Clinical significance of cachexia index determined by bioelectrical impedance analysis in patients with gastrointestinal cancer

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Abstract. Cancer cachexia is a complex disorder characterized by skeletal muscle loss, which may influence the prognosis of patients with cancer. The cachexia index (CXI) is a new index for cachexia. The present study aimed to assess whether the CXI determined by bioelectrical impedance analysis (BIA) is valuable for predicting survival in patients with gastrointestinal cancer. A total of 54 patients with gastrointestinal cancer undergoing BIA at the time of diagnosis at Fukuchiyama City Hospital (Kyoto, Japan) were retrospectively recruited. CXI values were calculated as follows: CXI=skeletal muscle index (SMI) x serum albumin concentration/neutrophil-to-lymphocyte ratio. The SMI was measured using BIA values. The patients were classified into low- and high-CXI groups. The median patient age was 72 years and 63.0% of patients were male. A total of 20 patients with colorectal cancer were enrolled, 12 with pancreatic cancer, 11 with gastric cancer, 6 with esophageal cancer, 4 with biliary tract cancer and 1 with liver cancer. The cumulative one-year overall survival (OS) rate was significantly worse in the low-CXI group compared with that in the high-CXI group (58.3 vs. 88.5%; P=0.012). By contrast, the SMI had no significant effect on OS. Thus, CXI values using BIA may predict survival in patients with gastrointestinal cancer.

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Introduction

Advances in cancer treatments have improved the prognosis of patients with gastrointestinal cancer. However, gastrointestinal cancer accounts for >30% of cancer mortalities (1). In advanced gastrointestinal cancers, a high prevalence of cachexia can lead to a lower quality of life (2). Cancer cachexia is a complex disorder characterized by skeletal muscle loss. In cancer cachexia, inflammatory cytokines released by the tumor can cause systemic inflammation, deteriorated nutritional status and skeletal muscle loss (3). Skeletal muscle depletion and systemic inflammation can influence the outcomes of patients with cancer. Indeed, our previous studies demonstrated that the neutrophil-to-lymphocyte ratio (NLR) and the decrease of the psoas muscle index (PMI) were notably associated with survival in unresectable pancreatic cancer (4,5).

The cachexia index (CXI) is a novel index of cachexia (6), evaluated using the skeletal muscle index (SMI), serum albumin (ALB) levels and NLR values. Thus, the CXI can reflect the skeletal muscle mass, nutritional status and systemic inflammation in patients with cancer. In clinical settings, the CXI has been associated with survival in gastrointestinal cancers, including gastric, biliary tract, pancreatic, colorectal and hepatocellular cancer (7-14). In previous studies, the SMI was calculated using computed tomography (CT) images for CXI assessment (7-14). In recent years, bioelectrical impedance analysis (BIA) has been widely used to evaluate body composition, as it is a simple and inexpensive method without radiation exposure (15,16).

Overall, BIA is a widely used method to evaluate sarcopenia in patients with cancer (15). However, few studies have assessed the use of the CXI using BIA (16). Therefore, the present study aimed to evaluate whether CXI values calculated using BIA could predict survival in gastrointestinal cancer.

Materials and methods

A total of 54 patients with gastrointestinal cancer (colorectal, pancreatic, gastric, esophageal, biliary tract and liver cancer) who underwent BIA at diagnosis between May 2021 and

Table I. Baseline characteristics of the patients in the present study.[a]

Characteristic	All cases, n=54	Resectable group, n=31	Unresectable group, n=23	P-value[b]
Age, years	72 (45-96)	72 (49-96)	74 (45-91)	0.581
Sex				0.254
Male	34 (63.0)	22 (71.0)	12 (52.2)	
Female	20 (37.0)	9 (29.0)	11 (47.8)	
ECOG-PS				>0.999
0 or 1	47 (87.0)	27 (87.1)	20 (87.0)	
≥2	7 (13.0)	4 (12.9)	3 (13.0)	
BMI, kg/m^2	21.5 (14.6-32.2)	21.8 (14.6-32.2)	21.1 (14.9-27.6)	0.916
Follow-up, days	469 (31-684)	561(148-684)	267 (31-677)	<0.001
Total mortalities	17 (31.5)	2 (6.5)	15 (65.2)	<0.001
Primary tumor site				0.204
Colorectal cancer	20 (37.0)	14 (45.2)	6 (26.1)	
Pancreatic cancer	12 (22.2)	6 (19.4)	6 (26.1)	
Gastric cancer	11 (20.4)	8 (25.7)	3 (13.0)	
Esophageal cancer	6 (11.1)	2 (6.5)	4 (17.4)	
Biliary tract cancer	4 (7.4)	1 (3.2)	3 (13.0)	
Liver cancer	1 (1.9)	0 (0.0)	1 (4.3)	
Treatment				<0.001
Surgery	28 (51.9)	28 (90.3)	0 (0.0)	
Chemotherapy	19 (35.2)	1 (3.2)	18 (78.3)	
Chemoradiotherapy	4 (7.4)	1 (3.2)	3 (13.0)	
BSC	3 (5.6)	1 (3.2)	2 (8.7)	
WBC, /μl	6,320 (3,210-21,840)	6,100 (3,210-8,440)	6,930 (3,930-21,840)	0.120
Hb, g/dl	12.3 (8.3-15.8)	11.9 (8.3-15.4)	13.1 (9.6-15.8)	0.041
PLT, x10^3/μl	22.7 (11.9-51.9)	24.0 (11.9-43.6)	22.5 (12.0-51.9)	0.649
CRP, mg/dl	0.295 (0.020-14.100)	0.190 (0.020-4.930)	1.110 (0.020-14.100)	0.033
ALB, g/dl	4.0 (2.3-4.8)	4.0 (2.7-4.8)	3.8 (2.3-4.4)	0.099
NLR	3.11 (0.72-9.53)	2.61 (0.72-5.65)	4.59 (1.36-9.53)	0.001
Body fat, %	24.65 (3.70-45.60)	24.90 (3.70-42.50)	22.80 (9.90-45.60)	0.643
ECW/TBW	0.394 (0.361-0.426)	0.391 (0.361-0.426)	0.395 (0.372-0.418)	0.323
SMI, kg/m^2				
Male	6.9 (5.1-8.9)	6.85 (5.1-8.9)	6.95 (6.2-8.2)	0.986
Female	5.45 (4.60-8.80)	5.30 (4.60-6.60)	5.70 (4.70-8.80)	0.303
CXI				
Male	9.22 (1.94-39.25)	11.19 (3.70-39.25)	5.48 (1.94-21.29)	0.068
Female	6.24 (1.66-27.26)	12.05 (2.77-27.26)	5.08 (1.66-10.00)	0.025

[a]Data are presented as median (range) or n (%). [b]P-values were calculated by comparing the resectable and unresectable groups. ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; BSC, best supportive care; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; ECW/TBW, extracellular water/total body water; SMI, skeletal muscle index; CXI, cachexia index.

April 2022 at Fukuchiyama City Hospital (Kyoto, Japan) were retrospectively enrolled, regardless of their age, cancer staging, presence of metastasis or prior medical history, including previous cancer diagnoses. All medical records were retrospectively reviewed.

Evaluation of the SMI was performed using BIA with an InBody770 body composition analyzer (InBody Co., Ltd.) at diagnosis. In addition to SMI, the body fat percentage and extracellular water/total body water ratio (ECW/TBW) was evaluated. Baseline characteristics, such as age, sex, primary tumor site, resectability, and treatment were assessed. Biochemical test results were also assessed, including white blood cell (WBC) counts, neutrophil counts, lymphocyte counts, hemoglobin levels, platelet counts, C-reactive protein (CRP) levels and ALB levels. The SMI values were calculated using BIA. CXI values

Table II. Clinical characteristics of the patients in the low- and high-skeletal muscle index groups.[a]

Characteristic	Low-SMI group (n=30)	High-SMI group (n=24)	P-value
Age, years	74 (45-96)	7 (49-83)	0.559
Sex			0.778
Male	18 (60.0)	16 (66.7)	
Female	12 (40.0)	8 (33.3)	
ECOG-PS			0.443
0 or 1	25 (83.3)	22 (91.7)	
≥2	5 (16.7)	2 (8.3)	
BMI kg/m^2	20.2 (14.6-26.1)	24.2 (17.9-32.2)	<0.001
Follow-up, days	475 (31-684)	461 (83-677)	0.993
Total mortalities	10 (33.3)	7 (29.2)	0.777
Primary tumor site			0.112
Colorectal cancer	10 (33.3)	10 (41.7)	
Pancreatic cancer	8 (26.7)	4 (16.7)	
Gastric cancer	8 (26.7)	3 (12.5)	
Esophageal cancer	4 (13.3)	2 (8.4)	
Biliary tract cancer	0 (0.0)	4 (16.7)	
Liver cancer	0 (0.0)	1 (4.2)	
Resectability			0.410
Resectable	19 (63.3)	12 (50.0)	
Unresectable	11 (36.7)	12 (50.0)	
WBC, /μl	6,435 (3,930-17,920)	5,855 (3,210-21,840)	0.870
Hb, g/dl	12.4 (8.7-15.4)	11.9 (8.3-15.8)	0.814
PLT, x10^3/μl	23.8 (11.9-41.3)	22.5 (12.3-51.9)	0.781
CRP, mg/dl	0.35 (0.02-12.86)	0.21 (0.02-14.10)	>0.999
ALB, g/dl	4.0 (2.6-4.8)	4.0 (2.3-4.8)	0.422
NLR	3.63 (0.86-9.26)	2.84 (0.72-9.53)	0.802
Body fat, %	24.65 (3.70-37.70)	24.25 (9.90-45.60)	0.560
ECW/TBW	0.394 (0.361-0.426)	0.391 (0.379-0.416)	0.958

[a]Data are presented as median (range) or n (%). SMI, skeletal muscle index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; ECW/TBW, extracellular water/total body water.

were calculated using the following: SMI (kg/m^2) x ALB (g/dl)/NLR. Overall survival (OS) was assessed from the date of BIA at diagnosis to the date of the last follow-up or mortality.

Firstly, the patients were divided into groups based on their SMI values for each sex: Patients with low SMI (low-SMI group) and patients with high SMI (high-SMI group). The SMI cut-off values were determined as 7.0 kg/m^2 for male patients and 5.7 kg/m^2 for female patients in accordance with the Asian Working Group for Sarcopenia report (17,18). The clinical features and prognoses of the two groups were then assessed. Secondly, the patients were divided based on the median CXI values for each sex: Low CXI (low-CXI group) and high CXI (high-CXI group). The clinical features and prognoses of the two groups were then assessed.

The present study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committee of Fukuchiyama City Hospital (approval no. 5-57).

Statistical analysis. Statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing) and SPSS Statistics 27 (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference. Continuous data are presented as median (range) and categorical data are expressed as n (%). Statistical analysis was performed using the Mann-Whitney U test, Fisher's exact test or χ^2 test. OS rates were evaluated using the Kaplan-Meier method and the log-rank test.

Results

Baseline characteristics of enrolled patients. Table I presents the baseline characteristics of the patients in the present study. A total of 34 (63.0%) male patients and 20 (37.0%) female patients were enrolled. The median patient age was 72 years (range, 45-96). The median follow-up period was 469 days (range, 31-684). There were 20 patients (37.0%) with colorectal

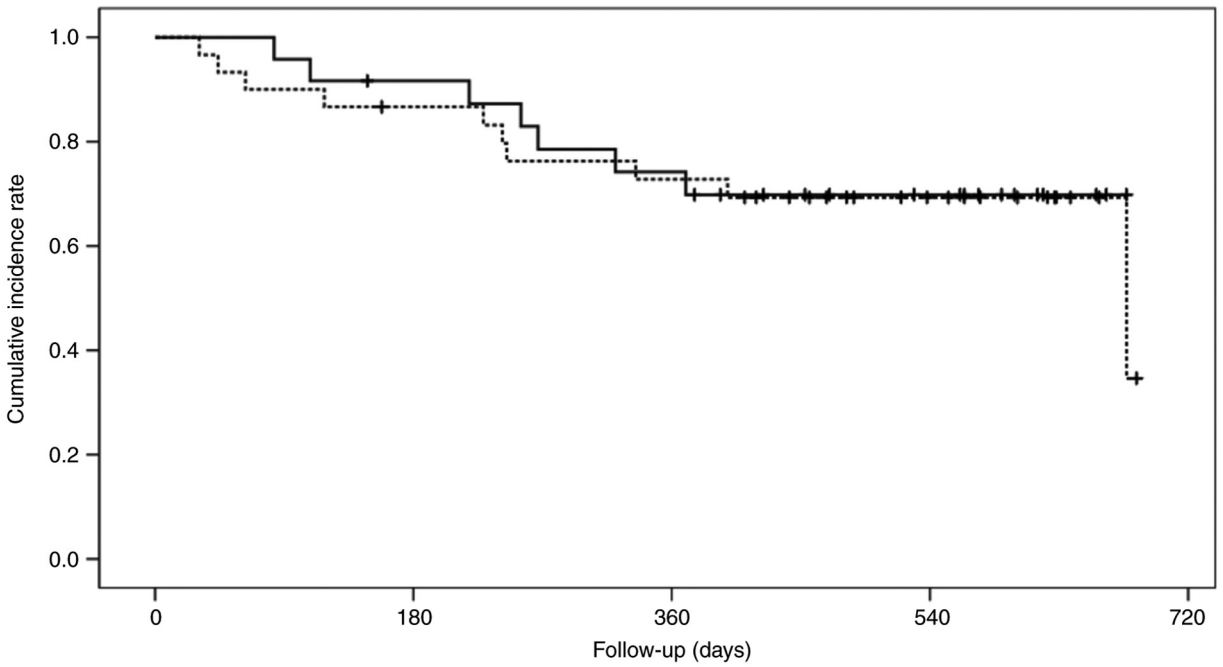

Figure 1. Overall survival of the low- and high-SMI groups. SMI, skeletal muscle index.

cancer, 12 (22.2%) with pancreatic cancer, 11 (20.4%) with gastric cancer, 6 (11.1%) with esophageal cancer, 4 (7.4%) with biliary tract cancer and 1 (1.9%) with liver cancer. A total of 31 patients (57.4%) were diagnosed with resectable cancer (resectable group) and 23 patients (42.6%) were diagnosed with unresectable or recurrent cancer (unresectable group). In the resectable group, 1 patient with gastric cancer refused surgery, resulting in chemotherapy, and 1 patient with gastric cancer received the best supportive care (BSC). Furthermore, 1 patient with esophageal cancer underwent chemoradiotherapy in addition to endoscopic submucosal dissection. In the resectable group, 2 patients died, 1 patient with gastric cancer receiving BSC died of pneumonia and 1 patient with gastric cancer undergoing surgery died of recurrent peritoneal dissemination. In the unresectable group, 18 patients (78.3%) underwent chemotherapy, 3 patients (13.0%) underwent chemoradiotherapy and 2 patients (8.7%) received BSC. The hemoglobin concentration was significantly higher in the unresectable group compared with the resectable group (13.1 vs. 11.9 g/dl; P=0.041). The CRP levels was also significantly higher in the unresectable group compared with the resectable group (1.11 vs. 0.19 mg/dl; P=0.033). Furthermore, the NLR was significantly higher in the unresectable group compared with the resectable group (4.59 vs. 2.61; P=0.001). However, no significant differences were demonstrated for SMI values between the unresectable and resectable group in both female and male patients. Furthermore, in female patients, the CXI was significantly lower in the unresectable group compared with the resectable group (5.08 vs. 12.05; P=0.025). However, in male patients, no significant difference in CXI was observed between the unresectable and resectable groups (5.48 vs. 11.19; P=0.068).

Clinical characteristics of the low- and high-SMI groups. Table II presents the clinical characteristics of the patients in the low- and high-SMI groups. Body mass index (BMI) was significantly lower in the low-SMI group compared with the high-SMI group (20.2 vs. 24.2; P<0.001). However, there were no significant differences in age, sex, primary tumor site, resectability, ALB or NLR between the two groups. Fig. 1 presents the OS of the low- and high-SMI groups. The cumulative 1-year OS rates in the low- and high-SMI groups were 72.8 and 74.2%, respectively (P=0.782).

Clinical characteristics of the low- and high-CXI groups. Table III presents the clinical characteristics of the patients in the low- and high-CXI groups. Using the medians, the low-CXI group was classified as patients with a CXI value <9.22 (male patients) or <6.24 (female patients), while the high-CXI group was classified as those with a CXI value ≥9.22 (male patients) or ≥6.24 (female patients). There were no significant differences in age, sex, primary tumor site or resectability between the two groups.

The ALB levels were significantly lower in the low-CXI group compared with the high-CXI group (3.8 vs. 4.0 g/dl; P=0.025), whilst the NLR was significantly higher in the low-CXI group compared with that in the high-CXI group (5.03 vs. 2.09; P<0.001). In male patients, the SMI was significantly lower in the low-CXI group compared with the high-CXI group (6.6 vs. 7.4; P=0.009). However, in female patients, no significant differences in SMI were observed between the low- and high-CXI groups (5.15 vs. 5.6; P=0.425). Additionally, WBC counts were significantly higher in the low-CXI group compared with the high-CXI group (6,930 vs. 5,590 WBC/μl; P=0.034) and CRP was also significantly higher in the low-CXI group compared with the high-CXI group (1.11 vs. 0.17 mg/dl; P=0.005). Fig. 2 shows the OS of the low- and high-CXI groups. The cumulative 1-year OS rate was significantly lower in the low-CXI group compared with the high-CXI groups (58.3 vs. 88.5%; P=0.012).

Table III. Clinical characteristics of the patients in the low-and high-cachexia index groups.[a]

Characteristic	Low-CXI group (n=27)	High-CXI group (n=27)	P-value
Age, years	74 (50-96)	71 (45-91)	0.709
Sex			1.000
Male	17 (63.0)	17 (63.0)	
Female	10 (37.0)	10 (37.0)	
ECOG-PS			0.100
0 or 1	21 (77.8)	26 (96.3)	
≥2	6 (22.2)	1 (3.7)	
BMI kg/m^2	21.0 (14.6-27.6)	21.8 (17.1-32.2)	0.416
Follow-up, days	399 (31-638)	564 (148-684)	0.002
Total mortalities	12 (44.4)	5 (18.5)	0.077
Primary tumor site			0.894
Colorectal cancer	9 (33.3)	11 (40.7)	
Pancreatic cancer	5 (18.6)	7 (25.9)	
Gastric cancer	6 (22.2)	5 (18.5)	
Esophageal cancer	4 (14.8)	2 (7.4)	
Biliary tract cancer	2 (7.4)	2 (7.4)	
Liver cancer	1 (3.7)	0 (0.0)	
Resectability			0.098
Resectable	12 (44.4)	19 (70.4)	
Unresectable	15 (55.6)	8 (29.6)	
WBC, /μl	6,930 (3,960-21,840)	5,590 (3,210-8,440)	0.034
Hb, g/dl	12.1 (8.7-15.8)	12.9 (8.3-15.1)	0.345
PLT, x10^3/μl	22.8 (11.9-51.9)	22.6 (12.0-43.6)	0.972
CRP, mg/dl	1.11 (0.02-14.10)	0.17 (0.02-2.35)	0.005
ALB, g/dl	3.8 (2.3-4.7)	4.0 (3.3-4.8)	0.025
NLR	5.03 (2.69-9.53)	2.09 (0.72-3.25)	<0.001
SMI, kg/m^2			
Male	6.6 (5.1-8.2)	7.4 (6.3-8.9)	0.009
Female	5.15 (4.60-8.80)	5.60 (5.20-6.60)	0.425
Body fat, %	24.9 (6.8-45.6)	23.6 (3.7-42.5)	0.802
ECW/TBW	0.395 (0.361-0.426)	0.391 (0.372-0.411)	0.197

[a]Data are presented as median (range) or n (%). CXI, cachexia index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; SMI, skeletal muscle index; ECW/TBW, extracellular water/total body water.

Discussion

In the present study, SMI and CXI values using BIA in patients with gastrointestinal cancer were assessed. The results demonstrated that the SMI had a lower impact on OS, whereas the CXI at diagnosis was closely associated OS in gastrointestinal cancer. Therefore, calculating CXI values using BIA may be valuable for predicting OS in patients with gastrointestinal cancer.

Cancer cachexia is closely related to advanced gastrointestinal cancer. The prevalence of cachexia is 88.9% in patients with advanced pancreatic cancer, 76.5% in those with advanced gastric cancer and 52.9% in those with advanced esophageal cancer (2). Cancer cachexia may reduce the effects of chemotherapy and increase chemotherapy-related toxicities, particularly in older patients with cancer (19). However, previous studies have reported that skeletal muscle loss at diagnosis may not influence the survival in advanced pancreatic cancer (5,20). Recently, the CXI has emerged as an improved prognostic index due to its ability to reflect systemic inflammation and nutritional status in addition to skeletal muscle mass, which are closely associated with cancer cachexia (3,21).

The CXI is frequently associated with the prognosis of patients with certain malignancies (6-14,16,22-24). Jafri *et al* (6) first established the CXI using the SMI calculated from CT images and reported that a lower CXI was associated with worse clinical outcomes of patients with metastatic non-small cell lung cancer. Thereafter, previous studies have reported that preoperative CXI may be a prognostic factor for OS (7-10).

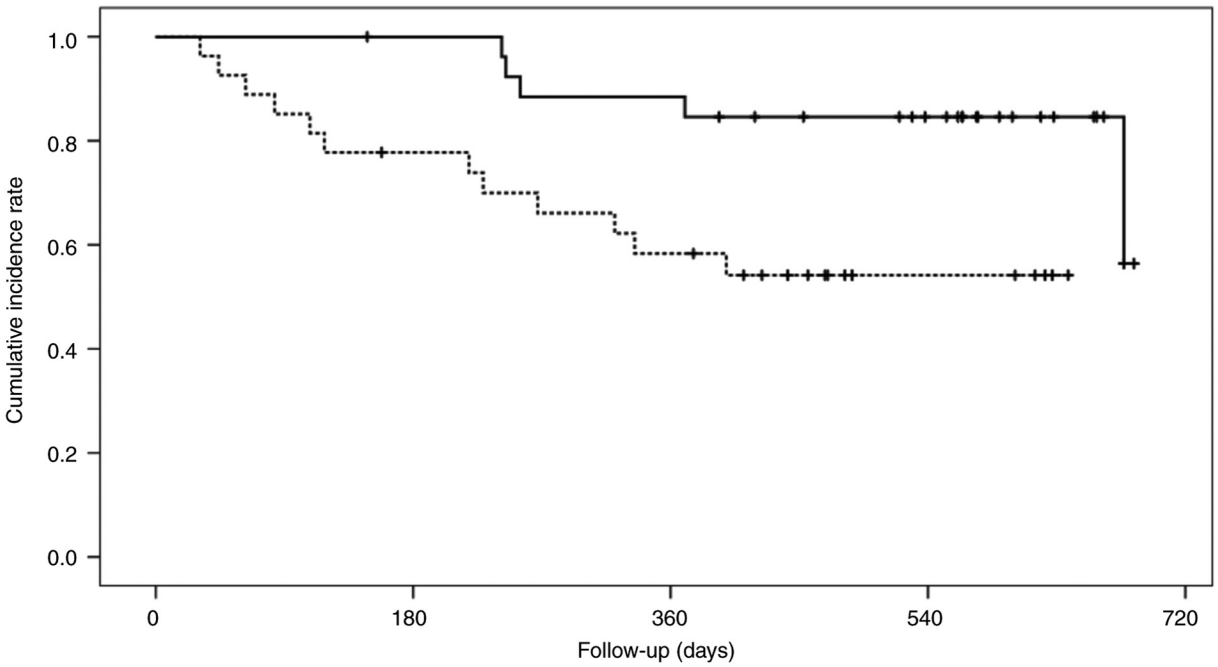

Figure 2. Overall survival of low- and high-CXI groups. CXI, cachexia index.

Furthermore, in patients with unresectable hepatocellular carcinoma and gastric cancer undergoing chemotherapy, the CXI may be a beneficial indicator to predict treatment response and prognosis (11,12). Although the progression or prognosis may differ among several gastrointestinal cancers, the CXI could be a pivotal factor influencing prognosis across gastrointestinal cancers. The present study included patients with resectable and unresectable different gastrointestinal cancers as a preliminary analysis due to the limited number of enrolled patients. Subsequently, the results demonstrated that the OS rate of patients in the low-CXI group was significantly lower compared with the high-CXI group. By contrast, no differences were reported for age, primary tumor site or resectability between the high- and low-CXI groups. Collectively, the data demonstrate that the CXI could be useful for predicting the prognosis of gastrointestinal cancer, regardless of the treatment strategy.

In previous reports, the SMI in the evaluation of CXI values was calculated by analyzing the skeletal muscle area at the L3 level on CT images (7-14); however, Okubo *et al* (16) reported that CXI calculations using BIA may be a prognostic indicator in elderly patients with non-Hodgkin's lymphoma. Notably, BIA is a cost-effective, quick and non-invasive method that does not involve radiation exposure. By contrast, a specialized software is required when calculating the SMI using CT images. In addition, BIA can provide other body composition data such as body fat percentage and ECW/TBW. Collectively, BIA is an attractive and accurate modality for measuring CXI or sarcopenia (15,25). The findings of the present study also suggest that CXI calculations using BIA could be an acceptable prognostic indicator of gastrointestinal cancer. However, in patients with significant ascites or edema, the SMI can be overestimated using the BIA method (26). Moreover, BIA cannot be performed in patients with a lower performance status, as it requires maintaining a standing position for a few minutes (16).

The present study has certain limitations. Firstly, the present study was a retrospective, single-center analysis with a limited number of cases, which introduced the possibility of selection bias. Secondly, the observation period was short and the number of patients in the resectable group who experienced relapse or mortality was too small to determine the clinical significance. Therefore, a larger prospective study with a longer follow-up period is necessary in the future. Thirdly, the results of the present study cannot be easily generalized to all types of gastrointestinal cancer, as the primary tumor sites, patterns of tumor progression and treatment modalities can vary widely.

Overall, the present study demonstrated that CXI values determined using BIA may predict survival in patients with gastrointestinal cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NI, KoO and JS contributed to the study's conception and design. Collection and assembly of data were performed by TOh, NI, KoO, KeO, HS, TTs, TOk and JS. Data analysis and interpretation were performed by TOh, NI, KoO, JS, TD, KI,

OD and MM. TOh and NI drafted the manuscript. KK, NY, KY, KU, TI, TTa, HK and YI revised the manuscript. TTs, TOk and JS confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committee of Fukuchiyama City Hospital (Kyoto, Japan; approval no. 5-57). The opt-out method was used to obtain informed consent due to the retrospective design of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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