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Prognostic impact of low skeletal muscle mass in stage I-III colon cancer: A retrospective study

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Abstract. Colon cancer (CC) is a common malignancy. Although the TNM staging system is widely employed for prognosis, its ability to predict individual patient outcomes is limited. In recent years, however, low skeletal muscle mass (SM) has emerged as a marked prognostic factor in patients with cancer. The present study aimed to investigate the prognostic value of low SM in patients with stage I-III CC. The present retrospective analysis included 230 patients with CC who underwent tumor resection at Lanzhou University Second Hospital (Lanzhou, China). The skeletal muscle index (SMI) was assessed using preoperative abdominal CT scans. Patients were stratified into low SM and non-sarcopenia groups based on their SMI. The primary outcome was overall survival (OS). The prognostic significance of low SM was evaluated using Kaplan-Meier survival curves, Cox regression modeling and time-dependent receiver operating Characteristic analysis. Furthermore, a combined TNM and low SM model was developed. Among the 230 patients, results showed that 24.34% exhibited low SM. Kaplan-Meier curves indicated that patients in the low SM group exhibited significantly lower OS rates compared with the normal SM group (P<0.001). Cox regression identified low SM as an independent adverse prognostic factor (hazard ratio: 1.70; 95% CI: 1.05-2.75). Incorporating low SM into the TNM model increased the Harrell's C-index from 0.570 to 0.604 (likelihood ratio P=0.027), with improved predictive performance at 1, 3 and 5-year time points. Overall, the present study concluded that low SM was an independent prognostic factor for OS in patients with stage I-III CC and a valuable supplement to existing prognostic tools, further contributing to personalized treatment strategies.

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Abbreviations: HR, hazard ratio; ROC, receiver operating characteristic; AUC, area under the curve; AJCC, American Joint Committee on Cancer; SMA, skeletal muscle area; SMI, skeletal muscle index; OS, overall survival

Key words: colon cancer, low skeletal muscle mass, prognosis, survival

Introduction

Colon cancer (CC) is globally, one of the most common malignant tumors in the digestive tract, with adenocarcinoma accounting for ~95% of cases. According to GLOBOCAN 2022 data, there were ~1.93 million new cases of colorectal cancer and 904,000 deaths reported globally, with colon cancer accounting for the majority of cases (1).

CC is the third most common cancer globally and the second leading cause of cancer-associated mortalities, presenting a notable challenge to public health. Currently, the standard treatment for stage I-III CC involves extensive tumor resection followed by adjuvant chemotherapy, such as 5-fluorouracil/folinic acid + oxaliplatin or capecitabine + oxaliplatin regimens (2). While this treatment approach has markedly improved overall survival (OS) rates, notable prognostic disparities persist in clinical practice. This is particularly evident in the ongoing debate surrounding adjuvant chemotherapy for patients with stage II CC. The debate centers on the following: in contrast to the well-established survival benefit of adjuvant chemotherapy in stage III colon cancer (10-15% improvement in 5-year OS), the absolute survival benefit in stage II patients remains very limited (2-3% improvement in 5-year DFS). Furthermore, reliable biomarkers to identify patients most likely to benefit are lacking, the criteria for defining high-risk features vary across different guidelines, and the additional value of oxaliplatin in high-risk stage II patients remains unproven (3-5).

Although TNM staging is an established tool for risk stratification based on tumor anatomy and offers certain prognostic value, it fails to account for key factors such as the nutritional status, metabolic condition and overall physiological state of the patient. This limitation hinders its ability to fully reflect tumor biology and restricts its application in precision medicine (6,7). Previous studies have highlighted the important role of nutritional status and body composition (particularly changes in skeletal muscle mass (SM) in the prognosis of patients with cancer (8,9). Protein-energy malnutrition impairs immune function, increases the risk of treatment-associated toxicity and postoperative complications and markedly reduces patient survival (10-12). In addition, micronutrients such as vitamin D, zinc and selenium modulate the tumor microenvironment through regulation of the barrier-microbiota-inflammation axis, which consists of three core components: Intestinal barrier dysfunction, gut microbial dysbiosis and chronic inflammation (13,14).

In recent years, low skeletal muscle mass (SM) has attracted notable attention as a clinical indicator that reflects the overall functional status and nutritional condition of the patient (15,16). Numerous studies have demonstrated that low SM is associated with adverse outcomes following surgical intervention in patients with cancer, including higher rates of complication, reduced quality of life and reduced OS (17,18). An important prospective cohort study conducted in China determined that low SM is an independent predictor of poor postoperative prognosis in patients with gastrointestinal cancer (19). Notably, a study by Lieffers *et al* (20) demonstrated that, for patients with CC undergoing surgery, low SM was markedly associated with a prolonged postoperative hospital stay, heightened chemotherapy toxicity and reduced OS, underscoring its importance in preoperative risk assessment. While certain studies (21-23) have suggested an association between preoperative low SM and unfavorable outcomes in patients with CC, research specifically targeting stage I-III CC remains relatively limited.

Therefore, the present study aimed to thoroughly investigate the prognostic value of low SM in patients with stage I-III CC and clarify its impact on OS. In addition, the present study constructed a combined prognostic prediction model, integrating low SM with traditional TNM staging, to assess the incremental value of low SM in predicting the prognosis of patients with CC beyond TNM staging alone. Ultimately, the present study sought to provide clinicians with evidence to stratify patient risk and guide individualized treatment decisions.

Patients and methods

Patients and inclusion criteria. A retrospective review was performed on 230 patients with CC who underwent primary tumor resection at Lanzhou University Second Hospital (Lanzhou, China) between January 2018 and December 2019. None of these patients received neoadjuvant therapy and all underwent routine abdominal CT scans within 1 month prior to surgery. The 8th edition of the American Joint Committee on Cancer (AJCC) staging system was applied, as its publication in 2018 coincided with the initiation of patient data collection for the present study (24). The inclusion criteria were as follows: i) Initial diagnosis of CC with subsequent curative surgery; ii) age >18 years; iii) postoperative pathological diagnosis of CC with TNM stages I-III; iv) at least 12 lymph nodes detected in the surgical specimen after radical surgery; v) availability of complete follow-up and clinical-pathological records; and vi) availability of complete preoperative CT imaging data. The exclusion criteria were as follows: i) Received neoadjuvant therapy prior to surgery; ii) presence of rectal cancer; iii) history of other malignancies; and iv) concurrent malignant tumors. The final study cohort consisted of 230 patients, including 128 males (55.65%) and 102 females (44.35%). The mean age of the study cohort was 60.00±13.63 years (range, 33-89 years). Specifically, 112 patients (48.70%) were aged ≤60 years and 118 patients (51.30%) were aged >60 years.

The present study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Lanzhou University Second Hospital (Lanzhou, China; approval no. 2025A-638). As a retrospective study, patient privacy and personal identity information were protected and the Medical Ethics Committee waived the requirement for informed consent.

Assessment of low SM. A CT scan, routinely performed within 1 month prior to surgery, utilized parameters including contrast-enhanced or non-enhanced multi-phase acquisition with a 5 mm slice thickness. For the assessment of low SM, two adjacent non-contrast CT images of the third lumbar vertebra (L3) were selected from the same series (25). ImageJ2 software (version 2.0.0-rc-11; National Institutes of Health) was used to measure the total skeletal muscle area (SMA) on the two slices within the range of -29 to +150 Hounsfield units (26). The SMA was averaged for each patient. The outlined regions for SMA measurement are shown in Fig. 1. The skeletal muscle index (SMI) was defined as SMA divided by the square of height.

According to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) consensus (27), sarcopenia requires the presence of both low muscle mass and reduced muscle strength/function. Given that the present study was retrospective, preoperative muscle function measurements (such as handgrip strength) were unavailable. Consequently, the present assessed low SM instead of full sarcopenia.

The Global Leadership Initiative on Malnutrition (GLIM) criteria (28) recognize low muscle mass as a phenotypic criterion for malnutrition, which can be evaluated using CT-derived SMI. The GLIM criteria recommend using ethnicity- and sex-adjusted cut-off values for low muscle mass. A Chinese population-specific normative L3 SMI database is currently lacking, primarily due to the following reasons: Most existing studies are based on regional samples, cutoff values vary considerably across studies (for example, ranging from 38.89 to 44.77 cm^2/m^2 for males and from 31.6 to 33.28 cm^2/m^2 for females), and age-stratified reference standards have not yet been standardized (29,30). The present defined low SM as an SMI below the sexspecific lowest quartile of the present study population. This approach aligns with the GLIM framework and has been validated in a large prospective Chinese cohort of patients with digestive tract cancer (19). Specifically, low SM was defined as SMI <40.6 cm^2/m^2 for men and <34.9 cm^2/m^2 for women. According to this criterion, patients were categorized into low SM and normal SM groups (Fig. 1).

Data collection. Preoperative demographic and clinical data collected included age, sex, height, SMI, CEA levels and cancer location. Tumor location was classified as right-sided or left-sided CC based on established anatomical and embryological criteria (31). Right-sided CC encompassed the cecum, ascending colon, hepatic flexure and transverse colon (originating from the midgut), while left-sided CC included the splenic flexure, descending colon and sigmoid colon (originating from the hindgut) (32). Postoperative data comprised T stage, N stage, differentiation grade, neurovascular invasion, tumor maximum diameter, Ki67 (%) and cancer staging according to the AJCC 8th edition staging system. The outcome of interest

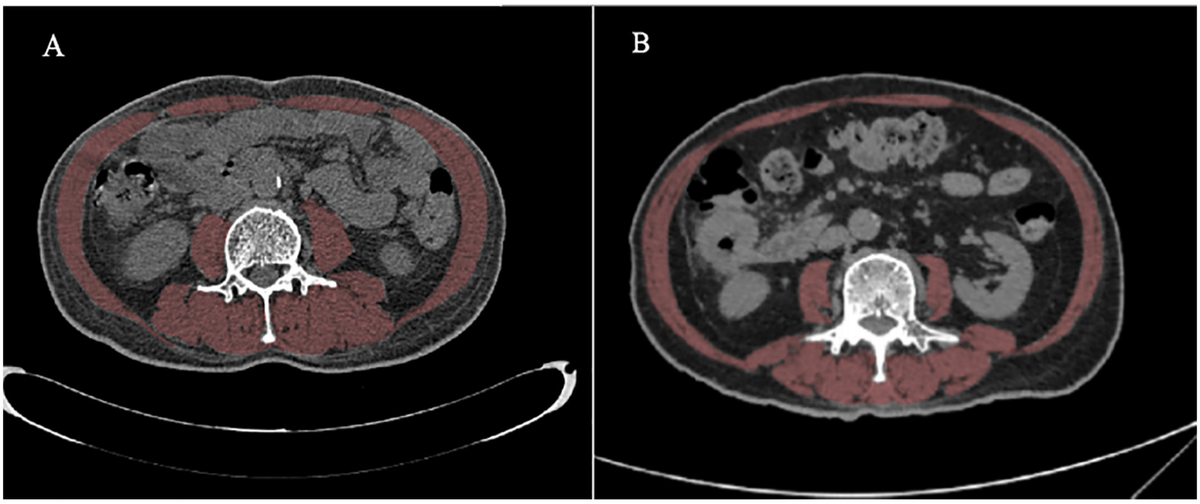

Figure 1. Representative diagram of the total skeletal muscle area outlined at the L3 level for (A) patients without low SM and (B) patients with low SM. SM, skeletal muscle mass.

was OS, defined as the time from surgery to mortality from any cause. Patients underwent follow-up within 1 month after surgery and subsequently every 3 months. The most recent follow-up was conducted in December 2024.

Statistical analysis. Normality of clinical characteristics was assessed using the Shapiro-Wilk test. For baseline characteristics, continuous variables are reported as the mean ± SD and categorical variables are presented as frequencies and percentages. Continuous variables were analyzed using independent t-tests or Mann-Whitney U tests, depending on their normality distribution. Categorical variables were analyzed using χ^2 tests.

Univariate and multivariate Cox regression analyses were performed to identify potential independent prognostic factors for OS. Survival analysis involved the construction of Cox proportional hazards models and Kaplan-Meier analyses. Model performance was evaluated using Harrell's C statistic and likelihood ratio P-values were utilized to compare the performance of risk prediction models.

For risk stratification, samples were divided into high-risk and low-risk groups based on the median risk score derived from the respective multivariate Cox regression models (TNM alone and TNMlow SM). The discriminative ability of this stratification was assessed using Kaplan-Meier survival curves with the logrank test. Hazard ratios (HRs) between the two risk groups were calculated using univariate Cox regression.

Time-dependent receiver operating characteristic (ROC) analysis was performed to assess the predictive performance of the models at specific time points (1, 3 and 5 years). The 'timeROC' package (version 0.4) (33) in R software was utilized, employing 1,000 bootstrap resamples to estimate the area under the curve (AUC) and its 95% CIs. The AUC, ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination), quantified predictive accuracy. Subgroup analysis was conducted to explore the impact of low SM within each subgroup. All data analyses were performed using R software (version 4.2.1; Posit Software, PBC) and Python (version 3.7.12; Python Software Foundation). P<0.05 was considered to indicate a statistically significant difference.

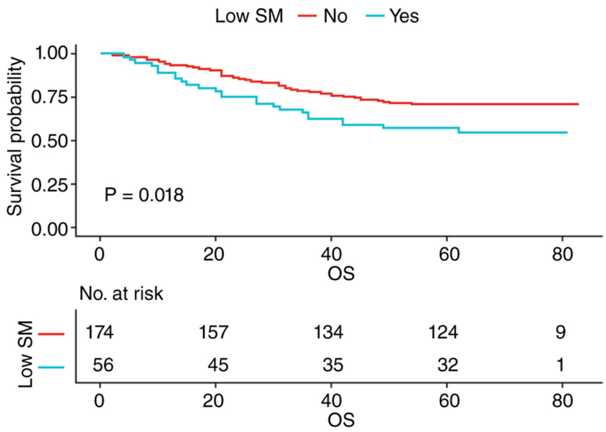

Figure 2. Kaplan-Meier survival curves estimating OS in patients stratified by low SM status. OS, overall survival; SM, skeletal muscle mass.

Results

Baseline characteristics of patients. A total of 230 patients with CC who underwent initial tumor resection at the Second Hospital of Lanzhou University (Lanzhou, China) were included in the present study. Low SMI was defined by sex-specific L3 SMI cut-offs, representing the lowest quartile: 40.6 cm^2/m^2 for males and 34.9 cm^2/m^2 for females. Among these patients, low SMI was identified in 56 individuals (24.34%). Baseline characteristics are presented in Table I. While patients with low SMI exhibited no statistically significant difference from those with normal SMI regarding age, sex, differentiation degree or AJCC stage, they experienced significantly poorer prognosis, shorter OS and higher mortality (all, P<0.05).

Low SM on OS. Kaplan-Meier survival curve analysis (Fig. 2) indicated that the OS of patients with low SM was significantly lower compared with that of patients without low SM (log-rank P<0.001). The risk factors for OS in patients with stage I-III CC are listed in Table II. Univariate

Table I. Baseline characteristics of the participants.

Variable	Total (n=230)	Normal SM (n=174)	Low SM (n=56)	P-value
Age, n (%)				0.252
≤60 years	112 (48.70)	81 (46.55)	31 (55.36)	
>60 years	118 (51.30)	93 (53.45)	25 (44.64)	
Sex, n (%)				0.959
Female	102 (44.35)	77 (44.25)	25 (44.64)	
Male	128 (55.65)	97 (55.75)	31 (55.36)	
CEA, n (%)				0.144
≤5 μg/l	114 (49.57)	91 (52.30)	23 (41.07)	
>5 μg/l	116 (50.43)	83 (47.70)	33 (58.93)	
Height	165.72±7.84	165.61±7.85	166.04±7.85	0.728
Tumor location, n (%)				0.224
Left hemicolon	123 (53.48)	97 (55.75)	26 (46.43)	
Right hemicolon	107 (46.52)	77 (44.25)	30 (53.57)	
Tumor maximum diameter, n (%)				0.662
≤6 cm	180 (78.26)	135 (77.59)	45 (80.36)	
>6 cm	50 (21.74)	39 (22.41)	11 (19.64)	
Neural or vascular invasion, n (%)				0.861
No	84 (36.52)	63 (36.21)	21 (37.50)	
Yes	146 (63.48)	111 (63.79)	35 (62.50)	
Grade, n (%)				0.156
Poor/undifferentiated	39 (16.96)	26 (14.94)	13 (23.21)	
Moderately differentiated	178 (77.39)	136 (78.16)	42 (75.00)	
Well differentiated	13 (5.65)	12 (6.90)	1 (1.79)	
T stage, n (%)				0.398
T1-2	46 (20.00)	37 (21.26)	9 (16.07)	
T3-4	184 (80.00)	137 (78.74)	47 (83.93)	
Lymph node metastasis, n (%)				0.886
N0	166 (72.17)	126 (72.41)	40 (71.43)	
N1-2	64 (27.83)	48 (27.59)	16 (28.57)	
TNM stage, n (%)				0.798
I	44 (19.13)	35 (20.11)	9 (16.07)	
II	122 (53.04)	91 (52.30)	31 (55.36)	
III	64 (27.83)	48 (27.59%)	16 (28.57)	
Overall survival, months	55.29±23.11	57.33±22.07	48.95±25.25	0.018
Survival status, n (%)				0.027
Survival	155 (67.39)	124 (71.26	31 (55.36)	
Mortality	75 (32.61)	50 (28.74)	25 (44.64)	

P-values for categorical variables were calculated using the χ^2 test; continuous variables were analyzed using independent t-tests or Mann-Whitney U tests as appropriate. Data are presented as n (%) for categorical variables and mean ± SD for continuous variables.

analysis revealed that CEA >5, lymph node metastasis and low SM were significantly associated with poorer OS (all P<0.05). Multivariate analysis demonstrated that lymph node metastasis (N1-2; HR=1.63; 95% CI: 1.01-2.62; P=0.0460) and low SM (HR=1.70; 95% CI: 1.05-2.75; P=0.0321) were independent predictors of OS.

Prognostic value of low SM. Within the present study, two Cox proportional hazards models were developed to assess OS in patients with CC, one based solely on the TNM staging system and another that incorporated low SM as an additional prognostic factor. Analysis revealed that the traditional TNM model yielded a C-index of 0.570 (95% CI: 0.508-0.631), whereas the TNM-low SM model achieved a higher C-index of 0.604 (95% CI: 0.540-0.669). Therefore, the inclusion of low SM significantly enhanced the predictive performance of the traditional TNM model (likelihood ratio P=0.027), demonstrating that low SM provided significant

Table II. Univariate and multivariate Cox regression analyses.

	Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years				
≤60	1.00			
>60	0.89 (0.56-1.40)	0.6067		
Sex				
Female	1.00			
Male	0.93 (0.59-1.47)	0.7691		
CEA, μg/l				
≤5	1.00	1.0000		
>5	1.63 (1.03-2.59)	0.0373	1.43 (0.89-2.30)	0.1363
Tumor location				
Left hemicolon	1.00			
Right hemicolon	1.16 (0.74-1.83)	0.5152		
Tumor maximum diameter, cm				
≤6	1.00			
>6	1.02 (0.58-1.76)	0.9562		
Neural or vascular invasion				
No	1.00			
Yes	1.62 (0.98-2.68)	0.0612		
Grade				
Poor/undifferentiated	1.00			
Moderately differentiated	0.87 (0.48-1.55)	0.6320		
Well differentiated	0.58 (0.17-2.01)	0.3876		
T stage				
T1-2	1.00			
T3-4	1.38 (0.74-2.55)	0.3105		
Lymph node metastasis				
N0	1.00	1.0000		
N1-2	1.76 (1.10-2.80)	0.0185	1.63 (1.01-2.62)	0.0460
TNM stage				
I	1.00			
II	1.19 (0.61-2.34)	0.6141		
III	2.00 (1.00-4.02)	0.0515		
Low SM				
No	1.00	1.0000		
Yes	1.76 (1.09-2.85)	0.0204	1.70 (1.05-2.75)	0.0321

HR, hazard ratio; SM, skeletal muscle mass.

prognostic value for OS in patients with stage I-III CC (Table III).

To further evaluate the prognostic value of low SM, patients were stratified into high-risk and low-risk groups using HRs from the Cox model. The discriminatory performance of these groups was then assessed using Kaplan-Meier analysis (Fig. 3). The results demonstrated that the TNM-low SM model (log-rank P=0.001) outperformed the TNM model (log-rank P=0.017) in identifying high-risk patients. To comprehensively assess and compare the predictive performance of the TNM-low SM and TNM models, time-dependent ROC analysis was conducted at 1, 3 and 5 years (Table SI). The results showed that the TNM-low SM model outperformed the TNM model at all time points (Fig. S1).

Subgroup analysis. Subgroup analyses and interaction tests were further performed to examine potential effect modifications by factors (such as age and sex) on the independent association between low SM and OS (Table IV). Subgroup analyses consistently demonstrated an increased mortality

Table III. Multivariate analysis of two models in patients with stage I-III disease.

Model	Overall survival index, HR (95% CI)	P-value	Concordance, HR (95% CI)
TNM-low SM model			0.604 (0.540-0.669)
T	1.13 (0.59-2.16)	0.7056	
N	1.70 (1.05-2.77)	0.0325	
Low SM	1.75 (1.08-2.83)	0.0222	
TNM-model			0.570 (0.508-0.631)
T	1.17 (0.61-2.22)	0.6395	
N	1.70 (1.04-2.76)	0.0332	

SM, skeletal muscle mass; HR, hazard ratio.

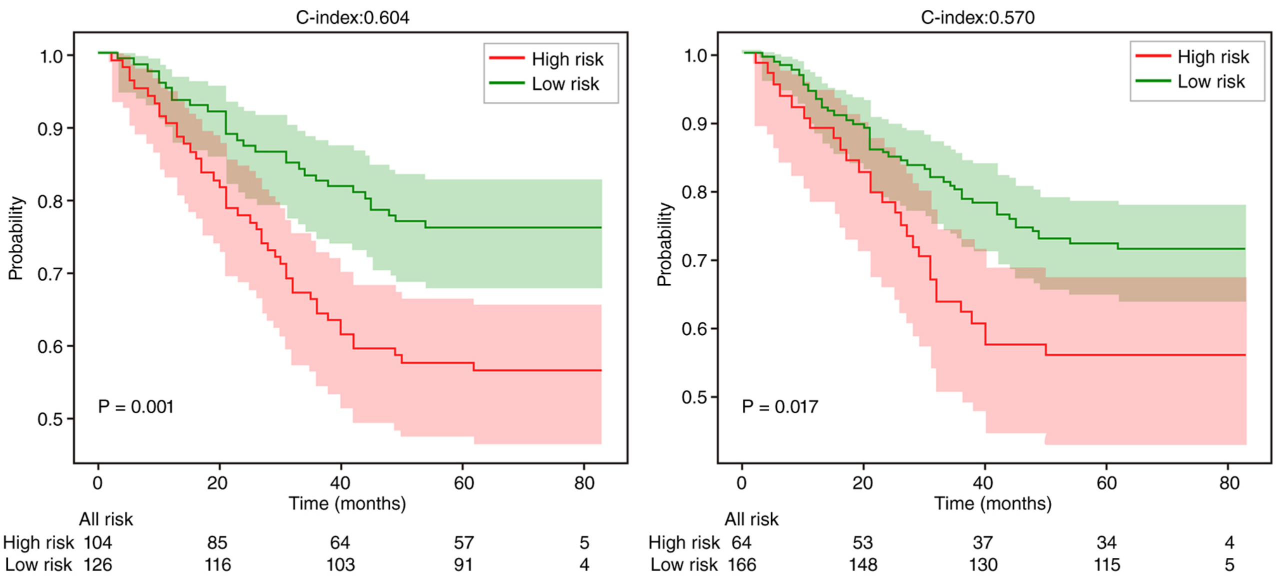

Figure 3. Kaplan-Meier curve analysis of the high-risk and low-risk groups, indicating the differences in overall survival between the high-risk and low-risk groups according to both the TNM-low skeletal muscle mass model and the TNM staging model.

risk associated with low SM across all predefined subgroups of patients with stage I-III CC. While this association was broadly observed, statistically significant findings for poorer survival were specifically noted in patients with left-sided CC (HR=2.03; 95% CI: 1.02-4.03; P=0.0423), T3-4 stage disease (HR=1.81; 95% CI: 1.08-3.05; P=0.0244) and TNM stage II (HR=2.18; 95% CI: 1.12-4.27; P=0.0225). Despite these specific observations, no statistically significant interaction effects were detected across any subgroups (all, interaction P>0.05).

Prognostic value of low SM in stage II CC. Table V details the baseline clinical characteristics of patients with stage II CC, stratified by low SM status. The present study further explored the prognostic importance of low SM on OS in these patients, utilizing Kaplan-Meier survival analysis and both unadjusted and multivariate Cox proportional hazard regression models. The Kaplan-Meier survival curves (Fig. 4) revealed that OS for patients with stage II CC in the low SM group was significantly shorter compared with the normal SM group (P=0.019).

Among patients with stage II tumors (n=122), Cox regression analysis revealed that low SM was associated with shorter OS (HR=2.18; 95% CI: 1.12-4.27; P=0.0225), an association that remained consistent in the adjusted model after controlling for sex, age, CEA level, tumor location, differentiation grade, maximum tumor diameter, neurovascular invasion and T stage (Table VI). These findings suggested that low SM may serve as an independent prognostic factor for OS in patients with stage II CC.

Discussion

Low SM is a common metabolic abnormality in patients with malignant tumors, previously associated with poor outcomes across a number of cancer types (34,35), including lung, gastric, pancreatic and CC. Expanding upon this, the present study investigated the impact of low SM on OS in patients with stage I-III CC, determining its role as an independent prognostic factor. The results demonstrated a significant association between low SM and poorer survival outcomes in patients with CC, with its impact remaining evident in multivariate Cox

Table IV. Effect of low skeletal muscle mass on overall survival in patients with stage I-III colon cancer across different subgroups.

Variable	n	HR (95% CI)	P-value	Interaction P-value
Age, years				0.7331
≤60	112	1.84 (0.95-3.59)	0.0714	
>60	118	1.65 (0.82-3.32)	0.1636	
Sex				0.3738
Female	102	1.37 (0.66-2.87)	0.3988	
Male	128	2.15 (1.14-4.06)	0.0186	
CEA, μg/l				0.1718
≤5	114	2.55 (1.21-5.36)	0.0137	
>5	116	1.28 (0.68-2.41)	0.4414	
Tumor location				0.5301
Left hemicolon	123	2.03 (1.02-4.03)	0.0423	
Right hemicolon	107	1.50 (0.76-2.94)	0.2414	
Tumor maximum diameter, cm				0.2733
≤6	180	1.56 (0.90-2.69)	0.1116	
>6	50	2.88 (1.04-7.93)	0.0411	
Neural or vascular invasion				0.7536
No	84	1.59 (0.64-3.94)	0.3171	
Yes	146	1.89 (1.07-3.32)	0.0282	
Histological grade				0.6226
Poor/undifferentiated	39	1.64 (0.57-4.74)	0.3585	
Moderately differentiated	178	1.81 (1.05-3.14)	0.0338	
Well differentiated	13	0.00 (0.00-Inf)	0.9991	
T stage				0.7243
T1-2	46	1.40 (0.38-5.17)	0.6142	
T3-4	184	1.81 (1.08-3.05)	0.0244	
Lymph node metastasis				0.4618
N0	166	2.02 (1.11-3.66)	0.0206	
N1-2	64	1.39 (0.61-3.16)	0.4291	
TNM stage				0.6808
I	44	1.49 (0.39-5.60)	0.5591	
II	122	2.18 (1.12-4.27)	0.0225	
III	64	1.39 (0.61-3.16)	0.4291	

HR, hazard ratio; CI, confidence interval.

regression analysis (HR=1.70; 95% CI: 1.05-2.75; P=0.0321). Subgroup analyses further revealed that low SM exerted a more notable effect on survival in patients with left-sided CC, T3-4 stage and N1-2 stage disease.

To enhance prognostic predictive capability, the present study developed a novel TNM-low SM model based on the existing TNM staging system. This new model exhibited an improved predictive performance, with higher C-index and AUC values compared with the standard TNM model. This suggests the marked potential of incorporating low SM into the prognostic assessment of CC.

Notably, low SM is a common metabolic abnormality in patients with malignant tumors and previous studies have shown that it is associated with poor outcomes in a number of cancer types, including lung, gastric, pancreatic and CC (36-39). While previous studies have investigated the impact of preoperative low SM on short- and long-term outcomes in CC, a meta-analysis by Trejo-Avila *et al* (40) further clarified its role as a notable predictor of increased postoperative complications and reduced survival. An additional study demonstrated that low SM was an objective and reliable predictive factor, outperforming current nutritional, functional, biochemical and clinical indicators in predicting postoperative complications and cancer recurrence after radical resection for CC (41). However, to date, research on its prognostic value in patients with stage I-III CC is insufficient. Therefore, the findings of the present study may further support the need for clinical intervention for low SM in patients with stage I-III CC.

The present study showed that patients with low SM exhibited significantly lower OS rates compared with those without

Table V. Baseline clinical characteristics of stage II colon cancer patients by SM status.

Variable	Normal SM (n=91)	Low SM (n=31)	P-value
Sex, n (%)			0.840
Female	43 (47.25)	14 (45.16)	
Male	48 (52.75)	17 (54.84)	
Age, n (%)			0.009
≤60 years	51 (56.04)	9 (29.03)	
>60 years	40 (43.96)	22 (70.97)	
CEA, n (%)			0.254
≤5 μg/l	46 (50.55)	12 (38.71)	
>5 μg/l	45 (49.45)	19 (61.29)	
Tumor location, n (%)			0.340
Left-sided colon	53 (58.24)	15 (48.39)	
Right-sided colon	38 (41.76)	16 (51.61)	
Tumor maximum diameter, n (%)			0.064
≤6 cm	30 (32.97)	16 (51.61)	
>6 cm	61 (67.03)	15 (48.39)	
Neurovascular invasion, n (%)			0.486
No	29 (31.87)	12 (38.71)	
Yes	62 (68.13)	19 (61.29)	
Differentiation grade, n (%)			0.438
Poor/undifferentiated	11 (12.09)	5 (16.13)	
Moderately differentiated	76 (83.52)	26 (83.87)	
Well differentiated	4 (4.40)	0 (0.00)	
Overall survival, n (%)			0.027
Survival	69 (75.82)	17 (54.84)	
Deaths during follow-up	22 (24.18)	14 (45.16)	

P-values for categorical variables were calculated using the χ^2 test; continuous variables were analyzed using independent t-tests or Mann-Whitney U tests as appropriate. Data are presented as n (%) for categorical variables and mean ± SD for continuous variables. SM, skeletal muscle mass.

(P=0.018) and low SM was identified as an independent risk factor for OS (HR=1.70; P=0.0321), further demonstrating its reliability as a prognostic indicator for long-term outcomes in patients with stage I-III CC. However, the mechanisms through which low SM influences the long-term prognosis of CC patients are not fully understood. This may be associated with the chronic inflammatory state, impaired immune function and reduced antitumor capacity associated with low SM (42). Low SM in patients with cancer is hypothesized to result from skeletal muscle atrophy due to metabolic abnormalities associated with tumor cachexia (43). Dietary supplements and appetite stimulants alone are insufficient to reverse this underlying metabolic abnormality, which may partially explain the low prognostic role of SM for poor outcomes in patients with cancer (43).

Patients with low SM often exhibit elevated levels of systemic inflammatory factors, such as C-reactive protein and IL-6. These inflammatory markers accelerate tumor progression and compromise treatment outcomes by stimulating tumor cell proliferation, suppressing antitumor immune responses and enhancing tumor resistance via chronic inflammation-driven NF-κB activation (44,45). In addition, studies (46-48) have demonstrated a notable association between low SM and elevated IL-23 levels. This combination effectively predicts prognosis, suggesting that IL-23 and systemic inflammation may serve key roles in poor survival outcomes. High levels of inflammation are closely associated with a poor prognosis in patients with CC. Low SM may exacerbate this inflammatory state, initiating a cascade of reactions that further reduce patient survival rates. Furthermore, low SM has been associated with malnutrition in patients with cancer, impairing immune function and reducing treatment tolerance. Given the particular prevalence of malnutrition in patients with CC, appropriate nutritional supplementation is important in achieving favorable short-term outcomes and long-term survival (49,50). Previous studies have shown that patients with low SM experience a higher incidence of complications after surgery or chemoradiotherapy, slower postoperative recovery and difficulties in treatment implementation (18,51). Despite the present study having not directly analyzed the impact of treatment modalities on patient outcomes, the present results

Table VI. Multivariate analysis of low SM in patients with stage II colon cancer.

Variable	Overall survival, HR (95% CI)	P-value	Concordance index, (95% CI)
Unadjusted Cox regression			0.584 (0.507-0.661)
Low SM	2.18 (1.12-4.27)	0.0225	
Multivariable Cox regression			0.649 (0.567-0.730)
Low SM	2.19 (1.08-4.42)	0.0289	
Sex	1.14 (0.58-2.23)	0.7012	
Age	0.87 (0.42-1.80)	0.7037	
CEA, µg/l	1.36 (0.67-2.75)	0.3887	
Tumor location	1.18 (0.59-2.35)	0.6387	
Histological grade	1.16 (0.37-3.64)	0.7951	
Tumor maximum diameter, cm	1.02 (0.46-2.25)	0.9593	
Neural or vascular invasion	1.61 (0.74-3.50)	0.2308	
T stage	1.57 (0.67-3.64)	0.2976	

SM, skeletal muscle mass.

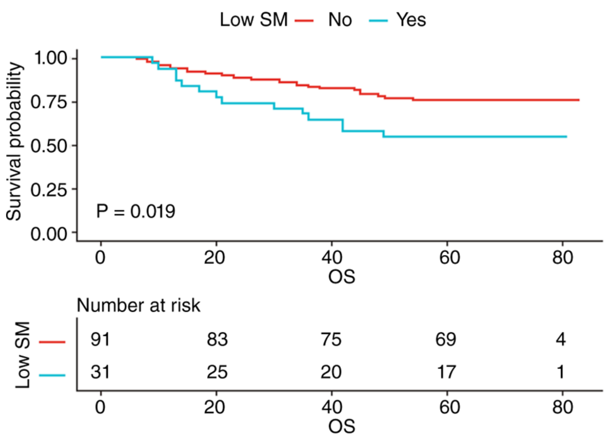

Figure 4. Kaplan-Meier survival curves evaluating the OS based on low SM status in patients with stage II colon cancer. OS, overall survival; SM, skeletal muscle mass.

indicated poorer survival outcomes for patients with low SM. This suggested that clinical practice should prioritize screening for and intervening in low SM to improve patient outcomes.

While the TNM staging system is currently a standard tool for treatment decision-making and prognosis assessment in CC, it still presents limitations in individualized prediction (52). To overcome this limitation, CC has been classified into molecular subtypes based on gene expression, aiming to guide treatment decisions more effectively. However, these classifications currently offer limited practical value in routine clinical practice (53). Due to complex CC development, a single genetic marker is unlikely to predict prognosis. Therefore, international validation analysis, initiated by the International Immuno-Scoring A study from Consortium (54), assessed the prognostic value of total and cytotoxic tumor-infiltrating T cell counts in patients with stage I-III CC, employing a consensus immuno-scoring assay. Results indicated that patients with high immuno-scores experienced the lowest 5-year recurrence risk and the assay could effectively identify patients at a high-risk of tumor recurrence, particularly in stage II cancer. However, the AUC value for predicting OS in this model, which combined all clinical variables with the immune score, remained <0.65. This underscored the need for further exploration of additional prognostic predictors.

Based upon this, the present study subsequently constructed both a traditional TNM model and a modified TNM-low SM model to assess and validate the predictive ability of low SM in patients with stage I-III CC. The TNM-low SM model demonstrated an improved predictive performance. The resulting C-index (0.604) was higher compared with that of the standalone TNM model (0.570). Furthermore, the AUC values for the TNM-low SM model at 1, 3 and 5 years consistently exceeded those of the TNM model, with the most significant improvement observed being observed at 3 years (TNM-low SM model AUC=0.629 vs. TNM model AUC=0.588). These findings indicated that incorporating low SM factors enhanced the predictive capability of the model, further validating the role of low SM in CC prognosis assessment. Kaplan-Meier survival analysis additionally showed that the TNM-low SM model demonstrated an improved stratified predictive capability compared with the standalone TNM model. These results suggested that, in clinical practice, the TNM-low SM model, by incorporating low SM factors, may offer more precise survival predictions and effectively identify patients at a high-risk, thereby aiding individualized treatment decisions.

Subgroup analysis in the present study further demonstrated that low SM had a more significant impact on survival in patients with left-sided CC, as well as those with T3-4 and N1-2 stages. This observation may be associated with known differences in gut microbiota, tumor microenvironment and metabolic characteristics among patients with left-sided CC, as previous studies (55,56) have reported marked biological differences and long-term prognostic distinctions between left-sided and right-sided CC (57). A retrospective study indicated that low SM (15) as assessed by CT, independently predicts shorter OS and recurrence-free survival in patients with left-sided colon or rectal cancer after curative surgery. These results were consistent with the subgroup analysis. Furthermore, patients with T3-4 and N1-2 stage disease already bear a greater disease burden and thus low SM may further exacerbate their survival disadvantage. Therefore, in clinical practice, prioritizing the screening and management of low SM in these high-risk subgroups is important in optimizing survival outcomes.

Although the present study reported the adverse impact of low SM on OS in patients with stage I-III CC (particularly those with stage II disease), a number of limitations must be acknowledged. Firstly, a full diagnosis of sarcopenia, according to the EWGSOP2 consensus, requires the simultaneous assessment of both muscle mass and muscle function (including both grip strength and walking speed). Due to the retrospective design of the present study, preoperative functional measurements could not be obtained; thus, the exposure variable in the present study was low SM rather than comprehensive sarcopenia. Secondly, a number of body composition components, such as skeletal muscle and visceral fat, are interrelated through adipose, muscular and metabolic factors and should not be assessed in isolation. The present study focused solely on low SM and did not assess visceral adipose tissue (VAT) at the L3 level or trunk fat, which could have provided an improved prognostic stratification through combined phenotypes (such as sarcopenic obesity, defined as low SM combined with high VAT). This omission was due to limitations in the storage of imaging data, preventing the quantification of VAT or trunk fat (58,59). Thirdly, as a retrospective, single-center analysis, the present study was susceptible to selection bias. Furthermore, survival outcomes in patients with low SM who received different treatment regimens (such as adjuvant chemotherapy or intensive nutritional intervention) were not analyzed and other potential confounding factors (including nutritional intake or inflammatory status) were not accounted for.

To overcome these limitations, future prospective studies should be conducted in larger, multicenter cohorts, incorporating functional assessments, standardized CT cut-offs, comprehensive body composition analysis (including VAT and trunk fat) and detailed treatment and nutritional data.

In conclusion, low SM may be an independent prognostic factor for OS in patients with stage I-III CC. When incorporated into a combined model with TNM staging, it markedly enhanced prognostic prediction, particularly in patients with stage II CC, by more effectively identifying high-risk populations. Therefore, low SM may represent a robust prognostic biomarker to facilitate risk stratification and individualized treatment.

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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

CM and FC designed the present study, collected the data and conducted the data analysis. HY conceived the research idea, supervised the entire research process, participated in the interpretation and validation of the results, provided critical oversight of the statistical methods, and was responsible for the final review, revision and approval of the manuscript. All authors read and approved the final version of the manuscript. CM and HY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the Second Hospital of Lanzhou University (Lanzhou, China; approval no. 2025 A-638). As the present study was retrospective and the privacy and personal identity information of the patients were protected, the need for informed consent was waived by the Medical Ethics Committee of the Second Hospital of Lanzhou University.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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