

Influencing factors of serum lactate in patients undergoing partial hepatectomy with fluid restriction: a prospective cohort study

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Research article

Keywords: serum lactate, lactate clearance rate, portal triad clamping, hepatectomy, fluid restriction

Posted Date: August 20th, 2019

DOI: <https://doi.org/10.21203/rs.2.13242/v1>

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Abstract

Background: This prospective cohort study was designed to investigate the factors related to serum lactate in hepatectomy patients with fluid restriction before resection of liver lesions. **Methods:** Patients for an open procedure for elective partial hepatectomy were chosen for this study. Limited fluid was infused at a rate of $6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ before liver resection. The infusion speed was increased after resection of liver lesion. Stable hemodynamics was maintained by additional fluid infusion or vasoconstrictor drug. An additional infusion of 200 ml crystalloid liquid over ten min was given when urine output was less than 20ml/h, and/or when systolic blood pressure was less than 90mmHg for 1 minute and for more than 3 times. An injection of 6mg Ephedrine was given when the systolic blood pressure was less than 90 mm Hg for 1 minute. The duration of portal triad clamping, the central venous pressure (CVP), the frequency of additional fluid infusion, the frequency of ephedrine, and the intraoperative blood loss were recorded. The serum lactate was measured from arterial blood-gas analysis at 4 time points: T1: before anesthesia; T2: after liver dissection, and immediately before liver resection; T3: 10 min after the liver lesion was removed; and T4: before the patient was discharged from the post-anesthesia care unit. The lactate clearance rate was calculated and linear regression analysis was employed to identify the relationship between serum lactate level and the influence factors. **Results:** The highest serum lactate was observed at T3 in all 110 patients. Lactate clearance rate averaged $14.4\pm 17.2\%$ in all patients. The influence factors contributed to the highest serum lactate listed by level of importance: duration of portal triad clamping, frequency of ephedrine, operation time. **Conclusions:** Hepatic portal clamping can result in the increase of serum lactate. The inadequate perfusion of organ during the fluid restriction may be due to increased serum lactate. Accelerated fluid infusion after resection of liver lesions can improve the tissue perfusion. **Trial registration:** The registration number is ChiCTR1900023167. Retrospectively registered on 14th, May, 2019

Background

Arterial lactate concentration has been considered as a factor related to tissue oxygenation and perfusion state. Lactate clearance rate has been used as an indicator of tissue perfusion and oxygenation improvement [1]. Both serum lactate and lactate clearance rate could be used to guide clinical treatment and as a precise evaluation of the prognosis [2,3,4]. Decreased lactate clearance was related to liver disease during early sepsis resuscitation [5]. It was reported that serum lactate might be associated with peak post-operative bilirubin, prothrombin time, renal dysfunction, length of hospital stays and 90-day mortality. Compared to patients with a post-operative lactate $\leq 2 \text{ mmol/L}$, the 90-day mortality in patients with lactate $\geq 6 \text{ mmol/L}$ increased from 0.7% to 28% [6].

To reduce bleeding during liver resection, hepatic portal triad clamping (PTC, referring to the temporary clamping of hepatic artery, portal vein, and bile duct) is routinely used in half of medical centers [7]. Intermittent PTC during hepatectomy may induce warm ischemia in the whole liver parenchyma, which causes higher intraoperative lactate levels [2,3].

Minimizing blood loss should be a consideration of both the surgeon and anesthesiologist [7,8]. It is now accepted that massive blood loss and blood transfusion is more damageable to liver parenchyma than prolonged continuous warm ischemia [9,10]. Several studies have shown that the fluid restriction before hepatectomy was necessary for reducing bleeding [11,12]. Intravascular volume plays a prominent role in maintaining tissue perfusion and lactate level within a normal range. Previous research showed no significant increase in lactate level during esophagus surgery with fluid restriction [13]. However, the effect of limited infusion on the lactate concentration in patients undergoing partly hepatectomy is not clear.

This study was designed to investigate the effect of perioperative care on serum lactate and lactate clearance in hepatectomy patients. Fluid infusion was restricted before liver lesions being removed. A stable hemodynamics was maintained by additional fluid infusion or vasoconstrictor drug. The serum lactate was measured during the perioperative period.

Materials And Methods

1. The study was approved by the ethics committee of Peking University Cancer Hospital & Institute Beijing, China on Dec. 2017. The protocol number is 2017KT107. The trial was registered at Chinese Clinical Trial Registry. The registration number is ChiCTR1900023167. The patients undergoing elective partial hepatectomy by open procedure during 2018.12 - 2019.7 were chosen as the candidate for this study in our hospital. Written informed consent was taken from each participant before surgery. The patients with no cirrhosis or with cirrhosis grading below CHILDA were selected. The disease types included primary hepatocellular carcinoma and colorectal cancer liver metastasis. Exclusion criteria were an age of 17 years younger, age older than 75 years, a hemoglobin level of lower than 9g/dL, repeated liver resections or general condition \geq III on American Society of Anesthesiologists (ASA) scale. Patients with a history of hypertension or diabetes with uncontrolled hypertension/ blood glucose were excluded from this study. One hundred and ten patients were enrolled prospectively in the study and no one dropped out. The central venous catheter was inserted in the internal jugular vein or subclavian vein one day before surgery, and the position of the catheter was tested by chest X ray. The routine monitoring of ECG, pulse oxygen saturation, end-tidal carbon dioxide, invasive arterial pressure, urine output, CVP, and bispectrum index (BIS) were performed after the patient entered the operation room.

2. Fluid regimen and anesthetic techniques Intraoperative fluid was maintained by colloid and crystalloid. The rate of fluid infusion was limited to 6 ml·kg⁻¹·h⁻¹ from the moment of patient entering the operating room to right before the liver lesion was removed. When urinary output was less than 20 ml/h, an additional fluid infusion of 200 ml crystalline solution was given over a period of 10 mins. When systolic blood pressure (SBP) was below 90mmHg for 1 min, and more than 3 times, an additional fluid infusion of 200 ml crystalline solution was given over a period of 10 mins. When the liver lesion was removed, the fluid infusion rate was increased to 1000–1500 ml/h. Packed red blood cells were transfused when the hemoglobin was less than 8g/dl.

Anesthesia was induced with midazolam 1mg intravenous (IV), sufentanil 0.4–0.5ug/kg IV, CIS atracurium 0.2 mg/kg IV, propofol 2–2.5mg/kg IV followed by endotracheal intubation. General anesthesia was maintained with inhalation of 1% sevoflurane and intravenous infusion of propofol and remifentanil to keep BIS between 40 and 50. Mechanical ventilation in all patients was performed with 50% oxygen, which was adjusted to maintain end-tidal carbon dioxide between 35–45mm Hg. Ephedrine 6mg was injected when SBP was less than 90 mm Hg for 1 minute. All patients were sent to the post-anesthesia care unit (PACU) after surgery. The patient was moved back to the ward after the endotracheal tube was removed in the PACU.

3. Patients' Demographic data, surgical treatment, operation time, frequency of ephedrine, frequency of additional fluid infusion of 200ml crystalline solution, intraoperative urine output, and blood loss were recorded. The extent of liver resections was divided into major resection and minor resection. The major hepatic resection was defined as resection of more than three or more segments. The extent of liver resections was assessed by hepatobiliary surgeons. The overall duration of PTC and the value of CVP were recorded. The serum lactate was measured from an arterial blood-gas analysis at the following time points: before anesthesia (T1), after liver dissection and immediately before liver resection (T2), 10 min after the liver lesion was removed (T3), and before the patient was discharged from the PACU (T4). Lactate clearance was calculated as following: $\text{Lactate clearance} = \frac{\text{serum lactate at T3} - \text{serum lactate at T4}}{(\text{time interval (h) of T3 and T4} * \text{serum lactate at T3})} * 100\%$. The mean values of the maximum and minimum values of CVP measured during liver resection was used as CVP values.

4. Outcome and sample size calculation: The primary outcome of interest was serum lactate. The secondary outcomes were frequency of ephedrine, frequency of additional fluid infusion of 200ml crystalline solution, intraoperative blood loss, duration of PTC, the mean value of CVP during hepatectomy.

Sample size was estimated with PASS software (version 11.0; NCSS, LLC, Kaysville, UT, USA). Sample size was calculated based on preliminary trial for 10 patients conducted by the authors, and estimated standard deviation of serum lactate was 2.0 mmol/L. The procedure of confidence intervals for one mean was selected with a confidence interval of 95% with a distance from the mean to the limits of 0.5. The sample size calculated was 96 patients. Therefore, a total of 110 patients were recruited for possible dropouts.

5. Statistical analyses: All statistical analyses were performed by SPSS software (SPSS 18.0 for Windows; SPSS Inc., Chicago, IL, USA). All data were tested for a normal distribution. Data that were normally distributed were expressed as mean value \pm standard deviation ($X \pm SD$). Repeated measures ANOVA was used to compare mean differences of serum lactate at T1, T2, T3, T4. Non-normally distributed data were expressed by median and interquartile range. Multivariate linear regression analysis was employed as the primary analysis to identify the relationship between serum lactate level or lactate clearance and influencing factors. The influencing factors includes presence of cirrhosis, mean CVP value during hepatectomy, the duration of all PTC, the frequency of ephedrine, the frequency of additional fluid

infusion, blood transfusion requirement, the extent of liver resections, operation time, intraoperative blood loss and output. Selection of variables was based on literature and physiologically and clinically valid model of the phenomenon being studied. A subgroup analysis was performed. All the patients were divided into two subgroups according to portal triad clamping or not. The independent sample t test was used to compare data between two subgroups. A value of $P < 0.05$ was considered statistically significant.

1. Demographic data

There were 90 males and 20 females, a total of 110 patients, with an age range of 26 - 70 years enrolled in this study. No patient dropped out, thus data from 110 patients was available for analysis. The patients were selected for elective partial hepatectomy by open procedure due to primary liver carcinoma ($n = 50$) or liver metastases following colorectal cancer ($n = 60$) in our hospital. Demographic data are shown in table 1. Thirty-two patients with hepatitis B virus (HBV) and 2 patients with hepatitis C virus (HCV) related chronic hepatitis presented liver cirrhosis. Three patients with HBV infection related chronic hepatitis did not present liver cirrhosis. Drug induced liver cirrhosis was found in 1 patient. Alcohol abuse induced liver cirrhosis was found in 2 patients. Liver cirrhosis was determined by pathology diagnosis.

Insert table 1

2. Clinical details

Intraoperative events and anesthesia details are presented in Table 2. There were 86 patients treated with PTC and 24 patients without PTC. The longest total PTC duration was 76 mins and the shortest was 4 mins. The operation time ranged from 51 mins to 464 mins. The maximum and minimum intraoperative blood loss was 1200 ml and 50 ml respectively. Fifty-three patients didn't require ephedrine, and the most frequent administration of ephedrine was 5 times. The mean value of CVP during hepatectomy ranged from 1 to 9 mm Hg.

Insert table 2

3. In all 110 patients, the highest level of serum lactate was observed at T3. As shown in figure 1. The result of repeated measures ANOVA showed that serum lactate differed significantly ($F = 108.233$, $P < 0.001$) at T1, T2, T3, and T4.

Insert figure 1

4. Influence factors contributed to the high levels of serum lactate at T3, listed by level of importance: duration of PTC, the frequency of ephedrine, operation time. No significant correlation was detected at any time point between lactate concentrations and other factors such as presence of cirrhosis, mean CVP value during hepatectomy, blood transfusion requirement, the extent of liver resections, intraoperative blood loss, and intraoperative output. The coefficients of linear regression see table 3.

Insert table 3

5. Lactate clearance rate was positive in 100 of the 110 patients. Lactate clearance rate averaged $14.4 \pm 17.2\%$ in all patients, with a maximum value of 67.1%, and a minimum value of -67.3% . Data from patients with negative lactate clearance rate is listed in table 4.

Insert table 4

6. Subgroup analysis: Subgroup analysis was performed for subgroups according to portal triad clamping or not. In this study, 86 of the 110 patients were treated with PTC and 24 patients without PTC. As shown in Figure 2, compared with patients without PTC, a significant increase in the level of serum lactate in the patients with PTC was observed at both T3 and T4 ($t = 4.143$, $P < 0.05$ and $t = 4.273$, $P < 0.05$).

Insert figure 2

Discussion

In this study, the duration of hepatic portal obstruction ranged from 4 min to 76 min. The highest serum lactate level was observed 10 mins after the end of resection of liver lesion (T3). Serum lactate at T3 increased in accordance with the prolongation of PTC. During a hepatectomy, the clamping of inflowing blood vessel and squeezing of liver parenchyma lead to a malfunction of liver to metabolism lactate, which could lead to an increase of serum lactate and a decrease of lactate clearance. On the other hand, anaerobic metabolism caused by hepatic warm ischemia during the period of PTC is most likely another reason of high serum lactate [2,6].

Our study showed that hepatic portal clamping had an obvious effect on the level of serum lactate. Eighty-six of the 110 patients underwent PTC. Compared with the 24 patients without PTC, serum lactate increased significantly at 10 minutes after the liver lesion was removed in patients with PTC. Pietsch UC et. al [2] showed that Pringle maneuver significantly increased arterial lactate levels during liver resection with a maximum at 10 mins after the end of liver resection, and the intraoperative serum lactate in the patients without clamping increased gradually. In our study, we didn't observe the tendency of serum lactate increasing after liver resection in patients without PTC. This discrepancy might be due to a difference in the grouping of patients. In Pietsch UC's study, the patients were randomly divided into 2 groups either to be or not to be treated with the Pringle maneuver. In the present study, the use of PTC was determined according to the location and size of the liver mass by surgery. Thus, the choice of surgical procedures and PTC was not based on the purpose the present study. This might cause the different results from the previous study.

There were 37 cases of cirrhosis in our study. The increase of serum lactate at 10 mins after the end of liver resection showed no correlation with cirrhosis. This result is consistent with previous research, which showed that the serum lactate level was not higher in abnormal liver parenchyma after liver resection [3].

However, it is worth noting that patients with cirrhosis above grade CHILDA were excluded from this study.

A central venous pressure (CVP) of less than 5mm Hg was an optimal level for reducing blood loss during hepatic resection [14–18]. To maintain a low CVP, fluid restriction before live resection was used in 85% medical centers [7]. In this study, CVP was reduced by fluid restriction before the removing of hepatic lesion. The mean CVP value was 4.3 ± 1.6 mm Hg during liver resection for all participants. There was no correlation between serum lactate and CVP value observed during resection. We limited infusion at $6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ before resection of liver lesions in this study. CVP failed to drop below 5 mm Hg in 27 patients of 110 patients. The limitation of our study is that the CVP of some patients cannot be reduced to less than 5 mm Hg by limited infusion alone.

Our study showed that the high dose of ephedrine required for blood pressure support was associated with the increase of serum lactate level. Ephedrine 6mg was injected when the systolic blood pressure was less than 90 mm Hg for more than 1 minute. The more frequency of ephedrine was given the more frequency of hypotension was observed. It's likely that the inadequate perfusion of organ during the fluid restriction contributed to the increased serum lactate.

In this study, the longer operation time was related to increased serum lactate at T3. All patients were treated by the same surgery team. Therefore, the duration of operation depended on the difficulty of operation, which was decided by the size and/or the location of the lesions. A longer operation time means longer squeezing of liver parenchyma or longer clamping of inflowing blood vessel, which impaired the ability of the liver to metabolism lactate [2].

The lactate clearance rate was the rate of decline in serum lactate level from T3 to T4 in this study. In 100 of the 110 patients, the highest concentration of serum lactate was observed at 10 minutes after liver resection, and the lactate clearance rate was positive. A positive lactate clearance rate suggested that tissue perfusion and oxygen supply were improved after the liver lesion was removed. The cause of the decline in serum lactate may be related to the accelerated fluid infusion after the resection of liver, and /or the recovery of liver blood flow. In the rest 10 patients, lactate clearance rate showed a negative value, and the highest serum lactate level was observed at the time of leaving PACU. The pulse oxygen saturation in 1 of the 10 patients decreased after extubation in the PACU, which was considered as atelectasis, and the pulse oxygen saturation was improved after treatment. The lactate clearance was negative for a patient with post-operation shiver. In 3 of the remaining 8 patients, the negative lactate clearance rate may be due to large blood loss and blood transfusion. The other 5 patients with negative lactate clearance rate had no specific events during operation and in PACU. It is worth noting that a relatively low level of serum lactate ranging from 0.8mmol/L to 1.5 mmol/L was observed when leaving the PACU in the other 5 patients. All patients returned to the ward and were discharged smoothly.

In conclusion, hepatic portal clamping can result in increased serum lactate. The inadequate perfusion of organ during the fluid restriction may lead to increased serum lactate. Accelerated fluid infusion after

resection of liver lesions can improve oxygen metabolism and tissue perfusion.

List Of Abbreviations

CVP: central venous pressure

PTC: portal triad clamping

SBP: systolic blood pressure

PACU: postanesthesia care unit

BIS: bispectral index

ETCO₂: end-tidal carbon dioxide

IV: intravenous

HBV: hepatitis B virus

HCV: hepatitis C virus

Declarations

Ethics approval and consent to participate: We declare that this study has obtained the report of ethics board approval and informed consent obtained from each participant has been written before surgery. The study was approved by the ethics committee of Peking University Cancer Hospital & Institute, Beijing, China on Dec. 2017. The protocol number is 2017KT107.

Consent for publication: Not applicable

Availability of data and material: The datasets generated during the current study are available in the <http://www.medresman.org/login.aspx>, and the number is ChiCTR1900023167.

Competing interests: non-financial competing interests

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions: Hongyu Tan, as a corresponding author, substantially contributed to the article as the conception and design of the work and manuscript revision. Ling Yu, as the first author, substantially contributed to the article as literature research, case collection and writing the manuscript. Hongwei Sun was a major contributor in case collection and interpretation of data. Huangmo Jin was a major contributor in literature research, case collection and manuscript preparation. All authors read and approved the final manuscript.

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Tables

Table 1 Demographic data of 110 patients undergoing liver resection

Variable	Data
Age (X±SD) (years)	54.9±9.5
Chronic HBV infection (n)	35
Chronic HCV infection (n)	2
Presence of cirrhosis (n)	37
Primary liver carcinoma (n)/liver metastases (n)	50/60
Major liver resection (n)/ minor liver resection	40/70
Comorbidities (n)	
Hypertension/ Coronary artery disease/ Diabetes/ chronic bronchitis/ Alcohol abuse	19/10/7/2/2

HBV: hepatitis B virus; HCV: hepatitis C virus

Table 2 Intraoperative events and anesthesia details

Variable	Data
The duration of all PTC (N=86) X±SD min	28.1±16.3
blood transfusions requirement(n)	6
The duration of operation X±SD min	192.2±71.3
Urine output, M (P25, P75) ml	200 (100,300)
Blood loss, M (P25, P75) ml	200 (100,400)
Mean CVP during resection (X±SD mm Hg)	4.3±1.6
Frenquency of additional infusion (0/1/2/more than 3) (n)	68/32/9/1
Frequency of ephedrine (0/1/2/more than 3) (n)	53/21/20/16

PTC: portal triad clamping; CVP: central venous pressure.

Table 3 The coefficients^a of multivariate linear regression

	Unstandardized		Standardized	T-value	P-value
	Coefficients		Coefficients		
	B	Std. Error	Beta		
Constant	.998	.305		3.266	.001
0=no cirrhosis 1=cirrhosis	-.065	.152	-.032	-.427	.670
mean CVP value during hepatectomy	-.062	.047	-.103	-1.339	.184
Duration of all PTC	.030	.005	.576	6.002	.000
frequency of additional fluid infusion	-.228	.124	-.174	-1.841	.069
frequency of ephedrine	.172	.060	.217	2.889	.005
0=minor resection; 1=major resection	-.002	.166	-.001	-.013	.990
0=no blood transfusion 1=blood transfusion	-.357	.440	-.085	-.812	.419
intraoperative blood loss	.000	.001	-.086	-.591	.556
operation time	.003	.001	.255	2.277	.025
intraoperative output	.000	.001	.064	.706	.482

a: dependent variable: serum lactate at 10 min after the liver lesion was removed. CVP: central venous pressure; PTC: portal triad clamping

Table 4 Data from patients with negative lactate clearance rate

Lactate clearance rate	Serum lactate at T3 (mmol/L)	Serum lactate at T4 (mmol/L)	blood loss(ml)	Blood transfusions	Duration of PTC(mins)	Events in PACU
-67.3%	1.6	2.3	1200	4u	35	None
-36.7%	2.5	4.0	100	0	19	Postoperative shivering
-17.5%	2.3	3.3	150	0	15	SpO2 decreased after extubation
-12.1%	3.2	3.6	800	4u	40	None
-11.2%	0.8	1.1	100	0	0	None
-9.7%	2.2	2.8	1000	2 u	21	None
-9.6%	0.8	0.9	100	0	0	None
-6.6%	1.1	1.3	100	0	0	None
-3.7%	1.4	1.5	400	0	12	None
-3.3%	1.3	1.4	300	0	0	None

T3: 10 min after the liver lesion was removed; T4: before the patient was discharged from the PACU; PTC: portal triad clamping; PACU: postanesthesia care unit; SpO2: pulse oxygen saturation

Figures

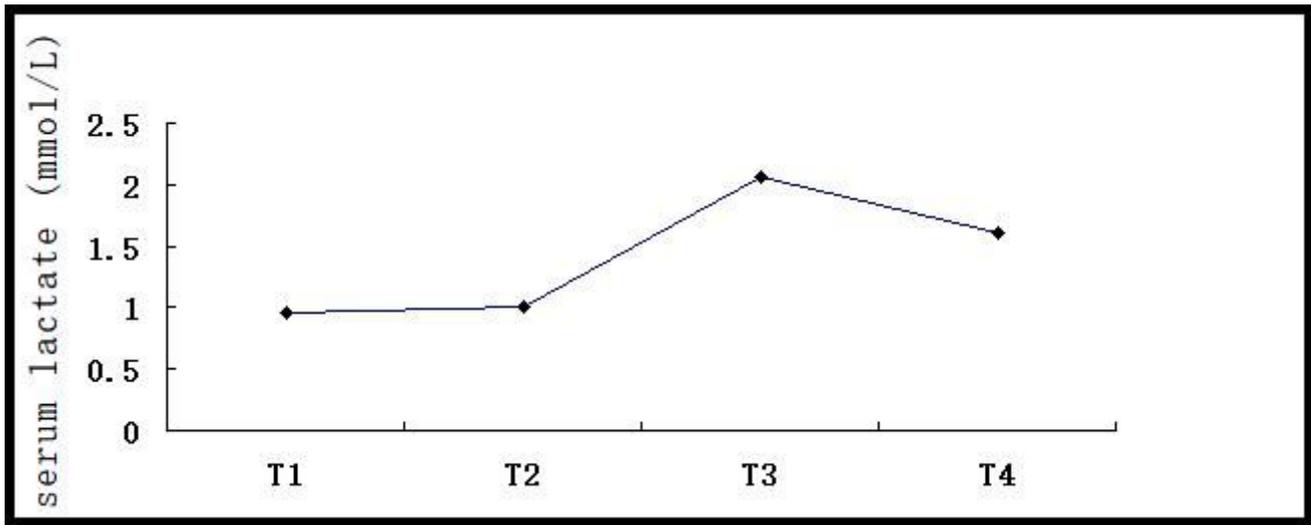


Figure 1

Serum lactate in all patients (n=110). T1: before anesthesia, T2: after liver dissection and immediately before liver resection, T3: 10 min after the liver lesion was removed, T4: before the patient was discharged from the PACU.

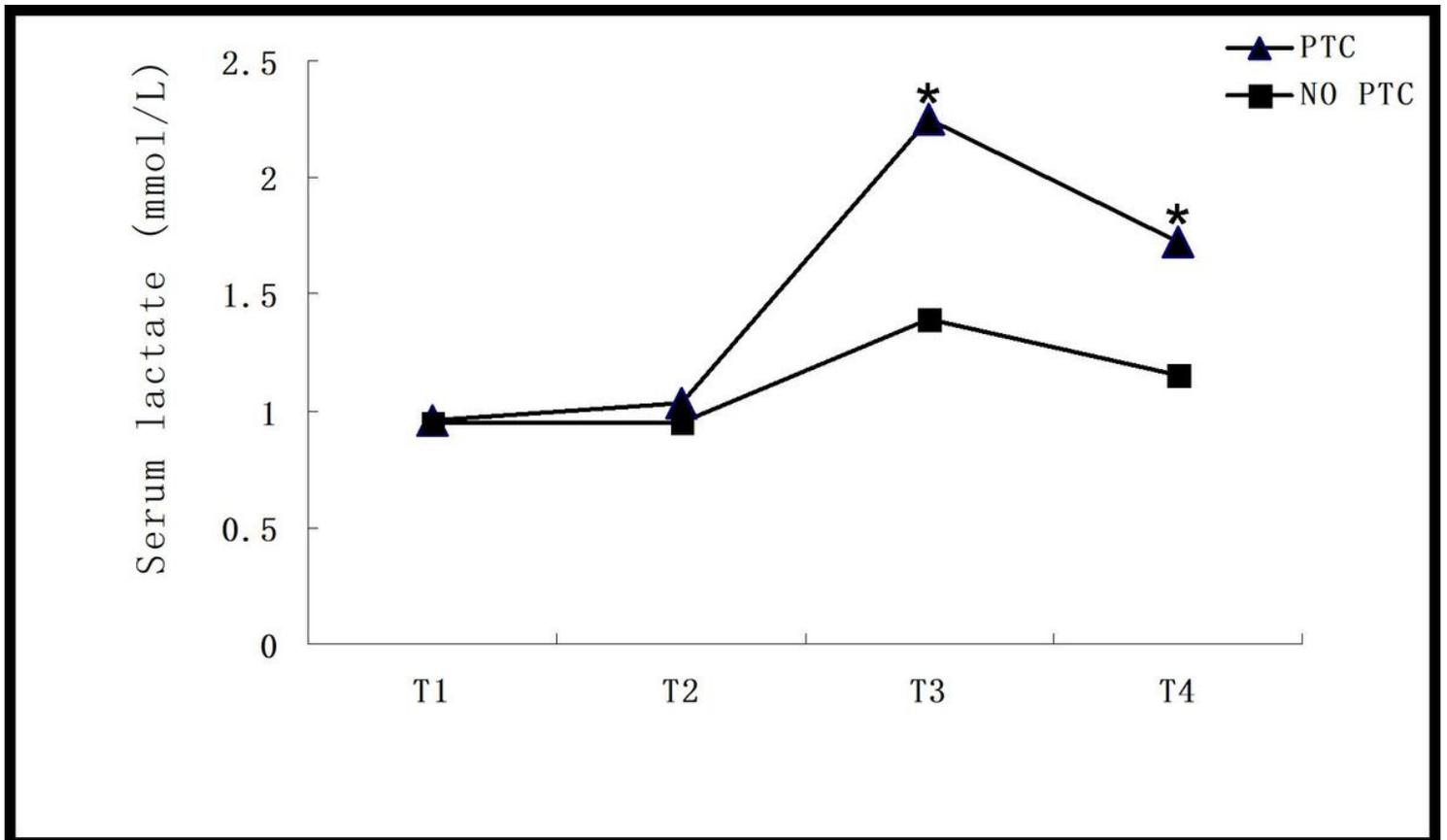


Figure 2

Serum lactate in patients with and without PTC at perioperation. Comparison between patients with and without PTC * $P < 0.05$ T1: before anesthesia, T2: after liver dissection and immediately before liver

resection, T3: 10 min after the liver lesion was removed, T4: before the patient was discharged from the PACU.

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