Asia-Pacific Journal of Science and Technology: Volume: 27. Issue: 06. Article ID.: APST-27-06-04. Research Article

APST

Asia-Pacific Journal of Science and Technology

https://www.tci-thaijo.org/index.php/APST/index

Published by the Research and Technology Transfer Affairs Division,
Khon Kaen University, Thailand

Predictors for sarcopenia in biliary tract cancer patients

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Received 18 July 2021
Revised 9 October 2021
Accepted 14 November 2021

Abstract

Here, we report the clinical predictors for sarcopenia. Sarcopenia is a common condition in patients with cancer and is associated with treatment toxicity and poorer outcomes. However, there are limited data available on its differential clinical features in biliary tract cancer (BTC) patients with and without sarcopenia. Our primary analysis showed that decreased muscle mass was associated with shorter overall survival. This was a retrospective analysis of a prospective cohort of BTC patients who received chemotherapy between January 2016 and December 2017. Factors associated with sarcopenia were examined using uni- and multivariate logistic regression. During the study period, a total of 71 participants, including 45 with sarcopenia (63%) and 26 without sarcopenia (27%), were included. Four significant factors differed between those with and without sarcopenia including age (61.9 vs 55.3 years), the proportion of male patients (87% vs 65%), body mass index (20.6 vs 23.2 kg/m^2), and skeletal muscle density (53.9 vs 59.2 HU). There were two independent predictors for sarcopenia in BTC patients: body mass index (BMI) and skeletal muscle density, with adjusted odds ratios (95% confidence interval) of 0.683 (0.530, 0.880) and 0.811 (0.700-0.944), respectively. Our study concludes that low body mass index and low skeletal muscle density on computed tomography (CT) imaging are suggestive of sarcopenia in biliary tract cancer patients.

Keywords: Body composition, Cholangiocarcinoma, Fat-free mass, Skeletal muscle mass, Body imaging

1. Introduction

Sarcopenia is a condition characterized by the depletion of lean body mass and impaired physical function [1-3]. It was originally used to describe muscle loss associated with the aging process [4,5]. In other conditions, such as malignancy, a decline in muscle mass can also occur regardless of age. This latter form is termed secondary sarcopenia [2,3]. In recent years, there have been many studies demonstrating the detrimental impact of sarcopenia on cancer survival and treatment-related toxicity [6-10].

The standard methods of evaluating body composition and diagnosing sarcopenia are dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). CT imaging is a convenient, routinely used method of investigation for various cancers. The cross-sectional area of skeletal muscle at the level of the third vertebra correlates well with total skeletal muscle, a finding that has been validated in several studies [1,3,11-13].

CT imaging can also be used to evaluate muscle quality by measuring skeletal muscle density (SMD) in Hounsfield units (HUs). Lower values indicate more fat infiltration or myosteatosis, which may result in decreased physical function [14,15] and is associated with poor prognosis in several cancers [16-18].

Biliary tract cancer (BTC) is an aggressive tumor with a dismal prognosis. Patients suffer from loss of appetite, obstructive jaundice, and abdominal pain, all of which lead to sarcopenia and eventually poor survival. Recent studies have reported low muscle mass as a factor related to poor prognosis in patients with biliary tract cancer [19-21].

This study investigated the differences in the clinical characteristics between BTC patients with and without sarcopenia in order to determine the clinical predictors for sarcopenia.

2. Materials and methods

2.1 Study design and patients

This was a secondary analysis of a single-center, prospective study that included biliary tract cancer patients undergoing chemotherapy from January 2016 to September 2017. Eligibility criteria, as reported previously [19], included age ≥18 years and having been diagnosed with either intra- or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma. Patients also had to have received at least one cycle of chemotherapy. Patients were excluded if the baseline contrast-enhanced CT scan did not cover the L3 vertebrae before the start of chemotherapy.

Baseline CT scans for tumor assessment were performed within 60 days before the initiation of chemotherapy and were used to evaluate body composition. Two radiologists (PT and PT), blinded to patient data, performed the measurement independently. Skeletal muscle density (SMD), which signifies muscle quality, was measured using the average radiation attenuation Hounsfield unit (HU) of cross-sectional imaging of all skeletal muscles at the L3 landmark. A lower HU indicated greater infiltration of fat. Subcutaneous adipose tissue was measured and reported as thickness (cm). The interrater reliability was assessed, and the average intraclass correlation coefficient was 0.90 (0.84-0.94) with a 95% confidence interval. Sarcopenia was defined according to the Asian Working Groups for Sarcopenia (AWGS) criteria [1].

2.2 Statistical analysis

Baseline and clinical characteristics of biliary tract cancer patients with and without sarcopenia were compared using descriptive statistics. When appropriate, a Chi-square/ Fisher's exact test or a Student's t-test/ Wilcoxon rank-sum test were used to compare the differences between the two groups in terms of proportions and numbers, respectively. The crude odds ratio (OR) for individual variables was calculated using univariate logistic regression analysis. Clinically significant variables and factors with p values of less than 0.20 by univariate logistic regression analysis and were included in the multivariate logistic regression analysis. The results are presented as crude OR, adjusted OR, and 95% confidence intervals. The goodness of fit of the model was tested. The Pearson correlation coefficient was used to determine the level of correlation.

3. Results

3.1 Patients' clinical characteristics

There were 71 biliary tract cancer patients included in the study, 45 of whom had sarcopenia (63.3%). Baseline characteristics and body composition (as observed using CT and DXA) of patients with and without sarcopenia are shown in Tables 1-2. The sarcopenia group was significantly older (61.9 vs 55.3 years) and had a higher proportion of male patients (86.7% vs 65.4%). Tumor type and staging, neck and waist circumference, and handgrip strength were comparable between the two groups. Sarcopenia was associated with a lower mean BMI (20.6 vs 23.2).

Table 1 Comparison of sarcopenia and non-sarcopenia patient characteristics.

Clinical factors	Non-sarcopenia (n=26)	sarcopenia (n=145)	*p*-value
Mean age, years (SD)	55.3 (8.2)	61.9 (8.3)	<0.01*
Male sex	17 (65.4)	39 (86.7)	0.03*
Intrahepatic CCA	15 (57.7)	19 (42.2)	0.23
Node positive	18 (69.2)	29 (64.4)	0.80
Metastasis	15 (57.7)	32 (71.1)	0.25
AJCC Stage			1.0
Stage 2/3	4 (15.4)	7 (15.6)	
Stage 4	22 (84.6)	38 (84.4)	
Weight loss (%), median (IQR)	3.7 (1.4, 14.8)	14.0 (6.4, 22.5)	0.008*
BMI, kg/m^2	23.2 (3.5)	20.6 (3.1)	<0.01*
Neck circumference, cm	37.2 (4.3)	36.3 (3.6)	0.33
Waist circumference, cm	86.5 (12.9)	83.6 (12.0)	0.76
Handgrip strength, kg	18.2 (5.7)	17.9 (5.7)	0.62

SD: standard deviation, CCA: cholangiocarcinoma, AJCC: American Joint Committee on Cancer, BMI: body mass index, *statistical significance

The median SMD for the entire group was 56.1 HU (range: 36.0-71.2 HU). Appendicular skeletal mass and SMD were significantly lower in those with sarcopenia (16.0 vs 18.2 kg and 53.9 vs 59.2 HU, respectively). Total fat mass and subcutaneous fat thickness were comparable between the two groups. There was a weak correlation between SMD and ASMI, r=0.12, *p*=0.33 (Figure 1).

Table 2 Distribution of body composition by CT scan and DXA.

Body composition	Non-sarcopenia (n=26)	Sarcopenia (n=45)	*p*-value
Skeletal mass, kg			
Upper extremity	4.7 (1)	4.3 (0.9)	0.04*
Lower extremity	13.5 (2.2)	11.8 (1.8)	<0.01*
Appendicular muscle	18.2 (3.2)	16 (2.6)	<0.01*
Total muscle	42.0 (5.9)	39.5 (5.2)	0.07
ASMI, kg/m^2	7.1 (0.9)	6.0 (0.7)	<0.01*
Skeletal muscle density, HU	59.2 (6.0)	53.9 (7.4)	<0.01*
Total fat, kg	14.5 (7.9)	11.9 (9.3)	0.13
Subcutaneous fat thickness, cm	15.7 (8.1)	15.2 (7.4)	0.81

SD: standard deviation, ASMI: Appendicular skeletal muscle index, HU: Hounsfield unit, *statistical significance.

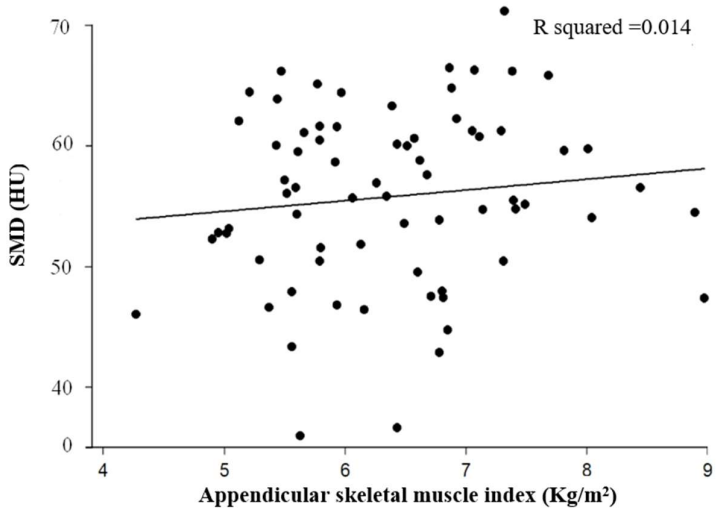

Figure 1 The relationship between skeletal muscle density (SMD) and appendicular skeletal muscle index (ASMI) in biliary tract cancer patients.

There were two independent predictors for sarcopenia in biliary tract cancer patients according to multivariate regression analysis: BMI and SMD (Table 3), with odds ratios (95% confidence intervals) of 0.683 (0.530, 0.880) and 0.811 (0.700-0.944), respectively.

Table 3 Factors associated with sarcopenia according to univariable and multivariable analyses.

Variables	Unadjusted OR	95% CI	Adjusted OR	95% CI
Age (years)	1.103	1.032 - 1.180	1.071	0.981 - 1.169
Male	3.441	1.058-11.195	3.222	0.639-16.247
BMI (kg/m^2)*	0.788	0.671 - 0.926	0.683	0.530 - 0.880
Weight loss (kg)	1.126	1.022 - 1.241	1.061	0.939 - 1.200
Metastasis	1.805	0.657 - 4.958	0.984	0.155 - 6.256
Surgery	1.042	0.379 - 2.869	1.014	0.159 - 6.461
Albumin (g/dL)	0.505	0.188 - 1.357	0.928	0.212 - 4.059
SMD (HU)*	0.887	0.816 - 0.965	0.811	0.700 - 0.944

OR: Odds ratio, BMI: body mass index, HU: Hounsfield unit

4. Discussion

In this study, we evaluated the clinical predictors of sarcopenia in biliary tract cancer. We found that skeletal muscle density (SMD) and body mass index (BMI) were two independent factors for sarcopenia among these patients.

Low BMI was a significant predictor of sarcopenia, indicating low nutritional status, low muscle mass, and low physical function. This is consistent with reports in both cancer patients and older adults without cancer [22-24]. A recent study by Sugawara et al. on esophageal cancer also showed that BMI was significantly correlated with fat mass, skeletal muscle mass, and skeletal muscle index [25]. Being underweight is not only indicative of low muscle mass but is also a significant prognostic factor for poor survival [21]. However, some reports have shown an association between sarcopenia and high BMI in older adults and sarcopenic obesity in cancer [26,27]. Since most of the patients in our cohort were under- or normal weight, no cases of sarcopenic obesity were observed.

Skeletal muscle density reflects muscle quality and has been shown to be another predictor of both sarcopenia and survival [16-17,28-29]. By measuring muscle radiation attenuation, one can compare the degree of fat infiltration into skeletal muscle. Although the mechanism underlying fat infiltration remains elusive, inflammation has been proposed in both cancer and non-cancer patients. In a study of nearly 2,500 colorectal cancer patients, pre-diagnosis neutrophil-lymphocyte ratio was significantly associated with sarcopenia and risk of death [30]. Moreover, in a study of advanced ovarian cancer patients, muscle area was significantly correlated with multiple inflammatory markers including IL-10 and Eotaxin [31].

We chose the L3 landmark for the cross-sectional image because it is the standard site for measuring skeletal muscle area, which signifies sarcopenia, and is usually covered in routing imaging for biliary tract cancer. Moreover, this landmark is used widely in the study of muscle attenuation in both cancer patients and healthy individuals.

Unlike skeletal muscle area, SMD does not correspond to the total lean muscle in the body. Since SMD represents muscle quality, it is not surprising that the correlation between SMD and appendicular skeletal muscle is weak. This is consistent with a report in breast cancer, which found that SMD has a weak correlation with skeletal muscle index [32]. Differences in timing of skeletal muscle evaluation after cancer diagnosis could lead to different results [22]. Hayashi et al. proposed that decreases in muscle density can be detected earlier than decreases in muscle mass [17].

Advanced age is known to be an important risk factor for sarcopenia. There have been numerous reports of progressive loss of muscle mass in older adults, both with chronic disease and in the general population [23,27]. However, after adjusting for other factors, age was not significantly associated with sarcopenia in this cohort. This could be explained by the narrow range of age in our study. The mean age was 59.4 years, and the maximum was 77 years, with only nine patients over 70 years old. This is likely because we included only patients who were eligible for chemotherapy, resulting the exclusion of many older patients.

This model included only clinical symptoms/signs and albumin level with no other laboratory results. While this simple clinical model can be employed in oncological clinics with limited resources, further study with larger sample sizes and longitudinal prospective monitoring of muscle depletion throughout the chemotherapy course is warranted to truly understand quantitative/qualitative skeletal and muscle change in cancer patients.

5. Conclusion

Low body mass index and low skeletal muscle density on CT scans of the L3 vertebra region were suggestive of sarcopenia in biliary tract cancer patients.

6. Ethical approval

All patients provided written informed consent, and the study was approved by the Khon Kaen University Faculty of Medicine Ethics Committee according to good clinical practice, the Declaration of Helsinki, and applicable regulations (Number HE581060).

7. Conflict of interests

The authors declare that they have no conflict of interest.

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