SARS-CoV-2 pneumonia: association between findings of CT and SF ratios in inpatients and critically ill patients

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Abstract

Introduction

We aim to evaluate the association between CT findings and SpO_2/FiO_2 (SF) in hospitalized patients with SARS-CoV-2 pneumonia. Our secondary purpose was to assess the predictive value of the SF ratio to identify critically ill patients and mortality.

Methods

A prospectively recorded electronic database for all hospitalized patients with SARS-CoV-2 pneumonia was used. CT findings and SF ratio were evaluated on admission. In the clinical course, they were divided into 2 groups as inpatients and critically ill patients to compare.

Results

During the study period, 256 patients with suspected SARS-CoV-2 were admitted to the hospital. The final cohort consisted of 87 patients. There is a significant moderate to strong negative correlation between the SF ratio and not-, and poorly-inflated lung ratios in critically ill patients ($r = -0.591$, $p = < .001$ and $r = -0.549$, $p = < .001$). There is a significant moderate negative correlation between the SF ratio and FWHM ($r = -0.417$, $p = .024$) in critically ill patients. The optimal cut-off point of the SF ratio for admission to the ICU was determined as 445 (87.1% sensitivity, 91.1% specificity, 84.4% PPV, and 92.7% NPV).

Conclusions

Lung involvement on chest CT in critically ill patients shows heterogeneity and FWHM could be used to estimate the lung heterogeneity. The SF ratio is significantly associated with CT findings and SF ratio on admission can be used alone to identify critically ill patients and mortality.

Introduction

The majority of patients with SARS-CoV-2 infection have experienced mild symptoms with a good prognosis. Approximately 14% of whom have had severe disease presented with pneumonia. Some patients with pneumonia have suffered acute hypoxemic respiratory failure with acute respiratory distress syndrome (ARDS), which is a syndrome associated with high mortality. [1] The severity of hypoxemia and lung involvement seen on chest CT appears to be the determining factors for severe disease. CT findings of SARS-CoV-2 pneumonia are most commonly ground-glass opacity with or without consolidation, consistent with viral pneumonia.[2,3] However, lung involvement is more heterogeneous in the critically ill patients with pneumonia. Since there can be both ground glass and consolidation at the same time, the evaluation of lung heterogeneity by CT seems more important in order to define disease severity.

In extraordinary situations such as the pandemic, as sufficient number of experienced intensivists may not be available, junior doctors may be required to work in unfamiliar intensive care settings. Therefore, objective parameters are needed to identify critically ill patients with pneumonia. The ratio between PaO_2 and FiO_2 (PF ratio) and SpO_2 are the two commonly used parameters of the oxygen status that are needed for invasive mechanical ventilation and to predict mortality in patients with SARS-CoV-2 pneumonia. [4,5] However, invasive arterial sampling requires the calculation of the PF ratio, which increases the risk of complications as well as physician workload. The ratio between SpO_2 and FiO_2 (SF ratio) is a non-invasive alternative to the PF ratio. In a previous study, the SF ratio was shown to be correlated with the PF ratio. The results of that study showed an SF ratio of 235 corresponding with a PF ratio of 200 for ARDS, while an SF ratio of 315 corresponded with a PF ratio of 300 for acute lung injury (ALI).[6]

Therefore, we aim to evaluate the association between CT findings and SF ratios on admission in inpatients and critically ill patients with SARS-CoV-2 pneumonia. Our secondary purpose was to assess the predictive values of the SF ratio to identify critically ill patients and mortality.

Methods

A prospectively recorded electronic database for all SARS-CoV-2 patients that were followed in the SARS-CoV-2 inpatient clinic and the ICU at Hacettepe University Hospital since 20 March 2020 was used. Approval for the study was granted by the local ethics committee (approval number: 2020/12–48, project number: GO 20/629).This observational study included patients with SARS-CoV-2 pneumonia admitted to Hacettepe University Hospital (Ankara, Turkey), from March 20 to April 20, 2020. No immunomodulatory therapy was used until April 20. The diagnosis of SARS-CoV-2 infection was determined using the following methods in addition to CT findings of SARS-CoV-2 pneumonia:

- A positive result of real-time reverse transcriptase-polymerase chain reaction testing (RT-PCR).
- The initial RT-PCR was negative, but clinical suspicion of SARS-CoV-2 pneumonia remained, a follow up RT-PCR testing was performed up to 3 times.

The demographic characteristics of patients including age, gender, height and weight were obtained from the in-hospital electronic database. BMI was calculated using a person's height and weight. PA information, which acts as a long-term lifestyle indicator, was determined by asking either the patient or relative by phone. We classified the PA levels into 3 groups; sedentary, daily PA and WHO (World health organization) PA. Sedentary PA was defined as spending more than 50% of the day in bed; daily PA was defined as being capable of doing daily activities such as house work; WHO PA was defined as, in addition to daily activities, performing 30 minutes of exercise 5 days a week.[7] The CT findings and SF ratio of hospitalized patients on admission were evaluated. In clinical course, they were divided into 2 groups as inpatients and critically ill patients to compare.

Unenhanced chest CT scans were obtained in a supine position with arms raised during an inspiratory breath-hold on a third-generation dual-source CT scanner (Somatom Force, Siemens Healthineers, Germany). Scanning parameters were as follows: tube voltage 70–110 kV, modulated mA with a reference mAs of 50 mAs (CareDose 4D, Siemens Healthineers), pitch 3, detector collimation 192x0.6 mm and a slice thickness of 3 mm. Image reconstruction was performed with a slice thickness of 1 mm. Quantitative CT analyses were performed on a workstation using a dedicated software (CT Pulmo3D, Syngo.via VB30, Siemens Healthineers, Germany). After automatic lung segmentation, lung contours and segmentation were checked and manual corrections were made if necessary. For the total, right and left lung, the volume (ml) and mean lung density (HU) were calculated. Total lung full width at half maximum (FWHM) (HU) that shows the width of frequency distribution at the half of the maximum CT value was measured to evaluate distribution of density and heterogeneity of viral pneumonia.[8] After the segmentation, a subrange analysis method based on CT density was used to demonstrate the relative volume of non-, poorly- and well-inflated lung within the segmented lung. Values of CT density for normal parenchyma (well-aerated) was determined as density values between − 950 HU to -750 HU.[9] While density threshold for ground-glass opacity (poorly-inflated) was set from − 30 HU to -750 HU, density values higher than − 300 HU were accepted as consolidation and/or atelectasis (non-inflated). Threshold values for CT scans obtained during insufficient inspiration were increased by 100 HU.[10] 3D VRT (volume rendering) subrange images and quantitative analysis curves were noted for all patients, examples of an inpatient and a critically ill patient are presented in Fig. 1.

The parameters of oxygen status on admission day recorded include, the types of oxygen support therapy (nasal cannula, simple mask, non-rebreather mask, high flow therapy) with flow setting, FiO_2 receiving noninvasive (NIV) and invasive mechanical ventilation, and the oxygen saturation value measured via pulse oximetry, namely SpO_2 on admission day. The SF ratio was subsequently calculated and recorded. If arterial blood gases were taken from the patient, the PF ratio was calculated as well. In addition, the worst arterial blood gases of critically ill patients, whether or not the patients were in the prone position, type of oxygen support therapy, both positive end-expiratory pressure (PEEP) and static compliance (Cstat) of the applied invasive mechanical ventilation were recorded in critically ill patients.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics software version 22.0. Normally distributed continuous variables are expressed as the mean ± standard deviation (SD). Non-normally distributed continuous variables are reported as the median and interquartile range (IQR, 25%-75%). Categorical variables were presented as numbers and percentages. The difference between two independent groups (inpatients and critically ill patients groups) was examined by using the Chi-square test for categorical variables and independent samples t-test or Mann Whitney U test for continuous numerical variables. Correlation between the continuous variables was analyzed with Spearman's correlation coefficient. The ROC curve was drawn and the area under the ROC curve was calculated to examine the performance of the SF ratio in determining ICU admission and to determine the best cutoff point for SF. Sensitivity, specificity, PPV and NPV statistics were calculated according to the determined cut-off point. Two-sided $p < 0.05$ was considered statistically significant.

Results

During the study period, 256 patients with suspected SARS-CoV-2 were admitted to the hospital, 62 of whom were transferred to the ICU. After using the inclusion diagnostic criteria, the final cohort consisted of 87 patients (Table I). The other 169 patients were excluded from this analysis because of missing SpO_2 value, missing chest CT or a non-COVID-19 final diagnosis. The involvement of the lung lobes according to the inflated lung ratios and density is shown in Fig. 2.

There appears to be a significant positive correlation between total LV, left LV, right LV and height in inpatients (Table II). A spearman correlation analysis between characteristics of patient and inflated lung ratios is presented in Table II. Spearman rho correlation show a significant moderate to strong negative correlation between the SF ratio and not- and poorly-inflated lung in critically ill patients. Also, there is a significant moderate negative correlation between the SF ratio and FWHM ($r = -0.417$, $p = .024$) in critically ill patients. Values of the SF ratio were tested as predictors to identify critically ill patients using receiver operating characteristic (ROC) curve analysis in Fig. 3. Values of the SF ratio were used to identify critically ill patients and mortality in Table III.

Oxygen support therapy (highest level of support) for critically ill patients is outlined as follows; 9 nasal cannula, 4 simple masks, 2 non-rebreather masks, and 1 high flow oxygen therapy. In the ICU, 15 patients received mechanically ventilator support; 2 NIV, and 13 invasive mechanical ventilation. The mean age of critically ill patients who were intubated was 69.2 ± 11.3 years and 8 patients were female. In critically ill patients, the median SF ratio on CT day (n = 31) was 452.0 (IQR, 342.0-461.0) and the median PF ratio on CT day (n = 14) was 155.0 (IQR, 86–225). During the ICU stay the median worst SF ratio (n = 31) was 184.0 (IQR, 127.0-240.0), the median worst PF ratio (n = 31) was 140.0 (IQR, 85.0-191.0). In the ICU, 15 critically ill patients were placed in the prone position. In the inpatients that received NIV or invasive mechanical ventilation (n = 15), the median PEEP was 10 cmH_2O (IQR, 7–10). In the inpatients that received invasive mechanical ventilation (n = 13), the median Cstat was 31.0 $L.cmH_2O^{-1}$(IQR, 28–40). The hospital mortality rate of SARS-CoV-2 patients was 10.3% and ICU mortality rate was 29.0%.

Discussion

We found a statistically significant moderate to strong negative correlation between the SF ratio and not-, and poorly-inflated lung ratios in critically ill patients with SARS-CoV-2 pneumonia. Actually, an increased not- and poorly-inflated lung, FWHM, lung density and a decreased SF ratio were observed in critically ill patients when compared to inpatients. During the SARS-CoV-2 pandemic, it is important to identify the critically ill patient, thus, CT findings could be used to evaluate the lung heterogeneity and to define disease severity. However, SF ratio is an easier and cheaper noninvasive method when compared to CT, as its overuse during the SARS-CoV-2 pandemic raises concerns about radiation-induced adverse health effects, both in patients and in healthcare workers.

Lung heterogeneity are associated with ARDS severity and independently associated with outcome.[11] Different CT scoring systems were presented to estimate the lung heterogeneity and to define disease severity. Our results indicated that increased FWHM in patients with viral pneumonia could be used to estimate the lung heterogeneity. In addition, the current study elicited a significant moderate negative correlation between the SF ratio and FWHM in these patients. Ragap et al. found a strong negative correlation between a high CT severity score by HRCT and oxygen saturation ($r = -0.73$, $p = .001$).[12] Similarly, Wang et al. reported a significant moderate negative correlation between oxygen saturation and CT findings ($r = -0.446$, $p < 0.05$), but heterogeneity index was not used.[13] Unfortunately, both authors did not report as to when the timing of the values of oxygen saturation were obtained, i.e. on the same day with chest CT or not. In addition, they did not clarify whether the oxygen saturation values were recorded while using oxygen support therapy. [12,13]

It has been previously reported that there is a strong and significant association between the square root of the SF ratio value and the risk for death, with a unit decrease in the marker corresponding to a 1.82 fold increase in mortality risk (95% CI: 1.56–2.13). Thus, the SF ratio can be used to define disease severity and mortality risk.[14] Optimal cut-off point of SF ratio to identify critically ill patients with viral pneumonia is not found in the literature. In our cohort, a SF ratio cut-off < 445 identified critically ill patients. Interestingly, when the cut-off is taken as < 325, which is close to the ARDS limit-, its selectivity decreases. It is important to evaluate patient breathing effort in addition to SF or PF ratio in the decision of intubation in critically ill patients with viral pneumonia. *Bauer et. al.* showed that delayed intubation (after two days) was associated with a greater risk of death after 10 days of ICU stay, than early intubation. [15]

ICU mortality rates reported in patients with severe SARS-CoV-2 range from 20–62%. In our study, most of the patients with SARS-CoV-2 pneumonia admitted to the ICU with acute respiratory failure survived; the cumulative mortality rate was around 29% in the ICU. Despite the global efforts to reduce it, ICU mortality remains high and varies from country to country, and across different regions within each country, even between hospitals in the same region depending on the level of experience in the managing of critically ill patients. Similar to previous reports, our critically ill patients were typically older, male gender and more sedentary than inpatients.[16] It is well known that the majority of older adults are sedentary. A large cohort study showed that consistently meeting PA guidelines was strongly associated with a reduced risk for severe COVID-19 outcomes among infected adults.[17] PA is an important and modifiable risk factor for severe COVID-19 outcomes according to the results of this study.

Our results indicated that lower lobes were more affected than the middle and upper lobes. Indeed, inpatients had more well inflated lung ratios. These lung ratios also showed a significant negative correlation with age and BMI. In contrast, critically ill patients had more not- and poorly-inflated lung ratios, and did not correlate with age and BMI. This could be explained by positive pressure ventilation, applied NIV or invasive mechanical ventilation, and limiting or preventing atelectasis especially in older and obese critically ill patients. The application of supraphysiological PEEP (> 5 cmH_2O) with invasive mechanical ventilation decreases atelectasis, improves alveolar ventilation and V/Q mismatch.

This study has several limitations. First, only 87 patients with a positive of RT-PCR were included, 169 patients with a negative of RT-PCR were ruled out in the analysis. The study started on March 20, when the first patient was admitted to the COVID-ICU. It was conducted until April 20, 2021 when immunomodulatory treatments began. Patients who did not receive immunomodulatory therapy were included; therefore there is a time limitation (only 1 month). The degree of PA was determined subjectively by referring to statements made by patients or relatives. In addition, optimal inspiration was not achieved in some CT scans especially in the ICU patients. Inadequate inspiration may falsely result in higher parenchymal CT density. Moreover, some CT scans could not be segmented or accurately segmented by the radiological software. Although manual corrections were performed in inadequately segmented scans, this could not be achieved in cases that segmentation failed. Since patients usually had a single CT during their hospitalization, correlation analysis could not be performed between the findings of CT and the worst P/F and SF values in the ICU. The value of the SF ratio as a predictor to determine the need for ICU admission may be high. Patients who might need intubation were admitted to the ICU for close monitoring.

Conclusion

The SF ratio is significantly associated with CT findings and can be used alone to evaluate critically ill patients with SARS-CoV-2 pneumonia. Lung involvement on chest CT shows heterogeneity and FWHM could be used to estimate the lung heterogeneity. The SF ratio can be used alone to identify critically ill patients with viral pneumonia and mortality.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Author contributions: Serpil Öcal was the principal investigator, designed the study, interpreted data, drafted the manuscript, and takes responsibility for the content of the manuscript, including the data and analysis. Serpil Öcal, Selin Ardalı Düzgün, and Meltem Gülsün Akpınar conceived the work. Selin Ardalı Düzgün and Meltem Gülsün Akpınar analyzed the radiological findings. Serpil Öcal, Erdem karabulut and İsmail Tuna geldigitti conducted the analysis and interpreted data. Burcu Çelikten and İsmail Tuna Geldigitti collected data. Nursel Çalık Başaran and Ömrüm Uzun interpreted data, and drafted the manuscript. All authors critically reviewed and approved the final manuscript.

Ethics approval

Approval for the study was granted by the local ethics committee (approval number: 2020/12-48, project number: GO 20/629).

Patient consent

Consent was obtained from patients for Figure 1A and 1B.

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Tables

Table I. Patient characteristics of inpatients and critically ill patients with SARS-CoV-2 pneumonia on admission

PA = physical activity; WHO = World Health Organization; BMI = Body mass index; LV = lung volume; SF ratio = SpO_2/FiO_2; CT = computed tomography; FWHM = full width at half maximum.

*p value of less than 0.05 was considered statistically significant

Table II. Spearman correlation analysis between characteristics of inpatients and critically ill patients

Patient characteristics	Inpatients (n = 56)	Critically ill patients (n = 31)	p value*
Age, median(IQR),y	45(29–53)	63 (52–77)	<.001
Male, n (%)	23(41.1)	20(64.5)	.036
PA, n (%)			
WHO PA	21(45.7)	8(25.8)	
Daily PA	24(52.2)	18(58.1)	.035
Sedentary	1(2.2)	5(16.1)	
Height, median(IQR),cm	169(165–176)	166(160–180)	.456
BMI, mean(±SD),kg/m^2	27.0(±4.9)	28.0(±6.1)	.431
Total LV mean(±SD),ml	4234.1(±1173.5)	3850.2(±1399.6)	.185
Left LV mean(±SD),ml	1991.0(±587.7)	1746.1(±701.5)	.092
Right LV mean(±SD),ml	2243.1(±545.4)	2103.5(±715.4)	.342
SF ratio, median(IQR),	321.0(236.0–409.0)	166.0(160.0–180.0)	<.001
FWHM, median(IQR), HU	85.0(68.0–108.0)	140.0(98.0–192.0)	<.001
Total lung density, median(IQR), HU	-819.5(-843.0–780.5)	-732.0(-810.0–656.0)	<.001
Not- inflated lung, median(IQR), %	1.3(1.0–2.2)	5.0(3.0–13.5)	<.001
Poorly- inflated lung, median(IQR), %	5.0(3.5–7.2)	12.9(7.0–17.7)	<.001
Well- inflated lung, median(IQR), %	93.4(90.5–95.4)	83.6 (69.9–87.2)	<.001
Left lung density, median(IQR), HU	-822.5(-847.5 – -779.5)	-746.0(-805.0 – -636.0)	<.001
Not- inflated left lung, median(IQR), %	1.3(1.0–2.1)	4.9(2.0–14.8)	<.001
Poorly- inflated left lung, median(IQR), %	5.0(3.7–7.2)	13.2(8.5–18.3)	<.001
Well- inflated left lung, median(IQR), %	93.7(90.9–95.4)	82.6(66.9–88.5)	<.001
Right lung density, median(IQR), HU	-815.5(-844.0 – -776.0)	-737.0(-804.0– -656.0)	<.001
Not- inflated right lung, median(IQR), %	1.3 (0.9–2.3)	4.7 (2.9–12.2)	<.001
Poorly- inflated right lung, median(IQR), %	5.0 (3.2–7.1)	12.4 (7.1–18.6)	<.001
Well- inflated right lung, median(IQR), %	93.4 (9.1–95.6)	82.0 (68.8–88.7)	<.001

Characteristics		Inpatients			Critically ill patients		
		Total LV	Left LV	Right LV	Total LV	Left LV	Right LV
Age	Rho	0.050	0.051	0.039	-0.257	-0.270	-0.256
	p*	.712	.709	.773	.142	.122	0.144
Height	Rho	0.477	0.481	0.472	0.781	0.786	0.784
	p*	.001	.001	.001	< .001	< .001	< .001
BMI	Rho	-0.017	-0.047	0.007	-0.091	-0.120	-0.032
	p*	.914	.763	.966	0.640	0.536	0.863
Characteristics		**Inpatients**			**Critically ill patients**		
		Not-inflated lung	**Poorly-inflated lung**	**Well-inflated lung**	**Not-inflated lung**	**Poorly-inflated lung**	**Well-inflated lung**
Age	Rho	0.318	0.386	-0.395	-0.023	0.034	-0.037
	p*	.017	.003	.003	.896	.850	.834
Height	Rho	0.183	0.154	-0.179	-0.127	-0.019	0.053
	p*	.234	.318	.244	.513	.921	.784
BMI	Rho	0.533	0.540	-0.569	0.000	-0.073	0.054
	p*	.000	<.001	<.001	.999	.708	.780
SF ratio	Rho	-0.057	-0.018	0.039	-0.591	-0.549	0.566
	p*	.679	.894	.774	<.001	<.001	<.001
FWHM	Rho	0.677	0.420	-0.509	0.409	0.564	-0.529
	p*	<.001	.001	<.001	.028	.001	.003
Total LV	Rho	-0.407	-0.198	0.276	-0.521	-0.432	0.484
	p*	.002	.144	.039	.002	.011	.004
Left LV	Rho	-0.411	-0.181	0.261	-0.509	-0.451	0.496
	p*	.002	.182	.052	.002	.007	.003
Right LV	Rho	-0.398	-0.213	0.287	-0.488	-0.380	0.435
	p*	.002	.114	.032	.003	.027	.010

BMI = body mass index; SF ratio = SpO_2/FiO_2; CT = computed tomography; FWHM = full width at half maximum, LV = lung volume.

*p value of less than 0.05 was considered statistically significant

Table III. Optimal cut-off SF ratios on admission for predicting critically ill patients and mortality

SF ratio cut-off	Sensitivity	Specificity	PPV	NPV	Predicting
<325	54.8	100.0	100.0	80.0	Critically ill patients
<445	87.1	91.1	84.4	92.7	
<325	66.7	85.9	35.3	95.7	Mortality
<445	88.9	69.2	25.0	98.2	

SF ratio = SpO_2/FiO_2, PPV = positive predictive value, NPV = negative predictive value

Figures

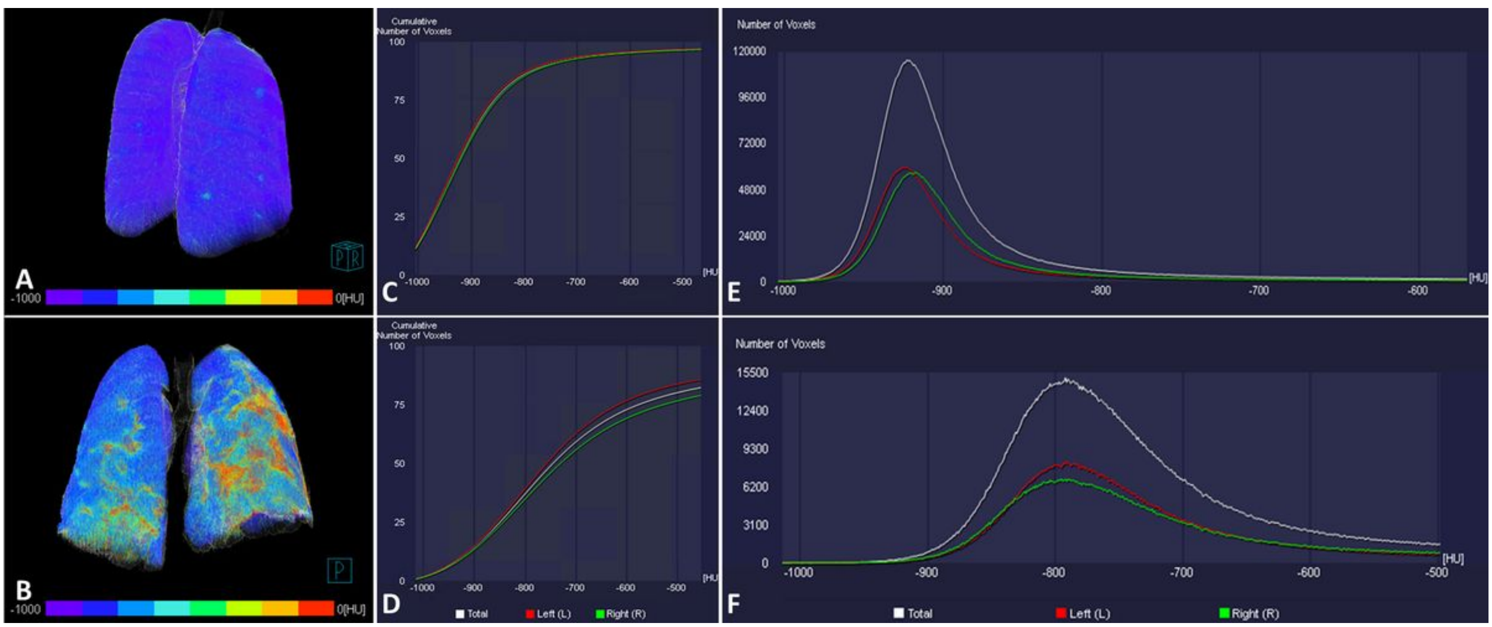

Figure 1

3D VRT (volume rendering) subrange images and quantitative analysis curves of a 46-year-old female inpatient (A, C, E) and a 52-year-old male critically ill patient (B, D, F).

3D VRT subrange images (A, B) are demonstrating the distribution and density of lung lesions. While the inpatient has a small number of ground glass opacities (A), the critically ill patient has more extensive and denser infiltrations consisting of mixed ground-glass opacities and consolidations (B). In the percentile curve images (C, D), relative well-aerated lung volume under the curve is lower in the critically ill patient (D). CT histogram curves (E, F) are showing the parenchymal distribution of Hounsfield units

(HU). The critically ill patient (F) has a higher MLD (mean lung density) (-652 HU) causing the histogram curve to shift to the right compared to the inpatient (E) with normal MLD (-874 HU).

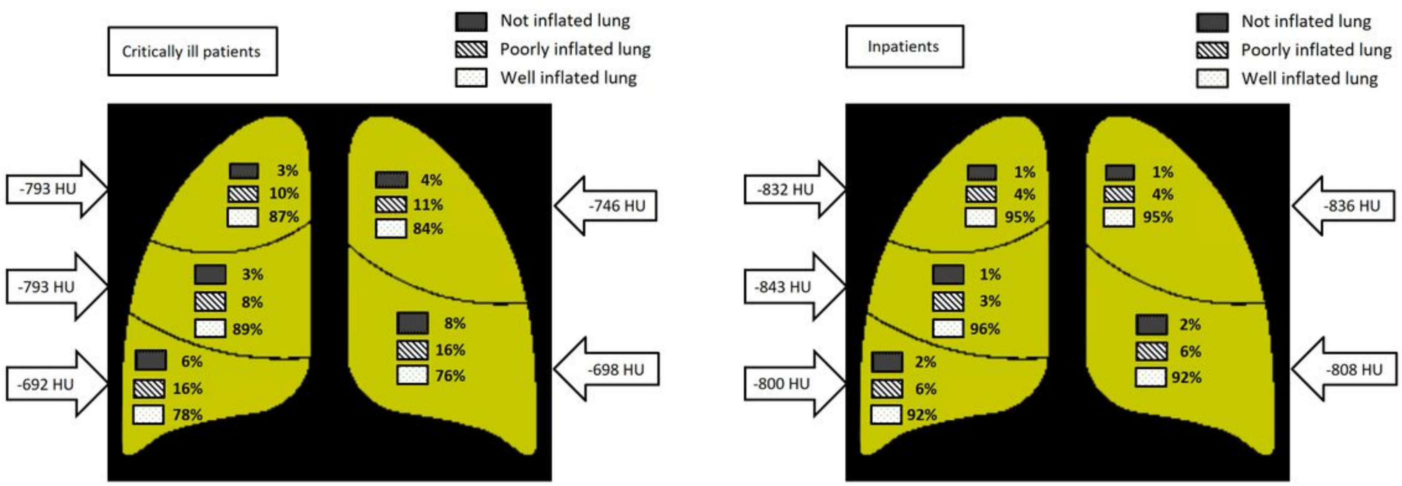

Figure 2

The involvement of the lung lobes according to the inflated lung ratios and density in inpatients and critically ill patients with SARS-CoV-2 pneumonia.

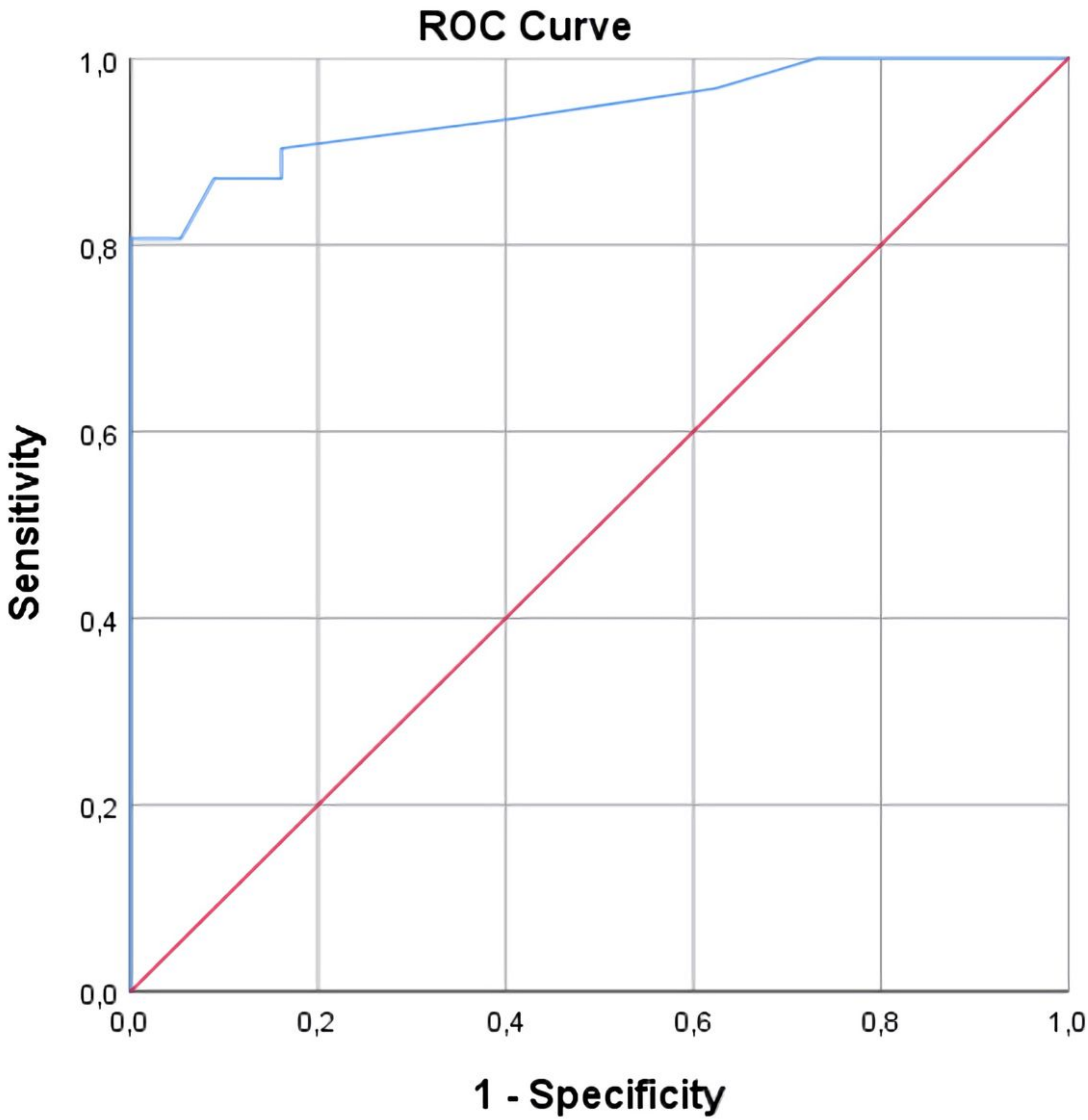

Figure 3

ROC curves for SF ratios on admission for predicting critically ill patients with pneumonia