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# Feasibility of assessment of skeletal muscle mass on a single cross-sectional image at the level of the fourth thoracic vertebra

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ABSTRACT

*Background:* Skeletal muscle mass (SMM) determined on computed tomography (CT) is emerging as a novel imaging biomarker. Cross-sectional area (CSA) of SMM at the level of the third lumbar vertebra (L3) on abdominal imaging is considered the clinical reference standard for measuring SMM. In certain patient groups, such as those with oncological or non-oncological lung disease like COVID-19, a chest CT may be available while an abdominal CT is not. The purpose of this study was to investigate whether determining SMM on a chest CT is a feasible alternative to abdominal CT.

*Research question:* What is the correlation between SMM measurements at the level of L3 and the level of the fourth thoracic vertebra (Th4)?

*Study design and methods:* In this study we retrospectively analyzed abdominal and thoracic series of whole-body CT-scans of trauma patients (N = 47) and head and neck cancer patients (N = 194). All abdominal muscles were delineated on a single axial slice at the level of L3. The erector spinae, levator scapulae, rhomboideus minor and major and pectoralis minor and major muscles were delineated on a single axial slice at the level of Th4. CSA of the muscles at Th4 and the L3 level were compared using linear regression, and a multivariate linear regression model was established.

*Results:* Muscle CSA at level Th4 strongly correlates with L3 muscle CSA ($r = 0.791$, $p < 0.05$). A multivariate model incorporating the patient characteristics arm positioning, age, sex, and weight achieved a stronger correlation ($r = 0.856$, $p < 0.05$).

*Interpretation:* Skeletal muscle CSA measured at the level of Th4 is a feasible alternative to measurements at L3. This allows diagnosing low SMM using clinically available thoracic CT-scans. SMM measurements at the level of Th4 may become a prognostic or triage tool when faced with mechanical ventilator shortage.

## 1. Introduction

Sarcopenia and low skeletal muscle mass (SMM) are important factors in patient outcome. The European Workgroup on Sarcopenia in Older People (EWGSOP) defines sarcopenia as both low SMM and low muscle function[1]. However, many studies have shown that low SMM by itself is an adverse predictive and prognostic factor for certain outcomes in patients. In cancer patients, this includes higher toxicity in patients treated with chemotherapy, more complications in surgically treated patients and reduced survival[2–5]. Patients suffering from head and neck-cancer (HNC) are especially prone to developing low SMM, due to dysphagia caused either by the tumor and subsequent treatment or due to pre-existent risk conditions (namely poor diet, alcohol use and smoking) and low SMM is gaining ground as a predictive and prognostic biomarker in HNC-patients[6]. Additionally, low SMM has also been shown to negatively affect ventilator-free days, ICU-free days and mortality in mechanically ventilated ICU-patients[7–10].

The effect of low SMM on patient outcomes is most commonly

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assessed using computed tomography (CT) or magnetic resonance imaging (MRI). Total body SMM can be assessed using a single axial abdominal CT-image at the level of the third lumbar vertebra (L3)[11]. In studies on the effect of SMM in patients, this method is often used and is considered a clinical reference standard. The main advantage of this method is that it can be retrospectively performed on images used for routine diagnostics and requires no additional investigations. Because imaging at the level of L3 may not be available in some patient groups, measurements at other levels have also been validated to assess SMM [12,13].

Earlier studies have used SMM at the level of the fourth thoracic vertebra (Th4) as a measurement for patients where L3 imaging is not available and correlated these measurements to outcome factors in cancer patients and non-cancer patients[14–21]. To our knowledge, there is one study analyzing the correlation between skeletal muscle cross-sectional area (CSA) al level Th4 and L3 in a cohort of patients with non-small cell lung cancer[22]. This study described only the correlation between Th4 and L3 measurements and did not include additional clinical variables to establish a prediction model for a more accurate assessment.

In the present study, we correlated the muscle CSA at the level of Th4 with L3 and established a prediction rule to accurately assess muscle CSA at the level of L3 using a chest CT.

## 2. Materials and methods

### 2.1. Patients and data

Total body CT-scans performed between 2010 and 2018 in the University Medical Center Utrecht, Utrecht, The Netherlands were randomly selected from two groups of patients. The first group underwent whole body unenhanced or contrast-enhanced CT-imaging in a trauma setting and were presumed to be otherwise healthy controls. The second group were HNC patients who underwent a whole-body (un) enhanced PET-CT scan for radiotherapy planning and disease staging. We collected age, sex, weight, and BMI when available. For HNC patients AJCC TNM staging (7th Edition) was recorded as well. These patients have been described previously in a study to validate SMM measurements at the level of C3[12].

### 2.2. Ethical considerations

CT-scans and other recorded patient information were coded before analysis. In accordance with Dutch “Best Practice” guidelines no informed consent or ethical approval was necessary. This study was performed under our hospital’s institutional review board approval number 17–365.

### 2.3. Radiological assessment

For CT-image analysis at the level of Th4 two researchers (HvH and JES) used 3D Slicer, a free open-source software application[23]. The majority (80%) of scans had a slice thickness of 0.7–1.5 mm, with the remaining percentage having a varying thickness of 1.5–4.0 mm. Slice thickness has previously been shown to slightly influence skeletal muscle area, where an increment of 3 mm results in a variance of 1%, which was deemed as an acceptable variance[24]. Image series were matched for scanning phase, i.e. in each patient the scan depicting the level of L3 was performed in the same phase as the scan at the level of Th4. Earlier research has shown that surface area measurements of muscle mass are relatively unaffected by contrast enhancement, allowing us to use both contrast enhanced and contrast unenhanced scans [25,26]. Although the noise was slightly higher in the CT scans from the PET, in our opinion this did not influence the area measurement significantly.

Both researchers segmented scans of half of all patients. Twenty scans were randomly selected and segmented by both researchers to determine the interobserver agreement. Th4 was chosen as a reference point. Image selection was performed by scrolling in a caudad to cephalad fashion and selecting the first slice showing the head of both ribs connecting to the vertebral body of Th4. The position of each arm of the patient during the scan (upward or downward) was recorded. The researchers then manually segmented three muscle groups separately: (1) the left pectoralis minor and major muscle, (2) the right pectoralis minor and major muscle and (3) the combined bilateral muscles of the erector spinae, levator scapulae, rhomboideus minor and major, and transversospinalis groups (later referred to as ‘back muscles’). Two examples are shown in Fig. 1. Shoulder muscles were excluded due to the variation in arm positioning (upward or downward) and in some instances only partial inclusion in the field of view of the scan. These muscles were therefore deemed unreliable. SMM at the level of L3 was composed of all muscles visible at the transverse process of the third lumbar vertebra and had already been determined for these patients in a previous study[11].

After visual segmentation of the muscles, automated thresholding was performed to only include the pixels between −29 and + 150 HU to prevent overestimation of muscle CSA[27]. The sum of pixels within the three segmentations were then automatically retrieved from Slicer and summed to represent the total muscle mass at the level of Th4.

### 2.4. Statistical analyses

The characteristics of the two patient groups were compared using independent-samples t-tests for normally distributed variables and independent-samples median tests for non-normally distributed variables. Normality was investigated using the Kolmogorov-Smirnov test. Pearson-correlation coefficients were used to determine the degree of correlation between CSA measurements. A Pearson-correlation coefficient of 0.40–0.69 was rated as moderate, a coefficient in the range of 0.70–0.89 as strong and 0.90–1.0 as very strong[28]. Interobserver agreement was determined using intraclass correlation coefficients (ICC), using a two-way mixed single measures model with absolute agreement. An ICC of less than 0.5 was indicative of poor reliability, a value between 0.5 and 0.75 as moderate, a value between 0.75 and 0.9 as good and an ICC greater than 0.90 as excellent[29].

To establish a model of the relation between Th4 and L3, missing data were handled using 10 multiple imputed data sets. Age, weight and Th4 were determined to be independent covariates. Additionally, we used age, weight, BMI and L3 as predictors for the imputation of the missing values. Multivariate linear regression was performed using the backward selection method and Akaikes information criterion ($p = 0.157$) for in- and exclusion of the predictors.

A two-tailed p-value of $< 0.05$ was chosen as statistically significant for all other analyses. SPSS Statistics version 26.0 (IBM) was used to perform the statistical analyses. In all prediction rules value 0 was used for male sex and 1 for female sex, age was used in years, weight was used in kg and CSA in $cm^2$. For arm position, two dummy variables were created. The value 1 was entered for the corresponding category (1 arm up or 2 arms up) if applicable and a 0 if this was not applicable.

## 3. Results

### 3.1. Patient characteristics

Patient characteristics are shown in Table 1. In total, 245 whole-body CT-scans were screened. Four scans were excluded from further analyses either due to impaired scan quality (for instance because of artifacts) or impacting pathology on the muscles at level Th4. We included 47 (20%) trauma patients and 194 (80%) HNC patients. There were no significant differences in sex distribution, weight, and BMI for the two groups. Weight was not recorded for 34 cases (14%) cases, and BMI could not be calculated in 36 cases (15%). HNC patients were significantly older than

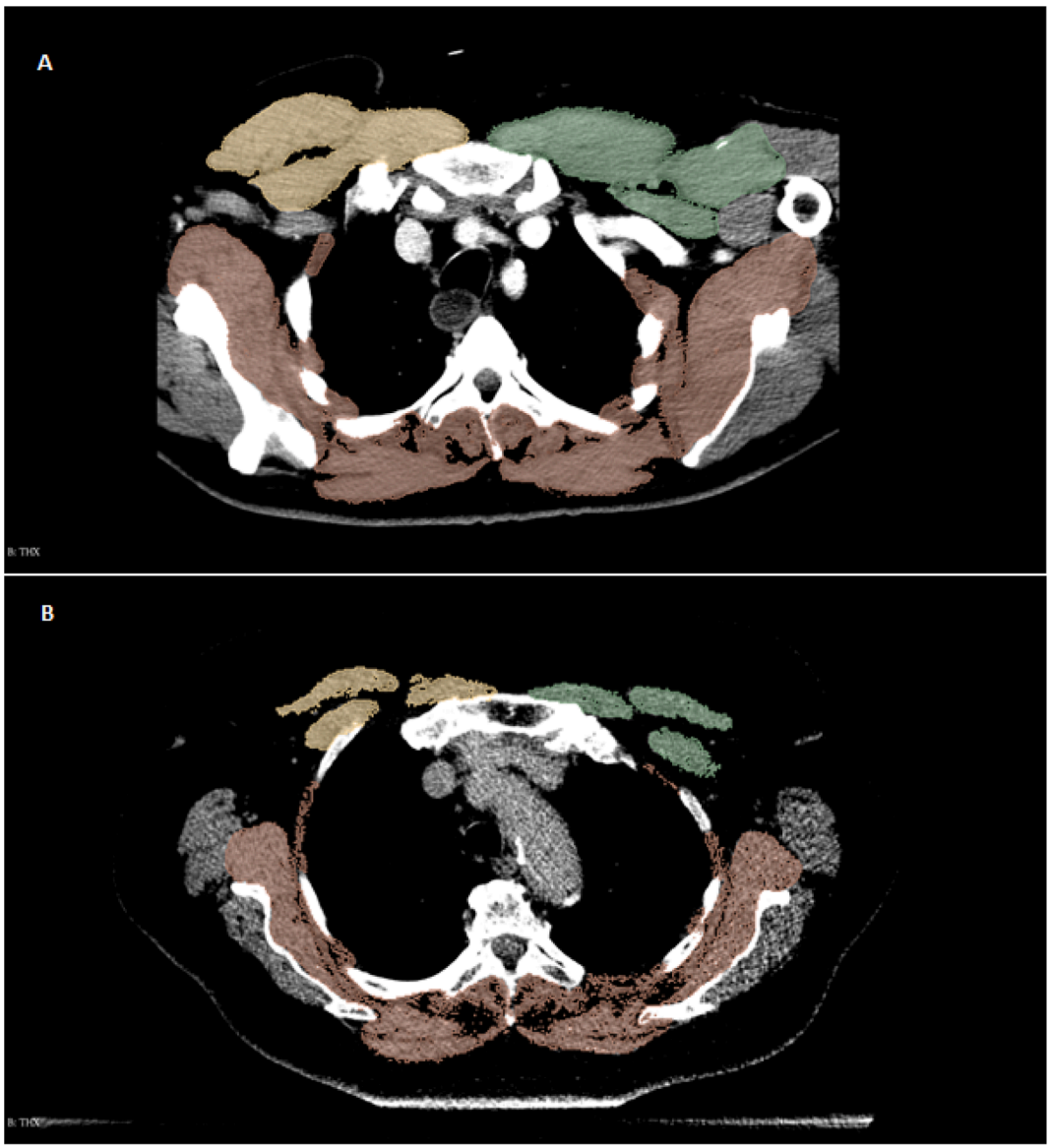


**Fig. 1.** Example of muscle segmentation using 3D Slicer A shows a patient positioned with the left arm downwards and the right arm upwards. B shows a patient positioned with their arms upwards.

trauma patients ($p < 0.05$). There were significant differences in arm positioning between the two groups. HNC patients were routinely scanned with both arms up, where the arm positioning in trauma patients varied more often ($p < 0.05$). There was no significant effect modification between the HNC and trauma patient groups, meaning the cohort could be analyzed as a single population (p-value for interaction variable Category*Th4 muscle CSA $> 0.05$).

### 3.2. Skeletal muscle measurements

The results of the image analyses are shown in Table 2. L3 muscle CSA was not significantly different between HNC and trauma patients. All measurements at the level of Th4, bilateral pectoralis muscle CSA, back muscle CSA and CSA of the pectoralis and back muscles combined were significantly lower in the HNC patients ($p < 0.05$ corrected for age, sex and arm positioning). For HNC patients, there was no significant difference in CSA measured at the level of L3 and Th4 in patients with N0 versus N + disease (L3: 131.9 vs 137.6 $cm^2$; Th4: 122.8 vs 128.7 $cm^2$) and T0-2 versus T3-4 patients (L3: 134.5 vs 136.9 $cm^2$; Th4: 127.4 vs 125.5 $cm^2$).

### 3.3. Interobserver agreement

The interobserver agreement for CSA measured at Th4 was good 0.852 (95% CI 0.633–0.941). For back muscle measurements the interobserver agreement was good as well (0.769 (0.444–0.907)). For measurements of left (0.913 (0.797–0.964)) and right (0.871 (0.707–0.947) pectoralis muscles the interobserver agreement was excellent and good, respectively.

### 3.4. Correlation of L3 and Th4

The Pearson correlation coefficients for muscle mass measurements are shown in Table 3. In patients with their arms positioned upwards, the largest subgroup of patients, L3 CSA correlated strongest with the CSA of the back muscles and both pectoralis muscles followed by the CSA of the back muscles ($r = 0.805$ and $r = 0.777$ respectively). In the second largest subgroup of patients, where both arms were positioned downwards, L3 CSA had an equal measure of correlation with the CSA of the back muscles and the combined CSA of the back muscles and pectoralis muscles ($r = 0.826$). In the smallest subgroup of patients, where

**Table 1**
Baseline patient characteristics.

| Variable | Trauma patients (n = 47) | HNC patients (n = 194) | p-value |
|---|---|---|---|
| **Sex** | | | NS |
| *Male* | 30 (63.80) | 134 (69.10) | |
| *Female* | 17 (36.20) | 60 (30.90) | |
| **Age** | 54.33 (16.09) | 61.64 (12.00)* | **<0.05** |
| **Weight** | 78.77 (17.72) | 72.16 (18.99)* | NS |
| **BMI** | 26.12 (5.19) | 24.28 (4.55) | NS |
| **Arm positioning** | | | **<0.05** |
| *Both arms up* | 8 (17.0) | 180 (92.78) | |
| *One arm up* | 10 (21.30) | 1 (0.52) | |
| *Both arms down* | 29 (61.70) | 13 (6.70) | |
| T-classification | NA | | NA |
| *T0-2* | | 102 (52.60) | |
| *T3-4* | | 92 (47.40) | |
| N-classification | NA | | NA |
| *N0* | | 72 (37.10) | |
| *N+* | | 122 (62.90) | |
| M- classification | NA | | NA |
| *M0* | | 189 (97.40) | |
| *M+* | | 5 (2.60) | |
| Tumor localization | NA | | NA |
| *Oropharynx* | | 124 (63.90) | |
| *Other* | | 70 (36.10) | |

*Not normally distributed, shown as median (IQR).
NS: not statistically significant, NA: not applicable

**Table 2**
Cross-sectional area measurements.

| Muscle groups | Trauma patients (n = 47) | HNC patients (n = 194) | p-value |
|---|---|---|---|
| L3 | 143.9 (38.6) | 135.5 (30.5) | NS |
| Th4 | 154.0 (36.6) | 126.5 (29.6) | **<0.05** |
| Both pectoralis muscles | 49.1 (21.0) | 36.9 (12.4) | **<0.05** |
| Back muscle | 104.9 (22.4) | 89.6 (19.2) | **<0.05** |

All values are shown in $cm^2$ (sd). p-values are corrected for age and sex (L3 measurements) and age, sex, and arm positioning (Th4 measurements)

**Table 3**
Pearson-correlation coefficients for L3 and Th4 measurements.

| Patient selection | Measurement | Correlation with L3 muscle CSA (p-value) |
|---|---|---|
| Whole cohort (n = 241) | Pectoralis muscles | 0.669 (<0.05) |
| | Pectoralis + back muscles | 0.791 (<0.05) |
| | Back muscles only | 0.766 (<0.05) |
| Both arms up (n = 188) | Pectoralis muscles | 0.743 (<0.05) |
| | Pectoralis + back muscles | 0.805 (<0.05) |
| | Back muscles only | 0.777 (<0.05) |
| Both arms down (n = 42) | Pectoralis muscles | 0.537 (<0.05) |
| | Pectoralis + back muscles | 0.826 (<0.05) |
| | Back muscles only | 0.826 (<0.05) |
| One arm up (n = 11) | Pectoralis muscles | 0.822 (<0.05) |
| | Pectoralis + back muscles | 0.813 (<0.05) |
| | Back muscles only | 0.645 (<0.05) |

one arm was positioned upwards, the CSA of the pectoralis muscle was strongly correlated with L3 CSA (r = 0.822) followed by the combined CSA of the back muscles and pectoralis muscles (r = 0.813). For all patients, independent of arm positioning, the strongest correlation was between L3 CSA and the CSA of the back muscles and pectoralis muscles (r = 0.791). The relationship between the CSA of the skeletal muscles at level L3 and the described measurements is shown in Fig. 2.

### 3.5. Regression analyses

The regression analyses are shown in Table 4. Model 1 describes the prediction rules of the total Th4 muscle CSA (pectoral and back muscles combined). Model 1 (only Th4 muscle CSA) could moderately predict CSA at L3 (r = 0.791). In the multivariate analysis the variables age, sex, weight and BMI were introduced in model 2. BMI was excluded using backward selection. The multivariate model provided a highly accurate estimate of CSA at L3 (r = 0.847).

Model 3 describes the prediction rules when incorporating arm positioning. In the multivariate model the variables age, sex, weight, BMI and arm position were introduced in the model. BMI was again excluded using backward selection. This final multivariate model provides a highly accurate estimate of CSA at L3 (r = 0.856). As an additional analysis only in the HNC cohort, the variables T- and N-stage were added to Model 3 and did not have a significant contribution to the model ($p > 0.05$).

## 4. Discussion

We investigated the correlation between the CSA of muscles at the level of Th4 with the CSA of muscles at level L3. We found that there was a strong correlation between the combined CSA of all muscles measured at level Th4 and CSA at the level of L3. When one of the muscle groups was omitted (i.e., pectorales only or back muscles only) the correlation was slightly lower. We found that our multivariate prediction rule incorporating patient characteristics resulted in the most accurate assessment of muscle CSA at the level of L3. Since CSA at L3 is considered to be the clinical reference standard, our findings suggest that chest CTs can be used to predict CSA at level L3.

Patients suffering from HNC are at increased risk of developing low SMM compared to patients compared diagnosed with other types of cancer[6]. Because of this low SMM is considered an important emerging prognostic marker for these patients. While ideally whole-body CT or MR imaging is used to assess SMM, earlier research has shown that assessment using a single axial slice at the level of L3 strongly correlates to whole body SMM and is since considered the clinical reference standard[11]. This poses an issue for diseases where abdominal imaging is often unavailable, such as HNC or pulmonary disease. Previous research performed by our group has established C3 as an alternative to L3 measurements. However post-surgical or post-radiotherapeutic treatment effects may influence these measurements. In those cases measurements at the level of Th4 can be an alternative in patients with extensive localized disease or post-treatment necks.

The correlation between L3 and Th4 is stronger than reported by Grønberg et al[21]. One possible explanation may lie in the choice of muscles that were segmented. The authors reported missing muscle circumference because of the field of view from the scan. It may be that our selection of muscle groups that were segmented (back and pectorales muscles only, excluding the shoulder muscles) are less influenced by patient positioning and the scan field of view. Although the rate to which muscles were cut off from the field of view was not reported by the authors, this may have impacted their measurements. Additionally, arm positioning was not described or corrected for in the measurements of Grønberg et al. Moreover, our multivariate prediction rule incorporating patient characteristics results in a better estimation of muscle CSA at level L3.

Several points in the current study should be addressed. First, we describe a multivariate prediction rule to assess SMM in patients with thoracic CT-imaging, for instance patients with COVID-19. While SMM may be assessed in these patients using this prediction rule, it has not been validated in patients with pulmonary diseases. To broaden the

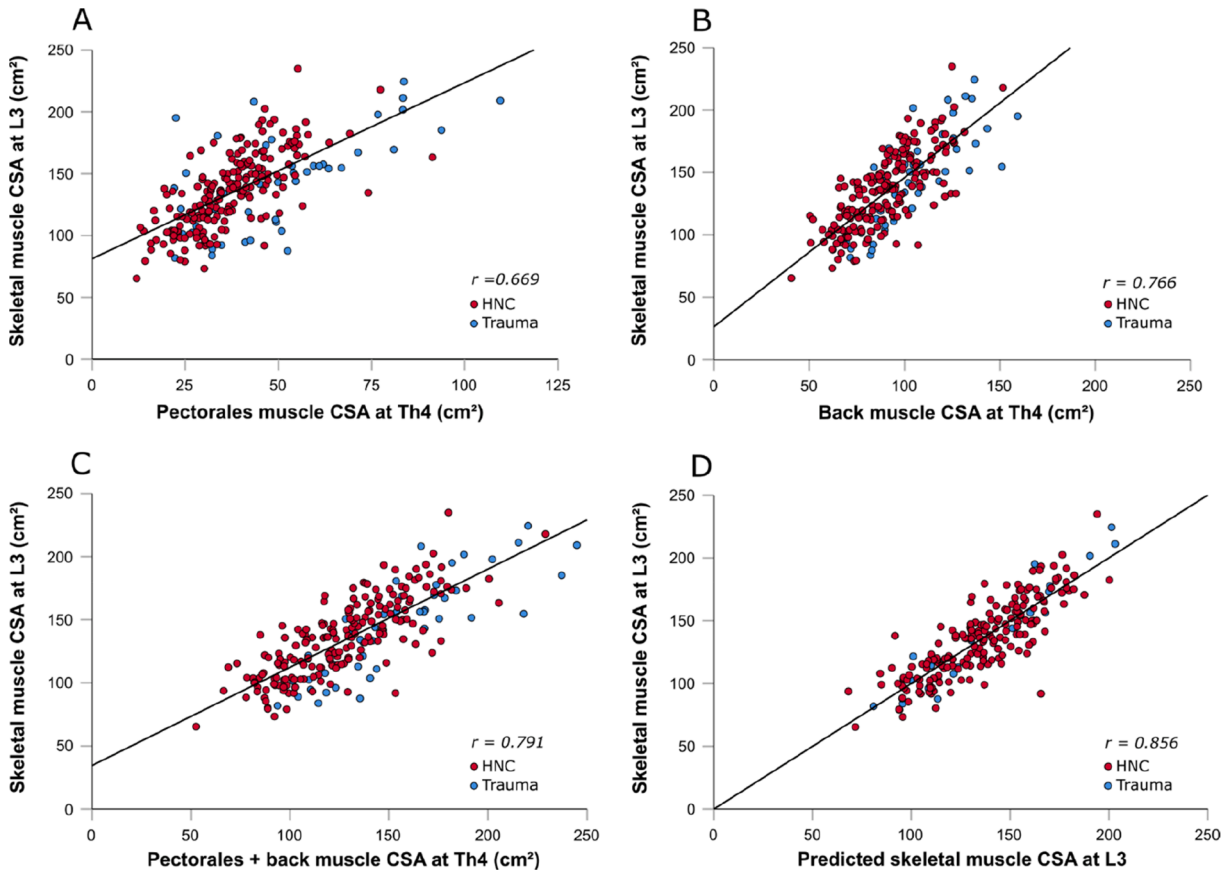


**Fig. 2.** Scatterplots of Th4 and L3 measurements Analysis of muscle CSA at the level of L3 and the pectorales muscles only at the level of Th4 (A), back muscles only at the level of Th4 (B), pectoralis and back muscles at the level of Th4 (C), and the estimated skeletal muscle using prediction rule 3 in Table 4.

applicability of our prediction rule, we also included a cohort of trauma patients in the study and found no significant effect modification between the two groups. However, the prediction rule should still be validated in a cohort of patients with lung diseases.

Second, especially in the trauma patient cohort the arm positioning of the patients varied. The majority of patients were scanned with arms in upward position. We found varying correlation coefficients based on arm positioning for the analyzed muscle groups. Arm positions had the greatest effect of how the pectoralis muscle was depicted, and we believe that this explains the large variance of correlation of pectoralis muscle CSA with L3 muscle CSA. Adding patient arm position to the statistical model resulted in a slightly better assessment of L3 muscle CSA and this should be taken into account when using Th4 SMM measurements. Alternatively, only the back muscle CSA at Th4 can be used although this has a slightly less strong correlation to L3 muscle CSA.

Third, weight and subsequently BMI data were missing for a minority of patients. To counteract this missing data we used multiple imputation, which has been shown to be provide a more accurate assessment than a complete case analysis even with a high proportion of missing data[30,31].

Other thoracic levels have been previously investigated, such as SMM at the level of the twelfth thoracic vertebra (Th12). Ishida et al found a comparable correlation between L3 and Th12 in 161 hospitalized patients aged 65 years and older (r = 0.858)[32]. Matsuyama et al describe a slightly superior correlation between L3 and Th12 in 164 Japanese oral squamous cell carcinoma patients aged 40 and over (r = 0.915)[33]. These studies were both performed at Japanese hospitals and therefore most patients were likely of Asian ethnicity. Earlier research has shown that Asian populations have a significantly differing body composition to other ethnicities[34]. Therefore, it is not clear whether their prediction rule can be extrapolated to Caucasian patients.

Moreover, these studies did not include healthy controls in their analysis, which may have possibly skewed the results. In our study we did include trauma patients as presumed otherwise healthy controls to extrapolate our findings to other patient populations than only HNC. Ishida et al did not describe the indications for performing thoracic and abdominal imaging, therefore it is not clear whether this is a homogeneous or heterogeneous patient cohort. Finally, the median age of patients in their study was slightly higher than in our study, which could also affect measurements. Another study in 157 American patients undergoing transcatheter aortic valve replacements showed a slightly poorer correlation between L3 and Th12 (r = 0.724) [35]. The authors did not report on patient ethnicity. It should be noted that L3 CSA, Th4 CSA and similar measurements are all derivatives of whole-body muscle SMM. Future efforts should be made to correlate measurements on these levels to whole body SMM on CT or MRI

In conclusion, assessing SMM at level Th4 appears to be a valid method of determining total body SMM, due to the strong correlation with CSA at L3. The CSA of back and pectoralis muscles at Th4 could serve as a substitute for L3 SMM assessment when abdominal cross-sectional imaging is not available and may also be used to study the prognostic effect of SMM in cases where thoracic image is generally the only available modality, such as in COVID-19 patients.

Further prospective research should investigate the relationship between muscle mass at level Th4 in patients with pulmonary disease, such as COVID-19, and its relationship between ICU stay, ventilator free days and mortality. Moreover, our SMM prediction rule may also be relevant in establishing prediction models for ICU survival, to assess which patients have the best odds of survival in the case of an ICU shortage.

**Table 4**
Regression models.

| Model | | Covariates | Unstandardized B (95% CI) | p-value | Model R* |
|---|---|---|---|---|---|
| 1. | Basic prediction rule all muscles at level Th4 | Th4 CSA | 0.78 (0.70–0.85) | <0.05 | 0.791 |
| | Prediction rule | CSA at L3 = 34.48 + 0.78 * Th4 CSA | | | |
| 2. | Backward selected multivariate model | Th4 CSA | 0.50 (0.40–0.59) | <0.05 | 0.847 |
| | | Age | −0.43 (−0.68 – −0.18) | <0.05 | |
| | | Sex | −17.85 (−23.37 – −12.33) | <0.05 | |
| | | Weight | 0.42 (0.25–0.60) | <0.05 | |
| | Prediction rule | CSA at L3 = 71.6 + 0.5 * Th4 CSA – 0.43 *age –17.85 * sex + 0.42 * weight | | | |
| 3. | Backward selected multivariate model including arm position | Th4 CSA | 0.55 (0.45–0.64) | <0.05 | 0.856 |
| | | Age | −0.45 (−0.69 – −0.21) | <0.05 | |
| | | Sex | −15.85 (−21.30 – −10.40) | <0.05 | |
| | | Weight | 0.41 (0.24–0.58) | <0.05 | |
| | | 1 arm up | 11.02 (5.08–16.96) | <0.05 | |
| | | 2 arms up | −0.55 (−12.12–11.02) | NS | |
| | Prediction rule | CSA at L3 = 58.21 + 0.55 * Th4 CSA – 0.45 * age – 15.85 * sex + 0.41 * weight + 11.02 * 1 arm up – 0.55 * 2 arms up | | | |

Statistical models to calculate L3 CSA based on the Th4 CSA in univariate or multivariate analysis. Pooled values from all imputed databases are shown where available. R-squared change between model 2 and 3 was significant, therefore we advise to use model 3 when applying the prediction rule.
* An R-value for the whole model is not produced from the pooled analysis. The R-value of the first imputed model is shown.

## CRediT authorship contribution statement

**Hugo C. van Heusden:** Investigation, Software, Writing - original draft. **Justin E. Swartz:** Conceptualization, Investigation, Formal analysis, Software, Writing - original draft. **Najiba Chargi:** Investigation, Writing - review & editing. **Pim A. de Jong:** Methodology, Writing - review & editing. **Mark C.P.M. van Baal:** Investigation, Writing - review & editing. **Inge Wegner:** Methodology, Formal analysis, Validation, Writing - review & editing. **Remco de Bree:** Conceptualization, Supervision, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Guarantor of the contents: JES, RdB;

Author contributions: JES and RdB conceived the idea for this study, HvH and JES performed the measurements, JES and IW performed the analyses, all authors contributed significantly to the study design and writing of the manuscript;

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