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Food Aversion, Systemic Inflammation and Intramuscular Adipose Tissue are Mortality Predictors in Advanced Lung Cancer Patients

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ABSTRACT

Background: Cancer cachexia, systemic inflammation and muscle wasting are associated with poor survival in non-small cell lung cancer (NSCLC) patients (pts). We hypothesized whether neutrophil-to-lymphocyte ratio (NLR) and intramuscular adipose tissue/skeletal muscle index (IMAT/SMI) would predict prognosis in metastatic NSCLC (mNSCLC). In addition, we verified the role of a cancer cachexia questionnaire (EORTC-QLQ-CAX24) in the survival prediction.

Methods: We analysed a prospective cohort of 128 treatment-naïve mNSCLC pts (April 2017 to May 2020). We evaluated QoL using the EORTC-QLQ-C30 and EORTC-QLQ-CAX24 scales. We used the baseline NLR as a surrogate of systemic inflammation. We did evaluate IMAT/SMI using baseline plain computed tomography imaging. Cox multivariate regression, including age, sex, ECOG-PS and histology as covariates, was performed.

Results: Elevated NLR (hazard ratio [HR] 1.26, 95% confidence interval [CI]: 1.01–1.59, $p=0.038$), IMAT/SMI ratio (HR 1.37, 95% CI: 1.03–1.84, $p=0.032$) and high CAX24 scores for food aversion (HR 1.52, 95% CI: 1.13–2.03, $p=0.006$) were associated with worse prognosis in mNSCLC. Indeed, higher ECOG-PS (Spearman $\rho=0.208$, $p=0.027$), CAX24 scores for food aversion (Spearman $\rho=0.197$, $p=0.036$), loss of control (Spearman $\rho=0.212$, $p=0.024$) and eating and weight loss worry domains (Spearman $\rho=0.219$, $p=0.020$) were associated with elevated NLR levels.

Conclusions: Elevated NLR, IMAT/SMI ratio and CAX24 score for food aversion are independently associated with worse survival in mNSCLC. These data underscored the importance of cachexia features as negative prognostic factors in mNSCLC and revealed the EORTC-QLQ-CAX24 questionnaire as a new tool for helping clinical decision-making.

Trial Registration: ClinicalTrials.gov identifier: NCT03960034 and NCT04306094

1 | Introduction

Lung cancer is the leading cause of death and the most frequently diagnosed cancer worldwide [1]. Non-small cell lung

cancer (NSCLC) represents 85% of lung cancer cases [2], and advanced disease accounts for 70% [3]. In an advanced stage, the estimated prognosis is poor, and the median overall survival is less than 1 year [4]. In addition, patients with

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metastatic NSCLC (mNSCLC) experience a high symptom burden and a quickly declining performance status (PS). Pain, dyspnoea, cough, anorexia and fatigue are the most common and distressing symptoms that negatively impact their quality of life (QoL) [5, 6].

Moreover, lower QoL is associated with shorter survival among patients with mNSCLC [4, 7]. Evaluation of QoL using QLQ-C30 questionnaires demonstrated that global QoL and physical function were overall survival predictors [8]. These questionnaire domains are related to the patient's functioning, the severity of symptoms and financial problems, among other aspects related to the cancer disease and its treatment [9]. A relationship exists between poorer QoL and muscle wasting in mNSCLC patients who received chemotherapy [10]. Muscle wasting is present in cancer cachexia, a multifactorial syndrome characterized by unintentional weight loss and anorexia not reversed by nutritional support. Most advanced cancer patients present cachexia leading to fatigue, loss of skeletal muscle mass and function and decreased survival; there is an association between muscle wasting and cachexia with decreasing survival before and after chemotherapy [11].

Cachectic patients frequently present with systemic inflammation [12]. The hypermetabolism caused directly by tumours or tumour-mediated effects, such as systemic inflammation, is attributed to cancer cachexia [13]. Systemic inflammation is associated with deteriorating functional status and QoL, chemotherapy intolerance, poor tumour response and decreasing survival [14]. The relationship between cancer cachexia and inflammation is bidirectional. Chronic inflammation contributes to the development and progression of cachexia, while cachexia exacerbates systemic inflammation [15]. In NSCLC patients, neutrophil-to-lymphocyte ratio (NLR) is a systemic inflammation marker and a prognostic predictor [16]. Intramuscular adipose tissue (IMAT) increase and inflammation are linked; it predicts muscle and mobility function in older adults and is a prognostic predictor in colorectal cancer patients [17, 18]. Together, inflammation, QoL and cachexia have a nasty cycle with one another that negatively influences the prognosis of mNSCLC patients.

As the importance of cachexia in patient prognosis is notable, the EORTC developed a questionnaire named QLQ-CAX24. It is a cancer cachexia-specific questionnaire for QoL assessment in clinical trials and practice. It contains five multi-item scales (food aversion, eating worry, weight-loss worry, eating difficulties, loss of control and physical decline) and four single items [19]. It is worth highlighting that no data exist on the relationship between this new questionnaire and patients' prognoses. Therefore, this study aimed to investigate QoL assessed via the EORTC-QLQ-CAX24 questionnaire, cachexia, and inflammation as predictors of mortality in patients diagnosed with mNSCLC.

2 | Materials and Methods

2.1 | Ethics, Study Population, and Design

The prospective cohort of lung cancer patients was recruited between April 2017 and May 2020 at Instituto do Cancer do Estado de São Paulo (ICESP). This cohort is a combination of

two studies, and both were approved by the Human Research Ethics Committee at the University of São Paulo (CEP-FMUSP; protocol: 2.286.563 and 2.286.753) and registered in [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03960034 and NCT04306094). The inclusion criteria used were as follows: (1) histologically proven diagnosis of Stage IV NSCLC (TNM eighth edition); (2) treatment-naïve for NSCLC; (3) normal renal and hepatic functions; and (4) able to read, understand and sign the consent form. The exclusion criteria included (1) patients with psychiatric diseases; (2) patients with two different cancers; and (3) patients under 18 years of age. One hundred twenty-eight patients were included, and we obtained written informed consent from all participants. After signing informed consent, we assessed clinical and demographic characteristics, including body weight, height, body mass index (BMI, kg/m²), age, sex, educational level, body weight, histological type, ECOG performance status, smoking status, tobacco load, metastatic sites and comorbidities.

2.2 | Assessment of Cachexia

Patients with weight loss > 5% over the past 6 months or BMI < 20 (in the absence of simple starvation and any degree of weight loss > 2%) were classified as cachectic [13].

2.3 | Assessment of the EORTC-QLQ-C30 and EORTC-QLQ-CAX24 Scales

Patient QoL was evaluated using the EORTC-QLQ-C30 [20] and EORTC-QLQ-CAX24 [19] scales. All patients answered the EORTC-QLQ-C30 and EORTC-QLQ-CAX24 scales. The EORTC QLQ-C30 questionnaire was developed to evaluate the quality of life in cancer patients. It has five functional measures (physical, role, emotional, social and cognitive), eight symptom scales (fatigue, pain, nausea/vomiting, appetite loss, constipation, diarrhoea, insomnia and dyspnoea), a global health/QoL evaluation and financial impact. Most items use a 4-item scale from *not at all* to *very much*. Raw scores are transformed to a 0–100 scale, with higher scores representing a high level of functioning, whereas a high score for a symptom scale/single item represents a high symptom burden [20].

The EORTC QLQ-CAX24 is a cachexia-specific questionnaire. It contains five multi-item scales (food aversion, eating and weight-loss worry, eating difficulties, loss of control and physical decline) and four single items. All items use a 4-item scale from *not at all* to *very much*. Raw scores are transformed to a 0–100 scale, with a high score indicating more problems, except for item 54, where a high score represents adequate information about weight loss [19].

2.4 | Assessment of the Body Composition Using Abdominal Computed Tomography Scans

Abdominal CT scans, performed routinely as part of diagnostic investigations or staging work-ups, were used to analyse body composition. We used the cross-sectional area of the abdominal CT imaging at the level of the third lumbar vertebra (L3) to measure

TABLE 1 | Patients characteristics ($n = 128$).

| Characteristics | <i>n</i> | % |
|----------------------------|----------|---------------|
| Age, median | 65 | 23–86 (range) |
| Sex | | |
| Men | 79 | 61.72 |
| Women | 49 | 38.28 |
| Race | | |
| White | 81 | 63.28 |
| Black | 14 | 10.94 |
| Brown | 30 | 23.44 |
| Yellow | 3 | 2.34 |
| Smoking story | | |
| Nonsmoker | 15 | 11.72 |
| 1–9 pack-years | 4 | 3.13 |
| ≥ 10 pack-years | 109 | 85.16 |
| Body weight loss | | |
| Without weight loss | 7 | 5.47 |
| $< 5\%$ | 13 | 10.16 |
| $> 5\%$ | 107 | 83.59 |
| Unknown | 1 | 0.78 |
| Death | 101 | 78.91 |
| Loss to follow-up | 2 | 1.56 |
| ECOG-PS status | | |
| 0 | 7 | 5.47 |
| 1 | 20 | 15.63 |
| 2 | 57 | 44.53 |
| 3 | 32 | 25.00 |
| 4 | 12 | 9.38 |
| Metastasis | | |
| Lung | 43 | 33.59 |
| Pleura | 43 | 33.59 |
| Central nervous system | 25 | 19.53 |
| Adrenal | 34 | 26.56 |
| Liver | 14 | 10.94 |
| Bone | 50 | 39.06 |
| Others | 9 | 7.03 |
| Tumour histology | | |
| Adenocarcinoma | 84 | 65.63 |
| Squamous cell carcinoma | 33 | 25.78 |
| Non-small cell lung cancer | 11 | 8.59 |

(Continues)

TABLE 1 | (Continued)

| Characteristics | <i>n</i> | % |
|--------------------------|----------|------|
| Chemotherapy | | |
| Yes | 75 | 58.6 |
| No | 53 | 41.4 |
| Regimen | | |
| Carboplatin + paclitaxel | 64 | 85.3 |
| Cisplatin + pemetrexed | 1 | 1.3 |
| Cisplatin + gemcitabine | 2 | 2.7 |
| Cisplatin + etoposide | 2 | 2.7 |
| Gemcitabine | 2 | 2.7 |
| Gefitinib | 3 | 4 |
| Alectinib | 1 | 1.3 |

Note: Patient characteristics was expressed in number and percentages.

the skeletal muscle index (SMI), psoas index, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and intramuscular adipose tissue (IMAT) contents. We used image analysis software (sliceOmatic V5.0; TomoVision, Magog, QC, Canada; Alberta protocol) to measure specific tissue demarcation by the Hounsfield unit (HU). The skeletal muscle index consists of the psoas, erector spinae, quadratus lumborum, transversus abdominis, internal oblique, external oblique and rectus abdominis. The L3 skeletal muscle and adipose area were normalized by height squared (cm^2) [21].

2.5 | Assessment of the NLR

Laboratory data were collected from the electronic medical records system when patients were evaluated for staging. The NLR was determined by dividing the total neutrophils by the total lymphocyte count.

2.6 | Statistical Analysis

We eliminated 15 of 128 patients with missing data for at least one of the variables. The variables were normalized by the Z-score method. We performed an individual Cox survival analysis with each muscle and Cax24 variable. Then, we adjusted for confounding factors (age, ECOG PS, histology and sex) with p values less than 0.05 in the chi-square proportion tests. Those variables that showed a significant relationship with survival were selected to perform a multivariate Cox analysis with all variables. We discretized the variables using the third quartile as a Kaplan–Meier analysis threshold. To verify the relationship between NLR ECOG and CAX24 variables, we used Spearman's correlation test. For all tests, we consider the significance level equal to 5%.

3 | Results

Table 1 presents the patient characteristics. The median age of the study population was 65 years, and 61.72% were male. The

predominant race was White (63.28%). In our cohort, 85.16% were heavy smokers, and 83.59% of the cohort experienced weight loss higher than 5% in the last 6 months of inclusion. We lost the follow-up of two patients (1.56%), and 101 patients (78.91%) died in the follow-up period. The most common ECOG-PS status in our sample was ECOG-PS 2 (44.5%), and the most common metastatic site was the bones (39.06%), followed by lung (33.59%) and pleura (33.59%). Adenocarcinoma was the most prevalent histologic type (65.63%).

We performed univariate analysis to determine the relationship between each tested variable and prognosis (Table S1). NLR ($p=0.023$), IMAT/SMI (intramuscular adipose tissue normalized by skeletal muscle index; $p=0.042$) and food aversion ($p=0.002$) are associated with the patient's prognosis in terms of overall survival. But not the psoas area, skeletal muscle

index, adipose tissue and other QoL-related questions. We adjusted for confounding factors, including age, histology type, ECOG-PS status and sex, and performed a multivariate Cox analysis (Table 2). NLR, IMAT/SMI, and food aversion presented significant differences ($p<0.05$, $p<0.02$ and $p<0.00$, respectively), showing an association with survival. As expected, ECOG-PS status and histological type also affected prognosis (Table S2).

The survival analysis for NLR, IMAT/SMI and food aversion. Patients with NLR > 7.4 present lower survival (Figure 1, Panel A; $p=0.03$). According to the IMAT/SMI ratio, patients with worse survival had values superior to 0.16 (Figure 1, Panel B; $p=0.004$). Finally, patients with a food aversion score greater than 46.66 also present lower survival rates (Figure 1, Panel C; $p=0.0001$).

We performed a Person correlation test to test collinearity among NLR, food aversion and IMAT/SMI. We noted that the correlation between those variables is weak (>0.1) and not statistically significant ($p>0.05$), which means no collinearity was detected (Table S2). However, the NLR presented a significant correlation with ECOG-PS status ($p=0.027$; Figure 2, Panel A), food aversion ($p=0.036$; Figure 2, Panel B), eating and weight loss worry ($p=0.020$; Figure 2, Panel C) and loss of control ($p=0.024$; Figure 2, Panel D). On the other hand, inflammation was not correlated with the psoas area, SMI, IMAT, IMAT/SMI or physical decline ($p=0.447$, 0.337, 0.915 and 0.674, respectively; Table S3).

4 | Discussion

We demonstrated food aversion, one item present in EORTC-QLQ-CAX24, as an independent mortality predictor. The other findings we summarize are as follows: First, except for food aversion, the other items in the QoL scale have no association with survival. Second, IMAT/SMI and NLR can predict survival, but not psoas area, SMI, and adipose tissue. Finally, there was a correlation between inflammation, ECOG-PS status, and food aversion. Our data add broad knowledge of prognosis predictors in mNSCLC patients and may help clinical decision-making.

Trejo et al. [7] indicated an association between survival and patient-reported outcomes, as measured by EORTC-QLQ30, confirming that the QoL of patients is an important prognostic

TABLE 2 | Multivariate Cox analysis for prognosis prediction.

| | HR | 95% CI for HR (LL - UL) | p |
|------------------------------|------|----------------------------|--------|
| NLR | 1.26 | 1.008–1.582 | 0.0427 |
| IMAT/SMI | 1.41 | 1.059–1.881 | 0.0186 |
| Food aversion | 1.48 | 1.111–1.962 | 0.0072 |
| Eating and weight loss worry | 1.01 | 0.772–1.322 | 0.941 |
| Loss of control | 1.03 | 0.74–1.436 | 0.8566 |
| Physical decline | 0.9 | 0.665–1.223 | 0.5066 |
| Age | 0.98 | 0.956–1.012 | 0.2444 |
| ECOG-1 | 1.22 | 0.298–4.96 | 0.786 |
| ECOG-2 | 2.62 | 0.723–9.509 | 0.1426 |
| ECOG-3 | 2.89 | 0.772–10.838 | 0.1152 |
| ECOG-4 | 8.55 | 1.893–38.614 | 0.0053 |
| Histology (NSCLC) | 3.86 | 1.467–10.144 | 0.0062 |
| Sex (female) | 0.7 | 0.38–1.303 | 0.2635 |
| Race (Black) | 0.46 | 0.208–1.006 | 0.0516 |
| Race (brown) | 0.66 | 0.378–1.167 | 0.1548 |

Abbreviations: CI=confidence interval, HR=hazard ratio, LL=lower limit, UL=upper limit.

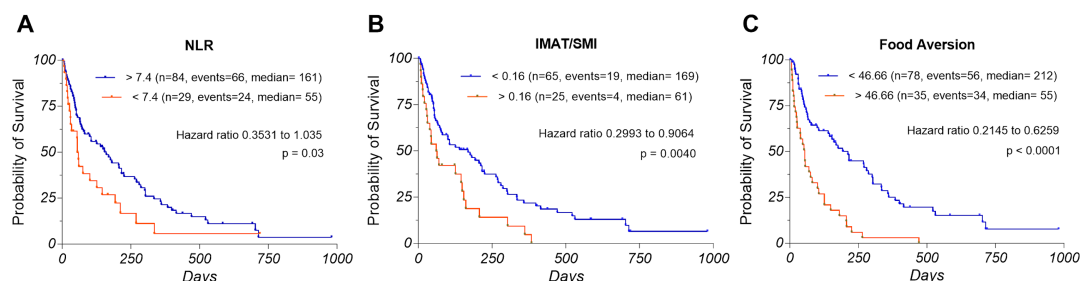


FIGURE 1 | Survival analysis using the third quartile as a cut-off of NLR, IMAT/SMI and food aversion. Each measurement was divided into quartile and probability of survival was compared using the third quartile as a cut-off. (A) Neutrophil-to-lymphocyte ratio < 7.4 ($n=84$) and > 7.4 ($n=29$). (B) Intramuscular adipose tissue divided by skeletal muscle index < 0.16 ($n=65$) and > 0.16 ($n=25$). (C) Food aversion < 46.66 ($n=78$) and > 46.66 ($n=35$). Comparisons were performed using the log-rank test and presented as Kaplan–Meier curves.

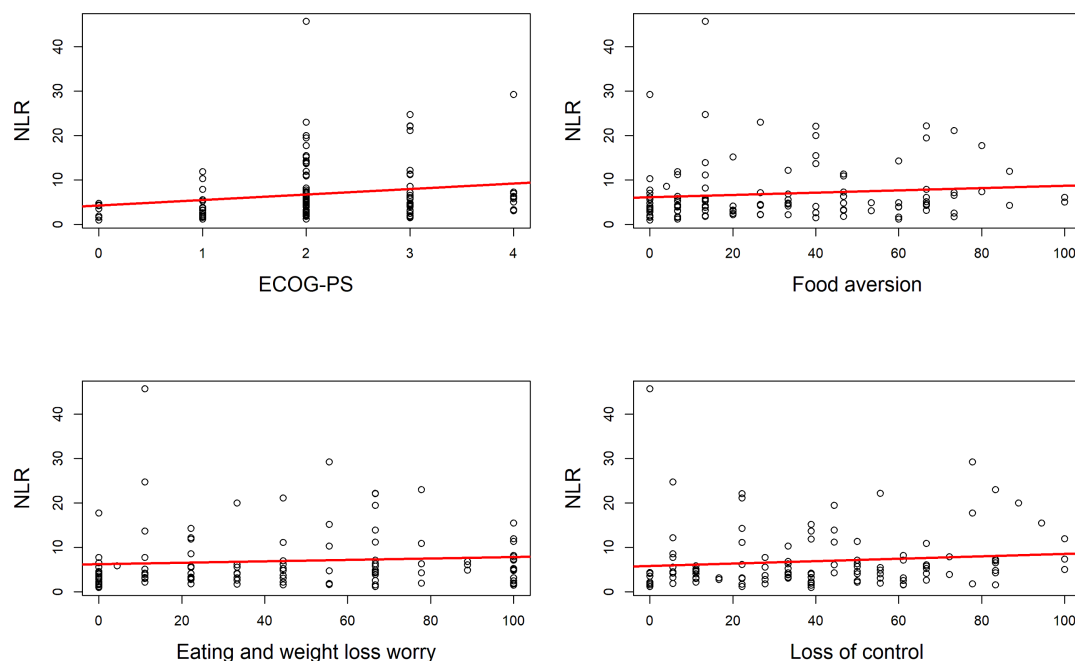


FIGURE 2 | Correlation between NLR, ECOG-PS status, food aversion, eating and weight loss worry and loss of control. Spearman correlation coefficient was performed to test the association between variables. Neutrophil-to-lymphocyte ratio was compared with (A) ECOG-PS status, (B) food aversion, (C) eating and weight loss worry and (D) loss of control. *p* values lower than 0.05 were considered for statistically significant.

indicator in oncology [22]. Braun et al. [8] showed that EORTC-QLQ30 global QoL and physical function at admission are significant predictors of lung cancer survival. Brown et al. [23] found that EORTC global QoL, role functioning, fatigue, appetite loss, and constipation were prognostic survival predictors in patients with NSCLC 12 weeks after starting the treatment. Here, we demonstrated that food aversion, present in EORTC-QLQ-CAX24, is an independent mortality predictor in metastatic lung cancer patients.

Cachectic patients present muscle depletion and systemic inflammation, whereas several papers use a CT scan to measure skeletal muscle and adipose tissue [10, 24]. Contrary to some studies [10, 25–28], we report that skeletal muscle index, psoas area, and adipose tissue are not associated with survival. In contrast, our results showed that IMAT is an independent predictor of mortality when normalized by the SMI (IMAT/SMI). Grönberg et al. [29] and Aubrey et al. [30] indicated that skeletal muscle quality is more clinically significant than quantification, which explains why IMAT/SMI is an independent predictor of mortality and psoas area and SMI is not. Therefore, correcting the infiltrated adipose tissue by the skeletal muscle index is a reasonable way to understand the increase in skeletal muscle adipose tissue infiltration concomitant with decreased skeletal muscle mass.

No data in the literature use this normalization to evaluate prognosis; however, some studies suggest that IMAT regulates insulin sensitivity and glucose tolerance and is associated with muscle performance measured with hand grip and knee extension [31–33]. Recently, Shen et al. [34] showed that IMAT is a predictor of in-hospital death in older inpatients. In frail individuals, there is an association between muscular expression of IL6 and IMAT; the authors also demonstrated a relationship between inflammation and muscle performance [35].

The NLR is an inflammatory marker and a prognostic predictor in cancer patients [36]. Rapoport et al. [37] showed that patients with recurrent mNSCLC have poor outcomes after nivolumab treatment when presented with $\text{NLR} \geq 5$. Furthermore, the efficacy of immune checkpoint inhibitors decreases in lung cancer patients with brain metastasis and $\text{NLR} \geq 5$ [38]. The advantage of the NLR is its ease of calculation through a blood count [39]. In this study, we reported that a diminished NLR is associated with poor prognosis in patients with mNSCLC.

There is evidence to link inflammation with food intake [40, 41]. Chronic or sustained inflammation may compromise nutrition status and immune function [42]. A previous study that analysed advanced cancer, including gastrointestinal and lung cancer, suggested that the systemic inflammatory response was independently associated with symptoms such as fatigue, appetite loss, physical functioning, and the QoL score [43]. Considering food aversion as a symptom of lack of appetite, affected by inflammation, and both present in cancer cachexia syndrome, our results elucidate the EORTC-QLQ-CAX24 questionnaire as a QoL marker in cachectic patients.

Our study has limitations. First, we did not include the treatment in our study, and the treatment choice can directly interfere with the patient's prognosis. Second, although more than 80% of our cohort presented weight loss $> 5\%$ at the time of inclusion, we did not include cancer cachexia in the statistical analysis. Cachectic patients could have higher food aversion and inflammation, mainly if it is refractory cachexia. Third, although solid evidence indicates a link between inflammation and NLR, it is not a direct measurement of inflammation. Finally, this study is a cohort study with metastatic lung cancer patients at a single institution. Future cohorts with larger sample sizes and other

cancer populations would benefit from extending beyond the analysis and confirming food aversion and IMAT/SMI as independent mortality predictors.

In conclusion, our data collaborate with the literature showing NLR as a mortality predictor. In addition, we provide clinical evidence that EORTC-QLQ-CAX24 and intramuscular adipose tissue normalized by skeletal muscle index can predict prognosis in metastatic lung cancer patients. Thus, these clinical tools can be helpful in a better choice of palliative care for this population. However, further studies are needed to understand the prognostic role of the EORTC-QLQ-CAX24 questionnaire and IMAT/SMI in cachectic patients and other cancer populations.

Author Contributions

G.C.J., A.P.S.B. and W.N. designed the study. W.N. and A.P.S.B. carried out the data collection. V.J.C. and A.F. performed the statistical analysis. All authors interpreted the results. W.N. wrote the manuscript. All authors approved the final manuscript.

Ethics Statement

The study complies with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia, and Muscle [44]. The authors declared that the appropriate ethics committee approved the study and that it had been performed according to the ethical standards in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent prior to their inclusion in the study.

Conflicts of Interest

G.C.J. is a consultant or advisor for Boehringer Ingelheim, Pfizer, Bayer, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Yuhan, Merck Serono, Janssen, Libbs, Sanofi and Novartis. G.C.J. is a speakers' bureau for AstraZeneca, Bayer, Novartis, Roche, Merck Serono, Bristol-Myers Squibb, Merck Sharp & Dohme, Boehringer Ingelheim, Pfizer, Janssen and Amgen. G.C.J. received travel payments, accommodations and expenses from Merck Sharp & Dohme, Novartis, Pfizer, Roche, AstraZeneca, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb and Merck Serono. The other authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.