


ORIGINAL ARTICLE

Simple systemic index associated with oxaliplatin-induced liver damage can be a novel biomarker to predict prognosis after resection of colorectal liver metastasis

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Abstract

Aim: Oxaliplatin, an anticancer drug for advanced colorectal cancer, causes liver sinusoidal damage, sometimes with portal hypertension. We conducted a retrospective comparative study of the relationship of liver sinusoidal disorders and liver function with the prognosis in patients who underwent hepatectomy for colorectal liver metastasis (CRLM).

Methods: In total, 158 patients who underwent hepatectomy for CRLM were included in the study, and the effect of chemotherapy-associated liver damage on the prognosis was examined.

Results: Preoperative oxaliplatin was used in 75 of 158 patients; of these 75 patients, 26 had intraoperative blue liver (BL). In a comparison of the BL group (n = 26) and non-BL group (n = 132), patients in the BL group had a significantly lower serum albumin concentration and a significantly higher indocyanine green test result, aspartate aminotransferase-to-platelet ratio index (APRI), and FIB-4 score. Operative morbidities were not significantly different between the two groups. The overall survival rate after hepatectomy was significantly worse in the BL group than in the non-BL group. In the univariate analysis, the serum albumin concentration, indocyanine green test, a high tumor burden score (TBS), and the APRI were statistically significant poor prognostic factors. In the multivariate analysis, the APRI and a high TBS were independent poor prognostic factors.

Conclusion: The APRI and TBS in patients with CRLM are prognostic predictors after hepatectomy for metastatic liver cancer. This study indicated that liver damage in patients treated with preoperative oxaliplatin has an effect on the prognosis.

KEYWORDS

aspartate aminotransferase to platelet ratio index, blue liver, colorectal liver metastasis, oxaliplatin, tumor burden score

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1 | INTRODUCTION

Colorectal cancer is the third most common neoplasm worldwide and the second leading cause of cancer-related mortality.¹ The liver is the most common site of colorectal cancer metastasis, and 15% to 25% of patients have colorectal liver metastasis (CRLM) at the time of diagnosis.² Surgical resection of CRLM has been shown to improve survival significantly, with a reported 5-year survival rate of ~50%.³ Additionally, complete resection of both the primary tumor and CRLM improves the survival expectancy compared with systemic therapies.⁴ To increase the chance of long-term survival even in patients with unresectable liver metastasis, radical resection is selected as conversion therapy when the tumor shrinks or becomes resectable by chemotherapy.⁵ In past reports, oxaliplatin-based fluorouracil + folinic acid + oxaliplatin (FOLFOX) therapy was often the first choice because FOLFOX therapy has a higher hepatectomy rate than irinotecan-based FOLFIRI therapy.⁶

However, oxaliplatin sometimes causes liver damage. One study showed that in about half of the hepatectomy procedures performed in patients with CRLM who underwent neoadjuvant chemotherapy including oxaliplatin, dilation of the sinusoid and changes mainly due to congestion were observed in the normal part of the resected liver.⁷ Since then, this change has been referred to as “blue liver” (BL) because intraoperative examination shows that the liver has a macroscopically blue tone. Because neoadjuvant therapy is not commonly performed for patients with colorectal cancer in Japan, there are many reports of conversion therapy. The above-mentioned change in the sinusoid is a venous obstructive disease called sinusoidal obstruction syndrome (SOS), which was previously known as a serious complication that occurs mainly after allogeneic hematopoietic cell transplantation. In severe cases, this syndrome results in sinusoid and intravenous fibrin deposition, fibroblast proliferation, and collagen deposition in the extracellular matrix, resulting in obstruction of the sinusoid. Portal hypertension, hepatorenal syndrome, and multiple organ failure subsequently occur.

Long-term chemotherapy including oxaliplatin can be expected to have a high tumor shrinkage effect, but the risk of liver failure after radical surgery increases because of the accompanying liver sinusoidal disorder. In fact, it has been reported that hepatectomy after chemotherapy with oxaliplatin is associated with a significantly higher incidence of postoperative complications than is hepatectomy without preoperative chemotherapy.⁸ Although there are methods for quantitatively evaluating liver function, such as the indocyanine green (ICG) test and liver receptor scintigraphy, these procedures cannot be performed every time chemotherapy is considered. Additionally, the presence or absence of BL is helpful information to have when determining the indication for surgery; however, this information cannot be obtained until the abdomen is opened for direct observation. Therefore, there is a demand for a simple method to confirm the status of the patient's hepatic sinusoidal disorder and

the presence or absence of BL at the time of decision-making regarding chemotherapy and surgery.

In the present retrospective comparative study, we used the aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4 score, which are independent predictors of SOS in the resected liver after using oxaliplatin,⁸ to examine the relationship between liver sinusoidal disorders and the prognosis in patients who underwent hepatectomy for CRLM.

2 | METHODS

2.1 | Study design

The medical records of 158 Japanese patients who met the following inclusion criteria were enrolled in the present study: treatment with radical surgery for CRLM from January 2014 to June 2021, initial diagnosis of colorectal cancer with liver metastasis, and histological diagnosis of CRLM. The patients had no organ metastasis other than liver metastasis prior to surgery.

Resected hepatic tissues were pathologically examined by an independent pathologist. No specimens contained cancer cells within the resected margins. After surgery, the patients were followed up in the hospital at 3-mo intervals. At these visits, the patients underwent measurement of liver function indices, the carcinoembryonic antigen (CEA) concentration, and the carbohydrate antigen 19-9 concentration along with other blood analyses; they also underwent enhanced computed tomography (CT) and/or magnetic resonance imaging.

The treatment strategy for each patient was decided by the institutional Cancer Board, comprising medical oncologists, gastrointestinal surgeons, and liver surgeons, who discussed the treatment plan at each patient's first visit and when significant treatment effects were achieved. For patients with resectable CRLMs and primary tumors, resection followed by chemotherapy was carried out according to institutional guidelines. The criteria for clearly unresectable, not optimally resectable, and not suitable for curative resection were as follows: (i) synchronous metastases in multiple organs; (ii) expectation of insufficient residual liver volume or function after liver resection; (iii) CRLM invasion of critical structures of the liver, such as the hilum and root of the hepatic vein, making their resection difficult without leaving residual metastasis; and (iv) Japanese Classification of Colorectal Category H2 or H3 (more than five liver metastatic lesions and/or a maximum diameter larger than 5 cm), which is associated with a poorer prognosis for patients undergoing liver resection than for those in Category H1. These patients were treated with chemotherapy, and the decision of the chemotherapy regimen was made mainly by the oncologist according to the patient's condition.⁵

We evaluated the clinicopathological factors and overall survival (OS) to specifically determine the association of liver sinusoidal disorders and liver function with the prognosis in patients who underwent hepatectomy for CRLM.

2.2 | Definitions

As previously reported by Calistri et al, BL referred to parenchymal venous congestion resulting from blockage of blood outflow, macroscopically characterized by an intraoperative subcapsular livid appearance and a similar "marble" bluish-red discoloration on the cut surface.⁹ Therefore, three or more surgeons determined the presence or absence of oxaliplatin-associated BL by confirming the color of the liver during the operation.^{10,11} The findings of BL in this study are shown in Figure S1.

Imaging findings of collateral circulation and splenomegaly were assessed using preoperative CT by radiologists. Spleen volume was determined by loading the CT images. The outline of the spleen on each axial images was determined and the resulting sum of the areas, after taking into account the slice thickness, was used to calculate the volume of the spleen.¹² A splenic volume $>314.5 \text{ cm}^3$ was defined as splenomegaly.¹²

In patients with multiple nodules, the tumor size was defined by the size of the largest lesion. Major hepatectomy was defined as resection of three or more Couinaud segments.¹³ The tumor burden score (TBS) was defined as the distance from the origin of a Cartesian plane and comprised two variables¹⁴: the maximum tumor size (x-axis) and the number of tumors (y-axis); thus, $\text{TBS}^2 = (\text{maximum tumor diameter})^2 + (\text{number of tumors})^2$. For each patient, the maximum tumor diameter and number of tumors were obtained from the final pathological report.

The following biologic data were assessed before surgery: platelet count, serum creatinine concentration, serum aspartate aminotransferase (AST) concentration, serum alanine aminotransferase (ALT) concentration, gamma-glutamyl transferase concentration, alkaline phosphatase concentration, serum total bilirubin concentration, and prothrombin time. Finally, the APRI^{8,15} and FIB-4 score¹⁶ were calculated to determine their correlation with the pathologic findings. The formulas used for these calculations are shown below. When the future liver remnant was thought to be insufficient to ensure satisfactory postoperative liver function, preoperative liver volumetry was performed using 3D CT to ensure a safe hepatectomy procedure.

$\text{APRI} = (\text{AST [U/L]} / \text{upper limit of reference range}) \times 100 / \text{platelet count } (10^9/\text{L})$.

$\text{FIB-4 score} = (\text{age (y)} \times \text{AST (U/L)}) / (\text{platelet count } (10^9/\text{L}) \times \text{ALT (U/L)}^{1/2})$.

2.3 | Statistical analysis

The clinicopathological records of all 158 patients were collected and retrospectively reviewed. Differences between groups (BL group vs non-BL group and high TBS group vs low TBS group) were assessed by the Mann-Whitney *U* test. Comparisons of the same patient were made by the paired Student's *t* test. Associations between variables were determined by Fisher's exact test or the χ^2 test. The diagnostic performance of potential biomarkers was

assessed by analyzing receiver operating characteristic (ROC) curves. A stepwise multivariate analysis was conducted to identify parameters that significantly contributed to OS after hepatectomy for CRLM.

Disease-free survival (DFS) and OS curves were calculated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. Univariate and multivariate logistic regression analyses were performed to identify independent determinants of OS. Statistical analyses were performed using GraphPad Prism, v. 7.0 (GraphPad Software, San Diego, CA, USA) and JMP Pro 15.1 (SAS Institute, Cary, NC, USA). $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

The patients' characteristics were as follows. Their mean age was 64.5 y (range, 36–84 y). The male:female ratio was 83:75. The mean (\pm standard deviation) body mass index and serum albumin concentration before hepatectomy were $22.8 \pm 0.2 \text{ kg/m}^2$ and $4.0 \pm 0.1 \text{ mg/dL}$, respectively. The primary tumor was located in the right colon (proximal to the splenic flexure) in 34 patients and in the left colon (distal to the splenic flexure) in 66 patients, and 58 patients had rectal cancer. The mean preoperative serum CEA and carbohydrate antigen 19–9 concentrations were $186.4 \pm 145.2 \text{ ng/mL}$ and $95.6 \pm 27.8 \text{ ng/mL}$, respectively. With respect to the location of CRLM, 93 patients had unilobar CRLM and 65 patients had bilobar CRLM. As for the timing of recognizing CRLM, 82 patients had synchronous CRLM and 76 patients had metachronous CRLM (Table S1). Preoperative oxaliplatin was used in 75 of 158 patients; of these 75 patients, 26 (35%) had BL, as shown by intraoperative examination.

Postoperative complications occurred in 23 (14.6%) of the 158 patients, including wound infection ($n = 4$), pulmonary infection ($n = 1$), biloma ($n = 3$), delirium ($n = 5$), pleural effusion ($n = 4$), ascites ($n = 5$), deep vein thrombosis ($n = 1$), and portal vein thrombus ($n = 1$) (Table S1). The postoperative mortality rate was 0% after hepatectomy for CRLM.

3.2 | Comparison between BL and non-BL groups

Comparison of the BL group ($n = 26$) and non-BL group ($n = 132$) showed that the serum albumin concentration and platelet count were significantly lower and that the ICG 15-min value and serum CEA concentration were significantly higher in the BL group than in the non-BL group. The APRI was significantly higher in the BL than non-BL group (6.2 ± 0.6 vs 4.8 ± 0.3 , $P = .025$), and the FIB-4 score was significantly higher in the BL than the non-BL group (24.8 ± 2.0 vs 19.2 ± 0.9 , $P = .010$) (Table 1). The cases using oxaliplatin of six cycles or more suffered from liver damage, and the findings of blue

TABLE 1 Comparative analysis of clinicopathological parameters between the BL group and non-BL group

| Variable | Non-BL group (n = 132) | BL group (n = 26) | P value |
|----------------------------------------------------|------------------------|-------------------|---------|
| Gender (male/female) | 67/65 | 16/10 | .314 |
| Age (y) ^a | 64.5 ± 0.9 | 64.8 ± 2.0 | .880 |
| BMI (kg/m ²) ^a | 22.9 ± 0.3 | 22.0 ± 0.6 | .177 |
| Neoadjuvant chemotherapy (yes/no) | 68/64 | 26/0 | <.001 |
| Neoadjuvant chemotherapy with oxaliplatin (yes/no) | 49/83 | 26/0 | <.001 |
| Numbers of cycles (0–5/≥6) | 86/46 | 11/15 | .029 |
| CRC location (right/left/rectum) | 33/52/47 | 1/14/11 | .053 |
| CRC histology (well/moderate/poor) | 2/128/2 | 1/25/0 | .601 |
| Esophageal or gastric varices (yes/no) | 2/130 | 0/26 | .528 |
| Splenomegaly (yes/no) | 5/127 | 1/25 | .989 |
| Portal hypertension (yes/no) | 6/126 | 1/25 | .874 |
| Maximum tumor size (cm) ^a | 2.6 ± 0.2 | 2.7 ± 0.3 | .841 |
| Number of liver metastasis ^a | 3.7 ± 0.5 | 4.6 ± 1.0 | .455 |
| TBS ^a | 5.1 ± 0.4 | 5.8 ± 1.0 | .505 |
| Serum albumin (g/dL) ^a | 4.0 ± 0.1 | 3.8 ± 0.1 | .007 |
| Total bilirubin (mg/dL) ^a | 0.7 ± 0.1 | 0.7 ± 0.1 | .536 |
| ICG test (%) ^a | 7.9 ± 0.4 | 10.5 ± 0.8 | .008 |
| Platelet (×10 ⁴ /μL) ^a | 20.5 ± 0.5 | 17.0 ± 1.2 | .008 |
| AST (IU/L) ^a | 26 ± 1 | 30 ± 2 | .100 |
| ALT (IU/L) ^a | 25 ± 1 | 24 ± 3 | .988 |
| Cr (mg/dL) ^a | 0.8 ± 0.1 | 0.7 ± 0.1 | .236 |
| CEA (ng/mL) ^b | 7.2 (3.4–27.6) | 9.4 (5.7–29.0) | .027 |
| CA19-9 (ng/mL) ^b | 16.5 (5.8–45.3) | 17.0 (7.8–60.5) | .509 |
| Distribution (unilobar/bilobar) | 83/49 | 10/16 | .021 |
| Timing of resection (synchronous/metachronous) | 66/66 | 16/10 | .282 |
| Operative time (min) ^a | 234.2 ± 7.3 | 258.3 ± 16.4 | .183 |
| Blood loss (g) ^a | 213.1 ± 24.6 | 209.3 ± 55.5 | .950 |
| Postoperative complication CD (0–1/≥2) | 115/17 | 20/6 | .178 |

TABLE 1 (Continued)

| Variable | Non-BL group (n = 132) | BL group (n = 26) | P value |
|--------------------------------|------------------------|-------------------|---------|
| Adjuvant chemotherapy (yes/no) | 76/56 | 17/9 | .460 |
| APRI score ^a | 4.8 ± 0.3 | 6.2 ± 0.6 | .025 |
| FIB-4 score ^a | 19.2 ± 0.9 | 24.8 ± 2.0 | .010 |

Note: Boldface P values are statistically significant.

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BL, blue liver; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CD, Clavien–Dindo classification; CEA, carcinoembryonic antigen; Cr, creatinine; CRC, colorectal cancer; ICG, indocyanine green; TBS, tumor burden score.

^aData are expressed as mean ± standard error.

^bData are expressed as median (25th–75th percentile).

liver were observed (Table 1). There was no significant difference in short-term results (postoperative complications) between the two groups ($P = .178$) (Table 1).

In the present study, imaging findings of collateral circulation and splenomegaly were assessed using preoperative CT by radiologists. The preoperative CT showed portal hypertension such as esophageal or gastric varices and splenomegaly in seven cases, of which one case showed blue liver (Table 1). There was no significant association between preoperative portal hypertension and blue liver.

The survival rate of patients with metastatic liver cancer after hepatectomy was significantly worse in the BL group than in the non-BL group ($P = .046$) (Figure 1A). There was no significant difference in DFS between the two groups (Figure 1B).

Comparison of the BL group ($n = 26$) and the non-BL group ($n = 49$) who received preoperative oxaliplatin therapies showed that the serum albumin concentration was significantly lower in the BL group than in the non-BL group. Also, the APRI and the FIB-4 scores were significantly higher in the BL than non-BL group (Table S2). The BL group using oxaliplatin was characterized by a high rate of postoperative complications (Table S2).

3.3 | Derivation of cutoff points of APRI, FIB-4 score, ICG test result, and platelet count for BL prediction

We used ROC curve analyses to evaluate the diagnostic performance of the APRI, FIB-4 score, ICG test result, and platelet count for BL. In the assessment of the APRI for BL prediction, the area under the curve (AUC), sensitivity, and specificity of BL were 0.704, 65.4%, and 74.2%, respectively (Figure 2A, Table S3). Similarly, in the assessment of the FIB-4 score for BL prediction, the AUC, sensitivity, and specificity of BL were 0.719, 73.1%, and 65.2%, respectively (Figure 2B). In the assessment of the ICG

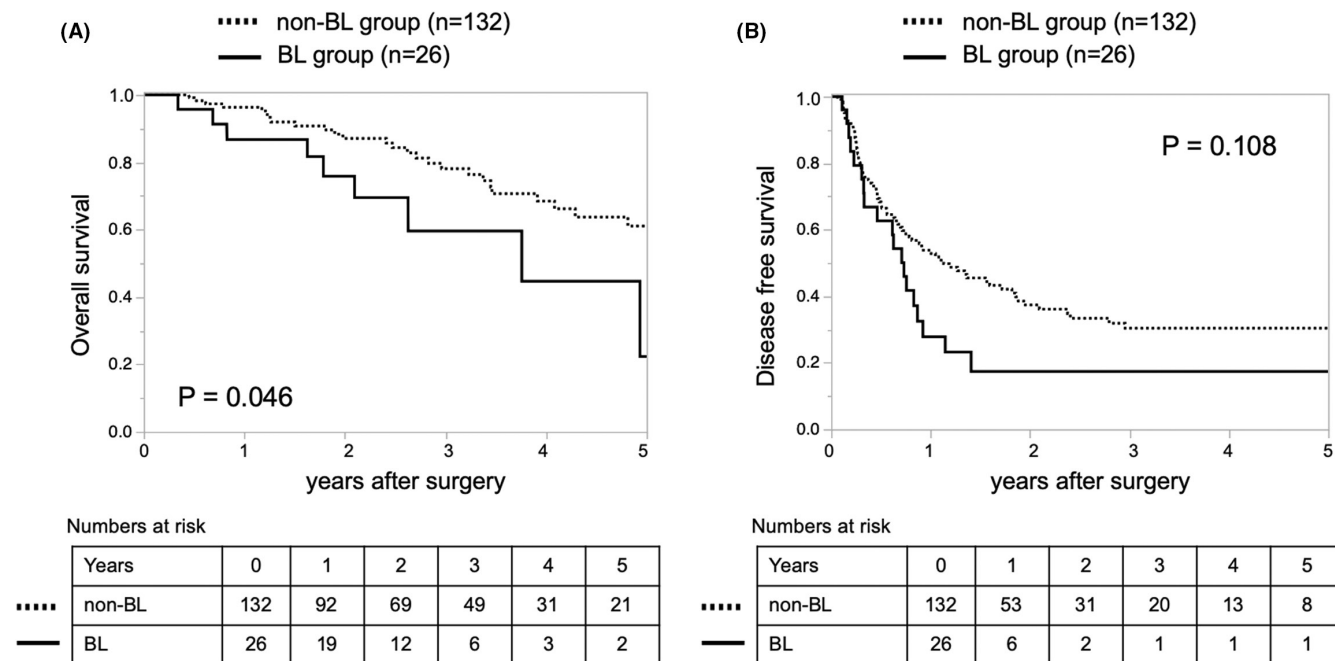


FIGURE 1 Kaplan–Meier analysis of (A) OS and (B) DFS in patients with CRLM divided into the BL group (n = 26) and non-BL group (n = 132). BL, blue liver; CRLM, colorectal liver metastasis; DFS, disease-free survival; OS, overall survival

test result for BL prediction, the AUC, sensitivity, and specificity of BL were 0.661, 61.5%, and 66.7%, respectively (Figure 2C). In the assessment of the platelet count for BL prediction, the AUC, sensitivity, and specificity of BL were 0.664, 80.8%, and 53.0%, respectively (Figure 2D).

3.4 | Establishment of APRI cutoff point for BL

The optimal cutoff point was 5.64 to classify patients into the high and low APRI groups (Figure 2A, Table S3). When comparing the two groups, the high APRI group had a worse prognosis than the low APRI group ($P = .012$) (Figure 3A). There was no significant difference in DFS between the two groups ($P = .199$) (Figure 3B). Therefore, even when classified by the APRI, the high APRI group showed no difference in DFS but had a significantly worse prognosis than the low APRI group.

3.5 | Poor DFS and OS in high TBS group

The 158 patients were divided into two groups using the overall mean of the TBS as a cutoff. The optimal cutoff point of the TBS was 5.2 to classify the patients into the high and low TBS groups. When comparing the two groups, the high TBS group had significantly worse DFS than the low TBS group ($P = .001$) (Figure S2A). Additionally, the high TBS group had significantly worse OS than the low TBS group ($P = .046$) (Figure S2B). These results were similar to those reported previously,¹⁴ indicating that the high TBS group had a high recurrence rate and a poor prognosis.

3.6 | APRI and TBS as independent predictors of OS after hepatectomy for CRLM

The univariate analysis showed that a high TBS ($P = .009$), the serum albumin concentration ($P = .009$), the ICG test result ($P = .034$), and the APRI ($P = .020$) were significantly associated with OS after resection for CRLM (Table 2). The multivariate analysis confirmed that the APRI (hazard ratio, 1.08; 95% confidence interval, 1.00–1.16; $P = .045$) and a high TBS (hazard ratio, 1.93; 95% confidence interval, 1.01–3.71; $P = .047$) were independently associated with OS in patients who underwent hepatectomy for CRLM (Table 2). APRI, not FIB-4, remained as a prognostic factor for OS among CRLM patients in univariate and multivariate analysis.

In this case, adjuvant chemotherapy was not a determinant of OS among patients treated with hepatectomy for colorectal liver metastasis in univariate and multivariate analysis (Table 2). As confirmed by the Kaplan–Meier curve, there was no difference regarding OS between the two groups with and without adjuvant chemotherapy (Figure S3).

4 | DISCUSSION

Oxaliplatin has previously been shown to cause liver sinusoidal injury and increase the APRI and FIB-4 score,⁸ and similar results were obtained in this study (Table 1). In a recent case report, oxaliplatin caused portal hypertension with resultant esophageal varices, gastric varices, and splenomegaly.¹⁷ Of course, portal hypertension in which collateral circulation appears can develop by other pathological mechanisms in patients with cancer. For example, patients with

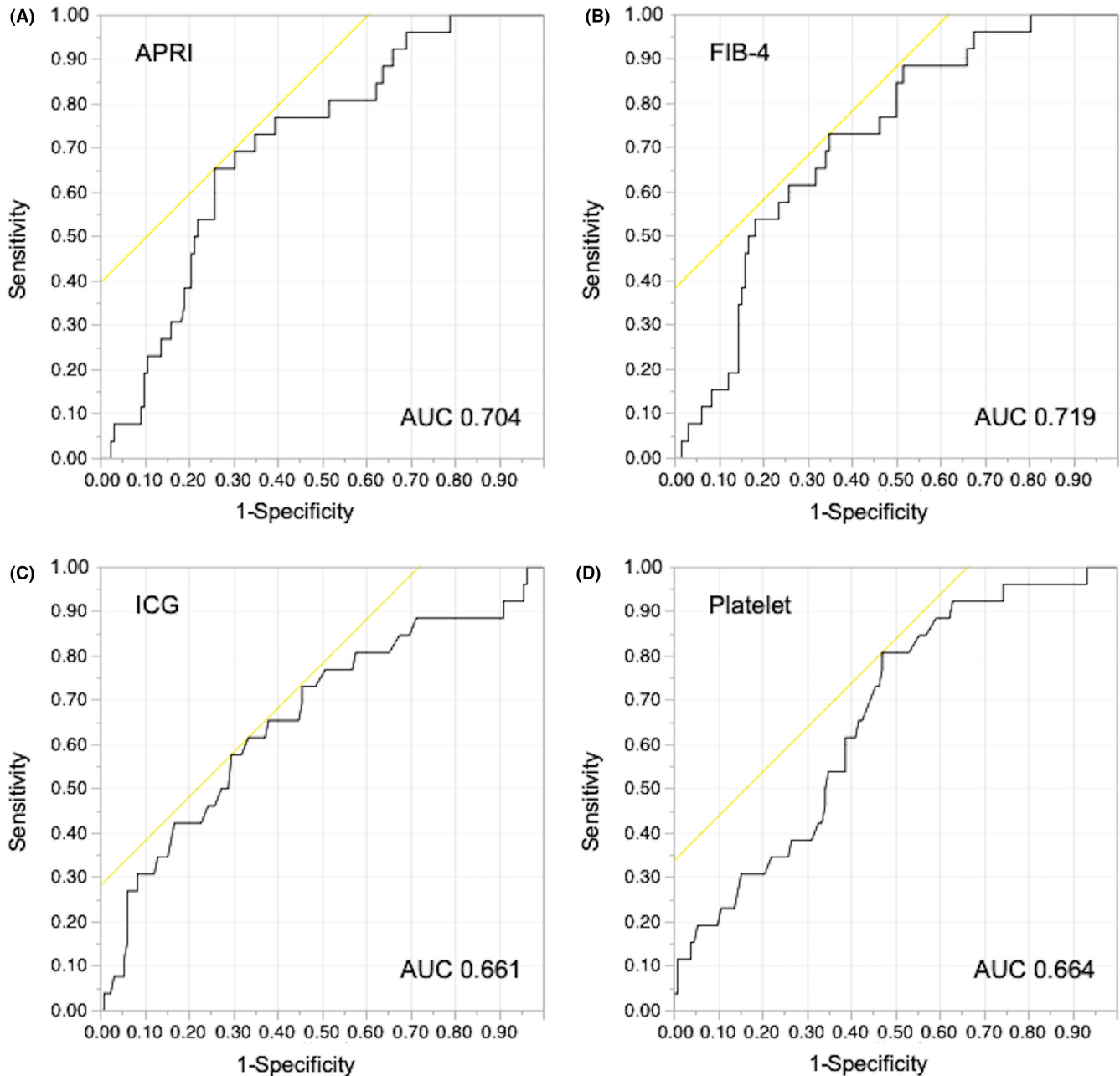


FIGURE 2 Receiver operating characteristic curves evaluating the accuracy of the (A) APRI, (B) FIB-4 score, (C) ICG test result, and (D) platelet count for the prediction of blue liver. APRI, aspartate aminotransferase to platelet ratio index; ICG, indocyanine green

liver sinusoid disorder (cancer-related portal hypertension) can develop acute liver failure owing to liver metastasis of cancer and portal hypertension.^{18,19} The main mechanism of this condition is that the portal vein is blocked by infiltration or a thrombus of the tumor itself, or the portal hypertension may be caused by extraductal compression of the portal vein by the tumor or lymphoid tissue; regardless, liver sinusoid disorder is considered a rare condition.¹⁹ According to previous studies, however, thrombocytopenia is an immunosuppressive and myelosuppressive mechanism that can be seen with ordinary chemotherapy, and portal hypertension caused by hepatic sinus disorder causes splenomegaly and prolongs thrombocytopenia.²⁰ Miura et al reported that the APRI is correlated with

the degree of increase in the spleen volume caused by oxaliplatin-induced SOS and that the APRI is useful for predicting SOS.²¹

Various *in vivo* studies have been conducted to examine the mechanism of SOS. One such study showed that oxaliplatin caused F-actin depolymerization in liver sinusoidal endothelial cells, increased the expression of matrix metalloproteinase (MMP)-9 and MMP-2, and destroyed the extracellular matrix in the space of Disse; additionally, erythrocytes reportedly penetrated the endothelium and occluded the downstream microvasculature.²² Therefore, it has been suggested that SOS may be prevented by inhibiting MMP-9 and preventing coagulation of the microvascular system. However, these findings have not been consistent. For

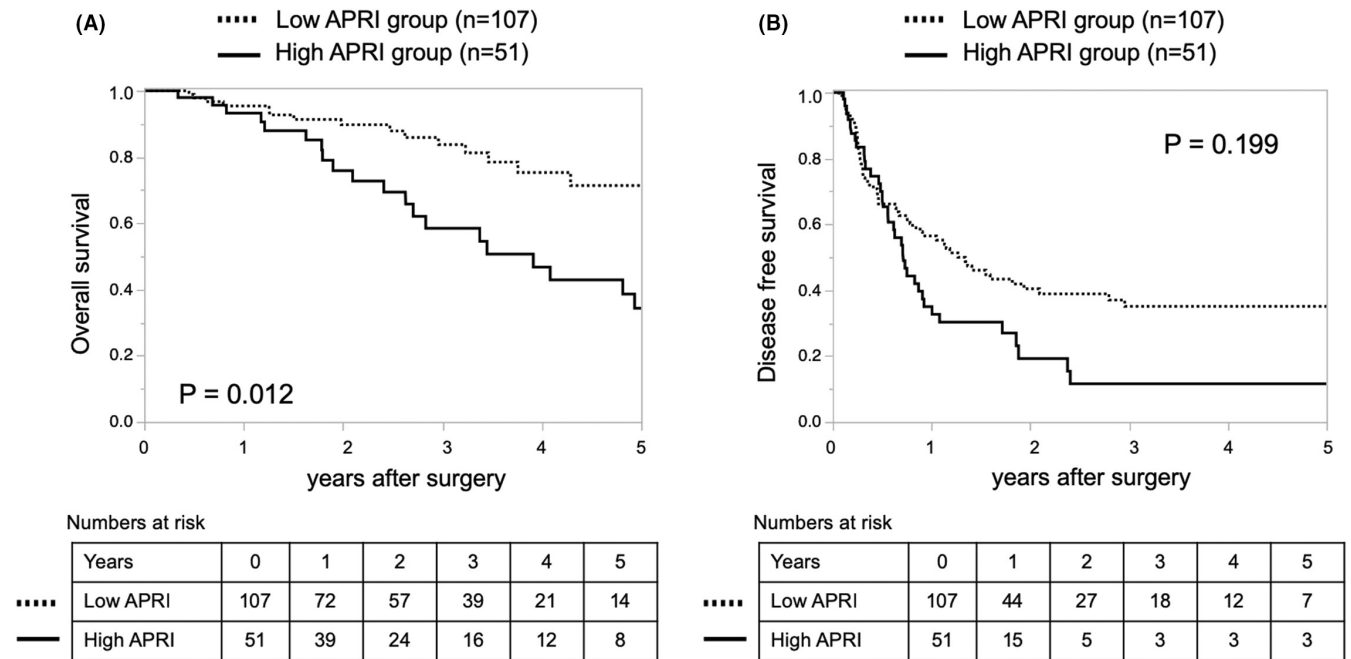


FIGURE 3 Kaplan–Meier analysis of (A) OS and (B) DFS for patients with CRLM stratified by the APRI (grouped by 5.64 as the cutoff value). APRI, aspartate aminotransferase to platelet ratio index; CRLM, colorectal liver metastases; DFS, disease-free survival; OS, overall survival

TABLE 2 Univariate and multivariate Cox regression analyses for overall survival

| Variable | Univariate analysis | | | Multivariate analysis | | |
|------------------------------------------------|---------------------|-----------|-------------|-----------------------|-----------|-------------|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Gender (male/female) | 1.05 | 0.56–1.98 | .879 | | | |
| Age (y) | 1.01 | 0.98–1.05 | .549 | | | |
| BMI (kg/m ²) | 1.02 | 0.92–1.13 | .640 | | | |
| CRC location (colon/rectum) | 0.58 | 0.31–1.10 | .097 | | | |
| CRC histology (well/moderate and poor) | 0.53 | 0.13–2.21 | .382 | | | |
| TBS (≥ 5.2 vs < 5.2) | 2.33 | 1.24–4.41 | .009 | 1.93 | 1.01–3.71 | .047 |
| Serum albumin (g/dL) | 0.32 | 0.14–0.74 | .009 | 0.47 | 0.19–1.18 | .108 |
| Total bilirubin (mg/dL) | 0.88 | 0.29–2.41 | .810 | | | |
| ICG test (%) | 1.08 | 1.01–1.15 | .034 | 1.06 | 0.98–1.13 | .134 |
| Platelet ($\times 10^4/\mu\text{L}$) | 0.97 | 0.91–1.02 | .236 | | | |
| AST (IU/L) | 1.03 | 0.99–1.05 | .080 | | | |
| ALT (IU/L) | 1.01 | 0.99–1.03 | .103 | | | |
| Cr (mg/dL) | 0.41 | 0.09–1.58 | .208 | | | |
| CEA (ng/mL) | 0.99 | 0.99–1.00 | .605 | | | |
| CA19-9 (ng/mL) | 1.00 | 0.99–1.00 | .408 | | | |
| Distribution (unilobar/bilobar) | 0.63 | 0.33–1.18 | .147 | | | |
| Timing of resection (synchronous/metachronous) | 1.09 | 0.58–2.07 | .771 | | | |
| Operative time (min) | 1.00 | 0.99–1.00 | .722 | | | |
| Blood loss (g) | 1.00 | 0.99–1.00 | .218 | | | |
| Postoperative complication CD (0–1/ ≥ 2) | 0.61 | 0.19–1.98 | .407 | | | |
| Adjuvant chemotherapy (yes/no) | 0.78 | 0.40–1.53 | .469 | | | |
| APRI score | 1.10 | 1.02–1.18 | .020 | 1.08 | 1.00–1.16 | .045 |
| FIB-4 score | 1.03 | 0.99–1.05 | .051 | | | |

Note: The high and low TBS groups were separated by a mean TBS of 5.2 (n = 158).

Boldface P-values are statistically significant.

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CD, Clavien–Dindo classification; CEA, carcinoembryonic antigen; CI, confidence interval; Cr, creatinine; CRC, colorectal cancer; HR, hazard ratio; ICG, indocyanine green; TBS, tumor burden score.

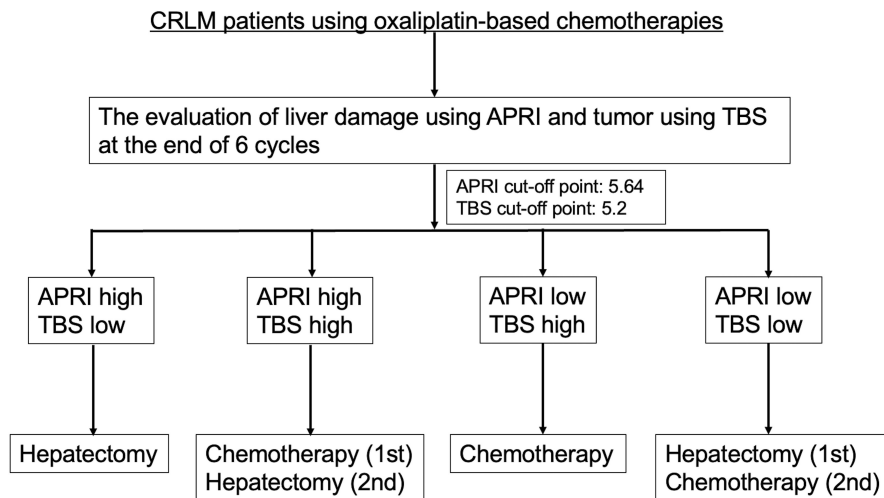


FIGURE 4 Treatment strategies for CRLM patients using oxaliplatin-based chemotherapies. CRLM, colorectal liver metastases

example, bevacizumab, an anti-vascular endothelial growth factor inhibitor that is often used in combination with oxaliplatin in patients with colorectal cancer, has been reported to either reduce SOS²³ or worsen SOS.²⁴ Although some reports have described experimental oxaliplatin-induced SOS,²⁵ the reproducibility of the results is questionable,^{26,27} and the exact mechanism has not yet been determined.

In this study we investigated the prognostic effects of oxaliplatin on liver damage. Preoperative oxaliplatin was used in 75 (47%) patients, 26 of whom were found to have BL during the operation. The APRI and FIB-4 score, which have been reported to be predictive markers for SOS, were significantly higher in the BL group than in the non-BL group (Table 1). The presence of BL cannot be determined immediately or regularly during chemotherapy. However, the APRI is reportedly useful for predicting the prognosis of BL.^{28,29} Using an ROC curve, we determined the cutoff value of the APRI as a factor to predict BL. When the patients were classified into two groups according to the APRI cutoff value, the high APRI group showed no difference in DFS but had a significantly worse prognosis than the low APRI group (Figure 3A,B). Univariate and multivariate analyses of OS of patients undergoing hepatectomy for CRLM revealed that the APRI and TBS were independent prognostic factors (Table 2). The TBS has been reported as an OS-independent factor in patients undergoing hepatectomy for CRLM,¹⁴ and a novel finding of the present study is that the APRI may also be an OS-independent factor in these patients. The reasons why the APRI was a prognostic factor include the possibility that postoperative adjuvant chemotherapy or second-line treatment could not be sufficiently performed because of liver damage. The use of oxaliplatin resulted in BL, which may reduce the dose intensity of chemotherapy or reduce the indication for re-hepatectomy.

It has been reported that FOLFOX therapy increases the risk of complications³⁰ and sinusoidal dilation³¹ after hepatectomy after six cycles or more. As shown in Table 1, the cases using oxaliplatin of six cycles or more suffered from liver damage, and the findings of blue liver were observed. Therefore, as shown in Figure 4, it is suggested that in CRLM patients using

oxaliplatin-based chemotherapies, it may be useful to evaluate liver damage using APRI at the end of six cycles. Based on the results of this study, we propose the following treatment strategies (Figure 4). If APRI is high and TBS is low, the treatment is hepatectomy, not continuing chemotherapy. If APRI is high and TBS is high, the treatment method is to continue chemotherapy as the first choice and hepatectomy as the second line, and consider according to each individual case. If APRI is low and TBS is high, the treatment is to continue chemotherapy. If APRI is low and TBS is low, the treatment method is hepatectomy as the first choice and to continue chemotherapy as the second line, and consider according to each individual case.

Our study had several limitations. First, it was a single-center retrospective study involving only 158 patients; therefore, the statistical power may be low. Second, because this was a retrospective study, it was not possible to compare blood data and imaging findings owing to differences in the number of chemotherapy courses and the contents of chemotherapy. Third, the degree of liver sinusoidal damage after chemotherapy was evaluated by the APRI; no supportive pathological data were available. However, previous studies have already shown that the APRI is an independent predictor of SOS in the resected liver after oxaliplatin use,⁸ and other studies have included it as an existing marker in SOS.^{28,29,32} On the basis of these findings, we considered it appropriate to adopt the APRI as an index of liver sinusoidal disorder. However, the fact that other diseases, such as idiopathic portal hypertension, could not be completely excluded because of a lack of pathological support that was considered a major limitation.

In conclusion, this study showed that the APRI and TBS in patients with CRLM were prognostic predictors after hepatectomy for metastatic liver cancer and that liver damage in patients treated with preoperative oxaliplatin had an effect on the prognosis.

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Ethical statements: This study protocol complied with the ethical guidelines of human clinical research established by the Japanese Ministry of Health, Labour and Welfare, as well as with the 1964 Helsinki Declaration and its later amendments, and was approved by the Ethics and Indications Committee of the National Hospital Organization Kyushu Cancer Center (No. 2019-54).

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SUPPORTING INFORMATION

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