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Original Article

# The Association of Sarcopenia with Inflammatory Biomarkers, Postoperative Complications, and Hospitalization Duration in Patients Undergoing Treatment for Pancreatic Cancer

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## ABSTRACT

**Objective:** This retrospective study investigated the association between pre-treatment sarcopenia values and inflammatory biomarkers in patients with pancreatic cancer (PC), and assessed the relationship of sarcopenia with postoperative complications, survival, and the duration of hospitalization and intensive care unit (ICU) stay.

**Methods:** Radiological images, demographic data, and laboratory parameters were perused retrospectively. The skeletal muscle area, considered an indicator of muscle mass, was measured utilizing the OsiriX software system on the computed tomography scans acquired at diagnosis. Thus, the skeletal muscle index was obtained by dividing the skeletal muscle area by the square of the body height ($cm^2/m^2$). The inflammatory biomarkers, postoperative complications, and durations of hospitalization and ICU stays were investigated.

**Results:** A total of 104 patients, including 36 females and 68 males, were classified into 2 main categories: sarcopenic (72 patients) and non-sarcopenic (32 patients). The durations of hospitalization and ICU stay were 14.7 days and 5.6 days, respectively, for sarcopenic individuals and 7 days and 1.6 days, respectively, for non-sarcopenic individuals. Of the 72 patients experiencing postoperative complications, 9 were non-sarcopenic, while 63 were sarcopenic. In terms of the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio, the patients were compared. Both ratios of the sarcopenic group were significantly higher compared to those of the non-sarcopenic category ($P < .001$).

**Conclusion:** In patients undergoing PC treatment, sarcopenia increases postoperative complications and prolongs hospital and ICU stays.

**Keywords:** Computerized tomography, inflammatory markers, muscle mass area, pancreatic cancer, sarcopenia

## INTRODUCTION

Pancreatic cancer (PC) is notably aggressive and is one of the most fatal malignancies worldwide.[1,2] Curative surgery is the only and most effective treatment for extending the lifespan of patients with PC.[3,4]

Sarcopenia refers to the loss of skeletal muscle mass and strength.[5] Recent research has shown a link between skeletal muscle density and disease outcomes in cancer patients.[6] Appetite loss, accelerated catabolic metabolism, and triggered systemic inflammation are considered to contribute to the development of sarcopenia.[7] In sarcopenic patients (SP), increased risk of infection is associated with a functional decline and increased mortality.[8,9]

In patients with PC, thoraco-abdominopelvic computed tomography (CT) is the reference imaging modality for

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staging the disease and determining lymph node involvement and distant metastases.[9]

A previous study indicated that inflammation is an important contributor to cancer development and progression and revealed an association between inflammatory responses and cancer prognosis.[10,11] Recent studies have demonstrated that biomarkers such as monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are associated with cancer prognosis.[12,13] In patients receiving surgical treatment for PC, sarcopenia also elevates postoperative complications (POC).[14,15]

This retrospective study aimed to examine the relationship between pre-treatment sarcopenia measurements and inflammatory biomarkers in individuals diagnosed with PC, and to assess the relationship of sarcopenia with postoperative complications, survival, and the duration of hospitalization and intensive care unit (ICU) stay.

## MATERIAL AND METHODS

This study was carried out in compliance with the principles outlined in the Declaration of Helsinki from 1975 (revised in 2013), and the protocol received approval from the Ethics Committee of University of Health Sciences Bursa Yüksek İhtisas Training & Research Hospital (Date: 08/03/2023; Number: 2011-KAEK-25 2023/03-05).

### Study Sample

A total of 104 patients diagnosed with PC through pathological evaluation at the oncology department between September 2017 and December 2022, and who remained after applying the exclusion criteria, were reviewed retrospectively. The contrast-enhanced chest and abdominal CT scans acquired at diagnosis for all patients included in this study were available.

In this study, the demographic data of the patients (gender, age, height), CT images, tumor size and location, tumor stage, treatment modality (surgery, adjuvant chemotherapy, and neoadjuvant chemotherapy), and POC comprising respiratory system complications, cardiovascular system complications, and wound site complications were perused. The durations of hospitalization and ICU stay during both surgery and treatment, and the survival of patients during the treatment period were investigated.

### MAIN POINTS

- Systemic inflammation and inflammatory markers are closely linked to cancer development, with their elevation associated with a poorer prognosis in cancer.
- Values for monocytes, lymphocytes, neutrophils, and platelet, as well as their ratios (monocyte-to-lymphocyte, neutrophil-to-lymphocytes, and platelet-to-lymphocyte), are associated with cancer stage and prognosis.
- Sarcopenia indicates muscle loss and is associated with a poor prognosis and survival in patients with cancer.
- The presence of sarcopenia is associated with prolonged hospitalization and intensive care unit stays.

### Inclusion Criteria

Patients older than 18 years of age who were pathologically diagnosed with PC and had available CT images, demographic data, and laboratory data were included in the study.

### Exclusion Criteria

Patients with malignancies apart from PC, those with widespread mesenteric and subcutaneous edema, and those with extensive muscle metastasis, particularly at the lomber 3 (L3) vertebra level, were excluded.

### Review of Computed Tomography Scans and Quantification of Skeletal Muscle Area

Computed tomography scan of the abdomen was conducted with a 128-slice multi-row CT system (Toshiba Aquillion, Japan). Contrast-assisted thoraco-abdomino-pelvic CT images that had been obtained in the portal venous phase prior to surgery or chemotherapy and were presented in the hospital's records were used for skeletal muscle area measurements. Measurements were taken on axial slices that intersected the L3 vertebra, including the paravertebral muscles. Previous studies have established an association between the measurement of muscle mass at the L3 vertebra and total body muscle mass.[16] Two radiologists carried out the measurements utilizing the OsiriX digital system with automatic boundary detection and intensity calibration (Figure 1). Cut-off values in Hounsfield units (HU) were defined as varying from −29 to +150 for muscle tissue.[6]

Skeletal muscle area ($cm^2$) was assessed at the L3 vertebra, and to determine the skeletal muscle index ($cm^2/m^2$), the value is divided by the height squared ($m^2$). The cut-off values for sarcopenia, determined using receiver operating characteristic (ROC) analysis, were found to be similar to the reference range of sarcopenia indices reported in a previous study conducted with an Asian population, physically similar to the Turkish population.[17] The reference intervals of 38 $cm^2/m^2$ for females and 42 $cm^2/m^2$ for males were compared with those determined in another study undertaken in the institute for gastric cancer.

### System-Wide Inflammatory Indicators

Organism-wide inflammatory markers, including leukocytes, erythrocytes, platelets, neutrophils, monocytes, lymphocytes, NLR, PLR, and MLR, were assessed from blood values obtained within 4 weeks prior to surgery or

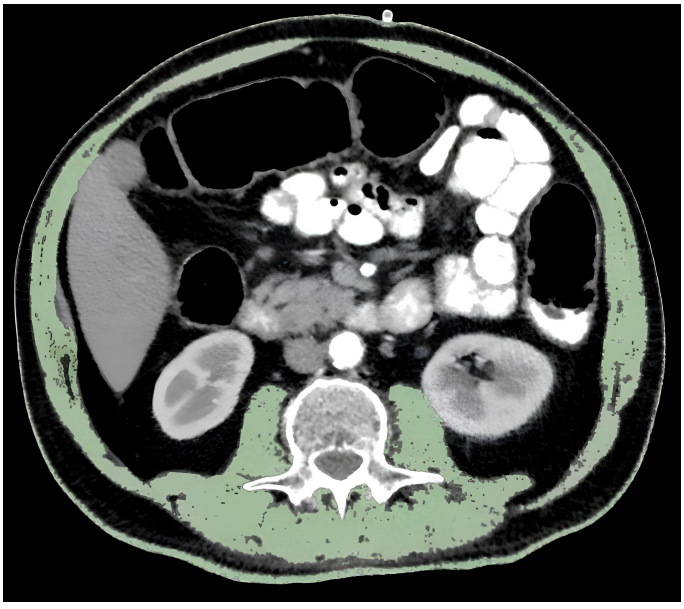

**Figure 1.** Measurements performed by OsiriX on the axial computed tomography image taken at the L3 vertebra in a patient with pancreatic cancer: skeletal muscle area.

chemotherapy (simultaneously with CT). With reference to previous studies, the cut-off values were accepted as 1.46 for MLR, 150 for PLR, and 3 for NLR.[10,12,13]

### Statistical Analysis

The uniformity of distributions across groups was evaluated using the Kolmogorov–Smirnov test. Average, variability, and central tendency were acquired for groups with normal and skewed distributions. The cut-off values for sarcopenia were determined separately for the female and male genders using the ROC analysis and the Youden test. Spearman's test was conducted to assess the relationship between sarcopenia and survival time. The correlation between POC and NLR, PLR, and MLR was investigated using the chi-square test, while the link of local and metastatic disease with NLR, PLR, and MLR was assessed using the Mann–Whitney and chi-square tests. Binary regression analysis, including both univariate and multivariate, was performed to survey the association of NLR and PLR with the risk of developing sarcopenia. Kaplan–Meier survival curves were generated to illustrate overall survival in both SP and non-sarcopenic patients (NSP). To calculate the adequacy of the sample size used in this study, a post-hoc *t*-test analysis was performed using the G*POWER program, and the power value for sarcopenia was found to be 100%. A *P*-value less than .05 was regarded as statistically significant.

## RESULTS

This study included a total of 104 patients diagnosed with pancreatic cancer, with an average age of 66.3 years. Among these patients, 68 were male, with an average age of 64.9 ± 9.7 years, and 36 were female, with an average age of 67.5 ± 10.7 years. The individuals were divided into 2 main categories: SP and NSP. Sarcopenia was ascertained in 72 patients (27 females and 45 males) (Table 1).

In terms of NLR, the individuals were categorized into 2 categories: NLR ≥ 3 (n = 65) and NLR < 3 (n = 39). The mean NLR value was considerably elevated in the SP population compared to the NSP population ($P < .001$, $r = 0.680$). The patients were also evaluated in 2 groups according to their PLR values being ≥150 (n = 64) or <150 (n = 40). In the SP group, the mean PLR value was considerably greater compared to the NSP population ($P < .001$, $r = 0.584$). In terms of MLR, the individuals were separated into 2 categorizes: ≥1.5 and <1.5. However, due to only 2 patients having an MLR value of ≥1.5, these 2 groups showed no significant difference.

A considerable negative correlation was acquired among survival time and inflammatory markers, namely NLR, PLR, and MLR ($r = 0.512$, $r = 0.493$, and $r = 0.447$ for MLR, sequentially; $P < .001$).

Complications developed in 72 of the 104 patients and included respiratory system disorders (n = 45), cardiovascular system disorders (n = 16), and wound site complications or postoperative leakage (n = 11). The presence of POC was notably greater in the SP population than in the NSP population ($P < .001$, $r = 0.580$) (Table 2).

The mean durations of hospitalization and ICU stay subsequent to treatment were 14.7 days and 5.6 days, respectively, in the SP group and 7 days and 1.6 days, respectively, in the NSP group. This indicates significantly higher values for both parameters in the SP group ($r = 0.731$ and $r = 0.801$, respectively) ($P < .001$) (Table 2).

A binary regression test was conducted for NLR and PLR. In the analysis of a single variable, individuals with an NLR

**Table 1.** Basic Demographic Data and Clinical Characteristics According to Gender in Pancreatic Cancer Patients

| | Female | Male |
|---|---|---|
| Number of patients (n) | 36 | 68 |
| Age† | 67.5 ± 10.2 | 64.9 ± 9.7 |
| Disease Stage | | |
| Early stage disease§ | 15 | 29 |
| Locally advanced-metastatic§ | 21 | 39 |
| SMI ($cm^2/m^2$)† | 38 ± 8.3 | 42 ± 11.7 |

SMI, skeletal muscle index.
†Mean ± SD.
§n (Number of patients).

**Table 2.** Postoperative Complications and Hospitalization in Sarcopenic and Non-Sarcopenic Individuals

| Characteristics | Sarcopenic Individuals | Non-sarcopenic Individuals | *P* |
|---|---|---|---|
| Complication | | | |
| Respiratory system† | 39 | 6 | **<.001** |
| Cardiac† | 14 | 2 | **<.001** |
| Postoperative leakage† | 10 | 1 | **<.001** |
| Hospitalization after treatment§ | 14.7 | 7 | **<.001** |
| Intensive care unit stay after treatment§ | 5.6 | 1.6 | **<.001** |

Chi-square test.
†Number of patients.
§Mean day.

of >3 were found to have a 68-fold increased risk of sarcopenia ($P < .001$, 95% CI = 12.6-368), while those with a PLR of >150 had a 48.5-fold elevated risk of sarcopenia ($P < .001$, 95% CI = 9.4-250). According to the multivariate analysis, patients with an NLR of >3 had a 17.9-fold increased risk of sarcopenia ($P = .007$, 95% CI = 2.2-14), and those with a PLR of >150 had a 6.8-fold increased risk of sarcopenia.

Pursuant to the CT characteristics, the individuals were categorized into 2 groups: local disease and locally advanced or metastatic disease. Forty-four patients had local disease and underwent surgery (Whipple procedure), while 60 patients were considered to have locally advanced or metastatic disease and were referred for a CT evaluation (Table 1).

Patients with local disease and locally advanced disease received adjuvant gemcitabine, capecitabine, or FOLFIRINOX regimens, either alone or in combination. Patients with metastatic disease received FOLFIRINOX or gemcitabine plus nab-paclitaxel treatments.

Due to the variability in chemotherapy protocols among patients, all blood parameters and CT measurements were compared based on pre-treatment values.

Among the 60 patients with advanced or metastatic disorders, chemotherapy was primarily administered. Among them, 15 PC patients deemed locally advanced underwent the Whipple procedure after treatment. Throughout the treatment, all patients underwent CT scans every 3 months. The follow-up period for patients who completed treatment was extended to 6 months.

The NLR, PLR, and MLR values were significantly higher among the individuals with locally advanced or metastatic disease compared to those with local disease ($P < .001$).

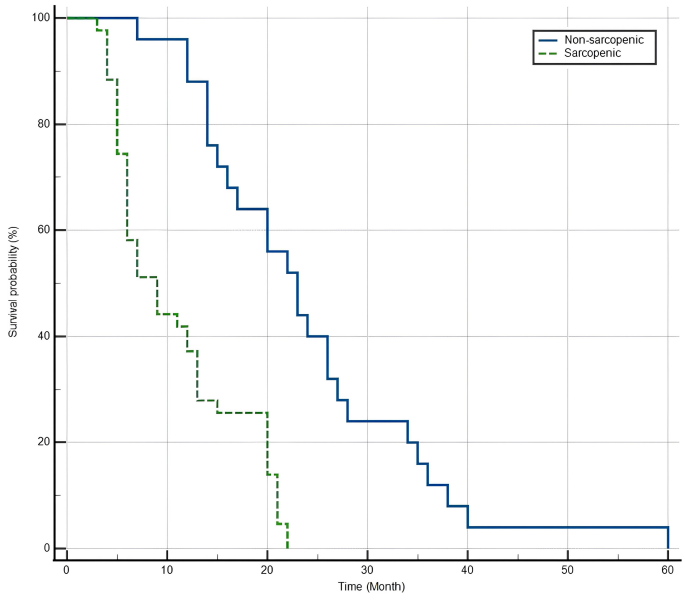


**Figure 2.** Kaplan–Meier survival curves of sarcopenic and non-sarcopenic individuals ($P < .001$; $r = 28.04$).

In the analysis of a single variable, the survival rate of the SP population was notably worse than that of the NSP population ($P < .001$, $r = 0.622$) (Figure 2). The survival rate of the SP group was [0.99%] (10.9) with a 95% CI of [8.95-12.85], and this result was statistically significant ($P < .05$). The survival rate of the NSP group was [2.32%] (24.1) with a 95% CI of [19.55-28.68], and this result was statistically significant ($P < .05$).

## DISCUSSION

For this investigation, inflammatory biomarkers, such as NLR and PLR, were shown to be considerably greater in SP compared to NSP. In research conducted by Iawi et al,[13] inflammatory biomarkers were observed to be considerably greater in locally advanced or metastatic disease compared to early-stage disease.[13]

Systemic inflammation is closely associated with carcinogenesis. The tumor microenvironment consists of tumor cells that release various cytokines, chemokines, and inflammatory cytokines. Monocytes are capable of killing tumor cells directly, and they can induce tumor cell death by phagocytosis through secondary activation.[18,19] Research has shown that monocytes may contribute to both primary tumors and lung metastases, particularly in breast cancer and colorectal cancer, depending on the monocyte chemoattractant protein-1.[10] The results obtained from this study were consistent with this idea, as we detected higher levels of inflammatory biomarkers in advanced-stage patients compared to early-stage patients. Neutrophils have a stimulating effect on the tumor microenvironment and

the host immune system.[13] Inflammatory cytokines are further important determinants of cancer progression and survival. Cholangiocarcinoma cells continuously secrete interleukin (IL)-6, which plays a significant role in survival signaling pathways and the growth of these cells.[16] Increased PLR values can be observed in conjunction with both thrombocytosis and lymphopenia, and thrombocytosis has been correlated with tumor growth and decreased survival in malignant diseases.[20] Previous studies have revealed that platelets contribute to hematogenous metastasis by trapping tumor cells in blood vessels, promoting tumor cell proliferation, and facilitating the escape of tumor cells from vessels.[20] Moreover, lymphopenia is capable of activating inhibitory immunological mechanisms, such as IL-10 and transforming growth factor beta, and impairing lymphocyte function.[13]

Cancer is a catabolic process generally characterized by muscle loss and cachexia, arising from a combination of decreased nutrient intake, imbalanced metabolism, and inflammation. In patients with cancer, systemic inflammation triggered by cytokines, hormones, and neurotransmitters appears to be activated from the early stages. Pancreatic cancer, in particular, results in severe muscle loss due to both mechanical factors and systemic inflammation. POC induced by sarcopenia frequently occurs in patients with PC. By anticipating this scenario, supportive special measures can be taken to address the condition effectively.[14]

In this study, the periods of hospitalization and ICU stay were substantially higher in SP compared to NSP. The increase in the periods of hospitalization and ICU stay is probably due to the prolonged healing process associated with the inflammatory process triggered in these patients and the development of POC. As a result, survival time was shorter in SP compared to NSP.

There are several limitations to this study. Firstly, the sample size was restricted, which hindered the separate evaluation of patients with local and metastatic disease. Due to the retrospective nature of the current study, information regarding the patients' nutritional programs was not available. Secondly, since the muscle parameters were solely assessed using CT scans in this study, the functional and strength aspects of muscles were not explored. Furthermore, due to the limited number of patients, a gender-based evaluation could not be performed. Lastly, recurrence was not assessed post-treatment. The impact of sarcopenia on recurrence in patients with PC could be a subject of investigation for further studies.

In patients with PC, sarcopenia can precipitate a cascade of adverse effects during treatment. Sarcopenia may exacerbate POC, as well as prolong hospitalization and ICU stays.

This awareness will allow them to consider interventions such as nutritional support and exercise programs while formulating treatment strategies.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of University of Health Sciences Bursa Yüksek İhtisas Training & Research Hospital (Date: 08/03/2023, Number: 2011-KAEK-25 2023/03-05).

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