Serum Creatinine/Cystatin C Ratio as a Surrogate Marker for Sarcopenia in Patients with Gastric Cancer

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Abstract

Background: Sarcopenia is an age-related syndrome that may negatively impact surgical outcomes and long-term survival in patients with gastric cancer. Serum creatinine/cystatin C (Cr/CysC) ratio has attracted attention as a surrogate marker for sarcopenia, but the ratio has not been adequately studied in patients with gastric cancer. Our objective was to investigate the validity of serum Cr/CysC ratio as a predictor of sarcopenia, determine a statistical cut-off value, and assess the relationship between Cr/CysC ratio and prognosis in patients with gastric cancer.

Methods: We retrospectively evaluated 269 patients who underwent surgery for gastric cancer from June 2009 to October 2017. Skeletal muscle mass index (SMI) was calculated using computed tomography (CT). We determined the relevance of serum Cr/CysC ratio as a surrogate maker for sarcopenia by comparing the ratio with various biomarkers. The C-index was calculated to determine whether Cr/CysC ratio can predict the prognosis of patients with gastric cancer.

Results: Serum Cr/CysC ratio was significantly correlated with SMI ($r=0.269$, $p<0.001$) and skeletal muscle area ($r=0.277$, $p<0.001$). The area under the curve for sarcopenia was significantly larger for serum Cr/CysC ratio than for other biomarkers (Cr/CysC: 0.665, CysC: 0.441, Cr: 0.572). Patients in the high-Cr/CysC group had longer survival times than in the low-Cr/CysC group, defined by a cutoff value of 0.67. The C-index for both Cr/CysC ratio and SMI with overall survival was 0.63.

Conclusions: Serum Cr/CysC ratio can be used accurately, inexpensively, and easily to evaluate sarcopenia in patients with gastric cancer. Our study showed that sarcopenia is possible in patients with Cr/CysC <0.67, indicating a poor prognosis.

Background

Gastric cancer is one of the most common malignant tumors worldwide. The incidence (5.7%) and mortality (8.2%) rates were fifth and third, respectively in 2018 [1]. Although technological developments have led to progress in tumor diagnosis, surgical methods, and adjuvant treatment, the survival rate of patients with gastric cancer remains low [2].

Sarcopenia is an age-related syndrome characterized by progressive and extensive loss of skeletal muscle mass and strength [3]; this has a negative impact on surgical outcomes and long-term survival in patients with gastric cancer [4]. Studies have shown that weight loss and malnutrition are common problems in patients with gastric cancer [5–6]. Recently, researchers have proposed a new method to predict muscle mass. Routinely measured serum creatinine (Cr) and serum cystatin C (CysC) concentrations were used to assess renal function. Because serum Cr concentration is affected by muscle mass, patients with decreased muscle mass have decreased serum Cr [7, 8]; while serum CysC is not affected by muscle mass [9, 10]. According to these characteristics, dividing serum Cr by serum CysC can be used to predict muscle mass. This method has been confirmed in the research of several diseases [11–14]; however, to our knowledge, no studies have evaluated the effectiveness of Cr/CysC in patients

with gastric cancer. For these reasons, we evaluated the ability of Cr/CysC to indicate muscle mass in gastric cancer patients, and we determined the best cut-off value for Cr/CysC ratio to predict sarcopenia and its impact on survival time in patients with gastric cancer.

Materials And Methods

Patients and study design.

We obtained the included patients' data from the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University from June 2009 to October 2017. Inclusion criteria were as follows: (a) pathological diagnosis of gastric adenocarcinoma, (b) radical gastrectomy, (c) computed tomography (CT) imaging within 1 month preoperatively, and (d) serum Cr and CysC concentrations measured preoperatively. The exclusion criteria were as follows: (a) metastatic or remnant gastric cancer, (b) preoperative chemotherapy or radiotherapy, (c) incomplete or inaccurate medical records, and (d) renal function impairment (estimated glomerular filtration rate: < 60 mL/min/1.73 m^2). After applying these criteria, 278 patients were enrolled. The flowchart of patient admission is presented in Figure S1. In this study, gastric cancer treatment was performed in accordance with the 2010 Japanese Gastric Cancer Treatment Guidelines [15]. Each patient provided written informed consent to participate in this study, and the research protocol was approved by our institution's ethics committee. This research was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

We collected the following clinical information for each patient: (1) preoperative characteristics, namely age, sex, height, American Society of Anesthesiologists (ASA) grade, complications, and preoperative serum Cr and CysC concentrations; (2) postoperative characteristics, namely tumor location, tumor size, tumor histological type (tumor differentiation divided into high, medium, and low categories), pathological tumor-node-metastasis (pTNM) staging, and chemotherapy. Tumor staging conformed to the 8th edition of the American Joint Committee on Cancer guidelines [16]. To reduce bias, all evaluations were performed by two independent, well-trained researchers, and all other data were ignored.

Definition of sarcopenia

Abdominal CT was routinely performed preoperatively, and skeletal muscle mass was estimated by calculating the area of all skeletal muscles on the cross-section of the third lumbar vertebra (L3) [17] using ImageJ software. Tissues with a specific Hounsfield unit threshold of 29–150 HU were considered skeletal muscles and were standardized according to height (m^2). Skeletal muscle mass was evaluated by calculating the skeletal muscle mass index (SMI) (cm^2/m^2) [18].

The criteria for sarcopenia were low skeletal muscle mass, low muscle strength, and/or poor physical function according to the European Working Group on Sarcopenia in Older People (EWGSOP) [19] and the Asian Working Group for Sarcopenia (AWGS) [20]. We used the following cut-off values to define

sarcopenia: SMI (L3) < 40.8 cm^2/m^2 for men and SMI < 34.9 cm^2/m^2 for women, considering possible ethnic differences regarding low muscle mass [21].

Follow-up

All patients were followed-up in our outpatient department 1 month after surgery, and by telephone or at the outpatient clinic every 36 months, thereafter. Overall survival (OS) was defined as the time between surgery and death from any cause or the date of the last follow-up. All patients were followed-up for at least 3 years, and the last follow-up date was in October 2020.

Laboratory measurements

Serum Cr concentrations were measured in our hospital laboratory using an enzymatic method. Serum CysC concentrations were determined using a particle-enhanced immunoturbidimetric assay, and Cr/CysC ratio was calculated by diving serum Cr by serum CysC.

Statistical analysis

All continuous data in this study were non-normally distributed according to the Kolmogorov–Smirnov test. Therefore, continuous data were presented as median and interquartile range (IQR). Kaplan–Meier survival analysis was used to calculate the effects of Cr/CysC ratio on OS. Receiver operating characteristic (ROC) curve analysis was used to evaluate the utility of the Cr/CysC ratio for identifying low SMI, according to the area under the ROC curve (AUC) and 95% confidence interval (CI). Youden's index (sensitivity + specificity − 1) was calculated to determine the optimal cutoff points for the Cr/CysC ratio. The C-index was calculated to measure the impact of Cr/CysC ratio and SMI on prognosis. All P values were two-sided, and a P value of < 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences, version 26.0 (IBM Corp., Armonk, NY, USA) and R version 3.5.3 (The R Foundation, Vienna, Austria).

Results

Patient characteristics

We enrolled 278 adults from June 2009 to October 2017. Some participants were excluded because of an estimated glomerular filtration rate of < 60 mL/min/1.73m^2 (n = 9). A total of 269 participants (median age: 64 years, range 20–89 years) were considered eligible for the analysis, namely 191 men and 78 women, whose characteristics are shown in Table 1. There were 22 male sarcopenia patients (11.5%) and 14 female sarcopenia patients (17.9%).

Table 1
Clinical characteristics of the male and female groups

Factors	Male(n = 191)	Fmale(n = 78)
Age (y)	62.9 ± 11.0	59.2 ± 12.5
Weight (kg)	61.3 ± 10.2	54.7 ± 7.7
Height (m)	1.67 ± 0.1	1.58 ± 0.1
BMI (kg/m2)	21.5 ± 3.1	21.8 ± 3.0
SMA (CT scan, kg)	138.7 ± 20.1	102.7 ± 18.5
SMI (kg/m2)	48.9 ± 7.3	40.9 ± 7.3
Serum Cystatin C (mg/L)	1.0 ± 0.3	0.8 ± 0.2
Serum Creatinine (mg/dL)	0.8 ± 0.2	0.6 ± 0.1
Serum Cr/Cys C	0.8 ± 0.2	0.7 ± 0.1
Sarcopenia,n%	11.5%	17.9%

Correlation between clinical factors and sarcopenia

We performed logistic regression analysis to evaluate whether Cr/CysC is related to sarcopenia. Univariate analysis showed that Cr/CysC, age, lower body mass index (BMI), preoperative anemia, tumor size, and pTNM stage predicted sarcopenia. Cr/CysC (odds ratio = 0.096; $p < 0.001$) remained an independent predictor of sarcopenia in the multivariate analysis (Table 2). In addition, age ≥ 75 years, lower BMI, and preoperative anemia were associated with an increased risk of sarcopenia (all $p < 0.05$).

Table 2
Univariate and multivariate analyses the risk of sarcopenia

Factors	Odds ratio for sarcopenia (95%CI)			
	Univariate analysis	P value	Multivariate analysis	P value
Age				
>75/≤75	5.641(1.724–18.462)	0.004*	12.725(2.970-54.532)	0.001*
Sex				
Male/Female	0.595(0.287–1.234)	0.163		
BMI, kg/m2				
18.5–25/<18.5	0.112 (0.039–0.332)	< 0.001*	0.525 (0.276–1.003)	0.049*
> 25/<18.5	0	0.998	0	0.998
Hypoproteinemia				
Yes/No	2.785 (1.933–4.013)	< 0.001*	1.968 (1.308–2.961)	0.001*
Tumor location				
Corpus/Cardia	1.500(0.335–6.726)	0.596		
Pylorus/Cardia	1.091(0.285–4.183)	0.899		
Mixed or total/Cardia	0	0.999		
Tumor size				
≥4.75/<4.75	5.146(1.871–14.153)	0.002*	8.324(2.515–27.543)	< 0.001*
Type of differentiation				
Moderate/Well	2.752(0.342–22.158)	0.341		
Poor/Well	2.315(0.257–20.865)	0.454		
pTNM stage				
II/I	1.796 (1.071–3.011)	0.027	2.205(0.529–6.564)	0.295
III/I	2.504 (1.630–3.846)	0.021	2.143(0.644–7.125)	0.214
Serum Cr/Cys C				
Low/High	0.096	< 0.001*		< 0.001*

Association between various biomarkers and sarcopenia severity

Serum Cr/CysC ratio was positively correlated with SMI ($r = 0.269$, $p < 0.001$) and skeletal muscle area (SMA) ($r = 0.277$, $p < 0.001$). Serum Cr was positively correlated with SMI ($r = 0.217$, $p = 0.002$) and SMA ($r = 0.275$, $p < 0.001$), while serum CysC had no significant correlation with SMI and SMA ($p > 0.05$) (Fig. 1). We calculated the AUC of each biomarker using ROC curves (Fig. 2), and used the DeLong test to evaluate the effectiveness of each biomarker as a predictor of sarcopenia. The serum Cr/CysC ratio, CysC, and Cr AUCs were 0.665 (95% confidence interval (CI): 0.565–0.765), 0.441 (95% CI: 0.338–0.543), and 0.572 (95% CI: 0.462–0.681), respectively. The AUC of the Cr/CysC ratio was significantly greater than the AUC of all other biomarkers ($p < 0.01$).

Cutoff value for serum Cr/CysC regarding sarcopenia

We calculated the serum Cr/CysC cutoff as 0.67 using Youden's index, which was associated with a sensitivity, specificity, positive predictive value, and negative predictive value of 0.50, 0.81, 0.29, and 0.91, respectively. As shown in Fig. 3, 91% of the patients with serum Cr/CysC ratio above the cutoff did not have sarcopenia.

Survival outcomes

We used the calculated optimal AUC cut-off value to create the Kaplan–Meier curve for serum Cr/CysC and OS after excluding two patients who died within 1 month after surgery, to reduce the impact of postoperative acute complications on survival time. As shown in Fig. 4, serum Cr/CysC was highly correlated with OS; OS of the high serum Cr/CysC group was significantly longer than that of the low serum Cr/CysC group ($p = 0.02$). Using R software, we calculated the height-calibrated Cr/CysC ratio, SMI, and survival C-index value. The C-index for SMI and OS was 0.62, and after calibration by height, the C-index for Cr/CysC ratio and OS was 0.56. When both variables were included, we calculated the C-index as 0.63, which was higher than that for SMI, alone.

Discussion

Baumgartner et al. first proposed the concept of "sarcopenia" [22] in 1998 to describe muscle mass decrease in older patients, as they age. Sarcopenia is closely related to age and specific physiological conditions, and has recently received extensive attention. Several studies have shown that sarcopenia is associated with an increased risk of recurrence [23], shortened survival time [24–25], and increased other causes of death [26] after gastric cancer resection. Weight loss and malnutrition are issues that are very worthy of our attention in all stages of gastric cancer treatment. More than half of patients with gastric cancer have some degree of weight loss owing to the impact of the tumor at the time of diagnosis [27]. Furthermore, an inability to maintain weight is considered a poor prognostic factor that affects long-term survival during neoadjuvant therapy or chemotherapy [28–29].

The relationship between Cr/CysC ratio and sarcopenia in different populations has been discussed. Tetsuka et al. reported that the Cr/CysC ratio of patients with amyotrophic lateral sclerosis was lower than that of healthy people [30]. In Japanese older people without severe renal impairment, Cr/CysC ratio

is positively correlated with muscle mass and physical function [31]. Low Cr/CysC ratio is considered a predictor of sarcopenia in patients with type 2 diabetes and chronic obstructive pulmonary disease (COPD) [32–33]. Recent studies showed that Cr/CysC ratio can also predict malnutrition, weakness, and poor clinical outcomes in intensive care unit patients [34–36]. However, to our knowledge, no reports have confirmed an association between Cr/CysC ratio and sarcopenia in patients with gastric cancer.

This study showed that serum Cr/CysC ratio is a useful predictor of sarcopenia compared with other biomarkers, such as serum Cr and CysC, individually. In addition, the best cut-off value for serum Cr/CysC ratio was 0.67, and in patients with a Cr/CysC ratio ≥ 0.67, sarcopenia can essentially be ruled out.

We found that the Cr/CysC ratio is the most predictive of sarcopenia in patients with gastric cancer, and that the ratio was positively correlated with SMI and SMA among the three biomarkers, serum Cr, serum CysC, and serum Cr/CysC ratio. Previous studies have shown that serum Cr is related to muscle mass [37–38]. In our study, serum Cr was positively correlated with SMI and SMA, consistent with findings in previous studies. Serum CysC showed no correlation with muscle mass. As an indicator of renal function, serum CysC has recently received greater attention. Serum CysC is a low-molecular-weight protein with a stable production rate and it can be freely filtered by glomeruli [39]. Therefore, Cr/CysC ratio is not affected by muscle mass and can predict sarcopenia.

We found that the best cut-off value for the optimal serum Cr/CysC ratio for predicting sarcopenia in patients with gastric cancer is 0.67. A previous study found that the optimal cut-off value for Cr/CysC ratio in diabetic patients for predicting sarcopenia was 0.9 [32], while another study found that the optimal cut-off value was 0.71 in COPD patients [33]. However, to our knowledge, no studies have determined the optimal cut-off value for sarcopenia in gastric cancer patients.

The OS of the high serum Cr/CysC group defined by the optimal cut-off value was significantly longer than that of the low serum Cr/CysC group. Sarcopenia shortened gastric cancer patients' OS as an independent factor affecting the prognosis. And the results of both are consistent. We also determined the height-calibrated Cr/CysC ratio and SMI, and created survival models. Studies have shown that although Cr/CysC ratio is related to OS, the correlation is not as good as with SMI. However, the ratio's correlation is greater than that for SMI when the ratio is used with SMI as an indicator of prognosis in patients with gastric cancer. This means that the prognosis of gastric cancer patients can be predicted using the Cr/CysC ratio and SMI as a combined index.

In this study, we used the area of all skeletal muscle on CT images at the L3 level as the standard for estimating a patient's skeletal muscle mass. Several studies have confirmed that CT is effective for assessing body composition, and that CT can predict sarcopenia in the general population. CT is widely used in oncology as a highly feasible method; however, CT is limited clinically as a method of evaluating body composition because of the high radiation level and cost. As an alternative, measuring grip strength and pace is often used to assess sarcopenia, but this method is very dependent on patient compliance and is often difficult to implement clinically. However, early diagnosis and intervention for sarcopenia are very important because sarcopenia can significantly affect the prognosis of patients with gastric cancer.

Serum Cr/CysC ratio is a simple, easy and low-cost method that can be used to screen patients for sarcopenia and assist in determining subsequent treatment and intervention. If the Cr/CysC ratio is < 0.67, detailed examinations must be performed, such as bioelectrical impedance analysis, dual energy X-ray absorptiometry, CT, or magnetic resonance imaging.

This study has certain limitations. First, this was a retrospective study, and there were deficiencies when collecting the patients' follow-up information. Second, the sample size was insufficient because we included data only from a tertiary center, for the statistical analysis. Additionally, serum Cr and serum CysC measurements are affected by reagents and instruments. Future prospective studies in multiple centers are needed to address these issues. Third, this study involved only the Chinese population, and different criteria for sarcopenia limit the applicability of our conclusions, especially for Western populations. Studies determining appropriate standards for determining sarcopenia according to different populations are very important.

Abbreviations

Cr/CysC
Serum creatinine/cystatin C
CT
Computed tomography
ASA
American Society of Anesthesiologists
SMI
Skeletal muscle mass index
EWGSOP
European Working Group on Sarcopenia in Older People
AWGS
Asian Working Group for Sarcopenia
OS
Overall survival
IQR
interquartile range
ROC
Receiver operating characteristic
AUC
Area under the ROC curve
CI
confidence interval
COPD
Chronic obstructive pulmonary disease
ICU

Intensive care unit
MRI
Magnetic resonance imaging

Declarations

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Authors' contributions

ZS and XS are the main authors of manuscript and have made substantial contributions to the conception and design of study. XY, TC, HY, XW, CZ,TZ,DC, ZS and JP have been involved in collection and analysis of the data, ZS and XS gave fnal approval and revised of the manuscript. All authors read and approved the fnal manuscript.

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Availability of data and materials

The data that support the fndings of this study are available from the corresponding author upon reasonable request. Emails could be sent to the address below to obtain the shared data:shenxian@wmu.edu.cn.

Ethics approval and consent to participate

The research was in compliance with the Declaration of Helsinki. Ethical approval was obtained from the Second Affiliated Hospital, Wenzhou Medical University(ID: 2014063) and the necessity for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

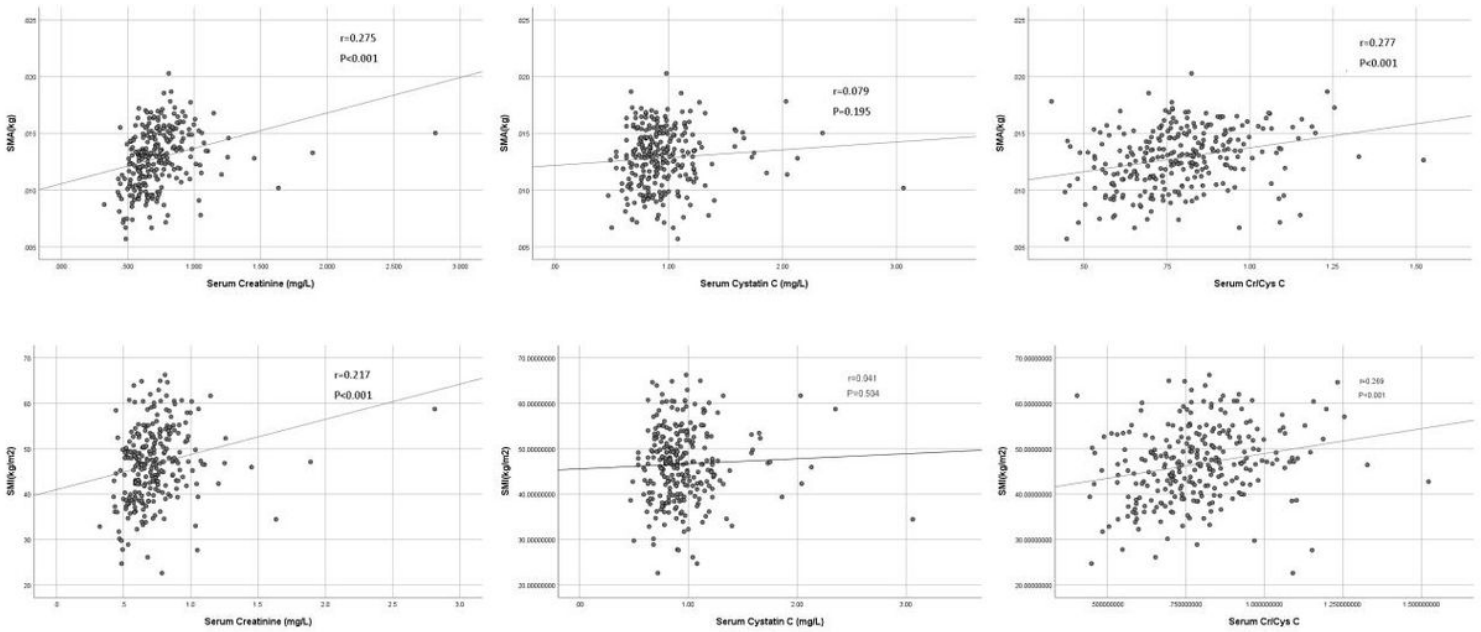

Figure 1

Linear correlation between the skeletal muscle mass index (SMI), skeletal muscle area(SMA) and cystatin C,creatinine and creatinine/cystatin C ratio in the group

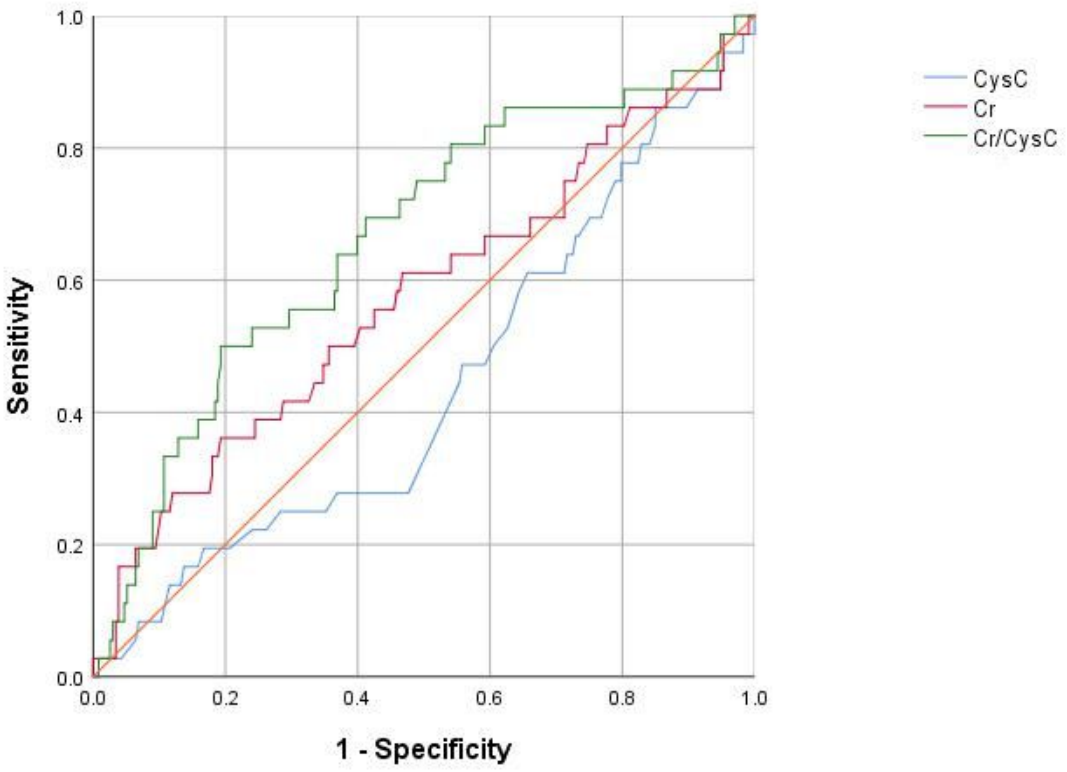

Figure 2

Receiver operator characteristic curves presenting sarcopenia according to serum creatinine (Cr)/cystatin C (CysC) ratio, serum CysC and serum Cr levels.

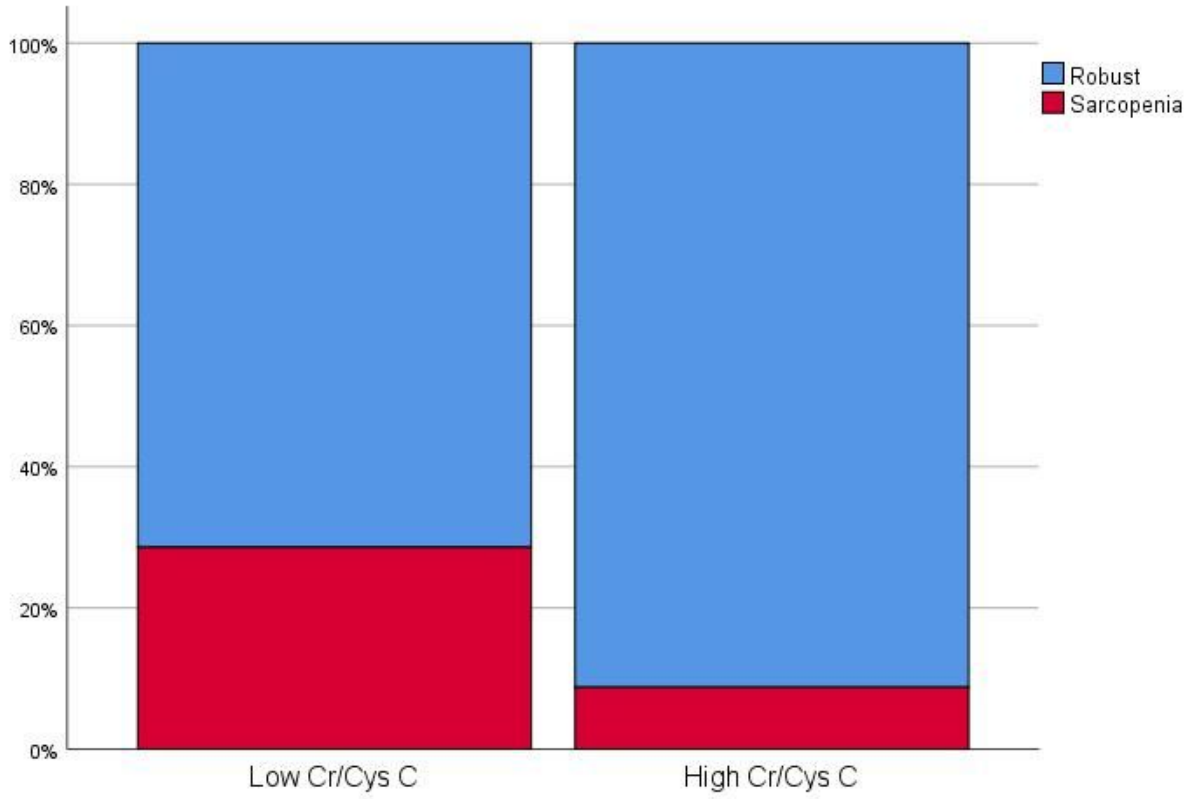

Figure 3

Frequency of sarcopenia in patients with low and high serum creatine (Cre)/ cystatin C (Cys C) ratio. Cr/CysC <0.67 was defined as low Cr/CysC, and Cr/CysC S 0.67 was defined as high Cr/CysC.

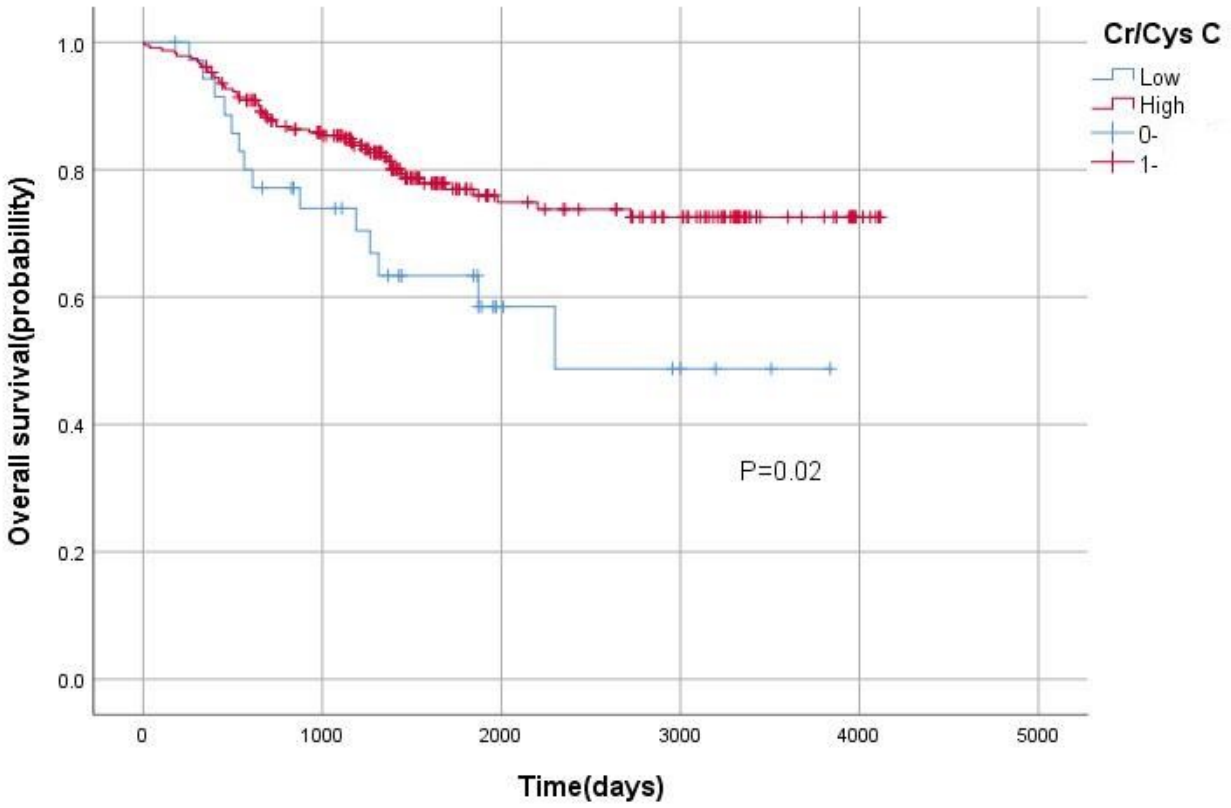

Figure 4

Kaplan–Meier survival analyses of patients in low and high serum creatine (Cre)/ cystatin C (Cys C) ratio. Cr/CysC <0.67 was defined as low Cr/CysC, and Cr/CysC S 0.67 was defined as high Cr/CysC

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Fig.S1.jpg