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Research article

Body composition on low dose chest CT is a significant predictor of poor clinical outcome in COVID-19 disease - A multicenter feasibility study

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ABSTRACT

Purpose: Low-dose computed tomography (LDCT) of the chest is a recommended diagnostic tool in early stage of COVID-19 pneumonia. High age, several comorbidities as well as poor physical fitness can negatively influence the outcome within COVID-19 infection. We investigated whether the ratio of fat to muscle area, measured in initial LDCT, can predict severe progression of COVID-19 in the follow-up period.
Method: We analyzed 58 individuals with confirmed COVID-19 infection that underwent an initial LDCT in one of two included centers due to COVID-19 infection. Using the ratio of waist circumference per paravertebral muscle circumference (FMR), the body composition was estimated. Patient outcomes were rated on an ordinal scale with higher numbers representing more severe progression or disease associated complications (hospitalization/ intensive care unit (ICU)/ tracheal intubation/ death) within a follow-up period of 22 days after initial LDCT.
Results: In the initial LDCT a significantly higher FMR was found in patients requiring intensive care treatment within the follow-up period. In multivariate logistic regression analysis, FMR ($p < .001$) in addition to age ($p < .01$), was found to be a significant predictor of the necessity for ICU treatment of COVID-19 patients.
Conclusion: FMR as potential surrogate of body composition and obesity can be easily determined in initial LDCT of COVID-19 patients. Within the multivariate analysis, in addition to patient age, low muscle area in proportion to high fat area represents an additional prognostic information for the patient outcome and the need of an ICU treatment during the follow-up period within the next 22 days.
This multicentric pilot study presents a method using an initial LDCT to screen opportunistically for obese patients who have an increased risk for the need of ICU treatment. While clinical capacities, such as ICU beds and ventilators, are more crucial than ever to help manage the current global corona pandemic, this work introduces an approach that can be used for a cost-effective way to help determine the amount of these rare clinical resources required in the near future.

1. Introduction

Coronavirus disease (COVID-19) has been identified as an outbreak of severe acute respiratory syndrome in Wuhan, Hubei Province, China in the beginning of December 2019. It is caused due to a highly pathogenic human coronavirus, actually named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. While the real-time reverse-transcription polymerase chain reaction test (RT-PCR) is considered the gold standard for the diagnosis of COVD-19, additional low-dose chest computed tomography (LDCT) is often performed, as CT is nearly ubiquitously available for diagnostic of COVID-19 with a high sensitivity and short acquisition time [3]. Due to early disease detection

Abbreviations: LDCT, Low dose computed tomography; FMR, Fat to muscle ratio; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ICU, Intensive care unit; RT-PCR, Reverse-transcription polymerase chain reaction test; SD, Standard deviation; MRI, Magnetic resonance imaging; AIC, Akaike-Information-Criterion.

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and possible quantification of lung involvement in COVID-19 pneumonia, chest CT is recommended in many guidelines within the scope of immediate diagnostics for suspected SARS-CoV-2 infections [4,5]. Thus, the initial workup of patients with suspected COVID-19 pneumonia frequently includes an early LDCT chest examination for quantification of the pulmonary involvement and to exclude other diagnoses [6]. The degree of pulmonary involvement quantified in these CT examinations may be associated with the progression and prognosis of COVID-19, but is also affected by a large variance regarding the individual stage of the disease or other clinical parameters [7,2]. In addition, demographic factors, especially age, but also comorbidities including cardiovascular diseases and chronic obstructive pulmonary disease, are major determinants of patients outcome in COVID-19 infection [8,9].

Several studies hinted that obesity is a risk factor for greater severity and hospitalization in COVID-19 patients [10–12]. One of the factors explaining this phenomenon might be an upregulated expression of angiotensin-converting enzyme 2 - the functional receptor for SARS-CoV-2 - in adipocytes of obese and diabetic patients. Thus, adipose tissue might present a potential target for SARS-CoV-2 and turn into a viral reservoir, leading to a more severe manifestation of the disease [13]. In general and also particularly in connection with infectious diseases, obesity can increase the risk of thrombosis, leading to disseminated intravascular coagulation and venous thromboembolism [14–16]. Apart from thrombotic consequences, obesity has adverse effects on lung function, as the forced expiratory volume and the forced vital capacity decrease in general [17–19]. Other studies found that obesity in general is associated with aggravated processes and increased treatment complications in COVID-19 disease [12,19].

To determine body composition in clinical routine, bioelectrical impedance analysis is a widely used method to determine body composition; however, it sets high standards for examination conditions and patient preparation. These requirements cannot always be fulfilled in the case of a patient admission with suspected acute respiratory infection, especially since certain hygienic standards must be observed due to the increased risk of contamination [20–24]. Other established methods to determine body composition are dual-energy X-ray absorptiometry, magnetic resonance imaging (MRI) and CT.

Different approaches have been described to determine body composition in a CT scan: While some approaches use a skeletal muscle index approximating body size, others examine the paravertebral or psoas muscle area at lumbar height in axial CT slices [25–28]. While waist circumference in abdominal CT can easily be measured in a cross-sectional area of the patient's body and is highly correlated with total abdominal fat tissue as the sum of visceral and abdominal subcutaneous fat, muscle mass may also be a variable affecting the individual waist circumference [27–29]. For this reason, some authors suggest that the waist circumference should be considered in relation to muscle mass in order to gain more precise information on the amount of abdominal fat tissue [27,30–32]. Hence, the standardized CT-based measurements of the body composition we applied provide a high degree of validity with regard to the physiologically present body composition [26,30,31,33].

Since, as described above, LDCT is clinically performed in patients with suspected COVID-19 infection, information regarding body composition might be obtained opportunistically. However, assessment of body composition in those patients has not been utilized so far.

Considering the above-mentioned theory that obesity as well as a comparatively lower muscle area represented in a high FMR may have an unfavorable influence on the outcome of an acute SARS-CoV-2 infection, the purpose of this study was to analyze the FMR as an early biomarker in an early LDCT of the chest for a poor clinical outcome and the necessity of intensive care treatment within the follow up period.

2. Material and methods

The methodology used in this study involving human participants was in accordance with the ethical standards of the institutional and national research committee as well as the Declaration of Helsinki of 1964. This retrospective study was approved by the institutional review board (No. 20-1216), University of Cologne). No scan was conducted explicitly for the purpose of this study. Imaging was only performed in case of a clinical indication.

2.1. Patient enrollment and follow up

We screened our database for consecutive patients from the first confirmed case of COVID-19 at University Hospital of Cologne (center 1) and from HELIOS Schmidt Hospital, Wiesbaden (center 2) in March and April 2020. Inclusion criteria were a) main reason for clinical admission is due to a symptomatology associated with a COVID-19 infection, b) parallel LDCT and c) a positive RT-PCR SARS-CoV-2 test.

Exclusion criteria were:

a) Other acute pathology at the time of admission responsible for the respiratory symptoms including acute pulmonary artery embolism, acute coronary syndrome and aspiration.
b) Children and adolescents under 18 years.

Under consideration of the inclusion and exclusion criteria, 58 patients were finally enrolled in the investigation.

The outcome and clinical development were evaluated on an ordinal scale from 1 to 5 for each patient with higher numbers representing higher severity of progression or disease associated complications (no hospitalization = 1 / hospitalization = 2 / intensive care unit (ICU) = 3 / tracheal intubation = 4 / death = 5). The highest achieved status during the observation period of 22 days beginning with admission to the hospital was collected. 22 days was the maximum survival time of deceased patients recently published in The Lancet 4/2020 (median 18.5 days, 15.0–22.0) [34]. All patients who were rated 4 or 5 on the scale in the observation period had previously been on an intensive care unit, so condition 3 or higher can be considered as "intensive care obligation", which was the focus in the present investigation. In addition, the respective radiological stage of a COVID-19 disease was recorded and divided into corresponding established four stages of lung CT findings: ground-glass opacities, crazy-paving pattern, consolidation, resolution of consolidation [35].

2.2. Scanning protocol LDCT and image reconstruction

The scans were performed on state-of-the-art multi-slice CT scanner; iCT 256 (Philips, Amsterdam, Netherlands; center 1) and SOMATOM Definition AS+ (SIEMENS, Erlangen, Germany); center 2). Patients were placed in a head-first supine position. No contrast agent was admitted.

Scan parameters for the Philips scanner in center 1: 29.4 ± 9.4 mAs, collimation 80 × 0.625 mm, pitch 0.763, tube voltage 120 kV, mean CTDIvol 2.1 ± 0.6 mGy, mean DLP 86.2 ± 26.8 mGy*cm. For center 2 (SIEMENS scanner): 116.3 ± 41.3 mAs; collimation 38.4 × 0.6 mm; pitch 1,2; tube voltage 100 kV; CTDIvol 7.6 ± 2.5 mGy. Mean DLP 262 ± 90.2 mGy*cm.

For the Philips scanner, images were reconstructed in a 512 × 512 matrix containing pixels of 0.68 × 0.68 mm. Slice thickness was 2 mm with an overlap of 1 mm (SIEMENS: 512 × 512 pixels of 0.64 × 0.64 mm, slice thickness 1 mm, overlap 0 mm).

2.3. Measurements of muscle area to body fat composition

We followed the proposed procedure and determined the fat mass on the basis of the body's circumference common to literature [27,31]. Subsequent exact determination of the fat content by calculation on the basis of a suggested formula had to be omitted, as it provides a gender-specific weighting, which according to our procedure should only be performed within the multivariate regression analysis, so that the influence of gender and fat or muscle mass can be considered separately [31]. Measurements were performed by a radiologist (reader 1, more than one year of experience in CT abdominal imaging) using the institute's standard DICOM viewing software (Impax EE R20, XVII SU1, Agfa Healthcare, Mortsel, Belgium) [26,30,31]. In each case, the complete body circumference was measured in the initial CT scan, no clipping of tissue occurred. The 12th thoracic vertebra was recognized as the last vertebral body in the sagittal plane to be completely depicted on all CT scans. The measurements were performed in axial plane oriented at the center of the 12th thoracic vertebra. Using a freehand region of interest tool, the circumference of the autochthonous spine muscles as well as the whole cross-sectional circumference of the patient were determined (see Fig. 1). Mean muscle area was determined by averaging both sides. The FMR was calculated from the ratio of the average muscle area and the whole cross-sectional area of the patient (see formula 1). To determine inter- and intrareader reliability, 10 patients were randomly selected from the data set and measured twice by reader 1. Furthermore, another 10 randomly selected patients were measured by a second radiologist (reader 2, more than one year experience in abdominal CT imaging).

$$FMR = \frac{C_{waist}}{C_{spine\ muscle\ right} + C_{spine\ muscle\ left}/2}$$

Formula 1: Estimation of the fat to muscle ratio measuring the waist and autochthonous spine muscle circumference (C).

2.4. Statistics

Statistical data analysis was performed using R version 3.6.2 on Rstudio version 1.2.5033 [36]. Figures were plotted using the *ggplot2* package [37]. To predict the categorical variable of intensive care treatment, a multivariate logistic regression analysis was used. The *glm()* function was used in "*binomial*" specification taking the independent variables of age, gender, and body composition into account. To illustrate the accuracy of fit, pseudo-R^2 according to Nagelkerke / Cragg & Uhlers was calculated using the *descr* package (.2 > acceptable, .4 > good, .5 > very good) as well as the Akaike-Information-Criterion (AIC; low value indicates a higher informativeness of the model) [38]. Continuous variables were reported as mean ± standard deviation (SD). Intra- and interreader reliability was tested using the intraclass correlation coefficient in two-way random-effects model (<.5 poor, >.5 moderate, > .75 good, > .9 excellent) using the *irr* package. Statistical significance was defined as $p \leq .05$.

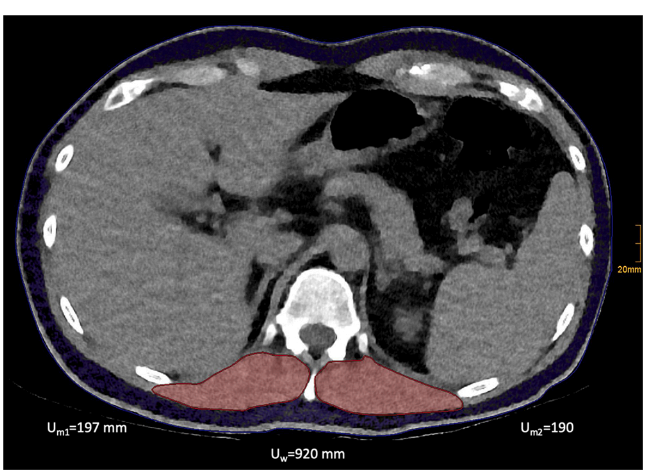

Fig. 1. Measurement method.
Fig. 1 Exemplary measurement of the paraspinal muscle circumference (red) and waist circumference (blue) in a 36-year-old male patient. Mean muscle circumference (U_m) = 193.5 mm, waist circumference (U_w) = 920 mm resulting in a muscle-to-fat ratio of 4.8. No intensive care treatment was necessary for the patient.

3. Results

3.1. Patient characteristics and clinical outcome

Due to acute pulmonary artery embolism (n = 1), acute coronary syndrome (n = 1) and aspiration (n = 1), 3 patients were excluded, resulting in 58 patients, 37 were male and 21 female. The mean age was 59.3 (SD ± 16.2). All patients underwent a throat swab and a clinically indicated LDCT due to suspected COVID-19 infection. In 51 (87.9 %) of the patients, RT-PCR tests were immediately positive for SARS-CoV-2, in a further 5 (8.2 %) patients tests were positive within the next two days and 2 (3.5 %) patients showed a positive sputum result within the next three days - in total, all patients included in the study were tested positive for SARS-CoV-2. All patients showed clinical symptoms such as malaise, fever, cough or shortness of breath upon admission to the hospital.

Among the patients included, 45 (78 %) had to be hospitalized, where of 26 (45 %) had to receive intensive care. 12 (21 %) of these individuals were placed on mechanical ventilation and 6 (10 %) died (three without having been mechanically ventilated prior to their passing) within the observation period of 22 days. Since not all patients in this study arrived at the hospital at the beginning of the infection, the stages vary accordingly. The following radiological stages were assessed: ground-glass opacities 31 (53 %), crazy-paving pattern 8 (14 %), consolidation 14 (24 %), resolution of consolidation 5 (9%). Due to the non-ordinal character of the different radiological scales of corona infection, this was not included in the logistic regression model (for instance consolidation vs. resorption stage). Since the prognostic value of the amount of lung involvement is depending on the individual stage, assessment of the individual lung involvement would therefore not result in an added prognostic value between the stages in the present study design [35,39,40]. Detailed information on patient characteristics are listed in Table 1.

3.2. CT measurements

CT measurements resulting in a mean muscle circumference of 175.3 mm (SD ± 29.8), waist circumference of 1018.2 mm (SD ± 134.9) resulting in a mean FMR of 5.9 (SD ± 1.3). Man showing a mean muscle

Table 1
Patient characteristics.

	mean (SD)	count (%)	Fat muscle ratio (SD)
age (y)	59.3 (± 16.2)		
sex_{female}		21 (36.2 %)	
mean muscle circumference (mm)	175.3 (± 29.8)		
waist circumference (mm)	1018.2 (± 134.9)		
fat muscle ratio	5.9 (± 1.3)		
outcome			
no hospitalization		13 (22.5 %)	5.2 (± 1.2)
hospitalization		45 (77.5 %)	5.6 (± 0.8)
…ICU		26 (44.8 %)	6.2 (± 0.5)
…mech. ventilation		12 (20.7 %)	6.6 (± 1.4)
…death		6* (10.3 %)	7.2 (± 1.4)

Table 1 Patient characteristics given in mean value (SD) or count (%). *Six patients died, three without having been mechanically ventilated prior to their passing.

circumference of 185.4 mm (SD ± 32.6), waist circumference of 1030.3 (SD ± 112.2), FMR of 5.7 (SD ± 1.2). Women showing a mean muscle circumference of 164.8 mm (SD ± 25.1), waist circumference of 1015.4 (SD ± 174.3), FMR of 5.7 (SD ± 6.3). Dividing the patient group in two equal sized age groups, the older than 55-years-old patients showing a mean muscle circumference of 172.9 mm (SD ± 35.1), waist circumference of 1050.4 (SD ± 136.7), FMR of 6.3 (SD ± 1.5). Younger than 55-year-old patients showing a mean muscle circumference of 183.7 mm (SD ± 24.7), waist circumference of 990.8 (SD ± 135.6), FMR of 5.5 (SD ± 1.1). A significantly higher muscle circumference ($p < .01$) was found in men, with no significant difference in waist circumference and FMR ($p > .05$) compared to women. Also, the comparison of the two age groups showed a significant difference in terms of muscle and waist circumference as well as FMR ($p < .01$). A higher FMR was documented according to the respective degree of medical care (see Table 1 and the following regression analysis below).

3.3. Prediction of the outcomes using the CT parameters

Considering gender (dummy coded as 0 for female, 1 for male), age, and CT measurements of body composition within the independent variables, we fit a logistic regression model to predict if the patient would require intensive care within a period of 22 days. In a multivariate model, considering the independent variables of gender and age, FMR was a significant regressor for the prognosis of intensive care obligation with a pseudo R^2 to the Nagelkerke Index of .53 ($p < .001$), and an AIC of 58.5 (see Table 2 and Fig. 2). In comparison, a logistic regression model without including FMR achieved a pseudo R^2 to the Nagelkerke Index of .32 ($p < .001$) and an AIC of 79.8.

According to the intraclass correlation coefficient, intra- and inter-reader reliability achieved values in the range of “excellent” (see Table 3).

3.4. Discussion

The course and severity of a SARS-CoV-2 infection depends on various factors such as the patient’s age, basic physical condition and possible comorbidities [8,9]. Several studies hinted that additionally, obesity might be a risk factor for greater severity and hospitalization in COVID-19 patients [10–12]. The exact quantification of obesity would involve complex procedures that cannot be performed at the time of an initial infection. Hence alternative measures approximating the degree of obesity should be considered [20,24]. Since several studies showed a strong correlations between body composition and measurements on axial CT slices, we used these established methods to quantify obesity in the initial LDCT-scan of COVID-19 patients to predict the clinical course of the COVID-19 patients [30–32]. This clinical course was observed for 22 days at both centers included in this study according to previously published recommendations [34]. Using the FMR measured in the initial LDCT examination - derived from the ratio of total cross-sectional circumference to muscle area - it was possible to predict whether a patient would need intensive care treatment in the period following admission. The ratio of fat per muscle area was an additional significant predictor next to age and gender within a logistic regression analysis. Here, a pseudo R^2 of .53 was calculated, which means that the predictive value of the model was in the range of "very good", and 53 % of the variance in necessity of intensive care treatment was explained by the model [38]. In comparison, only 32 % of this variance was explained by a model based solely on age and gender. This means that an additional assessment of the body composition has a substantial prognostic added value with regard to the course of the disease and the potentially required intensive care resources. Considering the logistic regression graph, the probability of a potential ICU treatment drops below 50 % at a FMR of 5.5 and is going down in the range of less than 10 % at a FMR of under 5. In contrast, the probability of the necessity for an ICU treatment increases to about 80 % at a FMR of 7 and higher (see Fig. 2).

Table 2
Parameters of the multivariate logistic regression analysis.

	estimate	standard error	z-value
intercept***	−12.07	3.27	−3.69
age*	0.05	0.03	2.0
sex*	2.10	0.94	2.2
fat muscle ratio**	1.22	0.44	2.76

Table 2 Estimates for the multivariate logistic regression model to predict intensive care obligation. *** = $p < .001$; **=$p < .01$; *=$p<.05$.

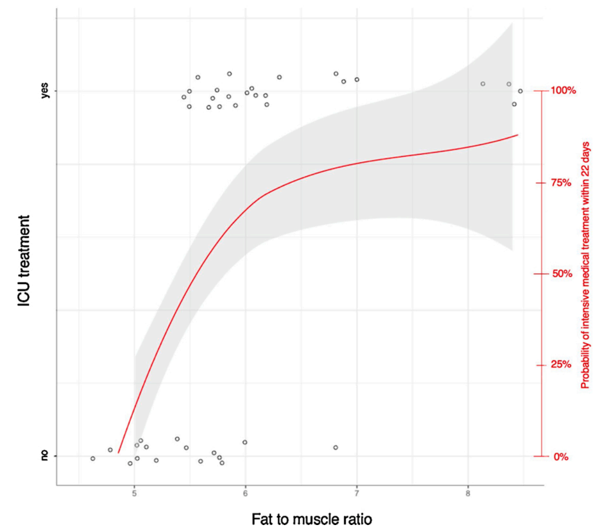

Fig. 2. Multivariate logistic regression model.
Fig. 2 Multivariate logistic regression model to predict whether intensive care treatment was necessary within the 22 days following LDCT. X-axis: measured muscle to fat ratio, left Y-axis: representation of the need for intensive care treatment. Right-y-axis (red:) Probability (based on logistic regression model) of intensive care treatment being necessary depending on the muscle to fat ratio (95 % confidence interval in grey).

Table 3
Intraclass correlation coefficient to determine the inter- and intrarater reliability.

	Intraraterreliability	Interraterreliability
mean muscle circumference (mm)	.94	.91
waist circumference (mm)	.95	.93

Table 3 Intraclass Correlation Coefficient to determine the inter- and intrarater reliability, (<.5 poor, >.5 moderate, > .75 good, > .9 excellent).

The results of the present study go along with observational findings which determine that obesity is associated with an increased risk of severe COVID-19 disease [12,19]. In addition to cardiometabolic complications in obese patients, reduced lung function is also discussed as a complication-causing component [15,17,19]. Physiological as well as virologic explanations argue with an upregulated expression of angiotensin-converting enzymes 2 - the functional receptor for SARS-CoV-2 - and turn adipose tissue into a viral reservoir, leading to a more severe manifestation of the disease. Regardless of which, or which possible combination of the ultimate physiological cause is responsible, these findings are reflected in our data. To the best of our knowledge, we provide a fast and reliable way to determine the FMR as a surrogate variable of the body composition in SARS-CoV-2 infected patients using an initial LDCT scan to estimate the future need for ICU treatment. The analyses showed that the measurements of muscle and waist circumference provided a very good inter- and intrareader reliability and can be considered as robust and well reproducible.

This study has several limitations that need to be considered. First, most previous studies assessing body composition on axial CT images, measurements of the muscle and fat areas were usually performed in the lumbar area. Since this area was not available on the LDCT examinations of the thorax, we had to modify our approach to the height of the 12th thoracic vertebrae. However, there is also evidence - admittedly not so numerous - of good correlations between thoracic muscle areas and body composition [26,41,42]. Furthermore, no additional measurements were performed using other methods, such as bioelectrical impedance analysis or dual X-ray absorptiometry. Additionally, data on BMI was not available for all patients in our study. Nevertheless, other studies have shown that the use of CT-based measurement provide a high degree of validity with regard to the physiologically present body composition [26,30,31]. Furthermore, it should be noted that although body composition and BMI are correlated, they should be considered in a differentiated manner. We consider an analysis that includes the proportional fat content more valuable in terms of an assessment of obesity and sarcopenia than only putting the weight in relation to body size. In addition, it should be noted that an opportunistic evaluation of CT data is a more feasible option for detecting obesity than measuring the height and weight of potentially infectious patients in the emergency room. Comorbidities have not been accounted for within the current investigation, although they have a significant impact on the outcome and disease-related complications. In addition to methodologically justified decisions, we also decided on the basis of the fact that some relevant pre-existing diseases might potentially be undiagnosed at the time of the initial CT scan. While several pre-existing conditions or comorbidities can certainly be regarded as causally linked to obesity (i.e. they could potentially be a cause or a consequence of obesity, or share a common cause with it), the prognostic relevance of obesity measured by our method with regard to the outcome of the COVID-19 disease remains unchanged. The present study considers only a small patient population within the context of a retrospective design. Additional studies should verify our hypotheses on the basis of a larger prospective patient collective. Since not all patients in this study arrived at the hospital at the beginning of the infection and received their initial CT scan within different times of the disease, the included stages vary accordingly. Assessment of the individual lung involvement would only provide a benefit if patients in a radiologically identical stage of disease were included in an analysis. Future studies with larger patient collectives should focus on a corresponding disease-stage-related analysis, or correct for the specific disease stage and severity in a regression analysis. In addition, future studies should take the conventional body mass index into account and evaluate its additional value to CT-based FMR measurements.

Furthermore, an automated determination of the body composition in COVID-19 patients should be considered. In this sense, data from our pilot study is suggesting that adding FMR measurements to AI tools for automatic characterization of lung infiltrations in COVID-19 patients might provide additional value and perform a risk classification for upcoming ICU treatment.

4. Conclusions

In summary, our retrospective multicentric pilot study emphasizes the prognostic relevance of obesity and body composition as a prognostic factor for SARS-CoV-2 infected patients. Furthermore, we present a method using an initial LDCT to screen opportunistically for obese patients who have an increased risk for the need of intensive care treatment. While clinical capacities, such as ICU beds and ventilators, are more crucial than ever to help manage the current global corona pandemic, this work introduces an approach that can be used for a cost-effective way to help determine the amount of these rare clinical resources required in the near future.

CRediT authorship contribution statement

Jonathan Kottlors: Conceptualization, Methodology, Writing - original draft. **David Zopfs:** Methodology, Conceptualization, Writing - review & editing. **Philipp Fervers:** Conceptualization, Investigation. **Johannes Bremm:** Investigation. **Nuran Abdullayev:** Data curation, Writing - review & editing, Conceptualization. **David Maintz:** Writing - review & editing, Conceptualization. **Stephanie Tritt:** Data curation. **Thorsten Persigehl:** Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

David Maintz received speaker's Honoria from Philips Healthcare, unrelated to the presented work. David Zopfs received exemption from clinical duties for research outside this project as a part of a research agreement between Philips Healthcare and University Hospital Cologne. Furthermore, no funding or financial contributions were received from third parties concerning the present investigation.

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The authors declare that they have no conflict of interest. The present study was conducted without any support from third parties.

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