Combined ultrasound of m. quadriceps and diaphragm to determine the occurrence of sarcopenia and prolonged ventilation in a COVID-19 ICU cohort : the COVID-SARCUS trial

Combined ultrasound of m. quadriceps and diaphragm to determine the occurrence of sarcopenia and prolonged ventilation in a COVID-19-ICU cohort.

The COVID-SARCUS trial.

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Highlights:

- Muscle wasting and weakness occur unevenly in COVID-19 ventilated ICU patients.
- Relative preservation of diaphragm compared to quadriceps femoris muscle group.
- Increased muscle thickness and higher echo-intensity have a worse prognosis.
- The greatest loss of muscle thickness occurred between day 5 and day 10.
- Reduction in average pennation angle from day 0 up to discharge from ICU of 13.30%.
- The very low hand grip strength in this COVID19 cohort correlates with muscle mass.
- A higher BMI correlates positively with survival, but not with functional outcome.

Keywords: muscle ultrasound, diaphragm ultrasound, COVID-19 (SARS-CoV-2), sarcopenia, hand grip strength, ICU

Introduction

By March 2023, over 676 million cases of coronavirus disease (COVID-19), caused by the Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2), have been registered worldwide.[1] *(accessed on March 10, 2023; last day of data collection by John Hopkins University)*. Symptoms and severity of acute COVID-19 vary widely, ranging from asymptomatic or mild to severe critical illness with a need for mechanical ventilation. Myalgia and muscle loss are frequently present. Both symptoms coupled with prolonged mechanical ventilation and immobilization, can lead to severe sarcopenia and intensive care unit - acquired weakness (ICU-AW), continuing during the recovery period following COVID-19. The underlying mechanisms of muscle wasting are likely multifactorial and include altered substrate metabolism, anabolic resistance, hypoxia, inflammation, immobilization and nutritional inadequacy [2, 3]. People at highest risk appear to be those with comorbidities, more particularly diabetes, hypertension, and those smoking and of older age. There is also a delay in the diagnosis of ICU-AW due to the inability of patients to follow commands to enable accurate volitional strength testing.

Sarcopenia in the intensive care unit (ICU), defined by low skeletal muscle mass and function, is associated with negative clinical outcomes and increased mortality in survivors of critical illness.[4] There has been a growing interest in measuring the thickness of the skeletal and diaphragmatic muscles in critically ill patients since muscle wasting occurs early and rapidly during the ICU stay and contributes significantly to the development of ICU-AW, occurring in 50 to 100% of survivors.[5] Ultrasound (US) quadriceps femoris muscle assessment may constitute a convenient tool to evaluate muscle wasting. [6, 7] Mid-thigh muscle measurement is a good predictor of whole body muscle volume, and one of the tools used in sarcopenia diagnosis.[8] Ultrasonography is a nonvolitional measure that can be easily performed at the bedside – without requirement for a critically ill patient's transport nor radiation risk such as with CT. It is non-invasive and inexpensive and has little infection control implications. The assessment by ultrasonography of the quadriceps muscles thickness (MT) shows a good intra- and inter-observer reliability. [7, 9]

The aim of this study is to determine the prevalence and development of sarcopenia during prolonged ventilation in the COVID-ICU patient population by sequential quadriceps and diaphragm ultrasound parameters and its relationship with hospital outcomes.

Materials and Methods:

Design, setting and participants:

This single-centre prospective observational study was conducted in a mixed ICU in the university teaching hospital of Antwerp (Belgium) from October 2020 to April 2021. The study was in accordance with the ethical principles of the Declaration of Helsinki of 1964. Ethical approval was obtained from the University of Antwerp – Antwerp University Hospital ethics committee (B3002020000159). A waiver of informed consent was used as ultrasonography forms part of daily practice in the ICU.

Mechanically ventilated critically ill adult patients (age ≥ 18 years) with confirmed COVID-19 disease and anticipated to be intubated longer than 72h were included. We evaluated the relationship between muscle US parameters and measures of muscle function and length of mechanical ventilation, during the first 10 days in ICU and at ICU discharge. We recorded anthropometric data, serum inflammatory markers, ICU severity scores, respiratory mechanics and gas exchange parameters, daily fluid balance, and the number of calories and proteins administered. The clinical frailty scale was used to screen for the overall level of fitness.[10, 11]

Ultrasound measurements

The right rectus femoris muscle and the right hemidiaphragm were studied with US (Sonosite X-Porte, FUJIFILM SonoSite Inc., USA). US has the advantage over dual-energy X-ray absorptiometry and bio-impedance analysis to give both quantitative and qualitative information on muscle.[12] Ultrasound parameters that were studied included muscle thickness (MT) and cross-sectional area (CSA), fascicle length (Lf), pennation angle (PA) and echo-intensity (EI). PA and EI were evaluated offline with Horos (Nimble Co LLC d/b/a Purview in Annapolis, MD USA) on exported images.

The density of the tissue identifies whether there is loss of muscle fibre. Additionally, we evaluated the ultrasound index (USI).[13] This index diagnoses sarcopenia based on changes in muscle geometric proportions. Unlike Narici et al.[13] we evaluated the USI in de m. rectus femoris and not the m. vastus lateralis.

Parameters of muscle quantity and quality

Muscle mass of the diaphragm and quadriceps muscle were assessed ultrasonographically within 48h after intubation, at day 5, day 10 of mechanical ventilation and on the day of ICU discharge. All values are means over three repeated measurements.

Diaphragm thickness was measured with a high frequency linear transducer (12-15MHz) on the right chest wall in the ninth intercostal space mid-way between the anterior and mid-axillary line and held perpendicular to the chest wall.[14, 15] In this location, the diaphragm was identified as a three-layered structure just superficial to the liver, consisting of a relatively non-echogenic muscular layer bounded by the echogenic membranes of the diaphragmatic pleura and peritoneum. Temporary markings were applied to the skin to guarantee an identical positioning on subsequent days. Subjects were positioned on their back, with their upper body in a 30° angle, arms next to the upper body. The registration was done at end-expiratory lung volume. Digital images were stored and re-interpreted by a separate, blinded interpreter. We performed intra- and inter-operator reliability tests for each person performing these measurements prior to starting the inclusions. All diaphragm measurements were done by 1 operator (TS) who was trained in using bedside US in the ICU.

The quadriceps femoris is a group of muscles composed by three vastus muscles (medialis, intermedius, and lateralis) and the rectus femoris which presents a proximal insertion in the anterior inferior iliac spine and other insertion in the supra-acetabular sulcus. Lower limbs muscles are more subject to early disuse atrophy among critically ill patients than those of the upper [16] limbs, hence the m. rectus femoris was measured in this study.

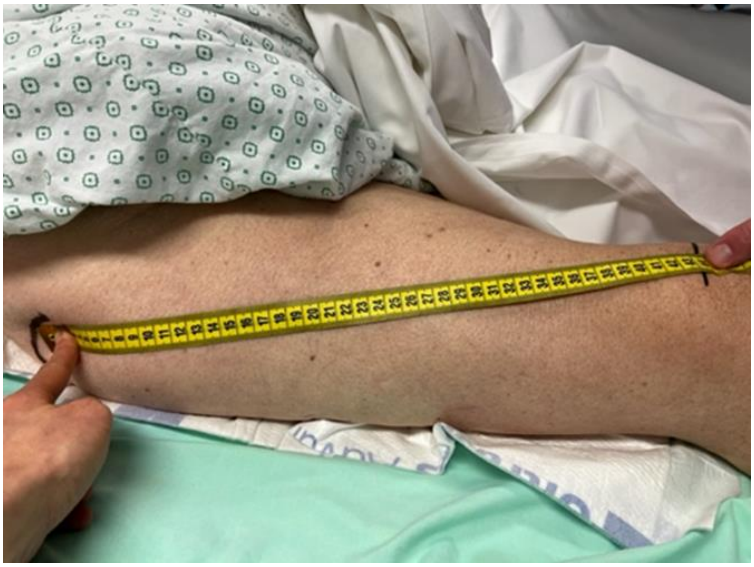
Quadriceps measurements were performed in supine, full extension, relaxed position of the right leg (dominant/non-dominant side mentioned) and no physiotherapy was executed 30 minutes before. The measurements were done at the middle point between the greater trochanter and the proximal border of the patella as proposed by the SARCUS group.[12] There is a strong correlation between the two legs in the analysis of muscle mass loss, the difference in muscle wasting between the legs being exceedingly small.[17] Given this fact, we evaluated the right leg. Temporary markings were applied to the skin to guarantee an identical positioning on subsequent days. (Figure 1) A generous amount of contact gel was used to minimize the required pressure of the transducer on the skin. Oblique scanning can lead to incorrect MT and EI and was avoided by adjusting the angle of measurement, as much perpendicular to the skin as possible, until the best image of the underlying bone was obtained. Rectus femoris CSA and MT were measured using a curvilinear probe (SonoSite© C60 60 mm broadband

curved array probe with frequency range of 5-2 MHz). Images for PA, Lf and EI were made with a linear transducer probe (SonoSite© HFL 38X linear transducer of with frequency range 13-6 MHz), depth was adjusted to view both muscle layers and femur. Thicknesses and areas were measured on frozen images. Our US system cannot perform all measurements on-screen. For the measurements after the 'live' examination we used Horos™. All quadriceps measurements were done by one operator (KD) who was trained in ICU ultrasound techniques.

The pennation angle is defined as the angle of insertion of muscle fiber fascicles into the deep aponeurosis.[18] Pennation angle was measured in the central portion of the image where the pennation angles are usually uniform, as opposed to the periphery.[19] The smaller the angle, the shorter is the muscle length and the lower is the strength.[20]

Figure 1 A and B: Quadriceps measurements.

Figure 1A. 3 measuring points are marked on the right leg. Landmarks: the middle of the upper border of the greater trochanter is marked; the middle of the superior border of the patella is marked; between these 2 points we mark the middle with the help of a measuring tape.



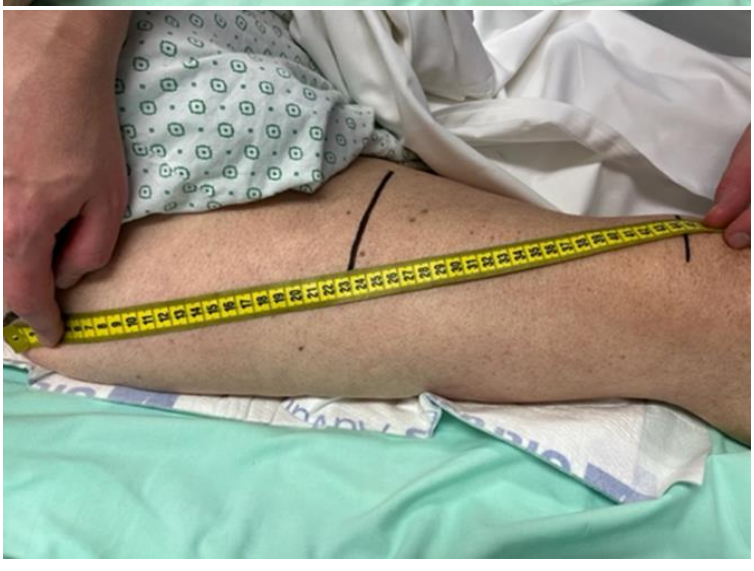
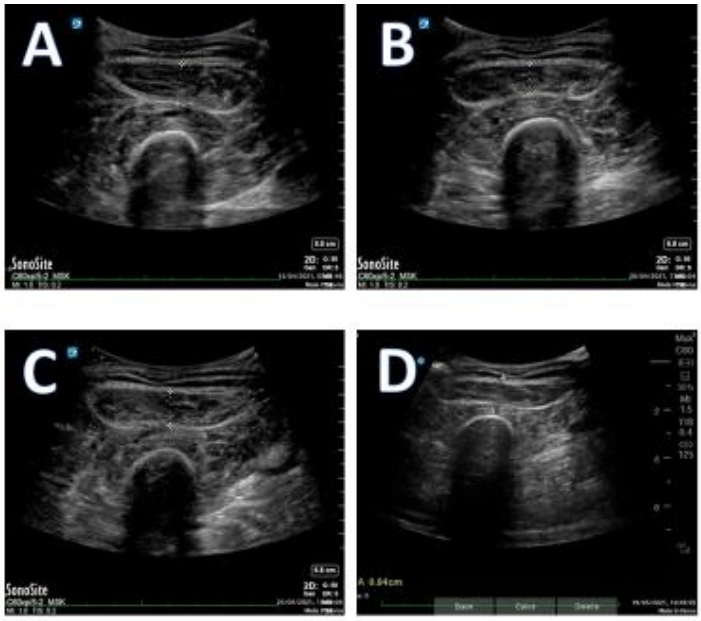


Figure 1B: Muscle mass of m. quadriceps was assessed ultrasonographically within 48h after intubation (panel A), at day 5 (panel B), day 10 (panel C) and on the day of discharge (panel D).



Fascicle length (Lf) was defined as the length of the fascicular path between the insertions of the fascicle into the superficial and deep aponeuroses. In those cases where the fascicle extended outside of the acquired ultrasound image, the length of the missing portion of the fascicle was estimated by extrapolating linearly both the fascicular path, visible in the image, and the aponeurosis.[18] Measurements were executed in Horos™, when direct measurements and if the extrapolation was not feasible, Lf was calculated using the following formula[18]:

Lf (mm) = MT (mm) * sin (PA)$^{-1}$ (Lf = fascicle length, MT = muscle thickness and PA = pennation angle).

Echo-intensity was determined by computer-assisted gray-scale analysis using Horos™. First, a region of interest was manually selected in each muscle to include as much of the muscle as possible without any bone or surrounding fascia. Second, echo intensity was calculated as the mean greyscale level of the pixels within the region of interest. Third, an average was determined from the three images. US system settings were kept unchanged throughout the study.

USI is an ultrasound imaging method for diagnosing sarcopenia based on changes in muscle geometric proportions. The values are independent of sex, height and body mass.

A total of 3 US measures per item (CSA, MT of m. rectus femoris and diaphragm, pennation angle, echogenicity, fascicle length) per patient and per evaluation day (day 0, day 5, day 10, discharge) were analysed.

Digital images were stored and re-interpreted by a separate, blinded interpreter. It has been previously shown that quadriceps femoris muscle and diaphragm thickness on US are reproducible techniques with high intraclass correlation coefficient.[21]

The study population was categorized into decreased thickness, increased thickness, and unchanged group, respectively in diaphragm and intercostal muscles. These categories were based on the change

in muscle thickness over the study period, based on previous studies.[22] Changes of thickness of 10 % or more were considered as relevant : The decreased thickness group was defined as those exhibiting more than 10% decrease in thickness from day one to the lowest value over the measurement period. The increased thickness group was defined as more than 10% increase in thickness without more than 10% decrease, and the remaining patients were categorized into an unchanged group.

Other recorded parameters

Patients or their next-of-kin were interviewed by using established questionnaires for their pre-hospitalization nutritional risk (NRS 2002) and functional status (clinical frailty scale CFS), [10, 23]

Fluid balance was evaluated daily and calculated automatically (Metavision v5, iMDSoft, Düsseldorf, Germany). The recorded intake consisted of enteral and parenteral nutrition and intravenous fluids, also including blood products. Output was calculated as the sum of urine (and/or ultrafiltration in case of renal replacement therapy), blood loss, drain output and gastric aspirates.

Hand grip strength was measured by an electronic hand dynamometer DynEx1™ (MD Systems, Inc. Ohio, USA). The recommendations for the handgrip strength test of the American Society of Hand Therapists were followed [24]: the patient was in sitting position with the non-dominant hand resting on the thigh. The patient was instructed to keep the ipsilateral shoulder in a neutral position, elbow in 90° flexion, and the forearm in neutral rotation. The patients were instructed to grip the dynamometer with maximum strength in response to a standardized voice command.[25]. There was at least one minute of rest between three consecutive measurements. The maximum of the three values was considered for analysis.

Statistical analysis

Data was entered into an electronic database (Microsoft Excel; Microsoft, Redmond, Washington) and analysed using SPSS v28 (IBM, Armonk, NY, USA).

Inclusion ended after 30 patients. An a priori sample size calculation was performed based on the primary variable in this study, the cross-sectional area of the rectus femoris muscle (RF-CSA). According to previous studies performed with the ultrasound technique on this muscle[5], we calculated the sample size with the following reference data: a mean RF-CSA of 514 mm^2 with standard deviation of 66mm. A 15% cut-off (77mm) was used to define clinically relevant muscle wasting. With an α level of .05 and a β level of .20, the suitable sample size was calculated to be 13 subjects for each group. Accordingly, we set the total sample size at 26 patients.

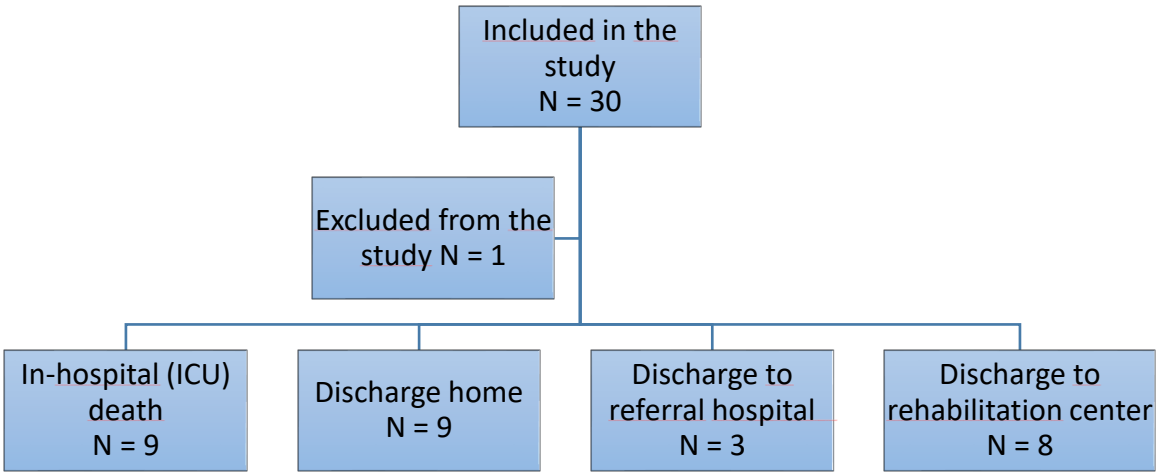
Normally distributed variables are expressed as mean with standard deviation. Other data are presented as median with range or count with proportion. Normality was tested with the Kolmogorov-Smirnov test. Association between ultrasound measurement variables was assessed by linear regression and Pearson correlation coefficient. Association of various parameters with mortality was analysed using a logistic regression model.

Results

Thirty critically ill patients were prospectively included within 48 hours following intubation (Table 1). One patient was excluded as COVID-19 disease was suspected on imaging, but PCR-testing turned out to be negative. (Figure 2)

The characteristics of our patient population (Table 1) show an overweight population with male predominance and arterial hypertension, chronic kidney disease and diabetes mellitus as most prevalent comorbidities. All patients had a NRS score > 3. Survival after 1 year was 69% (20 out of 29 of patients). Overall ICU mortality in the study period was 29.0% .

Figure 2 Diagram of the study



The median length of mechanical ventilation was 28.45 days (min 1.95 d – max 72.79 d), with nineteen out of twenty-nine patients who were already intubated on admission, however, we only included patients who were intubated for < 72h. All patients were under continuous sedation and twenty patients received continuous neuromuscular-blocking agents. All but one patient received corticosteroids.

All patients were monitored by a multidisciplinary team including ICU physicians, nurses, dietician and physiotherapists. The hospital has a feeding and early mobilization protocol for critically ill patients.

Table 1: Patient characteristics

	Global (patients/total number of patients n=29)	Min; max	Reference value
Ratio male/female (%)	65.5/34.5		
Age (years)	60.9	29; 79	
CFS	2,7	1; 6	
North African race	8/29		
Caucasian race	21/29		
BMI (kg/m^2)	29.7	20.76; 42.30	

Right leg dominance	27/29		
Smoking	3/29		
Alcohol abuse	3/29		
Co-morbidities: Ischemic heart disease	4/29		
Diabetes mellitus (100% type 2)	7/29		
Obesity	15/29		
COPD	2/29		
OSAS	5/29		
Immunocompromised: 1 CVID/1 chemotherapy/1 kidney transplant	3/29		
Chronic liver disease	2		
LOS prior to ICU admission	4.25 days	56 min; 25.6 days	
Inflammation parameters: IL-6 (pg/ml)	131.4	2.7; 752	< 7
CRP (mg/l)	162.6	10.3; 405.8	< 10
Use of: NMB Corticosteroids: - No steroids: - Dexamethasone 6 mg - High dose [26] (Meduri) - Combination dexamethasone + high dose:	 20/29 1/29 18/29 19/29 10/29		
LOS ICU (days)	4.25	2.3; 25.6	
LOS Hospital after ICU discharge (days)	10.66	max 37.7	
Time to intubation after admission (days)	1.8	max 9.6	
Already intubated on admission	19/29		
LOV (days)	28.45	1.95; 72.79	
PaO_2/FiO_2 (mmHg)	126,4	54; 250	
Prone positioning	21/29		
ECMO	4/29		
Time from COVID positivity to ICU admission	8.6 days	4.01 hours; 15.0 days	
Max CK level at discharge (U/L)	873.8	29; 4035	46-171
APACHE II (points)	15.5	9; 30	
SOFA (points) Day 0 Day 5 Day 10	 8.3 10.2 9.0	 1; 15 1; 17 3; 16	

List of abbreviations, alphabetically: Acute Physiology and Chronic Health Evaluation II score (APACHE II) ; BMI Body Mass Index; CFS Clinical Frailty Score; CK Creatine Kinase; COPD Chronic Obstructive Pulmonary Disease;

CRP C-reactive Protein; CVID Common Variable Immunodeficiency Disorder; ECMO Extracorporeal Membrane Oxygenation; ICU Intensive Care Unit; IL-6 Interleukin-6; LOS Length Of Stay; LOV Length Of Ventilation; min Minimum; max Maximum; NMB Neuromuscular-Blocking drugs; P/ F the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen; OSAS Obstructive Sleep Apnoea Syndrome; SOFA Sequential Organ Failure Assessment

Table 2 Nutritional parameters

	Day 5	*Day 10*	*ICU discharge*
% daily caloric target reached (min – max)	60.5% (0 - 95.5%)	77.4% (0 - 139%)	51.0% (13.1 – 122.9%)
% daily protein target reached (min – max)	56.2% (0 - 100%)	70.3% (0 - 136%)	37% (4-100.9%)
Cumulative fluid balance (ml/day) (min – max)	6361 (-1720 – 14210)	8665 (-2970 – 21010)	11116 (-1920 – 43470)
Hand grip strength (kg) (min – max)			6.89 (0 - 29.9)

Muscle measurements on ultrasound

The evolution of the muscle thickness of the m. rectus femoris and the diaphragm in our patient population can be divided into 3 groups and a distinct pattern between the two muscles was observed: stable in 36.8% of the patients, a loss of > 10% in 36.8% and an increase of > 10% in 26.3% for the diaphragm; there was an increase of > 10% in 26.3% of patients, in 21.1% a decrease of > 10% and in 52.6% the m. rectus femoris remained stable. (Figure 3) The changes between both muscles were not correlated (Pearson-Chi Square 3.91, p = 0.419).

Mean baseline m. rectus femoris thickness was 1.36 ± 0.4 cm (95% CI 1.21 – 1.51 cm). Between day 0 and day 5 we measured an increase in muscle thickness in 15 out of 29 patients (51,7%). All these patients had a positive fluid balance (6.87 l on average (min 0.5 l, max 13.71 l)) and 60% of these patients had one or more sessions of prone ventilation. We detected a correlation between muscle thickness on day 10 and ICU mortality, but only for m. rectus femoris (Figure 4): patients with increased muscle thickness had a worse prognosis. Difference in muscle thickness is linked to outcome for both the m. rectus femoris and diaphragm, with the best survival seen in the group with stable muscle thickness (<10% change in thickness from baseline).

Figure 3 Change in rectus femoris thickness from baseline in survivors and non-survivors.

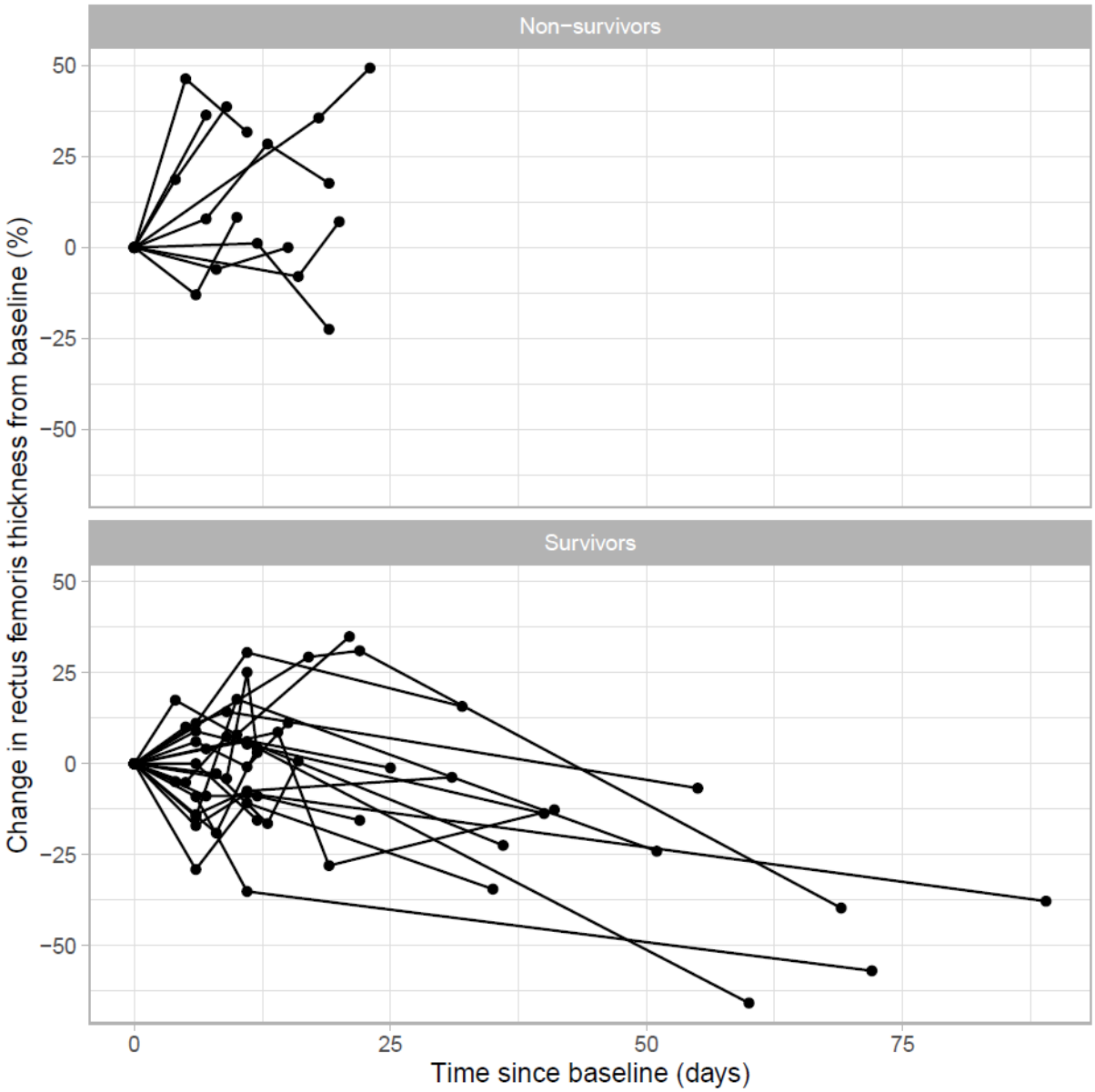
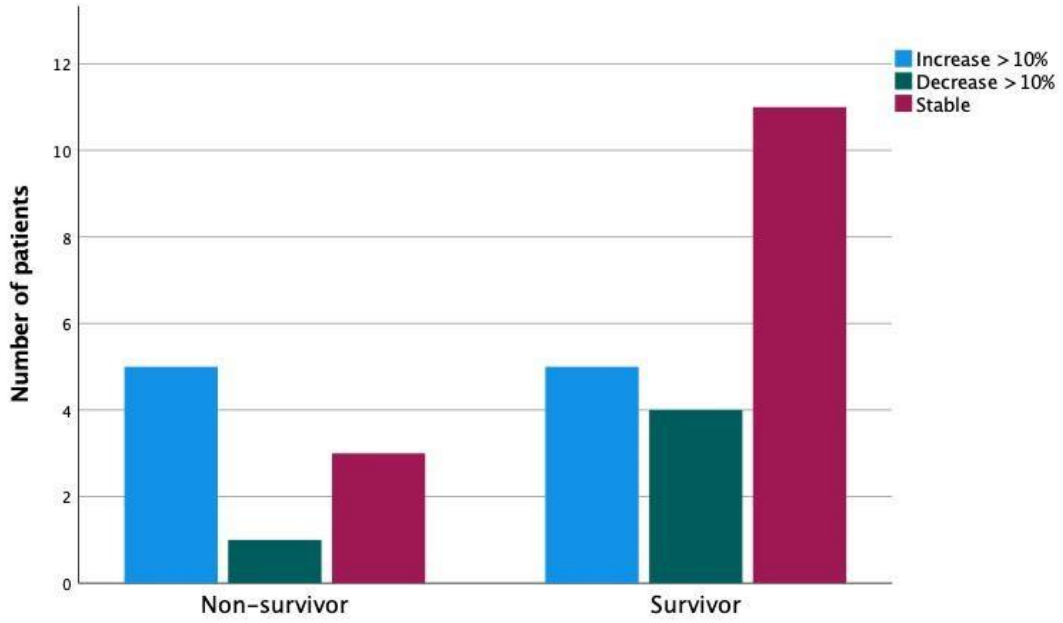


Figure 4 Correlation between change in muscle thickness of m. rectus femoris and outcome in non-survivors and survivors, each divided in the 3 patient groups of decreased thickness, increased thickness, and a stable group.



There was a correlation between CSA on day 5 and handgrip strength (r = 0.290, p = 0.010). There was no correlation between CSA on day 10 and pennation angle nor echo-intensity nor outcome (p = 0.581 and p = 0.852).

Echo-intensity

In our population no statistically significant difference could be seen between day 0 and day 5, nor between day 5 and 10, but there was a correlation between day 0 and day 10 (p 0,0049; r= 0,5348; 95% CI 0.1860 to 0.7639) and day 0 and discharge (p 0,0049; r= 0,4860; 95% CI 0.09226 to 0.7483) and with outcome. On day 5 there was a higher echo-intensity in the group of patients with an increase in muscle thickness.

There was no correlation between echo-intensity on day 10 and discharge destination (home, referral hospital, rehabilitation centre)(Kruskal-Wallis p=0.245).

Diaphragm

The included patients started with a low value of diaphragm thickness (median 1.8mm, IQR 1.5 – 2.2mm), which is an independent predictor of worse outcome. [27] The average diaphragm thickness was stable through the disease course in 52.6% of patients.

We found no correlation between the difference in muscle thickness of the m. rectus femoris and diaphragm and no correlation either between diaphragm change and pennation angle on day 10 (p = 0.331).

Pennation angle

We found a significant correlation between baseline pennation angle and muscle thickness of m. rectus femoris (r=0.476; p=0.02) We measured a change in average pennation angle from day 0 up to discharge from ICU of 13.30%.

Fascicle length Lf and USI

The ratio of Lf/MT was calculated to obtain an ultrasound index (USI) of the loss of muscle mass associated with sarcopenia [13] In our cohort we found no correlation between USI and age. USI was not associated with the need for reintubation or length of ventilation. There was no correlation found between USI and LOS (p = 0.646).

Hand grip strength

We measured hand grip strength on discharge in nearly all the survivors (19/20). All patients have very low values (mean 7.65; min 0-max 31; SD 6.66). We did find a correlation with CSA on day 5 (r=0.53; p=0.33).

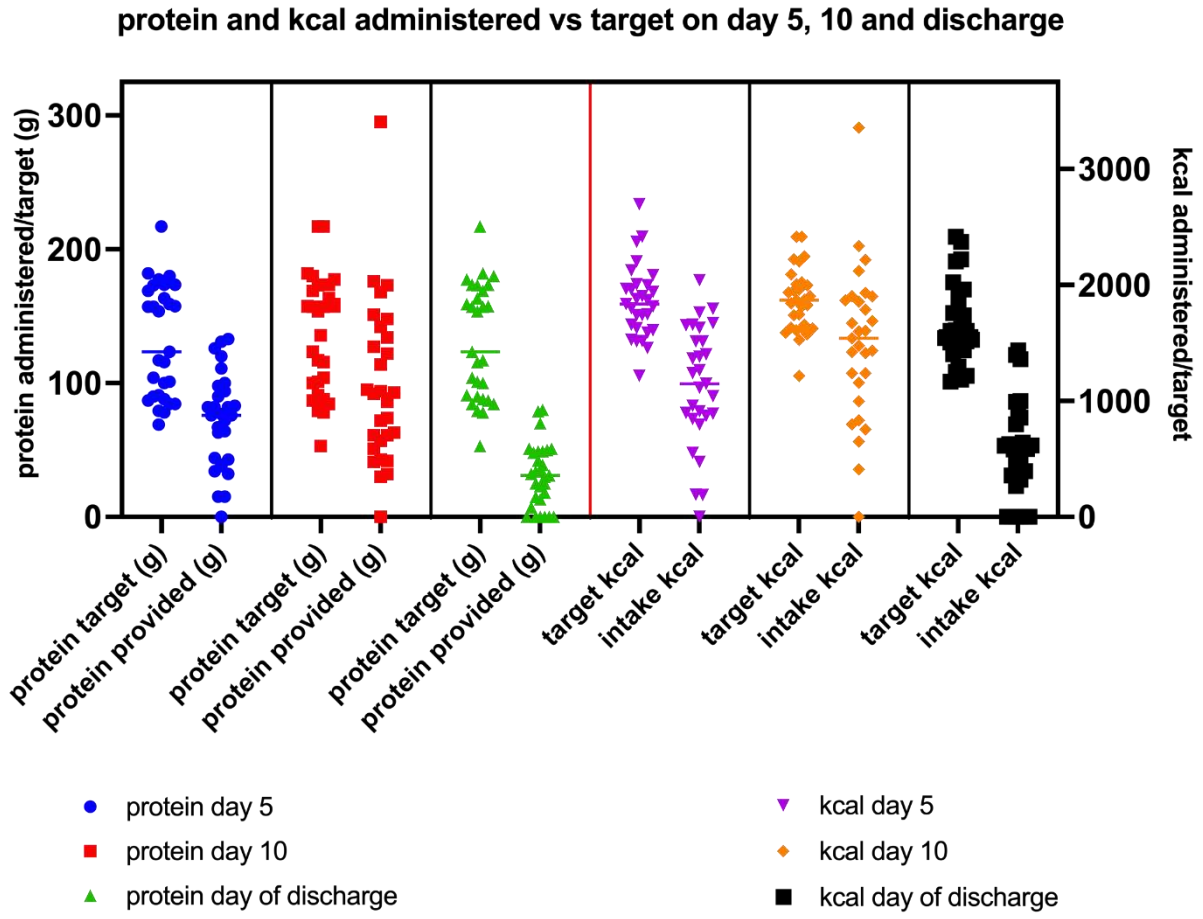
There was no correlation between handgrip strength and m. rectus femoris echo-intensity (p = 0.948).

Nutrition parameters

Each patient received an individual nutrition plan with protein and calories according to personal clinical needs. As an index of adequacy of the nutritional support, the cumulative energy and protein deficits were calculated, as the difference between the calorie or protein target and the amount actually delivered to the patient. (Table 2, Figure 5)[28]

A correlation between BMI with outcome was demonstrated (p = 0.022; unadjusted Odds ratio 1.27).

Figure 5 Difference between protein and kcal administered versus target set on day 5, 10 and discharge.



Discussion

To test our hypothesis of a relationship between muscle US parameters of both diaphragm and quadriceps and measures of muscle function and length of mechanical ventilation we studied a homogeneous, phenotypically well characterized cohort of ICU patients (Table 1). Since they all suffered from the same disease, we could assume consistency in the drugs they received during their stay. Patients received different doses of steroids (Table 1). In an earlier study [29], however, there was no correlation between the hydrocortisone dose with rectus femoris cross-sectional area, muscle thickness and echo-intensity.

Our data add to the knowledge on sarcopenia in the critically ill COVID-19 patient. Indeed, to date, there are only two other studies, from the same study group, which investigated the time course of both respiratory and limb muscle mass and quality in critically ill patients with COVID-19, and to relate the findings with the nutritional strategy and the outcomes. [30, 31] Our study is the only one to stretch beyond the first week of ICU stay, with repeated ultrasound measurements and follow-up until ICU discharge.

MT, CSA and echo-intensity

In the present study a different evolution of the muscle thickness (MT) of the diaphragm and the m. rectus femoris (RF) was observed, the changes between the two muscles were not correlated. In more than half of the patients MT of RF remained stable. The group with increased MT had worse outcomes. The greatest loss of MT occurred between day 5 and day 10.(Figure 3) This finding is partially different from Umbrello M et al. where both RF CSA and diaphragm thickness were significantly reduced after one week of ICU stay, with a more pronounced reduction in non-survivors [31].

Possible explanations for these differences are: selective oedema in muscles, effect of prone positioning, inflammation and infection, or an acute disuse phenomenon.

Muscle is mainly composed of water and may significantly change with dehydration and fluid overload.[32] We found no correlation between the different evolution groups in MT change (stable, increase, decrease) and fluid balance. The subgroup of patients with an increased MT of RF on day 5 had a positive cumulative fluid balance (ranging from + 0,5 L to + 13,6 L) and 66,7% of these patients were ventilated in prone position for minimum 16 hours of the day due to severe hypoxemia despite IMV. This might lead to fluid shift to the anterior compartment of the thigh, which might have influenced the US measurements when the patient was put back in the supine position.

Muscle ultrasound echo-intensity is normally low: healthy tissue contains little fibrous tissue, leading to little sound reflection. In disease, replacement of muscle with fat or fibrous tissue increases echo-intensity. Increased echo-intensity correlates with reduced strength and function with age [33, 34] and is expressed in grey scales (0-255).[18] The echo-intensity was higher in the patients with increased muscle thickness, who also had a worse prognosis. This finding is in line with the two previous studies on this topic [30, 31] which also found a significantly lower echogenicity score for rectus femoris and diaphragm in survivors as compared with those wo did not survive. It could be suggested that the increase in RF echo-intensity may be representative of the infiltration of fatty and connective tissue and muscle necrosis associated with the remodelling of muscle fibres leading to qualitative impairment [3, 5, 29, 35, 36]. Excessive fluid resuscitation with a positive fluid balance in septic shock patients may partly account for unspecific muscle oedema in the acute stage of the disease. In later stages of COVID-disease and ICU stay, fluid balances are more balanced. However, there was no correlation between echo-intensity and fluid balance, nor between MT and CSA and fluid balance.

Systemic inflammation may contribute to damage to the respiratory and peripheral muscle groups. Markers of systemic inflammation such as IL-6 and TNF-α are associated with myosin loss and have the potential to induce skeletal muscle proteolysis. COVID-19 is characterized by an exacerbated cytokine response that can amplify inflammatory and immobility-induced changes in muscle and have secondary effects that propagate damage.[16, 37] The patients in our cohort had markedly increased IL-6 values (Table 1), which is the best early biomarker for disease severity and has pleiotropic pro-inflammatory effects. Systemic inflammation might have played a role in muscle loss in this cohort. COVID-19 can act as a catabolic stimulus on muscles with a high risk of developing acute sarcopenia. Muscle enzymes were elevated in our patients (Table 1), there might be a direct effect of viral infection to muscular structures that may be exacerbated by inflammatory disease.[30]

Muscle atrophy and decline in muscle strength appear very rapidly with prolonged disuse after acute hospitalization. The greatest rate of muscle strength decline and atrophy occurred in the earliest stages of bed rest (first ten days) and plateaued later. Bed rest degradation is progressive but not linear.[38] The first day of ICU admission does not necessarily reflect the first day of critical illness, as patients were already sick for some days (median time from positive COVID-19 test to ICU admission was 8,6 d) the greatest muscle loss might already have taken place before ICU admission in this population, hence the low starting values and the less pronounced loss.

Only 31.03% (9/29) of our patients were able to return to their preadmission residence on discharge from their acute hospital stay without any additional rehabilitation, which suggests that muscle loss and weakness detected in the ICU could be a predictor of patients' discharge disposition or level of independence.

Diaphragm

Most of the patients started off with a low value of diaphragm thickness (<2 mm) and during ICU stay and disease course the average diaphragm thickness remained stable in 52.6% of patients. There are several possible explanations for this stability and low start value: patients were already ill for several days/weeks prior to admission in ICU (median of 4.25 days in hospital before ICU admission, Table 1). Patients might still have had spontaneous diaphragm activity despite widespread use of neuromuscular blocking agents, as the diaphragm is the most difficult muscle to paralyze. The survivors all had preserved diaphragm thickness.

In a study of US measures in mechanically ventilated patients with sepsis, these patients had no significant difference in diaphragm thickness, when compared with healthy controls, but do have significantly less thigh muscle thickness.[16]

Pennation angle

Muscles with bigger pennation angles are thicker, as they have greater numbers of sarcomeres in parallel with the direction of the fascicle. It is possible that these parallel sarcomeres are lost first, causing loss of pennation angle as an (early?) indicator of muscle wasting.[20] We measured a change in average pennation angle from day 0 up to discharge from ICU of 13.30%. The hypothesis is that this is linked to a larger amount of myosteatosis and/or fibrosis.[12]

Fascicle length (Lf) and USI

We calculated the ratio of Lf/MT to obtain an USI for diagnosing sarcopenia based on changes in muscle geometric proportions. In the article of Narici et al.[13], USI is specific for m. vastus lateralis and values are used to stratify patients to their muscle sarcopenic status. As we measured m. rectus femoris we cannot stratify our patient cohort according to the same values. This is the first study to evaluate the USI in m. rectus femoris.

Some of our patients might have suffered from pre-existing sarcopenia, the prevalence of which is relatively high in patients who need invasive mechanical ventilation (up to 43% in a study of Jiang T et al.)[39] Patients with sarcopenia have a longer duration of mechanical ventilation (LOV) and LOS in ICU and hospital.[40] The combination of possible pre-existing sarcopenia and a small cohort makes it difficult to evaluate cut-off values for the rectus femoris USI as was proposed for the m. vastus lateralis in the article of Narici et al.[13]

Hand grip strength

This cohort demonstrated a substantial floor effect, with very low hand grip strength values, which makes further differentiation difficult. We do find a (weak) correlation with CSA on day 5, mainly due

to the low values of the handgrip strength. However, this suggests that there exists a correlation between muscle strength (hand grip strength) and muscle mass on day 5 too. Ultrasound measurement of RF-CSA has been shown to be correlated with muscle strength previously.[41]

A decline in muscle strength is a common consequence of prolonged disuse and muscle atrophy is generally considered as the major cause of this phenomenon. A 30 % fall in CSA occurs within 90 days of strict bed rest. However, the decrease in CSA is smaller than the decline in force, indicating deterioration in force per unit CSA.[42]

Hand grip strength and muscle mass have been shown previously to be predictive of clinical outcomes, such as hospital length of stay (LOS) and mortality. [40] We were not able to measure hand grip strength on inclusion as patients were mechanically ventilated and sedated. No study attempted to control for prehospital muscle function or overall functional status as a predictor of ICU acquired weakness, the impact of which is still unknown.[20] The patients in this study have a mean Clinical Frailty Score of 2.7, which indicates they are somewhere between fit and managing well, assuming the acute disease state itself can be held responsible for the very low hand grip strength values.

Nutrition parameters

Patients with COVID-19 have a high prevalence of nutritional complaints with a high risk of developing acute sarcopenia.[43] In our study the mean BMI of survivors is 31,82 and 24,95 for the non-survivors. BMI is associated with an improved outcome, a phenomenon known as the “obesity paradox”, and has been supported from large meta-analyses and recent studies. Main pathophysiologic mechanisms related to obesity that could explain this phenomenon include higher energy reserves, inflammatory preconditioning, anti-inflammatory immune profile, endotoxin neutralization, adrenal steroid synthesis, renin-angiotensin system activation, cardioprotective metabolic effects, and prevention of muscle wasting. [44-46]

In our study, BMI was not associated with better functional outcome, we found no correlation between BMI and hand grip strength.

There is a considerable difference in percentage of reached target kcal and protein between day 10 and day of discharge from ICU. A possible explanation is the preparation for transition to the ward with (too early) removal of the nasogastric tube.

Quadriceps muscle assessment by US might be a promising tool to evaluate the effect of nutritional-based interventions on muscle wasting in critically ill patients.

Limitations and strengths:

This study has some limitations. This is a single-centre study, and the findings may not be generalizable to other settings. However, this may also be seen as a strength, because the sedation, ventilator settings and weaning and early mobilization protocols are similar across the whole patient group.

Although this study is adequately powered to detect changes in the selected outcomes, it is still a small cohort. A total of 235 patients was admitted to our ICU during the study period, however, as we are a referral centre, a lot of these patients were already intubated for several days upon admission and could not be included. One of the strengths of our study is that this group has been followed from admission until discharge from ICU, data are not limited to the first week of ICU stay.

Most of the patients were already ill for some days (8,6 days from positive COVID-19 testing to admission in ICU, Table 1). It is not possible to say which patients had lost muscle as a result of their illness and others before onset of disease.

Volitional muscle strength measurements were impossible on admission as patients were sedated.

There are some specific limitations regarding the use of ultrasound: there is still a lack of standardization of the ultrasound methodology, and the ICU setting poses challenges to making reliable ultrasound measures. However, in our study we had a single trained person to execute all m. quadriceps measurements and another single trained person to do all diaphragm measurements. We did take additional factors such as hydration, the use of corticosteroids and neuromuscular blocking agents into account.

The lack of a control group limits the comparison with other critical illnesses. Despite this, the objective of this study was to document muscle loss in this specific COVID-19 population who all needed IMV.

CONCLUSION

Critically ill patients with COVID-19 had a high risk of developing sarcopenia with the greatest loss of muscle thickness occurring between day 5 and day 10 of ICU stay. There was no correlation between the evolution of the muscle thickness of the diaphragm and the m. rectus femoris. The group with increased muscle thickness had higher echo-intensity scores and worse outcomes. The best survival was seen in the group with stable muscle thickness. Hand grip strength results showed very low values, and were correlated with muscle mass.

Muscle wasting and weakness may occur unevenly in patients recovering from COVID-19 and an extended period of mechanical ventilation.

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