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.

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
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 (χ²) 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).
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®, 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.

| Factor                                      | 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/m²)                                 | 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                   | 273.±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.
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.

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.

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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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