



## Retrospective Study

# Evaluating the influence of sarcopenia and myosteatosi

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## Abstract

### BACKGROUND

The development and progression of gastric cancer (GC) are closely linked to the nutritional status of patients. Although immunotherapy has been demonstrated to be clinically effective, the relationships of sarcopenia and myosteatosi

### AIM

To assess the effects of sarcopenia and myosteatosi

### METHODS

We performed a retrospective study of patients who were undergoing immunotherapy for GC. For the evaluation of sarcopenia, the optimal cut-off value for the skeletal muscle index was established using receiver operating characteristic analysis of data obtained from pre-treatment computed tomography images at the L3 vertebral level. Myosteatosi

## RESULTS

We studied 115 patients who were undergoing ICI therapy for GC, of whom 27.4% had sarcopenia and 29.8% had myosteatos. Patients with sarcopenia or myosteatos had significantly shorter PFS and OS than those without these conditions. Furthermore, both sarcopenia and myosteatos were found to be independent predictors of PFS and OS in patients with GC administering an ICI. The prediction models created for PFS and OS were associated with C-indexes of 0.758 and 0.781, respectively.

## CONCLUSION

The presence of sarcopenia or myosteatos is a reliable predictor of the clinical outcomes of patients with GC who are undergoing treatment with an ICI.

**Key Words:** Gastric cancer; Sarcopenia; Myosteatos, Immune checkpoint inhibitor; Prognostic factor; Overall survival; Progression-free survival

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**Core Tip:** We performed a retrospective study to evaluate the use of sarcopenia and myosteatos for the prediction of the prognosis of patients with gastric cancer who are being treated with an immune checkpoint inhibitor (ICI). We studied 115 patients with complete sets of clinical data and imaging information and analyzed their muscle cross-sectional area at the L3 Level. We determined the optimal cut-off area value to identify sarcopenia, and myosteatos was defined using mean skeletal muscle densities of < 41 Hounsfield units (HU) for patients with a body mass index (BMI) < 25 kg/m<sup>2</sup> and < 33 HU for those with a BMI ≥ 25 kg/m<sup>2</sup>. We found that muscle loss and muscle steatosis are independent predictors of the outcomes of patients with gastric cancer being treated with an ICI.

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## INTRODUCTION

Gastric cancer (GC) is the fifth most prevalent cancer globally and is a major global health concern[1]. Although the global incidence and mortality rate associated with GC are decreasing, particularly because of advancements in preventive measures, such as a reduction in the prevalence of *Helicobacter pylori* and improvements in food preservation and storage, East Asia retains high incidence and mortality rates[2-7]. The therapeutic options for GC are expanding, with the inclusion of immune checkpoint inhibitors (ICIs) alongside conventional chemotherapy and targeted agents[8]. For instance, navulizumab in combination with chemotherapy is now a first-line treatment for GC, and pembrolizumab in combination with trastuzumab and chemotherapy is the first-line treatment for patients with HER2-positive GC[9,10]. The advent of ICIs has prompted extensive research aimed at identifying prognostic factors for the success of ICI therapy, and parameters including programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) expression, microsatellite instability (MSI), tumor mutational load (TMB), and Epstein-Barr virus (EBV) infection status, have been considered. However, the assessment of these parameters is often expensive and complex[11-13]. Consequently, there is a compelling need for straightforward, cost-effective predictors of the prognosis of patients with advanced GC who are undergoing ICI therapy.

Sarcopenia, which is commonly recognized in patients with cancer, is characterized by the gradual depletion of skeletal muscle and its degeneration. This condition has detrimental effects on metabolism and immunity, resulting in compromised tolerance of, and a poor prognosis associated with, various cancer treatments, including chemotherapy, targeted therapy, and immunotherapy[14,15]. Skeletal muscle mass represents a quantitative and objective measure of the nutritional status of a patient and has been shown to be of prognostic value in patients with a range of cancers, such as GC, hepatocellular carcinoma, and esophageal carcinoma[16-21].

In addition to muscle loss, the presence of myosteatos, which is characterized by increases in inter- and intramuscular fat content, is also of relevance[22]. This pathological change often accompanies excessive muscle loss and is exacerbated by factors such as aging and obesity, which lead to metabolic abnormalities that can affect the outcomes of treatments[23, 24]. Myosteatos has been shown to be associated with inferior overall survival (OS) in patients with several types of cancer, including hepatocellular carcinoma, GC, and colorectal cancer[25].

In the present study, we used cross-sectional computed tomography (CT) images obtained at the level of the third lumbar vertebra (L3) to evaluate the sarcopenia and myosteatos of patients with GC who were undergoing immunotherapy, with the aim of investigating the prognostic value of the presence of these conditions with respect to the clinical outcomes of the patients.

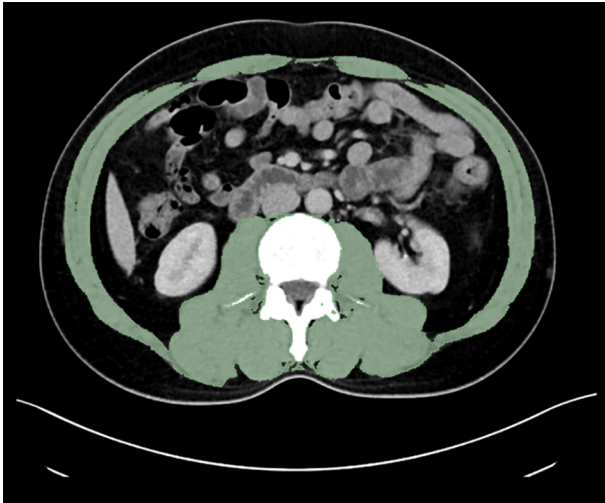


Figure 1 Example of a computed tomography image used for skeletal muscle measurements.

## MATERIALS AND METHODS

### Participants

Patients diagnosed with GC who underwent immunotherapy with an ICI between February 2016 and October 2022 at our institution were eligible for inclusion in the study. A comprehensive set of data, including demographics, clinical attributes, tumor characteristics (tumor size and stage), laboratory parameters, L3 skeletal muscle area, and mean CT radiodensities, were extracted from the medical records of each participant. The institutional review board provided approval for this analysis, and the requirement for informed consent was waived owing to its retrospective nature. Patients undergoing ICI immunotherapy with a PD-1 blocking antibody, including anti-PD-1 and anti-PD-L1 antibodies, with combination therapy including one of these, or with an ICI in conjunction with chemotherapy and/or other agents in phase III clinical trials, were included in the study. The exclusion criteria comprised prior immunotherapy and the inability to undergo pre-treatment CT examination.

### Data collection

The primary endpoints of the study were progression-free survival (PFS) and OS. The timing of these endpoints was determined through telephone follow-up, and the final follow-up consultation was held in December 2022. PFS was defined as the difference between the timing of random assignment to a clinical trial and that of disease progression, which was primarily assessed using enhanced CT. If no evidence of disease progression was identified, the final date of follow-up was used to calculate PFS. OS was calculated as the difference between the timing of the commencement of immunotherapy and the death of the patient.

### Evaluation of sarcopenia and myosteatorsis

Sarcopenia and myosteatorsis were evaluated by a radiologist with over a decade of experience and no knowledge of the clinical outcomes of the participants. The CT data for the participants were imported into 3D Slicer (version 4.10.2, [www.slicer.org](http://www.slicer.org)) to measure the cross-sectional area of the skeletal muscle at the L3 level and the mean skeletal muscle density [SMD, in Hounsfield units (HU)] across the entire muscle region. Skeletal muscle was identified and quantified using HU thresholds ranging from -29 to 150[26]. The L3 muscle region included the psoas major, erector spinae, quadratus lumborum, transversus abdominis, internal and external abdominal oblique muscles, and rectus abdominis. The cross-sectional area was automatically calculated by adding the data for each tissue pixel together and multiplying this by the pixel surface area (Figure 1). Skeletal muscle index (SMI) was calculated as the total L3 skeletal muscle area (cm<sup>2</sup>) divided by the square of the participant's height (m<sup>2</sup>). Given the lack of established diagnostic criteria for sarcopenia, the optimal cut-off value was determined using receiver operating characteristic (ROC) analysis, and participants with an SMI below this threshold were classified as having sarcopenia. The optimal cut-off value for SMI was calculated to be 27.36 for men and 31.10 for women. Myosteatorsis was defined using a mean SMD < 41 HU for participants with a BMI < 25 kg/m<sup>2</sup> and < 33 HU for those with a BMI ≥ 25 kg/m<sup>2</sup>[27].

### Statistical analysis

Data are presented as mean ± SD for normally distributed continuous data or median for non-normally distributed continuous data. Categorical data were analyzed using Pearson's chi-square or Fisher's exact tests, and continuous datasets for participants with or without sarcopenia and myosteatorsis were compared using Student's *t*-test or the Mann-Whitney *U*-test, as appropriate. Kaplan-Meier survival curves were used to evaluate survival outcomes, and Cox's regression analysis was used to identify potential prognostic factors for PFS and OS in univariate analyses. Cox's regression analysis and the parameters that were significant on univariate analysis were then used to identify

independent prognostic factors associated with OS and PFS. Multivariate logistic regression analyses were then performed to construct models for the prediction of 1-, 3-, and 5-year OS and PFS. We used the R statistical package (version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 25.0, IBM, Inc., Armonk, NY, United States) to analyze the data. A two-sided  $P$ -value  $< 0.05$  was considered to represent statistical significance.

## RESULTS

### **Characteristics and laboratory parameters of participants with or without sarcopenia and myosteatosi**

A total of 115 patients with GC who were undergoing ICI treatment were included in the study [89 (77.4%) men and 26 (32.6%) women]. Of these, 29 (25.2%) had stage III GC and 86 (74.8%) had stage IV GC. When we compared the participants with or without sarcopenia, we found that the former were significantly older ( $P < 0.001$ ), had a lower BMI ( $P < 0.001$ ), and were predominantly male ( $P < 0.001$ ). The participants with myosteatosi tended to be older than those without ( $P = 0.001$ ) (Table 1).

Analysis of the laboratory indices showed that participants with sarcopenia had lower creatinine (Crea) concentrations ( $P = 0.004$ ) than those without. In addition, the participants with myosteatosi had higher globulin (GLOB) concentrations ( $P = 0.047$ ), lactate dehydrogenase (LDH) activities ( $P = 0.012$ ), and D-dimer (DDi) concentrations ( $P = 0.002$ ), and lower pre-albumin (PALB) concentrations ( $P = 0.010$ ) than those without (Table 2).

### **Results of the univariate and multivariate Cox's regression analyses**

Univariate analysis identified BMI, total protein (TP), PALB, eosinophil count (Eosi), carbohydrate antigen 724 (CA724) concentration, carbohydrate antigen 125II (CA125II) concentration, sarcopenia, and myosteatosi as potential prognostic factors for OS. Similarly, BMI, alkaline phosphatase (ALP) activity, total bilirubin (TBIL) concentration, indirect bilirubin (IDBIL) concentration, PALB, lymphocyte count (Lym), Eosi, CA724, CA125, TNM stage, sarcopenia, and myosteatosi were identified as potential prognostic factors for PFS. All these potential prognostic factors were then included in multivariate analyses. In these, TP, Eosi, CA724, CA125, sarcopenia, and myosteatosi were found to be independent prognostic factors for OS; ALP, Eosi, CA724, CA125, TNM stage, sarcopenia, and myosteatosi were found to be independent prognostic factors for PFS (Table 3).

### **Effects of sarcopenia and myosteatosi on survival**

The participants with sarcopenia had significantly shorter PFS (median, 15.40 months *vs* 26.20 months,  $P < 0.001$ ) and OS (median, 25.97 months *vs* 38.78 months,  $P < 0.001$ ) than those without (Figure 2). Similarly, the participants with myosteatosi had shorter PFS (median, 16.43 months *vs* 24.30 months,  $P = 0.011$ ) and OS (median, 21.43 months *vs* 33.57 months,  $P = 0.001$ ) than those without (Figure 3).

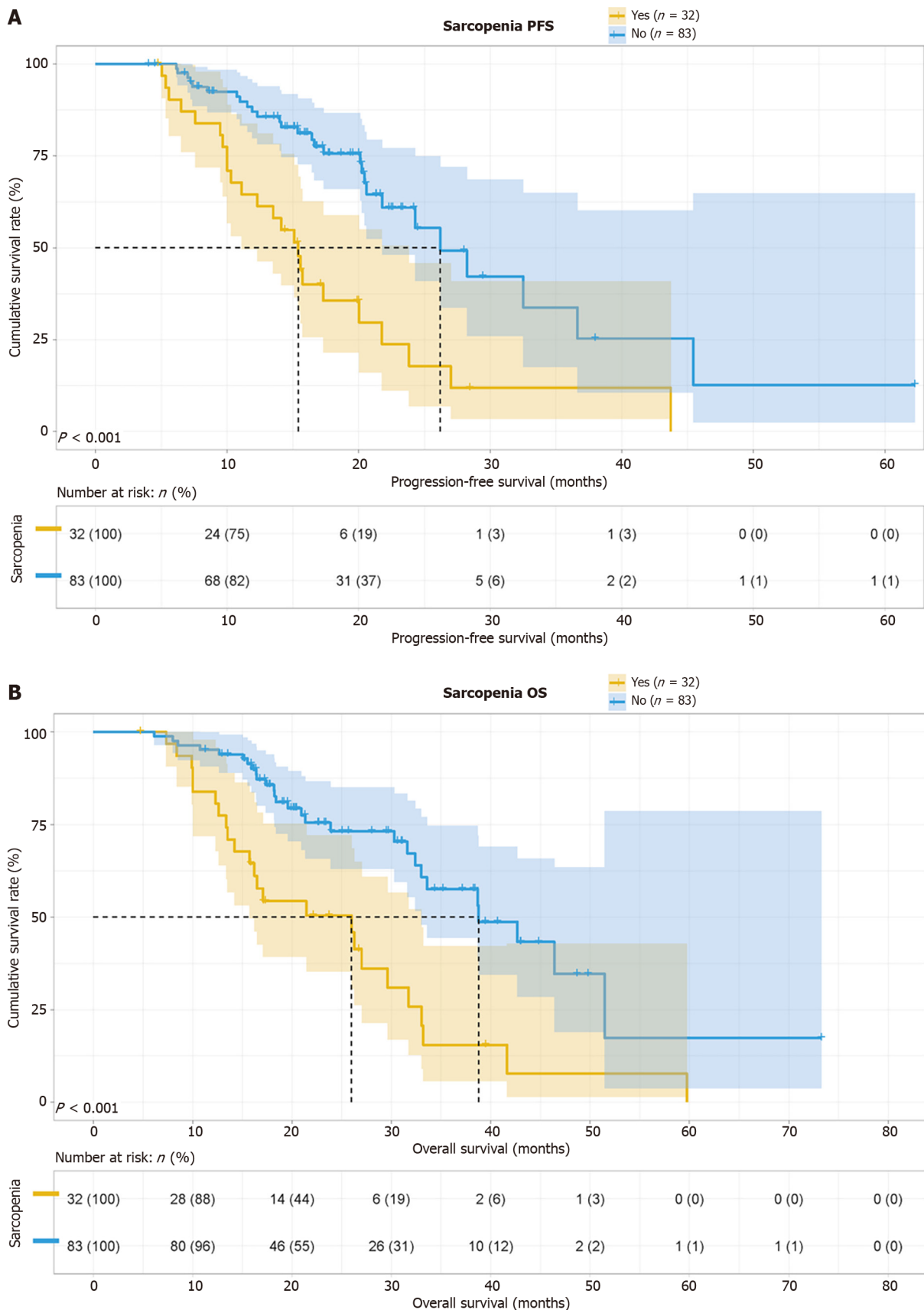
Given that 74.8% of the participants had stage IV GC, a subgroup analysis was conducted, and this yielded results that confirmed the adverse effects of sarcopenia and myosteatosi on both PFS ( $P = 0.002$  *vs*  $P = 0.011$ , respectively) and OS ( $P < 0.001$  *vs*  $P = 0.005$ , respectively) in this subset of participants (Figures 4 and 5).

### **Nomograms**

We used multivariate Cox regression analysis to construct an optimized prediction model for PFS. In addition to the presence of sarcopenia and myosteatosi, ALP, Eosi, CA724, CA125, and TNM stage were identified to be predictors of PFS, and we used these variables to construct a nomogram for PFS (Figure 6A). Similarly, for OS, the predictive model constructed included sarcopenia and myosteatosi, as well as TP, Eosi, CA724, and CA125 (Figure 7A). Both the predictive models for PFS and OS exhibited good C-indexes of 0.758 and 0.781, respectively. First-year calibration curves showed a close alignment of the observed outcomes and those predicted using the presence of sarcopenia or myosteatosi (Figures 6B and 7B). To validate the predictive utility of these parameters, the nomograms were subjected to area under the curve (AUC) analysis for 1- and 3-year intervals, yielding AUC values of 0.769 and 0.850 for PFS, and 0.843 and 0.904 for OS, respectively (Figures 6C and 7C). In addition, decision curve analysis (DCA) including diverse threshold probabilities demonstrated that the net benefit for the prediction of PFS was maximal within the range 0.040–0.978, peaking at 0.282. Similarly, for OS, the optimal DCA threshold was within the range 0.022–0.900, peaking at 0.260 (Figures 6D and 7D). This meticulous analysis affirmed the robustness and clinical utility of the predictive models for the outcomes of patients undergoing ICI therapy.

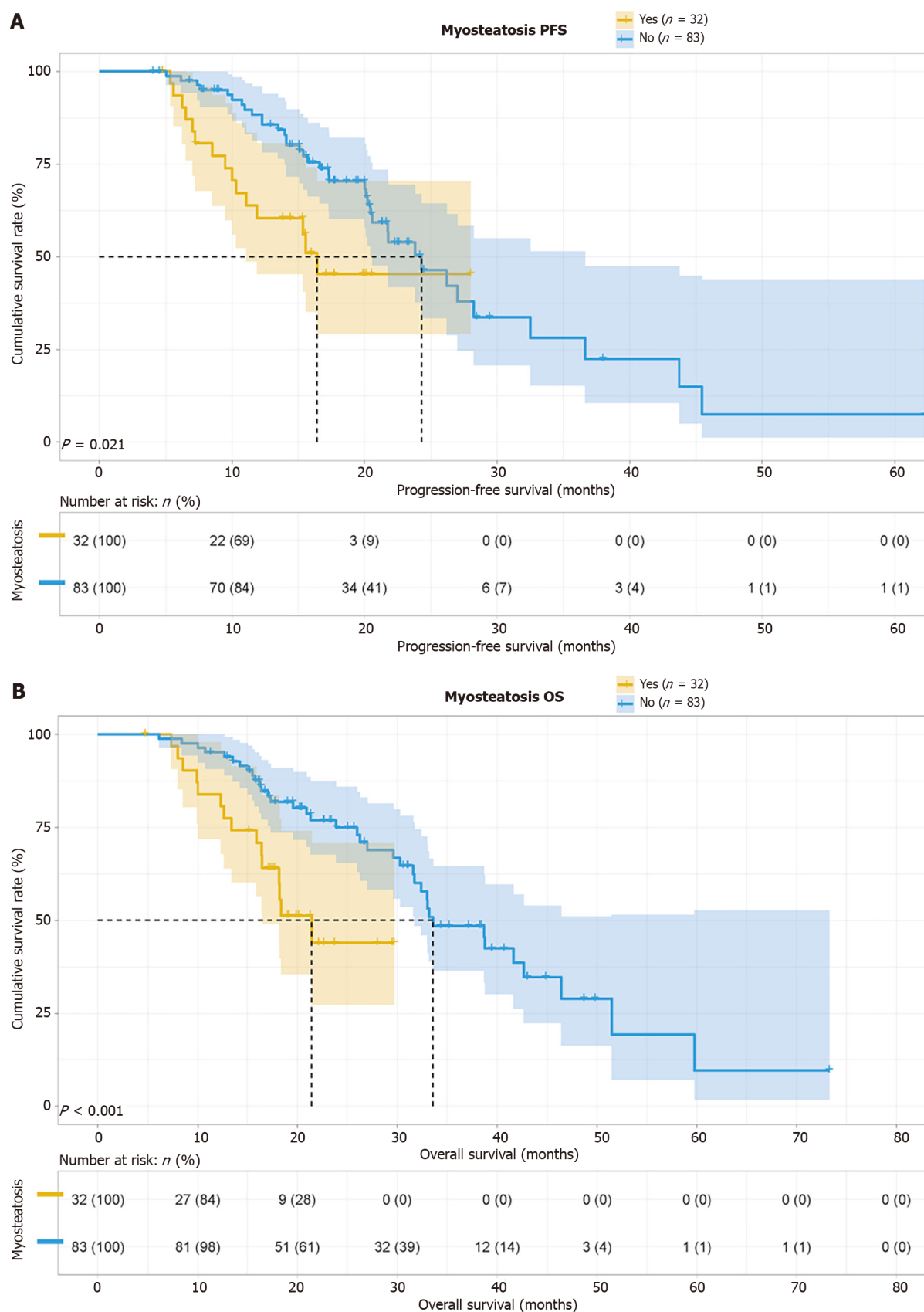
## DISCUSSION

GC is highly prevalent but often presents with non-specific clinical features, resulting in a delay to diagnosis and the administration of ineffective treatments, especially in older patients[28,29]. Systemic chemotherapy has been the primary approach to the treatment of advanced GC, but it yields limited survival benefits, with a median survival of approximately 1 year[30,31]. In recent years, ICIs have emerged as promising therapeutic options for patients with advanced cancer, showing efficacy and safety in clinical trials. Some ICIs, such as pembrolizumab, avelumab, sindilizumab, tirilizumab, and ipilimumab, have been approved for administration in combination with targeted therapies for advanced GCs[32–34]. Notably, nabulizumab in combination with chemotherapy yielded excellent outcomes in the Chinese subgroup of the CheckMate 649 clinical trial[12]. To date, parameters such as PD-1/PD-L1 expression, MSI, TMB, and

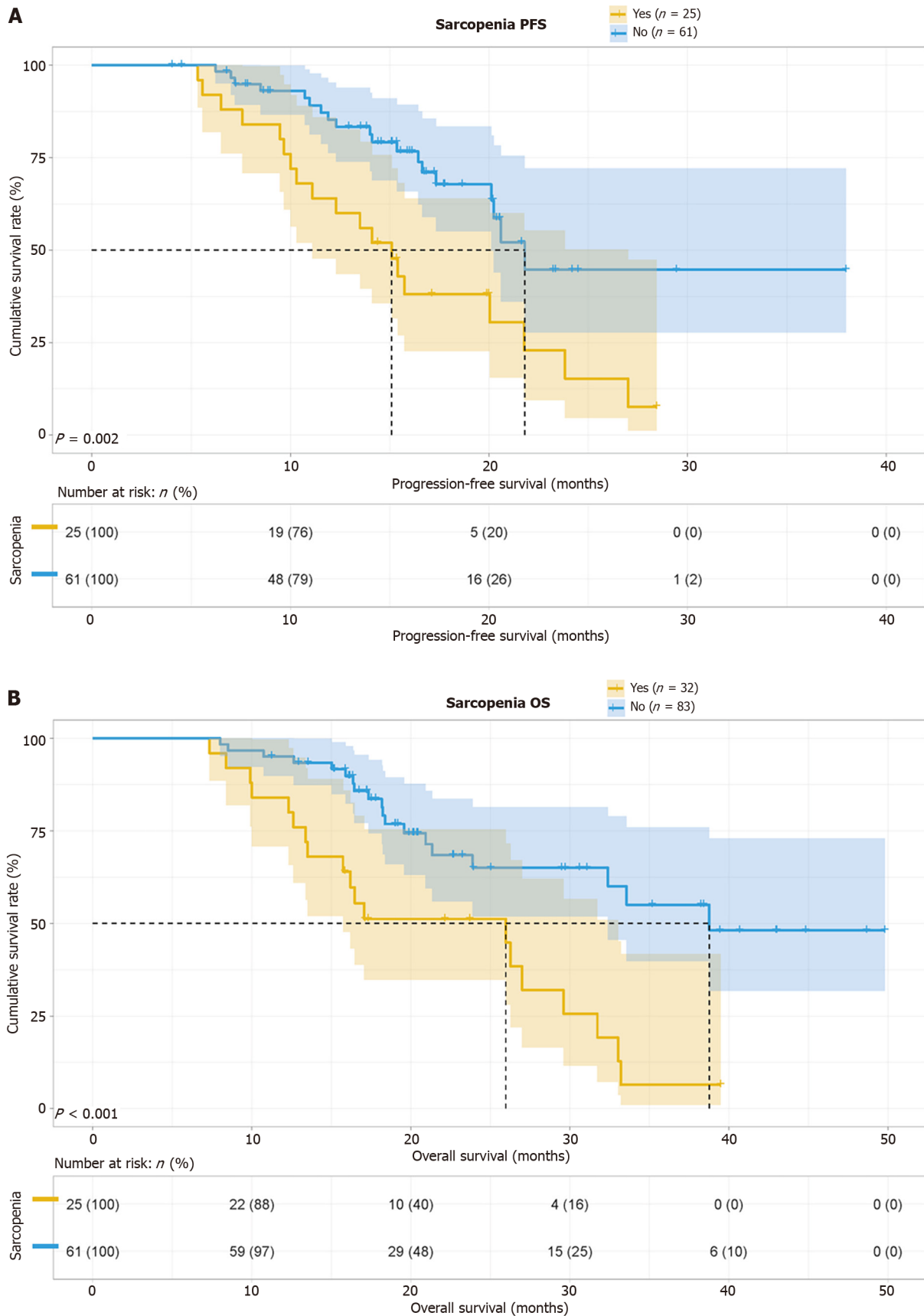


**Figure 2** Survival curves for (A) progression-free survival and (B) overall survival in the presence or absence of sarcopenia. PFS: Progression-free survival; OS: Overall survival.

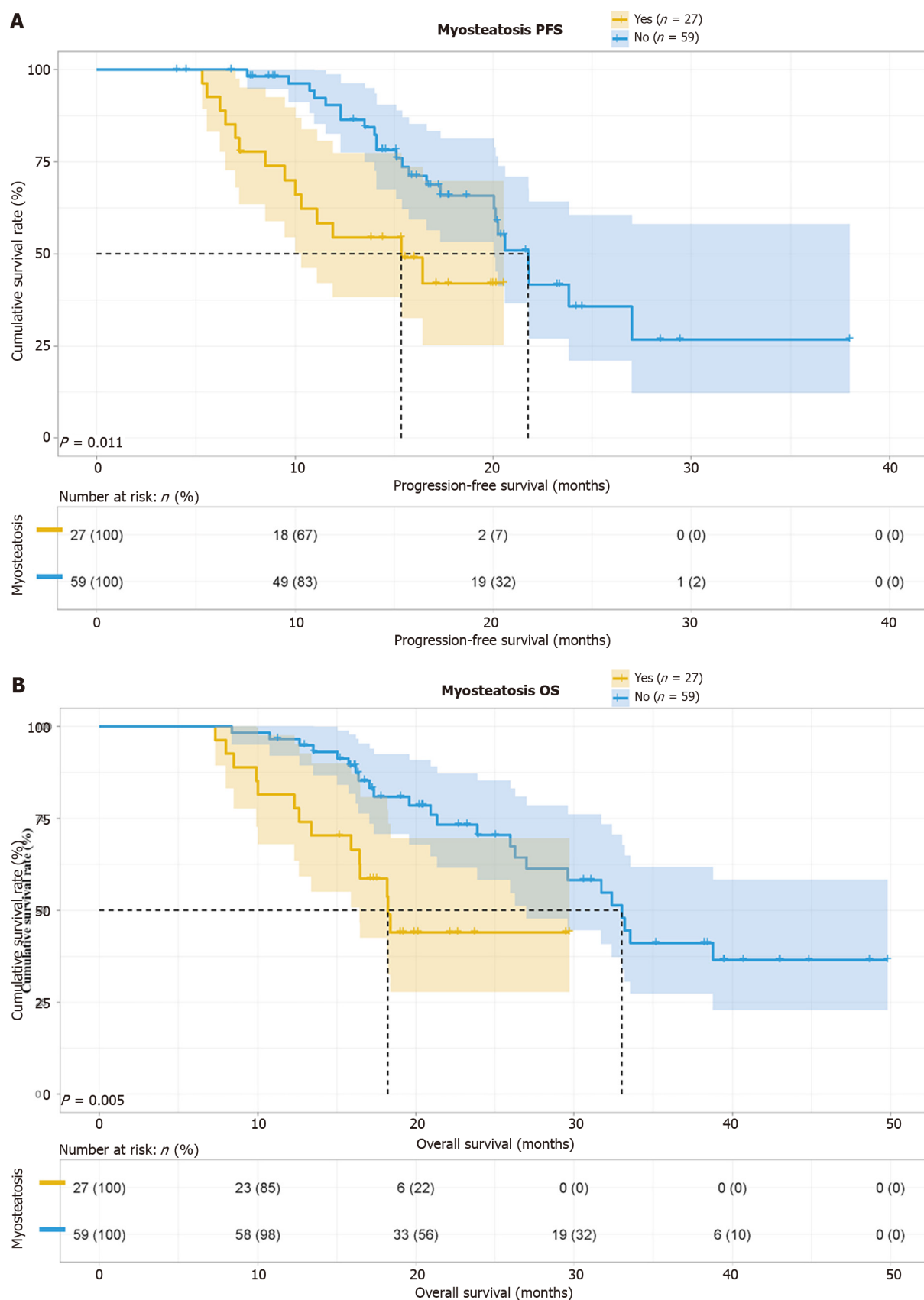




**Figure 3** Survival curves for (A) progression-free survival and (B) overall survival in the presence or absence of myosteatosi. PFS: Progression-free survival; OS: Overall survival.

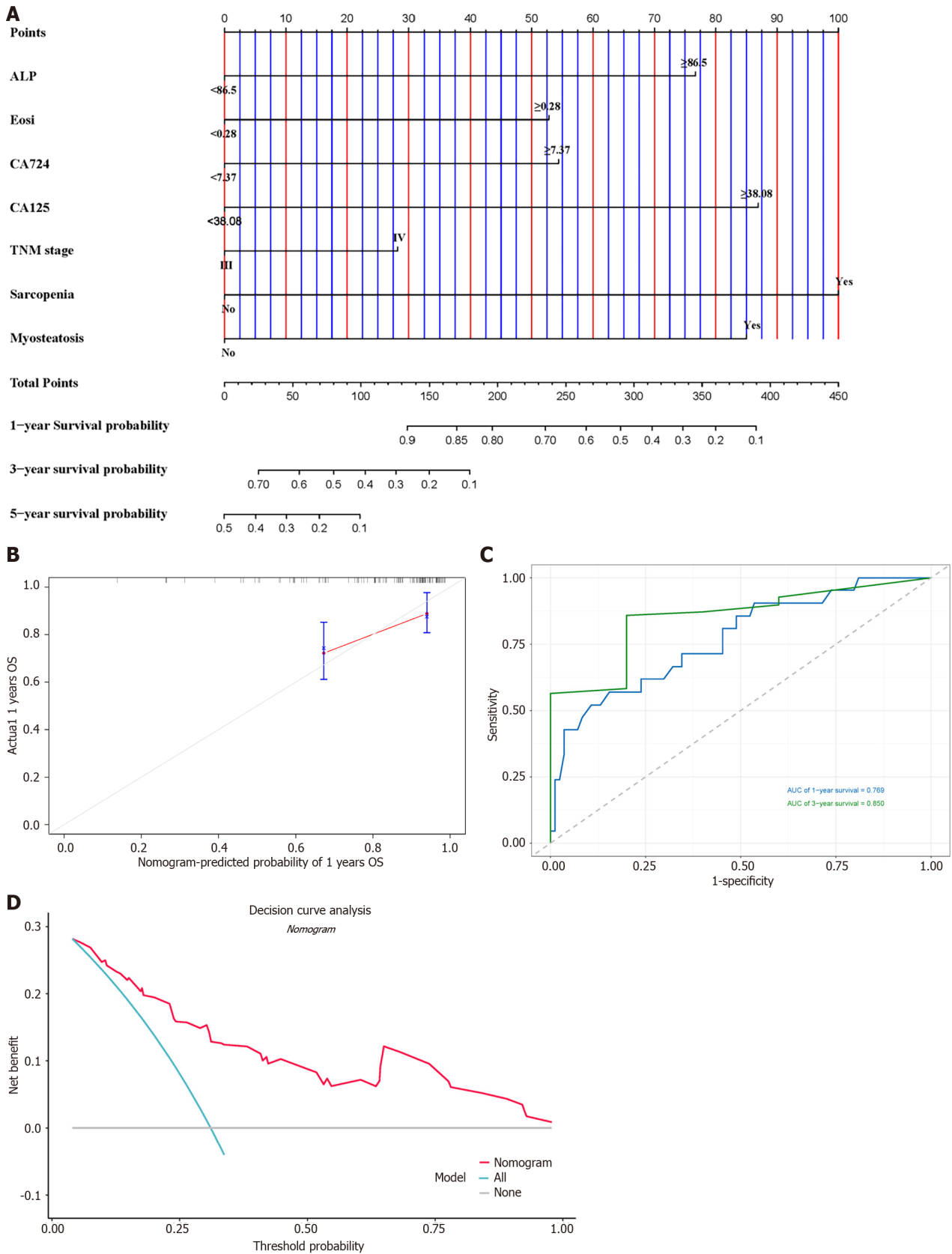


**Figure 4** Survival curves for (A) progression-free survival and (B) overall survival in participants with gastric cancer in the presence or absence of sarcopenia. PFS: Progression-free survival; OS: Overall survival.

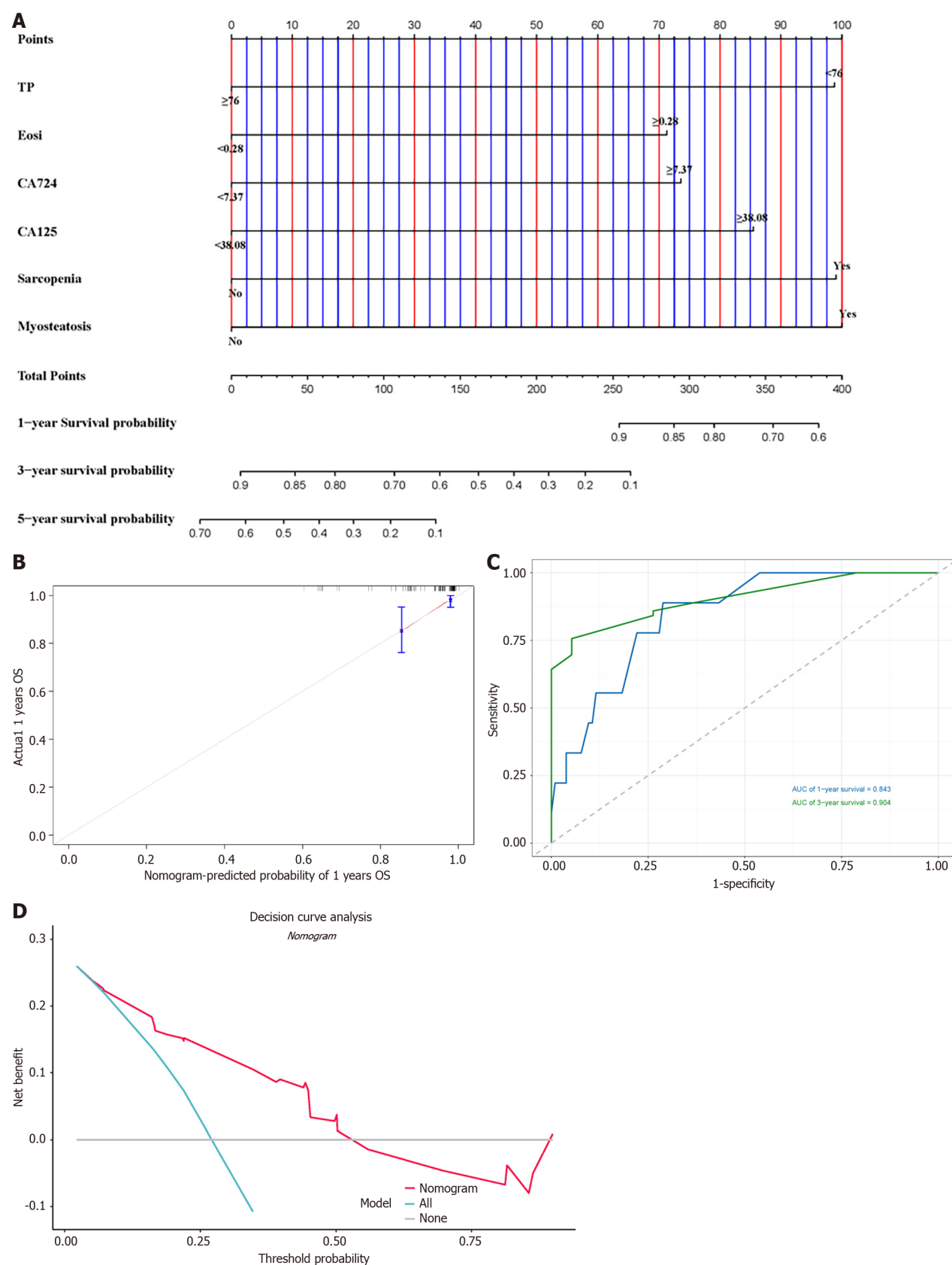


**Figure 5** Survival curves for (A) progression-free survival and (B) overall survival in participants with advanced gastric cancer in the presence or absence of myosteatos. PFS: Progression-free survival; OS: Overall survival.





**Figure 6** Nomogram for progression-free survival. A: Nomogram for progression-free survival (PFS); B: One-year and 3-year area under the curves for PFS; C: Calibration curves for PFS; D: Decision curve analysis for PFS. AUC: Area under the curve; PFS: Progression-free survival; OS: Overall survival; ALP: Alkaline phosphatase; Eosi: Eosinophil count; CA724: Carbohydrate antigen 724; CA125: Carbohydrate antigen 125.



**Figure 7 Nomogram for overall survival.** A: Nomogram for overall survival (OS); B: One-year and 3-year area under the curves for OS; C: Calibration curves for OS; D: Decision curve analysis for OS. AUC: Area under the curve; OS: Overall survival; TP: Total protein; Eosi: Eosinophil count; CA724: Carbohydrate antigen 724; CA125: Carbohydrate antigen 125.

Table 1 Participant characteristics

	Sarcopenia			Myosteatosi		
	Yes (n = 32)	No (n = 83)	P value	Yes (n = 32)	No (n = 83)	P value
Item, mean (SD)						
Age	57.44 (11.18)	57.40 (8.57)	< 0.001	62.31 (7.69)	55.52 (9.24)	0.001
BMI	19.88 (4.39)	22.75 (3.07)	< 0.001	22.04 (3.85)	21.91 (3.85)	0.986
Sex, n (%)			< 0.001			0.703
Male	15 (46.9)	74 (89.2)		24 (75.0)	65 (78.3)	
Female	17 (53.1)	9 (10.8)		8 (25.0)	18 (21.7)	
Primary tumor site, n (%)			0.900			0.640
Upper 1/3	6 (18.8)	13 (15.7)		5 (15.6)	14 (16.9)	
Middle 1/3	7 (21.9)	23 (27.7)		6 (18.8)	24 (28.9)	
Low 1/3	18 (56.2)	45 (54.2)		20 (62.5)	43 (51.8)	
Whole	1 (3.1)	2 (2.4)		1 (3.1)	2 (2.4)	
Pathology, n (%)			0.166			0.344
Adenocarcinoma	6 (18.8)	22 (26.5)		5 (15.6)	23 (27.7)	
Others <sup>†</sup>	5 (15.6)	4 (4.8)		2 (6.3)	7 (8.4)	
Unknown	21 (65.6)	57 (68.7)		25 (78.1)	53 (63.9)	
TNM stage, n (%)			0.608			0.141
III	7 (21.9)	22 (26.5)		5 (15.6)	24 (28.9)	
IV	25 (78.1)	61 (73.5)		27 (84.4)	59 (71.1)	
PD-1, n (%)			0.281			0.698
Positive	5 (15.6)	5 (6.1)		4 (12.5)	6 (7.2)	
Negative	2 (6.3)	7 (8.4)		2 (6.3)	7 (8.4)	
Unknown	25 (78.1)	71 (85.5)		26 (81.2)	70 (84.4)	
PD-L1, n (%)			0.281			0.710
Positive	5 (15.6)	5 (6.1)		4 (12.5)	6 (7.2)	
Negative	2 (6.3)	8 (8.4)		2 (6.3)	8 (9.6)	
Unknown	25 (78.1)	70 (85.5)		26 (81.2)	69 (83.2)	
AFP, n (%)			0.702			0.221
< 2.92 ng/mL	19 (59.4)	46 (55.4)		21 (65.6)	44 (53.0)	
≥ 2.92 ng/mL	13 (40.6)	37 (44.6)		11 (34.4)	39 (47.0)	
CEA, n (%)			0.933			0.315
< 4.24 ng/mL	9 (28.1)	24 (28.9)		7 (21.9)	26 (31.3)	
≥ 4.24 ng/mL	23 (71.9)	59 (71.1)		25 (78.1)	57 (68.7)	
CA199, n (%)			0.859			0.295
< 17.63 U/L	21 (65.6)	53 (63.9)		23 (71.9)	51 (61.4)	
≥ 17.63 U/L	11 (34.4)	30 (36.1)		9 (28.1)	32 (38.6)	
CA724, n (%)			0.704			0.955
< 4.40 U/L	20 (62.5)	55 (66.3)		21 (65.6)	54 (65.1)	
≥ 4.40 U/L	12 (37.5)	28 (33.7)		11 (34.4)	29 (34.9)	
CA125II, n (%)			0.811			0.756
< 21.94 U/L	26 (81.3)	69 (83.1)		27 (81.9)	68 (84.4)	

≥ 21.94 U/L	6 (18.8)	14 (16.9)	5 (18.1)	15 (15.6)	
Sarcopenia, <i>n</i> (%)					0.057
Yes			13 (59.4)	19 (22.9)	
No			19 (40.6)	64 (77.1)	
Myosteatosi, <i>n</i> (%)					0.057
Yes	13 (40.6)	19 (22.9)			
NO	19 (59.4)	64 (77.1)			

<sup>1</sup>Others comprised mucinous carcinoma, signet ring cell carcinoma, and mixed carcinoma. BMI: Body mass index; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199; CA724: Carbohydrate antigen 724; CA125II: Carbohydrate antigen 125II; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1.

EBV infection status have been used to identify suitable candidates for ICI therapy, but the nutritional status of the patients has a significant effect on their treatment outcomes[11-13]. Malnutrition and the related symptoms negatively affect the prognosis and the quality of life of patients with cancer. Therefore, we conducted a study using CT-derived data to assess the muscle status of patients with GC undergoing immunotherapy, and especially of those who were negative for prognostic markers such as PD-1 and PD-L1.

Sarcopenia, which reflects malnutrition and involves chronic inflammation, is common in patients with cancer, and features muscle loss and a decrease in fat mass[35]. It significantly impacts quality of life, induces anxiety and depression, and results in poorer clinical outcomes[36,37]. Furthermore, patients with sarcopenia may experience more severe toxic side effects during chemotherapy, owing to alterations in body composition and muscle loss caused by tumor-specific therapy[38-40]. In the present study, sarcopenia in patients with GC who were undergoing ICI therapy was shown to be associated with both PFS and OS. A previous study similarly showed that sarcopenia is associated with shorter PFS and OS in patients with microsatellite-stable GC being treated with a PD-1 inhibitor[41]. In 2021, Kim *et al*[42] also studied patients with advanced GC who were being treated with naviluzumab and pabulizumab. They divided the patients into those with or without sarcopenia and discussed the prognostic value of the neutrophil-to-lymphocyte ratio between the groups[42], but did not evaluate the relationship between sarcopenia and prognosis.

Myosteatosi is characterized by excessive fat accumulation in skeletal muscle and is often used to describe low muscle mass in patients[43]. It has predictive value in patients with various diseases and is consistently associated with poor prognoses, including for colon, liver, and pancreatic cancer[44-47]. Several previous studies of the relationship between immunotherapy and myosteatosi have generated important findings. In patients with metastatic melanoma who were being treated with nivolumab, low SMD was found to be associated with shorter OS[48], and another study of patients being treated with ipilimumab revealed that patients with high SMD experienced more immunity-related adverse events but superior objective responses to treatment, whereas low SMD was found to be associated with a worse prognosis[49]. The skeletal muscle microenvironment plays a critical role in skeletal muscle repair, and this involves monocytes, neutrophils, and lymphocytes. Myosteatosi, which reflects low muscle mass, is associated with impaired muscle repair, leading to compromised immunity[50]. This, in turn, may result in poorer responsiveness to immunotherapy, a higher risk of toxic side effects, and poorer clinical outcomes. However, the specific mechanisms involved and the variations in the effects of myosteatosi in patients with various types of cancer warrant further investigation.

Accumulating evidence indicates the involvement of immune cell mitochondria in the effects of ICIs, as well as in the development of sarcopenia and myosteatosi. Previous studies have shown that cancer cells can appropriate the mitochondria of immune cells, thereby facilitating their survival within the immune microenvironment, the evasion of immune surveillance, and resistance to therapeutic interventions[51]. The commandeering of mitochondria from immune cells, and particularly T cells, has been shown to increase the expression of PD-1, which contributes to its anti-tumor effects[52]. Moreover, compromised mitochondrial function can lead to the overexpression of PD-1 in T cells[53], and the inhibition of the hijacking of mitochondria by immune cells has been demonstrated to improve anti-tumor responses in mice with mammary cancer that were treated with an anti-PD-1 antibody[54]. Notably, a previous study has also shown that muscle loss and muscle fat degeneration are indicative of poor mitochondrial function in muscle cells, which can be extrapolated to other normal human cells, including immune cells[55]. Consequently, the presence of sarcopenia and muscle steatosi may present challenges for successful therapy with ICIs.

There are several important considerations regarding studies of the prognostic implications of sarcopenia and myosteatosi. For instance, there is no well-established value of SMI that can be used in the diagnosis of sarcopenia, and therefore in most studies, ROC-derived cut-off values have been used[22]. This approach, in combination with the use of differing cut-off values in patients with different types of cancer, may affect the identified relationships between muscle-related conditions and clinical outcomes. In the case of myosteatosi, mean SMD is an objective index, but some studies have shown variations in mean SMD according to whether measurements were made using unenhanced contrast-enhanced CT images or those obtained during the arterial or portal venous phases of enhancement. Thus, the CT protocol used can introduce bias into SMD measurements. To minimize such bias, we consistently obtained images during the portal-venous phase. In future investigations of the relationships between muscle conditions and cancer, two key challenges should be addressed: The standardization of CT protocols and the optimal diagnostic criteria for sarcopenia and myosteatosi.

**Table 2 Laboratory data for the participants, *n* (%)**

Item, mean (SD)	Sarcopenia		<i>P</i> value	Myosteatosi		<i>P</i> value
	Yes ( <i>n</i> = 32)	No ( <i>n</i> = 83)		Yes ( <i>n</i> = 32)	No ( <i>n</i> = 83)	
ALT (U/L)	20.31 (16.87)	22.89 (21.41)	0.404	20.07 (15.82)	22.98 (21.70)	0.660
AST (U/L)	27.41 (23.12)	25.99 (18.25)	0.954	29.84 (28.16)	25.05 (15.15)	0.831
γ-GGT (U/L)	66.22 (159.76)	60.37 (88.60)	0.378	97.19 (174.69)	48.43 (72.81)	0.067
ALP (U/L)	115.02 (109.27)	114.35 (67.34)	0.216	116.33 (66.18)	113.84 (85.98)	0.651
TBIL (μmol/L)	14.47 (9.57)	14.44 (8.10)	0.584	14.56 (9.70)	14.40 (8.04)	0.350
DBIL (μmol/L)	3.69 (4.51)	3.18 (2.43)	0.476	3.49 (3.51)	3.26 (3.00)	0.627
IDBIL (μmol/L)	10.79 (5.90)	11.26 (6.19)	0.554	11.08 (6.65)	11.15 (5.90)	0.438
TP (g/L)	70.80 (7.83)	68.31 (7.55)	0.077	69.42 (7.63)	68.84 (7.74)	0.798
ALB (g/L)	39.45 (4.70)	38.61 (6.41)	0.189	37.44 (4.50)	39.38 (6.40)	0.053
GLOB (g/L)	31.30 (4.86)	30.15 (5.00)	0.184	31.93 (4.76)	29.91 (4.96)	0.047
PALB (g/L)	200.44 (66.25)	210.51 (65.47)	0.640	182.16 (59.81)	217.55 (65.33)	0.010
Urea (mmol/L)	5.75 (1.89)	5.94 (1.63)	0.501	6.31 (1.98)	5.73 (1.56)	0.182
CREA (μmol/L)	72.00 (15.17)	79.40 (16.50)	0.013	78.78 (15.45)	76.78 (16.83)	0.375
UA (μmol/L)	297.28 (88.63)	316.28 (92.69)	0.169	318.66 (92.09)	308.04 (91.78)	0.636
LDH (U/L)	229.03 (204.48)	233.55 (213.03)	0.836	301.75 (274.39)	205.52 (173.55)	0.012
WBC (10 <sup>9</sup> /L)	7.28 (3.82)	7.59 (5.32)	0.769	7.58 (3.60)	7.48 (5.39)	0.280
NEU (10 <sup>9</sup> /L)	4.91 (3.57)	4.72 (2.17)	0.658	5.26 (3.36)	4.59 (2.26)	0.208
Lym (10 <sup>9</sup> /L)	1.69 (0.58)	1.60 (0.56)	0.476	1.57 (0.53)	1.65 (0.58)	0.493
Mono (10 <sup>9</sup> /L)	0.47 (0.22)	0.53 (0.21)	0.150	0.55 (0.18)	0.49 (0.22)	0.113
Eosi (10 <sup>9</sup> /L)	0.12 (0.13)	0.13 (0.11)	0.173	0.13 (0.10)	0.12 (0.12)	0.364
Baso (10 <sup>9</sup> /L)	0.03 (0.02)	0.02 (0.01)	0.145	0.03 (0.02)	0.02 (0.01)	0.276
Hb (g/L)	124.03 (21.17)	126.69 (27.63)	0.575	121.03 (30.31)	127.85 (23.97)	0.245
RBC (10 <sup>12</sup> /L)	4.19 (0.66)	4.45 (0.73)	0.103	4.26 (0.80)	4.42 (0.68)	0.363
Plt (10 <sup>9</sup> /L)	255.41 (98.83)	256.23 (91.47)	0.967	279.75 (110.41)	246.84 (84.53)	0.213
Fbg (g/L)	3.67 (0.98)	4.04 (2.78)	0.902	4.78 (4.13)	3.61 (1.14)	0.051
DDi (mg/L)	1.54 (2.90)	1.28 (2.14)	0.135	1.83 (3.18)	1.17 (1.96)	0.002

ALT: Alanine transaminase; AST: Aspartate aminotransferase; γ-GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase; TBIL: Total bilirubin; DBIL: Direct bilirubin; IDBIL: Indirect bilirubin; TP: Total protein; ALB: Albumin; GLOB: Globulin; PALB: Pre-albumin; Urea: Urea nitrogen; CREA: Creatinine; UA: Uric acid; LDH: Lactate dehydrogenase; WBC: White blood cell count; NEU: Neutrophil count; Lym: Lymphocyte count; Mono: Monocyte count; Eosi: Eosinophil count; Baso: Basophil count; Hb: Hemoglobin; RBC: Red blood cell count; Plt: Platelet count; Fbg: Fibrinogen; DDi: D-dimer.

In the present study, we found that 27.4% of patients with GC who were undergoing ICI treatment had sarcopenia, 29.8% had myosteatosi, and 10.5% of those with sarcopenia also had concurrent myosteatosi. Furthermore, Kaplan–Meier analysis demonstrated that patients with sarcopenia and/or myosteatosi had shorter PFS and OS. Multivariate analysis identified TP, Eosi, CA724, CA125, sarcopenia, and myosteatosi as independent prognostic factors for OS; and TBIL, DBIL, Eosi, CA125, sarcopenia, and myosteatosi were found to independently affect PFS. We were able to develop models that can accurately predict the prognosis of patients undergoing ICI treatment, with C-indexes of 0.758 for PFS and 0.781 for OS. In the future, the accuracy of the prediction may be improved by using multidimensional integrated analyses based on CT radiomics, body composition, markers of inflammation, and gene expression.

Although valuable insights have been provided by the present study, certain limitations should also be acknowledged. First, it was a retrospective, single-center study, and therefore the results require corroboration by multicenter prospective studies. Second, the inclusion of patients treated with a range of ICI regimens introduced variability regarding treatment efficacy, and therefore the results may need validation using a cohort undergoing a uniform treatment regimen. However, to date, there have been few studies of the prognostic implications of sarcopenia and myosteatosi in patients with GC who are undergoing ICI therapy, and the present study has provided novel insight into the prediction of the prognosis of such patients and has improved understanding of the relevance of these muscle

**Table 3 Results of the univariate and multivariate analyses to identify parameters predictive of progression-free survival and overall survival**

Parameters	OS				PFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value
ALT (U/L)	1.191 (0.680-2.088)	0.541			1.312 (0.748-2.301)	0.343		
AST (U/L)	3.316 (0.457-24.065)	0.236			4.063 (0.560-29.469)	0.165		
γ-GGT (U/L)	0.914 (0.522-1.601)	0.753			0.907 (0.511-1.610)	0.739		
ALP (U/L)	1.673 (0.933-2.998)	0.084			1.962 (1.096-3.513)	0.023	1.540 (0.722-3.282)	0.264
TBIL (μmol/L)	1.578 (0.861-2.893)	0.140			2.108 (1.155-3.848)	0.015	3.752 (1.104-12.750)	0.034
DBIL (μmol/L)	1.245 (0.705-2.197)	0.450			1.337 (0.763-2.343)	0.310		
IDBIL (μmol/L)	1.383 (0.785-2.434)	0.261			1.870 (1.066-3.281)	0.029	0.847 (0.276-2.603)	0.772
TP (g/L)	0.389 (0.165-0.917)	0.031	0.310 (0.126-0.765)	0.011	0.502 (0.214-1.179)	0.114		
ALB (g/L)	0.985 (0.542-1.791)	0.961			1.212 (0.667-2.201)	0.528		
GLOB (g/L)	0.380 (0.118-1.223)	0.105			0.345 (0.107-1.114)	0.075		
PALB (g/L)	0.518 (0.293-0.915)	0.024	0.757 (0.414-1.384)	0.366	0.524 (0.299-0.919)	0.024	0.560 (0.288-1.088)	0.087
Urea (mmol/L)	0.693 (0.362-1.328)	0.269			0.711 (0.369-1.368)	0.307		
CREA (μmol/L)	0.882 (0.486-1.600)	0.679			1.007 (0.557-1.822)	0.981		
UA (μmol/L)	0.571 (0.256-1.275)	0.172			0.641 (0.284-1.446)	0.284		
LDH (U/L)	1.094 (0.556-2.152)	0.794			1.056 (0.543-2.051)	0.873		
WBC (10 <sup>9</sup> /L)	1.500 (0.835-2.696)	0.175			1.450 (0.809-2.598)	0.212		
NEU (10 <sup>9</sup> /L)	1.352 (0.728-2.512)	0.339			1.334 (0.719-2.475)	0.360		
Lym (10 <sup>9</sup> /L)	0.581 (0.323-1.043)	0.069			0.555 (0.308-0.998)	0.049	0.692 (0.345-1.391)	0.301
Mono (10 <sup>9</sup> /L)	0.727 (0.418-1.262)	0.257			0.730 (0.421-1.267)	0.264		
Eosi (10 <sup>9</sup> /L)	3.205 (1.520-6.758)	0.002	2.398 (1.116-5.153)	0.025	2.856 (1.374-5.936)	0.005	3.022 (1.341-6.809)	0.008
Baso (10 <sup>9</sup> /L)	1.151 (0.656-2.019)	0.625			1.408 (0.797-2.489)	0.239		
Hb (g/L)	1.062 (0.604-1.866)	0.835			1.010 (0.576-1.772)	0.973		
RBC (10 <sup>12</sup> /L)	0.951 (0.542-1.667)	0.860			0.946 (0.538-1.666)	0.849		
Plt (10 <sup>9</sup> /L)	0.578 (0.308-1.085)	0.088			0.590 (0.314-1.110)	0.102		
Fbg (g/L)	0.044 (0.000-	0.282			0.44 (0.000-	0.238		



	12.949)				7.917)			
DDi (mg/L)	1.906 (0.978-3.715)	0.058			1.883 (0.978-3.627)	0.058		
AFP ng/mL	0.830 (0.473-1.454)	0.514			0.871 (0.496-1.529)	0.631		
CEA ng/mL	1.507 (0.796-2.855)	0.208			1.175 (0.622-2.219)	0.620		
CA199 U/L	1.605 (0.927-2.780)	0.091			1.756 (1.015-3.037)	0.044	1.395 (0.719-2.706)	0.325
CA724 U/L	2.051 (1.176-3.578)	0.011	2.459 (1.334-4.534)	0.004	1.846 (1.055-3.228)	0.032	1.951 (1.056-3.606)	0.033
CA125 II U/L	2.408 (1.294-4.482)	0.006	2.763 (1.302-5.862)	0.008	2.735 (1.445-5.179)	0.002	2.419 (1.094-5.348)	0.029
BMI (kg/m <sup>2</sup> )	0.533 (0.309-0.921)	0.024	1.165 (0.584-2.322)	0.665	0.467 (0.268-0.815)	0.007	1.232 (0.581-2.610)	0.586
Age (< 53.50 <i>vs</i> ≥ 53.50)	0.978 (0.550-1.737)	0.939			1.276 (0.721-2.256)	0.403		
Sex (Male <i>vs</i> Female)	1.288 (0.689-2.410)	0.428			1.275 (0.682-2.385)	0.447		
TNM stage (III <i>vs</i> IV)	1.586 (0.820-3.067)	0.170			2.044 (1.031-4.052)	0.041	2.313 (1.007-5.317)	0.048
Sarcopenia (Yes <i>vs</i> No)	2.896 (1.670-5.021)	< 0.001	3.569 (1.808-7.045)	< 0.001	3.021 (1.737-5.253)	< 0.001	4.036 (1.959-8.316)	< 0.001
Myosteatosi (Yes <i>vs</i> No)	2.662 (1.357-5.225)	0.004	3.172 (1.471-6.839)	0.003	2.104 (1.118-3.962)	0.021	2.624 (1.256-5.483)	0.010

ALT: Alanine transaminase; AST: Aspartate aminotransferase; γ-GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase; TBIL: Total bilirubin; DBIL: Direct bilirubin; IDBIL: Indirect bilirubin; TP: Total protein; ALB: Albumin; GLOB: Globulin; PALB: Pre-albumin; Urea: Urea nitrogen; CREA: Creatinine; UA: Uric acid; LDH: Lactate dehydrogenase; WBC: White blood cell count; NEU: Neutrophil count; Lym: Lymphocyte count; Mono: Monocyte count; Eosi: Eosinophil count; Baso: Basophil count; Hb: Hemoglobin; RBC: Red blood cell count; Plt: Platelet count; Fbg: Fibrinogen; DDi: D-dimer; PFS: Progression-free survival; OS: Overall survival.

conditions to the outcomes of immunotherapy.

## CONCLUSION

Sarcopenia and myosteatosi, which reflect the body's response to trophic inflammation, are useful predictors of the prognosis of patients with GC who are undergoing treatment with ICI. The clinical course of patients with sarcopenia and myosteatosi has the potential to involve a number of unfavorable outcomes, including shorter PFS and OS. In summary, the evaluation of muscle mass by CT imaging has the potential to yield robust predictors of the prognosis of patients with GC being treated with ICIs.

## ARTICLE HIGHLIGHTS

### Research background

The evolution and progression of gastric cancer (GC) is closely associated with the nutritional status of patients. The laboratory indices currently used to assess the nutritional status of patients have limitations.

### Research motivation

The presence or absence of sarcopenia and myosteatosi are objective indicators of the nutritional status of patients, and muscle mass status influences the effectiveness of immune checkpoint inhibitors (ICIs) therapy.

### Research objectives

This study aims to investigate the effects of sarcopenia and sarcopenia on the clinical prognosis of patients with GC being treated with ICIs.

## Research methods

We studied 115 patients with GC who underwent ICI therapy between 2016 and 2022. The third lumbar vertebrae skeletal muscle cross-sectional area and the mean skeletal muscle density were assessed using 3D Slicer. We then analyzed the relationships of sarcopenia and myosteatorsis with the prognosis of the patients.

## Research results

Patients exhibiting sarcopenia and/or myosteatorsis demonstrated poorer clinical outcomes, and nomograms formulated on the basis of these conditions had substantial prognostic value.

## Research conclusions

The presence of sarcopenia and/or myosteatorsis was validated for the prediction of the clinical outcomes of patients with GC undergoing ICI therapy.

## Research perspectives

Screening for sarcopenia and myosteatorsis should help identify patients with advanced GC who would benefit from treatment with ICIs.

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## FOOTNOTES

**Co-first authors:** Gui-Ming Deng and Hai-Bin Song.

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**Author contributions:** Deng GM and Song HB contributed equally to this work; Deng GM, Song HB, Du ZZ, Xue YW, Song HJ and Li YZ designed the research study; Deng GM, Song HB, Du ZZ and Li YZ performed the research; Xue YW, Song HJ and Li YZ provided data and funding for the experiment; Deng GM and Song HB analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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