Original Article

Computed Tomography–Determined Sarcopenia Is a Useful Imaging Biomarker for Predicting Postoperative Outcomes in Elderly Colorectal Cancer Patients

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Purpose

This study aimed to establish whether computed tomography (CT)–determined sarcopenia is a useful imaging biomarker for postoperative outcome in elderly colorectal cancer (CRC) patients, and construct sarcopenia-based nomograms to predict individual outcomes after surgery.

Materials and Methods

CT imaging data of 298 elderly CRC patients who underwent surgery in 2012-2014 were retrospectively analyzed. Skeletal muscle mass was determined by CT, and sarcopenia was diagnosed based on the optimal cutoff value determined by X-tile program. The correlation between sarcopenia and risk of preoperative nutrition and postoperative complications was evaluated. A Cox proportional hazards model was used to determine survival predictors. Sarcopenia-based nomograms were developed based on multivariate analysis, and calibrated using concordance index and calibration curves.

Results

A total 132 patients (44.3%) had sarcopenia based on the optimum cutoff values (29.9 cm²/m² for women and 49.5 cm²/m² for men). Sarcopenia was an independent risk factor for preoperative nutrition (p < 0.001; odds ratio [OR], 3.405; 95% confidence interval [CI], 1.948 to 5.954) and postoperative complications (p=0.008; OR, 2.192; 95% CI, 1.231 to 3.903). Sarcopenia was an independent predictor for poor progression-free survival (p < 0.001; hazard ratio [HR], 2.175; 95% CI, 1.489 to 3.179) and overall survival (p < 0.001; HR, 2.524; 95% CI, 1.721 to 3.703). Based on multivariate analysis, we produced four nomograms that had better predictive performance.

Conclusion

CT-determined sarcopenia is a useful imaging biomarker for predicting preoperative nutritional risk, postoperative complications, and long-term outcomes in elderly CRC patients. The sarcopenia-based nomograms can provide a scientific basis for guiding therapeutic schedule and follow-up strategies.

Introduction

Colorectal cancer (CRC) is one of the malignancies with the highest morbidity and mortality worldwide. According to Global Cancer Epidemiological Statistics (GLOBOCAN) 2018, there are about 1.8 million new cases and 881,000 cancer-related deaths worldwide, with the third highest incidence and second highest mortality rate worldwide, which accounts for about one tenth of all cancer cases and deaths [1]. In China, CRC has high morbidity and mortality rates and is one of the five most common tumors and one of the fourth most fatal tumors [2]. As the prevalence of CRC increases with age, the proportion of elderly CRC patients

gradually increases with the acceleration of population aging [3]. According to the Surveillance, Epidemiology, and End Results database, approximately 70% of CRC patients are aged > 65 years and about 40% are > 75 years old. Although there has been a significant improvement in follow-up and treatment strategies for CRC, overall survival (OS) in elderly CRC patients remains low [4,5]. Surgery is still a powerful tool for treating CRC, but treatment of elderly patients can be challenging. These patients have a higher incidence of post-treatment complications and mortality [6]. In addition, they are also reported to be at risk of functional decline after treatment, with an incidence of > 60% in elderly patients [7]. Therefore, the prognostic assessment of elderly CRC patients is critical for guiding therapeutic schedule and follow-up strategies.

Recently, there has been increasing evidence that the gradual decline in nutrition and function is associated with disease progression and is one of the leading causes of poor treatment outcomes. Sarcopenia, as an objective nutrient assessment index independent of body mass index (BMI), is of increasing concern. Sarcopenia is a progressive and pervasive disease that is characterized by reduced skeletal muscle mass and function throughout the body, reduced physical ability, decreased quality of life, and increased risk of adverse events such as death [8]. Sarcopenia was first proposed by Rosenberg in 1989 [9]. It is worth noting that systemic inflammation is reported to be a risk factor for muscle loss, and muscle loss may be a useful external marker of systemic inflammatory response. Wallengren et al. [10] found that high NLR was associated with lower muscle mass. Malietzis et al. [11] found that patients with elevated C-reactive protein had increased muscle loss and that muscle loss was accelerated. Skeletal muscle mass reduction measured on computed tomography (CT) is considered the gold standard in diagnosing sarcopenia [12]. There is increasing evidence that preoperative CT-determined sarcopenia is associated with postoperative adverse short-term and long-term outcomes in CRC patients [13,14]. Most of the current research on sarcopenia in CRC is based on the general population. There are still no clear guidelines for treatment decisions in elderly CRC patients. Compared with general patients, elderly CRC patients are more susceptible to sarcopenia due to both cancer invasion and body aging. Thus, it is imprecise to infer the results from the general population to older patients who have sarcopenic changes due to aging and cancer.

Therefore, this study retrospectively analyzed the medical history of elderly CRC patients to explore the relationship of CT-determined sarcopenia with muscle loss and preoperative nutritional risk, postoperative complications and long-term prognosis in elderly CRC patients.

Materials and Methods

1. Patients

This retrospective study included data from the hospital records of 670 consecutive patients who underwent surgery for CRC at the First Affiliated Hospital of Guangxi Medical University, Nanning, China, between January 2012 and December 2014. We excluded eight patients were lost during follow-up, 342 patients aged < 60 years when they underwent CRC resection, and 22 patients were not available for measurement of the area of skeletal muscle in the third lumbar spine by preoperative abdominal CT. In total, 298 elderly CRC patients were eligible for the study (Fig. 1). All patients included in this study did not receive preoperative chemoradiotherapy, and 118 patients received postoperative chemoradiotherapy.

2. Survival follow-up

Postoperative follow-up was performed every 3 months within 2 years after surgery and then every 3-6 months thereafter. The final follow-up visit occurred on September 1, 2019. The follow-up mainly included contacting the patient by telephone and investigating the patient in the clinic. The follow-up plan included physical examination, laboratory examination (tumor markers, blood routine, liver function test, kidney function test, etc.), imaging examination (flat, CT and magnetic resonance imaging) and endoscopy. Progression-free survival (PFS) was determined as the duration between surgery and recurrence, death, or last follow-up. OS was determined as the duration between surgery and death or last follow-up.

3. Data extraction

The data collected included the following: general patient information, including sex, age, BMI (low, < 18.5; normal, ≥ 18.5 and < 24; and high, 24), Nutrition Risk Screening 2002 (NRS-2002), American Society of Anesthesiologists (ASA) grade, Surgical method, and postoperative chemoradiotherapy; preoperative blood tests, including serum carcinoembryonic antigen (CEA) (normal, < 5 ng/mL), lymphocyte counts and serum albumin concentration (< 35 g/L was defined as hypoproteinemia); clinicopathological factors, including tumor location, pathological tumor stage (pT category), pathological node stage (pN category), preoperative metastasis, pathological tumor-node-metastasis stage (pTNM stage), tumor perineural/vascular invasion, tumor differentiation, tumor pathological type, and tumor size; postoperative outcomes, including postoperative complications, Cla-
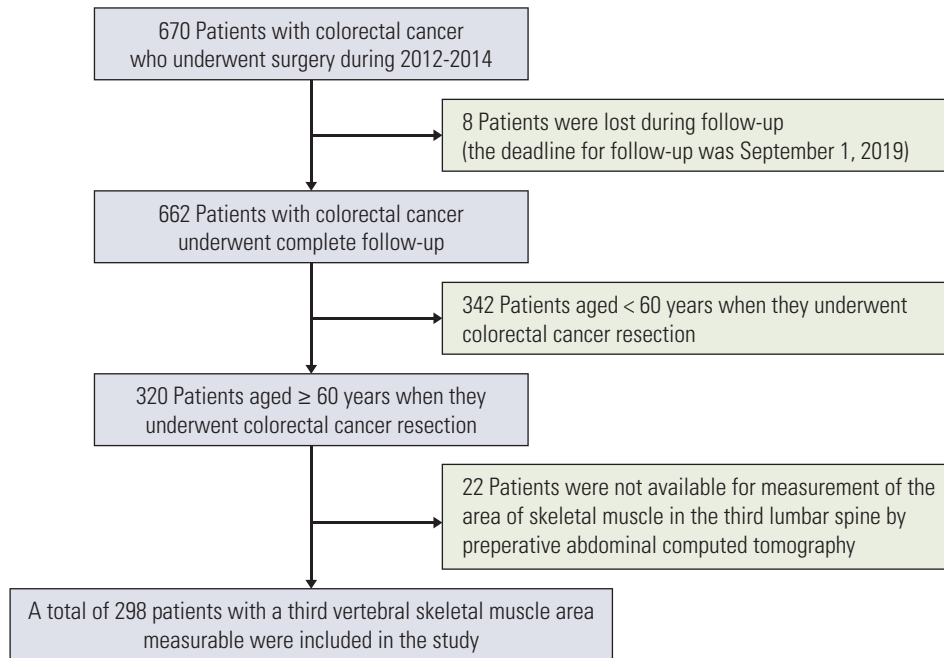
Fig. 1. The process of patients' inclusion and exclusion in elderly colorectal cancer patients.

vien-Dindo classification [15], length of hospital stays, PFS, and OS.

4. Definition of skeletal muscle mass

Abdominal CT was taken within 1 month before surgery. We selected a cross-sectional CT image of the third lumbar vertebra (L3) to estimate muscle mass and adjusted the CT threshold range from –29 to 150 HU to separate skeletal muscle from other tissues. Psoas major, erector spine, quadratus psoas, transverse abdominis, internal and external oblique muscles, and rectus abdominis in the L3 region were measured. Then, referring to the BMI, the L3 muscle cross-sectional area calculated for each image was normalized by the square of the patient's height (m^2), and the skeletal muscle index (SMI, cm^2/m^2) was obtained [16].

5. Statistical analysis

The X-tile program [17] was used to determine the cutoff values of SMI for male and female patients, respectively. The chi-square test or t test was used to compare clinical variables. Kaplan-Meier analysis with the logarithmic rank test was used to construct a survival curve. Cox proportional hazards analysis was used to determine the prognostic factors of PFS and OS. Factors that were significant in multivariate analysis were used for nomograms, and the concordance

index (C-index) and calibration curves were used to evaluate the accuracy of the nomograms. Statistical analysis was performed using IBM SPSS ver. 24.0 (IBM Corp., Armonk, NY) and R software ver. 3.5.3 (http://www.r-project.org). A two-tailed value of $p < 0.05$ was considered to be statistically significant.

6. Ethical statement

This research was approved by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University of China and strictly complied with the provisions of the Helsinki Declaration (approval number: 2019 (KY-E-022)). All patients in this research have signed informed consent.

Results

1. Clinicopathological factors

Sex-specific cutoff values for SMI associated with OS were 29.9 cm^2/m^2 for women and 49.5 cm^2/m^2 for men. Using these cutoff values, 44.3% of patients were found to have sarcopenia. The clinicopathological features of the 298 elderly CRC patients are shown in Table 1. There were 197 (66.1%)

Table 1. The relationships between the sarcopenic and clinicopathological factors of elderly colorectal cancer patients

Feature	Case (n=298)	Sarcopenic (n=132)	Nonsarcopenic (n=166)	X/t	p-value
Sex (male/female)	197 (66.1)/101 (33.9)	119 (90.2)/13 (9.8)	78 (47.0)/88 (53.0)	61.143	< 0.001
Age (yr)	68.46±6.67	70.14±7.434	67.13±5.67	3.846	< 0.001
ALB (g/L)	35.81±4.12	34.81±4.26	36.60±3.84	-3.819	< 0.001
BMI (kg/m²)	22.10±6.67	20.43±3.23	23.42±3.01	-8.220	<0.001
NRS2002 (non-malnutrition/malnutrition)	185 (62.1)/113 (37.9)	57 (43.2)/75 (56.8)	128 (77.1)/38 (22.9)	35.953	< 0.001
ASA grade (I-II/III-IV)	141 (47.3)/157 (52.7)	62 (47.0)/70 (53.0)	79 (47.6)/87 (52.4)	0.011	0.915
pT category (T1-2/T3-4)	88 (29.5)/210 (70.5)	42 (31.8)/90 (68.2)	46 (27.7)/120 (72.3)	0.596	0.440
pN category (N0/N1/N2)	178 (59.3)/79 (26.5)/41 (14.2)	84 (63.6)/33 (25.0)/15 (11.4)	94 (56.6)/46 (27.7)/26 (15.7)	1.796	0.407
Preoperative metastasis (no/yes)	273 (91.6)/25 (8.4)	122 (92.4)/10 (7.6)	151 (91.0)/15 (9.0)	0.204	0.651
Tumor location (colon/rectal)	146 (49.0)/152 (51.0)	69 (52.3)/63 (47.7)	77 (46.4)/89 (53.6)	1.020	0.313
Tumor size (cm)	4.91±2.04	5.00±2.19	4.84±1.92	0.683	0.495
Perineural/vascular invasion (negative/positive)	245 (82.2)/53 (17.8)	112 (84.8)/20 (15.2)	133 (80.1)/33 (19.9)	1.124	0.289
Pathological type (protrude/infiltrating/ulcerative)	67 (22.5)/36 (12.1)/195 (65.4)	36 (27.3)/13 (9.8)/83 (62.9)	31 (18.7)/23 (13.9)/112 (67.4)	3.632	0.163
Differentiation (poor/medium and high)	21 (7.0)/277 (93.0)	6 (4.5)/126 (95.5)	15 (9.0)/151 (91.0)	2.264	0.132
CEA (normal/high)	165 (55.4)/133 (44.6)	75 (56.8)/57 (43.2)	90 (54.2)/76 (45.8)	0.201	0.654
Hospital stays (day)	14.69±7.45	15.25±7.74	14.25±7.20	1.148	0.252
Total complications	66 (22.1)	39 (13.1)	27 (9.1)	11.400	0.001
Clavien-Dindo classification grade I	23 (7.7)	13 (4.4)	10 (3.4)	1.510	0.219
Clavien-Dindo classification grade II	34 (11.4)	20 (6.7)	14 (4.7)	3.283	0.070
Clavien-Dindo classification grade III	3 (1.0)	2 (0.7)	1 (0.3)	0.615	0.433
Clavien-Dindo classification grade IV	6 (2.0)	4 (1.3)	2 (0.7)	1.242	0.265

Values are presented as number (%) or mean±standard deviation. ALB, albumin; BMI, body mass index; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen.

Table 2. Univariate and multivariate logistic regression analysis of factors associated with malnutrition in elderly CRC

Feature	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female sex	0.920 (0.560-1.512)	0.743	-	-
Age (≥ 70 yr)	1.537 (0.951-2.483)	0.079	-	-
ALB (≥ 35 g/L)	0.319 (0.195-0.520)	< 0.001	0.418 (0.244-0.716)	0.001
BMI		< 0.001		0.037
Low	1.000		1.000	
Normal	0.233 (0.115-0.472)	< 0.001	0.381 (0.179-0.813)	0.013
High	0.164 (0.075-0.359)	< 0.001	0.390 (0.162-0.938)	0.036
Sarcopenia (no)	4.142 (2.515-6.823)	< 0.001	3.405 (1.948-5.954)	< 0.001
ASA grade (I-II/ III-IV)	0.688 (0.430-1.101)	0.119	-	-
pT category (T3-4)	0.895 (0.537-1.491)	0.670	-	-
pN category		0.673		
N0	1.000		-	-
N1	0.783 (0.450-1.361)	0.385	-	-
N2	0.869 (0.431-1.756)	0.696	-	-
Preoperative metastasis (yes)	2.237 (0.978-5.116)	0.056	-	-
Tumor location (colon/rectal)	1.462 (0.913-2.339)	0.114	-	-
Tumor size (< 5 cm/≥ 5 cm)	1.694 (1.031-2.784)	0.038	1.505 (0.856-2.645)	0.155
Perineural/Vascular invasion (positive)	0.733 (0.390-1.378)	0.335	-	-
Pathological type		0.590		
Protrude	1.000		-	
Infiltrating	0.741 (0.322-1.706)	0.481	-	-
Ulcerative	0.750 (0.427-1.319)	0.318	-	-
Differentiation (medium and high)	0.636 (0.239-1.688)	0.363	-	-
CEA (high)	1.095 (0.684-1.752)	0.707	-	-

CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; ALB, albumin; BMI, body mass index; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen.

men and 101 (33.9%) women. Their median age was 67 years (range, 60 to 92 years). Sixty-eight patients (22.8%) were diagnosed with stage I CRC, 101 (33.9%) with stage II, 103 (34.6%) with stage III, and 26 (8.7%) with stage IV. The median follow-up time was 62 months (range, 1 to 80 months). Seventy-four (24.8%) and 124 (41.6%) patients experienced recurrence and death, respectively.

2. Association of sarcopenia with clinicopathological factors

The main features of elderly CRC patients with sarcopenia were male sex (p=0.002), older age (p < 0.001), lower serum albumin (p=0.002), lower BMI (p < 0.001), and higher malnutrition risk (p < 0.001). Other factors such as ASA grade, pT category, pN category, preoperative metastasis, tumor location, tumor size, perineural/vascular invasion, tumor differentiation, pathological type, and CEA were not related to the presence of sarcopenia (Table 1).

3. Risk factors for preoperative malnutrition and postoperative complications in elderly CRC patients

Currently, the most commonly used preoperative nutritional assessment method is NRS2002. All patients were assessed for NRS2002 before surgery, and 113 were diagnosed with malnutrition. In univariate logistic regression analysis, serum albumin (p < 0.001), BMI (p < 0.001), sarcopenia (p < 0.001), and tumor size (p=0.038) were considered to be correlated with preoperative malnutrition. In multivariate logistic regression analysis, only serum albumin (p=0.001; odds ratio [OR], 0.418; 95% confidence interval [CI], 0.244 to 0.716), BMI (p=0.037) and sarcopenia (p < 0.001; OR, 3.405; 95% CI, 1.948 to 5.954) were independent risk factors for predicting preoperative nutritional risk in elderly CRC patients (Table 2).

Sixty-six patients (22.1%) suffered from postoperative complications, including anastomotic leak (4 cases), postoperative bowel obstruction (12 cases), wound problems (25 cases), pulmonary complications (12 cases), and other complications

Table 3. Univariate and multivariate logistic regression analysis of factors associated with complications in elderly CRC

Feature	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female sex	0.739 (0.407-1.343)	0.322	-	-
Age (≥ 70 yr)	1.083 (0.618-1.898)	0.780	-	-
ALB (≥ 35 g/L)	0.557 (0.321-0.968)	0.038	-	-
BMI		0.142		-
Low	1.000		-	
Normal	1.095 (0.511-2.349)	0.815	-	-
High	0.552 (0.225-1.353)	0.194	-	-
Sarcopenia (yes)	2.159 (1.237-3.766)	0.007	2.192 (1.231-3.903)	0.008
ASA grade (III-IV)	1.395 (0.802-2.429)	0.239	-	-
pT category (T3-4)	2.484 (1.230-5.015)	0.011	2.337 (1.127-4.847)	0.023
pN category		0.890		-
N0	1.000		-	
N1	1.167 (0.622-2.187)	0.631	-	-
N2	1.036 (0.456-2.357)	0.932	-	-
Preoperative metastasis (yes)	2.583 (1.102-6.058)	0.029	1.988 (0.811-4.874)	0.133
Tumor location (colon/rectal)	1.053 (0.609-1.820)	0.853	-	-
Tumor size (< 5 cm/≥ 5 cm)	0.906 (0.517-1.588)	0.731	-	-
Perineural/Vascular invasion (positive)	1.332 (0.673-2.638)	0.410	-	-
Pathological type		0.139		-
Protrude	1.000		-	
Infiltrating	1.140 (0.378-3.440)	0.816	-	-
Ulcerative	1.966 (0.933-4.140)	0.075	-	-
Differentiation (medium and high)	0.541 (0.209-1.402)	0.206	-	-
CEA (high)	1.129 (0.652-1.954)	0.665	-	-
Surgical method (open)	2.035 (1.141-3.629)	0.016	1.693 (0.929-3.084)	0.086

CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; ALB, albumin; BMI, body mass index; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen.

(13 cases). There were 23 patients (23.0%) with grade I complications, 34 (9.6%) with grade II complications, three (1.3%) with grade III complications, and six (2.2%) with grade IV complications by Clavien-Dindo classification. Patients with sarcopenia had a higher incidence of total complications (13.1% vs. 9.1%, p=0.001) (Table 1). Logistic regression analysis found that sarcopenia (p =0.008; OR, 2.192; 95% CI, 1.231 to 3.903) was a useful indicator for predicting short-term postoperative complications in the elderly CRC patients (Table 3).

4. Associations of sarcopenia with survival outcomes

In univariate Cox proportional hazards analysis, patients with sarcopenia had significantly lower PFS and OS than those with non-sarcopenia, respectively (p=0.008; hazard ratio [HR], 1.607; 95% CI, 1.133 to 2.279 and p=0.001; HR, 1.785; 95% CI, 1.252 to 2.545). After adjustment for clinicopathological factors, multivariate Cox proportional hazards

analysis showed that sarcopenia was an independent risk factor for predicting long-term survival outcomes (PFS: p < 0.001; HR, 2.175; 95% CI, 1.489 to 3.179 and OS: p < 0.001; HR, 2.524; 95% CI, 1.721 to 3.703) (Table 4).

In Kaplan-Meier analysis, patients in the sarcopenia group had poorer clinical outcomes in terms of PFS (48.5% vs. 64.5%, log-rank p=0.007) and OS (47.7% vs. 66.9%, log-rank p=0.001) than those in the non-sarcopenia group had (Fig. 2A and B). We also compared survival curves for each pathological TNM stage between the sarcopenia and non-sarcopenia groups. There were significant differences in both PFS (65.7% vs. 87.9%, log-rank p=0.042) and OS (62.9% vs. 90.9%, log-rank p=0.010) in TNM stage I (Fig. 3A and D). Similar results were also found for PFS (57.8% vs. 76.8%, log-rank p=0.036) and OS (57.8% vs. 80.4%, log-rank p=0.010) in TNM stage III (Fig. 3B and E). However, there were no significant differences in TNM stage I (Fig. 3C and F) and IV patients (data not shown).

To correct confounding factors, we performed a subgroup

Table 4. Univariate and multivariate survival analyses of clinicopathological characteristics in elderly colorectal cancer patients

Feature	Progression-free survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Female sex	0.914 (0.629-1.329)	0.639	-	-	0.916 (0.627-1.339)	0.652	-	-
Age (≥ 70 yr)	1.180 (0.829-1.679)	0.359	-	-	1.209 (0.846-1.727)	0.297	-	-
ALB (≥ 35 g/L)	0.649 (0.458-0.920)	0.015	0.813 (0.563-1.175)	0.271	0.651 (0.458-0.927)	0.017	0.797 (0.550-1.156)	0.232
BMI		0.262		-		0.393		-
Low	1.000				1.000			
Normal	1.305 (0.781-2.181)	0.309	-	-	1.160 (0.700-1.920)	0.565	-	-
High	0.955 (0.536-1.702)	0.876	-	-	0.870 (0.491-1.540)	0.633	-	-
Sarcopenia (yes)	1.607 (1.133-2.279)	0.008	2.175 (1.489-3.179)	< 0.001	1.785 (1.252-2.545)	0.001	2.524 (1.721-3.703)	< 0.001
ASA grade (I-II/III-IV)	1.705 (1.192-2.438)	0.003	0.919 (0.595-1.419)	0.702	1.753 (1.219-2.521)	0.002	0.944 (0.606-1.469)	0.797
pT category (T3-4)	2.317 (1.474-3.640)	< 0.001	1.330 (0.811-2.181)	0.259	2.217 (1.409-3.488)	0.001	1.238 (0.750-2.044)	0.404
pN category		< 0.001		< 0.001		< 0.001		< 0.001
N0	1.000		1.000		1.000		1.000	
N1	2.067 (1.378-3.099)	< 0.001	1.824 (1.141-2.916)	0.012	2.061 (1.366-3.110)	0.001	1.822 (1.129-2.941)	0.014
N2	4.247 (2.727-6.615)	< 0.001	3.382 (1.955-5.851)	< 0.001	4.289 (2.744-6.703)	< 0.001	3.442 (1.995-5.936)	< 0.001
Preoperative metastasis (yes)	6.559 (4.153-10.361)	< 0.001	5.028 (2.999-8.431)	< 0.001	6.498 (4.109-10.275)	< 0.001	5.387 (3.208-9.046)	< 0.001
Tumor location (colon)	0.923 (0.651-1.307)	0.651	-	-	-	0.325	-	-
Tumor size (< 5 cm/≥ 5 cm)	1.117 (0.775-1.609)	0.554	-	-	1.069 (0.741-1.541)	0.722	-	-
Perineural/Vascular invasion (positive)	1.612 (1.070-2.428)	0.022	0.949 (0.603-1.494)	0.822	1.458 (0.952-2.234)	0.083	-	-
Pathological type		0.199		-		0.270		-
Protrude	1.000		-		1.000		-	
Infiltrating	1.416 (0.743-2.696)	0.290	-	-	1.405 (0.738-2.677)	0.301	-	-
Ulcerative	1.534 (0.962-2.446)	0.072	-	-	1.470 (0.920-2.349)	0.107	-	-
Differentiation (medium and high)	0.453 (0.260-0.790)	0.005	0.433 (0.239-0.782)	0.006	0.461 (0.259-0.820)	0.008	0.442 (0.240-0.814)	0.009
CEA (high)	2.140 (1.503-3.049)	< 0.001	1.414 (0.962-2.080)	0.078	2.039 (1.427-2.913)	< 0.001	1.397 (0.951-2.053)	0.089
Surgical method (open)	1.294 (0.907-1.848)	0.155	-	-	1.267 (0.885-1.814)	0.197	-	-
Postoperative chemoradiotherapy	1.117 (0.785-1.590)	0.539	-	-	1.142 (0.800-1.631)	0.463	-	-

HR, hazard ratio; CI, confidence interval; ALB, albumin; BMI, body mass index; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen.
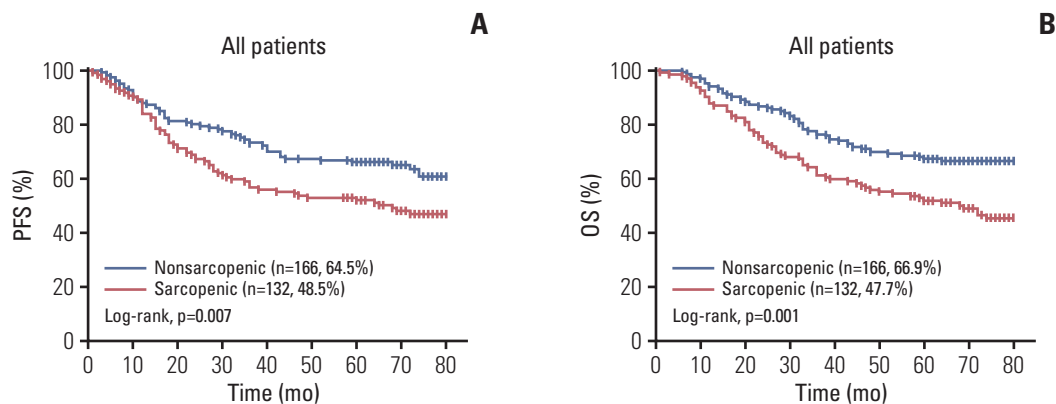
Fig. 2. Kaplan-Meier survival curves of sarcopenia and non-sarcopenia groups of all elderly colorectal cancer patients. (A) Kaplan-Meier progression-free survival (PFS) curves of all patients. (B) Kaplan-Meier overall survival (OS) curves of all patients.

multivariate analysis of each factor. 28 of the 35 subgroups indicated that sarcopenia was an independent risk factor for prognosis in PFS (Fig. 4A). Similarly, 28 of the 35 subgroups indicated that sarcopenia was an independent risk factor for prognosis in OS (Fig. 4B).

5. Construction of sarcopenia-based nomograms

Factors with $p < 0.05$ in univariate analysis were included in multivariate analysis. Based on multivariate analysis, we built four nomograms (A, nutritional risk model; B, complication risk model; C, PFS model; D, overall survival model) (Fig. 5). SMI was utilized as a continuous variable to improve the predictive accuracy of the nomograms, and the C-index value and calibration curves were used to evaluate the accuracy of the model. The C-index for nutritional risk prediction was 0.738 (95% CI, 0.679 to 0.797), complication risk prediction was 0.635 (95% CI, 0.560 to 0.710), PFS prediction was 0.717 (95% CI, 0.669 to 0.765), and OS prediction was 0.718 (95% CI, 0.672 to 0.764). The calibration curves for the probability of nutritional risk, complication risk, PFS, and OS demonstrated optimal consistency between the prediction by sarcopenia-based nomograms and actual observation (Fig. 6). By calculating the score of each factor, the preoperative nutritional risk, the risk of postoperative complications, and the PFS and OS of the elderly CRC patients could be predicted.

Discussion

The latest research suggests that sarcopenia in cancer patients is the result of local muscle inflammation. During tumor progression, tumor cells or surrounding cells are stimulated to produce tumor necrosis factor and interleukin-6 inflammatory cytokines [18]. Tumor necrosis factor inhibits skeletal muscle cell differentiation and promotes muscle atrophy [19]. Interleukin-6 can further reduce muscle protein synthesis by promoting protein degradation and reducing synthesis [20]. An increase in inflammatory cytokines can also lead to insulin resistance and muscle wasting by activating the ubiquitin proteasome proteolytic pathway, which further exacerbates systemic inflammation and muscle degeneration [21].

Gastrointestinal malignancies are often associated with the occurrence of dyscrasia. Studies have shown that about 80% of gastrointestinal cancer patients experience varying degrees of weight loss and muscle loss [22]. They are prone to obstruction, bleeding, and decreased food intake, which leads to increased glycogen decomposition and decreased synthesis of skeletal muscle, resulting in sarcopenia. In this study, approximately 44.3% of patients were considered to have sarcopenia. Patients with advanced age, hypoalbuminemia, low BMI, malnutrition were more likely to develop sarcopenia. We explored the relationship between sarcopenia and nutritional risk through logistic regression analysis and demonstrated that sarcopenia is a factor that can independently predict the preoperative nutritional risk of elderly CRC patients. As can be seen from the nutritional risk nomogram, sarcopenia has a higher impact on nutritional risk than serum albumin and BMI. Based on the above results, CT-determined sarcopenia can be used as a new indicator of pre-
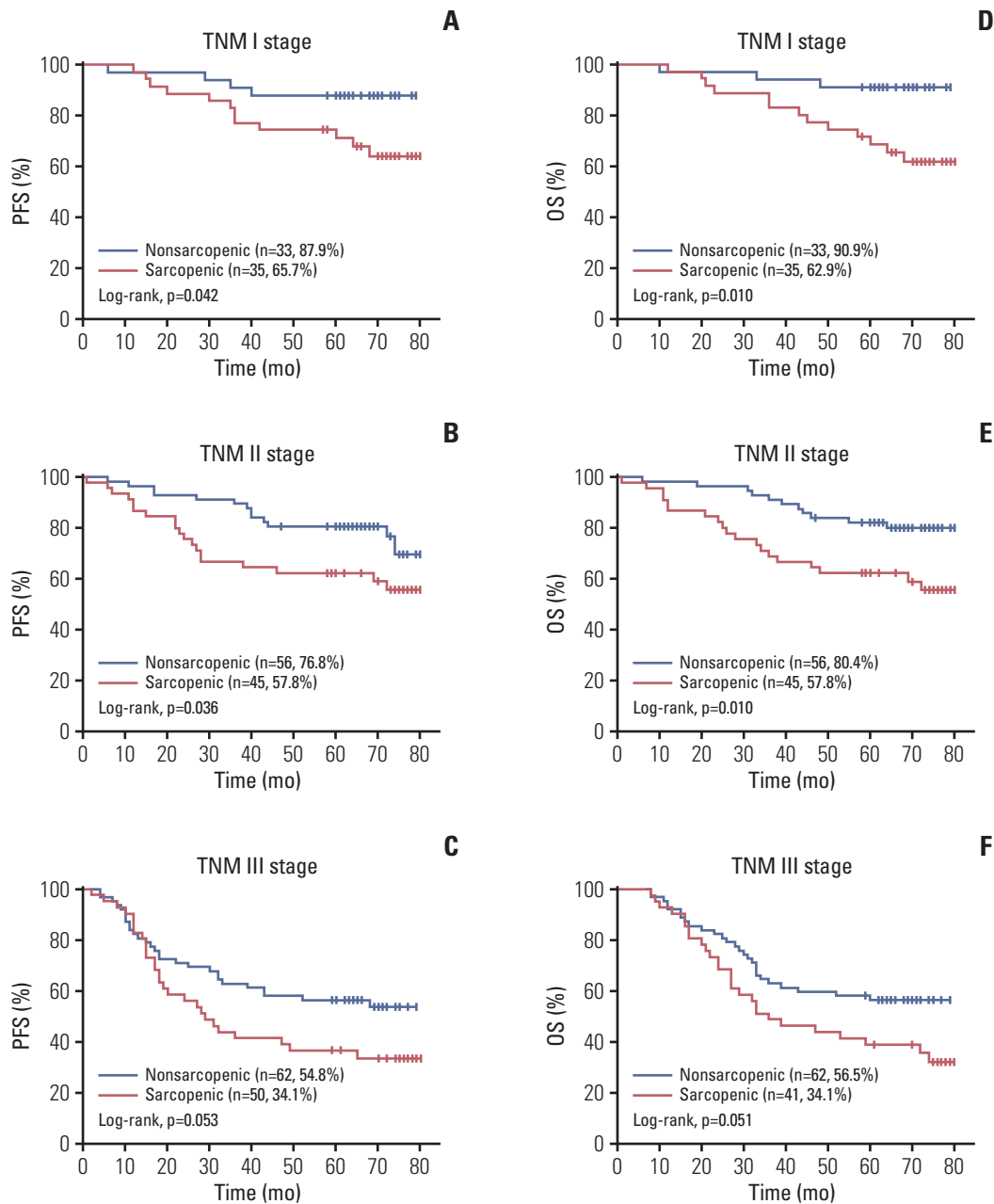
Fig. 3. Kaplan-Meier survival curves of sarcopenia and non-sarcopenia groups of elderly colorectal cancer patients based on each TNM stage. (A) Kaplan-Meier progression-free survival (PFS) curves of TNM I stage patients. (B) Kaplan-Meier PFS curves of TNM II stage patients. (C) Kaplan-Meier PFS curves of TNM III stage patients. (D) Kaplan-Meier overall survival (OS) curves of TNM I stage patients. (E) Kaplan-Meier OS curves of TNM II stage patients. (F) Kaplan-Meier OS curves of TNM III stage patients.

operative nutritional assessment. In elderly CRC patients with sarcopenia, approximately 16.8% had normal BMI and serum albumin. Although these patients appeared to be sufficiently healthy based on their appearance and preoperative examination and could undergo surgical resection, the true

malnutrition status and unacceptable organ function were often ignored. In multivariate subgroup analysis, sarcopenia could be used to assess poor prognosis in patients with normal BMI and serum albumin. The above results indicated that CT-determined sarcopenia might be useful in identify-

A

Sarcopenic (PFS)			
Subgroup	Yes	No	HR (95% CI)
Sex			
Male	119	78	2.435 (1.459-4.064)
Female	13	88	2.543 (1.052-6.146)
Age (yr)			
< 70	73	112	5.370 (2.779-10.379)
≥ 70	59	54	2.375 (1.272-4.435)
ALB			
Low	64	52	1.518 (0.852-2.704)
High	68	114	2.586 (1.561-4.286)
BMI			
Low	39	7	1.514 (0.276-8.306)
Normal	74	90	2.520 (1.508-4.213)
High	19	69	2.849 (1.033-7.859)
ASA grade			
I-II	62	79	1.477 (0.800-2.726)
III-IV	70	87	2.581 (1.573-4.235)
pT category			
T1-2	42	46	4.386 (1.499-12.834)
T3-4	90	120	1.903 (1.253-2.889)
pN category			
N0	84	94	2.683 (1.483-4.853)
N1	33	46	2.208 (1.124-4.337)
N2	15	26	1.525 (0.674-3.450)
Preoperative metastasis			
No	122	151	2.101 (1.380-3.198)
Yes	10	15	2.507 (0.611-10.288)
Tumor location			
Rectal	63	89	2.247 (1.330-3.797)
Colon	69	77	1.862 (1.037-3.343)
Tumor size (cm)			
< 5	51	61	2.259 (1.183-4.312)
≥ 5	81	105	2.134 (1.307-3.483)
Perineural/Vascular invasion			
Negative	112	133	2.055 (1.350-3.128)
Positive	20	33	2.401 (0.901-6.398)
Pathological type			
Protrude	36	31	2.831 (0.786-10.195)
Lnfiltrating	13	23	10.075 (2.238-41.833)
Ulcerative	83	112	1.915 (1.222-2.999)
Differentiation			
Poor	6	15	5.462 (1.219-24.464)
Medium and high	126	151	2.347 (1.282-2.860)
CEA			
Normal	75	90	2.514 (1.345-4.700)
high	57	76	2.289 (1.168-3.182)
Surgical method			
Open	83	81	1.749 (1.035-2.957)
Laparoscopy	49	85	3.374 (1.833-6.209)
Postoperative chemotherapy			
No	86	94	1.942 (1.197-3.149)
Yes	46	72	2.524 (1.385-4.602)

● p ≥ 0.05   ■ p < 0.05
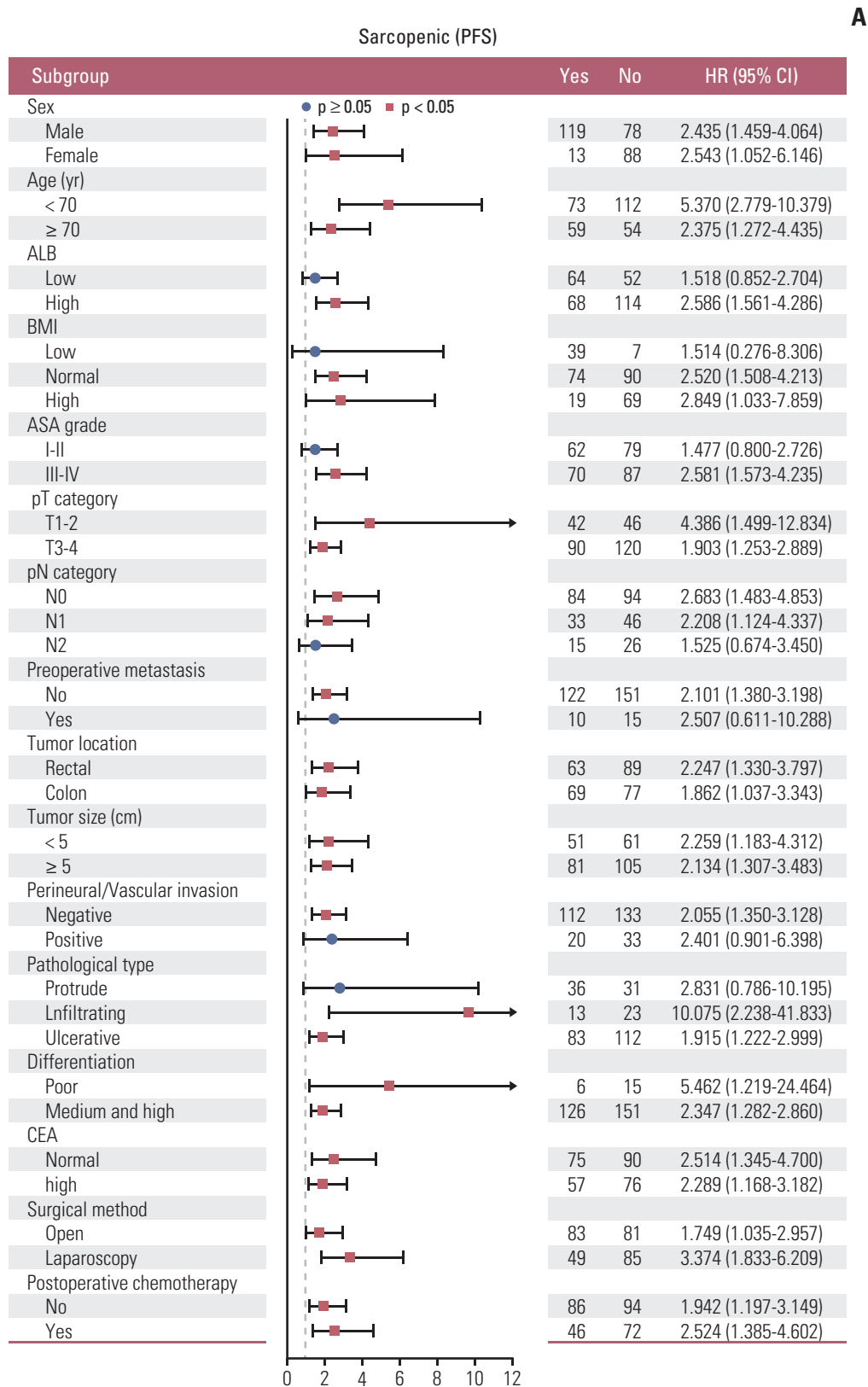
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Fig. 4. Subgroup multivariate survival analysis of sarcopenia in elderly colorectal cancer patients. (A) Subgroup multivariate progression-free survival (PFS) analysis of sarcopenia. *(Continued to the next page)*
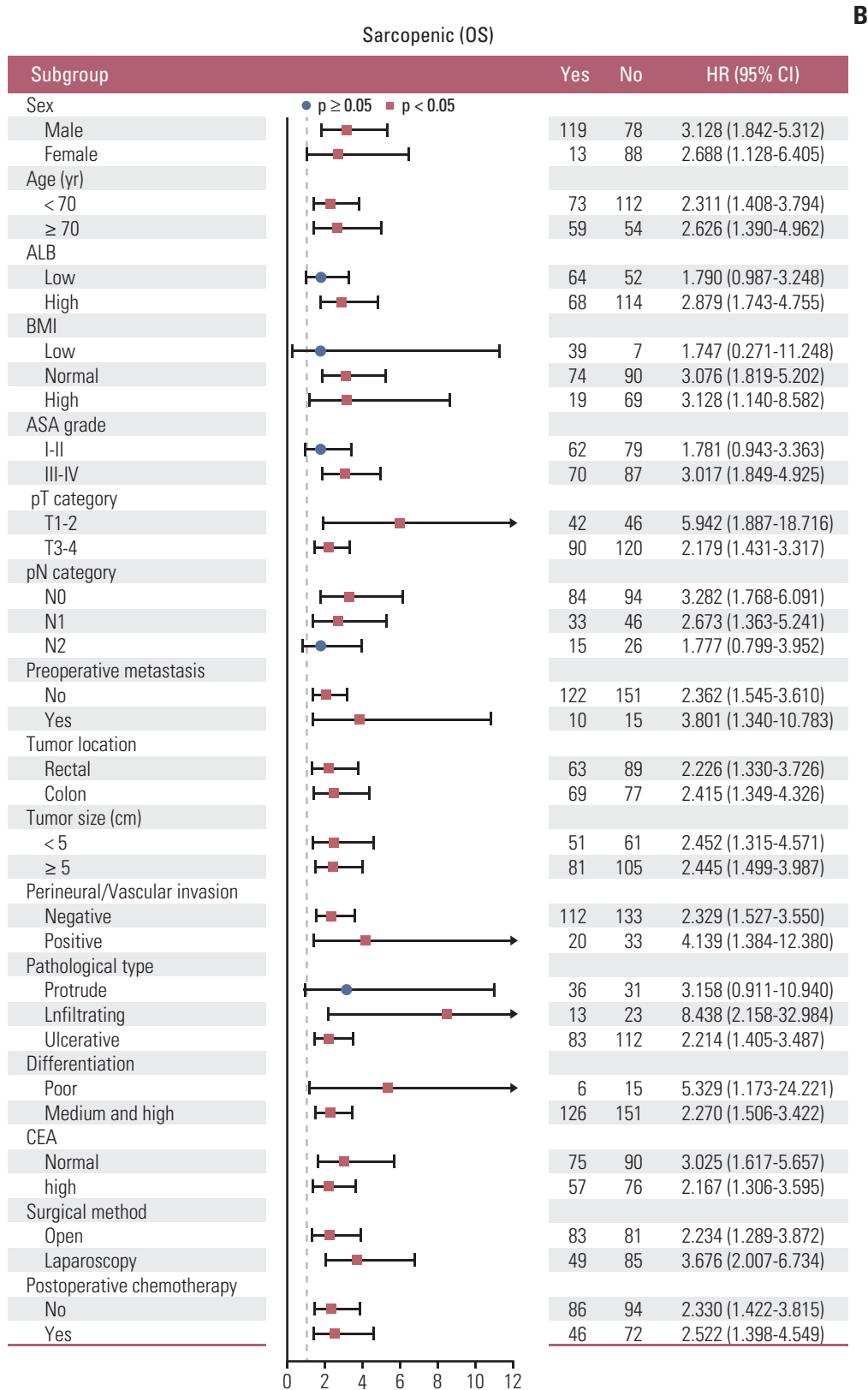
B

Sarcopenic (OS)

Subgroup		Yes	No	HR (95% CI)
Sex	● p ≥ 0.05 ■ p < 0.05			
Male		119	78	3.128 (1.842-5.312)
Female		13	88	2.688 (1.128-6.405)
Age (yr)				
< 70		73	112	2.311 (1.408-3.794)
≥ 70		59	54	2.626 (1.390-4.962)
ALB				
Low		64	52	1.790 (0.987-3.248)
High		68	114	2.879 (1.743-4.755)
BMI				
Low		39	7	1.747 (0.271-11.248)
Normal		74	90	3.076 (1.819-5.202)
High		19	69	3.128 (1.140-8.582)
ASA grade				
I-II		62	79	1.781 (0.943-3.363)
III-IV		70	87	3.017 (1.849-4.925)
pT category				
T1-2		42	46	5.942 (1.887-18.716)
T3-4		90	120	2.179 (1.431-3.317)
pN category				
N0		84	94	3.282 (1.768-6.091)
N1		33	46	2.673 (1.363-5.241)
N2		15	26	1.777 (0.799-3.952)
Preoperative metastasis				
No		122	151	2.362 (1.545-3.610)
Yes		10	15	3.801 (1.340-10.783)
Tumor location				
Rectal		63	89	2.226 (1.330-3.726)
Colon		69	77	2.415 (1.349-4.326)
Tumor size (cm)				
< 5		51	61	2.452 (1.315-4.571)
≥ 5		81	105	2.445 (1.499-3.987)
Perineural/Vascular invasion				
Negative		112	133	2.329 (1.527-3.550)
Positive		20	33	4.139 (1.384-12.380)
Pathological type				
Protrude		36	31	3.158 (0.911-10.940)
Lnfiltrating		13	23	8.438 (2.158-32.984)
Ulcerative		83	112	2.214 (1.405-3.487)
Differentiation				
Poor		6	15	5.329 (1.173-24.221)
Medium and high		126	151	2.270 (1.506-3.422)
CEA				
Normal		75	90	3.025 (1.617-5.657)
high		57	76	2.167 (1.306-3.595)
Surgical method				
Open		83	81	2.234 (1.289-3.872)
Laparoscopy		49	85	3.676 (2.007-6.734)
Postoperative chemotherapy				
No		86	94	2.330 (1.422-3.815)
Yes		46	72	2.522 (1.398-4.549)

0   2   4   6   8   10   12

Fig. 4. *(Continued from the previous page)* (B) Subgroup multivariate overall survival (OS) analysis of sarcopenia. HR, hazard ratio; CI, confidence interval; ALB, albumin; BMI, body mass index; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen.
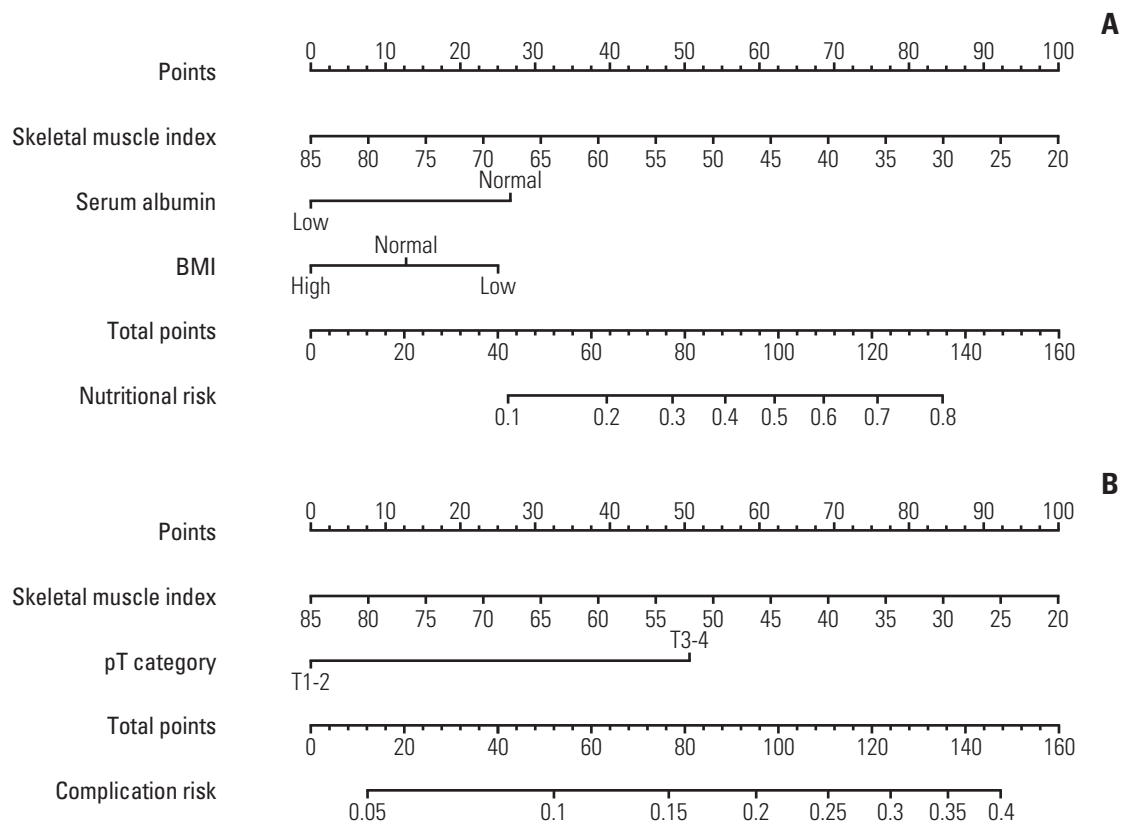
Fig. 5. Construction of sarcopenia-based nomograms in elderly colorectal cancer patients. (A) Sarcopenia-based nomograms of nutritional risk. (B) Sarcopenia-based nomograms of complication risk. *(Continued to the next page)*

ing patients with occult malnutrition.

In the present study, about 22.1% of the elderly patients experienced varying degrees of postoperative complications. We determined that sarcopenia is an independent risk factor for postoperative complications, which is consistent with previous studies [14,23]. Sarcopenia leads to an increase in postoperative complications, which may be related to the following reasons. On the one hand, sarcopenia reflects malnutrition, and perioperative malnutrition in patients greatly increases the incidence of postoperative complications [24]. On the other hand, muscle mass and strength are key factors in maintaining body function, flexibility and vitality. Sarcopenia delays the early postoperative movement and early feeding time, which leads to impaired postoperative recovery [25].

Sarcopenia has been reported to have good prognostic value in many tumors, such as gastric cancer, hepatocellular carcinoma, and pancreatic cancer. However, different studies on the relationship between sarcopenia and long-term prognosis of CRC have yielded inconsistent results [23,26-28]. A multicenter study showed that sarcopenia is not associated with long-term prognosis, but is associated with short-term

postoperative complications. The study showed that age had a greater impact than sarcopenia after the reduction of cancer load *in vivo* [27]. Since sarcopenia is related to human aging, skeletal muscle mass, skeletal muscle strength, and dysfunction undergo degenerative changes with age. In our study, we investigated the effects of sarcopenia on prognosis by screening elderly CRC patients aged > 60 years, which to some extent reduced the bias caused by different ages. We showed that age was not an independent factor influencing survival outcomes, while sarcopenia was a good predictor of short- and long-term prognosis.

In survival analysis, we confirmed that sarcopenia is an independent risk factor for long-term outcomes, whether in PFS or OS. Besides, it can be seen from the survival nomograms that sarcopenia has a good impact efficiency, but comparing these risk-related factors, the effects of pN category and metastasis were greater than sarcopenia. It is well known that advanced tumor stages are associated with poor long-term prognosis of malignant tumors, but the prognosis of patients with the same stage is often different. We performed a stratified analysis of patients based on TNM staging and compared survival rates in patients with sarcopenia and non-
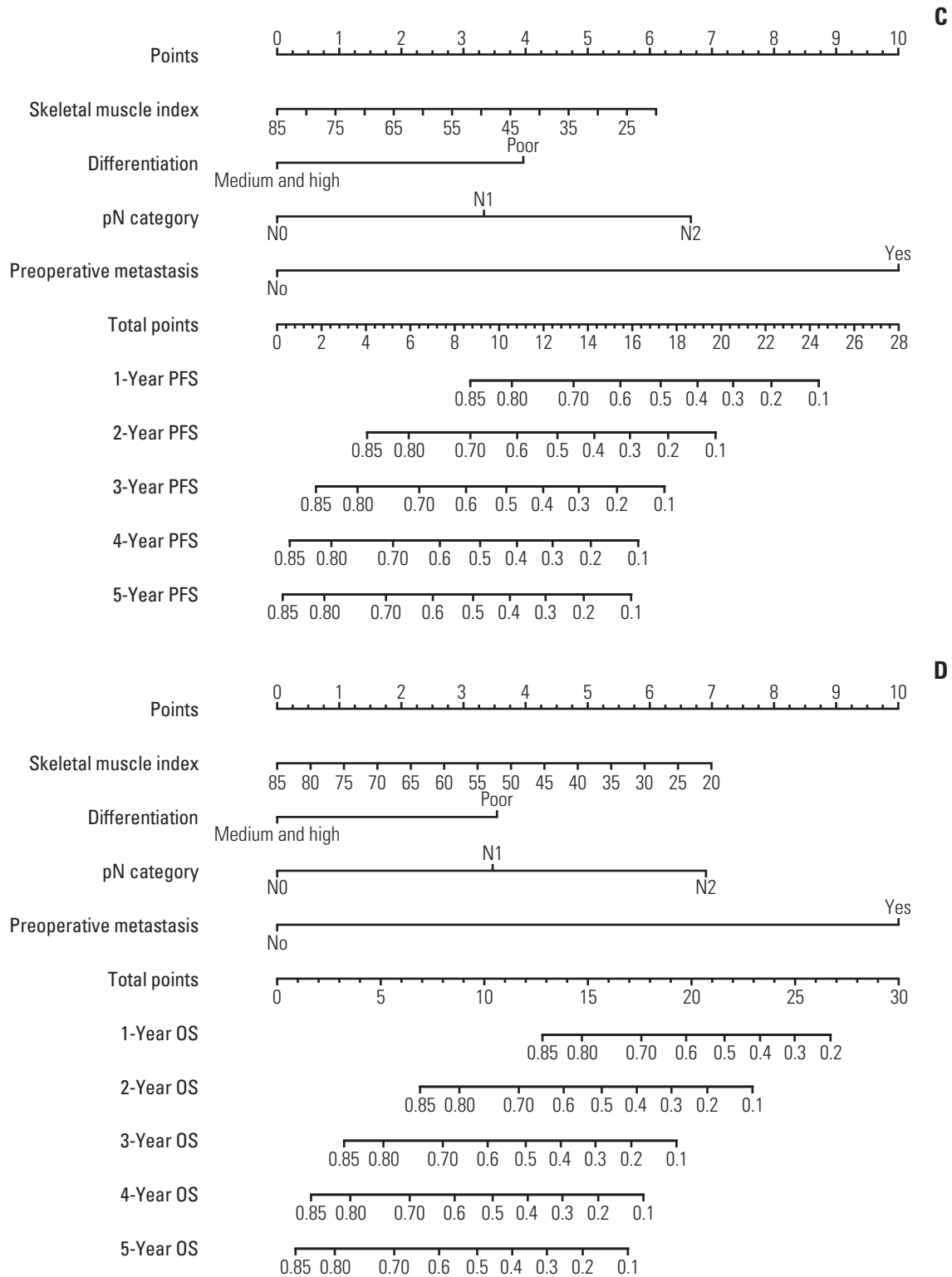
C

Points		0 1 2 3 4 5 6 7 8 9 10
Skeletal muscle index		85 75 65 55 45 35 25
Differentiation		Poor / Medium and high
pN category		N1 / N0 ... N2
Preoperative metastasis		Yes / No
Total points		0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
1-Year PFS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1
2-Year PFS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1
3-Year PFS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1
4-Year PFS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1
5-Year PFS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1

D

Points		0 1 2 3 4 5 6 7 8 9 10
Skeletal muscle index		85 80 75 70 65 60 55 50 45 40 35 30 25 20
Differentiation		Poor / Medium and high
pN category		N1 / N0 ... N2
Preoperative metastasis		Yes / No
Total points		0 5 10 15 20 25 30
1-Year OS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2
2-Year OS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1
3-Year OS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1
4-Year OS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1
5-Year OS		0.85 0.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1

Fig. 5. *(Continued from the previous page)* (C) Sarcopenia-based nomograms of progression-free survival (PFS) (D) Sarcopenia-based nomograms of overall survival (OS). BMI, body mass index.
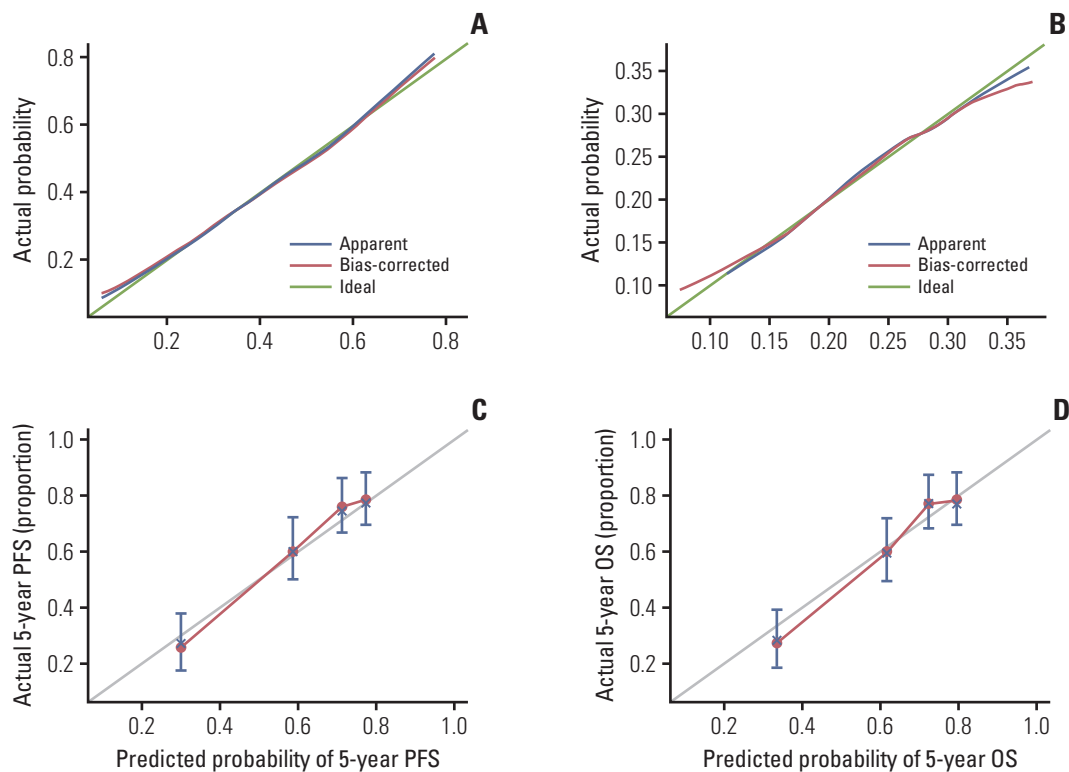
Fig. 6. The calibration curves for predicting nutritional risk (A), complication risk (B), progression-free survival (PFS) (C), and overall survival (OS) (D) in elderly colorectal cancer patients. The X axis presents the predicted probability and the Y axis shows the actual probability. The calibration lines fit along with the 45 reference.

sarcopenia. The results showed that OS and PFS of the sarcopenia group were significantly lower than those of the non-sarcopenia group in TNM stage I and II, but not in stage IIII and IV. Although in TNM III stage, Patients with sarcopenia still tend to have a poor prognosis, but it is not the main factor affecting prognosis. This may be because, in the early stage of the tumor, sarcopenia has a large impact on the prognosis of the patient. As the tumor progresses, the tumor invasion and metastasis gradually occupy the main position.

Nomograms are considered to be a direct tool for individualized risk assessment for each patient. We constructed four novel and effective nomograms based on sarcopenia for individualized assessment of preoperative nutritional risk, postoperative complications, PFS, and OS in elderly CRC patients. It is worth noting that the results of the C-index and the calibration chart confirm that the nomograms have good prediction accuracy. These four sarcopenia-based nomograms, combining clinically easy-to-use clinicopathological factors, are viable and reliable risk prediction tools for individualized prediction of elderly CRC patients, which may contribute to individualized postoperative follow-up and treatment options. Using sarcopenia-based nomograms to

help screen high-risk patients can facilitate early treatment interventions, which is beneficial to improve the prognosis of elderly CRC patients. Resistance training [29], and anti-inflammatory drugs [30] have been reported to be safe and effective in maintaining and increasing muscle mass and function in cancer patients. Early application of these measures can improve the quality of life and achieve longer survival.

CT is considered clinically as an accurate method for assessing skeletal muscle mass. It provides important quantitative information about muscle composition and distribution through high-quality images, spatial accuracy, and location features, as well as the ability to measure muscle mass from a cross-section of an abdomen. Before CRC surgery, an abdominal CT scan or enhanced examination is usually performed to evaluate tumor staging. If the L3 skeletal muscle mass is measured at the same time, it will not increase any cost, which can reduce the burden on the patient. Other detection methods for skeletal muscle reduction include dual-energy X-ray absorption, nuclear magnetic resonance imaging, and bioelectrical impedance. Due to the complexity of the other methods, the testing process requires additional

patient inspection costs. The prospects for clinical application are far from good than CT examinations. However, the measurement of skeletal muscle mass is still not a routine measurement item in CT examination. More studies are still needed to elucidate the importance of preoperative skeletal muscle mass measurement.

There were some limitations to our study. First, as a single-center and retrospective study, there were problems such as insufficient sample size and selection bias. Second, the definition of sarcopenia was based on muscle mass on CT, and we did not investigate muscle strength or function. Based on the overall survival and overall survival time, this study used the X-tile program to determine the optimal cutoff value, which may have certain subjectivity. However, there are no clear diagnostic criteria for CT-determined sarcopenia in elderly CRC patients. In our opinion, this method can provide some reference value for subsequent research. Finally, sarcopenia-based nomograms are designed based on a limited population. Although the calibration curve suggested that they have good effectiveness, it is not verified by other independent teams. Therefore, the validity and practicability of the nomograms should be verified in the multicenter and large-sample population in the future.

This study is believed to be the first to explore the relationship between sarcopenia and preoperative nutrition, postoperative complications, and long-term outcomes of elderly CRC patients. The results suggest that CT-determined sarcopenia is a useful imaging biomarker for predicting preoperative nutritional risk, postoperative complications, and long-term outcomes in elderly CRC patients. The sarcopenia-based nomograms can provide a scientific basis for guiding therapeutic schedule and follow-up strategies.

Conflicts of Interest

Conflicts of interest relevant to this article was not reported.

Acknowledgments

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