overall postoperative complication rate, incidence of postoperative liver failure and postoperative hospital stay (P＞0. 05). Conclusion: Compared with PVE, The ALPPS procedure was associated with good postoperative outcomes with insufficient FLR. However, the clinical application of ALPPS and PVE has some limitations. Large, multicenter prospective randomized controlled trials are needed to validate these findings.

Background

Hepatic resection has become the standard treatment for patients with liver tumours and remains the only potentially curative therapy in most instances. Extended liver resections are frequently necessary to achieve tumour-free resection margins[1]. A low future liver remnant volume-to-total liver volume (FLR) is associated with higher postoperative morbidity and mortality rates in patients undergoing hepatectomy[2]. In the 1980s, Makuuchi et al 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[3]. However, even though PVE can increase the volume of the FLR by up to 40% within 3 to 8 weeks, but the second stage of the procedure was not always performed[4]. In 2012, Schnitzbauer et al described a novel approach: associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). This method seems to increase FIR in a much shorter time. However, according to preliminary reports, this improvement comes at the cost of increased postoperative morbidity and mortality, which justifies further investigation into technique modification. Safety concerns in ALPPS have been highly controversial[5].

At present, there are different clinical views on the effect of ALPPS and PVE, and there is still lack of sufficient evidence-based medicine (EBM) to its their advantages. Therefore, we compared the safety, feasibility and effectiveness of ALPPS and PVE with a meta-analysis system by retrieving the clinical

comparison study of ALPPS and PVE, in order to provide help to guide further research and clinical practice in the field of hepatobiliary surgery.

Methods

2.1. Literature Search Strategies

We conducted a comprehensive systematic literature search of online database in PubMed from January 2010 to January 2020 to identify all of RCTs and observational studies. We searched for published data using the following terms: ((((((((((((associating liver partition and portal vein ligation for staged hepatectomy)) OR ALPPS) AND portal vein embolization) OR PVE) OR portal vein ligation) OR PVI) OR portal vein occlusion) OR PVO) AND hepatectomy) OR staged hepatectomy) OR staged liver resection) OR liver resection) OR two-stage hepatectomy) OR hepatic resection. All the search results were evaluated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) statement (supplementary material)[6]. We also reviewed the references of included articles and related systematic reviews to identify additional studies. Ethical approval was not necessary, because available data were collected from the previous published studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the included literature should contain the abstract and full text of the published literature from January 2010 to January2020; (2) literature design type: Cohort studies, case-control studies, and randomized controlled studies with strict inclusion and exclusion criteria[7]; (3) The number of cases in the literature was ≥5, and the subjects were FLR-deficient patients with intermediate or advanced liver cancer, including primary or metastatic tumor cases, without restrictions of radiotherapy and chemotherapy; (4) Major indicators such as FLR growth rate and two-step surgical completion rate have been recorded in the literature.

The exclusion criteria were as follows: (1) the type of literature design is not clear, and the general situation of the included patients is not clear; (2) the included study language is limited to English; (3) data duplication; (4) the grouping description in the included literature is not clear, and some items are missing.

2.3. Data Extraction and Quality Assessment

Data extraction and the evaluation of literature quality were conducted independently by 2 investigators. A Microsoft excel database was used to record all available information, including: The perioperative completion rate of two-step surgery, FLR growth rate, two-step surgery interval time of ALPPS group and PVE group, R0 resection rate, mortality rate within 90 days, overall complication rate, postoperative liver failure rate and , length of stay, etc. All studies were assessed by Newcastle-Ottawa Scale (NOS). The quality scores ranged from 6 to 9, suggesting that the methodological quality was high[8].

2.4. Statistical Analysis

Statistical analysis was performed using *RevMan* (version 5.3; Cochrane Collaboration, Oxford, UK) and *STATA*, version 12.0 (Stata Corporation, College Station, TX). Heterogeneity among studies was tested using Cochran Chi-square test and I^2. And when I^2>50%, a random-effects model was chosen to pool the results, while a fixed-effects model was used when I^2<50%. Publication bias was detected using the Funnel plots tests and Egger tests. Counts and measures were analyzed by Odds ratio (OR) and weighted mean difference (WMD) with 95% confidence intervals (CI)[10]. The methodological quality of the included studies was assessed using the Newcastle–Ottawa scale (NOS). *P* values of <0.05 were considered statistically significant.

Results

3.1. Literature Search and Study Characteristics

According to the previous search strategy, 25961 citations were obtained from the online database from January 2010 to January 2020. Then, 1325 records were excluded by viewing title and abstract. Among the remaining 187 records, 175 citations were removed with various reasons. Finally, 11 full-text studies were suitable for this meta-analysis[9-19](Fig.1). Besides the characteristics, quality evaluation, and demographics of the included studies are summarized in Table 1.

3.2. Data Analysis

3.2.1. The second stage hepatectomy

Eleven literatures described the completion rate of two-step surgery in two groups, including a total of 867 patients[9-19]. There were 247 cases in ALPPS group and 620 cases in PVE group. The completion rate of two-step surgery was significantly different between the two groups (OR=11.25, 95%CI: 5.64~22.43, Z=6.87, *P*□0.001) (Fig. 2A).

3.2.2. The sufficient FLR growth

The rate of FLR after the first operation was described in 10 articles, including 845 patients[9-14, 16-19]. There were 239 cases in ALPPS group and 606 cases in PVE group. The difference in FLR growth rate between the two groups was statistically significant (MD=46.85, 95% CI:4~89.70, Z=2.41, *P*=0.03) (Fig. 2B).

3.2.3. The time to stage II operation

A total of 671 patients were included in 9 articles describing the time to stage II operation[9, 11, 12, 14-19]. There were 188 cases in ALPPS group and 483 cases in PVE group. The difference between the two groups was statistically significant (MD=-22.85, 95% CI:-33.87~-11.84, Z=4.07, *P*□0.001) (Fig. 2C).

3.2.4. The rate of R0 resection

The R0 removal rate was described in five literatures, involving a total of 307 patients[9, 10, 13, 14, 18]. There were 128 cases in ALPPS group and 179 cases in PVE group. The difference of R0 removal rate between the two groups was statistically significant (OR=2.29, 95%CI: 1.07~4.90, Z=2.13, *P*=0.03) (Fig. 2D).

3.2.5. Mortality within 90 days of perioperative period

All included literatures described the case fatality rate within 90 days of the perioperative period, including a total of 791 patients[9-19]. Among them, 240 cases in ALPPS group and 451 cases in PVE group showed no significant difference in case fatality rate within 90 days between the two groups (OR=1.31, 95%CI: 0.73~2.34, Z=0.91, *P*=0.36) (Fig. 2E).

3.2.6. Overall postoperative complication rate

All included literatures described the overall incidence of postoperative complications (including biliary fistula, sepsis, abdominal infection, etc.), including a total of 791 patients[9-19]. Among them, 240 cases in ALPPS group and 451 cases in PVE group showed no significant difference in the overall complication rate between the two groups (OR=1.14, 95%CI: 0.63~2.07, Z=0.44, *P*=0.66) (Fig. 2F).

3.2.7. The incidence of postoperative liver failure

The incidence of postoperative liver failure was described in 7 literatures, involving a total of 428 patients[11-17]. There were 119 cases in ALPPS group and 309 cases in PVE group, and there was no significant difference in the incidence of postoperative liver failure between the two groups (OR=0.83, 95%CI: 0.42~1.63, Z=0.54, *P*=0.59) (Fig. 2G).

3.2.8. Postoperative hospital stay

The total length of stay was described in 4 articles, including 283 patients. There were 77 cases in ALPPS group and 206 cases in PVE group. There was no significant difference in total hospitalization time between the two groups (OR=4.71, 95%CI: -1.25~10.66, Z=1.55, *P*=0.12) (Fig. 2H).

3.2.9. Immunohistochemical analysis of Ki-67 in tumor tissue

Only one literature described the expression of ki-67 after surgery[13]. At first hepatectomy, Ki-67 expression was evident in 28.2±42.7% of cells in the ALPPS group and 51.7±35.6% in the PVE group (*P*=0.09). At second hepatectomy, expression was 20.5±24.7% in the ALPPS group and 54.5±26.9% in the PVE group (*P*=0.01). No difference of Ki-67 expression in liver tumor cells was seen at first hepatectomy, but expression at second hepatectomy was greater in the PVE group than the ALPPS group.

3.3. Publication Bias and Sensitivity Analysis

On the basis of the overall incidence of perioperative complications in the ALPPS group and the PVE group, the Bgger's test was performed to assess the publication bias of the literature. Funnel plots

indicated a symmetric distribution of included studied. Begg tests demonstrated that there was no potential publication bias among studies (Begg test, *P*=0.94). Sensitivity analyses have confirmed the robustness of the results (Fig. 3).

Discussion

Hepatectomy is the main method to treat various benign and malignant liver tumors. With the development of surgical techniques, anesthesia, radiology, and oncology, the indications for hepatectomy gradually relaxed[20]. But the future liver remnant (FLR), have become the limit the implementation of the main causes of radical resection of liver tumor[21].How to obtain enough FLR has long been a hot topic in hepatic surgery. Portal vein embolization (PVE) leads to sufficient FRL hypertrophy in about 80% of patients, allowing them to undergo surgery from which they were initially rejected[22].

However, a small percentage of patients still do not get enough FLR after PVE[23]. Furthermore, studies have shown that PVE can increase the invasiveness of tumors at the later stage of treatment[24]. Associating liver partition and portal vein ligation for stage hepatectomy (ALPPS) is thought to induce rapid FLR hypertrophy, that in turn, decreases the time for the second stage hepatectomy. But, it can potentially increase postoperative complications[25]. Currently, there are few studies examining postoperative complications and surgical effect after LAPPS and PVE. Therefore, we systematically evaluated the differences in postoperative complications and surgical effect between LAPPS and PVE to guide further research and clinical selection of patients for treatment. Adequate FLR is a prerequisite for reducing the incidence of postoperative liver failure, especially in patients with bilateral hepatic tumors requiring a two-step hepatectomy. Usually, if FLR accounts for more than 25% of the original liver volume after hepatectomy, the patient can fully recover without any serious consequences. For patients with liver damage (fatty liver, cholestasis, etc.), the FLR is required to be at least 40%[26]. The data reviewed showed that the FLR growth rate of the ALPPS group was faster than that of the PVE group, and the FLR growth rate of the ALPPS group could be induced to increase in a short time to reach R0 resection. We think an increase in FLR after ALPPS may be related to the redistribution of portal vein blood flow after hepatic separation. It may also be related to the stimulation of liver regeneration caused by local trauma. In addition, the possible mechanism of ALPPS inducing FLR proliferation has been proved by many studies. (1) Yutaro Kikuchi et al. demonstrated through mouse model experiments that ALPPS induced accelerated hyperplasia of the liver, in which the high expression of inflammatory mediators tumor necrosis factor (TNF-α), transforming growth factor (TGF-β), and hepatocyte growth factor (HGF) was involved in the process of liver hyperplasia[27]. (2) Dipok Kumar Dhar et al. detected 29 cytokines in the rat model by protein chip, and found that an advantage of the ALPPS procedure over PVL group in terms of early regeneration. In addition, cytokine induced neutrophil chemoattractant-1 had the highest expression whereas IL-6 had the highest fold (>6 vs PVL group) expression at the early phase of regeneration in the ALPPS group[28]. (3) Martin DE Santibanes et al. found that the ratio of proliferating cell nuclear antigen (PCNA) and terminal deoxynucleotidyl transferase dUTP significantly increased in the second stage[29]. With the growing body of research, the detailed mechanism of liver regeneration induced by ALPPS will be further elucidated.

In this enrollment study, the completion rate of perioperative two-step surgery in the ALPPS group was significantly higher than that in the PVE group (97.1% vs 72.7%).

We believe that the main reason is that FLR enlargement in the PVE group takes 4–8 weeks, during which there may be a risk of liver metastasis or extrahepatic metastasis. Another reason can be due to some patients do not have enough FLR to undergo second stage hepatectomy. However, in the included study, the number of cases of ALPPS group was small, and there was greater heterogeneity in statistical analysis compared with PVE group, so it was difficult to determine which method was better. In addition, Maulat C et al. reported 7 cases of insufficient FLR after PVE due to portal vein recanalization, collateral circulation obstruction and cholestasis. R0 resection was achieved in 6 cases after rescue ALPPS. Therefore, it is suggested that rescue ALPPS may be an alternative after unsuccessful PVE and could allow previously unresectable patients to reach surgery[30].

This meta-analysis showed that there were no significant differences were observed between ALPPS and PVE in terms of mortality within 90 days of perioperative period, overall postoperative complication rate, incidence of postoperative liver failure and postoperative hospital stay (P–0. 05). However, some included studies showed that the ALPPS group had a higher complication rate and mortality than the PVE group[10, 12, 15-18]. To analyze the reasons, it may be that some patients in the PVE group did not receive the second stage hepatectomy, and the incidence of complications and mortality were not related to the number of the second stage hepatectomy. In order to reduce the perioperative complications and mortality, surgeons have made many efforts: (1) The classic ALPPS requires two open operations, while Machado MA et al. believed that Laparoscopic ALPPS was feasible as the default procedure for patients with very small FLR, and it was not inferior to the open approach. Surgeons experienced with complex laparoscopy should be encouraged to use a laparoscopic approach to ALPPS[31]. (2) Robles R reported in 2014 in the first stage ALPPS, through a tourniquet was placed around the parenchymal transection line, and the right portal vein was ligated and cut (associating liver tourniquet and portal ligation for staged hepatectomy, ALTPS) that creates the new technology. This technique reduces the invasiveness of the first stage and alters the relative invasiveness of the operation by avoiding the separation of liver parenchyma in the first stage[32]. (3) Linecker M et al. reported that partial transection of at least 50% induced comparable hypertrophy (137% vs 156%) and hepatocyte proliferation compared to complete transection[33]. Therefore, partial ALPPS can avoid liver injury caused by complete transection, reduce surgical trauma and effectively reduce *postoperative complications*. (4) In 2014, Chan et al from the University of Hong Kong Queen Mary Hospital reported for the first time that ALPPS was implemented in a patient with a background of chronic liver disease using a pre-approach approach, which specifically included complete hepatic parenchyma separation to IVC, without moving the liver and not dissociating the right half of the liver, retaining the right Hepatic ducts and right hepatic arteries showed reduced adhesion around the liver and inferior vena cava, and reduced the risk of iatrogenic tumor spread[34]. However, only one case of this method was reported, and its clinical feasibility and safety require further investigation. (5) Biological tissue fibrin glue and absorbable collagen membrane were used to wrap the right third liver instead of the traditional plastic bag to reduce abdominal adhesion after the first operation[35]. The above improvements to traditional ALPPS provide more appropriate options

for different patients, improve surgical safety, and reduce the incidence of postoperative complications and mortality.

The Ki-67 protein is present during all active phases of the cell cycle (G(1), S, G(2), and mitosis), but is absent from resting cells (G(0)). Ki-67 protein has been widely used as a proliferation marker for human tumor cells for decades[36]. The included studies showed no difference of Ki-67 expression in liver tumor cells was seen at first hepatectomy, but expression at second hepatectomy was greater in the PVE group than the ALPPS group[13]. We think that the reason for this difference may be compared with PVE, the short treatment period of ALPPS is less likely to cause tumor progression. Moreover, due to the application of neoadjuvant chemotherapy before surgery, the expression level of ki-67 index in ALPPS group was relatively low. The Ki-67 expression was lower in the ALPPS group than in the PVE group after two-step surgery, showing the oncological benefits of ALPPS in *inhibition* of *tumor* growth and *tumor progression.*

Our systematic review summarizes most of the available evidence in this field. However, it has the following limitations: (1) The number of cases of ALPPS is relatively small, and the conclusions are inevitably biased. (2) In the literature included in this article, about 80% of patients with metastatic liver cancer and about 10% of patients with primary liver cancer. There is no detailed comparative data between patients with metastatic liver cancer and primary liver cancer in the literature, so a subgroup analysis of two groups cannot be performed. (3) Despite having searched only one database, we included an extensive number of studies. (4) The total number of cases included in this study was relatively small and there were regional differences. Therefore, large sample, multicenter, and standardized prospective randomized controlled trials are needed to validate these findings.

Conclusion

Compared with PVE group, the perioperative FLR growth rate was faster in ALPPS group, and the completion rate of two-step surgery was higher. Meanwhile, the interval of two-step surgery was shorter, the tumor progression was not obvious, and the average R0 resection rate was higher in ALPPS group. However, no significant differences were observed between ALPPS and PVE in terms of mortality within 90 days of perioperative period, overall postoperative complication rate, incidence of postoperative liver failure and postoperative hospital stay (P 0. 05). Compared to the PVE procedures, ALPPS appears an effective treatment method for liver tumor with insufficient FLR.

Abbreviations

FIR = Function of the future liver remnant

PVE = Portal vein embolization

ALPPS= Associating liver partition and portal vein ligation for staged hepatectomy

NOS=Newcastle-Ottawa Scale

Declarations

Ethics approval and consent to participate

Ethical approval was not necessary, because available data were collected from the previous published studies.

Consent to publish

Not applicable.

Availability of data and materials

All the data are available without restriction. Researchers can obtain data from the corresponding author.

Competing interests

The author(s) declare that they have no competing interests.

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Authors' Contributions

Protocol/project development: Z.-H.L. Data acquisition and interpretation of data: Q.-Y.Z. Statistics analysis of data: Q.-Y.Z and Y.-X.X. Manuscript drafting: Q.-Y.Z and Y.-X.X. Manuscript Revision and accountable for all aspects of the study: Q.-Y.Z. All authors read and approved the final manuscript.

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Table

Due to technical limitations, Table 1 is only available for download from the Supplementary Files section.

Figures

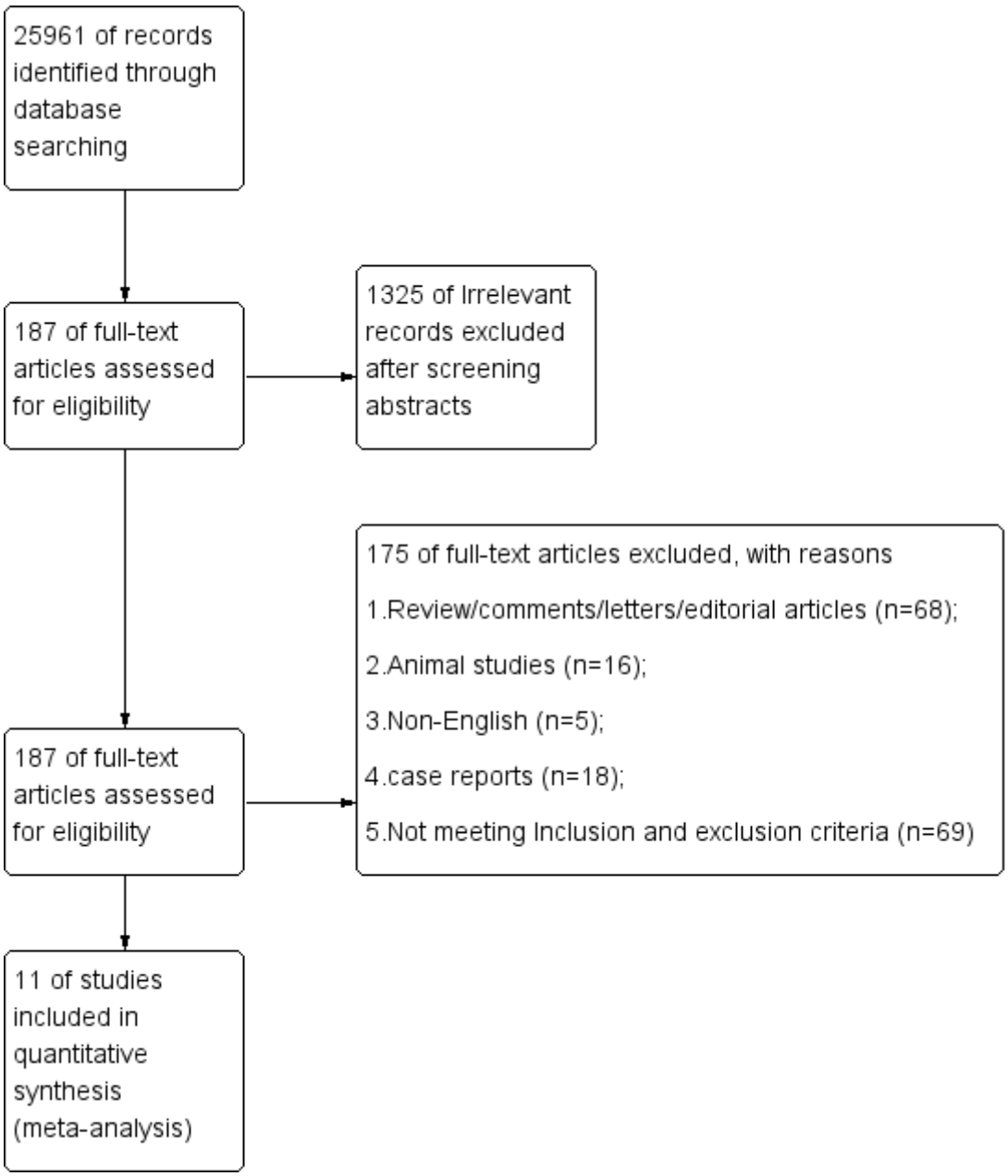

Figure 1

11 full-text studies were suitable for this meta-analysis[9-19].

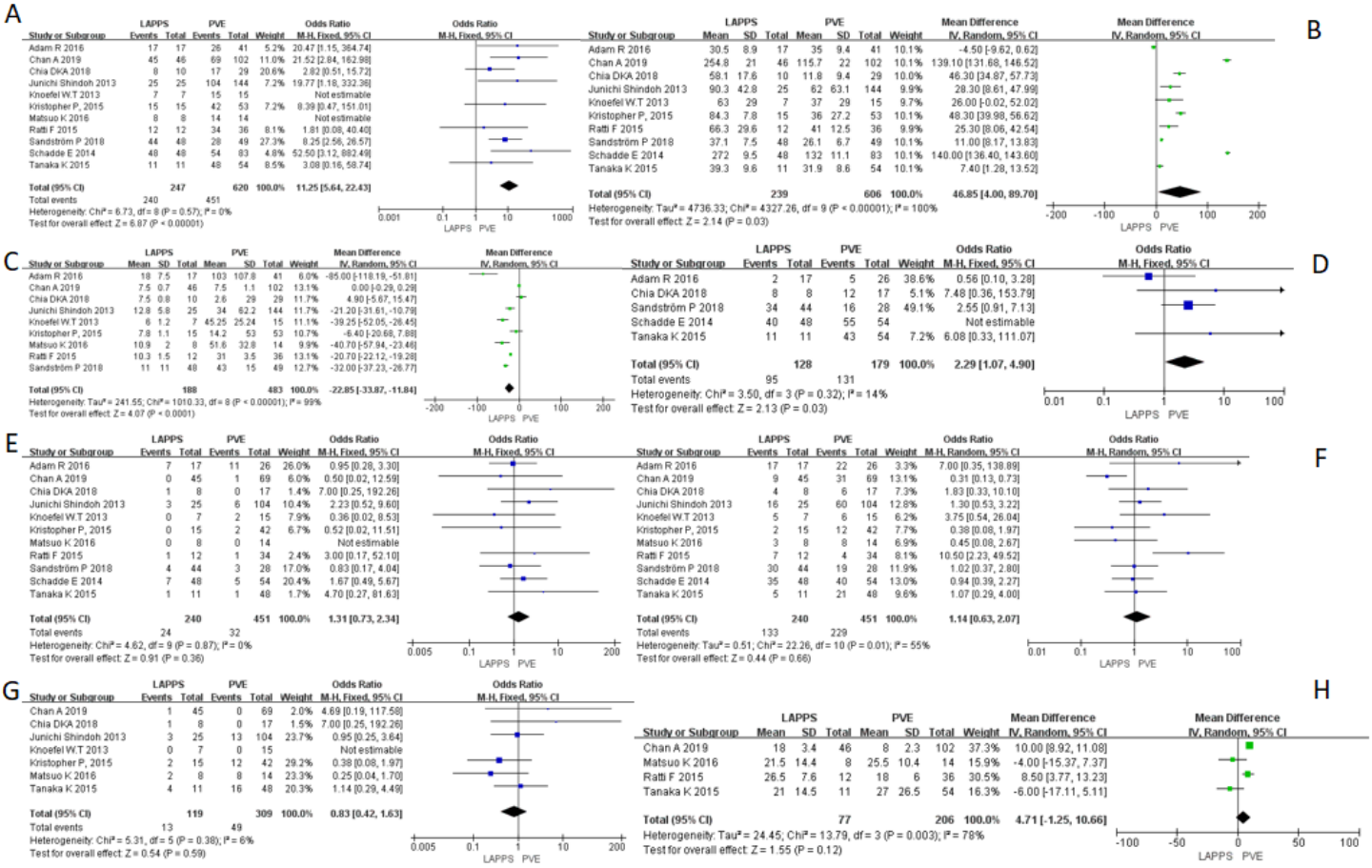

Figure 2

2A) The second stage hepatectomy ; 2B) The sufficient FLR growth; 2C) The time to stage II operation; 2D) The rate of R0 resection; 2E) Mortality within 90 days of perioperative period; 2F) Overall postoperative complication rate; 2G) The incidence of postoperative liver failure; 2H) Postoperative hospital stay (see details in manuscript)

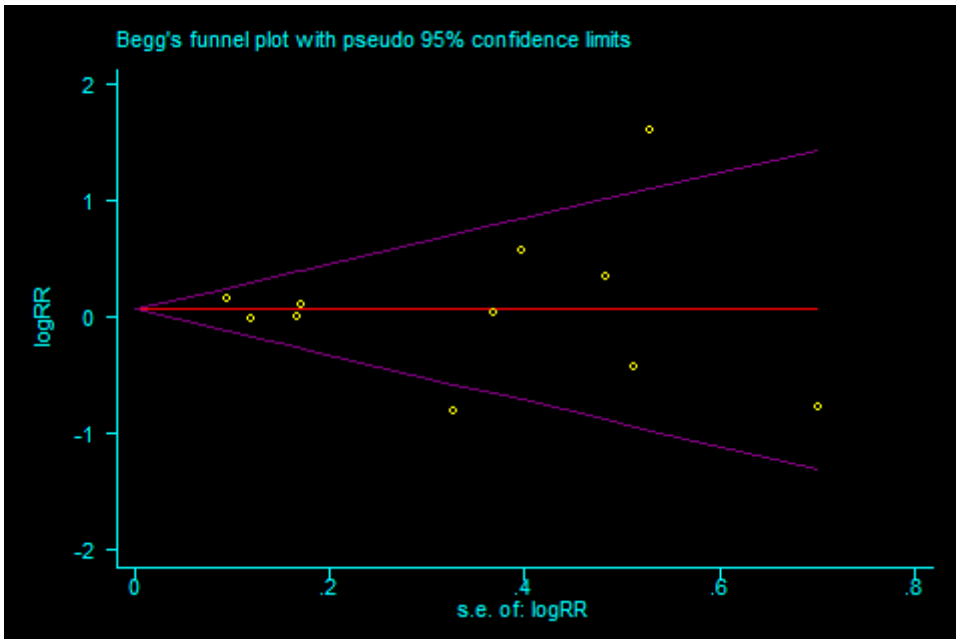

Figure 3

On the basis of the overall incidence of perioperative complications in the ALPPS group and the PVE group, the Bgger's test was performed to assess the publication bias of the literature. Funnel plots indicated a symmetric distribution of included studied. Begg tests demonstrated that there was no potential publication bias among studies (Begg test, P=0.94). Sensitivity analyses have confirmed the robustness of the results.

Supplementary Files

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- supplementarymaterial.docx
- Table1.docx