Original Article

DOI: 10.5582/bst.2018.01004

Neither ischemic parenchymal volume nor severe grade complication correlate transient high transaminase elevation after liver resection

Tokio Higaki, Shintaro Yamazaki*, Yusuke Mitsuka, Masaru Aoki, Nao Yoshida, Yutaka Midorikawa, Hisashi Nakayama, Tadatoshi Takayama

Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan.

Summary **To clarify whether high transient elevation of serum transaminase predicts severe complications and is related to the ischemic area on CT. Postoperative laboratory data and ischemia area on CT were analyzed on the basis of the presence of high transaminase elevation (aspartate aminotransferase (AST) > 1,000 IU/L within postoperative day (POD) 2 after liver resection. In the high elevation group, volume of ischemic areas was assessed by CT on POD2. The 538 patients were divided into a high transaminase group (n = 51) and a control group (n = 487). Median operation time (527 min *vs*. 360 min, $p < 0.01$) and liver ischemia time (121 min *vs*. 70 min, $p < 0.01$) were significantly longer, and intraoperative blood loss (478 mL [85-1572 mL] *vs*. 269 mL [5-4491 mL], $p < 0.01$) was significantly greater in the high transaminase group. No significant differences observed in frequency of severe complications (Clavien-Dindo classification Grade III or more) or postoperative hospitalization. Operation time (> 500 min; odds ratio (OR), 4.86; 95% confidence interval (CI), 2.40-9.89; $p < 0.01$) and liver ischemia time (> 120 min; OR, 3.47; 95%CI, 1.67-7.17; $p < 0.01$) were independent predictors of high transaminase elevation. No relationship was observed between degree of transaminase elevation and ischemic area (correlation coefficients: AST, $R^2 < 0.001$; alanine aminotransferase, $R^2 = 0.005$) CT volumetry on POD2. In conclusions, high transaminase elevations do not predict severe complications or reflect remnant ischemic area.**

Keywords: CT volumetry, serum transaminase level, clavien-dindo classification

1. Introduction

Recent liver resection for cancer has been performed with satisfactory operative morbidity and mortality (*1-5*). Serum transaminase levels are a most convenient and reliable indicator of liver ischemia following surgery (*6-7*). Serum transaminase levels easily increase following liver transection, hepatic pedicle clamping during liver resection and other operation-related factors (*6,8,9*). However, the increase in serum transaminases was commonly transient and recovered to within normal ranges for the first 7 days postoperatively.

**Address correspondence to:*
Dr. Shintaro Yamazaki, Department of Digestive Surgery, Nihon University School of Medicine, 30-1 Oyaguchikami-machi, Itabashigh ku, Tokyo 173-8610, Japan.
E-mail: yamazaki-nmed@umin.ac.jp

High elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in the early postoperative period are considered one of the phenomena reflecting severe complications. Because, the lack of remnant liver parenchyma or wide ischemic area in the remnant liver after resection may be the principal issues leading to severe complications (*5*). Therefore, surgeons pay attention to high postoperative transaminase levels as a marker of crisis.

In clinical situation, we sometimes encountered high elevation of transaminase (≥ 1,000 IU/L) after liver resection however, the importance of this issue remains unsettled. (*6*) No studies to date have analyzed the area of ischemia at the time of high transaminase elevation. Thus, we routinely checked the postoperative liver ischemic area on POD2 to clarify whether a high transaminase elevation predicts severe complications and reflects the ischemic area on CT.

2. Patients and Methods

2.1. *Patients*

We retrospectively analyzed the data of consecutive patients who underwent liver resection for cancers. Perioperative laboratory data were collected before the operation, just after the operation, and on postoperative day (POD) 1, 2, 3, 5, 7, 30, 90 and 180. Then, the patients were divided into two groups according to the presence of high transaminase elevation (AST > 1,000 IU/L) on POD2. Operation-related variables (tumor factors, operation time, liver ischemia time, intraoperative blood loss and procedure) and outcomes in the early period (all complications, severe grade comprications according to Clavien-Dindo classification > grade3 and duration of postoperative hospital stay) were analyzed (10).

2.2. *Volumetry*

On POD2 all patients were routinely performed to check ischemic area and portal vein thrombus. Volumetric analysis was performed when the serum AST level reached ≥ 1,000 IU/L within POD2. Three-phase contrast-enhanced dynamic CT scans (unenhanced and hepatic arterial, portal venous, and liver parenchymal phases) were performed using a 64-detector row scanner (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan). The total dose of nonionic iodinated contrast medium was 600 mgI/kg body weight of iomeprol (350 mgI/mL), administered over the course of 30 s using an automatic injector. Scanning was performed in the arterial phase (37 s), in the portal venous phase (60 s), and in the delayed phase (150 s). Portal-phase images were used for volumetry. When ischemic regions were confirmed on CT, CT-based volumetry was performed using portal venous phase images. The calculation of ischemic liver area has been described elsewhere (*11-13*). Follow-up CT was performed at 1 week and at 1, 3, and 6 months after operation.

2.3. *Surgical procedures*

Anatomical resection of Couinaud's segment was the first-line operative procedure for hepatocellular carcinoma (HCC) when the patient had sufficient functional reserve. In cases of metastatic liver tumor, partial resection with adequate surgical margins was the first-line procedure. Details of the indications and procedures have been described previously (*14-16*). Minor hepatectomy was defined as limited resection or resection of up to two Couinaud's segments. Hepatic parenchymal transection was guided ultrasonographically and performed by the clamp-crushing method with the inflow-blood-occlusion technique, and Glisson's pedicle was tied and divided with silk thread. Standard systemic antibiotic therapy with cefazolin was routinely administered immediately before surgery, then twice daily on POD1-3.

2.4. *Statistical analysis*

Data are expressed as median and range or as absolute value and percentage. Student's t test, the χ^2 test, and Fisher's exact test were used for univariate analysis, as required. Multivariate analysis was performed using logistic regression. Odds ratios with 95% confidence intervals derived from logistic regression analysis were calculated. The period until the onset of infection was analyzed using the Kaplan-Meier method, with comparison by the log-rank test. Values of $P < 0.05$ were considered indicative of statistical significance. All analyses were performed using a statistical software package (JMP version 9.0; SAS Institute, USA).

3. Results

3.1. *Patients*

Between January 2008 and December 2010, a total of 538 patients underwent liver resection for malignancy. These patients were divided into a high transaminase group (n = 51) and a control group (n = 487) according to laboratory data on POD1 (Table 1). Age (median, 64 years [range, 41-84 years] *vs*. 69 years [range, 20-84 years], p = 0.006), proportion of patients with cancer. (HCC, 26 patients [51.0%] *vs*. 342 [70.0%]; p = 0.005 or liver metastasis, 21 [41.1%] *vs*. 112 [22.9%], p = 0.007) differed significantly between groups. Preoperative platelet count was significantly higher (21.2 $mm^3/\mu L$ [range, 6.2-39.5 $mm^3/\mu L$] *vs*. 16.6 $mm^3/\mu L$ [range, 4.2-54.9 $mm^3/\mu L$], p = 0.006), total bilirubin level was lower (0.57 mg/dL [range, 0.31-1.39 mg/dL] *vs*. 0.59 mg/dL [range, 0.19-1.83], p = 0.006) and indocyanine green retention rate at 15 min was better (7.8% [range, 2.3-22.8%] *vs*. 11.45% [range, 1.1-82.3%], p < 0.001) in the high transaminase group. Preoperative serum AST level (p = 0.743), preoperative serum ALT level (p = 0.484) and proportion of Child-Pugh class B cases (p = 0.746) did not differ significantly between groups (Table 1).

3.2. *Surgical outcomes and transaminase levels*

Operation time (527 min [range, 310-752 min] *vs*. 360 min [range, 112-831 min], p < 0.001) and liver ischemia time (121 min [range, 45-243 min] *vs*. 70 min [range, 0-222 min], p < 0.001) were significantly longer in the high transaminase elevation group. Intraoperative blood loss (478 mL [range, 85-1572 mL] *vs*. 269 mL [range, 5-4491 mL], p < 0.001) was significantly greater and number of liver resections (2 [range, 1-20] *vs*. 1 [range, 1-4], p = 0.013) was higher in the high transaminase

Table 1. Characteristics of patients

Items	High transaminase >1,000 IU/L (n = 51)	Control < 1,000 IU/L (n = 487)	p value
Age (years)	64 (41-84)	69 (20-84)	0.006
Sex (male/female)	39/12	340/147	0.323
Presenting illness			
Hepatocellular carcinoma	26 (51.0%)	342 (70.2%)	0.005
Metastatic liver cancer	21 (41.1%)	112 (23.0%)	0.007
Intrahepatic cholangiocarcinoma	2 (3.9%)	14 (2.9%)	0.636
Gallbladder cancer	0 (0%)	7 (1.4%)	0.314
Others	2 (3.9%)	12 (2.5%)	0.571
Platelet account (mm^3/uL)	21.2 (6.2-39.5)	16.6 (4.2-54.9)	0.006
Aspartate aminotransferase (IU/L)	28 (12-213)	36 (9-265)	0.742
Alanine aminotransferase (IU/L)	28 (8-217)	28 (5-296)	0.484
Total bilirubin (mg/dL)	0.57 (0.31-1.39)	0.59 (0.19-1.83)	0.006
Albumin (g/dL)	4.1 (2.7-5.3)	4.0 (2.0-5.3)	0.112
Prothrombin time (%)	100 (78-100)	100 (52-100)	0.347
ICGR15 (%)	7.8 (2.3-22.8)	11.45 (1.1-82.3)	< 0.001
Child-Pugh class B	1 (2.0%)	7 (1.4%)	0.746

Values represent median with range. ICGR15, indocyanine green retention test at 15 min.

Table 2. Surgical outcomes

Items	High transaminase >1,000 IU/L (n = 51)	Control < 1,000 IU/L (n = 487)	p value
Operation time (min)	527 (310-752)	360 (112-831)	< 0.001
Ischemic time (min)	121 (45-243)	70 (0-222)	< 0.001
Intraoperative blood loss (g)	478 (85-1572)	269 (5-4491)	< 0.001
Multiple liver resection	21 (41.2%)	117 (24.0%)	0.013
Anatomical resection	23 (45.1%)	163 (33.5%)	0.097
Major hepatectomy	6 (11.7%)	34 (7.0%)	0.218
Complications (Total)	21 (41.2%)	136 (27.9%)	0.047
Complications (Severe)*	9 (17.6%)	68 (14.0%)	0.474
Postoperative hospital stay (days)	14 (8-38)	12 (8-62)	0.072

Values represent median with range. *Clavien classification grade III or more.

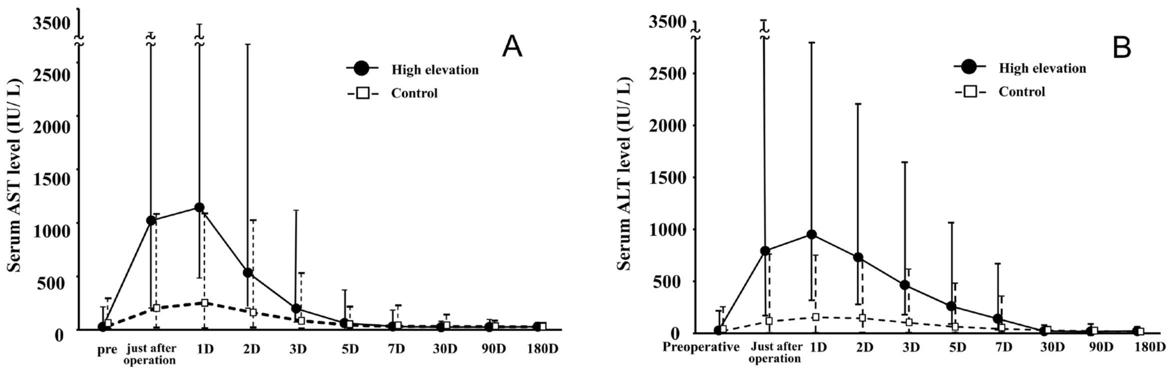

Figure 1. Trends in perioperative serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Transaminase levels increased rapidly just after operation and peaked by POD2 in AST **(A)** and ALT **(B)**. Concentrations then gradually decreased and returned to within normal range by POD7.

elevation group (Table 2). Total number of postoperative complications was significantly higher in the high transaminase elevation group (9 [17.6%] *vs*. 68 [14.0%], p = 0.04), whereas the number of severe complications according to the Clavien-Dindo classification (> Grade III) (p = 0.474) and duration of postoperative hospital stay (p = 0.07) did not differ significantly.

Transaminase levels increased rapidly just after operation and peaked by POD2 (Figure 1A,B). Concentrations then gradually decreased and returned to within normal range by POD7.

3.3. *Multivariate analysis for high transaminase elevation*

Operation-related variables were further analyzed by

Table 3. Multivariate analysis for high transaminase elevation

Items	Odds ratio	95%CI (Hi-Low)	*p* value
Operation time (> 500 min)	4.86	2.40-9.89	< 0.001
Liver ischemia time (> 120 min)	3.47	1.67-7.17	< 0.001
Number of liver resections (single)	1.33	0.67-2.60	0.401
Intraoperative blood loss (> 1,000 mL)	1.24	0.50-3.31	0.642

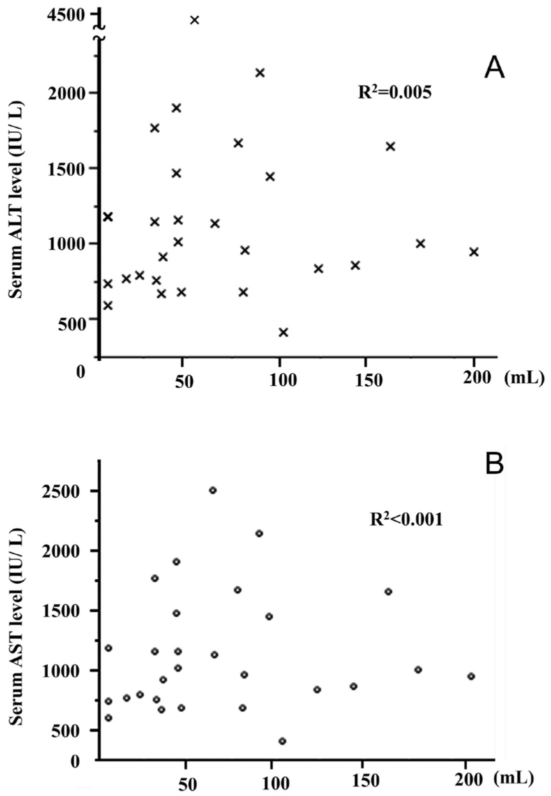

Figure 2. Relationship between serum transaminase level and ischemia area after high transaminase elevation by volumetry. Correlation coefficients are $R^2 = 0.00049$ for serum AST **(A)** and $R^2 = 0.0049$ for ALT **(B)**. No relationship is apparent between transaminase level and liver ischemia area by volumetry.

multivariate analysis regarding influences on high transaminase elevation (Table 3). Operation time > 500 min (odds ratio, 4.86; 95% confidence interval, 2.40-9.89; $p < 0.001$) and liver ischemia time >120 min (odds ratio, 3.47; 95% confidence interval, 1.97-7.17; $p < 0.001$) were independent predictors of high transaminase elevation.

3.4. *Volumetry*

The median volume of ischemia was 63 mL (ranged, 4-210 mL) when the high transaminase elevation was confirmed on POD2. The correlation coefficient of AST was $R^2 < 0.001$ and ALT was $R^2 = 0.005$. No causal relationships were observed between each transaminase level and volume of ischemic area on POD2 (Figure 2A,B).

4. Discussion

We identified operation time (> 500 min) and liver ischemia time (> 120 min) as significant predictors for high transaminase elevation, although this elevation was only transient and did not predict severe complications. Moreover, the ischemic area just after operation did not correlate with the concentration of transaminase.

High serum transaminase levels after liver resection strongly suggest severe damage to the liver parenchyma. Severe liver injury in which transaminase levels exceeded 1,000 IU/L just after the operation has been considered to predict secondary liver failure. The mechanism of injury mainly depends on ischemic reperfusion injury during liver resection or the presence of an ischemic area in the remnant liver at a result of liver resection and other reasons related to the operative procedure. However, whether a significant correlation exists between high transaminase elevation and severe complications remains unclear (*17-19*). Moreover, which factor is the main cause of high transaminase elevation is unclear. The present study revealed that the main cause of high elevation did not reflect the ischemic area in the remnant liver, but rather ischemia time during the operation.

Multivariate analysis revealed operation time (> 500 min) and liver ischemia time (> 120 min) as the significant prognostic factor for high transaminase elevation. However, the occurrence of severe complications and postoperative hospital stay did not differ significantly between groups, because this population had significant better liver functional reserve. Therefore, complex or large-scale liver resections were performed for patients with sufficient liver function. As a result, a large release of liver enzymes is seen from livers with good functional reserve.

Elevation of transaminases is well known to be transient and to subside within one week. In contrast, the recovery of liver parenchyma after liver resection is not fully understood. In the present study, three-phase enhanced CT enabled visualization of the ischemic area in liver parenchyma. This enabled to confirm blood flow in the liver parenchyma phase by phase. Ischemic areas may recover with hypertrophy of the remnant parenchyma or apoptosis of the ischemic liver parenchyma. However, no previous study has shown the relationship between high elevation of transaminases and ischemic area on CT. We found that the median ischemic area on CT volumetry was only 63 mL, even if transaminase level exceeded 1,000 IU/L.

In conclusion, postoperative routine CT on POD2 is useful to check the ischemic area and portal vein thrombus due to the operation procedure. High elevation of transaminases reflects mainly the length of liver resection and does not predict severe complications, even for > 1,000 IU/L. Because it is not correlate to the liver ischemic area after operation.

References

1. Reissfelder C, Rahbari NN, Koch M, Kofler B, Sutedja N, Elbers H, Büchler MW, Weitz J. Postoperative course and clinical significance of biochemical blood tests following hepatic resection. Br J Surg. 2011; 98:836-844.
2. Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, Massucco P. Liver resection for hepatocellular carcinoma on cirrhosis: Analysis of mortality, morbidity and survival – A European single center experience. Eur J Surg Oncol. 2005; 31:986-993.
3. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: Analysis of 1222 consecutive patients from a prospective database. Ann Surg. 2004; 240:698-710.
4. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, Takayama T, Makuuchi M. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg. 2003; 138:1198-1206.
5. Rahbari NN, Garden OJ, Padbury R,*et al*. Posthepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011; 149:713-724.
6. Teramoto K, Nakamura N, Ito K, Kudo A, Noguchi N, Takamatsu S, Kawamura T, Tanaka S, Arii S. Strong association between frequency of intermittent inflow occlusion and transient increase in serum liver enzymes after hepatic resection. Hepatogastroenterology. 2008; 55:636-640.
7. Pelton J, Hoffman J, Eisenberg. Comparison of liver function tests hepatic lobectomy and hepatic wedge resection. Am Surg. 1998; 64:408-414.
8. Noun R, Jagot P, Farges O, Sauvanet A, Belghiti J. High preoperative serum alanine transferase levels: Effect on the risk of liver resection in Child grade a cirrhotic patients. World J Surg. 1997; 21:390-395.
9. Giovannini I1, Chiarla C, Giuliante F, Vellone M, Ardito F, Sarno G, Nuzzo G. Analysis of the components of hypertransaminasemia after liver resection. Clin Chem Lab Med. 2007; 45:357-60.
10. Dindo D, Demartines N, Clavien PA. Classification of Surgical complications. Ann Surg. 2004;240:205-213.
11. Costello P, Duszlak EJ, Lokich J, Matelski H, Clouse ME. Assessment of tumor response by computed tomography liver volumetry. J Comput Tomogr. 1983; 7:323-326.
12. Kawasaki S, Makuuchi M, Matsunami H, Hashikura Y, Ikegami T, Chisuwa H, Ikeno T, Noike T, Takayama T, Kawarazaki H. Preoperative measurement of segmental liver volume of donors for living related liver transplantation. Hepatology. 1993; 18:1115-1120.
13. Honda H, Onitsuka H, Masuda K, Nishitani H, Nakata H, Watanabe K. Chronic liver disease: Value of volumetry of liver and spleen with computed tomography. Radiat Med. 1990; 8:222-226.
14. Yamazaki S, Takayama T, Moriguchi M, Okada S, Hayashi Y, Nakayama H, Higaki T, Sugitani M. Validation of biological and clinical outcome between with and without thoracotomy in liver resection: A matched cohort study. World J Surg. 2012; 36:144-150.
15. Hayashi Y, Takayama T, Yamazaki S, Moriguchi M, Ohkubo T, Nakayama H, Higaki T. Validation of perioperative steroids administration in liver resection: A randomized controlled trial. Ann Surg. 2011; 253:50-53.
16. Yamazaki S, Takayama T, Kimura Y, Moriguchi M, Higaki T, Nakayama H, Fujii M, Makuuchi M. Transfusion criteria for fresh frozen plasma in liver resection. Arch Surg. 2011; 146:1293-1299.
17. Gerald Y Minuk. Canadian Association of Gastroenterology Practice Guidelines: Evaluation of abnormal liver enzyme tests. Can J Gastroenterol. 1998; 12:417-421.
18. Man K, Fan ST, Ng IO, Lo CM, Liu CL, Yu WC, Wong J. Tolerance of the liver to intermittent pringle maneuver in hepatectomy for liver tumors. Arch Surg. 1999; 134:533-539.
19. Wu CC, Hwang CR, Liu TJ, P'eng FK. Effects and limitations of prolonged intermittent ischaemia for hepatic resection of the cirrhotic liver. Br J Surg. 1996; 83:121-124.

(Received January 23, 2018; Revised February 13, 2018; Accepted February 16, 2018)