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Fatty Liver Does Not Increase the Risk of Postoperative Liver Damage Following Hepatectomy

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Abstract. *Background/Aim: The number of patients with fatty liver due to alcohol consumption, metabolic syndrome, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis is increasing. Since there is no consensus on the risk of hepatectomy for patients with fatty liver, this study examined the clinical outcomes of hepatectomy for fatty liver patients via evaluation of transaminase. Patients and Methods: Patients (n=164) who underwent hepatectomy for primary liver tumors from January 2014 to March 2019 were included in the study. Patients were divided into steatohepatitis (n=19), steatosis (n=20), and control (n=30) groups. Serum values of aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin (TB), prothrombin time (PT), white blood cells, and platelets were compared before and immediately after surgery, and on postoperative days 1-5, 7, and 10. And their rates of change were compared using the preoperative value as a reference value. Results: Overall, AST and ALT elevation rates were higher in the control group than in the steatosis and steatohepatitis groups from postoperative days 2-7. There was no difference in postoperative hepatic dysfunction between the steatosis and steatohepatitis groups. Univariate analysis revealed significant differences in liver stiffness, operative time, mobilization, and Pringle time. Multivariate analysis indicated low liver stiffness and longer Pringle time as independent risk factors. Postoperative change in TB, PT, and albumin levels did not differ between the groups. There was no difference in postoperative complications and hospital stay between the groups. Conclusion: Fatty liver does not increase the risk of postoperative liver damage following hepatectomy.*

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In liver tumor resection, the indications for hepatectomy and resection volume are determined according to the condition of the underlying liver disease. Previously, preoperative evaluation of liver function has mainly been performed for viral hepatitis. But recently, the rate of liver cancer developing secondary to non-alcoholic fatty liver disease (NAFLD) has increased, and the incidence of hepatectomy is increasing. Some studies have reported reduction in liver regeneration after fatty liver resection (1), whereas others have reported no related problems (2, 3).

Herein, we focus on the factors involved in postoperative transient elevation of transaminase, emphasizing the involvement of fatty liver. This study aimed to examine the clinical outcomes of performing hepatectomy for patients with fatty liver *via* evaluation of transaminase.

Patients and Methods

Patients. This study was conducted under the ethical approval of the Kurume University Ethics Committee (the ethical approval number 19228) and all the patients provided informed consent. Data were obtained from patients who underwent primary liver tumor resection at our hospital from January 2014 to March 2019. Patients with intrahepatic cholangiocarcinoma were excluded. Patients (n=19) with steatohepatitis (≥10%) were included in the steatohepatitis group and those (n=20) with steatosis without inflammation (without hepatitis B or C infection) were included in the steatosis group. Further, 30 patients with viral hepatitis (without steatosis) were included in the control group.

Extent of liver resection. The extent of liver resection was comprehensively evaluated according to the extent of tumor progression, liver functional status, and the general condition of the patient. Liver function impairment was assessed by measuring liver biochemical parameters, determining Child-Pugh (CP) scores, and performing indocyanine green retention test.

Blood analysis. Routine blood analysis was performed at our Hospital. The values of aspartate transaminase (AST), alanine transaminase (ALT), albumin (Alb), total bilirubin (TB), prothrombin time (PT), white blood cells (WBCs), and platelets (Plts) in peripheral blood were compared. Samples were taken

Table I. *Patient characteristics*.

	Viral hepatitis	Steatohepatitis	Steatosis	*p*-Value (viral hepatitis *vs*. steatohepatitis)	*p*-Value (viral hepatitis *vs*. steatosis)	*p*-Value (steatohepatitis *vs*. steatosis)
N	30	19	20			
Age (years)	74.1±7.0	71.6±10.3	69.0±11.2	0.3758	0.0614	0.3721
Sex (male/female)	23/7	11/8	14/6	0.1648	0.5985	0.4309
BMI (kg/m^2)	23.0±3.3	27.3±6.9	26.5±2.9	**0.0019**	**0.0085**	0.6044
Alcohol use	14/16	7/12	12/8	0.1481	0.3552	0.1481
DM	8/22	8/11	14/5	0.2165	**0.0013**	0.0487
DM (HbA1c level)	5.5±1.6	6.3±1.8	5.9±2.0	0.0757	0.3185	0.4875
Hypertension	22/8	14/6	12/8	0.7809	0.4933	0.7150
Child-Pugh A (5/6)	25/5	18/1	18/2	0.2354	0.5057	0.5790
ICG 15 (%)	16.9±9.1	21.1±14.9	18.3±10.3	0.2551	0.6908	0.4811
Fibroscan score (kPa)	13.6±10.3	11.1±4.1	15.2±10.9	0.4004	0.5652	0.1989
AFP (ng/mL)	69.3±148.7	153.8±637.2	19.9±30.1	0.4154	0.6287	0.2361
DCP (mAU/mL)	1385.3±4001	265.2±272.4	235±558.0	0.1553	0.1388	0.9712
Tumor size (mm)	24.1±18.6	30.6±16.9	35.1±21.5	0.2709	0.0588	0.4708
Tumor stage (I/II/III)	13/13/3	3/13/2	3/11/6	0.1287	0.0507	0.3557
Operative time (min)	324.7±124.6	385.9±133.8	357.2±133.8	0.1126	0.3896	0.492
Pringle time (min)	55.4±37.0	64.2±30.6	60.7±39.0	0.4079	0.6095	0.7653
Blood loss (ml)	385.4±457.5	557.4±568.0	513.6±715.1	0.3089	0.4403	0.812
Hepatectomy (partial/more than sectionectomy)	10/20	8/11	10/10	0.5349	0.2386	0.6211
Operative method (laparotomy/laparoscopic)	17/13	14/5	14/6	0.2286	0.3413	0.7983
Resection volume	274.4±229.5	273±170.1	224.8±199.7	0.9820	0.4080	0.4682
Resection rate (%)	23.7±17.2	21.7±12.6	15.5±13.7	0.6606	0.0657	0.2041
Histological grade (F;0/1/2/3/4)	0/7/14/1/8	3/3/6/5	5/5/1/7	0.0172	0.6206	0.1808
Histological grade (A; 0/1/2/3)	0/17/12/1	0/12/4/0	0/8/10/0	0.4138	0.4685	0.0708
Histological steatotic rate (%)	0	32.9±17.7	33.3±17.8	<0.0001	<0.0001	0.9244

Continuous variables are expressed as the mean±standard deviation (SD). BMI, Body mass index; DM, diabetes mellitus; HbA1c, glycated hemoglobin; ICG 15, indocyanine green retention rate at 15 min; AFP, alpha fetoprotein; DCP, des-γ-carboxy prothrombin; *vs*., *versus*; F, fibrosis (F0, no fibrosis in the portal tract; F1, portal fibrosis without septa; F2, portal fibrosis with a few septa; F3, numerous septa without cirrhosis; and F4cirrhosis); A, activity (A0, no activity, A1, mild activity of necroinflammatory reaction, A2, moderate activity of necroinflammatory reaction, A3, sever activity of necroinflammatory reaction).

within 7 days before the operation, immediately after the surgery, and on postoperative days 1-5, 7, and 10, and their rates of change were compared using the preoperative value as a reference value.

Histology. The diagnosis of NAFLD was made using the Matteoni classification and NAFLD activity score (NAS). In this study, the fibrosis rate was equally classified into five stages for both viral and non-viral hepatitis (including NAFLD) according to the degree of fibrosis as follows: F0, no fibrosis in the portal tract; F1, portal fibrosis without septa; F2, portal fibrosis with a few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis.

Statistical analyses. Statistical analyses were performed using the JMP 14.0 (SAS Institute Inc.). For continuous variables, comparisons were made using analysis of variance.

The Student's *t*-test, Chi-square (χ^2) test, and Fisher's exact test were used for univariate analyses. Multivariate analyses were performed by logistic regression using odds ratios with 95% confidence intervals. Variables are expressed as means±standard deviation (SD) and significance was set at $p<0.05$.

Results

Patient characteristics. Body mass index was higher in the steatohepatitis and steatosis groups, and there were significantly more patients with diabetes mellitus in the steatosis group. No other significant differences were found in other patient characteristics (Table I). Serum AST and ALT levels before the operation were significantly higher in the steatosis and steatohepatitis groups than in the viral hepatitis group. The WBC levels were significantly higher in the steatosis group than in the viral hepatitis group. Cholinesterase was significantly lower in the viral hepatitis group than in the steatohepatitis and steatosis groups. (Table II).

Table II. *Preoperative laboratory data*.

	Viral hepatitis	Steatohepatitis	Steatosis	*p*-Value (viral hepatitis *vs*. steatohepatitis)	*p*-Value (viral hepatitis *vs*. steatosis)	*p*-Value (steatohepatitis *vs*. steatosis)
N	30	19	20			
AST level (U/L)	29.5±12.7	40.6±10.0	40.6±14.7	**0.0040**	**0.0034**	0.9959
ALT level (U/L)	22.0±13.4	40.3±14.5	39.2±16.9	**<0.0010**	**0.0002**	0.8149
TB level (mg/dl)	0.69±0.2	0.84±0.3	0.73±0.2	**0.0460**	0.5140	0.2087
Alb level (g/dl)	4.0±0.4	4.03±0.3	4.0±0.4	0.6113	0.9551	0.6060
LDH level (U/L)	195.7±43.2	194.7±32.4	184.3±39.0	0.9359	0.3178	0.4077
ChE level (U/L)	222±75.2	284.4±55.1	277.0±77.7	**0.0167**	**0.0111**	0.9151
ALP level (U/L)	326.5±361.3	233.0±60.7	276±100	0.2022	0.4824	0.5894
PT	96.4±20.3	90.8±15.3	94.8±18.4	0.4086	0.9097	0.5124
WBC count (/µL)	4966.7±1438	5510.5±998.3	6035±1391.4	0.1641	**0.0066**	0.2187
Plt count (×10^3/µL)	139±50.1	685.7±2352.8	164.4±31.9	0.1340	0.9431	0.1901
CRP level (mg/dl)	0.22±0.5	0.34±0.5	0.34±0.46	0.3764	0.3611	0.9893

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; TB, total bilirubin; Alb, albumin; LDH, lactate dehydrogenase; ChE, cholinesterase; ALP, alkaline phosphatase; PT, prothrombin time; WBC, white blood cell; Plt, platelet; CRP, C-reactive protein; *vs*., *versus*.

Table III. *Postoperative course and complications*.

	Viral hepatitis without steatosis or steatohepatitis	Steatohepatitis	Steatosis	*p*-Value (viral hepatitis *vs*. steatohepatitis)	*p*-Value (steatohepatitis *vs*. steatosis)	*p*-Value (steatohepatitis *vs*. steatosis)
N	30	19	20			
All complications	6	2	4	0.3820	1	0.4124
Minor	6	2	4	0.3820	1	0.4124
Major	0	0	0			
PHLF	2	3	0	0.3040	0.2386	0.0664
Transfusion during the operation	2	3	1	0.3040	0.8079	0.2670
Postoperative bleeding (ml)	0	0	0			
Ascites	0	1	0	0.2042		0.2986
Bile leakage	2	0	1	0.2505	0.8079	0.3234
PVT	4	0	3	0.0967	0.8679	0.0789
SSI	0	1	0	0.2042		0.2986
Abdominal abscess	0	0	0			
Pulmonary complication	0	0	0			
Cardiac complication	0	0	0			
Renal failure	0	0	0			
Hospital stay (days)	15.9±11.4	15.2±8.4	12.4±6.3	0.8023	0.1994	0.3517

Minor, Clavien Dindo classification less than grade III; major, Clavien Dindo classification grade III or higher; PHLF, post-hepatectomy liver failure was based on International Study Group of Liver Surgery criteria; PVT, portal vein thrombus; SSI, surgical site infection; *vs*., *versus*.

Postoperative changes. The serum AST and ALT elevation rates remained significantly higher in the viral hepatitis group than in the steatosis and steatohepatitis groups from day 2 to day 7 postoperatively. The postoperative WBC elevation rates remained significantly higher in the steatohepatitis group (Figure 1). All patients were discharged from the hospital without significant postoperative complications or a markedly prolonged hospital stay (Table III).

Univariate analysis of the effect of each factor on postoperative transaminase. Table IV shows the effect of several factors associated with postoperative peak ALT elevation rate (postoperative peak ALT/preoperative ALT). The liver stiffness, as measured by transient elastography (Fibroscan^R, Echosens), was significantly lower in the high ALT group than in the low ALT group (p=0.0176). The operative time (p=0.0036) and Pringle time (p=0.0012) were

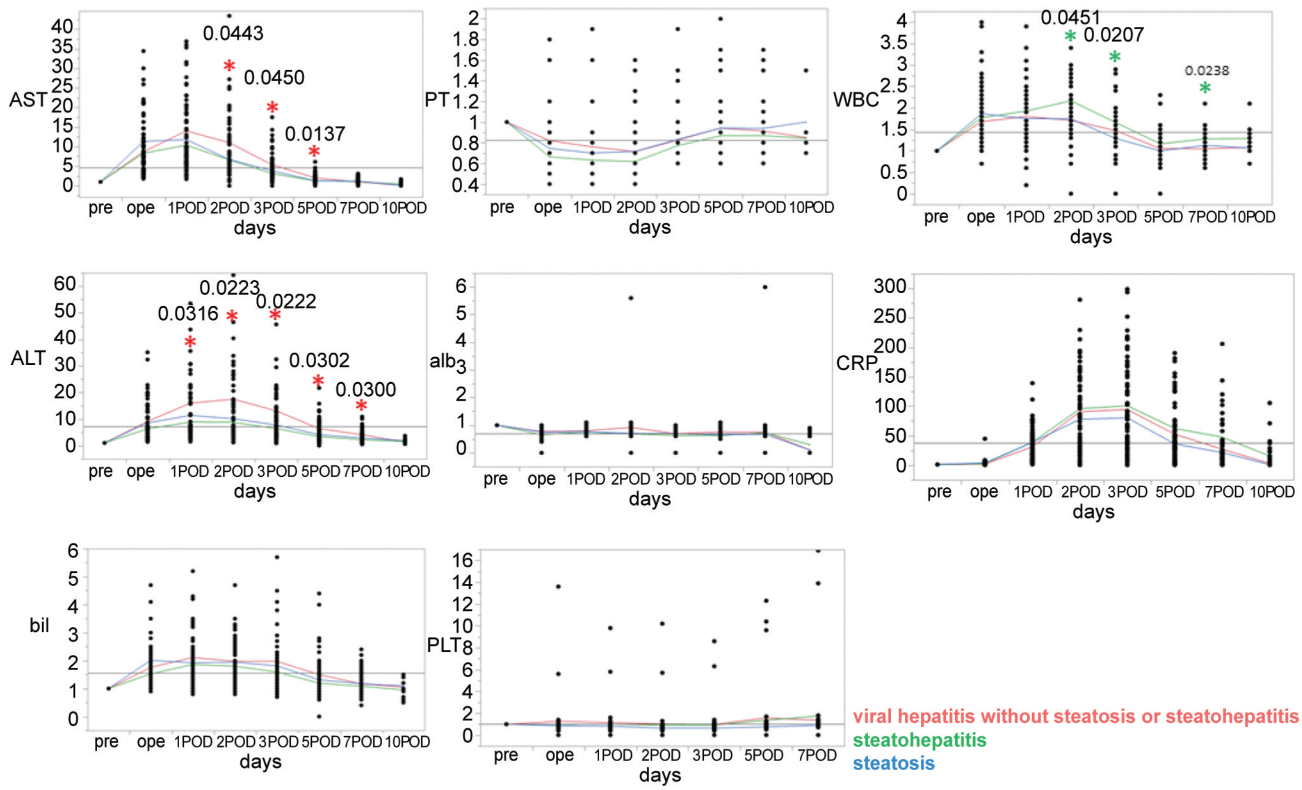

Figure 1. *Postoperative serum biochemistry test results. Elevation rates of AST, ALT, bilirubin, prothrombin time, albumin, platelets, WBCs, and C-reactive protein were measured in the serum of patients from each group. *p<0.05.*

Table IV. *Results of univariate analysis of the effect of each factor on the postoperative peak ALT elevation rate.*

	Peak ALT/preoperative ALT >8	Peak ALT/preoperative ALT <8	*p*-Value
Age (years)	72.2±9.5	71.7±9.5	0.8055
Sex (male/female)	26/5	22/16	**0.0197***
BMI (kg/m^2)	24.6±3.0	25.7±5.9	0.3318
DM (HbA1c level)	5.7±1.7	5.9±1.9	0.5414
HT	21/8	26/10	0.9863
ICG 15 (%)	15.6±7.1	20.7±13.3	0.0908
Tumor size (mm)	331.9±19.7	27.3±19.1	0.3534
Tumor stage (I/II/III)	5/18/7	14/19/4	0.1094
Hepatectomy (partial/more than sectionectomy)	9/22	19/19	0.0777
Operative method (laparotomy/laparoscopy)	24/14	21/10	0.6909
AFP (ng/ml)	58.3±133.9	95.1±458.4	0.6674
DCP (mAU/ml)	840.9±2451.9	615.0±2801.3	0.7311
Operative time (min)	400.6±113.1	310.6±131.0	**0.0036***
Operative blood loss (ml)	588.1±663.2	373.4±465.1	0.1194
Resection volume (g)	310.9±204.9	217.8±196.8	0.0509
Resection rate (%)	24.1±14.8	18.0±15.3	0.0971
Pringle time (min)	74.3±33.5	47.1±32.9	**0.0012***
Steatotic rate (%)	13.9±19.8	22.7±21.5	0.0851
Liver stiffness (kPa)	10.2±6.3	15.9±10.4	**0.0176***
Mobilization	18/13	13/25	**0.0475***

BMI, Body mass index; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HT, hypertension; ICH 15, indocyanine green retention rate at 15 min; AFP, alpha fetoprotein; DCP, des-γ-carboxy prothrombin.

Table V. *Results of multivariate analysis of the effect of each factor on the postoperative peak ALT elevation rate.*

	Odds ratio	95% CI (low)	95% CI (high)	*p*-value (Probability>chi-square)
Sex (male/female)	2.4958	0.5510	11.3050	0.2245
Operative time (min)	1.0014	0.0995	1.0076	0.6617
Pringle time (min)	1.0309	1.0062	1.0561	0.0055*
Liver stiffness (Kpa)	0.8932	0.8082	0.9822	0.0111*
Mobilization of the liver during transection	2.3654	0.2211	0.5957	0.2190

CI, Confidence interval.

longer in the high ALT group than in the low ALT group. Additionally, there were significantly more cases of mobilization (as a surgical method) in the high ALT group than in the low ALT group (p=0.0475).

Multivariate analyses. The effects of several factors associated with the postoperative peak ALT elevation rate analyzed by multivariate analysis are shown in Table V. Odds ratio analysis revealed that lower liver stiffness and a longer Pringle time were associated with a higher postoperative peak of ALT. The degree of steatosis had no effect on transient postoperative ALT elevation.

Discussion

In recent years, the incidence of fatty liver caused by alcohol consumption, metabolic syndrome, NAFLD, and non-alcoholic steatohepatitis (NASH) has increased. Additionally, the administration of irinotecan-based chemotherapeutic regimens for colorectal cancer has been shown to correlate with the development of steatohepatitis (4, 5), and it increases the need for hepatectomy to remove metastatic carcinoma from steatotic livers. The influence of steatosis following resection of fatty liver tissue remains uncertain, despite numerous reports.

Elevated serum transaminase indicates the volume of hepatocytes that were impaired during surgery, and the changes in TB and PT are considered to have a significant effect on liver regeneration. Although the transaminase level showed the most noticeable changes, ALT elevation correlated with a longer Pringle time and lower preoperative liver stiffness, and was not related to the degree of steatosis. The negative correlation of the value of liver stiffness value to the ALT value is consistent with a previous report that postoperative transaminase elevation was uncommon in patients with cirrhosis. Sugiyama *et al*. reported that cirrhotic remnant liver and that with marked fibrosis, may release smaller amounts of aminotransferase than normal livers after warm ischemia-reperfusion (IR) (6). They observed the presence of collateral circulation and suggested that the absence of portal congestion in patients with cirrhotic livers may explain the improved tolerance to the Pringle maneuver.

However, in transplantation, hepatic steatosis is reported to be a risk factor for postoperative graft dysfunction (7, 8). In cases of transplantation, macrovesicular steatosis affecting more than 30% of hepatocytes, which is thought to be associated with metabolic syndrome and alcohol abuse (9), was reported to be associated with an increased risk of primary graft dysfunction and graft loss due to IR injury (7, 8, 10-13). Macrovesicular steatosis, which is characterized by intracellular lipid accumulation and increases in hepatocyte volume, leads to obstruction of the adjacent sinusoid spaces, and increasing vascular resistance in hepatic microcirculation leads to mitochondrial dysfunction during reperfusion (9, 14, 15). IR during transplantation is generally cold IR, but in case of hepatectomy, warm IR is used. There are fundamental differences between warm and cold IR. Warm IR injury is caused by inflow occlusion during transection of the liver and leads to hepatocyte damage, while cold IR injury damages liver sinusoidal endothelial cells (LSEC) (16-18). Some studies have reported that liver regeneration requires increased expression of hepatocyte growth factor by LSECs and increased LSEC proliferation (3, 19, 20). Therefore, liver regeneration is suppressed by cold IR.

This study was not without limitations. First, the number of hepatectomies performed in patients with cirrhosis was small and the Pringle time seemed to have been short. Second, this study was based on a review of patients at a single institution. Thus, it is necessary to perform further studies on the effects of hepatectomy on fatty liver and to determine the volume of tissue that can be safely excised from patients with fatty liver.

In conclusion, the transient increase in transaminase, which can peak out within a few days after surgery, did not necessarily reflect liver damage. This increase in transaminase was associated with a soft liver and a long pringle time. From this result, it can be said that hepatectomy for fatty liver is not a risk enough to consider reducing the resection volume, but further cases need to be accumulated.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

All Authors contributed to the writing of the manuscript.

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