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

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Abstract

Background

The number of patients with fatty liver due to alcohol consumption, the metabolic syndrome, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis is increasing. Because there is no consensus on the risk of hepatectomy in patients with fatty liver, this study examined the clinical outcomes of hepatectomy in fatty liver patients by evaluation their transaminase levels.

Methods

Patients (n = 164) who underwent hepatectomy for primary liver tumors from January 2014 to March 2019 were included in the study. They were divided into the steatohepatitis (n = 19), steatosis (n = 20), and viral hepatitis (n = 30) groups. Serum values of aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin (TB), white blood cells, and platelets level and the prothrombin time (PT) were compared before and immediately after surgery, and on postoperative days 1–5, 7, and 10.

Results

Overall, the AST and ALT elevation rates were higher in the control group than in the steatosis and steatohepatitis groups during 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 the Pringle time. Multivariate analysis indicated low liver stiffness and a longer Pringle time as independent risk factors. Postoperative changes in the TB and albumin levels and the PT did not differ between the groups. There was no difference in the postoperative complications and hospital stay length between the groups.

Conclusions

Fatty liver does not increase the risk of postoperative liver damage following hepatectomy.

Background

In liver tumor resection, the indications for hepatectomy and the 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. However recently, the incidence of liver cancer developing secondary to non-alcoholic fatty liver disease (NAFLD) has increased, and accordingly, the incidence of hepatectomy is increasing.

NAFLD, which involves triglyceride accumulation into the hepatocytes, results in a broad spectrum of liver injury and is graded based on the degree of inflammation and the degrees of fibrosis. [1] Steatohepatitis causes graft loss after liver transplantation, because it prevents postoperative liver regeneration. [2–5] Therefore, NAFLD-specific risks are also a concern in hepatectomy. Some studies have reported reductions in liver regeneration after fatty liver resection, [6] whereas others have reported no problems. [4, 7] Similarly, there are conflicting results regarding the risk of postoperative acute liver injury after hepatectomy. [1, 8–10]

Herein, we have focused on the factors involved in the postoperative transient elevation of transaminase level, which emphasizes the involvement of fatty liver. This study aimed to examine the clinical outcomes of performing hepatectomy in patients with fatty liver via the evaluation of transaminase.

Methods

Patients

This study was conducted under the ethical approval of the Kurume University Ethics Committee (the ethical approval number-19228), and all 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. Tumor progression was assessed by preoperative enhanced computed tomography (CT), gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid magnetic resonance imaging, and ultrasonography (US). Liver function impairment was assessed by measuring the liver biochemical parameters, determining the Child-Pugh (CP) scores, and performing indocyanine green retention tests. As a quantitative assessment of liver function, future liver remnant (FLR) volume was calculated by CT volumetry. The minimum FLR volume required was over 35% in normal livers, over 50% in mildly impaired livers, and over 60% in cirrhotic livers. In patients with normal liver function or mild liver impairment, portal vein embolization was performed when the FLR volume was insufficient.

Blood analysis

Routine blood analysis was performed at our hospital. The serum levels of aspartate transaminase (AST), alanine transaminase (ALT), albumin (Alb), total bilirubin (TB), white blood cells (WBCs), and platelets (PLT) in the peripheral blood and the prothrombin time (PT) were compared. Samples were collected 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

All specimens were reviewed by at least two pathologists. 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 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

The body mass index was higher in the steatohepatitis and steatosis groups than in the viral hepatitis group. There were significantly more patients with diabetes mellitus in the steatosis group than in the other groups; however, the hemoglobin A1c levels were controlled in all groups. No other significant differences were found in other patient characteristics (Table 1).

Table 1
Patient characteristics

	Viral hepatitis group	Steatohepatitis group	Steatosis group	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	0.38	0.06	0.37
Sex (male/female)	23/7	11/8	14/6	0.16	0.60	0.43
BMI (kg/m^2)	23.0 ± 3.3	27.3 ± 6.9	26.5 ± 2.9	0.002*	0.009*	0.60
Alcohol use	14/16	7/12	12/8	0.15	0.36	0.15
DM	8/22	8/11	14/5	0.22	0.001*	0.05
DM (HbA1c level)	5.5 ± 1.6	6.3 ± 1.8	5.9 ± 2.0	0.076	0.32	0.49
Hypertension	22/8	14/6	12/8	0.78	0.49	0.72
Child-Pugh A (5/6)	25/5	18/1	18/2	0.24	0.51	0.58
ICG 15 (%)	16.9 ± 9.1	21.1 ± 14.9	18.3 ± 10.3	0.26	0.69	0.48
Fibroscan score (kPa)	13.6 ± 10.3	11.1 ± 4.1	15.2 ± 10.9	0.40	0.57	0.20
AFP (ng/mL)	69.3 ± 148.7	153.8 ± 637.2	19.9 ± 30.1	0.42	0.63	0.24
DCP (mAU/mL)	1385.3 ± 4001	265.2 ± 272.4	235 ± 558.0	0.16	0.14	0.97
Tumor size (mm)	24.1 ± 18.6	30.6 ± 16.9	35.1 ± 21.5	0.27	0.06	0.47
Tumor stage (I/II/III)	13/13/3	3/13/2	3/11/6	0.13	0.05	0.36
Operative time (min)	324.7 ± 124.6	385.9 ± 133.8	357.2 ± 133.8	0.11	0.39	0.49
Pringle time (min)	55.4 ± 37.0	64.2 ± 30.6	60.7 ± 39.0	0.41	0.61	0.77
Blood loss (ml)	385.4 ± 457.5	557.4 ± 568.0	513.6 ± 715.1	0.31	0.44	0.81
Hepatectomy (partial/more than sectionectomy)	10/20	8/11	10/10	0.53	0.24	0.62
Operative method (laparotomy/laparoscopic)	17/13	14/5	14/6	0.23	0.34	0.80
Resection volume	274.4 ± 229.5	273 ± 170.1	224.8 ± 199.7	0.98	0.41	0.47
Resection rate (%)	23.7 ± 17.2	21.7 ± 12.6	15.5 ± 13.7	0.66	0.07	0.20
Histological grade (F;0/1/2/3/4)	0/7/14/1/8	3/3/6/5	5/5/1/7	0.02	0.62	0.18

	Viral hepatitis group	Steatohepatitis group	Steatosis group	p-value (viral hepatitis vs steatohepatitis)	p-value (viral hepatitis vs steatosis)	p-value (steatohepatitis vs steatosis)
Histological grade (A; 0/1/2/3)	0/17/12/1	0/12/4/0	0/8/10/0	0.41	0.47	0.07
Histological steatotic rate (%)	0	32.9 ± 17.7	33.3 ± 17.8	< 0.0001	< 0.0001	0.92

AFP, alpha fetoprotein; BMI, body mass index; DCP, des-γ-carboxy prothrombin; DM, diabetes mellitus; HbA1c, glycated hemoglobin; ICG 15, indocyanine green 15 min test; N, number of patients; vs, versus

Postoperative 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. Biochemical examination did not reveal any significant differences between the steatosis and steatohepatitis groups (Table 2).

Table 2
Preoperative laboratory data

	Viral hepatitis group	Steatohepatitis group	Steatosis group	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	0.004	0.003	0.99
ALT level (U/L)	22.0 ± 13.4	40.3 ± 14.5	39.2 ± 16.9	< 0.001	< 0.001	0.81
TB level (mg/dl)	0.69 ± 0.2	0.84 ± 0.3	0.73 ± 0.2	0.046	0.51	0.21
Alb level (g/dl)	4.0 ± 0.4	4.03 ± 0.3	4.0 ± 0.4	0.61	0.96	0.61
LDH level (U/L)	195.7 ± 43.2	194.7 ± 32.4	184.3 ± 39.0	0.94	0.32	0.41
ChE level (U/L)	222 ± 75.2	284.4 ± 55.1	277.0 ± 77.7	0.017	0.011	0.92
ALP level (U/L)	326.5 ± 361.3	233.0 ± 60.7	276 ± 100	0.20	0.48	0.59
PT	96.4 ± 20.3	90.8 ± 15.3	94.8 ± 18.4	0.41	0.91	0.51
WBC count (/μ[illegible])	4966.7 ± 1438	5510.5 ± 998.3	6035 ± 1391.4	0.16	0.007	0.22
Plt count ($\times 10^3$/μ[illegible])	139 ± 50.1	685.7 ± 2352.8	164.4 ± 31.9	0.13	0.94	0.19
CRP level (mg/dl)	0.22 ± 0.5	0.34 ± 0.5	0.34 ± 0.46	0.38	0.36	0.99

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

Postoperative changes

The serum AST and ALT elevation rates remained significantly higher in the viral hepatitis group than in the steatosis and steatohepatitis groups during postoperative days 2–7. However, the TB, PT, and PLT values were not significantly different between the three groups. The postoperative WBC elevation rates remained significantly higher in the steatohepatitis group (Fig. 1). All patients were discharged from the hospital without significant postoperative complications or a markedly prolonged hospital stay (Table 3).

Table 3
Postoperative course and complications

	Viral hepatitis group	Steatohepatitis Group	Steatosis group	p-value (viral hepatitis vs steatohepatitis)	p-value (viral hepatitis vs steatosis)	p-value (steatohepatitis vs steatosis)
N	30	19	20			
All complications	6	2	4	0.38	1	0.41
Minor	6	2	4	0.38	1	0.41
Major	0	0	0			
PHLF	2	3	0	0.30	0.24	0.07
Transfusion during the operation	2	3	1	0.30	0.81	0.27
Postoperative bleeding (ml)	0	0	0			
Ascites	0	1	0	0.20		0.30
Bile leakage	2	0	1	0.25	0.81	0.32
PVT	4	0	3	0.10	0.87	0.08
SSI	0	1	0	0.20		0.30
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	0.80	0.20	0.35

Minor, Clavien–Dindo classification less than grade □; Major, Clavien–Dindo classification grade □ or higher; N, number of patients; PHLF, post-hepatectomy liver failure based on the International Study Group of Liver Surgery criteria; PVT, portal vein thrombus; SSI, surgical site infection; vs., versus

Univariate analysis of the effect of each factor on postoperative transaminase

Table 4 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 (postoperative peak ALT/ preoperative ALT > 8) than in the low ALT group (postoperative peak ALT/ preoperative ALT < 8) ($p = 0.0176$). The operative time ($p = 0.0036$) and the Pringle time ($p = 0.0012$) were 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).

Table 4
Results of the univariate analysis of the 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	0.81
Sex (male/female)	26/5	22/16	0.019*
BMI (kg/m^2)	24.6 ± 3.0	25.7 ± 5.9	0.33
DM (HbA1c level)	5.7 ± 1.7	5.9 ± 1.9	0.54
HT	21/8	26/10	0.98
ICG 15 (%)	15.6 ± 7.1	20.7 ± 13.3	0.09
Tumor size (mm)	331.9 ± 19.7	27.3 ± 19.1	0.35
Tumor stage (I/II/III)	5/18/7	14/19/4	0.11
Hepatectomy (partial/more than sectionectomy)	9/22	19/19	0.08
Operative method (laparotomy /laparoscopy)	24/14	21/10	0.69
AFP (ng/mL)	58.3 ± 133.9	95.1 ± 458.4	0.67
DCP (mAU/mL)	840.9 ± 2451.9	615.0 ± 2801.3	0.73
Operative time (min)	400.6 ± 113.1	310.6 ± 131.0	0.004*
Operative blood loss (mL)	588.1 ± 663.2	373.4 ± 465.1	0.12
Resection volume (g)	310.9 ± 204.9	217.8 ± 196.8	0.05
Resection rate (%)	24.1 ± 14.8	18.0 ± 15.3	0.10
Pringle time (min)	74.3 ± 33.5	47.1 ± 32.9	0.001*
Steatotic rate (%)	13.9 ± 19.8	22.7 ± 21.5	0.09
Liver stiffness (kPa)	10.2 ± 6.3	15.9 ± 10.4	0.018*
Mobilization	18/13	13/25	0.048*

AFP, alpha fetoprotein; ALT, alanine aminotransferase; BMI, body mass index; DCP, des-γ-carboxy prothrombin; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HT, hypertension; ICG 15, indocyanine green 15 min test

Multivariate analyses

The effects of several factors associated with the postoperative peak ALT elevation rate (postoperative peak ALT/preoperative ALT > 8), as analyzed by multivariate analysis are shown in Table 5. 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.

Table 5
Results of the multivariate analysis of the 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	11.305	0.22
Operative time (min)	1.0014	0.09952	1.0076	0.66
Pringle time (min)	1.0309	1.0062	1.0561	0.006*
Liver stiffness (Kpa)	0.8932	0.8082	0.9822	0.011*
Mobilization of the liver during transection	2.3654	0.2211	0.5957	0.22

ALT, alanine aminotransferase; CI, confidence interval

Discussion

In recent years, the incidence of fatty liver caused by alcohol consumption, the 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, [11–12] and it increases the need for hepatectomy to remove the metastatic carcinoma from steatotic livers. The influence of steatosis following resection of fatty liver tissue remains uncertain, despite numerous reports.

In clinical practice, elevated serum transaminase and TB levels, decreased PT, and decreased PLT count of the peak value rates are used to estimate the approximate surgical damage to the liver. Elevated serum transaminase indicates the volume of hepatocytes that were impaired during surgery, and the changes in the TB level and PT are considered to have a significant effect on liver regeneration. In this study, AST and the ALT elevation rate after hepatectomy were significantly higher in patients with viral hepatitis, and there was no significant difference between patients with steatohepatitis and steatosis. Postoperative transitions in the TB and Alb levels and the PT did not differ between the groups, and there were no significant differences in the postoperative complications and hospital stay length between the groups.

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 between the liver stiffness value and the ALT value is consistent with a previous report that postoperative transaminase elevation was uncommon in patients with cirrhosis. Sugiyama et al. reported that a cirrhotic remnant liver, including one with marked fibrosis, may release smaller amounts of aminotransferase as compared to normal livers after warm ischemia-reperfusion (IR). [13] 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. There were no differences in the postoperative course, including the complication rate, post-hepatectomy liver failure rate, [14] and length of hospital stay after surgery between patients with viral hepatitis, steatosis, and steatohepatitis.

However, hepatic steatosis is reported to be a risk factor for postoperative graft dysfunction in transplantation. [2, 15] In cases of transplantation, macrovesicular steatosis affecting more than 30% of the hepatocytes which is thought to be associated with the metabolic syndrome and alcohol abuse,[16] was reported to be associated with an increased risk of primary graft dysfunction and graft loss due to IR injury. [2–3, 5, 15, 17–18] Macrovesicular steatosis, which is characterized by intracellular lipid accumulation and increases in the hepatocyte volume, leads to obstruction of the adjacent sinusoid spaces, and increasing vascular resistance in the hepatic microcirculation leads to mitochondrial dysfunction during reperfusion. [16, 19–20]

Generally cold IR ins used in transplantation, while warm IR is used in hepatectomy. There are fundamental differences between warm and cold IR. Warm IR injury is caused by inflow occlusion during transection of the liver and damages the hepatocytes, while cold IR injury damages liver the sinusoidal endothelial cells (LSEC). [21–23] Some studies have reported that liver regeneration requires increased expression of the hepatocyte growth factor by the LSECs and increased LSEC proliferation. [4, 24–25] Therefore, liver regeneration is suppressed by cold IR.

Most patients in this study had serum blood test abnormalities, which improved to normal ranges by the fifth or seventh postoperative day. They were discharged without significant postoperative complications, long-term hospital admission, or death from postoperative liver failure.

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

Conclusion

In conclusion, due to changes in blood chemistry tests results and the frequency of postoperative complications following hepatectomy in patients with NAFLD and viral hepatitis, it is likely that the indication criteria for liver resection and the resection volume will be similar when determined using existing preoperative liver function assessments. We found that compared to viral hepatitis, fatty liver does not increase the risk of postoperative liver damage after hepatectomy, thereby highlighting the potential for patients with fatty liver to undergo hepatectomy when necessary, without the added risk of adverse outcomes.

Abbreviations

AST, aspartate aminotransferase; ALT, alanine transaminase; TB, total bilirubin; PT, prothrombin time; WBC, white blood cell; NAFLD, non-alcoholic fatty liver disease; CT, computed tomography; Gd-EOB-MRI, gadolinium ethoxybenzyl diethylenetriamine pentacetic acid magnetic resonance imaging; US, ultrasonography; CP, Child-Pugh; FLR, future liver remnant; NAS, non-alcoholic fatty liver disease activity score; BMI, body mass index; IR, ischemia reperfusion; LSCE, liver sinusoidal endothelial cells

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. This study was reviewed and approved by the Ethics Committee of the Kurume University Hospital (the ethical approval number-19228).

Consent for publication

Written informed consent was obtained from the patient and her family for the publication of this report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YN collected the data and wrote the manuscript. HS and TH provided instructions for surgery. YN also performed the preoperative examination and diagnosis. JA and HY made histological diagnoses. YA and KO contributed to the study concept and review of the final manuscript. All authors read and approved the final manuscript.

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Figures

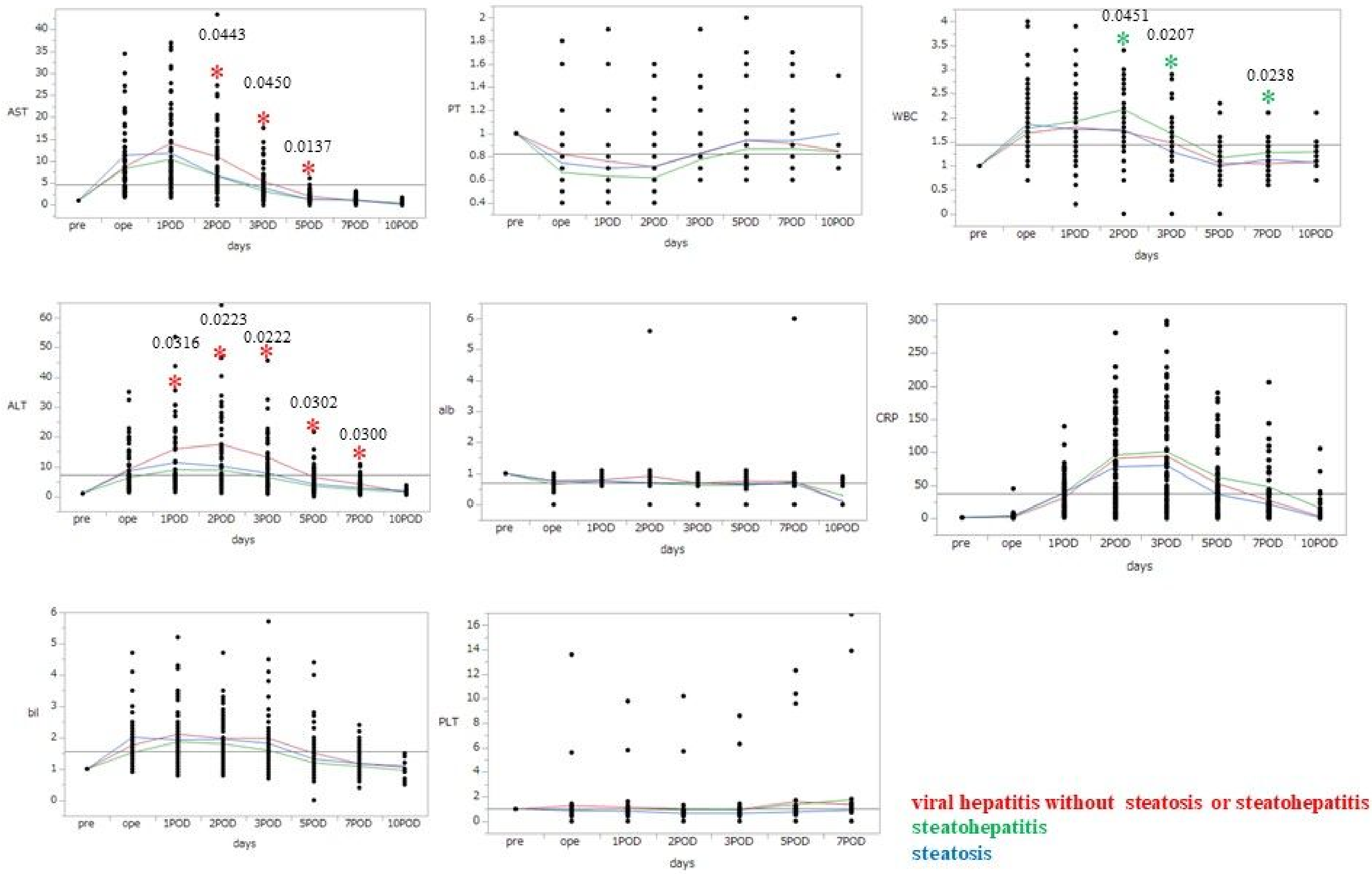

Figure 1

Changes in the postoperative serum biochemistry test results Elevation rates of AST, ALT, bil, PT, alb, plt, WBCs, and CRP were measured in the serum of patients from each group. The serum AST and ALT elevation rates remain significantly higher in the viral hepatitis group than in the other groups from day 2 to day 5 after surgery. In the steatohepatitis group, the high postoperative WBC rate remains significant. ALT, alanine transaminase; AST, aspartate aminotransferase; bil, total bilirubin; prothrombin time, PT; alb, albumin; WBC, white blood cell; C-reactive protein, CRP * indicates $p < 0.05$.