Intramuscular adipose tissue at level Th12 is associated with survival in COVID-19

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Introduction

Body composition refers to the amount and distribution of skeletal muscle, adipose tissue and bone in the human body. Sarcopenia, as an example of abnormal body composition, is defined as a significant loss of skeletal muscle mass (muscle wasting) and muscle strength and infiltration of muscle by fat and connective tissue.[1,2] Body composition has been studied using a single computed tomography (CT) slice, which is considered the reference standard for quantitative body composition studies.[3,4] Abnormal body composition, and in particular sarcopenia, has been associated with survival in patients with cancer[5] or an increased cardiometabolic risk.[6]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic of coronavirus disease 19 (COVID-19). In COVID-19 patients, age is associated with lower survival,[7] and a higher body mass index (BMI) is associated with invasive ventilation.[8] Regarding abnormal body composition, an increase of visceral fat has been associated with ICU admission of COVID-19 patients.[9] Effects of abnormal body composition on survival are currently unknown. We hypothesized that abnormal body composition, as measured on standard chest CT images, is associated with lower survival in COVID-19 patients. The aim of our study was to examine the association between body composition measures and survival in COVID-19 patients.

Materials and methods

Patients

We prospectively included consecutive patients admitted to the Amsterdam University Medical Centers, location Academic Medical Center, between March 2020 and June 2020. Inclusion criteria were a polymerase chain reaction-confirmed COVID-19 infection, age ≥18 years, need for hospitalization, availability of a CT scan of the chest and availability of clinical outcome data.

This study has been conducted in accordance with the ethical principles set out in the declaration of Helsinki and all participants provided written informed consent, if applicable. Ethics approval was obtained from the Amsterdam UMC Biobank Committee (202_065#A202029).[10]

Clinical data

We collected the following demographic and clinical variables: age, sex, length, weight and BMI and survival status at Day 21.

Image acquisition and body composition measurements

CT images were obtained using standard multi-slice CT scanners and a clinical non-contrast enhanced low-dose CT chest protocol. The first scan, at the day of admission, was used if more scans were acquired. Body composition is typically estimated at the level of vertebra L3/L4.[11] As these levels were not available on standard CT chest examinations, measurements were performed at level Th12, in the cross-sectional slice that showed both transverse processes.

Images were anonymized and stored in 512 × 512 matrix, 16-bit Digital Imaging and Communications in Medicine (DICOM) format. Muscle segmentation was performed using manual outlining and semi-automated thresholding using the Horos DICOM viewer (version 3.3.6, www.horosproject.org) by an experienced operator. In all examinations, skeletal muscle and subcutaneous adipose tissue (SAT) were segmented manually, carefully excluding bone, cartilage and intra-abdominal/thoracic tissues (*Figure* 1A–D).

For segmentation, previously used thresholds in Hounsfield units (HU) were applied: −29 to +150 HU for muscle and −190 to −30 HU for SAT.[12] Cross-sectional area (CSA; cm^2) and mean radiodensity (HU) of muscle and SAT were calculated. As an indicator for fatty muscle degeneration, the CSA (cm^2) of intramuscular adipose tissue (IMAT) was determined

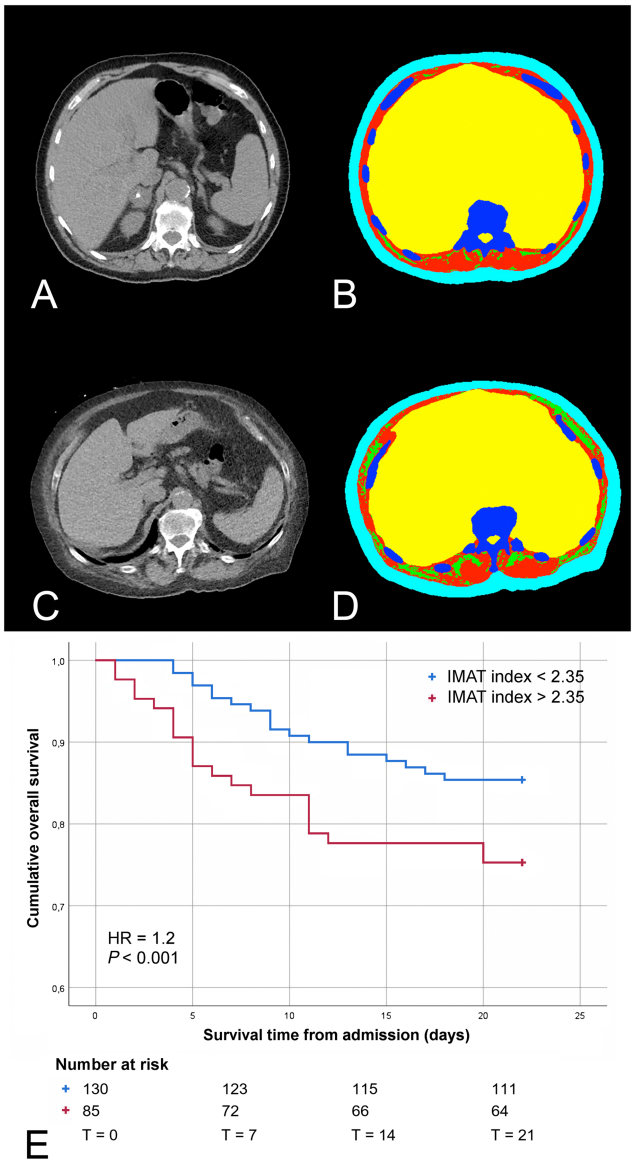

Figure 1 Axial CT slices of two patients at level Th12, segmented in subcutaneous adipose tissue (SAT, cyan), muscle (red), intramuscular adipose tissue (IMAT, green), bone (blue) and other (yellow). (*A*,*B*) A COVID-19 survivor. (*C*,*D*) Images of a deceased patient: Notice the increased amount of IMAT (green). (*E*) Kaplan–Meier analysis of the effect of the cross-sectional area of the intramuscular adipose tissue (IMAT) index at level Th12 on survival in COVID-19 patients. Groups are based on a median split of the IMAT index. Blue line = patients with IMAT index $<$ 2.35; red line = patients with IMAT index $>$ 2.35. Log-rank test for equality of survival functions, $P < 0.05$.

by measuring fat pixels (below −29 HU) within the muscle contours. In order to correct for body size, the skeletal muscle index (SMI) was computed (cm^2/m^2) by dividing cross-sectional muscle area (cm^2) by squared patient length (m). The same correction for body size was applied to CSA of IMAT and SAT, creating IMAT and SAT indices (cm^2/m^2).

Statistical analysis

Descriptive statistics were reported as percentages, means and standard deviations or, when appropriate, median and interquartile range (IQR). We performed logarithmic transformation on non-normal distributed data and used Fisher exact test, independent *t*-test and Mann–Whitney *U* test, where appropriate. All tests assumed a two-tailed probability and a *P*-value of $<$0.05 indicated statistically significant difference. Kaplan–Meier survival analysis was performed with groups based on median split and the log-rank test. We used a multivariate Cox proportional hazards model with, age, BMI, muscle density and IMAT index (Enter method) as explanatory variables.

Results

Patients

We included 215 of the eligible 278 COVID-19 patients (see Supporting Information, *Data S2*). Eighty-six patients (40.0%) were female; mean age at hospital admission was 61.1 (SD 14.3) years, and mean BMI was 28.9 (SD 6.1).

Fifty-eight patients (27.0%) were admitted to MCU/ICU, of whom 56 received invasive ventilation during a median of 11.5 days (IQR 7.8–17.3). In total, 192 (89.3%) patients had oxygen therapy, and 16 (7.4%) patients had non-invasive ventilation. Forty patients (18.6%) died within 21 days. Compared with non-deceased patients, patients who died were older (66.9 [SD 12.0] vs. 59.8 [SD 14.5] years; $P < 0.005$) and more often invasively ventilated; BMI was similar between these two groups (*Table* 1).

Body composition measures

Non-survivors had a larger CSA of IMAT (median 10.1 cm^2 [IQR 5.0–18.0] vs. 6.2 cm^2 [IQR 3.7–11.4], $P < 0.01$) and a larger IMAT index (median 3.6 cm^2/m^2 [IQR 1.6–8.1] vs. 2.1 cm^2/m^2 [1.2–3.9], $P < 0.05$) as compared with survivors (*Table* 1). No statistically significant differences were observed for CSA or mean radiodensity (HU) of muscle, SMI or CSA of SAT (*Table* 1). *Figure* 1E shows the Kaplan–Meier curve of the two groups divided by the median IMAT index (2.35, $P < 0.05$). The Cox proportional hazards model including age, BMI, muscle density and IMAT index showed an effect of IMAT index only (HR = 1.2, 95% CI 1.1–1.3, $P < 0.001$). See Supporting Information, *Data S3*, for the complete model.

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Table 1 Patient characteristics of COVID-19 patients based on outcome after 3 weeks of admission

Clinical feature	Dead $n = 40$	Alive $n = 175$	*P*-value
No. (%) of female patients	13 (32.5%)	73 (41.7%)	0.371[a]
Age at admission	66.9 (12.0)	59.8 (14.5)	0.004
Length (cm)	172.0 (11.7)	171.8 (9.7)	0.948
Weight (kg)	86.5 (18.8)	85.4 (18.5)	0.760
Body mass index	29.0 (5.8)	28.8 (6.2)	0.841
Clinical outcome measures			
No. (%) of patients admitted to MCU/ICU	24 (60.0%)	34 (19.4%)	<0.001[a]
No. (%) of patients with oxygen therapy	39 (97.5%)	153 (87.4%)	0.086[a]
No. (%) of patients with non-invasive ventilation[b]	4 (10.0%)	12 (6.9%)	0.506[a]
No. (%) of patients with invasive ventilation	22 (55.0%)	34 (19.4%)	<0.001[a]
Duration of invasive ventilation, median days (median, IQR)[c]	10.0 (7.8–13.0)	14.0 (7.5–21.8)	0.046
Body composition measures			
Muscle cross section area (cm^2), median (IQR)[c]	104.0 (83.3–116.7)	108.0 (86.5–124.4)	0.704
Skeletal muscle index (cm^2/m^2)	35.7 (9.5)	36.1 (9.1)	0.820
Muscle density (HU)[c]	24.0 (10.1)	27.6 (10.9)	0.067
IMAT cross sectional area (cm^2), median (IQR)[c]	10.1 (5.0–18.0)	6.2 (3.7–11.4)	0.009
IMAT index (cm^2/m^2), median (IQR)[c]	3.6 (1.6–8.1)	2.1 (1.2–3.9)	0.013
SAT cross-sectional area (cm^2), median (IQR)[c]	160.4 (115.7–198.8)	133.1 (97.9–190.6)	0.219
SAT index (cm^2/m^2), median (IQR)[c]	52.6 (35.1–79.7)	41.7 (31.3–68.7)	0.193

Scores are presented as mean (SD), except where stated otherwise. Independent *t*-test was used except where stated otherwise. HU = Hounsfield units; IMAT = intermuscular adipose tissue; SAT = subcutaneous adipose tissue.
[a]Fisher's exact test.
[b]Bilevel positive airway pressure or continuous positive airway pressure.
[c]Normally distributed after logarithmic transformation.

Discussion

Our findings indicate that a larger CSA of intramuscular adipose tissue at Th12 is a risk factor for survival in COVID-19 patients. This association was independent of age, BMI and muscle density.

Our finding is in line with studies in non-COVID patients, showing a relation between abnormal body composition, in particular sarcopenia, and survival in patients with malignancies or other conditions.[5,6]

Our study adds to previously reported associations in COVID-19 patients between visceral fat and ICU admission.[8,9] Our data suggest that survival in COVID-19 is related to a marker of fatty muscle degeneration. At Th12, muscles of both inspiration (external intercostals) and active expiration (abdominal muscles, quadratus lumborum) contribute to optimal breathing function. We did not examine the diaphragm, pulmonary function tests or muscle biopsies. Consequently, we can only speculate on mechanisms explaining how fatty muscle degeneration at the low thoracic level leads to lower survival, which may include respiratory muscle impairment (e.g. ineffective cough leading to more progressive pulmonary disease). In addition, our findings may be of interest in relation to a description of a severe diaphragm myopathy with increased fibrosis in a post-mortem study of severely ill COVID-19 patients.[13]

The most frequently used level for measurements of body composition is L3, because the CSA of muscles and adipose tissue at L3 correlates well with total body volumes of skeletal muscle and adipose tissue.[14] Our approach seems valid, however, as a strong correlation between CSA of muscle at Th12 and L3 has been reported.[15]

Our study has some limitations. As only COVID-19 patients with the availability of chest CT were included, some admitted patients with mild disease were not included. Second, only clinical data and outcome during the first 21st days were available, as many patients were transferred to other centers. Finally, not for all patients, other variables of interest (e.g. diabetes or cardiovascular disease) were present.

Conclusions

Our findings indicate that intramuscular adipose tissue is associated with survival in COVID-19 patients. Quantification of IMAT on chest CT examinations might be a tool for risk assessment in COVID-19 patients.

Author contributions

A.R. Viddeleer: Conceptualization, methodology, software, formal analysis, investigation, writing—original draft preparation, resources. M. Min: Formal analyses, writing—review

and editing preparation. J. Raaphorst: Conceptualization, writing—review and editing preparation. L.F.M. Beenen: Resources, writing—review and editing preparation. M.J. Scheerder: Resources, writing—review and editing preparation. A.P.J. Vlaar: Writing—review and editing preparation. M. Beudel: Conceptualization, writing—review and editing preparation. R. Hemke: Conceptualization, methodology, formal analysis, investigation, writing—original draft preparation, resources, project administration management.

Amsterdam UMC COVID-19 Biobank: Data acquisition.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplement 1. Collaborators Amsterdam UMC Covid-19 Biobank.

Data S2. Supplement 2. Study Flow Chart.

Data S3. Supplement 3. Cox proportional hazards model.

Conflict of interest

None declared.

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References

1. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: current concepts and imaging implications. *Am J Roentgenol* 2015;**205**: W255–W266.
2. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* 2010;**29**:154–159.
3. Hemke R, Buckless C, Torriani M. Quantitative imaging of body composition. *Semin Musculoskelet Radiol* 2020;**24**: 375–385.
4. Brown JC, Cespedes Feliciano EM, Caan BJ. The evolution of body composition in oncology—epidemiology, clinical trials, and the future of patient care: facts and numbers. *J Cachexia Sarcopenia Muscle* 2019;**9**:1200–1208.
5. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *European Journal of Cancer* 2016;**57**:58–67.
6. Li Y, Liu B, Li Y, Jing X, Deng S, Yan Y, et al. Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2019;**18**.
7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**:1054–1062.

8. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity* 2020;**28**:1195–1199.
9. Kottlors J, Zopfs D, Fervers P, Bremm J, Abdullayev N, Maintz D, et al. Body composition on low dose chest CT is a significant predictor of poor clinical outcome in COVID-19 disease - a multicenter feasibility study. *Eur J Radiol* 2020;**132**:109274.
10. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the journal of cachexia, sarcopenia and muscle: update 2017. *J Cachexia Sarcopenia Muscle* 2017;**8**:1081–1083.
11. Murray TÉ, Williams D, Lee MJ. Osteoporosis, obesity, and sarcopenia on abdominal CT: a review of epidemiology, diagnostic criteria, and management strategies for the reporting radiologist. *Abdom Radiol* 2017;**42**:2376–2386.
12. Rutten IJG, van Dijk DPJ, Kruitwagen RFPM, Beets-Tan R, Olde Damink S, van Gorp T, et al. Loss of skeletal muscle during neoadjuvant chemotherapy is related to decreased survival in ovarian cancer patients. *J Cachexia Sarcopenia Muscle* 2016;**7**:458–466.
13. Shi Z, de Vries HJ, Vlaar APJ, van der Hoeven J, Boon RA, Heunks LMA, et al. Diaphragm pathology in critically ill patients with COVID-19 and postmortem findings from 3 medical centers. *JAMA Intern Med* 2021;**181**:122–124.
14. Shen W, Punyanitya M, Wang Z, Gallagher D, St.Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* 2004;**97**:2333–2338.
15. Nemec U, Heidinger B, Sokas C, Chu L, Eisenberg RL, et al. Diagnosing sarcopenia on thoracic computed tomography: quantitative assessment of skeletal muscle mass in patients undergoing transcatheter aortic valve replacement. *Acad Radiol* 2017;**24**:1154–1161.