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Enhanced recovery after surgery strategy for cirrhosis patients undergoing hepatectomy: experience in a single research center

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Purpose: To evaluate the safety and effectiveness of an enhanced recovery after surgery (ERAS) programme after curative liver resection in cirrhotic hepatocellular carcinoma (HCC) patients.
Methods: One hundred sixty-two patients were enrolled in the study; 80 patients whose data were collected prospectively were assigned to the ERAS group, and 82 patients whose data were collected retrospectively were assigned to the control group. Preoperative clinicopathologic factors, surgical factors, and postoperative outcomes of the 2 groups were compared. Logistic regression was applied to explore potential predictors of hospital stay and morbidity.
Results: The postoperative hospital stay, postoperative complication rate, and recovery of liver function on postoperative day 5 seemed to be better in the ERAS group. The composition of complications was different in the 2 groups; pleural effusion and postoperative ascites were more common in the control group, and indocyanine green retention at 15 minutes, operation time, preoperative alanine aminotransferase, and number of liver segmentectomies were associated with postoperative complications rather than ERAS intervention.
Conclusion: The ERAS programme is safe and effective for HCC patients with chronic liver disease undergoing hepatectomy, but it seems that surgical factors, such as operation type, have a greater impact on morbidity than other factors. Operative characteristics such as the method of blood loss control and the volume of liver resection should be augmented into ERAS protocol of hepatectomy.
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Key Words: Enhanced recovery after surgery, Hepatectomy, Hepatitis, Hepatocellular carcinoma, Liver cirrhosis

INTRODUCTION

For patients with hepatocellular carcinoma (HCC), hepatic resection is the main curative treatment [1]; however, hepatic resection is associated with a high postoperative complication rate (approximately 30%) [2]. Complications include haemorrhage, coagulopathy, and renal failure, in addition to the inherent complications of hepatic resection, such as biliary fistula and postoperative liver failure [3]. Liver cirrhosis is an independent risk factor for perioperative liver failure and death in HCC patients with positive HBsAg [4]. For cirrhotic hepatitis patients, the mortality rate is increased because of decreased reticuloendothelial system function and impaired regeneration [5]. Fibrotic parenchyma, irregular vascular structure, elevated portal pressure, and impaired coagulation in cirrhosis patients would cause excessive bleeding, and a more severe impact on

recovery of liver function postoperatively, or liver and renal failure. However, with the development of technology, the results of liver resection for HCC in patients with cirrhosis has improved over time [6]. A study [7] showed that for elderly cirrhosis patients, major hepatectomy was as safe as for noncirrhosis patients. In brief, hepatectomy is still the most important option for HCC cirrhosis patients, even with higher risk of postoperative complication. Some surgeons prefer the Glissonean approach rather than the Pringle maneuver in cirrhosis patients [8] for preservation of liver function; some studies strictly controlled central venous pressure (CVP) and intravenous fluid in cirrhosis patients. Therefore, perioperative management of hepatic resection requires additional attention in cirrhosis patients.

Enhanced recovery after surgery (ERAS), also called fast-track surgery, is a multistep strategy in the perioperative period used to improve recovery and reduce complications [9]. The essence of ERAS is to maintain homeostasis, reduce unnecessary operative stress and increase the speed of recovery in patients [10]. In recent years, many studies have demonstrated that ERAS is safe and effective for colorectal [11], orthopedic, and gynecological surgery patients, and ERAS is coincident with clinical practice. ERAS has also been proven effective for hepatectomy patients in some analyses [12]. Currently, the ERAS strategy for hepatectomy patients is similar to that for colorectal surgery patients and includes no preoperative fasting for more than 6 hours, no need for oral bowel preparation, a reduction in the use of opioids, early intake, and mobilization [13]. However, most surgical centers have not applied ERAS to cirrhosis patients, so whether the colorectal ERAS strategy is safe for cirrhosis patients undergoing hepatectomy is unknown.

In our center, most hepatectomies are performed on cirrhosis patients; therefore, we have attempted to apply an ERAS strategy similar to that for colorectal surgery patients in our clinical practice to confirm its safety and effectiveness. The primary aim of this study was to evaluate the safety and effectiveness of ERAS for cirrhotic liver resection patients in a single, high-volume liver unit. The second aim was to investigate the factors that influence postoperative hospital stay and complications.

METHODS

This study was approved by the Independent Ethics Committee of the National GCP Center for Anticancer Drugs, Cancer Hospital, Chinese Academy of Medical Sciences (IRB No. NCC2017-YL-002). This is a prospective and historical case-control study.

Patients

All enrolled patients were managed by the same single-surgeon team. All patients in the ERAS group and the control group were screened for the following inclusion criteria: (1) the patient was diagnosed with HCC, (2) the patient had current hepatitis or previous hepatitis, (3) the patient had cirrhosis confirmed by imaging or an operation record with a pathological evaluation with a Scheuer S score ≥ 1 (an S score < 3 was recognized as mild fibrosis and ≥ 3 was considered severe fibrosis or cirrhosis), (4) the patient had a class A Child-Pugh score and an indocyanine green retention at 15 minutes (ICG15) rate <15%, and (5) the patient's comorbidities were controlled well. The exclusion criteria were as follows: (1) the patient could not be informed of the study due to mental or physical factors, (2) the patient had other organ cancers, (3) the patient had other severe diseases, and (4) the patient had a Scheuer S score = 0 in the pathological report. Patients were then divided into 2 groups. This was a historical case-control study that compared a prospective cohort (ERAS group: October 2017 to November 2018) with a historical standardized care pathway cohort (control group: January 2017 to August 2017). Written and verbal informed consent was obtained from each patient before inclusion in the study. Based on an expected hospital stay of 6 days in the ERAS group and 7 days in the conventional treatment group (the standard deviation of the hospital stay was 2 days), we performed a sample size calculation with an α of 0.05 and power of 0.8 and determined that 60 patients were needed in each group to detect a difference in-hospital stay and postoperative morbidity using the PASS software (ver. 11, NCSS, LLC, Kaysville, UT, USA).

ERAS group

The ERAS group consisted of 80 patients whose data were collected prospectively and who were undergoing the ERAS strategy perioperatively for hepatectomy from October 2017 to November 2018.

Control group

The historical control group consisted of 82 consecutive patients who underwent hepatectomy with routine (non-ERAS) perioperative management from January 2017 to August 2017, before the implementation of the ERAS strategy. Control group patients also served as a control group in another prospective clinical trial studying the perioperative application of corn peptide in HCC patients with chronic liver disease (2016YFD0400604-03) in our center. Data from the control group were collected retrospectively from the medical records.

Intervention

The ERAS protocol was based on experience in colorectal surgery and review of the current literature on liver surgery. The key factors for ERAS were minimization of the time interval with no oral intake, absence of a gastric tube and

bowel preparation; control of intraoperative CVP, minimization of intraoperative and postoperative intravenous fluids, minimization of total opioids by multimodal analgesia, early mobilization, and standardized postoperative care.

The basic protocols of the ERAS and control groups are summarized below (Table 1). The attending surgeons, resident physicians, midlevel providers, and nurses were educated on the new protocol.

Evaluated factors

The controlling nutritional status (CONUT) score is an objective tool that is considered an established assessment model for evaluating nutritional aspects in surgically treated patients, and it reflects liver functional reserve especially well [14,15]; therefore, the CONUT score as well as body mass index

(BMI) were used to evaluate the perioperative nutrition state in this study.

Postoperative opioids were converted to morphine equivalent units (MEU). The visual analogue score (VAS) was used to evaluate pain. The liver fibrosis-cirrhosis degree was evaluated by pathologists and surgeons with the Scheuer S score. The Scheuer score classifies fibrosis into 4 stages: minimal, mild, moderate, or severe/cirrhosis [16].

Liver resection was defined as a resection in which the lesion(s) was/were anatomically removed on the basis of Couinaud classification, including single segmentectomy, 2 combined segmentectomies, and major hepatectomy. Major hepatectomy was defined as 3 combined segmentectomies, hemihepatectomy, and caudate lobe hepatectomy. Morbidities such as liver failure were classified according to the Clavien-

Table 1. Summary of the ERAS protocol and comparison with the control group

Operation	ERAS group	Control group
Preoperation	Antiviral therapy at least 2 wk before surgery	Antiviral therapy at least 2 wk before surgery
	Preoperative education	-
	No routine bowel preparation before surgery	Routine bowel preparation (by laxative or glycerol enema) one day before surgery
	Consumed carbohydrate drinks (10% dextrose solution mixture, 500 mL) until 2 hr before surgery	Fasted from food and water 12 hr before surgery
	Intravenous antibiotics 30 min before surgery	Intravenous antibiotics 30 min before surgery
	No nasogastric tube administered	Nasogastric tube administered 30 min before surgery
During operation	Controlled SVV <13% and CI >3 L/min with LiDCO monitoring	Controlled CVP < 5 cmH$_2$O through central venous catheter
	Hypothermia avoided using a heater	Thick quilt used
	Mainly hemihepatic vascular control with ischemic preconditioning	Pringle maneuvres and hemihepatic vascular control
	If a sufficient edge was present, local hepatectomy was preferred	-
Postoperation	Pain control: POD 0: PCA + NSAIDS every 12 hr POD 1–3: removal of PCA, NSAIDS i.v. every 12 hr + necessary opioids i.m. POD 4: discontinuation of NSAIDS i.v. every 12 hr, only necessary occasional NSAIDs i.v. or opioids i.m.	Pain control: POD 0–3: PCA + necessary opioids i.m. POD 4: necessary opioids i.m.
	Preventive use of metoclopramide for postoperative nausea and vomiting	-
	Clear liquid diet allowed 6 hr after surgery	Food and drink allowed after bowel movement
	Approximately 50 mL/kg i.v. infusion volume per day on POD 0–3, as diet was advanced with the goal of discontinuation of intravenous infusion on POD 4	-
	Diet: POD 1: oral intake of rice gruel at evening meal, approximately 200 mL POD 2: semiliquid diet of more than 500 mL per day POD 3: normal diet	Normal diet after bowel movement
	Postoperative glycaemic control	-
	Mobilization POD 1: patient mobilized off bed at least 2 hr per day POD 2-: more than 2 hr of off-bed activity	No special recommendation

ERAS, enhanced recovery after surgery; SVV, stroke volume variation; CI, cardiac index; CVP, central venous pressure; PCA, patient-controlled analgesia; NSAIDS, non-steroidal anti-inflammatory drugs; POD, postoperative day; i.v., intravenously; i.m., intramuscularly.

Dindo definition as grade I to V [17]. All morbidities were assessed by 2 experienced surgeons (FW and LW) who were masked to the group assignments. Postoperative hospital stay was defined as the day when the patient was medically fit for discharge.

Patients were deemed stable for discharge once they could tolerate half-stream food, have bowel movements, and had no serious complications. The discharge criteria were based on the Chinese hepatectomy guideline as follows: white blood cell count < 1.2 times the normal value, albumin (ALB) > 30 g/L, ALT/AST < 3 times the normal value, serum total bilirubin (TBIL) < 2 times the normal value, and prothrombin activity (PTa) > 60%.

The preoperative factors (age, sex, ICG15 value, Scheuer S score, BMI, preoperative laboratory indexes), operative factors (blood loss, operation time, operation type, hepatectomy type, blood transfusion) and postoperative factors (postoperative hospital stay, bowel movement time, drain removal time, postoperative complication [Clavien-Dindo grade] rate, total morphine usage after surgery, postoperative day [POD] 1/3/5 CONUT score, and postoperative laboratory indexes) for all patients were recorded. All factors were analyzed to identify risk factors for delayed recovery after surgery.

The primary endpoint was the day when the patients could be discharged. Secondary endpoints included morbidity and recovery of liver function on POD 5.

Statistical analyses

Data on patient characteristics, intraoperative parameters, and postoperative courses were collected. Continuous data with a normal distribution were statistically tested for group differences using a 2-sample Student t-test. Data without a normal distribution were analyzed using the Mann-Whitney U-test. Complication and mortality rates were analyzed using the chi-square test or Fisher exact test. The median postoperative hospital stay was compared across the same factors using Mann-Whitney or Kruskal-Wallis tests for categorical factors and Spearman correlation for continuous factors. Logistic regression multivariate analysis was performed to determine the association between risk factors and complications. A P-value of <0.05 was considered to be statistically significant. Statistical analyses were performed with IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA).

RESULTS

During the study period, 85 patients who met the inclusion criteria were included in the ERAS group, and 5 patients whose

Table 2. Perioperative characteristics of HCC patients in the ERAS and control groups

Variable	ERAS	Control	P-value
Age (yr)	55 (42–69)	59 (45–70)	0.339
Sex, female:male	16:64	23:59	0.491
ICG15 (%)	4.00 (1.70–10.42)	5.05 (2.20–10.73)	0.281
Preoperative PLT (×10^9 L)	177.50 (104.10–253.50)	153.00 (87.90–272.40)	0.125
Preoperative PTa (%)	88.10 (74.00–103.10)	82.50 (67.60–99.43)	0.533
Preoperative TBIL (μmol/L)	13.30 (8.61–21.78)	11.80 (7.16–20.22)	0.054
Preoperative ALT (U/L)	22.50 (13.00–49.50)	24.50 (13.30–61.50)	0.090
Preoperative AST (U/L)	23.00 (17.00–43.00)	23.50 (15.30–43.00)	0.418
Preoperative ALB (g/L)	45.20 (40.14–49.90)	43.90 (38.99–48.59)	0.080
Preoperative CONUT score	2.00 (0.00–3.40)	2.00 (0.10–4.00)	0.290
Preoperative BMI (m²/kg)	23.43 (20.18–28.26)	24.64 (20.92–29.13)	0.062
Tumor size (cm²)	11.52 (3.04–38.08)	12.00 (3.00–45.43)	0.993
Scheuer S score			0.651
<3	27 (33.75)	24 (29.27)	
≥3	53 (66.25)	58 (70.73)	
Type of procedure			0.500
Laparoscopic surgery	21 (26.25)	14 (17.07)	
Open surgery	59 (73.75)	68 (82.93)	
Type of hepatectomy			0.728
Single segmentectomy	25 (31.25)	28 (34.14)	
Two combined segmentectomies	25 (31.25)	33 (40.24)	
Major hepatectomy	30 (37.50)	21 (25.62)	

Values are presented as median (IQR)[a] or number (%)[b].
IQR, interquartile range; HCC, hepatocellular carcinoma; ERAS, enhanced recovery after surgery; ICG15, indocyanine green retention at 15 minutes; PLT, platelet; PTa, prothrombin activity; TBIL, total bilirubin; ALB, albumin; CONUT, controlling nutritional status; BMI, body mass index.
P-value: [a]Mann-Whitney test. [b]Chi-square test.

Scheuer S scores were 0 were excluded in the end; 82 patients were included in the control group.

The baseline characteristics and perioperative results of the patients are displayed in Table 2. There were no significant differences between the 2 groups for sex, age, preoperative liver function (ICG15 rate, serum ALB level, TBIL level, ALT level, and platelet count), CRP level, preoperative CONUT score/BMI, tumor size, Scheuer S score, type of procedure and type of hepatectomy.

Clinical short-term outcomes after surgery are summarized in Table 3.

The median postoperative hospital stay was 5 days in the ERAS group and 7 days in the control group (P < 0.001). Patients in the ERAS group had a shorter postoperative hospital stay than those in the control group. The control group was comparable to the ERAS group regarding the use of different types of postoperative pain management, which is shown in Table 1. The MEU value was significantly lower in the ERAS group, resulting in a higher POD 1/2 pain score; the pain score was 2 in the ERAS group and 1 in the control group. The median time to return of bowel function was earlier in the ERAS group, and abdominal drains were removed 3 days postoperatively in

Table 3. Comparison of short-term outcomes between the ERAS and control groups

Variable	ERAS	Control	P-value
Intraoperative blood loss (mL)	200 (100–500)	300 (175–400)	0.064
Total blood transfusion (mL)	0 (0–400)	0 (0–400)	0.89
Postoperative hospital stay (mL)	5 (4–6)	7 (6–8)	<0.001*
Abdominal drainage tubes removed day (day)	3 (3–4)	4 (3–5)	0.005*
Bowel movement time (day)	2 (2–3)	3 (3–3)	<0.001*
Morphine equivalents units (MEU)	83.33 (48.75–92.50)	250 (167.50–280.00)	<0.001*
POD 1 VAS score	2 (1–2)	1 (1–2)	0.002*
POD 2 VAS score	2 (1–2)	1 (1–2)	0.001*
POD 1 CONUT score	7 (5.75–8)	7 (6–8)	0.689
POD 3 CONUT score	7 (5–8)	7 (5.5–8)	0.927
POD 5 CONUT score	5 (4–6)	7 (4–8)	0.113

Values are presented as median (interquartile range).
Data are the mean/medians with ranges in parentheses for continuous variables, with P-values from Mann-Whitney test or 2-sample Student t-test.
ERAS, enhanced recovery after surgery; POD, postoperative day; VAS, visual analogue scale; CONUT, controlling nutritional status.
*P < 0.05, statistically significant differences.

Table 4. Univariate and multivariate logistic regression analysis of the risk factors for prolonged hospital stay

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Control group	2.093	0.757–5.792	0.155	-	-	-
Age	1.051	0.991–1.115	0.100	1.037	0.990–1.087	0.128
ICG15	1.009	0.854–1.192	0.919	-	-	-
Operation time	1.014	1.004–1.024	0.008*	1.010	1.003–1.017	0.006*
Tumor size	0.996	0.965–1.029	0.826	-	-	-
Intraoperative blood loss	0.998	0.996–1.001	0.226	-	-	-
Preoperative ALB	1.045	0.905–1.208	0.547	-	-	-
Preoperative ALT	1.063	1.008–1.120	0.023*	1.026	1.000–1.053	0.051
Preoperative AST	0.972	0.922–1.025	0.289	-	-	-
Open surgery	1.551	0.372–6.475	0.547	-	-	-
Single segmentectomy	0.368	0.094–1.436	0.150	0.300	0.094–0.958	0.042*
Combined 2 segmentectomies	0.319	0.085–1.200	0.091	0.512	0.173–1.511	0.225
Major hepatectomy	-	-	0.190	-	-	0.127
Postoperative complication	0.148	0.041–0.538	0.004*	0.067	0.024–0.185	<0.001*

Results from the logistic regression model, with prolonged hospital stay as the dependent variable.
CI, confidence interval; ICG15, indocyanine green retention at 15 minutes; ALB, albumin.
*P < 0.05, statistically significant differences.

the ERAS group, which was significantly sooner than that in the control group under the same standard of drain removal.

Based on the median hospital stay of 6 days in all patients, we dichotomized hospital stay into 2 groups (prolonged hospital stay > 6 days). Logistic regression analysis was applied to identify risk factors of prolonged hospital stay (Table 4). Patients with single segmentectomy had shorter hospital

Table 5. Comparison of morbidity after surgery between the ERAS and control groups

Variable	ERAS	Control	P-value
Any complication	17 (21.25)	30 (36.59)	0.041*
Clavien-Dindo grade			
I	4 (5.00)	13 (15.85)	0.018*
II	7 (8.75)	9 (10.84)	0.467
III	2 (2.50)	5 (6.02)	0.157
IV	4 (5.00)	3 (3.66)	0.705
Any complication	-	-	-
Liver/renal failure	5 (6.30)	3 (3.70)	0.480
Biliary leak/abdominal infection	1 (1.30)	2 (2.40)	0.564
Incision infection	2 (2.50)	-	-
Pneumonia	-	2 (2.40)	-
Pleural effusion	4 (5.00)	10 (12.20)	0.029*
Acute blood loss	1 (1.30)	1 (1.20)	>0.999
Postoperative ascites	3 (3.80)	12 (14.60)	0.046*
Hospital readmission	10 (12.50)	20 (24.39)	0.051

Values are presented as number (%).
ERAS, enhanced recovery after surgery.
*P < 0.05, statistically significant differences. P-values from chi-square test.

stay, meanwhile longer operation time and postoperative complication were associated with prolonged hospital stay.

Sixteen patients (20.00%) in the ERAS group and 30 patients (36.59%) in the control group had at least one complication (P < 0.05) (Table 5); most complications were classified as grade 1–2, accounting for 68.75% of the total complications in the ERAS group and 70.65% in the control group. Grade I complications were significantly different in the 2 groups (patients in the ERAS group had fewer grade I complications), while complications of other grades were similar. The differences in the rates of pleural effusion and postoperative ascites (referring to ascites needing intervention, such as diuretics or paracentesis) were significant; the control group rates were approximately 3 times higher than those in the ERAS group. Risk factors for complications are shown in Table 6 (logistic regression analysis). ICG15, operation time, preoperative ALT, and number of liver segmentectomies were associated with postoperative complications (Fig. 1).

Recovery of liver function was evaluated by the Child-Pugh score, and postoperative biochemical parameters including liver enzymes are shown in Fig. 2. The median hospital stay was 5 days in the ERAS group; therefore, recovery of liver function on POD 5 was compared between the 2 groups (Table 7). The Child-Pugh score on POD 5 was lower in the ERAS group (6 vs. 7) (P < 0.001), while the ALT, AST, and TBIL levels did not show significant differences between the 2 groups. In repeated measurement analysis of variance, the postoperative PTa (P < 0.001) and ALB (P = 0.007) levels were higher in the ERAS group than in the control group.

The CRP concentration in the ERAS group was lower than that in the control group, and the POD 5 CRP level was

Table 6. Univariate and multivariate logistic regression analysis of the risk factors for postoperative complications

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Control group	2.496	1.247–4.996	0.010*	2.756	0.970–7.828	0.057
Age	1.017	0.982–1.053	0.338	-	-	-
ICG15	1.194	1.059–1.346	0.004*	1.235	1.047–1.458	0.012*
Operation time	1.010	1.005–1.015	<0.001*	1.011	1.002–1.021	0.020*
Tumor size	1.011	0.996–1.027	0.150	-	-	-
Intraoperative blood loss	1.003	1.001–1.004	<0.001*	1.002	1.000–1.004	0.051
Preoperative ALB	0.872	0.798–0.953	0.003*	1.011	0.885–1.154	0.873
Preoperative ALT	1.019	1.000–1.038	0.045*	1.035	1.007–1.064	0.014*
Preoperative AST	1.001	0.993–1.009	0.877	-	-	-
Laparoscopic surgery	0.390	0.151–1.011	0.053	0.500	0.099–2.529	0.402
Single segmentectomy	0.426	0.187–0.973	0.043	0.092	0.022–0.387	0.001*
Combined 2 segmentectomies	0.504	0.214–1.191	0.118	0.487	0.138–1.725	0.265
Major hepatectomy	-	-	0.110	-	-	0.004*

Results from the logistic regression model, with prolonged hospital stay as the dependent variable.
CI, confidence interval; ICG15, indocyanine green retention at 15 minutes; ALB, albumin.
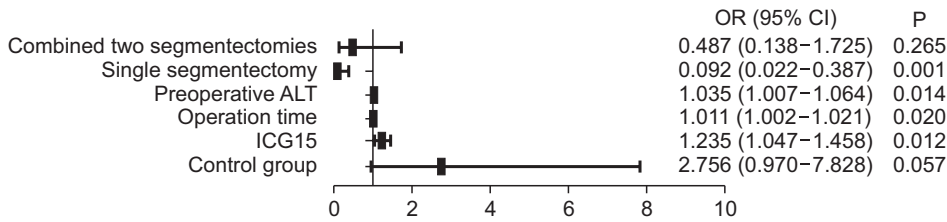*P < 0.05, statistically significant differences.

Fig. 1. Forest plot of multivariate analysis of the risk factors for postoperative complications. OR, odds ratio; CI, confidence interval; ICG15, indocyanine green retention at 15 minutes.
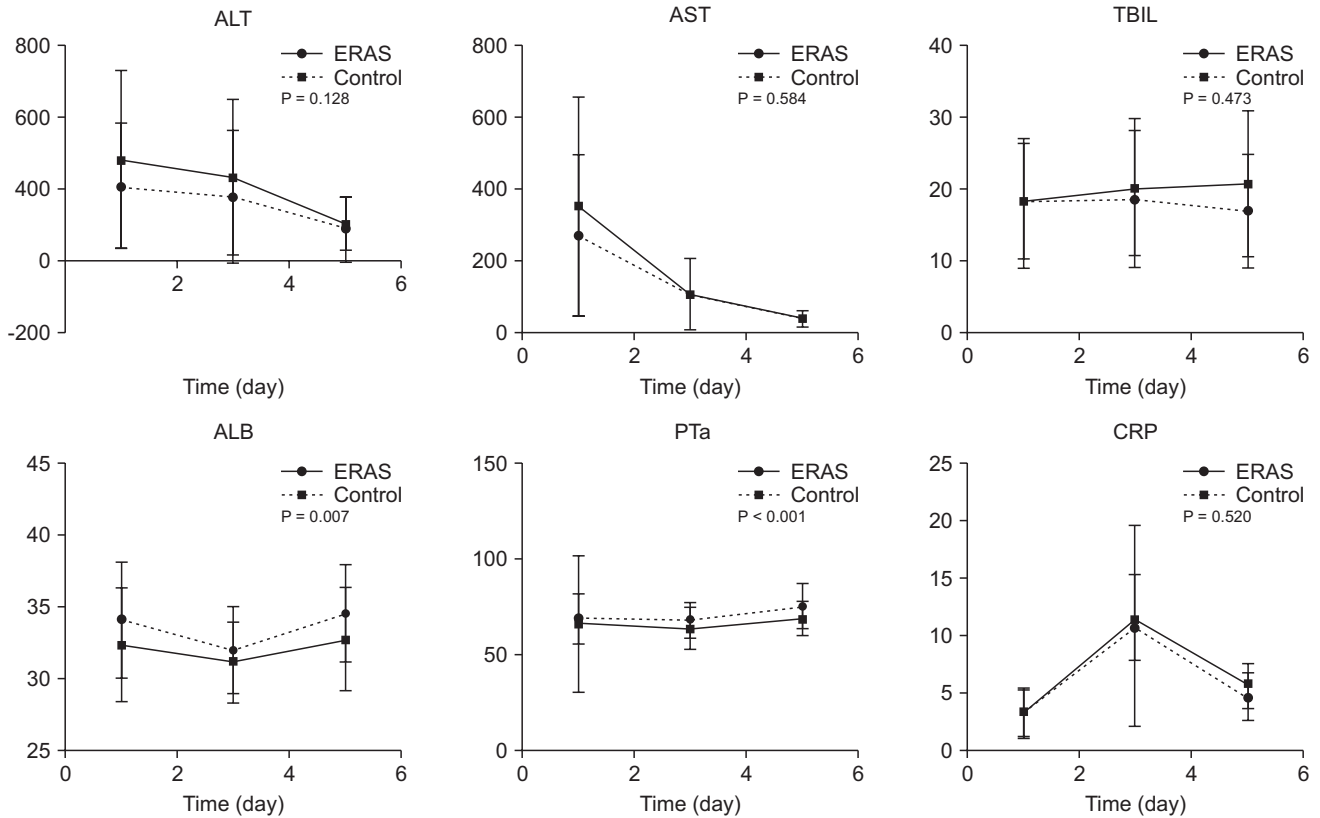

Fig. 2. Postoperative biochemical parameters of the 2 groups. Mean ± standard deviation of ALT/AST/TBIL/ALB/PTa/CRP in the ERAS and control groups on POD 1/3/5. Squares represent the control group and circles represent the ERAS group. P-values from repeated measurement analysis of variance. TBIL, total bilirubin; ALB, albumin; PTa, prothrombin activity; ERAS, enhanced recovery after surgery; POD, postoperative day. *P < 0.05, statistically significant differences.

Table 7. Comparison of POD5 liver/renal function between the ERAS and control groups

Variable	ERAS	Control	P-value
Child-Pugh score	6 (5–6)	7 (6–7)	<0.001*
ALT (U/L)	110.3881 ± 106.02100	133.3077 ± 94.57991	0.171
AST (U/L)	35.9254 ± 17.79369	37.6026 ± 20.02229	0.597
TBIL (μmol/L)	18.8866 ± 11.09306	20.2423 ± 11.25989	0.468
DBIL (μmol/L)	9.7955 ± 5.74821	11.0385 ± 6.17238	0.214
PLT (×10⁹ L)	149.8824 ± 58.36108	140.7949 ± 52.94652	0.326
CRE (μmol/L)	71.9552 ± 34.13273	66.0649 ± 12.21985	0.159
K (mmol/L)	3.8999 ± 0.38684	3.8247 ± 0.40474	0.258

Values are presented as mean ± standard deviation.
POD, postoperative day; ERAS, enhanced recovery after surgery; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; CRE, creatinine.
*P < 0.05, statistically significant differences. P-values from t-tests.

significantly different between the groups (4.62 ± 0.296 *vs.* 5.60 ± 0.314, P = 0.027).

DISCUSSION

This study showed that using an evidence-based multimodal enhanced program similar to that for colorectal surgery patients was safe for hepatectomy patients, including those with cirrhosis undergoing major hepatectomy. Patients in the ERAS group had a shorter postoperative hospital stay and fewer complications than those in the control group, indicating that the ERAS strategy was effective in cirrhotic hepatitis patients. Unlike in colorectal surgery, ERAS protocol in liver resection took more consideration regarding remnant liver metabolism, especially in cirrhosis patients. In view of impaired coagulation and possible epidural hematoma, epidural anesthesia was not performed in our ERAS protocol; instead, the way of blood loss control, the volume of liver resection, more specific fluid therapy, and protection of postoperative liver and renal function were augmented.

Quality of life seemed to be better in the ERAS group than in the control group based on 3 aspects. First, the MEU value was significantly reduced in the ERAS group, while the postoperative VAS pain score was not clinically different (VAS scores of 1 and 2 both represent minimal pain); therefore, the side effects of morphine, such as gastrointestinal motility disturbance, were reduced in the ERAS group. Second, reduced morphine use may have accelerated bowel movements in the ERAS group, and the normal oral intake time was earlier, which is an important factor in the General Comfort Questionnaire for the Kolcaba score [18] to evaluate quality of life. Additionally, under the same standard of drain tube removal (drainage < 50 mL, no blood present), the drain removal time was significantly reduced in the ERAS group, which could potentially be explained by the policy of early drain removal in ERAS patients [19]. This result coincides with a study [20] that used the validated MD Anderson Symptom Inventory to show that ERAS group patients seemed to have a better quality of life.

A study in 2010 [5], which explored risk factors for complications associated with hepatectomy, concluded that the independent relative risk for morbidity was influenced by operation time and blood loss. Another study concluded that improvements in surgical technology and techniques and perioperative management resulted in marked reductions in mortality and morbidity over time [3]. As for the type of surgery procedure, laparoscopic liver resection for HCC is feasible and safe but not inferior to open liver resection in regard to operative outcome [21]. In our center, in order to prevent bias, we did not deliberately perform more laparoscopic surgery in the ERAS group. Coincidentally, ERAS showed an advantage in reducing morbidity in our study, though in the multivariate

analysis, it was not an outstanding factor. Preoperative liver function, such as ICG15 rate and ALT levels, and operative characteristics, such as operation time and number of liver segmentectomies, were associated with postoperative complications in the multivariate analysis rather than the intervention. Improvements of the factors in operation, such as hemihepatic vascular control and local hepatectomy, do have positive impacts on recovering after surgery. Our team's previous study [22] showed that intraoperative factors, such as hemihepatic vascular control, could result in better postoperative outcomes. In this study, patients in ERAS group had lower POD5 Child-Pugh score and lesser postoperative hospital stay. Based on earlier studies regarding hepatobiliary surgery in our center [23,24], hemihepatic vascular control and local hepatectomy combined with necessary radiotherapy showed no difference in survival of HCC. In colorectal surgery, surgical procedure is relatively constant compared with irregular hepatectomy, and operative characteristics have not changed much between the surgeries. Different HCC patients require specific liver resection, with different liver metabolism status, and it might be the reason why preoperative liver function and operative characteristics have greater impact in multivariate analysis of morbidity. Regardless, for some specific postoperative complications, such as pleural effusion and ascites, ERAS had a significant preponderance. This may be due to perioperative goal-directed fluid therapy changes. In the ERAS group, the anaesthesiologists controlled the intravenous fluid by stroke volume variation and cardiac index rather than CVP during the operation. This is unique in the liver surgery ERAS strategy, particularly regarding anesthesia, because goal-directed fluid therapy can effectively reduce operative bleeding and postoperative pleural effusion. After the operation, strict control of postoperative fluid through the veins was applied, and further oral intake was encouraged.

Liver function recovery was not different according to the trends of ALT and AST levels, while postoperative PTa and ALB levels were notably higher and the POD5 Child-Pugh score was lower in the ERAS group than in the control group. These results may indicate that liver function recovery was faster in the ERAS group than in the control group. In the ERAS group, surgeons paid more attention to avoiding Pringle maneuvres and preserving as much of the remnant liver as possible. Although hemihepatic vascular control was performed more often in the ERAS group, there was no difference in intraoperative blood loss and total blood transfusion, which indicates that hemihepatic vascular control is safe and effective in cirrhotic patients.

Malnutrition is a common complication after hepatectomy in cirrhosis patients. Although some research found that nutritional support is less related to postoperative morbidity, most research reports that nutrition support is beneficial

to cirrhosis patients undergoing liver surgery [25], and early enteral feeding is advantageous in reducing the complication rate after major hepatic resection [26]. In particular, early enteral nutrition on POD 1 was verified to be beneficial in shortening the recovery period of intestine and liver functions in patients with HCC, even in a situation of liver cirrhosis [27]. There are a few methods, such as the subjective global assessment, nutritional risk index, and CONUT score, that can be used to evaluate the nutritional state of postoperative patients [28]. Considering that weight is not a reliable indicator of malnutrition because of the presence of ascites and edema, and that early postoperative CONUT scores are associated with complications after hepatectomy in HCC patients [29], it seems reasonable to use the CONUT score to assess the nutritional state of a patient. However, in our study, the postoperative nutritional state in the 2 groups was not different according to the CONUT scores. It seems that the ERAS strategy cannot improve nutrition state recovery. However, the ERAS group may have experienced less stress because the POD 5 CRP levels and POD 3 neutrophil to lymphocyte ratios were lower in the ERAS group than in the control group. One study noted that the ERAS protocol seemed to modulate perioperative insulin sensitivity, reducing operative stress and accelerating the return of baseline function [30]. More detailed laboratory studies are needed to validate this theory.

One limitation of this study was that it was not conducted as a randomized blind trial because in the trial test, the ERAS protocol showed sufficient safety and efficacy, and the trial could not be performed in a double-blind manner. Data from patients in the ERAS group were collected prospectively, and the principal aim was to assess the impact of implementing ERAS in routine clinical practice. Another limitation was that our ERAS protocol was very basic compared to that used in other studies involving the administration of branched-chain amino acids, and data of perioperative intravenous fluid were not analyzed in our study, for the anesthetists in our group have done a deeper study about goal-fluid therapy and metabolism.

In conclusion, this study has demonstrated that ERAS is a safe and effective intervention for cirrhosis patients undergoing complex liver resection surgery. ERAS, with a high level of compliance with the different elements, can result in a significant reduction in postoperative hospital stay and fewer postoperative medical complications, together with improved quality of life in the hospital. Patients undergoing cirrhotic hepatectomy with an ERAS protocol might have better recovery of liver function after surgery. In ERAS protocol for hepatectomy, operative characteristics such as the method of blood loss control and the volume of liver resection should be brought into consideration.

Conflict of Interest

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

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