Prognostic Implication of Baseline Sarcopenia for Length of Hospital Stay and Survival in Patients with Coronavirus Disease 2019

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Background: The impact of sarcopenia on clinical outcomes of coronavirus disease 2019 (COVID-19) is not clearly determined yet. We aimed to investigate the association between baseline sarcopenia and clinical outcomes in patients with COVID-19.

Methods: All hospitalized adult patients with COVID-19 who had baseline chest computed tomography (CT) scans at a Korean university hospital from February 2020 to May 2020 were included. The main outcome was time from hospital admission to discharge. Death was considered as a competing risk for discharge. Baseline skeletal muscle cross-sectional area at the level of the 12th thoracic vertebra was measured from chest CT scans. The lowest quartile of skeletal muscle index (skeletal muscle cross-sectional area divided by height-squared) was defined as sarcopenia.

Results: Of 121 patients (median age, 62 years; 44 men; 29 sarcopenic), 7 patients died and 86 patients were discharged during the 60-day follow-up. Patients with sarcopenia showed a longer time to discharge (median, 55 vs. 28 days; $p<0.001$) and a higher incidence of death (17.2% vs. 2.2%; $p=0.004$) than those without sarcopenia. Baseline sarcopenia was an independent predictor of delayed hospital discharge (adjusted hazard ratio [aHR], 0.47; 95% CI, 0.23-0.96), but was not independently associated with mortality in patients with COVID-19 (aHR, 3.80; 95% CI, 0.48-30.26). The association between baseline sarcopenia and delayed hospital discharge was consistent in subgroups stratified by age, sex, comorbidities, and severity of COVID-19.

Conclusion: Baseline sarcopenia was independently associated with prolonged hospital stay in patients with COVID-19. Sarcopenia could be a prognostic marker in COVID-19.

Keywords: COVID-19; severe acute respiratory syndrome coronavirus 2; sarcopenia; prognosis; length of stay

Introduction

In the absence of specific treatments for coronavirus disease 2019 (COVID-19), the COVID-19 pandemic has become a tremendous threat to human health worldwide. Most patients with COVID-19 experience mild to moderate disease, but some patients can develop severe respiratory illness and finally death. Older age, chronic comorbid conditions, and higher concentrations of d-dimer, interleukin-6, or C-reactive protein have all been associated with higher mortality in COVID-19 (1-6). However, factors associated with prolonged hospitalization in survivors of COVID-19 are not fully investigated. Because prolonged hospital stay increases the burden to public health under limited hospital resources, identifying these factors would be useful.

Sarcopenia is a muscle disorder characterized by low muscle strength combined with low muscle quantity or quality (7). Sarcopenia is highly associated with aging, but illness, malnutrition, and physical inactivity can also contribute to the development of sarcopenia (7). The adverse health effects of sarcopenia include poor quality of life, disability, and increased risk of falls, fractures, and hospitalization (8-10). In addition, the presence of sarcopenia is a proven predictor of treatment outcomes in patients with acute or chronic illness and those undergoing surgery (11-16). On computed tomography (CT), sarcopenia defined by the muscle mass at the level of the 3rd lumbar vertebra (L3) has predicted survival in patients with hepatocellular carcinoma and in liver transplant recipients (11, 12). CT-defined sarcopenia also predicted survival and length of intensive care unit (ICU) stay in patients requiring ICU admission after traumatic injuries (13).

CT is a useful tool for identifying sarcopenia by measuring muscle area in cross-sectional images, most commonly at the L3 level, which well represents the total body skeletal muscle mass (17, 18). The skeletal muscle mass can also be measured at the level of

the 12th thoracic vertebra (T12), which is highly correlated with the skeletal muscle mass at L3 and can also reflect clinical outcomes (19).

The association between sarcopenia and treatment outcomes in COVID-19 has not been examined. Therefore, we investigated the association between baseline sarcopenia and length of hospital stay and survival in hospitalized patients with COVID-19 by assessing for baseline sarcopenia using chest CT scans that were initially performed to evaluate COVID-19 pneumonia.

Methods

Patients

All patients with COVID-19 who were hospitalized at Daegu Catholic University Medical Center from February 17 to May 19, 2020 and had chest CT scans at baseline were eligible for this retrospective cohort study. Patients who did not have CT scans at baseline and those younger than 19 years were excluded from the study. The diagnosis of COVID-19 was based on positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swab specimens. The study was approved by the Institutional Review Board of Daegu Catholic University Medical Center (CR-20-110). Informed consent was waived because of the retrospective study design.

Estimation of skeletal muscle index by chest computed tomography

Cross-sectional images were obtained from chest CT scans that were performed for evaluation of COVID-19 pneumonia at the time of admission. Cross-sectional areas of muscle and fat were measured from the axial CT image nearest to the inferior border of the T12 vertebral body by using AsanJ-Morphometry software (Seoul, South Korea), including erector spinae, external and internal oblique, latissimus dorsi, rectus abdominis, and external

and internal intercostal muscles. Tissue Hounsfield Unit (HU) thresholds were 0 to 100 HU for skeletal muscle and –190 to –30 HU for subcutaneous and visceral fat tissues. Total muscle area (cm^2) was determined after excluding the total intramuscular fat area (total intramuscular fat area = total fat area – subcutaneous fat area – visceral fat area; **Figure 1**). The skeletal muscle index (cm^2/m^2) was calculated as total muscle area adjusted for height. Sarcopenia was defined as the lowest quartile of skeletal muscle index, which was ≤24 cm^2/m^2 for men and ≤20 cm^2/m^2 for women. The reference values for sarcopenia were ≤29 cm^2/m^2 for men and ≤23 cm^2/m^2 for women in the COVID-19 survivors (for sensitivity analysis).

The muscle and fat areas were determined by two physicians (J.W.K. and J.S.Y.) who were blinded to the patients' clinical information, and an intraclass correlation coefficient of 0.976 (95% confidence interval [CI], 0.959-0.986) indicated excellent reliability. We also selected 15 patients who had both chest and abdominal CT scans at baseline and confirmed a positive correlation between the measurements of the cross-sectional muscle areas at T12 and L3 (Spearman's rho=0.732, p=0.003).

Main outcome and clinical parameters

Main outcome was time from hospital admission to discharge. Time to reaching study endpoint (discharge or death) was assessed until 60 days after admission. COVID-19 patients discharged alive are those who meet the criteria of 1) negative conversion of SARS-CoV-2 RNA from nasopharyngeal and oropharyngeal swabs (detection of two consecutive negative RT-PCR results), and 2) improvement of clinical symptoms and vital signs and/or resolution

of pneumonia. Most people who discharged met both the PCR-negative and clinical criteria for discharge within a week apart.

Data on age, sex, comorbidities (diabetes, hypertension, cardiovascular disease, chronic lung disease, and chronic kidney disease), duration of symptoms before admission, symptoms (cough, sputum, fever, dyspnea, diarrhea, etc.), oxygen support, chest CT findings, and laboratory values at baseline were obtained from the medical records. National Early Warning Score 2 (NEWS2, range 0 to 20) was determined from respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, and temperature at baseline (20). A higher score indicates greater clinical risk, with 0 to 4 = low risk; 5 to 6 = medium risk; and 7 or more = high risk. Data on treatment with antibiotics, glucocorticoids, or IV immunoglobulin, use of nasal prong, high-flow nasal cannula, or mechanical ventilation, and complications such as acute respiratory distress syndrome (ARDS) and shock were also collected retrospectively. ARDS was defined using the Berlin definition (21) and shock was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (22).

Statistical analysis

Comparison of two groups was conducted using Mann-Whitney U test for continuous variables and Chi-Square test or Fisher's exact test for categorical variables. We executed a competing risk model for discharge outcome. Death was considered as a competing risk for discharge. Patients still hospitalized 60 days after admission and those who were transferred before study endpoint were censored. Cumulative incidence plots for discharge (or death) between patients with and without sarcopenia were drawn and compared by using Gray's test.

The association between baseline sarcopenia and hospital discharge was investigated using a Fine and Gray proportional subdistribution hazards regression model. Subgroup analyses stratified by age, sex, comorbidities, disease severity, and treatment were also performed to estimate the predictive performance of sarcopenia on hospital discharge. All statistical analyses were performed using R software, version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Total 121 patients were included in this study after excluding 7 patients who did not have chest CT scans at baseline and 2 patients who were under the age of 19 (**Figure 2**). Characteristics of the patients are described in **Table 1**. The median age was 62 years and 44 patients (36.4%) were men. The median duration of symptoms before admission was 7 (interquartile range [IQR], 3-10) days. Median NEWS2 at baseline was 2 (IQR, 1-5). Seventy patients (57.9%) had bilateral multifocal ground-glass opacities (GGOs) and/or consolidations on baseline chest CT images and 42 patients (34.7%) required oxygen support at baseline.

Of 121 patients, 29 patients (24%) met the study criteria for sarcopenia at baseline. Patients with sarcopenia presented with more severe disease at baseline, as indicated by higher NEWS2, more frequent oxygen support, and higher C-reactive protein (CRP) levels, than those without sarcopenia (**Table 1**). Sarcopenic individuals were older and had more frequent prevalence of hypertension and cardiovascular disease than those who were not sarcopenic. However, the duration of symptoms before admission and the presence of

bilateral multifocal GGOs and/or consolidations on baseline CT images did not differ between patients with and without sarcopenia.

Seven patients (5.8%) died and 86 patients (71.1%) were discharged during the 60-day period. Median length of hospital stay was 26 (IQR, 16-39) days. Characteristics of non-survivors, survivors with prolonged hospital stay (length of hospital stay ≥26 days), and survivors without prolonged hospital stay (length of hospital stay <26 days) are described in **Supplementary Table S1**. Among 7 non-survivors, 5 patients (71.4%) were sarcopenic. Sarcopenia was more common in patients with prolonged hospital stay than in patients without prolonged hospital stay (28.8% vs. 12.7%; p = 0.035).

Baseline sarcopenia as a predictor of length of hospital stay in COVID-19

To determine whether baseline sarcopenia could predict the length of hospital stay, cumulative incidence curves for discharge or death were depicted separately in patients with and without sarcopenia (**Figure 3**). Patients with sarcopenia had significantly longer hospital stay than those without sarcopenia (median, 55 vs. 28 days; Gray's test, p <0.001). In addition, patients with sarcopenia had a significantly higher death rate than those without sarcopenia (17.2% vs. 2.2%; Gray's test, p = 0.004).

Next, Fine and Gray proportional subdistribution hazards regression model for competing risks was performed to determine whether baseline sarcopenia had an independent effect on predicting length of hospital stay in patients with COVID-19 (**Table 2**). After adjusting for age, sex, diabetes, hypertension, cardiovascular disease, chronic lung disease, oxygen support at baseline, and CRP levels at baseline, baseline sarcopenia was significantly associated with delayed hospital discharge (adjusted HR [aHR], 0.47; 95% CI, 0.23-0.96). In

addition, baseline sarcopenia tended to be associated with high mortality in patients with COVID-19, but without statistical significance (aHR, 3.80; 95% CI, 0.48-30.26). We then conducted additional analyses to determine whether sarcopenia was a consistent predictor of length of hospital stay in different subgroups (**Supplementary Figure S1**). Patients with sarcopenia at baseline were likely to experience delayed hospital discharge consistently in subgroups according to age, sex, comorbidities, disease severity, and steroid treatment.

Sensitivity analysis

For sensitivity analysis, we investigated the association between sarcopenia and length of hospital stay only in survivors of COVID-19 (excluding 7 non-survivors). Sarcopenia was an independent predictor of delayed hospital discharge after adjusting for age, sex, diabetes, hypertension, cardiovascular disease, chronic lung disease, oxygen support at baseline, and CRP levels at baseline (aHR, 0.60; 95% CI, 0.37-0.96), which was in line with the results from the primary analysis.

Discussion

The main question of this study was whether baseline sarcopenia was associated with the prognosis of COVID-19 in terms of length of hospital stay and survival. We used chest CT scans, which were performed to evaluate the presence and severity of pneumonia, to determine the presence of sarcopenia at baseline. Sarcopenia was an independent predictor of prolonged hospital stay in patients with COVID-19. The impact of sarcopenia on length of hospital stay was consistently observed in subgroups with regards to age, sex, comorbidities, and severity of COVID-19. In addition, sarcopenia tended to be associated with high

mortality in patients with COVID-19, although the association was not statistically significant due to small numbers of patients who died. Our analysis showed an association between baseline sarcopenia and prognosis in COVID-19.

The interplay between skeletal muscle and the immune system may validate the association between sarcopenia and the clinical course of COVID-19. Skeletal muscle is now regarded as an organ that can release multiple soluble factors (myokines) deriving autocrine and paracrine effects (23). Myokines not only induce muscle regeneration and homeostasis, but also maintain immune function. Interleukin (IL)-15 is a myokine that stimulates proliferation and activation of natural killer (NK) cells and $CD8^+$ T lymphocytes and induces activation and phagocytosis of neutrophils (24, 25). NK cells and $CD8^+$ T lymphocytes provide essential defense against viral pathogens, therefore, a lack of IL-15 signaling might contribute to poor immune responses against SARS-CoV-2. Indeed, defects in NK cells and $CD8^+$ T lymphocytes and impaired antiviral responses have been observed in IL-15-deficient mice (26). Furthermore, impaired signaling of other myokines can cause a shift toward a proinflammatory environment (27, 28). Taken together, the integral role of skeletal muscle in immune function indicates that sarcopenia could be a prognostic factor in the treatment of COVID-19.

The association between sarcopenia and adverse outcomes of COVID-19 has been supported by other studies that examined CT-defined sarcopenia or clinical frailty scores in patients with COVID-19 (29-31). Low pectoralis muscle index (obtained by measuring the area of the pectoralis muscle on axial chest CT images) in patients with COVID-19 was associated with prolonged hospital stay and death (29). In a multi-center study in Europe, higher frailty scores in patients with COVID-19 were linked to higher mortality risk and longer duration of hospital stay compared with lower frailty scores (30). The presence of

diabetes, hypertension, and coronary artery disease was not associated with mortality or duration of hospital stay, indicating that frailty is a better predictor of the clinical course of COVID-19 than comorbidities (30). Our results, along with those of the other studies, suggest that evaluating muscle area on chest CT can be a simple and useful tool for predicting outcomes in patients with COVID-19.

Sarcopenia might also explain the heterogeneity of disease course in the context of aging. Generally, increasing age is considered to be a prognostic factor in multiple diseases. However, individually, age alone may have variable and inconsistent effects in predicting clinical outcomes (32). Being old does not always mean being unhealthy, and conversely, younger people may experience poor health-related outcomes (32). Sarcopenia, as well as frailty, might be a latent prognostic factor which partially accounts for the heterogeneity of associations between age and clinical outcomes (33). The clinical course of COVID-19 in older patients with the disease differs according to their frailty status. Frail patients have a higher mortality risk and experience severe disease more frequently than non-frail patients (31, 34). Our study found that sarcopenia was a reliable marker of prolonged hospital stay in a subgroup of older patients with COVID-19, confirming that not all older people have similar outcomes in COVID-19. Sarcopenia and frailty also predict mortality in patients with various other medial or surgical conditions, regardless of age (14, 35-37). Sarcopenia, which reflects body composition better than body mass index, is a key physical component of frailty (38). The present study demonstrated that baseline sarcopenia serves as a predictor of adverse outcomes in COVID-19 independently of age.

There are some limitations of this study. First, our study was conducted within a retrospective design. Further large, prospective study would be required to support our findings. Second, sarcopenia was defined based on only muscle mass in our study, while the

current definition of sarcopenia is based on muscle mass and function (7). Third, reference values for sarcopenia measured from CT scans at thoracic levels are not determined in Korean population. However, cutoffs for height-adjusted cross-sectional area (skeletal muscle index) measured at the T12 level in our study population were quite similar to those in a healthy group in the United States (39). Fourth, we could not measure the skeletal muscle index at L3 across the study group because most of the patients had only chest CT scans. Instead, we checked the correlation between skeletal muscle indices from T12 and L3 levels in patients who had both chest and abdominal CT scans (n=15) and found a close relationship between them. Fifth, length of hospital stay might be influenced by several external factors such as social support, living environment, and services. However, we set the criteria for discharge in case of patients with COVID-19 (aforementioned in the methods section), and most patients followed these criteria. To overcome this possible limitation, mortality risk, as well as length of hospital stay, was evaluated in our study, because both mortality and hospital discharge are commonly selected outcomes in clinical studies of COVID-19 (3, 29, 30).

In conclusion, baseline sarcopenia was independently associated with duration of hospital stay in hospitalized patients with COVID-19. Patients with sarcopenia had increased mortality, but the association was not statistically significant. Although chest CT was originally conducted to evaluate the presence and severity of pneumonia in patients with COVID-19, it provided an additional value to assess for sarcopenia, which is a prognostic marker of COVID-19.

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Conflict of interest

All authors declare that they have no conflict of interest.

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Table 1 Characteristics of the patients with and without sarcopenia

Variables	Total (n = 121)	Sarcopenia[a,b] (n = 29)	No sarcopenia[a,b] (n = 92)	*P* value[a]
Age, median (IQR), y	62.0 (49.0;75.0)	80.0 (72.0;83.0)	57.5 (46.0;69.0)	**<0.001**
Male sex, No. (%)	44 (36.4)	11 (37.9)	33 (35.9)	0.841
Comorbidities, No. (%)				
Diabetes	24 (19.8)	5 (17.2)	19 (20.7)	0.893
Hypertension	30 (24.8)	12 (41.4)	18 (19.6)	**0.034**
Cardiovascular disease[c]	24 (19.8)	11 (37.9)	13 (14.1)	**0.011**
Chronic lung disease[d]	21 (17.4)	8 (27.6)	13 (14.1)	0.165
Chronic kidney disease	9 (7.4)	3 (10.3)	6 (6.5)	0.781
Duration of symptoms before admission, median (IQR), d	7.0 (3.0;10.0)	6.0 (2.0;10.0)	7.0 (4.0;10.0)	0.492
Symptoms, No. (%)				
Cough	93 (76.9)	21 (72.4)	72 (78.3)	0.690
Fever	81 (67.5)	20 (69.0)	61 (67.0)	1.000
Sputum	74 (61.2)	16 (55.2)	58 (63.0)	0.589
Dyspnea	67 (55.4)	21 (72.4)	46 (50.0)	0.057
Diarrhea	41 (34.2)	9 (31.0)	32 (35.2)	0.854
Myalgia	28 (23.3)	3 (10.3)	25 (27.5)	0.100
Sore throat	25 (20.8)	3 (10.3)	22 (24.2)	0.182
Rhinorrhea	21 (17.5)	5 (17.2)	16 (17.6)	1.000
Chest pain	16 (13.3)	5 (17.2)	11 (12.1)	0.691
NEWS2 at baseline, median (IQR)	2.0 (1.0;5.0)	5.0 (2.0;9.0)	2.0 (0.0;4.0)	**<0.001**
Oxygen support at baseline, No. (%)	42 (34.7)	17 (58.6)	25 (27.2)	**0.004**
Bilateral multifocal GGOs and/or consolidations on baseline chest CT images, No. (%)	70 (57.9)	16 (55.2)	54 (58.7)	0.905
Laboratory values at baseline, median (IQR)				
White blood cell count, /μL	5300 (4300;6400)	6300 (4600;7800)	5200 (4100;6050)	**0.010**
Lymphocyte count, /μL	1153.4 (852.0;1572.1)	889.0 (691.2;1264.2)	1215.7 (932.4;1596.3)	**0.001**
C-reactive protein, mg/L	13.8 (1.0;48.2)	38.2 (10.6;70.7)	7.1 (0.8;31.1)	**0.005**
Aspartate aminotransferase, U/L	24.0 (18.0;34.0)	26.0 (18.0;36.0)	24.0 (18.0;32.5)	0.766

Alanine aminotransferase, U/L	18.0 (13.0;28.0)	16.0 (11.0;22.0)	19.0 (13.5;28.0)	0.129
Serum creatinine, mg/dL	0.7 (0.7;0.9)	0.7 (0.6;0.9)	0.8 (0.7;0.9)	0.174
Concomitant treatment, No. (%)				
Antibiotic agent	94 (77.7)	27 (93.1)	67 (72.8)	**0.042**
Glucocorticoid	20 (16.5)	10 (34.5)	10 (10.9)	**0.007**
IV immunoglobulin	17 (14.0)	7 (24.1)	10 (10.9)	0.137
Nasal prong	53 (43.8)	17 (58.6)	36 (39.1)	0.103
HFNC	14 (11.6)	8 (27.6)	6 (6.5)	**0.006**
MV	8 (6.6)	3 (10.3)	5 (5.4)	0.618
Complications, No. (%)				
ARDS	14 (11.6)	8 (27.6)	6 (6.5)	**0.006**
Shock	7 (5.8)	3 (10.3)	4 (4.3)	0.453
ICU stay	10 (8.3)	4 (13.8)	6 (6.5)	0.393

NEWS2, national early warning score 2; GGO, grand-glass opacity; CT, computed tomography; IV, intravenous; HFNC, high-flow nasal cannula; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome; ICU, intensive care unit

[a]Values are compared between patients with and without sarcopenia using Mann-Whitney U test, Chi-square test, or Fisher's exact test, as appropriate.

[b]Sarcopenia was defined as the lowest quartile of skeletal muscle index at the level of the 12th thoracic vertebra.

[c]Cardiovascular disease includes ischemic heart disease, heart failure, valvular heart disease, arrhythmia, and cerebrovascular accident.

[d]Chronic lung disease includes asthma, chronic obstructive pulmonary disease, interstitial lung disease, lung cancer, and tuberculosis-associated lung damage.

Table 2 Baseline sarcopenia as a predictor of delayed hospital discharge and death in COVID-19

Outcome	No. of events/No. of population	Incidence rate	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[a,b]
Discharge at day 60				
Sarcopenia	14/29	48.3%	0.34 (0.18-0.64)	0.47 (0.23-0.96)
No sarcopenia	72/92	78.3%	Reference	Reference
Death at day 60				
Sarcopenia	5/29	17.2%	6.25 (1.18-33.04)	3.80 (0.48-30.26)
No sarcopenia	2/92	2.2%	Reference	Reference

HR, hazard ratio; CI, confidence interval.

[a]HRs were determined using the Fine and Gray proportional subdistribution hazards regression model for competing risks.

[b]Adjusted for age, sex, diabetes, hypertension, cardiovascular disease, chronic lung disease, oxygen support at baseline, and CRP at baseline.

Figure legends

Figure 1 Measurement of muscle area on axial CT images at the level of the 12th thoracic vertebra in (A) non-sarcopenic and (B) sarcopenic COVID-19 patients with the same BMI

The purple area represents the skeletal muscle. The skeletal muscle indices are 37.1 cm^2/m^2 and 15.5 cm^2/m^2 for patients A and B, respectively. The lower density of the purple area (patient B) indicates the smaller skeletal muscle area.

Figure 2 Flow chart of the study population

[a]Sarcopenia was defined as the lowest quartile of skeletal muscle index at the level of the 12^{th} thoracic vertebra.

Figure 3 Cumulative incidence curves indicating the rate of discharge or death in accordance with absence or presence of sarcopenia in patients with COVID-19

Figure 1

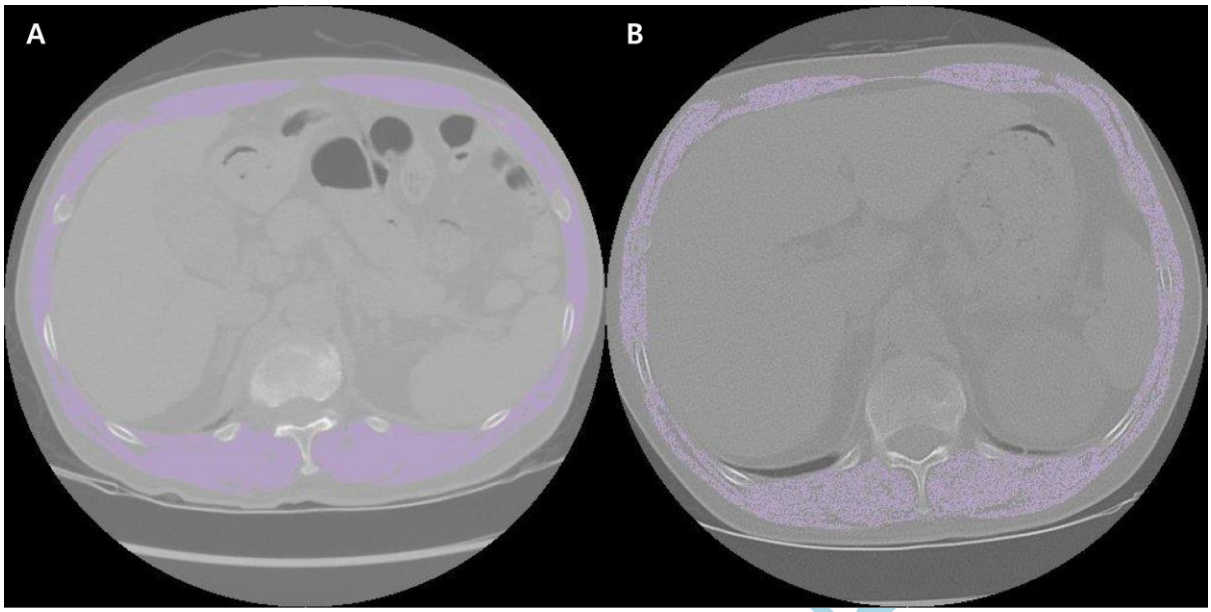

Figure 2

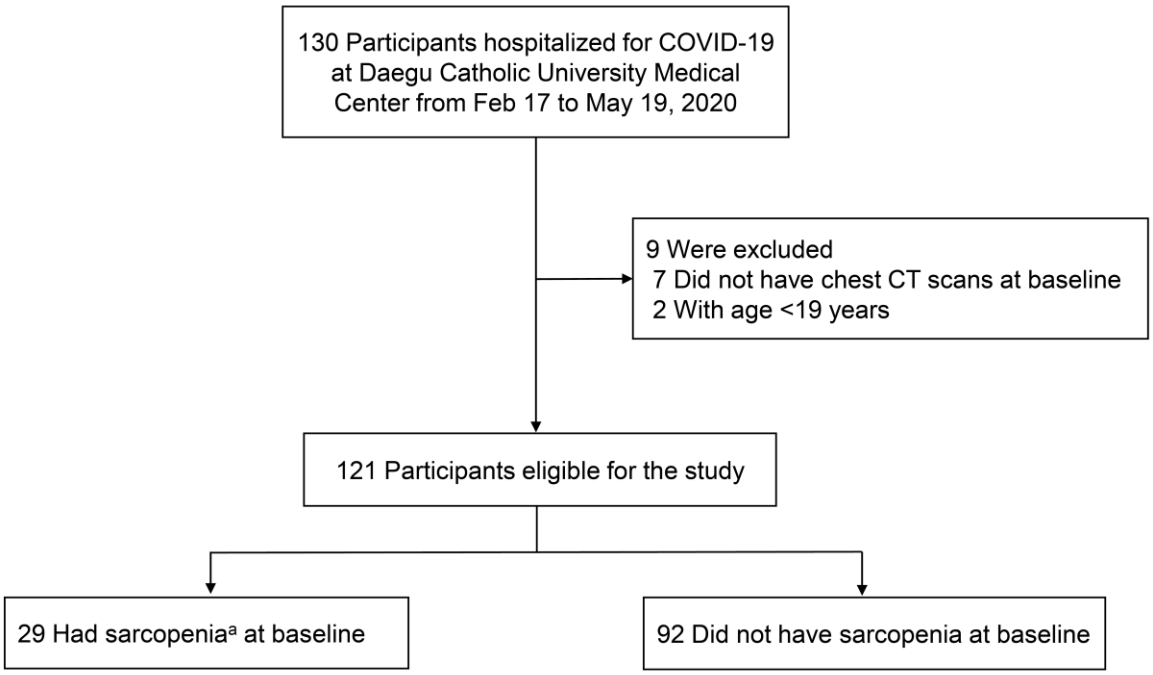

Figure 3