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Possible underestimation of blood loss during laparoscopic hepatectomy

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Background: Previous studies have documented potential advantages of laparoscopic hepatectomy in decreasing blood loss compared with open surgery. This study aimed to compare intraoperative blood loss estimated using four different methods in open *versus* laparoscopic hepatectomy.

Methods: Patients undergoing liver resection between 2014 and 2017 were evaluated prospectively, differentiating between the laparoscopic and open approach. Groups were compared using univariable and multivariable analyses. Intraoperative blood loss was estimated using three formulas based on the postoperative decreases in haematocrit, haemoglobin or red blood cell volume, and using the conventional method of the sum of suction fluid amounts and gauze weight. In addition, blood loss per hepatic transection area was calculated to compare groups.

Results: Some 125 patients who underwent hepatectomy were selected, including 56 open hepatectomies and 69 laparoscopic liver resections. Intraoperative blood loss per hepatic transection area estimated by the conventional method was significantly less in the laparoscopic than the open group (3·6 (range 0·2–50·0) *versus* 6·6 (1·2–82·5) ml/cm^2 respectively; $P < 0·001$). In contrast, there were no significant differences between groups in blood loss estimated based on the decrease in haematocrit (12·9 (0–65·2) *versus* 8·1 (0–123·7) ml/cm^2; $P = 0·818$), haemoglobin or red blood cell volume. Blood loss estimation using three formulas showed significant linear correlations with the blood loss estimated by the conventional method in the open group ($r_S = 0·758$ to 0·762), but not in the laparoscopic group ($r_S = -0·019$ to 0·031).

Conclusion: The conventional method of calculating blood loss in laparoscopic hepatectomy can underestimate losses.

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Introduction

Major advantages of laparoscopy over the open approach in liver surgery include minimized trauma to the abdominal wall, decreased postoperative pain and decreased operative blood loss (BL); this benefit could possibly be due to the pneumoperitoneum pressure suppressing capillary and venous bleeding[1,2]. The majority of comparative studies have demonstrated decreased BL during laparoscopic surgery compared with open surgery[3–5], particularly for hepatectomy[6], where venous bleeding during hepatic dissection accounts for most BL. However, venous bleeding can also be well controlled during open hepatectomy with anaesthetic management to maintain a low vena cava pressure and with mobilization of the liver by the surgeon.

In orthopaedic surgery, several formulas based on circulating blood volume and changes in blood counts have been used for the accurate estimation of intraoperative BL, and applied in clinical settings[7–11]. In surgical procedures where direct measurement of intraoperative BL is technically difficult, the potential BL underestimation has led to development of the concept of 'hidden BL'[7].

The aim of this study was to estimate intraoperative BL using blood count-based formulas in patients undergoing open *versus* laparoscopic hepatectomy.

Methods

Consecutive patients who underwent open or laparoscopic hepatectomy for primary liver cancer, liver metastases or benign disease between April 2014 and December 2017 at the Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, a teaching hospital for cancer treatment, were enrolled prospectively. Patients scheduled for extended hemihepatectomy with bile duct resection and reconstruction were excluded because these procedures were considered a contraindication to laparoscopic surgery in terms of technical complexity and unfavourable surgical outcomes compared with hepatectomy without bile duct reconstructions. The indication for laparoscopic surgery was determined by a multidisciplinary team according to tumour size and location. In general, open surgery was indicated for tumour(s) larger than 5 cm and/or those requiring four or more hepatic resections. All clinical, demographic and surgical data were recorded, including estimation of intraoperative BL (main outcome measure), surgical margins, postoperative severe morbidity (at least grade III in the Clavien–Dindo classification[12]), bile leak, postoperative mortality, hospital stay and costs (calculated in euros). Patients were grouped according to the surgical approach (open or laparoscopic).

Surgical techniques

All procedures were performed by a single surgeon as an operator and/or teaching assistant. Open hepatectomy was done using an inverted L-shaped incision, restricted fluid infusion and respiratory volume controlled by anaesthetists, mobilization of the hepatic lobe to be resected[13,14], and hepatic dissection by the clamp-crushing technique with concomitant use of bipolar coagulation and a vessel sealing system (LigaSure™; Medtronic, Minneapolis, Minnesota, USA) under intermittent inflow occlusion[15,16].

For laparoscopic hepatectomy, patients were placed in reverse-Trendelenburg position and the pneumoperitoneum pressure was set at 12 mmHg[17]. Intercostal trocars were used for hepatic lesions located in segments VII and/or VIII[18]. The hepatic parenchyma was transected by the same technique as in open surgery, including the use of intermittent inflow occlusion and the clamp-crushing technique employing a bipolar forceps and a vessel sealing system[17].

Estimation of intraoperative blood loss

In both groups, any abdominal fluids in the visible surgical fields were aspirated during and after hepatectomy.

Table 1 Formulas used to calculate intraoperative blood loss

BL estimation method	Formula
Hct-based BL (ml)	Hct-based BL = $V_{loss\ total}/Hct_{mean}$ $V_{loss\ total} = BV \times (Hct_{preop} - Hct_{postop}) + V_t$ $BV = (k_1 \times H^3 + k_2 \times W + k_3) \times 1000$ For men: $k_1 = 0{\cdot}3669$, $k_2 = 0{\cdot}03219$, $k_3 = 0{\cdot}6041$ For women: $k_1 = 0{\cdot}3561$, $k_2 = 0{\cdot}03308$, $k_3 = 0{\cdot}1833$ 1 unit of banked blood was considered to be 200 ml of RBCs
Hb-based BL (ml)	Hb-based BL = $Hb_{loss\ total}/Hb_{preop} \times 1000$ $Hb_{loss\ total} = BV \times (Hb_{preop} - Hb_{postop}) \times 0{\cdot}001 + Hb_t$ 2 units of banked blood was considered to contain mean(s.d.) 52(5·4) g Hb
OSTHEO BL (ml)	OSTHEO BL = $V_{loss\ total}/Hct_{preop}$ $V_{loss\ total} = V_{initial} - V_{final} + V_t$ $V_{initial} = BV_2 \times Hct_{preop}$ $V_{final} = BV_2 \times Hct_{postop}$ $BV_2 = Z \times k$ For men: k = 2530 For women: k = 2430 $Z\ (m^2) = 0{\cdot}0235 \times H^{0{\cdot}42246} \times W^{0{\cdot}51456}$ 1 unit of banked blood was considered to be 150 ml of RBCs

BL, blood loss; Hct, haematocrit; $V_{loss\ total}$, total volume of blood lost (ml); Hct_{mean}, mean haematocrit (%); BV, patient blood volume before surgery (ml); Hct_{preop}, preoperative Hct (%); Hct_{postop}, postoperative Hct (%); V_t, total volume of blood transfusion (ml); H, height (m); W, weight (kg); RBC, red blood cell; Hb, haemoglobin; $Hb_{loss\ total}$, amount of Hb loss (g); Hb_{preop}, preoperative Hb (g/l); Hb_{postop}, postoperative Hb (g/l); Hb_t, total amount of Hb transfusion (g); OSTHEO, Orthopedic Surgery Transfusion Hemoglobin European Overview; $V_{initial}$, RBC volume before surgery (ml); V_{final}, RBC volume after surgery (ml); BV_2, patient blood volume before surgery (calculated using different formula from BV) (ml).

Intraoperative BL was calculated in accordance with the conventional method, as the sum of intraoperative suction fluid amounts (after subtracting the amount of irrigation fluids) and increase in operative gauze weight (conventional BL). In addition, three established formulas were used to estimate BL based on changes in haematocrit (Hct-based BL)[7,19,20], haemoglobin (Hb-based BL)[9,11], and red blood cell volume as proposed by Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO BL)[8,10,21,22] (*Table 1*). BL per hepatic transection area, based on the raw surface areas of the resected specimens, was also calculated to compare groups[15,18,23].

Statistical analysis

Continuous data are expressed as median (range) and were compared using Wilcoxon's rank-sum test, whereas Fisher's exact test was used for analysis of categorical variables. Correlations between the formula-based BL/area values (Hct-based BL/area, Hb-based BL/area, OSTHEO

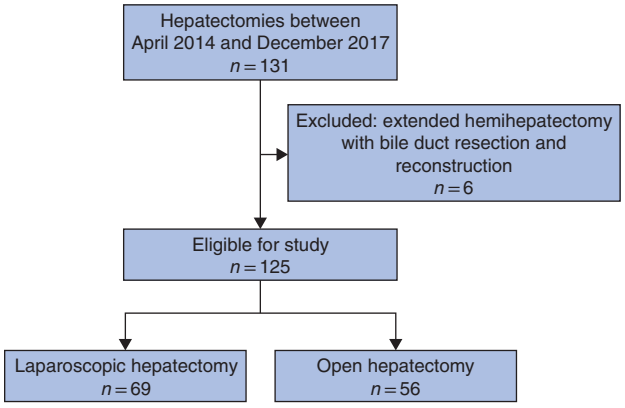

Fig. 1 Study flow diagram

BL/area) and conventional BL/area were evaluated using Spearman's rank correlation test. After conversion of continuous into categorical data using median values, logistic regression analyses were performed to identify variables associated with increased blood loss. To include as many potential confounders as possible, potential independent variables with $P < 0{\cdot}100$ in univariable analyses were included in the multivariable models[24]. Statistical analyses were undertaken using SPSS® version 24.0 (IBM, Armonk, New York, USA) and $P < 0{\cdot}050$ was considered statistically significant.

Results

Between April 2014 and December 2017, some 131 patients underwent liver resection. Six patients who

Table 2 Demographic characteristics and intraoperative factors

	Laparoscopic hepatectomy ($n = 69$)	Open hepatectomy ($n = 56$)	P†
Age (years)*	66 (37–92)	64·5 (35–88)	0·525‡
Sex ratio (M : F)	41 : 28	36 : 20	0·458
BMI (kg/m^2)*	22·5 (14·7–39·4)	21·7 (18·1–36·6)	0·418‡
Preoperative haemoglobin (g/l)*	13·4 (9·3–17·2)	12·7 (9·7–17·7)	0·777‡
Haematocrit (%)*	40·6 (28·9–50·9)	39·0 (28·8–54·2)	0·638‡
Prothrombin activity (%)*	100 (80–100)	96 (71–100)	0·093‡
Serum albumin (g/dl)*	4·2 (3·1–5·0)	4·1 (2·6–4·7)	0·001‡
Preoperative chemotherapy	9 (13)	13 (23)	0·161
Cirrhosis	4 (6)	5 (9)	0·513
Tumour pathology			0·085
Primary liver cancer	12 (17)	19 (34)	
Metastatic liver cancer	53 (77)	33 (59)	
Benign lesion	4 (6)	4 (1)	
Maximum tumour size (mm)*	20 (2–50)	30 (10–160)	< 0·001‡
Synchronous colorectal resection	16 (23)	6 (11)	0·098
Tumour location (liver segment)			0·221
I	2 (3)	7 (13)	
II	7 (10)	4 (7)	
III	10 (14)	4 (7)	
IV	7 (10)	6 (11)	
V	11 (16)	4 (7)	
VI	6 (9)	2 (4)	
VII	12 (17)	15 (27)	
VIII	14 (20)	14 (25)	
Difficult tumour location (segment I, IVa, VII, VIII)	31 (45)	39 (70)	0·007
Proximity to major blood vessel	16 (23)	28 (50)	0·002
Repeat hepatectomy	7 (10)	21 (38)	< 0·001
No. of resections			0·104
1	55 (80)	37 (66)	
≥ 2	14 (20)	19 (34)	
Anatomical resection	11 (16)	28 (50)	< 0·001
Major hepatectomy	4 (6)	17 (30)	< 0·001
Duration of operation (min)*	252 (75–891)	364 (135–876)	< 0·001‡
Transection speed (cm^2/min)*	0·60 (0·16–1·36)	1·07 (0·23–2·84)	< 0·001‡
Hepatic transection area (cm^2)*	41 (8–188)	73 (8–184)	< 0·001‡

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Fisher's exact test, except ‡Wilcoxon rank-sum test.

Table 3 Postoperative outcomes

	Laparoscopic hepatectomy ($n = 69$)	Open hepatectomy ($n = 56$)	P‡
Surgical margins (mm)*	9 (0–28)	5 (0–40)	0·119
Morbidity (Clavien–Dindo ≥ grade III)	3 (4)	4 (7)	0·700§
Bile leak	0 (0)	0 (0)	–
Death	0 (0)	0 (0)	–
Duration of postoperative hospital stay (days)*†	7 (4–17)	9 (5–46)	0·001
Costs of surgery (€)*	5700 (3600–15 000)	5700 (3500–14 000)	0·072
Costs of hospitalization (€)*	12 000 (8200–46 000)	13 000 (8400–36 000)	0·771

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Excluding patients who underwent synchronous colorectal resection. ‡Wilcoxon rank-sum test, except §Fisher's exact test.

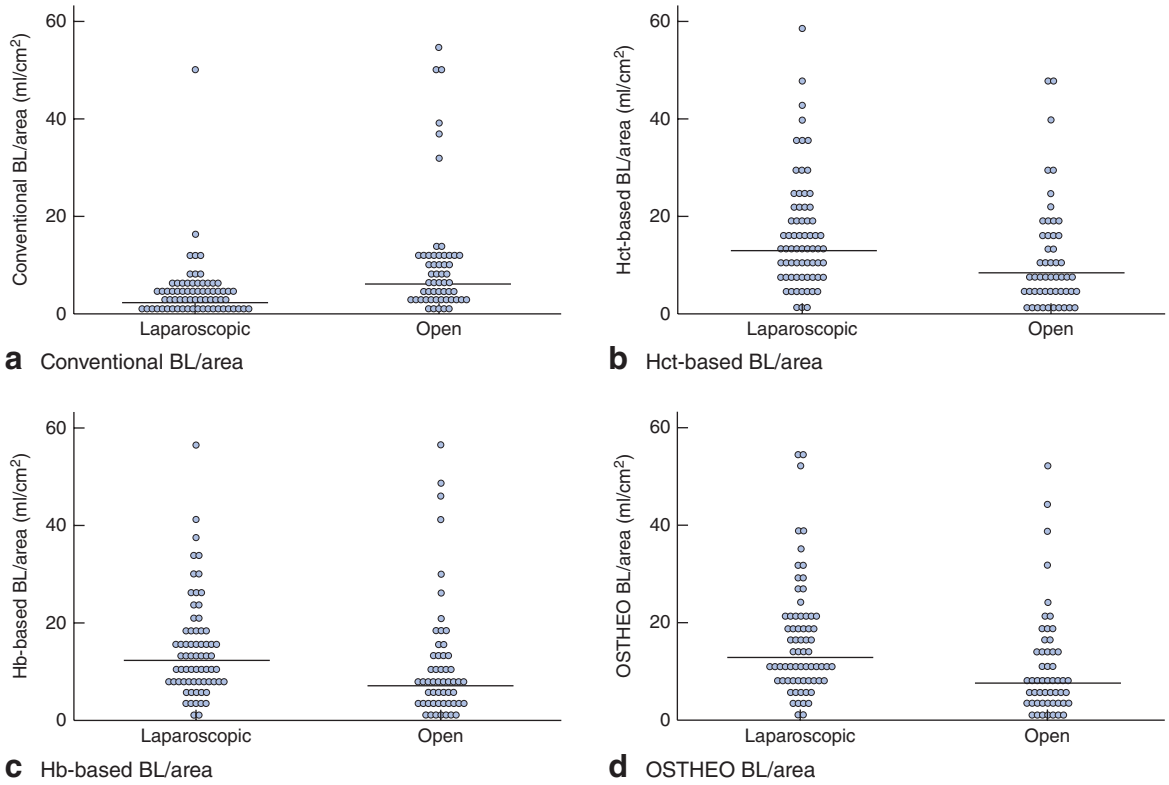

Fig. 2 Intraoperative blood loss in the laparoscopic and open hepatectomy groups estimated using the conventional method and blood count-based calculations. **a** Conventional blood loss (BL) per hepatic transection area; **b** haematocrit (Hct)-based BL/area; **c** haemoglobin (Hb)-based BL/area; **d** Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) BL/area. Outliers are not shown in this figure. Horizontal lines indicate median values. **a** $P < 0·001$, **b** $P = 0·818$, **c** $P = 0·633$, **d** $P = 0·575$ (Wilcoxon signed-rank test)

had extended hemihepatectomy with bile duct resection were excluded, leaving 56 patients treated using an open approach and 69 treated by laparoscopy for analysis (*Fig. 1*). Only one laparoscopic procedure was converted to open surgery; hepatic mobilization and transection was performed using open approach because intraoperative laparoscopic ultrasonography identified a deeply located tumour that was not diagnosed before operation. This patient was included in the open group for analysis.

Patient demographics and surgical data are summarized in *Table 2*. Patients in the open group had larger resection volumes and more complicated procedures owing to difficult tumour location, proximity to major blood vessels, and rate of repeat and major hepatectomies. Operating time was significantly shorter in the laparoscopic group than the open group, despite the significantly larger transection areas in the laparoscopic group.

Blood transfusions were required in four patients in the open group compared with none in the laparoscopic group. *Table 3* shows postoperative outcomes in the two groups. Postoperative hospital stay was significantly shorter in the laparoscopic group, but there were no significant differences between the two groups in surgical margins, complications or treatment costs.

Blood loss estimation

Although the conventional BL calculation and conventional BL/area were significantly lower in the laparoscopic group than the open group ($P < 0{\cdot}001$), there were no significant differences between groups in Hct-based BL/area (12·9 (0–65·2) *versus* 8·1 (0–123·7) ml/cm^2; $P = 0{\cdot}818$), Hb-based BL/area (12·3 (0–64·1) *versus* 7·3 (0–101·2) ml/cm^2; $P = 0{\cdot}633$) or OSTHEO BL/area (12·8 (0–53·4) *versus* 7·7 (0–109·7) ml/cm^2; $P = 0{\cdot}575$) (*Fig. 2*, *Table 4*).

Table 4 Blood loss according to surgical approach

	Laparoscopic hepatectomy ($n = 69$)	Open hepatectomy ($n = 56$)	P*
Conventional BL (ml)	130 (5–1800)	490 (50–2650)	< 0·001
Conventional BL/area (ml/cm^2)	3·6 (0·2–50·0)	6·6 (1·2–82·5)	< 0·001
Hct-based BL/area (ml/cm^2)	12·9 (0–65·2)	8·1 (0–123·7)	0·818
Hb-based BL/area (ml/cm^2)	12·3 (0–64·1)	7·3 (0–101·2)	0·633
OSTHEO BL/area (ml/cm^2)	12·8 (0–53·4)	7·7 (0–109·7)	0·575

Values are median (range). BL, blood loss; Hct, haematocrit; Hb, haemoglobin; OSTHEO, Orthopedic Surgery Transfusion Hemoglobin European Overview. *Wilcoxon rank-sum test.

Fig. 3 shows correlations between blood count-based BL/area values and the conventional BL/area. In the open

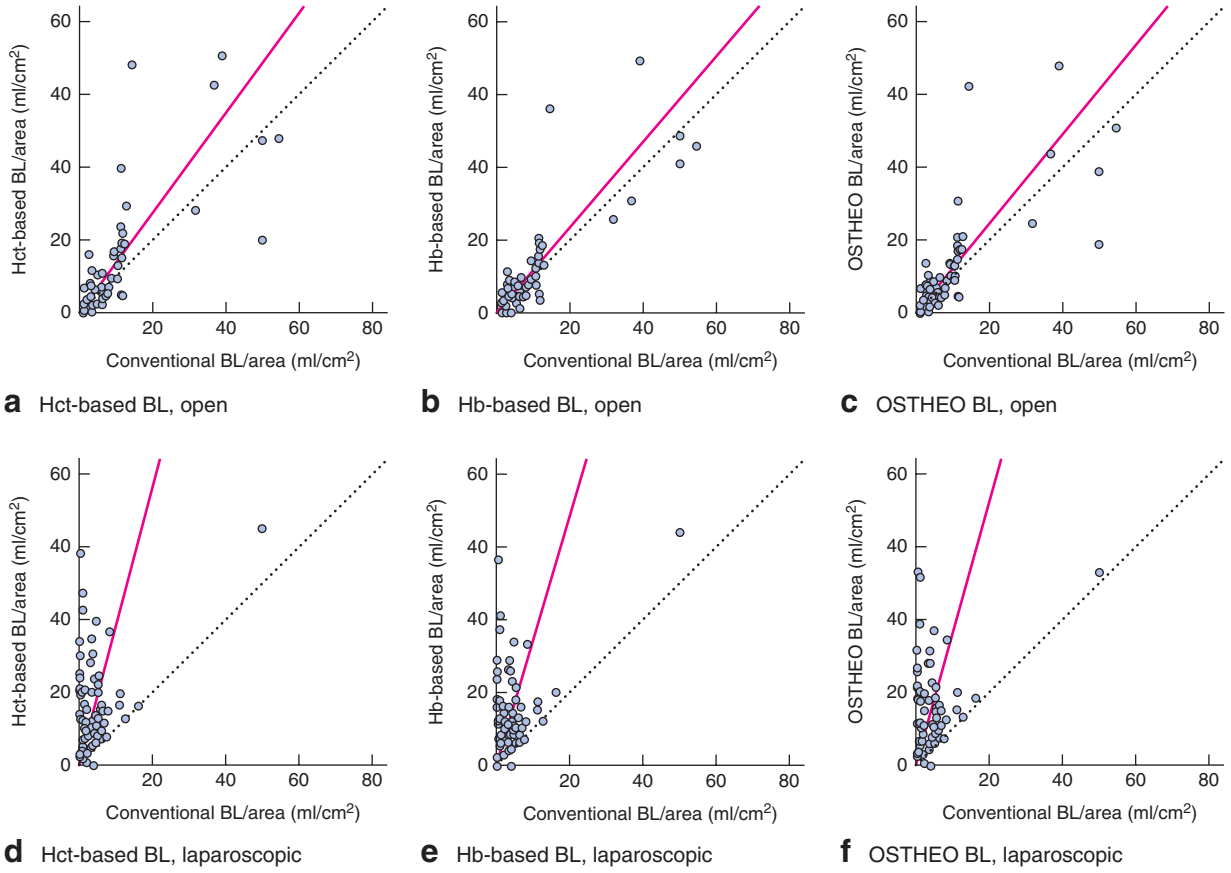

Fig. 3 Correlations between blood loss estimated by the conventional method and blood count-based calculations in the open and laparoscopic hepatectomy groups. Correlations between conventional blood loss (BL) per hepatic transection area and **a**,**d** haematocrit (Hct)-based BL/area, **b**,**e** haemoglobin (Hb)-based BL/area and **c**,**f** Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) BL/area in **a**–**c** open and **d**–**f** laparoscopic surgery. Solid lines indicate best-fit lines obtained by linear regression. **a** $r_S = 0{\cdot}762$, $P < 0{\cdot}001$; **b** $r_S = 0{\cdot}758$, $P < 0{\cdot}001$; **c** $r_S = 0{\cdot}760$, $P < 0{\cdot}001$; **d** $r_S = -0{\cdot}019$, $P = 0{\cdot}879$; **e** $r_S = 0{\cdot}031$, $P = 0{\cdot}802$; **f** $r_S = 0{\cdot}001$, $P = 0{\cdot}996$

Table 5 Univariable and multivariable logistic regression analyses of clinical factors affecting increased conventional blood loss per unit area (ml/cm^2)

	Univariable	Multivariable analysis	
	P	Hazard ratio	*P*
Age > 66 years	0·437		
Male sex	0·137		
BMI > 22 kg/m^2	0·029	10·99 (2·70, 43·48)	0·001
Preoperative haemoglobin > 12·9 g/l	0·520		
Preoperative haematocrit > 39·3%	0·637		
Preoperative albumin > 4·1 g/dl	0·955		
Preoperative prothrombin > 98%	0·999		
Cirrhosis	0·853		
Preoperative chemotherapy	0·172		
Tumour size > 30 mm	0·079	1·09 (0·32, 3·70)	0·890
Open hepatectomy	< 0·001	6·92 (1·90, 25·19)	0·003
Major hepatectomy	0·002	9·09 (1·76, 47·62)	0·008
Anatomical resection	0·140		
≥ 2 resections	0·308		
Repeat hepatectomy	< 0·001	9·25 (2·47, 34·70)	0·001
Synchronous colorectal resection	0·077	1·61 (0·26, 10·00)	0·608
Difficult tumour location	0·789		
Proximity to major blood vessel	0·030	1·58 (0·37, 6·75)	0·540

Values in parentheses are 95 per cent confidence intervals. Conventional blood loss was estimated using conventional methods as the sum of intraoperative suction fluid amounts (after subtracting the amount of irrigation fluids) and increase in operative gauze weight.

Table 6 Univariable and multivariable logistic regression analyses of clinical factors affecting increased haematocrit-based blood loss per unit area (ml/cm^2)

	Univariable	Multivariable analysis	
	P	Hazard ratio	*P*
Age > 66 years	0·815		
Male sex	0·105		
BMI > 22 kg/m^2	0·508		
Preoperative haemoglobin > 12·9 g/l	0·798		
Preoperative haematocrit > 39·3%	0·406		
Preoperative albumin > 4·1 g/dl	0·231		
Preoperative prothrombin > 98%	0·154		
Cirrhosis	0·303		
Preoperative chemotherapy	0·667		
Tumour size > 30 mm	0·129		
Open hepatectomy	0·126		
Major hepatectomy	0·178		
Anatomical resection	0·025	2·33 (0·75, 7·17)	0·142
≥ 2 resections	0·432		
Repeat hepatectomy	0·083	3·00 (1·11, 8·11)	0·030
Synchronous colorectal resection	0·094	2·65 (0·91, 7·73)	0·074
Difficult tumour location	0·546		
Proximity to major blood vessel	0·054	1·84 (0·67, 5·07)	0·241

Values in parentheses are 95 per cent confidence intervals.

group, there were significant linear and positive correlations between conventional BL/area and Hct-based BL/area ($r_S = 0·762$, $P < 0·001$), Hb-based BL/area ($r_S = 0·758$, $P < 0·001$) and OSTHEO BL/area ($r_S = 0·760$, $P < 0·001$). In contrast, conventional BL/area correlated poorly with the three formula-based BL estimations in the laparoscopic group ($r_S = -0·019$ to $0·031$).

Results of multivariable analyses with the endpoint of increased conventional BL/area and Hct-based BL/area are shown in *Tables 5* and *6* respectively. When BL was estimated by the conventional method, open surgery (odds ratio (OR) 6·92, 95 per cent c.i. 1·90 to 25·19; $P = 0·003$), high BMI (OR 10·99, 2·70 to 43·48; $P = 0·001$), major hepatectomy (OR 9·09, 1·76 to 47·62; $P = 0·008$) and repeat hepatectomy (OR 9·25, 2·47 to 34·70; $P = 0·001$) correlated significantly with increased BL.

However, when the Hct-based BL formula was applied, open surgery was not found to be a significant variable predicting increased BL (OR 0·52, 0·23 to 1·20; $P = 0·126$).

Discussion

Regarding surgical approach, controversy exists over whether laparoscopic hepatectomy leads to decreased intraoperative BL compared with open surgery. During the Second International Consensus Conference of Laparoscopic Liver Resection (ICCLLR), 82 comparative studies and 12 meta-analyses were reviewed to evaluate the short-term outcomes of laparoscopic *versus* open hepatectomy[25]. Intraoperative BL was significantly less for laparoscopic compared with open hepatectomy in 40 comparative studies and eight meta-analyses, whereas it was similar for both approaches in 30 comparative studies and one meta-analysis[25]. The second ICCLLR concluded that 'estimated blood loss was considered by the jury to be an unreliable metric', and strongly recommended researchers to 'consider performing studies to standardize method of blood loss measurement'[25]. Following the second ICCLLR, three case-matched studies with propensity score analysis using Japanese multicentre series[26,27] or National Clinical Database information[28] demonstrated

significantly less intraoperative BL in laparoscopic *versus* open hepatectomy. However, the intraoperative BL was equivalent for laparoscopic and open hepatectomy in comparative studies using propensity score matching reported from Korea[29] and China[30], and in an RCT[31] from Norway focusing on minor hepatectomy for colorectal liver metastases.

In the present study, a laparoscopic approach was associated with significantly decreased BL during hepatectomy when BL was measured by the conventional method as the sum of intraoperative suction fluid amounts and increase in operative gauze weight. However, when BL was estimated using formulas based on changes in blood counts, the surgical approach (laparoscopic *versus* open) did not significantly affect BL during hepatectomy. Blood count-based formulas have mainly been applied in orthopaedic surgery[7–11]; the accuracy of these formulas in hepatectomy could be validated by the significant positive and almost one-to-one linear correlations documented between conventional BL and BL estimated by the blood count-based formulas in the open group. In contrast, in the laparoscopic group, BL estimated by the blood count-based formulas showed no significant correlations and tended to be roughly three times higher than the conventional BL.

A possible explanation could be related to limitations in suctioning of fluids throughout the abdominal cavity during laparoscopic procedures, especially when patients are placed in the reverse-Trendelenburg position. Another possible reason is the tendency for pneumoperitoneum pressure to decrease the amount of ascitic fluids, which is a potential advantage of laparoscopic surgery; however, based on the present results, this seems unlikely because of the 1 : 1 linear relationship between conventional BL and blood count-based BL in the open group.

The major limitation of the present study is the significant difference in hepatectomy procedures between groups, which could have caused bias in BL estimation, even after adjustment by use of BL per hepatic transection area. The potential underestimation of BL during laparoscopic hepatectomy should be investigated further in larger prospective studies using blood count-based BL estimation in addition to the conventional method. An unbiased method for estimating BL during hepatectomy would be required, especially for the purpose of designing clinical studies for evaluating the benefits of laparoscopic surgery.

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