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Albumin-myosteatosis gauge as a novel prognostic risk factor in patients with non-metastatic colorectal cancer

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Abstract

Background Myosteatosis and systemic inflammation are well-known prognostic factors in patients with colorectal cancer (CRC). The serum albumin level is a reflection of malnutrition and systemic inflammation, which in turn plays a key role in the development of myosteatosis. However, few studies have been conducted on these synergistic effects. This study aimed to examine the individual and synergistic effects of different prognostic markers related to skeletal muscle quality and serum albumin levels in patients with CRC.

Methods This study enrolled patients with stage I–III CRC who underwent surgical resection between July 2006 and February 2014. Skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) were calculated using computed tomography at the L3 level obtained within 2 months prior to surgery. The albumin-myosteatosis gauge (AMG) was defined as SMD × albumin. Patients were divided into sex-specific quartiles (G1 to G4) according to the AMG, and analysis of variance for continuous variables and chi-square test for categorical variables were used to compare variables among quartiles. Cox proportional hazard models were constructed and integrated receiver operating characteristic curve (iAUC) analysis was used to compare the prognostic performance of SMD, albumin and AMG.

Results Among the 906 participants, the median (interquartile) age was 64 (55–72) years, and 365 (40.3%) were female. AMG was significantly correlated with the occurrence of complications, albumin level, SMI and SMD (all $P < 0.001$). Overall survival (OS) differed significantly according to the AMG group, with 5-year OS for G1–G4 being 73.4%, 86.2%, 91.1% and 95.5%, respectively ($P < 0.0001$). Although SMI, SMD, albumin and AMG were all significant individual prognostic markers of OS in the univariable analysis, AMG remained the only independent prognostic factor in the multivariable analysis (G1 vs. G2, $P = 0.045$, G1 vs. G3, $P = 0.005$, G1 vs. G4, $P < 0.001$, respectively). The iAUC value of AMG [0.681, 95% confidence interval (CI) = 0.638–0.723] was superior to that of SMD (0.610, 95% CI = 0.566–0.654) (bootstrap iAUC mean difference = 0.071, 95% CI = 0.034–0.106), SMI (0.551, 95% CI = 0.511–0.594) (bootstrap iAUC mean difference = 0.129, 95% CI = 0.076–0.181) and albumin (0.627, 95% CI = 0.585–0.668) (bootstrap iAUC mean difference = 0.053, 95% CI = 0.010–0.098).

Conclusions In patients with stage I–III CRC, AMG is a meaningful predictor of survival, with superior prognostic value compared to SMI, SMD or albumin alone. Further studies are needed to determine their significance in different ethnic groups.

Keywords myosteatosis; albumin; albumin-myosteatosis gauge; colorectal cancer; sarcopenia; inflammation

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Introduction

Colorectal cancer (CRC) is the third most common malignancy and one of the leading causes of cancer-related death worldwide. Despite much progress in the surgical and medical treatment of CRC, 20–30% of patients with stage I–III disease still develop recurrence, and it is the third highest cause of cancer-related mortality in South Korea.[1,2] Many studies have focused on identifying clinical and treatment-related factors associated with prognosis in patients with CRC.[3]

Cancer cachexia, a syndrome characterized by multiple factors including reduced nutritional status and a chronic inflammatory response, is associated with poor survival.[4] Skeletal muscle wasting is an important factor in cancer cachexia. The definition of sarcopenia used by the European Working Group on Sarcopenia in Older People (EWGSOP) has recently been changed to highlight that both muscle mass and muscle quality, reflected in part by intermuscular or intramyocelluar fat deposition (myosteatosis), are important.[5] A meta-analysis showed that myosteatosis was a major prognostic factor for survival in a variety of cancer types, reporting 73% higher mortality in cancer patients with myosteatosis than in those without myosteatosis [hazard ratio (HR) 1.73, 95% confidence interval (CI) 1.58–1.90, $P < 0.0001$].[6]

Systemic inflammation is also a promising factor for predicting the outcome of CRC, as well as a key component in the pathogenesis of muscle wasting by pro-inflammatory cytokines, such as interleukin 1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor (TNF)-α, which influence muscle progenitor cells and muscle turnover.[7,8] These cytokines also affect the production of albumin in the liver, which is an indicator of malnutrition, as well as a factor for inflammation.[9] Taking this into consideration, muscle quality and albumin share a common pathway; however, the synergistic effects of both in patients with cancer have not been thoroughly investigated.

Therefore, this study aimed to examine and compare different prognostic markers for overall survival (OS) related to skeletal muscle quality and serum albumin in patients with CRC.

Methods

Study population

This retrospective study enrolled patients diagnosed with CRC who were surgically treated between July 2006 and February 2014 at Gangnam Severance Hospital, Yonsei University College of Medicine. This study was approved by the Institutional Review Board of our hospital. The requirement for informed consent was waived owing to the retrospective nature of the study.

The following patients were eligible for study inclusion: (i) diagnosed with stage I–III CRC, (ii) underwent blood testing within 1 month prior to surgery, including serum albumin measurements, and (iii) underwent routine abdominal-pelvic computed tomography (CT) within 2 months prior to surgery. The exclusion criteria were as follows: (i) neuroendocrine or gastrointestinal stromal tumour, (ii) appendiceal or anal cancer, (iii) double primary cancers, (iv) preoperative chemoradiotherapy or radiotherapy, (v) emergency operations and (vi) hereditary non-polyposis syndrome, familial adenomatous polyposis, ulcerative colitis and Crohn's disease. Details of the inclusion and exclusion criteria are shown in *Figure* S1.

Clinical variables

Patient source data were obtained from a review of electronic medical records (EMR) and included information on disease stage, tumour characteristics such as tumour location, size, histological grade, lymphovascular invasion (LVI), total lymph nodes, receipt of chemotherapy and demographic characteristics, including sex, age, American Society of Anesthesiologists (ASA) grade and body mass index (BMI). Height and weight measured at the clinical visit closest to the diagnostic CT scan were used to calculate BMI, expressed as weight in kilograms (kg) divided by height in meters squared (m^2). Other relevant covariates, such as carcinoembryonic antigen (CEA) and serum albumin levels, and complications, were retrieved from the EMR.

Measurement of skeletal muscle index and skeletal muscle radiodensity

Abdominopelvic CT images were obtained within 2 months prior to surgery. The CT protocol is described in *Supplementary Paragraph* 1. CT images taken at the level of the third lumbar vertebra (L3) were used to measure skeletal muscle area (SMA) and skeletal muscle density (SMD). To measure SMA, we used in-house open-source software 'BMI_CT' available at https://sourceforge.net/projects/muscle-fat-area-measurement.[10] The SMD was measured using 3DSlicer, which is also available online at https://www.slicer.org.[11] The SMA was segmented using a threshold of −29 to 150 Hounsfield units (HU). SMA normalized to height (cm^2/m^2) was defined as the skeletal muscle index (SMI). The SMD was assessed by estimating the mean HU value of the SMA. The intra-class correlation coefficients pre-determined via this software by two investigators of SMD and SMI were reported to be 0.99 (range, 0.97–0.99) and 0.97 (range, 0.95–0.99), respectively, in our previous report.[12]

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Albumin-myosteatosis gauge

The albumin-myosteatosis gauge (AMG) was calculated using the following formula: serum albumin (g/dL) × SMD (HU). For simplicity, an arbitrary unit was used in the study instead of g/dL × HU as the AMG unit.

Defining low and high level of SMD and albumin

In this study, SMD was divided into low and high according to the criteria suggested by Martin et al., which was 41 in patients with BMI $<$ 25 kg/m^2 and 33 in patients with BMI $\geq$ 25 kg/m^2.[13] Albumin was classified into low and high groups based on the median value.

Patient follow-up

Patient follow-up was performed regularly every 3 months at outpatient clinics for the first 3 years post-operatively and then every 3–6 months for the next 2 years. Routine chemistry and complete blood counts, including serum CEA levels, were recorded during follow-up. Chest and abdominopelvic CT images were obtained every 6 or 12 months, considering the patient's pathological stage, for 5 years. Procedures, such as colonoscopy, pelvic magnetic resonance imaging and other imaging studies, were performed according to the judgement of the physician.

Statistical analysis

Patients were divided into sex-specific quartiles based on their AMG levels at the time of enrolment. Clinicopathological characteristics between the groups were compared using analysis of variance for continuous variables and chi-square test for categorical variables. Bonferroni's post hoc test was performed to assess the magnitude of the differences.

The primary outcome of the study was OS, which was defined as the time from the date of surgery to the date of death from any cause or the date of the last follow-up. Patients with OS periods longer than 5 years were censored. OS was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Cox proportional hazard models were used to test the relationship of between AMG and OS. Variables that were significant ($P < 0.05$) in the univariable analyses were entered into a multivariable analysis using backward selection. The results were reported using HR with corresponding 95% CIs.

To compare the prognostic capabilities of AMG, albumin and SMD, the integrated areas under the time-dependent receiver operating characteristic (ROC) curves (iAUC) were calculated. The time-dependent ROC curve is the weighted average of the AUC in a specific time period and is used as a continuous marker to evaluate the discriminatory power for time-dependent disease outcomes. The time-dependent ROC curve was used to measure the predictive value of the model during a certain period, mostly during follow-up. We used bootstrapping to assess between-group risk differences. All analyses were repeated according to sex, as shown in the *Supporting Information*.

All statistical analyses were performed using R version 4.1.0 (R-project, Institute for Statistics and Mathematics, Vienna, Austria). Statistical significance was set at $P < 0.05$.

Results

Distribution of AMG according to the sex

The study sample consisted of 906 patients with stage I–III CRC. The median values of albumin, SMD and AMG differed considerably according to sex (*Figure* S2). With respect to AMG, each quartile was divided into 158.66, 189.95 and 219.52 in male patients and 138.43, 174.06 and 200.54 in female patients, respectively (*Table* S1). We divided AMG into four subgroups according to sex quartile methods: G1, G2, G3 and G4. The numbers of male patients in groups G1, G2, G3 and G4 were 136, 135, 135 and 135, respectively. The number of female patients in groups G1, G2, G3 and G4 was 96, 95, 95 and 95, respectively.

Clinicopathological characteristics according to the quartile of AMG

Analysis of variance for continuous variables and chi-square test for categorical variables were used to detect correlations between quartile AMG groups and clinicopathological characteristics, such as sex, age, BMI, ASA grade, CEA level, tumour location, tumour size, histologic grade, LVI, total lymph nodes, stage, complications, chemotherapy, albumin level, SMI and SMD. Patients in the lowest quartile AMG group were older (age ≥70 years; 64.5%, 38.5%, 21.2% and 5.3%, $P < 0.001$), had higher ASA grade (grades III and IV, 17.5%, 10.6%, 8.8% and 4%, $P < 0.001$; G1 vs. G4, $P < 0.05$; G2 vs. G3, $P < 0.05$), higher CEA (≥5 ng/mL, 36%, 27%, 21.7% and 21.2%, $P < 0.001$; G1 vs. G3, $P < 0.05$; G1 vs. G4, $P < 0.05$), larger tumour size (≥5 cm, 53.5%, 42%, 27.4% and 28.3%, $P < 0.001$; G1 vs. G3, $P < 0.05$; G1 vs. G4, $P < 0.05$; G2 vs. G3, $P < 0.05$; G2 vs. G4, $P < 0.05$), more complications (32%, 19.9%, 17.3% and 16.8%, $P < 0.001$; G1 vs. G2, $P < 0.05$; G1 vs. G3, $P < 0.05$; G1 vs. G4, $P < 0.05$), lower mean serum albumin levels (g/dL) (3.8, 4.2, 4.4 and 4.6, $P < 0.001$; G1 vs. G2, $P < 0.05$; G1 vs. G3, $P < 0.05$; G1 vs. G4, $P < 0.05$; G2 vs. G3, $P < 0.05$; G2 vs.

G4, $P < 0.05$; G3 vs. G4, $P < 0.05$), lower mean SMI (cm^2/m^2) (47.1, 47.9, 49.3 and 49.8, $P < 0.001$; G1 vs. G3, $P < 0.05$; G1 vs. G4, $P < 0.05$) and lower mean SMD (HU) (32.2, 40.3, 45.6 and 50.9, $P < 0.001$; G1 vs. G2, $P < 0.05$; G1 vs. G3, $P < 0.05$; G1 vs. G4, $P < 0.05$; G2 vs. G3, $P < 0.05$; G2 vs. G4, $P < 0.05$; G3 vs. G4, $P < 0.05$) than those in the other groups (*Table* 1).

We compared SMD and albumin levels among the AMG groups in men and women. There were significant differences in the median SMD values according to the AMG group in both men and women (all $P < 0.001$). In addition, there were significant differences in the median albumin level according to the AMG group in the men and women (all $P < 0.001$) (*Figure* S3).

Kaplan–Meier survival curve according to the quartiles of AMG

Kaplan–Meier analysis showed significant differences in 5-year OS among the AMG groups (G1–73.4%, G2–86.2%, G3–91.1% and G4–95.5%), respectively ($P < 0.0001$; G1 vs. G2, $P = 0.005$; G1 vs. G3, $P < 0.001$; G1 vs. G4, $P < 0.001$; G2 vs. G3, $P = 0.592$; G2 vs. G4, $P = 0.051$; G3 vs. G4, $P = 0.400$) (*Figure* 1). In subgroup analysis of stage II and III patients, the 5-year OS rates for G1, G2, G3 and G4 were 69.6%, 83.2%, 87.9% and 94.7%, respectively ($P < 0.0001$) (*Figure* S4).

Univariable and multivariable analyses of factors associated with OS

Univariable analysis showed that age, BMI, CEA level, tumour size, complications, histologic grade, total lymph nodes, LVI, stage, SMI, SMD, albumin level and AMG were all significantly associated with OS (*Table* 2). In a multivariable analysis adjusted for age, sex, BMI, CEA level, tumour size, histologic grade, complications, total lymph nodes, LVI, stage, SMI, SMD and albumin level, AMG was identified as

Table 1 Patient characteristics according to the quartile of albumin-myosteatosis gauge

Variables	Categorization	G1 group(n = 228) n (%)	G2 group(n = 226) n (%)	G3 group(n = 226) n (%)	G4 group(n = 226) n (%)	P
Sex	Female	92 (40.4)	91 (40.3)	91 (40.3)	91 (40.3)	
	Male	136 (59.6)	135 (59.7)	135 (59.7)	135 (59.7)	>0.999
Age (years)	<70	81 (35.5)†‡§	139 (61.5)*‡§	178 (78.8)*†§	214 (94.7)*†‡	
	≥70	147 (64.5)	87 (38.5)	48 (21.2)	12 (5.3)	<0.001
BMI (kg/m^2)	Mean (SD)	23.7 (3.5)	23.6 (2.9)	23.5 (2.8)	23.0 (2.9)	0.051
ASA grade	I	84 (36.8)§	95 (42)‡	108 (47.8)†	135 (59.7)*	
	II	86 (37.7)	96 (42.5)	87 (38.5)	73 (32.3)	
	III and IV	40 (17.5)	24 (10.6)	20 (8.8)	9 (4)	
	Unknown	18 (7.9)	11 (4.9)	11 (4.9)	9 (4)	<0.001
CEA (ng/mL)	<5	141 (61.8)‡§	158 (69.9)	158 (69.9)*	164 (72.6)*	
	≥5	82 (36)	61 (27)	49 (21.7)	48 (21.2)	
	Unknown	5 (2.2)	7 (3.1)	19 (8.4)	14 (6.2)	<0.001
Tumour location	Colon	174 (76.3)§	163 (72.1)	156 (69)	140 (61.9)*	
	Rectum	54 (23.7)	63 (27.9)	70 (31)	86 (38.1)	0.008
Tumour size	<5	106 (46.5)‡§	131 (58.0)‡§	164 (72.6)*†	162 (71.7)*†	
(cm)	≥5	122 (53.5)	95 (42.0)	62 (27.4)	64 (28.3)	<0.001
Histologic grade	G1 and G2	204 (89.5)	208 (92.0)	215 (95.1)	211 (93.4)	
	G3 and MC and SRC	24 (10.5)	18 (8.0)	11 (4.9)	15 (6.6)	0.134
LVI	Absent	162 (71.1)	164 (72.6)	184 (81.4)	174 (77.0)	
	Present	60 (26.3)	56 (24.8)	36 (15.9)	40 (17.7)	
	Unknown	6 (2.6)	6 (2.7)	6 (2.7)	12 (5.3)	0.029
Total lymph	<12	36 (15.8)	28 (12.4)	34 (15.0)	32 (14.2)	
nodes	≥12	192 (84.2)	198 (87.6)	192 (85.0)	194 (85.8)	0.756
Stage	I and II	128 (56.1)	132 (58.4)	138 (61.1)	124 (54.9)	
	III	100 (43.9)	94 (41.6)	88 (38.9)	102 (45.1)	0.560
Complications	No	155 (68.0)†‡§	181 (80.1)*	187 (82.7)*	188 (83.2)*	
	Yes	73 (32.0)	45 (19.9)	39 (17.3)	38 (16.8)	<0.001
Chemotherapy	No	105 (46.1)	94 (41.6)	93 (41.2)	87 (38.5)	
	Yes	123 (53.9)	132 (58.4)	133 (58.8)	139 (61.5)	0.432
Albumin (g/dL)	Mean (SD)	3.8 (0.5)†‡§	4.2 (0.3)*‡§	4.4 (0.3)*†§	4.6 (0.3)*†‡	<0.001
SMI (cm^2/m^2)	Mean (SD)	47.1 (8.8)‡§	47.9 (7.6)	49.3 (8.6)*	49.8 (9.2)*	<0.001
SMD (HU)	Mean (SD)	32.2 (7.1)†‡§	40.3 (4.2)*‡§	45.6 (3.7)*†§	50.9 (4.1)*†‡	<0.001

ASA, American Society of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen; HU, Hounsfield unit; LVI, lymphovascular invasion; MC, mucinous adenocarcinoma; SD, standard deviation; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; SRC, signet-ring cell.
*$P < 0.05$ vs. G1 group.
†$P < 0.05$ vs. G2 group.
‡$P < 0.05$ vs. G3 group.
§$P < 0.05$ vs. G4 group.

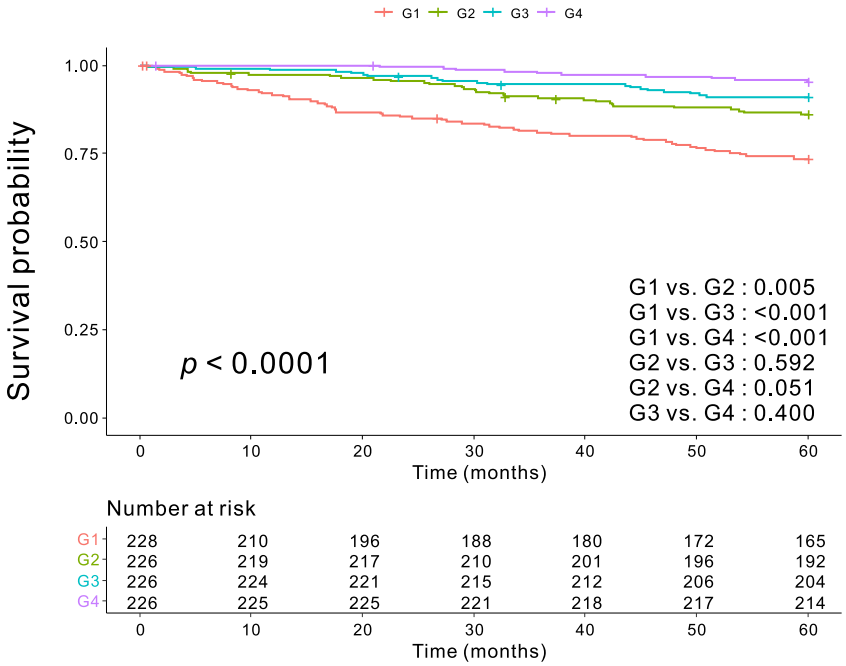

Figure 1 Kaplan–Meier survival curve. The 5-year overall survival for G1, G2, G3 and G4 were 73.4%, 86.2%, 91.1% and 95.5%, respectively ($P < 0.0001$).

an independent prognostic factor for OS (G1 vs. G2, $P = 0.045$; G1 vs. G3, $P = 0.005$; G1 vs. G4, $P < 0.001$) (*Table* 3).

Comparison between AMG and albumin, SMI and SMD

We compared iAUC values to evaluate the predictive power of AMG as a prognostic factor during the follow-up period. The integrated AUC value of AMG (0.681, 95% CI = 0.638–0.723) was superior to that of SMD (0.610, 95% CI = 0.566–0.654) (bootstrap iAUC mean difference = 0.071, 95% CI = 0.034–0.106), SMI (0.551, 95% CI = 0.511–0.594) (bootstrap iAUC mean difference = 0.129, 95% CI = 0.076–0.181) and albumin (0.627, 95% CI = 0.585–0.668) (bootstrap iAUC mean difference = 0.053, 95% CI = 0.010–0.098) (*Table* S2).

Clinical significance of AMG according to sex

We have added statistical analyses according to sex to the supplementary file (*Tables* S3–S8). In male patients, AMG was identified as a significant prognosticator, whereas albumin level and SMD were not selected in the final multivariable model with backward selection (*Tables* S3 and S4). Based on the integrated AUC comparison (*Table* S5), the discriminatory ability of AMG may be better than that of albumin level, SMD and SMI in male patients.

In female patients, AMG was also identified as an independent indicator of survival in multivariable analysis (*Tables* S6 and S7). The discriminatory ability of AMG was better than that of SMD and SMI but similar to that of albumin level (*Table* S8).

Clinical significance of category-based combination of albumin and SMD

In addition, the patients were divided into four groups as follows: low SMD and low albumin level (LL), low SMD but high albumin level (LH), high SMD but low albumin level (HL) and high SMD and high albumin level (HH). Five-year OS was significantly different among the four groups (72.1%, 86.1%, 84.9% and 93.7%, respectively ($P < .0001$); LL vs. LH, $P = 0.047$; LL vs. HL, $P = 0.010$; LL vs. HH, $P < 0.001$; LH vs. HL, $P > 0.05$; LH vs. HH, $P = 0.084$; HL vs. HH, $P = 0.003$) (*Figure* S5). Univariable analysis according to categorical classification showed statistical significance (LL vs. LH, $P = 0.005$; LL vs. HL, $P < 0.001$; LL vs. HH, $P < 0.001$), whereas multivariable analysis showed significance only for LL versus HH ($P < 0.001$) (*Table* S9).

Discussion

This study demonstrated the superior predictive capability of AMG as a predictor of OS compared with serum albumin, SMI

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Table 2 Univariable analysis of factors associated with overall survival

Variables	Categorization	Univariable analysis	
		HR (95% CI)	*P*
Sex	Female	1	
	Male	1.343 (0.921–1.957)	0.125
Age (years)	<70	1	
	≥70	2.757 (1.927–3.943)	<0.001
BMI (kg/m^2)	<25	1	
	≥25	0.524 (0.330–0.832)	0.006
ASA grade	I	1	
	II	1.181 (0.798–1.748)	0.405
	III and IV	1.006 (0.524–1.931)	0.985
	Unknown	1.721 (0.873–3.389)	0.117
CEA (ng/mL)	<5	1	
	≥5	1.940 (1.340–2.807)	<0.001
	Unknown	1.031 (0.415–2.558)	0.946
Tumour location	Colon	1	
	Rectum	0.944 (0.637–1.4)	0.777
Tumour size	<5	1	
(cm)	≥5	2.184 (1.526–3.126)	<0.001
Complications	No	1	
	Yes	2.043 (1.402–2.977)	<0.001
Histologic grade	G1 and G2	1	
	G3 and MC and SRC	1.862 (1.084–3.197)	0.024
Total lymph	<12	1	
nodes	≥12	0.636 (0.409–0.987)	0.043
LVI	Absent	1	
	Present	2.456 (1.698–3.552)	<0.001
	Unknown	0.605 (0.148–2.468)	0.484
Stage	I and II	1	
	III	2.644 (1.822–3.837)	<0.001
Chemotherapy	No	1	
	Yes	1.044 (0.726–1.501)	0.815
SMI (cm^2/m^2)	Low	1	
	High	0.607 (0.417–0.885)	0.009
SMD (HU)	Low	1	
	High	0.387 (0.271–0.552)	<0.001
Albumin	Low	1	
	High	0.351 (0.239–0.514)	<0.001
AMG	G1	1	
	G2	0.472 (0.306–0.729)	<0.001
	G3	0.296 (0.178–0.491)	<0.001
	G4	0.144 (0.073–0.281)	<0.001

AMG, albumin-myosteatosis gauge; ASA, American Society of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; HU, Hounsfield unit; LVI, lymphovascular invasion; MC, mucinous adenocarcinoma; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; SRC, signet-ring cell.

Table 3 Multivariable analysis of factors associated with overall survival

Variables	Categorization	HR (95% CI)	*P*
AMG	G1	1	
	G2	0.627 (0.397–0.989)	0.045
	G3	0.457 (0.263–0.794)	0.005
	G4	0.223 (0.107–0.464)	<0.001

AMG, albumin-myosteatosis gauge; CI, confidence interval; HR, hazard ratio.
Multivariable analysis was adjusted for age, sex, body mass index, carcinoembryonic antigen, tumour size, histologic grade, complications, lymph node numbers, lymphovascular invasion, stage, skeletal muscle index, skeletal muscle radiodensity and albumin.

and SMD in patients with stage I–III CRC. AMG can be used as a novel prognostic biomarker that reflects the risk of cachexia and nutritional status of patients with CRC.

Sarcopenia was initially suggested to represent muscle loss observed in older people.[14] The EWGSOP currently defines sarcopenia according to muscle mass, strength and physical performance. When CT is performed, sarcopenia can be estimated using the SMI obtained from a cross-sectional CT image at the L3 level.[5] Myosteatosis is the infiltration of adipose tissue into the skeletal muscle and is associated with muscle strength per size.[15] Due to CT examination being routinely performed in most patients with CRC, the assessment of muscle quality has also been extensively studied.[6,16–18] Although the exact pathophysiology of myosteatosis is yet to be discovered, some clinical data suggest that sarcopenia and myosteatosis may partially share systemic inflammation as a common mechanism underscored by IL-6-mediated catabolic activity.[7,8] The prognostic value of sarcopenia and myosteatosis in patients with cancer is well known.[19–21]

The prognostic impacts of SMI and SMD are often not directly compared, and studies to date have reported contradictory results. Cortellini et al. found that, whereas SMI was significantly associated with progression-free survival in patients with CRC (HR, 0.54; 95% CI: 0.31–0.93), low SMD was not (HR, 0.67; 95% CI: 0.36–1.24).[22] Malietzis et al. reported that, in patients who received surgical treatment of CRC, SMI was a prognostic factor for OS and disease-free survival (DFS) ($P < 0.001$ and $P = 0.011$, respectively), whereas SMD was not ($P = 0.069$ and $P = 0.622$, respectively).[7] In contrast, other studies have demonstrated that SMD is a better prognostic factor than SMI.[23,24] Maurits et al. reported that higher SMD was associated with better OS, although no significant association with SMI was found in patients with renal cell carcinoma.[23] Another study that enrolled patients with gastric cancer treated with radical gastrectomy showed similar findings, with SMD being significantly associated with OS and DFS and SMI was excluded in a multivariate analysis using forward stepwise selection.[24] Although it is very difficult to determine the reason underscoring the contradictory associations of SMI and SMD evident from prior studies, the absence of definite criteria to diagnose sarcopenic status using SMI or SMD may be one fundamental reason. A recent review observed diverse SMI cut-off values for the 156 included studies with 39 (25%), 47 (30.1%) and 70 (44.9%) using the criteria put forth by Martin et al., Prado et al. and their own, respectively.[25] Also, a review of 73 studies described the use of 32 different cut-off values when determining the prognostic value of myosteatosis.[17] These situations may hinder the reliable determination of the prevalence of sarcopenia using SMI and/or SMD and the incorporation of these biomarkers in the process of clinical decision in patients with cancer. Therefore, future investigations are required to identify additional universal biomarkers of CRC prognosis.

Serum albumin, which is produced in the liver and is abundant in the blood, is a well-known marker of systemic inflammation and nutritional status.[26] Gastrointestinal tumours, including CRC, can influence serum albumin levels in two ways. Malnutrition due to impaired food absorption is associated with decreased survival in patients with cancer.[27,28] Systemic inflammation secondary to cancer also lowers serum albumin levels,[29,30] and this anti-tumour response even promotes cancer growth and progression,[31] resulting in a worse prognosis.[26] A meta-analysis of 29 studies showed that serum albumin measured before cancer treatment was a meaningful prognostic factor for better survival, supporting this hypothesis.[32] In addition, Haskins et al. showed that serum albumin was independently associated with higher 30-day mortality post-operatively in patients with CRC.[33] Although albumin acts as an independent prognostic marker in CRC, non-tumour factors such as diet and hydration state influence albumin levels, which can hinder the clinical applications of this marker for risk stratification in patients with CRC.

Post-operative complications are associated with poor survival and disease recurrence in patients with CRC.[34,35] Similarly, complications were identified as independent prognostic factors for OS in our multivariable analysis (data not shown). The percentage of patients with complications was highest in the G1 group, at 32.0%, 19.9%, 17.3% and 16.8% for G1–G4, respectively ($P < 0.001$). With regard to age and tumour size, all variables were identified as independent prognostic factors in the multivariable analysis. Our study showed that the sex–quartile AMG was significantly associated with age ($P < 0.001$) and tumour size ($P < 0.001$). Thus, we believe that the relationship between AMG groups and these clinical situations may explain, in part, the survival discrimination among the AMG groups.

Myosteatosis and serum albumin levels are associated with tumour-induced inflammation and cancer cachexia. Recent studies have suggested that muscle proteolysis and inhibition of hepatic albumin production are caused by increased production of pro-inflammatory mediators such as IL-6.[7,8,29,30] The tumour microenvironment produces pro-inflammatory cytokines such as TNF-α and IL-6.[36] These cytokines may mediate the redistribution of adipose tissue and intramuscular fat infiltration by inducing the differentiation of muscle progenitor cells to an adipocyte-like phenotype.[37,38] Based on these observations, myosteatosis and albumin may reflect cachexic status in different ways; thus, integrating these two factors may have a synergistic effect on the stratification of prognosis. In our study, although albumin, SMI, SMD and AMG had a significant prognostic impact at the univariate level, only AMG remained an independent prognostic risk factor in the multivariable analysis. Furthermore, the discriminatory ability of AMG outperformed that of serum albumin, SMI and SMD.

Our study has several limitations. Fat infiltration of the skeletal muscle increases with obesity,[39] the prevalence of which differs between ethnicities. Whether our results are applicable to ethnicities other than those of self-reported Asian ancestry requires further investigation. This was a retrospective cross-sectional study; therefore, we could not examine the causal relationship between AMG and risk factors for poor OS, such as post-operative complications. Since each patient received different post-operative treatments depending on their pathological stage, we could not determine how this affected the prognosis of each patient. However, this could have been corrected to some extent in our multivariable analysis. Our study included the receipt of post-operative chemotherapy as a covariant. Based on the Kaplan–Meier survival curves according to patients with stage II and III CRC, which are potential candidates for adjuvant chemotherapy, survival also significantly differed according to AMG. Weight loss might be associated with prognosis in patients with various types of cancer.[13] Thus, consideration of this parameter might be necessary when evaluating the effect of nutritional status or body composition. However, we did not include weight loss as a clinical parameter in this study. Further research is needed to overcome these limitations.

In conclusion, AMG, which is calculated using serum albumin levels and SMD, is a meaningful and novel prognostic risk factor for patients with stage I–III CRC. AMG can be used as a more reliable prognostic marker than SMI and SMD alone. Because albumin levels and SMD are both readily accessible, the potential role of AMG as an easily accessible and affordable measure for predicting patient outcomes is promising. Further evaluation of AMG in different ethnicities is required.

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The authors certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia, and Muscle*.[40]

Conflicts of interest

The authors declare that they have no conflict of interest.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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