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Clinical Nutrition 41 (2022) 2918–2923

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Covid-19

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J. Koehler [a], Y. Boirie [b], L. Bensid [a], B. Pereira [c], N. Ghelis [a], C. Dupuis [d], A. Tournadre [e], L. Boyer [f], L. Cassagnes [f, *]

[a] Service de Radiologie, CHU Clermont-Ferrand Clermont-Ferrand, France
[b] Université Clermont Auvergne, CHU Clermont-Ferrand, Service de Nutrition Clinique, Unité de Nutrition Humaine, INRAe, CRNH Auvergne, F-63000, Clermont-Ferrand, France
[c] CHU Clermont-Ferrand, Service de Bio Statistique, Clermont-Ferrand, France
[d] CHU Clermont-Ferrand, Service de Réanimation Médicale, Clermont-Ferrand, France
[e] Service de Rhumatologie, CHU Clermont-Ferrand, Unité de Nutrition Humaine, UMR 1019 INRA, Clermont-Ferrand, France
[f] Service de Radiologie, CHU Clermont-Ferrand, Institut Pascal, TGI, UMR6602 CNRS SIGMA UCA, Faculté Médecine, Clermont-Ferrand, France

ARTICLE INFO

Article history:
Received 14 September 2021
Accepted 24 January 2022

Keywords:
COVID
SARS-COV2
Sarcopenia
SMI
SMD
Malnutrition

SUMMARY

Purpose: Evaluation of CT sarcopenia as a predictor of intensive care hospitalization during SARS-COV2 infection.

Materials and methods: Single-center retrospective study of patients admitted to hospital with SARS-COV2 infection. The estimation of muscle mass (skeletal muscle index (SMI)) for sarcopenia, measurement of muscle density for muscle quality and body adiposity, were based on CT views on the T4 and L3 levels measured at admission. Demographic data, percentage of pulmonary parenchymal involvement as well as the orientation of patients during hospitalization and the risk of hospitalization in intensive care were collected.

Results: A total of 162 patients hospitalized for SARS-COV2 infection were included (92 men and 70 women, with an average age of 64.6 years and an average BMI of 27.4). The muscle area measured at the level of L3 was significantly associated with the patient's unfavorable evolution (124.4cm2 [97; 147] vs 141.5 cm^2 [108; 173]) ($p = 0.007$), as was a lowered SMI ($p < 0.001$) and the muscle area measured in T4 (OR = 0.98 [0.97; 0.99]), ($p = 0.026$). Finally, an abdominal visceral fat area measured at the level of L3 was also associated with a risk of hospitalization in intensive care (249.4cm2 [173; 313] vs 147.5cm2 [93.1; 228] ($p < 0.001$).

Conclusion: This study demonstrates that thoracic and abdominal sarcopenia are independently associated with an increased risk of hospitalization in an intensive care unit, suggesting the need to assess sarcopenia on admission during SARS-COV2 infection.

1. Introduction

Coronavirus 19 disease (Covid-19) is an emerging disease due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that started in Wuhan in Hubei Province in China in December 2019. This pathology is a major public health problem in France and worldwide. It has been observed that, among others, obesity, diabetes and hypertension were common comorbidities among patients hospitalized for COVID-19 [1–3].

Approximately 5–10% of patients develop a severe form of ARDS or multi-visceral failure. Of those patients who develop severe forms, 71–75% require mechanical ventilation and approximately 50% die [4,5].

Several studies have demonstrated a relationship between obesity and the unfavorable evolution of infection in intensive care, particularly when sarcopenia coexisted with overweight [6–8]. These observations suggest that beyond weight, muscle loss, particularly in the chest, may contribute to the poor evolution of COVID-19 infection.

Recent studies have shown the importance of chest CT-scan, in the diagnosis of COVID-19, particularly in the case of false negative RT-PCR examination [9] and report a CT sensitivity of 98% [10].

* Corresponding author.
E-mail address: lcassagnes@chu-clermontferrand.fr (L. Cassagnes).

https://doi.org/10.1016/j.clnu.2022.01.022

Chest CT is therefore part of the initial systematic check-up in patients who are symptomatic or require hospitalization [11].

The analysis of computed tomography (CT) images now allows the evaluation of muscle mass, fat mass and its distribution: subcutaneous or visceral adipose mass and proportion of intramuscular fat (myosteatosis) by measuring muscle attenuation.

The French Society of Radiology (SFR) and the French of Thoracic Imaging Society (SIT), in view of the incidence of renal insufficiency in acute disease patients and the risks of infection during abdominal ultrasound, recommend that the kidneys be explored during thoracic acquisition in order to eliminate obstructive urinary syndrome during the initial assessment of these patients [12,13].

It is now accepted that the evaluation of muscle and fat surface area measured at the L3 level is strongly correlated with the occurrence of complications in many pathologies, particularly neoplastic ones [14–18]. In addition, several studies have shown that the assessment of the thoracic muscle surface area measured on the T4 level was an independent factor in the survival and occurrence of complications in bronchial cancer surgery [19].

We therefore hypothesize that the assessment of thoracic and abdominal muscle surface area would be a potential indicator of severity or unfavorable evolution in the patient with COVID-19.

2. Material and methods

This monocentric retrospective observational study performed at the University Hospital Clermont-Ferrand has received ethics committee approval (IRB Number: CRM-2005-085).

2.1. Population

Patients were retrospectively included in the study during the investigation period.

The inclusion criteria were adults patients with a SARS-CoV-2 infection confirmed by RT-PCR and who had a chest CT scan at their admission (Fig. 1) also exploring the renal region (L3) according to the SFR recommendations between March 1, 2020 and October 31, 2020 at the Clermont-Ferrand University Hospital (CHU). The exclusion criteria were the absence of a CT scan and the absence of diagnostic confirmation by RT-PCR (see Fig. 2).

The criteria used for a hospitalization in intensive care unit was: respiratory with hypoxemia (>6 L/min O2) or respiratory depression, neurological with a GCS<12 and degradation kinetics of organ failure [20].

2.2. Data analysis

Muscle surface area and mean muscle density were measured with SliceOmatic Software V 5.0 (Tomovision, Magog, Canada) on native CT sections at the T4 and L3 levels at diagnosis. These measurements were analyzed separately. Muscle structures were quantified with a preset threshold of Hounsfield unit (−29 to 150 HU). The skeletal muscle index (SMI) was calculated as the ratio of muscle surface area (cm^2) to height (m^2). A decreased SMI in L3 was defined as <38.6 cm^2/m2 for women and <52.3 cm^2/m2 for men with a body mass index (BMI) < 30 and 46.6 cm^2/m2 for women and 54.3 cm^2/m2 for men with a BMI>30. Decreased skeletal muscle density (SMD) was defined as <32.5 HU for women and <35.5 UH for men [21].

Height and weight of patients were measured at the hospitalization's admission.

For the T4 level, no reference threshold is available in the literature.

Percentage of involvement was measured with ADW Server, Thoracic VCAR software with a − 600 UH threshold on the initial CT-scan.

The sarcopenia was defined like a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes: physical disability, and death. The European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia [22].

Our main objective was to analyze sarcopenia as a predictive criterion for an intensive care hospitalization during a SARS-COV2 infection.

Our secondary objectives concerned abdominal adiposity as a risk factor for intensive care hospitalization.

2.3. Statistical analysis

Continuous data were expressed as mean and standard-deviation, or median and interquartile range, according to their statistical distribution. The assumption of normality was assessed with the Shapiro–Wilk test. Demographic and scanographic characteristics and muscular and adipose characteristics were compared between conventional hospitalization and intensive care groups. The comparisons between groups were performed using Chi-squared or Fisher's exact tests for categorical variables whereas Student t-test or the Mann–Whitney test, when assumptions

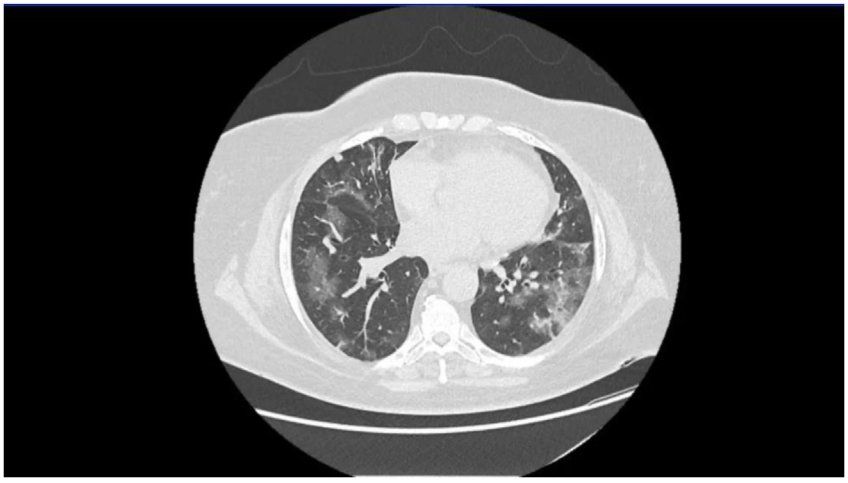

Fig. 1. Typical Covid CT scan.

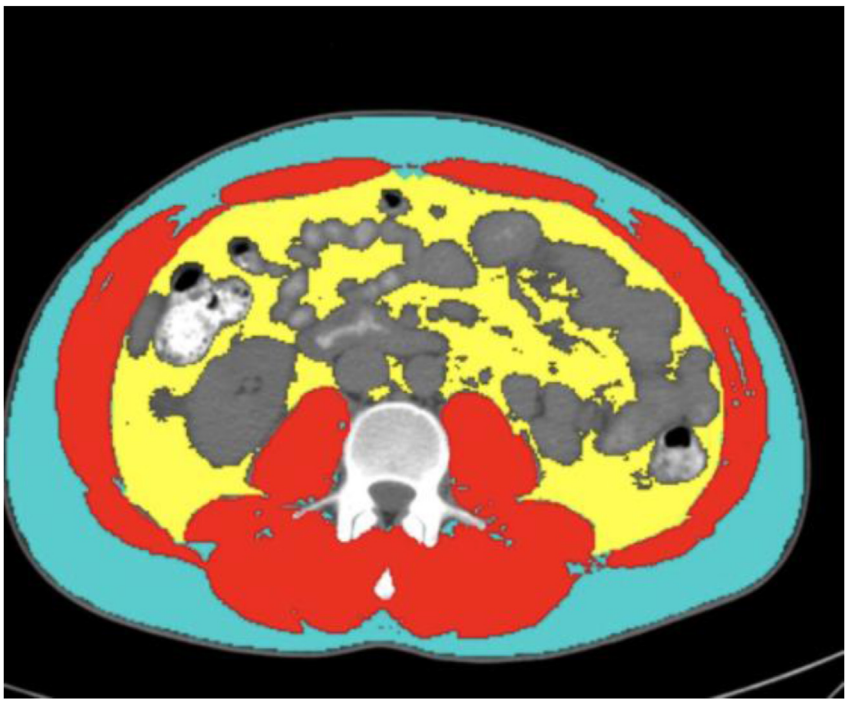

Fig. 2. SliceOmatic analysis on an L3 section.

required for the t-test were not met, were applied for quantitative variables. The homoscedasticity was analyzed using the Fisher–Snedecor test. Then, to determine muscular and adipose parameters (independent variables) associated to ICU admission (dependent variable), multivariable analysis was carried out using generalized linear model (i.e. logistic for dichotomous endpoint) taking into account possible confounding factors: sex (dichotomous variable), BMI (continuous variable), percentage of lung damage (continuous variable) and associated pulmonary embolism (dichotomous variable). The covariates were chosen according to univariate results and to their clinical relevance. Hence, no specific statistical strategy approach, such as stepwise, was conducted. The covariates were chosen with caution due to sample size according to the univariate results and to clinical relevance [24]. The testing and parameter estimation performed using a statistical model clearly depends on the variables included in the model. It is therefore crucial for confounding adjustment that known clinically and biologically significant variables are included in the regression model. A significant variable may well be an important confounder also when it is statistically insignificant [25]. A particular attention was paid to possible multicollinearity between covariates using Farrar–Glauber test. The results were expressed using odds-ratios and 95% confidence intervals. The statistical analyses were carried out using Stata software version 15 (StataCorp, College Station, US). Statistical tests were two-sided with a type-I error set at 5%. As analyses were exploratory, the individual p-values have been reported without applying systematically mathematical correction but with a specific attention paid on the magnitude of differences.

3. Results

3.1. Population

A total of 162 patients were included in the study during the investigation period. In this study a patient requiring a hospitalization in intensive care during hospitalization was classified in the intensive care arm.

Hospitalization in intensive care was required for 55 (34%) patients. Characteristics were mostly comparable between the two groups (Table 1).

Nevertheless, we found a significant difference in the proportion of men admitted to intensive care 41 (75%) patients compared to conventional hospitalization 51 (48%) patients ($p = 0.001$). The percentage of pathologic pulmonary parenchyma was also higher in the intensive care group 50.4% (±22.8) compared to the conventional hospitalization group 20.8% (±14.9) ($p < 0.01$), as was the association of pulmonary embolism with the diagnosis 8 (15%) patients in intensive care and 4 (3.7%) patients in conventional hospitalization ($p = 0.013$).

3.2. Univariate analysis

3.2.1. Measurement of sarcopenia

In univariate analysis, patients in intensive care had a significantly low L3 muscle surface area 124.4 cm^2 [97; 147] than those in a conventional unit 141.5 cm^2 [108; 173] ($p = 0.007$). Similarly, a low SMI was more frequently found in patients hospitalized in an intensive care unit 42 (76%) patients compared to 41 (38%) patients in a conventional hospitalization ($p < 0.001$). On the other hand, there was no significant difference in muscle mass density measured in L3 between our two groups: 30.5 HU [24.6; 34.2] for patients hospitalized in the intensive care unit and 32.6 HU [26.1; 38.8] for those hospitalized in a conventional unit ($p = 0.06$). The low SMD differed significantly according to the hospitalization department: 42 (78%) patients in intensive care versus 62 (56%) patients in a conventional department ($p = 0.006$).

Muscle density measured in T4 appeared significantly lower in intensive care patients 34.7 HU [30.6; 38.4] compared to 37.8 HU [31.4; 43.2] in conventional care ($p = 0.026$).

Finally, the thoracic muscle surface area measured on T4 did not differ according to patient orientation: 147.8 cm^2 [110; 193] in the intensive care unit compared with 154.6 cm^2 [134; 187] in the conventional unit ($p = 0.18$) (Table 2).

Table 1
Initial demographic and scanographic characteristics.

	Total (n = 162)	Conventional hospitalization (n = 107)	Intensive care (n = 55)	p value
Age, (years) average and SD	64.6 (14.6)	63.8 (±16.3)	66.2 (±10.5)	0,26
Sex (Man) n (%)	92 (56,8)	51 (48%)	41 (75%)	0,001
BMI (kg/m^2) average and SD	27.4 (6.00)	26.7 (±6.39)	28.8 (±4.96)	0,032
diabetes, n (%)	41 [3,26]	24 (22%)	17 (31%)	0,24
Hypertension, n (%)	60 (37)	36 (34%)	24 (44%)	0,21
Dyslipidemia n (%)	27 [7,16]	17 (16%)	10 (18%)	0,71
Smoke n (%)	36 [7,22]	22 [6,21]	14 [26]	0,733
Pulmonary lesions				
% of lesion, median and RQI	30.8 (±22.7)	20.8 (±14.9)	50.4 (±22.8)	<0,001
Pulmonary embolism n (%)	12 [4,7]	4 (3.7%)	8 (15%)	0,013

SD: Standard deviation; BMI: Body Mass Index; RQI: Interquartile range

Table 2
Muscular and adipose characteristics.

	Total (n = 162)	Conventional hospitalization (n = 107)	Intensive care (n = 55)	p value
Muscular density L3(HU) Med (RQI)	31,6 [25,3; 37,2]	32,6 [26,1; 38,8]	30,5 [24,6; 34,2]	0,06
Muscular surface L3 (cm^2) Med (RQI)	129,8 [106; 161]	141,5 [108; 173]	124,4 [97; 147]	0,007
Low SMI L3, n (%)	83 (51,2)	41 (38)	42 (76)	<0,001
Low SMD L3, n (%)	105 (64,8)	62 (56)	43 (78)	0,006
Superficial L3 fat (cm^2) med (RQI)	202 [140; 292]	198 [138; 296]	205 [146; 286]	0,69
Visceral L3 fat (cm^2) Med (RQI)	176,5 [119; 269]	147,5 [93,1; 228]	249,4 [173; 313]	<0.001
Muscular density T4 (HU) Med (RQI)	36,1 [31.2; 42.1]	37,8 [31,4; 43,2]	34,7 [30,6; 38,4]	0,026
Muscular surface T4 (cm^2) Med (RQI)	152 [129; 188]	154,6 [134; 187]	147,7 [110; 193]	0,18

IQR: intervalle interquartile,; SMD: Skeletic Mass Density; SMI: Skeletic Mass Index; HU: Hounsfield Unity.

3.2.2. *Measurement of abdominal adiposity*

The visceral adipose surface area measured on an L3 section differed significantly between our groups, being measured at 249.5 cm^2 [173; 313] in the intensive care unit and 147.5 cm^2 [93.1; 228] in the conventional unit ($p < 0.001$). On the other hand, the subcutaneous fat surface area did not differ between the groups analyzed, measured at 205 cm^2 [146; 286] in the intensive care unit versus 198 cm^2 [138; 296] in the conventional unit ($p = 0.69$).

3.2.3. *Multivariate analysis* Table 3

After adjusting our different results on gender, BMI, percentage of parenchymal involvement, and presence of associated pulmonary embolism, we found a significant difference in muscle surface area measured on a L3 CT section with OR = 0.97 [0.95; 0.98] ($p < 0.001$) as well as on the SMI evaluation: OR = 5.32 [1.90; 14.87] ($p < 0.001$).

Moreover, the visceral adipose surface area measured on an L3 section appears significantly higher in the intensive care patients with OR = 1.01 [1.001; 1.02] ($p = 0.015$).

These analyses show a significant difference in muscle surface area measured in T4, which appears to be lower in the intensive care patients with OR = 0.98 [0.97; 0.99] ($p = 0.004$).

Finally, we did not find a significant difference in estimated muscle density in L3 (OR = 0.98 [0.94; 1.03]) ($p = 0.5$), SMD assessment in L3 (OR = 1.81 [0.64; 5.15]) ($p = 0.26$), or estimated muscle density in T4 (OR = 0.98 [0.926; 1.04]) ($p = 0.47$). Similarly, the subcutaneous abdominal fat surface area did not differ between groups (OR = 0.98 [0.93; 1.05]) ($p = 0.69$).

These multivariate analyses were also conducted in order to compare the evaluation of muscle surface area measured in T4 and the one measured in L3, which found a superiority of the abdominal measurement with OR = 0.97 [0.95; 0.99] ($p = 0.006$) to the thoracic measurement OR = 0.99 [0.98; 1.01] ($p = 0.87$).

Table 3
Evaluation of the different parameters measured in multivariate analysis.

	Ajusted Odds-Ratio[a]	p
a. Adjustment		
Muscle density L3	0.98 [0.94; 1.03]	0.5
Muscle surface L3	0.97 [0,95; 0,98]	<0.001
SMI	5,32 [1,90; 14,87]	0.001
SMD	1,81 [0,64; 5,15]	0,26
Superficial fat L3	0.98 [0,93; 1,05]	0.69
Visceral fat L3	1.01 [1001; 1,02]	0.015
Muscle density T4	0.98 [0,926; 1,04]	0.5
Muscle surface T4	0.98 [0,97; 0,99]	0.004
b. Comparison of T4 and L3 muscle surface area		
Muscle surface T4	0,99 [0,98; 1,01]	0,87
Muscle surface L3	0,97 [0,95; 0,99]	0,006
Sex	6,92 [2,1; 22,82]	0,001
BMI	1,11 [1,01; 1,21]	0,026
Percentage of lesion	1,08 [1,05; 1,11]	<0,0001
Pulmonary embolism	0,66 [0,05; 8,01]	0,73

SMD: Skeletic Mass Density; SMI: Skeletic Mass Index.
[a] After adjusting to sex, BMI, percentage of lung damage and associated pulmonary embolism.

4. Discussion

In this study we investigated the impact of sarcopenia and visceral adiposity on the severity of progression of SARS-COV2 infection and the occurrence of intensive care management in a hospitalized patient cohort. Decreased muscle surface area and muscle index measured in L3 were independent risk factors for intensive care hospitalization.

In addition, multivariate analyses performed after adjusting to gender, patient BMI, percentage of pulmonary parenchyma and associated diagnosis of pulmonary embolism concluded that muscle surface area measured in T4 was also an independent risk factor for intensive care hospitalization.

Conversely, the assessment of muscle density in T4 and the assessment of SMD did not appear to be significant in multivariate analyses showing their interdependencies with the various associated poor criteria.

Finally, we demonstrated that the visceral abdominal adipose surface measured at L3 was significantly higher in patients hospitalized in the intensive care unit.

To our knowledge, this study is the first to evaluate CT-measured thoracic sarcopenia as a predictor of the evolution of a COVID-19 infection.

Our results are in agreement with several studies on the importance of sarcopenia in the unfavorable evolution of patients in many diseases [14–17].

T4 sarcopenia has been evaluated in a carcinological context [19]. The fact that it appears as a predictive criterion of evolution independently of the other unfavorable criteria classically retained in the context of a pulmonary viral infection is a new fact. It suggests the importance of respiratory muscles in the quality of ventilation and its impact on the evolution of respiratory pathologies. Therefore, this criterion should be evaluated in all patients receiving chest CT scans, alerting clinicians to the potential negative clinical evolution of the patient and reflecting an increased risk of hospitalization in intensive care.

Similarly, lowered MSI and L3 sarcopenia evaluated in a multivariate study appear to be independent prognostic factors. This finding at the thoracic and abdominal level is indicative of systemic muscle damage and suggests the possibility of a common etiological cause of muscle loss [26].

The study conducted by Yang et al. [27] found a risk of poor evolution of an SARS-COV2 infection in cases of abdominal obesity. Our results corroborate these data and demonstrate the need to go beyond BMI with a more precise measurement of adipose tissue distribution. Indeed, it is known that the virulence of adipose tissue depends on its location and its capacity to produce inflammatory mediators that contribute to the evolutionary severity of COVID-19, probably increasing the “cytokine storm".

There was no difference in terms of age, BMI and risk factors between the 2 ″ intensive care/conventional hospitalization " groups, underlining the importance of sarcopenia, which does not only concern the elderly but also younger patients, especially when they are suffering of chronic diseases [28]. Furthermore, these data underline the importance of evaluating sarcopenia in the screening and diagnosis of malnutrition, as shown by the latest consensus meetings in France (HAS 2019) and worldwide [23].

However, our study has several weaknesses. Indeed, it is monocentric and the decision to admit a patient to an intensive care unit may vary depending on the teams and the number of beds available in the centers. Moreover, we did not include the different biological characteristics of the patients in our cohort, which could themselves be predictive factors for hospitalization in the intensive care unit.

5. Conclusion

Our study reveals a statistically significant association between sarcopenia and the risk of progression to intensive care hospitalization for SARS-COV2 infection. This association is independent of other known risk factors for aggravation of COVID-19.

Visceral abdominal adiposity is also an independent risk factor for a poor evolution of the patient.

All these parameters related to body composition suggest that an alteration in adipo-muscular status beyond weight and corpulence reveal a vulnerability of patients with COVID-19 that must be assessed at hospital admission. Finally, these results suggest that any respiratory pathology can be analyzed to determine the prognosis and that early action can be initiated to limit the evolution of the disease, particularly by using an individualized multimodal approach combining nutritional, physical and pharmacological intervention in the context of rehabilitation.

Conflict of Interest

None.

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