

# Serum Lactate Clearance as a Predictive Biomarker for Optimal Graft Perfusion in Living Donor Liver Transplantation

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# Serum Lactate Clearance as a Predictive Biomarker for Optimal Graft Perfusion in Living Donor Liver Transplantation

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## ABSTRACT

**Background:** The optimal balance between the graft volume (GV) and portal venous flow (PVF) in living donor liver transplantation (LDLT) is unclear. As lactate is mainly metabolized in the liver, perioperative lactate levels are reportedly a useful biomarker for early graft dysfunction (EGD). The present study analyzed perioperative lactate levels according to the PVF.

**Methods:** The PVF/GV (mL/min per 100 g GV) of 97 recipients from 1996 to 2022 was retrospectively classified as low (LPVF; PVF/GV  $\leq 100$ , N = 29), moderate (MPVF; PVF/GV 100–250, N = 40), or high (HPVF; PVF/GV > 250, N = 28). Lactate levels were obtained preoperatively (L0), immediately after graft reperfusion (L1), 4 h after reperfusion (L2), and on postoperative day 3 (L3). The lactate clearances were then calculated.

**Results:** The lower the PVF/GV ratio, the younger the age at LDLT and the higher the graft-to-recipient weight ratio. The median L2 and L3 in the HPVF group were significantly higher than those in the other groups ( $p = 0.019$  and  $p = 0.003$ , respectively). The median  $\Delta L1$  in the HPVF group was lower than that in the LPVF and MPVF groups (0.23 vs. 0.50,  $p < 0.0001$  and 0.23 vs. 0.41,  $p = 0.011$ , respectively).  $\Delta L1$  was negatively correlated with the PVF/GV. Although no patient had EGD, three patients with HPVF with low  $\Delta L1$  developed small-for-size syndrome.

**Conclusions:** Graft hyperperfusion may delay the recovery of the graft function and result in poor lactate clearance. The combination of the PVF/GV and lactate clearance may be useful as a prognostic marker for optimal graft perfusion in LDLT.

**Level of evidence:** IV.

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## 1. Introduction

Sufficient graft perfusion is essential for successful liver transplantation (LT). The optimal balance between graft size and perfusion volume is crucial for ensuring a good graft function in recipients with partial grafts in living donor LT (LDLT). According to a histopathological study by Demetris et al., small-for-size syndrome (SFSS) occurs when excessive portal venous flow (PVF) damages sinusoidal endothelial cells and reduces the hepatic

arterial blood flow owing to the arterial buffer response, which causes hepatocellular damage and bile duct ischemia [1]. However, the appropriate PVF for graft weight (GV) is unknown. Gastaca et al. reported that PVF/GV < 80 mL/min per 100 g GV is associated with EGD and graft loss [2]. Maramba et al. reported that intraoperative PVF/GV > 123 mL/min per 100 g GV contributed to the 5-year patient survival [3]. In a previous study, the maximum PVF/GV was 100 mL/min per 100 g GV in patients with insufficient portal venous inflow [4]. In contrast, Troisi et al. reported that a PVF/GV greater

**Abbreviations:** LT, liver transplantation; LDLT, living donor liver transplantation; PVF, portal venous flow; HAF, hepatic arterial flow; GV, graft volume; EGD, early graft dysfunction; SFSS, small-for-size syndrome; APOLT, auxiliary partial orthotopic liver transplantation; PT-INR, prothrombin time-international normalized ratio; IQR, interquartile range; GRWR, graft-to-recipient weight ratio; CIT, cold ischemic time; WIT, warm ischemic time; BAR score, balance of risk score.

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than 250 mL/min per 100 g GV is a risk factor for SFSS [5]. In the present study, we hypothesized an optimal PVF/GV ratio of 100–250 mL/min per 100 g GV.

As most lactate is metabolized in the liver, lactate levels in the perioperative period of LT have recently attracted attention as biomarkers for early graft dysfunction (EGD). Golse et al. proposed that the balance of risk (BAR) score combined with lactate levels at the end of transplantation could predict the early prognosis [6]. The BAR score has been reported to be a prognostic score in deceased donor liver transplantation, calculated from recipient age, MELD score, previous liver transplantation, life support at transplantation, cold ischemic time (CIT), and donor age [7].

As such, the present study analyzed the perioperative serum lactate levels according to the graft perfusion volume and examined the relationship between excessive or deficient PVF and perioperative lactate levels.

## 2. Patients and methods

The medical records of patients who underwent LDLT at the Department of Pediatric Surgery, Kyushu University Hospital, from October 1996 to September 2022 were reviewed, and perioperative data were obtained retrospectively, including the clinical data of the recipients, donor age, intraoperative data, perioperative lactate levels, and clinical outcomes. No major changes were made in the surgical techniques or perioperative management during the long period under review. Therefore, the data were comprehensively examined. Portal vein anastomosis was performed using absorbable continuous sutures. Venoplasty was performed by using a patch graft in the recipient with a narrow portal vein. End-to-end arterial reconstruction was performed under a microscope. After reperfusion, the PVF and hepatic artery flow (HAF; mL/min) were measured using an ultrasonic transit time flow meter (Transonic System, Ithaca, NY, USA). The PVF and HAF values divided by the GV (mL/min per 100 g GV) were calculated as parameters of graft perfusion, as previously reported [4]. We performed portal inflow modulation intraoperatively, such as splenectomy in cases with a low platelet count or remarkable splenomegaly, or splenic artery ligation in cases with an obviously high PVF. Based on the PVF/GV, recipients were classified into three groups: low PVF (LPVF; PVF/GV  $\leq$  100 mL/min per 100 g GV), moderate PVF (MPVF; PVF/GV 100–250 mL/min per 100 g GV), and high PVF (HPVF) (PVF/GV > 250 mL/min per 100 g GV). Arterial lactate levels (mg/dL) were obtained at 4 points: at the preoperative phase (L0), immediately after graft reperfusion (L1), 4 h after reperfusion (L2), and on postoperative day 3 (L3). The clearance of arterial lactic acid was assessed based on the rate of change in the lactate levels. The clearance from L1 to L2 ( $\Delta L1 = [L1 - L2]/L1$ ), from L1 to L3 ( $\Delta L2 = [L1 - L3]/L1$ ), and from L2 to L3 ( $\Delta L3 = [L2 - L3]/L2$ ) was calculated.

Some diseases and conditions demonstrate high lactate levels preoperatively and such lactate levels may continue to increase before performing graft reperfusion, ostensibly improving lactate clearance. To eliminate these effects, the following patients were excluded: patients with fulminant hepatitis, urea cycle disorder, congenital metabolic disorder, or mitochondrial disease; and patients with preoperative hypoxemia or severe acidemia. Conversely, surgical complications, such as hepatic artery, hepatic vein, or portal thrombus identified by the timing of L3 measurement, can have negative impacts on the lactate clearance. Patients with these complications were therefore also excluded. In addition, recipients undergoing auxiliary partial orthotopic liver transplantation (APOLT) and those without intraoperative lactate level, portal flow volume, or graft volume data were excluded.

In accordance with Dahm et al., SFSS was defined as the presence of two of the following three criteria on 3 consecutive days at 1 week postoperatively without other complications: (1) total Bil >5.84 mg/dL, (2) the prothrombin time-international normalized ratio (PT-INR) >2.0, and (3) Grade  $\geq$ 3 encephalopathy [8].

The differences among the groups were compared using the Kruskal–Wallis test or Fisher's exact test for continuous variables and the Steel–Dwass test for multiple comparisons among the predefined groups. The factors affecting lactate clearance were examined using a simple regression analysis. P was set at  $p < 0.05$ .

This study was approved by the local institutional ethics committee (No. 22322-00) and complied with the 1964 Declaration of Helsinki (revised in 2013).

## 3. Results

A total of 149 LDLT procedures were performed in the study term. Fifty-two recipients were excluded, and 97 recipients were included in this study. They were assigned to groups by the PVF/GV as described above: 29 to the LPVF group, 40 to the MPVF group, and 28 to the HPVF group (Fig. 1). Indications were biliary atresia in 77 cases, hepatoblastoma in 10 cases, Alagille syndrome in 3 cases, transient abnormal myelopoiesis in 3 cases, neonatal hemochromatosis in 2 cases, Langerhans cell histiocytosis in 1 case, and microvillus inclusion disease in 1 case, with no marked differences noted among the 3 groups. The lower the PVF/GV ratio, the younger the age at LDLT (LPVF vs. MPVF,  $p = 0.005$ ; LPVF vs. HPVF,  $p < 0.0001$ ; MPVF vs. HPVF,  $p = 0.019$ , respectively) and the higher the graft-to-recipient weight ratio (GRWR) (LPVF vs. MPVF,  $p = 0.002$ ; LPVF vs. HPVF,  $p < 0.0001$ ; MPVF vs. HPVF,  $p = 0.014$ , respectively). Donor age was higher in the HPVF group than in the other groups (vs. LPVF,  $p < 0.0001$ ; vs. MPVF,  $p = 0.019$ , respectively). There were no significant differences among the groups in biological sex, PELD or MELD scores, ABO compatibility, anhepatic time, cold ischemic time (CIT), warm ischemic time (WIT), or HAF/GV. No right lobe was transplanted in the LPVF. The HPVF had fewer left lateral segments and more extended left lobes as grafts. In the LPVF group, the patient survival rate was lower than that in the other groups (Table 1). Only one patient with HPVF underwent retransplantation eight years after primary liver transplantation due to graft failure.

### 3.1. Perioperative arterial lactate levels

Overall, the median lactate level increased from the preoperative phase (L0) to post-reperfusion (L1) (from 9 to 37 mg/dL,  $p < 0.0001$ ). After reperfusion, it gradually decreased to below preoperative levels (L0) by the third postoperative day (L3) (9 vs. 7 mg/dL,  $p = 0.008$ ) (Fig. 2). The median L0 was not significantly different among the 3 groups ( $p = 0.817$ ). The median L1 level in the LPVF group was higher than that in the HPVF group (46 vs. 34 mg/dL,  $p = 0.034$ ). In contrast, the median L2 level in HPVF was significantly higher than that in the LPVF group (27.5 vs. 17 mg/dL,  $p = 0.026$ ), and the median L3 level was significantly higher than that in both the LPVF and MPVF groups (10 vs. 6 mg/dL,  $p = 0.005$ ; 10 vs. 6,  $p = 0.013$ , respectively) (Fig. 3).

While the values of  $\Delta L1$  in the LPVF group were all positive, some patients with MPVF and HPVF had negative  $\Delta L1$  values. The median values of  $\Delta L1$  in the LPVF, MPVF and HPVF groups were 0.50 (interquartile range [IQR]: 0.33–0.76), 0.41 (IQR: 0.16–0.56), and 0.23 (IQR: –0.10–0.32), respectively. The  $\Delta L1$  in the HPVF group was significantly lower than that in both the LPVF and MPVF groups ( $p < 0.0001$  and  $p = 0.011$ , respectively) (Fig. 4A). The  $\Delta L2$  in the HPVF group was also significantly lower than that in the LPVF group ( $p = 0.034$ ) but did not differ from that in the MPVF group (Fig. 4B).

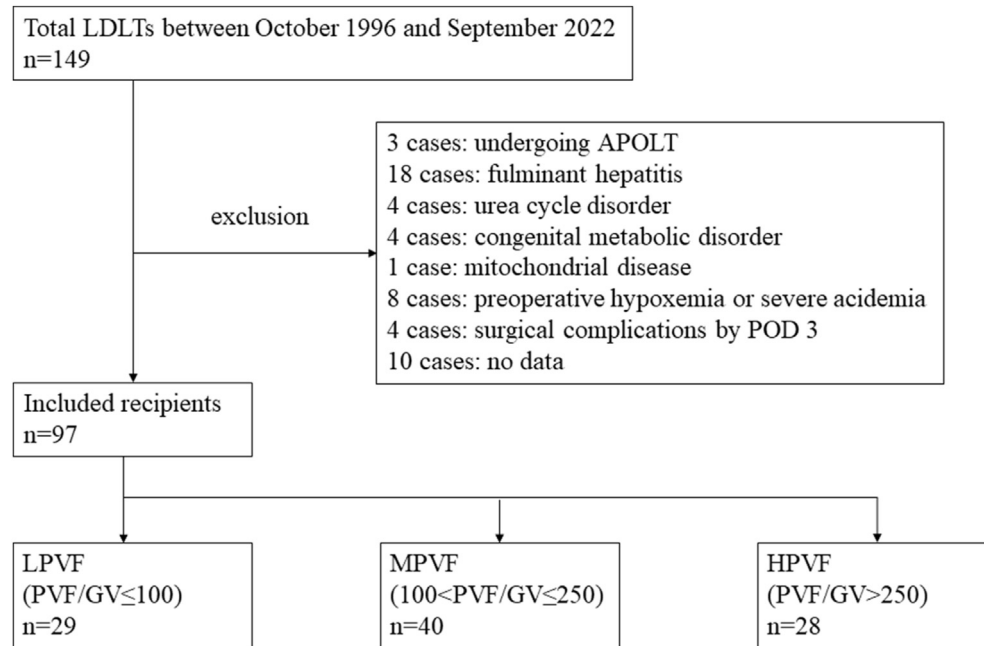


Fig. 1. Enrollment flow chart.

Table 1

The characteristics and clinical data of LDLT recipients by group.

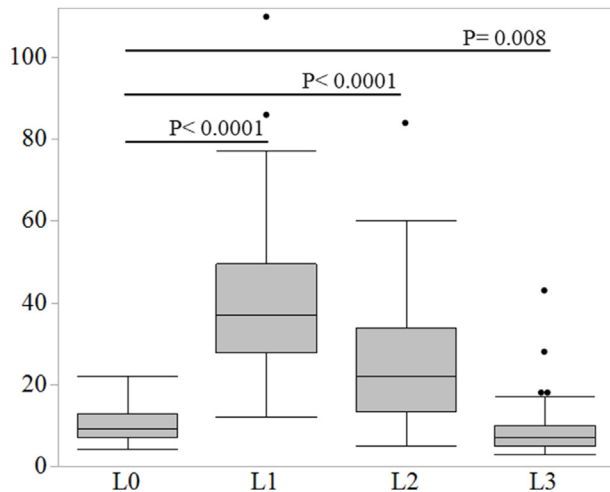
|                                    | LPVF (n = 29) median (IQR) | MPVF (n = 40) median (IQR) | HPVF (n = 28) median (IQR) | p-value <sup>a</sup> |
|------------------------------------|----------------------------|----------------------------|----------------------------|----------------------|
| Biological sex (male), n (%)       | 10 (34.5%)                 | 12 (30%)                   | 13 (46.4%)                 | 0.394                |
| Age at LDLT, years                 | 0.8 (0.5–1.5)              | 2.0 (0.8–5.9)              | 8.6 (1.8–18.3)             | <0.0001              |
| Indication of LDLT, n (%)          |                            |                            |                            | 0.975                |
| Biliary atresia                    | 22 (75.9%)                 | 31 (77.5%)                 | 24 (85.7%)                 |                      |
| Hepatoblastoma                     | 3 (10.3%)                  | 5 (12.5%)                  | 2 (7.1%)                   |                      |
| Alagille syndrome                  | 2 (6.9%)                   | 1 (2.5%)                   | 0                          |                      |
| Transient abnormal myelopoiesis    | 1 (3.4%)                   | 1 (2.5%)                   | 1 (3.6%)                   |                      |
| Neonatal hemochromatosis           | 1 (3.4%)                   | 0                          | 1 (3.6%)                   |                      |
| Langerhans cell histiocytosis      | 0                          | 1 (2.5%)                   | 0                          |                      |
| Microvillus inclusion disease      | 0                          | 1 (2.5%)                   | 0                          |                      |
| PELD/MELD                          | 14.5 (11–21.8)             | 13.5 (2.5–19)              | 11 (5–22.5)                | 0.395                |
| Donor age, years                   | 33 (28–37)                 | 35 (31.3–39)               | 41 (31–48.8)               | 0.011                |
| ABO compatibility, n (%)           |                            |                            |                            | 0.2774               |
| Identical                          | 20 (69%)                   | 20 (50%)                   | 13 (46.4%)                 |                      |
| Compatible                         | 5 (17.2%)                  | 8 (20%)                    | 9 (32.1%)                  |                      |
| Incompatible                       | 4 (13.8%)                  | 10 (25%)                   | 6 (21.4%)                  |                      |
| Unknown                            | 0                          | 2 (5%)                     | 0                          |                      |
| Graft type                         |                            |                            |                            | <0.0001              |
| Left lateral segment               | 19 (65.5%)                 | 28 (70%)                   | 8 (28.6%)                  |                      |
| Reduced left lateral segment       | 9 (31%)                    | 4 (10%)                    | 4 (14.3%)                  |                      |
| Left lobe                          | 1 (3.4%)                   | 1 (2.5%)                   | 2 (7.1%)                   |                      |
| Extended left lobe                 | 0                          | 3 (7.5%)                   | 11 (39.3%)                 |                      |
| Right lobe                         | 0                          | 4 (10%)                    | 3 (10.7%)                  |                      |
| Graft-to-recipient weight ratio, % | 3.16 (2.55–3.55)           | 2.33 (1.57–3.14)           | 1.24 (0.95–2.45)           | <0.0001              |
| Anhepatic time, minutes            | 148 (115.5–199)            | 131.5 (96.3–167.3)         | 107 (71–176)               | 0.221                |
| Cold ischemic time, minutes        | 102 (66–140)               | 97.5 (55.8–145.8)          | 86 (59–135)                | 0.778                |
| Warm ischemic time, minutes        | 51 (46–61)                 | 50 (45–56)                 | 46 (39–56)                 | 0.151                |
| PVF/GV                             | 64.8 (51–86.6)             | 180.2 (147.2–208.0)        | 321.2 (281.2–394.4)        | <0.0001              |
| HAF/GV                             | 32.3 (20.0–50.8)           | 34.4 (24.4–52.9)           | 33.5 (24.8–50.3)           | 0.8425               |
| Patient survival                   | 21 (72.4%)                 | 38 (95%)                   | 26 (92.9%)                 | <0.0001              |

<sup>a</sup> p-value for Fisher's exact test or Kruskal–Wallis test.

There was no significant difference in the  $\Delta L3$  among the three groups (Fig. 4C).

None of the 97 patients had primary nonfunction or EGD. There was no significant difference in the liver function test results among the groups. Three patients developed SFSS, all of whom had HPVF.

Two patients had negative  $\Delta L1$  values. One patient with SFSS was a nine-year-old boy with biliary atresia. The left lobe of the patient's father was transplanted into the patient. The GRWR was 1.12%, and the PVF/GV was 798.2 mL/min per 100 g GV, which was remarkably high. In the postoperative period, ascites gradually increased,



**Fig. 2.** Perioperative lactate levels of the whole cohort. Lactate levels that had increased by the time of reperfusion dropped to preoperative levels by three days after transplantation. P-values for Steel test.

reaching >10 L/day at 2 weeks after LDLT. Splenectomy was performed on postoperative day 20. After splenectomy, the massive ascites improved dramatically.

### 3.2. An examination for the correlation between intraoperative factors and the lactate clearance

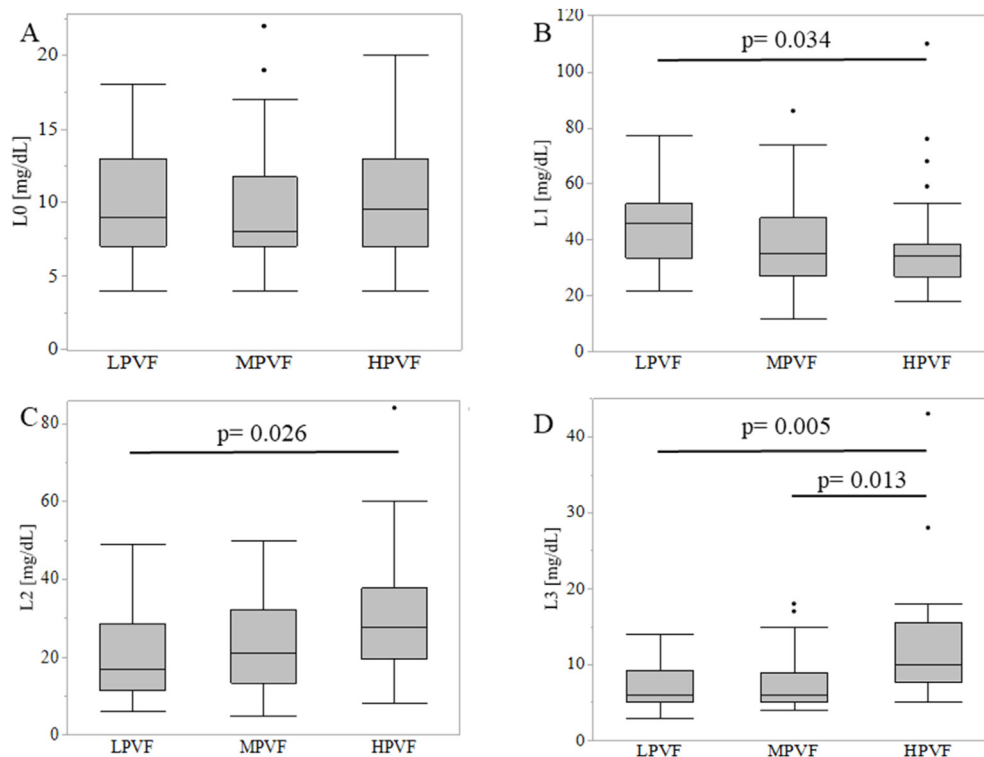
Since the comparison of lactate clearance showed the most significant difference in  $\Delta L1$  (intraoperative clearance of lactate),

the intraoperative findings regarding ischemia and reperfusion were examined for their effect on  $\Delta L1$ . A simple regression analysis for the correlation between intraoperative factors and  $\Delta L1$  is shown in Fig. 5. (PVF + HAF)/GV represents the whole perfusion blood flow volume per GV. The  $\Delta L1$  was negatively correlated with the PVF/GV and (PVF + HAF)/GV ( $p < 0.001$ ,  $R^2 = 0.187$  and  $p < 0.001$ ,  $R^2 = 0.053$ , respectively) and positively correlated with the HAF/GV ( $p = 0.027$ ,  $R^2 = 0.151$ ).  $R^2$ , which is the coefficient of determination, was the highest between  $\Delta L1$  and PVF/GV. There was no association between  $\Delta L1$  and either the anhepatic or ischemic time.

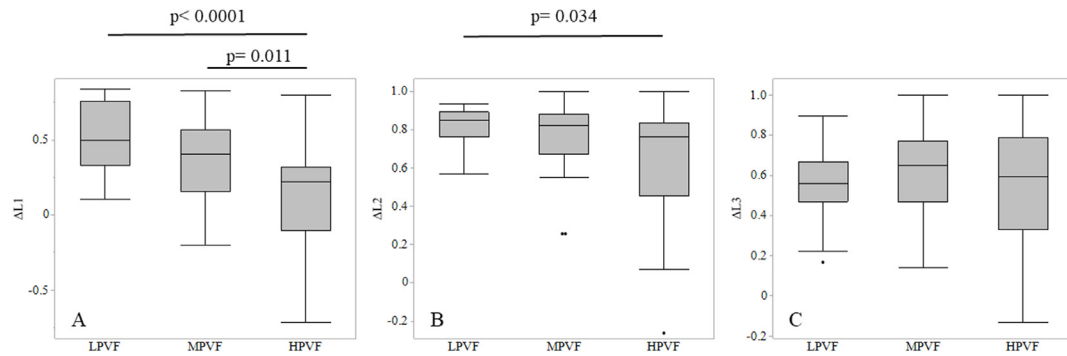
## 4. Discussion

Lactic acid is a hydroxycarboxylic acid that is produced as a metabolite of pyruvate during glycolysis. Lactate levels result from a dynamic balance between lactate production and clearance. Under normal conditions, lactate is metabolized predominantly in the liver and converted back to pyruvate through lactate dehydrogenase, although the kidneys and skeletal muscles are involved in lactate clearance [9]. Preoperatively, lactate dynamics in patients undergoing liver surgery may be confounded by the presence of preexisting liver diseases. In LT, graft cold preservation and reperfusion affect ischemia-reperfusion injury of the liver graft and subsequently lactate levels. Overall, the liver accounts for up to 70% of lactate clearance, and consequently, liver surgery, particularly if complicated by liver failure, can have significant effects on lactate levels.

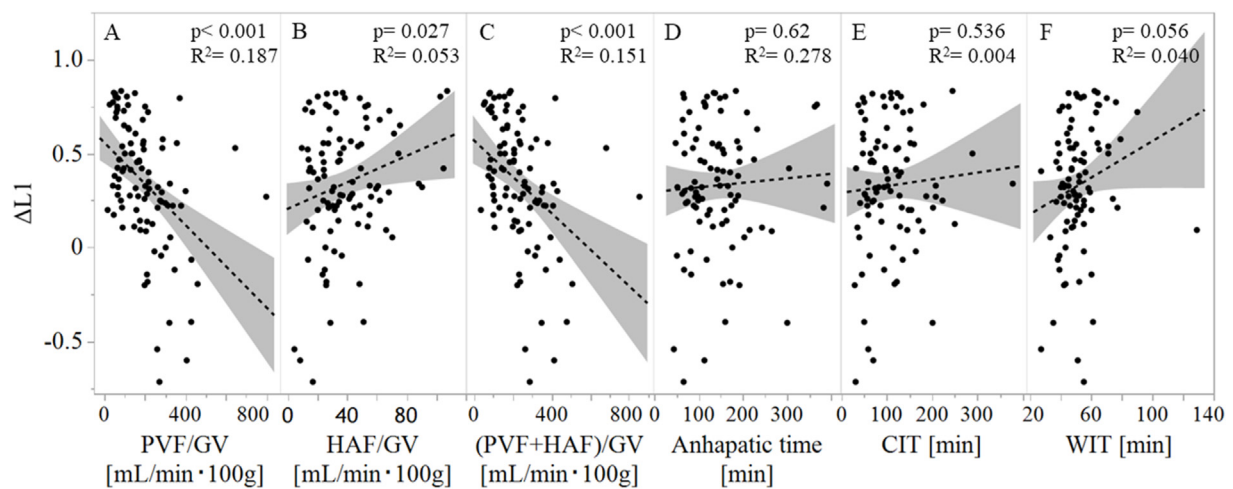
In clinical practice, the ideal target PVF for LDLT has been regarded as twice the perfusion observed in the full-sized graft (250 mL/min per 100 g of GV) or twice that observed in a healthy donor (180 mL/min per 100 g of GV). Shimamura et al. reported that LDLT recipients with a PVF/GV  $\geq 260$  mL/min per 100 g GV showed a higher peak of total bilirubin and longer hospital stay than those



**Fig. 3.** Lactate levels by group at each time point. Levels (A) at the preoperative phase (L0) and (B) immediately after graft reperfusion (L1); the L1 in the LPVF group was higher than in the HPVF group. Levels (C) 4 h after reperfusion (L2); the L2 in the HPVF group was higher than in the LPVF group. Levels (D) on postoperative day 3 (L3); the L3 in the HPVF group was higher than in both the LPVF and MPVF groups. P-values for Steel–Dwass test.



**Fig. 4. Lactate clearance by group.** Clearance (A) from L1 to L2 ( $\Delta L1$ ); the lactate clearance in the HPVF group was lower than in both the LPVF and MPVF groups. Clearance (B) from L1 to L3 ( $\Delta L2$ ); the lactate clearance in the HPVF group was lower than in the LPVF group. (C) from L2 to L3 ( $\Delta L3$ ). P-values for Steel–Dwass test.



**Fig. 5. Results of a simple regression analysis for the correlation between the intraoperative factors and  $\Delta L1$ .** (A) The PVF/GV had a negative correlation with  $\Delta L1$ . (B) The HAF/GV had a positive correlation with  $\Delta L1$ . (C) The (PVF + HAF)/GV had a negative correlation with  $\Delta L1$ . (D) Anhepatic time, (E) CIT, (F) WIT were not associated with  $\Delta L1$ .

with a PVF/GV < 260 mL/min per 100 g GV [10]. Sainz-Barriga et al. reported that the median PVF value was 130 mL/min per 100 g GV for full-size grafts and 180 mL/min per 100 g GV for partial liver grafts (such as LDLT grafts) in their analysis of whole and partial graft hemodynamics [11,12]. Their group showed that recipients with a low PVF (defined as <90 mL/min per 100 g GV) were likely to suffer more severe ischemia-reperfusion injury. They also reported that the average HAF of a healthy living donor is approximately 25 mL/min per 100 g GV. Following these reports, in the present study, we defined PVF  $\leq$  100 mL/min per 100 g GV as LPVF and >250 mL/min per 100 g GV as HPVF and stratified the recipients into three groups. Our data showed that the lactate clearance early after reperfusion ( $\Delta L1$ ) was poor in the HPVF group. This result may reflect that excessive portal blood flow delays the recovery of the graft liver function and reduces the lactate metabolic capacity. Excessive portal venous flow relative to the liver graft puts the graft at risk of SFSS and early graft dysfunction due to hepatocellular injury and bile duct ischemia. The three SFSS cases observed in our cohort were all in the HPVF group, and two of them had negative  $\Delta L1$  and relatively poor lactate clearance in the HPVF group.

Several researchers have reported the utility of lactate concentration as a prognostic biomarker after liver transplantation. Combinations of lactate concentration and various biomarkers have been investigated to predict the prognosis after liver transplantation, including the MELD score, platelet count, blood gas

analysis results, and biomarkers of acute kidney injury [13–16]. Gasperi et al. reported that, in the primary nonfunction group, lactate levels continued to rise from reperfusion to the end of surgery, and lactate excretion was stagnant for 48 h postoperatively [17]. Takahashi et al. reported that delayed lactate clearance is an independent risk factor for EGD [18]. However, these were all prognostic predictors, based primarily on postoperative laboratory data. The optimal portal pressure to prevent SFSS has also been studied and is generally considered to be < 15 mmHg [19,20]. In the present study, we stratified recipients based on the PVF/GV immediately after reperfusion and found that a low  $\Delta L1$  in the HPVF group was associated with a risk of SFSS. Both the PVF/GV and  $\Delta L1$  values used in this study were obtained intraoperatively, and PVF can be measured noninvasively using an ultrasound flowmeter without puncturing the vessel. These data may be used to improve the postoperative prognosis with the addition of portal inflow modulation procedures, such as splenic artery ligation and splenectomy. The highlight of this study is the finding that, focusing on the association between PVF/GV and lactate clearance, we can predict the graft prognosis and determine the need for portal inflow modulation from simple intraoperatively obtained data.

In the present study, lactate levels immediately after reperfusion were higher in the LPVF group than in the other groups; the LPVF group also included more infants than the other groups. Lactate metabolism involves the kidneys in addition to the liver; however,

infants may have an immature renal function, which may lead to an increased accumulation of lactate during the anhepatic period. In addition, this study did not include intraoperative infusions and blood glucose levels, and the possibility that these may be confounding factors cannot be ruled out.

Several limitations associated with the present study warrant mention. First, it was a retrospective study. Second, this was a single-center study, and the number of patients was insufficient. Furthermore, as no EGD cases were included, we could not examine the association between EGD and the parameters of this study. Because graft loss was observed in only one case, the effect of perioperative lactate levels on the graft survival could not be adequately analyzed in this study. Therefore, future large-scale studies are warranted.

## 5. Conclusion

Recipients with excessive portal venous flow to the graft volume showed decreased lactate clearance early after reperfusion. In the cases with hyper graft perfusion and poor lactate clearance, portal inflow modulation procedures, such as splenic artery ligation, should be considered intraoperatively, and it is necessary to be wary of graft dysfunction. The combination of PVF/GV and lactate clearance may be useful as a prognostic marker for optimal graft perfusion in LDLT.

## Previous communication

The contents of this manuscript were previously presented as a short oral presentation at the Pacific Association of Pediatric Surgeons 57th annual meeting.

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## Conflict of interest

The authors declare no conflicts of interest in association with the present study.

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