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Original

Intraoperative increased plasma lactate concentration as a prognostic factor for liver transplant recipients: a retrospective cohort study

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Abstract

Liver transplantation for patients with end-stage liver diseases has become a standard, life-saving procedure. The aim of this retrospective cohort study was to analyze the perioperative clinical course and laboratory data of liver transplant recipients within the context of anesthesia management for the prevention of postoperative mortality and morbidity.

Forty-three adult patients with liver failure who underwent living donor liver transplantation were divided into two groups based upon their 90-day mortality. Group 1 comprised patients who were alive 90 days after surgery (n = 34); Group 2 comprised those who died within 90 days after surgery (n = 9).

Ninety days after transplant surgery, the overall survival rate was 79.1%. Pre-anesthetic blood urea nitrogen (BUN) concentration was significantly higher ($p < 0.05$), chloride ion concentration was lower ($p < 0.05$), and the pre-anesthetic model for end-stage liver disease (MELD) score was higher in Group 2 ($p < 0.05$). BUN concentrations in Group 2 were significantly higher after anesthesia induction, at the end of surgery, and at admission to the intensive care unit (ICU) ($p < 0.05$). The raw data of plasma lactate concentration during anesthesia showed no significant difference between Groups 1 and 2; however, in Group 2 there was a significantly increased lactate concentration after reperfusion and at the end of surgery ($p < 0.05$). This increase in lactate concentration negatively affected postoperative 90-day mortality as determined by logistic regression analysis ($p < 0.05$).

An increased blood lactate concentration after reperfusion of the transplanted liver might be a predictor of postoperative clinical prognosis.

Key words : *liver failure, liver transplantation, lactate, prognosis*

I. Introduction

Liver transplantation is one of the life-saving therapies available for end-stage liver diseases, but the results of postoperative outcomes are not satisfactory [1-3]. Indications for liver transplantation depend on several factors including clinical symptoms, laboratory data, and imaging studies. Among those factors, the model for end-stage liver disease (MELD) score is often used to assess the need for liver transplantation [4-7].

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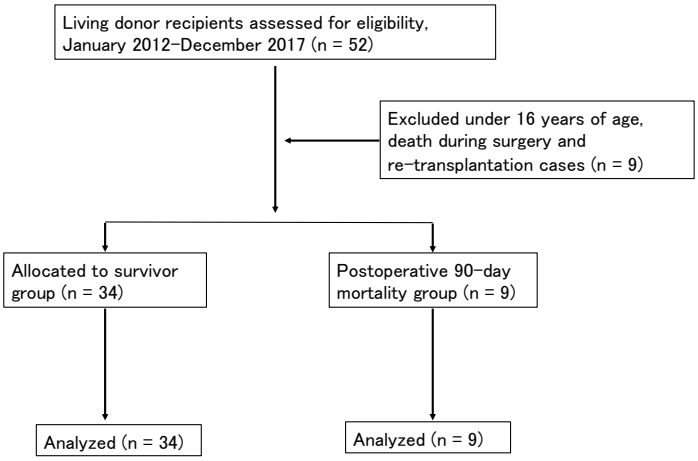

Fig. 1. Patients selection and cohorting

In Japan, liver transplantation is performed on 400-500 patients per year, and the 1-year post-transplant survival rate is about 80% [2]. In addition, liver transplantation has a high therapeutic cost compared to other treatments.

Arguments related to the precise prognostic factors of liver transplantation are controversial, and have thus been the focus of many studies [8-13]. Although MELD score is a useful predicting factor for liver failure, it is not a useful predictive factor of recovery after the liver transplantation [5, 8]. Therefore, we conducted this study to clarify a useful index for recovery after liver transplantation.

In the present study we compared peri-operative clinical data between survivors and non-survivors to evaluate which index is the most precise prognostic determinant. To consider the predictors for prognosis after liver transplantation we looked at the time periods before anesthesia, during anesthesia and just after anesthesia.

II. Patients and methods

This study was approved by the ethics committee of Iwate Medical University School of Medicine (MH2018-043).

Clinical data of decompensated cirrhosis patients, who had undergone liver transplantation from living donors in our hospital between January 2012 and December 2017, were obtained from electronic clinical records and anesthetic records. Patients under 16 years of age, cases of re-implantation surgery, and patients who died of massive bleeding during surgery were excluded. A total of 43 patients were enrolled in the present study. These subjects were divided into two groups based upon their 90-day mortality; Group 1 comprised patients who were alive 90 days after surgery (n = 34), and Group 2 comprised those who died within 90 days after surgery (n = 9) (Fig. 1). We collected the data of the patients'

Abbreviations
PT-INR: prothrombin time-international normalized ratio
APTT: activated partial thromboplastin time
AT III: anti-thrombin III
AST: aspartic aminotransferase
ALT: alanine aminotransferase
BUN: blood urea nitrogen
MELD: model for end-stage liver disease
ICU: intensive care unit

Table 1. Demographic profile

	Group 1 (n = 34)	Group 2 (n = 9)	p value
Age	48.6 ± 12.2	54.6 ± 6.6	0.169
M/F	17/17	4/5	0.767
Height (cm)	162.7 ± 10.2	159.8 ± 7.4	0.436
Weight (kg)	63.7 ± 11.9	63.7 ± 13.8	0.995
BMI	24.0 ± 3.6	24.8 ± 4.3	0.576

Values are mean ± S.D. or number.

Table 2. Indication diseases of recipients

	Group 1 (n = 34)	Group 2 (n = 9)
Cholestatic Diseases	7	1
Hepatocellular Diseases	20	8
Vascular Diseases	3	0
Neoplastic Diseases	1	0
Acute Liver Failure	2	0
Metabolic diseases	0	0
Others	1	0

Values are numbers of patients .
Chi-square p-value is 0.0672.

characteristics, and anesthesia data throughout the time course, i.e., blood and urine output values, infused fluid volume, and administered medications. Additionally, we collected the perioperative blood laboratory data including blood gas analysis (PF ratio, pH, base excess, and HCO_3^- concentration), blood cell counts (hemoglobin concentration, hematocrit, and platelet count), coagulation function (prothrombin time-international normalized ratio, activated partial thromboplastin time, anti-thrombin III, and fibrinogen concentration), liver biochemical tests (total bilirubin, aspartic aminotransferase, and alanine aminotransferase), renal function (blood urea nitrogen and creatinine), electrolytes (sodium, potassium, and chloride) and other blood biochemical examinations (total protein and albumin, MELD score, MELD-Na score, and MELD-lactate score). These data were compared between the two groups.

Statistical analyses were performed using SPSS version 22 (SPSS Inc, Chicago, IL, USA). The Shapiro-Wilk test was used to assess whether the data were normally distributed. Continuous data were expressed as median (interquartile range) or mean ± SD, and categorical variables were expressed as raw number of patients. The Mann-Whitney U test or unpaired Student's t-test were used to compare the continuous variables. The categorical data were assessed using a Chi-square test. The logistic method was used for the regression analysis. P-values < 0.05 were considered statistically significant.

III. Results

In Group 1, the mean duration of postoperative intensive care unit (ICU) stay and hospital stay were 14.7 ± 9.4 days and 81.3 ± 48.4 days, respectively, and the duration of mechanical ventilation after surgery was 38.2 ± 115.3 hours. In Group 2, the mean postoperative survival was 34.8 ± 21.0 days and death certification was performed under mechanical ventilatory management. The postoperative 90-day survival rate was 79.1%. In Group 2, the causes of death were severe infectious disease (n = 4), postoperative bleeding (n = 3) and acute cellular rejection (n = 2).

All patients received fentanyl and/or remifentanil for pain prevention during general anesthesia. For sedation, anesthesia was induced by intravenous administration of propofol, and maintained by inhalation of 0.5-1.0% isoflurane or 3-6% desflurane with 40-80% oxygen mixed with air. Rocuronium was continuously administered at 0.2-0.4 mg/kg/h as a muscle relaxant during

Table 3. Pre-anesthetic laboratory data

	Group 1 (n = 34)	Group 2 (n = 9)	p value
Blood gas analysis			
PF ratio	406.7 (365.2, 512.4)	398.8 (378.6, 450.1)	0.876
pH	7.46 (7.45, 7.49)	7.48 (7.47, 7.48)	0.644
Base excess (mmol/L)	1.45 (0.00, 2.00)	2.10 (2.00, 2.90)	0.184
HCO_3^- (mmol/L)	25.1 (23.9, 26.0)	26.6 (25.0, 28.6)	0.237
Blood count			
Hemoglobin (g/dl)	10.1 (9.2, 11.3)	9.7 (8.8, 9.9)	0.101
Hematocrit (%)	30.9 (27.7, 33.8)	29.0 (26.0, 29.0)	0.124
Platelet (/mm^3)	86.0 (52.0, 118.0)	77.0 (54.0, 128.8)	0.948
Coagulation function			
PT-INR	1.41 (1.20, 1.59)	1.61 (1.15, 2.14)	0.483
APTT (sec)	39.5 (34.4, 51.5)	39.5 (33.6, 49.7)	0.999
Fibrinogen (mg/dl)	281.4 (195.0, 320.0)	225.0 (139.8, 380.5)	0.780
Anti-thrombin III (%)	56.5 (44.0, 81.8)	41.0 (32.3, 57.3)	0.095
Liver biochemical tests			
Total bilirubin (mg/dl)	2.30 (1.13, 6.33)	3.30 (1.10, 9.70)	0.731
AST (IU/L)	50.0 (33.0, 68.0)	59.5 (39.3, 87.3)	0.316
ALT (IU/L)	34.0 (18.0, 52.0)	29.5 (25.5, 42.8)	0.705
Renal function			
Creatinine (mg/dl)	0.71 (0.56, 0.88)	0.85 (0.62, 1.05)	0.232
BUN (mg/dl)	14.5 (9.2, 16.2)	25.7 (16.3, 31.8)*	0.041
Electrolytes			
Na (mmol/L)	136.0 (132.9, 138.8)	133.2 (131.9, 136.0)	0.244
K (mmol/L)	3.82 (3.53, 4.06)	3.90 (3.40, 4.50)	0.403
Cl (mmol/L)	105.0 (103.3, 107.7)	100.0 (99.0, 104.0)*	0.046
Others			
Total protein (g/dl)	6.40 (5.80, 7.00)	6.65 (6.30, 7.12)	0.293
Albumin (g/dl)	2.70 (2.30, 3.40)	2.85 (2.55, 3.13)	0.882
MELD score	10.54 (6.63, 13.79)	18.10 (12.64, 18.61)*	0.032
MELD-Na score	13.00 (11.35, 17.28)	22.65 (12.64, 18.61)	0.069

Values are expressed as the median (25% quartile, 75% quartile). *: $p<0.05$ vs Group 1

anesthesia. We routinely prepared dopamine and noradrenaline for vasopressor activity and prostaglandin E1 for perfusion maintenance of the transplanted liver. Anesthesia-related drugs and cardiovascular agents were used at the discretion of the anesthesiologist.

There was no significant difference between Group 1 and Group 2 regarding age, gender, height, weight, and BMI (Table 1). Indication diseases of liver transplantation, such as cholestatic, hepatocellular, and vascular diseases did not differ either (Table 2).

Comparison of pre-anesthetic laboratory data between Group 1 and Group 2 are shown in Table 3. Blood urea nitrogen (BUN) concentration was significantly higher and chloride ion concentration was lower in Group 2 ($p < 0.05$). Moreover, MELD score was significantly higher in Group 2 ($p < 0.05$). As for other factors mentioned in Patients and methods, there was no significant difference between the two groups.

Table 4. Intra-anesthetic data

	Group 1 (n=34)	Group 2 (n=9)	p value
Operation time (min)	735.5 (682.3, 823.8)	679.0 (653.0, 944.0)	0.835
Anesthesia time (min)	845.0 (783.5, 923.0)	722.0 (768.0, 1055.0)	0.591
Blood loss (g)	3704 (2202, 7106)	4260 (1510, 16681)	0.743
Urine output (ml)	1,795 (908, 2731)	1,225 (540, 2155)	0.221
Infusion volume (ml)	13,530 (10430, 16850)	14,820 (10570, 34540)	0.720
Total balance (ml/kg/hr)	9.12 (6.98, 12.12)	12.3 (10.3, 12.7)	0.089

Values are expressed as the median (25% quartile, 75% quartile).

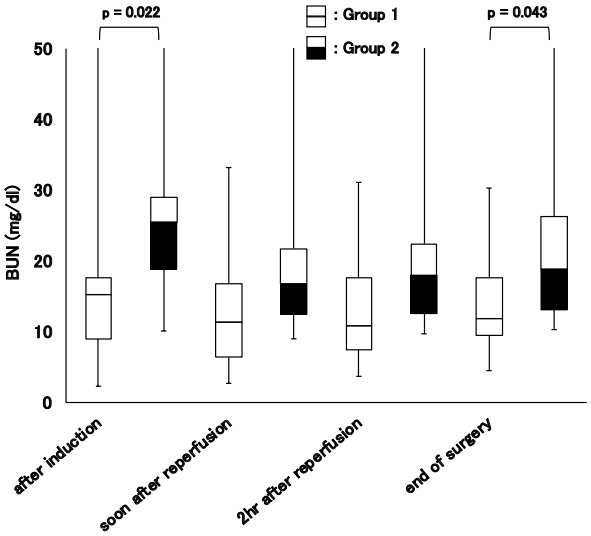

Fig. 2. Changes of blood urea nitrogen (BUN) concentration during anesthesia

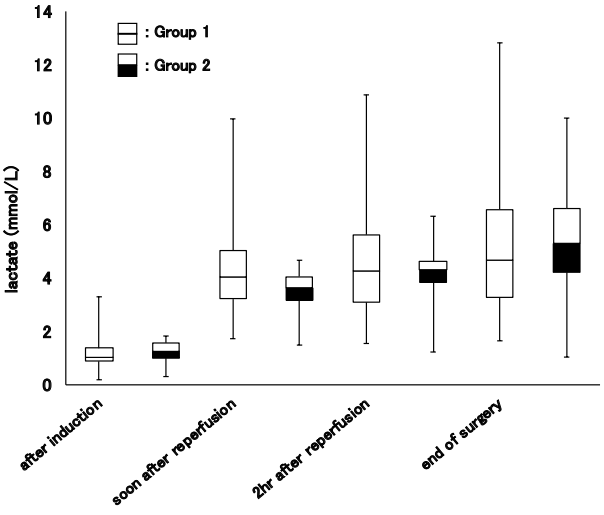

Fig. 3. Changes of lactate concentration during anesthesia

Intra-anesthetic data involving fluid balance are shown in Table 4, and there was no significant difference between the groups. Although BUN concentrations were significantly higher in Group 2 after anesthesia induction and at the end of surgery ($p < 0.05$, Fig. 2), other laboratory data such as examination with pre-anesthetic data did not differ between the two groups during anesthesia. Although the changes of plasma lactate concentration during anesthesia did not differ between the groups (Fig. 3), it seemed to be different about the way of changes of the lactate level of both groups as shown in Fig. 4. And the increased rate of

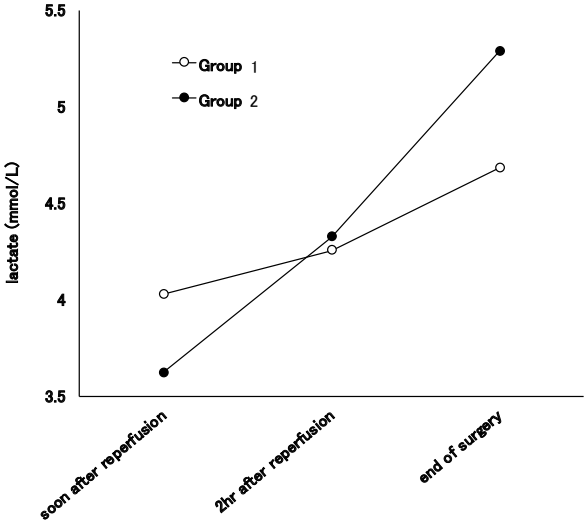

Fig. 4. Changes of median value of lactate concentration after liver reperfusion

Table 5. Increased rates of plasma lactate concentration

	Group 1 (n = 34)	Group 2 (n = 9)	p value
Soon after reperfusion-2hr after reperfusion	0.057 (−0.048, 0.138)	0.198 (−0.043, 0.276)	0.357
Soon after reperfusion-end of surgery	0.085 (−0.034, 0.315)	0.448 (0.040, 0.785)*	0.034
2hr after reperfusion-end of surgery	0.058 (−0.011, 0.140)	0.251 (0.060, 0.399)	0.215

Values are expressed as the median (interquartile range). *: $p<0.05$ vs. Group 1

Table 6. Laboratory data at the admission to ICU

	Group 1 (n=34)	Group 2 (n=9)	p value
Blood gas analysis			
PF ratio	406.2 (349.8, 466.0)	343.8 (233.5, 441.2)	0.550
pH	7.39 (7.36, 7.43)	7.39 (7.35, 7.40)	0.748
Base excess (mmol/L)	−1.30 (−2.40, 0.10)	−2.10 (−3.40, 0.50)	0.999
HCO_3^- (mmol/L)	23.7 (22.6, 24.7)	24.1 (22.3, 25.8)	0.592
Blood count			
Hemoglobin (g/dl)	9.3 (8.7, 10.2)	9.1 (8.8, 9.9)	0.713
Hematocrit (%)	27.0 (25.4, 30.0)	27.0 (26.0, 29.0)	0.736
Platelet (/mm^3)	82.0 (64.0, 99.0)	81.5 (67.3, 106.3)	0.681
Coagulation function			
PT-INR	1.48 (1.39, 1.57)	1.40 (1.29, 1.59)	0.456
APTT (sec)	41.8 (38.1, 41.8)	41.5 (37.5, 48.3)	0.948
Fibrinogen (mg/dl)	165.0 (142.0, 197.0)	216.0 (179.0, 219.0)	0.164
Anti-thrombin III (%)	76.0 (62.0, 89.0)	66.5 (56.0, 80.8)	0.459
Liver function	4.1 (3.1, 5.5)	4.5 (3.2, 7.2)	0.405
Total bilirubin (mg/dl)	341.5 (202.8, 546.3)	357.5 (308.8, 474.8)	0.710
AST (IU/L)	212.0 (142.5, 394.3)	234.5 (188.0, 319.5)	0.774
ALT (IU/L)			
Renal function	0.74 (0.58, 1.03)	0.81 (0.65, 1.07)	0.325
Creatinine (mg/dl)	11.9 (9.5, 17.7)	18.9 (13.1, 26.2) *	0.043
BUN (mg/dl)			
Electrolytes	141.6 (137.9, 143.8)	141.7 (139.3, 143.5)	0.988
Na (mmol/L)	3.46 (3.27, 3.88)	3.45 (2.95, 3.68)	0.702
K (mmol/L)	107.0 (104.0, 109.0)	106.0 (104.0, 107.0)	0.342
Cl (mmol/L)			
Others	5.00 (4.90, 6.00)	5.10 (4.80, 5.60)	0.606
Total protein (g/dl)	3.80 (3.50, 4.30)	3.90 (3.75, 3.90)	0.859
Albumin (g/dl)	4.69 (3.29, 6.59)	5.29 (4.22, 6.61)	0.624
Lactate (mmol/L)	13.40 (11.46, 16.92)	15.05 (12.31, 22.02)	0.633
MELD scoreMELD-Na score	11.94 (10.69, 17.49)	12.37 (11.02, 20.45)	0.492
MELD-lactate score	20.71 (17.78, 24.00)	21.41 (19.55, 25.54)	0.478

Values are expressed as the median (25% quartile, 75% quartile). *: $p < 0.05$ vs Group 1

Table 7. Logistic analysis for postoperative 90-day survival

	OR	95% CI	p value
Preanesthetic agent MELD score	1.087	0.908-1.205	0.114
Intranesthetic agent Increased rate of plasma lactate*	6.117	1.002-37.351	0.048
Postanesthetic agent BUN	1.147	0.997-1.319	0.055

*: $p<0.05$

plasma lactate concentration after reperfusion and at the end of surgery, that was provided in the following calculating formulas, was significantly higher in Group 2 ($p < 0.05$, Table 5).

Increased rate of *LA = [(LA at the end of surgery) – (LA soon after reperfusion)] / (LA soon after reperfusion)

*LA = plasma lactate concentration

Laboratory data at the start of ICU admission are shown in Table 6. BUN was significantly higher in Group 2, but there was no difference between the groups in other values shown in the Patients and methods ($p < 0.05$).

Logistic single regression analysis comparing the groups was performed on the factors in which the p-value was the smallest. These factors included the pre-anesthetic value measuring the MELD score, the intra-anesthetic value of increased rate of plasma lactate concentration after reperfusion and at the end of surgery, and the post-anesthetic value of BUN at admission to the ICU. The increased rate of plasma lactate concentration after reperfusion and at the end of surgery was determined to affect postoperative 90-day survival ($p < 0.05$, Table 7).

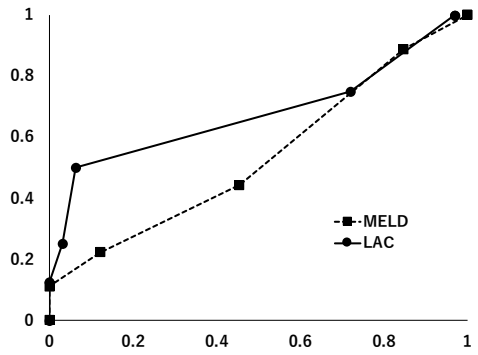

Fig. 5. Receiver operating characteristic (ROC) curve for prediction of liver transplantation on the MELD score at the 2hr after reperfusion (MELD) and the increased ratio of plasma lactate concentration (LAC), Area under the curve (AUC); MELD score: 0.53; increased ratio of lactate: 0.65

IV. Discussion

Liver transplantation has become the standard life-saving procedure for patients with end-stage liver disease in Japan. However, treatment outcomes are not satisfactory [1-3]. One cause of poor outcomes is the difficulty of predicting patient recovery. Many papers on the prognostic factors of liver disease have been published, but to date no reliable factors have been identified [4-7]. Previous studies have mainly demonstrated that it can be difficult to predict the clinical outcomes of individual patients after liver transplantation. Furthermore, most reports have focused on the prognosis of recipients scheduled for liver transplantation, concluding that it is not critical for the indicators of postoperative prognosis [14-17]. Hence, we must consider how

liver transplant patients' prognosis is related to the effect of various agents on liver function and the general condition of liver transplant patients [8, 13].

The MELD score is one of the representative indices of liver damage, specifically the MELD-Na and the MELD-lactate scores [9-12]. Previously, blood concentrations of liver enzymes, bilirubin, and lactate have been used as indicators of transplanted liver function, especially blood lactate levels and acid-base balance [14-17]. However, the model of early allograft function score and liver graft assessment following transplantation risk score, in addition to the MELD score, have been reported to be more accurate predictors of transplanted liver function [18, 19].

In the present study, we assessed the causes of postoperative 90-day mortality from the perspective of perioperative factors. Figure 5 shows the receiver operating characteristic (ROC) curve of the MELD score at 2 hours after reperfusion, and the increased rate of lactate level until the end of surgery after reperfusion. The areas under the curve (AUC) are 0.53 in the MELD score and 0.65 in the increased lactate concentration. It is a few higher in the increased rate lactate concentration, but it cannot be said to be extremely accurate by ROC in both parameters because of the small AUC.

Although there was no difference in the raw data of lactate concentrations (Fig. 3), the increased rate of lactate concentration affected postoperative 90-day mortality (Table 7, $p < 0.05$). Despite differences in several factors between groups, no factors other than the increased lactate rate had an apparent effect on mortality. The cases with a continuous rise in lactate concentration during surgery had a poor prognosis and this was considered to be due to insufficient blood perfusion of the transplanted liver or the malfunction of the replacement graft. More recently, it was demonstrated that lactate clearance after reperfusion of liver graft is useful for predicting early allograft dysfunction [20, 21]. However, these studies evaluated serum lactate concentration 6 hours after reperfusion, while we evaluated the changes in lactate concentration during anesthesia, specifically after reperfusion, and until the end of surgery. As lactate is mainly metabolized in the liver, serum lactate concentration is elevated when the liver is defective. In addition, the damaged liver can become the production source of lactate, which is a waste product of cellular metabolism [8]. These are the reasons for our supposition that the postoperative survival rate was low in patients who showed a large increase in lactate concentration. We have routinely administered catecholamine and prostaglandin E1 to maintain the graft's blood perfusion, but we suggest that the doses of these drugs should be increased if the patients' lactate levels continue to increase [22].

There have been reports that the risk of complications experienced by liver failure patients is increased in patients with a MELD score $\geqq$ 18, and is even higher post-transplantation [5-7]. On the other hand, liver transplantation is indicated in patients with higher MELD score, in which case that treatment is the only life-saving method. In our cohort, pre-anesthetic MELD score was significantly higher in the non-survivor group ($p = 0.032$, Table 3), but it did not statistically affect the 90-day mortality rate (Table 7). Although BUN values were statistically different between the

groups both before and during anesthesia, other factors, i.e., chloride and MELD score, were not statistically different during anesthesia. Instead, those results could be ascribed to treatments with fluid resuscitation and administration of the formulations during anesthesia. In addition, the higher BUN value of Group 2 may be due to preoperative renal function deteriorating in many cases in Group 2. In fact, there were many patients with abnormal value of the creatinine level in Group 2. Although there was no significant difference in pre-anesthetic creatinine level between the two groups, the number of patients who were more than 1.5 mg/dl of serum creatinine concentration was larger in Group 2 (5.9% in Group 1, 22.2% in Group 2) ($p < 0.05$).

The most important finding of this study was that an increased blood lactate concentration, after reperfusion of the transplanted liver, affected the 90-day survival of transplant recipient patients.

This retrospective study has some inherent limitations. First, there were few patients and the numbers in each group were different. Therefore, we could not perform multivariate logistic analysis and had to adopt a single regression analysis. Second, the patients were divided into two groups based on postoperative 90-day survival. In the present study, we selected 90-day survival as the grouping criterion because the length of hospital stay after surgery in Group 1 was 81.3 ± 48.4 days, a value close to 90 days. However, it is unclear whether our classification was appropriate or not. Third, we did not analyze the quality of donor grafts. Fourth, we did not measure pre-operative lactate levels, so we could not compare the pre-anesthetic raw numerical value to the lactate level during anesthesia. Furthermore, our lactate data could not be standardized based on preoperative values.

The number of liver transplants in Japan, especially from brain dead donors, remains small compared to Europe or the US because the concept of brain death is not agreed upon. However, the total number of liver transplant surgeries has been steadily increasing. Hence, further analyses of liver transplantation in Japan will be necessary in the future.

In conclusion, the increased blood lactate concentration after reperfusion of transplanted liver was shown to be a predictor of post-operative clinical severity.

Acknowledgments

This was a retrospective cohort study and the research was approved by the ethics committee of Iwate Medical University Graduate School of Medicine (approval number; MH2018-043).

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KSS designed the study. TH bone the main responsibility for preparing the manuscript, and analyzed and interpreted the data. All authors took charge of anesthetic management and contributed to writing the manuscript.

Conflict of interest: The authors have no conflict of interest to declare.

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生体肝移植レシピエントにおける 術中乳酸値の上昇率は予後予測の指標となりうる

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要旨

肝移植レシピエント患者の予後予測因子を明らかにする目的で後ろ向きに検討した.

当施設で 2012 年 1 月～ 2017 年 12 月の期間に施行された生体肝移植術のレシピエント患者 43 名を対象とし, 移植後 90 日での生存群:1 群（n = 34）と死亡群:2 群（n = 9）に振り分けた.

90 日生存率は 79.1％であった．術前血中尿素窒素濃度（BUN）および model for end-stage liver disease score（MELD スコア）は 2 群で有意に高く，血中 Cl^{-1} 濃度は 2 群で有意に低かった．麻酔導入後および手術終了時の BUN は 2 群で有意に高かった．術中の血中乳酸濃度（Lac）に群間差はなかったが，移植肝再灌流後から手術終了時の Lac 上昇率は 2 群で有意に高かった（いずれも $p < 0.05$）．麻酔前因子・麻酔中因子・麻酔後因子に分けて施行したロジスティック回帰分析では麻酔中移植肝再灌流後の Lac 上昇率のみが有意な影響因子であった（OR = 6.117，95％CI = 1.002 – 37.351，$p = 0.048$）.

肝移植における再灌流後の Lac 上昇率は予後予測の指標となりうることが示唆された.