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Impact of Sarcopenia on Survival of Patients With Malignant Salivary Glands Tumors

Vincenzo Abbate, MD[1], Stefania Troise, MD[1], Giulia Togo, MD[1], Simona Barone, MD[1], Paola Bonavolontà, MD, PhD[1], Daniela Pacella, PhD[2], Luigi Angelo Vaira, MD[3], Umberto Committeri, MD[1], Alessandro Tel, MD[4], Lorenzo Ugga, MD[5], Massimo Robiony, MD, PhD[4], Luigi Califano, MD PhD[1], and Giovanni Dell'Aversana Orabona, MD, PhD[1]

Abstract

Objective. Malignant salivary glands tumors (MSGTs) are a quite rare and heterogeneous group of tumors. Management of these lesions remains controversial and challenging. Thus, finding new prognostic factors that can help to guide the decision-making process, appears to be paramount. The aim of this study was to evaluate the prognostic performance of preoperative sarcopenia to stratify MSGTs patients at high risk of disease progression.

Study Design. Retrospective study.

Setting. A single-institution analysis (Maxillo-facial Surgery Unit, University of Naples Federico II).

Methods. The study consists of a retrospective analysis of 74 patients surgically treated for MSGTs. For all patients, the skeletal muscle index (SMI) was calculated and sarcopenia was defined as SMI < 41 in females and <43 in males. The correlation between sarcopenia and tumor variables was analyzed. The prognostic performance of sarcopenia was evaluated through survival Kaplan-Meier curves.

Results. Sarcopenia resulted statistically related to age ($P < .001$), tumor size ($P < .001$), lymph node metastases ($P < .001$), and American Joint Committee on Cancer tumor, node, metastasis stage ($P < .001$). Kaplan-Meier survival curves show that 47.3% of sarcopenic patients died before their final follow-up.

Conclusion. Data obtained from our study seem to confirm the correlation between sarcopenia and other high-risk features. The early detection of sarcopenia in patients with negative prognostic factors could be used to implement the support therapeutic strategies aimed at restore the clinical conditions of the patients. Sarcopenia may be routinely investigated before surgery to suggest the implementation of precautionary therapeutic strategies to improve the standard treatment response, reducing possible complications.

Keywords

inflammatory biomarkers, prognostic factors, sarcopenia, salivary glands tumors, skeletal muscle index

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Malignant salivary glands tumors (MSGTs) are quite rare, accounting for 1% to 3% of head and neck tumors and 0.3% of all malignant tumors. Their low incidence and wide variety of histological entities and grades make it difficult to define standardized guidelines for their management.[1,2] According to the literature, neck lymph node involvement is considered the worst prognostic factor in patients with MSGTs and occult metastases are detected in about the 12% to 48% of patients.[3] The American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system has been recognized as the main prognostic indicator for MSGTs and for other malignant tumors.[4] Nevertheless, several authors have shown that, for different types of

[1]Department of Neurosciences, Reproductive and Odontostomatological Sciences, Maxillofacial Surgery Unit, University of Naples Federico II, Naples, Italy
[2]Department of Public Health, University of Naples Federico II, Naples, Italy
[3]Department of Medicine, Surgery and Pharmacy, Maxillo Facial Unit, University Hospital of Sassari, Sassari, Italy
[4]Department of Medicine, Maxillofacial Surgery Unit, University Hospital of Udine Santa Maria della Misericordia, Udine, Italy
[5]Department of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy

Corresponding Author:
Vincenzo Abbate, MD, Department of Neurosciences, Reproductive and Odontostomatological Sciences, Maxillofacial Surgery Unit, University Federico II, Via Pansini 5, Naples, Italy.
Email: vincenzo.abbate@unina.it

cancer, patients with the same disease stage may still have varying prognoses, suggesting that additional factors could affect tumor progression.[5-7] Thus, the challenge in recent years has been to find new effective prognostic indicators that could act as a supplement to TNM staging for preoperative risk stratification in MSGT patients. Pretreatment hematological markers have emerged as prognostic factors for several cancers, including head and neck cancer (HNC).[8-12] In a preliminary study, Abbate et al[13] have demonstrated the prognostic performance of a combination of hematological inflammatory biomarkers in MSGTs. Likewise, several authors have recently pointed out the prognostic value of patient nutritional status and sarcopenia in different cancers, including HNC.[14-16] Sarcopenia is defined by the European Working Group on Sarcopenia in Older People as a decrease of skeletal muscle mass (skeletal muscle index [SMI]) mass and function; sarcopenia is a crucial component of cancer cachexia and it is a predictor of worse outcomes in HNC.[17-21] To date and to our knowledge, there are no existing studies that analyze the role of sarcopenia as a prognostic indicator for MSGTs. Based on these assumptions, our study aims to investigate the prognostic performance of SMI as an indicator of overall survival (OS) in patients surgically treated for MSGTs.

Materials and Methods

Study Population

This is a retrospective single-center study on patients who underwent surgery for MSGTs at the Maxillo-facial Surgery Unity of the University Federico II of Naples, between January 2011 and June 2018.

Patients who satisfied the following inclusion criteria were enrolled in the study:

- Preoperative investigation with fine needle aspiration cytology; ultrasound examination for cervical node status; computed tomography (CT)/magnetic resonance imaging (MRI) of head and neck area.
- Minimum follow-up of 36 months.
- Postoperative histology for MSGTs.
- No previous/simultaneous cancer at any other site
- No clinical conditions that might affect the patients' inflammatory status and eating disorders (eg, inflammatory, autoimmune, acute or chronic infectious disease, hematological disorder, a history of corticosteroid therapy or chronic renal insufficiency, celiac disease, anorexia).
- No radiotherapy or chemotherapy in the patient's clinical history.

Patients who did not satisfy the inclusion criteria or met the following criteria were excluded from this study:

- Serious complications or death that occurred within 15 days of the surgery.
- Administration of neoadjuvant chemotherapy.
- Lack of preoperative inflammation status data.

Considering the aforesaid criteria, 74 patients were enrolled in the study.

Data Collection

Relevant demographic and clinical variables were collected from patients' medical records including age, sex, height and weight at diagnosis, body mass index, alcohol consumption and smoking habits, pretreatment blood inflammatory biomarkers, tumor site, surgical treatment, and SMI.[15,18] All tumors were classified according to the AJCC classification (eighth edition).[4] The surgical treatment was performed according to current guidelines: superficial parotidectomy was performed in T1 or T2 low-grade superficial tumors; high-grade or T3 to T4 parotid gland tumors underwent total parotidectomy.[22] Patients with any tumor located in the submandibular gland underwent sialoadenectomy and patients with any tumor in minor salivary glands underwent local excision with a healthy margin. Neck dissection was performed in select cases according to the literature: early stage patients (cN0 T1 or T2 low-grade tumor) were subjected to a *wait-and-see* approach; while in cN0 high-grade tumors or low-grade T3/T4 tumors, an elective neck dissection was performed. cN+ Patients underwent a Modified Radical Neck Dissection.[23]

Sarcopenia Evaluation

According to the method published by Swartz et al[14] the SMI (cm^2/m^2) was measured as a cross-sectional area of muscle (CSA cm^2) on head and neck CT/MRI at the third cervical vertebrae (C3). The CSA was obtained considering the area of paravertebral and sternocleidomastoid muscles, showing a radiodensity between −29 and + 150 Hounsfeld Units (HU).[15] The segmentation of the muscular area and the CSA measurement was performed using the CoreSlicer.com software (free and open source web-based interface, Jonathan Afilalo and Louise Mullie© 2014-2022).

The cut-off to define a low SMI is already established in literature[18]:

- Male: SMI < 43.
- Female: SMI < 41.

Our sample was divided in sarcopenic and nonsarcopenic patients according to SMI cut-off value.[18]

Blood parameters such as platelet count, neutrophil count, lymphocyte count, and monocyte count, were calculated 1 week before the surgery. The preoperative patients' inflammatory status was assessed by inflammatory biomarker measurements: the neutrophil-to-lymphocyte ratio (NLR) was obtained as the ratio of neutrophil count to lymphocyte count; the platelet-to-lymphocyte ratio

(PLR) was obtained as the ratio of platelet count to lymphocyte count; the systemic immune inflammation index (SII) was defined as the neutrophil count multiplied by the platelet count divided by the lymphocyte count; and the systemic inflammation response index (SIRI) was defined as the neutrophil count multiplied by the monocyte count divided by the lymphocyte count.

Follow-Up and Outcome

Patients' outcome was determined via clinical follow-up every 6 months for up to 5 years followed by telephone calls every year or until death. The latest outcome for the final patient was recorded in February 2023. The outpatient outcome assessment included a physical examination, neck ultrasonography, and/or a maxillofacial/neck/total body CT scan. OS was calculated as time in months from surgery to death or to the date of the latest follow-up.

Statistical Analysis

Continuous variables are reported as mean and standard deviations. Categorical variables are reported as absolute frequencies and percentages. Comparisons between 2 groups were performed using Student's t test or Mann-Whitney U test, as appropriate. Comparisons between groups for categorical variables are performed with the χ^2 test or with Fisher's exact test, as appropriate. Survival curves were estimated using the Kaplan-Meier method and the difference between survival curves was computed using log-rank test. Cox regression was used to investigate, as a secondary outcome, whether the inflammatory biomarkers predicted OS in the cohort. The proportional hazard assumption was tested using the Schoenfeld residuals. Inflammatory markers that showed statistical significance at the univariable model were added to a multivariable model. For all analyses, a $P < .05$ was considered statistically significant. Analyses were performed using the statistical software R, version 4.0.3.

Results

Patients Characteristics

The main features of the 74 patients are shown in **Table 1**. In our sample, 38 patients (51.4%) were male and 36 (48.6%) were female, with a median age of 56 years [interquartile range (IQR): 13-85 years]. The tumors were located in the parotid gland in 49 patients (66.2%), in the minor salivary glands in 15 patients (20.3%), and in the submandibular gland in 10 patients (13.5%). The size of the tumor was greater than 4 cm in 11 patients (15%), although none of these patients showed involvement of the facial nerve. cT1 was observed in 22 patients (30%), cT2 in 41 (55%), and cT3 was observed in 11 (15%). Fifty-three patients (72%) presented with a cN0; a neck dissection was performed in 24 cases (32.4%). Among these 24 cases, lymph nodes were positive for metastasis in

Table 1. General Population Features

Variables	Total cases 74
Age (years)	
≤60	45
	– Sarcopenic 16 (35.5%)
	– Nonsarcopenic 29 (65.5%)
>60	29
	– Sarcopenic 22 (75.9%)
	– Nonsarcopenic 7 (24.1%)
Gender	
Female	36
	– Sarcopenic 16 (44.4%)
	– Nonsarcopenic 20 (56.6%)
Male	38
	– Sarcopenic 22 (57.9%)
	– Nonsarcopenic 16 (42.1%)
Tumor location	
Major salivary glands	59
	– Sarcopenic 34 (57.6%)
	– Nonsarcopenic 25 (42.4%)
Minor salivary glands	15
	– Sarcopenic 4 (26.7%)
	– Nonsarcopenic 11 (73.3%)
Tumor size (cm)	
≤4	63
	– Sarcopenic 28 (44.4%)
	– Nonsarcopenic 35 (56.6%)
>4	11
	– Sarcopenic 10 (90.9%)
	– Nonsarcopenic 1 (9.1%)
Lymph node metastasis	
Negative	53
	– Sarcopenic 17 (32.1%)
	– Nonsarcopenic 36 (67.9%)
Positive	21
	– Sarcopenic 21 (100%)
	– Nonsarcopenic 0 (0%)
pTNM stage	
I	20
	– Sarcopenic 5 (25%)
	– Nonsarcopenic 15 (75%)
II	28
	– Sarcopenic 9 (32.1%)
	– Nonsarcopenic 19 (67.9%)
III	23
	– Sarcopenic 21 (91.3%)
	– Nonsarcopenic 2 (8.7%)
IV	3
	– Sarcopenic 3 (100%)
	– Nonsarcopenic 0 (0%)
Adjuvant therapy	
No	41
	– Sarcopenic 13 (31.7%)
	– Nonsarcopenic 28 (68.3%)

(*continued*)

Table 1. (continued)

Variables	Total cases 74
Yes	33 – Sarcopenic 25 (75.8%) – Nonsarcopenic 8 (24.2%)

Abbreviation: TNM, tumor, node, metastasis.

21 patients; thus 21 patients were found to be pN+ while 3 patients were found to be pN0. The patients were divided based on the AJCC TNM stage: a total of 20 patients were at stage I (27%), 28 at stage II (38%), 23 at stage III (31%), and 3 at stage IV (3%). Moreover, as shown in **Table 1**, for each variable the patients were further divided into sarcopenic and nonsarcopenic. Thirty-eight (51.4%) patients were sarcopenic (SMI < 43 for males and SMI < 41 for females). Twenty-nine patients were over 60 years of age, of which 22 (75.9%) were sarcopenic. Fifty-nine patients had major salivary gland tumors, of which 34 (57.6%) were sarcopenic. Eleven patients presented with a tumor size >4 cm, of which 10 (90.9%) were sarcopenic. Twenty-one patients were pN+, of which all were sarcopenic. Twenty-six patients presented in an advanced AJCC TNM stage (III/IV), of which 24 (92.3%) were sarcopenic. Thirty-three patients received adjuvant therapy after surgery, of which 25 (75.8%) were sarcopenic.

Association Between Sarcopenia and Tumor Variables

The results are shown in **Table 2**. Among sarcopenic patients, the average age was 62 years old; 26% (10 cases) had tumor size >4 cm; 55% displayed lymph node metastasis, and 64% (24 cases) presented in an advanced AJCC TNM stage (III/IV). Therefore, the univariate analysis of the correlation between the variables and sarcopenia resulted in statistically significant for age ($P < .001$), tumor size ($P < .001$), lymph node metastasis ($P < .001$), and AJCC TNM stage ($P < .001$).

Association Between Sarcopenia and Inflammatory Biomarkers

The results are shown in **Table 3**. In sarcopenic patients, the mean values of NLR, SII, and SIRI resulted statistically higher ($P < .016$, $P < .041$, $P < .04$, respectively) compared to nonsarcopenic patients. PLR value resulted not statistically significant. The mean values for NLR, SII, and SIRI in sarcopenic patients were 4.01, 913, and 2.29, respectively. Comparatively, mean values for nonsarcopenic patients were 2.60, 605, and 1.26, respectively.

Overall and Disease-Specific Survival Analysis

The mean follow-up time was 74.5 months (IQR: 6-135 months). During the follow-up period, the death rate was

Table 2. Difference Between Sarcopenic and Nonsarcopenic Patients With Respect to Demographics and Tumor Variables

Variable	Not Sarcopenic, N = 36	Sarcopenic, N = 38	*P* value
Sex			.355
Female	20 (56%)	16 (42%)	
Male	16 (44%)	22 (58%)	
Age	49 (14)	62 (17)	**<.001**
pTNM stage			**<.001**
I	15 (42%)	5 (13%)	
II	19 (53%)	9 (24%)	
III	2 (5%)	21 (55%)	
IV	0 (0%)	3 (8%)	
Tumor location			.064
Major	25 (69%)	34 (89%)	
Minor	11 (31%)	4 (11%)	
Tumor size			**.001**
≤4	36 (100%)	28 (74%)	
>4	0 (0%)	10 (26%)	
Lymph node metastasis			**<.001**
N–	35 (97%)	17 (45%)	
N+	1 (2.8%)	21 (55%)	
Smoke			.520
No	28 (78%)	26 (68%)	
Yes	8 (22%)	12 (32%)	
Alcohol			.670
No	33 (92%)	36 (95%)	
Yes	3 (8.3%)	2 (5.3%)	
BMI	26.8 (4.3)	26.2 (3.7)	.526
Adjuvant radiotherapy	8 (22%)	25 (66%)	**<.001**

Data presented as frequency (%) or as mean (SD). *P* values computed with Student's *t* test or with Mann-Whitney for continuous variables, with χ^2 test or Fisher's exact test for categorical variables. Significant *P* values are marked in bold.

Abbreviations: BMI, body mass index; N, node; TNM, tumor, node, metastasis.

Table 3. Differences in Inflammatory Biomarkers Between Sarcopenic and Not Sarcopenic Patients

Variable	Not sarcopenic, N = 36	Sarcopenic, N = 38	*P* value
NLR	2.60 (1.45)	4.01 (3.16)	**.016**
PLR	125 (54)	154 (76)	.064
SII	605 (275)	913 (859)	**.041**
SIRI	1.26 (0.74)	2.29 (2.99)	**.046**

Data presented as mean (SD). *P* values computed with Student's *t* test. Significant *P* values are marked in bold.

Abbreviations: NLR, neutrophils on lymphocytes ratio; PLR, platelets on lymphocytes ratio; SII, systemic immune inflammation index; SIRI, systemic inflammation response index.

24% (18 patients). Among these, 15 (83.3%) were AJCC TNM advance staged (III-IV) and 3 (16.7%) were early stage (I-II). Three patients died due to cardiovascular diseases, 3 patients due to unknown causes, and 12 patients died due to MSGT progression. The Kaplan-Meier survival curves (**Figure 1**) show the OS of sarcopenic patients in comparison with nonsarcopenic patients: of the 38 sarcopenic patients, 18 (47.4%) died before the last investigation, while 0 nonsarcopenic patients died (log-rank test $P < .001$); the first event was registered at a 6-month follow-up, the last one at a 62-month follow-up. This significant difference also emerged in the disease-specific survival analysis (**Figure 2**), since 12 sarcopenic patients (31.6%) died due to MSGT progression, while 0 nonsarcopenic patients died (log-rank test $P < .001$). All inflammatory markers also showed a significant association with OS (**Table 3**) at univariate analysis, and, in particular, multivariate analysis showed that higher values of NLR independently predicted mortality (hazard ratio: 1.38, 95% confidence interval: 1.03-1.84, $P = .028$) (**Table 4**).

Discussion

MSGTs are a rare and heterogeneous group of cancers with diverse histological pictures. The World Health Organization (WHO) identified 25 different histotypes and 50 different gene mutations.[24] The rarity and the extreme heterogeneity of these neoplasms make it difficult to identify the best treatment.

In general, the decision-making process underlying the treatment of malignancies is based on the stratification of patients according to the risk of disease progression. Defining a prognosis early allows the clinician to define the appropriate treatment and follow-up in order to maximize patient survival and quality of life.

For MSGTs, the literature has already widely discussed the topic and has identified the following as valid prognostic factors: tumor grading, lymph node involvement, positive resection margins, and TNM staging, with the latter representing the most effective prognostic factor.[25] However, as reported by several authors, patients with the same TNM stage may still display different disease progression.[5-12]

Hence, the need to identify early prognostic indicators, that can effectively and inexpensively predict disease progression, is paramount.

Previous studies have highlighted how inflammatory status can be used as a supplement to TNM staging, to further stratify the prognostic prediction in many cancer types.[5-7] Recently, blood inflammatory indices have also been recognized as prognostic indicators for MSGTs.

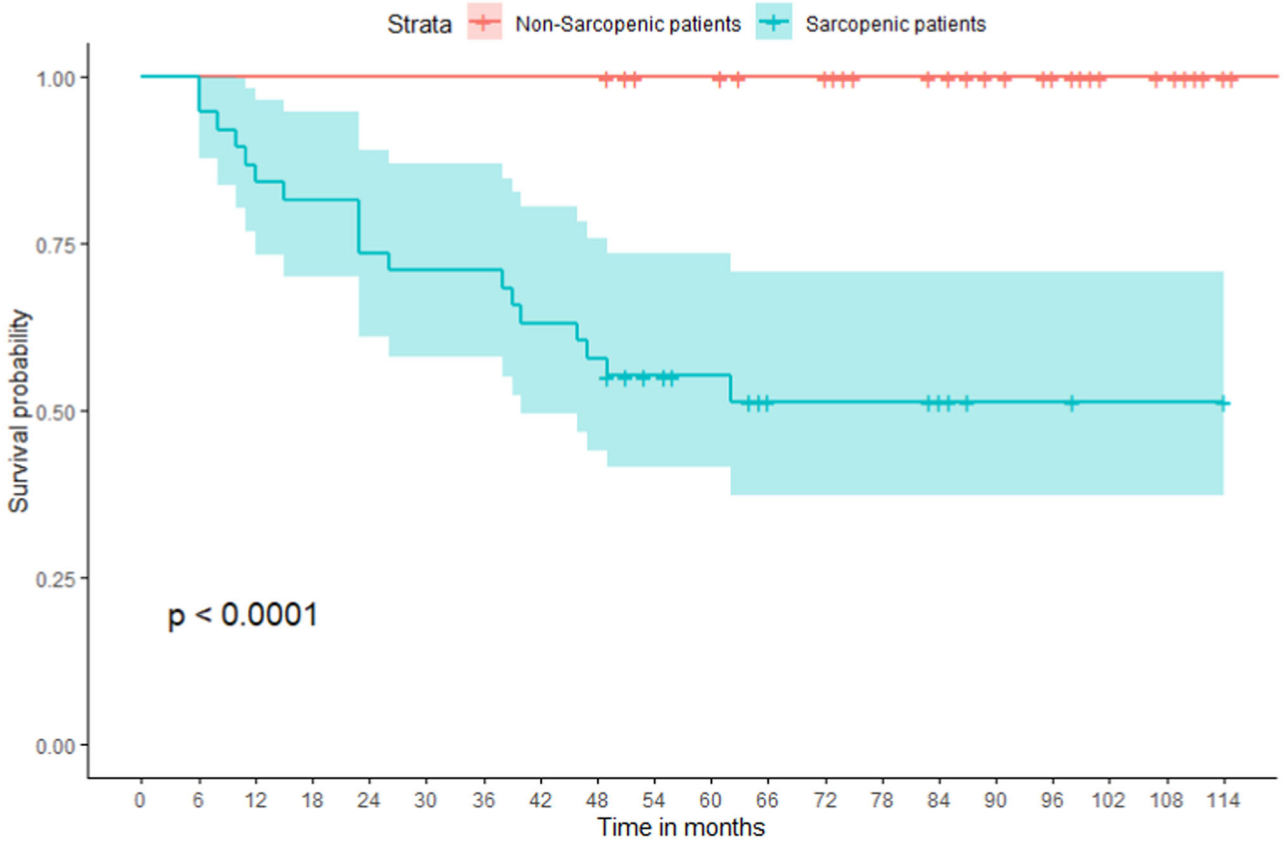

Figure 1. Kaplan-Meier overall survival curves. The figure shows the difference in estimated overall survival probability between sarcopenic and nonsarcopenic patients.

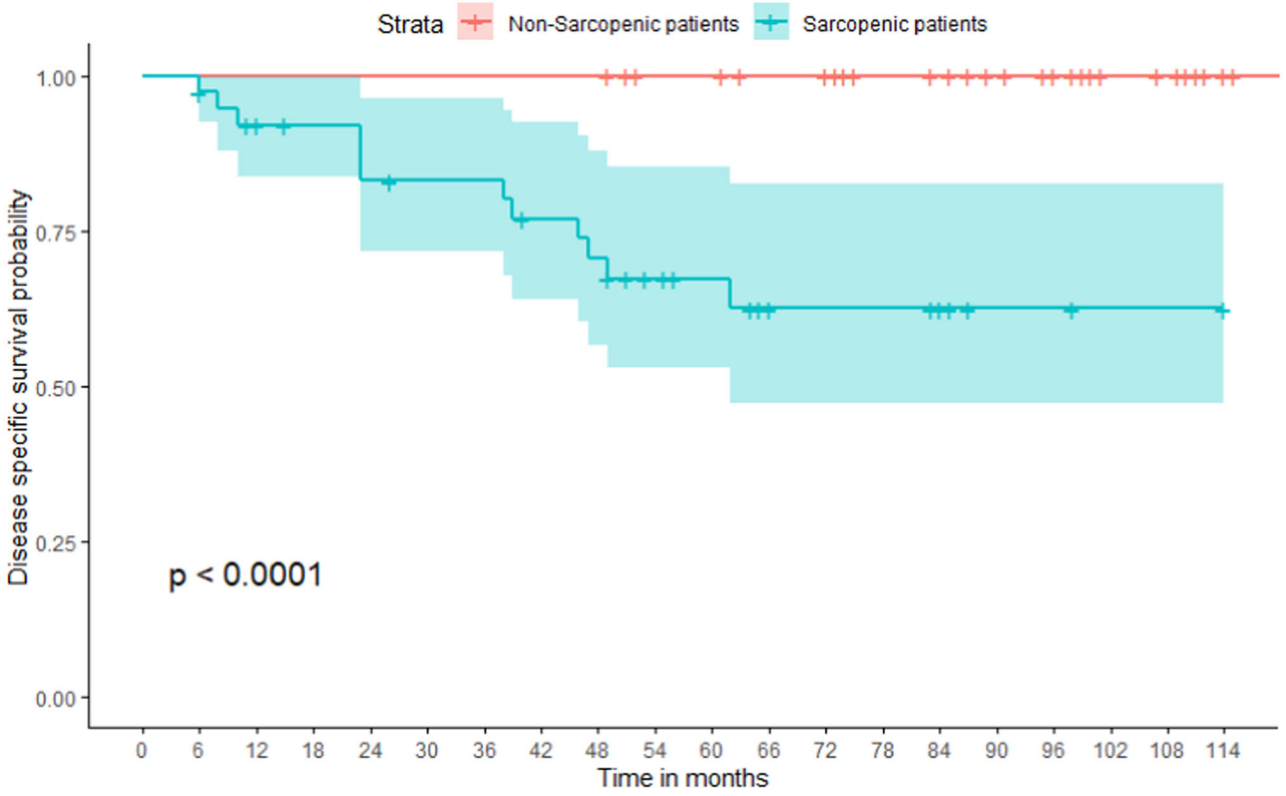

Figure 2. Kaplan-Meier disease-specific survival curves. The figure shows the difference in estimated disease-specific survival probability between sarcopenic and nonsarcopenic patients.

Table 4. Crude and Adjusted Cox Regression Analysis to Investigate the Predictive Capability of Inflammatory Biomarkers on Overall Survival

Overall survival	HR (univariate)	95% CI (univariate)	*P* value	HR (adjusted)	95% CI (adjusted)	*P* value
NLR	1.48	1.30, 1.69	**<.001**	1.38	1.03, 1.84	**.028**
PLR	1.01	1.01, 1.02	**<.001**	1.00	0.99, 1.01	.811
SII	1.00	1.00, 1.00	**<.001**	1.00	1.00, 1.00	.446
SIRI	1.23	1.11, 1.35	**<.001**	0.86	0.62, 1.17	.336

P values computed with Cox proportional hazard regression model. Significant *P* values are marked in bold.
Abbreviations: CI, confidence interval; HR, hazard ratio; NLR, neutrophils on lymphocytes ratio; PLR, platelets on lymphocytes ratio; SII, systemic immune inflammation index; SIRI, systemic inflammation response index.

Abbate et al[13] have demonstrated that the combination of SII + SIRI is a valid, fast, and low-cost prognostic system to stratify patients at a higher risk of disease progression.

Similarly, sarcopenia has been recently identified as an effective prognostic factor in several cancers.[17,26] However, to the best of our knowledge, there is no evidence regarding the prognostic performance of sarcopenia in MSGTs. So, the aim of the present study was to investigate how sarcopenia may affect the OS in MSGTs patients.

The most relevant aspect emerging from the study results is the correlation between sarcopenia and prognosis in our sample. Eighteen sarcopenic patients in the study died within 62 months of surgery. Furthermore, sarcopenia was statistically related to age >60, tumor size >4 cm, positive neck nodes, and advanced AJCC TNM stage (stage III/IV).

Moreover, it was interesting to see how in sarcopenic patients, the mean values of the inflammatory indices NLR, SII, and SIRI were statistically higher than in nonsarcopenic patients. Only PLR resulted as not statistically relevant.

These results could be explained by the correlation between inflammatory status and catabolism. Previous studies have emphasized the role of systemic inflammation as a driver of muscle degradation in cancer patients. Muscle wasting may be due to increased protein catabolism (hypercatabolism) or decreased protein synthesis (hypoanabolism). The simultaneous presence of both, results in greater muscular atrophy.[27] Evidence in the

literature shows how the inflammatory response is closely related to the development of sarcopenia: cytokines, tumor necrosis factor (TNF), and interleukin-6 (IL-6) are produced by tumor or surrounding cells and promote both the protein degradation and decreased synthesis. Elevated muscle metabolism results in increased cytokine levels which will further induce protein catabolism in muscles.[28] Indeed, Ding et al have demonstrated the correlation between elevated inflammatory biomarkers values and sarcopenia in patients with locally advanced gastric tumors.[29] The mechanistic explanation for the higher inflammatory indices values in sarcopenic patients depends on the fact that proinflammatory cytokines, such as TNF and IL-6, stimulate the increase of neutrophils and monocytes, decreasing the value of lymphocytes; therefore biomarkers such as NLR, SII, and SIRI are increased.[30]

Data obtained to our study seem to confirm that sarcopenia is related to already-known negative prognostic factors. Therefore, the correlation between sarcopenia and other high-risk features has been demonstrated. The early detection of sarcopenia in patients with negative prognostic factors could be used to implement the support therapeutic strategies aimed at restore the clinical conditions of the patients. Pamoukdjian et al in their review demonstrated that nutritional support, vitamin D supplementation, and neuromuscular rehabilitation influence improve the prognosis in sarcopenic cancer patients.[31]

This is a retrospective study in which data were obtained from the hospital's digital and clinical archives. For this reason, the sample may have been subjected to selection bias. Furthermore, the study collects the cases of a single center subjecting the analysis to possible epidemiological bias. Prospective studies with a larger population from different centers and longer follow-ups are required in order to confirm these preliminary data. Another limitation of the present study is that in our sample of nonsarcopenic patients no death occurred. For this reason, it was not possible to estimate hazard ratios neither crude or adjusted using time-to-event regression models to quantify the independent impact of sarcopenia on overall and disease-specific survival.

Our future aim will be to carry out a prospective study in order to verify whether the administration of precautionary strategies in sarcopenic patients will prevent the disease progression of MSGT patients.

Conclusion

Data obtained to our study seem to confirm the correlation between sarcopenia and other high-risk features. The early detection of sarcopenia in patients with negative prognostic factors could be used to implement the support therapeutic strategies aimed at restore the clinical conditions of the patients. Sarcopenia may be routinely investigated before surgery to suggest the implementation of precautionary therapeutic strategies to improve the standard treatment response, reducing possible complications.

Author Contributions

Vincenzo Abbate, conceptualization and validation; **Stefania Troise**, writing—review and editing; **Giulia Togo**, writing—original draft preparation; **Simona Barone**, resources and data curation; **Paola Bonavolontà**, investigation; **Daniela Pacella**, methodology and formal analysis; **Luigi Angelo Vaira**, design of the study; **Umberto Committeri**, software analysis; **Alessandro Tel**, software analysis; **Lorenzo Ugga**, resources and data curation; **Massimo Robiony**, visualization; **Luigi Califano**, supervision; **Giovanni Dell'Aversana Orabona**, project administration. All authors have read and agreed to the published version of the manuscript.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

ORCID iD

Vincenzo Abbate http://orcid.org/0000-0002-7905-0531

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