





Clinical significance of sarcopenia in patients undergoing treatment for gastric cancer

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the impact of sarcopenia on prognosis in patients with gastric cancer in order to explore the relationship between sarcopenia and postoperative complications as well as durations of hospital stay and intensive care unit.

METHODS: A total of 175 patients who visited the oncology clinic between 2017 and 2022 with respect to their radiological images, demographic data, and laboratory parameters were perused. The OsiriX software was used to measure the skeletal muscle area that was divided by the body height in order to obtain the skeletal muscle index.

RESULTS: A total of 50.28% of 175 patients (41 females and 134 males, with a mean age of 63.5 years) who met the inclusion criteria in the study were sarcopenic. Significant differences appeared between sarcopenic and non-sarcopenic patients with respect to durations of both hospital stay ($p<0.01$) and intensive care unit stay ($p<0.01$) (multivariate analysis). Furthermore, patients with sarcopenia had significantly frequent postoperative complications in comparison with those without sarcopenia. Among the patients with sarcopenia, decreased levels of hemoglobin and albumin as well as lymphocytes were encountered in terms of inflammatory markers; nevertheless, no significant differences were determined among other inflammatory markers.

CONCLUSION: In patients undergoing treatment for gastric cancer, sarcopenia increases postoperative complications and prolongs hospital and intensive care stays during the treatment process.

KEYWORDS: Albumins. Biomarker. Intensive care units. Sarcopenia. Skeletal muscle. Stomach neoplasm.

INTRODUCTION

Gastric cancer is the fifth most common type of cancer in the world¹. Gastric carcinoma (GC) ranks third in cancer-related deaths worldwide². Despite the decrease in the incidence of GC in recent years as well as the increase in endoscopic detection and screening in the early phase, GC poses still a significant clinical challenge³. More than 950,000 new diagnoses are performed annually across the world⁴. Gastric cancer comprises 10.4% of cancer deaths worldwide⁵. Surgical resection remains the only potential curative treatment². Chemotherapy is commonly used in addition to surgery in order to improve patient outcomes³.

Gastric cancer can be assorted into three groups with respect to its etiology and localization: (a) distal type gastric cancer associated with chronic gastritis and *Helicobacter pylori* infection, (b) proximal type cancer associated with obesity and gastroesophageal reflux disease and being more aggressive, and (c) signet-ring cell type cancer that is diffusely infiltrative and not associated with gastritis⁶.

Nowadays, due to the increase in life comfort and the development of screening methods, patients are generally diagnosed with endoscopy for symptoms such as dyspepsia and reflux⁷. However, patients may rarely present with advanced symptoms such as gastrointestinal bleeding, dysphagia, anorexia, weight loss, abdominal pain, and nausea^{4,7}.

Optimal diagnosis for gastric cancer appears to be a staging process with computed tomography (CT) after biopsy taken with endoscopy and diagnosed². Sufficient surgical resection is the only curative option for gastric cancer⁴. Recent studies have substantiated a negative association between sarcopenia and postoperative complications as well as the duration of hospital stay, survival, and early- and long-term outcomes of patients after surgery¹.

Sarcopenia is defined as a condition characterized by the loss of skeletal muscle mass and strength⁵. It is commonly observed in elderly individuals, but it can also occur in younger ages with chronic diseases or prolonged bed rest⁵. European Working

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Group on Sarcopenia determines sarcopenia in elderly people as weak muscle mass, either as low muscle strength or as low physical performance¹. Sarcopenia has been associated with an increased risk of complications following surgery and poorer outcomes in various types of cancers¹. Recent studies have proposed that systemic inflammatory markers such as hypoalbuminemia, anemia, lymphopenia, thrombocytopenia, and neutrophil/lymphocyte ratio (NLR) have prognostic consideration in the course of the disease and adherence to treatment when evaluated together with sarcopenia². The study published in the *Annals of Surgical Oncology* emphasizes that sarcopenic patients had a higher incidence of postoperative complications, such as surgical site infection, anastomotic leaks, and delayed gastric emptying, following surgery for gastric cancer, and cardiac and pulmonary complications⁸. Furthermore, it adverted that patients with sarcopenia had a longer hospital stay and a higher mortality rate than those without sarcopenia⁸.

In sarcopenia diagnosis, the skeletal muscle index, which is derived from muscle mass area acquired by using CT, is utilized. Measurements of each patient were performed using contrast-enhanced abdominal CT scans.

The objective of this study was to assess the association between sarcopenia and postoperative complications as well as the durations of hospital stay and intensive care unit (ICU) in patients with gastric cancer.

METHODS

The study was conducted in accordance with the Declaration of Helsinki as well as reviewed and approved by the ethics committee of our hospital (Approval date and no: 2011-KAEK-25 2023/03-04).

The preoperative data of the patients who participated in the study, including medical records, age, gender, height, weight, body mass index, blood parameters, surgery date, use of neo-adjuvant chemotherapy, and patients' comorbidities, were collected from the hospital system. Patients who underwent surgery as well as those who were inoperable and received adjuvant therapy were screened. Sarcopenia indexes were calculated based on CT images taken before surgery or chemotherapy. Surgical methods, the extent of the disease, lymph node involvement during surgery, and surgical stages were surveyed. As postoperative information, the duration of hospital stay and cardio-pulmonary system complications after surgery were investigated.

Study population

We assessed 175 of 217 patients who visited the Oncology Department between September 2017 and December 2022 and who were diagnosed with pathologically gastric cancer.

Inclusion criteria for the study

(1) Patients diagnosed with gastric cancer by biopsy, (2) patients who had a CT examination in the hospital system within a maximum of 4 weeks before the surgery or chemotherapy, (3) patients with blood parameters taken within a maximum of 4 weeks before the surgery or chemotherapy present in the system, and (4) patients whose weight and height data present in the system within a maximum of 4 weeks before the surgery or chemotherapy were investigated.

Exclusion criteria

(1) Patients with significant subcutaneous and mesenteric edema, (2) patients with widespread metastases in muscle tissue and intra-abdominal adipose tissue, and (3) patients with widespread intra-abdominal implants were excluded from the study.

A total of 17 patients with subcutaneous and mesenteric edema, 17 patients with the absence of preoperative CT images, and 8 patients with the absence of preoperative blood parameters in the hospital system were excluded from the study. In 175 patients, measurements were executed and images were analyzed. Blood counts, body weight and height, and serum tumor markers were also collected.

Analyses of computed tomography images and skeletal muscle mass measurement

All abdomen CT scans were performed by using a 128-slice multi-detector-row CT scanner (Toshiba Aquilion, Japan). All CT images were acquired at deep inspiration in the supine position, and all thoracic and abdominal sections were scanned in the soft tissue window, using thin section and contrast-enhanced scans. CT scans were analyzed using the OsiriX version 5.6.2 open-source software. The cross-sectional skeletal muscle area (cm²) was measured by using a standardized approach¹. The cross-sectional skeletal muscle surface area (cm²) was measured at the level of the third lumbar vertebra (L3)² (Figure 1).

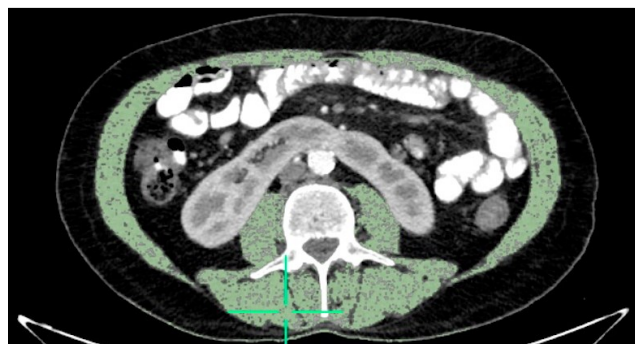


Figure 1. Axial computed tomography image crossing from the level of the third lumbar vertebrae of the gastric cancer patient. Skeletal muscle (green) was measured by using the OsiriX software semi-automatically.

In the axial plane, the section in which both transverse processes were displayed was selected and measurements were performed from this section⁴. L3 skeletal muscles comprise the paraspinal muscles, psoas major, rectus abdominis, and internal and external oblique and transverse abdominal muscles⁴ (Figure 1). During muscle area measurement, Hounsfield values varying from -29 to +150 were used in the OsiriX Program¹. The skeletal muscle index was also acquired by dividing the skeletal muscle area measured by Osirix to height in metric unit (cm^2/m^2)⁸. By conducting descriptive analysis, the cutoff value for sarcopenia was determined to be 34.7 ± 8.5 (mean \pm SD) in males and 29.3 ± 6.51 (mean \pm SD) in females, and patients who had below these values were considered sarcopenic.

Markers of systemic inflammation

Systemic inflammatory markers such as hemoglobin, leukocyte, neutrophil, lymphocyte, monocyte, CRP, NLR, and platelet/lymphocyte ratio (PLR) were investigated. In recent studies, NLR and PLR have started to attract more attention as indicators of systemic inflammatory response⁹. Studies demonstrated that these markers can be used as predictable biomarkers in determining the likelihood of advanced-stage disease in cancer patients, the presence of lymphatic metastasis, and the response to treatment and prognosis⁹. A pilot study exposed that PLR is superior to other biomarkers¹⁰.

Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS ver. 25 for Windows, Chicago, IL, USA) software was used for all statistical analyses. The Kolmogorov-Smirnov test was performed in order to observe the homogeneity and normality among the groups. Descriptive analysis and receiver operating characteristic (ROC) curve were used to calculate the sarcopenia value. A parametric Mann-Whitney U test was executed to determine the differences between sarcopenic and non-sarcopenic patients in terms of albumin, hemoglobin, and lymphocyte levels, as well as differences in postoperative hospital and ICU stay durations. The Youden index calculation was performed to compare the duration of hospital stay and postoperative complications between sarcopenic and non-sarcopenic patients. ROC analysis was conducted to compare inflammatory markers between sarcopenic and non-sarcopenic groups. An independent t-test was used for intergroup comparisons in normally distributed groups. $p < 0.05$ was considered a level of significance for the study.

RESULTS

A total of 175 patients with CT images and blood parameters were included, of whom 41 (24.41%) were females and 134 (75.58%) were males. The mean ages were 62.17 years for

females and 64.83 years for males, respectively. The calculation of sarcopenia indexes was based on CT images acquired within a maximum of 4 weeks before chemotherapy or surgery.

Based on radiological imaging, 55 patients were deemed inoperable and were considered to have locally advanced or metastatic disease. These inoperable patients were directly referred to chemotherapy. Total gastrectomy on 85 patients, distal gastrectomy on 25 patients, and proximal gastrectomy on 10 patients were carried out (Table 1).

During the investigation of tumor locations, 27 patients had tumor at the cardia, 10 at the fundus, 113 at the corpus (greater and lesser curvature), 15 at the antrum, and 10 at the pylorus (Table 1).

By using the descriptive analysis, the cutoff value for sarcopenia was determined to be 34.7 ± 8.5 (mean \pm SD) for males and 29.3 ± 6.51 (mean \pm SD) for females. Patients with values less than the determined cutoff value were considered sarcopenic.

Table 1. Demographic and pathological data of patients with and without sarcopenia.

Characteristics	Sarcopenic	Non-sarcopenic	p-value
Age (years)*	64.96	62.18	0.395 ^a
Sex**			
Male	68	66	
Female	20	21	
Height (cm)***	168.50 \pm 8.9	170.44 \pm 7.5	0.421 ^a
Tumor site****			0.354 ^b
Cardia	15	12	
Fundus	5	5	
Corpus	58	55	
Antrum	7	8	
Pylorus	3	7	
Stage****			0.428 ^b
1	24	30	
2	24	17	
3	15	10	
4	25	30	
Type of surgery****			0.127
Total gastrectomy	45	40	
Distal gastrectomy	13	12	
Proximal gastrectomy	5	5	
Inoperable	25	30	

*Mean value, **mean value of age, ***mean \pm SD, and ****quantity of patients.

^aIndependent t-test and ^bChi-square test.

Accordingly, 88 patients had sarcopenia, comprising 20 females (49%) and 68 males (50.75%).

During the postoperative or chemotherapy period, respiratory complications developed in 62 (36%) of patients, comprising 55 sarcopenic and 7 non-sarcopenic individuals. Cardiac complications developed in 20 (11.4%) patients during the postoperative or post-chemotherapy period, all of whom belonged to the sarcopenic group. Postoperative complications were significantly higher in comparison with non-sarcopenic patients ($p < 0.01$).

The means of hospital stay duration were 12.14 ± 3.4 days for sarcopenic and 7.23 ± 2.3 days for non-sarcopenic patients, respectively, while the means of ICU stay duration were 3.11 ± 1.6 days for sarcopenic and 1.48 ± 1.2 days for non-sarcopenic patients, respectively (Table 2). A significant difference occurred in hospital (Figure 2) and ICU stay durations between the two groups ($p < 0.01$) (Figure 3).

Table 2. Complications and hospitalization durations of sarcopenic and non-sarcopenic patients.

Outcomes	All patients	Sarcopenia	Non-sarcopenia	p-value
Pulmonary complications	62	55	7	<0.01
Cardiac complications	20	20	0	<0.01
Duration of hospital stay	9.69	12.14	7.23	<0.01
Duration of intensive care stay	2.30	3.11	1.48	<0.01

The numbers used in the table correspond to the number of patients in the complication sections and the durations of hospital and intensive care stays. p-value denoted in bold are statistically significant.

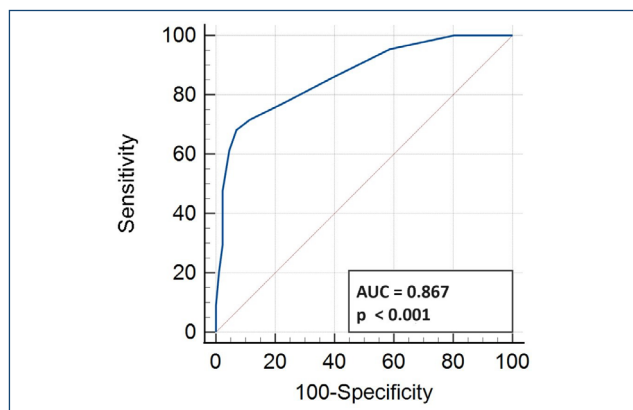


Figure 2. Receiver operating characteristic analysis of postoperative hospital stay.

Inflammatory parameters like albumin, hemoglobin, platelet, lymphocyte, and neutrophil values were investigated, and NLR and PLR ratios were calculated.

The mean albumin values were 2.64 ± 1.7 g/dL for sarcopenic and 3.08 ± 1.1 g/dL for non-sarcopenic patients, while the mean hemoglobin values were 9.8 ± 3.5 g/dL for sarcopenic and 10.4 ± 4.1 g/dL for non-sarcopenic patients. The mean platelet values were 262.09 ± 113.7 cells/mL for sarcopenic and 268.21 ± 90.06 cells/mL for non-sarcopenic patients, whereas the mean lymphocyte values were 1160.61 ± 990.0 μ l for sarcopenic and 1520.90 ± 1030.1 μ l for non-sarcopenic patients, while the mean neutrophil values were 4250.34 ± 365.6 μ l for sarcopenic and 3380.69 ± 284.1 μ l for non-sarcopenic patients, respectively.

By using the Youden test, statistically significant low-grade correlations were observed in sarcopenic patients in terms of albumin, hemoglobin, and lymphocyte ratios in comparison with non-sarcopenic patients (Figure 4) ($p = 0.087$). No significant difference was observed between the two groups with reference to neutrophil values, NLR, and PLR.

DISCUSSION

In this study, contrary to many previous studies, the inflammatory markers commonly used to measure NLR and PLR did not indicate significant differences between sarcopenic and non-sarcopenic patients. This could be attributed to the majority of early-stage operable patients in this study, with fewer patients having advanced-stage disease (100 of 172 patients underwent surgery). Supporting this, advanced-stage patients included in the study exhibited significantly higher NLR and PLR values compared with other stages ($p = 0.042$). Furthermore, patients with lymph node metastasis also possessed significantly higher NLR and PLR values ($p = 0.036$). In sarcopenic patients, other

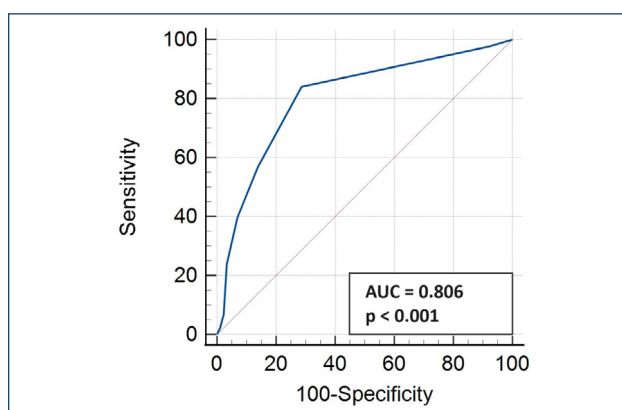


Figure 3. Receiver operating characteristic analysis of postoperative intensive care unit stay.

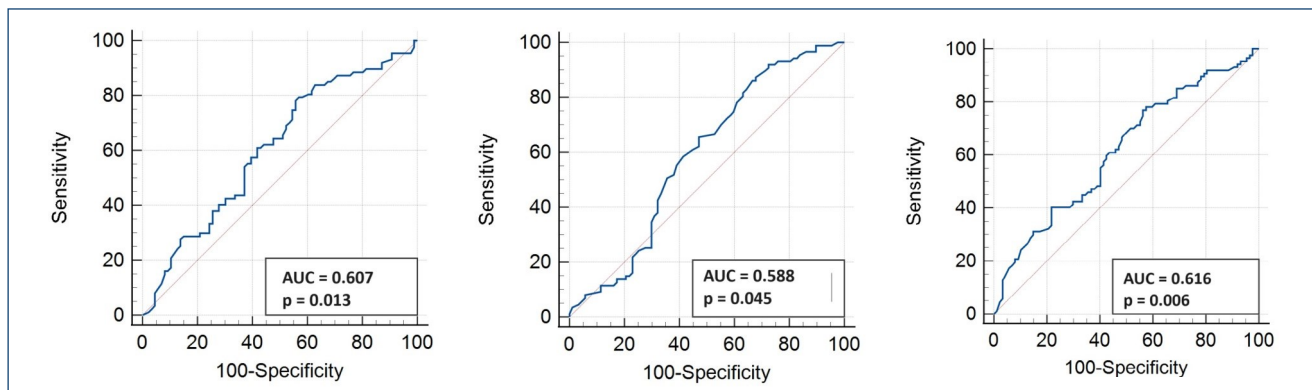


Figure 4. Receiver operating characteristic analysis of albumin, hemoglobin, and lymphocytes, respectively.

inflammatory biomarkers such as albumin, hemoglobin, and lymphocyte values were acquired to be lower compared with the non-sarcopenic patients.

Chronic inflammation plays a significant role in carcinogenesis. This association has been investigated since the 19th century when Virchow discovered the presence of leukocytes in tumor tissues and identified a potential association between tumors and inflammation^{11,12}.

According to a theory related to cancer cases, approximately one-fourth of cancer cases develop due to chronic inflammation and infection¹¹. Neutrophils play a role in both the innate and adaptive immune responses, while monocytes transform into macrophages in the tissue microenvironment to combat tumor cells. Platelets facilitate the migration and extravasation of leukocytes. Lymphocytes can recognize and eliminate tumor cells by influencing their proliferation and thus impacting further disease progression¹².

Previous studies have demonstrated that systemic inflammation is particularly a negative prognostic marker in advanced-stage cancer patients¹³. In this study, lower levels of albumin, hemoglobin, and lymphocyte ratios were obtained in sarcopenic patients, while higher NLR and PLR ratios were noticed in patients with cancer in more advanced stages.

There is no definitive cutoff value defined in the literature for these NLR and PLR¹³. For instance, in a study conducted on patients with metastatic renal cell carcinoma and tumor thrombus who underwent cytoreductive nephrectomy, the patients with $NLR < 4$ had higher survival rates compared with those with $NLR > 4$ ¹⁴.

Despite previous studies in the literature investigating individual inflammatory markers, postoperative complications, hospitalization durations, and ICU stays in sarcopenic patients and various types of cancers, this study is the pioneer to comprehensively consider all these parameters, particularly in Turkish patients. Additionally, this study has identified mean

values for hospitalization durations and ICU stays after treatment in sarcopenic patients, which can serve as a pioneering step in determining a cutoff value with larger quantities of patients in prospective studies.

In sarcopenic patients composed of 50.28% of the total patients in this study, the durations of hospitalization and ICU stay were observed to be significantly higher compared with the non-sarcopenic group.

The skeletal muscle is one of the essential structures responsible for body movement and respiration, and it constitutes the largest protein reservoir in the body¹⁵. Loss of muscle mass and cachexia lead to protein loss and exercise intolerance, which play a significant role in various diseases, especially in conditions such as cancer, affecting the recovery time, tolerance to treatment, and post-treatment rehabilitation process¹⁵.

Cancer often presents with rapid and aggressive weight loss and deterioration of muscle mass. In cancer patients, muscle mass loss varies depending on the type of cancer and stage of the disease. Muscle mass loss in the body leads to an increase in tumor progression incidence and an increased risk of chemotherapy toxicity, resulting in decreased tolerance to treatment and longer hospital stays¹⁶. In this study, patients with sarcopenia had longer hospitalization and ICU stays during treatment compared with others.

As an additional observation, sarcopenic patients had a significantly higher incidence of complications during treatment compared with the non-sarcopenic group. Among these complications, respiratory system complications and cardiac complications were prominent. The cause of respiratory complications is attributed to decreased muscle mass and impaired respiratory function, leading to ineffective cough and subsequently resulting in atelectasis and effusion¹⁷. Alongside the respiratory muscles, cardiac complications also increase due to the involvement of the heart muscles¹⁸. Furthermore, increased inflammatory stimuli can lead to acute lung injury^{18,19}.

There are some limitations in this study. The patients were heterogeneous in terms of stages, and due to the heterogeneity in the quantity of early-stage and advanced-stage patients, optimal comparisons of inflammatory markers, in particular, could not be performed. Due to the absence of some laboratory parameters, all inflammatory markers could be surveyed. The pre-treatment weight values of all patients were not available in the system; therefore, a comparison between body mass index and sarcopenia values could not be executed, and the analysis of sarcopenic obesity could not be conducted.

CONCLUSION

The presence of sarcopenia in gastric cancer patients prolongs hospitalization and ICU stay during treatment and increases postoperative complications. As clinicians are aware

of the presence of sarcopenia in patients with gastric cancer before starting treatment, they can determine treatment strategies accordingly.

AUTHORS' CONTRIBUTIONS

SGGO: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **TK:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **NKK:** Conceptualization, Data curation, Project administration. **BG:** Data curation. **IHV:** Data curation. **SO:** Data curation.

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