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Early View

Original article

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Title

Chest computed tomography and alveolar-arterial oxygen gradient as rapid tools to diagnose and triage mildly symptomatic COVID-19 pneumonia patients

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Take Home Message

Low dose chest CT and alveolar-arterial oxygen gradient appear rapid and accurate tools to diagnose COVID-19 pneumonia and to select mildly symptomatic patients in need for hospitalization.

Abstract

Purpose In pandemic COVID-19, a rapid clinical triage is crucial to determine which patients are in need for hospitalization. We hypothesized that chest CT and alveolar-arterial oxygen (A-a) gradient may be useful to triage these patients, since it reflects the severity of the pneumonia-associated ventilation/perfusion abnormalities.

Methods A retrospective analysis was performed in consecutive patients (n=235) suspected for COVID-19. The diagnostic protocol included low-dose chest CT and arterial blood gas analysis. In patients with CT-based COVID-19 pneumonia, the association between "need for hospitalization" and A-a gradient was investigated by multivariable logistic regression model; and, the A-a gradient was tested as predictor for need for hospitalization using ROC curve analysis and logistic regression model.

Results 72 out of 235 patients (mean±SD age 55.5±14.6 years, 40% female) screened by chest CT showed evidence for COVID-19 pneumonia. In these patients, A-a gradient was shown to be a predictor of need for hospitalization, with an optimal decision level ("cut-off") of 36.4 mmHg (95% CI 0.70 - 0.91, $p < 0.001$). The A-a gradient was shown to be independently associated with need for hospitalization (OR 1.97 [95% CI 1.23 – 3.15], p=0.005, A-a gradient per 10 points) from CT-SS (OR 1.13 [95% CI 0.94 – 1.36], p=0.191), NEWS (OR 1.19 [95% CI 0.91 – 1.57], p=0.321) or peripheral oxygen saturation (OR 0.88 [95% CI 0.68 – 1.14], p=0.345).

Conclusion Low dose chest CT and the alveolar-arterial oxygen gradient may serve as rapid and accurate tools to diagnose COVID-19 pneumonia and to select mildly symptomatic patients in need for hospitalization.

Introduction

In the COVID-19 pandemic, large amounts of symptomatic patients require acute medical attention. To avoid the risk of burdening the healthcare system, effective triage of disease severity is essential to identify patients in need of hospitalization. Diagnosing COVID-19, however, is time consuming, and testing with reverse transcription polymerase chain reaction (RT PCR) techniques take several hours. Computer Tomography (CT) has been validated as an accurate tool to diagnose symptomatic patients with a COVID-19 pneumonia.[1,2] Subsequently, rapid clinical triage is of major importance to decide whether hospitalization is indicated and, even more importantly, whether a patient can be discharged home safely with a low chance of subsequent deterioration. At current, however, clinical guidelines are still lacking, and this decision making is merely based upon clinical judgement. Based upon WHO guidelines in pneumonia, breathing frequency and saturation are important indicators of disease severity. Hospitalization in these patients is advised if respiratory frequency exceeds 30/min or periphery oxygen SpO2 is below 93%.[3,4]

Where SpO2 is an accurate tool for measuring tissue oxygenation, however, it neither reflects ventilatory drive, nor oxygen uptake efficiency. We hypothesized that the alveolar-arterial oxygen tension ratio (A-a) gradient may be useful to triage these patients, since it reflects the severity of the pneumonia-associated ventilation/perfusion abnormalities. [5] The A-a gradient can be derived from the arterial oxygen and carbon dioxide pressures. Previously, various studies showed that the A-a gradient can be used as indicator for disease severity in patients with pneumonia and can predict clinical outcomes in hospitalised patients with community acquired pneumonia (CAP).[6,7]

Therefore, in the present study, we investigated whether the combination of low dose chest CT and the calculated A-a gradient could be used to diagnose COVID-19 and to predict the need for hospitalization and to support safe discharge of patients with COVID-19 pneumonia.

Materials and Methods

This retrospective observational analysis included patients suspected for COVID-19 infection admitted from March 25th to April 22th 2020 to a mobile triage unit, the Corona Screening Unit (CSU) of the OLVG Hospital Amsterdam, the Netherlands. The CSU was used to determine whether not-critically ill patients suspected for COVID-19 pneumonia were in need for hospital admission. Patients were suspected for COVID-19 if they had fever, cough and/or shortness of breath. In all patients vital parameters were measured (saturation of peripheral oxygen (SpO2), respiratory frequency (Rf), blood pressure (RR) and heart rate (Hr)), underwent low dose chest CT and ABG analysis. National Early Warning Score (NEWS)[8] was calculated. Pregnant women and patients in critical condition were directly referred to the emergency care unit and excluded for the purpose of this study. A critical condition was defined by SpO2 < 88%, Rf > 30/min, systolic blood pressure < 100 mmHg or mean arterial pressure (MAP) < 60 mmHg and/or oxygen requirements > 5 litres/min. Comorbidities were reported by the patient when entering CSU including: Chronic Obstructive Pulmonary Disease (COPD), hypertension, Diabetes Mellitus, immunocompromised status and/or obesity. The study was approved by the advisory committee for scientific research of OLVG Hospital.

COVID-19 diagnosis

All patients underwent a low dose chest CT scan. Scans were performed with a 16-slice multidetector CT scanner (Philips Brilliance, temporarily rented from Philips, Best, the Netherlands). The low-dose screening protocol did not include the use of intravenous contrast medium. Patients were scanned in caudocranial direction, from lung bases including posterior recess to lung apex, with the help of a scout view. A single breath hold protocol of 100 mAs and 120 Kv was used, with pitch 0.938, rotation time 0.5s and and (for an average patient) a general effective radiation dose of 2,5 mSv. Axial images were reconstructed with 1.0 mm slice thickness and 0.5 mm increments (16 seconds breath hold scan). For dyspneic patients the protocol comprised 2.0 mm slices with 1.0 mm increments (8 seconds breath hold scan). Scans were read in consensus by teams of two radiologists on service at the CSU (between 6 and 21 years of experience) for the presence of COVID-19-related pneumonia. After consensus the chest CT-severity score (CT-SS) (range 0-25) and COVID-19 Reporting and Data System (CO-RADS) score was reported, ranging from 1 (very unlikely) to 5 (very likely).[9,10]Based on previous reports, CO-RADS scores 4 and 5 were considered positive for COVID-19 infection. Diagnosis was confirmed in admitted patients by RT-PCR testing. When the initial RT-PCR was negative or indeterminate, but clinical suspicion of COVID-19 remained, repeat RT-PCR testing was performed. In this study, COVID-19 was defined by 1) a positive RT-PCR result, 2) indeterminate or negative RT-PCR results but laboratory findings and clinical signs supportive for COVID-19. Laboratory findings supportive for COVID-19 infection included lymphopenia, elevated lactate dehydrogenase, creatine kinase and C-reactive protein.[11,12]

Need for hospital admission

Patients in **need for hospitalization** were, retrospectively, defined when their length of stay (LOS) was more than 2 days. Patients directly discharged from CSU and patients with a LOS ≤ 2 days were considered in **no**

need for hospitalization. In particular, since the latter group was admitted because of more observational purpose or non-somatic reasons, without any need for additional treatment.

Standard of discharge

Admitted patients were discharged if their respiratory symptoms had improve, they had normal SpO2 on room air and were hemodynamically stable. Readmission within 30 days after discharge was registered for all patients.

A-a gradient

The A-a gradient was calculated as the difference between the alveolar oxygen partial pressure (PAO2) and the measured arterial oxygen pressure (PaO2) obtained by an automatic gas analyser (ABL90 Flex blood gas analyser, Radiometer). The fraction oxygen inspired O2 (FIO2) was 21% (patient breathing room air). The PAO2 was calculated as FIO2 x (atmospheric pressure- partial pressure of water vapor) - (partial pressure of carbon dioxide/0.8)). Analyses were performed using MedCalc for Windows, version 19.3.1 (MedCalc Software).

Since the A-a oxygen gradient increases with age[13] we also adjusted the calculated A-a gradient for age (*i.e.* age adjusted A-a gradient). A conservative estimate of a normal A-a gradient for age is (years + 10)/4. The exact expected A-a gradient for age was calculated using MedCalc Software. With the following formula the age adjusted A-a gradient was measured: calculated A-a gradient – expected A-a gradient for age.

Statistical analysis

The primary outcome of the present study was to determine whether A-a gradient in patients with COVID-19 pneumonia can predict the need for hospital admission. Normally distributed variables were summarized by means ± standard deviations and categorical variables by their frequencies and proportions. Group comparison was done with independent t-test or chi-square test, as appropriate. Multivariable logistic regression models were applied to independently assess the need of hospitalization by an increasing A-a gradient. A Receiver Operator Curve was created and an area under the curve (AUC) was calculated to assess an optimal cut-off value of the A-a gradient and the CT-SS. Variables with a P value of less than 0.05 were considered significantly different. Statistical analysis was performed retrospectively using SPSS Statistics Software (version 22; IBM, New York, USA).

Results

During the study period, 235 patients with suspected COVID-19 were referred to CSU. After using the exclusion criteria detailed above, the final cohort consisted of 232 subjects of which 160 were excluded for this analysis because of CO-RADS < 4 (n=141), missing ABG analysis (n=16), missing data (n=2) or a non-COVID-19 final diagnosis (n=1). A total of 72 patients with CO-RADS 4 or 5 were included in this study, 20 (28%) were discharged from the CSU, 52 (72%) were admitted to the hospital (Figure 1). Five were transferred to ICU and 3 died after initial ward admission.

In total, 31 patients were either discharged (I) or had a LOS ≤ 2 days (II) and were for these analyses retrospectively classified as in **“no need for hospitalization”**. A total of 41 patients were hospitalised for > 2 day (III) and were identified as in “**need for hospitalization”** (Figure 1, Table 1). Among the latter group of patients median length of hospital stay was 5.0 (IQR 3.0-8.0). Age, gender and number of days since first symptoms were similar in both groups. Both NEWS and A-a gradients were significantly higher in the group that was in **need for hospitalization** (A-a 26.5 mmHg (SD 12.7) vs 40.6 mmHg (SD 13.4) (p<0.001), NEWS 2.8 (SD 2.0) vs 4.1(SD 2.2) (p= 0.011). Peripheral oxygen saturation was significant lower in the group in **need for hospitalization** (SpO2 97.2% (SD 1.7) vs 95.2% (SD 3.1) (p= 0.003).

Table 1: Patients characteristics

	No need for hospitalization	**Need for hospitalization***	**P-value**
N	**31 (100%)**	**41 (100%)**	
Age (y)	52.2 ± 16.1	57.9 ± 12.8	0.098
Gender (Female)	12 (38.7%)	17 (41.5%)	0.814
Number of days since first symptoms	10.9 ± 5.2	10.2 ± 6.2	0.606
NEWS score (scale 0-20)	2.8 ± 2.0	4.1 ± 2.2	0.011
Mean arterial blood pressure (mmHg)	94.0 ± 10.0	100.0 ± 10.1	0.214
Body temperature (°C)	37.5 ± 1.0	37.5 ± 1.1	0.812
Heart rate (beats/min)	93.4 ± 20.5	94.2 ± 16.9	0.868
Respiratory frequency (breaths/min)	22.4 ± 5.4	25.0 ± 5.7	0.061
Peripheral oxygen saturation (%)	97.2 ± 1.7	95.2 ± 3.1	0.003
Comorbid conditions			
Hypertension	4(12.9%)	13 (31.7%)	0.063
Diabetes Mellitus type II	4 (12.9%)	7 (17.1%)	0.626
Obesity	2 (6.5%)	7 (17.1%)	0.177
COPD	1 (3.2%)	2 (4.9%)	0.728
Immune compromised	1 (3.2%)	1 (2.4%)	0.841
A-a gradient (mmHg)	26.5 ± 12.7	40.6 ± 13.4	<0.001
CT-SS (scale 0-25)	9.2 ± 3.39	11.8 ± 3.38	0.002

Numbers are presented as n (%) for categorical variables; mean ± standard deviation for continuous and normally distributed variables. P values were derived from χ^2 test for frequencies and t-test for continuous variables. *Need for hospitalization was defined as hospital admission for >2 days; no need for hospitalization was defined as either discharge or ≤ 2 days hospitalization. . Comorbidities were reported by a physician when entering CSU including. CT-SS: CT Severity Score

Multivariable logistic regression model demonstrated A-a gradient was associated with **need for hospitalization** (odds ratio 1.97 [95% CI 1.23 – 3.15], p=0.005, A-a gradient per 10 points), independently from CT-SS (odds ratio 1.13 [95% CI 0.94 – 1.36], p=0.191), NEWS (odds ratio 1.19 [95% CI 0.91 – 1.57], p=0.321) or peripheral oxygen saturation (odds ratio 0.88 [95% CI 0.68 – 1.14], p=0.345).

The value of A-a gradient and CT-SS were both tested as predictors for **need for hospitalization** using ROC curve analysis. The ROC curve of A-a gradient achieved an area under the curve (AUC) of 0.81(95% confidence interval (CI) 0.70 - 0.91 p < 0.001) (Figure 2) and therefore was a stronger predictor for **need for hospitalization** than CT-SS (AUC of 0.71 (0.59-0.84), p=0.002) (Figure 3).

For A-a gradient, based on the optimal sensitivity (0.73) and specificity (0.81), a decision level ("cut-off") of 36.4 mmHg (< 36.4 mmHg to predict no need for hospital admission and ≥ 36.4 mmHg to predict need for hospitalization) was established. The positive predictive value (PPV), *i.e.* the probability that someone with an A-a gradient > 36.4 mmHg was hospitalized is 83%. Whilst the negative predictive value (NPV) is 69%.

For the calculated age adjusted A-a gradient the ROC was 0.77 (95% confidence interval (CI) 0.66– 0.88, p < 0.001) (Figure 4). An optimum age adjusted A-a gradient of 19.5 mmHg was calculated to predict need for hospital admission (specificity 0.77 and sensitivity 0.68) with a PVV of 75% and NPV of 55%.

Discussion

In this study we demonstrated that a low dose chest CT scan combined with the alveolar-arterial oxygen gradient may serve as a rapid and accurate tool to diagnose and triage mildly symptomatic patients with COVID-19 pneumonia in need for hospitalization. A-a gradient is associated with need for hospitalization. Since chest CT is not mandatory in patients with an already positive COVID-19 test, the A-a gradient can be used to assess **need for hospitalization.** Moreover, A-a threshold over 36.4 mmHg, or age adjusted A-a gradient ≥ 19.5 mmHg, identified patients at risk for hospitalization. In reverse, in our cohort, all patients with A-a gradient < 36.4 mmHg (or age adjusted A-a ≤ 19.5 mmHg) could be discharged home safely. In support, during a 30-day follow-up in the 31 patients in the group **no need for hospitalization** there were no patients readmitted to the hospital with an A-a gradient at screening of < 36.4mmHg. Two patients in this group were readmitted after discharge and both patients had A-a gradients > 36.4 mmHg (40.0 mmHg and 42.0 mmHg respectively).

The potential clinical value of the A-a gradient was previously recognized in patients with CAP and was proven to be correlated with the pneumonia severity index (PSI).[6,7] Moammar et al.[6] showed that in CAP, an A-a gradient ≥ 89mmHg correlated with moderate-to-high risk, *i.e*. PSI classes IV and V. In our study, however, the more severely affected COVID-19 patients were excluded; so, we did not test whether the A-a gradient correlates with the severity of disease. However, A-a gradient appeared to reflect severity of disease as defined by the need for hospitalization. As the A-a gradient is dependent of age, we also studied the predictive value of the age adjusted A-a. The age adjusted A-a gradient might be more accurate for the detection of disease severity, as for the young and older patients' the A-a gradient significantly differs. In this study, we were unable to show a difference in the predictive value for hospitalization between the A-a gradient or the age adjusted A-a gradient. Although this might be due to the relatively small sample size, our study is the first to suggest that both age adjusted A-a- and A-a gradient appear to be of clinical use as quick screening tool in moderate COVID-19 patients to predict need of hospitalization.

For this study, we created 3 different groups: group I discharged directly; group II hospitalization ≤ 2 days, and group III hospitalised > 2 days. The reason for separating hospitalized patients based upon their length of hospital stay into two groups (II and III) was to distinguish patients with a hospitalization just for safety reasons, *i.e*. mere clinical observation period of 24-48 hours without any need for additional treatment, from patients that were truly in need for hospitalization and received additional oxygen, antibiotics and/or potential other drug therapies for COVID-19. In fact, retrospectively, these patients could have been discharged home. Therefore, for this study, they were considered as in no need for hospitalization.

This retrospective study has several limitations. First, the decision to hospitalize and discharge patients with COVID-19 pneumonia was left to the judgment of the clinician. This has led to a wide variation in criteria used for admission and discharge based on physician experience and bias. However, this provides a good reflection of daily practice. Second, due to the shortness of tests at the beginning of the COVID-19 pandemic in the Netherlands, RT-PCR conformation was performed strictly in hospitalized patients. In patients with negative or indeterminate RT-PCR, however, the final diagnose was established among at least three pulmonologist based on chest CT and laboratory findings. Nevertheless it cannot be excluded that some COVID-19 diagnoses were missed. Third, after discharge at CSU, follow-up was documented only in the patients who received subsequent medical attention in our hospital. In theory, patients could be hospitalised or readmitted at another hospital afterwards. We recommended, however, all patients after discharge to use our mobile national corona app ("De Corona Check") to monitor their symptoms.[14] Moreover, we instructed patients in case of deterioration, to come to our hospital at any time. Fourth, an increased A-a gradient has more causes next to V/Q mismatch as reflection of the extend of parenchymal damage. Also dead space ventilation (*i.e*. pulmonary embolism) may contribute to V/Q mismatch. In this study, we were not informed about possible pulmonary embolism as non-contrast chest CT was performed at the time of diagnosis. Lastly, this study was conducted on a relative small sample size of 72 patients, Therefore, external validation of the A-a gradient and the proposed threshold in a larger number of patients is needed to warrant its clinical validity.

During the recent COVID-19 pandemic the burden on the limited hospital capacity was high. Therefore, hospitalization should be reserved for patients in true need of supportive care and an increased risk for subsequent deterioration. At the time of the pandemic no clinical prediction rule was presented yet. Our hospital built a CSU for rapid triage, and by doing so, tried to keep the emergency unit and healthcare system accessible. By using chest CT, a quick recognition of pulmonary involvement of COVID-19 was established. Although confirmation of our results in other and larger series of patients is warranted, the combination of a CT and an arterial blood gas analysis may provide within minutes all information needed to triage patients in the need for hospitalization. Despite other biomarkers[11,12] shown to correlate with clinical outcomes, most of these are not suitable for rapid screening because they are time consuming. Our approach takes less than 10 minutes to select patients in true need for hospitalization.

Based on latest WHO clinical management of COVID-19, patients with moderate illness, *i.e*. clinical signs of pneumonia but no signs of severe pneumonia, with SpO2 ≥ 93% may not require hospitalization. Severe pneumonia is defined as fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2≤ 93% on room air. In the present study, however, only 7 of 41 patients who were in need for hospitalization had a SpO2 <93% and fulfilled the WHO criteria. All other patients turned out to be more seriously ill than estimated based on SpO2 alone. Since SpO2 merely reflect tissue oxygenation, in our view, additional blood gas analysis is mandatory in all dyspnoeic patients. Moreover, an ABG is easy to perform and provides next to PaO2, information on ventilatory drive (PaCO2) and allows for calculating the A-a gradient. In addition since our study was performed in ambulant, mildly symptomatic patients presenting with low NEWS scores of 1-4 (range 0-20), no decisions for hospitalization could have been made based on NEWS. In conclusion, based upon our findings, we suggest that the combination of chest CT and the A-a gradient may serve as rapid and accurate tools to diagnose COVID-19 pneumonia and to assess the need for hospital admission. However, our observations warrant prospective validation studies in larger cohorts of patients to assess the clinical validity of the A-a gradient and the proposed thresholds, *i.e.* A-a < 36.4 mmHg or an age adjusted A-a ≤ 19.5 mmHg, respectively.

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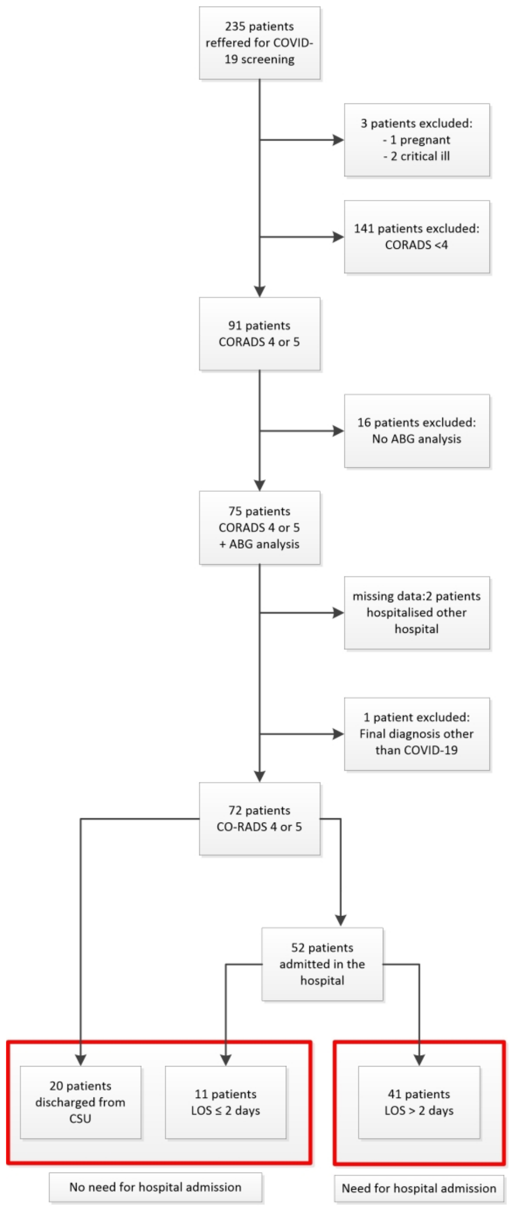

Flowchart CSU

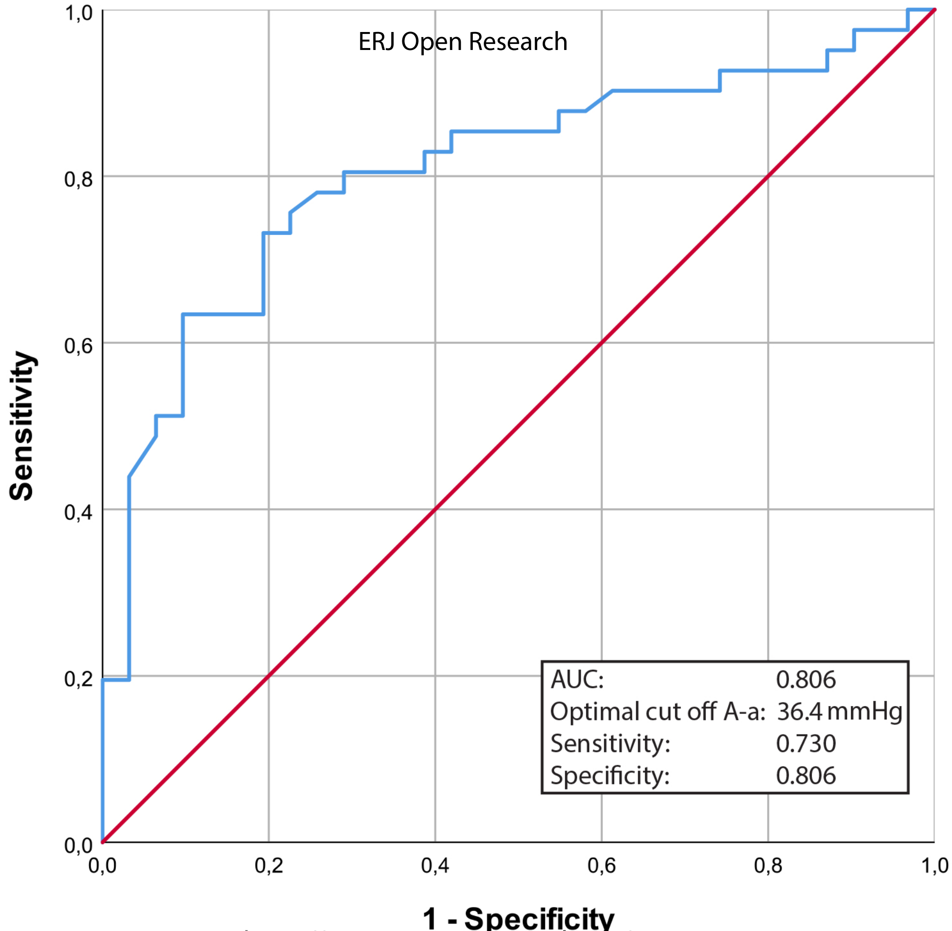

Figure 2: A-a gradient to predict the need for hospitalization in COVID-19 patients

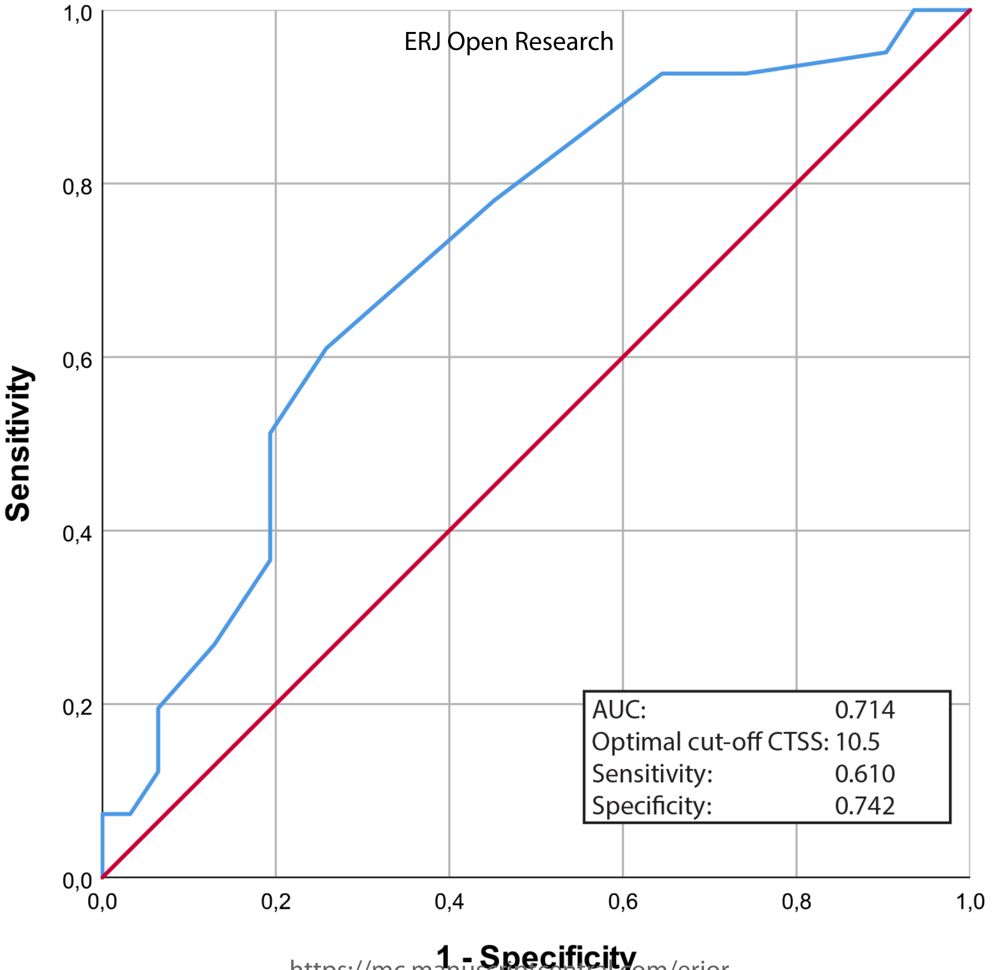

Figure 3: CT severity score to predict the need for hospitalization in COVID-19 patients

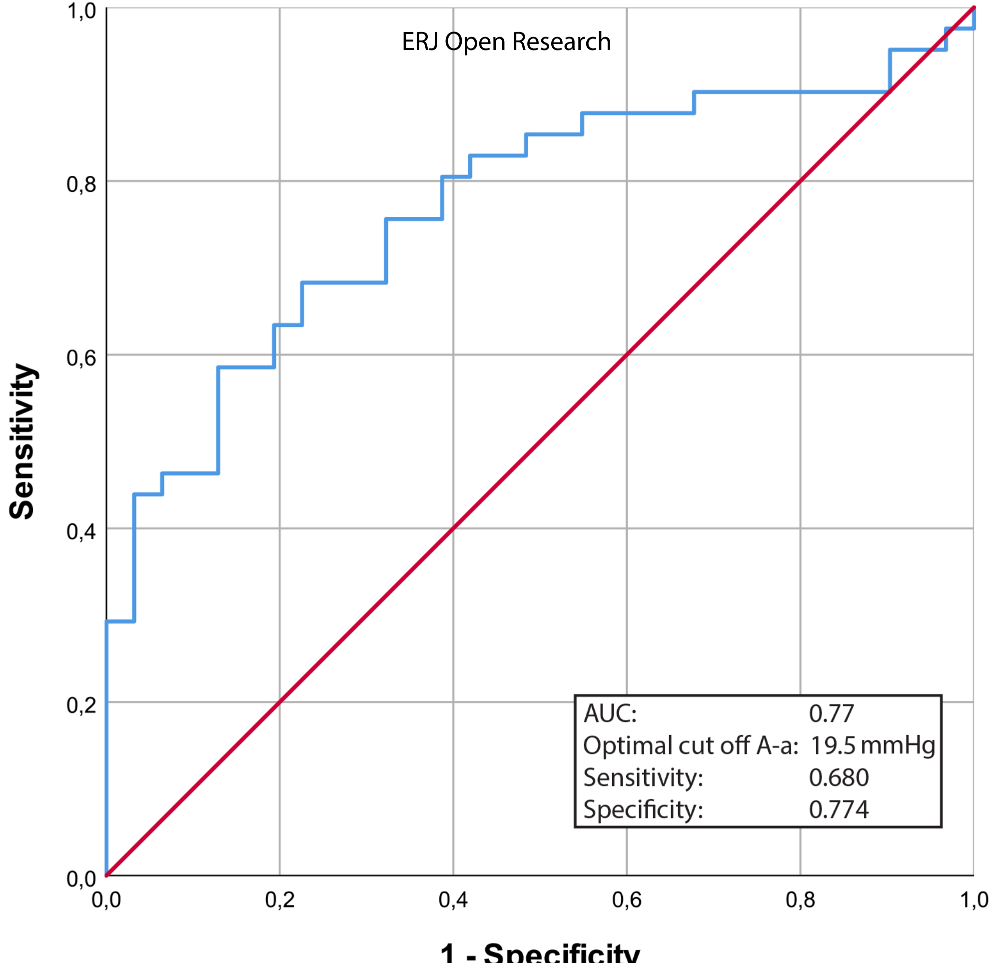

Figure 4: Age adjusted A-a gradient to predict the need for hospitalization in COVID-19 patients