JCSM Communications

WILEY

Original Article OPEN ACCESS

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

Willian das Neves[1,2,3] | Ana Paula de Souza Borges[1] | Vinicius Jardim Carvalho[2] | André Fujita[4] | Gilberto de Castro Jr[1]

[1]Hospital das Clínicas HC FMUSP, Faculdade de Medicina da Universidade de Sao Paulo, Instituto Do Cancer do Estado de São Paulo (ICESP), Sao Paulo, Brazil | [2]Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA | [3]Neuroscience Program, Harvard Medical School, Boston, Massachusetts, USA | [4]Department of Computer Science, Institute of Mathematics and Statistics, University of Sao Paulo, Sao Paulo, Brazil

Correspondence: Willian das Neves (willian.dasneves@alumni.usp.br) | Gilberto de Castro Jr (gilberto.castro@usp.br)

Received: 30 January 2024 | **Revised:** 20 August 2024 | **Accepted:** 30 August 2024

Funding: The São Paulo Research Foundation (FAPESP) supported this work (Grant 2015/22814-5, 2016/20187-6, and 2019/17009-7).

Keywords: cachexia | lung cancer | myosteatosis | prognostic | quality of life | sarcopenia

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-naive 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

Willian das Neves and Ana Paula de Souza Borges share the first authorship. Presented in a mini-oral session in the European Society for Medical Oncology (ESMO) Virtual Congress in 2020.

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 (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/m^2), 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	*n*	%
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
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).

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.

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

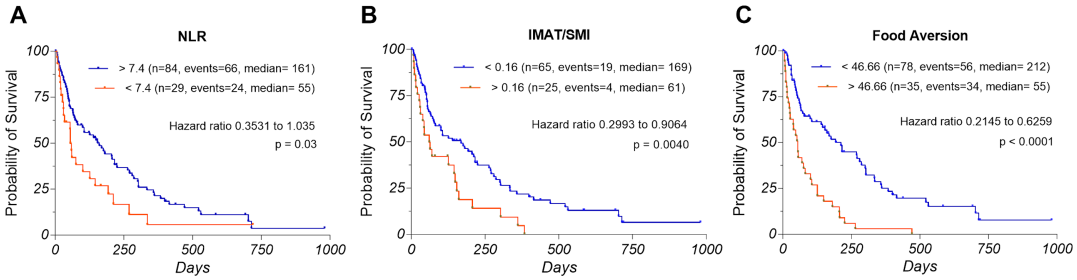

FIGURE 1 | Survival analysis using the third quartile as a cut-off of NLR, IMAT/SMI and food aversion. Each measurement was divided into quartile and probability of survival was compared using the third quartile as a cut-off. (A) Neutrophil-to-lymphocyte ratio < 7.4 ($n = 84$) and > 7.4 ($n = 29$). (B) 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.

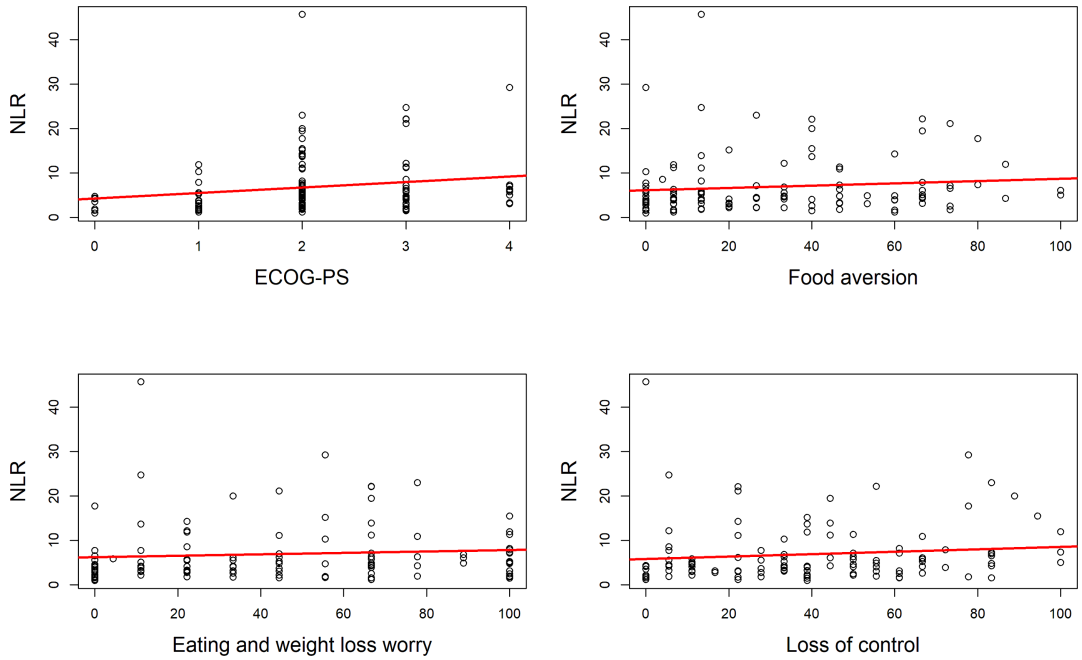

FIGURE 2 | Correlation between NLR, ECOG-PS status, food aversion, eating and weight loss worry and loss of control. Spearman correlation coefficient was performed to test the association between variables. Neutrophil-to -lymphocyte ratio was compared with (A) ECOG-PS status, (B) food aversion, (C) eating 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). Grønberg 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 NLR ≥ 5. Furthermore, the efficacy of immune checkpoint inhibitors decreases in lung cancer patients with brain metastasis and NLR ≥ 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. Cachexic 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.

References

1. H. Sung, J. Ferlay, R. L. Siegel, et al., "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," *CA: A Cancer Journal for Clinicians* 71, no. 3 (2021): 209–249, https://doi.org/10.3322/caac.21660.

2. W. D. Travis, E. Brambilla, A. G. Nicholson, et al., "The 2015 World Health Organization Classification of Lung Tumors," *Journal of Thoracic Oncology* 10, no. 9 (2015): 1243–1260, https://doi.org/10.1097/JTO.0000000000000630.

3. C. M. Jones, A. Brunelli, M. E. Callister, and K. N. Franks, "Multimodality Treatment of Advanced Non-Small Cell Lung Cancer: Where are We With the Evidence?," *Current Surgery Reports* 6, no. 2 (2018): 5, https://doi.org/10.1007/s40137-018-0202-0.

4. J. S. Temel, J. A. Greer, A. Muzikansky, et al., "Early Palliative Care for Patients With Metastatic Non–Small-Cell Lung Cancer," *New England Journal of Medicine* 363, no. 8 (2010): 733–742, https://doi.org/10.1056/NEJMoa1000678.

5. J. S. Temel, W. F. Pirl, and T. J. Lynch, "Comprehensive Symptom Management in Patients With Advanced-Stage Non–Small-Cell Lung Cancer," *Clinical Lung Cancer* 7, no. 4 (2006): 241–249, https://doi.org/10.3816/CLC.2006.n.001.

6. D. Chandrasekar, E. Tribett, and K. Ramchandran, "Integrated Palliative Care and Oncologic Care in Non-Small-Cell Lung Cancer," *Current Treatment Options in Oncology* 17, no. 5 (2016): 23, https://doi.org/10.1007/s11864-016-0397-1.

7. M. J. Trejo, M. L. Bell, H. M. Dhillon, and J. L. Vardy, "Baseline Quality of Life is Associated With Survival Among People With Advanced Lung Cancer," *Journal of Psychosocial Oncology* 38, no. 5 (2020): 635–641, https://doi.org/10.1080/07347332.2020.1765065.

8. D. P. Braun, D. Gupta, and E. D. Staren, "Quality of Life Assessment as a Predictor of Survival in Non-Small Cell Lung Cancer," *BMC Cancer* 11, no. 1 (2011): 353, https://doi.org/10.1186/1471-2407-11-353.

9. J. Franceschini, J. R. Jardim, A. L. G. Fernandes, S. Jamnik, and I. L. Santoro, "Reprodutibilidade da versão em português do Brasil do European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire em conjunto com seu módulo específico para câncer de pulmão," *Jornal Brasileiro de Pneumologia* 36, no. 5 (2010): 595–602, https://doi.org/10.1590/S1806-37132010000500011.

10. J. H. R. J. Degens, K. J. C. Sanders, E. E. C. de Jong, et al., "The Prognostic Value of Early Onset, CT Derived Loss of Muscle and Adipose Tissue During Chemotherapy in Metastatic Non-Small Cell Lung Cancer," *Lung Cancer* 133 (2019): 130–135, https://doi.org/10.1016/j.lungcan.2019.05.021.

11. M. Kimura, T. Naito, H. Kenmotsu, et al., "Prognostic Impact of Cancer Cachexia in Patients With Advanced Non-Small Cell Lung Cancer," *Supportive Care in Cancer* 23, no. 6 (2015): 1699–1708, https://doi.org/10.1007/s00520-014-2534-3.

12. J. U. Lim, C. D. Yeo, H. S. Kang, et al., "Elevated Pretreatment Platelet-To-Lymphocyte Ratio is Associated With Poor Survival in Stage IV Non-Small Cell Lung Cancer With Malignant Pleural Effusion," *Scientific Reports* 9, no. 1 (2019): 4721, https://doi.org/10.1038/s41598-019-41289-9.

13. K. Fearon, F. Strasser, S. D. Anker, et al., "Definition and Classification of Cancer Cachexia: An International Consensus," *Lancet Oncology* 12, no. 5 (2011): 489–495, https://doi.org/10.1016/S1470-2045(10)70218-7.

14. S.-I. Go, M. J. Park, H. N. Song, et al., "Sarcopenia and Inflammation are Independent Predictors of Survival in Male Patients Newly Diagnosed With Small Cell Lung Cancer," *Supportive Care in Cancer* 24, no. 5 (2016): 2075–2084, https://doi.org/10.1007/s00520-015-2997-x.

15. G. D. Mangano, M. Fouani, D. D'Amico, V. Di Felice, and R. Barone, "Cancer-Related Cachexia: The Vicious Circle between Inflammatory Cytokines, Skeletal Muscle, Lipid Metabolism and the Possible Role of Physical Training," *International Journal of Molecular Science* 23, no. 6 (2022): 3004, https://doi.org/10.3390/ijms23063004.

16. Y. Yin, J. Wang, X. Wang, et al., "Prognostic Value of the Neutrophil to Lymphocyte Ratio in Lung Cancer: A Meta-Analysis," *Clinics* 70, no. 7 (2015): 524–530, https://doi.org/10.6061/clinics/2015(07)10.

17. R. Vettor, G. Milan, C. Franzin, et al., "The Origin of Intermuscular Adipose Tissue and its Pathophysiological Implications," *American Journal of Physiology Endocrinology and Metabolism* 297, no. 5 (2009): E987–E998, https://doi.org/10.1152/ajpendo.00229.2009.

18. N. Horii, Y. Sawda, T. Kumamoto, et al., "Impact of Intramuscular Adipose Tissue Content on Short- and Long-Term Outcomes of Hepatectomy for Colorectal Liver Metastasis: A Retrospective Analysis," *World Journal of Surgical Oncology* 18, no. 1 (2020): 68, https://doi.org/10.1186/s12957-020-01836-5.

19. S. J. Wheelwright, J. B. Hopkinson, A. S. Darlington, et al., "Development of the EORTC QLQ-CAX24, a Questionnaire for Cancer Patients With Cachexia," *Journal of Pain and Symptom Management* 53, no. 2 (2017): 232–242, https://doi.org/10.1016/j.jpainsymman.2016.09.010.

20. N. W. Scott, P. M. Fayers, N. K. Aaronson, et al., "EORTC QLQ-C30 Reference Values This Manual Presents Reference Data for the QLQ-C30 Based Upon Data Provided by EORTC Quality of Life Group Members and Other Users of the QLQ-C30 Sprangers on Behalf of the EORTC Quality of Life Group EORTC Quality of Life Group," (2008).

21. W. Shen, M. Punyanitya, Z. M. Wang, et al., "Total Body Skeletal Muscle and Adipose Tissue Volumes: Estimation From a Single Abdominal Cross-Sectional Image," *Journal of Applied Physiology* 97, no. 6 (2004): 2333–2338, https://doi.org/10.1152/japplphysiol.00744.2004.

22. C. Quinten, C. Coens, M. Mauer, et al., "Baseline Quality of Life as a Prognostic Indicator of Survival: A Meta-Analysis of Individual Patient Data From EORTC Clinical Trials," *Lancet Oncology* 10, no. 9 (2009): 865–871, https://doi.org/10.1016/S1470-2045(09)70200-1.

23. J. Brown, H. Thorpe, V. Napp, et al., "Assessment of Quality of Life in the Supportive Care Setting of the Big Lung Trial in Non–Small-Cell Lung Cancer," *Journal of Clinical Oncology* 23, no. 30 (2005): 7417–7427, https://doi.org/10.1200/JCO.2005.09.158.

24. A. Tolonen, T. Pakarinen, A. Sassi, et al., "Methodology, Clinical Applications, and Future Directions of Body Composition Analysis Using Computed Tomography (CT) Images: A Review," *European Journal of Radiology* 145 (2021): 109943, https://doi.org/10.1016/j.ejrad.2021.109943.

25. N. Fujiwara, H. Nakagawa, Y. Kudo, et al., "Sarcopenia, Intramuscular fat Deposition, and Visceral Adiposity Independently Predict the Outcomes of Hepatocellular Carcinoma," *Journal of Hepatology* 63, no. 1 (2015): 131–140, https://doi.org/10.1016/j.jhep.2015.02.031.

26. S. M. R. Kazemi-Bajestani, V. C. Mazurak, and V. Baracos, "Computed Tomography-Defined Muscle and Fat Wasting are Associated With Cancer Clinical Outcomes," *Seminars in Cell & Developmental Biology* 54 (2016): 2–10, https://doi.org/10.1016/j.semcdb.2015.09.001.

27. Y. Yamada, Y. Shimada, Y. Makino, et al., "Clinical Utility of Psoas Muscle Volume in Assessment of Sarcopenia in Patients With Early-Stage Non-Small Cell Lung Cancer," *Journal of Cancer Research and Clinical Oncology* 149 (2022): 3277–3285, https://doi.org/10.1007/s00432-022-04234-4.

28. K. Katsui, T. Ogata, S. Sugiyama, et al., "Sarcopenia is Associated With Poor Prognosis After Chemoradiotherapy in Patients With Stage III Non-Small-Cell Lung Cancer: A Retrospective Analysis," *Scientific Reports* 11, no. 1 (2021): 11882, https://doi.org/10.1038/s41598-021-91449-z.

29. B. H. Grønberg, C. D. Valan, T. Halvorsen, B. Sjøblom, and M. S. Jordhøy, "Associations Between Severe Co-morbidity and Muscle Measures in Advanced Non-Small Cell Lung Cancer Patients," *Journal of Cachexia, Sarcopenia and Muscle* 10, no. 6 (2019): 1347–1355, https://doi.org/10.1002/jcsm.12469.

30. J. Aubrey, N. Esfandiari, V. E. Baracos, et al., "Measurement of Skeletal Muscle Radiation Attenuation and Basis of its Biological Variation," *Acta Physiologica* 210, no. 3 (2014): 489–497, https://doi.org/10.1111/apha.12224.

31. A. Shiny, Y. S. Bibin, C. S. Shanthirani, et al., "Association of Neutrophil-Lymphocyte Ratio With Glucose Intolerance: An Indicator of Systemic Inflammation in Patients With Type 2 Diabetes," *Diabetes Technology & Therapeutics* 16, no. 8 (2014): 524–530, https://doi.org/10.1089/dia.2013.0264.

32. S. Sachs, S. Zarini, D. E. Kahn, et al., "Intermuscular Adipose Tissue Directly Modulates Skeletal Muscle Insulin Sensitivity in Humans," *American Journal of Physiology Endocrinology and Metabolism* 316, no. 5 (2019): E866–E879, https://doi.org/10.1152/ajpendo.00243.2018.

33. M. Harris-Love, K. Benson, E. Leasure, B. Adams, and V. McIntosh, "The Influence of Upper and Lower Extremity Strength on Performance-Based Sarcopenia Assessment Tests," *Journal of Functional Morphology and Kinesiology* 3, no. 4 (2018): 53, https://doi.org/10.3390/jfmk3040053.

34. Y. Shen, L. Luo, H. Fu, et al., "Chest Computed Tomography-Derived Muscle Mass and Quality Indicators, In-Hospital Outcomes, and Costs in Older Inpatients," *Journal of Cachexia, Sarcopenia and Muscle* 13, no. 2 (2022): 966–975, https://doi.org/10.1002/jcsm.12948.

35. O. Addison, M. J. Drummond, P. C. Lastayo, et al., "Intramuscular fat and Inflammation Differ in Older Adults: The Impact of Frailty and Inactivity," *Journal of Nutrition, Health & Aging* 18, no. 5 (2014): 532–538, https://doi.org/10.1007/s12603-014-0019-1.

36. Y. Yu, L. Qian, and J. Cui, "Value of Neutrophil-To-Lymphocyte Ratio for Predicting Lung Cancer Prognosis: A Meta-Analysis of 7,219 Patients," *Molecular and Clinical Oncology* 7, no. 3 (2017): 498–506, https://doi.org/10.3892/mco.2017.1342.

37. B. L. Rapoport, A. J. Theron, D. A. Vorobiof, et al., "Prognostic Significance of the Neutrophil/Lymphocyte Ratio in Patients Undergoing Treatment With Nivolumab for Recurrent Non-Small-Cell Lung Cancer," *Lung Cancer Management* 9, no. 3 (2020): LMT37, https://doi.org/10.2217/lmt-2020-0014.

38. A. Lauko, B. Thapa, M. Sharma, et al., "Neutrophil to Lymphocyte Ratio Influences Impact of Steroids on Efficacy of Immune Checkpoint Inhibitors in Lung Cancer Brain Metastases," *Scientific Reports* 11, no. 1 (2021): 7490, https://doi.org/10.1038/s41598-021-85328-w.

39. B. A. Derman, J. N. Macklis, M. S. Azeem, et al., "Relationships Between Longitudinal Neutrophil to Lymphocyte Ratios, Body Weight Changes, and Overall Survival in Patients With Non-Small Cell Lung Cancer," *BMC Cancer* 17, no. 1 (2017): 141, https://doi.org/10.1186/s12885-017-3122-y.

40. L. Gautron, "Neurobiology of Inflammation-Associated Anorexia," *Frontiers in Neuroscience* 4 (2009): 59, https://doi.org/10.3389/neuro.23.003.2009.

41. F. Bergeron, M. Bouin, L. D'Aoust, M. Lemoyne, and N. Presse, "Food Avoidance in Patients With Inflammatory Bowel Disease: What, When and Who?," *Clinical Nutrition* 37, no. 3 (2018): 884–889, https://doi.org/10.1016/j.clnu.2017.03.010.

42. K. Gonda, M. Shibata, Y. Sato, et al., "Elevated Neutrophil-To-Lymphocyte Ratio is Associated With Nutritional Impairment, Immune Suppression, Resistance to S-1 Plus Cisplatin, and Poor Prognosis in Patients With Stage? IV Gastric Cancer," *Molecular and Clinical Oncology* 7 (2017): 1073–1078, https://doi.org/10.3892/mco.2017.1438.

43. L. E. Daly, R. D. Dolan, D. G. Power, et al., "Determinants of Quality of Life in Patients With Incurable Cancer," *Cancer* 126, no. 12 (2020): 2872–2882, https://doi.org/10.1002/cncr.32824.

44. S. von Haehling, A. J. S. Coats, and S. D. Anker, "Ethical Guidelines for Publishing in the *Journal of Cachexia, Sarcopenia and Muscle*: Update 2021," *Journal of Cachexia, Sarcopenia and Muscle* 12, no. 6 (2021): 2259–2261, https://doi.org/10.1002/jcsm.12899.

Supporting Information

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