



# The efficacy and safety of controlled low central venous pressure for liver resection: a systematic review and meta-analysis

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**Background:** Application of controlled low central venous pressure (LCVP) in liver resection growing in popularity, but its efficacy and safety are still controversial. Our objectives were to assess and compare the efficacy, feasibility, and safety of controlled LCVP in patients undergoing liver resection.

**Methods:** The PubMed, Cochrane library, and EMBASE databases were systematically searched for all the relevant studies regardless of study design. We evaluated the methodological quality of the included studies and excluded studies of poor quality. Moreover, we applied a systematic review and meta-analysis by using RevMan 5.3 software to compare the efficacy and safety of LCVP *vs.* standard CVP for liver resection. Outcomes included operation time, blood loss, blood infusion, fluid infusion, urinary volume, postoperative complication rates, and hospital stay.

**Results:** In total, 10 studies, involving 324 patients undergoing liver resection with controlled LCVP, were identified. Meta-analysis displayed that blood loss in the LCVP group was dramatically less than that in the control group (standard CVP group, mean difference (MD): -581.68; 95% CI: -886.32 to -277.05;  $P=0.0002$ ). Moreover, blood transfusion in the LCVP group was also markedly less than that in the control group (MD: -179.16; 95% CI: -282.00 to -76.33;  $P=0.0006$ ). However, there was no difference between LCVP group and control group in operation time (MD: -16.24; 95% CI: -39.56 to 7.09;  $P=0.17$ ), fluid infusion (MD: -287.89; 95% CI: -1,054.47 to 478.69;  $P=0.46$ ), urinary volume (MD: -26.88; 95% CI: -87.14 to 33.37;  $P=0.38$ ), ALT (MD: -58.66; 95% CI: -153.81 to 36.50;  $P=0.23$ ), TBIL (MD: -0.32; 95% CI: -3.93 to 3.28;  $P=0.86$ ), BUN (MD: -0.13; 95% CI: -0.73 to 0.47;  $P=0.67$ ), CR (MD: 1.87; 95% CI: -4.90 to 8.63;  $P=0.59$ ), postoperative complication rates (MD: 0.62; 95% CI: 0.44 to 0.90;  $P=0.01$ ) and hospital stay (MD: -0.61; 95% CI: -1.68 to 0.46;  $P=0.26$ ).

**Conclusions:** Compared with the control, controlled LCVP showed comparable efficacy and safety for the treatment during liver resection.

**Keywords:** Low central venous pressure (LVCP); hepatectomy; meta-analysis

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## Introduction

Hepatectomy is an effective method for the treatment of benign and malignant liver diseases. With recent improvements in surgical treatment, hepatectomy has been

validated as an effective and safe surgical procedure and is widely recommended (1,2). Although preoperative strict selection criteria in patients and recent progress in surgical techniques and perioperative management have reduced the

morbidity and mortality after hepatectomy, intraoperative bleeding is one of the major factors affecting the outcome of hepatectomy (3). A large number of studies have shown that operative mortality is related to intraoperative blood loss, and large blood loss can increase the incidences of postoperative complications and mortality (4).

Currently, the most commonly used method of hepatic blood flow occlusion in clinical practice is the Pringle method, but this method has a great impact on liver function and can cause hepatic ischemia-reperfusion injury (5). In addition, after blocking the blood flow into the liver, the main source of bleeding is the hepatic vein, how to control the hepatic vein bleeding is also the key to the operation. Therefore, the use of timely and effective bleeding control is of great clinical significance and practical value for rapid postoperative recovery and competent immune function in patients with benign and malignant liver diseases undergoing hepatectomy. Previous studies have shown that blood loss volume during hepatectomy is related to central venous pressure (CVP) (6). Intraoperative control of low central venous pressure (LCVP) is increasingly popular in hepatectomy, but its effectiveness and safety remain controversial. This study aimed to assess the role of controlled LCVP during hepatectomy and undertook the purpose of providing objective evidence for clinical decision-making.

## Methods

### *Literature search strategy*

As of December 2015, computer searches were performed on PubMed, EMBASE, Cochrane Library, and Google Scholar. The search words used were “central venous pressure” and “hepatectomy” or “hepatic dissection” or “liver resection”. In addition, we conducted a comprehensive manual search of the bibliography for each peer-reviewed paper selected. No language or date restrictions were imposed. Furthermore, there are no restrictions on the form of publication.

### *Study selection*

All articles were independently reviewed by two authors (Wang and Sun). Any differences in whether a study should be chosen to be resolved by consensus. Inclusion criteria were established at the beginning of the study and were as follows: (I) population: patients with hepatectomy; (II)

intervention: any method of LCVP; (III) results: operation time, blood loss, blood infusion, fluid infusion, urinary volume, alanine transaminase (ALT), total bilirubin (TBIL), blood urea nitrogen (BUN), creatinine (CR), postoperative complication rates and hospital stay; Methods: randomized controlled trials.

### *Data extraction*

The two authors (Wang and Sun) conducted data extraction for each study. Any disagreement in data extraction is resolved by consensus. Detailed data, population, intervention, and outcome were recorded, including sample size, surgical procedure, LCVP control, operation time, blood loss, blood infusion, fluid infusion, urinary volume, ALT, TBIL, BUN, CR, postoperative complication rates and hospital stay.

### *Statistical analysis*

The main result of the analysis was to reduce blood loss and blood infusion. Secondary outcomes included operative time, fluid infusion, urine volume, ALT, TBIL, BUN, CR, postoperative complication rates and length of hospital stay. Statistical analysis was employed using RevMan 5.3 software (Cochrane Collaboration, Oxford, England). The results of all studies were measured by mean  $\pm$  standard deviation. If there is significant heterogeneity between the results ( $P < 0.05$ ), a random-effects model is used. A fixed-effect model was performed when there was no significant heterogeneity ( $P > 0.05$ ). Heterogeneity was evaluated using the Cochrane  $\chi^2$  test (using a 10% significance level) and  $I^2$  statistic (the higher the percentage change in heterogeneity indicates a greater degree of heterogeneity). The OR of the result is 95% CI.

## Results

### *Quality assessments*

We generated a risk of bias graphs to identify the risk of bias of all included studies. The graphs showed that the studies included in our meta-analysis presented generally good methodological quality. The selection bias of all studies experienced low risk especially the generation of random sequences. The unclear risk of bias was mainly focused on performance bias (blinding of participants and personnel). In a word, the included studies generally experienced good

quality. The results of the risk of bias assessment are shown in *Figure 1*.

**Characteristics of included studies**

We identified 205 studies through an electronic search. Ten studies fulfilled the inclusion criteria of the meta-analysis (*Figure 2*). The characteristics of the 10 selected studies are shown in *Table 1*. Ten studies involved subjects, including 324 patients who underwent LCVP, and 393 who served as controls. The methods of controlled LCVP included Trendelenburg’s posture, nitroglycerine, furosemide, fentanyl, control of infusion speed, and clamping the intrahepatic vena cava (IVC) (17).

**Outcome measures**

**Operation time**

Six studies reported the data for the operative time and the difference between the LCVP and Control groups was not significant (MD: -16.24; 95% CI: -39.56 to 7.09; P=0.17; *Figure 3A*), with marked heterogeneity (P=0.005; I<sup>2</sup>=70%).

**Blood loss**

The meta-analysis of seven studies indicated that the volume of intraoperative blood loss in LCVP group was notably lower than that in Control group (MD: -581.68; 95% CI: -886.32 to -277.05; P=0.0002; *Figure 3B*), with marked heterogeneity (P<0.00001; I<sup>2</sup>=96%).

**Blood infusion**

Five trials reported information on blood infusion. The meta-analysis of the studies on blood infusion showed that blood infusion (MD: -179.16; 95% CI: -282.00 to -76.33; P=0.0006; *Figure 3C*) in LCVP group were significantly lower than in Control group (P=0.009; I<sup>2</sup>=70%).

**Fluid infusion**

Three studies reported the data for the fluid infusion and the difference between the LCVP and Control groups was not significant (MD: -287.89; 95% CI: -1,054.47 to 478.69; P=0.46; *Figure 3D*), with marked heterogeneity (P<0.00001; I<sup>2</sup>=99%).

**Urinary volume**

Two studies reported the data for the urinary volume and there was almost no difference between the LCVP and

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dong ZT 2012	?	?	?	+	+	+	?
Essam A.Eid 2005	?	?	?	+	+	+	+
Herbert Chell 2000	+	?	?	+	+	-	+
Kazuhisa Uchiyama 2007	?	?	?	+	+	+	+
Lin CX 2013	+	+	?	?	-	+	+
Liu HZ 2005	+	?	?	+	+	+	?
Liu YY 2007	?	?	+	+	+	+	+
Masato Kato 2008	+	?	?	+	-	+	+
Wang WD 2006	+	+	?	+	+	+	+
Zhao H 2015	+	?	?	+	+	+	?

**Figure 1** Risk of bias summary in included studies. Each risk of bias was described as low risk (+), high risk (-) or unclear risk (?).

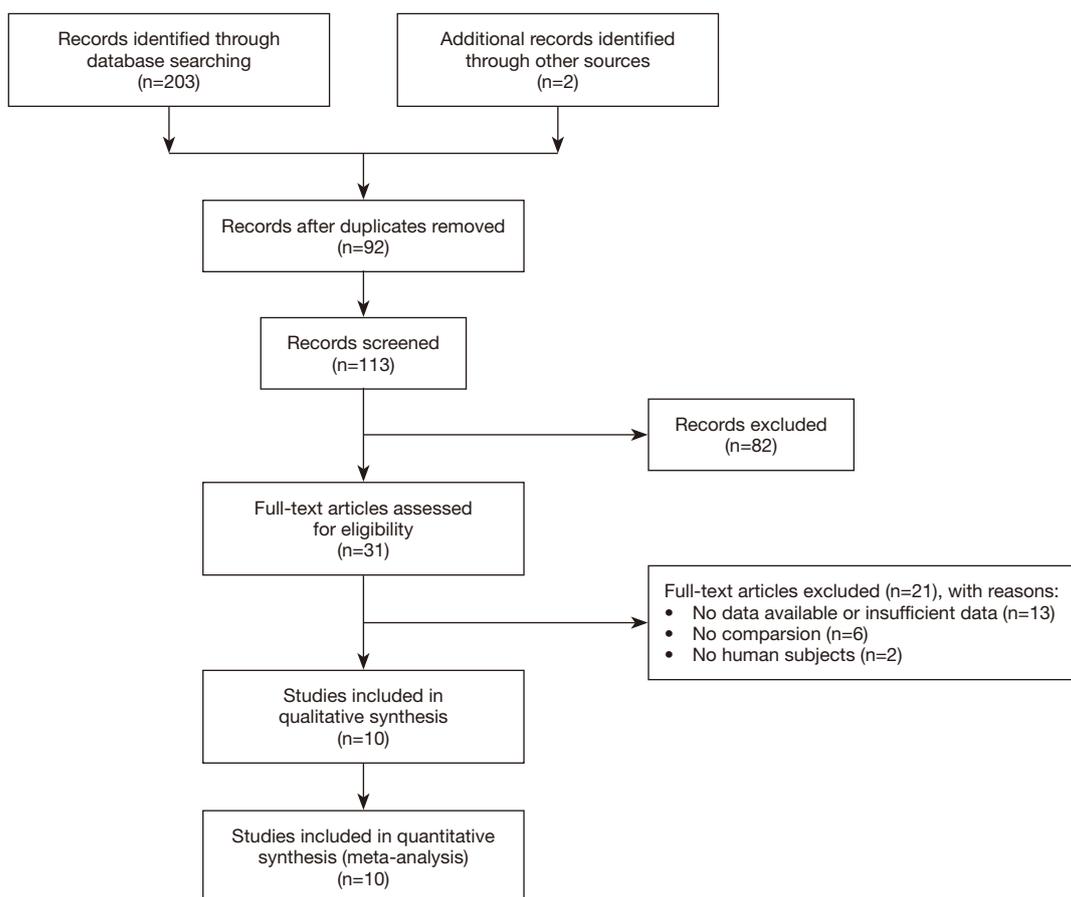
Control groups (MD: -26.88; 95% CI: -87.14 to 33.37; P=0.38; *Figure 3E*), with no heterogeneity (P=0.80; I<sup>2</sup>=0%).

**ALT and TBIL**

Three trials reported information on ALT, and two trials reported information on TBIL. Three studies reported the data for the ALT and the difference between the LCVP and Control groups was not significant (MD: -58.66; 95% CI: -153.81 to 36.50; P=0.23; *Figure 4A*), with marked heterogeneity (P=0.05; I<sup>2</sup>=67%). TBIL did not show a statistically significant difference between LCVP and Control groups (MD: -0.32; 95% CI: -3.93 to 3.28; P=0.86; *Figure 4B*), with no heterogeneity (P=0.61; I<sup>2</sup>=0%).

**BUN and CR**

Four trials were each reported information about BUN and



**Figure 2** The flowchart showed the literature search and study selection process according to the PRISMA guidelines.

CR. Four studies reported the data for the BUN and the difference between the CLCVP and Control groups was not significant (MD:  $-0.13$ ; 95% CI:  $-0.73$  to  $0.47$ ;  $P=0.67$ ; *Figure 4C*), with no heterogeneity ( $P=0.99$ ;  $I^2=0\%$ ). CR also showed no statistically significant difference between LCVP and control group (MD:  $1.87$ ; 95% CI:  $-4.90$  to  $8.63$ ;  $P=0.59$ ; *Figure 4D*) with no heterogeneity ( $P=0.30$ ;  $I^2=18\%$ ).

### Postoperative complication rates

Five studies reported the data for the postoperative complication rates and there was no difference between the LCVP and Control groups (MD:  $0.62$ ; 95% CI:  $0.44$  to  $0.90$ ;  $P=0.01$ ; *Figure 5A*), with no heterogeneity ( $P=0.87$ ;  $I^2=0\%$ ).

### Hospital stay

Two studies reported the data for the hospital stay and there was no difference between the LCVP and Control groups

(MD:  $-0.61$ ; 95% CI:  $-1.68$  to  $0.46$ ;  $P=0.26$ ; *Figure 5B*), with no heterogeneity ( $P=0.66$ ;  $I^2=0\%$ ).

## Discussion

The incidence of liver disease is getting higher and higher, and surgical resection is the preferred method of treatment (18). Because the liver itself has a rich blood supply, hepatectomy has often led to massive bleeding during surgery. Clinical studies have shown (19) that the average blood loss in patients undergoing hepatectomy is 700 mL, and 30% of patients require an intraoperative blood transfusion to maintain Blood perfusion of vital organs of the body. There are various complications and increased risk of malignant tumor metastasis during intraoperative and postoperative transfusion (20). Therefore, how to improve the safety and feasibility of hepatectomy has always been a problem. With the development of anesthesia techniques and concepts,

**Table 1** Characteristics of the included studies

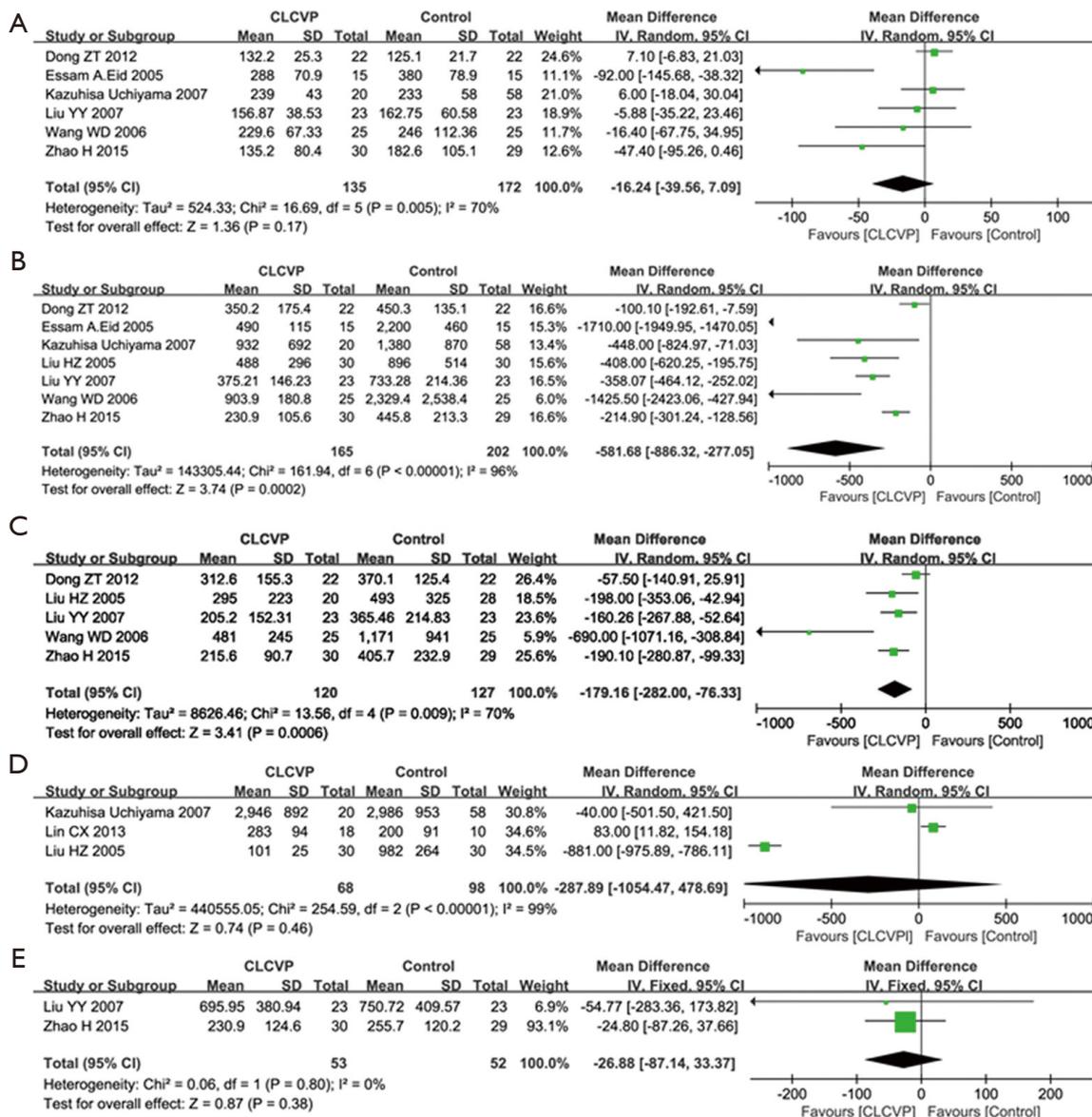
Author/year	Country	Disease	No. of patients		Gender	Lost to follow-up	LCVP technique
			LCVP	Control	(M/F)		
Zhao H (2015) (7)	China	HCC, HH	30	29	48/11	0/60	Limiting the volume of infusion, nitroglycerine, fentanyl
Liu H (2005) (8)	China	Not reported	30	30	Not reported	0/60	Trendelenburg's posture, nitroglycerine, isoflurane, fentanyl, limiting the volume of infusion
Dong ZT (2013) (9)	China	HCC, HH, liver abscess, hepatolithiasis	22	22	29/15	0/44	Trendelenburg's posture, control of infusion speed, nitroglycerine, fentanyl
Liu Y (2008) (10)	China	HCC	23	23	30/16	0/46	Trendelenburg's posture, limiting the volume of infusion, nitroglycerine, fentanyl
Kato M (2008) (11)	Japan	PLC, MLT, ICC, Hepatolithiasis, GBC	43	42	Not reported	0/85	Clamping the intrahepatic inferior vena cava
Uchiyama K (2009) (12)	Japan	HCC, ICC, MCC, Other diseases	20	58	59/19	0/78	Half clamping the intrahepatic inferior vena cava
Chen H (2000) (13)	America	Not reported	78	90	81/87	0/168	Trendelenburg's posture, limiting the volume of infusion
Eid EA (2005) (14)	Egypt	Not reported	15	15	15/15	0/30	Limiting the volume of infusion, nitroglycerine, fentanyl
Wang WD (2006) (15)	China	HCC	25	25	40/10	0/50	Trendelenburg's posture, nitroglycerine, isoflurane, limiting the volume and speed of infusion
Lin CX (2012) (16)	China	HCC	38	59	87/10	0/97	Limiting the volume and speed of infusion, nitroglycerine, isoflurane

HCC, hepatocellular carcinoma; HH, hepatic hemangioma; PLC, primary liver carcinoma; MLT, metastatic liver tumor; ICC, intrahepatic cholangiocellular carcinoma; GBC, gallbladder carcinoma; MCC, metastasis of colorectal carcinoma.

lowering CVP can reduce the pressure in the hepatic vein and hepatic sinus and reduce the bleeding when the liver parenchyma is broken. This is the theoretical basis for the control of LCVP to reduce hepatic resection and hemorrhage (21). In this meta-analysis, when liver resection was performed in Trendelenburg's position that is an effective technical aspect of LCVP, the drug was treated by maintaining the CVP below 5 mmHg, the infusion rate was controlled, and the IVC under the liver was clamped. We analyzed the efficacy and safety of LCVP by blood loss, blood infusion, fluid infusion, operation time, urinary volume, ALT, TBIL, BUN, CR, postoperative complication rates and hospital stay.

First of all, this study presented that blood loss and blood infusion in the LCVP group were significantly lower than the control group. A large number of studies have reported (22,23), LCVP technique is used for hepatectomy and liver

transplantation, which can reduce hepatic venous pressure, thus effectively reducing intraoperative blood loss and blood transfusion, and reducing surgical risk. According to the Poiseuille laminar flow formula, the amount of hemorrhage caused by hepatic vein injury is proportional to the pressure difference of the vessel wall and the fourth power of the vessel radius. When the CVP decreases, the inferior vena cava pressure follows. When CVP decreases, the pressure of inferior vena cava, hepatic vein and hepatic sinus also decrease, which reduces the pressure difference of blood vessel wall and the radius of the blood vessel, and thus significantly reduces the intraoperative blood loss of patients (24). However, some studies (25,26) have reported that CVP has nothing to do with blood loss from hepatectomy, and intraoperative blood loss is not significantly reduced in patients with relatively low CVP. The differences between these studies may be due to differences in patient

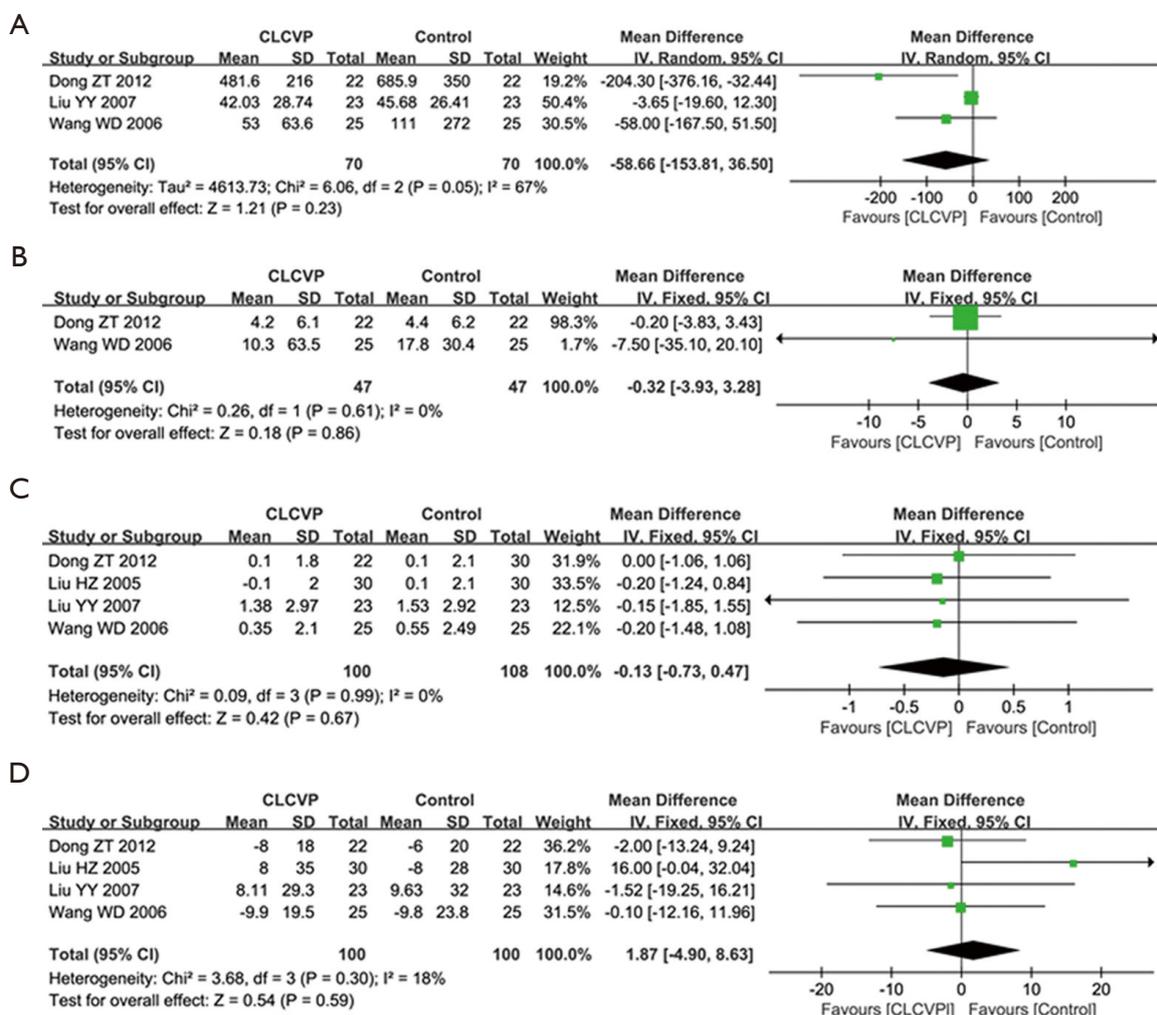


**Figure 3** Forest plot of meta-analysis for intraoperative outcomes: (A) operative time, (B) blood loss, (C) blood infusion, (D) fluid infusion, (E) urinary volume.

populations. And the bleeding tendency of patients with benign or malignant liver damage may be different.

Moreover, this meta-analysis showed that there was no difference in fluid infusion between the LCVP group and the control group. We found that in one study (27), patients in the LCVP and control group had a fluid infusion of 283 mL and 200 mL. However, another study (23) reported fluid infusion of 101 and 982 mL in the LCVP and control group. Hence, fluid infusion varied widely in different studies. Further large RCTs are needed.

In addition, regarding the operation time, this meta-analysis showed no significant difference between the low CVP group and the control group. There are many factors that affect the operation time, such as intraoperative bleeding, the difficulty of surgery, and so on. It is understandable that less blood loss is favorable for the surgical visual field and procedure, and reduces the duration of operation, reducing the operation time. However, difficult surgery usually takes longer, resulting in more blood loss, blood transfusion, and higher blood transfusion



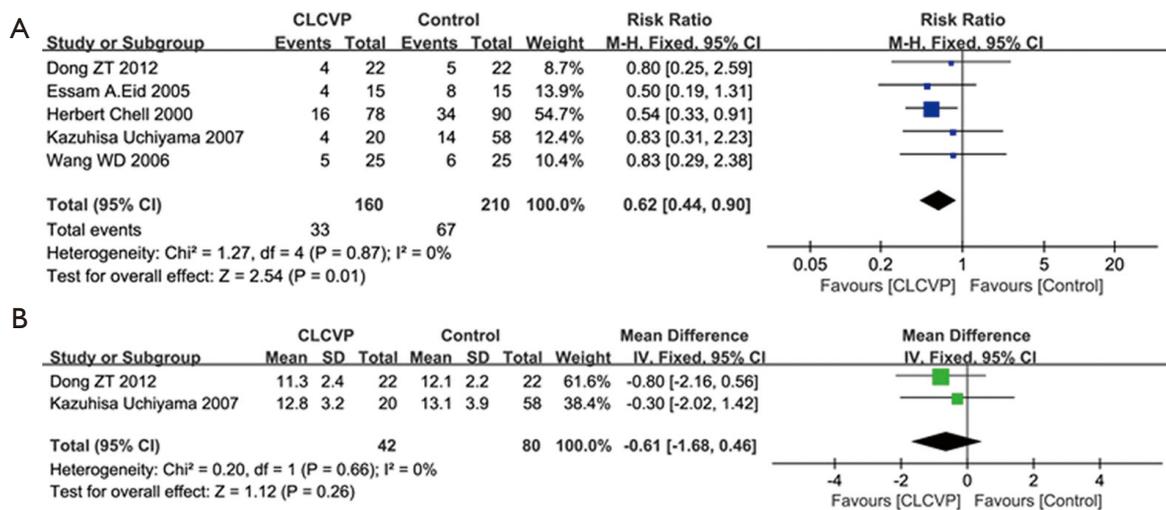
**Figure 4** Forest plot of meta-analysis for postoperative outcomes: (A) ALT, (B) TBIL, (C) BUN, (D) CR. ALT, alanine transaminase; TBIL, total bilirubin; BUN, blood urea nitrogen; CR, creatinine.

rates. Therefore, LCVP is necessary for difficult operations. For uncomplicated surgery, especially experienced surgeons, LCVP may not be needed.

Although the use of LCVP in hepatectomy has become increasingly popular, its widespread use is still limited. There is concern about the possibility that the lack of abdominal organ perfusion during LCVP during liver resection may lead to morbidity (28). In particular, the effects of relative hypotension and potential hypoperfusion on liver and kidney function have been listed as limiting factors. Our results showed no significant difference in ALT, TBIL, BUN, CR, and urine volume between the two groups. The results revealed that all tissues and organs were still effectively performed without affecting liver and

kidney function in the case of LCVP. There is no significant effect on systemic hemodynamics, which is safe and reliable. The above results of our analysis are consistent with many reported studies (10,15,28).

Regarding the incidences of postoperative complications and postoperative hospital stay, this meta-analysis showed no significant difference between the low CVP group and the control group. This is also consistent with many studies (15,17). We hypothesize that the use of LCVP in hepatectomy may result in changes in cardiac preload and insufficient capacity, which may, in turn, affect the perfusion of vital organs, which may offset the benefits of low CVP and low blood loss surgery. However, some studies (27,29) pointed out that LCVP is performed during hepatectomy,



**Figure 5** Forest plot of meta-analysis for postoperative complication rates (A) and length of postoperative hospital stay (B).

and the reperfusion is guided by cardiac stroke volume variation. Compared with conventional infusion, less infusion volume is safe for patients and can reduce the incidence of postoperative complications. We believe that how to choose a better control of LCVP has a certain significance in the reduction of postoperative complication rate and the shortening of postoperative hospital stay.

This meta-analysis also has some limitations. First, one limitation of this meta-analysis is that the controls in each eligible study are various, and the number of tests is insufficient; Second, heterogeneity exists between trials, and there are many factors contributing to heterogeneity, such as differences in LCVP methods. Third, another limitation of this study is that it is based on retrospective studies with inherently unavoidable selection bias. Hence, further large randomized controlled trials are needed.

## Conclusions

The present systematic review and meta-analysis found that the LCVP technique is safe and effective in hepatectomy. It has further clinical research and application value.

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## Footnote

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/gs.2020.03.07>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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