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Review Article

Low versus standard central venous pressure during laparoscopic liver resection: A systematic review, meta-analysis and trial sequential analysis

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To compare the outcomes of low central venous pressure (CVP) to standard CVP during laparoscopic liver resection. The study design was a systematic review following the PRISMA statement standards. The available literature was searched to identify all studies comparing low CVP with standard CVP in patients undergoing laparoscopic liver resection. The outcomes included intraoperative blood loss (primary outcome), need for blood transfusion, mean arterial pressure, operative time, Pringle time, and total complications. Random-effects modelling was applied for analyses. Type I and type II errors were assessed by trial sequential analysis (TSA). A total of 8 studies including 682 patients were included (low CVP group, 342; standard CVP group, 340). Low CVP reduced intraoperative blood loss during laparoscopic liver resection (mean difference [MD], −193.49 mL; 95% confidence interval [CI], −339.86 to −47.12; p = 0.01). However, low CVP did not have any effect on blood transfusion requirement (odds ratio [OR], 0.54; 95% CI, 0.28–1.03; p = 0.06), mean arterial pressure (MD, −1.55 mm Hg; 95% CI, −3.85–0.75; p = 0.19), Pringle time (MD, −0.99 minutes; 95% CI, −5.82–3.84; p = 0.69), operative time (MD, −16.38 minutes; 95% CI, −36.68–3.39; p = 0.11), or total complications (OR, 1.92; 95% CI, 0.97–3.80; p = 0.06). TSA suggested that the meta-analysis for the primary outcome was not subject to type I or II errors. Low CVP may reduce intraoperative blood loss during laparoscopic liver resection (moderate certainty); however, this may not translate into shorter operative time, shorter Pringle time, or less need for blood transfusion. Randomized controlled trials with larger sample sizes will provide more robust evidence.

Key Words: Laparoscopy; Hepatectomy; Central venous pressure

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INTRODUCTION

Despite advances in surgical techniques, intraoperative bleeding during liver surgery remains a concern. Intraoperative blood loss is considered a cause of perioperative complications in patients undergoing liver surgery [1]; hence, several operative and non-operative strategies are applied to reduce the risk of bleeding. The strategies include intermittent clamping the portal vein and hepatic artery (Pringle manoeuvre) [2], sophisticated liver dissection techniques, use of stapling devices, ultrasonic dissectors, bipolar cautery, and hydrodissectors

for parenchymal transection [3], and maintaining a low central venous pressure (CVP) during parenchymal transection [4,5].

Although the learning curve is steep and there are technical challenges, laparoscopic liver resection has become more popular in the past decade even for lesions in anatomically challenging segments [6,7]. However, the application of haemostasis techniques may be more challenging during laparoscopic liver resections compared with the open approach [8]. It has been shown that low CVP can reduce intraoperative bleeding during liver resection [5]; however, the impact of low CVP on intraoperative bleeding, specifically in laparoscopic liver resection is not known. Therefore, this systematic review and meta-analysis aimed to compare the outcomes of low CVP to standard CVP during laparoscopic liver resection.

MATERIALS AND METHODS

The design of the study was according to the Preferred Reporting Items for systematic reviews and Meta-Analyses statement standards [9], and followed a predefined protocol.

Criteria for eligibility

Study design: Comparative cohort studies and randomized controlled trials (RCTs) that compared low CVP with standard CVP in patients undergoing laparoscopic liver resection were of interest to this review.

Population: Adult patients undergoing laparoscopic liver resection for any indications were eligible. The liver resection procedures of interest comprised both anatomical and non-anatomical resections.

Intervention and comparison: Low CVP, defined as pressure ≤ 5 cmH$_2$O, was the eligible intervention and standard CVP, defined as pressure > 5 cmH$_2$O, was the eligible comparison.

Outcomes: Intraoperative blood loss was the primary outcome. The secondary outcomes comprised the need for blood transfusion, mean arterial pressure, operative time, Pringle time, and total complications.

Literature search strategy

Using proper keywords, thesaurus headings, and search limits, a literature search strategy was constructed by two separate authors who had adequate experience in evidence synthesis (Appendix 1). There were no language restrictions. The date for the last search was 15 July 2023. The electronic sources searched comprised MEDLINE, CINAHL, Scopus, International Standard Randomised Controlled Trial Number Registry, World Health Organization International Clinical Trials Registry, CENTRAL, ClinicalTrials.gov, the European Association for Grey Literature Exploitation, and System for Information on Grey Literature. The reference lists of the relevant original studies and reviews were also evaluated.

Selection of the eligible studies and data collection

Two separate authors reviewed the titles and abstracts of the articles, obtained the full texts of potentially eligible articles, and included the eligible studies. The following relevant data from the eligible studies were recorded on an electronic data collection sheet:
- First author's name
- Publication year
- Journal name
- Study design
- Included population
- Study sample size
- Definitions of low and standard CVP
- Outcomes

Any disagreements about study selection or data collection were resolved by a third author when required.

Risk of bias assessment

The risk of bias (RoB) of RCTs was judged using the Cochrane RoB tool [10], and the RoB of observational studies was evaluated using the Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool [11]. Two independent authors conducted the RoB assessment and a third author resolved the disagreements when required.

Data analysis

Review Manager 5.4 software and trial sequential analysis (TSA) 0.9.5.5 Beta software were used. Random effects modelling was used to compute mean difference (MD) with 95% confidence level for continuous variables and odds ratio (OR) with 95% confidence for dichotomous variables. An individual patient was the unit of analysis and we based the analyses on intention to treat data. The I^2 using the Cochran Q test (χ^2) was calculated to measure statistical heterogeneity and was interpreted as below:
- I^2 0%–25% suggests low heterogeneity
- I^2 25%–75% suggests moderate heterogeneity
- I^2 75%–100% suggests high heterogeneity

When an outcome was reported by ten studies, we aimed to construct funnel plots for publication bias risk assessment. TSA was modelled to explore the possibility of type I and type II errors in the primary outcome analysis as long as it was adequately reported (by at least five RCTs). The possibility of type I and II errors was determined using the O'Brien-Fleming α-spending function and futility boundaries, respectively.

Additional analyses

Leave-one-out analysis and independent meta-analysis of studies with low RoB were planned as sensitivity analyses of the primary outcome.

Certainty of evidence

The GRADE system was followed to determine the certainty

of evidence for each outcome [12].

RESULTS

The literature search yielded 277 articles; 266 studies were excluded due to irrelevance. After full-text review, three more articles were excluded as they were systematic reviews (Fig. 1). The remaining eight articles [13-20] met the eligibility criteria of this study. The eligible studies included 7 RCTs and 1 retrospective cohort study, enrolling a total of 682 patients; 342 in the low CVP group and 342 in the standard CVP group (Table 1).

Risk of bias assessment

The outcomes of RoB assessment based on the aforementioned tools are shown in Fig. 2.

Primary outcome

Intraoperative blood loss: Examination results of 682 individuals (8 studies) demonstrated that low CVP reduced intraoperative blood loss (MD, –193.49 mL; 95% confidence interval [CI], –339.86 to –47.12; $p = 0.01$). The heterogeneity (statistical) was high ($I^2 = 99\%$, $p < 0.001$) and the GRADE system suggested moderate certainty (Fig. 3). The information size calculated via TSA (950 patients) was not achieved; however, Z-curve intersected the conventional and alpha-spending boundaries in favour of low CVP, hence the possibility of type I and II errors was minimal and the conclusion was robust (Fig. 4).

Secondary outcomes

Need for blood transfusion: Examination results of 416 individuals (4 studies) demonstrated comparable need for blood transfusion between low CVP and standard CVP (OR, 0.54; 95% CI, 0.28–1.03; $p = 0.06$) (Fig. 3). The heterogeneity (statistical) was low ($I^2 = 0\%$, $p = 0.85$) and the GRADE system suggested moderate certainty.

Mean arterial pressure: Examination results of 364 individuals (3 studies) demonstrated comparable mean arterial pressure between low CVP and standard CVP (MD, –1.55 mm Hg; 95% CI, –3.85–0.75; $p = 0.19$) (Fig. 3). The heterogeneity (statistical) was low ($I^2 = 0\%$, $p = 0.75$) and the GRADE system suggested moderate certainty.

Pringle time: Examination results of 404 individuals (3 studies) demonstrated comparable Pringle time between low CVP and standard CVP (MD, –0.99 minutes; 95% CI, –5.82–3.84; $p = 0.69$) (Fig. 3). The heterogeneity (statistical) was high ($I^2 = 96\%$, $p < 0.001$) and the GRADE system suggested moderate certainty.

Operative time: Examination results of 454 individuals (4 studies) demonstrated comparable operative time between low CVP and standard CVP (MD, –16.38 minutes; 95% CI, –36.68–3.39; $p = 0.11$) (Fig. 3). The heterogeneity (statistical) was high ($I^2 = 95\%$, $p < 0.001$) and the GRADE system suggested low certainty.

Total complications: Examination results of 274 individuals (4 studies) demonstrated comparable risks of total complications between low CVP and standard CVP (OR, 1.92; 95% CI, 0.97–3.80; $p = 0.06$) (Fig. 3). The heterogeneity (statistical) was low
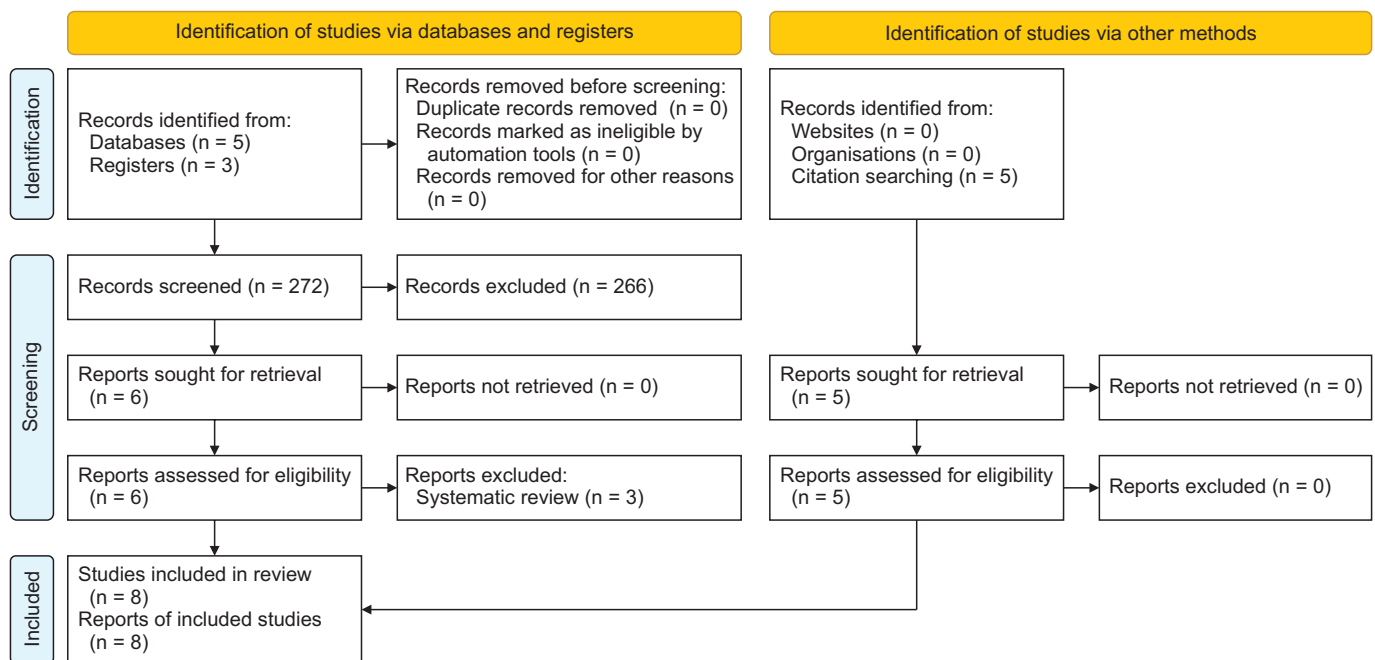

Fig. 1. Study PRISMA flow diagram.

Table 1. Baseline characteristics of the included studies

Study	Country	Journal	Design	Included population	Sample size			Low CVP definition	Standard CVP definition	Interventions for maintaining low CVP in the low CVP group
					Total	Low CVP	Standard CVP			
Zhang et al. [13], 2023	China	*Signa Vitae*	RCT	Patients undergoing laparoscopic liver resection	90	45	45	CVP between 2–4 cmH$_2$O	CVP between 6–12 cmH$_2$O	Intravenous nitroglycerin Dorsal elevated position
Wu et al. [14], 2021	China	*American Journal of Translational Research*	Retrospective cohort	Patients undergoing laparoscopic major liver resection	168	84	84	CVP between 1–5 cmH$_2$O	CVP between 6–10 cmH$_2$O	15° head over feet position Limiting infusion volume Vasoactive drugs
Pan et al. [15], 2020	China	*Surgery*	RCT	Patients undergoing laparoscopic liver resection	146	73	73	CVP between 0–5 cmH$_2$O	CVP higher than 5 cmH$_2$O	Nitro compounds Diuretics Opioids
Gan [16], 2020	China	*Modern Chinese Medicine*	RCT	Patients undergoing laparoscopic liver resection	100	50	50	CVP between 3–5 cmH$_2$O	CVP between 6–12 cmH$_2$O	Limiting infusion volume Intravenous nitroglycerin Diuretics
Chen et al. [17], 2018	China	*China Journal of Minimally Invasive Surgery*	RCT	Patients undergoing laparoscopic liver resection	52	27	25	CVP between 2–4 cmH$_2$O	CVP between 5–10 cmH$_2$O	Limiting infusion volume Intravenous nitroglycerin
Chen et al. [18], 2017	China	*Journal of Hepatobiliary Surgery*	RCT	Patients undergoing laparoscopic liver resection	36	18	18	CVP between 0–5 cmH$_2$O	CVP between 6–12 cmH$_2$O	Reversed Trendelenburg's position Intravenous nitroglycerin Diuretics
Deng et al. [19], 2017	China	*Lingnan Modern Clinics in Surgery*	RCT	Patients undergoing laparoscopic liver resection	40	20	20	CVP between 0–5 cmH$_2$O	CVP between 6–12 cmH$_2$O	Limiting infusion volume
Zhang et al. [20], 2017	China	*Lingnan Modern Clinics in Surgery*	RCT	Patients undergoing laparoscopic liver resection	50	25	25	CVP between 3–5 cmH$_2$O	CVP between 6–12 cmH$_2$O	Limiting infusion volume Intravenous nitroglycerin

RCT, randomized controlled trial; CVP, central venous pressure.

A Randomized controlled trials
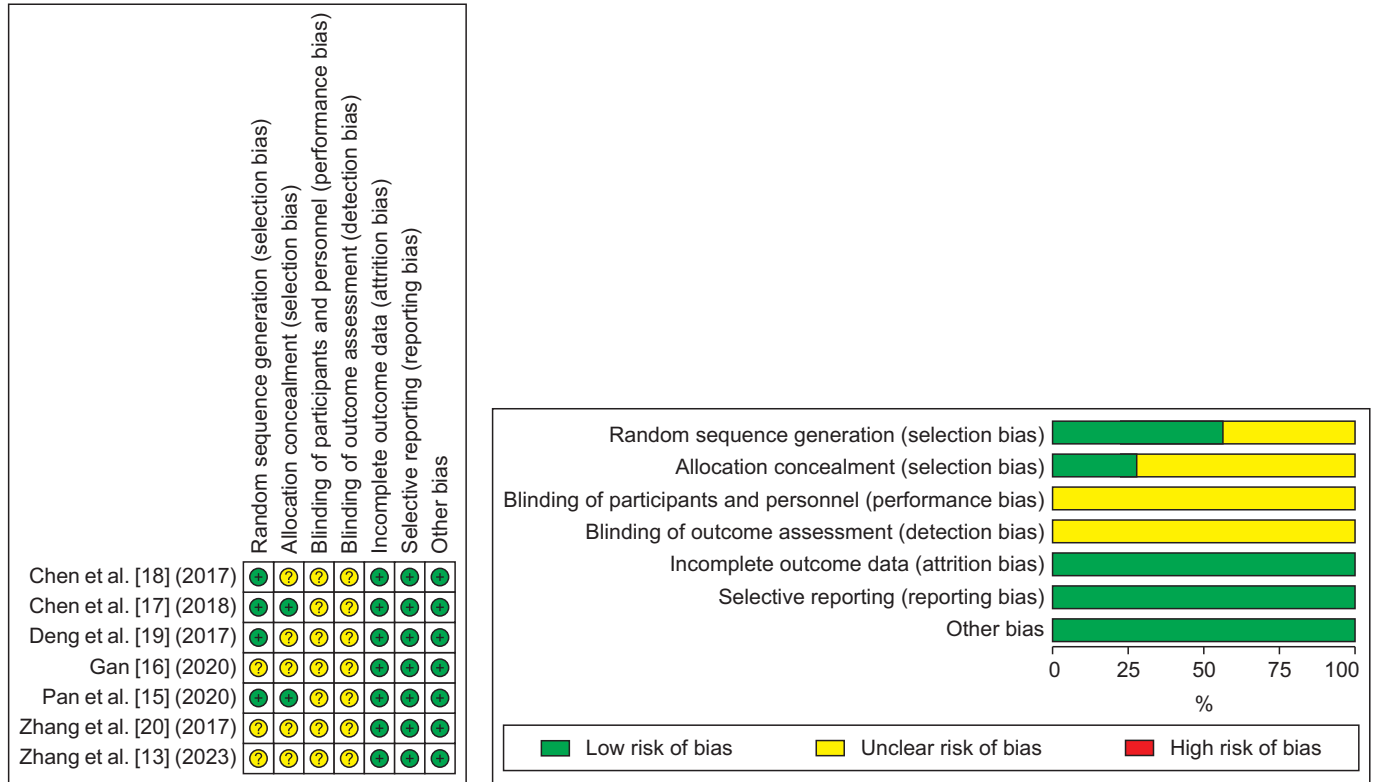
B Observational studies

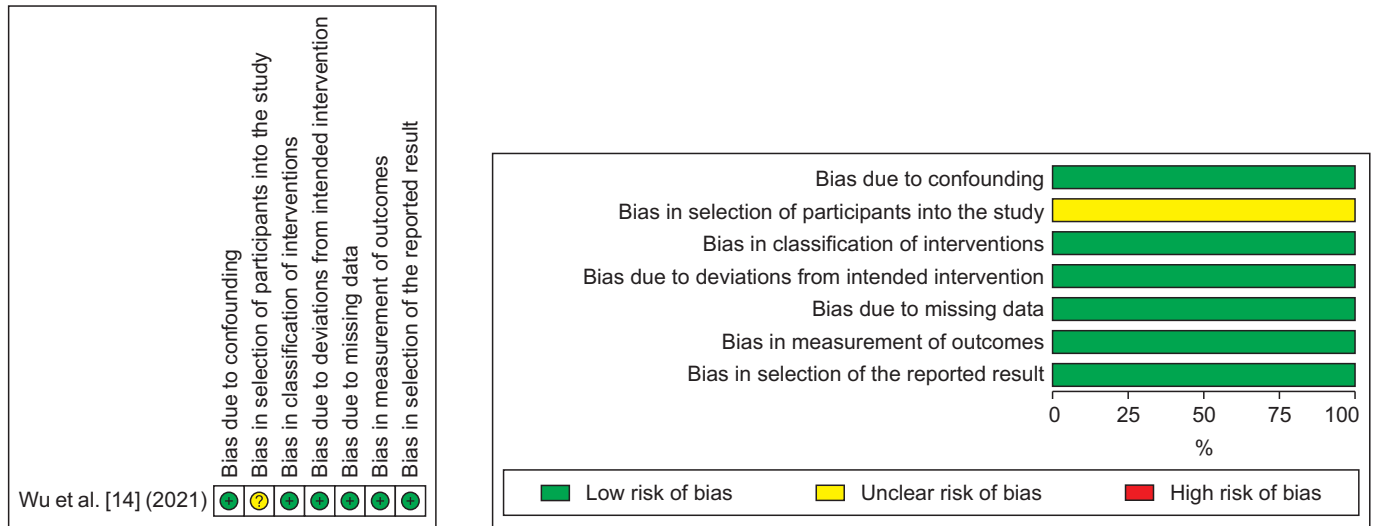**Fig. 2.** Risk of bias summary and a graph showing the authors' judgements about each risk of bias item for randomized controlled trials (A) and observational studies (B).

(I^2 =0%, p = 0.66) and the GRADE system suggested moderate certainty.

Additional analyses

Leave-one-out analysis and independent analysis of studies with low RoB confirmed robust results for the primary outcome.
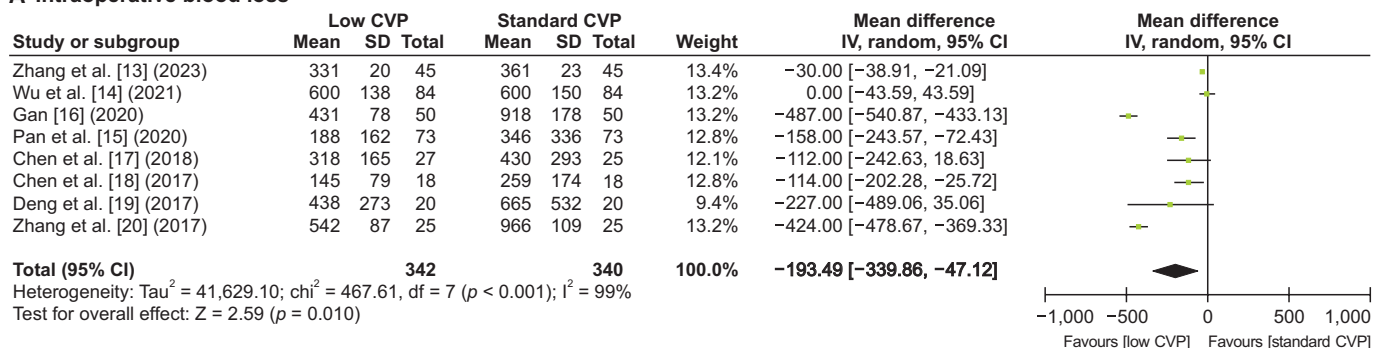
DISCUSSION

We conducted a systematic review to compare the outcomes of low CVP and standard CVP during laparoscopic liver resection. Analysis of 8 studies including 682 patients showed that low CVP reduced intraoperative blood loss during laparoscopic liver resection; however, it did not have any effects on the need for blood transfusion, mean arterial pressure, Pringle time, operative time, or total complications. Sensitivity analysis suggested consistency of the results for intraoperative blood loss
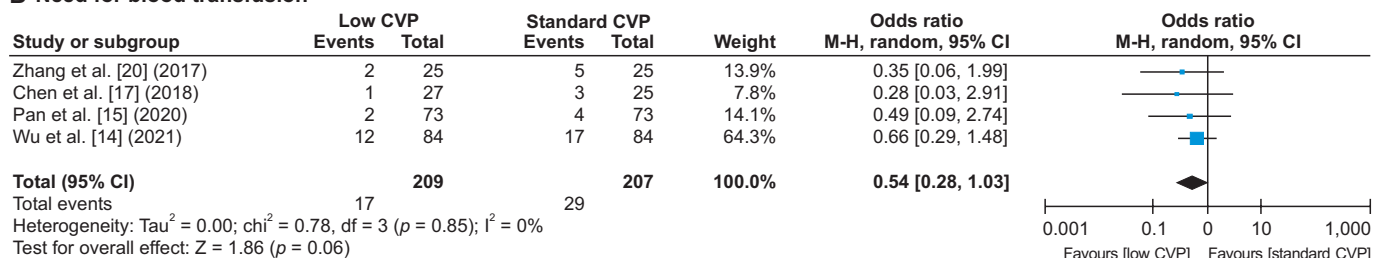
and TSA suggested that meta-analysis for intraoperative blood loss was not subject to type I or II errors. The GRADE system suggested moderate certainty.

For the first time in the literature, the current study assessed the impact of low CVP on intraoperative bleeding, specifically during laparoscopic liver resection. However, the results of the current study can be compared with the results of previous reviews, which did not limit the included population to laparoscopic liver resection. Liu et al. [5] conducted a systematic review including patients who had open or laparoscopic liver
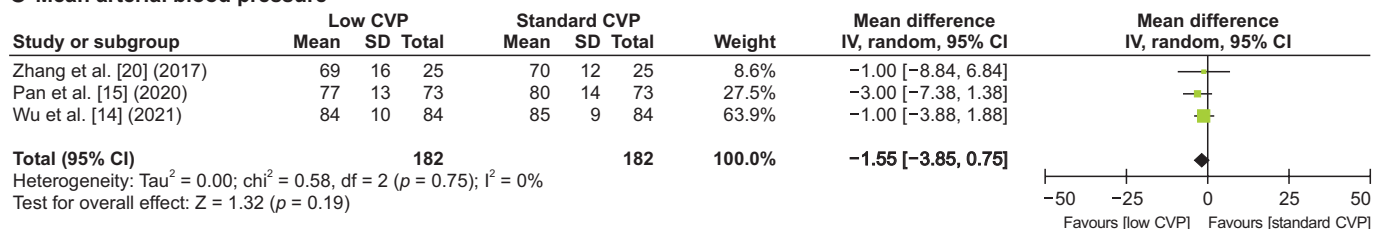
A Intraoperative blood loss

Study or subgroup	Low CVP Mean	SD	Total	Standard CVP Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Zhang et al. [13] (2023)	331	20	45	361	23	45	13.4%	−30.00 [−38.91, −21.09]
Wu et al. [14] (2021)	600	138	84	600	150	84	13.2%	0.00 [−43.59, 43.59]
Gan [16] (2020)	431	78	50	918	178	50	13.2%	−487.00 [−540.87, −433.13]
Pan et al. [15] (2020)	188	162	73	346	336	73	12.8%	−158.00 [−243.57, −72.43]
Chen et al. [17] (2018)	318	165	27	430	293	25	12.1%	−112.00 [−242.63, 18.63]
Chen et al. [18] (2017)	145	79	18	259	174	18	12.8%	−114.00 [−202.28, −25.72]
Deng et al. [19] (2017)	438	273	20	665	532	20	9.4%	−227.00 [−489.06, 35.06]
Zhang et al. [20] (2017)	542	87	25	966	109	25	13.2%	−424.00 [−478.67, −369.33]
Total (95% CI)			342			340	100.0%	−193.49 [−339.86, −47.12]

Heterogeneity: Tau^2 = 41,629.10; chi^2 = 467.61, df = 7 (p < 0.001); I^2 = 99%
Test for overall effect: Z = 2.59 (p = 0.010)

B Need for blood transfusion

Study or subgroup	Low CVP Events	Total	Standard CVP Events	Total	Weight	Odds ratio M-H, random, 95% CI
Zhang et al. [20] (2017)	2	25	5	25	13.9%	0.35 [0.06, 1.99]
Chen et al. [17] (2018)	1	27	3	25	7.8%	0.28 [0.03, 2.91]
Pan et al. [15] (2020)	2	73	4	73	14.1%	0.49 [0.09, 2.74]
Wu et al. [14] (2021)	12	84	17	84	64.3%	0.66 [0.29, 1.48]
Total (95% CI)		209		207	100.0%	0.54 [0.28, 1.03]
Total events	17		29			

Heterogeneity: Tau^2 = 0.00; chi^2 = 0.78, df = 3 (p = 0.85); I^2 = 0%
Test for overall effect: Z = 1.86 (p = 0.06)

C Mean arterial blood pressure

Study or subgroup	Low CVP Mean	SD	Total	Standard CVP Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Zhang et al. [20] (2017)	69	16	25	70	12	25	8.6%	−1.00 [−8.84, 6.84]
Pan et al. [15] (2020)	77	13	73	80	14	73	27.5%	−3.00 [−7.38, 1.38]
Wu et al. [14] (2021)	84	10	84	85	9	84	63.9%	−1.00 [−3.88, 1.88]
Total (95% CI)			182			182	100.0%	−1.55 [−3.85, 0.75]

Heterogeneity: Tau^2 = 0.00; chi^2 = 0.58, df = 2 (p = 0.75); I^2 = 0%
Test for overall effect: Z = 1.32 (p = 0.19)

D Pringle time

Study or subgroup	Low CVP Mean	SD	Total	Standard CVP Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Pan et al. [15] (2020)	15	6	73	10	7	73	32.8%	5.00 [2.89, 7.11]
Wu et al. [14] (2021)	51	8	84	57	8	84	32.2%	−6.00 [−8.42, −3.58]
Zhang et al. [13] (2023)	14	1	45	16	1	45	35.0%	−2.00 [−2.41, −1.59]
Total (95% CI)			202			202	100.0%	−0.99 [−5.82, 3.84]

Heterogeneity: Tau^2 = 17.36; chi^2 = 52.10, df = 2 (p < 0.001); I^2 = 96%
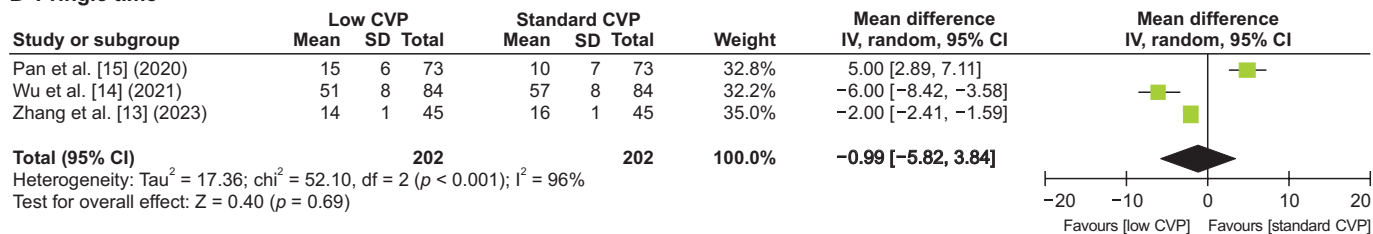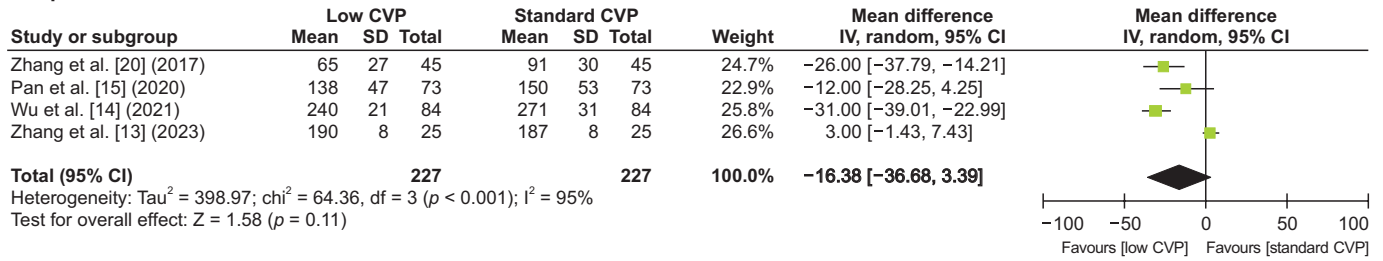Test for overall effect: Z = 0.40 (p = 0.69)

Fig. 3. Forest plots for the comparison between low CVP and standard CVP. (A) Intraoperative blood loss. (B) Need for blood transfusion. (C) Mean arterial blood pressure. (D) Pringle time. (E) Operative time. (F) Total complications. CVP, central venous pressure; SD, standard deviation; CI, confidence interval; IV, inverse variance; M-H, Mantel-Haenszel.

E Operative time

Study or subgroup	Low CVP Mean	SD	Total	Standard CVP Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Zhang et al. [20] (2017)	65	27	45	91	30	45	24.7%	−26.00 [−37.79, −14.21]
Pan et al. [15] (2020)	138	47	73	150	53	73	22.9%	−12.00 [−28.25, 4.25]
Wu et al. [14] (2021)	240	21	84	271	31	84	25.8%	−31.00 [−39.01, −22.99]
Zhang et al. [13] (2023)	190	8	25	187	8	25	26.6%	3.00 [−1.43, 7.43]
Total (95% CI)			**227**			**227**	**100.0%**	**−16.38 [−36.68, 3.39]**

Heterogeneity: Tau^2 = 398.97; chi^2 = 64.36, df = 3 (p < 0.001); I^2 = 95%
Test for overall effect: Z = 1.58 (p = 0.11)

Mean difference IV, random, 95% CI — axis: −100, −50, 0, 50, 100. Favours [low CVP] / Favours [standard CVP]

F Total complications

Study or subgroup	Low CVP Events	Total	Standard CVP Events	Total	Weight	Odds ratio M-H, random, 95% CI
Chen et al. [18] (2017)	1	18	0	18	4.4%	3.17 [0.12, 83.17]
Deng et al. [19] (2017)	10	20	4	20	23.7%	4.00 [0.98, 16.27]
Chen et al. [17] (2018)	7	27	5	25	27.5%	1.40 [0.38, 5.16]
Pan et al. [15] (2020)	10	73	7	73	44.4%	1.50 [0.54, 4.17]
Total (95% CI)		**138**		**136**	**100.0%**	**1.92 [0.97, 3.80]**
Total events	28		16			

Heterogeneity: Tau^2 = 0.00; chi^2 = 1.59, df = 3 (p = 0.66); I^2 = 0%
Test for overall effect: Z = 1.87 (p = 0.06)

Odds ratio M-H, random, 95% CI — axis: 0.002, 0.1, 0, 10, 500. Favours [low CVP] / Favours [standard CVP]
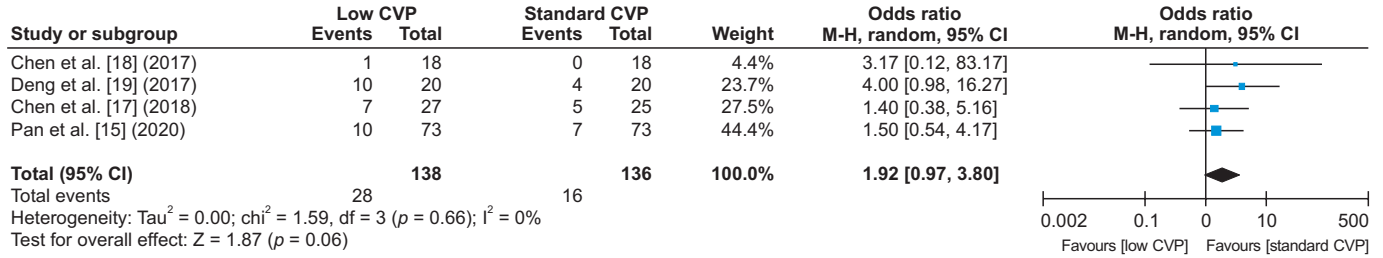
Fig. 3. Continued.

resection and concluded that low CVP is effective in reducing blood loss during liver resection. In another study, Hughes et al. [21] concluded that low CVP reduced intraoperative bleeding during open liver resection. Our findings are consistent with those of the aforementioned reviews.

The reduced intraoperative blood loss associated with low CVP during laparoscopic liver resection can be simply explained. It is well-recognized that venous bleeding is the main source of bleeding during liver resection, especially when he-

patic inflow is reduced via Pringle manoeuvre or hepatic hilum occlusion [22,23]. Considering that CVP is directly related to the hepatic sinusoidal pressure, reducing the pressure in the inferior vena cava will reduce the former resulting in a drop of the pressure in hepatic sinusoids hence reducing intraoperative blood loss [22,23]. The findings of the current study support the above mechanism.

The current study is subject to the following limitations. Although most of the included studies had a randomized de-
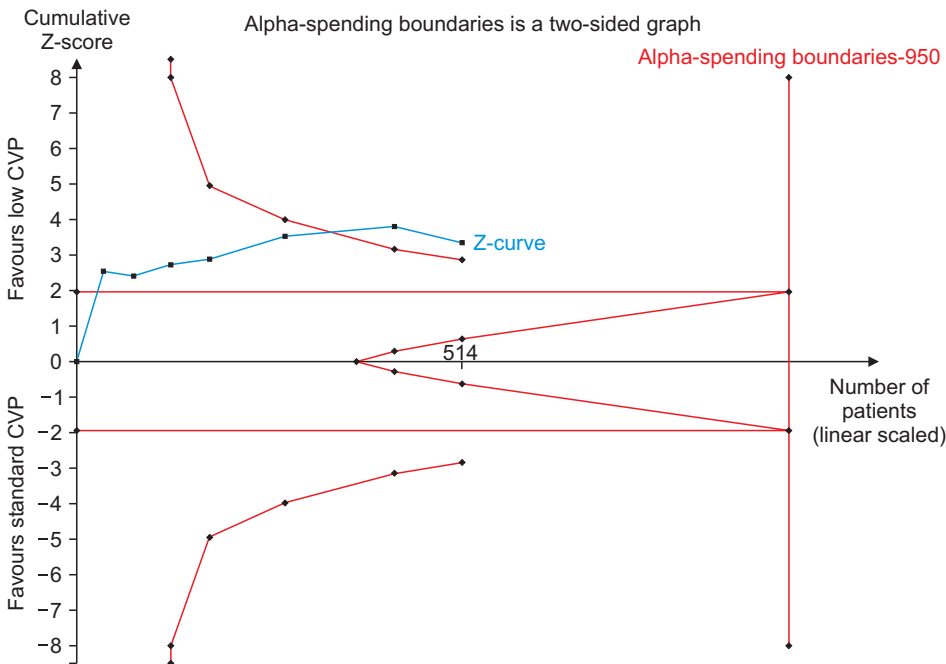

Fig. 4. Results of trial sequential diagnosis for intraoperative blood loss. CVP, central venous pressure.

sign, the included population characteristics, detail of liver resections, and detail of randomizations were poorly reported. Moreover, the available evidence is limited to studies from the same country, which may affect the generalisability of the findings. Consequently, the available data was not adequate for performing meta-regression analysis or subgroup analyses based on the baseline characteristics of the included population and type of liver resection; hence, confounding bias and selection bias cannot be excluded. Laparoscopic insufflation pressure may help to reduce intraoperative blood loss when it exceeds CVP pressure during laparoscopic liver resection. Therefore, variation in insufflation pressure among the included studies and between the treatment arms may be an important confounding factor. The insufflation pressure used during laparoscopic pressure was poorly reported by the included studies; consequently, it was not possible to perform meta-regression analysis or subgroup analyses based on insufflation pressure; this can be considered as another potential source of confounding bias. Although the intraoperative blood loss as the primary outcome was well-reported by the included studies, the secondary outcomes were not reported by all of the included studies; hence, our secondary outcomes results are less robust. The statistical heterogeneity was high for the primary outcome; nevertheless, the findings remained consistent through sensitivity analyses and TSA. Moreover, we downgraded evidence certainty due to high statistical heterogeneity. Because we included less than 10 studies, we were not able to assess publication bias risk.

CONCLUSIONS

While the available evidence may be subject to confounding bias and selection bias, the best available evidence suggests that low CVP may reduce intraoperative bleeding during laparoscopic liver resection (moderate certainty); however, this may not translate into shorter operative time, shorter Pringle time, or less need for blood transfusion. RCTs with larger sample sizes will provide more robust evidence. The results of the current study provide a robust basis for power analysis and hypothesis synthesis for future randomised trials.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: TS, Shahab H. Data curation: MS, Shahab H. Methodology: All authors. Writing - original draft: All authors. Writing - review & editing: All authors.

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Appendix 1. Literature search strategy

Search No.	Search strategy[a]
#1	liver near 2 resection: TI,AB,KW
#2	wedge resection OR tumorectomy OR sectionectomy OR segmentectomy OR bisegmentectomy OR trisegmentectomy OR lobectomy OR hepatectomy: TI,AB,KW
#3	#1 OR #2
#4	low near 2 venous pressure: TI,AB,KW
#5	central venous pressure: TI,AB,KW
#6	MeSH descriptor: [central venous pressure] explode all trees
#7	#4 OR #5 OR #6
#8	MeSH descriptor: [laparoscopic surgery] explode all trees
#9	laparoscop*: TI,AB,KW
#10	#8 OR #9
#11	#3 AND #7 AND #10

[a]This search strategy was adopted for following databases: MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL).