Computed Tomography Determined Sarcopenia is a Significant Predictor of Poor Clinical Outcome in Gastric Cancer

Yasar YILDIZ (dryasar2706@yahoo.co.uk)
İzmir Kâtip Çelebi Üniversitesi Tip Fakültesi: Izmir Katip Celebi Universitesi Tip Fakultesi
https://orcid.org/0000-0002-2912-3835

sebnem karasu
Izmir Katip Celebi Universitesi Tip Fakultesi

utku Oflazoglu
Izmir Katip Celebi Universitesi Tip Fakultesi

Kenan cetinoglu
Izmir Katip Celebi Universitesi Tip Fakultesi

Burcin Dalkılınc
Izmir Katip Celebi Universitesi Tip Fakultesi

Yüksel Kucukzeybek
Izmir Katip Celebi Universitesi Tip Fakultesi

Ahmet Alacacıoglu
Izmir Katip Celebi Universitesi Tip Fakultesi

Sinan Unal
Izmir Katip Celebi Universitesi Tip Fakultesi

Zeynep Guc
Izmir Katip Celebi Universitesi Tip Fakultesi

betül kücükzeybek
Izmir Katip Celebi Universitesi Tip Fakultesi

tarık salman
Izmir Katip Celebi Universitesi Tip Fakultesi

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Abstract

Background

Sarcopenia is defined as a progressive and extensive loss of muscle mass and function. This study aimed to investigate the impact of sarcopenia and body composition on survival outcomes in patients with newly diagnosed gastric carcinoma (GC).

Materials and methods

Skeletal muscle area was measured at the level of the third lumbar vertebra (L3) using baseline CT images in patients with GC. Sarcopenia was defined as a L3 Skeletal muscle index (SMI) of < 41.6 cm^2/m^2 for men and < 32 cm^2/m^2 for women using van der Werf's cutoffs. The disease free survival (DFS), overall survival (OS) and clinical characteristics of patients with and without sarcopenia were compared.

Results

A total of 226 patients were included. The median age of patients was 62 years (range 18–85) and 154 patients (68.1%) were men. Of the patients 37.6% were metastatic. Sarcopenia was present in 75 patients (33.2%) and was at significantly higher frequencies in men, metastatic disease, lower body mass index (BMI < 30), and higher ages (≥ 65 years) (respectively; all $p < 0.05$). The median DFS was 27 months (95% CI, 1.5 to 52.4) in patients with sarcopenia and *non-appliceable* in patients without sarcopenia in patients undergoing curative surgery for gastric cancer (p=0.041). The median OS was 10 months (95%CI, 7.730 to 12.270) in patients with sarcopenia and 29 months (95%CI, 21.307 to 36.693) in patients without sarcopenia (p<0.0001). In the multivariate Cox regression model, sarcopenia (with or without) (B=1.101; p<0.0001), stage (1-3 vs 4) (B=1.087; p=0.016) and surgical resection margin (R0 vs R1-2) (B=1.029; p<0.0001) were statistically significant predictors for OS.

Conclusion

Sarcopenia is an independent clinical predictor for poor prognosis in patients with GC. Early diagnosis and screening of sarcopenia may have a positive effect on survival outcomes.

Introduction

Gastric cancer is the fifth most common cancer and third leading cause of cancer-related deaths in the world[1]. Due to the aggresiveness of disease and the lack of effective screening methods, the majority of patients are diagnosed at advanced stage, and the 5-year overall survival rate is generally less than 20%[2]. There is a number of clinical indicators which are related to prognosis in GC. Tumor stage is the most important predictor of the long-term prognosis[3]. In addition, studies have demonstrated well-known clinical and pathological features such as the presence of lymph node involvement, lymphovascular

invasion, perineural invasion, D2 plus lymphadenectomy, RO resection margin and performance status of the patient[3–5]. Despite that, there is still a need for the detection of potentially modifiable prognostic factors. Recently, sarcopenia has been identified as a negative prognostic factor which has an effect on morbidity and mortality in many cancer types[6–8].

Sarcopenia was firstly described in the 1980s as an age-related decrease in lean body mass affecting nutritional status, mobility and independence[9]. The definition of sarcopenia has been since developed. Sarcopenia is a syndrome defined as a progressive and generalised skeletal muscle disorder that is related to increased probability of adverse outcomes including physical deformity, falls, fractures, treatment complications and mortality by The European Working Group on Sarcopenıa in Older People 2 (EWGSOP2) and European Society of Parenteral and Enteral Nutrition (ESPEN)[10]. Primary causes of sarcopenia are nutritional factors and age related inactivity. Cancer-related diseases are the secondary cause. The risk of sarcopenia is higher in untreated cancer patients due to wasting syndrome (cachexia), which is a characteristic feature of many malignancies, and its incidence is between 16 and 75%.[11–12]. The gold standard method recommended by international working groups for the detection of sarcopenia is computed tomography (CT)[13–14]. The Skeletal muscle index (SMI) is a semiquantitative parameter which is calculated by dividing the muscle area given by CT with the square of the patient's height. Sex-specific SMI cut-offs are used to diagnose sarcopenia[13,15].

There are numerous studies reporting the impact of CT-determined sarcopenia in various cancers[6,15–19]. Presence of CT-determined sarcopenia in cancer patients increases perioperative comorbidity such as a higher risk of postoperative infections, longer hospitalization periods and high hospital costs[7,15,20–23]. Sarcopenia can also cause early termination of neoadjuvant chemotherapy because of dose-limiting effect[24–25].

Additionally, sarcopenic patients show significantly worse survival than non-sarcopenic patients[6,15–19]. Presence of sarcopenia statistically reduces both DFS and OS in patients undergoing curative radical gastric surgery[7–8] and predicts survival in patients with advanced gastric cancer[26].

Data about effects of sarcopenia on DFS and OS reported from Europe is more limited than eastern Asia and there is not any study on this subject in Turkish population. In this study,we aimed to evaluate the effect of CT- dedected sarcopenia on prognosis in gastric cancer patients.

Materials And Methods

Patient selection

This study is approved by the local Institutional Review Board and conducted in accordance with Helsinki declaration. The medical records of patients with gastric adenocarcinoma who were admitted to the medical oncology department of Izmir Katip Celebi University Faculty of Medicine Ataturk Training and Research Hospital between 2008 and 2020 were retrospectively reviewed. Among these patients, those

with CT examination at the time of diagnosis were included. The clinical and histopathological features of all patients, including sex, age, body mass index (BMI), serum albumin level, Eastern cooperative oncology group performance status (ECOG PS), survival outcomes were recorded. Patients with severe chronic inflammatory or autoimmune disease, having steroid treatment and having severe comorbidity were excluded.

Definition of CT-Based Sarcopenia

Computed tomography scans which were performed for staging at the time of diagnosis were used. A transverse abdominal CT image passing through the L3 vertebra level was transferred to an open access software program (sliceOmatic 5.0 visual c 14.0 update 3) available at https://coreslicer.com, and paravertebral and abdominal wall muscle areas (cm2) was measured. Skeletal muscle index (SMI, cm^2/m^2) was determined by dividing of SMA (cm^2) to the square of the patient's height (m^2). van der Werf's cutoff values were used[13] and sarcopenia was defined as a SMI of < 41.6 cm^2/m^2 for men and < 32 cm^2/m^2 for women.

Evaluation of histopathological and clinical features

The TNM staging was performed according to the American Joint Committee on Cancer (AJCC 2018) classification and coded as binary variables metastatic or non-metastatic[5,26]. Histological grade (well/moderate/ vs high), nodal status (N0 vs N1-3), tumor invasion dept (T1-2 vs T3-4), surgical resection margin (R0 vs R1-2), lymphadenectomy type (D1 vs D 2-3), lymphovascular invasion (negative vs positive), perineural invasion (negative vs positive), serum albumin level (low: <3.5 vs high: ≥3.5 mg/dL), Eastern cooperative oncology group performance status (0-1 vs 2-4), age (young: <60 vs old: ≥60) were recorded. Body mass index was calculated by dividing the patient's weight by the square of height (kg/m^2)[27]. The patients were categorized according to BMI as follows: BMI > 30 kg/m^2: obese; 25.0-29.9 kg/m^2: overweight; 20.0-24.9 kg/m^2: normal weight; < 20.0 kg/m^2: underweight.

Treatment endpoints

Disease free survival (DFS) was defined as the time from randomization (pathological diagnosis) to the first event of either recurrent disease or death.

Overall Survival (OS) was defined as the time from randomization (pathological diagnosis) to death from any cause or the final follow-up visit.

Statistical analyses

Statistical analyses were made by using the Statistical Package of Social Science (SPSS) version 16.0 software (Chicago, IL). The Kaplan–Meier method was performed to estimate survival outcomes and groups were compared by the log-rank test. Cox proportional hazards models were fit to determine the association between sarcopenia with survival outcomes after adjustment for patient and disease characteristics. The 95% confidence interval (CI) was used to quantify the relationship between survival

time and each independent factor and all statistical tests were carried out two-sided and a P value ≤0.05 was considered statistically significant.

Results

Four hundred eighty GC patients were found and 226 of them who met the inclusion criteria were included. Of the patients, 154 (68.1%) were men and 72 (31.9%) were women and median age was 62 years (range 17-85). 141 patients (62.4%) presented at non-metastatic and 85 (37.6%) patients presented at metastatic stages. The clinicopathological features of the patients are listed in Table 1.

Table 1
Clinicopathological characteristics of patients.

Characteristics	Number of patients	%
Age		
Age < 60 years	101	44.7
Age ≥ 60 years	125	55.3
Sex		
Male	154	68.1
female	72	31.9
ECOG PS		
0	113	50
1	80	35.4
2	12	5.3
3	21	9.3
BMI		
<20	41	18.1
20-24.9	78	34.5
25-29.9	75	33.2
>30	32	14.2
sarcopenia		
Non- sarcopenia	151	66.8
sarcopenia	75	33.2
Albumın		
≥3.5	152	67.3
<3.5	74	32.7
Nuclear grade		
Grade 1-2	80	35.4
Grade 3	75	33.2
Lymphovascular invasion		

ECOG PS: **Eastern cooperative Oncology Group (ECOG) Performance Status BMI:Body Mass Index**

Characteristics	Number of patients	%
Negative	42	18.6
Positive	86	38.1
Perıneural ınvasion		
Negative	42	18.6
Positive	82	36.3
Tumor invasıon dept		
T1	17	7.5
T2	16	7.1
T3	64	28.3
T4	49	21.7
Lymph node metastasis		
N0	38	16.8
N1	21	9.3
N2	36	15.9
N3	51	22.6
surgical resection margin		
R0	110	48.7
R1-2	36	15.9
Lymphadenectomy type	86	60.1
D1	54	37.8
D2	3	2.1
D3		
Stage		
1	21	9.3
2	19	8.4
3	101	44.7
4	85	37.6

ECOG PS: **Eastern cooperative Oncology Group (ECOG) Performance Status BMI:Body Mass Index**

Characteristics	Number of patients	%
Exitus		
No	63	27.9
Yes	163	72.1
ECOG PS: **Eastern cooperative Oncology Group (ECOG) Performance Status BMI:Body Mass Index**		

Seventy-five patients (33.2%) were sarcopenic. Among them, 18.1% were categorized as underweight and 14.2% as obese. The sarcopenic patients tended to be older ($p<0.001$), men ($p=0.001$), at metastatic stage ($p<0.001$), have lower BMI ($p=0.023$) and have lower ECOG PS ($p<0.001$) compared with non-sarcopenic patients (Table 2). The prevalence of sarcopenia was 20.6% (n:22; $p<0.0001$) in patients with BMI≥25 and was 15.6% (n:5; $p=0.023$) in patients with BMI≥30. The sarcopenia prevalence was 47.2% (n:59) in patients older than 60 years, while it was 15.8% (n:16) in younger patients ($p<0.0001$).

Table 2
Clinical characteristics of the patients with gastric cancer by sarcopenic status

	No sarcopenia, n (%)	Sarcopenia, n (%)	p value
Gender	92(59.7%)	62 (40.3%)	**0.001**
Men	59 (81.9%)	13 (18.1%)	
Women			
BMI status,	124 (63.9)	70 (36.1)	**0.023**
< 30	27 (84.4)	5 (15.6)	
≥ 30			
Age	85(84.2)	16(15.8)	**<0.001**
< 60	66(52.8)	59 (47.2)	
≥ 60			
Metastatic status	107 (75.9)	34 (24.1)	**<0.001**
No	44 (51.8)	41 (48.2)	
Yes			
ECOG status	138 (71.1)	56 (28.9)	**0.001**
<2	13 (40.8)	19 (59.4)	
≥2			
Albumine level	49(66.2)	25(33.8)	0.505
<3.5	102(67.1)	50(32.9)	
≥3.5			
ECOG PS: **Eastern cooperative Oncology Group (ECOG) Performance Status BMI:Body Mass Index**			

The median DFS was 27 months (95%CI, 1.5-52.4) in patients with sarcopenia and non-appliceable in patients without sarcopenia in patients undergoing curative surgery for gastric cancer (p=0.041) (Figure.1). The median OS was 10 months (95%CI, 7.7-12.2) in patients with sarcopenia and 29 months (95%CI, 21.3-36.6) in patients without sarcopenia (p<0.0001) (Figure 2).

In the univariate Cox regression model, high nuclear grade, lymphovascular invasion, perineural invasion, tumor invasion depth, lymph node metastasis, resection margin, stage, and presence of sarcopenia were associated with shorter DFS; age, ECOG PS, grade, lymphovascular invasion, perineural invasion, tumor invasion depth, lymph node metastasis, resection margin, stage and presence of sarcopenia were statistically associated with shorter OS (all, p<0.05 (Supplementary Table1).

In the multivariate Cox regression model, presence of sarcopenia (B=0.850; p=0.024), lymphovascular invasion (B=1.941; p=0.002) and positive surgical resection margin (B=1.092; p=0.002) were statistically significant predictors for DFS (Table 3). Presence of sarcopenia (B=0.988; p=0.001), lymphovascular invasion (B=0.904; p=0.018), positive surgical resection margin (B=0.996; p=0.001) and tumor stage (B=1.006; p=0.026) were statistically significant predictors for OS (Table 4).

Table 3
Univariate analysis of factors associated with disease free survival and Cox proportional hazards regression model of clinical factors predicting disease free survival in patients with gastric cancer

	Log Rank (Mantel Cox)		***Cox-proportional Hazard***	
	Chi-square	*p*	*B (95%CI)*	*p*
Sarcopenia (non-sarcopenia vs. sarcopenia)	4.44	0.035	0.850(1.11-4.89)	0.024
Lymphovascular invasion (negative vs.positive)	15.7	0.000	1.941(2.08-23.23)	0.002
Surgical resection margin (R0 vs R1-2)	9.06	0.003	1.092 (1.51-5.87)	0.002

Table 4
Univariate analysis of factors associated with overall survival and Cox proportional hazards regression model of clinical factors predicting overall survival in patients with gastric cancer

	Log Rank (Mantel Cox)		***Cox-proportional Hazard***	
	Chi-square	*p*	*B (95%CI)*	*p*
Sarcopenia (non-sarcopenia vs. sarcopenia)	9.549	0.002	0.988(1.49-4.81)	0.001
Lymphovascular invasion (negative vs.positive)	6.546	0.011	0.904(1.17-5.20)	0.018
Surgical resection margin (R0 vs R1-2)	10.237	0.001	0.996(1.51-4.84)	0.001
Tumor stage (non-metastatic vs. metastatic)	3.962	0.047	1.006(1.12-6.63)	0.026

Discussion

In this study, we analyzed the CT-determined sarcopenia retrospectively in gastric cancer patients. Male gender, advanced age, lower BMI, metastatic stage and lower ECOG PS were significantly related to sarcopenia. CT determined sarcopenia was independently associated with a worse DFS and OS.

Frailty is a condition of increased vulnerability to poor resolution of homoeostasis after a stressor event, resulting in an increased risk of developing adverse health outcomes[28]. Although the definition of frailty is controversial and its assessment is subjective, in various studies, sarcopenia has been defined as an accurate and objective measure of frailty[28–29]. It is important to identify and assess sarcopenia at the time of diagnosis. The detection of an optimal sarcopenia cut-off value on CT imaging depends on the type of disease and patient factors like sex, age, and race[30]. Zhuang et al. used SMI cut-offs to define sarcopenia (L3 muscle area: men, 40.8 cm^2 /m^2; women, 34.9 cm^2/m^2), while Nishigori et al. reported cut-off values for skeletal muscle mass impacting on OS of patients with advanced gastric cancer as 53 cm^2/m^2 in men and 41 cm^2/m^2 in women[20,7,39]. We used the cut-off values of a European Werf's study[13] as we thought it would be more suitable for the anthropometric structure of the Turkish people. Amoung the our patients, 75 (33.2%) of them were sarcopenic. Tegels et al. found the sarcopenia ratio of 57.7% in the patients undergoing surgery for gastric cancer[12]. They used the cut-off values of American patients and the cut-off values were higher than the European study of Werf's and we think it explains the high prevalence of sarcopenia in their series[12].

The prevalence of sarcopenia also depends on the type and stage of cancer, the gender, age, BMI and the ECOG PS of the patient[7,11,30–33]. Haiducu et al. evaluated the prevalence of sarcopenia in digestive cancers and they reported the highest prevalence of sarcopenic patients was in esophageal (70.4%) and hepatic (60.3%) cancers, following by biliary tract (49.3%), pancreatic (45.70%) and gastric cancer (32.05%)[31]. The prevalence of sarcopenia is higher in patients with locally advanced disease compared to patients with early-stage disease[32,34]. In our study, while the prevalence of sarcopenia was 24% in the group with non-metastatic disease, this rate was found to be 42.2% in the group with metastatic disease. This is because tumors that have progressed from local disease to metastatic stage may also produce more cancer-related cytokines, more oral intake disturbance due to the local effect of the tumor that may induce sarcopenia[33]. Hong-Bo Zou found the sarcopenia ratio as 20.0% in non-metastatic stage gastric cancer patients[32].

We found a higher prevalance of sarcopenia in men (40.3%) than women (18.1%). Fukuda et al. reported that the prevalance of men in the sarcopenic group was higher than in the non-sarcopenic group in elderly gastric cancer patients undergoing gastrectomy (28.7% vs. 6.06%; $p = 0.009$)[35]. In another study including 276 newly diagnosed cancer patients, the prevalence of sarcopenia in men was found to be statistically higher than in women (25.4% vs 5,9%.; $p<0.0001$)[36]. Our results were also similar to the literature data.

Another common indicator of a patient's general condition is BMI. We found that sarcopenia prevalence was lower in obese group (15.6%) compared to non-obese group (36.1%). Zhuang et al. reported that

sarcopenia was negatively correlated with lower BMI in patients undergoing radical gastrectomy for GC[7]. Similarly, Oflazoglu et al. reported the prevalence of sarcopenia was lower in obese and overweight patients compared to normal and underweight ones with newly diagnosed cancer[11].

In this study the prevalence of sarcopenia was found to be lower in the group with good ECOG status (28.9% in ECOG PS 0-1) than the worse one (59.4% in ECOG PS 2-3). Similarly, Prado et al. investigated the prevalence of sarcopenia in patients with solid tumors of the respiratory and gastrointestinal tract and they found lower ratios in patients with good functional scores (ECOG PS 0-1) compared to patients with poor functional scores (ECOG PS2-3) (47% vs 53%, respectively P=0.009)[30]. A similar result was observed in the study of Oflazoğlu et al. While the rate of sarcopenia was 14.3% in patients with ECOG PS 0, the rate of sarcopenia was significantly higher at 23% in patients with ECOG PS 1-2 (p=0.026)[11]. Oflazoglu et al. hypothesized that the reason for the higher prevalence of sarcopenia in the group of patients with low performance scores might be because of less physical activity and less food intake, which eventually caused loss of muscle mass[11].

In the present study, sarcopenia prevalence was higher in patients over 60 years (47.2%) than those under 60 years (15.8%). It has been shown in previous studies that the prevalence of sarcopenia increases with aging[11,20,32,34]. The possible reasons for the accelerated loss of muscle mass in elderly people, can be the higher prevalance of chronic diseases, aging, drug usage and more sedentary lifestyle.

Many reports have suggested that sarcopenia was associated with both short and long-term survival outcomes[7,8,15,20,37,39], but in fewer studies no significant relation was found between sarcopenia and short[12,34,38] or long-term outcomes in GC [12,24]. In both univariate and multivariate analyses we found that the sarcopenic patients have poor DFS and OS. Zhuang et al. evaluated the effect of sarcopenia on short-term and long-term survival outcomes after radical gastrectomy using preoperative abdominal CT scanning[7]. Patients with sarcopenia had worse both OS and DFS[7]. Kudou et al. evaluated the prognostic significance of sarcopenia in patients with esophagogastric junction cancer or upper GC and they showed that sarcopenia was reducing both short-term and long-term survival outcomes[8]. Our findings were similar with their results. In O'Brien's study, which included 56 patients who underwent resection for gastric adenocarcinoma, no statistically significant difference was observed in recurrence-free survival (RFS) which defined as the length of time from the date of first therapy to the date of detection of tumor recurrence, death, or loss to follow-up of sarcopenic patients, while there was a statistically significant difference in OS with reduced survival[38]. A study by Nishigori et al. demonstrated that sarcopenia was an independent predictor of DFS (p = 0.035) and OS (p = 0.005) in the 177 eligible patients with advanced GC[39]. Hong-Bo Zou found that three-year OS was 66.1% in sarcopenia group and 80.6% in non-sarcopenia group in the operated gastric cancer (p=0.014)[32]. Lee at al. reported shorter OS (median, 6.8 months) in sarcopenic patients than those non-sarcopenic ones (median 10.3 months) with advanced gastric cancer[37]. We found similar survival outcomes with the above mentioned study in the metastatic group (median, 7 months in sarcopenic vs. 14 months in non-sarcopenic groups).

However, Tegels et al. did not find a significant correlation between sarcopenia and short or long term survival in patients undergoing surgery for GC[12]. This may be due to the cut-off values used for the definition of sarcopenia and the demographic and clinical characteristics of the patients[12]. Another study by Kuwada et al. evaluated sarcopenic and non-sarcopenic short-term and long-term survivals in 491 gastrectomy patients[34]. While sarcopenia did not contribute significantly to short-term outcomes, sarcopenic patients had significantly worse survival[34]. The cutoff values used to define sarcopenia were 69.7 and 54.2 cm2/m2 for men and women, respectively. This may have affected the short-term results. Palmela at al. found that sarcopenia was not associated with poor survival in patients with locally advanced gastric cancer[24]. The higher rate of sarcopenic obese patients in this study, as well as the low overall number of patients at 48, may explain the relative survival relationship of sarcopenia.

Our study has several limitations. First, only 226 of the 480 total patients screened were included because they met the available abdominal CT data or inclusion criteria at baseline. This may have led to selection bias. Second, this is a retrospective, single-center study; therefore, there may be bias in the population and the results of this study need to be validated in future by multicenter prospective studies. To improve the comparability of studies, it is important to standardize the definition of CT-assessed sarcopenia and outcome-related thresholds adjusted for tumor type, age, sex and ethnicity.

In conclusion, CT determined sarcopenia is a significant predictor of poor clinical outcome s in gastric cancer. Each gastric cancer patient should also be evaluated in terms of sarcopenia besides clinical, radiologic and histopatologic examination.

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

Author contributions Study concept: Y. Yildiz and S. Karasu Study design: Y. Yildiz and S. Karasu Data acquisition:Y. Yildiz, S. Karasu, K. Cetinoglu, B. Dalkılınc, Y. Kucukzeybek, A. Alacacioglu, S. Unal, Z. Guc, B. Kucukzeybek, T. Salman. Quality control of data:Y. Yildiz, U. oflazoglu and S. Karasu. Data analysis and interpretation: Y. Yildiz and S. Karasu, U. Oflazoglu Statistical analysis: Y. Yildiz, U. Oflazoglu and A Alacacioglu. Manuscript preparation: Y. Yildiz and S. Karasu Manuscript editing:Y. Yildiz and S. Karasu . Manuscript review: Y. Yildiz and S. Karasu, U. oflazoglu and Y. Kücükzeybek

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Figures

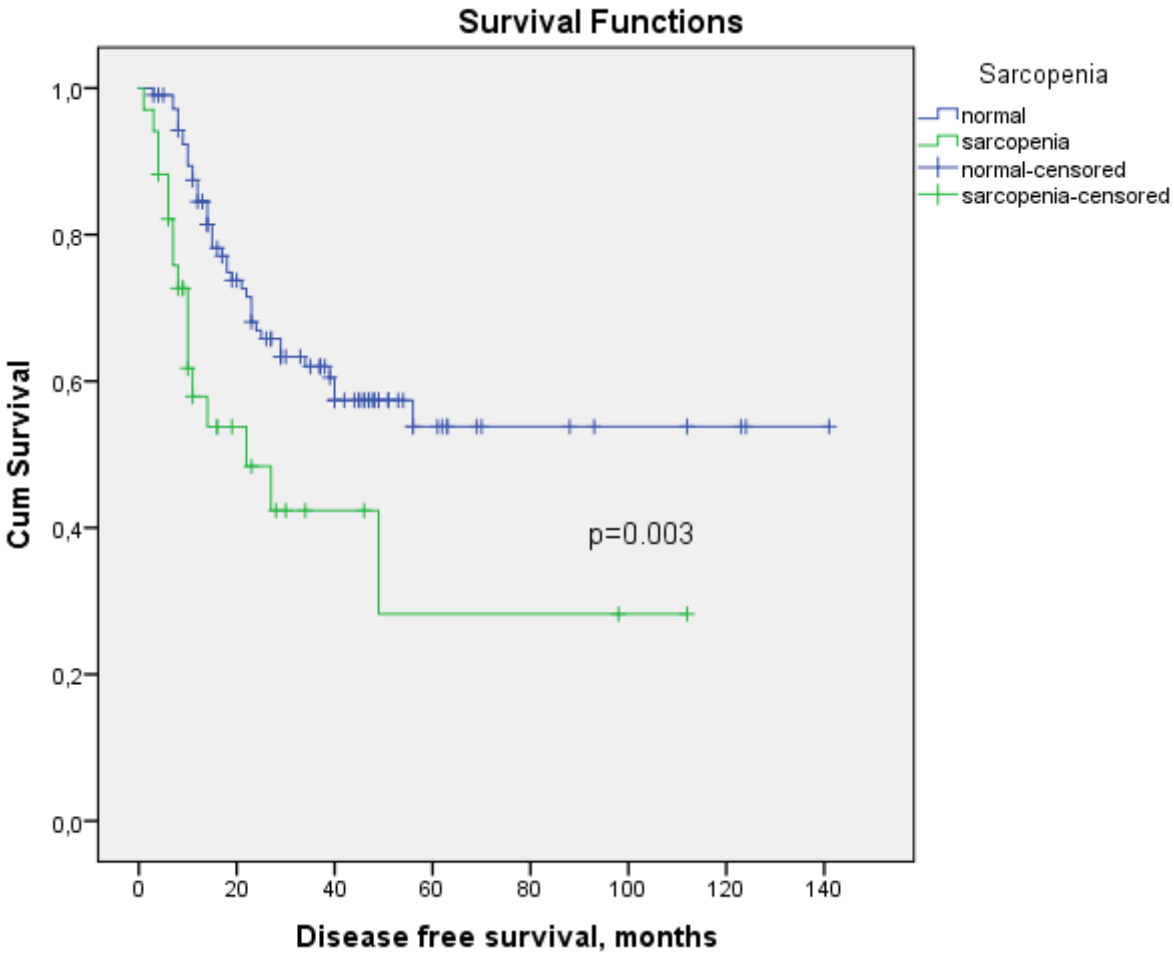

Figure 1

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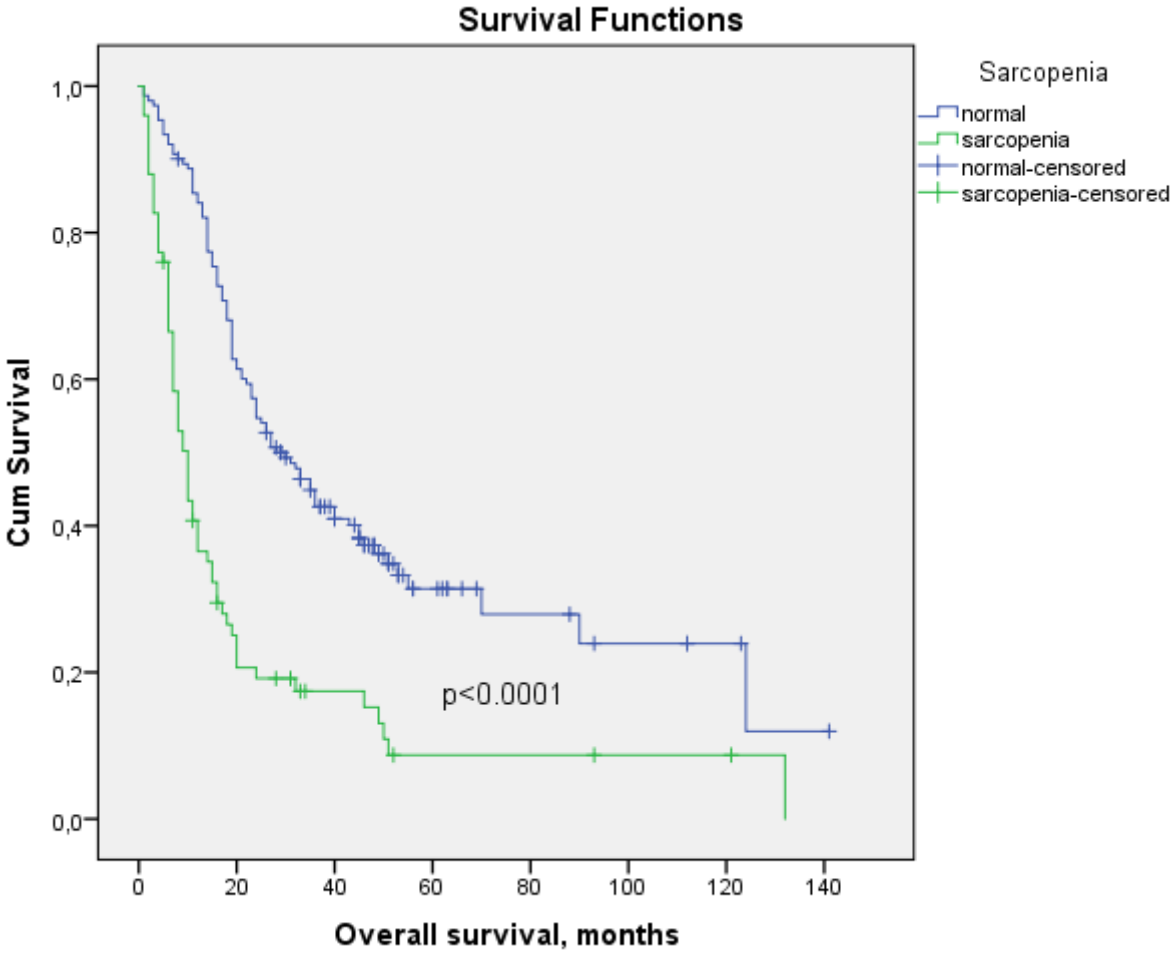

Figure 2

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- SupplementaryTable1.docx