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Original Article

Sarcopenia as an independent prognostic factor in patients following surgery for gallbladder cancer

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Abstract: Background: Sarcopenia has been identified as a poor prognostic factor for various diseases. The aim of this study is to determine whether sarcopenia is a prognostic factor for gallbladder cancer (GBC). *Methods*: We evaluated 88 consecutive patients with primary GBC. The skeletal muscle cross-sectional area was measured by computed tomography at the third lumbar vertebra (L3), from which the L3 skeletal muscle index was obtained. Clinicopathological, surgical outcome and long-term survival data were analyzed. *Results*: Sarcopenia was present in 33 (37.5 percent) of 88 patients, and was significantly correlated with female, lower body mass index and serum albumin levels. In patients with, and without sarcopenia, the 5-year overall survival rate was 31.4 and 60 percent respectively, and the 5-year recurrence-free survival rate was 28 and 41.4 percent respectively. Multivariable analysis revealed that reduced skeletal muscle mass was predictive of an unfavorable prognosis. *Conclusion*: Sarcopenia is an independent prognostic factor. Intervention to prevent muscle wasting might be an effective strategy for improving the outcome of GBC.

Keywords: Sarcopenia, gallbladder cancer, prognostic factor

Introduction

Gallbladder cancer (GBC) is the most common malignant tumor of the biliary system, presenting features such as high degree of malignancy, difficult early diagnosis, poor therapeutic effects and prognosis, and with a dismal survival rate of 0-12% in most reports [1]. The morbidity rate from GBC and cholangiocarcinoma in Chinese cancer registration areas was 4.31/100,000, and the population-standardized incidence rate was 1.93/100,000 [2], a rate which was equal to global levels. Radical resection has been shown to be an effective therapeutic method to increase the 5-year survival rate in patients with GBC [3]. Unfortunately, most of patients with GBC have lost an opportunity for radical resection when visiting, less than 10 percentages of patients have tumors that can be resected at the time of surgery.

Sarcopenia, a novel concept reflecting the degenerative loss of skeletal muscle mass and strength, has recently been an indispensable element in the definition of cancer cachexia [4, 5]. In recent years, sarcopenia has been gradually recognized to be associated with negative prognosis after colorectal [6], pancreatic [7], urothelial [8], and hepatic [9] surgery. Thus, sarcopenia, which can be evaluated from computed tomography (CT) images [10], is expected to predict the prognosis of cancer patients. The assessment of sarcopenia is based on the consensuses of the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia (AWGS) [11, 12]. To date, there have been no reports on the relationship between sarcopenia and the prognosis of patients with GBC following gallbladder cancer surgery.

Previous studies regarding the association of sarcopenia with postoperative prognosis were mostly conducted in Western countries [13], and the diagnostic criteria of sarcopenia were based on the characteristics of the Western population [5]. Considering the different patient characteristics between Asia and the West, it is necessary to conduct a study using Asian diagnostic criteria of sarcopenia.

A retrospective study was performed at the authors' institution to investigate the outcome of patients with sarcopenia who underwent sur-

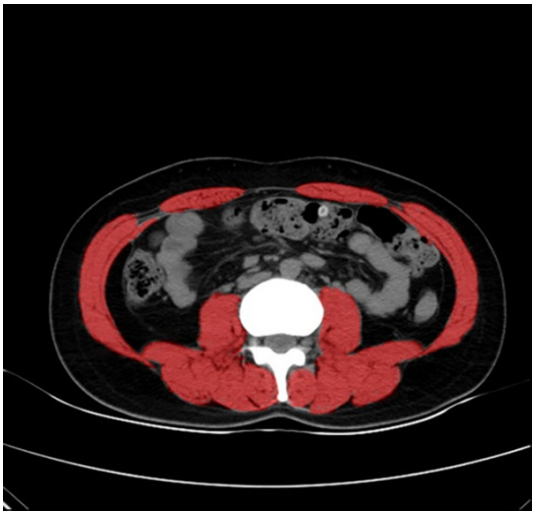

Figure 1. Computed tomogram showing the area of skeletal muscle mass in the L3 region (highlighted red).

gery for GBC. The outcome of these patients was compared with that of patients without sarcopenia undergoing surgery during the same period.

Patients and methods

Patients

We evaluated 217 consecutive primary GBC patients with any cancer stage who underwent initial treatment for GBC in our hospital between 2006 and 2012. The inclusion criteria included patients who (1) were ≥e18 years old; (2) had American Society of Anesthesiologists grade ≤8III; (3) planned to receive elective surgery for GBC with curative intent; (4) had preoperative abdominal CT scans available for review (no more than 1 months before surgery); and (5) agreed to take part in the study and signed the informed consent.

Image analysis of skeletal muscle mass

A cross-sectional CT image at the third lumbar vertebra (L3) in the inferior direction was analyzed as described previously. All patients had preoperative computed tomography (CT). Skeletal muscle was identified and quantified by Hounsfield unit (HU) thresholds of -29 to +150 (water is defined as 0HU, air as 1000 HU). The distinction between different tissues was based on Hounsfield Units (HU), using INFINITT PACS software version 3.0.11.3 BN17 32 bit (INFINITT Healthcare Co., Ltd., Seoul, Korea). Multiple muscles were quantified, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominal muscle, and rectus abdominis muscle (**Figure 1**). The cross-sectional areas of muscle (cm^2) at the L3 level computed from each image were normalized by the square of the height (m^2) to obtain the L3 skeletal muscle index (L3 SMI, cm^2/m^2).

Diagnosis of sarcopenia

Sarcopenia was diagnosed according to the consensuses of EWGSOP and AWGS. Based on the characteristics of the Asian population, the cut-off values for reduced skeletal muscle mass were L3 MI <36.0 cm^2/m^2 for men, and L3 MI <29.0 cm^2/m^2 for women [14]. Based on this cut-off, patients were assigned to one of two groups, depending on the presence or absence of sarcopenia. The clinicopathological background and rates of overall and recurrence-free survival were compared between the two groups.

Data collection

The prognostic factors were examined with respect to overall and recurrence-free survival on the basis of the following variables: sarcopenia (absence *versus* presence); skeletal muscle mass; age; sex (male *versus* female); body mass index (BMI); serum albumin level; serum total bilirubin level; platelet number; White blood cell count; tumour size; gallstone history (absence *versus* presence); Nevin stage; tumour node metastasis (TNM) stage according to the American Joint Committee on Cancer (AJCC) (7th edition) [15]; tumour differentiation (well differentiated + moderately differentiated *versus* poorly differentiated); microvascular invasion (MVI) (absence *versus* presence); serum α-fetoprotein level (AFP); serum carcinoembryonic antigen (CEA); serum carbohydrate antigen 199 (CA199) and postoperative complications (absence versus presence). Postoperative complications within 1 month after GBC surgery included liver failure, gastrointestinal bleeding, intraperitoneal abscess, abdominal hemorrhage, bile leakage, pleural effusion, intractable ascites and wound infection.

Follow-up strategy

After discharge, patients were followed-up on an outpatient basis by assessing the levels of serum tumor markers such as alpha-fetopro-

Table 1. Clinicopathological factors in patients with, and without sarcopenia

	Sarcopenia (*n*=33)	No sarcopenia (*n*=55)	*P*#
Age (years)	64.7±14.7	64.3±12.6	0.918
Sex ratio (M:F)	6:27	26:29	0.006*
Skeletal muscle mass (cm^2/m^2)	27.3±2.9	34.4±3.2	<0.001
Body mass index (kg/m^2)	19.6±1.4	23.4±2.0	<0.001
Albumin (g/dl)	36.3±1.7	39.0±1.5	<0.001
Total bilirubin (mg/dl)	1.0±0.5	0.8±0.3	0.098
Platelet count ($\times 10^9$/L)	247.2±90.2	239.4±83.4	0.572
White blood cell count ($\times 10^9$/L)	7.7±3.5	8.2±4.2	0.786
α-Fetoprotein level (ng/ml)	3.5±1.7	6.8±15.5	0.200
Carcinoembryonic antigen	20.2±41.9	8.6±11.1	0.979
carbohydrate antigen 199	939.7±2551.7	819.3±2165.3	0.789
Tumour size (cm)	3.1±2.4	3.1±1.7	0.576
Gallstone history (Y:N)	18:15	33:22	0.616*
TNM stage			0.368*
I	5	6	
II	4	4	
III	17	34	
IV	7	11	
Nevin stage			0.101*
I	0	0	
II	9	8	
III	5	13	
IV	0	6	
V	28	19	
Differentiation of GBC			0.635*
Well	4	4	
Moderate	14	28	
Poor	15	23	
Postoperative complications (Y:N)	6:27	8:47	0.652*
Microvascular invasion(Y:N)	4:29	5:50	0.650*

Values are mean ± s.d. unless indicated otherwise: values in parentheses are percentages. TNM, tumour node metastasis; GBC, gallbladder cancer; Y, yes; N, no; #Mann-Whitney *U* test, except *Fisher's exact test or χ^2 test.

tein (AFP) and using imaging modalities such as abdominal ultrasonography, dynamic CT scanning, or dynamic MRI every 3 months. By these means, we could monitor the healthy condition of patients and decide whether they should come back to hospital for further examination and treatment.

Statistical analysis

All data were analyzed using SPSS statistics version 22.0. Associations of continuous and categorical variables with relevant outcome variables were assessed using the Mann-Whitney *U* test and Fisher's exact test respectively. To identify prognostic factors after GBC surgery, all variables were included in the overall multivariable Cox proportional model in the analyses of both overall and recurrence-free survival using the backward selection method. The overall and recurrence-free survival curves were analyzed by the Kaplan-Meier method and compared with the log rank test. $P<0.05$ was considered statistically significant.

Results

The baseline characteristics and laboratory data of the 88 patients (32 men and 56 women; median age, 64.4 years) are shown in **Table 1**. Women were more likely to have sarcopenia than men. Patients with sarcopenia were sig-

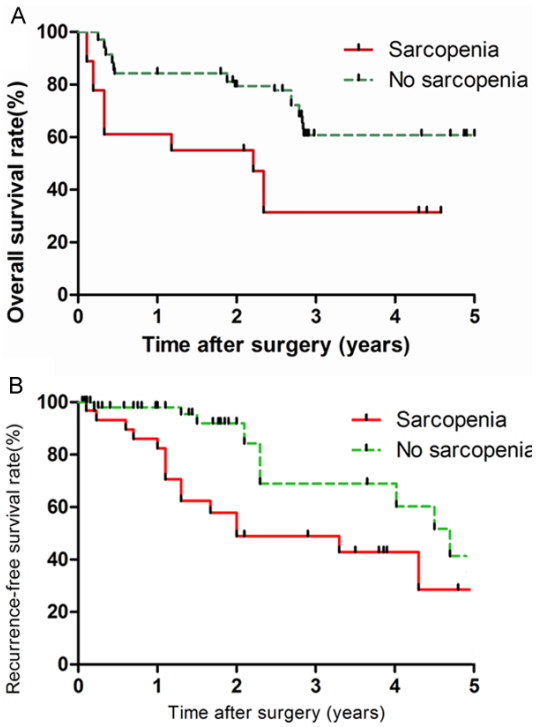

Figure 2. A: Overall survival curves after GBC surgery in patients with and without sarcopenia. *P*=0.001. B: Recurrence-free survival curves after GBC surgery in patients with and without sarcopenia. *P*=0.015 (log rank test).

nificantly lower in BMI and serum albumin levels than those without. Other factors such as age, total bilirubin, platelet count, white blood cell count, α-Fetoprotein level, carcinoembryonic antigen, carbohydrate antigen 199 and gallstone history were not related to the presence of sarcopenia. There were no significant differences in tumour-related factors or surgical outcomes between the two groups.

Overall and recurrence-free survival curves for patients with and without sarcopenia are shown in **Figure 2**. Overall and recurrence-free 5-year survival rates were 31.4 and 28 per cent respectively in patients with sarcopenia, and 60 and 41.4 per cent in patients without sarcopenia (**Figure 2**). Patients with sarcopenia had a significantly worse prognosis than those without in terms of both overall (*P*=0.001) and recurrence-free survival (*P*=0.015).

In invariable analysis, significant prognostic factors for overall survival were low skeletal muscle mass, microvascular invasion and postoperative complications (**Table 2**). Significant prognostic factors for recurrence-free survival were lower skeletal muscle mass, serum albumin level, poorly differentiated GBC, microvascular invasion, tumour stage, and serum CA199 levels (**Table 3**). Multivariable analysis identified four poor prognostic factors (low skeletal muscle mass, poorly differentiated GBC, microvascular invasion and postoperative complications) that influenced overall survival, and three poor prognostic factors (low skeletal muscle mass, stage III+IV, and stage IV+V disease) that influenced recurrence-free survival (**Tables 2** and **3**).

Discussion

According to the consensus of EWGSOP, sarcopenia is defined as “a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death” [11]. However, muscle function is difficult to evaluate, and thus low muscle mass was investigated in the present study. sarcopenia patients with malignancy or other chronic diseases often coexists with cachexia [16]. Cachexia is a syndrome defined as “a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle mass with or without loss of fat mass”. Sarcopenia is attributed to a decrease in protein synthesis and increase in protein degradation [17]. Sarcopenia is usually accompanied by muscle atrophy and is frequently seen in patients with cancer [11]. It is also thought to be a bad factor in the prognosis of malignant tumors such as respiratory and gastrointestinal cancers, melanoma, pancreatic cancer and liver metastasis from colorectal cancer [4, 18-20]. The decrease in protein synthesis depends on anorexia and the low nutritional status caused by side effects of the treatment and progression of the disease. Meanwhile, the increase in protein degradation is induced by catabolic drivers such as systemic inflammation.

A CT scan is a highly precise modality to estimate human body composition with a reported precision error of 1.4% [21]. CT is the standard procedure for quantifying skeletal muscle mass, enabling objective and detailed nutritional and metabolic assessment of patients.

Table 2. Univariable and multivariable analysis of clinicopathological factors and overall survival following GBC surgery

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P**	Hazard ratio	*P*#
Age	1.01	0.297		
Female sex	0.83	0.64		
Skeletal muscle mass	0.99	0.005	0.98	0.003
Body mass index	0.98	0.231		
Albumin	0.49	0.095		
Platelet	1.00	0.417		
α-Fetoprotein	1.00	0.538		
CEA	1.01	0.521		
CA199	1.03	0.161		
TNM stage III+IV	1.53	0.147		
Nevin stage IV+V	1.36	0.112		
Poor differentiation	2.15	0.064	1.89	0.037
Microvascular invasion	2.36	0.029	3.14	0.023
Postoperative complications	1.15	0.023	1.23	0.019

TNM, tumour node metastasis; CEA, serum carcinoembryonic antigen; CA199, serum carbohydrate antigen 199. *Log rank test; #Cox proportional model.

Table 3. Univariable and multivariable analysis of clinicopathological factors and recurrence-free survival following GBC surgery

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P**	Hazard ratio	*P*#
Age	1.02	0.189		
Female sex	1.03	0.923		
Skeletal muscle mass	1.11	0.045	1.02	0.012
Body mass index	0.98	0.093		
Albumin	0.53	0.003		
Platelet	0.54	0.532		
α-Fetoprotein	1.01	0.471		
CEA	1.12	0.632		
CA199	1.05	0.002		
TNM stage III+ IV	2.41	0.003	2.15	0.003
Nevin stage IV+V	2.21	0.002	2.11	0.001
Poor differentiation	1.49	0.037		
Microvascular invasion	2.41	0.041		
Postoperative complications	1.02	0.714		

TNM, tumour node metastasis; CEA, serum carcinoembryonic antigen; CA199, serum carbohydrate antigen 199. *Log rank test; #Cox proportional model.

In cancer patients with sarcopenia, there may be some harmful effects. Sarcopenia is associated with chemotherapy toxicities, leading to dose reductions, dose delays, or the termination of chemotherapy [22, 23]. Therefore, chemotherapy may not be fully effective in sarcopenia patients undergoing chemotherapy. Furthermore, patients with sarcopenia are also susceptible to infections [24]. Thus, sarcopenia itself can cause poor prognosis in cancer patients through these mechanisms.

Sarcopenia reflects many clinical conditions, such as frailty, low nutritional status, active catabolism, and systemic inflammation. First, nutrition: Decreased protein intake has a direct effect on muscle disease. The body's vitamin D comes from the effects of diet and ultraviolet light on the skin [25]. Skeletal muscle is also a target for vitamin D [26]. Some in vitro studies have found that vitamin D regulates the proliferation and differentiation of skeletal muscle cells [27]. Second, Sports: Studies have shown that elderly people who lack physical activity are more likely to have reduced skeletal muscle mass and reduced muscle strength, and the risk of developing muscle disease is increased [28]. Fiatarone *et al.* found that the strength movement was beneficial to the recovery of skeletal muscle strength and quality of life in the elderly [29]. Third, hormone: The role of growth hormone is to promote protein synthesis through insulin-like growth factor 1 [30]. Generally, the growth hormone of the elderly is lower in general, and the frequency and amplitude of the impulsive secretion are significantly reduced. Studies have shown that testosterone therapy increases muscle size, and studies have shown that there is a further improvement in muscle strength [31].

The molecular mechanism of sarcopenia remains unclear. Skeletal muscle was recently identified as an endocrine organ [32]. Skeletal

muscles can produce and release cytokines and other peptides. For example, interleukin (IL) 6 is released from skeletal muscle [32]. Furthermore, Levels of insulin-like growth factor (IGF) 1 stimulate the development and regulation of skeletal muscle mass. IGF-1 is reduced in patients with sarcopenia.

In modern society, the number of overweight or obese patients is increasing [33]. Sarcopenic obesity, the coexistence of obesity and low muscle mass, is considered to be a worst-case scenario due to the combination of two health-related risk factors [34, 35]. Sarcopenic obesity has been reported to be associated with poor survival in patients with several types of cancers [36]. Screening of sarcopenic overweight is significant because sarcopenia is present as a covert condition in HCC patients with any BMI [37].

Sarcopenia is easily assessed in conventional CT scans, and is a useful and objective biomarker for predicting overall and recurrence-free survival of cancer patients.

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Disclosure of conflict of interest

None.

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