Skeletal muscle mass predicts the prognosis of patients with intrahepatic cholangiocarcinoma

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ABSTRACT

Background: We studied the prognostic impact of sarcopenia after hepatic resection for intrahepatic cholangiocarcinoma (ICC).
Methods: Sixty-one patients who underwent surgery for ICC during 2000—2017 were analyzed retrospectively. Psoas muscle areas were measured on CT scans at the third lumbar vertebra. Areas less than the sex-specific median were deemed low skeletal muscle masses (SMMs).
Results: Low-SMM patients were significantly more often older ($p = 0.002$) than high-SMM patients, had lower serum albumin ($p = 0.004$), higher serum C-reactive protein (CRP) ($p = 0.002$), and higher carbohydrate antigen 19-9 ($p < 0.001$). Five-year overall survival rates were 72.5% and 17.6% and 5-year recurrence-free survival rates were 58.6% and 21.1%, respectively, in high- and low-SMM patients. Multivariable analysis revealed that low SMM predicted unfavorable prognoses. SMM was associated with immune nutritional status (e.g., prognostic nutritional index, Glasgow prognostic score, CRP/albumin ratio).
Conclusion: Low SMM was related to worse surgical outcomes in patients with ICC following hepatic resection.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver tumor after hepatocellular carcinoma (HCC) and a major cause of cancer mortality and morbidity worldwide.[1] ICCs are estimated to account for approximately 5%—15% of all primary liver cancers, and their incidence has been increasing.[2] The only potentially curative treatment if ICC is surgical resection, although many patients develop recurrence afterward. Although combined systemic chemotherapy has been shown to improve patients' survival, the etiology and pathogenesis remain poorly understood.[2—5] Recently, several reports have addressed tumor-specific factors, such as the TNM stage, number of tumors present, tumor differentiation, and vascular invasion.[5,6]

Sarcopenia was described in 1989, by Irwin Rosenberg, as an age-related involuntary loss of muscle mass.[7] Currently, sarcopenia is defined as a complex syndrome characterized by progressive, generalized loss of skeletal muscle mass and strength.[8,9] Sarcopenia can be observed at any age and may have multifactorial etiologies, including immobility, altered endocrine functions, and chronic inflammatory diseases (including malignancy).[10] Sarcopenia has been identified as a factor that indicates a poor prognosis after several types of liver resection, including HCC, colorectal metastasis, and liver transplantation.[11—14]

Recently, we reported that decreased skeletal muscle quality was closely related to outcomes after liver transplantation and HCC resection,[11,13,14] but its impact on outcomes after ICC resection remains unknown. We have found little evidence concerning the prognostic value of sarcopenia with ICC in patients who have undergone hepatic resection.[15] The purpose of this study was to assess the prognostic significance of sarcopenia in patients undergoing hepatic resection for ICC. We investigated the skeletal muscle mass (SMM) determined from the psoas muscle mass area (PMA), which was calculated based on computed tomography (CT) imaging data from patients with ICC.

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Material and methods

We retrospectively enrolled 61 patients who underwent open hepatic resection for ICC between May 2000 and October 2017 at Kyushu University. CT was performed within 1 month before surgery. All relevant data, including the patients' clinical, surgical, and pathology records, were collected retrospectively from the database at our hospital. We analyzed cross-sectional, non-contrast-enhanced, plain CT images at the level of the third lumbar vertebra to determine the area of the psoas muscle to assess. The psoas muscle mass area (PMA) was calculated using the formula

$$PMA = a \times b \times \pi$$

where a and b are the radii of the major and minor axes, respectively (Fig. 1).[16] For this study, we defined "low PMA" as "low SMM" if it was smaller than the established sex-specific median size.

In our institution, major hepatectomy with bile duct resection was performed when bile duct invasion by ICC was suspected to affect the first hepatic duct. Partial hepatectomy was performed in cases of peripheral ICC without bile ductal invasion. If the surgical margin was suspected to be infiltrated by carcinoma cells, we sent the resected stump for frozen pathology. Lymph node dissection was performed according to whether lymph node metastasis was suspected on the preoperative abdominal CT scan.

Standard statistical analyses were used to evaluate descriptive statistics, such as means, medians, frequencies, and percentages. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using a χ^2 test or Fisher's exact test. Univariate and multivariate survival analyses were performed using a Cox proportional hazard models, respectively. Cumulative overall survival (OS) and recurrence-free survival (RFS) rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. OS was calculated in days from the date of surgery to the date of last follow-up or death. All statistical tests were two-sided, and a value of $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using JMP12 software (SAS Institute, Cary, NC, USA).

Results

The calculated median PMA was 34.6 cm^2 (12.7–70.0 cm^2) for men and 18.1 cm^2 (10.7–40.2 cm^2) for women. When we defined the cutoff values as 34.6 cm^2 for men and 18.1 cm^2 for women, 30 of the 61 patients (49.2%)—including 47.6% (20/44) of men and 52.6% (10/19) of women—were diagnosed with low SMM. The clinicopathological characteristics of patients with high and low SMM are
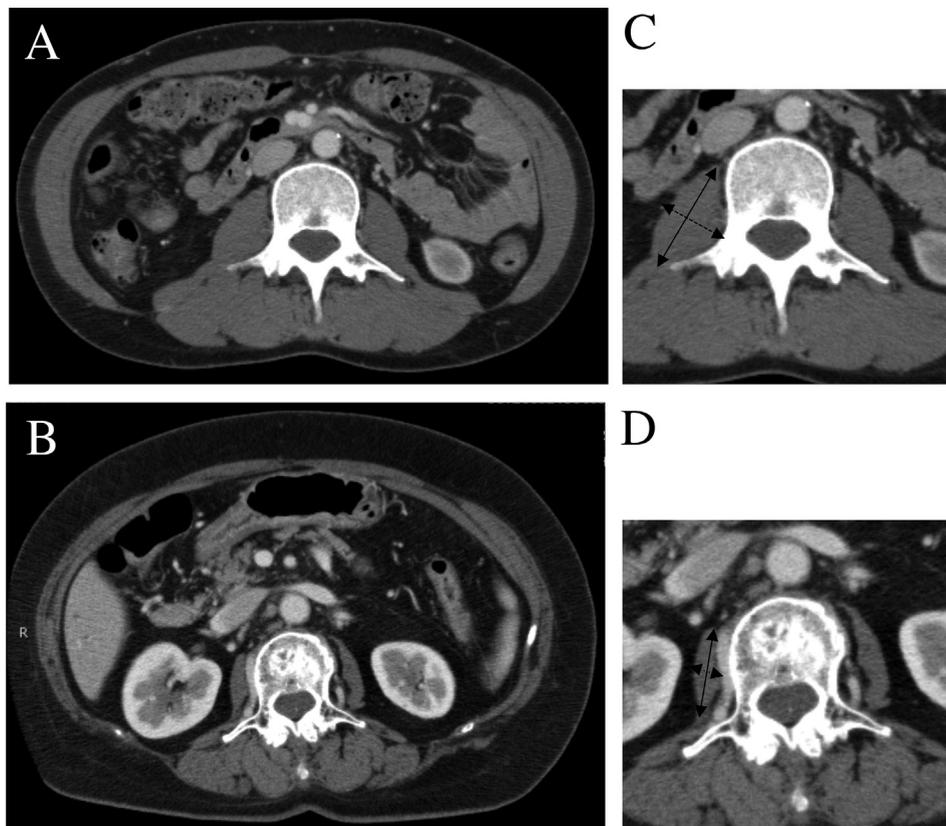
Fig. 1. Measurement of psoas muscle mass at the level of the third lumbar vertebra on a CT scan image. Axial CT scan image at the level of the third lumbar vertebra in patients with non-sarcopenia (A) and sarcopenia (B). Details on measurement of the psoas muscle mass by radii of the major (continuous line) and minor (dotted line) axes, respectively (C and D).

Table 1
Comparison of the clinicopathological factors between patients with high and low skeletal muscle mass (SMM) following hepatic resection of intrahepatic cholangiocarcinoma.

| Factors	High SMM (n = 31)	Low SMM (n = 30)	P value
Age (yr)	60 (39–82)	69 (53–87)	0.002
Sex (male/female)	22/9	20/10	0.716
BMI (kg/m^2)	22.5 (16.2–35.5)	22.6 (15.9–29.0)	0.497
Albumin (g/dL)	4.2 (3.3–5.3)	4.0 (3.3–4.7)	0.004
Total bilirubin (mg/dL)	0.7 (0.2–1.2)	0.7 (0.4–1.6)	0.571
CRP (mg/dL)	0.08 (0.01–1.9)	0.24 (0.01–4.01)	0.002
Total number of lymphocytes (/μL)	1546 (526–3950)	1375 (699–2789)	0.152
Platelets (x10^4/μL)	18.0 (9.9–40.2)	18.4 (5.2–44.0)	0.644
CA19-9 (U/ml)	18.1 (0.6–329.9)	62.8 (6.2–40795)	<0.001
HBsAg positive (%)	3/31 (10.0%)	3/30 (9.7%)	0.967
HCVAb positive (%)	3/31 (9.7%)	4/30 (13.3%)	0.654
Tumor size (cm)	3.8 (1.2–9.4)	5.3 (0.5–12.0)	0.219
Tumor localization (peripheral type/hilar type)	27/4	22/8	0.176
Poor differentiation (%)	17 (54.8%)	19 (63.3%)	0.500
Vascular invasion (%)	15 (48.3%)	13 (43.3%)	0.692
Bile duct invasion (%)	15 (48.3%)	14 (46.6%)	0.893
Intrahepatic metastasis (%)	7 (22.5%)	13 (43.3%)	0.106
Lymph node metastasis (%)	3 (9.6%)	8 (26.6%)	0.105
Histological liver cirrhosis (%)	5 (16.1%)	3 (10.0%)	0.707
Histological inflammatory activity (A0/A1/A2)	10/18/3	13/12/5	0.354
R0 resection (%)	27/31 (87.1%)	23/30 (76.7%)	0.256
Adjuvant chemotherapy (%)	10/31 (32.3%)	6/30 (20.0%)	0.274

BMI: body mass index, CA19-9: carbohydrate antigen 19-9, CRP: C-reactive protein.

shown in Table 1. Elderly patients were more likely to have low SMM than younger patients (median younger vs. older age = 60 vs. 69 years; $p = 0.002$). Overall, the serum albumin level was significantly lower (median 4.2 vs. 4.0 g/dL, $p = 0.004$), and C-reactive protein (CRP) and carbohydrate antigen (CA) 19-9 levels were significantly higher [median 0.08 vs. 0.24 U/mL ($p = 0.002$) and 18.1 vs. 62.8 U/mL ($p < 0.001$), respectively] in patients with low SMM than those with high SMM. Other host-related factors—e.g., sex, body mass index (BMI), chronic liver disease, tumor size, primary tumor location, differentiation type, biological malignancy (invasion or metastasis), resection margin, adjuvant chemotherapy—were not related to the presence of low SMM (all $p > 0.05$).

We investigated the relation between low skeletal muscle and nutritional scores [i.e., Glasgow prognostic score (GPS); prognostic nutritional index (PNI); controlling nutrition status (CONUT); CRP albumin ratio (CAR)]. The PNI was significantly lower (mean 51.0 vs. 47.3; p = 0.004) and the GPS and CAR significantly higher (12/31, 38.7% vs. 22/30, 73.3%; p = 0.006 and 0.05 vs. 0.20; p = 0.014, respectively) in patients with low SMM than those with high SMM (Table 4).

The OS and RFS curves for patients with high and low SMM are shown in Fig. 2. The 5-year OS and RFS rates were, respectively, 21.1% and 17.6% for patients with low SMM and 72.5% and 58.6% for patients with high SMM (Fig. 2). Patients with low SMM had a significantly worse prognosis than those with high SMM for both OS ($p < 0.001$) and RFS ($p < 0.001$). A univariable analysis showed that the significant prognostic factors for OS were low skeletal mass, BMI ≥ 25 kg/m^2, relatively large tumor size (≥ 3.8 cm), hilar localization, and positive for vascular invasion, intrahepatic metastasis, and lymph node metastasis (Table 2). Significant prognostic factors for RFS were low skeletal mass, BMI ≥ 25 kg/m^2, serum high CA19-9 level (≥ 31.3 U/mL), relatively large tumor size (≥ 3.8 cm), hilar localization, and positivity for intrahepatic metastasis and nodal metastasis (Table 3). We defined the serum CA19-9 cutoff levels using the receiver operating characteristic analysis (area under the curve 0.788), and the sensitivity and specificity were 79.3% and 69.0%, respectively (p = 0.0002). The multivariable analysis identified only one prognostic factor (low SMM) that influenced OS and three poor prognostic factors (low SMM, large tumor size, hilar localization) that influenced RFS (Tables 2 and 3).

In addition, we created a score, using significant prognostic
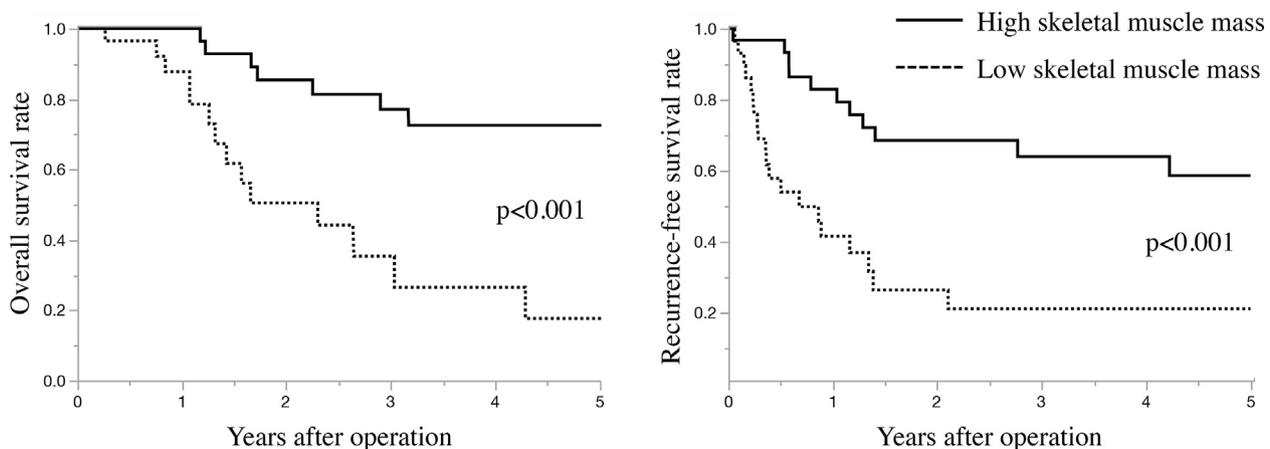
Fig. 2. Overall and recurrence-free survival rates after hepatic resection for intrahepatic cholangiocarcinoma in patients with high and low skeletal muscle mass.

Table 2
Univariate and multivariate analyses of risk factors for overall survival following hepatic resection of intrahepatic cholangiocarcinoma.

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Low skeletal muscle mass	3.43 (1.68–7.34)	<0.001	2.35 (1.11–5.22)	0.024
Age (>65)	0.91 (0.45–1.81)	0.795		
Male	1.25 (0.61–2.77)	0.540		
BMI (≥25 kg/m^2)	3.17 (1.56–6.39)	0.001	1.94 (0.80–4.67)	0.139
Albumin (<3.5 g/dL)	1.19 (0.06–5.62)	0.863		
CRP (≥1.0 mg/dl)	1.71 (0.62–4.00)	0.240		
CA19-9 (≥31.3 U/mL)	2.24 (0.98–5.55)	0.055		
Tumor size (≥3.8 cm)	2.93 (1.39–6.76)	0.004	1.98 (0.73–5.54)	0.175
Hilar type	3.16 (1.45–6.54)	0.004	2.30 (0.77–6.66)	0.132
Poor differentiation	1.09 (0.55–2.21)	0.791		
Vascular invasion (+)	2.67 (1.30–5.78)	0.006	1.58 (0.60–4.28)	0.346
Bile duct invasion (+)	1.23 (0.61–2.53)	0.555		
Intrahepatic metastasis (+)	2.87 (1.40–5.86)	0.003	1.28 (0.49–3.45)	0.603
Lymph node metastasis (+)	3.15 (1.40–6.63)	0.003	1.51 (0.54–4.01)	0.417
Histological liver cirrhosis (+)	1.18 (0.34–3.05)	0.750		
Adjuvant chemotherapy (−)	2.18 (0.95–5.90)	0.086		

BMI: body mass index, CA19-9: carbohydrate antigen 19-9, CRP: C-reactive protein.

factors, for the outcome of patients who underwent ICC resection. We stratified the score over 0–3 points by calculating three prognostic factors (low SMM, large tumor size, hilar localization), with one point for each factor. OS and RFS curves for stratified scores for patients with ICC are shown in Fig. 3A and B. The patients' scores who had significant prognostic factors were as follows: score 0: 14/61 patients; score 1: 21/61 patients; score 2: 23/61 patients; score 3: 3/61 patients. The 2-year OS and 1-year RFS rates were, respectively, 74.3% and 79.1% for score 1; 52.3% and 32.3% for score 2; and 33.3% and 33.3% for score 3 (Fig. 3A and B). The higher score of patients with ICC predicted the worse prognoses for both OS and RFS (p < 0.001). We also classified patients according to these scores in a low-score group (n = 35, scores 0/1) and a high-score group (n = 26, scores 2/3) to predict the outcome of patients with ICC. OS and RFS rates were, respectively, 76.5% and 63.5% for the low-score group and 11.2% and 11.2% for the high-score group. Patients with high scores of previously described prognostic factors had significantly worse prognoses than those with low scores for both OS and RFS (p < 0.001) (Fig. 3C and D).

Discussion

Sarcopenia plays an important role as a significant prognostic factor for various tumorous entities. The survival rate for sarcopenic patients with a malignancy (determined by CT-identified low SMM) was significantly lower than that of patients who were not sarcopenic.[15,17–21] Our present findings suggest that sarcopenia is an independent prognostic factor for OS and RFS in patients with ICC following partial hepatectomy. We found that low SMM was an independent risk factor for a poor prognosis, which is compatible with a previous report of patients who had undergone surgery for ICC.[22] We also established a scoring system by calculating points for our identified prognostic factors (including low SMM) and classified the patients into low- and high-score groups. The results suggested that preoperative scoring using our identified factors made it possible to predict outcomes for patients with ICC.

Several recent studies reported that the loss of skeletal muscle was associated with a poor prognosis. The molecular mechanism for sarcopenia, however, remains unclear. Inflammatory conditions, inactivity, nutritional factors, and aging have been postulated as potential causes.[23,24] Skeletal muscle is considered a secretory organ as it produces myokines and several proinflammatory cytokines.[25] Myocytes increase proinflammatory cytokine levels, a condition associated with chronic inflammation and carcinogenesis.[26] These reports suggest that loss of muscle predicts poor survival through weakened immune functioning.

Table 3
Univariate and multivariate analyses of risk factors for recurrence-free survival following hepatic resection of intrahepatic cholangiocarcinoma.

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Low skeletal muscle mass	4.01 (1.77–9.46)	0.001	2.47 (1.06–6.01)	0.036
Age (>65)	1.12 (0.49–2.47)	0.780		
Male	1.32 (0.57–3.41)	0.518		
BMI (≥25 kg/m^2)	3.44 (1.55–7.81)	0.002	1.74 (0.74–4.04)	0.204
Albumin (<3.5 g/dL)	1.88 (0.30–3.22)	0.266		
CRP (≥1.0 mg/dl)	1.50 (0.43–4.03)	0.461		
CA19-9 (≥31.3 U/mL)	2.49 (1.21–5.49)	0.012	0.76 (0.30–1.99)	0.567
Tumor size (≥3.8 cm)	2.35 (1.01–6.10)	0.045	2.62 (1.10–6.69)	0.030
Hilar type	4.28 (1.80–9.89)	<0.001	3.11 (1.19–7.99)	0.021
Poor differentiation	0.95 (0.42–2.11)	0.911		
Vascular invasion (+)	2.10 (0.90–5.24)	0.091		
Bile duct invasion (+)	2.16 (0.93–5.58)	0.071		
Intrahepatic metastasis (+)	3.58 (1.61–8.31)	0.001	1675 (0.24–1.49)	0.264
Lymph node metastasis (+)	5.33 (2.06–13.0)	0.001	1.30 (0.49–3.22)	0.589
Histological liver cirrhosis (+)	1.49 (0.43–3.99)	0.483		
Adjuvant chemotherapy (−)	1.23 (0.50–3.46)	0.648		

BMI: body mass index, CA19-9: carbohydrate antigen 19-9, CRP: C-reactive protein.

Table 4
Correlation for the nutritional scores between patients with high and low skeletal muscle mass (SMM) following hepatic resection of intrahepatic cholangiocarcinoma.

Nutritional scores	High SMM (n = 31)	Low SMM (n = 30)	P value
GPS (albumin<3.5 or CRP≧1.0)	12/31 (38.7%)	22/30 (73.3%)	0.006
PNI	51.0 (49.3−52.8)	47.3 (45.5−49.1)	0.004
CAR	0.05 (0.00−0.13)	0.20 (0.12−0.28)	0.014
CONUT	1.38 (0.95−1.83)	1.70 (1.25−2.15)	0.320

CAR: CRP albumin ratio, CONUT: controlling nutrition status, GPS: glasgow prognostic score, CRP: C-reactive protein: PNI: prognostic nutritional index, SMM: skeletal muscle mass.

Our findings showed that the serum albumin level was significantly lower in individuals with sarcopenia than in those without it, indicating a poor nutritional condition in sarcopenic individuals. Moreover, the CRP level was higher in patients with sarcopenia than those without it, suggesting that low SMM weakens immune functions, such as down-regulation of several proinflammatory cytokines. Furthermore, as shown in Table 4, our findings suggested that sarcopenia was associated with a worse nutritional condition (including a low serum albumin level) and/or systemic inflammation (including a high serum CRP level or mobilization of inflammatory cells). Thus, the nutritional status could be a key element of sarcopenia. One of the tumor markers, CA19-9, was present at a
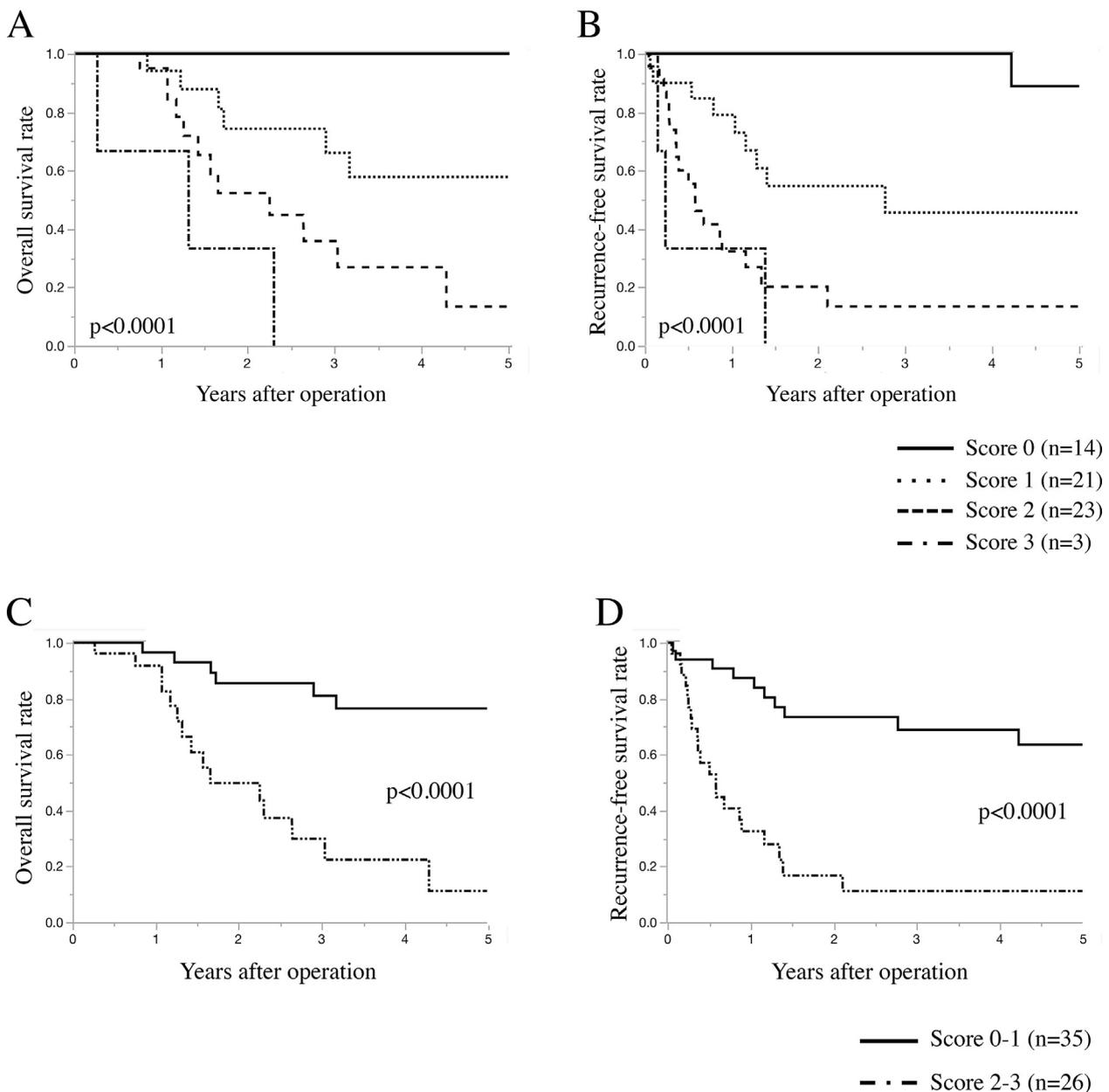
Fig. 3. Use of the prognostic score to predict overall survival (A and C) and recurrence-free survival (B and D) rates in patients who underwent surgery for ICC.

higher level in patients with sarcopenia than in those without it, indicating that low-SMM has malignant-change ability. Considering these results, low SMM, as a parameter of sarcopenia, is a comprehensively poor prognostic factor in sarcopenic patients after surgery for ICC.

Numerous studies have suggested that postoperative outcomes correspond with the serum albumin level. In fact, low serum albumin is associated with poor survival in the presence of malignancy.[27,28] In this study, patients with sarcopenia were also hypoalbuminemic and had greater alterations in body composition, including markedly decreased skeletal muscle. Even though low albumin has not been established as a marker of survival, sarcopenia is a powerful negative prognostic factor.

Although a univariate analysis identified tumor-specific factors—including tumor size, vascular invasion, and intrahepatic and lymph node metastasis—as predictors of poor survival, these factors, although strongly correlated with sarcopenia, are only potentially able to predict malignancy. The multivariate analysis identified hilar ICC as being related to RFS, which was compatible with a previous report.[29]

We acknowledge that this study had several limitations. First, the study was retrospective and conducted in a single institution with a relatively small sample size. Our results should be confirmed in larger prospective studies. Second, we did not measure the PMA during the early postoperative period, so we could not clarify exactly when the skeletal muscle mass decreased postoperatively. If the PMA decreased early in the postoperative period, the cause of the muscle mass loss may have been the invasiveness of the surgery. Finally, BMI is one of the most common parameters used to represent nutritional status, but we did not evaluate changes in this parameter. The prognostic impact of sarcopenia on survival has been demonstrated for various malignancies. Although varying cutoff points regarding skeletal muscle mass have been used, the definition of sarcopenia remains controversial, with a variety of claimed appropriate diagnostic cutoff values. In the present study, we based the cutoff value on the median value for this population.

The physical ability of patients with sarcopenia is reduced, and their activities of daily living functions are weakened. Thus, sarcopenia effectively affects their quality of life. Supportive therapy focusing on nutrition and rehabilitation would be applicable for ICC patients. Further study of the most effective supportive therapy must be encouraged.

Conclusions

We found that the preoperative quantity of skeletal muscle was closely related to postoperative survival in patients who underwent surgery for ICC. Thus, the evaluation of skeletal muscle may be useful for risk stratification and clinical decision-making for patients with ICC. Nutritional support and physical exercise represent new strategies to improve outcomes after ICC resection.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.03.010.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics. *Ca - Cancer J Clin*. 2014;64(2014):9–29.
2. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology*. 2001;33:1353–1357.
3. Kato I, Kuroishi T, Tominaga S. Descriptive epidemiology of subsites of cancers of the liver, biliary tract and pancreas in Japan. *Jpn J Clin Oncol*. 1990;20: 232–237.
4. Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? *J Hepatol*. 2004;40: 472–477.
5. Sakamoto Y, Kokudo N, Matsuyama Y, et al. Proposal of a new staging system for intrahepatic cholangiocarcinoma: analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. *Cancer*. 2016;122: 61–70.
6. Farges O, Fuks D, Le Treut YP, et al. AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma: by the AFC-IHCC-2009 study group. *Cancer*. 2011;117: 2170–2177.
7. Rosenberg IH. Sarcopenia: origins and clinical relevance. *Clin Geriatr Med*. 2011;27:337–339.
8. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. *Age Ageing*. 2010;39:412–423.
9. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc*. 2011;12:249–256.
10. Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian working group for sarcopenia. *J Am Med Dir Assoc*. 2014;15:95–101.
11. Harimoto N, Shirabe K, Yamashita YI, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg*. 2013;100:1523–1530.
12. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg*. 2012;99:550–557.
13. Harimoto N, Yoshizumi T, Izumi T, et al. Clinical outcomes of living liver transplantation according to the presence of sarcopenia as defined by skeletal muscle mass, hand grip, and gait speed. *Transplant Proc*. 2017;49:2144–2152.
14. Itoh S, Shirabe K, Yoshizumi T, et al. Skeletal muscle mass assessed by computed tomography correlates to muscle strength and physical performance at a liver-related hospital experience. *Hepatol Res*. 2016;46:292–297.
15. Okumura S, Kaido T, Hamaguchi Y, et al. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. *Surgery*. 2015;157:1088–1098.
16. Masuda T, Shirabe K, Ikegami T, et al. Sarcopenia is a prognostic factor in living donor liver transplantation. *Liver Transplant*. 2014;20:401–407.
17. Begini P, Gigante E, Antonelli G, et al. Sarcopenia predicts reduced survival in patients with hepatocellular carcinoma at first diagnosis. *Ann Hepatol*. 2017;16: 107–114.
18. Peng P, Hyder O, Firoozmand A, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. *J Gastrointest Surg*. 2012;16: 1478–1486.
19. Psutka SP, Carrasco A, Schmit GD, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. *Cancer*. 2014;120:2910–2918.
20. Fujiwara N, Nakagawa H, Kudo Y, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol*. 2015;63:131–140.
21. Itoh S, Shirabe K, Matsumoto Y, et al. Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma. *Ann Surg Oncol*. 2014;21: 3063–3068.
22. Okumura S, Kaido T, Hamaguchi Y, et al. Impact of skeletal muscle mass, muscle quality, and visceral adiposity on outcomes following resection of intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2017;24:1037–1045.
23. Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases:

from sarcopenic obesity to cachexia. *Clin Nutr*. 2014;33:737–748.

24. Cosquéric G, Sebag A, Ducolombier C, Thomas C, Piette F, Weill-Engerer S. Sarcopenia is predictive of nosocomial infection in care of the elderly. *Br J Nutr*. 2007;96.

25. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol*. 2012;8:457–465.

26. Charles T, et al. Sarcopenia, obesity, and natural killer cell immune senescence in aging: altered cytokine levels as a common mechanism. *Ading*. 2012;4: 535–546.

27. van Stijn MFM, Korkic-Halilovic I, Bakker MSM, van der Ploeg T, van Leeuwen PAM, Houdijk APJ. Preoperative nutrition status and postoperative outcome in elderly general surgery patients. *J Parenter Enteral Nutr*. 2012;37: 37–43.

28. Souza Cunha M, Wiegert EVM, Calixto-Lima L, Oliveira LC. Relationship of nutritional status and inflammation with survival in patients with advanced cancer in palliative care. *Nutrition*. 2018;51–52:98–103.

29. Orimo T, Kamiyama T, Mitsuhashi T, et al. Impact of tumor localization on the outcomes of surgery for an intrahepatic cholangiocarcinoma. *J Gastroenterol*. 2018;53:1206–1215.