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Immuno-Oncology

Combined Effect of Sarcopenia and Systemic Inflammation on Survival in Patients with Advanced Stage Cancer Treated with Immunotherapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Sarcopenia • Inflammation • Immunotherapy • Biomarkers • Risk stratification

Abstract

Background. Sarcopenia and inflammation have been associated with poor survival in patients with cancer. We explored the combined effects of these variables on survival in patients with cancer treated with immunotherapy.

Methods. We performed a retrospective review of 90 patients enrolled on immunotherapy-based phase I clinical trials at Emory University from 2009 to 2017. Baseline neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio (PLR) were used as surrogates of inflammation. The skeletal muscle index (SMI) was derived from the skeletal muscle density calculated from baseline abdominal computed tomography images. Optimal cutoffs for continuous inflammation biomarkers and SMI were determined by bias-adjusted log-rank test. A four-level risk stratification was used to create low-risk (PLR <242 and nonsarcopenic), intermediate-risk (PLR <242 and sarcopenic), high-risk (PLR ≥242 and nonsarcopenic), and very-high-risk (PLR ≥242 and sarcopenic) groups with subsequent association with survival.

Results. Most patients (59%) were male, and the most common cancers were melanoma (33%) and gastrointestinal (22%). Very high-risk, high-risk, and intermediate-risk patients had significantly shorter overall survival (hazard ratio [HR], 8.46; 95% confidence interval [CI], 2.65–27.01; $p < .001$; HR, 5.32; CI, 1.96–14.43; $p = .001$; and HR, 4.01; CI, 1.66–9.68; $p = .002$, respectively) and progression-free survival (HR, 12.29; CI, 5.15–29.32; $p < .001$; HR, 3.51; CI, 1.37–9.02; $p = .009$; and HR, 2.14; CI, 1.12–4.10; $p = .022$, respectively) compared with low-risk patients.

Conclusion. Baseline sarcopenia and elevated inflammatory biomarkers may have a combined effect on decreasing survival in immunotherapy-treated patients in phase I trials. These data may be immediately applicable for medical oncologists for the risk stratification of patients beginning immunotherapeutic agents. ***The Oncologist*** 2020;25:e528–e535

Implications for Practice: Sarcopenia and inflammation have been associated with poor survival in patients with cancer, but it is unclear how to apply this information to patient care. The authors created a risk-stratification system that combined sarcopenia and platelet-to-lymphocyte ratio as a marker of systemic inflammation. The presence of sarcopenia and systemic inflammation decreased progression-free survival and overall survival in our cohort of 90 patients who received immunotherapy in phase I clinical trials. The data presented in this study may be immediately applicable for medical oncologists as a way to risk-stratify patients who are beginning treatment with immunotherapy.

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Introduction

The effects of body composition on prognosis in patients with cancer is gaining increasing interest as a topic of research. Cachexia is a multifactorial syndrome characterized by weight loss in patients with underlying pathologic states such as cancer [1]. This syndrome has been associated with poor responses to cancer treatment, decreased survival, and poor quality of life [2–4]. Cachexia has been linked to systemic inflammation, which is consistent with inflammation being recognized as a hallmark of cancer [5, 6]. Although patients with cancer presenting with weight loss and clinical signs of wasting have a poor prognosis, recent statistics from the Centers for Disease Control and Prevention estimate that 40% of cancer diagnoses in the U.S. (55% in women and 24% in men) can be linked to obesity [7]. Thus, weight may not be the most effective measure of body composition in predicting outcomes in patients with cancer.

Sarcopenia, decreased levels of skeletal muscle mass and function, has gained interest as a measure of body composition as it relates to human pathology and is defined as a skeletal mass index (SMI) more than two SDs below the mean for a healthy adult (male patients, <55 cm^2/m^2; female patients, <39 cm^2/m^2) [1, 8]. It can be observed in patients with chronic inflammatory conditions such as autoimmune diseases, and patients with cancer and sarcopenia have been shown to have higher levels of C-reactive protein (CRP) [9–12]. Chronic inflammation contributes to muscle catabolism via cytokines such as interleukin (IL)-6, tumor necrosis factor alpha (TNF-α), and transforming growth factor beta (TGF-β) [13, 14]. Furthermore, sarcopenia at cancer diagnosis is associated with shorter overall survival (OS), cancer-specific survival, and disease-free survival [15]. Hence, there is an interplay between inflammation and sarcopenia that likely affects clinical outcomes in patients with cancer, although causality is not yet determined.

Sarcopenia may be an effective prognostic body composition indicator, particularly in overweight or obese patients with cancer, given that they are unlikely to be presenting with wasting. The interaction between chronic inflammation and body composition is particularly important in the era of immunotherapy, given that immune checkpoint inhibitors (ICIs) rely on the host immune system for their efficacy [16]. We investigated the combined effect of inflammation and sarcopenia on clinical outcomes in patients with solid tumors treated with immunotherapy-based treatment regimens on phase I clinical trials.

Materials and Methods

Patients and Data

All patients (n = 90) treated on immunotherapy-based phase I clinical trials at Winship Cancer Institute from 2009 to 2017 with available baseline computed tomography (CT) images were included. CT scans were deemed acceptable if they were performed within 2 months of starting immunotherapy if patients received no other systemic treatment since the scans. Axial images from the middle of the third lumbar vertebrae (mid-L3) were retrieved from the electronic medical record, a validated muscular measurement source. Two authors (D.J.M., J.M.S.) were trained to correctly identify mid-L3 on CT and quantify skeletal muscle quantity and density by using the Hounsfield unit threshold (−29 to +150) using SliceOmatic (version 5.0; TomoVision, Magog, Canada) [17]. Low intraobserver variation of 1.3% was required to confirm adequate training. Skeletal muscle density was converted to SMI by dividing by height (m) squared [18]. Baseline platelet, absolute neutrophil, monocyte, and lymphocyte counts were obtained from the complete blood count within 2 weeks before immunotherapy initiation. Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) were then calculated. Other data collected included gender, race, medication allergies, histology, prior lines of systemic therapy, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and number and sites of metastatic disease. Royal Marsden Hospital (RMH) risk groups (albumin <3.5 g/dL, lactate dehydrogenase above the upper limit of normal, more than two metastatic sites) were used to risk-stratify patients (0–1 risk factors, good risk; 2+ risk factors, poor risk) [19].

The study was approved by the Emory University Institutional Review Board and was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. Informed consent for publication has been obtained and the consent forms are held by the authors. All data generated or analyzed during this study are included in this published article.

Statistical Analysis

OS was calculated from first dose of immunotherapy to date of death or hospice referral. Progression-free survival (PFS) was measured from first dose to date of clinical or radiographic progression or death. PFS was set as the primary outcome because of the higher number of events at the time of analysis. The nonlinear relationship between each biomarker (NLR, MLR, and PLR) and PFS was examined by the martingale residual plot, and an optimal cutoff value of each biomarker was determined by a bias-adjusted log-rank test after searching all possible cuts in terms of PFS [20]. An optimal cutoff value for SMI was determined for each gender by the same method described above. A four-level risk group system was then defined by combining sarcopenia (sarcopenic vs. nonsarcopenic) and inflammation (high vs. low biomarker based on optimal cutoff), as has been done for localized cancer [21]. A Cox regression model was carried out to associate the risk group with OS or PFS separately, and the multivariable model controlled for gender, checkpoint indication, number of previous treatments, RMH risk group, age, ECOG PS, race, number of metastatic sites, and histology. All analyses were done in SAS 9.4 and SAS macros developed by Winship Biostatistics and Bioinformatics Shared Resource [22] with significance level set at .05.

Results

Baseline demographic and disease characteristics are presented in Table 1. More than one-half (n = 53, 59%) of patients were male, and 20 patients (22%) were nonwhite.

Table 1. Demographic information and disease characteristics

Variable	*n* (%)
Gender	
Male	53 (59)
Female	37 (41)
Race	
White	70 (78)
Black	16 (18)
Asian or unknown	4 (4)
Histology	
Melanoma	30 (33)
Gastrointestinal	20 (22)
Lung or head and neck	18 (20)
Breast	11 (12)
Other	11 (12)
Checkpoint Indication	
Yes	49 (54)
No	41 (46)
ECOG PS	
0	34 (38)
1	55 (62)
Unknown	1 (1)
Number of prior systemic therapies in the metastatic setting	
0–1	28 (31)
2+	62 (69)
Prior treatment with ICI	
Yes	27 (30)
No	63 (70)
RMH risk group	
Good	71 (81)
Poor	17 (19)
Unknown	2 (2)
Treatment regimen	
FDA-approved ICI + experimental combination	46 (51)
Anti–PD-L1 monotherapy	25 (28)
Experimental IO monotherapy	19 (21)
SMI, median (range), cm^2/m^2	47.42 (27.64–71.74)
Sarcopenia cutoff, cm^2/m^2	
For male patients	55.97
For female patients	37.39
PLR, median (range)	182.65 (52.94–1,373.08)
Inflammation cutoff	242

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, U.S. Food and Drug Administration; ICI, immune checkpoint inhibitor; IO, immunotherapy; PD-L1, programmed death ligand 1; PLR, platelet-to-lymphocyte ratio; RMH, Royal Marsden Hospital; SMI, skeletal muscle index.

The most common histologies were melanoma (33%), gastrointestinal (22%), lung and head and neck (20%), and breast (12%). Most patients (*n* = 63, 70%) were ICI-naïve. Only 31% of patients had received fewer than two lines of

Table 2. UVA and MVA[a] of PLR-based risk groups and survival

	UVA				MVA			
	OS		PFS		OS		PFS	
Group	HR (CI)	*p* value	HR (CI)	*p* value	HR (CI)	*p* value	HR (CI)	*p* value
Group 1: low risk PLR <242 and nonsarcopenic (*n* = 27)	—	—	—	—	—	—	—	—
					Median survival: 24.3 months		Median survival: 4.8 months	
Group 2: intermediate risk PLR <242 and sarcopenic (*n* = 29)	1.67 (0.83–3.35)	.148	1.40 (0.80–2.44)	.242	4.01 (1.66–9.68)	.002[b]	2.14 (1.12–4.10)	.022[b]
					Median survival: 9.4 months		Median survival: 2.8 months	
Group 3: high risk PLR ≥242 and nonsarcopenic (*n* = 8)	2.78 (1.17–6.60)	.021[b]	2.72 (1.20–6.15)	.016[b]	5.32 (1.96–14.43)	.001[b]	3.51 (1.37–9.02)	.009[b]
					Median survival: 7.6 months		Median survival: 1.7 months	
Group 4: very high risk PLR ≥242 and sarcopenic (*n* = 15)	3.56 (1.65–7.68)	.001[b]	5.32 (2.64–10.73)	<.001[b]	8.46 (2.65–27.01)	<.001[b]	12.29 (5.15–29.32)	<.001[b]
					Median survival: 4.6 months		Median survival: 1.6 months	

[a]The multivariable model was built by controlling for gender, checkpoint indication, number of previous treatment lines, Royal Marsden Hospital risk group, age, Eastern Cooperative Oncology Group performance status, race, number of metastatic sites, and histology.
[b]Statistical significance at α < .05.
Abbreviations: —, reference; CI, 95% confidence interval; HR, hazard ratio; MVA, multivariable analysis; OS, overall survival; PLR, platelet-to-lymphocyte ratio; PFS, progression-free survival; UVA, univariable analysis.

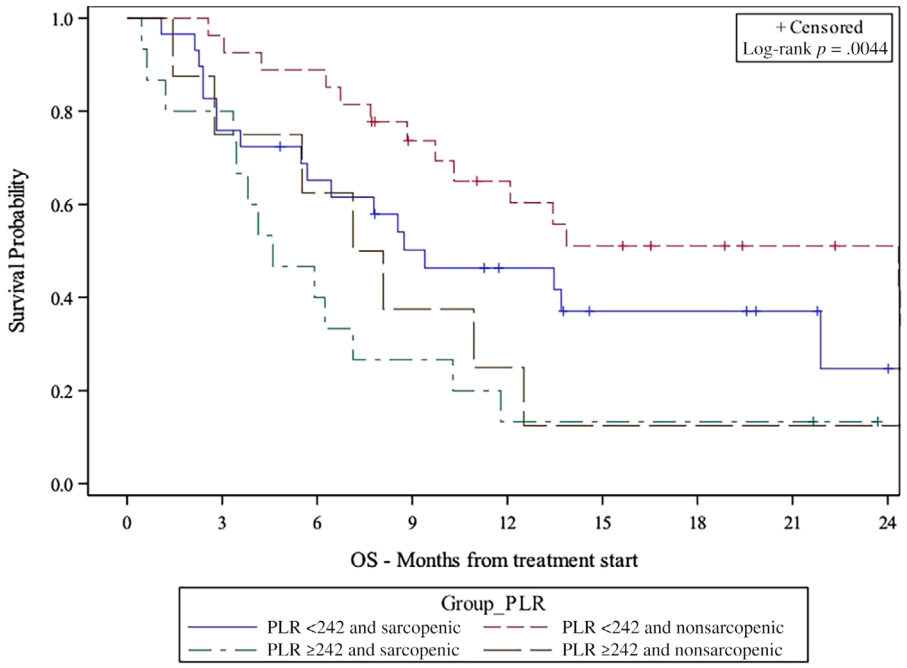

Figure 1. Kaplan-Meier plot of association between risk group and OS.
Abbreviations: OS, overall survival; PLR, platelet-to-lymphocyte ratio.

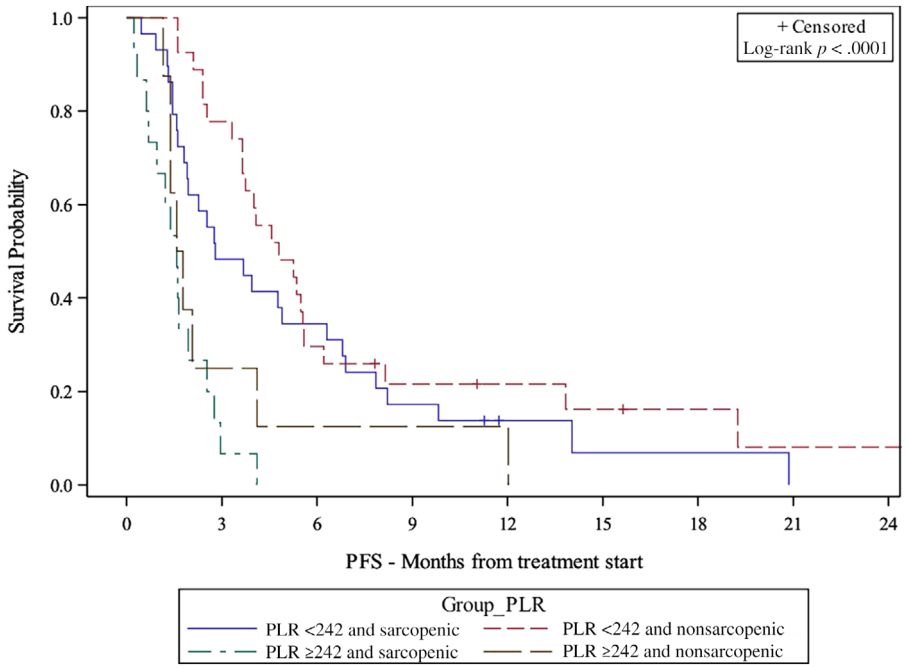

Figure 2. Kaplan-Meier plot of association between risk group and PFS.
Abbreviations: PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio.

prior systemic therapy. Most patients (81%) were RMH good risk. The immunotherapy treatment regimens are shown in Table 1. The median baseline SMI was 47.42, and the median NLR, MLR, and PLR were 3.63, 0.49, and 182.65, respectively. The optimal cutoffs for SMI that defined sarcopenia in our model were 55.97 for male patients and 37.39 for female patients, which closely correspond to previously reported cutoffs [1, 21]. NLR, MLR, and PLR were highly correlated (Pearson correlation coefficients ≥0.67, all $p < .0001$, not shown).

The univariable analysis and multivariable analysis (MVA) of the PLR-based risks groups and survival are shown in Table 2. NLR- and MLR-based risk group analyses are provided in supplemental online Tables 1 and 2. In PLR-based MVA, very high-risk patients (PLR ≥242 and sarcopenic) had significantly shorter OS (hazard ratio [HR], 8.46; 95%

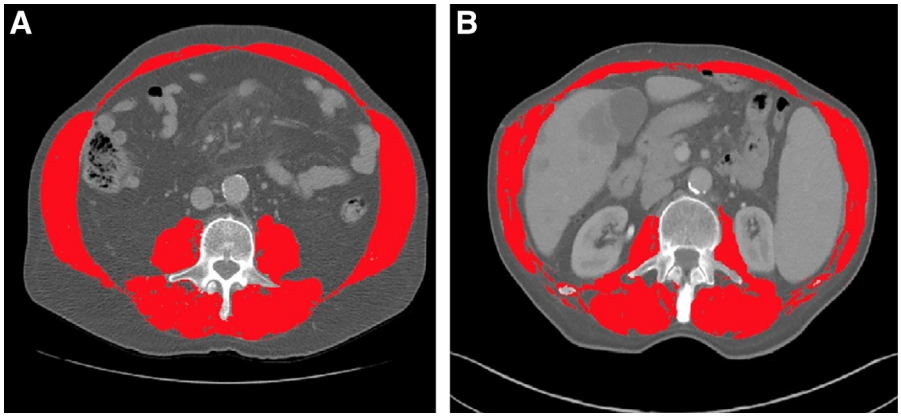

Figure 3. Segmented computed tomography images comparing clinical outcomes of two overweight patients (25 ≤ body mass index [BMI] < 30). **(A):** Baseline BMI, 26.5. Baseline skeletal muscle index (SMI), 59.6. Best response to immunotherapy: stable disease maintained for 11 months. **(B):** Baseline BMI, 26.0. Baseline SMI, 42.8. Best response to immunotherapy: progressive disease on first reimaging scan.

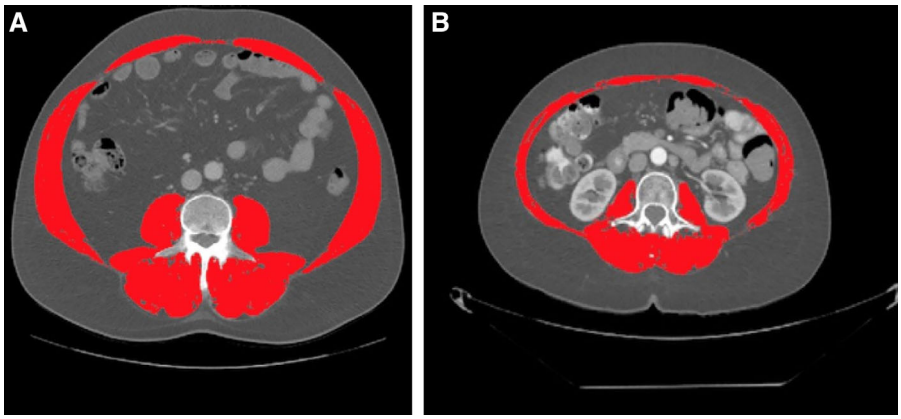

Figure 4. Segmented computed tomography images comparing clinical outcomes of two patients without inflammation (platelet-to-lymphocyte ratio [PLR] <242). **(A):** Baseline PLR, 160.19. Baseline skeletal muscle index (SMI), 66.38. Best response to immunotherapy: partial response. **(B):** Baseline PLR, 192.95. Baseline SMI, 31.71. Best response to immunotherapy: progressive disease.

confidence interval [CI], 2.65–27.01; $p < .001$) and PFS (HR, 12.29; CI, 5.15–29.32; $p < .001$) compared with low-risk patients (PLR <242 and nonsarcopenic). High-risk (PLR ≥242 and nonsarcopenic) and intermediate-risk (PLR <242 and sarcopenic) patients also had shorter OS (high-risk HR, 5.32; CI, 1.96–14.43; $p = .001$; intermediate-risk HR, 4.01; CI, 1.66–9.68; $p = .002$) and shorter PFS (high-risk HR, 3.51; CI, 1.37–9.02; $p = .009$; intermediate-risk HR, 2.14; CI, 1.12–4.10; $p = .022$) compared with low-risk patients. The median OS and PFS were longer for low-risk patients (24.3 months and 4.8 months) than intermediate-risk (9.4 months and 2.8 months), high-risk (7.6 months and 1.7 months), and very-high-risk patients (4.6 months and 1.6 months) per Kaplan-Meier estimation (Figs. 1, 2, both $p < .005$). SMI was negatively correlated with PLR ($p = .0387$, not shown).

Discussion

We showed that sarcopenia and PLR have a combined effect on decreasing survival in this population of patients treated with immunotherapy on phase I clinical trials. These results build upon previous data showing that sarcopenia and systemic inflammation are independently associated with poor survival in patients with cancer [15, 23]. This is the first study, to our knowledge, investigating the combined effect of sarcopenia and inflammation in patients with solid tumors treated with immunotherapy. This study is also novel in that it included heavily pretreated patients enrolled on phase I clinical trials using novel immunotherapeutic agents.

The effect of sarcopenia and inflammation on clinical outcomes has been explored in patients with malignancies. In a previous analysis, we showed that increased NLR, MLR, and PLR were associated with worse clinical outcomes in this group of patients treated with immunotherapy on phase I clinical trials [24]. A study of 117 male patients with small cell lung cancer treated with chemotherapy or chemo-radiotherapy showed that sarcopenia and high NLR were independently associated with shorter OS and PFS [25]. Patients with melanoma with sarcopenia were found to be more likely to experience ipilimumab-related toxicity, whereas a cohort of patients with advanced non-small cell lung cancer treated with nivolumab or pembrolizumab appeared to have poorer survival outcomes and response rates if they were sarcopenic [26, 27].

These clinical findings in immunotherapy-treated populations in particular may be explained by the interplay between skeletal muscle and the immune system. Chronic inflammation has been posited to play a role in both the development of sarcopenia and resistance to immune checkpoint inhibitors. The same cytokines implicated in sarcopenia such as TGF-β and IL-6 have also been cited as mediators of T-cell exhaustion [28]. Increased TGF-β signaling in urothelial cell tumors of patients unresponsive to the anti–programmed death ligand 1 agent atezolizumab has been correlated with the sequestering of $CD8^+$ T cells in the peritumoral stroma rather than in the tumor itself [29]. It is also known that skeletal muscle produces anti-inflammatory cytokines with increased production during times of exercise. IL-15 is one such cytokine, also known as myokine, and is known to decrease the activity of proinflammatory TNF-α during cachexia [30]. In addition, skeletal muscle undergoes necrosis in response to injury and releases intracellular contents, including chemotactic factors, which recruit immune cells to mediate regeneration of skeletal muscle [31]. Thus, the decreased muscle mass of sarcopenia may have a direct link to immune dysregulation, resistance to ICIs, and poorer outcomes in patients with cancer treated with these agents.

The inclusion of both sarcopenia and inflammatory biomarkers in these risk groups better accounts for the multifactorial contribution of prognostic indicators in oncology patients. Risk groups provide clinicians with a tool to assess the clinical outcomes of individual patients before they begin treatment. The data presented in this study may be immediately applicable for medical oncologists. For example, these results suggest that sarcopenia may be an important consideration in further risk-stratifying patients without laboratory signs of inflammation such as a low PLR. Furthermore, recent validated work has shown that sarcopenia can be measured in the clinic setting using standard picture archiving and communication system tools without the need for advanced software [21], making sarcopenia an easily determined prognostic marker.

The utility of sarcopenia as a biomarker of response to immunotherapy is particularly appealing in patients who are overweight or obese. Although increased body mass index (BMI) has been shown to be protective for some patients with cancer [32, 33], there is evidence suggesting that obesity contributes to oncologic development and progression via chronic inflammation [34]. It suffices to say that BMI is an imperfect biomarker of body composition as it relates to cancer outcomes [35]. Recently, Young et al. (2019) examined the role of skeletal muscle mass and adiposity on clinical outcomes in a cohort of patients with melanoma who received anti–programmed cell death protein 1 monotherapy. Interestingly, high skeletal muscle gauge (SMG), a composite of muscle area and density, was the best predictor of clinical outcomes, as the cohort with high SMG and high adiposity achieved superior OS and PFS, whereas patients with low SMG and high adiposity had the worst outcomes [36]. Therefore, a simple calculation of BMI that relies heavily on adiposity may understandably fall short as a prognostic marker.

Sarcopenia may be a better predictor of clinical outcomes in obese and overweight patients, which is supported by two patients with lung cancer presented in Figure 3. The first patient had a BMI of 26.5 and an SMI of 59.6 (Fig. 3A). His baseline NLR, MLR, and PLR were 4.26, 0.60, and 174.45, respectively. He maintained a best response of stable disease without progression for 11 months. The second patient (Fig. 3B) had a similar BMI (26.0) and lower baseline inflammatory markers but had a lower SMI (42.8). This patient had similar inflammatory markers as the first patient (NLR, 4.25; MLR, 0.55; and PLR, 142.11). This patient experienced progressive disease (PD) on their first restaging scans after starting immunotherapy. This suggests that sarcopenia may be a more valuable measure of body composition than BMI in this subset of patients. The fact that these patients had comparable inflammatory markers also highlights the importance of using SMI along with an inflammatory marker such as PLR when risk-stratifying oncology patients treated with immunotherapy.

In this study, sarcopenia was useful in distinguishing low- and intermediate-risk patients without laboratory signs of inflammation (PLR <242). This highlights another clinical situation in which sarcopenia may be a useful measure for clinicians. The clinical utility of sarcopenia in this situation is illustrated in Figure 4, which compares the baseline SMI of two patients who had PLR <242. One patient who had a baseline PLR of 160.19 at baseline and an SMI of 66.38 (Fig. 4A). This patient received an immunotherapy-based experimental treatment regimen on the phase I clinical trial as sixth-line systemic therapy and has sustained a partial response for 16 months. The second patient had a baseline PLR of 192.95 and an SMI of 31.71 (Fig. 4B). Unfortunately, this patient experienced PD as best response on an immunotherapy-based experimental treatment regimen and passed away 12 months after the first dose of immunotherapy. These two patients highlight a second clinical situation where sarcopenia can be used as a biomarker of response to immunotherapy.

Despite the novelty of this study, there are several limitations that should be noted. First, this is a retrospective study and is subject to selection bias. We attempted to mitigate the effect of selection bias by including all patients with available clinical data and baseline CT images who were treated on phase I clinical trials at our center, regardless of their primary malignancy or baseline characteristics. We did not investigate some markers of inflammation, such as CRP, given that it is not routinely collected. Finally, we only included skeletal muscle as a surrogate of body composition and did not include other markers.

Conclusion

In this study of patients with advanced stage cancer treated with immunotherapy-based treatment regimens on phase I clinical trials, sarcopenia and inflammation had a combined effect on decreasing survival. The inclusion of both sarcopenia and inflammatory biomarkers better accounts for the multifactorial contribution of prognostic indicators in patients with advanced cancer. The data presented in this study may be immediately applicable for medical oncologists, given that these risk groups may be used for risk stratification for patients who are beginning treatment with immunotherapy. Future studies should further elucidate the biological relationship between body composition and

inflammation in patients with cancer treated with immunotherapeutic agents.

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Disclosures

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