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Clinical Research

Intraoperative lactic acid concentration during liver transplantation and cutoff values to predict early mortality: a retrospective analysis of 3,338 cases

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Background: We aimed to explore the distribution of intraoperative lactic acid (LA) level during liver transplantation (LT) and determine the optimal cutoff values to predict post-LT 30-day and 90-day mortality.

Methods: Intraoperative LA data from 3,338 patients were collected between 2008 to 2019 and all-cause mortalities within 30 and 90 days were retrospectively reviewed. Of the three LA levels measured during preanhepatic, anhepatic, and neohepatic phase of LT, the peak LA level was selected to explore the distribution and predict early post-LT mortality. To determine the best cutoff values of LA, we used a classification and regression tree algorithm and maximally selected rank statistics with the smallest P value.

Results: The median intraoperative LA level was 4.4 mmol/L (range: 0.5–34.7, interquartile range: 3.0–6.2 mmol/L). Of the 3,338 patients, 1,884 (56.4%) had LA levels > 4.0 mmol/L and 188 (5.6%) had LA levels > 10 mmol/L. Patients with LA levels > 16.7 mmol/L and 13.5–16.7 mmol/L showed significantly higher 30-day mortality rates of 58.3% and 21.2%, respectively. For the prediction of the 90-day mortality, 8.4 mmol/L of intraoperative LA was the best cutoff value.

Conclusions: Approximately 6% of the LT recipients showed intraoperative hyperlactatemia of > 10 mmol/L during LT, and those with LA > 8.4 mmol/L were associated with significantly higher early post-LT mortality.

Keywords: Intraoperative hyperlactatemia; Lactic acid; Liver transplantation; Mortality.

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INTRODUCTION

The liver plays a key role in lactate metabolism. Hyperlactatemia is generally considered as an increase in lactate production due to anaerobic metabolism in a state of reduced organ perfusion. However, measured lactic acid (LA) concentrations are the sum of metabolic and catabolic process, therefore hyperlactatemia may be due to an increase in production or a reduction in clearance in liver disease [1,2].

Additionally, the liver can be transformed into a lactate-producing organ in cases of hypoxia, sepsis, or liver surgery [1–4]. Therefore, given the enhanced lactate produc-

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tion, reduction in clearance, and lactate-producing liver itself after reperfusion of the allograft, extremely high intraoperative LA levels are expected in patients undergoing liver transplantation (LT). However, compared to those of critically ill patients, characteristics of intraoperative LA concentrations during LT have been poorly studied in a large cohort of LTs. In addition, although there are studies that found that lactate clearance shortly after reperfusion of an allograft is associated with short-term prognosis [5–7], research on cutoff levels of intraoperative LA to predict early mortality remains poorly investigated [8,9].

To better understand the changes in LA concentration during LT, we thoroughly explored both preoperative and intraoperative LA and, furthermore, determined optimal cutoff values of intraoperative LA to predict post-LT 30-day and 90-day mortality.

MATERIALS AND METHODS

Study population

The Institutional Review Board approved the study design and a waiver of informed consent for participants (no. 2021-0664). Data from the institution's LT Registry, which prospectively registered patients who underwent LT, was extracted via the software, a fully computerized and automatic data extraction program. From January 2008 to December 2019, there were 4,604 potentially eligible LT recipients. Among them, 3,338 patients with measured intraoperative LA levels were chosen. We included the majority of heterogenous LT recipients because we aimed to characterize intraoperative LA and determine optimal cutoff values of hyperlactatemia to predict early post-LT mortality.

Data collection

Patient demographics, medical history, Model for End-stage Liver Disease score (MELDs), and preoperative laboratory variables were obtained automatically using the hospital software. All-cause mortality data were obtained from patients' electronic medical records and the updated record of the institution's LT Registry, which regularly follows all the registerd LT recipients.

Measurement of intraoperative LA during LT

Intraoperative LA levels were measured three times during the preanhepatic, anhepatic, and neohepatic periods as per the institution's routine intraoperative protocol. Of these, the peak level of intraoperative LA was used to analyze its distribution and predict early post-LT mortality. Preoperative LA concentration was also measured before LT as a routine work-up.

Study end-point

Primary and secondary end-points were 30-day and 90-day mortality, respectively.

Statistical analysis

Data are expressed as the mean ± standard deviation or median (1st quartile, 3rd quartile) for continuous variables, and numbers and percentages for categorical variables. Analyses between groups were performed using the Student's *t*-test, the Mann–Whiney *U* test, analysis of variance, or the Kruskal–Wallis test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate. The Kolmogorov–Smirnov test was used to test the normality assumption. To determine the best cutoff values of LA, we used a classification and regression tree (CART) algorithm of recursive partitioning and maximally selected rank statistics with the smallest P value ('caret' and 'maxstat' R package).

Briefly, in maximally selected rank statistics. The prognostic cutoff point was determined by evaluating every possible cutoff point classifying all patients into two groups according to their level and selecting the most discriminant threshold for death, corresponding to the minimum P value according to the log-rank test [10–12]. The Kaplan–Meier (KM) survival curve was used to depict the risk of 30-day and 90-day mortality.

RESULTS

The mean age of the 3,338 LT recipients included was 53.3 ± 9.0 years. Of the patients, 2,443 (73.2%) were men. The mean MELDs was 18.2 ± 10.9 (Table 1). The primary causes of liver disease were virus-related liver cirrhosis (63.1%) and alcoholic liver disease (20.3%), followed by others (18%).

Distribution of preoperative and intraoperative LA

The preoperative median LA level was 1.9 mmol/L (range:

Table 1. Patients' Demographics according to the Intraoperative Lactic Acid Levels

Variable	LA ≤ 8.4 mmol/L (n = 2,997)	LA > 8.4 mmol/L (n = 341)	Total (n = 3,338)	P value
Demographic data				
Age (yr)	53.2 ± 9.1	54.0 ± 8.8	53.3 ± 9.0	0.123
Sex, male	2,171 (72.4)	272 (79.8)	2,443 (73.2)	0.005
Body mass index (kg/m^2)	24.2 ± 3.7	24.8 ± 3.7	24.3 ± 3.7	0.003
Diabetes	731 (24.4)	69 (20.2)	800 (24.0)	0.102
Hypertension	559 (18.7)	60 (17.6)	619 (18.5)	0.688
MELD score	18.1 ± 10.8	18.9 ± 12.0	18.2 ± 10.9	0.262
MELDs				0.138
MELD < 15	1,619 (54.0)	188 (55.1)	1,807 (54.1)	
MELD 15–35	1,062 (35.4)	107 (31.4)	1,169 (35.0)	
MELD > 35	316 (10.5)	46 (13.5)	362 (10.8)	
Causes for liver disease				
Viral	1,874 (62.5)	231 (67.7)	2,105 (63.1)	0.067
Alcoholic	620 (20.7)	56 (16.4)	676 (20.3)	0.074
Biliary	99 (3.3)	4 (1.2)	103 (3.1)	0.047
Others	543 (18.1)	57 (16.7)	600 (18.0)	0.572
Malignancy	1,363 (45.5)	185 (54.3)	1,548 (46.4)	0.003
Comorbidities				
Fulminant hepatic failure	136 (4.5)	25 (7.3)	161 (4.8)	0.032
Intractable ascites	951 (31.7)	96 (28.2)	1,047 (31.4)	0.198
Hepatic encephalopathy	473 (15.8)	64 (18.8)	537 (16.1)	0.179
Pleural effusion	401 (13.4)	41 (12.0)	442 (13.2)	0.538
Spontaneous bacterial peritonitis	123 (4.1)	15 (4.4)	138 (4.1)	0.908
Laboratory variables				
Intraoperative	4.1 (2.9, 5.6)	10.4 (9.2, 12.2)	4.4 (3.0, 6.2)	< 0.001
Lactic acid (mmol/L)				
Hemoglobin (g/dl)	10.4 (8.9, 12.2)	10.7 (9.0, 12.7)	10.4 (8.9, 12.3)	0.052
Leukocytes (× 10^3/μl)	3.6 (2.5, 5.3)	3.5 (2.5, 5.6)	3.6 (2.5, 5.3)	0.739
Platelet count (× 10^3/μl)	61 (42, 94)	60 (41, 91)	61 (42, 94)	0.786
Total bilirubin (mg/dl)	2.1 (1.0, 9.6)	2.0 (1.8, 4.8)	2.1 (1.0, 9.8)	0.844
Albumin (g/dl)	3.1 (2.7, 3.5)	3.1 (2.7, 3.6)	3.1 (2.7, 3.5)	0.158
Prothrombin time (INR)	1.4 (1.2, 1.8)	1.4 (1.2, 1.9)	1.4 (1.2, 1.9)	0.507
Creatinine (mg/dl)	0.80 (0.7, 1.0)	0.84 (0.7, 1.1)	0.80 (0.7, 1.1)	0.012
Preoperative therapy				
Vasopressor support	145 (4.8)	36 (10.6)	181 (5.4)	< 0.001
Mechanical ventilation	245 (8.2)	54 (15.8)	299 (9.0)	< 0.001
Renal replacement therapy	297 (9.9)	52 (15.2)	349 (10.5)	0.003
Operative variables				
Deceased-donor	475 (15.8)	51 (15.0)	526 (15.8)	0.726
Operation time (min)	740.8 ± 142.4	754.4 ± 140.6	742.2 ± 142.3	0.096
Total ischemic time (min)	147.5 ± 71.7	130.5 ± 53.4	140.8 ± 65.6	< 0.001
Transfusion				
pRBC (unit)	11.3 ± 14.1	13.1 ± 16.4	11.5 ± 14.3	0.052
FFP (unit)	11.7 ± 14.0	12.7 ± 14.9	11.8 ± 14.1	0.193

Values are expressed as mean ± SD, number (%), or median (1Q, 3Q). LA: lactic acid, MELD score: Model for End-stage Liver Disease score, pRBC: packed red blood cells, FFP: fresh frozen plasma, INR: international normalized ratio.

0.4–24.6, interquartile range [IQR]: 1.5–2.6 mmol/L, n = 1,741), but it was markedly increased intraoperatively to a median LA level of 4.4 mmol/L (range: 0.5–34.7, IQR: 3.0–6.2 mmol/L, n = 3,338) (Fig. 1).

A total of 1,884 (56.4%) patients had intraoperative LA levels > 4.0 mmol/L, and while 188 (5.6%) had intraoperative LA levels > 10 mmol/L.

Distribution of intraoperative LA according to MELDs

When the patients were grouped according to MELDs of < 15 (n = 1,807, 54.1%), 15–35 (n = 1,169, 35%), and > 35 (n = 362, n = 10.8%), preoperative LA levels increased and separated clearly along with the increase of MELDs (1.8, IQR: 1.4–2.3 vs. 2.0, IQR: 1.5–2.6 vs. 2.6, IQR: 1.9–4.2 mmol/L, respectively; P < 0.001), whereas, despite the marked increase of intraoperative LA levels, the separation of LA levels were modest and somewhat inversed (4.5, IQR: 3.2–6.3 vs. 4.3, IQR: 2.9–6.2 vs. 4.1, IQR: 2.7–6.0, respectively; P = 0.002) compared to preoperative LA (Fig. 2).

Prognostic cutoff values of intraoperative LA

To predict 30-day all-cause mortality, tree-structured survival analysis using CART of a recursive partitioning algorithm demonstrated that intraoperative LA cutoffs of 13.5% and 16.7% were found to be optimal. In addition, maximally selected log-rank statistics of the "maxstat" R package revealed that LA cutoffs of 8.4% were the best cutoff for predicting for 90-day all-cause mortality (Fig. 3).

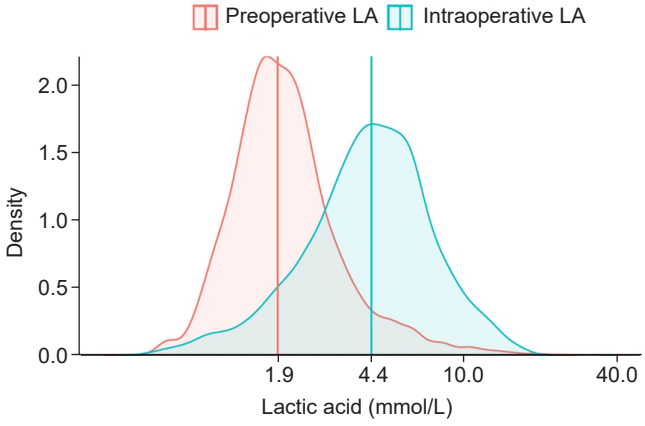

Fig. 1. Distribution of preoperative and intraoperative lactic acid. Vertical line indicate median lactic acid level. LA: lactic acid.

Application of thresholds of LA to predict early mortality

The 30-day and 90-day mortality rates were 2.5% (n = 83) and 4.7% (n = 157), respectively.

When the patients were grouped according to the best cutoff values of 8.4 mmol/L, those with LA > 8.4 mmol/L yielded a 30-day mortality rate of 6.7% and a 90-day mortality rate of 9.4% (P < 0.001) (Fig. 4). In particular, derived LA cutoffs of 16.7% and 13.5% by CART to predict 30-day mortality showed a wide separation of the KM curve. Patients with LA levels > 16.7 mmol/L and 13.5–16.7 had significantly higher 30-day mortality rates of 58.3% and 21.2%, respectively, compared to those with LA < 13.5 mmol/L, who had a 2.1% 30-day mortality rate (log-rank P < 0.001) (Fig. 4).

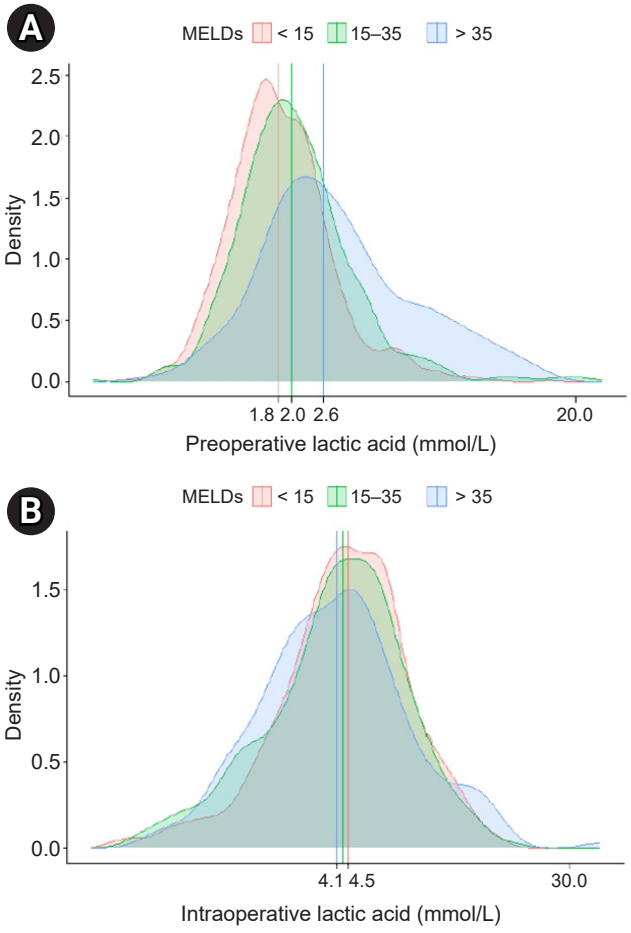

Fig. 2. Distribution of (A) preoperative and (B) intraoperative lactic acid levels according to liver disease severity. Vertical lines indicate median lactic acid. MELDs: model for end-liver disease score.

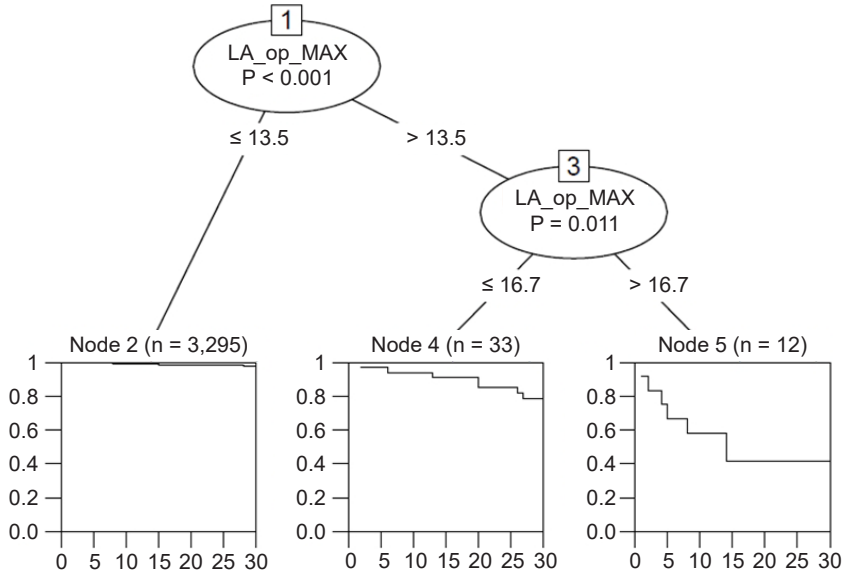

Fig. 3. Decision tree diagram for 30-day mortality, showing intraoperative lactic acid cutoffs of 13.5 mmol/L and 16.7 mmol/L as optimal cutoffs in predicting 30-day all-cause mortality. LA: lactic acid, LA_op_MAX: lactic acid_intraoperative_maximal value.

DISCUSSION

It has long been known that LA levels might reflect critically ill hepatic patients and are independently associated with the short-term mortality affiliated with end-stage liver disease (ESLD) [6,13,14].

In fact, the LA levels and its clearance are known predictors of the outcome of critically ill patients in the intensive care unit [15]. There has been widespread research, especially in septic patients, that evaluate the use of LA as a potential resuscitation marker or prognosticator. Therefore, the Surviving Sepsis Campaign Bundle suggested that if the initial LA is > 2 mmol/L, it should be remeasured within 2–4 h. Moreover, if the LA is > 4 mmol/L in those with sepsis, the initiation of rapid administration of > 30 ml/kg crystalloid is strongly recommended in sepsis [16].

However, lactate metabolism in cirrhosis differs substantially from that in patients without hepatic impairment. In the current study, we found that approximately 50% patients are associated with preoperative LA > 2 mmol/L, confirming that the LA level in patients with ESLD is quite different from those without ESLD. Therefore, management guidelines proposed "repeated measurement of blood lactate levels, even though the interpretation may be complicated by impaired clearance in cirrhosis" [17].

Furthermore, we found that 1,884 (56.4%) patients showed intraoperative LA > 4.0 mmol/L, and 188 (5.6%) exceeded intraoperative LA of 10 mmol/L. These rates are surprisingly high, given that LA levels > 10 mmol/L are associated with high mortality rates of 80% or more in critically ill patients [15,18]. In the current study on intraoperative LA exploration, patients with LA > 16.7 mmol/L and 13.5–16.7 mmol/L demonstrated significantly higher 30-day mortality rates of 58.3% and 21.2%, respectively.

LT is often an extremely difficult event for ESLD patients because LT recipients frequently suffer from severe hypotension, acute blood loss with extreme anemia, massive transfusion, inferior vena cava clamping, prolonged refractory hypotension with high-dose vasopressors, perturbed hemodynamics shortly after graft reperfusion, and/or pr-existing multiple organ failures, such as circulatory, respiratory, and kidney failures [12,19]. Additionally since initial grafts can poorly handle lactate load and may serve as a lactate-producing organ, intraoperative LA concentration is not only extremely high compared with preoperative LA, but also remains high regardless of increasing MELDs during LT surgery. It is thought that high intraoperative LA levels regardless of MELDs are likely to be due to the initial poor graft function and lactate-producing liver itself.

On the other hand, given that acidosis and hyperlactatemia can occur independently, hyperlactatemia might only be moderately predictive for acidosis. Both acidosis and lactate independently predicted mortality in critically ill patients suffering from sepsis [20]. Additionally, it has been reported that lactate clearance calculated at 6 h after reperfusion of an allograft was associated with the development of

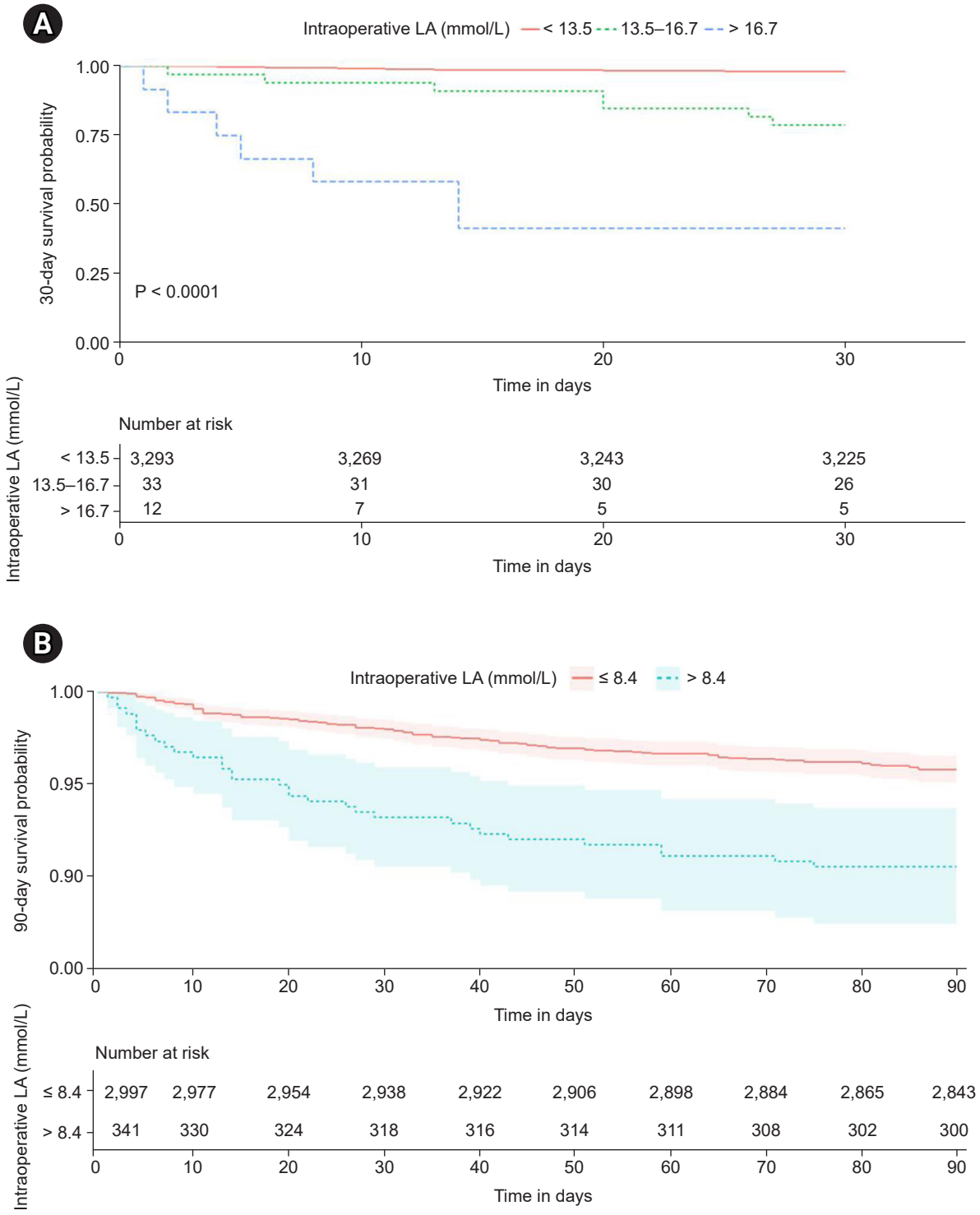

Fig. 4. Kaplan-Meier survival plot shows 30-day mortality according to intraoperative lactic acid > 16.7 mmol/L, 13.5-16.7 mmol/L and < 13.5 mmol/L (A) 90-day mortality according to intraoperative lactic acid > 8.4 mmol/L and 8.4 ≤ mmol/L (B). LA: lactic acid.

early allograft dysfunction and in-hospital and 6 m mortalities after deceased donor liver transplantation [5]. In the current study, we did not evaluate the combining acidosis and hyperlactatemia and lactate clearance; therefore, further study including both of the aforementioned in a model will yield higher predictiveness of the short-term outcome in patients undergoing LT.

This study has several limitations. The enrolled patients

are from the observational cohort study in a single center and retrospective observational design. Therefore, further prospective randomized control studies are warranted to validate our results. Additionally, higher LA resulted in higher mortality rates, but did not completely exclude factors other than LA. Therefore, future study is needed to consider non-LA factors in patients with LT.

In conclusion, in this large cohort LT study determining cutoff levels of intraoperative LA, patients with LA > 13.5 mmol/L showed significantly higher 30-day mortality rates, and > 8.4 mmol/L was the optimal cutoff value for the 90-day mortality. Therefore, identifying intraoperative cutoffs of LA and correction of hyperlactatemia may play a potential role in lowering early mortality rates after LT.

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable reques.

AUTHOR CONTRIBUTIONS

Conceptualization: Gyu-Sam Hwang. Data curation: Kyoung-Sun Kim. Formal analysis: Sang-Ho Lee. Methodology: Sang-Ho Lee, Bo-Hyun Sang. Writing - original draft: Kyoung-Sun Kim. Writing - review & editing: Gyu-Sam Hwang. Investigation: Sang-Ho Lee, Bo-Hyun Sang. Supervision: Bo-Hyun Sang, Gyu-Sam Hwang.

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