**ORIGINAL ARTICLE**
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# Clinical significances of liver fibrotic markers in patients with cholangiocarcinoma after radical resections

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## ABSTRACT

**Objective:** We examined the relation between several fibrotic markers reflecting liver parenchymal injury and conventional liver function or surgical outcomes in 67 patients with cholangiocarcinoma who underwent biliary drainage for obstructive jaundice followed by surgical resection.

**Material and Methods:** We examined conventional clinicopathological factors, six hepatic fibrosis parameters, including platelet count, hyaluronic acid, Mac-2 binding protein glycosylation isomer (M2BPGi), type IV collagen 7S, aspartate aminotransferase-to-platelet ratio index (APRI), and FIB-4 index before hepatectomy, and surgical outcomes or long-term prognosis.

**Results:** Obstructive jaundice was observed in 57% of the patients, a history of biliary diseases in 7.5%, and chronic hepatic injuries in 17.9%. M2BPGi was significantly higher in patients with obstructive jaundice as the primary sign ($p< 0.05$), the FIB-4 index was significantly correlated with patient age ($p< 0.01$), and serum hyaluronic acid and T4C7 levels were significantly increased in distal cholangiocarcinoma (CC). No markers were associated with the histological hepatic fibrotic index, tumor-related factors, or postoperative morbidities. Tumor relapse was observed in 37% of patients, and cancer-related death was observed in 25%. A higher FIB-4 index was significantly associated with shorter cancer-free survival ($p< 0.05$). Cox multivariate analysis showed that bilirubin levels, poor histological cancer differentiation, and absence of fibrotic markers were associated with cancer-free, cancer-specific overall, and overall survival.

**Conclusion:** Although a sufficient relation exists between these markers and elastographic or histological fibrotic indexes, the clinical significance of measuring conventional fibrotic markers might no longer be necessary in future studies.

**Keywords:** Cholangiocarcinoma, obstructive jaundice, fibrotic markers, liver dysfunction, surgical outcomes, patient prognosis

## INTRODUCTION

In biliary tract carcinomas (BTC) with biliary obstruction and jaundice, the liver parenchyma or sinusoidal functions often show a macroscopically injured appearance, as black, dull, and fragile texture even after preoperative biliary drainage until the total bilirubin level is 2-3 mg/dL (1). This induces severe postoperative liver dysfunction and related biliary sepsis or hepatic failure (2,3) which are more unexpected based on the preoperative liver functional tests (2,3). In comparison with hepatocellular carcinoma (HCC) which has chronic background liver disease, rapid liver injury in BTC seems to be caused by different mechanisms. However, to date, it has been difficult to distinguish these different hepatic pathogeneses using conventional liver functional parameters such as indocyanine green (ICG) clearance test and liver scintigraphy (4).

Hepatic fibrosis is a significant potential factor among the impaired function causes of acute and chronic liver injury (5-10). Except for needle biopsy and resected specimen histology, representative direct liver fibrosis-associated surrogate markers in serum samples, such as type IV collagen hyaluronic acid (HA) and mac-2 binding protein glycosylation isomer (M2BPGi), have been investigated for decades (8-10). Furthermore, as non-invasive scoring systems based on liver functional parameters, decreased platelet count, increased aspartate aminotransferase-to-platelet ratio index (APRI), and FIB-4 index are often used to evaluate hepatic fibrosis and patient prognosis (9-11). These markers show not only the degree of fibrosis but also non-parenchymal cell or tissue damage of the liver, which is a useful surrogate marker of liver elastography (12). As previously reported, HA levels are well correlated with changes during liver failure after hepatectomy; M2BPGi is also a promising parameter for acute liver injury and a novel marker for assessing hepatic fibrosis that induces inflammatory cytokines

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and increases extracellular collagen or fibronectin levels (7,13). Bekki et al. have reported that stellate cells are a source of M2BPGi and that M2BPGi levels reflect the activation of these cells during acute liver fibrosis. To the best of our knowledge, the relation between these fibrotic markers and surgical outcomes in patients with BTC and obstructive jaundice has not been fully elucidated (14).

Therefore, we aimed to clarify which fibrotic markers are significantly related to postoperative lethal liver dysfunction. To achieve this aim, we collected data on fibrosis parameters and investigated the relation between conventional liver function or postoperative hepatic-related complications and these candidate markers in 67 patients with cholangiocarcinoma who underwent preoperative biliary drainage due to complete obstruction at a single academic cancer institute at the University of Miyazaki, Japan.

## MATERIAL and METHODS

### Patients

This study included 67 consecutive patients with BTC who were scheduled for surgery and admitted to the Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, University of Miyazaki Faculty of Medicine, Miyazaki, Japan for 7.5 years between April 2015 and September 2022. Patients with distant metastases or double cancer during surgery were excluded from the study. A radical hepatectomy was performed, and the hepatic tumors were completely resected without macroscopic exposure of the amputated sections to the remaining liver tissue. Before and after the primary treatment, serum tumor levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were measured as tumor markers of BTC every three months, and enhanced computed tomography (CT) of the liver was performed every six months after hepatectomy to monitor tumor recurrence. Mean follow-up period after hepatic resection in patients with cholangiocarcinoma (CC) who survived was 39 months (range, 12-86.5 months). This study adhered to the Declaration of Helsinki statement on the ethical principles for medical research involving human participants, including research on identifiable human materials and data. All the study protocols were approved by the Human Ethics Review Board of our institution (Approval number: O-1469; 22.12.2023). Patient agreement to participate in the study was obtained via an opt-out procedure for one month at the website and outpatient clinic of our institution. Anesthesia and patient data were retrieved from the the University of Miyazaki Hospital database.

### Measurement of Tumor Markers and Histological Findings

Patient clinicopathological data were retrieved from the archives of our institute. At our hospital, the normal levels of CEA, CA19-9, and Duke pancreas II monoclonal antibody (DUPAN-II) were determined to be <5 ng/mL, <37 U/mL, and 150 U/mL, respectively. Elevated levels were defined as those that exceeded the normal levels. Tumor-related factors were compared with the histopathological findings of the resected specimen. For the clinicopathological assessment of biliary tract carcinomas, we used the general rules for clinical and pathological studies on cancer of primary liver cancer and the biliary tract cancer (15,16).

### Measurement of Fibrotic Markers

Peripheral blood samples were collected from each patient early in the morning before surgery when the patient was stable. The blood samples were centrifuged at 3000 rpm for 15 min, and the obtained serum was stored at -80°C. HA was assayed using the sandwich binding protein assay by SRL Inc. (Tokyo, Japan) (7). The normal serum HA level reported by SRL Inc. is <50 ng/mL. M2BPGi levels were measured using a chemiluminescent enzyme immunoassay with anti-Wisteria floribunda agglutinin and anti-M2BP antibodies using a fully automated HSCL-2000i Immunoanalyzer (Sysmecs Co., Hyogo, Japan) (13). The cutoff value was set at <1 cutoff index (COI) according to the company's data. The serum 7S collagen concentration was measured using a type IV collagen 7S domain RIA kit (Diaiatron Co., Tokyo, Japan), which uses a polyclonal antibody against the 7S domain of type IV collagen isolated from the human placenta. The normal value was set at <8.0 ng/mL, according to company data. (17). The FIB-4 score was calculated as follows: age (years) × aspartate aminotransferase (AST) level (U/L)/platelet count ($10^9$/L) × alanine transaminase level (1/2 IU/L). According to the literature, the FIB-4 cutoff for fibrosis or cirrhosis (F3 and F4) is >3.25 (10). The APRI score was calculated by dividing the AST level by 30 (the upper limit of normal at our institute), multiplying it by 100, and dividing the total by the platelet count (11). We adopted the validated cutoff point with the presence of advanced fibrosis of 1.5, and a cutoff value of <0.5 predicted the absence of fibrosis. The histological fibrosis index was measured in some patients, following Knodell's method (18).

### Statistical Analysis

Differences in categorical data between the groups and prevalence were assessed using the Chi-square test, Fisher's exact test, or Dunnett's multiple comparison test. Differences in continuous data between the groups were evaluated using Student's t-test or the Mann-Whitney test. Continuous data was expressed as mean ± standard deviation, and median with quartile (25%, 75%). The correlation coefficient was calculated and tested for the correlation relation by Pearson's test. Disease-free interval and overall survival were calculated using the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test. Multivariate analysis was performed using a Cox proportional hazards

regression model. A two-tailed p value of <0.05 was considered significant. Statistical analyses were performed using the SAS software (Statistical Analysis System Inc., Cary, NC, USA).

## RESULTS

### Perioperative Parameters

Basic patient data were indicated as follows: The patients included 53 (79%) men and 14 (21%) women with a mean age of 71 ± 7.3 years [median 71 and (61, 75.8)] at the time of surgery. The tumor was located in the distal bile duct (Bd) in 24 patients, proximal bile duct in 14, both distal and proximal bile ducts (Bdp) in 12, and intrahepatic in 17. Obstructive jaundice was observed in 38 patients (57%), a history of biliary diseases in five (7.5%), chronic hepatic injuries in 12 (17.9%), diabetes in 20 (30%), smoking in 40 (59.7%), and other carcinomas in eight (11.9%). Mean levels of carcinoembryonic antigen (CEA) and cancer-antigen (CA) 19-9 were 6.3 ± 24 ng/mL (normal range: ≤5) and 4407 ± 32.735 ng/mL (normal range: ≤37) respectively, and median levels of these were 2.5 (1.7, 4.4) and 24 (7.5, 247), respectively. Preoperative liver functions showed that the mean and median ICGR15 were 10.3 ± 4.3 and 9.5% (6.6, 13.9), those of LHL15 were 0.94 ± 0.05 and 0.90 (0.90, 1.0), those of albumin level were 3.67 ± 0.59 and 3.69 mg/dL (3.42, 4.05), those of total cholesterol were 180 ± 58 and 176 mg/dL (152, 201), those of lymphocyte were 1461 ± 678 and 1320/mm$^3$ (974, 1816), those of CRP were 0.54 ± 0.72 and 0.24 mg/dL (0.10, 0.61), those of total bilirubin were 1.25 ± 2.28 and 0.70 mg/dL (0.6, 1.08), and those of prothrombin activity were 94 ± 20 and 91% (83, 103), respectively.

Operative procedures were pancreaticoduodenectomy (PD) in 34 patients (51%), partial or segmental hepatectomy in six (9%), hemihepatectomy with bile duct resection (BDR) in 26 (39%), and trisectionectomy with BDR in one. Combined resection of the hepatic artery in four (6%) patients, portal vein in one, and inferior vena cava in two. Macroscopic findings of the tumors were nodular in 24 patients (36%), flat in 23 (34%), papillary in 12 (18%), and mass-forming in 8 (12%). Mean and median tumor size was 4.0 ± 4.8 cm and 2.9 cm (2.1, 4.6), respectively. Histological differentiation was papillary in eight patients (12%), well in 23 (34%), moderate in 27 (41%), and poorly in nine (13%). The histological depth or extension of the tumor was Tis in two patients, T1 in eight (12%), T2 in 28 (42%), T3 in 27 (40%), and T4 in two. Histological vessel infiltration was positive in 12 patients (18%), which was portal veins in 11 patients (16%), and arteries in four (6%). Lymph node metastasis was observed in 18 patients (27%). Histological fibrosis was examined in 18 patients (27%), and the fibrotic grade was zero in seven, one in four, two in two, three in three, and four in two. Superficial extension >2 cm from the main tumor was observed in eight patients (12%). Surgical margin positivity was observed in eight patients (12%), including the hepatic duct side in six (9%), duodenal side in three (5%), and exposed margin in four (6%). Final tumor stage was I in 15 patients (22%), II in 39 (58%), III in seven (11%), and IV in six (9%). Curative resection was achieved in 59 patients (88%), and R1 in eight (12%). Postoperative complications of Clavien-Dindo III≤ were observed in 30 patients (45%) and mortality was nil. Adjuvant chemotherapy was not administered. Mean and median blood loss was 1202 ± 987 mL and 1010 mL (565, 1388), respectively, and those of operating time were 640 ± 655 minutes and 588 mL (491, 648), respectively. Postoperative complications were observed in 37 patients (55%), including hepatic failure in two, bile leakage in six (9%), pancreatic fistula in 14 (21%), uncontrolled ascites in nine (13%), and intra-abdominal abscess in 27 (40%).

Adjuvant chemotherapy was S-1 for six months in 19 patients (28%), gemcitabine and cisplatin for six months in one but nil in 47 patients (70%). Postoperative cancer recurrence was observed in 25 patients (37%), including the liver in eight, peritoneum in seven, lymph node in six, lung in four, local recurrence in two, and bone in one. Treatment for cancer recurrence included gemcitabine + cisplatin in 13 patients, gemcitabine + cisplatin + durvalumab in two, gemcitabine alone in one, gemcitabine +S-1 in one, and nil in 50 patients (75%). Mean and median cancer-free survival periods were 911 ± 610 and 809 days (380, 1257), respectively, and the overall survival periods were 1057 ± 580 and 924 days (575, 1446), respectively. A total of 37 patients (55%) were alive without cancer recurrence, ten (15%) were alive with cancer recurrence, 17 (2%) died due to cancer, and three (5%) died due to other causes.

### The Relation Between Clinicopathological Parameters and Each Fibrotic Marker

With respect to fibrotic markers, mean and median hyaluronic acid (HA) levels were 139 ± 332 and 81 ng/mL (40, 123), those of platelet count were 25 x $10^4$ ± 22 x $10^4$ and 21 x $10^4$/mm$^3$ (18 x $10^4$, 25 x $10^4$), those of M2BPGi level were 1.07 ± 0.54 and 1.00 C.O.I (0.71, 1.47), those of Type IV collagen 7S (T4C7) were 7.37 ± 5.61 and 5.5 ng/mL (5.03, 6.58), those of aspartate transaminase (AST) were 43 ± 77 and 25 IU/L (20, 35), those of alkaline phosphatase (ALP) were 455 ± 499 and 287 U/L (198, 405), those of APRI were 0.72 ± 1.46 and 0.40 (0.32, 0.61), and those of FIB-4 index were 4.09 ± 2.13 and 3.97 (2.38, 5.24), respectively. In 67 patients, relations of continuous data in each issue between the six types of fibrotic markers or scores and clinicopathological, surgical, and cancer recurrence after hepatectomy are shown in Table 1. In terms of patient demographics, M2BPGi was significantly higher in patients with obstructive jaundice as a primary sign ($p< 0.05$) but was not correlated with total bilirubin level just before surgery. The FIB-4 index significantly correlated with patient age ($p< 0.01$). With respect to tumor location, serum HA and T4C7 levels were significantly increased in distal CC (Bd) ($p< 0.01$). Although fibrotic markers were not associated with the histological fibrotic index, the number of patients examined was limited. Platelet count was significantly higher in

**Table 1.** Comparison of continuous parameters between fibrotic markers and clinicopathological parameters, surgical records, post-hepatectomy complications, and cancer recurrence in patients with cholangiocarcinoma (CC)

| | Platelet Count ($10^4$/mL) | HA (ng/mL) | Type4 collagen 7S (ng/mL) | M2BPGi (COI) | APRI | FIB-4 Index |
|---|---|---|---|---|---|---|
| Demographics | | | | | | |
| Sex, Male (n= 53) | 21.6 ± 6.9 | 152 ± 366 | 7.7 ± 6.1 | 1.08 ± 0.58 | 0.75 ± 1.62 | 4.1 ± 2.2 |
| Female (n= 14) | 35.8 ± 45.6* | 80 ± 57 | 5.9 ± 6.1 | 1.06 ± 0.78 | 0.61 ± 0.46 | 4.2 ± 2.1 |
| Obstructive jaundice, no (n= 29) | 28.8 ± 32.4 | 85 ± 52 | 6.4 ± 3.1 | 0.90 ± 0.46 | 0.53 ± 0.43 | 4.3 ± 2.1 |
| Yes (n= 38) | 22.2 ± 6.2 | 222 ± 527 | 8.7 ± 7.9 | 1.34 ± 0.62* | 0.86 ± 1.90 | 4.0 ± 2.2 |
| Chronic hepatitis, no (n= 55) | 22.3 ± 24 | 169 ± 415 | 7.7 ± 6.9 | 1.11 ± 0.60 | 0.74 ± 1.60 | 4.0 ± 2.1 |
| Yes (n= 12) | 21.0 ± 6.7 | 88 ± 54 | 6.9 ± 3.5 | 1.02 ± 0.51 | 0.62 ± 0.39 | 4.7 ± 2.4 |
| Diabetes, no (n= 47) | 26.2 ± 25.8 | 76 ± 49 | 6.7 ± 5.6 | 1.04 ± 0.58 | 0.78 ± 1.71 | 4.1 ± 2.3 |
| Yes (n= 20) | 20.6 ± 6.2 | 334 ± 662 | 9.8 ± 5.5 | 1.17 ± 0.53 | 0.57 ± 0.37 | 4.0 ± 1.6 |
| Tumor-factors | | | | | | |
| Location, Bd (n= 24) | 20.9 ± 6.6 | 1001 ± 1371** | 25 ± 9.9** | 1.99 ± 0.35 | 0.47 ± 0.37 | 4.3 ± 2.3 |
| Bp (n= 14) | 22.9 ± 9.3 | 79 ± 56 | 6.1 ± 1.6 | 1.16 ± 0.63 | 1.42 ± 0.35 | 4.6 ± 2.0 |
| Bpd (n= 12) | 22.0 ± 3.5 | 77 ± 11 | 5.2 ± 0.9 | 0.82± 0.50 | 0.61 ± 0.60 | 3.4 ± 1.5 |
| ICC (n= 17) | 32.8 ± 42 | 87 ± 51 | 6.4 ± 3.3 | 0.98 ± 0.45 | 0.58 ± 0.41 | 3.9 ± 1.3 |
| Vascular involvement, no (n= 55) | 25.1 ± 25 | 162 ± 416 | 8.1 ± 6.8 | 1.10 ± 0.60 | 0.76 ± 1.60 | 4.1 ± 2.2 |
| Yes (n= 12) | 21.8 ± 6.0 | 98 ± 58 | 6.1 ± 2.0 | 1.04 ± 0.50 | 0.55 ± 0.29 | 3.9 ± 2.0 |
| Node metastasis, no (n= 49) | 22.1 ±7.2 | 157 ± 373 | 6.9 ± 3.6 | 0.67 ± 0.48 | 1.07 ± 0.54 | 4.1 ± 1.8 |
| Yes (n= 18) | 31.2 ± 41 | 73 ± 31 | 9.5 ± 11 | 0.91 ± 0.55 | 1.07 ± 0.68 | 4.0 ± 2.9 |
| Fibrotic stage, 0 (n= 7) | 49.7 ± 63.4 | 55 ± 35 | 4.7 ± 0.8 | 0.69 ± 0.41 | 0.31 ± 0.14 | 2.9 ± 1.7 |
| 1 (n= 4) | 24.8 ± 4.5 | 101 ± 48 | 5.6 ± 1.1 | 1.31 ± 0.44 | 0.91 ± 0.55 | 5.1 ± 3.3 |
| 2 (n= 2) | 21.5 ± 3.5 | 79 ± 91 | 7.5 ± 1.0 | 1.16 ± 0.45 | 0.59 ± 0.32 | 3.2 ± 2.1 |
| 3 (n= 3) | 16.7 ± 10.3 | 144 ± 23 | 11 ± 5.5 | 0.84 ± 0.14 | 0.78 ± 0.48 | 4.9 ± 2.5 |
| 4 (n= 2) | 19.0 ± 2.8 | 129 ± 128 | 6.9 ± 2.4 | 1.23 ± 0.62 | 0.41 ± 0.05 | 4.8 ± 0.2 |
| Macroscopic finding, | | | | | | |
| Nodular (n= 24) | 22 ± 7.1 | 78 ± 49 | 6.9 ± 3.8 | 1.03 ± 0.68 | 0.43 ± 0.27 | 4.6 ± 2.1 |
| Mass-forming (n= 8) | 45 ± 60* | 95 ± 49 | 6.3 ± 1.9 | 1.12 ± 0.50 | 0.46 ± 0.28 | 5.7 ± 2.4 |
| Flat or ulcerative (n= 23) | 20 ± 4.2 | 275 ± 597 | 9.3 ± 9.0 | 1.16 ± 0.54 | 1.16 ± 2.41 | 4.2 ± 2.3 |
| Papillary (n= 12) | 26 ± 9.1 | 58 ± 43 | 5.8 ± 1.5 | 0.92 ± 0.58 | 0.25 ± 0.49 | 2.5 ± 1.6 |
| Histological differentiation | | | | | | |
| Papillary (n= 8) | 26.4 ± 8.5 | 63 ± 4.8 | 5.3 ± 1.1 | 1.06 ± 0.58 | 0.50 ± 0.39 | 3.5 ± 1.8 |
| Well (n= 23) | 19.3 ± 4.2 | 89 ± 47 | 6.8 ± 3.7 | 1.14 ± 0.57 | 1.04 ± 2.39 | 4.9 ± 2.1 |
| Moderately (n= 27) | 28.6 ± 33.6 | 200 ± 491 | 8.5 ± 8.0 | 0.98 ± 0.59 | 0.62 ± 0.58 | 3.8 ± 2.2 |
| Poorly (n= 9) | 23.8 ± 6.8 | 118 ± 78 | 7.5 ± 2.3 | 1.34 ± 0.53 | 0.39 ± 0.16 | 3.3 ± 1.7 |
| Tumor factor, ECC | | | | | | |
| 1 (n= 9) | 22.8 ± 3.9 | 52 ± 12 | 5.6 ± 1.0 | 0.97 ± 0.62 | 0.44 ± 0.21 | 4.2 ± 1.3 |
| 2 (n= 21) | 22.4 ± 8.6 | 68 ± 44 | 9.2 ± 9.3 | 1.12 ± 0.80 | 1.15 ± 2.53 | 4.7 ± 2.2 |
| 3 (n= 18) | 20.4 ± 6.1 | 95 ± 60 | 8.4 ± 6.5 | 1.27 ± 0.53 | 0.49 ± 0.38 | 3.7 ± 2.2 |
| 4 (n= 2) | 21.5 ± 2.2 | 61 ± 29 | 6.8 ± 2.1 | 1.44 ± 0.57 | 0.71 ± 0.28 | 2.2 ± 1.3 |
| ICC | | | | | | |
| 1 (n= 1) | 14 | 146 | 17.1 | 0.74 | 0.6 | 5.5 |
| 2 (n= 7) | 21.6 ± 8.2 | 97 ± 55 | 5.7 ± 0.8 | 1.08 ± 0.62 | 0.70 ± 0.52 | 5.5 ± 2.3 |
| 3 (n= 9) | 43.6 ± 56.2 | 73 ± 48 | 5.6 ± 2.1 | 0.92 ± 0.36 | 0.48 ± 0.38 | 2.5 ± 1.5 |
| Postoperative complication | | | | | | |
| No (n= 30) | 28.1 ± 32.2 | 184 ± 448 | 7.0 ± 4.3 | 1.01 ± 0.45 | 0.48 ± 0.35 | 4.3± 2.6 |
| Yes (n= 37) | 21.6 ± 5.1 | 85 ± 46 | 7.8 ± 7.1 | 1.15 ± 0.68 | 0.92 ± 1.93 | 3.9 ± 1.7 |
| CD≤ 2 (n= 12) | 19.8 ± 5.0 | 81 ± 44 | 11.7 ± 11.4 | 1.24 ± 0.72 | 0.77 ± 0.71 | 4.5 ± 2.1 |
| CD≥ 3 (n= 25) | 225 ± 5.0 | 87 ± 48 | 5.6 ± 1.1 | 1.10 ± 0.69 | 0.98 ± 2.31 | 3.6 ± 1.5 |
| Bile leakage, no (n= 31) | 21.9 ± 5.0 | 92 ± 48 | 8.5 ± 7.9 | 1.17 ± 0.64 | 0.92 ± 2.08 | 3.8 ± 1.7 |
| Yes (n= 6) | 20.2 ± 6.2 | 64 ± 30 | 5.4 ± 0.4 | 1.22 ± 0.70 | 0.89 ± 0.82 | 4.1 ± 2.1 |
| Pancreatic fistula, no (n= 23) | 22.7 ± 5.0 | 79 ± 46 | 8.1 ± 8.0 | 0.85 ± 0.56 | 0.68 ± 0.57 | 3.8 ± 2.0 |
| Yes (n= 14) | 19.9 ± 5.0 | 107 ± 36 | 6.7 ± 2.8 | 0.97 ± 0.56 | 1.31 ± 3.07 | 4.0 ± 1.3 |
| Long-term ascites, no (n= 28) | 21.1 ± 5.1 | 74 ± 34 | 8.7 ± 8.8 | 0.97 ± 0.59 | 1.02 ± 2.20 | 3.9 ± 1.8 |
| Yes (n= 9) | 23.0 ± 5.0 | 107 ± 59 | 6.2 ± 1.5 | 1.51 ± 0.75 | 0.59 ± 0.37 | 4.0 ± 1.5 |
| Intraabdominal abscess, no (n= 10) | 20.9 ± 4.8 | 108 ± 89 | 6.0 ± 1.5 | 1.00 ± 0.53 | 0.68 ± 0.37 | 3.7 ± 1.7 |
| Yes (n= 27) | 21.9 ± 5.3 | 88 ± 35 | 8.8 ± 8.8 | 1.22 ± 0.75 | 1.00 ± 2.25 | 3.9 ± 1.8 |

**Table 1.** Comparison of continuous parameters between fibrotic markers and clinicopathological parameters, surgical records, post-hepatectomy complications, and cancer recurrence in patients with cholangiocarcinoma (CC) (continue)

| | Platelet Count ($10^4$/mL) | HA (ng/mL) | Type4 collagen 7S (ng/mL) | M2BPGi (COI) | APRI | FIB-4 Index |
|---|---|---|---|---|---|---|
| Tumor recurrence, | | | | | | |
| No (n= 42) | 26.1 ± 27.3 | 86 ± 52 | 7.4 ± 6.5 | 1.18 ± 0.58 | 0.76 ± 1.80 | 4.5 ± 2.1 |
| Yes (n= 25) | 21.9 ± 6.4 | 231 ± 549 | 7.3 ± 3.9 | 0.88 ± 0.50 | 0.65 ± 0.54 | 3.3 ± 2.0 |
| Prognosis, alive (n= 37) | 26.4 ± 29.0 | 87 ± 52 | 7.6 ± 7.0 | 1.21 ± 0.61 | 0.80 ± 1.91 | 4.5 ± 2.1 |
| Recurrent alive (n= 10) | 23.6 ± 7.1 | 80 ± 55 | 6.4 ± 1.8 | 0.69 ± 0.29 | 0.44 ± 0.32 | 3.4 ± 2.3 |
| Cancer death (n= 17) | 21.9 ± 6.4 | 323 ± 722 | 7.7 ± 5.3 | 1.04 ± 0.57 | 0.72 ± 0.61 | 3.8 ± 0.8 |
| Other death (n= 3) | 19.0 ± 3.5 | 105 ± 63 | 7.5 ± 1.6 | 1.10 ± 0.43 | 0.64 ± 0.48 | 7.5 ± 2.0 |

The clinicopathological findings and TNM classification were based on the general rules for clinical and pathological studies on cancer of the biliary tract and primary liver cancer (15,16).
HA: Hyaluronic acid; M2BPGI: Mac-2 binding protein glycosylation isomer; APRI: Aspartate aminotransferase-to-platelet ratio.
n.s.: not significant with p-value >0.10, Wilcoxon test or Scheffe's multiple comparison test.
*p< 0.05, **p< 0.01

macroscopically mass-forming CC located in the liver or perihilar lesions (p< 0.05). No fibrotic markers were significantly different among other tumor-related factors, postoperative complications, or patient prognosis. Among the fibrotic parameters (Table 2), platelet count was negatively correlated with the FIB-4 index (p< 0.01), and T4C7 was positively correlated with the FIB-4 index (p< 0.05). HA was negatively correlated with serum albumin level and positively correlated with total bilirubin level (p< 0.01). The APRI was significantly associated with CRP and total bilirubin level (p< 0.01).

### The Relation Between Preoperative Fibrotic Parameter Levels and Post-Hepatectomy Disease-Free and Overall Survival

Table 3 shows the cancer-free, overall, and cancer-specific overall rates, and the differences in each clinicopathological parameter of the entire CC. Tumor relapse was observed in 25 (37%) patients, and the one-, three- and five-year cancer-free survival rates were 77%, 64%, and 57%, respectively, with a median survival of 57 months. Cancer deaths occurred in 17 patients (25%), and the three-, five-, and seven-year overall

**Table 2.** Correlative relation between fibrotic markers in patients with cholangiocarcinoma (CC)

| | Platelet Count ($10^4$/mL) | HA (ng/mL) | Type 4 Collagen 7S (ng/mL) | M2BPGi (COI) | APRI | FIB-4 Index |
|---|---|---|---|---|---|---|
| Correlations (r) | | | | | | |
| Demographics | | | | | | |
| Age | 0.094 | 0.017 | 0.036 | -0.019 | 0.149 | 0.312** |
| Tumor factors | | | | | | |
| Tumor size | 0.052 | -0.052 | -0.051 | 0.177 | 0.060 | 0.012 |
| Carcinoembryonic antigen | 0.046 | -0.057 | -0.0009 | 0.080 | 0.103 | -0.010 |
| Cancer antigen 19-9 | 0.029 | -0.017 | 0.106 | 0.243 | -0.029 | 0.174 |
| Surgical records | | | | | | |
| Blood loss | -0.038 | 0.144 | 0.192 | -0.027 | -0.015 | -0.165 |
| Fibrotic parameters | | | | | | |
| Platelet count | - | -0.104 | -0.179 | -0.004 | -0.100 | -0.328** |
| HA | -0.104 | - | 0.306 | 0.250 | 0.146 | 0.012 |
| Type IV collagen 7S | -0.179 | 0.306 | - | 0.067 | -0.003 | 0.407* |
| M2BPGi | -0.0004 | 0.250 | 0.067 | - | 0.055 | 0.308 |
| APRI | -0.100 | 0.146 | -0.003 | 0.055 | - | 0.012 |
| FIB-4 index | -0.328** | 0.012 | 0.407* | 0.308 | 0.012 | - |
| Immuno-nutritional index and tumor marker | | | | | | |
| Albumin | -0.008 | -0.345** | 0047 | -0297** | -0.113 | -0.109 |
| Total cholesterol | 0.007 | -0.080 | -0.002 | -0.135 | -0.075 | -0.014 |
| Lymphocyte count | -0.148 | 0.023 | 0.0003 | 0.152 | -0.023 | -0.007 |
| C-reactive protein | -0.054 | 0.213 | 0.052 | -0.020 | 0.439** | -0.099 |
| Total bilirubin | -0.044 | 0.560** | 0.199 | -0.153 | 0.609** | -0.091 |
| Prothrombin activity | 0.048 | -0.206 | -0.103 | -0.249 | -0.058 | -0.039 |

HA: Hyaluronic acid; M2BPGI: Mac-2 binding protein glycosylation isomer; APRI: Aspartate aminotransferase-to-platelet ratio.
*p< 0.05, **p< 0.01, Pearson correlation coefficient test.

**Table 3.** Relationship between fibrotic markers or parameters, and survivals in 67 patients with CC undergoing surgical resections using the log-rank test under Kaplan-Meier survival curves

| | Cancer-Free Survival (years) | Significance p | Cancer-Specific Overall Survival (years) | Significance p | Overall Survival (years) | Significance p |
|---|---|---|---|---|---|---|
| | 1 3 5 | | 3 5 7 | | 3 5 7 | |
| Age, <70 (n= 49) | 75 56 47 | 0.028 | 68 59 47 | 0.10 | 66 54 43 | 0.13 |
| ≥70 (n= 18) | 89 83 83 | | 89 89 - | | 81 81 - | |
| Sex, Male (n= 53) | 72 61 56 | 0.29 | 73 73 53 | 0.92 | 68 64 48 | 0.63 |
| Female (n= 14) | 100 77 64 | | 79 59 59 | | 79 59 59 | |
| Jaundice, no (n= 29) | 72 68 68 | 0.44 | 82 82 82 | 0.20 | 79 79 79 | 0.16 |
| Yes (n= 38) | 82 61 48 | | 67 57 38 | | 68 68 32 | |
| Chronic liver injury, no (n= 55) | 78 64 59 | 0.87 | 68 68 51 | 0.13 | 64 60 45 | 0.08 |
| Yes (n= 12) | 75 66 50 | | 100 67 67 | | 100 67 67 | |
| Diabetes, no (n= 47) | 78 66 62 | 0.39 | 76 67 67 | 0.55 | 73 64 64 | 0.25 |
| Yes (n= 20) | 75 59 47 | | 70 70 34 | | 65 54 27 | |
| Laboratory data | | | | | | |
| Platelet count ($10^4$/mL), ≥15 (n= 60) | 81 65 57 | 0.53 | 75 68 51 | 0.81 | 71 62 46 | 0.96 |
| <15 (n= 7) | 57 57 - | | 69 69 69 | | 69 69 69 | |
| HA (ng/mL), <100 (n= 29)† | 82 66 51 | 0.61 | 79 63 42 | 0.34 | 79 56 38 | 0.59 |
| ≥100 (n= 18) | 75 75 - | | 92 92 92 | | 82 82 82 | |
| Type IV collagen 7S (ng/mL), <5.5 (n= 44)† | 79 69 60 | 0.56 | 72 62 0 | 0.20 | 72 62 0 | 0.73 |
| ≥5.5 (n= 15) | 73 57 57 | | 82 82 82 | | 75 60 60 | |
| M2BPGi (COI), <1 (n= 16)†† | 69 61 51 | 0.43 | 88 58 58 | 0.67 | 82 54 54 | 0.69 |
| ≥1 (n= 17) | 88 74 55 | | 77 77 0 | | 77 64 0 | |
| APRI, ≥0.56 (n= 14) | 71 64 51 | 0.84 | 70 70 35 | 0.55 | 62 62 31 | 0.49 |
| <0.56 (n= 53) | 79 64 60 | | 75 66 66 | | 74 61 61 | |
| FIB-4 index, <2.5 (n= 34) | 88 81 76 | 0.012 | 68 68 45 | 0.49 | 63 56 38 | 0.36 |
| ≥2.5 (n= 33) | 68 48 40 | | 80 68 68 | | 77 66 66 | |
| Alkaline phosphatase (U/l), <450 (n= 48) | 75 61 56 | 0.34 | 75 62 62 | 0.88 | 73 57 57 | 0.92 |
| ≥450 (n= 19) | 84 73 63 | | 73 73 48 | | 67 67 44 | |
| Albumin (g/dL), ≥4 (n= 19) | 74 51 51 | 0.37 | 72 72 72 | 0.54 | 72 72 72 | 0.32 |
| <4 (n= 48) | 79 70 60 | | 75 66 44 | | 71 58 38 | |
| Total cholesterol (mg/dL), ≥180 (n= 28) | 85 63 56 | 0.81 | 65 43 43 | 0.28 | 65 43 43 | 0.63 |
| <180 (n= 39) | 72 64 59 | | 82 82 61 | | 74 70 52 | |
| Lymphocyte (/$mm^3$), ≥1500 (n= 28) | 82 71 61 | 0.48 | 79 79 40 | 0.53 | 79 70 35 | 0.49 |
| <1500 (n= 39) | 74 59 54 | | 71 61 61 | | 64 55 55 | |
| Total bilirubin (mg/dL), <1 (n= 49) | 86 69 63 | 0.040 | 80 80 53 | 0.058 | 78 74 49 | 0.053 |
| ≥1 (n= 18) | 56 50 40 | | 59 47 47 | | 51 41 41 | |
| Tumor-related factor | | | | | | |
| CEA, <5 ng/mL (n= 55) | 76 67 58 | 0.75 | 77 69 55 | 0.52 | 73 62 49 | 0.78 |
| ≥5 (n= 12) | 83 52 52 | | 63 63 - | | 64 64 - | |
| CA19-9, <37 U/L (n= 40) | 78 64 57 | 0.89 | 78 78 59 | 0.47 | 77 69 52 | 0.55 |
| ≥37 (n= 27) | 78 64 56 | | 66 55 55 | | 63 53 53 | |
| Location, distal BD (n= 24) | 66 57 57 | 0.39 | 69 69 69 | 0.68 | 59 59 59 | 0.51 |
| Proximal (n= 14) | 100 76 76 | | 75 75 75 | | 68 68 68 | |
| Proximal to distal (n= 12) | 83 75 50 | | 71 71 0 | | 71 54 0 | |
| Intrahepatic (n= 17) | 71 58 48 | | 86 57 57 | | 86 57 57 | |
| Tumor size, <30 mm (n= 35) | 74 56 50 | 0.16 | 74 59 59 | 0.72 | 66 53 53 | 0.55 |
| ≥30 mm (n= 32) | 81 73 65 | | 74 74 49 | | 74 68 46 | |
| Macroscopic finding, papillary (n= 12) | 92 83 83 | 0.40 | 83 83 83 | 0.41 | 74 62 62 | 0.63 |
| Nodular (n= 24) | 75 61 - | | 62 62 - | | 63 63 - | |
| Flat, ulcerative (n= 23) | 78 63 47 | | 75 64 32 | | 71 61 31 | |
| Mass-forming (n= 8) | 63 50 50 | | 88 88 88 | | 88 88 88 | |
| Node metastasis, no (n= 49) | 86 79 68 | <0.001 | 84 75 60 | 0.009 | 79 67 53 | 0.036 |
| Yes (n= 18) | 56 25 - | | 40 40 - | | 41 41 - | |
| Vascular involvement, no (n= 55) | 80 66 62 | 0.21 | 74 74 55 | 0.91 | 71 68 51 | 0.66 |
| Yes (n= 12) | 67 58 39 | | 73 37 37 | | 66 33 33 | |

**Table 3.** Relationship between fibrotic markers or parameters, and survivals in 67 patients with CC undergoing surgical resections using the log-rank test under Kaplan-Meier survival curves (continue)

| | Cancer-Free Survival (years) | | | Significance p | Cancer-Specific Overall Survival (years) | | | Significance p | Overall Survival (years) | | | Significance p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 3 | 5 | | 3 | 5 | 7 | | 3 | 5 | 7 | |
| Histological differentiation, papillary (n= 8) | 100 | 88 | - | 0.006 | 88 | 88 | 88 | 0.14 | 88 | 66 | 66 | 0.41 |
| Well (n= 23) | 96 | 90 | 68 | | 90 | 77 | 38 | | 78 | 68 | 34 | |
| Moderately (n= 27) | 63 | 42 | 42 | | 58 | 58 | 58 | | 58 | 58 | 58 | |
| Poorly (n= 9) | 55 | 44 | - | | 70 | 70 | 70 | | 70 | 70 | 70 | |
| Tumor factor, ECC t1 (n= 9) | 100 | 100 | - | 0.0017 | 100 | 100 | - | 0.14 | 100 | 80 | - | 0.28 |
| t2 (n= 21) | 86 | 75 | 75 | | 74 | 74 | 74 | | 62 | 62 | 62 | |
| t3 (n= 18) | 61 | 42 | - | | 50 | 50 | 50 | | 50 | 50 | 50 | |
| t4 (n= 2) | 100 | 50 | 0 | | 50 | 50 | 0 | | 50 | 50 | 0 | |
| ICC t1 (n= 1) | 100 | 100 | - | | 100 | - | - | | 100 | - | - | |
| t2 (n= 7) | 71 | 71 | - | | 100 | 100 | - | | 100 | 100 | - | |
| t3 (n= 9) | 67 | 40 | 40 | | 71 | 48 | 48 | | 71 | 47 | 47 | |
| Fibrotic stage, 0 (n= 7)[#] | 71 | 57 | 29 | 0.41 | 85 | 43 | - | 0.82 | 86 | 43 | - | 0.63 |
| 1 (n= 4) | 100 | 75 | - | | 75 | 75 | - | | 75 | 75 | - | |
| 2 (n= 2) | 100 | 50 | - | | 100 | 100 | - | | 100 | 100 | - | |
| 3 (n= 3) | 33 | 33 | - | | 100 | 100 | 100 | | 100 | 100 | 100 | |
| 4 (n=2) | 100 | - | - | | 100 | 100 | - | | 50 | 50 | - | |
| Superficial extension >2 cm, no (n= 59) | 78 | 65 | 58 | 0.94 | 75 | 69 | 55 | 0.81 | 71 | 65 | 52 | 0.42 |
| Yes (n= 8) | 75 | 63 | - | | 70 | 70 | - | | 70 | 0 | - | |
| Operation, PD (n= 34) | 70 | 61 | 61 | 0.56 | 68 | 68 | 68 | 0.28 | 64 | 57 | 57 | 0.28 |
| Hepatectomy (n= 33) | 85 | 67 | 56 | 0.95 | 81 | 69 | 46 | 0.56 | 78 | 67 | 44 | 0.19 |
| Limited resection (n= 3) | 67 | 67 | - | | 100 | 100 | - | | 100 | 100 | - | |
| Segmentectomy (n= 3) | 100 | 50 | - | | 100 | 100 | - | | 100 | 100 | - | |
| Hemihepatectomy (n= 27) | 85 | 68 | 56 | | 78 | 67 | 67 | | 75 | 64 | 43 | |
| Combined vascular resection | | | | | | | | | | | | |
| Hepatic artery (n= 4) | 75 | - | - | 0.65 | 0 | - | - | 0.18 | 0 | - | - | 0.21 |
| IVC, PV (n= 2) | 50 | - | - | | 100 | 100 | - | | 100 | 100 | - | |
| Morbidity, C-D 0-2 (n= 37) | 81 | 72 | 62 | 0.24 | 80 | 72 | 58 | 0.41 | 74 | 63 | 51 | 0.75 |
| C-D 34 (n= 30) | 73 | 53 | 53 | | 62 | 62 | - | | 62 | 62 | - | |
| Hepatic failure (n= 2) | 50 | 50 | - | 0.38 | 50 | - | - | 0.091 | 50 | - | - | 0.11 |
| Bile leakage (n= 6) | 67 | 25 | 25 | 0.039 | 42 | 42 | - | 0.013 | 42 | 42 | - | 0.023 |
| Pancreatic fistula (n= 14) | 72 | 72 | 72 | 0.0016 | 77 | 77 | 77 | 0.73 | 56 | 56 | 56 | 0.73 |
| Prolonged ascites (n= 9) | 89 | 51 | 51 | 0.67 | 77 | 70 | 56 | 0.43 | 72 | 63 | 51 | 0.61 |
| Intraabdominal abscess (n= 9) | 83 | 83 | 0 | 0.67 | 63 | 63 | 63 | 0.26 | 56 | 46 | 46 | 0.12 |
| Blood loss, <1500 mL (n= 51) | 100 | 100 | 0 | 0.87 | 85 | 77 | 58 | 0.00025 | 80 | 70 | 52 | 0.008 |
| ≥1500 mL (n= 16) | 50 | 25 | - | | 20 | 20 | - | | 20 | 20 | - | |
| Curability, R0 (n= 59) | 76 | 63 | 60 | 0.97 | 75 | 68 | 68 | 0.31 | 72 | 63 | 63 | 0.12 |
| R1 (n= 8) | 88 | 77 | 0 | | 73 | 73 | 0 | | 63 | 63 | 0 | |
| hm1 (n= 6) | 83 | 83 | 0 | 0.87 | 83 | 83 | 0 | 0.61 | 83 | 83 | 0 | 0.70 |
| dm1 (n= 3) | 100 | 100 | 0 | 0.81 | 100 | 100 | 0 | 0.93 | 67 | 67 | 0 | 0.33 |
| em1 (n= 4) | 50 | 25 | - | 0.028 | 25 | - | - | 0.00029 | 25 | - | - | 0.0006 |
| Adjuvant chemotherapy, no (n= 47) | 89 | 76 | 70 | 0.0004 | 81 | 81 | 60 | 0.030 | 75 | 71 | 53 | 0.095 |
| Yes (n= 20) | 50 | 37 | 25 | | 57 | 38 | 38 | | 57 | 38 | 38 | |
| Treatments for cancer recurrence, no (n= 50) | - | | | - | 92 | 83 | 83 | <0.0001 | 87 | 75 | 75 | <0.0001 |
| Yes (n= 17)[‡] | - | | | | 21 | 21 | 11 | | 21 | 21 | 11 | |

The clinicopathological findings and TNM classification were based on the general rules for clinical and pathological studies on cancer of the biliary tract and primary liver cancer. (15,16)

C-D: Clavien-Dindo classification (40)

Cancer recurrence: None (n= 40, 61%); peritoneal dissemination (n= 7); liver (n= 8); lymph node (n= 6); local (n= 3); lung (n= 3); or bone (n= 1).

Prognosis: Survival without recurrence (n= 37, 55%), survival with CC recurrence (n= 10), death from CC (n= 17), and other related deaths (n= 3).

[#]n= 18, [†]n= 59, [††]n= 33.

[‡]: Gemcitabine alone (n= 1), gemcitabine plus CDDP (n= 14), durvalumab plus gemcitabine plus CDDP (n= 2).

survival rates were 74%, 68%, and 54%, respectively, with a median survival period of 64.7 months. With respect to fibrotic markers, lower T4C7 levels tended to be associated with a shorter cancer-specific overall survival period, but this was not statistically significant. A higher FIB-4 index was significantly associated with shorter cancer-free survival ($p< 0.05$). Other fibrotic markers were not significantly associated with survival. With respect to other laboratory parameters, a total bilirubin level over 1 mg/dL was significantly associated with shorter cancer-free survival, cancer-specific survival, and overall survival periods. Table 4 shows the results of Cox multivariate analysis using significant prognostic factors (p-value less than 0.20 identified by univariate analysis) with respect to CC-free and cancer-specific overall survival rates, including the candidate fibrotic parameters. A preoperative total bilirubin level over 1 mg/dL, lower histological differentiation, increased T-factors, postoperative bile leakage, and exposed margin positivity were independently associated with cancer-free

**Table 4.** Multivariate analysis of prognostic factors influencing cancer-free, cancer-specific and overall survival using Cox proportional hazard test in 67 patients with CC undergoing surgical resection

| | Cancer-Free Survival | | Cancer-Specific Overall Survival | | Overall Survival | |
|---|---|---|---|---|---|---|
| **Variables** | **Rr* (95% CI)** | **p** | **Rr (95% CI)** | **p** | **Rr (95% CI)** | **p** |
| Age, <70 (n= 49) | | | | | | |
| ≥70 (n= 18) | 0.18 (0.03-1.00) | 0.050 | 0.11 (0.01-1.67) | 0.11 | 0.25 (0.06-1.01) | 0.056 |
| Jaundice, no (n= 29) | | | | | | |
| Yes (n= 38) | | | 7.72 (1.31-45.6) | 0.024 | 2.38 (0.86-6.59) | 0.094 |
| Chronic liver injury, no (n= 55) | | | | | | |
| Yes (n= 12) | | | 0.37 (0.03-4.30) | 0.43 | 0.28 (0.03-2.66) | 0.27 |
| Type IV collagen 7S (ng/mL),<5.5 (n= 44)† | | | | | | |
| ≥5.5 (n= 15) | | | 0.07 (0.01-1.29) | 0.074 | | |
| FIB-4 index, <2.5 (n= 34) | 0.85 (0.28-2.56) | 0.78 | | | | |
| ≥2.5 (n=33) | | | | | | |
| Total bilirubin (mg/dL), <1 (n= 49) | 4.85 (1.45-16.2) | 0.011 | 8.38 (1.92-36.6) | | | |
| ≥1 (n= 18) | | | | 0.005 | 3.14 (1.15-8.55) | 0.025 |
| Size of tumor (cm), <3 cm | 2.78 (1.01-7.69) | 0.048 | 1.55 (0.33-7.28) | | | |
| ≥3 cm | | | | | | |
| Lymph node metastasis, no (n= 49) | 2.69 (0.87-8.30) | 0.086 | 4.50 (0.88-23.0) | | | |
| Yes (n= 18) | | | | 0.58 | 2.18 (0.79-5.97) | 0.13 |
| Histological differentiation, | | | | | | |
| Papillary, well (n= 31) | 5.1 (1.58-16.5) | 0.006 | 4.89 (0.82-29.2) | | | |
| Moderately, poorly (n= 36) | | | | 0.071 | | |
| Tumor factor, t1, t2 (n= 38) | 6.03 (1.80-20.2) | 0.004 | 1.05 (0.07-16.6) | | | |
| t3, t4 (n= 29) | | | | 0.082 | | |
| Operation, PD (n= 34) | | | | | | |
| Hepatectomy (n= 33) | | | | | 0.61 (0.21-1.83) | 0.38 |
| Combined vascular resection, no (n= 59) | | | | 0.97 | | |
| Yes (n= 8) | | | | | | |
| Morbidity, C-D 0-2 (n= 37) | | | | | | |
| C-D 34 (n= 30) | | | | | | |
| Hepatic failure, yes (n= 2) | | | | 0.94 | 2.21 (0.21-23.2) | 0.51 |
| Bile leakage, yes (n= 6) | 5.97 (1.36-26.1) | 0.018 | 0.90 (0.05-14.9) | 0.008 | 9.10 (1.55-53.3) | 0.014 |
| Pancreatic fistula, yes (n= 14) | 0.52 (0.12-2.28) | 0.39 | 29.31(2.44-352.6) | | | |
| Intraabdominal abscess, yes (n= 9) | | | | | 1.02 (0.34-3.11) | 0.97 |
| Blood loss (mL), <1500 (n= 51) | | | | | | |
| ≥1500 (n= 16) | | | 16.07(3.52-73.4) | 0.003 | 6.02 (1.71-21.2) | 0.005 |
| Curability, R0 (n= 59) | | | | | | |
| R1 (n= 8) | | | | | | |
| em1 (n= 4) | 3.89 (0.65-23.2) | 0.14 | 10.76 (1.64-70.6) | 0.013 | 4.41 (1.10-17.7) | 0.037 |

Parameters less than p-value 0.20 by univariate analysis for patient survival, were selected for multivariable analysis.
The clinicopathological findings and TNM classification were based on the general rules for clinical and pathological studies on cancer of the biliary tract and primary liver cancer (15,16)
C-D: Clavien-Dindo classification (40),
RR: Risk ratio; CI: Confidence interval.
Cancer recurrence: None (n= 40, 61%); peritoneal dissemination (n= 7); liver (n= 8); lymph node (n= 6); local (n= 3); lung (n= 3); or bone (n= 1).
Prognosis: Survival without recurrence (n= 37, 55%), survival with CC recurrence (n= 10), death from CC (n= 17), and other related deaths (n= 3).

survival (p< 0.05), but no fibrotic markers were associated. The first signs of obstructive jaundice, higher total bilirubin level, postoperative bile leakage, increased blood loss over 1500 mL and exposed margin positivity were independently associated with cancer-specific overall survival (p< 0.05); however, no fibrotic markers were associated. Higher total bilirubin levels, postoperative bile leakage, increased blood loss over 1500 mL, and exposed margin positivity were independently associated with overall survival (p< 0.05), but no fibrotic markers were associated.

## DISCUSSION

Specific CC tumor markers such as CEA or CA19-9 are commonly used for cancer diagnosis or tumor aggressiveness (19). According to the abovementioned data, our previous study showed that not only tumor-associated markers but also background liver dysfunction was significantly correlated with poor prognosis in patients with CC undergoing hepatectomy as well as previous reports (20). In patients with extrahepatic CC, particularly distal CC (Bd), obstructive jaundice is frequently observed, and the liver is functionally or macroscopically injured according to the degree of hyperbilirubinemia or a longer period of jaundice, even though adequate biliary drainage is performed until radical operation (1-3,21). During laparotomy, unexpected liver fragility due to liver injury caused by jaundice or background liver disease is often found, which might be associated with postoperative morbidity (22). We hypothesized that severe postoperative morbidity or increased blood loss might also be associated with patient survival in the primary author's previous study; therefore, we attempted to examine liver injury markers, including liver fibrotic markers, to clarify predictive non-tumorous parameters in patients with CC who underwent radical surgery in the present study. Fibrotic markers permitted by Japan's health insurance system at this stage were examined in our study (12).

We also reported that serum HA, a hepatic fibrosis marker, was associated with poor survival, reflecting non-parenchymal liver function, injury, or the risk of post-hepatectomy uncontrolled ascites in patients with chronic hepatitis or cirrhosis (6,7) HA or its protein complex are increased not only in cirrhotic patients but also in patients with HCC and liver malignancies. The mechanism underlying the relation between HA and tumor progression has not been fully clarified; however, physiological stress in the liver parenchyma may stimulate the production of liver-derived growth factors and induce subsequent tumor progression (23,24). The principal author previously reported a close relation between HA and prognosis in patients with HCC However, drug chemotherapy, minimally invasive surgery, and radiological interventions have dramatically improved (25). The prognostic factors for non-tumorous markers have changed over the last decade. Based on these results, it is hypothesized that increased liver fibrosis and related liver dysfunction or latent injury influence patient prognosis after hepatectomy. We also examined the relation between fibrotic markers and prognosis in patients with HCC who underwent hepatectomy in the last decade (unpublished data). Furthermore, the latent progression of remnant cancer cells or multiple carcinogenesis of the liver would also influence the prognosis of patients with hepatobiliary malignancies, including cholangiocarcinoma, through physiological stress (26).

In the present study, five fibrotic candidate parameters and platelet counts, which were routinely examined in patients who underwent hepatectomy but not pancreatectomy, were retrospectively examined in 67 consecutive patients with ICC and ECC, with a minimum follow-up period of one year after surgery, to clarify the relation between these parameters and patient prognosis. Concerning differences or correlations between them, platelet counts and FIB-4 index were significantly noted in each. In patients with HCC with chronic liver damage, platelet counts are closely associated with background liver disease progression; however, platelet counts do not differ between the stages of fibrosis. Despite the low number of patients in this series, platelet counts were not associated with liver damage caused by obstructive jaundice. In the formula for the FIB-4 index, the platelet count is the parameter denominator, and a negative correlation is reasonable when the transaminase levels are stable (10).

HA and type 4 collagen are thought to be specific parameters of general fibrosis, which are increased in patients with distal CC with the first onset of obstructive jaundice. Obstructive biliary congestion may have influenced the increase in the levels of these markers. However, in our study, only HA was significantly correlated with liver dysfunction such as hyperbilirubinemia and hypoalbuminemia. This result shows that obstructive jaundice may not always induce hepatic fibrosis, but increased damage to the endothelium of the hepatic sinusoid due to bile congestion is thought to be an important factor in this mechanism (27). Type IV collagen is common in various tumors, and a positive correlation between type IV collagen expression and tumor metastasis has been reported (28). Native type IV collagen induces epithelial-to-mesenchymal transition-like processes, cell migration, and invasion in MCF10A human mammary epithelial cells, which are suitable for HCC progression. However, T4C7 was not correlated with tumor-related factors; therefore, contrary to our expectations, it was not related to cancer-specific parameters (29). M2BPGi, a secreted glycoprotein present in the extracellular matrix of several organs, is a novel marker for assessing hepatic fibrosis and induction of inflammatory cytokines. According to a report by Bekki et al., the different mechanism as a fibrotic marker from HA or T4C7, is different

the hepatic stellate cell is a source of M2BPGi and the higher biological activities of M2BPGi are associated with the development of hepatocellular carcinoma (12,14). Recent reports have shown that M2BPGi is more strongly associated with liver fibrosis than with other serum markers; however, M2BPGi was not correlated with other fibrotic markers in this series. M2GPGi was associated only with obstructive jaundice and lower albuminemia (12). Although our preliminary data on patients who underwent hepatectomy showed that this marker was closely correlated with textbook outcomes, no such correlation was observed in the present study (13). This might be due to the inclusion of pancreatectomy, and the severity of preoperative obstructive jaundice might not have been associated with postoperative morbidities. The APRI and FIB-4 index were influenced by the degree of hepatocyte injury because the included parameters were transaminase levels, age, and platelet counts. However, these have recently been used to evaluate liver fibrosis in patients with chronic hepatic injuries, although the underlying mechanism has not been fully elucidated (10,11). Except for the correlation with platelet counts and T4C7, these indices were not associated with any parameters, including jaundice or postoperative morbidities, which would not be useful for subacute liver injury, such as obstructive jaundice due to CC.

Concerning cancer recurrence or patient survival in the present study, Steffani et al. reported that histological liver fibrosis is associated with poorer overall survival and higher recurrence rates in patients with CC (30). Contrary to our hypothesis, no fibrotic markers were significantly associated with long-term prognosis, owing to the impaired background liver in our results. Furthermore, in the univariate survival analysis in our study, preoperative obstructive jaundice and two fibrotic markers (T4C7 and FIB-4 index), tumor markers reflecting malignant behavior, and operative stress were significantly associated, as expected. Regarding cancer-free survival, known tumor-related parameters and operative curability are independent factors, whereas liver dysfunction and fibrosis are not, as seen on multivariate analysis (31,32). In order to examine non-cancerous survival due to liver damage caused by CC obstruction, both cancer-specific and overall survival rates were examined. Although the fibrotic parameters were not associated, preoperative jaundice and dominant bile leakage were independent prognostic factors. This shows that preoperative liver damage due to obstructive jaundice might influence the long-term prognosis, as previously reported (33). However, our results do not recommend fibrotic markers as independent biomarkers. In hepatectomy or PD operations, it is speculated that the risk of bile leakage always remains in patients with CC, in which cholangitis-induced liver damage could occur in any situation, but there is no evidence so far. Contrary to our hypothesis, fibrotic markers were not predictive of postoperative bile leakage or associated patient prognosis. Preoperative total bilirubin level alone is a candidate prognostic parameter; therefore, immediate preoperative biliary drainage and sufficient decrease of total bilirubin at the time of operation, even in PD for distal CC located in the Bd, is necessary, although the necessity of preoperative biliary drainage is controversial worldwide (1-5,34,35) Intraoperative blood loss was also an independent risk factor for overall and cancer-specific survival. Allogeneic blood transfusion remained a poor prognostic factor in our previous studies among patients with HCC undergoing hepatectomy (11,33). It has been speculated that liver injury, stress, and transfusion-induced immunodeficiency may occur (36,37).

The limitations were as follows:

1) This study was performed in a consecutive cohort with a relatively small number of participants (67 patients with both ICC and ECC);

2) We did not perform any elastography evaluation to detect the degree of hepatic fibrosis in all patients with CC, which is a more reliable and less invasive parameter for evaluating intrahepatic fibrosis and surgical outcomes (11). Candidate parameters are usually correlated with this in patients with chronic liver injuries; and, therefore, we scheduled elastographic exams preoperatively even in obstructive biliary carcinomas if clinical significances with candidate parameters were observed in the next step;

3) Classical histological fibrotic evaluation was not examined in all, particularly in patients with ECC. If there is a correlation between candidate fibrotic markers and histological fibrosis of the liver injured by obstructive jaundice, we might prospectively examine histological fibrosis as well as elastography in the next step. Due to health insurance or manpower limitations, further advanced examinations for histological liver injuries cannot be performed. In the present study, the histological mechanism of non-tumorous liver injuries caused by obstructive jaundice (biliary congestive liver injury) or carcinogenesis of ICC in the small hepatic ducts did not seem to be different from those in chronic viral hepatitis or steatosis in patients with HCC (38).

4) The relation between candidate markers, tumor-related factors, or surgery-related adverse results was not clearly observed, and these markers might not be produced by CC. However, the precise relations between these factors remain unclear. Another study showed that type IV collagen 7s was correlated with the degree of malignant behavior in HCC and similar results were not observed in CC in this study (39). Because of the above results and limitations, the relation between any patient prognosis was not significantly associated with candidate markers more than other known tumor- or

surgery-related factors influencing patient prognosis by multivariable analyses, contrary to our hypothesis. However, the clinical significance of these markers remains unclear.

## CONCLUSION

We conducted a retrospective and consecutive analysis of the outcomes of 67 patients with ICC and ECC who underwent curative hepatectomy or pancreatectomy, including an analysis of the relation between six preoperative liver fibrosis or hepatic injury markers or conventional clinicopathological parameters, surgical outcomes, and patient prognosis. Among several fibrotic markers, M2BPGi was increased in patients with obstructive jaundice, serum HA and T4C7 were significantly increased in the distal CC (Bd), and no markers were significantly associated with tumor-related factors or postoperative complications. Although a higher FIB-4 index was significantly associated with shorter cancer-free survival, no candidate markers were independent prognostic markers for CC in multivariate analysis. Therefore, future studies might no longer be necessary.

**Ethics Committee Approval:** This study was approved by Chair of Research Institute Dean of University of Miyazaki Yoshitaka Hishikawa (Decision no: 0-1469, Date: 22.12.2023).

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**ORİJİNAL ÇALIŞMA-ÖZET**
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# Kolanjiyokarsinomlu hastalarda radikal rezeksiyon sonrası karaciğer fibrotik belirteçlerinin klinik önemi

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## ÖZET

**Giriş ve Amaç:** Obstrüktif sarılık nedeniyle biliyer drenaj ve ardından cerrahi rezeksiyon yapılan 67 kolanjiyokarsinomlu hastada karaciğer parenkim hasarını yansıtan çeşitli fibrotik belirteçler ile konvansiyonel karaciğer fonksiyonu veya cerrahi sonuçlar arasındaki ilişkiyi inceledik.

**Gereç ve Yöntem:** Konvansiyonel klinikopatolojik faktörleri, hepatektomi öncesi trombosit sayısı, hyalüronik asit, Mac-2 bağlayıcı protein glikozilasyon izomeri (M2BPGi), tip IV kollajen 7S, aspartat aminotransferaz-trombosit oranı indeksi (APRI) ve FIB-4 indeksi dahil olmak üzere altı hepatik fibrozis parametresini ve cerrahi sonuçları veya uzun dönem prognozu inceledik.

**Bulgular:** Hastaların %57'sinde obstrüktif sarılık, %7,5'inde safra yolu hastalığı öyküsü ve %17,9'unda kronik karaciğer yaralanması öyküsü gözlendi. Primer bulgu olarak obstrüktif sarılık olan hastalarda M2BPGi anlamlı olarak daha yüksekti ($p< 0,05$), FIB-4 indeksi hasta yaşı ile anlamlı olarak ilişkiliydi ($p< 0,01$) ve distal kolanjiyokarsinomda (CC) serum hyalüronik asit ve T4C7 düzeyleri anlamlı olarak artmıştı. Histolojik hepatik fibrotik indeks, tümörle ilişkili faktörler veya postoperatif morbiditeler ile ilişkili hiçbir belirteç yoktu. Hastaların %37'sinde tümör nüksü, %25'inde kansere bağlı ölüm gözlendi. Daha yüksek bir FIB-4 indeksi, daha kısa kansersiz sağkalım ile anlamlı olarak ilişkiliydi ($p< 0,05$). Cox çok değişkenli analizi, bilirubin düzeylerinin, zayıf histolojik kanser farklılaşmasının ve fibrotik belirteçlerin yokluğunun kansersiz, genel olarak kansere özgü ve genel sağkalım ile ilişkili olduğunu gösterdi.

**Sonuç:** Bu belirteçler ile elastografik veya histolojik fibrotik indeksler arasında yeterli bir ilişki olmasına rağmen, konvansiyonel fibrotik belirteçlerin ölçülmesinin klinik önemi gelecekteki çalışmalarda artık gerekli olmayabilir.

**Anahtar Kelimeler:** Kolanjiyokarsinom, obstrüktif sarılık, fibrotik belirteçler, karaciğer disfonksiyonu, cerrahi sonuçlar, hasta prognozu

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