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Prognostic Value of the Modified Cachexia Index in Colorectal Cancer Patients Undergoing Curative Surgery

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Abstract. *Background/Aim: The cachexia index (CXI) has been reported to be a useful indicator for predicting the prognosis of cancer patients. However, CXI calculation requires skeletal muscle index (SMI) measurements, which involves an analysis of computed tomography images using an imaging software program, which makes the calculation process highly complex and time-consuming. Recently, the modified cachexia index (mCXI), calculated using the urea-to-creatinine ratio (UCR) instead of SMI, has been reported to be a useful marker that is easier to calculate than CXI. This study aimed to evaluate the correlation between mCXI and the prognosis of patients with colorectal cancer (CRC). Patients and Methods: A total of 291 patients who underwent curative surgery for stage I-III CRC were enrolled. mCXI was calculated as the serum albumin concentration/neutrophil-to-lymphocyte ratio (NLR)/UCR. A receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value of the mCXI for predicting prognosis. Results: The median mCXI was 0.089 (range=0.012-0.354). The ROC curve analysis revealed that the appropriate cut-off value for mCXI was 0.113. The low mCXI group had significantly shorter relapse-free and overall survival rates than the high mCXI group (p=0.030 and p=0.014, respectively). Conclusion: mCXI, which does not require an image analysis, may be closely associated with prognosis in patients undergoing curative surgery for CRC.*

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Colorectal cancer (CRC) is the third most common cancer type worldwide, with more than 1.9 million cases annually, and the second leading cause of cancer-related deaths, resulting in more than 900,000 deaths each year (1). The risk of CRC recurrence is commonly assessed using the TNM classification, which is based on the pathological findings of resected specimens (2). However, previous studies have reported that, in addition to tumor-related factors, host-related factors also affect the prognosis of CRC (3-6).

Cachexia is a key host-related factor and an independent predictor of prognosis in cancer patients (7, 8). The prevalence of cachexia is relatively high, at approximately 50%, in patients with CRC (9, 10). Cachexia can also occur in patients who undergo curative surgery for CRC (11, 12). Therefore, screening for cachexia before treatment is important for risk stratification in patients with CRC.

Nonetheless, there are limited objective methods to evaluate cachexia. Although definitions and classifications have been proposed by Fearon *et al*., the diagnostic criteria for pre-cachexia remain ambiguous (13). In recent years, Jafri *et al*. proposed a scoring system for cachexia and the cachexia index (CXI) (14). The CXI was calculated as skeletal muscle index (SMI) × serum albumin concentration/neutrophil-to-lymphocyte ratio (NLR). Wan *et al*. reported that the CXI was superior to the Fearon criteria (weight loss >5% over the past six months; or BMI <20 and any degree of weight loss >2%; or sarcopenia and any degree of weight loss >2%) in predicting overall survival and could be a useful prognostic indicator in patients with stage I-III CRC (10, 13). However, calculating CXI requires the measurement of SMI, which must be analyzed on computed tomography (CT) images obtained before treatment using an imaging software program, making the calculation process highly complex and time-consuming.

We focused on the urea-to-creatinine ratio (UCR), which has been reported to be correlated with skeletal muscle mass

(15). Replacing SMI with UCR when calculating the CXI may allow for a simple assessment of cachexia using blood test data that are routinely measured in daily clinical practice. In the present study, we evaluated the clinical impact of a modified cachexia index (mCXI), which was calculated by dividing serum albumin concentration by both NLR and UCR, as a marker for predicting the prognosis of patients who underwent curative surgery for CRC.

Patients and Methods

Patients. We retrospectively evaluated 291 consecutive patients who underwent curative surgery for stage I-III CRC at the Department of Gastroenterological Surgery of Osaka City University Hospital between January 2017 and December 2019. This retrospective study was approved by the Ethics Committee of Osaka City University (approval number: 4182) and was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent for the treatment and data analysis.

Methods. The patients routinely underwent blood tests before surgery. mCXI was calculated as follows: [serum albumin concentration (g/dl)]/[NLR×UCR]. NLR was defined as the neutrophil-to-lymphocyte ratio (ratio of counts in mm^3). UCR was defined as the urea:creatinine ratio (ratio of concentrations in mg/dl). An appropriate cutoff value for mCXI was determined by a receiver operating characteristic (ROC) curve analysis, and the patients were then categorized into low and high mCXI groups. The associations between mCXI and the clinicopathological factors were analyzed using a chi-squared test or Fisher's exact test. Relapse-free survival was defined as the time from the date of operation until the date of the diagnosis of the first recurrence, death from any cause, or the last follow-up examination. Overall survival was defined as the time from the date of operation until the date of death from any cause or the last follow-up examination. Survival curves were estimated using the Kaplan–Meier method with a log-rank test. We used a multivariate Cox proportional hazards model to investigate the prognostic factors associated with survival. Variables with a *p*-Value of <0.1 in a univariate analysis were further analyzed using a multivariate analysis. Statistical significance was set at $p<0.05$.

Statistical analysis. All analyses were conducted using the IBM SPSS Statistics software program for Windows (ver. 26; IBM Corp., Armonk, NY, USA) and EZR on the R commander software program (ver. 1.55; Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

The study population included 167 men and 124 women with a median age of 71 years (range=27-100 years). The median mCXI was 0.089 (range=0.012-0.354). The median follow-up period was 44.6 months. Forty patients (19.8%) relapsed, and 28 patients (14.6%) died during the follow-up period.

Classification according to the mCXI. mCXI, as a continuous variable, was used as the test variable, and the 5-year survival was used as the state variable. A ROC curve analysis showed that the appropriate cutoff value for the mCXI was 0.113 (sensitivity: 85.7%, specificity: 42.6%) (Figure 1). Based on these cutoff values, 192 and 99 patients had low and high mCXI, respectively.

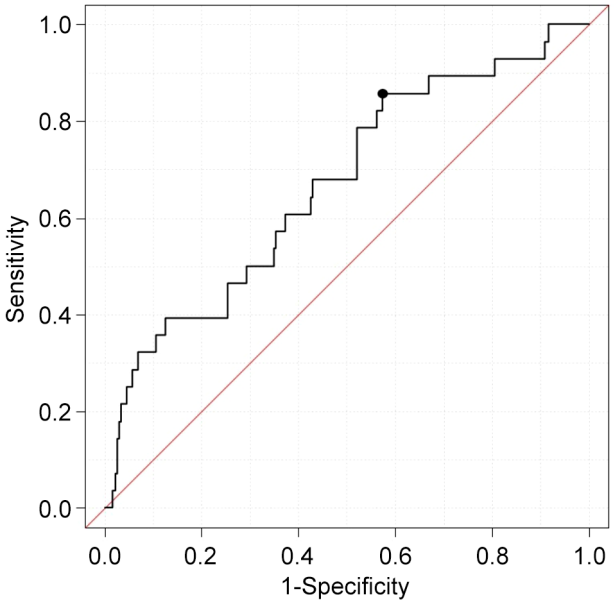

Figure 1. *A receiver operating characteristic (ROC) curve of the modified cachexia index (mCXI) for predicting death. Area under the curve (AUC): 0.668; 95% confidence interval=0.559-0.777.*

Associations between the mCXI and clinicopathological factors. Table I shows the association between the mCXI levels and clinicopathological factors. A low mCXI was significantly associated with female sex, age ≥75 years, and tumors located on the left side, relative to a high mCXI. In both groups, 22% of the patients experienced an ongoing weight loss of >2%. Twenty-seven patients (9.3%) did not know whether or not their weights had changed.

Results of a survival analysis according to the mCXI. The relapse-free and overall survival rates were significantly shorter in patients with low mCXI than in those with high mCXI ($p=0.030$ and $p=0.014$, respectively) (Figure 2).

Prognostic factors for the relapse-free/overall survival identified by univariate and multivariate analyses. Table II shows the associations between relapse-free survival and various clinicopathological factors. In the univariate analysis, relapse-free survival was significantly associated with tumor depth, lymph node metastasis, serum CEA concentration, and mCXI. In the multivariate analysis, higher T stage (T4), presence of lymph node metastasis, and low mCXI were independent and significant predictors of poor relapse-free survival. Table III

Table I. *Associations between the modified cachexia index (mCXI) and clinicopathological factors.*

Factors		Low mCXI group (n=192)	High mCXI group (n=99)	*p*-Value
Sex, n	Male	97	70	
	Female	95	29	0.001
Age (years), n	<75	112	72	
	≥75	80	27	0.021
Location of the tumor, n	Right side	76	27	
	Left side	116	72	0.039
Histological type, n	Well-/moderately differentiated	179	94	
	Poorly differentiated, Mucinous, Signet	13	5	0.798
Tumor diameter (cm), n	<5	126	72	
	≥5	66	27	0.235
Depth of tumor, n	T1-3	180	95	
	T4	12	4	0.590
The number of harvested lymph nodes, n	<12	58	30	
	≥12	134	69	>0.999
Lymph node metastasis, n	Negative	139	78	
	Positive	53	21	0.258
Serum CEA concentration (ng/ml), n	≤5.0	129	73	
	>5.0	63	26	0.284
Body weight loss (%), n	≤2	128	71	
	>2	43	22	0.881
	Unknown	21	6	

CEA: Carcinoembryonic antigen.

shows the association between overall survival and various clinicopathological factors. In a univariate analysis, overall survival was significantly associated with tumor depth, serum CEA concentration, and mCXI. In the multivariate analysis, age ≥75 years, higher T stage (T4), and low mCXI were independent and significant predictors of poor overall survival.

Discussion

In the present study, correlations were found between mCXI and long-term survival outcomes after curative surgery in patients with stage I-III CRC. This is consistent with previous studies reporting that cachexia status, based on CXI, was correlated with prognosis in patients who underwent curative surgery for CRC (10). Cancer cachexia was defined by the European Palliative Care Research Collaborative (EPCRC) as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without a loss of fat mass) that cannot be fully reversed by conventional nutritional support and which leads to progressive functional impairment (13). Cancer cachexia is classified into three stages: pre-cachexia, cachexia, and refractory cachexia. Pre-cachexia is the first stage prior to the onset of cachexia, characterized by anorexia and metabolic changes, despite weight loss of less than 5% over the past six months. Cachexia is the second stage and is characterized by systemic inflammation and a low food intake. The diagnostic criteria for cachexia, known as the Fearon criteria, are met if any of the following factors are present: (i) >5% loss of stable body weight over the past six months, (ii) body mass index (BMI) <20 kg/m^2 and ongoing weight loss >2%, or (iii) sarcopenia and ongoing weight loss >2%. Refractory cachexia is a more advanced stage of cachexia, and in such a situation, resistance to anticancer treatment is emerging. Refractory cachexia is a terminal stage that occurs when the individual has <3 months to live. Therapeutic interventions during the refractory cachexia stage are primarily focused on palliative care. The diagnostic criteria established by the EPCRC are widely recognized for cancer cachexia. However, the criteria for pre-cachexia are limited to clinical features, making objective assessment difficult. Furthermore, some patients lacked an awareness of their own weight. In this study, information on whether or not weight loss occurred was unavailable in 9.3% of the patients. In contrast, mCXI is an objective marker calculated from blood test data, including serum albumin concentration, NLR, and CUR. The proportion of patients with a >2% ongoing weight loss, as described in the Fearon criteria, was equivalent between the low and high mCXI groups. Therefore, weight loss may be insufficient to accurately assess cachexia, whereas mCXI could serve as a more clear-cut and useful index for the assessment of cachexia. Moreover, mCXI may be suitable for monitoring the status of cachexia during nutritional interventions.

In the present study, we used UCR as an indicator of skeletal muscle mass instead of SMI, which was used to

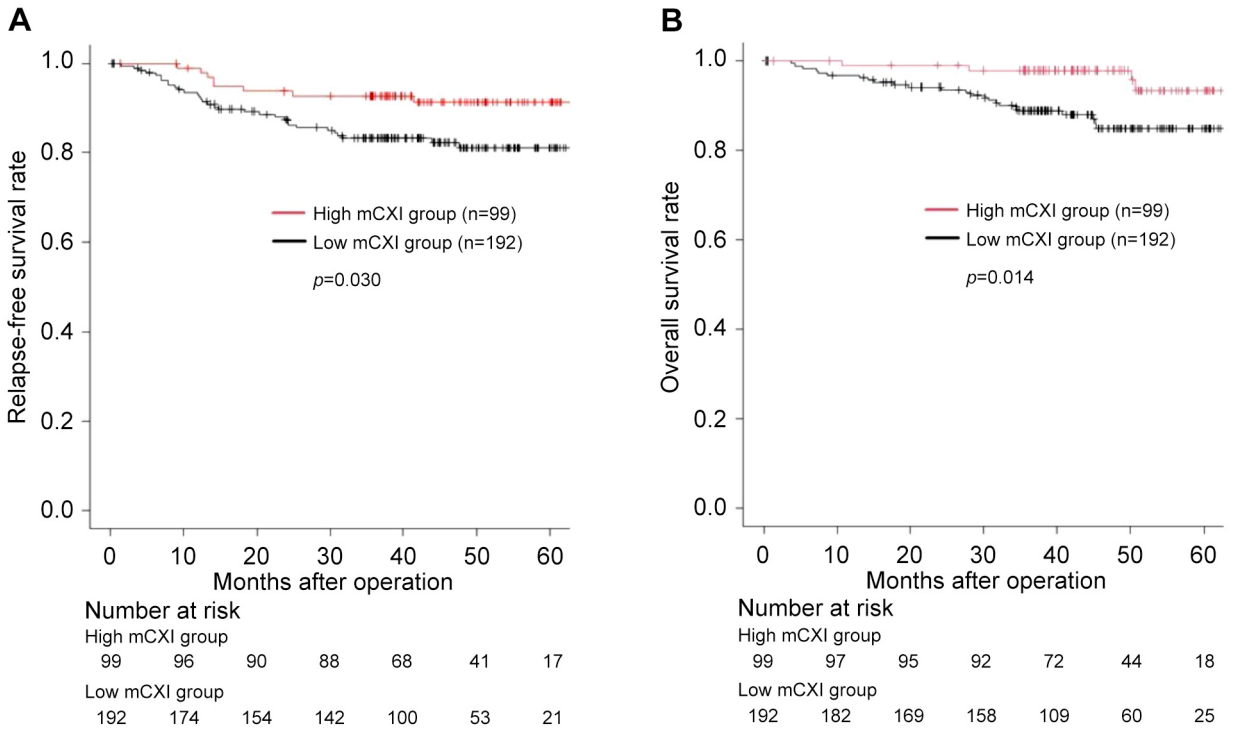

Figure 2. *Kaplan–Meier survival curves for the relapse-free survival rate (A) and overall survival rate (B) according to the modified cachexia index (mCXI).*

calculate the original CXI. Creatine, a precursor of creatinine, is a nitrogenous organic acid that is naturally present in vertebrates and which contributes to the supply of energy to muscle cells. Since approximately 95% of the human body's total creatine is located in skeletal muscle, the serum creatinine concentration and intramuscular creatine concentrations are closely linked (16, 17). A study by Haines *et al*. demonstrated that the UCR has lower sensitivity to factors unrelated to muscle atrophy, making it more suitable for reflecting the skeletal muscle mass (15, 18). An elevated UCR may reflect a combination of muscle catabolism/altered protein homeostasis, muscle bioenergetic failure, and persistent muscle wasting, representing a metabolic signature of the effects of prolonged critical illness (15, 19-21). Because the UCR is not only closely correlated with skeletal muscle mass but also easily calculated based on blood test data that are routinely measured in daily clinical practice, it could be useful as a surrogate marker for skeletal muscle mass.

Multivariate analyses revealed that the mCXI is an independent prognostic predictor after curative surgery in patients with stage I-III CRC, and host-related factors, as well as tumor-related factors, significantly affect the prognosis of CRC, which is consistent with previous reports (3, 5, 6). Cachexia is characterized by skeletal muscle wasting resulting from a complex combination of increased catabolism owing to metabolic changes and reduced energy intake caused by anorexia (22, 23). In cancer patients, systemic inflammation occurs because of the interaction between the tumor and the host. Activation of inflammatory cytokines, including IL-1, IL-6 and TNF-α, accelerates skeletal muscle degradation via various biological responses associated with inflammation (24, 25). Moreover, proteolysis-inducing factor (PIF), which is secreted by cancer cells, inhibits protein synthesis in skeletal muscles, leading to a reduction in skeletal muscle mass (22). Additionally, anorexia associated with cancer itself can lead to skeletal muscle wasting, which suppresses antitumor immunity (26, 27). Furthermore, systemic inflammation creates a microenvironment conducive to metastasis and growth of cancer cells through cytokines and chemokines, ultimately facilitating micrometastasis (6, 28, 29). Owing to these mechanisms, mCXI, which is determined from the skeletal muscle mass and inflammatory markers, may be correlated with the long-term prognosis after curative surgery in patients with CRC.

Study limitations. First, this was a retrospective study with a small cohort from a single center. Second, the cutoff value of mCXI used in this study was a provisional value calculated from the analyzed population. A large prospective study should be conducted to support our findings and establish an appropriate cutoff value. Third, the serum creatinine concentration, which serves as an index of skeletal muscle index, is susceptible to impairment of the renal

Table II. *Univariate and multivariate Cox regression analyses for relapse-free survival in the overall patient cohort.*

	Univariate			Multivariate		
	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Sex (Female *vs*. Male)	1.024	0.579-1.812	0.935			
Age (≥75 *vs*. <75 years)	1.473	0.832-2.607	0.183			
Location of the tumor (Right *vs*. Left side)	0.808	0.439-1.488	0.494			
Histological type (Poorly, Mucinous, Signet *vs*. Well, Moderately)	0.975	0.303-3.138	0.966			
Tumor diameter (>5 *vs*. ≤5 cm)	1.093	0.599-1.911	0.773			
Depth of tumor (T4 *vs*. T1-3)	6.619	3.196-13.708	<0.001	4.192	1.805-9.732	0.001
The number of harvested lymph nodes (<12 *vs*. ≥12)	0.860	0.455-1.626	0.643			
Lymph node metastasis (Positive *vs*. Negative)	2.922	1.655-5.157	<0.001	2.109	1.149-3.870	0.016
Serum CEA concentration (>5.0 *vs*. ≤5.0 ng/ml)	2.171	1.230-3.831	0.007	1.476	0.787-2.767	0.225
mCXI (<0.113 *vs*. ≥0.113)	2.890	1.352-6.177	0.006	2.833	1.321-6.076	0.007

CI: Confidence interval; CEA: carcinoembryonic antigen; mCXI: modified cachexia index.

Table III. *Univariate and multivariate Cox regression analyses for overall survival in the overall patient cohort.*

	Univariate			Multivariate		
	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Sex (Female *vs*. Male)	0.702	0.324-1.521	0.370			
Age (≥75 *vs*. <75 years)	2.029	0.965-4.266	0.062	2.184	1.013-4.710	0.046
Location of the tumor (Right *vs*. Left side)	0.730	0.322-1.658	0.452			
Histological type (Poorly, Mucinous, Signet *vs*. Well, Moderately)	1.176	0.279-4.957	0.825			
Tumor diameter (>5 *vs*. ≤5 cm)	0.699	0.297-1.644	0.412			
Depth of tumor (T4 *vs*. T1-3)	7.120	2.877-17.618	<0.001	6.331	2.204-18.190	0.001
The number of harvested lymph nodes (<12 *vs*. ≥12)	1.114	0.504-2.462	0.790			
Lymph node metastasis (Positive *vs*. Negative)	2.092	0.979-4.470	0.057	1.581	0.714-3.502	0.259
Serum CEA concentration (>5.0 *vs*. ≤5.0 ng/ml)	2.139	1.018-4.495	0.045	1.358	0.582-3.171	0.479
mCXI (<0.113 *vs*. ≥0.113)	3.498	1.213-10.088	0.021	3.075	1.046-9.042	0.041

CI: Confidence interval; CEA: carcinoembryonic antigen; mCXI: modified cachexia index.

function (18). Hence, its usefulness as a biomarker of muscle metabolism is limited in cases of renal dysfunction.

In conclusion, mCXI, which is calculated solely from routinely measured blood test data in daily clinical practice without the need for a CT image analysis, may be a useful marker for cachexia that sensitively reflects the prognosis after curative surgery in patients with CRC. Additionally, mCXI may be useful for monitoring cachexia in daily clinical practice.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

TN and MS designed the study, performed statistical analysis, and drafted the manuscript. HT, YS, SK, HK, TF, and KM collected clinical data and critically reviewed the manuscript.

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