

## Retrospective Study

## Assessment for the minimal invasiveness of laparoscopic liver resection by interleukin-6 and thrombospondin-1

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**statement:** This study was retrospective, non-interventional, which approved by the institutional ethics committee of Kumamoto University Hospital (approval No.2052) and was performed in accordance with the Helsinki Declaration of 1975.

**Informed consent statement:**

Written informed consent was obtained from all patients.

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**Abstract****BACKGROUND**

Laparoscopic surgery has been introduced as a minimally invasive technique for the treatment of various field. However, there are few reports that have scientifically investigated the minimally invasive nature of laparoscopic liver resection (LLR).

**AIM**

To investigate whether LLR is scientifically less invasive than open liver resection.

**METHODS**

During December 2011 to April 2015, blood samples were obtained from 30 patients who treated with laparoscopic ( $n = 10$ , 33%) or open ( $n = 20$ , 67%) partial liver resection for liver tumor. The levels of serum interleukin-6 (IL-6) and plasma thrombospondin-1 (TSP-1) were measured using ELISA kit at four time points including preoperative, immediate after operation, postoperative day 1 (POD1) and POD3. Then, we investigated the impact of the operative approaches during partial hepatectomy on the clinical time course including IL-6 and TSP-1.

**RESULTS**

Serum level of IL-6 on POD1 in laparoscopic hepatectomy was significantly lower than those in open hepatectomy (8.7 vs 30.3 pg/mL, respectively) ( $P = 0.003$ ). Plasma level of TSP-1 on POD3 in laparoscopic hepatectomy was significantly higher than those in open hepatectomy (1704.0 vs 548.3 ng/mL, respectively) ( $P = 0.009$ ), and have already recovered to preoperative level in laparoscopic approach. In patients with higher IL-6 Levels on POD1, plasma level of TSP-1 on POD3 was significantly lower than those in patients with lower IL-6 Levels on POD1.

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Multivariate analysis showed that open approach was the only independent factor related to higher level of IL-6 on POD1 [odds ratio (OR), 7.48; 95% confidence interval (CI): 1.28-63.3;  $P = 0.02$ ]. Furthermore, the higher level of serum IL-6 on POD1 was significantly associated with lower level of plasma TSP-1 on POD3 (OR, 5.32; 95%CI: 1.08-32.2;  $P = 0.04$ ) in multivariate analysis.

## CONCLUSION

In partial hepatectomy, laparoscopic approach might be minimally invasive surgery with less IL-6 production compared to open approach.

**Key Words:** Laparoscopic surgery; Liver resection; Hepatectomy; Minimal invasiveness; Interleukin-6; Thrombospondin-1

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**Core Tip:** Laparoscopic liver resection is less invasive than open liver resection and is becoming more popular worldwide. However, reports that have scientifically investigated the minimally invasive nature of laparoscopic surgery remain scarce. In the current study, we scientifically evaluated the minimally invasive nature of laparoscopic surgery using interleukin-6 and thrombospondin-1 as markers of tissue damage.

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## INTRODUCTION

Laparoscopic surgery has been introduced as a minimally invasive technique for the treatment of various field such as prostatectomy, hysterectomy, cholecystectomy and gastrectomy[1-5]. Nowadays, robot-assisted surgery is becoming more widespread in the hope of further minimizing invasiveness[6,7]. Laparoscopic surgery is considered to be a minimally invasive technique because of smaller size of skin incision and less bleeding loss than open surgery[8,9]. In fact, laparoscopic surgery results in less morbidity and a much shorter time to discharge compared to open surgery[10]. It is unclear whether laparoscopic technology is really contributing to minimally invasive surgery due to the development of other instruments and the remarkable effect of magnification.

Hepatic resection is the only curative treatment for hepatocellular carcinoma (HCC). It has been reported that laparoscopic hepatectomy is less invasive than open hepatectomy, with less blood loss, fewer postoperative complications, and less hospital stay[9]. However, there are few reports that have scientifically investigated the minimally invasive nature of laparoscopic liver resection (LLR)[11-14].

Surgery induces a systemic stress response and produces various cytokine such as interleukine-6 (IL-6) and IL-10. IL-6 is a proinflammatory cytokine that is produced by many tissues in response to injury. Peak level of L-6 and CRP consistently were associated with the magnitude of operative injury and operative method[15]. Thrombospondin-1 (TSP-1) is expressed during hepatic resection and acts as an inhibitor of liver regeneration[16,17]. It reflects the invasiveness when liver resection. Kuroki *et al*[18] reported that a decrease in TSP-1 after partial hepatectomy was associated with liver damage, and the less invasive the liver, the faster the recovery of TSP-1. Changes in plasma level of TSP-1 after liver resection may reflect surgical invasion.

This study aimed to investigate scientifically whether LLR is less invasive technique than open liver resection (OLR).

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## MATERIALS AND METHODS

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### **Patients**

From December 2011 to April 2015, all patients with tumors in liver (such as HCC, metastatic colorectal cancer, cholangiocellular carcinoma and benign tumor) treated with hepatic resection were enrolled. Patients were prospectively received either OLR or LLR in the department of gastroenterological surgery at hospital of Kumamoto university. The serum samples were collected early in the morning after an overnight fast. Blood samples that used to measure IL-6 and TSP-1 were taken at four time points: immediately before anesthetic induction (preoperative), immediately after closure of the skin incision (postoperative), postoperative day 1 (POD1) and POD3. Thirty patients were treated with partial liver resection and obtained blood samples at all four time points. Blood samples taken up to POD3 were used because previous studies had not found significant changes in TSP-1 Levels after POD5. Ten of 30 patients underwent laparoscopic partial hepatectomy and other 20 patients underwent open partial hepatectomy. All procedures were performed by the same surgical team, and the same surgical and oncological principles were followed in both groups. The patients received similar preoperative and postoperative management.

Patient data were separately collected and analyzed. This study was retrospective, non-interventional, which approved by the institutional ethics committee of Kumamoto University Hospital and was performed in accordance with the Helsinki Declaration of 1975.

### **Biomarker assays**

All serum and plasma biomarker (such as IL-6 and TSP-1) samples were stored at -80 °C until analysis. Serum and plasma samples concentrations were measured by commercially available ELISA kits for IL-6 and TSP-1 (R and D Systems; catalog numbers, D6050 and DTSP10, respectively), according to the manufacturers' instructions.

### **Estimated operative factors for higher level of IL-6 and lower level of TSP-1**

A total of 9 variables were analyzed: age, sex, operative method, the number of tumors, operative time, bleeding loss, the presence of complication, the kind of skin incision, and the presence of liver mobilization. Operative method was divided into OLR and LLR. The presence of complication was defined as more than Clavien-Dindo classification IIIa. The skin incision was divided into reverse L-sharp incision and others. The cut off value of age, operative time, bleeding loss and level of serum IL-6 and plasma TSP-1 was based on the median.

### **Statistical analysis**

All statistical analyses were carried out by using JMP® 14 (SAS Institute Inc., Cary, NC, United States). Continuous variables were compared using Student's *t* tests, and Categorical variables were compared using the Chi-square test. The multivariate analysis to estimate the risk factors was undertaken using the Cox proportional hazard model. The multivariate analysis to be identified clinical factors which related to high level of serum IL-6 on POD1 and lower level of plasma TSP-1 on POD3 was carried out using logistic regression analysis. Continuous variables were converted into two groups at the median. Statistical significance was defined as  $P < 0.05$ .

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## RESULTS

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### **Patient characteristics**

The median age was 71.0 years with age range from 31 years to 94 years. Among 30 patients, 18 (60.0%) were men and 12 (40%) were women. Two patients were HBs-Ag positive and 12 patients were HCV-Ab positive. The indication for hepatectomy were primary tumor in 20 patients, metastatic liver cancer in 8 patients, and benign tumor in 2 patients. Ten patients underwent LLR and 20 patients underwent OLR. No differences were detected in the clinical data between the LLR group and the OLR group (Table 1). Age, sex, hepatitis B infection, hepatitis C infection, preoperative blood tests (such as white blood cell, platelet, prothrombin time, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and cholinesterase, retention of indocyanine green at 15 min (ICG-R15), Child-Pugh classification and difficulty scoring system were similar. In operative and postoperative data, bleeding loss in LLR

Table 1 Clinical characteristics of study patients

Factors	LLR	OLR	P
	n = 10	n = 20	
Age, years	74 (31-94)	71 (35-83)	0.91
Sex (male/female)	6/4	12/8	1.0
HBs-Ag (positive/negative)	0/10	2/18	0.20
HCV-Ab (positive/negative)	4/6	8/12	1.0
White blood cell, × 10 <sup>3</sup> /uL	5.5 (3.1-6.0)	6.8 (2.5-10.6)	0.23
Platelet, × 10 <sup>4</sup> /uL	16.4 (11.2-21.2)	17.5 (8.3-88.0)	0.36
Prothrombin time, %	102 (69-122)	105 (65-126)	0.86
AST, U/L	23 (14-48)	27 (13-175)	0.52
ALT, U/L	23 (10-46)	26 (6-103)	0.31
ALP, U/L	221 (138-375)	243 (134-676)	0.36
ChE, U/L	263 (154-327)	231 (121-357)	0.39
ICG R15, %	10.4 (4.5-24.7)	10.6 (0.9-65.4)	0.84
Child-Pugh classification (A/B)	10/0	18/2	0.20
Difficulty scoring system	4 (2-5)	4 (2-6)	0.44
Operative time, min	290 (126-660)	385 (82-633)	0.88
Bleeding volume, mL	57 (5-750)	528 (116-9527)	0.003
Resected liver volume, g	66.5 (4-206)	77.5 (2-220)	0.76
Longest diameter of the tumor, mm	17 (6-53)	25 (7-55)	0.27
Number of resected lesion	1 (1-2)	2 (1-7)	0.1
Surgical margin, mm	5 (0-55)	1 (0-22)	0.24
Diagnosis(primary/metastasis/benign)	7/2/1	13/6/1	0.77
Postoperative hospital stay, d	10 (6-14)	14 (8-26)	0.003
Complications (no/yes)	10/0	17/3	0.1

No complication means less than IIIa at clavien-dindo classification. LLR: Laparoscopic liver resection; OLR: Open liver resection; HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C antibody; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ChE: Cholinesterase; ICG-R15: Retention of indocyanine green at 15 min.

group was significantly less than that in OLR group ( $P = 0.003$ ). Postoperative hospital stay in LLR group was significantly shorter than that in OLR group ( $P = 0.003$ ). In operative time, resected liver volume, longest diameter of the tumor, the number of tumors, surgical margin, primary diagnosis and complication, there was no significant difference between the two groups. The postoperative complications included one case of bile leakage, one case of refractory ascites, and one case of surgical site infection.

#### **Time course in levels of serum IL-6 and plasma TSP-1 according to operative approaches**

Time course of serum IL-6 Level and plasma TSP-1 Level before and after liver resection are shown in Table 2. Serum level of IL-6 on POD1 and POD3 in LLR group was significantly lower than those in OLR group (8.7 vs 30.3 pg/mL,  $P = 0.003$ , 9.3 vs 31.7 pg/mL,  $P = 0.03$ ). There was no significant difference in serum level of IL-6 on pre- and post-operation between the two groups. Plasma level of TSP-1 on POD3 in LLR group was significantly higher than those in OLR group (1704.0 vs 548.3 ng/mL,  $P = 0.009$ ), and have already recovered to preoperative level. There was no significant difference in plasma level of TSP-1 on pre-, post-operation and POD1 between the two groups.

**Table 2** Time course of circulating serum level of interleukin-6 and plasma level of thrombospondin-1 before and after laparoscopic and open liver resection

Factors	LLR	OLR	P
	n = 10	n = 20	
IL-6, pg/mL			
Preoperatively	3.9 (2.6-43.6)	3.7 (2.0-68.8)	0.50
Postoperatively	30.8 (4.9-189.8)	73.6 (4.7-348.8)	0.14
POD1	8.7 (4.8-359.3)	30.3 (10.8-376.3)	0.003
POD3	9.3 (4.1-99.7)	31.7 (7.0-212.3)	0.03
TSP-1, ng/mL			
Preoperatively	1817.1 (141.7-2985.7)	2025.1 (124.6-3815.0)	0.98
Postoperatively	1364.7 (84.1-2459.3)	684.4 (42.5-3580.3)	0.52
POD1	589.1 (139.3-3186.4)	233.6 (36.6-4058.3)	0.12
POD3	1704.0 (665.4-3399.2)	548.3 (30.4-2239.2)	0.009

TSP-1: Thrombospondin-1; IL-6: Interleukin-6; LLR: Laparoscopic liver resection; OLR: Open liver resection; POD: Postoperative days.

### **Changes in inflammatory and liver functional markers according to operative approaches**

At any point in time, the neutrophil ratio in LLR group was not significant differ compared with that in OLR group (Table 3). However, serum level of CRP on POD3, 5 and 7 in LLR group was significantly lower than that in OLR group (2.04 vs 5.93 mg/dL,  $P = 0.01$ , 1.18 vs 4.36 mg/dL,  $P = 0.01$ , 0.65 vs 2.77 mg/dL,  $P = 0.01$ ). In the liver functional biomarker (such as total bilirubin, bile acid and albumin), there was no significant difference between the two groups at any time (for example, pre-operation, POD3, POD5, and POD30).

### **Factors related to higher level of serum IL-6 in patients who had undergone partial hepatectomy**

Among the changes in postoperative serum level of IL-6 over time, the level of IL-6 on POD1 showed the most difference between the two groups. The median serum level of IL-6 on POD1 in 30 patients who had undergone hepatectomy was 17 pg/mL. The higher level of IL-6 group on POD1 was defined as 17 pg/mL or higher and divided into two groups. The statistically significant factors which related to higher level of IL-6 Level on POD1 by univariate analysis are listed in Table 4. The operative method as an operation-related factor and the number of tumors as a tumor-related factor was identified as factors which related to higher level of IL-6 on POD1. Multivariate analysis showed that open approach was the only independent factor related to higher level of IL-6 on POD1 [odds ratio (OR), 7.48; 95% confidence interval (CI): 1.28-63.3;  $P = 0.02$ ].

### **Relationship between serum level of IL-6 on POD1 and plasma level of TSP-1 on POD3**

Table 2 showed that the only plasma level of TSP-1 on POD3 was significant difference between the two groups. The median plasma level of TSP-1 on POD3 in 30 patients who had undergone hepatectomy was 898 ng/mL. The lower level of TSP-1 on POD3 was defined as 898 ng/mL or lower and divided into two groups. The statistically significant factors which related to lower level of TSP-1 on POD3 by univariate analysis are listed in Table 5. The higher level of IL-6 on POD1 and the skin incision (reverse-L sharp vs others) was identified as factors which related to lower level of TSP-1 on POD3 (Table 6). Multivariate analysis showed that the higher level of IL-6 than 17.0 pg/mL on POD1 was the only independent factor related to lower level of TSP-1 on POD3 (OR, 5.32; 95% CI: 1.08-32.2;  $P = 0.04$ ). The plasma level of TSP-1 on POD3 in higher IL-6 group was significantly lower than that in lower IL-6 group.

**Table 3 Comparison between changes in inflammatory and liver functional markers before and after laparoscopic and open liver resection**

Factors	LLR	OLR	P
	n = 10	n = 20	
Total bilirubin, mg/dL			
Preoperatively	0.8 (0.4-1.4)	0.8 (0.4-2.6)	0.69
POD5	0.7 (0.5-0.9)	0.9 (0.3-5.2)	0.11
POD30	0.7 (0.3-1.1)	0.7 (0.4-2.5)	0.95
Bile acid, $\mu$ mol/L			
Preoperatively	7.4 (0.8-16.8)	12.4 (0.7-82.1)	0.21
POD3	4.9 (0.6-20.8)	9.9 (1.6-56.7)	0.13
Albumin, g/dL			
Preoperatively	3.8 (3.5-4.5)	3.6 (2.9-4.4)	0.08
POD5	3.0 (2.4-3.3)	3.0 (2.3-3.5)	0.77
POD30	3.9 (3.4-4.6)	3.6 (2.2-4.4)	0.16
Neutrophil, %			
Preoperatively	62.1 (46.7-74.3)	67.3 (28.8-85.2)	0.17
POD1	82.5 (68.1-92.7)	83.1 (70.7 - 92.2)	0.86
POD3	70.9 (58.7-83.7)	76.3 (52.9-86.6)	0.20
POD5	69.2 (46.3-80.4)	67.6 (45.1-80.9)	0.95
POD7	67.3 (49.8-76.7)	69.3 (38.3-77.5)	0.42
CRP, mg/dL			
Preoperatively	0.07 (0.01-2.67)	0.07 (0.01-3.50)	0.57
POD1	0.96 (0.24-6.32)	1.48 (0.38-4.94)	0.28
POD3	2.04 (0.62-9.16)	5.93 (1.12-16.48)	0.01
POD5	1.18 (0.20-5.83)	4.36 (0.44-14.3)	0.01
POD7	0.65 (0.11-1.52)	2.77 (0.31-9.97)	0.01

LLR: Laparoscopic liver resection; OLR: Open liver resection; POD: Postoperative days; CRP: C-reactive protein.

## DISCUSSION

From the introduction of laparoscopic cholecystectomy in 1987, the number of laparoscopic procedures quickly increased due to its minimally invasive advantages over laparotomy[19]. Laparoscopic hepatectomy was also reported in 1992 and has been on the rise worldwide year after year[20]. The advantages of laparoscopic surgery include cosmetically attractive scars, less postoperative pain, and shorter hospital stay[21]. On the other hand, conventional laparotomy has good tactile sensation, hepatic mobilization, control of bleeding. LLR has also been reported to be less invasive than laparotomy on the basis of less blood loss, fewer postoperative complications, and shorter hospital stay[22]. Our study showed similar results, with less blood loss and shorter hospital stay in laparoscopic surgery compared to open surgery (57 vs 528 mL,  $P = 0.003$ , 10 vs 14 d,  $P = 0.003$ ). In fact, there are only a few reports that have scientifically investigated the minimally invasive nature of laparoscopic hepatectomy [12,23,24].

It has been reported that the degree of surgical trauma is reflected by the extent of systemic response[23]. IL-6 is a known hepatocyte-stimulating cytokine that is easily synthesized and activates the acute immune response in response to infection or tissue damage. IL-6 correlates with the degree of surgical trauma[25]. The present study showed this biochemical parameter of surgical trauma to compare the serum levels of IL-6 in laparoscopic with OLR by using ELISA kit. The serum level of IL-6 was highest

**Table 4 Univariate and multivariate analysis of factors that related with higher level of interleukin-6 on postoperative day 1 in 30 patients who has undergone hepatectomy**

Factors	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
Sex (male/female)	0.80	0.18-3.50	0.77			
Age ( $\geq 75$ / $< 75$ , yr)	1.289	0.30-5.57	0.73			
Operative method (OLR/LLR)	9.33	1.74-75.7	0.008	7.48	1.28-63.3	0.02
Number of tumors (single/multiple)	0.21	0.04-0.99	0.048	0.29	0.04-1.64	0.16
Operative time ( $< 369$ / $\geq 369$ , min)	2.31	0.54-10.7	0.29			
Bleeding loss ( $< 443$ / $\geq 443$ , mL)	3.00	0.70-14.3	0.14			
Complication (yes/no)	0.74	0.20-11.9	0.74			
Skin incision (reverse L-sharp/others)	1.94	0.43-9.62	0.39			
Liver mobilization (yes/no)	1.73	0.31-10.6	0.53			

IL-6: Interleukin-6; OR: Odds ratio; CI: Confidence interval; OLR: Open liver resection; LLR: Laparoscopic liver resection.

**Table 5 Univariate and multivariate analysis of factors that related with lower level of thrombospondin-1 on postoperative day 1 in 30 patients who has undergone hepatectomy**

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Sex (male/female)	0.57	0.12-2.48	0.46			
Age ( $\geq 75$ / $< 75$ , yr)	1.00	0.23-4.26	1.00			
Higher level of IL-6 on POD1 ( $\geq 17.0$ / $< 17.0$ , pg/mL)	5.50	1.22-29.4	0.03	5.32	1.08-32.2	0.04
Operative method (OLR/LLR)	3.50	0.73-20.3	0.29			
Number of tumor (single/multiple)	1.00	0.23-4.39	1.00			
Operative time ( $< 369$ / $\geq 369$ , min)	0.33	0.07-1.43	0.14			
Bleeding loss ( $< 443$ / $\geq 443$ , ml)	0.44	0.10-1.88	0.27			
Complication (yes/no)	1.63	0.23-14.0	0.62			
Skin incision (reverse L-sharp/others)	4.57	0.97-26.7	0.05	4.38	0.82-29.9	0.09
Liver mobilization (yes/no)	3.24	0.56-26.2	0.19			

TSP-1: Thrombospondin-1; IL-6: Interleukin-6; OR: Odds ratio; CI: Confidence interval; OLR: Open liver resection; LLR: Laparoscopic liver resection.

postoperatively in both groups, but there was no significant difference between the two groups at that time. IL-6 Levels on POD1 and 3 was significantly lower in the LLR group and decreased to preoperative values. In the OLR group, IL-6 Levels on POD1 and 3 decreased from the postoperative level, but the improvement to the preoperative level was not observed and was prolonged. The change in CRP levels showed a peak on POD3 in both groups. Thereafter, it decreased slowly and improved to baseline. CRP levels on POD3, 5, and 7 were significantly lower in the LLR group than in the OLR group. Shenkin *et al*[26] reported that in open cholecystectomy, IL-6 Levels reached a maximum level 1.5-4 h after skin incision and the CRP level was detectable 8-12 h after the skin incision. In this current study, IL-6 and CRP levels showed similar changes over time, and these changes were the same in both the LLR and OLR groups. There was no significant difference in the marker of liver function (such as Total-bilirubin, bile acids, and albumin levels) between the two groups. We showed that laparoscopic surgery was associated with lower IL-6 Levels on the first postoperative day, which was thought to reflect the minimally invasive procedure. In the present study, there was no relationship between operative time or blood loss and the

**Table 6** Time course of circulating plasma thrombospondin-1 levels according to serum interleukin-6 levels on postoperative day 1

Factors	Lower IL-6	Higher IL-6	P
	n = 14	n = 16	
TSP-1, ng/mL			
Preoperatively	2420.6 (223.0-3121.1)	893.9 (124.6-3815.0)	0.088
Postoperatively	1672.7 (42.5-2674.4)	504.8 (53.9-3580.3)	0.067
POD1	447.9 (101.7-3186.4)	246.2 (36.6-4058.3)	0.24
POD3	1432.4 (30.4-3399.2)	548.3 (53.3-3153.2)	0.026

TSP-1: Thrombospondin-1; IL-6: Interleukin-6; POD: Postoperative days.

minimally invasive procedure. There was also no relationship between the skin incision or liver mobilization and the minimally invasive procedure.

The only significant difference in the number of resected lesion was not observed in the multivariate analysis, but was observed in the univariate analysis. The number of resected lesion might be related to surgical invasiveness. Although there was no significant difference in the indications for surgery in this study, there was a tendency for patients with a large number of tumors to choose laparotomy. Complication was not observed in the univariate analysis of the factors that related with higher level of IL-6 on POD1 in 30 patients who has undergone hepatectomy. In present study, complications were not affected higher level of IL-6 on POD1.

TSP-1 is a matricellular protein which can be produced by a variety of cells, particularly by platelets and endothelial cells and can act as a negative regulator of liver regeneration by activating latent transforming growth factor- $\beta$ 1[17,27,28]. Kuroki *et al* [18] showed that the plasma level of TSP-1 decreased to the lowest level on POD1 compared with the pretreatment value, suggesting that a reduced plasma TSP-1 Level is required for a regenerative response in the liver after hepatectomy[16,18]. They expressed that a decrease in TSP-1 after partial hepatectomy was associated with liver damage, and the less invasive it is to the liver, the faster the improvement of TSP-1 Level. In our study, the plasma level of TSP-1 was the lowest on POD1 and showed improvement on POD3. Although the plasma TSP-1 values before and after LLR and OLR showed similar changes, the values on POD3 were significantly higher in LLR than in OLR and improved to the preoperative values. And multivariate analysis of factors associated with low level of plasma TSP-1 on POD3 showed that high level of serum IL-6 on POD1 were significant. Open approach was associated with a greater release of IL-6 on POD1 than laparoscopy approach, and this may contribute to liver regeneration by suppressing the increase in TSP-1 on POD3. This might indicate that laparoscopy is a less invasive procedure than laparotomy. Complication was not observed in the univariate analysis of the factors that related with lower TSP-1 on POD3. In present study, complications were not affected lower level of TSP-1 on POD3.

There are limitations to our research. The number of cases is small and it is not a randomized trial. It needs to be studied in a larger number of cases. However, as far as we could find, there were no reports using IL-6 and TSP-1 to evaluate the degree of invasiveness of the laparoscopic approach. Secondly, this study can't reveal the biological process to explain the relationship between IL-6 and TSP-1. There are no reports on it, and this is a future issue.

## CONCLUSION

In conclusion, laparoscopic hepatectomy might be minimally invasive surgery with less IL-6 production compared to open hepatectomy.



## ARTICLE HIGHLIGHTS

### Research background

There are few reports that have scientifically verified whether laparoscopic surgery is truly minimally invasive in liver resection.

### Research motivation

Evaluation of minimally invasive laparoscopic surgery will also be important when robot-assisted surgery becomes more widespread in the future. There are many unclear points, such as whether invasion reflects skin incision size or organ invasion.

### Research objectives

We aimed to verify whether the laparoscopic technique contributes to minimally invasive procedures in surgery using biomarkers of interleukin-6 (IL-6) and thrombospondin-1 (TSP-1).

### Research methods

This study is a retrospective study. Serum IL-6 and TSP-1 were measured and analyzed by ELISA using blood samples taken before and after surgery. We also evaluated the relationship between the operative approach, the size of the skin incision and the presence of liver mobilization.

### Research results

This study demonstrated that laparoscopic liver resection is likely to be scientifically less invasive than open liver resection. The lower IL-6 Level was significantly related to the operative methods. The limitation of this study is that the number of cases is small, so further accumulation and analysis is needed in the future.

### Research conclusions

In patients who undergo liver resection, laparoscopic approach that is less invasive than open approach is preferred whenever possible.

### Research perspectives

Studies conducted in the future should focus on evaluating whether biomarker such as IL-6 affected not only short-term outcomes but also long-term outcomes and how several biomarker change with robot-assisted techniques.

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