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Preoperative Myosteatosis and Prognostic Nutritional Index Predict Survival in Older Patients With Resected Biliary Tract Cancer

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Abstract. *Background/Aim: Sarcopenia accompanied by systemic inflammation is associated with poor prognosis in patients with cancer. This study evaluated the prognostic significance of sarcopenia (myopenia and myosteatosis) and systemic inflammatory markers in older patients (aged ≥80 years) with resected biliary tract cancer. Patients and Methods: Patients who underwent resection for biliary tract cancer between July 2010 and January 2023 at the NHO Fukuyama Medical Center were retrospectively reviewed. Preoperative computed tomography measured myopenia and myosteatosis, using the psoas muscle index and modified intramuscular adipose tissue content. Associations between clinicopathological characteristics, inflammation-based prognostic scores, and overall survival were analyzed using Cox proportional hazards models. Results: Univariate analysis revealed low C-reactive protein-to-albumin ratio (<0.125), low prognostic nutritional index (<42), low modified intramuscular adipose tissue content, higher T-stage (T3-4), lymph node metastasis, and postoperative complications associated with worse overall survival in older patients (aged ≥ 80 years) with resected biliary tract cancer (n=48). Multivariate analysis identified low prognostic nutritional index (<42) (p=0.007), low modified intramuscular adipose tissue content (p=0.015), higher T-stage (T3-4) (p<0.001), lymph node metastasis (p=0.001), and postoperative complications (p=0.017) as independent predictors of overall survival. Conclusion: Preoperative myosteatosis and low prognostic nutritional index are independent prognostic factors for overall survival in older patients (aged ≥80 years) with resected biliary tract cancer. These factors may be useful for risk stratification and clinical decision-making. Early interventions, such as nutritional support and physical exercise, may improve outcomes after resection of biliary tract cancer.*

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Biliary tract cancer, a rare aggressive malignancy, has demonstrated an increasing incidence over the past few decades (1). Surgical resection is the only curative treatment for biliary tract cancer; however, recurrence remains a major concern (2). Biliary tract cancer is often diagnosed at an advanced stage, at which point most patients cannot be considered as candidates for surgical resection. Despite advancements in surgical techniques and adjuvant chemotherapy (3, 4), the prognosis remains poor. Preoperative prognostic factors could enable a more effective risk–benefit assessment (5), and facilitates patient stratification for precision medicine. Therefore, the need to identify new predictive biomarkers is urgently required.

Japan has the most rapidly aging population in the world (6, 7). This has led to an increase in the number of older patients undergoing surgery for cancer. The efficacy of surgery among older patients has been investigated across various cancer types (8-10), including gastric cancer, pancreatic cancer, and hepatocellular carcinoma. However, few studies (11, 12) have investigated the efficacy of surgery in older patients with resected biliary tract cancer.

Sarcopenia was first used to describe the age-related decline in muscle mass and is now regarded as primary sarcopenia (13). Secondary sarcopenia arises because of underlying conditions (14-16), such as chronic inflammatory disease, advanced cancer, and malnutrition. In patients with cancer, sarcopenia may be associated with poor overall survival (17, 18).

Sarcopenia manifests in two primary patterns: myopenia and myosteatosis. Myopenia is classically characterized by decreased skeletal muscle mass regardless of age and underlying disease. Accumulating evidence (19) suggests a negative effect of myopenia on oncological outcomes. In contrast, myosteatosis is characterized by low-quality skeletal muscle. Myosteatosis has attracted attention as an indicator of sarcopenia, because the accumulation of intramuscular adipose tissue may diminish muscle strength and mobility, as well as increase the risk of morbidity, in older patients (20, 21). Intramuscular adipose tissue content (IMAC) and modified IMAC are closely related to aging and visceral fat accumulation (22, 23). Several studies (24, 25) have evaluated IMAC as a surrogate marker for myosteatosis and demonstrated the potential of preoperative IMAC as a negative prognostic marker in hepatobiliary cancer.

Sarcopenia is associated with aging and cancer-related inflammation (26). Several studies (27, 28) have shown that systemic inflammation and nutritional status are associated with poor prognosis in patients with cancer. Several markers have been used to assess systemic inflammation (29, 30), including the prognostic nutritional index, Glasgow Prognostic Score, C-reactive protein-to-albumin ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio.

Patients diagnosed with metastatic biliary tract cancer, hepatocellular carcinoma, gastric cancer, and colorectal cancer with high systemic inflammation and sarcopenia have worse overall survival (31-34). However, prognostic factors in older patients with resected biliary tract cancer have not been well studied. Therefore, this study aimed to evaluate the prognostic significance of sarcopenia (myopenia and myosteatosis) and systemic inflammatory markers in older patients (aged ≥80 years) with resected biliary tract cancer.

Patients and Methods

Patients. A total of 148 consecutive patients who underwent surgical resection for biliary tract cancer at the Department of Surgery of the NHO Fukuyama Medical Center, Fukuyama, Japan, between July 2010 and January 2023 were retrospectively reviewed. Biliary tract cancer, including gallbladder carcinoma, intrahepatic cholangiocarcinoma, distal cholangiocarcinoma, ampullary carcinoma, and perihilar cholangiocarcinoma, was confirmed by imaging and pathological examination. Patients were divided into two groups according to age: <80 and ≥80 years.

Ethics approval and consent to participate. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee, following the principle outlined in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study design was approved by the Ethical Review Board of the National Hospital Organization Fukuyama Medical Center, Fukuyama, Japan (approval number: ERB2022027). Informed consent was obtained from all individual participants included in the study. We confirmed that all methods were carried out in accordance with relevant guidelines and regulations.

Data collection. Data on demographic characteristics (age at surgery and sex), laboratory tests (serum albumin and C-reactive protein levels; platelet, neutrophil, and lymphocyte counts; and tumor markers), comorbidities (hypertension; diabetes mellitus; and cardiac, cerebral, and lung disease), preoperative cholangitis, surgical procedure (type of resection), operative time, blood loss, blood transfusion, Tumor-Node-Metastasis stage [Union for International Cancer Control classification (eighth edition)], tumor differentiation, and postoperative adjuvant chemotherapy were obtained from patients' medical records. Curative (R0) resection was defined as the complete removal of all macroscopic nodules with microscopically clear margins. R1 and R2 resections were defined as microscopic or macroscopic disease, respectively, involving at least one margin. Complications were defined according to the Clavien–Dindo classification (35). Postoperative complications were defined as complications of Clavien–Dindo Grade ≥IIIa. Postoperative mortality was defined as death from any cause within 30 days after surgery.

Sarcopenia. Preoperative computed tomography was performed within 1 month before surgery using a multidetector computed tomography scanner (Aquilion CXL 64; Canon Medical Systems, Tochigi, Japan). Using preoperative computed tomography at the level of the caudal end of the third lumbar vertebra, the cross-sectional area of the bilateral psoas muscles was measured by manual tracing. The psoas muscle index was used as a marker of myopenia, and IMAC and modified IMAC were used as markers of myosteatosis (17, 22).

The psoas muscle index was calculated as follows (17): psoas muscle index=cross-sectional area of the bilateral psoas muscles (cm^2)/height squared (m^2). A low psoas muscle index was indicative of low muscle volume. Given the variance in psoas muscle index between men and women, different cutoff values were established using receiver operating characteristic curves. Optimal cutoff values were determined based on achieving the best accuracy for the outcome. Specifically, the cutoff values for psoas muscle index in men and women were 5.10 and 3.69 cm^2/m^2, respectively (areas under the receiver operating characteristic curves: 0.587 and 0.625, respectively).

Subfacial muscular tissue in the multifidus muscle was estimated by manual tracing at the same level on preoperative plain computed tomography images and mean computed tomography values were calculated. Circles (n=4) were placed on areas of subcutaneous fat away from major vessels, serving as regions of interest. Mean computed tomography values were subsequently calculated for these regions.

IMAC was calculated as follows (22): IMAC=mean computed tomography value of the region of interest of the multifidus muscle [Hounsfield units (HU)]/mean computed tomography value of the region of interest of subcutaneous fat (HU). Modified IMAC was calculated as follows (23): modified IMAC=mean computed tomography value of the region of interest of the multifidus muscle (HU)–mean computed tomography value of the region of interest of subcutaneous fat (HU).

High IMAC and low modified IMAC are considered surrogates for low-quality skeletal muscle (myosteatosis). High IMAC and low modified IMAC were defined using sex-specific median values: –0.135 and –0.183 and 121.5 and 108.5 for men and women, respectively.

Prognostic nutritional index and other inflammation-based prognostic scores. Peripheral venous blood samples were collected within 2 weeks before surgery. The prognostic nutritional index was calculated as follows (36): prognostic nutritional index=10 × serum albumin (g/dl) + 0.05 × total lymphocyte count (/mm^3). The Glasgow Prognostic Score was defined as follows (37): 0, normal albumin (≥3.5 g/dl) and C-reactive protein (≤1.0 mg/dl); 1, low albumin (<3.5 g/dl) or high C-reactive protein (>1.0 mg/dl); and 2, low albumin (<3.5 g/dl) and high C-reactive protein (>1.0 mg/dl). The C-reactive protein-to-albumin ratio was calculated as follows (38): C-reactive protein-to-albumin ratio=C-reactive protein (mg/dl)/serum albumin (g/dl). The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were calculated by dividing the neutrophil and platelet counts by the lymphocyte count, respectively (29, 30).

Follow-up. All patients underwent routine follow-up until January 2023. Postoperative follow-up included medical history (symptoms and physical examination), laboratory tests, and imaging studies performed every 6 months for ≥5 years. Patients with lymph node metastasis or who underwent R1 or R2 resection received postoperative adjuvant chemotherapy (tegafur/gimeracil/oteracil) for approximately 6 months. None of the patients received neoadjuvant chemotherapy.

Outcomes. Associations between clinicopathological variables and overall survival were analyzed using Cox proportional hazards models. Disease-free survival and overall survival were defined as the intervals from surgery to recurrence and death or last follow-up, respectively.

Statistical analysis. All data were blinded before analysis. Categorical variables were expressed as percentages. Continuous variables were expressed as median (range). Univariate analysis was performed using the Mann–Whitney *U*-test and Chi-square test. Diagnostic accuracy was determined using the area under the receiver operating characteristic curve. The optimal cutoff values of the prognostic nutritional index and other inflammation-based prognostic scores were determined by maximizing the Youden index (sensitivity + specificity − 1). Disease-free survival and overall survival were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards models. Variables that were significant in the univariate analysis were included in the multivariate analysis. All statistical analyses were conducted using JMP 11 (SAS Institute, Cary, NC, USA). $p<0.05$ was considered statistically significant.

Results

Patient characteristics. The patient characteristics, according to age, are summarized in Table I. Of the 148 patients included in the study, 100 were aged <80 years, 48 patients were aged ≥80 years. Within the group aged ≥80 years, the median age of patients was 84 years (range=80-92). No differences in sex, body mass index, tumor markers, and type of cancer were observed between the two groups. Comorbidities were present in 60 patients aged <80 years and 36 patients aged ≥80 years. A higher proportion of patients aged ≥80 years had cardiac, cerebral, or lung disease (p=0.037, 0.005, and 0.030, respectively). Additionally, the prognostic nutritional index was lower in patients aged ≥80 years than in those aged <80 years (p=0.039). Patients aged ≥80 years exhibited higher IMAC and lower modified IMAC compared to those aged <80 years (both p<0.001). Furthermore, a higher proportion of patients aged ≥80 years had a high IMAC (p=0.027) and a low modified IMAC (p=0.002).

Surgical outcomes. The intraoperative and postoperative outcomes are presented in Table II. No differences in blood loss, postoperative complications, length of hospital stay, and cause of death were observed between the two groups. The operative time was shorter in patients aged ≥80 years than in those aged <80 years (p=0.036). A lower proportion of patients aged ≥80 years received postoperative adjuvant chemotherapy (p=0.038).

Long-term outcomes. The median follow-up was 46.7 (range=6.0-142.6) months. No difference in overall survival (62.2 *vs*. 41.2 months, respectively; p=0.667) (Figure 1A) or disease-free survival (76.8 *vs*. 46.3 months, respectively; p=0.321) (Figure 1B) was observed between patients aged ≥80 years and those aged <80 years.

Univariate and multivariate analyses of clinicopathological factors for overall survival in older patients (aged ≥80 years) with resected biliary tract cancer. Table III shows the relationship between clinicopathological variables and overall survival among older patients (aged ≥80 years) with resected biliary tract cancer. Univariate analysis revealed that a low C-reactive protein-to-albumin ratio (<0.125), a low prognostic nutritional index (<42), a low modified IMAC, a high T-stage (T3-4), lymph node metastasis, and postoperative complications were associated with worse overall survival in older patients (aged ≥80 years) with resected biliary tract cancer. A low prognostic nutritional index (<42) [hazard ratio (HR)=5.07, 95% confidence interval (CI)=1.55-18.87; p=0.007], a low modified IMAC (HR=4.03, 95% CI=1.31-13.78; p=0.015), a high T-stage (T3-4) (HR=12.51, 95% CI=3.21-62.76; p<0.001), lymph node metastasis (HR=8.78, 95% CI=2.83-31.51; p=0.001), and postoperative complications (HR=3.87, 95% CI=1.27-12.33; p=0.017) were independent predictors of overall survival in multivariate analysis.

Relationship between clinicopathological variables and modified IMAC in older patients (aged ≥80 years) with resected biliary tract cancer. Table IV shows the relationship between clinicopathological variables and modified IMAC among older patients (aged ≥80 years) with resected biliary tract cancer. Patient- and tumor-related factors were similar in both groups, except for the prognostic nutritional index and Glasgow Prognostic Score, which were lower in patients with a low modified IMAC than in those with a high modified IMAC (p=0.009 and 0.008, respectively).

Table I. *Clinicopathological characteristics of patients who underwent surgical resection for biliary tract cancer according to age.*

Characteristic	Aged <80 years (n=100)	Aged ≥80 years (n=48)	*p*-Value
Age (years), median (range)	72 (34-79)	84 (80-92)	<0.001***
Sex (male/female), n	62/38	27/21	0.505
Body mass index (kg/m^2), median (range)	22.8 (14.2-30.8)	22.7 (16.9-34.5)	0.641
Comorbidities, n (%)	60 (60.0)	36 (75.0)	0.069
Cerebral disease	1 (2.1)	16 (16.0)	0.005**
Cardiac disease	9 (9.0)	7 (14.3)	0.037*
Hypertension	29 (60.4)	46 (46.0)	0.099
Diabetes mellitus	9 (18.8)	19 (19.0)	0.971
Lung disease	5 (10.4)	2 (2.0)	0.030*
Carcinoembryonic antigen level (ng/ml), median (range)	2.86 (0.56-113.10)	3.16 (1.23-16.80)	0.270
Carbohydrate antigen 19-9 level (U/ml), median (range)	14.97 (2.00-10,046.00)	19.40 (2.00-120,000.00)	0.054
C-reactive protein level (mg/dl), median (range)	0.23 (0.01-12.96)	0.33 (0.03-24.18)	0.521
Inflammation-based prognostic scores			
Prognostic nutritional index, median (range)	46.6 (32.9-59.9)	44.7 (22.2-63.0)	0.039*
Glasgow Prognostic Score (0/1/2), n	69/21/10	24/18/6	0.071
C-reactive protein-to-albumin ratio, median (range)	0.062 (0.001-4.629)	0.092 (0.007-14.224)	0.311
Platelet-to-lymphocyte ratio, median (range)	137 (41-600)	131 (46-444)	0.580
Neutrophil-to-lymphocyte ratio, median (range)	2.19 (0.76-21.75)	2.33 (0.75-48.00)	0.324
Markers of sarcopenia			
Psoas muscle index (cm^2/m^2)	4.68 (1.61-9.23)	4.51 (1.97-7.44)	0.242
IMAC (HU)	–0.312 (–0.828-0.175)	–0.183 (–0.760-0.300)	<0.001***
Modified IMAC (HU)	134.6 (69.4-158.8)	116.8 (50.9-167.9)	<0.001***
Low psoas muscle index, n (%)	39 (39.0)	25 (52.1)	0.133
High IMAC, n (%)	60 (60.0)	37 (78.7)	0.027*
Low modified IMAC, n (%)	19 (19.0)	21 (44.7)	0.002**
Preoperative cholangitis (absent/present), n	61/39	27/21	0.584
Type of cancer, n (%)			
Intrahepatic cholangiocarcinoma	25 (25.0)	9 (18.8)	0.139
Gallbladder carcinoma	22 (22.0)	21 (43.8)	
Distal cholangiocarcinoma	21 (21.0)	10 (20.8)	
Ampullary carcinoma	19 (19.0)	5 (10.4)	
Perihilar cholangiocarcinoma	13 (13.0)	3 (6.3)	

*p<0.05; **p<0.01; ***p<0.001. HU: Hounsfield units; IMAC: intramuscular adipose tissue content.

Discussion

In this study, preoperative myosteatosis and low prognostic nutritional index were identified as independent prognostic factors for overall survival among older patients (aged ≥80 years) with resected biliary tract cancer. To our knowledge, this is the first study to investigate the prognostic value of the modified IMAC among older patients (aged ≥80 years) with resected biliary tract cancer. Although we analyzed markers of sarcopenia, including the psoas muscle index (myopenia), only the modified IMAC (myosteatosis) was a significant prognostic marker in older patients (aged ≥80 years) with resected biliary tract cancer, suggesting that the prognosis of these patients is highly dependent on the quality of skeletal muscle.

Regarding prognostic factors after resection of biliary tract cancer, several studies (2-4) have addressed tumor-specific factors, such as tumor size, tumor differentiation, lymph node metastasis, and resection margin status. In this study, tumor-specific factors, including lymph node metastasis and T-stage, were associated with poor prognosis, consistent with previous studies (2, 4). Notably, these factors are determined postoperatively; however, in clinic practice, preoperative prognostic factors may be more useful. Prognosis after resection of biliary tract cancer is multifactorial and is not only related to tumor-specific factors but also to patient characteristics, such as nutritional status and sarcopenia. Okumura *et al.* (25) demonstrated that preoperative IMAC and psoas muscle index were independent predictors of poor overall survival in patients with extrahepatic biliary tract cancer. Interestingly, in this study, these factors did not emerge as independent prognostic factors.

Adipose tissue deposition in skeletal muscle has gained attention. Previous studies (22, 24, 25) have shown that a high IMAC is a negative prognostic factor in various cancer types. However, the prognostic value of IMAC remains controversial. Kusunoki *et al.* (39) demonstrated no prognostic effect of preoperative IMAC in patients with colorectal cancer. Kitajima *et al.* (22) proposed IMAC as a

Table II. *Intraoperative and postoperative outcomes of patients who underwent surgical resection for biliary tract cancer according to age.*

Characteristic	Aged <80 years (n=100)	Aged ≥80 years (n=48)	*p*-Value
Surgical procedure, n (%)			
Cholecystectomy	11 (11.0)	13 (27.1)	
Bile duct resection without liver resection	0 (0.0)	1 (2.1)	
Type of liver resection			0.073
Liver bed resection	3 (3.0)	5 (10.4)	
Partial hepatectomy	1 (1.0)	0 (0.0)	
Subsegmentectomy	9 (9.0)	2 (4.2)	
Sectionectomy	4 (4.0)	3 (6.3)	
Hemihepatectomy	28 (28.0)	8 (16.7)	
Trisectionectomy	3 (3.0)	1 (2.1)	
Pancreaticoduodenectomy	39 (39.0)	15 (31.3)	
Hepatopancreaticoduodenectomy	2 (2.0)	0 (0.0)	
Resection (R0/R1-2), n	84/16	44/4	0.185
Operative time (minutes), median (range)	465 (45-793)	380 (107-738)	0.036*
Blood loss (ml), median (range)	395 (0-6,410)	271 (0-13,870)	0.968
Blood transfusion (no/yes), n	86/12	44/4	0.493
T-stage (T3-4), n (%)	49 (49.0%)	17 (35.4%)	0.118
Lymph node metastasis (absent/present), n	40 (40.0%)	16 (33.3%)	0.432
Tumor-Node-Metastasis stage[a] (I-II/III-IV), n	59/41	33/15	0.248
Tumor differentiation (well/other)	35/51	15/30	0.407
Postoperative complications[b] (absent/present), n	63/37	32/16	0.662
Length of hospital stay (days), median (range)	19.0 (4.0-78.0)	16.5 (4.0-122.0)	0.696
Postoperative adjuvant chemotherapy (no/yes), n	32/65	24/23	0.038*
Cause of death			
Cancer/other, n (%)	34 (82.9%)/7 (17.1%)	12 (63.2%)/7 (36.8%)	0.099

*$p<0.05$. [a]Union for International Cancer Control Tumor-Node-Metastasis classification (eighth edition); [b]Clavien–Dindo Grade ≥IIIa.

computed tomography value of the multifidus muscle-to-computed tomography value of subcutaneous fat ratio to normalize individual fat attenuation. However, computed tomography values for subcutaneous fat are usually negative, raising doubts about the effectiveness of this ratio as a normalization method. Kusunoki *et al*. (23) proposed a new normalization method (modified IMAC) that calculates the difference between computed tomography values of the multifidus muscle and subcutaneous fat, demonstrating its prognostic value in patients with gastric and colorectal cancer. Consistent with this study (23), modified IMAC was found to be a more reliable predictor of overall survival than IMAC.

The prognostic nutritional index (a marker of nutritional status and systemic inflammation) is another preoperative independent prognostic factor. The prognostic nutritional index is based on serum albumin levels and total lymphocyte counts (36), which can be easily obtained through routine blood tests. Serum albumin concentration in the PNI reflects the nutritional status of patients with cancer. Hypoalbuminemia is not only a syndrome of poor nutritional status but is also associated with a weakened host immune system (40). Thus, a low serum albumin concentration usually predicts poor prognosis in patients with cancer. A low PNI may be predictive of an unfavorable prognosis in patients with BTC. We previously investigated the prognostic significance of the prognostic nutritional index in patients with resected biliary tract cancer (40, 41) and demonstrated its potential clinical application. The mechanisms underlying the prognostic significance of the prognostic nutritional index in patients with resected biliary tract cancer were previously discussed (40).

Frailty is a state of impaired physiological reserve that increases vulnerability and the risk of adverse outcomes. Frailty markers are developed from nutritional markers (42), such as the prognostic nutritional index, serum albumin, and body mass index. Kusunoki *et al*. (23) established a positive correlation between modified IMAC and the prognostic nutritional index, serum albumin, and body mass index among patients with gastric and colorectal cancer. Furthermore, they identified modified IMAC as a novel surrogate marker for nutritional status and frailty (23). In this study, we demonstrated an association between modified IMAC and the prognostic nutritional index in older patients (aged ≥80 years) and found a correlation between myosteatosis and nutritional status, which may indicate frailty.

Supportive therapy focusing on nutrition and rehabilitation may improve outcomes after resection of biliary tract cancer in patients with myosteatosis and poor nutritional status. Perioperative nutritional support is recommended to improve the nutritional status of patients with hepatobiliary pancreatic carcinoma, who have a high prevalence of malnutrition (43).

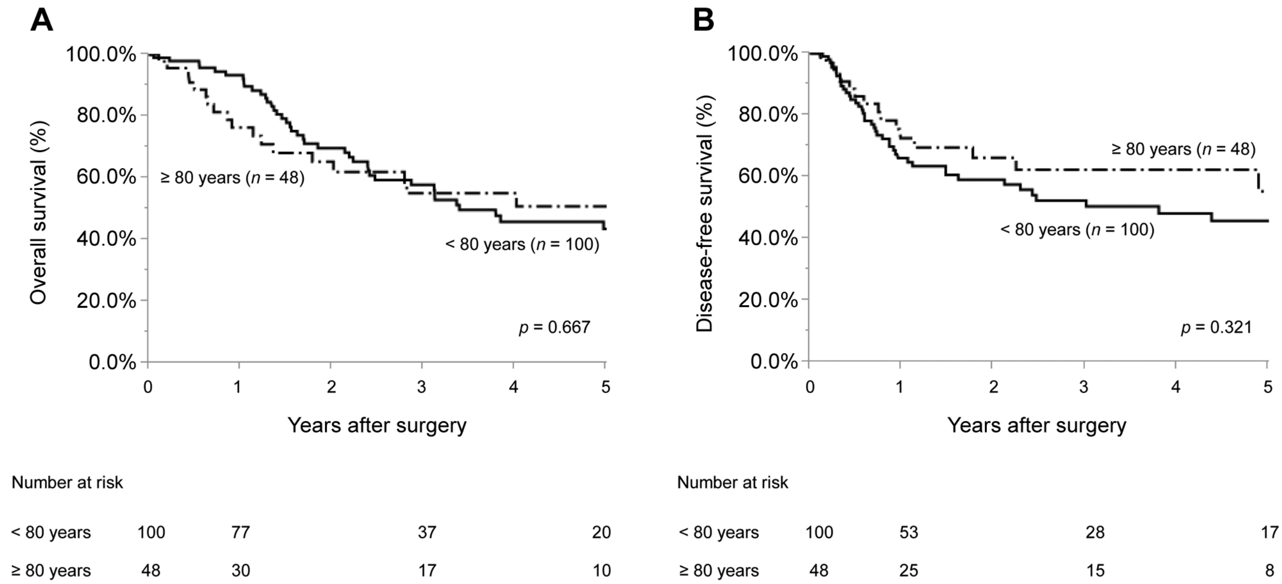

Figure 1. *Kaplan–Meier curves of (A) overall survival and (B) disease-free survival in patients who underwent surgical resection for biliary tract cancer according to age.*

Preoperative immunonutrition has been reported to suppress the perioperative inflammatory response (44). To improve prognosis, patients with a low PNI should be given immunonutrition. Further studies evaluating the relationship between immunonutrition and this inflammation-based prognostic score are required to improve the management of BTC patients with a low PNI. Also, Kaido *et al*. (45) reported the impact of nutritional therapy on prognosis after liver transplantation in patients with sarcopenia. Additionally, several other studies (46, 47) have reported the efficacy of preoperative rehabilitation in reducing postoperative complications in patients with various cancer types. Nonetheless, the efficacy of such therapies requires further evaluation in prospective studies.

Study limitations. First, its retrospective, observational design may have introduced bias. Second, the correlation between modified IMAC and physiological parameters, including skeletal muscle strength, could not be assessed due to the retrospective nature of the study. Notably, low IMAC may reflect not only intramuscular adipose tissue content but also reduced muscle mass because IMAC and modified IMAC are calculated as the ratio or subtraction of computed tomography values between skeletal muscle and subcutaneous fat. Third, optimal cutoff values from receiver operating characteristic curves differ according to sex and disease because modified IMAC is sex- and disease-specific in nature. Finally, patients were recruited from a single institution in Japan. Therefore, larger, multicenter, prospective studies are needed to validate our findings.

Conclusion

Preoperative myosteatosis and low prognostic nutritional index are independent prognostic factors for overall survival in older patients (aged ≥80 years) with resected biliary tract cancer. Preoperative myosteatosis and prognostic nutritional index may be useful for risk stratification and clinical decision-making. Early interventions, such as nutritional support and physical exercise, may improve outcomes after resection of biliary tract cancer.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

All Authors contributed to the study's design. MU, MI, KK, and NT treated the patients. MU conducted the literature search and drafted the manuscript. MI critically revised the manuscript. All Authors read and approved the final manuscript.

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Table III. *Univariate and multivariate analyses of clinicopathological factors for overall survival in older patients (aged ≥80 years).*

Clinicopathological factor	Univariate analysis		Multivariate analysis	
	n	*p*-Value	HR (95% CI)	*p*-Value
Sex				
Male	27	0.178	–	–
Female	21		–	
Body mass index (kg/m^2)				
≥20	33	0.852	–	–
<20	15		–	
Carcinoembryonic antigen level (ng/ml)				
≥9	7	0.740	–	–
<9	41		–	
Carbohydrate antigen 19-9 level (U/ml)				
≥20	16	0.798	–	–
<20	31		–	
Preoperative cholangitis				
Present	27	0.663	–	–
Absent	21		–	
Comorbidities				
Present	36	0.239	–	–
Absent	12		–	
Type of cancer				
Intrahepatic cholangiocarcinoma	9	0.218	–	–
Other	39		–	
Resection				
R0	44	0.274	–	–
R1-2	4		–	
Operative time (minutes)				
≥420	22	0.276	–	–
<420	26		–	
Blood loss (ml)				
≥300	22	0.630	–	–
<300	26		–	
Blood transfusion				
No	44	0.397	–	–
Yes	4		–	
T-stage				
T1-2	31	0.001**	12.51 (3.21-67.26)	<0.001***
T3-4	17		Reference	
Lymph node metastasis				
Present	16	<0.001***	8.78 (2.83-31.51)	0.001**
Absent	32		Reference	
Tumor differentiation				
Well	18	0.334	–	–
Other	29		–	
Myopenia				
Present (low psoas muscle index)	25	0.122	–	–
Absent (high psoas muscle index)	23		–	
Myosteatosis				
Present (high IMAC)	37	0.987	–	–
Absent (low IMAC)	11		–	
Present (low modified IMAC)	22	0.015*	4.03 (1.31-13.78)	0.015*
Absent (high modified IMAC)	26		Reference	
Prognostic nutritional index				
<42	16	<0.001***	5.07 (1.55-18.87)	0.007**
≥42	32		Reference	
Glasgow Prognostic Score				
0	24	0.318	–	–
1-2	24		–	

Table III. *Continued*

Table III. *Continued*

Clinicopathological factor	Univariate analysis		Multivariate analysis	
	n	*p*-Value	HR (95% CI)	*p*-Value
C-reactive protein-to-albumin ratio				
<0.125	21	0.016*	1.26 (0.41-3.71)	0.670
≥0.125	27		Reference	
Neutrophil-to-lymphocyte ratio				
<1.59	28	0.972	–	–
≥1.59	20		–	
Platelet-to-lymphocyte ratio				
<106	12	0.882	–	–
≥106	36		–	
Postoperative complications[a]				
Absent	32	0.035*	3.87 (1.27-12.33)	0.017*
Present	16		Reference	
Postoperative adjuvant chemotherapy				
No	24	0.885	–	–
Yes	24		–	

*$p<0.05$; **$p<0.01$; ***$p<0.001$. [a]Clavien–Dindo Grade ≥IIIa. CI: Confidence interval; HR: hazard ratio; IMAC: intramuscular adipose tissue content.

Table IV. *Clinicopathological characteristics of older patients (aged ≥80 years) with high or low modified IMAC.*

Characteristic	High modified IMAC (n=26)	Low modified IMAC (n=22)	*p*-Value
Age (years), median (range)	84 (80-92)	83 (80-91)	0.958
Sex (male/female), n	13/13	14/8	0.341
Body mass index (kg/m^2), median (range)	22.4 (17.7-30.4)	23.1 (16.9-32.5)	0.587
Carcinoembryonic antigen level (ng/ml), median (range)	2.94 (1.26-7.32)	3.93 (1.23-16.80)	0.144
Carbohydrate antigen 19-9 level (U/ml), median (range)	15.6 (2.0-6,392.7)	20.2 (2.0-120,000.0)	0.147
C-reactive protein level (mg/dl), median (range)	0.13 (0.03-3.70)	0.71 (0.04-24.18)	0.104
Prognostic nutritional index, median (range)	48.4 (36.9-62.9)	42.3 (22.2-58.2)	0.009**
Glasgow Prognostic Score (0/1/2), n	18/15/3	6/13/3	0.008**
C-reactive protein-to-albumin ratio, median (range)	0.033 (0.007-1.000)	0.180 (0.009-14.224)	0.945
Platelet-to-lymphocyte ratio, median (range)	0.12 (0.05-0.26)	0.17 (0.06-0.44)	0.054
Neutrophil-to-lymphocyte ratio, median (range)	2.25 (0.73-5.26)	2.46 (1.12-48.00)	0.137
Preoperative cholangitis (absent/present), n	15/11	12/10	0.827
Comorbidities (absent/present), n	4/22	8/14	0.093
Type of cancer (intrahepatic cholangiocarcinoma/other), n	4/22	5/17	0.517
Resection (R0/R1-2), n	24/2	20/2	0.862
Operative time (minutes), median (range)	341 (107-540)	421 (124-738)	0.244
Blood loss (ml), median (range)	207 (0-1,220)	345 (30-13,870)	0.112
Blood transfusion (no/yes), n	25/1	18/3	0.198
T-stage (T3-4), n (%)	9 (34.6)	8 (36.4)	0.900
Lymph node metastasis, n (%)	7 (26.9)	9 (40.9)	0.306
Tumor-Node-Metastasis stage[a] (I-II/III-IV), n	20/6	13/9	0.183
Tumor differentiation (well/other)	12/14	6/15	0.215
Postoperative complications[b] (absent/present), n	19/7	13/9	0.306
Postoperative adjuvant chemotherapy (no/yes), n	14/12	10/11	0.671

**$p<0.01$. [a]Union for International Cancer Control Tumor-Node-Metastasis classification (eighth edition); [b]Clavien–Dindo Grade ≥IIIa. IMAC: Intramuscular adipose tissue content.

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