

Impact of body composition parameters, age, and tumor staging on gastric cancer prognosis

Wei Li^{a,b,c,d,e,*}, Hai Zhu^{c,f,*}, Hai-Zheng Dong^b, Zheng-Kun Qin^b, Fu-Ling Huang^e, Zhu Yu^e, Shi-Yu Liu^{a,c,d}, Zhen Wang^{a,c,d} and Jun-Qiang Chen^{a,c,d,e}

Background Research studies on gastric cancer have not investigated the combined impact of body composition, age, and tumor staging on gastric cancer prognosis. To address this gap, we used machine learning methods to develop reliable prediction models for gastric cancer.

Methods This study included 1,132 gastric cancer patients, with preoperative body composition and clinical parameters recorded, analyzed using Cox regression and machine learning models.

Results The multivariate analysis revealed that several factors were associated with recurrence-free survival (RFS) and overall survival (OS) in gastric cancer. These factors included age (≥ 65 years), tumor-node-metastasis (TNM) staging, low muscle attenuation (MA), low skeletal muscle index (SMI), and low visceral to subcutaneous adipose tissue area ratios (VSR). The decision tree analysis for RFS identified six subgroups, with the TNM staging I, II combined with high MA subgroup showing the most favorable prognosis and the TNM staging III combined with low MA subgroup exhibiting the poorest prognosis. For OS, the decision tree analysis identified seven subgroups, with the subgroup featuring high MA combined with TNM staging I, II showing the best prognosis and the subgroup with low MA, TNM staging II,

III, low SMI, and age ≥ 65 years associated with the worst prognosis.

Conclusion Cox regression identified key factors associated with gastric cancer prognosis, and decision tree analysis determined prognoses across different risk factor subgroups. Our study highlights that the combined use of these methods can enhance intervention planning and clinical decision-making in gastric cancer. *European Journal of Cancer Prevention* 34: 267–275 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

European Journal of Cancer Prevention 2025, 34:267–275

Keywords: body composition, decision tree, gastric cancer, prognosis

^aDepartment of Gastrointestinal Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, ^bDepartment of Pediatric Surgery, The First Affiliated Hospital of Guangxi Medical University, ^cGuangxi Key Laboratory of Enhanced Recovery after Surgery for Gastrointestinal Cancer, ^dGuangxi Clinical Research Center for Enhanced Recovery after Surgery, ^eGuangxi Zhuang Autonomous Region Engineering Research Center for Artificial Intelligence Analysis of Multimodal Tumor Images and ^fDepartment of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

Correspondence to Jun-Qiang Chen, MD, Department of Gastrointestinal Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, No. 6, Shuangyong Road, Nanning 530021, Guangxi, China
Tel: +86 0771 5356552; e-mail: chenjunqiang@gxmu.edu.cn

*Wei Li and Hai Zhu contributed equally to the writing of this article.

Received 2 June 2024 Accepted 25 July 2024.

Introduction

China holds the unfortunate distinction of having the highest global incidence of gastric cancer, with an alarming age-standardized 5-year survival rate of only 27.4%. Gastric cancer in China constitutes a staggering 44.1% of new cases worldwide, with approximately 50% of global gastric cancer deaths attributed to the country (Gao and Wu, 2019). Gastric cancer, an upper gastrointestinal tumor, often leads to digestive absorption issues. Tumor cells trigger inflammatory responses and metabolic abnormalities, resulting in significant depletion of body

proteins and adipose tissue (Fearon *et al.*, 2011; Ryan *et al.*, 2016; Arends *et al.*, 2017a; Gascon-Ruiz *et al.*, 2021). Disease progression can ultimately lead to cachexia, a severe wasting syndrome (Arends *et al.*, 2017b; Zhang *et al.*, 2021a). Monitoring body composition becomes essential in evaluating tumor treatment, and assessing conditions like obesity, malnutrition, and muscle wasting (Fujiwara *et al.*, 2015; Brown *et al.*, 2020).

The current gold standard for assessing body composition parameters like skeletal muscle area, skeletal muscle density, subcutaneous adipose tissue area, and visceral adipose tissue area is through computed tomography (CT) scan analysis at the third lumbar level (Park *et al.*, 2018; Hacker *et al.*, 2020; Zhang *et al.*, 2021b). In patients with gastric cancer, sarcopenia, marked by reduced skeletal muscle mass and density, correlates with lower survival rates and increased chemotherapy toxicity (Bozzetti, 2017; Hacker *et al.*, 2020). However, the role of adipose

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.eurjancerprev.com).

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

tissue on the prognosis remains a subject of debate (Lin *et al.*, 2021).

Traditional survival analysis methods, such as the Cox proportional hazards model, are valuable for identifying a single independent predictor. However, these methods may not be useful for detecting multiple predictors in a patient subgroup and for capturing complex interactions between these predictors. In contrast, machine learning techniques based on decision tree algorithms are capable of identifying higher-order interactions between predictors that might otherwise be ignored, even with small sample sizes and numerous covariates (Audureau *et al.*, 2018). Therefore, this study aims to investigate how combined body composition parameters, age, and tumor staging influence the prognosis of gastric cancer patients. Additionally, it seeks to develop decision tree models for predicting outcomes in these patients.

Patients and methods

Patients

Inclusion criteria: (1) age ≥ 18 years old; (2) postoperative pathological diagnosis of gastric adenocarcinoma; (3) willingness to undergo gastric cancer treatment and consent for gastrectomy; (4) abdominal CT performed in our hospital within 1 month before surgery; (5) signed informed consent form to participate in the research.

Exclusion criteria: (1) confirmation of distant tumor metastasis during surgery or inability to undergo curative or palliative surgery; (2) presence of serious metabolic diseases or other systemic conditions, such as diabetes, severe heart failure, decompensated cirrhosis, etc. (3) incomplete or unclear CT images that prevent identification of skeletal muscle or adipose tissue; (4) preoperative neoadjuvant chemotherapy, immunotherapy, or molecular targeted therapy.

All patients received written informed consent, specifying that all clinical information collected for research purposes would be anonymized. The study protocol was approved by the Ethics Review Committee of the First Affiliated Hospital of Guangxi Medical University [approval number 2020 (KY-E-078)].

Clinical and anthropometric variables

Clinical data and anthropometric parameters were recorded within 1 week before surgery, and included the following: age, gender, BMI, hemoglobin, albumin, neutrophil-to-lymphocyte ratio (NLR), American Society of Anesthesiology score, Charlson Comorbidity Index score, and tumor-node-metastasis (TNM) staging according to the eighth edition of the Joint Commission on Cancer Staging manual.

All participants underwent radical gastrectomy with D₂ lymph node dissection. BMI was classified according to

Chinese standards: underweight (<18.5 kg/m²), normal weight (18.5 – 23.9 kg/m²), overweight (24 – 27.9 kg/m²), and obesity (≥ 28 kg/m²) (Zhang *et al.*, 2021c). Serum albumin <35 g/l was considered hypoalbuminemia (Ying *et al.*, 2019) and $\text{NLR} \geq 3$ is defined as an inflammatory state (Feliciano *et al.*, 2017).

Computed tomography analyses of body composition variables

To assess body composition parameters, the patient's third lumbar spine (L3) segment image was analyzed using the full abdomen image scanned by Siemens Somatom Definition Flash CT, and the image was uploaded to AW 4.5 (Advantage Workstation) area measurement software (GE Healthcare, Chicago, Illinois, USA). The measurement parameters included: skeletal muscle area, visceral adipose tissue area, and subcutaneous adipose tissue area. Different tissues were characterized using specific Hounsfield unit (HU) thresholds: skeletal muscle (29–150 HU), subcutaneous adipose tissue (190–30 HU), and visceral adipose tissue (150–50 HU) (Gomez-Perez *et al.*, 2016). To standardize measurements for individualization and comparison, the body composition variable was divided by the square of height and expressed as cm²/m². The ratio of visceral adipose tissue area to subcutaneous adipose tissue area, known as VSR, was calculated to assess fat distribution. The HU of muscle tissue vary among individuals, which can represent muscle density, also known as muscle attenuation, and the muscle attenuation value correlates to the adipose tissue infiltration into the muscles (Martin *et al.*, 2013). Finally, to assess the reproducibility and reliability of the measured data, we randomly selected data from 60 patients in the training set and ensured that the coefficient of variation among observers was $<1.3\%$.

Statistical analysis

Overall survival (OS) was defined as the duration from the patient's initial hospital admission for gastric cancer until death or 31 December 2021, whichever came first. Recurrence-free survival (RFS) was defined as the time from surgery to gastric cancer recurrence or until 31 December 2021. The normality of continuous data was checked using the Shapiro–Wilk test. Continuous data with a normal distribution are presented as means $\pm$ SD and compared using Student's *t*-test. Continuous data with non-normal distributions are expressed as median and interquartile range and compared using the Mann–Whitney *U* test. Categorical variables are expressed as numbers and percentages and analyzed using Pearson's chi-square test or Fisher's exact test.

All enrolled cases were randomly split in a 70/30 ratio to form training and validation sets. The optimal cutoff value for body composition variables related to prognosis was determined using maximally selected rank statistics. Based on this cutoff, cases were categorized into high or

Table 1 Baseline characteristic

Characteristic	Training set	Validation set	<i>P</i>
Age (years), mean $\pm$ SD			0.924
<65, <i>N</i> (%)	604 (78.0%)	281 (78.5%)	
≥ 65 , <i>N</i> (%)	170 (22.0%)	77 (21.5%)	
Sex			0.299
Male, <i>N</i> (%)	268 (34.6%)	112 (31.3%)	
Female, <i>N</i> (%)	506 (65.4%)	246 (68.7%)	
BMI (kg/m ²), median (IQR)			0.417
<18.5 (underweight), <i>N</i> (%)	65 (8.4%)	37 (10.3%)	
18.5–23.9 (normal weight), <i>N</i> (%)	369 (47.7%)	178 (49.7%)	
24.0–27.9 (overweight), <i>N</i> (%)	239 (30.9%)	106 (29.6%)	
≥ 28.0 (obesity), <i>N</i> (%)	101 (13.0%)	37 (10.3%)	
ALB (g/l)			0.555
≥ 35 , <i>N</i> (%)	189 (24.4%)	94 (26.3%)	
<35, <i>N</i> (%)	585 (75.6%)	264 (73.7%)	
Hemoglobin (g/l)			0.253
≥ 90 , <i>N</i> (%)	135 (17.4%)	52 (14.5%)	
<90, <i>N</i> (%)	639 (82.6%)	306 (85.5%)	
NLR			0.506
≥ 3 , <i>N</i> (%)	595 (76.9%)	268 (74.9%)	
<3, <i>N</i> (%)	179 (23.1%)	90 (25.1%)	
ASA score			0.753
<3, <i>N</i> (%)	742 (95.9%)	341 (95.3%)	
3, <i>N</i> (%)	32 (4.1%)	17 (4.7%)	
TNM staging			0.468
I, <i>N</i> (%)	289 (37.3%)	141 (39.4%)	
II, <i>N</i> (%)	224 (28.9%)	91 (25.4%)	
III, <i>N</i> (%)	261 (33.7%)	126 (35.2%)	
CCI			0.768
0–2, <i>N</i> (%)	583 (75.3%)	266 (74.3%)	
≥ 3 , <i>N</i> (%)	191 (24.7%)	92 (25.7%)	
Body composition, median (IQR)			
SATI (cm ² /m ²)	35.9 (23.5–49.3)	34.1 (20.9–47.2)	0.141
VATI (cm ² /m ²)	29.5 (14.8–47.1)	25.6 (13.3–43.9)	0.079
VSR	0.87 (0.56–1.27)	0.86 (0.54–1.21)	0.467
MA (HU)	39.8 (35.3–45.3)	40.5 (35.3–46.8)	0.645
SMI (cm ² /m ²)	39.1 (34.8–43.4)	40.1 (35.2–44.6)	0.053

ALB, albumin; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; HU, Hounsfield unit; IQR, interquartile range; MA, muscle attenuation; NLR, neutrophil-lymphocyte ratio; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; TNM, tumor-node-metastasis; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

Table 2 Optimal cutoff values for each body composition

	RFS		OS	
	Male	Female	Male	Female
SATI (cm ² /m ²)	30.31	39.31	32.18	41.20
VATI (cm ² /m ²)	34.09	26.80	34.47	26.50
VSR	1.15	1.11	1.25	1.14
MA (HU)	41.30	34.19	42.24	33.09
SMI (cm ² /m ²)	45.80	39.60	40.20	36.30

HU, Hounsfield unit; MA, muscle attenuation; OS, overall survival; RFS, recurrence-free survival; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

low groups, and the prognostic differences were assessed using Kaplan–Meier survival curves. Cox regression analysis was used to identify all prognostic factors in gastric cancer, with results presented as hazard ratios and 95% confidence intervals (CIs). In further analysis, prognostic factors were selected as covariates based on the Cox model. A decision tree was used to segment the subject population naturally according to survival time and these covariates. Node segmentation employed a significance criterion of $P < 0.05$. Various combinations of covariate subgroups with different prognosis were identified, and

for each subgroup, the decision tree generated Kaplan–Meier curves. The analysis was conducted using the Party and Survival packages, within the R software (<http://www.r-project.org/>). Statistical significance was defined as a two-tailed $P < 0.05$.

Results

Patient characteristics

Between June 2012 and June 2021, a total of 1249 gastric cancer patients were admitted to the First Affiliated Hospital of Guangxi Medical University for this study. Of these, 52 cases were excluded due to incomplete CT data or body composition measurements. Additionally, 31 cases underwent palliative resection for gastric cancer, 14 cases had serious metabolic diseases before surgery, and 20 cases underwent neoadjuvant chemotherapy or molecular targeted therapy before surgery. Finally, 1132 patients were randomly divided into a training set ($n = 774$) and validation set ($n = 358$) using a 70/30 split ratio. The case selection enrollment charts are illustrated in Supplementary Figure 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A490>, and the baseline characteristics of the patients are outlined in Table 1.

Optimal cutoff values for body composition

Optimal cutoff values of body composition variables were calculated separately for males and females, due to the known differences in body composition and distribution between genders. The cutoff values are depicted in Supplementary Figures S2–S5, Supplemental digital content 1, <http://links.lww.com/EJCP/A490> and summarized in Table 2.

Survival analysis of body composition high groups versus low groups

Continuous body composition variables were categorized into dichotomous groups using optimal cutoff values, and survival analysis compared high and low groups for each variable. The results are depicted in Supplementary Figures S6–S9, Supplemental digital

content 1, <http://links.lww.com/EJCP/A490> and summarized in Table 3. Our analysis suggests that factors influencing gastric cancer prognosis include muscle attenuation, skeletal muscle index (SMI), and VSR, whereas subcutaneous adipose tissue index (SATI) and visceral adipose tissue index (VATI) exhibit no significant impact.

Univariate and multivariate analysis of prognostic factors for gastric cancer

For RFS, independent predictors of poor prognosis included: age ≥65 years (hazard ratio 1.43, 95% CI: 1.12–1.82, *P* = 0.004), TNM staging (staging II, hazard ratio 2.04, 95% CI: 1.52–2.75, *P* < 0.001; staging III, hazard ratio 3.78, 95% CI: 2.90–4.94, *P* < 0.001), low muscle attenuation (hazard ratio 2.46, 95% CI: 1.96–3.10, *P* < 0.001), and

Table 3 Based on RFS and OS, the survival analysis results of the body composition high groups vs low groups

		SATI	VATI	VSR	MA	SMI
		(High vs low, <i>P</i>)	(High vs low, <i>P</i>)	(High vs low, <i>P</i>)	(High vs low, <i>P</i>)	(High vs low, <i>P</i>)
Training set	RFS	0.054	<0.001	<0.001	<0.001	<0.001
	OS	0.17	<0.001	<0.001	<0.001	<0.001
Validation set	RFS	0.2	0.56	0.003	<0.001	0.004
	OS	0.017	0.54	<0.001	<0.001	<0.001

MA, muscle attenuation; OS, overall survival; RFS, recurrence-free survival; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

Table 4 Univariate and multivariate analysis of risk factors affecting RFS of gastric cancer

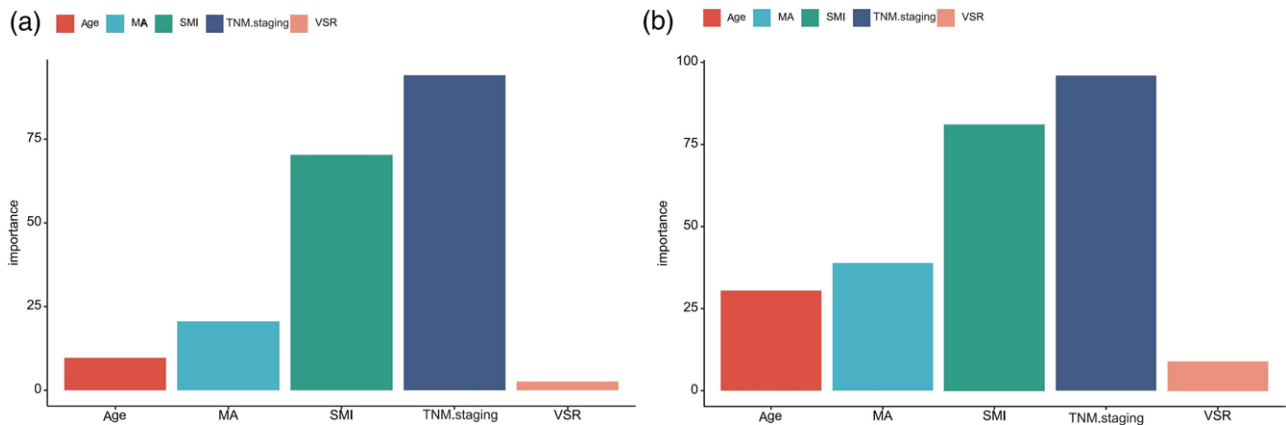
Variable	Categorization	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>
Age (years)	<65				
	≥65	1.92 (1.52–2.42)	0.001	1.43 (1.12–1.82)	0.004
Sex	Female				
	Male	1.07 (0.86–1.33)	0.572		
BMI	18.5.0–23.9				
	24.0–27.9	1.05 (0.83–1.34)	0.692		
	≥25.0	1.12 (0.81–1.54)	0.495		
	<18.5	1.19 (0.82–1.74)	0.358		
ALB (g/l)	≥35				
	<35	0.76 (0.60–0.96)	0.020		
Hemoglobin (g/l)	≥90				
	<90	0.74 (0.57–0.96)	0.023		
NLR	<3				
	≥3	1.19 (0.94–1.50)	0.156		
ASA	<III				
	III	1.27 (0.77–2.09)	0.355		
TNM staging	I				
	II	2.04 (1.52–2.74)	<0.001	2.04 (1.52–2.75)	<0.001
	III	3.93 (3.01–5.12)	<0.001	3.78 (2.90–4.94)	<0.001
CCI	<3				
	≥3	1.02 (0.80–1.29)	0.901		
SATI (cm²/m²)	High				
	Low	1.23 (1.00–1.51)	0.054		
VATI (cm²/m²)	High				
	Low	0.65 (0.52–0.81)	<0.001		
VSR	High				
	Low	0.59 (0.48–0.73)	<0.001	0.72 (0.55–0.93)	0.011
MA (HU)	High				
	Low	2.57 (2.08–3.17)	<0.001	2.30 (1.84–2.86)	<0.001
SMI (cm²/m²)	High				
	Low	2.41 (1.84–3.17)	<0.001	2.18 (1.63–2.93)	<0.001

ALB, albumin; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; HU, Hounsfield unit; MA, muscle attenuation; NLR, neutrophil–lymphocyte ratio; RFS, recurrence-free survival; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; TNM, tumor-node-metastasis; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

Table 5 Univariate and multivariate analysis of risk factors affecting OS of gastric cancer

Variable	Categorization	Univariate analysis		Multivariate analysis	
		HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age (years)	<65				
	≥65	2.21 (1.66–2.67)	<0.001	1.67 (1.31–2.15)	<0.001
Sex	Female				
	Male	1.06 (0.85–1.32)	0.603		
BMI	18.5.0–23.9				
	24.0–27.9	1.07 (0.84–1.36)	0.596		
	≥25.0	1.09 (0.78–1.51)	0.620		
	<18.5	1.16 (0.78–1.71)	0.466		
ALB (g/l)	≥35				
	<35	0.74 (0.58–0.94)	0.013		
Hemoglobin (g/l)	≥90				
	<90	0.72 (0.55–0.94)	0.016	0.81 (0.62–1.06)	0.131
NLR	<3				
	≥3	1.16 (0.92–1.48)	0.216		
ASA	<III				
	III	1.27 (0.76–2.13)	0.366		
TNM	I				
	II	2.19 (1.63–2.94)	<0.001	2.27 (1.68–3.05)	<0.001
	III	3.77 (2.88–4.93)	<0.001	3.58 (2.73–4.70)	<0.001
CCI	<3				
	≥3	1.02 (0.80–1.30)	0.876		
SATI (cm ² /m ²)	High				
	Low	1.26 (0.91–1.74)	0.169		
VATI (cm ² /m ²)	High				
	Low	0.65 (0.52–0.82)	<0.001		
VSR	High				
	Low	0.58 (0.47–0.73)	<0.001	0.72 (0.56–0.89)	0.003
MA (HU)	High				
	Low	2.73 (2.19–3.39)	<0.001	2.46 (1.96–3.10)	<0.001
SMI (cm ² /m ²)	High				
	Low	2.20 (1.76–2.75)	<0.001	1.86 (1.46–2.36)	<0.001

ALB, albumin; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; HU, Hounsfield unit; MA, muscle attenuation; NLR, neutrophil–lymphocyte ratio; OS, overall survival; SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; TNM, tumor-node-metastasis; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio.

Fig. 1

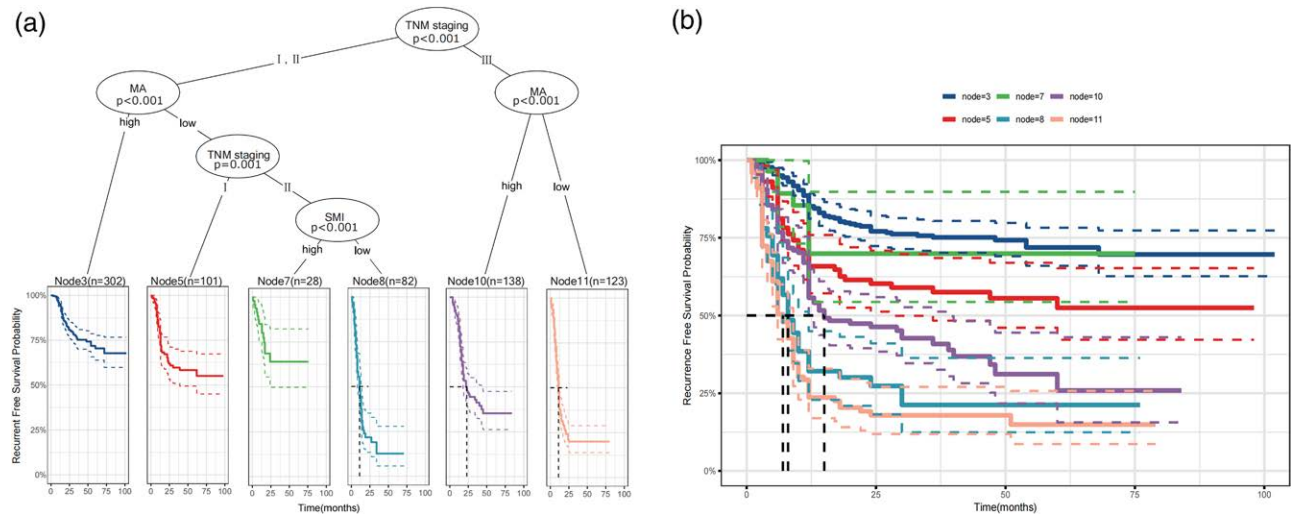
In the decision tree analysis, the important values of the prognostic factors affecting gastric cancer. (a) RFS model; (b) OS model. OS, overall survival; RFS, recurrence-free survival.

low SMI (hazard ratio 1.86, 95% CI: 1.46–2.36, $P < 0.001$). Conversely, low VSR was associated with better prognosis (hazard ratio 0.72, 95% CI: 0.56–0.89, $P = 0.003$) (Table 4).

For OS, independent predictors of poor prognosis included: age ≥ 65 years (hazard ratio 1.67, 95% CI:

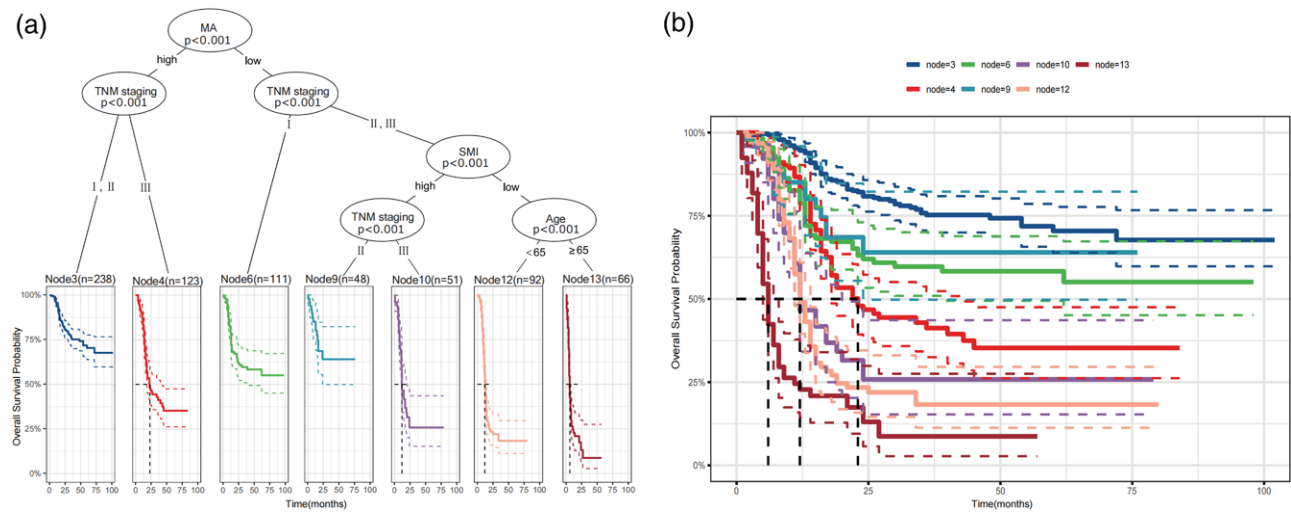
1.31–2.15, $P < 0.001$), TNM staging (staging II, hazard ratio 2.27, 95% CI: 1.68–3.05, $P < 0.001$; staging III, hazard ratio 3.58, 95% CI: 2.73–4.70, $P < 0.001$), low muscle attenuation (hazard ratio 2.46, 95% CI: 1.96–3.10, $P < 0.001$), and low SMI (hazard ratio 1.86, 95% CI: 1.46–2.36, $P < 0.001$), while low VSR (hazard ratio 0.72, 95% CI: 0.56–0.89, $P = 0.003$) was a protective factor (Table 5).

Fig. 2



Survival tree for RFS in gastric cancer. (a) Recursive partitioning of nodes in the RFS survival tree. (b) Kaplan–Meier RFS curves of terminal nodes. RFS, recurrence-free survival.

Fig. 3



Survival tree for OS in gastric cancer. (a) Recursive partitioning of nodes in the OS survival tree. (b) Kaplan–Meier OS curves of terminal nodes. OS, overall survival.

Developing decision tree models

Based on the results of univariate and multivariate regression analysis, age, TNM staging, muscle attenuation, SMI, and VSR were identified as independent predictors of gastric cancer prognosis. Consequently, a decision tree model utilizing these five variables was developed.

In the RFS model for the training set, TNM staging exhibited the highest importance value (94.06), followed by muscle attenuation (70.21), SMI (20.55), age (9.67),

and VSR (2.53) (Fig. 1a). The model comprised 11 nodes, dividing the training set into six groups five times, with significant differences observed between groups after each segmentation (Fig. 2a). Node 3, representing the combination of TNM staging I and II with high muscle attenuation, demonstrated the best prognosis, while node 11, representing TNM staging III with low muscle attenuation, had the worst prognosis (Fig. 2b). The model demonstrated a concordance index of 0.77, with a concordance index of 0.74 for 10-fold internal validation.

In the OS model, TNM staging was the most important predictor (95.85), followed by muscle attenuation (81.06), SMI (38.84), age (30.42), and VSR (8.92) (Fig. 1b). The model consisted of 13 nodes, dividing the training set into seven groups six times, with significant differences observed between groups after each segmentation (Fig. 3a). Node 3, representing high muscle attenuation with TNM staging I and II, exhibited the best prognosis, while node 13, representing low muscle attenuation, TNM staging II and III, low SMI, and age ≥ 65 , had the poorest prognosis (Fig. 3b). The concordance index for this model was 0.79, with a concordance index of 0.77 for 10-fold internal validation.

Discussion

Currently, there are no reports of decision tree prediction models for predicting the prognosis of gastric cancer patients based on age, TNM staging, and body composition. Our study found that among the body composition parameters considered, SMI, muscle attenuation, and VSR were associated with the prognosis of gastric cancer, whereas SATI and VATI did not show significant association.

Adipose tissue serves as the body's primary energy reservoir and reflects the patient's nutritional status. While visceral adipose tissue can fulfill disease-related energy demands, excess visceral fat may promote tumor growth (Greco *et al.*, 2020). In contrast, subcutaneous adipose tissue exhibits metabolic stability and produces leptin, which enhances insulin sensitivity and energy metabolism (Han *et al.*, 2023). Therefore, higher subcutaneous adipose tissue levels may shield against cachexia and insulin resistance, potentially reducing the risk of tumor recurrence (Kim *et al.*, 2021).

For instance, Harada *et al.* examined 507 patients with upper gastrointestinal tumors and found that individuals with low visceral fat had a higher overall mortality rate compared to those with high visceral fat (Harada *et al.*, 2015). In contrast, Dong *et al.* conducted a retrospective analysis involving 1147 patients who underwent gastric cancer resection. They concluded that a low subcutaneous adipose tissue area independently correlated with poorer OS and tumor-free survival. Interestingly, high visceral adipose tissue area negatively affected the survival rate of overweight patients ($\text{BMI} \geq 25$) but positively influenced the survival rate of non-overweight patients ($\text{BMI} < 25$). Although a high subcutaneous adipose tissue area did not significantly affect survival in overweight patients, it positively correlated with survival in non-overweight individuals (Dong *et al.*, 2021). However, Hacker *et al.* analyzed data from 761 cases of gastric cancer and found no association between subcutaneous adipose tissue, visceral adipose tissue, and prognosis (Hacker *et al.*, 2020). As depicted in Table 3, we computed optimal cutoff values for SATI and VATI based on prognosis. Despite

comparing the survival outcomes of high and low SATI/VATI groups, the conclusions from both the training and validation sets were inconsistent. Hence, we posit that merely discussing the quantity of subcutaneous and visceral adipose tissue does not directly correlate with gastric cancer prognosis.

In order to better evaluate the relationship between subcutaneous adipose tissue and visceral adipose tissue, some studies have introduced the concept of fat distribution ratio (VSR), that is, the area of visceral fat divided by the area of subcutaneous fat. A higher VSR indicates greater visceral obesity. In this study, both in the training set and the validation set, it was confirmed that VSR negatively correlated with the prognosis of gastric cancer. Therefore, it is more meaningful to measure VSR than to measure subcutaneous adipose tissue or visceral adipose tissue alone.

Gastric cancer primarily affects individuals in their middle to later years, and as age advances, there's often a decline in muscle quality and strength, leading to an increased risk of sarcopenia (Takahashi *et al.*, 2019; Huang *et al.*, 2021). Among those aged over 65 years, the incidence of gastric cancer complicated by sarcopenia can be as high as 28.8% (Zhou *et al.*, 2017), significantly surpassing the incidence of sarcopenia alone. Importantly, the prognosis of gastric cancer tends to worsen with advancing age (Sakurai *et al.*, 2017; Zhang *et al.*, 2021b). Our study's findings from both univariate and multivariate Cox regression analyses, as well as decision tree analysis, remained consistent. Specifically, age over 65 years emerged as a significant adverse prognostic factor, with its impact on prognosis outweighing that of the VSR. These results underscore the critical influence of age on gastric cancer prognosis and emphasize the importance of considering age-related factors in treatment planning and prognostic assessments.

According to the 2018 definition and diagnostic criteria for sarcopenia by the European Working Group on Sarcopenia in Older People 2 (EW-GSOP2), the detection of decreased muscle quantity and mass constitutes an important basis for diagnosing sarcopenia (Cruz-Jentoft *et al.*, 2019). As such, CT analysis of skeletal muscle at the third lumbar spine level has been widely used in clinical settings, focusing primarily on two measurements: SMI to quantify muscle mass and muscle attenuation to assess muscle quality. The impact of SMI on tumor prognosis has been supported by most studies. The level of muscle attenuation is closely related to ageing and visceral adipose tissue accumulation, with increased infiltration of intramuscular adipose tissue potentially leading to reduced muscle strength and abnormal metabolism (Waki *et al.*, 2019; Kusunoki *et al.*, 2021). In recent years, an increasing number of scholars have begun to pay attention to the impact of muscle attenuation on tumor prognosis. For example, Zhuang *et al.* analyzed 973 patients who

underwent gastrectomy, and 584 were matched for analysis. They found that compared to the non-myosteatosis group, the myosteatosis group had a significantly higher incidence of serious post-surgical complications and shorter OS and disease-free survival (Zhuang *et al.*, 2019). Wantanabe *et al.* analyzed 242 gastric cancer patients over the age of 65 who underwent gastrectomy and found that the high-intramuscular fat content group had a lower five-year survival rate and non-tumor-related survival compared with the low intramuscular fat content group (Watanabe *et al.*, 2021).

Both SMI and MA can provide insights into the prognosis of gastric cancer, yet research suggests that muscle attenuation has a more significant impact compared to SMI (Lu *et al.*, 2018; Waki *et al.*, 2019; Hacker *et al.*, 2020; Dong *et al.*, 2021). Our findings align with these observations. Multivariate analysis in our study revealed that muscle attenuation poses a greater risk to both RFS and OS than SMI. Moreover, in decision tree model, the importance values assigned to muscle attenuation for predicting RFS and OS outweigh those of SMI. A plausible explanation lies in the distinction between SMI and muscle attenuation measurements. SMI solely quantifies the cross-sectional area of the third lumbar vertebrae, encompassing both muscle and intramuscular fat content. Consequently, a high SMI might stem from increased intramuscular fat content. This could elucidate why the impact of muscle attenuation on gastric cancer prognosis surpasses that of SMI.

In our study, multivariate analysis revealed age, TNM staging, SMI, muscle attenuation, and VSR as independent predictors of both RFS and OS. Leveraging these five factors, we conducted machine learning decision tree analysis to construct a new prognostic model. By calculating the importance values of these variables in both RFS and OS, we determined their order of importance as follows: TNM staging > muscle attenuation > SMI > Age > VSR.

In both the RFS and OS models, our machine learning algorithms effectively segmented the training data into distinct groups for prognostic assessment. In the RFS model, 11 nodes were utilized to categorize the training set into six groups. Notably, patients with low tumor staging combined with high muscle attenuation exhibited the most favorable prognosis, while those with high tumor staging combined with low muscle attenuation showed the poorest prognosis. Age and VSR did not factor into the decision tree analysis, indicating their lesser impact on RFS prognosis. In the OS model, 13 nodes were employed to divide the training set into seven groups. Patients characterized by high muscle attenuation and low tumor staging demonstrated the most favorable prognosis, whereas those with high tumor staging, low SMI, and age ≥ 65 years exhibited the worst prognosis. Once again, VSR did not enter the decision tree analysis, suggesting its limited role in predicting OS outcomes.

These findings highlight the significance of tumor staging and muscle characteristics in determining both recurrence-free and OS in gastric cancer patients, underscoring the potential for personalized prognostic assessment and treatment planning.

This study introduces pioneering predictive models for long-term survival post-radical gastric cancer resection, using preoperative body composition data. However, limitations include the use of single-center data, conversion of continuous variables to dichotomous ones, and potential subjective biases. Future research should validate these models across diverse settings, refine variable categorization methods, and mitigate subjective biases. Despite limitations, these models offer valuable insights for clinical decision-making.

Conclusion

In summary, the Cox regression model effectively establishes the relationship between predictors and outcomes, while the decision tree model excels in analyzing prognostic relationships among subgroups with different risk factors. These methods complement each other in prognostic assessment. Muscle attenuation exhibits greater predictive value compared to SMI. Notably, SATI and VATI show no clear correlation with gastric cancer. However, VSR and age demonstrate certain predictive value in prognosis.

Acknowledgements

The authors are grateful to the patients who participated in the study and completed the survey.

This study was funded by the Guangxi Clinical Research Center for Enhanced Recovery after Surgery, Guangxi Science and Technology Base and Talent Project (grant no. AD19245196), Project of Provincial and Ministerial Key Laboratory of the First Affiliated Hospital of Guangxi Medical University (grant no. YYZS2020003), the Guangxi Key Research and Development Project (grant no. AB18126058), and the National Natural Science Foundation of China (no. 82060430, no. 82160128).

J.-Q.C. and Z.W. designed the study. H.-Z.D., Z.-K.Q., F.-L.H., Z.Y., and S.-Y.L. collected the data. W.L. and H.Z. did the analysis and interpretation of the data and wrote the article. J.-Q.C. revised the article and took the decision to submit the article for publication.

Conflicts of interest

There are no conflicts of interest.

References

- Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, *et al.* (2017a). ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* **36**:11–48.
- Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, *et al.* (2017b). ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr* **36**:1187–1196.

- Audureau E, Chivet A, Ursu R, Corns R, Metellus P, Noel G, *et al.* (2018). Prognostic factors for survival in adult patients with recurrent glioblastoma: a decision-tree-based model. *J Neurooncol* **136**:565–576.
- Bozzetti F (2017). Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann Oncol* **28**:2107–2118.
- Brown JC, Caan BJ, Prado CM, Cespedes Feliciano EM, Xiao J, Kroenke CH, Meyerhardt JA (2020). The association of abdominal adiposity with mortality in patients with stage I–III colorectal cancer. *J Natl Cancer Inst* **112**:377–383.
- Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, *et al.* (2019). Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* **48**:16–31.
- Dong QT, Cai HY, Zhang Z, Zou H-B, Dong W-X, Wang W-B, *et al.* (2021). Influence of body composition, muscle strength, and physical performance on the postoperative complications and survival after radical gastrectomy for gastric cancer: a comprehensive analysis from a large-scale prospective study. *Clin Nutr* **40**:3360–3369.
- Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, *et al.* (2011). Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* **12**:489–495.
- Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, *et al.* (2017). Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. *JAMA Oncol* **3**:e172319.
- Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, *et al.* (2015). Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol* **63**:131–140.
- Gao K, Wu J (2019). National trend of gastric cancer mortality in China (2003–2015): a population-based study. *Cancer Commun (Lond)* **39**:24.
- Gascon-Ruiz M, Casas-Deza D, Torres-Ramon I, Zapata-Garcia M, Alonso N, Sesma A, *et al.* (2021). Glim vs ESPEN criteria for the diagnosis of early malnutrition in oncological outpatients. *Clin Nutr* **40**:3741–3747.
- Gomez-Perez SL, Haus JM, Sheean P, Patel B, Mar W, Chaudhry V, *et al.* (2016). Measuring abdominal circumference and skeletal muscle from a single cross-sectional computed tomography image: a step-by-step guide for clinicians using National Institutes of Health ImageJ. *JPN J Parenter Enteral Nutr* **40**:308–318.
- Greco F, Mallio CA, Grippo R, Messina L, Vallesse S, Rabitti C, *et al.* (2020). Increased visceral adipose tissue in male patients with non-clear cell renal cell carcinoma. *Radiol Med* **125**:538–543.
- Hacker UT, Hasenclever D, Linder N, Stocker G, Chung H-C, Kang Y-K, *et al.* (2020). Prognostic role of body composition parameters in gastric/gastroesophageal junction cancer patients from the expand trial. *J Cachexia Sarcopenia Muscle* **11**:135–144.
- Han W, Wang L, Ohbayashi K, Takeuchi M, O'Farrell L, Coskun T, *et al.* (2023). Glucose-dependent insulinotropic polypeptide counteracts diet-induced obesity along with reduced feeding, elevated plasma leptin and activation of leptin-responsive and proopiomelanocortin neurons in the arcuate nucleus. *Diabetes Obes Metab* **25**:1534–1546.
- Harada K, Baba Y, Ishimoto T, Kosumi K, Tokunaga R, Izumi D, *et al.* (2015). Low visceral fat content is associated with poor prognosis in a database of 507 upper gastrointestinal cancers. *Ann Surg Oncol* **22**:3946–3953.
- Huang DD, Yu DY, Song HN, Wang W-B, Luo X, Wu G-F, *et al.* (2021). The relationship between the glim-defined malnutrition, body composition and functional parameters, and clinical outcomes in elderly patients undergoing radical gastrectomy for gastric cancer. *Eur J Surg Oncol* **47**:2323–2331.
- Kim JM, Chung E, Cho ES, Lee J-H, Shin S-J, Lee HS, *et al.* (2021). Impact of subcutaneous and visceral fat adiposity in patients with colorectal cancer. *Clin Nutr* **40**:5631–5638.
- Kusunoki Y, Okugawa Y, Toiyama Y, Kusunoki K, Ichikawa T, Ide S, *et al.* (2021). Modified intramuscular adipose tissue content as a feasible surrogate marker for malnutrition in gastrointestinal cancer. *Clin Nutr* **40**:2640–2653.
- Lin JX, Tang YH, Zhou WX, Desiderio J, Parisi A, Xie J-W, *et al.* (2021). Body composition parameters predict pathological response and outcomes in locally advanced gastric cancer after neoadjuvant treatment: a multicenter, international study. *Clin Nutr* **40**:4980–4987.
- Lu J, Zheng ZF, Li P, Xie J-W, Wang J-B, Lin J-X, *et al.* (2018). A novel preoperative skeletal muscle measure as a predictor of postoperative complications, long-term survival and tumor recurrence for patients with gastric cancer after radical gastrectomy. *Ann Surg Oncol* **25**:439–448.
- Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, *et al.* (2013). Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* **31**:1539–1547.
- Park HS, Kim HS, Beom SH, Rha SY, Chung HC, Kim JH, *et al.* (2018). Marked loss of muscle, visceral fat, or subcutaneous fat after gastrectomy predicts poor survival in advanced gastric cancer: single-center study from the classic trial. *Ann Surg Oncol* **25**:3222–3230.
- Ryan AM, Power DG, Daly L, Cushen SJ, Ni Bhuaichalla E, Prado CM (2016). Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc* **75**:199–211.
- Sakurai K, Kubo N, Tamura T, Toyokawa T, Amano R, Tanaka H, *et al.* (2017). Adverse effects of low preoperative skeletal muscle mass in patients undergoing gastrectomy for gastric cancer. *Ann Surg Oncol* **24**:2712–2719.
- Takahashi S, Shimizu S, Nagai S, Watanabe H, Nishitani Y, Kurisu Y (2019). Characteristics of sarcopenia after distal gastrectomy in elderly patients. *PLoS One* **14**:e0222412.
- Waki Y, Irino T, Makuuchi R, Notsu A, Kamiya S, Tanizawa Y, *et al.* (2019). Impact of preoperative skeletal muscle quality measurement on long-term survival after curative gastrectomy for locally advanced gastric cancer. *World J Surg* **43**:3083–3093.
- Watanabe J, Osaki T, Ueyama T, Koyama M, Iki M, Endo K, *et al.* (2021). The combination of preoperative skeletal muscle quantity and quality is an important indicator of survival in elderly patients undergoing curative gastrectomy for gastric cancer. *World J Surg* **45**:2868–2877.
- Ying J, Zhou D, Gu T, Huang J, Liu H (2019). Pretreatment albumin/fibrinogen ratio as a promising predictor for the survival of advanced non small-cell lung cancer patients undergoing first-line platinum-based chemotherapy. *BMC Cancer* **19**:288.
- Zhang Y, Li Z, Jiang L, Xue Z, Ma Z, Kang W, *et al.* (2021a). Impact of body composition on clinical outcomes in people with gastric cancer undergoing radical gastrectomy after neoadjuvant treatment. *Nutrition* **85**:111135.
- Zhang FM, Chen XL, Wu Q, Dong W-X, Dong Q-T, Shen X, *et al.* (2021b). Development and validation of nomograms for the prediction of low muscle mass and radiodensity in gastric cancer patients. *Am J Clin Nutr* **113**:348–358.
- Zhang Y, Li Z, Jiang L, Xue Z, Ma Z, Kang W, *et al.* (2021c). Marked loss of adipose tissue during neoadjuvant therapy as a predictor for poor prognosis in patients with gastric cancer: a retrospective cohort study. *J Hum Nutr Diet* **34**:585–594.
- Zhou CJ, Zhang FM, Zhang FY, Yu Z, Chen X-L, Shen X, *et al.* (2017). Sarcopenia: a new predictor of postoperative complications for elderly gastric cancer patients who underwent radical gastrectomy. *J Surg Res* **211**:137–146.
- Zhuang CL, Shen X, Huang YY, Zhang F-M, Chen X-Y, Ma L-L, *et al.* (2019). Myosteatosis predicts prognosis after radical gastrectomy for gastric cancer: a propensity score-matched analysis from a large-scale cohort. *Surgery* **166**:297–304.