Reduction of Central Venous Pressure in Elective Robotic and Laparoscopic Liver Resection

The PRESSURE Trial—A Randomized Clinical Study

Patrick Téoule, MD,†✉ Niccolo Dunker, MD,* Johanna Debatin, MS,*
Dorothée Sturm, DBiol,*† Svetlana Hetjens, DSc,‡ Valentin Walter, MD,§
Erik Rasbach, MD,*† Christoph Reissfelder, MD,*
Emrullah Birgin, MD,*† and Nuh N. Rahbari, MD*†*

Objective: To compare perioperative outcomes in patients undergoing minimally invasive liver surgery (MILR) with or without central venous pressure (CVP) reduction ($\leq$5 mm Hg).

Background: Reduction of CVP during parenchymal transection is widely accepted in open hepatectomy to reduce intraoperative blood loss, as a major predictor of postoperative outcomes. However, the effect of CVP reduction on blood loss in MILR remains unclear.

Methods: This study is a randomized controlled, double-blinded trial. Patients undergoing elective MILR between August 2020 and April 2023 were equally randomized to either no CVP reduction (No CVP reduction group) or CVP reduction by anesthesiological interventions (CVP reduction group). The remaining perioperative care was kept identical between groups. The primary endpoint was total intraoperative blood loss.

Results: In total, 120 patients were randomized and 112 were analyzed. Baseline characteristics did not differ between groups. Total intraoperative blood loss in MILR was equivalent between groups [No CVP reduction: 280 mL (120–560) vs CVP reduction: 360 mL (150–640); $P = 0.30$], despite higher CVP values during resection in the No CVP reduction group (9.3 mm Hg $\pm$ 4.2 vs 3.2 mm Hg $\pm$ 2.2; $P < 0.001$). Similarly, there was no difference in blood loss during parenchymal transection between the No CVP reduction (220 mL; 80–400) and the CVP reduction group (240 mL; 110–560; $P = 0.39$). Postoperative 90-day mortality (No CVP reduction: n = 3, 5% versus CVP reduction: n = 2, 4%; $P = 0.68$) and total morbidity rates (No CVP reduction: n = 10, 18% vs CVP reduction: n = 11, 20%; $P = 0.77$) were comparable. Intraoperative hemodynamic instability was less frequent in the No CVP reduction group (n = 7, 12% vs CVP reduction group: n = 16, 30%; $P = 0.03$).

Conclusions: MILR without CVP reduction during liver transection is safe and is not associated with increased intraoperative blood loss. Moreover, a no CVP reduction strategy might prevent potential adverse effects of fluid restriction in MILR, such as hemodynamic instability.

Key Words: anesthesiological CVP reduction, blood loos, hepatectomy, pneumoperitoneum, postoperative outcome

(*Ann Surg* 2025;282:210–218)

Intraoperative hemorrhage during liver resection (LR) is a major predictor of poor outcomes.[1,2] It is widely accepted that bleeding at the liver transection surface depends on the difference between the intraabdominal and the hepatic venous pressure, which in turn correlates with the central venous pressure (CVP). Therefore, most hepatobiliary centers apply a low CVP ($\leq$5 mm Hg) strategy to minimize blood loss in open and minimally invasive liver resection (MILR).[3–5] Current recommendations for bleeding control in MILR include (1) an intraabdominal pressure of $>$10 mm Hg, (2) inflow control (ie, portal triad clamping), and (3) outflow control (ie, low CVP).[6,7] CVP reduction is mainly accomplished by restrictive intraoperative fluid management, consequently posing the risk of inadequate peripheral organ perfusion and intraoperative hemodynamic instability, particularly in the event of acute hemorrhage.[8] Various randomized controlled trials (RCTs) have been performed aiming to reduce intraoperative hemorrhage and thus optimize the perioperative outcome after LR.[9–11] These studies have addressed methods of vascular control[12–16] and CVP reduction.[17] However, the effect of CVP reduction on blood loss in MILR remains unclear.

We hypothesized that elevated intraabdominal pressure in conjunction with inflow control can be harnessed during MILR to reduce intraoperative blood loss without CVP reduction in these patients. We here report the results from a RCT to assess the effect of low CVP ($\leq$5 mm Hg) by intraoperative fluid restriction, compared with standard CVP management, on intraoperative blood loss in elective MILR with an elevated intraabdominal pressure.

From the *Department of Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; †Department of General and Visceral Surgery, Ulm University Hospital, Ulm, Germany; ‡Department of Medical Statistics and Biomathematics, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; and §Department of Anesthesiology and Critical Care Medicine, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

✉patrick.teoule@uniklinik-ulm.de.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

P.T. and N.N.R.: conceptualization. P.T., N.D., J.D., D.S., V.W., E.R., C.R., E.B., and N.N.R.: data curation and investigation. P.T., N.D., S.H., C.R., E.B., and N.N.R.: formal analysis. P.T., N.D., D.S., E.B., and N.N.R.: methodology. P.T. and N.D.: project administration. N.N.R.: supervision. P.T., N.D., and N.N.R.: visualization. P.T., N.D., E.B., and N.N.R.: written the original draft. P.T., N.D., J.D., D.S., S.H., V.W., E.R., C.R., E.B., and N.N.R.: drafted the article or revised it critically for important intellectual content.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.

DOI: 10.1097/SLA.0000000000006721

METHODS

Study Design and Patients

This study was designed as a prospective randomized (DRKS00021748), controlled, single-center, observer-blinded, treating surgeon-blinded, and patient-blinded (double-blinded) trial with 2 parallel study groups (trial protocol in Supplemental 1, Supplemental Digital Content 3, http://links.lww.com/SLA/F456). The ethics committee of the Medical Faculty Mannheim, Heidelberg University (2020-575N) approved the study, and all surgeries were performed at the Department of Surgery, University Hospital Mannheim, Heidelberg University. Written informed consent was obtained from all patients before inclusion. Patients, aged $\geq$18 years and scheduled for elective MILR at the Department of Surgery, University Hospital Mannheim, were eligible for inclusion. Exclusion criteria included (1) need for extrahepatic resection based on preoperative imaging, (2) anticipated non-compliance, (3) child B or C liver cirrhosis, (4) atrial fibrillation, and (5) impaired mental state or language knowledge. The study was performed in agreement with the Declaration of Helsinki and Good Clinical Practice guidelines and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[18–20]

Randomization and Blinding

Patients entering the preoperative anesthesia unit were allocated to the study groups using block randomization by trial personnel who were not involved in the patient treatment. The groups included CVP reduction through anesthesiologic interventions (CVP reduction) or an experimental group (No CVP reduction) without CVP reduction with liberal CVP management. Allocation was performed using sealed, consecutively numbered opaque envelopes, which were opened after confirming patient identity and maintained confidentiality. Patients and the treating surgeon were blinded to the study intervention. Perioperative outcomes were documented by an independent study nurse who was unaware of the treatment groups.

Trial Interventions and Surgical Procedures

CVP reduction is recommended in guidelines on laparoscopic LR and can, therefore, be considered "standard of care." Therefore, in the CVP reduction group of our trial CVP reduction was carried out. Perioperative patient care was standardized and kept identically except for intraoperative CVP reduction ($\leq$5 mm Hg) during liver transection in the No CVP reduction group.[21] Central venous catheter (CVC) are not routinely required in all MILR (particularly in case of minor hepatectomies). However, for the purpose of the study and to ensure adequate CVP monitoring, all patients received a CVC at the level of the right atrium.[22]

All operations were conducted by expert surgeons in MILR with a minimum of 50 laparoscopic or robotic hepatectomies annually. Liver transection in patients randomized to CVP reduction through intravenous fluid restriction (CVP reduction group) was conducted with CVP lowered to $\leq$5 mm Hg. CVP was primarily reduced by fluid restriction and positive end-expiratory pressure (PEEP) below 5 mm Hg.[17] If needed, the anesthesiologist was permitted to use opioids within given ranges, nitro compounds, or diuretics at their discretion. In both study groups, patients were allowed to drink sweetened tea or clear fluids up to 2 hours before surgery. To compensate for the resulting intravascular deficit, patients undergoing MILR without CVP reduction (No CVP reduction group) received a standardized bolus of 500 mL crystalloid fluid during anesthesia induction. Intraoperative volume management included a basal infusion rate of 3 mL/kg/h. Pulse pressure variation was used as a dynamic preload parameter to assess volume responsiveness. A pulse pressure variation value exceeding 11% triggered the administration of a 250 mL crystalloid bolus.[23] In contrast, the CVP reduction group followed a restrictive fluid management approach, receiving fluids according to the formula: "$\geq$1 mL/kg body weight + 40 mL of any crystalloid fluid preparation per hour." Fluid loss through urine output was not replaced in both study groups. Acute blood loss was managed with colloidal solutions at a 1:1 ratio, while contraindications to colloids were addressed with crystalloid infusion at a 3:1 ratio.

In line with previous reports and current guidelines, liver transection in both study groups included a pneumoperitoneum of 15 to 18 mm Hg, patient placement in a reversed Trendelenburg position, and intermittent Pringle maneuver with 10 minutes of portal triad clamping followed by 5 minutes of reperfusion for all patients.[6,7,21,24–28] All procedures were performed as laparoscopic or robotic hepatectomy, depending on the availability of the robotic system. In laparoscopic and robotic LRs, parenchymal transection was performed by the crush-clamp technique in combination with an energy device[11,21,25,29] and monopolar scissors together with bipolar forceps,[26,27,30] respectively. Intraabdominal drains were not placed routinely. Additional information on anesthesiological and surgical care is detailed in Supplemental 2 (Supplemental Digital Content 3, http://links.lww.com/SLA/F456.).

Primary Outcome

The primary endpoint of the PRESSURE trial was total intraoperative blood loss (mL), defined as blood loss from skin incision to skin closure, determined by assessment of blood suction containers, including blood absorbed from all surgical swabs and textiles, excluding irrigation fluid and ascites.

Secondary Outcomes

All outcomes were predefined in the trial protocol. Secondary endpoints included blood loss during transection, transection surface area, operating time, perioperative transfusion, intraoperative gas embolism (defined as the occurrence of the following 3 clinical signs: decrease in end-tidal CO_2, hypotension, and hypoxemia), hemodynamic instability (defined as a shock index, ie, ratio of heart rate to systolic blood pressure, of $>$1), fluid and norepinephrine doses. Transection surface area was calculated using paper sheet imprints.[31] Hemodynamic instability was defined as a positive shock index, that is, heart rate exceeded systolic blood pressure. The IWATE score assessed the difficulty of LRs.[32] Major hepatectomy was defined as anatomic resection of at least 3 liver segments.[33] LR extent was categorized using the Brisbane nomenclature and Couinaud's segmentation.[34] Postoperative complications were graded by Clavien-Dindo and the Comprehensive Complication Index (CCI) until 90 ($\pm$7) days after surgery.[35–37] Specific complications after MILR were classified and reported in line with definitions of the International Study Group of Liver Surgery.[38–40]

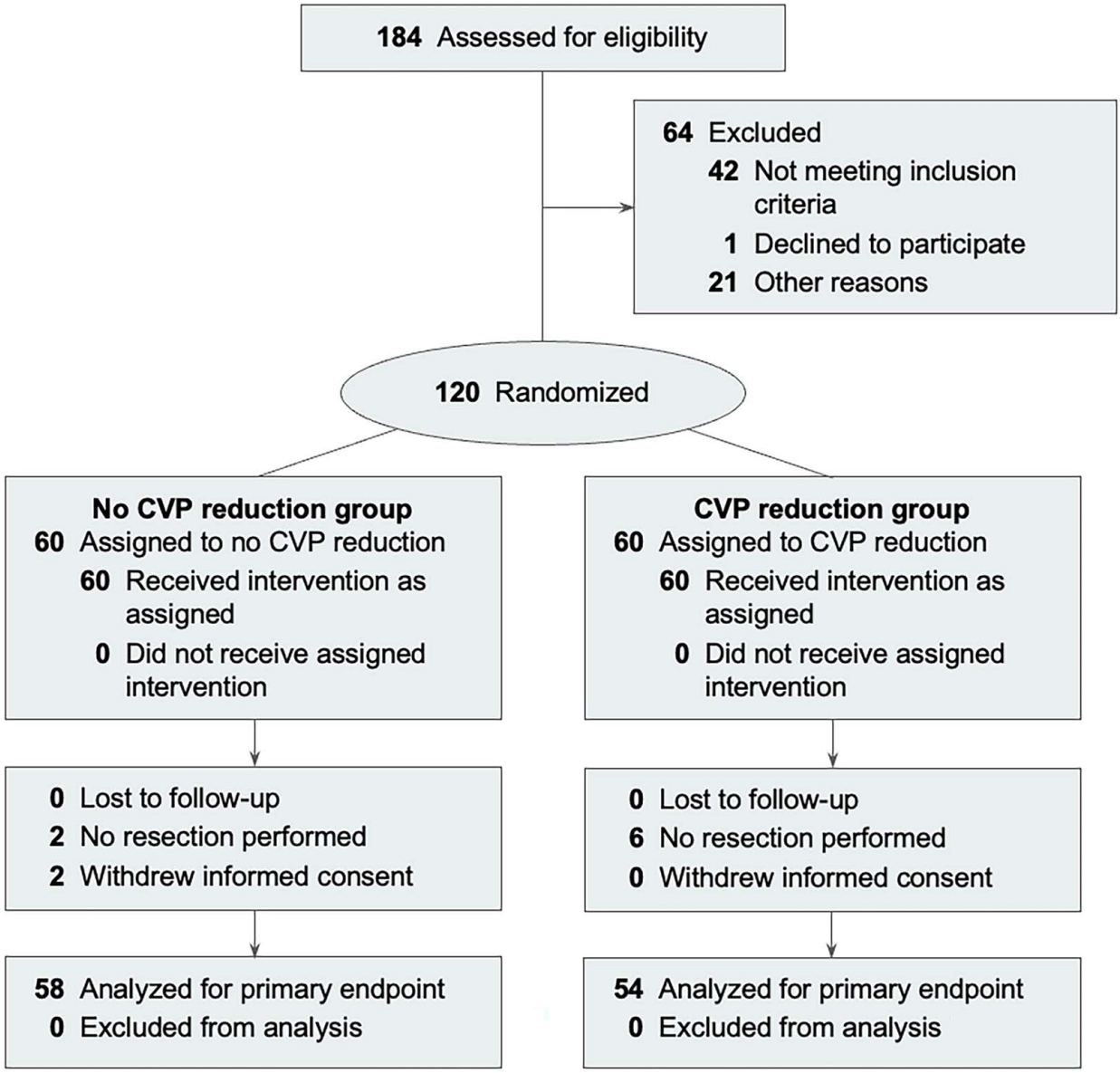

FIGURE 1. Flow diagram according to the CONSORT statement. CONSORT indicates Consolidated Standards of Reporting Trials.

Sample Size and Statistical Analysis

The sample size calculation was based on the primary endpoint, "total intraoperative blood loss." Literature reviews and internal observations indicated a mean intraoperative blood loss of 450 mL, with a SD of ~280 mL for patients undergoing MILR. A clinically relevant reduction of 30%, equivalent to 135mL, in blood loss after MILR was determined, as both literature reviews and internal observations showed that such a reduction was associated with clinically relevant outcomes.[41–46] Utilizing SAS "proc power" with 5% significance and 80% power, 54 patients per group were needed to detect a clinically relevant difference (accepted range between groups: 1.0%–30.0%). Assuming a 10% drop-out rate, the total sample size was set to 120 patients (60 per group).

Statistical analyses were conducted using SAS-Version 9.4 (SAS Institute). Categorical parameters were presented as frequencies (%), and continuous variables as mean (SD) or median [interquartile range (IQR)], depending on the distribution pattern determined by the Shapiro-Wilk test. For comparison, the appropriate tests, that is, 2-tailed t test or Mann-Whitney test for continuous variables and Pearson χ^2 test or Fisher exact test for categorical variables, were utilized. Confirmatory analysis was carried out based on an intention-to-treat (ITT) population adhering to ITT principles. Analysis of covariance (ANCOVA) was performed to assess treatment differences, with total intraoperative blood loss and blood loss during transection as dependent variable and CVP reduction as continuous covariate. Statistical significance was set at P values < 0.05.

RESULTS

Study Population

The study flow is shown in Figure 1. From August 2020 until April 2023, 184 patients were scheduled for

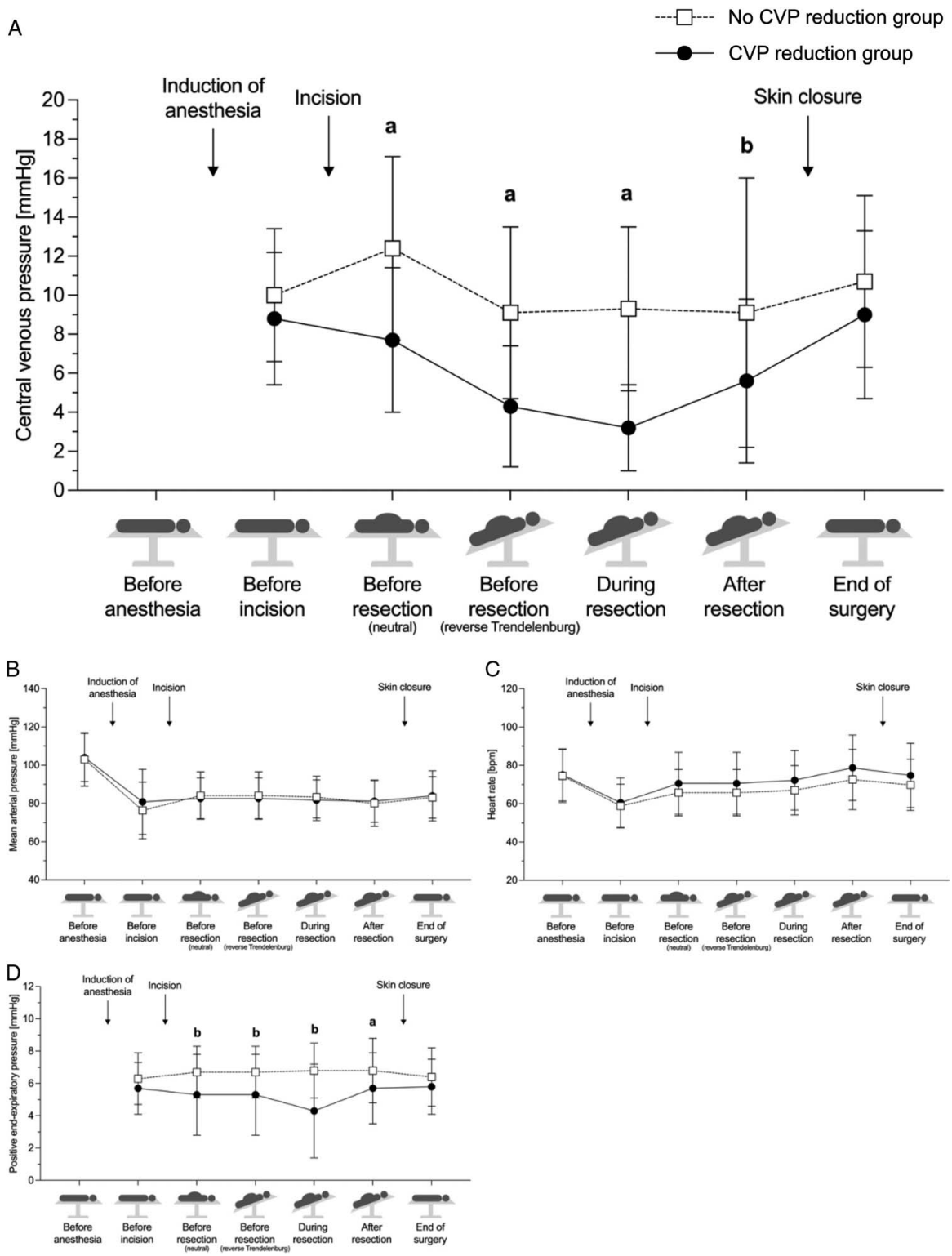

FIGURE 2. A–D, Intraoperative hemodynamic parameters and PEEP. All values are mean (standard deviation). a: $p < 0.001$; b: $p > 0.05$

elective MILR and screened for inclusion in this trial. Of 120 randomized patients, a total of 112 patients remained eligible for final analysis [54 allocated to CVP reduction (CVP reduction group) and 58 allocated to no CVP reduction (No CVP reduction group)]. Two patients in the No CVP reduction group withdrew their consent for further participation in the trial with permission to use the collected data and remained in the ITT analysis. Two patients in the

TABLE 1. Results of Primary Endpoint and Secondary Intraoperative Outcomes

	No CVP reduction group (N = 58)	CVP reduction group (N = 54)	Total (N = 112)	*P*
Primary endpoint				
Blood loss total (mL)	280 (120–560)	360 (160–640)	320 (160–640)	0.30
Secondary intraoperative endpoints				
Blood loss during transection (mL)	220 (80–400)	240 (110–560)	240 (80–480)	0.39
Blood loss per transection area (mL/cm^2)	4.3 (2.2–8.2)	3.8 (2.6–6.8)	4.0 (2.3–7.3)	0.86
Operating time (min)	168 (106–231)	196 (140–267)	184 (121–248)	0.09
Portal triad clamping	54 (93)	50 (93)	104 (93)	0.91
Need for intraoperative transfusion	10 (17)	16 (30)	26 (23)	0.12
Transfusion of PRBC	6 (10)	10 (19)	16 (14)	0.28
Transfusion of FFP	9 (16)	15 (28)	24 (21)	0.17
Transfusion of THC	1 (2)	1 (2)	2 (2)	>0.99
Gas embolism	5 (9)	6 (11)	11 (10)	0.76
Hemodynamic instability*	7 (12)	16 (30)	23 (21)	**0.03**
Infused crystalloid fluids (mL)	2500 (1900–3700)	2175 (1500–3500)	2400 (1700–3700)	0.17
Norepinephrine dose total operating time (µg/min)	3.5 (1.6–6.7)	5.8 (2.1–11.2)	4.9 (1.7–8.3)	**0.04**
Norepinephrine dose transection time (µg/min)	3.1 (1.7–5.9)	4.2 (2.3–8.8)	3.9 (1.8–6.8)	**0.04**
Conversion to open surgery	4 (7)	5 (9)	9 (8)	0.65

Bold values are statistically significant (P <0.05).
Data are shown as n (%) or median (interquartile range).
*Defined as positive shock index (heart rate/systolic blood pressure = >1).
FFP indicates fresh frozen plasma; PRBC, packed red blood cells; THC, thrombocyte concentrate.

No CVP reduction group and 6 in the CVP reduction group were randomized but excluded from the final analysis because no resection was performed. This exclusion was due to irresectability, caused by unexpected intraoperative findings of peritoneal carcinomatosis (3 patients) or to unforeseen progression of the liver tumor (5 patients), leading to subsequent irresectability.

Patients characteristics are outlined in Supplemental eTable 1 (Supplemental Digital Content eTable 1, http://links.lww.com/SLA/F456). Baseline characteristics were well balanced between both study groups, including preoperative anticoagulant medication of 28% (n = 15) in CVP reduction and 38% (n = 22) in No CVP reduction group (P = 0.25).

The performed surgical procedures were comparable between both study populations (Supplemental Digital Content eTable 2, http://links.lww.com/SLA/F456). No significant differences were observed in the extent of surgical resections, with similar proportions of major hepatectomies (P = 0.82) and comparable median transection surface area.

TABLE 2. ANCOVA on Factors Influencing Total and Blood Loss During Liver Transection

	Total blood loss		Blood during transection	
	F	*P*	F	*P*
Preoperative international normalized ratio	0.96	0.33	1.14	0.29
CVP reduction yes or no	0.55	0.46	0.30	0.59
Pneumoperitoneum flow (L/min)	2.72	0.10	2.74	0.10
Intraabdominal pressure (mm Hg)	0.72	0.40	0.31	0.58
PEEP (mm Hg)	0.10	0.75	0.30	0.59
CVP at time of transection (mm Hg)	0.5	0.48	0.34	0.56
Transection surface area (cm^2)	11.04	**0.001**	20.73	**<0.001**

Bold values are statistically significant (P <0.05).

Effectiveness of Trial Interventions

To evaluate the impact of CVP reduction on patient's hemodynamic status, we monitored CVP, heart rate, and mean arterial pressure from patients' entry to the anesthesia preparation room until the end of the surgical procedure. The results of these measurements are shown in Figure 2 and Supplemental eTable 3 (Supplemental Digital Content eTable 3, http://links.lww.com/SLA/F456). Indeed, the CVP reduction group demonstrated significantly lower CVP and PEEP values before, during, and after resection. Before resection, the CVP and PEEP values were 4.3 mm Hg (±3.1) and 5.3 mm Hg (±2.5) in CVP reduction group and 9.1 mm Hg (±4.4) and 6.7 mm Hg (±1.6) in the No CVP reduction group (P < 0.001; P = 0.01). During resection we observed 3.2 mm Hg (±2.2) and 4.3 mm Hg (±2.9) for CVP and PEEP values in CVP reduction group versus 9.3 mm Hg (±4.2) and 6.8 mm Hg (±1.7) in the No CVP reduction group (P < 0.001; P = 0.003). After resection, the values remained consistently lower with 5.6 mm Hg (±4.2) and 5.7 mm Hg (±2.2) in the CVP reduction versus No CVP reduction group: 9.1 mm Hg (±6.9) and 6.8 mm Hg (±2.0; P = 0.004; P < 0.001). These results validate the effectiveness of the trial interventions in reducing CVP among CVP reduction group. Of note, 4 patients of the CVP reduction group breached the ≤5 mm Hg CVP limit during transection with CVP levels of 7 mm Hg in 3 patients and 6 mm Hg in 1 patient.

Intraoperative Outcome Parameters

Table 1 summarizes the intraoperative outcomes. The analysis of the primary endpoint revealed no significant difference in total intraoperative blood loss between patients randomized to the CVP reduction group [360 mL (IQR: 160–640)] compared with those in the No CVP reduction group [280 mL (IQR: 120–560); P = 0.30]. Similarly, median blood loss during liver transection [CVP reduction group: 240 mL (IQR: 110–560) vs No CVP reduction group: 220 mL (IQR: 80–400; P = 0.39)] and blood loss normalized to transection surface area [CVP reduction

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 3. Postoperative Outcomes

	No CVP reduction group (N = 56)	CVP reduction group (N = 54)	Total (N = 110)	*P*
Postoperative complications*				
Presence of any complication	10 (18)	11 (20)	21 (19)	0.77
Grade ≤IIIa	3 (5)	3 (6)	6 (5)	0.94
Grade ≥IIIb	7 (12)	8 (15)	15 (13)	0.72
Grade I	0	1 (2)	1 (1)	0.31
Grade II	1 (7)	1 (2)	2 (2)	0.99
Grade IIIa	2 (4)	1 (2)	3 (3)	0.58
Grade IIIb	4 (7)	5 (9)	9 (8)	0.69
Grade IVa	0	0	0	—
Grade IVb	0	1 (2)	1 (1)	0.31
Grade V	3 (5)	2 (4)	5 (4)	0.68
CCI of patients with presence of any complication	20.9 (20.9–81.5)	33.7 (23.5–40.0)	26.2 (20.9–46.2)	0.52
Posthepatectomy complications†				
Posthepatectomy bile leakage	8 (14)	7 (13)	15 (13)	0.84
Grade A	1 (2)	0	1 (2)	—
Grade B/C	7 (13)	7 (13)	14 (13)	—
Posthepatectomy liver failure	4 (7)	4 (7)	8 (7)	0.96
Grade A	3 (5)	1 (2)	4 (4)	—
Grade B/C	1 (2)	3 (6)	4 (4)	—
Posthepatectomy hemorrhage‡	4 (7)	3 (6)	7 (6)	0.73
Specific complications				
Intraabdominal abscess	5 (9)	6 (11)	11 (10)	0.70
SSI	1 (2)	6 (11)	7 (6)	**0.04**
Renal failure	2 (4)	5 (9)	7 (6)	0.22
Pneumonia	2 (3)	4 (7)	6 (5)	0.38
PE	3 (5)	0	3 (3)	0.08
Myocardial infarction	0	1 (2)	1 (1)	0.31
Radiologic or endoscopic intervention	6 (11)	6 (11)	12 (11)	0.95
Relaparotomy	1 (2)	5 (9)	6 (5)	0.08
Postoperative transfusion	1 (2)	4 (7)	5 (4)	0.15
Transfusion of PRBC	1 (2)	3 (6)	4 (4)	0.28
Transfusion of FFP	0	4 (7)	4 (4)	**0.04**
Transfusion of THC	0	1 (2)	1 (1)	0.30
Readmission	8 (14)	4 (7)	12 (11)	0.25
90 d mortality rate	3 (5)	2 (4)	5 (4)	0.68
Postoperative length of stay (d)	5 (4–7)	6 (4–8)	5 (4–8)	0.56

Bold values are statistically significant ($P < 0.05$).
Data are shown as n (%) or median (interquartile range).
*In line with the Clavien-Dindo classification.
†In line with the International Study Group of Liver Surgery.
‡Posthepatectomy hemorrhage grade A.
FFP indicates fresh frozen plasma; PE, pulmonary embolism; PRBC, packed red blood cells; SSI, surgical site infection; THC, thrombocyte concentrate.

group: 3.8 mL/cm^2 (IQR: 2.6–6.8) vs No CVP reduction group: 4.3 mL/cm^2 (IQR: 2.2–8.2; $P = 0.86$)] did not significantly differ between groups. The intraoperative gas embolism frequency was comparable between groups (CVP reduction: n = 6, 11% vs No CVP reduction: n = 5, 9%; $P = 0.76$). Significantly fewer patients experienced hemodynamic instability during liver transection in the No CVP reduction compared with the CVP reduction group (n = 7, 12% vs n = 16, 30%; $P = 0.03$). Consistent with these data, the average administration of norepinephrine was lower in the No CVP reduction [3.5 µg/min (IQR: 1.6–6.7)] compared with the CVP reduction group [5.8 µg/min (IQR: 2.1–11.2); $P = 0.04$]. Intraoperative fresh frozen plasma (FFP) transfusion was required for 15 patients (28%) in the CVP reduction group and 9 patients (16%) in the No CVP reduction group ($P = 0.17$). However, the median of transfused FFP per patient was low, with 2 (IQR: 0) within the CVP reduction group and 1 (IQR: 0) in the No CVP reduction group ($P = 0.01$).

ANCOVA was conducted to determine factors with impact on total intraoperative blood loss and blood loss during liver transection following MILR (Table 2). These analyses demonstrated a significant association between transection surface area and both total intraoperative blood loss ($P = 0.001$) and blood loss during liver transection ($P < 0.001$). Of note, the ANCOVA did not reveal a significant reduction in total intraoperative blood loss ($P = 0.46$) or blood loss during liver transection ($P = 0.59$) under anesthesiologic CVP reduction compared with the No CVP reduction group. Furthermore, no significant associations were found between total blood loss and blood loss during liver transection and intraoperative parameters such as pneumoperitoneum, PEEP, and CVP at the time of liver transection, intraabdominal pressure, or preoperative International Normalized Ratio.

Postoperative Outcome Parameters

Table 3 summarizes postoperative outcomes for patients in both study groups. Clinically relevant

postoperative complications (Clavien-Dindo ≥ IIIB) were observed in 8 patients (13%) in the CVP reduction group and 7 patients (13%) in the No CVP reduction group (P = 0.72). Consistently, the overall morbidity rates between groups (CVP reduction: n = 11, 20% vs No CVP reduction: n = 10, 18%; P = 0.77), as well as median CCI of patients with the presence of any complication, were comparable between groups [CVP reduction: 33.7 (23.5–40.0) vs No CVP reduction: 20.9 (20.9–81.5); P = 0.52]. Mean and median CCI scores between all patients within CVP reduction group [8.7 ± 21.7; 0 (0)] and the No CVP reduction group [8.9 ± 23.8; 0 (0) (P = 0.94, P = 0.65)] did also not differ. The overall frequencies of posthepatectomy complications were similar in both study groups. Seven patients in each study group developed posthepatectomy bile leakage. Clinically significant posthepatectomy liver failure (Grade B/C) occurred in 3 patients (6%) in the CVP reduction and in 1 patient (2%) in the No CVP reduction group. All cases of posthepatectomy hemorrhage were Grade A, with 3 patients (6%) in the CVP reduction and 4 patients (7%) in the No CVP reduction group.

In the CVP reduction group, patients more frequently developed wound infections compared with the No CVP reduction group (n = 6, 11% vs n = 1, 2%; P = 0.04). Pulmonary embolism (PE) was exclusively observed in the No CVP reduction group (n = 3, 5%; P = 0.09), with a median detection time on postoperative day 12 (IQR: 9–20). The median age was 71 years (IQR: 63–77), and 1 and 2 patients were diagnosed with metastatic leiomyosarcoma and intrahepatic cholangiocarcinoma, respectively. One patient fully recovered with anticoagulation therapy, while the other 2 patients died on postoperative days 5 and 28 following cardiopulmonary reanimation. Other complications, such as intraabdominal abscesses, myocardial infarction, pneumonia, and renal insufficiency, as well as postoperative hepatic function and parenchymal injury (Supplemental Digital Content eFig. 1, http://links.lww.com/SLA/F456) were comparable in both study groups.

Although the number of revision surgeries was lower in the No CVP reduction group compared with the CVP reduction group (n = 1, 2% vs n = 5, 9%), this difference did not reach statistical significance (P = 0.08). Postoperative FFP transfusion was only required in patients of the CVP reduction group (n = 4, 7%; P = 0.04). There were no significant differences observed in the median length of postoperative stay [CVP reduction group: 6 days (IQR: 4–8) vs No CVP reduction group: 5 days (IQR: 4–7); P = 0.56] between both groups. In addition, postoperative readmission within 90 days after surgery did not differ between groups (CVP reduction: n = 4, 7% vs No CVP reduction: n = 8, 14%; P = 0.25). The 90-day mortality rate was comparable between the study groups (CVP reduction: n = 2, 4% vs No CVP reduction: n = 3, 5%; P = 0.68).

DISCUSSION

The PRESSURE trial is the first RCT in a western population to investigate the feasibility and safety of MILR with an elevated pneumoperitoneum without CVP reduction compared with MILR with low CVP (≤5 mm Hg) and restrictive intraoperative fluid management. Our study reveals that both total intraoperative blood loss and blood loss during parenchymal transection were not statistically different during MILR without CVP reduction (No CVP reduction group) as compared with the CVP reduction group. Our data provide, for the first time, evidence that a liberal fluid regime with an elevated pneumoperitoneum pressure of 15 to 18 mm Hg, patient placement in reversed Trendelenburg position, and intermittent Pringle maneuver during liver transection is sufficient for adequate bleeding control, even in the absence of low CVP conditions. These findings were substantiated through an ANCOVA assessing factors that affect total intraoperative blood loss and blood loss during liver transection. Notably, ANCOVA indicated a substantial impact of transection surface area on both intraoperative blood loss and blood loss during liver transection. In fact, the ANCOVA demonstrated no differences in blood loss between the two study groups and thereby confirmed the results of our primary analysis. In addition, the overall postoperative mortality and total morbidity rates were comparable between both study groups. When interpreting the trial results, it is important to consider that all resections were performed under elevated pneumoperitoneum. Future trials are needed to assess the effects of CVP reduction and No CVP reduction in patients undergoing MILR without elevated pneumoperitoneum.

To our knowledge, only one RCT has previously been conducted to investigate the effect of CVP reduction on blood loss in MILR.[47] The authors report a significant reduction of blood loss (188 ± 162 vs 346 ± 336 mL; P < 0.001) in patients with a low CVP compared with no CVP reduction.[47] Albeit, several key methodological differences between the previous study and our present trial hamper a side-by-side comparison. First, Pan and colleagues included exclusively patients with hepatocellular carcinoma, only 3% of whom underwent major hepatectomy, while we report a 6-fold higher frequency of major hepatectomies. Second, in the report by Pan and colleagues, data on the time period of perioperative morbidity and mortality recording is not defined (eg, 30 or 90 days), and data on the grading of postoperative complications (CCI), posthepatectomy complications according to the International Study Group of Liver Surgery definitions, difficulty of LRs, as well as readmission rates are missing, while all these data are reported in the PRESSURE trial. Third, it has to be taken into account that despite the nearly one-third smaller transection surface area reported in the study by Pan and colleagues compared with the PRESSURE trial (CVP reduction group: 39.3 vs 61.7 cm^2 and No CVP reduction group: 36.8 vs 51.3 cm^2), the blood loss per transection surface area was 1.5-fold and 3-fold higher, respectively, within the trial by Pan and colleagues compared with the PRESSURE trial (CVP reduction group: 5.94 vs 3.8 mL/cm^2 and 12.5 vs 4.3 mL/cm^2 in the No CVP reduction group). Furthermore, in the previous trial, the association between blood loss and transection surface area was not investigated using ANCOVA.

A possible reduction of intraoperative blood loss with a low CVP by a restrictive fluid administration comes at the cost of a higher risk of hemodynamic instability, which is particularly aggravated in the event of major blood loss. In this RCT, a significantly higher rate of hemodynamic instability was observed in the CVP reduction compared with the No CVP reduction group. Consequently, patients in the CVP reduction group required a significantly higher median dose of epinephrine during liver transection and whole procedure time compared with the No CVP reduction group. Taken together, the risk of sufficient peripheral organ

perfusion might be compromised.[17] In line with this observation, significantly more patients developed surgical site infections within the CVP reduction group (n = 6, 11% vs No CVP reduction group: n = 1, 2%; $P = 0.04$). This could be explained by the higher intraoperative blood loss within the CVP reduction group. In a systematic review by Marzoug et al.,[48] intraoperative blood loss has been identified as a risk factor for surgical site infection. We observed a higher rate of PE in the No CVP reduction group (n = 3, 5%; $P = 0.09$), with 2 patients succumbing to the complication on postoperative days 5 and 28, respectively. This finding warrants further examination because PE is a severe complication. All affected patients had risk factors for PE, including advanced age, immobility, and active cancer disease, and were in a hypercoagulable state. However, further studies are necessary, as we were unable to identify a clear explanation for this association between liberal CVP management in the No CVP reduction group and the occurrence of PE. To our knowledge, no previous studies have reported an association between postoperative PE and high intraoperative CVP levels. We observed no significant differences in the incidence of myocardial infarction, posthepatectomy liver failure, or renal failure, nor in the analyses of hepatic function and parenchymal injury.

Both study groups showed a high rate of suspected intraoperative gas embolism (CVP reduction: n = 6, 11% vs No CVP reduction group: n = 5, 9%; $P = 0.76$), detected by the appearance of clinical signs such as decrease in end-tidal CO_2, hypotension, or hypoxemia.[49] Although the parallel occurrence of 3 clinical criteria is highly suggestive of gas embolism, none of our patients had a major adverse event, and all cases were safely manageable with hyperventilation. Furthermore, gas embolism could not be detected by transesophageal echocardiography. Therefore, the incidence rates of gas embolism might be overestimated within the PRESSURE trial, but does not affect the comparability regarding the study intervention.

CVP monitoring requires CVC placement and comes with inherent risks, such as thrombosis, catheter malposition, and site or systemic infection, which may prolong hospital stay and even contribute to increased mortality rates.[50] In a retrospective cohort by O'Connor and colleagues, involving 2445 patients undergoing partial hepatectomy, including 404 patients (17%) with CVC placement, multivariate analysis revealed a significant association between the presence of CVC and all-cause mortality at 90 days (OR: 3.45, CI: 1.74–6.85, $P = 0.001$). Notably, CVC presence was associated with overall morbidity and infectious complications.[51] Our study findings indicate that omitting CVP reduction is safe during MILR and does not adversely affect intraoperative blood loss. Even though catheter-associated complications were not observed during this trial, abandonment of CVP monitoring during MILR might decrease the risk of perioperative complications associated with CVC placement.

A systematic review by Stephanos et al.[52] suggested that low CVP during MILR reduces blood loss without affecting mean arterial pressure but called for further RCTs. Based on our results, we disagree with these findings. Liberal CVP management in the No CVP reduction group resulted in reduced blood loss, lower norepinephrine doses, and more importantly, less hemodynamic instability, crucial for patient outcome.

There are limitations of our study. Blood loss, a good predictor of patient outcomes, was used as a primary endpoint. Although it was the primary aim of this trial to evaluate the effect of CVP reduction on blood loss, the effect on perioperative morbidity is of ultimate interest. However, our exploratory analyses of the secondary endpoints did not indicate a trend toward an advantage for either group. We observed a trend towards a higher transection surface area in the CVP reduction group, potentially biasing intraoperative blood loss results. To address this, we measured the blood loss per cm^2 of transection surface area, finding no difference between groups. Future studies could use stratified random sampling, to improve comparability. Finally, this study includes various underlying entities (ie, benign lesions, primary, and secondary liver tumors) and 2 surgical approaches (robotic and laparoscopic). Even though this approach might be perceived as a limitation as it introduces heterogeneity, we are convinced that it significantly enhances the generalizability of the results.

CONCLUSIONS

Our results provide substantial evidence that robotic and laparoscopic LRs can be performed safely without CVP reduction during liver transection without increased intraoperative blood loss. MILR without CVP reduction might prevent potential adverse effects of fluid restriction, such as hemodynamic instability, thereby providing a rationale for potentially improved patient outcomes that have yet to be investigated in RCTs.

REFERENCES

1. Poon RT, Fan ST, Lo CM, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg*. 2004;240:698–708.
2. Wei AC, Tung-Ping Poon R, Fan ST, et al. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. *Br J Surg*. 2003;90:33–41.
3. Chao YJ, Wang CJ, Shan YS. Technical notes: a self-designed, simple, secure, and safe six-loop intracorporeal Pringle's maneuver for laparoscopic liver resection. *Surg Endosc*. 2012;26:2681–2686.
4. Honda G, Kurata M, Okuda Y, et al. Totally laparoscopic hepatectomy exposing the major vessels. *J Hepatobiliary Pancreat Sci*. 2013;20:435–440.
5. Zacharoulis D, Sioka E, Tzovaras G, et al. Laparoscopic left lateral sectionectomy with the use of Habib 4X: technical aspects. *J Laparoendosc Adv Surg Tech A*. 2013;23:549–552.
6. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg*. 2015;261:619–629.
7. Tranchart H, O'Rourke N, Van Dam R, et al. Bleeding control during laparoscopic liver resection: a review of literature. *J Hepatobiliary Pancreat Sci*. 2015;22:371–378.
8. Birgin E, Mehrabi A, Sturm D, et al. Infrahepatic inferior vena cava clamping does not increase the risk of pulmonary embolism following hepatic resection. *World J Surg*. 2021;45:2911–2923.
9. Rahbari NN, Birgin E, Sturm D, et al. Randomized clinical trial of BioFoam Surgical Matrix to achieve hemostasis after liver resection. *HPB (Oxford)*. 2020;22:987–995.
10. Fritzmann J, Kirchberg J, Sturm D, et al. Randomized clinical trial of stapler hepatectomy versus LigaSure transection in elective hepatic resection. *Br J Surg*. 2018;105:1119–1127.
11. Rahbari NN, Elbers H, Koch M, et al. Randomized clinical trial of stapler versus clamp-crushing transection in elective liver resection. *Br J Surg*. 2014;101:200–207.
12. Belghiti J, Noun R, Malafosse R, et al. Continuous versus intermittent portal triad clamping for liver resection: a controlled study. *Ann Surg*. 1999;229:369–375.

13. Belghiti J, Noun R, Zante E, et al. Portal triad clamping or hepatic vascular exclusion for major liver resection. A controlled study. *Ann Surg*. 1996;224:155–161.
14. Clavien P-A, Selzner M, Rüdiger HA, et al. A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. *Ann Surg*. 2003;238:843–850.
15. Capussotti L, Muratore A, Ferrero A, et al. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. *Br J Surg*. 2006;93:685–689.
16. Rahbari NN, Wente MN, Schemmer P, et al. Systematic review and meta-analysis of the effect of portal triad clamping on outcome after hepatic resection. *Br J Surg*. 2008;95:424–432.
17. Rahbari NN, Koch M, Zimmermann JB, et al. Infrahepatic inferior vena cava clamping for reduction of central venous pressure and blood loss during hepatic resection: a randomized controlled trial. *Ann Surg*. 2011;253:1102–1110.
18. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191–2194.
19. ICH E6 (R2) Good clinical practice - Scientific guideline | European Medicines Agency. Accessed February 18, 2024. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline
20. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *Brit Med J*. 2010;340:c332.
21. Téoule P, Schmidt N, Rasbach E, et al. Laparoscopic infrahepatic inferior vena cava clamping during liver resection - a feasibility study. *J Gastrointest Surg*. 2023;27:794–797.
22. Magder S. Central venous pressure: a useful but not so simple measurement. *Crit Care Med*. 2006;34:2224–2227.
23. Miller's Anesthesia, 2-Volume Set - 8th Edition. Accessed February 22, 2020. https://www.elsevier.com/books/millers-anesthesia-2-volume-set/miller/978-0-7020-5283-5
24. Birgin E, Heibel M, Hetjens S, et al. Robotic versus laparoscopic hepatectomy for liver malignancies (ROC'N'-ROLL): a single-centre, randomised, controlled, single-blinded clinical trial. *Lancet Reg Health Eur*. 2024;43:100972.
25. Birgin E, Hartwig V, Rasbach E, et al. Minimally invasive mesohepatectomy for centrally located liver lesions-a case series. *Surg Endosc*. 2022;36:8935–8942.
26. Birgin E, Reissfelder C, Rahbari NN. Robotic left hepatectomy using the glissonean pedicle approach for the treatment of Caroli's syndrome. *Zentralbl Chir*. 2023;148:129–132.
27. Birgin E, Abdelhadi S, Seyfried S, et al. Robotic or laparoscopic repeat hepatectomy after open hepatectomy: a cohort study. *Surg Endosc*. 2024;38:1296–1305.
28. Birgin E, Heibel M, Téoule P, et al. Robotic sectionectomy versus robotic hemihepatectomy for anatomic liver resection: a comparative analysis of perioperative outcomes. *J Robot Surg*. 2024;18:197.
29. Rahbari NN, Koch M, Schmidt T, et al. Meta-analysis of the clamp-crushing technique for transection of the parenchyma in elective hepatic resection: back to where we started? *Ann Surg Oncol*. 2009;16:630–639.
30. Birgin E, Reißfelder C, Rahbari NN. Robot with the scissor-hands: scissor hepatectomy for parenchymal transection in robotic liver resection. *J Gastrointest Surg*. 2024;28:99–101.
31. Rahbari NN, Zimmermann JB, Koch M, et al. IVC CLAMP: infrahepatic inferior vena cava clamping during hepatectomy—a randomised controlled trial in an interdisciplinary setting. *Trials*. 2009;10:94.
32. Tanaka S, Kawaguchi Y, Kubo S, et al. Validation of index-based IWATE criteria as an improved difficulty scoring system for laparoscopic liver resection. *Surgery*. 2019;165:731–740.
33. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg*. 2005;12:351–355.
34. Wakabayashi G, Cherqui D, Geller DA, et al. The Tokyo 2020 terminology of liver anatomy and resections: updates of the Brisbane 2000 system. *J Hepatobiliary Pancreat Sci*. 2022;29:6–15.
35. Clavien P-A, Vetter D, Staiger RD, et al. The Comprehensive Complication Index (CCI): added value and clinical perspectives 3 years "down the line". *Ann Surg*. 2017;265:1045–1050.
36. Slankamenac K, Nederlof N, Pessaux P, et al. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. *Ann Surg*. 2014;260:757–763.
37. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
38. Rahbari NN, Garden OJ, Padbury R, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB (Oxford)*. 2011;13:528–535.
39. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery*. 2011;149:680–688.
40. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149:713–724.
41. Dagher I, O'Rourke N, Geller DA, et al. Laparoscopic major hepatectomy: an evolution in standard of care. *Ann Surg*. 2009;250:856–860.
42. Nomi T, Fuks D, Govindasamy M, et al. Risk factors for complications after laparoscopic major hepatectomy. *Br J Surg*. 2015;102:254–260.
43. Ratti F, Cipriani F, Ariotti R, et al. Laparoscopic major hepatectomies: current trends and indications. A comparison with the open technique. *Updates Surg*. 2015;67:157–167.
44. Yoon YI, Kim KH, Kang SH, et al. Pure laparoscopic versus open right hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a propensity score matched analysis. *Ann Surg*. 2017;265:856–863.
45. Elmahi E, Salama Y, Cadden F, et al. A literature review to assess blood loss in minimally invasive liver surgery versus in open liver resection. *Cureus*. 2021;13:e16008.
46. Komatsu S, Brustia R, Goumard C, et al. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis. *Surg Endosc*. 2016;30:1965–1974.
47. Pan YX, Wang JC, Lu XY, et al. Intention to control low central venous pressure reduced blood loss during laparoscopic hepatectomy: a double-blind randomized clinical trial. *Surgery*. 2020;167:933–941.
48. Marzoug OA, Anees A, Malik EM. Assessment of risk factors associated with surgical site infection following abdominal surgery: a systematic review. *BMJ Surg Interv Health Technol*. 2023;5:e000182.
49. Park EY, Kwon JY, Kim KJ. Carbon dioxide embolism during laparoscopic surgery. *Yonsei Med J*. 2012;53:459–466.
50. How-to Guide: Prevent Central Line-Associated Bloodstream Infection | IHI - Institute for Healthcare Improvement. Accessed July 7, 2023. https://www.ihi.org:443/resources/Pages/Tools/HowtoGuidePreventCentralLineAssociatedBloodstreamInfection.aspx
51. O'Connor DC, Seier K, Gonen M, et al. Invasive central venous monitoring during hepatic resection: unnecessary for most patients. *HPB (Oxford)*. 2020;22:1732–1737.
52. Stephanos M, Stewart CMB, Mahmood A, et al. Low versus standard central venous pressure during laparoscopic liver resection: a systematic review, meta-analysis and trial sequential analysis. *Ann Hepatobiliary Pancreat Surg*. 2024;28:115–124.