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RESEARCH

Prognostic Significance of Sarcopenia and Systemic Inflammatory Markers in Biliary Tract Cancer: A Retrospective Cohort Study

Masashi Utsumi[1] · Masaru Inagaki[1] · Koji Kitada[1] · Naoyuki Tokunaga[1] · Kosuke Yonoki[1] · Yuya Sakurai[1] · Hiroki Okabayashi[1] · Ryosuke Hamano[1] · Hideaki Miyasou[1] · Yousuke Tsunemitsu[1] · Shinya Otsuka[1]

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Abstract

Purpose To evaluate the prognostic significance of sarcopenia and systemic inflammatory markers in patients with surgically resected biliary tract cancer (BTC).

Methods Between July 2010 and December 2022, 146 patients were recruited. Sarcopenia was assessed using the psoas muscle index. Preoperative inflammatory markers were used to calculate the prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio. Cox regression analysis was performed to determine prognostic factors for overall survival (OS) and recurrence-free survival (RFS). $P < 0.05$ was considered statistically significant.

Results Sixty-four patients had sarcopenia. Sarcopenia was associated with body mass index (< 22 kg/m^2), lymph node metastasis, and low PNI (< 42). R1/R2 resection ($P = 0.02$), sarcopenia ($P < 0.001$), lymph node metastasis ($P = 0.007$), intrahepatic cholangiocarcinoma ($P < 0.001$), and low PNI ($P = 0.01$) were independent predictors of OS, while male sex ($P = 0.04$), R1/R2 resection ($P < 0.001$), lymph node metastasis ($P = 0.005$), intrahepatic cholangiocarcinoma ($P < 0.001$), tumor differentiation (other than well; $P = 0.003$), and low PNI ($P = 0.03$) were independent predictors of RFS. Patients were stratified into no sarcopenia and high PNI (≥ 42; A), sarcopenia or low PNI (B), and sarcopenia and low PNI (C) groups. Group C had worse OS than the other two groups ($P < 0.001$ and $P = 0.02$, respectively).

Conclusion Sarcopenia is associated with the PNI. Sarcopenia and the PNI are independent prognostic factors among patients with resected BTC. Sarcopenia may have better prognostic value when combined with the PNI.

Keywords Biliary tract cancer · Prognostic nutritional index · Sarcopenia · Surgical resection · Systemic inflammatory marker

Introduction

Biliary tract cancer (BTC), including gallbladder carcinoma, intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal cholangiocarcinoma, and ampullary carcinoma, is a rare aggressive malignancy that has been increasing in incidence in recent decades [1]. Resection is the only curative treatment for BTC. However, recurrence is a major concern [2]. Most patients are not eligible for surgical resection, because of the advanced stage of the disease at the time of diagnosis. Despite advances in surgical techniques and adjuvant chemotherapy, the prognosis remains poor [3]. Preoperative prognostic factors for BTC may allow better preoperative risk–benefit assessment and permit patient stratification for precision medicine [4].

Sarcopenia is characterized by the loss of skeletal muscle mass and strength. It is associated with aging, as well as pathological conditions, such as liver cirrhosis, renal failure, and cancer. The importance of sarcopenia in cancer has been recognized as low muscularity is an independent predictor of poor prognosis in various cancers [5]. Sarcopenia is associated with overall survival (OS) in patients with BTC [6]. Therefore, the prediction and early diagnosis of sarcopenia are crucial for the prognosis of patients with BTC.

Sarcopenia is associated with inflammation in cancer, as well as aging [7]. Several studies have shown that systemic inflammation and nutritional status are associated with poor prognosis in patients with cancer [8, 9]. Several markers have been used to assess systemic inflammation in the clinic, including the prognostic nutritional index (PNI), Glasgow Prognostic

✉ Masashi Utsumi
utsumi.masashi.vn@mail.hosp.go.jp

[1] Department of Surgery, NHO Fukuyama Medical Center, 4-14-17 Okinogami-Cho, Fukuyama, Hiroshima 720-8520, Japan

Score, C-reactive protein-to-albumin ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio [10, 11].

Patients with metastatic BTC and hepatocellular carcinoma with high systemic inflammation and sarcopenia have worse OS [12, 13]. However, the relationship between systemic inflammation and sarcopenia in patients with surgically resected BTC has not been well studied. This study aimed to evaluate the prognostic significance of sarcopenia and systemic inflammatory markers in patients with surgically resected BTC.

Materials and Methods

Patients

A total of 147 consecutive patients who underwent surgical resection for BTC at our institution between July 2010 and December 2022 were retrospectively reviewed. BTC, including gallbladder carcinoma, intrahepatic cholangiocarcinoma, distal cholangiocarcinoma, ampullary carcinoma, and perihilar cholangiocarcinoma, was confirmed by pathological examination. One patient who died of heart failure due to arrhythmia on postoperative day 18 was excluded. A total of 146 patients who underwent surgical resection for BTC were analyzed.

Data Collection

Data on demographic characteristics (age at surgery and sex), laboratory tests (serum albumin/C-reactive protein levels, platelet/neutrophil/lymphocyte counts, total bilirubin, conjugated bilirubin, and tumor markers), comorbidities (hypertension, diabetes mellitus, cardiac disease, and stroke), preoperative cholangitis, surgical procedure (type of resection), operative time, blood loss, transfusion, tumor stage (Union for International Cancer Control Tumor–Node–Metastasis classification [eight edition]), tumor differentiation, and postoperative adjuvant chemotherapy were obtained from patients' medical records. Liver resections were classified according to the Brisbane 2000 Terminology of Liver Anatomy and Resections [14]. Curative (R0) resection was defined as complete removal of all macroscopic nodules with microscopically clear margins. R1 and R2 resections were defined as microscopically or macroscopically positive margins, respectively. Complications were defined according to the Clavien–Dindo classification [15]. In this study, 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 Definition

Sarcopenia was assessed using the psoas muscle index, an alternative measurement of sarcopenia that has been adopted by the Japan Society of Hepatology [16]. Preoperative computed tomography imaging was performed within 1 month before surgery using a multidetector computed tomography scanner. 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 calculated as the cross-sectional area of the bilateral psoas muscles (cm^2) divided by height squared (m^2). A low psoas muscle index was considered a proxy for low muscle volume [16].

Because the psoas muscle index range differs between men and women, different cutoff values were established using receiver operating characteristic curves. The optimal cutoff values were determined based on the best accuracy in relation to outcome. The cutoff values for psoas muscle index in men and women were 5.10 and 3.69 cm^2/m^2, respectively (area under the receiver operating characteristic curve—0.587 and 0.625, respectively).

Systemic Inflammatory Markers

Peripheral venous blood samples were collected within 2 weeks before surgery. The PNI was calculated as 10 × serum albumin (g/dL) + 0.05 × total lymphocyte count ($/mm^3$) [17]. The Glasgow Prognostic Score was defined as follows: 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 [18]. The C-reactive protein-to-albumin ratio was calculated as C-reactive protein (mg/dL) divided by albumin (g/dL) [19]. The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were calculated by dividing the neutrophil and platelet counts by the lymphocyte count, respectively [10, 11].

Follow-Up

All patients underwent routine follow-up until December 2022. 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/R2 resection received postoperative adjuvant chemotherapy (tegafur/gimeracil/oteracil) for approximately 6 months. None of the patients received neoadjuvant chemotherapy.

Outcomes

The relationships between clinicopathological characteristics and OS and RFS were analyzed using univariate and multivariate Cox regression analyses. The duration between surgery and death or the last follow-up was defined as OS. The duration between surgery and recurrence which confirmed by radiology imaging was defined as recurrence-free survival (RFS).

Statistical Analysis

All data were blinded before analysis. Continuous data were presented as median (interquartile range). Categorical data were presented as numbers (percentage). 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 systemic inflammatory markers were determined by maximizing the Youden index (sensitivity + specificity − 1). OS was estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. Prognostic factors 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

Patient characteristics are summarized in Table 1. The median age was 74 (range, 38–92) years. 64 patients had sarcopenia. 43 patients had gallbladder carcinoma; 33, intrahepatic cholangiocarcinoma; 31, distal cholangiocarcinoma; 23, ampullary carcinoma; and 16, perihilar cholangiocarcinoma. Curative (R0) resection was achieved in 125 patients. Surgical procedures included liver resection in 67 patients (hemihepatectomy [$N = 36$], subsegmentectomy [$N = 11$], liver bed resection [$N = 8$], sectionectomy [$N = 7$], trisectionectomy [$N = 4$], and partial hepatectomy [$N = 1$]), pancreaticoduodenectomy in 52, cholecystectomy in 24, hepatopancreaticoduodenectomy in two, and bile duct resection without hepatectomy in one. Postoperative complications were observed in 51 patients: pancreatic fistula in 29, bile leakage in nine, abdominal abscess in eight, pleural effusion and chylous ascites in two each, and abdominal bleeding in one. The optimal cutoff values for the PNI, Glasgow Prognostic Score, C-reactive protein-to-albumin ratio, platelet-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio were 42 (sensitivity, 31.3%; specificity, 83.0%; area under the receiver operating characteristic curve, 0.560; and 95% confidence interval, 0.467–0.625), 1 (sensitivity, 26.6%; specificity, 80.3%; area under the receiver operating characteristic curve, 0.530; and 95% confidence interval, 0.462–0.623), 0.125 (sensitivity, 51.9%; specificity, 69.5%; area under the receiver operating characteristic curve, 0.590; and 95% confidence interval, 0.497–0.680), 106 (sensitivity, 79.7%; specificity, 31.8%; area under the receiver operating characteristic curve, 0.550; 95% confidence interval, 0.450–0.638), and 1.59 (sensitivity, 26.6%; specificity, 80.5%; area under the receiver operating characteristic curve, 0.467; and 95% confidence interval, 0.372–0.560), respectively.

Relationship Between Clinicopathological Characteristics and Sarcopenia

Patients were stratified into two groups according to the presence ($N = 64$) or absence ($N = 82$) of sarcopenia. Clinicopathological characteristics were compared between the two groups. Body mass index in the sarcopenia group was lower than that in the non-sarcopenia group [20.8 (18.9–23.3) *vs.* 23.6 (22.1–26.2) kg/m^2, respectively; $P < 0.001$]. PNI was also lower in the sarcopenia group than in the non-sarcopenia group [44.3 (40.0–48.6) *vs.* 48.5 (42.9–52.3), respectively; $P = 0.009$]. There were more patients with preoperative cholangitis in the sarcopenia group than in the non-sarcopenia group. The incidence of lymph node metastasis was higher in the sarcopenia group than in the non-sarcopenia group (46.9% *vs.* 29.3%, respectively; $P = 0.03$) (Table 2).

Univariate and Multivariate Analyses of Prognostic Factors for OS

The median OS was 47 (range, 6–147) months. The 1-, 3-, and 5-year OS rates were 87.7%, 57.2%, and 46.1%, respectively. In the Kaplan–Meier analysis, the sarcopenia group had worse OS than the non-sarcopenia group ($P = 0.001$; Fig. 1a), and the low PNI (< 42) group had worse OS than the high PNI (≥ 42) group ($P = 0.007$; Fig. 1b).

Table 3 shows the relationship between clinicopathological characteristics and OS after surgical resection. Univariate analysis showed that male sex, R1/R2 resection, sarcopenia, lymph node metastasis, intrahepatic cholangiocarcinoma, T stage ≥ 3, tumor differentiation, low PNI, C-reactive protein-to-albumin ratio ≥ 0.125, and carbohydrate antigen 19–9 levels ≥ 20 U/mL were associated with poor OS. R1/R2 resection ($P = 0.02$), sarcopenia ($P < 0.001$), lymph node metastasis ($P = 0.007$), intrahepatic cholangiocarcinoma ($P < 0.001$), and low PNI ($P = 0.01$) were independent predictors of OS in the multivariate analysis.

Table 1 Patient characteristics

Characteristic	Patients
Age (years), median (IQR)	75 (69–82)
Sex (male/female), N	91/58
Body mass index (kg/m^2), median (IQR)	22.8 (19.8–24.8)
Preoperative laboratory data	
Albumin (g/dL), median (IQR)	3.8 (3.4–4.2)
Platelet count ($\times 10^4$/mm^3), median (IQR)	21.4 (17.3–25.6)
Neutrophil count ($\times 10^3$/mm^3), median (IQR)	3.56 (2.67–4.52)
Lymphocyte count ($\times 10^3$/mm^3), median (IQR)	1.53 (1.15–1.93)
C-reactive protein (mg/dL), median (IQR)	0.80 (0.60–1.00)
Carcinoembryonic antigen (ng/mL), median (IQR)	3.02 (2.00–4.65)
Carbohydrate antigen 19–9 (U/mL), median (IQR)	16.55 (5.18–101.98)
Prognostic nutritional index, median (IQR)	45.9 (42.3–51.2)
Glasgow Prognostic Score (0/1/2), *N*	91/39/2
C-reactive protein-to-albumin ratio, median (IQR)	0.073 (0.027–0.234)
Platelet-to-lymphocyte ratio, median (IQR)	136 (104–198)
Neutrophil-to-lymphocyte ratio, median (IQR)	
Psoas muscle index (cm^2/m^2), median (IQR)	2.26 (1.71–3.30)
Type of cancer, *N* (%)	
Intrahepatic cholangiocarcinoma	33 (22.6)
Gallbladder carcinoma	43 (29.4)
Distal cholangiocarcinoma	31 (21.2)
Ampullary carcinoma	23 (15.7)
Perihilar cholangiocarcinoma	16 (10.9)
Preoperative cholangitis, *N* (%)	50 (40.4)
Comorbidities (absent/present), *N*	37/109
Surgical procedure, *N* (%)	
Cholecystectomy	24 (16.4)
Bile duct resection without liver resection	1 (0.7)
Liver bed resection	8 (5.5)
Partial hepatectomy	1 (0.7)
Subsegmentectomy	11 (7.5)
Sectionectomy	7 (4.8)
Hemihepatectomy	36 (24.7)
Trisectionectomy	4 (2.7)
Pancreaticoduodenectomy	52 (35.6)
Hepatopancreaticoduodenectomy	2 (1.3)
Operative time (min), median (IQR)	437 (305–525)
Blood loss (mL), median (IQR)	340 (144–713)
Blood transfusion, *N* (%)	16 (11.2)
T classification (1/2/3/4), *N*	29/51/58/8
Tumor–Node–Metastasis classification (eighth edition) (0/I/II/III/IV), *N*	7/27/57/37/18
Resection (R0/R1/R2), *N*	125/18/3
Lymph node metastasis (absent/present), *N*	54/92
Tumor differentiation (well/moderate/poor/pap/well pap/other/unknown), *N*	59/38/11/8/5/7/18
Mortality, *N* (%)	0 (0.0)
Postoperative adjuvant chemotherapy, *N* (%)	87 (61.3)
Postoperative complications (Clavien–Dindo Grade ≥ IIIa) (absent/present), *N*	51/95

Table 2 Patient characteristics according to the presence or absence of sarcopenia

Characteristic	Sarcopenia ($N=64$)	Non-sarcopenia ($N=82$)	P-value
Age (years), median (IQR)	77 (69–83)	74 (68.5–80.5)	0.09
Sex (male/female), N	44/22	47/35	0.31
Body mass index (kg/m^2), median (IQR)	20.8 (18.9–23.3)	23.6 (22.1–26.2)	< 0.001**
Carcinoembryonic antigen (ng/mL), median (IQR)	3.38 (2.34–4.98)	2.82 (1.95–4.65)	0.22
Carbohydrate antigen 19–9 (U/mL), median (IQR)	18.38 (6.5–163.1)	13.7 (4.4–77.3)	0.11
C-reactive protein (mg/dL), median (IQR)	0.32 (0.12–0.88)	0.22 (0.09–0.82)	0.25
Prognostic nutritional index, median (IQR)	44.3 (40.0–48.6)	48.5 (42.9–52.3)	0.009*
Glasgow Prognostic Score (0/1/2), *N*	37/18/9	54/21/7	0.48
C-reactive protein-to-albumin ratio, median (IQR)	0.093 (0.029–0.304)	0.056 (0.023–0.23)	0.21
Platelet-to-lymphocyte ratio, median (IQR)	141 (106–220)	131 (99–174)	0.17
Neutrophil-to-lymphocyte ratio, median (IQR)	2.39 (1.49–3.63)	2.16 (1.72–2.88)	0.79
Preoperative cholangitis (absent/present), *N*	32/32	55/27	0.04
Comorbidities (absent/present), *N*	16/48	22/60	0.80
Type of cancer (intrahepatic cholangiocarcinoma/other), *N*	12/52	22/60	0.25
Resection (R0/R1–2), *N*	52/12	74/8	0.12
Operative time (min), median (IQR)	426 (306–531)	458 (303–511)	0.96
Blood loss (mL), median (IQR)	325 (146–808)	346 (141–648)	0.38
Transfusion (no/yes), *N*	53/10	76/6	0.12
T classification (≥ 3), *N* (%)	33 (51.6)	33 (40.2)	0.17
Lymph node metastasis (absent/present), *N*	30 (46.9)	24 (29.3)	0.03*
Tumor–Node–Metastasis classification (eighth edition) (I–II/III–IV), *N*	30/34	57/25	0.04*
Tumor differentiation (well/other)	20/44	29/53	0.50
Postoperative complications (Clavien–Dindo Grade ≥ IIIa) (absent/present), *N*	44/20	51/31	0.41
Postoperative adjuvant chemotherapy (no/yes), *N*	41/23	46/36	0.24

*$P < 0.05$; **$P < 0.01$

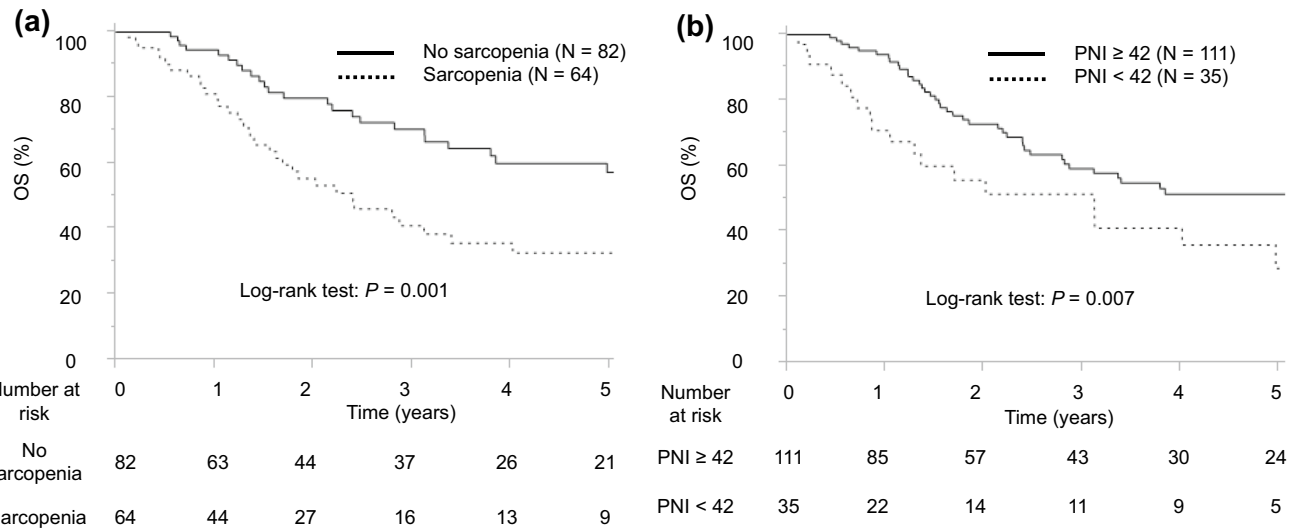

Fig. 1 Kaplan–Meier curves of overall survival (OS) stratified by **a** sarcopenia and **b** prognostic nutritional index (PNI)

Table 3 Univariate and multivariate analyses of clinicopathological characteristics for overall survival after resection of biliary tract cancer

Clinicopathological characteristic	Univariate analysis		Multivariate analysis	
	N	*P*-value	HR[a] (95% CI[b])	*P*-value
Age (years) ≥75 <75	76 70	0.79	–	–
Sex Male Female	89 57	0.02*	1.69 (0.97–3.07)	0.07
Body mass index (kg/m^2) ≥20 <20	95 51	0.40	–	–
Carcinoembryonic antigen (ng/mL) ≥9 <9	30 104	0.46	–	–
Carbohydrate antigen 19–9 (U/mL) ≥20 <20	53 91	0.05*	1.04 (0.57–1.83)	0.89
Preoperative cholangitis Present Absent	59 87	0.09	–	–
Comorbidities Present Absent	108 38	0.15	–	–
Type of cancer Intrahepatic cholangiocarcinoma Other	34 112	0.03*	3.33 (1.71–6.38)	0.005**
Resection R0 R1–2	126 20	<0.001***	2.35 (1.19–4.52)	0.02*
Operative time (min) ≥420 <420	80 66	0.55	–	–
Blood loss (mL) ≥300 <300	77 69	0.65	–	–
Transfusion No Yes	127 16	0.18	–	–
T classification <3 ≥3	91 55	<0.001***	1.56 (088–2.80)	0.13
Lymph node metastasis Present Absent	54 82	<0.001***	2.31 (1.26–4.28)	0.007**
Tumor differentiation Well Other	61 84	0.006**	1.61 (0.92–2.93)	0.10
Sarcopenia Present (low psoas muscle index) Absent (high psoas muscle index)	64 82	0.001**	2.55 (1.46–4.51)	<0.001***
Prognostic nutritional index <42 ≥42	35 111	0.007**	2.17 (1.21–3.82)	0.01*
Glasgow Prognostic Score 0 1–2	91 55	0.10	–	–
C-reactive protein-to-albumin ratio <0.125 ≥0.125	88 58	0.020*	1.00 (0.56–1.79)	0.99

Table 3 (continued)

Clinicopathological characteristic	Univariate analysis		Multivariate analysis	
	N	*P*-value	HR[a] (95% CI[b])	*P*-value
Neutrophil-to-lymphocyte ratio	24	0.93	–	–
< 1.59	122			
≥ 1.59				
Platelet-to-lymphocyte ratio	32	0.30	–	–
< 106	113			
≥ 106				
Postoperative complications (Clavien–Dindo Grade ≥ IIIa)	95	0.15	–	–
Absent	51			
Present				
Postoperative adjuvant chemotherapy	55	0.16	–	–
No	91			
Yes				

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

[a]*HR* hazard ratio

[b]*CI* confidence interval

Univariate and Multivariate Analyses of Prognostic Factors for RFS

The median RFS was 60 (range, 6–147) months. The 1-, 3-, and 5-year RFS rates were 68.1%, 55.4%, and 48.9%, respectively.

Table 4 shows the relationship between clinicopathological characteristics and RFS after surgical resection. Univariate analysis showed that male sex, R1/R2 resection, sarcopenia, lymph node metastasis, intrahepatic cholangiocarcinoma, T stage ≥ 3, tumor differentiation, low PNI, C-reactive protein-to-albumin ratio ≥ 0.125, carbohydrate antigen 19–9 levels ≥ 20 U/mL, and postoperative adjuvant chemotherapy were associated with poor RFS. Male sex ($P = 0.04$), R1/R2 resection ($P < 0.001$), lymph node metastasis ($P = 0.005$), intrahepatic cholangiocarcinoma ($P < 0.001$), tumor differentiation (other than well; $P = 0.003$), and low PNI ($P = 0.03$) were independent predictors of RFS in the multivariate analysis.

Impact of Sarcopenia and PNI on OS

Sarcopenia and PNI were independent predictors of OS in patients with BTC. Patients were stratified into three groups according to these two factors: Group A, no sarcopenia and high PNI; Group B, sarcopenia or low PNI; and Group C, sarcopenia and low PNI. In the Kaplan–Meier analysis, Group C had worse OS than the other two groups ($P < 0.001$ and $P = 0.02$, respectively) (Fig. 2).

As sarcopenia and PNI are strongly associated with OS, we performed a multivariate analysis of sarcopenia and PNI. Multivariate analysis showed that sarcopenia and low PNI and sarcopenia or low PNI were independent predictors of OS ($P < 0.001$ and $P = 0.047$, respectively) (Table 5).

Subgroup Analysis According to Tumor Location

The impact of sarcopenia and PNI on OS was also analyzed in relation to tumor location. Patients with gallbladder carcinoma and intrahepatic cholangiocarcinoma in Group C had worse OS than those in the other two groups (both, $P < 0.001$; Fig. 3). For patients with distal cholangiocarcinoma, ampullary carcinoma, and perihilar cholangiocarcinoma, the impact of sarcopenia and PNI on OS was not significant.

Discussion

In this study, we showed that sarcopenia and low PNI are independent predictors of poor OS in patients with surgically resected BTC. Patients in Group C had the worst OS among the three groups. To our knowledge, this is the first study to show that sarcopenia accompanied by low PNI is associated with poor OS in patients with BTC.

Sarcopenia is a hallmark of cancer cachexia and is a major factor leading to increased morbidity and mortality in patients with advanced gastrointestinal cancer [20]. The role of sarcopenia as a prognostic marker remains controversial. Therefore, there is an urgent need to investigate the prognostic significance of sarcopenia in patients with BTC. In this study, multivariate analysis showed that sarcopenia is associated with OS but not RFS. A previous study [6] confirmed that sarcopenia is an independent predictor of OS and RFS after surgical resection of BTC. Yoon et al. [21] analyzed the significance of sarcopenia in BTC and showed that sarcopenia (a low skeletal muscle index) was not associated with poor OS. Another study [13] showed that sarcopenia alone did not predict OS and RFS in multivariate analysis. However, sarcopenia and

Table 4 Univariate and multivariate analyses of clinicopathological characteristics for recurrence-free survival after resection of biliary tract cancer

Clinicopathological characteristic	Univariate analysis		Multivariate analysis	
	N	*P*-value	HR[a] (95% CI[b])	*P*-value
Age (years) ≥75 <75	76 70	0.20	–	–
Sex Male Female	89 57	0.01*	1.82 (1.04–3.32)	0.04*
Body mass index (kg/m^2) ≥20 <20	95 51	0.27	–	–
Carcinoembryonic antigen (ng/mL) ≥9 <9	30 104	0.73	–	–
Carbohydrate antigen 19–9 (U/mL) ≥20 <20	53 91	0.03*	1.12 (0.67–2.06)	0.54
Preoperative cholangitis Present Absent	59 87	0.08	–	–
Comorbidities Present Absent	108 38	0.11	–	–
Type of cancer Intrahepatic cholangiocarcinoma Other	34 112	0.003*	4.50 (2.27–8.89)	<0.001***
Resection R0 R1–2	126 20	<0.001***	4.66 (2.24–9.69)	<0.001***
Operative time (min) ≥420 <420	80 66	0.13	–	–
Blood loss (mL) ≥300 <300	77 69	0.29	–	–
Transfusion No Yes	127 16	0.39	–	–
T classification <3 ≥3	91 55	<0.001***	1.24 (069–2.27)	0.46
Lymph node metastasis Present Absent	54 82	<0.001***	2.53 (1.32–4.93)	0.005**
Tumor differentiation Well Other	61 84	0.002**	2.36 (1.32–4.35)	0.003**
Sarcopenia Present (low psoas muscle index) Absent (high psoas muscle index)	64 82	0.033*	1.62 (0.91–2.89)	0.11
Prognostic nutritional index <42 ≥42	35 111	0.003**	2.14 (1.09–4.18)	0.03*
Glasgow Prognostic Score 0 1–2	91 55	0.40	–	–
C-reactive protein-to-albumin ratio <0.125 ≥0.125	88 58	0.01*	1.02 (0.54–1.93)	0.94

Table 4 (continued)

Clinicopathological characteristic	Univariate analysis		Multivariate analysis	
	N	*P*-value	HR[a] (95% CI[b])	*P*-value
Neutrophil-to-lymphocyte ratio < 1.59 ≥ 1.59	24 122	0.12	–	–
Platelet-to-lymphocyte ratio < 106 ≥ 106	32 113	0.77	–	–
Postoperative complications (Clavien–Dindo Grade ≥ IIIa) Absent Present	95 51	0.43	–	–
Postoperative adjuvant chemotherapy No Yes	55 91	0.02*	1.31 (0.64–2.62)	0.44

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

[a]*HR* hazard ratio

[b]*CI* confidence interval

high neutrophil-to-lymphocyte ratio (> 3) were associated with poor OS and progression-free survival in patients with metastatic BTC. It is possible that BTC is more affected by tumor- than by patient-related factors (such as sarcopenia). Our findings support the prognostic value of sarcopenia in surgically resected BTC.

Systemic inflammation is a significant factor that can predict the prognosis of various cancers. Several inflammatory markers (Glasgow Prognostic Score, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio) are associated with poor prognosis in patients with BTC [13, 22, 23]. PNI, a marker of nutritional status and systemic inflammation, is based on serum albumin and lymphocyte count, both of which can be easily obtained from routine preoperative blood tests. Several studies [24, 25] have shown that the PNI can be used as a prognostic marker in patients with BTC. We previously investigated the prognostic significance of PNI in patients with surgically resected BTC and demonstrated its potential clinical application [22]. In this study, we obtained similar results with PNI. The mechanism(s) underlying the prognostic significance of PNI in patients with BTC have been discussed previously.

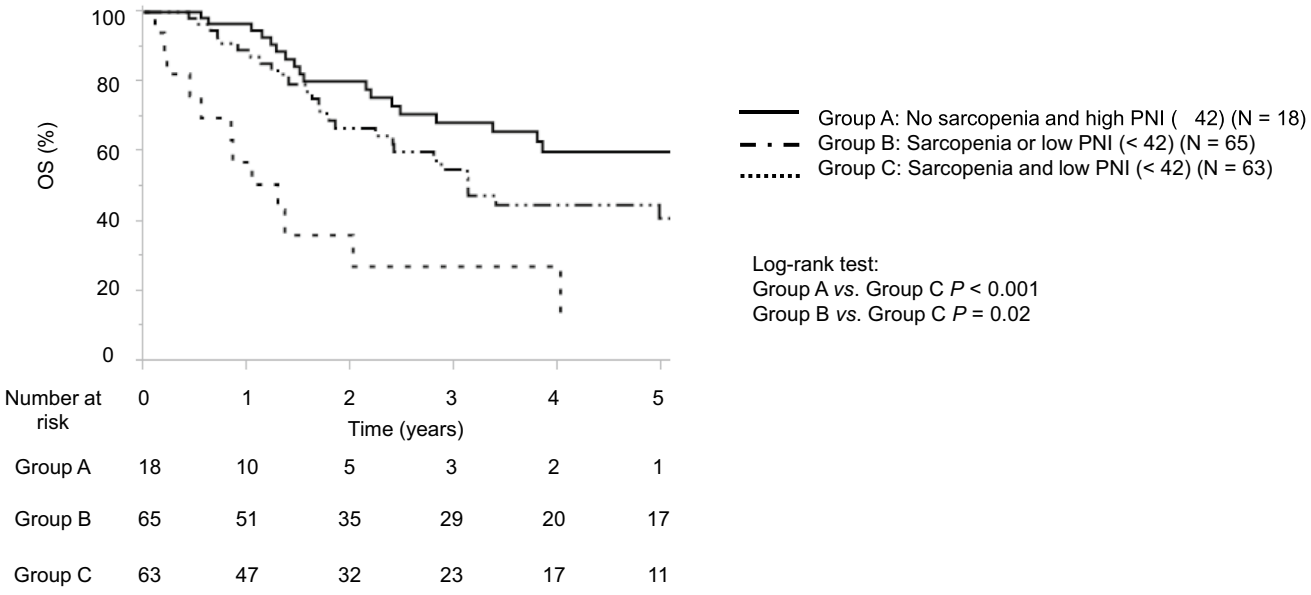

Fig. 2 Kaplan–Meier curves of overall survival (OS) for patients stratified into no sarcopenia and high prognostic nutritional index (PNI) (≥ 42; A), sarcopenia or low PNI (< 42; B), and sarcopenia and low PNI (C) groups

Table 5 Multivariate analysis of sarcopenia and PNI for overall survival

Variable	Multivariate analysis	
	HR[a] (95% CI[b])	*P*-value
Type of cancer (intrahepatic cholangiocarcinoma)	3.71 (2.01–6.71)	< 0.001***
Resection (R1–2)	2.07 (1.08–3.79)	0.029*
Lymph node metastasis (present)	3.03 (1.75–5.31)	< 0.001***
Sarcopenia and PNI[c]		
No sarcopenia and high PNI	Reference	
Sarcopenia or low PNI	1.84 (1.01–3.45)	0.047*
Sarcopenia and low PNI	5.48 (2.38–12.31)	< 0.001***

*$P < 0.05$; ***$P < 0.001$

[a]*HR* hazard ratio

[b]*CI* confidence interval

[c]*PNI* prognostic nutritional index

Patients with sarcopenia accompanied by inflammation have faster disease progression and worse OS than those without sarcopenia and inflammation. The relationship between sarcopenia and systemic inflammatory markers has attracted increasing attention. There is a strong correlation between systemic inflammatory markers and catabolic pathway activation [26]. Tumor necrosis factor and interleukin 6, which are released by the tumor and surrounding cells, can suppress protein synthesis, and stimulate protein degradation. The tumor itself also promotes inflammation, which facilitates tumor progression. The secretion of proinflammatory myokines induces muscle degeneration and exacerbates systemic inflammation [27]. A previous study [28] suggested that inflammation causes malnutrition, resulting in impaired immune responses and reduced muscle strength. Inflammation and malnutrition jointly lead to sarcopenia. In this study, patients with sarcopenia had low PNI and advanced disease compared to those without sarcopenia, suggesting that sarcopenia is associated with nutritional–inflammation status and tumor progression. Our findings are consistent with those of the aforementioned studies. Sarcopenia may have better prognostic value in patients with surgically resected BTC when combined with PNI.

In the subgroup analysis, sarcopenia and low PNI were associated with poor OS in patients with intrahepatic cholangiocarcinoma and gallbladder carcinoma but not distal cholangiocarcinoma, ampullary carcinoma, and perihilar cholangiocarcinoma. The reason may be that intrahepatic cholangiocarcinoma and gallbladder carcinoma have relatively high R0 resection rates. The R0 resection rates of intrahepatic cholangiocarcinoma and gallbladder carcinoma were 97.1% and 86.0%, respectively, while those

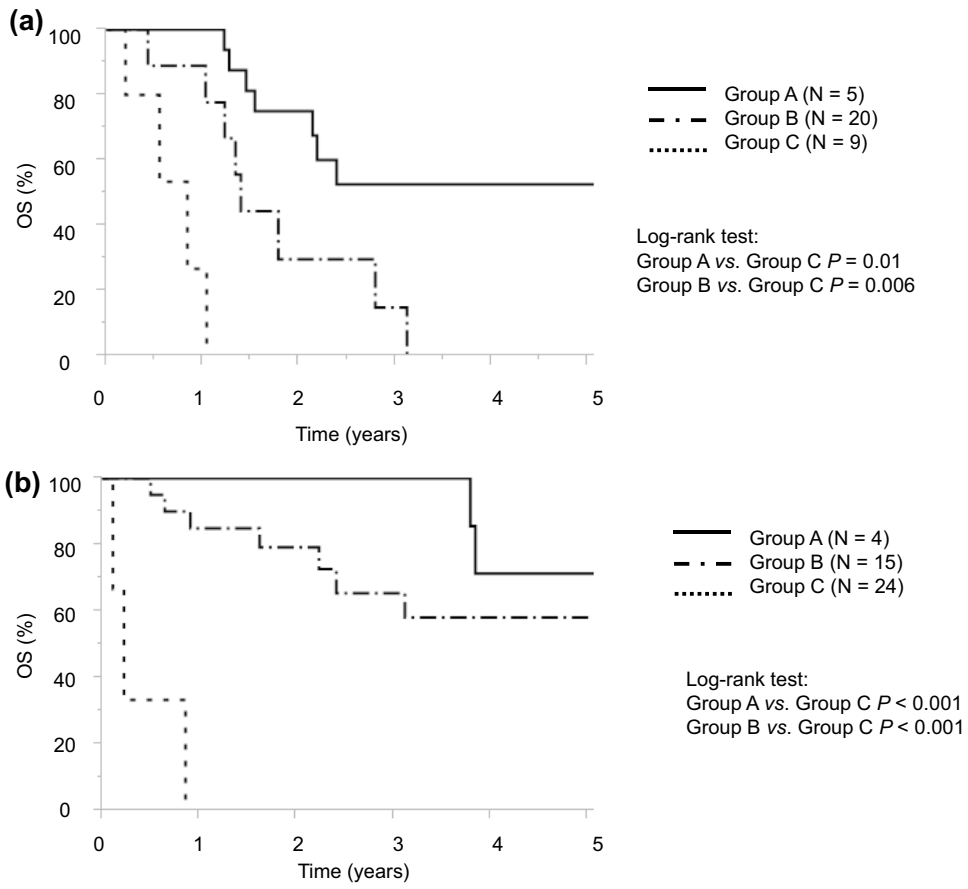

Fig. 3 Kaplan–Meier curves of overall survival (OS) for patients with **a** gallbladder carcinoma and **b** intrahepatic cholangiocarcinoma stratified into no sarcopenia and high prognostic nutritional index (PNI) (≥ 42; A), sarcopenia or low PNI (< 42; B), and sarcopenia and low PNI (C) groups

of distal cholangiocarcinoma, ampullary carcinoma, and perihilar cholangiocarcinoma were 80.0%, 95.1%, and 62.5%, respectively. Intrahepatic cholangiocarcinoma and gallbladder carcinoma may be more affected by patient-related factors (such as sarcopenia and PNI), whereas distal cholangiocarcinoma, ampullary carcinoma, and perihilar cholangiocarcinoma may be more affected by tumor-related factors and surgical outcomes.

Kaido et al. [29] reported the impact of nutritional therapy on prognosis after liver transplantation in patients with sarcopenia. Mayo et al. [30] reported that preoperative rehabilitation is effective in reducing postoperative complications in patients with various cancers. Supportive therapies focusing on perioperative nutrition and rehabilitation may be applicable to patients with surgically resected BTC. However, the efficacy of such therapies requires further evaluation in prospective studies.

This study has several limitations related to its single-center, retrospective design. The sensitivity, specificity, and areas under the receiver operating characteristic curves of the psoas muscle index and PNI were low. Further multicenter prospective studies are needed to validate our findings. Sarcopenia should be diagnosed not only by the detection of low muscle mass but also by reduced muscle strength. The diagnosis of sarcopenia in this study may not have been accurate enough.

Conclusions

Sarcopenia and low PNI are associated with poor OS in patients with surgically resected BTC. Both sarcopenia and PNI are independent predictors of OS in patients with BTC. Nutritional therapy and rehabilitation may enhance the survival of cancer patients with sarcopenia and inflammation.

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Author Contribution Conceptualization: Masashi Utsumi, Masaru Inagaki, Koji Kitada, Naoyuki Tokunaga, Kosuke Yonoki, Yuya Sakurai, Hiroki Okabayashi, Ryosuke Hamano, Hideaki Miyasou, Yousuke Tsunemitsu, and Shinya Otsuka. Formal analysis and investigation: Masashi Utsumi, Masaru Inagaki, Koji Kitada, and Naoyuki Tokunaga. Writing—original draft preparation: Masashi Utsumi. Writing—review and editing: Masaru Inagaki.

Data Availability No datasets were generated or analyzed during the current study.

Declarations

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the National Hospital Organization Fukuyama Medical Center, Fukuyama, Hiroshima, Japan (No. ERB2022027).

Consent to Participate The requirement for written informed consent was waived owing to the retrospective nature of the study.

Competing Interests The authors declare no competing interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34. https://doi.org/10.3322/caac.21551.
2. Hasegawa S, Ikai I, Fujii H, Hatano E, Shimahara Y. Surgical resection of hilar cholangiocarcinoma: analysis of survival and postoperative complications. World J Surg. 2007;31:1256–63. https://doi.org/10.1007/s00268-007-9001-y.
3. Buettner S, van Vugt JLA, Gaspersz MP, Coelen RJS, Roos E, Labeur TA, Margonis GA, Ethun CG, Maithel SK, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick BA, Weber SM, Salem A, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, IJermans JNM IJzermans, van Gulik TM, Pawlik TM, Groot Koerkamp B. Survival after resection of perihilar cholangiocarcinoma in patients with lymph node metastases. HPB (Oxford). 2017;19:735–40. https://doi.org/10.1016/j.hpb.2017.04.014.
4. Saito H, Noji T, Okamura K, Tsuchikawa T, Shichinohe T, Hirano S. A new prognostic scoring system using factors available preoperatively to predict survival after operative resection of perihilar cholangiocarcinoma. Surgery. 2016;159:842–51. https://doi.org/10.1016/j.surg.2015.10.027.
5. Hanai T, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, Takai K, Shimizu M, Moriwaki H. Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition. 2015;31:193–9. https://doi.org/10.1016/j.nut.2014.07.005.
6. Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Kobayashi A, Iida T, Yagi S, Taura K, Hatano E, Uemoto S. Impact of the preoperative quantity and quality of skeletal muscle on outcomes after resection of extrahepatic biliary malignancies. Surgery. 2016;159:821–33. https://doi.org/10.1016/j.surg.2015.08.047.
7. Fearon KC, Voss AC, Hustead DS, Cancer Cachexia Study Group. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr. 2006;83:1345–50. https://doi.org/10.1093/ajcn/83.6.1345.
8. Davis JL, Langan RC, Panageas KS, Zheng J, Postow MA, Brady MS, Ariyan C, Coit DG. Elevated blood neutrophil-to-lymphocyte ratio: a readily available biomarker associated with death due to disease in high risk nonmetastatic melanoma. Ann Surg Oncol. 2017;24:1989–96. https://doi.org/10.1245/s10434-017-5836-0.
9. Kao SC, Pavlakis N, Harvie R, Vardy JL, Boyer MJ, van Zandwijk N, Clarke SJ. High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. Clin Cancer Res. 2010;16:5805–13. https://doi.org/10.1158/1078-0432.CCR-10-2245.
10. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005;91:181–4. https://doi.org/10.1002/jso.20329.
11. Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, Ghaneh P. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected

pancreatic ductal adenocarcinoma. Am J Surg. 2009;197:466–72. https://doi.org/10.1016/j.amjsurg.2007.12.057.
12. Hayashi H, Shimizu A, Kubota K, Notake T, Masuo H, Yoshizawa T, Hosoda K, Sakai H, Yasukawa K, Soejima Y. Combination of sarcopenia and prognostic nutritional index to predict long-term outcomes in patients undergoing initial hepatectomy for hepatocellular carcinoma. Asian J Surg. 2023;46:816–23. https://doi.org/10.1016/j.asjsur.2022.07.122.
13. Lee BM, Cho Y, Kim JW, Jeung HC, Lee IJ. Prognostic significance of sarcopenia in advanced biliary tract cancer patients. Front Oncol. 2020;10:1581. https://doi.org/10.3389/fonc.2020.01581.
14. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg. 2005;12:351–5. https://doi.org/10.1007/s00534-005-0999-7.
15. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, De Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187–96. https://doi.org/10.1097/SLA.0b013e3181b13ca2.
16. Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, Hammad A, Mori A, Takaori K, Uemoto S. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. Surgery. 2015;157:1088–98. https://doi.org/10.1016/j.surg.2015.02.002.
17. Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg. 2011;98:268–74. https://doi.org/10.1002/bjs.7305.
18. Proctor MJ, Talwar D, Balmar SM, O'Reilly DS, Foulis AK, Horgan PG, Morrison DS, McMillan DC. The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome Study. Br J Cancer. 2010;103:870–6. https://doi.org/10.1038/sj.bjc.6605855.
19. Fairclough E, Cairns E, Hamilton J, Kelly C. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. Clin Med (Lond). 2009;9:30–3. https://doi.org/10.7861/clinmedicine.9-1-30.
20. Gullett NP, Mazurak VC, Hebbar G, Ziegler TR. Nutritional interventions for cancer-induced cachexia. Curr Probl Cancer. 2011;35:58–90. https://doi.org/10.1016/j.currproblcancer.2011.01.001.
21. Yoon SB, Choi MH, Song M, Lee JH, Lee IS, Lee MA, Hong TH, Jung ES, Choi MG. Impact of preoperative body compositions on survival following resection of biliary tract cancer. J Cachexia Sarcopenia Muscle. 2019;10:794–802. https://doi.org/10.1002/jcsm.12431.
22. Utsumi M, Kitada K, Tokunaga N, Kato T, Narusaka T, Hamano R, Miyasou H, Tsunemitsu Y, Otsuka S, Inagaki M. A combined prediction model for biliary tract cancer using the prognostic nutritional index and pathological findings: a single-center retrospective study. BMC Gastroenterol. 2021;21:375. https://doi.org/10.1186/s12876-021-01957-5.
23. Spolverato G, Maqsood H, Kim Y, Margonis GA, Luo T, Ejaz A, Pawlik TM. Neutrophil-lymphocyte and platelet-lymphocyte ratio in patients after resection for hepato-pancreatico-biliary malignancies. J Surg Oncol. 2015;111:868–74. https://doi.org/10.1002/jso.23900.
24. Wang J, Bo X, Li M, Nan L, Wang C, Gao Z, Suo T, Ni X, Liu H, Han J, Lu P, Liu H, Wang Y. Prediction efficacy for clinical outcome of prognostic nutritional index in patients with resectable biliary tract cancer depends on sex and obstructive jaundice status. Ann Surg Oncol. 2021;28:430–8. https://doi.org/10.1245/s10434-020-08728-8.
25. Yoo YJ, Kang CM, Choi M, Rho SY, Hwang HK, Lee WJ, Kim EW, Lee JA. Preoperative prognostic nutritional index as an independent prognostic factor for resected ampulla of Vater cancer. PLoS ONE. 2020;15: e0229597. https://doi.org/10.1371/journal.pone.0229597.
26. Kantola T, Klintrup K, Väyrynen JP, Vornanen J, Bloigu R, Karhu T, Herzig KH, Näpänkangas J, Mäkelä J, Karttunen TJ, Tuomisto A, Mäkinen MJ. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. Br J Cancer. 2012;107:1729–36. https://doi.org/10.1038/bjc.2012.456.
27. Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: a cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res Rev. 2017;35:200–21. https://doi.org/10.1016/j.arr.2016.09.008.
28. Lin J, Zhang W, Huang Y, Chen W, Wu R, Chen X, Lou N, Wang P. Sarcopenia is associated with the neutrophil/lymphocyte and platelet/lymphocyte ratios in operable gastric cancer patients: a prospective study. Cancer Manag Res. 2018;10:4935–44. https://doi.org/10.2147/CMAR.S175421.
29. Kaido T, Ogawa K, Fujimoto Y, Ogura Y, Hata K, Ito T, Tomiyama K, Yagi S, Mori A, Uemoto S. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant. 2013;13:1549–56. https://doi.org/10.1111/ajt.12221.
30. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, Stein B, Carli F. Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. Surgery. 2011;150:505–14. https://doi.org/10.1016/j.surg.2011.07.045.