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The prevalence of sarcopenia amongst non-small cell lung cancer patients, assessed using computed tomography, prior to treatment in a South African setting

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Background: Identification of sarcopenia in lung cancer is important to improve quality of life and treatment planning; however, clinical detection is challenging. Computed tomography (CT) may improve detection and assist with dose adjustment and prognostication.

Aim: To use CT to assess the prevalence of sarcopenia amongst non-small cell lung cancer (NSCLC) patients prior to treatment.

Setting: Non-small cell lung cancer patients ($n = 66$) attending Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) medical oncology clinic between 01 July 2017 and 01 July 2020 with staging CTs or CT chests including L3 level done at CMJAH prior to treatment.

Methods: The L3 skeletal muscle index (SMI L3) was assessed based on the cross-sectional muscle area at L3 vertebral level on CT. The prevalence of sarcopenia was determined based on gender-specific cut-offs defined by the International Consensus on Cancer Cachexia.

Results: The overall prevalence of sarcopenia was 69.7% ($n = 46$). There was a statistically significant difference in sarcopenia prevalence according to gender (males 82.2% [$n = 37$] compared to females 42.9% [$n = 9$] [$p = 0.00$]) and body mass index (BMI) (< 18.5 kg/m^2 [91.7%, $n = 11$], 18.5 kg/m^2 – 24.9 kg/m^2 [81.3%, $n = 26$], 25 kg/m^2 – 29.9 kg/m^2 [64.3%, $n = 9$], ≥ 30 kg/m^2 [0.0%, $n = 0$] [$p = 0.00$]), only noted between the ≥ 30 kg/m^2 BMI group and remainder of BMI groups on pairwise comparison. The median SMI L3 in men was 43.1 cm^2/m^2 (interquartile range [IQR]: 13.6 cm^2/m^2) whilst the median SMI L3 in women was 40.3 cm^2/m^2 (IQR: 11.5 cm^2/m^2). No statistically significant difference in sarcopenia prevalence was demonstrated according to age group, ethnicity, stage and histology.

Conclusion: There was a high overall prevalence of sarcopenia, as determined by CT, amongst NSCLC patients in a South African setting. The differences based on gender and BMI indicate potential avenues for future research.

Keywords: sarcopenia; non-small cell lung cancer; skeletal muscle index; cancer cachexia; CT assessment of sarcopenia.

Introduction

> Cancer cachexia is defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[1,2,3,4]

Specific criteria for the diagnosis of cancer cachexia include 'loss of more than 5% of body weight over a 6-month period, or a body mass index (BMI) less than 20 kg/m^2 and 2% ongoing weight loss, or sarcopenia and 2% ongoing weight loss'.[1,4,5] One of the major drawbacks of these criteria is the reliance on weight, as a patient may be cachectic without weight loss in cases where the patient has excessive adipose tissue (as in sarcopenic obesity).[1,4,6,7,8,9] It is thus suggested that a direct measure of muscularity (assessing for sarcopenia, rather than weight or BMI) should be used.[4,7,9]

The modality of choice for the assessment of sarcopenia in the oncology population is computed tomography (CT), considering the multiple routine CT scans that these patients undergo.[2,4,5,7,8,9,10,11,12] There is a strong correlation between the muscle area at the third lumbar

vertebral (L3) level and whole-body muscle mass, and it is thus considered the gold standard level for assessment on CT.[2,7,8,9,11,12,13,14] The skeletal muscle index is defined as the cross-sectional skeletal muscle area divided by the patients' height in metres squared (cm^2/m^2).[7,8] Although the most widely used cut-off values for sarcopenia at L3 level are 38.5 cm^2/m^2 for women and 52.4 cm^2/m^2 for men, thresholds of 39 cm^2/m^2 for women and 55 cm^2/m^2 for men have been used by the International Consensus on Cancer Cachexia.[1,4,10,11,15]

Cachexia and sarcopenia have been shown to be prognostic factors in multiple conditions, with their impact being accentuated in malignant diseases.[4,5,6,12,16] According to Von Haeling et al., 'mortality rates of patients with cachexia range from 10% to 15% per year (COPD), to 20–30% per year (CHF, CKD) and to 80% in cancer.'[4,5,16] Cancer cachexia has an approximate prevalence of 50% and accounts for approximately 20% of cancer related deaths.[1,3,4,17]

It has been shown in multiple studies that sarcopenia is not only linked to decreased overall survival in cancer, but also results in increased drug toxicity, decreased response to chemotherapy and can itself be induced by chemotherapy.[1,3,8,9,10,18,19]

The prevalence of sarcopenia amongst all non-small cell lung cancer (NSCLC) patients was shown to be as high as 47% in a systematic review in 2014 and 43% in a systematic review in 2019.[20,21]

Sarcopenia has been demonstrated to be a prognostic marker for survival in NSCLC patients.[22] Meta-analysis of 15 studies including a total of over 2500 patients found that those who were sarcopenic were two to three times more likely to die of their lung cancer than those who did not have sarcopenia.[22] This measurement performed well as a prognostic marker independently of the stage of tumour presentation; however, it is to be noted that early-stage disease is less likely to be associated with sarcopenia.[22]

Sarcopenia may also serve as a marker for the tolerance of surgery, and unsurprisingly predicts poor physiological reserve.[23,24] Several studies on patients with early-stage NSCLC have shown that sarcopenia was related to poor post-resection outcomes.[23,24] Although sarcopenia and cachexia are typically associated with more advanced cancer stages, this data highlights the value of assessing for sarcopenia in all stages of disease, particularly where curative treatment is being pursued. This marker may help in guiding clinicians where decision-making is problematic, as is often the case in patients with borderline operability. More conservative therapeutic strategies are justifiable under such circumstances.[23]

Aim

The primary aim of this study was to use CT to determine the overall prevalence of sarcopenia amongst NSCLC patients prior to treatment. Secondary aims were to assess the prevalence of sarcopenia with respect to age, gender, ethnicity, BMI, Eastern Cooperative Oncology Group (ECOG) performance status, histological subtype and stage of lung cancer (American Joint Committee on Cancer (AJCC) TNM [tumor-node-metastasis] 8th edition).

Methods

Research paradigm

The study design was a retrospective quantitative cross-sectional study.

Sample

The study population was all NSCLC patients who attended the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) medical oncology clinic between 01 July 2017 and 01 July 2020 who had staging CTs or CT chests performed at the same institution's radiology department which included L3 vertebral level. This sample comprised 154 patients.

Inclusion criteria

- Adults over the age of 18
- All patients who had staging CTs and CT chests which included L3 vertebral level done at CMJAH radiology department prior to treatment
- Non-small cell histological subtypes including squamous cell carcinoma and adenocarcinoma

Exclusion criteria

- The following histological subtypes were excluded: Small cell carcinoma, mesothelioma, neuroendocrine tumour of low or intermediate grade (including large cell carcinoma), pulmonary sarcoma and small blue round cell tumour
- Pulmonary metastases from extra-pulmonary cancers
- Patients who only had CT scans on treatment
- Patients with incomplete data, or illegible documentation were excluded.

Materials and methods

Image analysis and calculation of skeletal muscle index at L3 level (SMI L3)

Philips Ingenuity and Philips Brilliance 64 CT scanners were used for the muscle measurements. The scans were done with standard chest and abdomen protocols (120kV, 30mAs) with reconstructions in abdomen window (slice thickness of 3.03 mm and less). Images were timed as arterial phase chest (in the case of only CT chest including L3 level) and portovenous phase (in the case where full CT abdomens were performed). These were reconstructed using Philips Intellispace software into axial slabs at L3 vertebral level. Measurements were taken at L3 vertebral level (specific measurement technique described below) using the built-in Region of Interest Spline Contour function and entered into an Excel data sheet for each patient (see Figure 1).

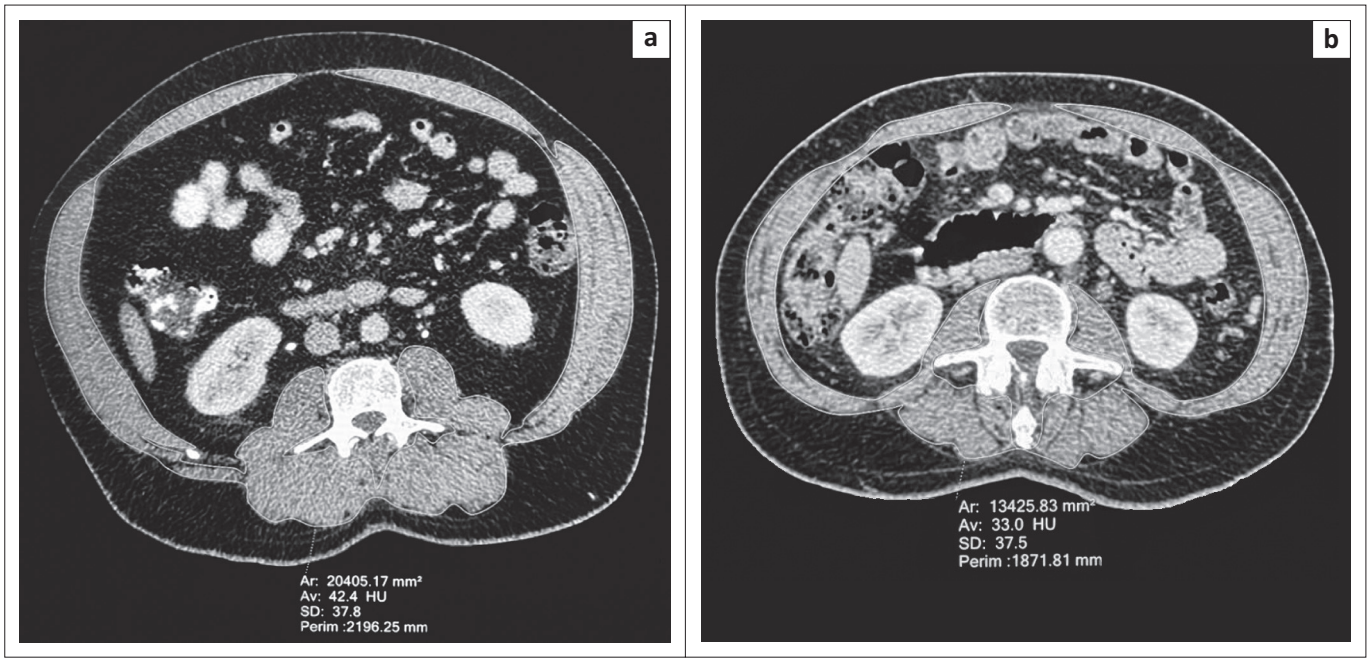


FIGURE 1: Two CTs (axial slices at L3 level) demonstrating the measurement of cross-sectional muscle area at L3 level (CSMA L3) (a) 54-year-old male with a BMI of 32.6 kg/m² with no sarcopenia: CSMA L3 204.1 cm², L3 skeletal muscle index (SMI L3) 73.2 cm²/m² and (b) 63-year-old male with a BMI of 26.0 kg/m² with sarcopenia: CSMA L3 134.3 cm², SMI L3 45.4 cm²/m².

The cross-sectional muscle area at L3 vertebral level (measured in cm²) was measured using a manual segmentation technique: manual outlining of the contours of psoas, erector spinae, quadratus lumborum, internal oblique, external oblique, transversus abdominus and rectus abdominus muscles at L3 level (these were measured on axial slices at the most cranial level where both L3 transverse processes are still visible) (see Figure 1).

In order to improve the reliability of the study, each measurement was performed twice by the principal investigator and the average of the two measurements was the final recorded value. During the CT measurement of the cross-sectional muscle area, the principal investigator was blinded to the radiology report and the collected clinical data, which was collected in a separate data collection tool, in order to prevent bias.

The cross-sectional muscle area at L3 level in cm² as measured on CT was divided by the patients' height in metres squared to calculate the skeletal muscle index at L3 level (SMI L3) in cm²/m². Sarcopenia was defined, according to the International Consensus of Cancer Cachexia, as SMI L3 less than 55 cm²/m² for men and less than 39 cm²/m² for women.[1]

Patient demographics and clinical information

The patients' outpatient records were used in order to obtain patient demographics and clinical information including age, gender, ethnicity, time between CT scan and onset of treatment, weight, height, ECOG performance status, histological subtype and stage (AJCC TNM 8th edition) (see supplementary material for details of data collection).

Data analysis and statistics

The data was analysed using Statistical Package for Social Sciences (SPSS) (IBM SPSS Statistics version 22). Descriptive statistics were presented as frequencies and percentages for categorical variables and in means, standard deviations, medians and ranges for continuous variables. The Pearson chi-squared test was used for comparisons of the prevalence of sarcopenia by age group, ethnicity, BMI and ECOG performance status. The Fishers exact test was used for comparisons of the prevalence of sarcopenia by gender, histological subtype and disease stage. Statistical significance testing was set at the 95% confidence level, with a *p*-value of less than 0.05 indicating statistical significance.

Ethical considerations

Human Research Ethics Committee of the University of the Witwatersrand approved the study (ethical clearance number: M201110).

Results

Demographics

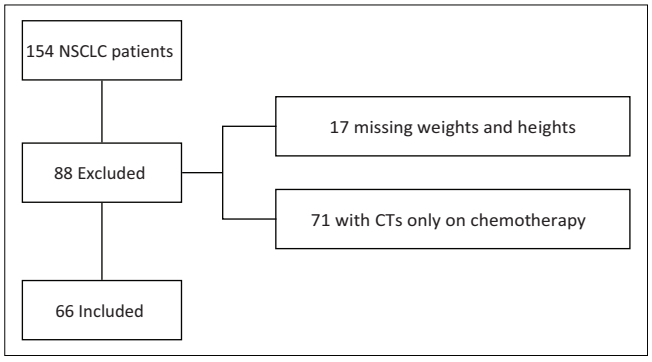
The information that follows is summarised in table format (see Table 1).

A total number of 154 NSCLC patients attended the CMJAH medical oncology clinic between 01 July 2017 and 01 July 2020. Of these patients, 88 were excluded (17 were missing weights and heights and 71 only had CT scans on chemotherapy) (as per the exclusion criteria). Therefore, a total number of 66 patients who had CT scans prior to treatment were included (see Figure 2).

TABLE 1: Demographics.

Variables	*n*	%
Gender		
Male	45	68.2
Female	21	31.8
Age groups (years)		
20–39	3	4.5
40–59	27	40.9
60–79	36	54.5
Ethnicity		
Black people	50	75.8
White people	9	13.6
Mixed race people	4	6.1
Asian people	3	4.5
BMI groups (kg/m²)		
< 18.5	12	18.2
18.5–24.9	32	48.5
25–29.9	14	21.1
≥ 30	8	12.1
ECOG performance status		
0	6	9.1
1	34	51.5
2	11	16.7
3	14	21.2
4	1	1.5
Histological subtype		
Adenocarcinoma	40	60.6
Squamous cell carcinoma	26	39.4
Stage (AJCC TNM 8th edition)		
IA	1	1.5
IB	0	0.0
IIA	1	1.5
IIB	3	4.5
IIIA	4	6.1
IIIB	8	12.1
IIIC	4	6.1
IVA	33	50.0
IVB	12	18.2

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; AJCC TNM, American Joint Committee on Cancer tumor-node-metastasis.



CTs, computed tomography; NSCLC, non-small cell lung cancer.

FIGURE 2: Flow diagram demonstrating patient disposition.

Amongst the 51 patients who received chemotherapy, the median time between the CT scan and onset of chemotherapy was 63 days (interquartile range [IQR] 127.5 days). Of the remaining 15 patients, 13 did not receive chemotherapy and 2 were lost to follow up.

The study population consisted of 45 males (68.2%) and 21 females (31.8%).

The study population consisted of 50 (75.8%) black, 9 (13.6%) white, 4 (6.1%) mixed race and 3 (4.5%) Asian patients.

The mean age was 59.6 years (standard deviation [s.d.]: 9.7 years). The majority of the patients, 36 (54.5%) were in the 60–79-year age group.

The median BMI was 22.9 kg/m² (IQR: 7.2 kg/m²). The BMIs ranged from 14.3 kg/m² to 43.9 kg/m². Most of the patients, 32 (48.5%), were in the 18.5 to 24.9 BMI group.

The most common ECOG performance status was 1, consisting of 34 (51.5%) patients.

The most common histological subtype was adenocarcinoma, consisting of 40 (60.6%) of the study population.

Most of the study population had stage IVA and IVB disease, 33 (50.0%) and 12 (18.2%) respectively.

Sarcopenia prevalence

The information that follows is summarised in table format (see Table 2).

Overall

The overall prevalence of sarcopenia was 69.7% ($n = 46$).

Gender

The prevalence of sarcopenia amongst males was 82.2% ($n = 37$) and amongst females was 42.9% ($n = 9$) ($p = 0.00$). Amongst males the median SMI L3 was 43.1 cm²/m² (IQR: 13.6 cm²/m²) and amongst females the median SMI L3 was 40.3 cm²/m² (IQR: 11.5 cm²/m²) (see Table 3).

Age

The highest prevalence of sarcopenia according to age group was 100.0% ($n = 3$) in the 18–39-year age group and 72.2% ($n = 26$) in the 60–79-year age group. There was no statistically significant difference in the prevalence of sarcopenia according to age group ($p = 0.37$).

Ethnicity

The highest prevalence of sarcopenia was in the mixed-race and black ethnic groups, 75% ($n = 3$) and 72% ($n = 36$), respectively. There was no statistically significant difference in the prevalence of sarcopenia according to ethnic group ($p = 0.79$).

Body mass index

The prevalence of sarcopenia according to BMI group was 91.7% ($n = 11$) in the < 18.5 kg/m² BMI group, 81.3% ($n = 26$) in the 18.5 kg/m² – 24.9 kg/m² BMI group, 64.3% ($n = 9$) in the 25.0 kg/m² – 29.9 kg/m² BMI group and 0% ($n = 0$) in the > 30.0 kg/m² BMI group ($p = 0.00$). The statistically significant difference was only between the > 30.0 kg/m² BMI group and each of the other BMI groups on the

TABLE 2: Sarcopenia prevalence.

Variables	Sarcopenia		No sarcopenia		*p*-value
	n	%	*n*	%	
Overall	46	69.7	20	30.3	-
Gender					
Male	37	82.2	8	17.8	0.00*
Female	9	42.9	12	57.1	
Age (years)					
18–39	3	100.0	0	0.0	0.37**
40–59	17	63.0	10	37.0	
60–79	26	72.2	10	27.8	
Ethnicity					
Black people	36	72.0	14	28.0	0.79**
White people	5	55.6	4	44.4	
Mixed race people	3	75.0	1	25.0	
Asian people	2	66.7	1	33.3	
BMI (kg/m²)					
< 18.5	11	91.7	1	8.3	0.00**
18.5–24.9	26	81.3	6	18.8	
25–29.9	9	64.3	5	35.7	
≥ 30	0	0.0	8	100.0	
ECOG performance status					
0	4	66.7	2	33.3	0.83**
1	23	67.6	11	32.4	
2	9	81.8	2	18.2	
3	9	64.3	5	35.7	
4	1	100.0	0	0.0	
Histological subtype					
Adenocarcinoma	28	70.0	12	30.0	1.00*
Squamous cell carcinoma	18	69.2	8	30.8	
Stage (AJCC TNM 8th edition)					
IA-IIIA	5	55.6	4	44.4	0.44*
IIIB-IVB	41	71.9	16	28.1	

*, Fishers exact test, **, Pearson chi-squared test.

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; AJCC TNM, American Joint Committee on Cancer tumor-node-metastasis.

TABLE 3: SMI L3 according to gender.

SMI L3 (cm²/m²)	Median	IQR	Range
Male	43.1	13.6	27.6–79.3
Female	40.3	11.5	29.8–57.2

pairwise comparisons ($p = 0.00$ in the comparison of the > 30.0 kg/m² BMI group to the < 18.5 kg/m² and 18.5 kg/m² – 24.9 kg/m² BMI groups and $p = 0.01$ in the comparison of the > 30.0 kg/m² BMI group to the 25.0 kg/m² – 29.9 kg/m² BMI group).

Eastern Cooperative Oncology Group performance status

The highest prevalence of sarcopenia according to ECOG performance status was 100.0% ($n = 1$) for ECOG performance status of 4. There was no statistically significant difference in the prevalence of sarcopenia according to ECOG performance status ($p = 0.83$).

Histological subtype

The prevalence of sarcopenia according to histological subtype was 70.0% ($n = 28$) amongst the adenocarcinoma group and 69.2% ($n = 18$) in the squamous cell carcinoma group ($p = 1.00$).

Stage

The prevalence of sarcopenia was 71.9% ($n = 41$) in the stage IIIB-IVB group and 55.6% ($n = 5$) in the stage IA-IIIA group ($p = 0.44$).

Discussion

This study demonstrated a high overall prevalence of sarcopenia 69.7% ($n = 46$) in a South African setting. To the knowledge of the author, these are the first available data collected on this topic in this population group.

This overall prevalence was higher than that reported by the meta-analysis and systematic review performed by Yang et al. in 2019 (43%).[21] Throughout the literature there were, however, multiple other studies which reported an overall sarcopenia prevalence greater than 50%.[14,21,25,26,27,28]

The reasons for these differences are unclear and may be influenced by several other external confounding variables specific to this population group such as co-morbidities, lack of representation of sample population with a possible lower normal range of SMI L3 and malnutrition. This is an area that presents substantial clinical ramifications in terms of chemotoxicity.

This study was similar to the other studies in the literature, as they all report the prevalence of sarcopenia prior to the commencement of chemotherapy.[14,25,26,27,28]

The criteria used to define sarcopenia differed in several analyses. In studies where similar overall prevalence was found to our own, including prevalence according to gender, the cut-offs used to define sarcopenia were based on those defined by the International Consensus on Cancer Cachexia.[1,14,25,28,29] These cut-offs are based on those determined by Prado et al. in their study on sarcopenic obesity amongst patients with respiratory and gastrointestinal tract solid tumours.[1,29] These specific cut-offs were used in this study as they were based on a population of advanced cancer patients (which included respiratory tract cancers) rather than a normal healthy population, were calculated using optimum stratification based on thresholds associated with mortality and were thus clinically relevant cut-offs and were used by the International Consensus on Cancer Cachexia to define sarcopenia.[1,29] Most of the current sarcopenia cut-off values are derived from a predominantly white, European or North American population. This produces some uncertainty in applying these criteria to other populations.[7]

Studies which also looked predominantly at late-stage disease such as those by Rossi et al., Stene et al. and Murphy et al. showed similar results to our own.[14,25,28]

There was a statistically significant difference in the sarcopenia prevalence according to gender (men 82.2% ($n = 37$)) compared to women (42.9% ($n = 9$)). This was further

supported by a median SMI L3 in males, 43.1 cm^2/m^2 (IQR: 13.6 cm^2/m^2), well below the sarcopenia cut-off value for males, 55.0 cm^2/m^2, compared to the median SMI L3 in females, 40.3 cm^2/m^2 (IQR: 11.5 cm^2/m^2), which was above the sarcopenia cut-off value for females, 39.0 cm^2/m^2.

The 18–39-year age group and stage IA-IIIA group demonstrated a high prevalence of sarcopenia, 100.0% (n = 3) and 55.6% (n = 5) respectively, with no statistically significant difference compared to the other groups in these categories. This is an interesting finding as it may signify a greater cachectic effect of NSCLC on these subgroups, which normally would be considered to have greater reserves considering their younger age and earlier stage of disease. These results should however be treated with reserve considering the small sample sizes in these subgroups.

Although a higher prevalence of sarcopenia was seen in the mixed race and black ethnic groups, 75% (n = 3) and 72% (n = 36) respectively, this was not a statistically significant difference and the sample size in the white, mixed race and Asian groups was small. Further research with larger sample sizes is required to further evaluate differences in sarcopenia prevalence according to ethnicity.

There was a statistically significant difference in the prevalence of sarcopenia between the obese BMI group, 0% (n = 0), and the remainder of the BMI groups. There was, however, no statistically significant difference in prevalence of sarcopenia between the underweight, normal and overweight BMI groups, with a high prevalence demonstrated in each of these groups, 91.7% (n = 11), 81.3% (n = 26) and 64.3% (n = 9), respectively. This study therefore demonstrates that BMI is not correlated with muscle mass, except in the case of very low BMI where most patients will be sarcopenic. This means that many patients with sarcopenia are not clinically assessable for this complication and demonstrates the value of CT in its detection.

The highest prevalence of sarcopenia was seen in the ECOG performance status of 4 group, 100% (n = 1). However, considering the absence of a statistically significant difference and small sample size in all ECOG performance status groups, except ECOG performance status of 1 group, this result should be treated with reserve. It may provide an avenue for future research as demonstrating a correlation between prechemotherapy sarcopenia and more advanced ECOG performance status may be a useful tool in assisting with decisions to de-escalate therapeutic intent, irrespective of the stage of the disease.

There was no difference in the prevalence of sarcopenia according to histological subtype, 70.0% (n = 28) amongst those with adenocarcinoma and 69.2% (n = 18) amongst those with squamous cell carcinoma.

Limitations of the study should be considered when interpreting this data and applying it to clinical scenarios. This was a retrospective study consisting of a small study population. There are no criteria available for defining cachexia which were developed specifically for a diverse ethnic population, made up predominantly of people of colour.[1] Therefore, it is not certain that the International Consensus on Cancer Cachexia criteria are necessarily accurate in detecting sarcopenia in the South African setting. Other studies have also demonstrated that different cut-offs should be applied according to BMI.[10] This approach was not adopted in this study.

Conclusion

This study demonstrated a high overall prevalence of sarcopenia amongst NSCLC patients in a South African setting. This information is useful in itself, but also shows how additional clinically useful information can be extracted from routine CT scans.

The majority of the patients in the study had a BMI $\geq$ 18.5 kg/m^2 with a high prevalence of sarcopenia in the normal and overweight BMI groups thus revealing the value of using CT to assess for sarcopenia in patients where muscle wasting may not be clinically evident.

Furthermore, sarcopenia was found to be more prevalent amongst men. The cause for this gender difference in alterations in body composition in response to NSCLC is not clear, and this may be an interesting avenue of investigation.

Supplementary material

Data collection

The patient register in the CMJAH medical oncology clinic was used to identify all lung cancer patients who attended the clinic between 01 July 2017 and 01 July 2020. Their details were recorded and used to retrieve the outpatient records from the folder archive. The patients' folder numbers and names were used to access their CT scans from the hospital Picture Archiving and Communications System (PACS).

In patients with multiple CT scans prior to chemotherapy, the earliest CT scan which included the L3 vertebral level was used.

Data from patient notes/folder included:

- Age (years): specific age as well as subdivided into age groups 18–39, 40–59, 60–79, 80–100 years
- Gender: male or female
- Ethnicity: black, white, mixed race, Asian
- Height (m) and weight (kg) recorded in the patients' notes at the time of diagnosis prior to the initiation of treatment
- Days between date of CT scan and date of onset of chemotherapy
- Eastern Cooperative Oncology Group performance status at time of CT: 0, 1, 2, 3, 4

- lung cancer stage (American Joint Committee on Cancer (AJCC) TNM 8th edition): IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, IVB
- non-small cell lung cancer histological subtype: adenocarcinoma or squamous cell carcinoma

Calculations

- Body mass index (kg/m^2): calculated using weight in kilograms over height in metres squared (kg/m^2), subdivided into four BMI groups as defined by the World Health Organisation (WHO): underweight (BMI < 18.5), normal weight (BMI = 18.5–24.9), overweight (BMI 25–29.9) and obese (BMI ≥ 30)
- Skeletal muscle index at L3 vertebral level (cm^2/m^2): cross-sectional muscle area at L3 vertebral level in centimetres squared divided by the height in metres squared. Sarcopenia was defined, according to the International Consensus of Cancer Cachexia, as L3 skeletal muscle index less than 55 cm^2/m^2 in men and less than 39 cm^2/m^2 for women.[1]

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

C.S. and D.B.-N supervised the project. L.D.M.-L. developed the study design and was involved in data collection and analysis. L.D.M.-L. took the lead in writing the manuscript, with C.S. and D.B.-N supervising and contributing to the final version submitted.

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Data availability

The findings of the study are supported by data which can be found within the article.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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