ORIGINAL ARTICLE

Effects of Sarcopenia on Prognosis After Resection of Gallbladder Cancer

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Abstract

Background This study aimed to determine the prognostic significance of radiographic sarcopenia (RS) in patients with gallbladder cancer (GBC).

Methods From March 2001 to December 2013, 158 GBC patients who underwent curative intent surgery were included. The presence of RS was determined by skeletal muscle mass index using abdominal computed tomography.

Results The 1-, 3-, and 5-year overall survival (OS) rates were 63.6%, 41.9%, and 36.4%, respectively, for patients with RS ($n = 88$), and 84.3%, 62.6%, and 54.3%, respectively, for those without RS ($n = 70$) ($P = 0.006$). Multivariate analysis showed that RS (hazard rate [HR] 1.704, $P = 0.024$) was a significant prognostic factor for patient survival, as well as disease stage (IV: HR 7.181, $P < 0.001$), radicality (HR 2.830, $P = 0.001$), adjuvant therapy (HR 0.537, $P = 0.017$), and intraoperative blood loss ≥ 1 L (HR 1.851, $P = 0.023$).

Conclusions This study showed a significant association between RS and OS in GBC patients. Because RS is the only significant prognostic factor that can be evaluated preoperatively, its assessment would be helpful to provide early preventive therapy allowing the maintenance of muscle mass and *patient-tailored treatment* based on their physiologic reserves (e.g., skeletal muscle mass).

Keywords Gallbladder cancer · Radiographic sarcopenia · Prognosis

Introduction

Gallbladder cancer (GBC) is the fifth most common malignancy of the gastrointestinal tract and the most common malignancy of the biliary tract.[1] Large gallstones (> 3 cm), extensive gallbladder calcification due to chronic cholecystitis (porcelain gallbladder), American Indian and Hispanic descent, chronic bacterial cholangitis (e.g., due to *Salmonella typhi*, *Salmonella paratyphi*), and an anomalous pancreaticobiliary duct junction are known risk factors of GBC.[2] GBC is commonly accompanied by regional lymph node (LN) involvement and liver invasion. Therefore, extended cholecystectomy, including cholecystectomy, liver parenchyma resection (segments IVb and V), and regional LN dissection could

improve surgical outcomes. Although surgical resection is recommended in possible cases, the prognosis is poor.

The most representative effect of aging is a change in body composition, i.e., an increase in the ratio of body fat to body weight and a decrease in lean body mass, especially skeletal muscle mass. In 1989, Rosenberg first described this age-associated skeletal muscle mass reduction as "sarcopenia," derived from the Greek words "sarx," which means "muscle" and "penia," which means "decrease."[3] Skeletal muscle mass decreases by 8% every 10 years after the age of 40 years, and by 15% every 10 years after the age of 70 years.[4, 5] In a previous report, sarcopenia was reported to increase the probability of functional limitations, disability, falls, loss of independence, and mortality in elderly patients.[6–10]

Recently, sarcopenia has received much attention as a prognostic factor in patients with various types of cancers such as colorectal cancer, esophageal cancer, gastric cancer, and hepatocellular carcinoma.[11–16] However, there have been few reports on the relationship between sarcopenia and postoperative oncologic outcomes in patients with GBC. The primary goal of this study is to elucidate the prognostic value of

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radiographic sarcopenia (RS), which is determined by computed tomography (CT), in patients with GBC.

Materials and Methods

Patients and Study Design

This study included 158 consecutive GBC patients who underwent surgery with curative intent at the National Cancer Center, Korea, from March 2001 to December 2013. Patients with double primary cancer of the gallbladder and other sites (e.g., hilar cholangiocarcinoma, mid/distal common bile duct cancer, pancreatic cancer, ampulla of Vater cancer, duodenal cancer) were excluded from this study, as well as patients with a history of treatment for any other types of cancer within the last 5 years. This study was approved by our Institutional Review Board (NCC2017-0256).

Definition and Surveillance

All the patients underwent CT as part of their presurgical evaluation. Cross-sectional skeletal muscle area (cm^2) evaluations were conducted at the level of the third lumbar vertebrae (L3). Two consecutive CT images both showing the vertebral spine at the L3 level were used to measure the muscle area, determined by semiautomatic segmentation. The mean value of the two measurements was regarded as the L3 skeletal muscle area (cm^2). The skeletal muscle area (cm^2), including the rectus abdominis, external oblique, internal oblique, transverse abdominis, psoas, and paraspinal muscles corresponding to the threshold, ranges between − 30 and + 110 Hounsfield units (Fig. 1).[17] The skeletal muscle index (SMI, cm^2/m^2) was defined as the skeletal muscle area (cm^2) at the L3 level divided by the square of the patient's height (m^2). RS was defined as SMI < 52.4 cm^2/m^2 for male patients and < 38.5 cm^2/m^2 for female patients.[18] All measurements were taken using OsiriX MD version 9.0 (http://www.osirix-viewer.com).

Body mass index (BMI, kg/m^2) was defined as the body weight (kg) divided by the square of the height (m^2) and BMI values were classified as low (< 18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), or obesity (≥ 25 kg/m^2).[19] For GBC staging, the 8th edition of the American Joint Committee on Cancer (AJCC) staging system was used.

Recurrence surveillance was performed every 3 or 6 months after discharge using CT or magnetic resonance imaging, and positron emission tomographic-CT scan was performed if necessary. Cancer recurrence was finally confirmed through biopsy in most patients. Patients for whom biopsies were not performed were considered to have recurrent cancer when their serial imaging results clearly indicated cancer
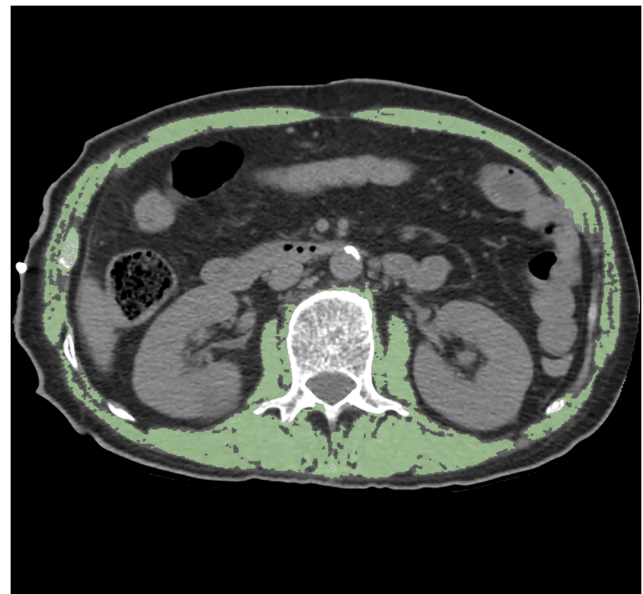

Fig. 1 Axial computed tomographic scan at the level of the third lumbar vertebra. Areas of total skeletal muscle (− 30 to + 110 HU) including rectus abdominis, transverse abdominal, external oblique, internal oblique, psoas, and paraspinal muscle were measured. The SMI (cm^2/m^2) was defined as the area of total skeletal muscle (cm^2) divided by the square of the height (m^2). HU, Hounsfield unit; SMI, skeletal muscle index

progression. Postoperative mortality was defined as death within 30 days after surgery.

Surgical Procedure

In most cases of early GBC (T1), laparoscopic/open cholecystectomy was performed. However, in patients with T1b GBC who were 65 years old or younger and had no severe comorbidity, extended cholecystectomy, including cholecystectomy, resection of segments IVb and V of the liver, and regional lymph node dissection, were considered. In cases of T2 GBC, extended cholecystectomy was performed. Further, in cases of T3/4 GBC, if the invasion of the surrounding organs was suspected, combined resection, including extended right hemihepatectomy, common bile duct resection, pancreaticoduodenectomy, and colectomy was performed along with extended cholecystectomy.

Adjuvant Therapy

Adjuvant therapy was performed as in our previous report.[20] Chemoradiation therapy consisted of 45 Gy of radiation in 25 fractions at 1.8 Gy per fraction daily, with concurrent continuous infusions of 5-fluorouracil and leucovorin (intravenous bolus injections of 5-fluorouracil, 400 mg/m^2/day and leucovorin, 20 mg/m^2/day for 3 days in the first and fifth weeks of radiotherapy).

Statistical Analysis

Continuous variables are given as mean ± standard deviation or median (interquartile range [IQR]) depending on the normality of the distribution. The cut-off values for the continuous variables were defined as the points with the most significant (log-rank test) split using the "maxstat" and "survival" packages of R. Survival was estimated using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional-hazards model was used for multivariate analysis, and a P value of less than 0.05 was considered statistically significant. All calculations were made using the SPSS 24.0 statistical software package (IBM Corporation, Armonk, NY, USA) and R 3.4.3 (https://www.r-project.org).

Results

Patient Characteristics

A total of 158 patients were included in this study, with 88 in the RS group and 70 in the no-RS group (Table 1). The median age was 64.5 years for the RS group and 63.5 years for the no-RS group ($P = 0.774$). In patients with RS, the proportion of males was higher than in those without RS ($n = 58$, 65.9% vs. $n = 15$, 21.4%; $P < 0.001$). There was a difference in BMI ($P < 0.001$), neutrophil to lymphocyte ratio ($P < 0.003$), and serum bilirubin level ($P = 0.031$) between the two groups. The American Society of Anesthesiologists (ASA) physical status ($P = 0.461$), Eastern Cooperative Oncology Group (ECOG) performance status ($P = 0.841$), type of surgery ($P = 0.385$), operation time ($P = 0.107$), and red blood cell (RBC) transfusion ($P = 0.345$) showed no significant differences between the two groups. Nevertheless, significant differences were observed in the Charlson comorbidity index (CCI; $P = 0.030$) and intraoperative blood loss ($P = 0.025$). No significant differences in pathologic variables such as tumor size ($P = 0.656$), tumor cell differentiation ($P = 0.424$), lymphatic invasion ($P = 0.987$), perineural invasion ($P = 0.363$), surgical radicality ($P = 0.512$), and disease stage ([AJCC, 8th edition] $P = 0.475$) were observed between the two groups. Adjuvant therapy was more commonly performed in patients without RS ($P = 0.045$). No significant differences in mortality ($P = 0.580$) and hospital stay ($P = 0.499$) were observed between the groups.

Univariate and Multivariate Analyses

Univariate analysis showed that the overall survival (OS) after surgery in patients with GBC was significantly associated with RS ($P = 0.008$), bilirubin level ($P = 0.001$), albumin level ($P = 0.042$), carcinoembryonic antigen (CEA) level ($P = 0.043$), carcinoembryonic antigen 19-9 (CA19-9) level

($P < 0.001$), type of surgery ($P = 0.016$), operation time ($P < 0.001$), intraoperative blood loss of ≥ 1 L ($P < 0.001$), RBC transfusion ($P = 0.001$), lymphatic invasion ($P < 0.001$), perineural invasion ($P < 0.001$), surgical radicality ($P < 0.001$), and disease stage ($P < 0.001$). Further, recurrence-free survival (RFS) was associated with CEA level ($P = 0.010$), CA19-9 level ($P < 0.001$), type of surgery ($P = 0.041$), operation time ($P = 0.004$), intraoperative blood loss of ≥ 1 L ($P = 0.004$), tumor size ($P = 0.031$), lymphatic invasion ($P < 0.001$), perineural invasion ($P < 0.001$), surgical radicality ($P < 0.001$), and disease stage ($P < 0.001$) (Table 2).

In multivariate analysis, significant prognostic factors for OS were RS (hazard ratio [HR] 1.704, $P = 0.024$), intraoperative blood loss of 1 L (HR 1.851, $P = 0.023$), surgical radicality (HR 2.830, $P = 0.001$), disease stage (IV: HR 7.181, $P < 0.001$), and adjuvant therapy (HR 0.537, $P = 0.017$). In addition, surgical radicality ($P = 0.022$) and disease stage ($P < 0.001$) were significant prognostic factors for RFS. The independent predictors for OS and RFS are summarized in Table 3.

Patient Survival and Recurrence

The 1-, 3-, and 5-year OS rates were 63.6%, 41.9%, and 36.4%, respectively, for patients in with RS, and 84.3%, 62.6%, and 54.3%, respectively, for patients without RS (Fig. 2a; $P = 0.006$). The 1-, 3-, and 5-year RFS rates were 59.8%, 49.0%, and 46.7%, respectively, for patients with RS and 68.1%, 51.8%, and 49.8%, respectively, for patients without RS (Fig. 2b; $P = 0.490$). In patients with GBC having RS, there was no difference between OS (Fig. 2c; $P = 0.552$) and RFS (Fig. 2d; $P = 0.821$) according to obesity status.

Discussion

The concept of sarcopenia was first proposed by Rosenberg in 1989,[3] but the worldwide consensus (e.g., European Working Group, International Working Group, and Asian Working Group) began to be established after 2010.[21–23] According to these, sarcopenia is a condition accompanied by a decrease in the muscle mass and a decrease in the muscle function (strength or performance). However, this retrospective study involved patients from March 2001 to December 2013 and included a significant number of patients without preoperative assessment of muscle function. In addition, in order to evaluate the effect of sarcopenia on the prognosis of patients with GBC, it is appropriate to investigate disease-specific survival rather than overall survival. However, in most cases, there was a legal restriction on the inquiry of the death certificate, making it difficult to identify the specific cause of death. The analysis using RS, which does not reflect muscle function, and overall survival rather than disease-specific survival

Table 1 Patient characteristics

Variables	RS (n = 88)	No RS (n = 70)	All (n = 158)	P
Age (years)	64.5 (56–70)	63.5 (54–71)	64 (55–70)	0.774
Sex (female/male)	30 (34.1)/58 (65.9)	55 (78.6)/15 (21.4)	85 (53.8)/73 (46.2)	< 0.001
BMI (kg/m^2)	22.2 ± 3.2	24.7 ± 3.9	23.3 ± 3.7	< 0.001
Laboratory values				
Neutrophil to lymphocyte ratio	2.2 (1.4–3.3)	1.5 (1.2–2.2)	1.9 (1.2–3.0)	0.003
Bilirubin (mg/dL)	0.6 (0.4–1.1)	0.6 (0.3–0.8)	0.6 (0.4–0.9)	0.031
Albumin (g/dL)	4.0 (3.8–4.3)	4.1 (3.9–4.3)	4.1 (3.9–4.3)	0.180
CEA (ng/mL) [15]	2.5 (1.5–3.9)	2.3 (1.3–4.0)	2.4 (1.4–3.9)	0.483
CA19-9 (U/mL) [9]	20.1 (7.9–42.0)	20.4 (9.9–79.0)	20.1 (8.2–53.3)	0.589
Charlson comorbidity index				0.030
0	49 (55.7)	50 (71.4)	99 (62.7)	
1	27 (30.7)	18 (25.7)	45 (28.5)	
2	12 (13..6)	2 (2.9)	14 (8.9)	
ASA physical status				0.461
1	23 (26.1)	19 (27.1)	42 (26.6)	
2	55 (62.5)	47 (67.1)	102 (64.6)	
≥ 0	10 (11.4)	4 (5.7)	14 (8.9)	
ECOG performance status (0, 1/≥ 2)	87 (98.9) / 1 (1.1)	68 (97.1) / 2 (2.9)	155 (98.1)/3 (1.9)	0.841
Type of surgery				0.385
LC	7 (8.0)	9 (12.9)	16 (10.1)	
OC	11 (12.5)	6 (8.6)	17 (10.8)	
OC + segments IVb and V + LND	31 (35.2)	33 (47.1)	64 (40.5)	
OC + segments IVb and V + LND + BDR/PD/colectomy	14 (15.9)	7 (10.0)	21 (13.3)	
OC + Ext. R(L)HH/central bisectionectomy + LND	19 (21.6)	13 (18.6)	32 (20.3)	
OC + Ext. RHH + LND + BDR/PD	6 (6.8)	2 (2.9)	8 (5.1)	
Operation time (min)	295 (192–395)	237.5 (165–330)	272.5 (175–385)	0.107
Intraoperative blood loss (mL)	525 (300–800)	375 (250–600)	500 (300–700)	0.025
RBC transfusion	13 (14.8)	6 (8.6)	19 (12.0)	0.345
Stage (AJCC 8th)				0.475
I, 0	14 (15.9)	12 (17.1)	26 (16.5)	
II	14 (15.9)	17 (24.3)	31 (19.6)	
III	43 (48.9)	32 (45.7)	75 (47.5)	
IV	17 (19.3)	9 (12.9)	26 (16.5)	
Tumor size (cm)	4.0 (2.9–5.5)	4.0 (2.5–5.5)	4.0 (2.7–5.5)	0.656
Differentiation				0.424
Well-differentiated, moderately differentiated	55 (62.5)	48 (68.6)	103 (65.2)	
Poorly differentiated, undifferentiated	24 (27.3)	13 (18.6)	37 (23.4)	
Others	9 (10.2)	9 (12.9)	18 (11.4)	
Lymphatic invasion [2]	43 (50.0)	34 (48.6)	77 (49.4)	0.987
Perineural invasion [2]	32 (37.2)	32 (45.7)	64 (41.0)	0.363
Radicality (R0 vs. R1, R2)	75 (85.2)/13 (14.8)	63 (90.0)/7 (10.0)	138 (87.3)/20 (12.7)	0.512
Adjuvant therapy	21 (23.9)	28 (40.0)	49 (31.0)	0.045
Mortality (< 30 days postoperatively)	2 (2.3)	0 (0.0)	2 (1.3)	0.580
Moderate to severe complications[†]	19 (21.6)	13 (18.6)	32 (20.3)	0.639
IIIa	16 (18.2)	13 (18.6)	29 (18.4)	0.950
Pleural effusion	2 (2.3)	2 (2.9)	4 (2.5)	
Pneumonia	1 (1.1)	0 (0.0)	1 (0.6)	
Bile leak	2 (2.3)	6 (8.6)	8 (5.1)	
Bile duct stenosis	1 (1.1)	2 (2.9)	3 (1.9)	

Table 1 (continued)

Variables	RS (*n* = 88)	No RS (*n* = 70)	All (*n* = 158)	*P*
Intra-abdominal abscess	3 (3.4)	2 (2.9)	5 (3.2)	
Wound infection	9 (10.2)	4 (5.7)	13 (8.2)	
IIIb	0 (0.0)	0 (0.0)	0 (0.0)	NA
IVa	2 (2.3)	0 (0.0)	2 (1.3)	0.503
Liver failure	1 (1.1)	0 (0.0)	1 (0.6)	
Acute myocardial infarction	1 (1.1)	0 (0.0)	1 (0.6)	
IVb	0 (0.0)	0 (0.0)	0 (0.0)	NA
V	2 (2.3)	0 (0.0)	2 (1.3)	0.503
Intra-abdominal bleeding	1 (1.1)	0 (0.0)	1 (0.6)	
Liver failure	1 (1.1)	0 (0.0)	1 (0.6)	
Hospital stay	12.5 (9.5–20.5)	11 (10–19)	12 (10–20)	0.499

Values are presented as number (%), mean ± standard deviation or median (interquartile range)

Numbers in parentheses are missing value

† Clavien-Dindo grade ≥ 3

AJCC, American Joint Committee on Cancer; *ASA*, American Society of Anesthesiologists; *BDR*, bile duct resection; *BMI*, body mass index; *CA19-9*, carcinoembryonic antigen 19-9; *CEA*, carcinoembryonic antigen; *ECOG*, Eastern Cooperative Oncology Group; *Ext.*, extended; *LC*, laparoscopic cholecystectomy; *LN*, lymph node; *LND*, lymph node dissection; *NA*, not applicable; *OC*, open cholecystectomy; *PD*, pancreaticoduodenectomy; *R(L) HH*, right (left) hemihepatectomy; *RBC*, red blood cell; *RS*, radiographic sarcopenia

constrains the interpretation of the results of this study, further highlighting the need for a *well-constructed* prospective study.

Meanwhile, sarcopenia in patients with cancer has been highlighted over the last decade. Recent studies have reported that sarcopenia has been identified as a poor prognostic factor in patients after several kinds of surgeries such as colectomy, hepatectomy, liver transplantation, esophagectomy, gastrectomy, and pancreatectomy.[11–16,24,25] However, little is known about the relationship between sarcopenia and postoperative prognosis in GBC patients. Okumura et al. have reported that sarcopenia is a poor prognostic factor for patient survival and cancer recurrence in patients with extrahepatic biliary malignancies, including hilar cholangiocarcinoma, GBC, distal bile duct cancer, and ampulla of Vater cancer.[26] However, because the study included only a small number of patients with GBC and different types of cancers with different pathophysiological properties, operation methods/range, and staging systems, it is inappropriate to conclude that the study accurately assessed the effect of sarcopenia on the postoperative outcome of patients with GBC.

In this study, significant prognostic factors for OS in patients with GBC were RS, intraoperative blood loss, surgical radicality, stage, and adjuvant therapy, and significant prognostic factors for RFS were surgical radicality and stage, respectively.

Gospodarowicz et al. classified the prognostic factors for cancer into tumor-related (e.g., tumor pathology, anatomic disease extent, tumor biology), host-related (e.g., age, gender, ethnicity, performance status, comorbidities, immune system), and environment-related (e.g., access to care, health-care policy, access to drugs or technology, choice of treatment, quality of treatment) factors. The study pointed out that the importance of host-related or environment-related factors might be overlooked by attention toward tumor-related factors.[27]

It is difficult to measure host-related factors, i.e., pretreatment physiologic reserves, among the prognostic factors for cancer. Comorbidity and performance indices, such as the ECOG performance status, ASA physical status, and CCI, which constitute such efforts, do not quantitatively reflect a patient's preoperative general condition because of their heterogeneities, subjectivity, and imprecision. Therefore, there have been criticisms that they exhibit limitations in predicting prognoses such as patient survival or toxicity after treatment of cancer.[28–30]

Here, RS, one of the host-related factors, should be noted in predicting postoperative survival in GBC patients. In this study, RS, along with stage, surgical radicality, intraoperative blood loss, and adjuvant therapy, was a significant prognostic factor for patient survival. On the other hand, other host-related factors such as age, ECOG performance status, ASA physical status, CCI, and BMI that were routinely collected before surgery were not helpful in predicting prognosis. Thus, the results of our study suggest that skeletal muscle mass may be more useful in assessing the preoperative physiologic reserves of patients with GBC than the conventional comorbidity and performance indices, such as ECOG performance status, ASA physical status, and CCI. Furthermore, among the significant prognostic factors for patient survival, SMI is the only factor that can be evaluated before surgery. Therefore,

Table 2 Univariate analysis of clinicopathologic variables associated with OS and RFS

Variables	Number (%)	OS			RFS		
		HR[†]	95% CI	P	HR[†]	95% CI	P
Age (years) (< 65 vs. ≥65)	81 (51.3)/77 (48.7)	1.096	0.718–1.673	0.671	1.062	0.666–1.692	0.801
Sex (female vs. male)	85 (53.8)/73 (46.2)	1.352	0.886–2.065	0.162	1.049	0.656–1.678	0.840
BMI (kg/m^2)				0.497			0.691
Under weight (< 18.5)	17 (10.8)	Reference			Reference		
Normal (≥ 18.5, < 23)	60 (38.0)	0.927	0.459–1.872	0.832	0.759	0.366–1.574	0.459
Overweight (≥ 23, < 25)	32 (20.3)	1.061	0.493–2.284	0.879	0.917	0.412–2.041	0.832
Obese (≥ 25)	49 (31.0)	0.679	0.322–1.436	0.311	0.671	0.314–1.433	0.302
RS (no vs. yes)	70 (44.3)/88 (55.7)	1.820	1.171–2.830	0.008	1.175	0.736–1.876	0.500
Laboratory values							
Neutrophil to lymphocyte ratio (< 4 vs. ≥ 4)	141 (89.2)/17 (10.8)	1.744	0.947–3.211	0.074	1.417	0.678–2.96	0.354
Bilirubin (mg/dL) (< 1.2 vs. ≥ 1.2)	132 (83.5)/26 (16.5)	2.320	1.400–3.844	0.001	1.424	0.763–2.657	0.266
Albumin (g/dL) (≥ 3.5 vs. < 3.5)	146 (92.4)/12 (7.6)	2.051	1.026–4.101	0.042	2.084	0.951–4.570	0.067
CEA (ng/mL) (< 5.0 vs. ≥ 5.0) [15]	119 (83.2)/24 (16.8)	1.722	1.016–2.919	0.043	2.154	1.203–3.858	0.010
CA19-9 (U/mL) (< 200 vs. ≥ 200) [9]	129 (86.6)/20 (13.4)	3.071	1.824–5.168	<0.001	3.508	1.944–6.328	<0.001
Charlson comorbidity index				0.507			0.980
0	99 (62.7)	Reference			Reference		
1	45 (28.5)	1.304	(0.821–2.071)	0.261	0.965	(0.565–1.646)	0.895
2	14 (8.9)	1.233	(0.584–2.600)	0.583	0.927	(0.396–2.171)	0.862
ASA physical status				0.187			0.873
1	42 (26.6)	Reference			Reference		
2	102 (64.6)	1.054	0.637–1.743	0.837	0.877	0.522–1.472	0.620
≥.	14 (8.9)	1.918	0.902–4.077	0.090	0.849	0.320–2.254	0.743
ECOG performance status (0, 1 vs. ≥ 2)	155 (98.1) / 3 (1.9)	0.559	0.078–4.016	0.563	0.600	0.083–4.319	0.612
Type of surgery				0.016			0.041
LC	16 (10.1)	Reference			Reference		
OC	17 (10.8)	7.842	1.737–35.412	0.007	3.198	0.645–15.862	0.155
OC + segments IVb and V + LND	64 (40.5)	4.629	1.109–19.317	0.036	3.316	0.791–13.902	0.101
OC + segments IVb and V + LND + BDR/PD/colectomy	21 (13.3)	7.831	1.777–34.506	0.007	5.488	1.225–24.579	0.026
OC + Ext. R(L)HH/central bisectionectomy + LND	32 (20.3)	8.187	1.917–34.956	0.005	4.753	1.092–20.691	0.038
OC + Ext. RHH + LND + BDR/PD	8 (5.1)	10.668	2.150–52.926	0.004	9.997	2.007–49.799	0.005
Operation time (min) (< 4 vs. ≥4)	68 (43.0) / 90 (57.0)	2.417	1.521–3.839	<0.001	2.097	1.272–3.456	0.004
Intraoperative blood loss (mL) (< 1000 vs. ≥ 1000)	133 (84.2) / 25 (15.8)	3.086	1.878–5.069	<0.001	2.356	1.320–4.205	0.004
RBC transfusion (no vs. yes)	139 (88.0) / 19 (12.0)	2.572	1.467–4.511	0.001	1.827	0.931–3.585	0.080
Stage (AJCC 8th)				<0.001			<0.001
I, 0	26 (16.5)	Reference			Reference		
II	31 (19.6)	1.369	0.435–4.316	0.591	1.556	0.372–6.513	0.545
III	75 (47.5)	5.480	2.181–13.774	<0.001	7.772	2.407–25.088	0.001
IV	26 (16.5)	12.586	4.722–33.550	<0.001	19.279	5.601–66.364	<0.001
Tumor size (cm) (< 2 vs. ≥2)	18 (13.4) / 116 (86.6)	1.670	0.803–3.471	0.170	3.589	1.124–11.463	0.031
Differentiation				0.173			0.170
Well-differentiated, moderately differentiated	103 (65.2)	Reference			Reference		
Poorly differentiated, undifferentiated	37 (23.4)	1.573	0.962–2.572	0.071	1.558	0.906–2.680	0.109
Others	18 (11.4)	1.347	0.703–2.583	0.369	1.608	0.807–3.206	0.177
Lymphatic invasion (no vs. yes) [2]	79 (50.6) / 77 (49.4)	3.190	2.020–5.036	<0.001	2.360	1.456–3.825	<0.001
Perineural invasion (no vs. yes) [2]	92 (59.0) / 64 (41.0)	2.811	1.828–4.325	<0.001	2.480	1.548–3.976	<0.001
Radicality (R0 vs. R1, R2)	138 (87.3) / 20 (12.7)	3.690	2.165–6.291	<0.001	3.752	2.007–7.015	<0.001

Table 2 (continued)

Variables	Number (%)	OS			RFS		
		HR†	95% CI	P	HR†	95% CI	P
Adjuvant therapy (no vs. yes)	109 (69.0) / 49 (31.0)	0.884	0.557–1.401	0.599	1.250	0.776–2.012	0.358
Moderate to severe complications‡ (no vs. yes)	126 (79.7) / 32 (20.3)	1.768	1.101–2.836	0.018	1.520	0.870–2.655	0.141

Numbers in parentheses are missing value

† The value on the left is the reference

‡ Clavien-Dindo grade ≥ 3

AJCC, American Joint Committee on Cancer; *ASA*, American Society of Anesthesiologists; *BDR*, bile duct resection; *BMI*, body mass index; *CA19-9*, carcinoembryonic antigen 19-9; *CEA*, carcinoembryonic antigen; *CI*, confidence interval; *ECOG*, Eastern Cooperative Oncology Group; *Ext.*, extended; *HR*, hazard ratio; *LC*, laparoscopic cholecystectomy; *LN*, lymph node; *LND*, lymph node dissection; *OC*, open cholecystectomy; *OS*, overall survival; *PD*, pancreaticoduodenectomy; *R(L) HH*, right (left) hemihepatectomy; *RBC*, red blood cell; *RFS*, recurrence-free survival; *RS*, radiographic sarcopenia

preoperative identification of patients with RS may be expected to improve prognosis by allowing preemptive treatment for maintaining or increasing muscle mass and may also help establish appropriate treatment strategies for individual patients by predicting preoperative physiologic reserves.[31]

Meanwhile, aging is associated with an increase in fat mass, particularly visceral fat, as well as skeletal muscle mass reduction. Accumulated adipose tissue secretes hundreds of pro-inflammatory cytokines called "adipokines" (e.g., leptin, adiponectin, apelin, chemerin, and vaspin) that cause chronic systemic inflammation in the body, as well as insulin resistance, atherosclerosis, and neurodegeneration.[32,33] This aging-associated obesity works synergistically with

sarcopenia, further increasing the risk of metabolic disorders, cardiovascular diseases, and mortality.[34]

The synergistic effects of sarcopenia and obesity have been reported to cause poor prognosis in patients with cancer.[18,35] However, in this study, in patients with GBC having RS, obesity tended to have an even slightly better effect on the prognosis for GBC, although there was no statistical significance (Fig. 2c, d). This observation is referred to as "obesity paradox."[36,37] Obesity paradox was first described in 1999 in overweight and obese patients receiving hemodialysis[38] and it has since been found in patients with heart failure and peripheral arterial disease.[37,39] According to those studies, obesity, defined as BMI alone, can be misleading because

Table 3 Multivariate analysis of clinicopathologic variables associated with OS and RFS

Variables	Number (%)	HR†	95% CI	P
OS				
RS (no vs. yes)	70 (44.3) / 88 (55.7)	1.704	1.072–2.710	0.024
Intraoperative blood loss (L) (<1 vs. ≥1)	133 (84.2) / 25 (15.8)	1.851	1.087–3.152	0.023
Radicality (R0 vs. R1, R2)	138 (87.3) / 20 (12.7)	2.830	1.548–5.175	0.001
Stage (AJCC 8th)				< 0.001
I, 0	26 (16.5)	Reference		
II	31 (19.6)	1.612	0.506–5.139	0.419
III	75 (47.5)	6.013	2.319–15.592	< 0.001
IV	26 (16.5)	7.181	2.526–20.413	< 0.001
Adjuvant therapy (no vs. yes)	109 (69.0)/49 (31.0)	0.537	0.322–0.894	0.017
RFS				
Radicality (R0 vs. R1, R2)	138 (87.3)/20 (12.7)	2.197	1.121–4.302	0.022
Stage (AJCC 8th)				< 0.001
I, 0	26 (16.5)	Reference		
II	31 (19.6)	1.415	0.338–5.922	0.635
III	75 (47.5)	6.480	2.000–20.994	0.002
IV	26 (16.5)	12.671	3.530–45.478	< 0.001

† The value on the left is the reference

AJCC, American Joint Committee on Cancer; *CI*, confidence interval; *HR*, hazard ratio; *OS*, overall survival; *RFS*, recurrence-free survival; *RS*, radiographic sarcopenia

Fig. 2 OS (**a**) and RFS (**b**) according to sarcopenia status in patients with GBC. OS (**c**) and RFS (**d**) according to obesity status in patients with GBC and RS. GBC, gallbladder cancer; OS, overall survival; RFS, recurrence-free survival; RS, radiographic sarcopenia
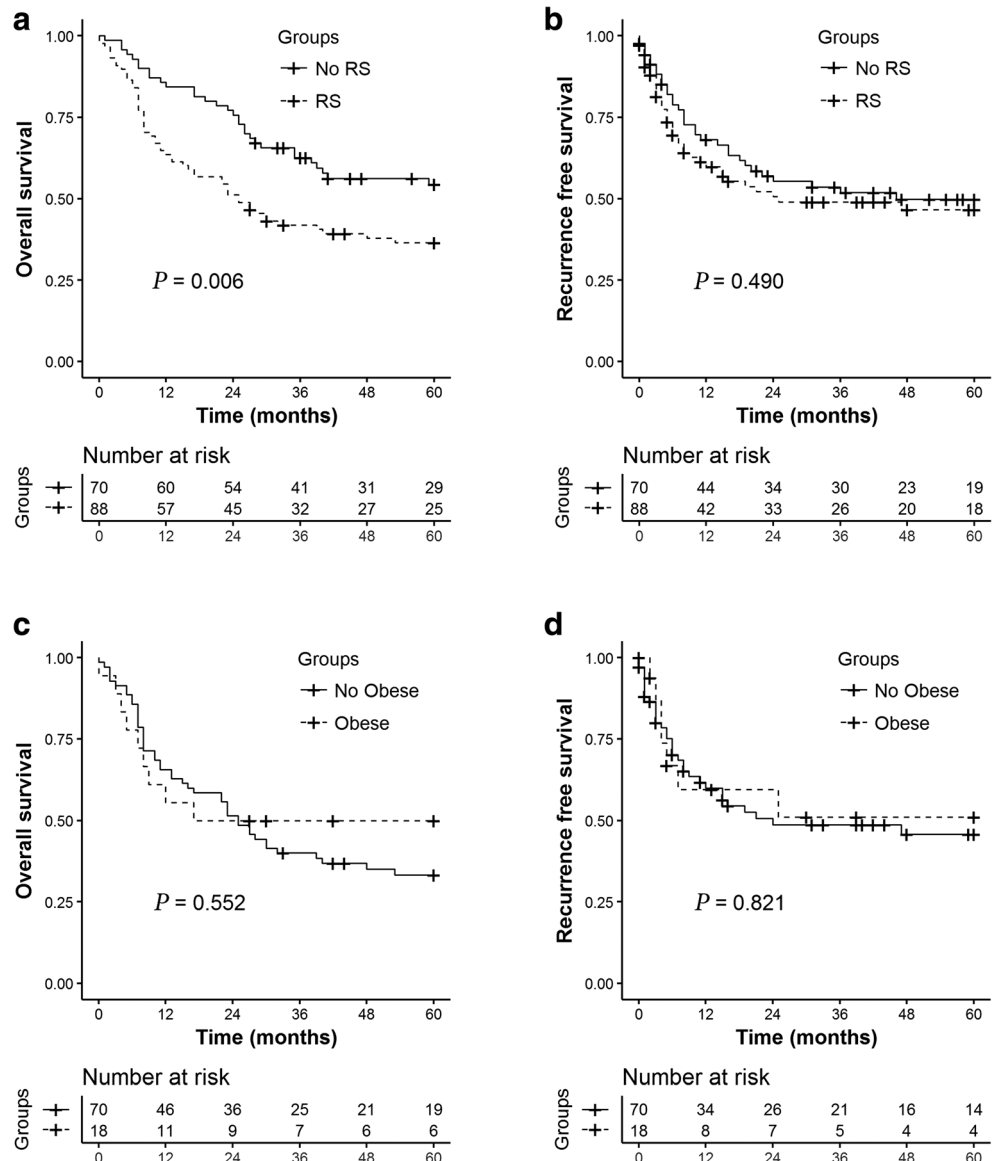
the height-adjusted weight is not a specific indicator of total body fat or abnormal body fat accumulation.[40] In other words, obesity means excess body fat, but people with excess lean body mass will have a higher BMI as well.[41,42] In addition, the differences in bone density depending on race, sex, and age can affect BMI.

This study has some limitations. First, this study was retrospective and conducted in a single institution. Our results should be confirmed in a larger multicenter prospective cohort. Second, despite our efforts, the complications that correspond to grade 1 or 2 of the Clavien-Dindo classification were difficult to investigate precisely and therefore were not presented in the results. Third, there are legal restrictions on the examination of death certificates of many patients included in this study, which makes it difficult to determine the exact cause of the death, and therefore disease-specific survival

could not be considered. Fourth, the semi-automated segmentation function built in OsiriX MD version 9.0 was used to measure the skeletal muscle area and then manually corrected for errors, but the possibility of measurement errors cannot be completely ruled out. Finally, in defining sarcopenia, functional parameters are not sufficiently considered due to the retrospective nature of this study.

Conclusion

This study showed that there was a significant association between RS and GBC patient survival. Furthermore, among the prognostic factors for patient survival, RS is the only factor that can be evaluated before surgery. Evaluation of RS in patients with GBC might be helpful in the development of

early prevention strategies to maintain or increase muscle mass, which would improve surgical outcomes and the establishment of appropriate treatment strategies according to the patient's physiologic reserves.

Author Contribution
-Study concepts and design: ECL, S-JP, SDL, S-SH, and SHK
-Data acquisition and analysis: ECL and SDL
-Manuscript preparation: ECL
-Manuscript review: ECL, S-JP, S-SH, and SHK

Compliance with ethical standards

Conflict of interest   The authors declare that they have no conflict of interest

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