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Spleen Volume as a Predictive Biomarker for Thrombocytopenia and Liver Dysfunction After Oxaliplatin-based Chemotherapy

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Abstract. *Background/Aim: We evaluated whether splenic volume (SV) predicts sinusoidal obstruction syndrome (SOS) in colorectal cancer (CRC) patients receiving capecitabine plus oxaliplatin (CapeOX) therapy. Patients and Methods: In this retrospective study, we measured SV in 41 patients receiving adjuvant CapeOX for CRC at five different time points. We compared the clinical data of the 18 patients who experienced ≥30% increases in SV immediately after vs. before CapeOX (group A) with data for the remaining 23 patients (group B). Results: Platelet numbers decreased and the levels of hepatobiliary enzymes increased significantly 1 year after CapeOX compared with before CapeOX in group A. However, in group B, significantly decreased platelet numbers and significantly increased aspartate transaminase levels were confirmed only immediately after CapeOX, with no significant subsequent changes. Conclusion: SV was significantly associated with thrombocytopenia and liver dysfunction in CRC patients, and predicted SOS.*

Oxaliplatin-based chemotherapies represent a mainstay of systemic treatment for colorectal cancer (CRC), and capecitabine plus oxaliplatin (CapeOX) is a recommended standard regimen in adjuvant chemotherapy for patients with high-risk stage II and stage III CRC (1, 2). However, hepatic sinusoidal obstruction syndrome (SOS) is a potentially problematic adverse effect of oxaliplatin (3).

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SOS is a drug-induced liver injury, and the development of SOS leads to tender hepatomegaly, fluid retention, hyperbilirubinemia and splenomegaly (4, 5). SOS is a less likely short-term obstacle; however, SOS may be a long-term treatment obstacle and requires attention, especially when liver metastases develop. SOS can decrease the effectiveness of chemotherapy (6). Moreover, SOS is significantly associated with higher morbidity and longer hospital stay in patients who undergo hepatectomy (7, 8). Preoperative assessment of SOS is necessary to improve complication rates following liver surgery; however, an effective strategy for SOS remains to be determined.

Conventionally, SOS is diagnosed exclusively according to liver histopathological findings (3, 5); however, this method is invasive. Recently, increased splenic volume (SV), which results from increased portal venous pressure (9), has been reported to be significantly associated with SOS (3, 10), which suggests that increased SV is a simple biomarker for predicting SOS.

To evaluate SV as a predictive biomarker for SOS, we measured SV at five different time points, before and after CapeOX for adjuvant chemotherapy in patients with high-risk stage II and stage III CRC after curative surgical resection, and investigated the relationships between SV, platelet counts and liver dysfunction as indicators of SOS.

Patients and Methods

Study design and enrolled patients. This was a retrospective study using the University of Kanazawa Medical Hospital (Ishikawa, Japan) database of CRC patients. The exclusion criteria were applied to 41 patients with high-risk stage II or stage III CRC who underwent radical resection at our hospital between January 2013 and December 2017, and who received CapeOX as adjuvant chemotherapy. According to the National Comprehensive Cancer Network Clinical Practice Guidelines: Colon Cancer. ver. 3, we defined high-risk stage II CRC as follows: T4 status; poorly differentiated histology; perforation; obstruction requiring

decompression before surgery or stoma; <12 lymph nodes examined; vascular invasion and neural invasion. We excluded patients who met the following criteria: less than five oxaliplatin adjuvant chemotherapy treatments without computed tomography (CT) imaging before adjuvant therapy or within 4 months of completion, development of metastatic disease during adjuvant therapy, administration of additional chemotherapy agents, prior splenectomy, known cirrhosis, presence of chronic viral hepatitis or prior liver surgery.

This study was approved by the Institutional Review Board of the Kanazawa Medical University Hospital.

Calculation of SV. Spleen size was determined using multi-detector raw CT scans (Hitachi Medical Corporation, Saitama, Japan). SV was calculated by uploading the CT images into a calculator software (Ziostation 2®; Zaiosoft, Tokyo, Japan; Figure 1). We measured SV five times: (i) before, (ii) immediately after, (iii) 6 months after, (iv) 1 year after and (v) 2 years after CapeOX therapy. Changes in SV were determined for each CT time point by comparing SV at that time point with the value before treatment at (i). Splenomegaly was defined as a 30% increase in SV at (ii) compared with (i).

Data collection. The data were retrospectively collected from patients' medical records and operative reports. We divided the patients into two groups as follows: patients who developed a ≥30% increase in SV at (ii) compared with (i) (group A) and patients whose SV did not increase by ≥30% (group B), and we compared outcomes for all patients and those between the groups. We evaluated the following patients' clinical characteristics: pathological oncological factors, SV, laboratory data and the correlation between the SV change ratio and the platelet numbers or liver enzyme levels change ratio. Thrombocytopenia was defined as a platelet count of <150,000 cells/mm^3. Additionally, we compared and examined the histopathological findings in the liver sinusoids in two patients in each group who underwent hepatectomy for recurrent liver metastasis >6 months after CapeOX. One patient in group A underwent hepatectomy 15 months after CapeOX therapy, and another patient in group B underwent hepatectomy 10 months after CapeOX.

Statistical analysis. Values are expressed as means±standard deviations. Statistical analyses were performed using the two-sided Student's *t*-test and the Mann–Whitney *U*-test for continuous data or Fisher's exact test. All statistical analyses were performed using the SPSS 10.0 software package (IBM Corp., Armonk, NY, USA). Significance was defined as $p<0.05$.

Results

Patient characteristics and preoperative findings. We performed curative surgery in 175 patients with high-risk stage II or stage III CRC. Of the 175 patients, we included 41 patients in this study and excluded 134. The average number of CapeOX courses was 7.5. Of the 41 patients, 18 patients in group A experienced a ≥30% increase in SV at (ii) compared with (i) *vs.* the 23 patients in group B who did not experience a ≥30% increase in SV. There was no difference in the clinical characteristics between the two groups (Table I).

Table I. *Patient characteristics.*

Characteristic	Group A (n=18)	Group B (n=23)	*p*-Value
Median age (years)	63	67	0.792
Range	35-76	46-78	
Gender (Male, n)	13	12	0.218
BMI			
Median, kg/m^2	21.6	23.1	0.427
Range	16.2-28.1	15.6-33.9	
Primary colorectal tumour site			
Right, n	6	7	1
Left, n	12	16	
TNM stage			
II	1	3	0.618
III	17	20	
Pathology			
Tub 1, tub 2	14	20	0.458
Pap	3	2	
Muc	1	1	
Number of cycles of oxaliplatin			
6	3	4	0.341
7	1	0	
8	14	19	

BMI: Body mass index; TNM: tumor–node–metastasis; tub: tubular; pap: papillary; muc: mucinous.

Changes in SV and laboratory data for all patients. Treatment with adjuvant CapeOX resulted in an increase in spleen size (Figure 2A), and the mean SV at (ii) increased significantly to 121.7% compared with SV at (i) ($p=0.023$; Figure 3A). Splenomegaly occurred in 18 patients (44%), and in 3 patients, SV increased by >200% (Figure 2A). Resolution of splenomegaly was confirmed when the mean SV at (iii) returned to 108.2% of the value at (i) ($p=0.177$); however, eight patients (20%) maintained an elevated SV of >30% at (iii) (Figure 2B). The mean percentage resolution in SV was 103.8% ($p=0.573$) at (iv) and 100.6% ($p=0.86$) at (v) (Figure 2C and D, and Figure 3A). Platelet counts decreased significantly ($p<0.001$), and aspartate aminotransferase (AST; $p<0.001$) and alkaline phosphatase (ALP; $p<0.001$) levels increased significantly at (ii) compared with (i). Platelet counts ($p<0.001$), and AST ($p=0.018$) and ALP ($p=0.015$) levels remained significantly changed at (iii) (Figure 3A). All patients' platelet counts improved with time, and there was no difference in platelet counts between (i) and (v) (Figure 3A). Moreover, the percentage change in SV from (i) to (ii) was related to the maximum percentage change in thrombocytopenia and the degree of decrease for all hepatobiliary enzymes, compared with (i) (Figure 4).

Correlation between splenomegaly and thrombocytopenia and liver disfunction. The changes in the laboratory data in

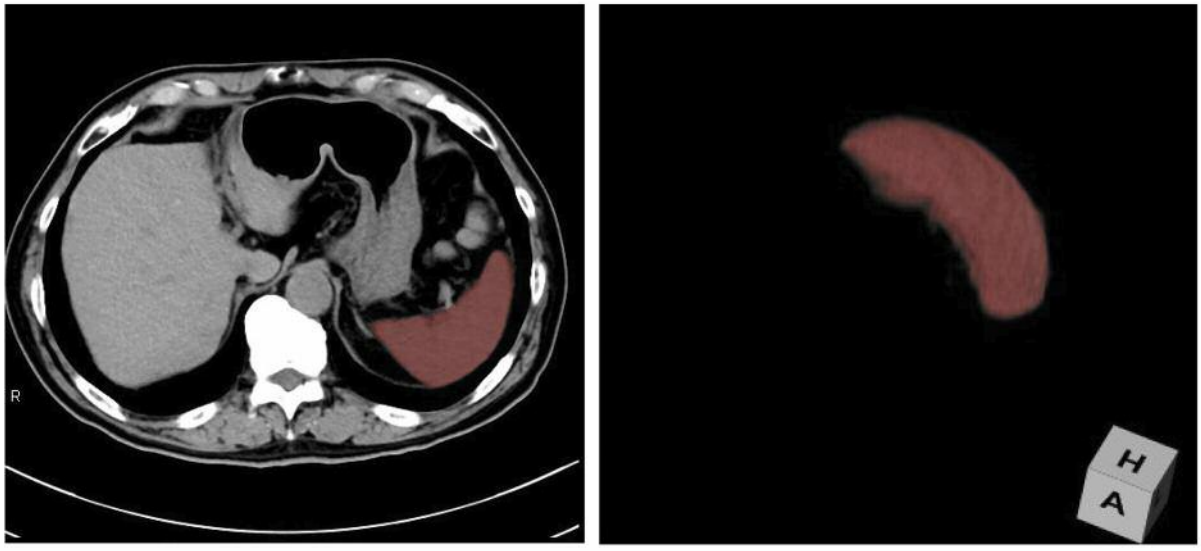

Figure 1. *Representative images of splenic volume. Splenic volume was measured using the calculator software Ziostation 2® (Zaiosoft, Tokyo, Japan), which can provide highly accurate measurements. The accurate three-dimensional image on the right was derived from the brown-colored area in the computed tomography image on the left.*

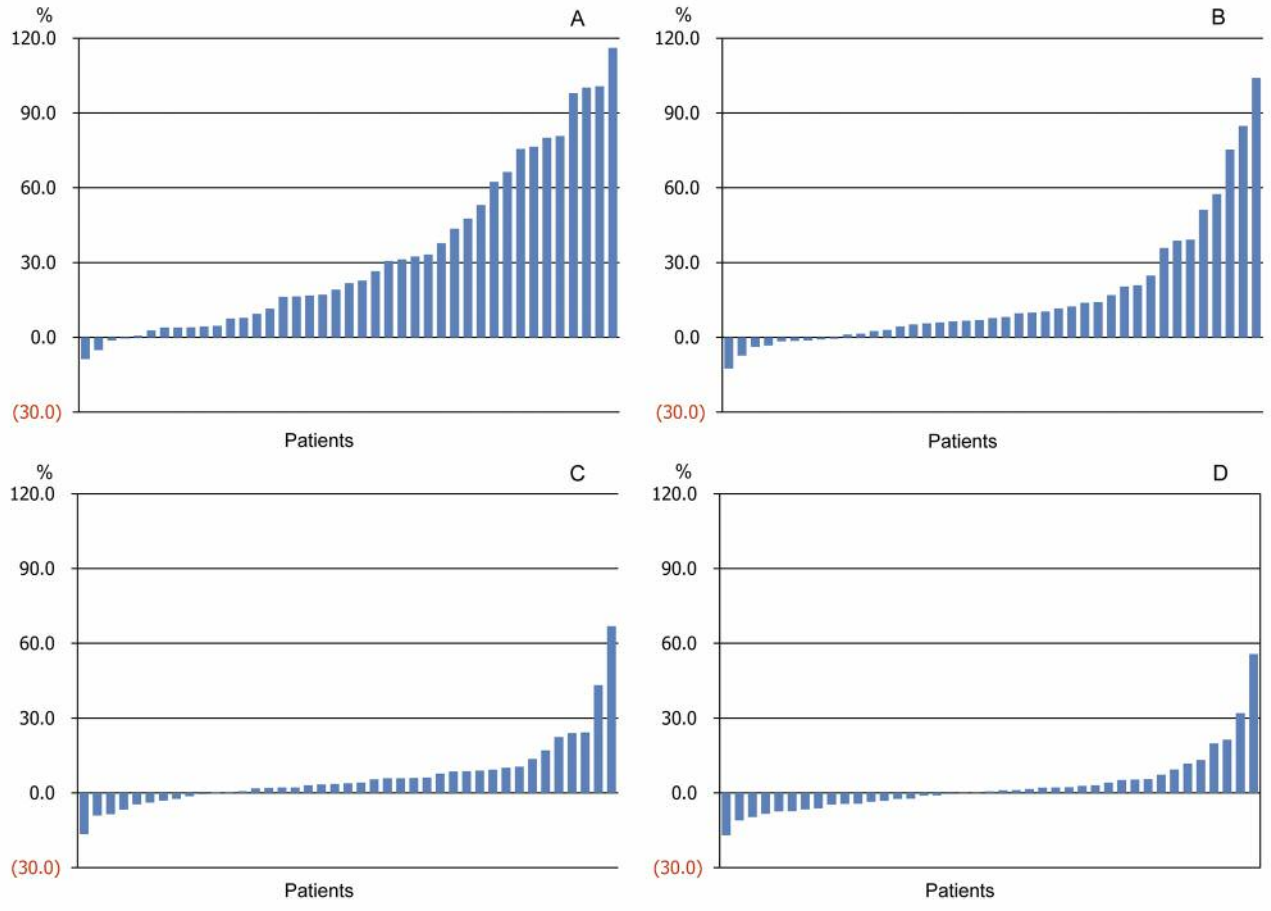

Figure 2. *Change in splenic volume (SV) after completing adjuvant capecitabine plus oxaliplatin (CapeOX) (A). SV increase ratio 6 months (B), 1 year (C) and 2 years after CapeOX therapy (D).*

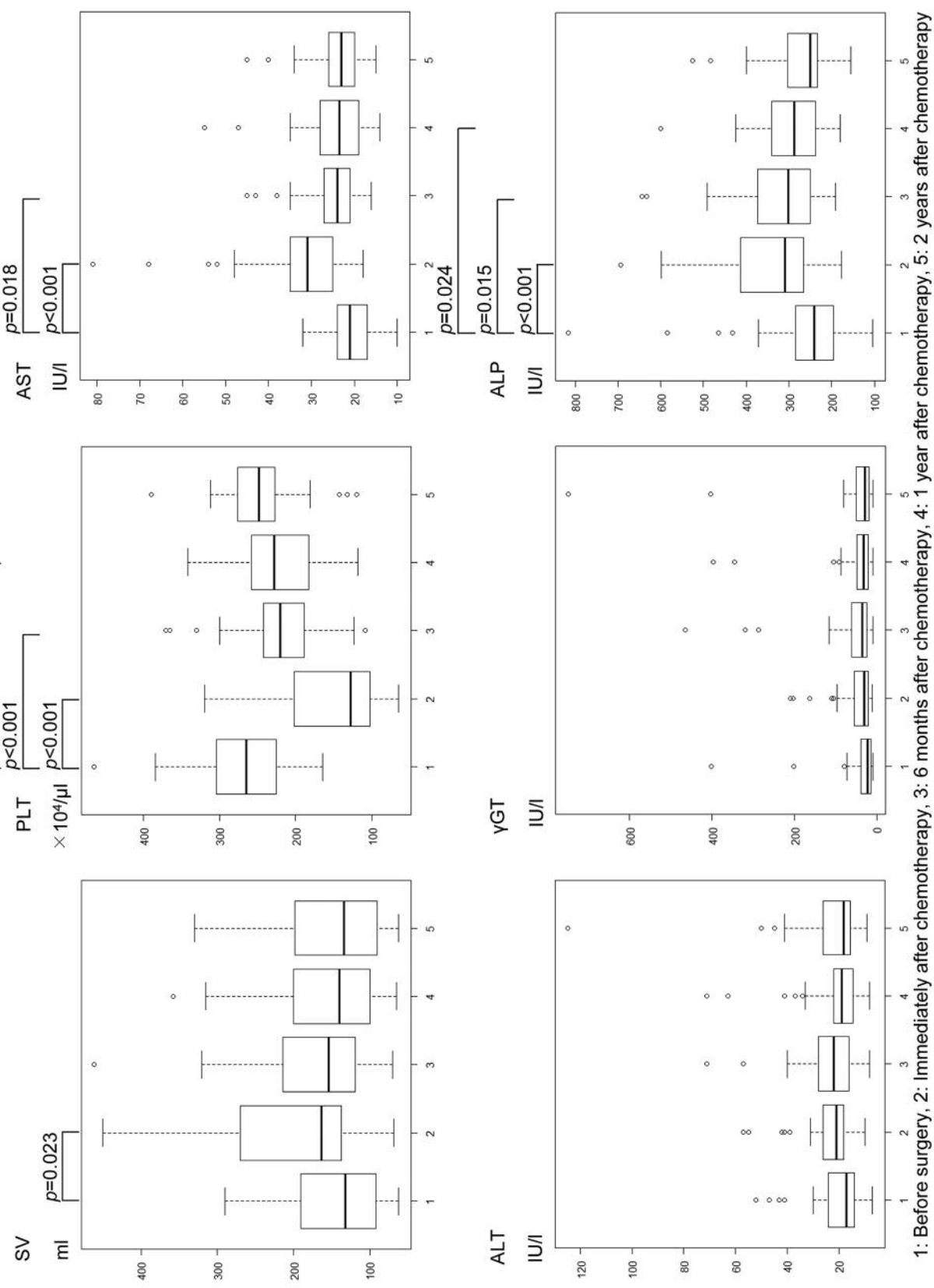

Figure 3. *Continued*

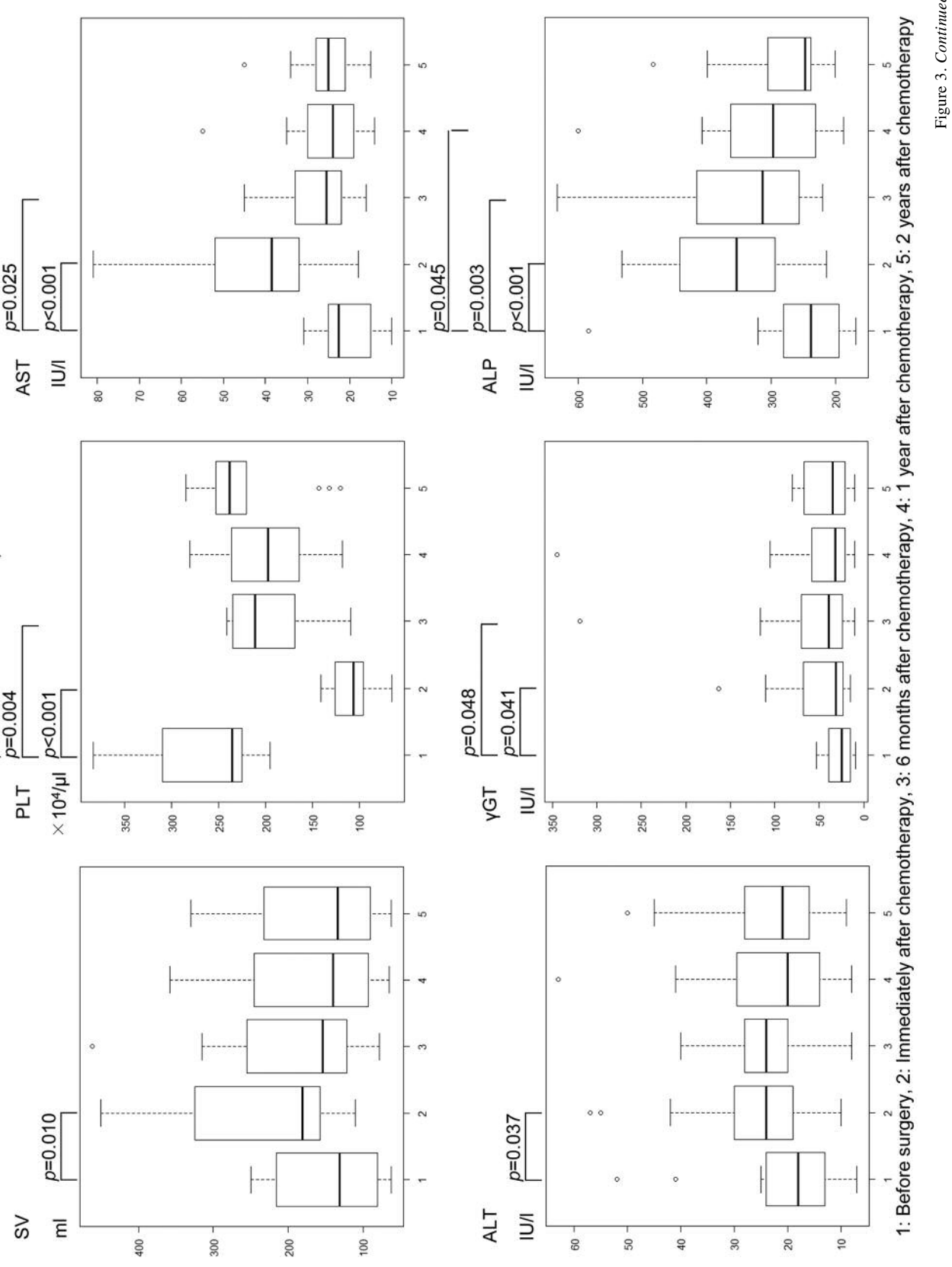

Figure 3. *Continued*

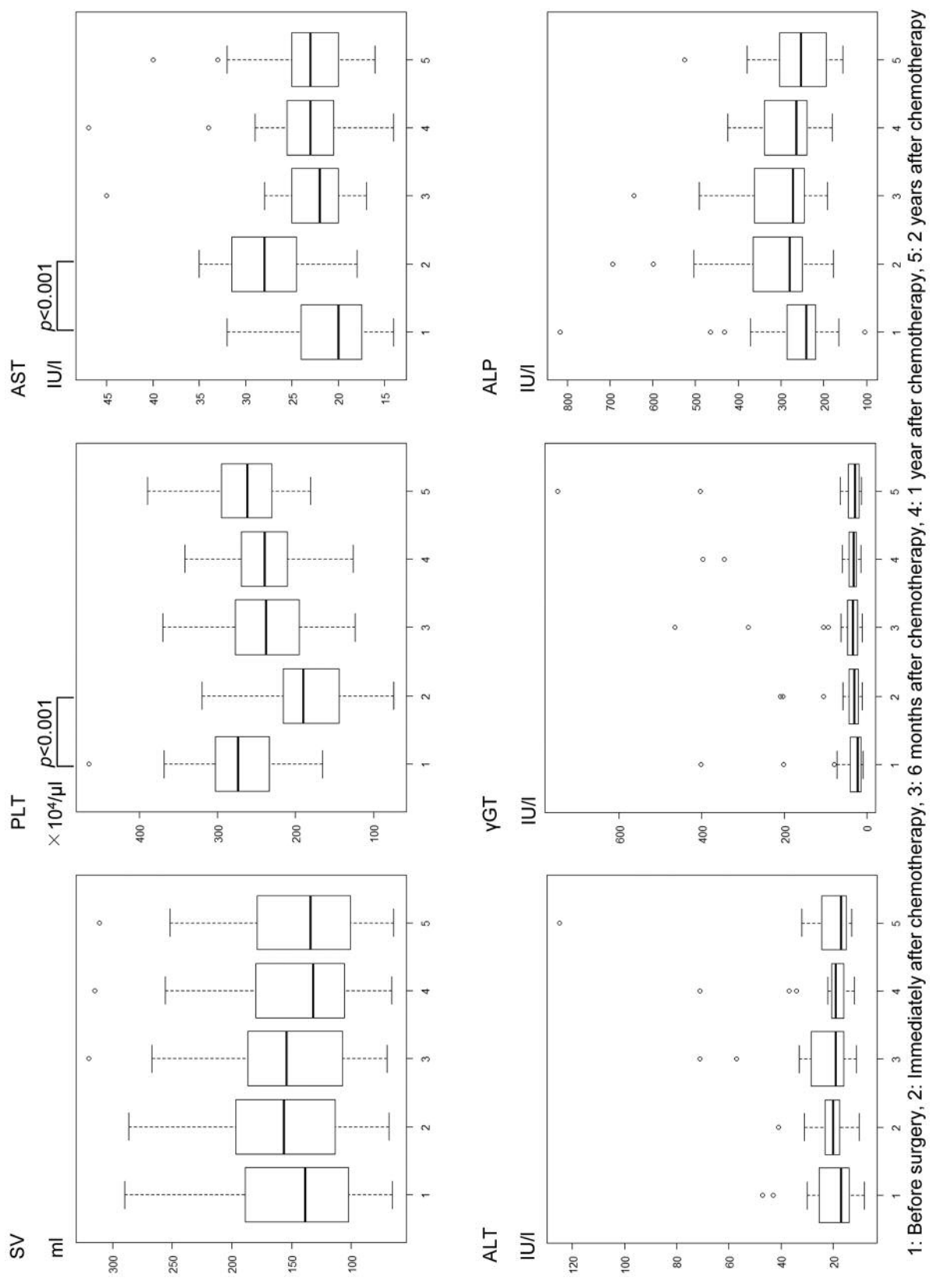

Figure 3. *Changes in laboratory data for all patients. B shows data for patients with a splenic volume (SV) increase of ≥30% after completing adjuvant chemotherapy with capecitabine plus oxaliplatin compared with before the treatment. C shows data for patients who did not develop an SV increase of ≥30%. PLT: Platelet count; AST: serum aspartate aminotransferase; alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; ALP: alkaline phosphatase.*

group A and B are shown in Figure 3 B and C. In group A, platelet counts decreased significantly ($p<0.001$), and AST ($p<0.001$), alanine aminotransferase (ALT; $p=0.034$), γ-glutamyl transpeptidase ($p=0.041$) and ALP ($p<0.001$) levels increased significantly at (ii) compared with (i). Platelet counts ($p=0.004$) and AST ($p=0.025$), γ-glutamyl transpeptidase ($p=0.048$) and ALP ($p=0.003$) levels remained significantly changed at (iii) (Figure 3B). Conversely, in group B, platelet counts decreased significantly ($p<0.001$), and AST levels increased significantly ($p<0.001$) at (ii) compared with (i); however, all data improved and did not change significantly at (iii) (Figure 3C). These results suggested that the degree of SOS was low in group B. The degree of thrombocytopenia during CapeOX treatment was significantly different in the 18 patients (100%) in group A and in 9 patients (39.1%) in group B ($p<0.001$; Table II). The degree of SV increase correlated strongly with decreasing platelet counts; resolution of thrombocytopenia was slower for patients in group A. Comparing platelet count improvement 1 year after adjuvant chemotherapy revealed a significant difference between the two groups; platelet counts in group A remained significantly changed at (iv) *vs*. (i) ($p=0.007$). Of note, thrombocytopenia in two patients in group A did not improve, even 2 years after CapeOX (data not shown).

Of the 41 patients, 7 patients (5 patients in group A and 2 patients in group B) experienced recurrences >6 months after completing chemotherapy (liver, 4; lung, 4; peritoneal dissemination, 2). Of the four patients with liver metastasis, two patients underwent hepatectomy (one in each group). There was no significant difference in the recurrence ratio between group A and B; however, in one patient in group A, SV changed by 180.8% at (ii), and SOS was confirmed during liver histopathology assessment (Figure 5). In another patient in group B, SV changed by 120.1%, and histopathology showed that the liver was normal.

Table II. *Comparison of minimum platelet counts during CapeOX treatment between the two groups.*

Platelet cell count	Group A (n=18)	Group B (n=23)	*p*-Value
$<15\times10^4$/μl (n)	18 (100%)	9 (39.1%)	<0.001

CapeOX: Capecitabine plus oxaliplatin.

Discussion

There are two novel and valuable findings in our study. First, SV increased significantly with adjuvant CapeOX therapy, and persistent decreases in platelet counts and liver dysfunction were recognized even 6 months to 1 year after this therapy. Second, patients with SV change ≥30% had higher rates of persistent liver dysfunction and remarkable thrombocytopenia during and even after CapeOX administration, which is indicative of SOS.

SOS, previously called veno-occlusive disease, is a drug-induced liver injury (5). Drugs such as busulfan that is used in haematopoietic stem cell transplantation are known to cause SOS, and the incidence of SOS after haematopoietic cell transplantation has been reported to be 70%, with fatality rates of up to 67% (11). Recently, SOS has been well-recognized as an adverse effect of oxaliplatin-based chemotherapy. Oxaliplatin-induced SOS is referred to as blue liver syndrome and is associated with higher risk for intraoperative bleeding and decreased hepatic functional reserve (5, 8, 12, 13). Therefore, it is important to evaluate the degree of SOS and to predict its risk, especially when liver metastases are identified.

CRC is a highly prevalent malignant tumour worldwide (14), and approximately 50% of patients develop liver metastases in the course of the disease (15). This indicates that a considerable number of patients who experience radical treatment have a possibility of liver recurrence and must be treated; therefore, early identification of SOS is needed for CRC patients. Several researchers state that oxaliplatin causes increased SV, and that SV is associated with SOS (3, 5, 10). However, patients in these studies already had liver metastasis, so evaluating SV change secondary to the effects of chemotherapy is biased. In our study, all patients were evaluated after radical resection only for CRC; therefore, increased SV in our study was secondary only to the effects of oxaliplatin, with no effect from liver metastasis.

Despite previous reports of oxaliplatin-induced SOS (3, 4, 8), clinically-useful predictive methods for this toxicity are poorly documented, although relevant reports have recently been published. Splenomegaly, which can be identified radiographically, and decreased platelet counts, both of which result from increased portal venous pressure, are clinical SOS biomarkers induced by oxaliplatin (16). Decreased platelet counts and increased liver enzymes have also been reported to indicate worsening SOS (5, 16, 17). Our analysis indicated that patients with an increase in SV of ≥30% had significantly higher rates of persistent liver dysfunction and remarkable thrombocytopenia during and after chemotherapy compared with patients without an SV increase of ≥30%.

This study focused on managing patients with CRC who underwent radical resection and who received oxaliplatin-based adjuvant chemotherapy. Thrombocytopenia persisted for approximately 1-2 years after only approximately 6 months of oxaliplatin-based chemotherapy. The most notable of our findings is that, in some patients with large increases in SV, thrombocytopenia and liver dysfunction persisted even

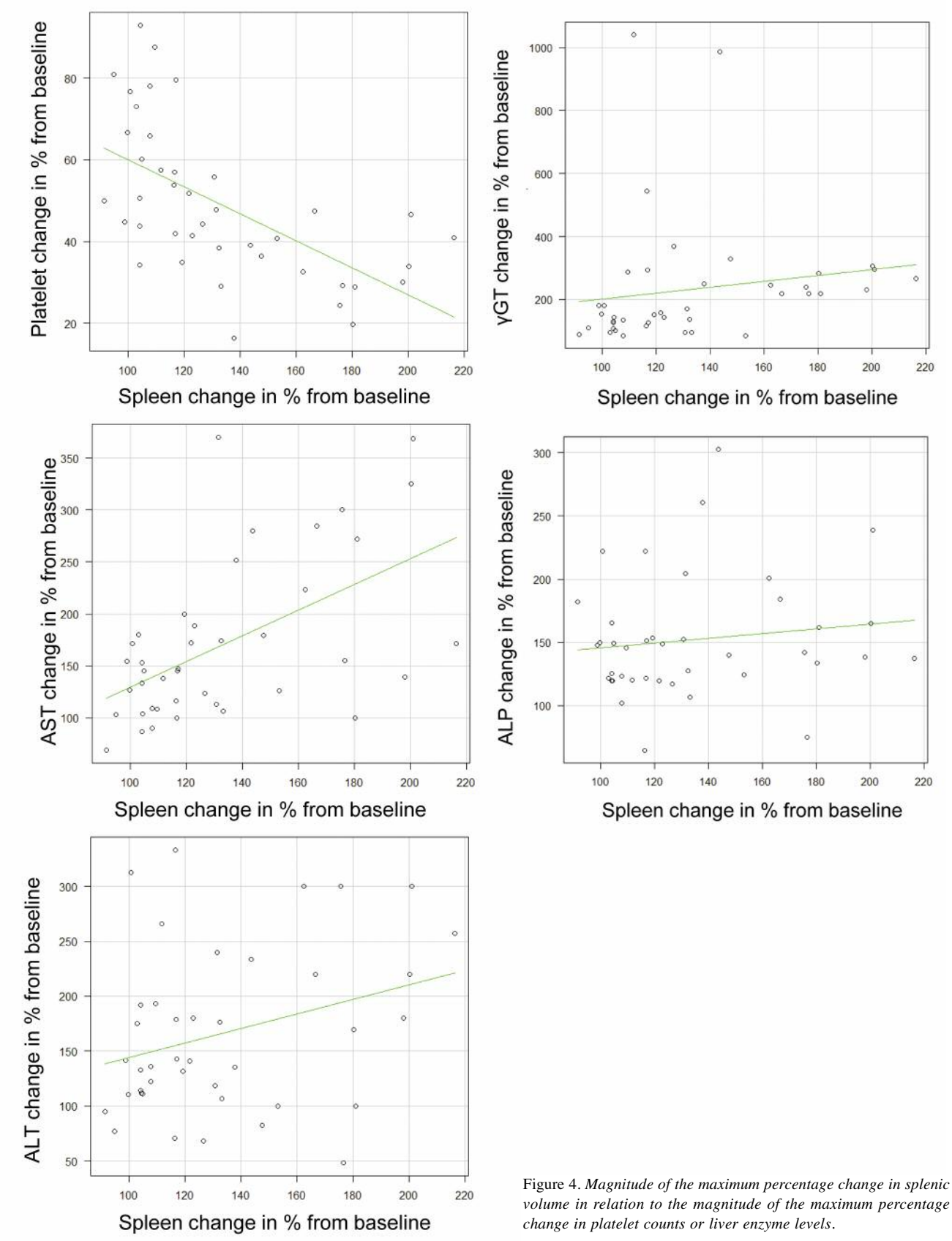

Figure 4. *Magnitude of the maximum percentage change in splenic volume in relation to the magnitude of the maximum percentage change in platelet counts or liver enzyme levels.*

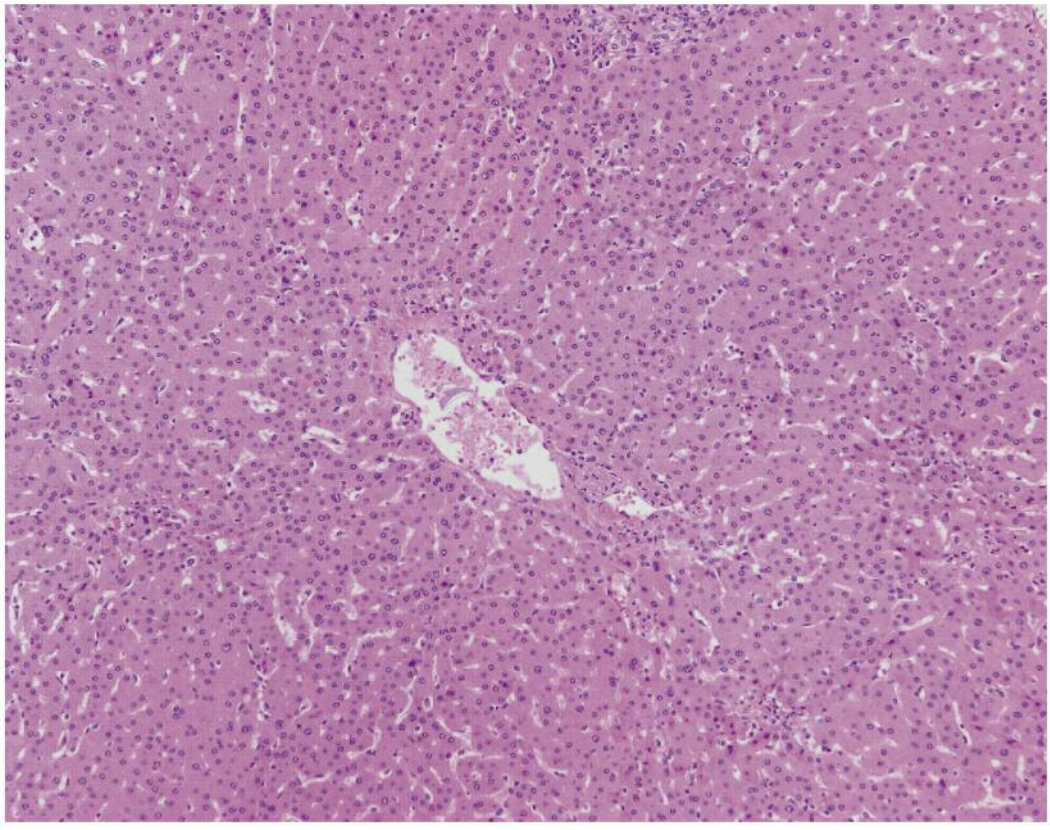

Figure 5. *Photomicrograph showing moderate sinusoidal dilation and atrophic hepatocytes, with moderate lymphocytic infiltration (magnification: ×200, haematoxylin and eosin).*

1 year after adjuvant chemotherapy. One of these patients had pathologically-confirmed SOS 15 months after adjuvant chemotherapy. Shigefuku *et al*. have reported a patient with oesophageal varices and hepatotoxicity caused by oxaliplatin 3.5 years after oxaliplatin-based chemotherapy (18). Considering these results, it is our firm belief that an SV increase immediately after oxaliplatin-based chemotherapy is a predictor of a higher risk of SOS, and affected patients should undergo surgery with careful monitoring, if liver metastasis develops, even in the long-term.

The present study had several limitations. First, this was a retrospective and non-randomized study. Second, we enrolled only a small number of patients from a single institution. Third, the correlation between splenomegaly secondary to chemotherapy and the development of hepatic sinusoidal injury identified during pathological examination remains to be fully clarified. A larger cohort study is needed to confirm our findings, using a different dataset that does not contain the original population involved in our study.

In conclusion, prominent thrombocytopenia and liver dysfunction were recognized after oxaliplatin-based adjuvant chemotherapy, possibly secondary to SOS. Increasing SV is a possible biomarker for the risk of SOS, and monitoring SV during the course of the treatment is useful in patients scheduled to undergo major hepatectomy.

Conflicts of Interest

The Authors declare they have no financial or other conflicts of interest regarding the content of this article.

Authors' Contributions

TM and HT designed the study. TM, HT, RK, HN, AH, YF, SM, JF, DK, YT, NN, HF, SK and NU performed data acquisition, analysis and interpretation. TM prepared the manuscript. HT and TK revised the paper critically. All Authors read and approved the final manuscript.

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