



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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ABSTRACT

Background: In the coronavirus disease 2019 (COVID-19) pandemic, rapid clinical triage is crucial to determine which patients need hospitalisation. We hypothesised that chest computed tomography (CT) and alveolar–arterial oxygen tension ratio (A-a) gradient may be useful to triage these patients, since they reflect the severity of the pneumonia-associated ventilation/perfusion abnormalities.

Methods: A retrospective analysis was performed in 235 consecutive patients 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 hospitalisation” and A-a gradient was investigated by a multivariable logistic regression model. The A-a gradient was tested as a predictor for need for hospitalisation using receiver operating characteristic curve analysis and a 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 hospitalisation, 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 hospitalisation (OR 1.97 (95% CI 1.23–3.15), $p=0.005$; A-a gradient per 10 points) from CT severity score (OR 1.13 (95% CI 0.94–1.36), $p=0.191$), National Early Warning Score (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 A-a gradient may serve as rapid and accurate tools to diagnose COVID-19 pneumonia and to select mildly symptomatic patients in need for hospitalisation.



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Low-dose chest CT and alveolar–arterial oxygen gradient appear to be rapid and accurate tools to diagnose #COVID19 pneumonia, and to select mildly symptomatic patients in need of hospitalisation <https://bit.ly/2N3rJlE>

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Introduction

In the coronavirus disease 2019 (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 hospitalisation. However, diagnosing COVID-19 is time consuming, and testing with reverse transcription (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 hospitalisation is indicated and, even more importantly, whether a patient can be discharged home safely with a low chance of subsequent deterioration. However, at present, clinical guidelines are still lacking, and this decision making process is merely based upon clinical judgement. Based on World Health Organization (WHO) guidelines in pneumonia, breathing frequency and saturation are important indicators of disease severity. Hospitalisation in these patients is advised if respiratory frequency is >30 breaths·min⁻¹ or periphery oxygen saturation measured by pulse oximetry (S_{pO_2}) is $<93\%$ [3].

Although S_{pO_2} is an accurate tool for measuring tissue oxygenation, it neither reflects ventilatory drive nor oxygen uptake efficiency. We hypothesised 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 [4]. The A-a gradient can be derived from the arterial oxygen and carbon dioxide pressures. Previously, various studies have shown that the A-a gradient can be used as an indicator for disease severity in patients with pneumonia and can predict clinical outcomes in hospitalised patients with community-acquired pneumonia (CAP) [5, 6].

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 hospitalisation 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 to a mobile triage unit, the Corona Screening Unit (CSU) of the OLVG Hospital (Amsterdam, the Netherlands), from 25 March to 22 April 2020. The CSU was used to determine whether patients suspected for COVID-19 pneumonia who were not critically ill needed 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 (S_{pO_2} , respiratory frequency, blood pressure and heart rate) and low-dose chest CT and arterial blood gas (ABG) analysis were performed. The National Early Warning Score (NEWS) [7] was calculated. Pregnant women and patients in a critical condition were directly referred to the emergency care unit and excluded for the purpose of this study. A critical condition was defined as $S_{pO_2} <88\%$, respiratory frequency >30 breaths·min⁻¹, systolic blood pressure <100 mmHg or mean arterial pressure <60 mmHg and/or oxygen requirements >5 L·min⁻¹. Comorbidities were reported by the patient when entering the CSU including: 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 0.5 s 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 s breath-hold scan). For dyspnoeic patients, the protocol comprised 2.0 mm slices with 1.0 mm increments (8 s breath-hold scan). Scans were read in consensus by teams of two radiologists on service at the CSU (with 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) [8, 9]. 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; or 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 [10, 11].

Need for hospital admission

Patients in need for hospitalisation were, retrospectively, defined when their length of stay (LOS) was >2 days. Patients directly discharged from the CSU and patients with a LOS ≤2 days were considered as no need for hospitalisation. In particular, the latter group was admitted because of more observational purposes or non-somatic reasons, without any need for additional treatment.

Standard of discharge

Admitted patients were discharged if their respiratory symptoms had improved, they had normal S_{pO_2} on room air and were haemodynamically 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 tension and the measured arterial oxygen tension obtained by an automatic gas analyser (ABL90 Flex blood gas analyser; Radiometer). The inspiratory oxygen fraction was 21% (patient breathing room air). The alveolar oxygen tension was calculated as $\text{inspiratory oxygen fraction} \times (\text{atmospheric pressure} - \text{partial pressure of water vapor}) - (\text{partial pressure of carbon dioxide}/0.8)$. Analyses were performed using MedCalc for Windows, version 19.3.1 (MedCalc Software).

Since the A-a oxygen gradient increases with age [12], 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 $(\text{years}+10)/4$. 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: $\text{calculated A-a gradient} - \text{expected A-a gradient for age}$.

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 presented as mean±SD and categorical variables as n (%). Group comparison was performed with independent t-tests or Chi-squared tests, as appropriate. Multivariable logistic regression models were applied to independently assess the need of hospitalisation 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 <0.05 were considered significantly different. Statistical analysis was performed retrospectively using SPSS Statistics Software (version 22; IBM, New York, NY, USA).

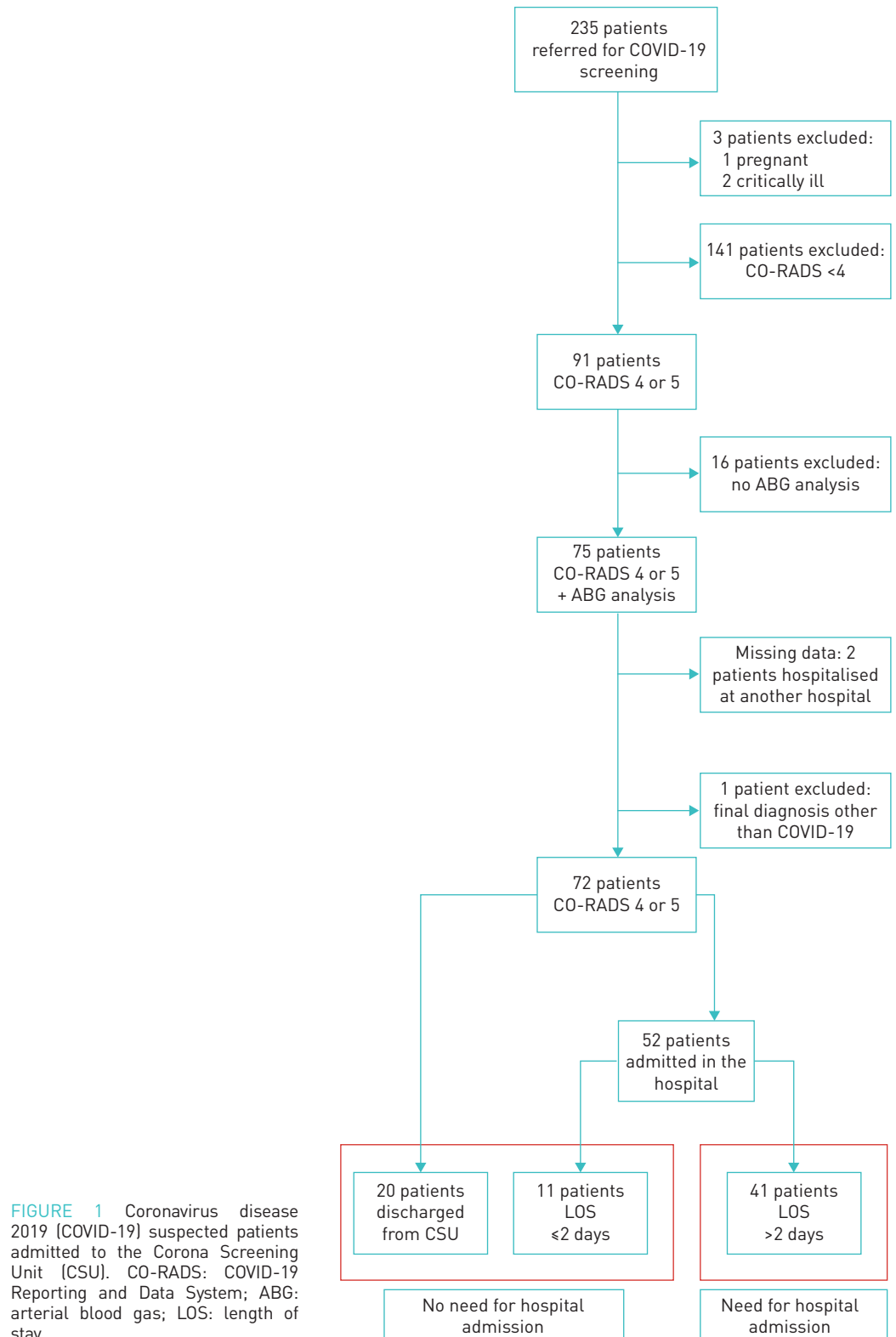
Results

During the study period, 235 patients with suspected COVID-19 were referred to the 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 the intensive care unit and three died after initial ward admission.

In total, 31 patients were either discharged (I) or had a LOS ≤2 days (II) and were retrospectively classified as in “no need for hospitalisation”. A total of 41 patients were hospitalised for >2 day (III) and were identified as in “need for hospitalisation” (figure 1, table 1). Among the latter group of patients median (interquartile range) length of hospital stay was 5.0 (3.0–8.0) days. Age, sex 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 hospitalisation (A-a 26.5 ± 12.7 mmHg *versus* 40.6 ± 13.4 mmHg ($p < 0.001$), NEWS 2.8 ± 2.0 *versus* 4.1 ± 2.2 ($p = 0.011$). Peripheral oxygen saturation was significantly lower in the group in need for hospitalisation (S_{pO_2} $97.2 \pm 1.7\%$ *versus* $95.2 \pm 3.1\%$ ($p = 0.003$)).

The multivariable logistic regression model demonstrated that the A-a gradient was associated with need for hospitalisation (OR 1.97 (95% CI 1.23–3.15), $p = 0.005$; A-a gradient per 10 points), independently 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), $p = 0.345$).

The value of the A-a gradient and CT-SS were both tested as predictors for need for hospitalisation using receiver operating characteristic (ROC) curve analysis. The ROC curve of A-a gradient achieved an AUC of 0.81 (95% CI 0.70–0.91, $p < 0.001$) (figure 2) and therefore was a stronger predictor for need for hospitalisation than CT-SS (AUC 0.71 (95% CI 0.59–0.84), $p = 0.002$) (figure 3).



For the 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 hospitalisation) was established. The positive predictive value (PPV), *i.e.* the probability that someone with an A-a gradient >36.4 mmHg was hospitalised was 83%. Whilst the negative predictive value (NPV) was 69%.

TABLE 1 Patient characteristics

	No need for hospitalisation [#]	Need for hospitalisation [¶]	p-value
Subjects	31 (100)	41 (100)	
Age years	52.2±16.1	57.9±12.8	0.098
Females	12 (38.7)	17 (41.5)	0.814
Days since first symptoms	10.9±5.2	10.2±6.2	0.606
NEWS 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 ⁻¹	93.4±20.5	94.2±16.9	0.868
Respiratory frequency breaths·min ⁻¹	22.4±5.4	25.0±5.7	0.061
Peripheral oxygen saturation %	97.2±1.7	95.2±3.1	0.003
Comorbidities*			
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

Data are presented as n (%) or mean±SD, unless otherwise stated. p-values were derived from Chi-squared tests for frequencies and t-test for continuous variables. NEWS: National Early Warning Score; A-a gradient: alveolar-arterial oxygen tension ratio; CT-SS: computed tomography-severity score. [#]: defined as either discharge or ≤2 days hospitalisation; [¶]: defined as hospital admission for >2 days; *: reported by a physician when entering the Corona Screening Unit.

For the calculated age adjusted A-a gradient, the ROC was 0.77 (95% 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 A-a gradient may serve as a rapid and accurate tool to diagnose and triage mildly symptomatic patients with COVID-19 pneumonia in need for hospitalisation. The A-a gradient is associated with need for hospitalisation. Since

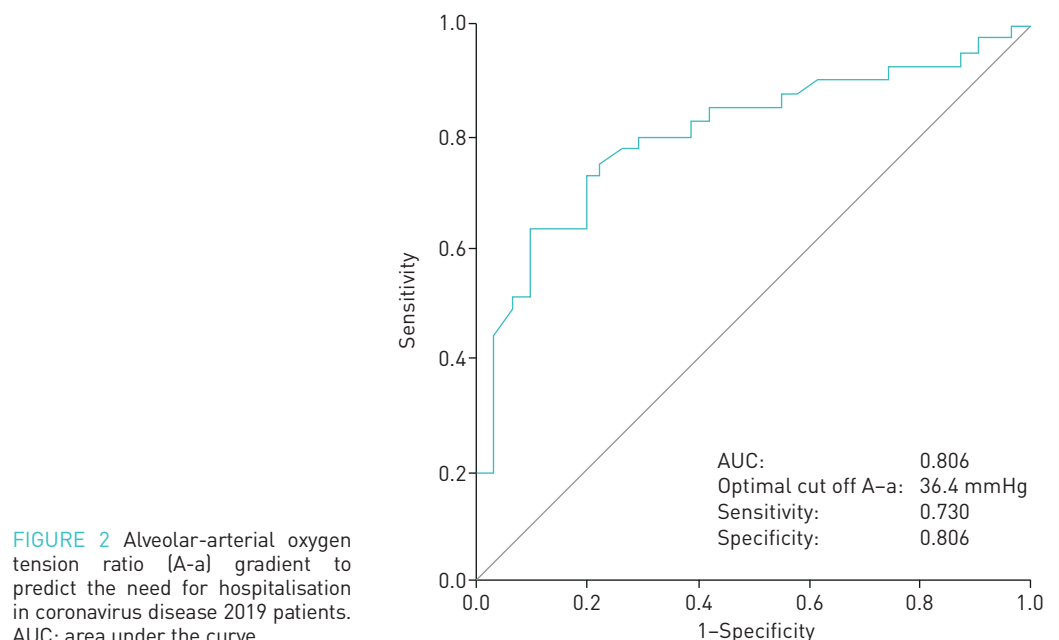
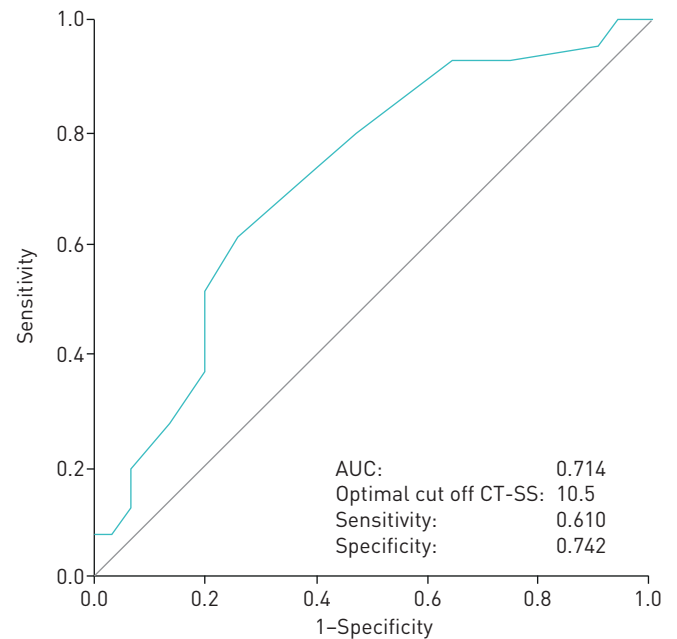


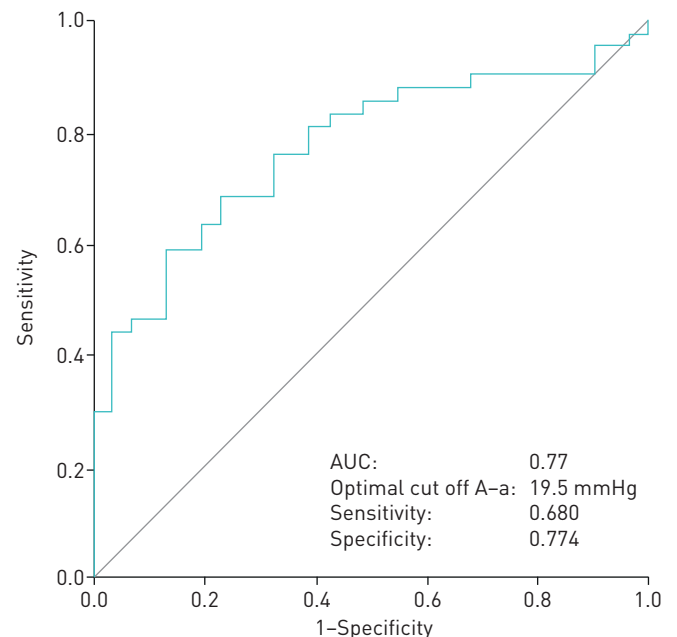
FIGURE 3 Computed tomography-severity score (CT-SS) to predict the need for hospitalisation in COVID-19 patients. AUC: area under the curve.



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 hospitalisation. Moreover, a A-a threshold >36.4 mmHg, or an age-adjusted A-a gradient ≥ 19.5 mmHg identified patients at risk for hospitalisation. In reverse, in our cohort, all patients with an A-a gradient <36.4 mmHg (or an age-adjusted A-a gradient ≤ 19.5 mmHg) could be discharged home safely. In support, during a 30-day follow-up in the 31 patients in the no need for hospitalisation group there were no patients readmitted to the hospital with an A-a gradient at screening of <36.4 mmHg. 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 recognised in patients with CAP and was proven to be correlated with the pneumonia severity index (PSI) [5, 6]. MOAMMAR *et al.* [5] showed that in CAP, an A-a gradient ≥ 89 mmHg 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, therefore, we did not test whether the A-a gradient correlates with the severity of disease. However, A-a gradient appeared to reflect

FIGURE 4 Age adjusted alveolar-arterial oxygen tension ratio [A-a] gradient to predict the need for hospitalisation in COVID-19 patients. AUC: area under the curve.



severity of disease as defined by the need for hospitalisation. As the A-a gradient is dependent on age, we also studied the predictive value of the age-adjusted A-a gradient. 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 hospitalisation 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 gradient and A-a gradient appear to be of clinical use as quick screening tools in moderate COVID-19 patients to predict need of hospitalisation.

For this study, we created three different groups: group I discharged directly; group II hospitalisation ≤ 2 days, and group III hospitalised > 2 days. The reason for separating hospitalised patients based upon their length of hospital stay into two groups (II and III) was to distinguish patients hospitalised just for safety reasons, *i.e.* clinical observation period of 24–48 h without any need for additional treatment, from patients that were truly in need for hospitalisation 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 hospitalisation.

This retrospective study has several limitations. First, the decision to hospitalise 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. Secondly, due to the shortness of tests at the beginning of the COVID-19 pandemic in the Netherlands, RT-PCR confirmation was performed strictly in hospitalised patients. In patients with negative or indeterminate RT-PCR, however, the final diagnose was established among at least three pulmonologists based on chest CT and laboratory findings. Nevertheless it cannot be excluded that some COVID-19 diagnoses were missed. Thirdly, after discharge from the CSU, follow-up was only documented 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, that all patients use our mobile national corona app ("De Corona Check") after discharge to monitor their symptoms [13]. Moreover, we instructed patients in case of deterioration, to come to our hospital at any time. Fourthly, an increased A-a gradient has more causes next to ventilation/perfusion mismatch as reflection of the extent of parenchymal damage, also dead space ventilation (*i.e.* pulmonary embolism) may contribute to ventilation/perfusion mismatch. In this study, we were not informed about possible pulmonary embolism as non-contrast chest CT was performed at the time of diagnosis. Finally, this study was conducted in a relatively 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, hospitalisation 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 had been presented. 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 scan and ABG analysis may provide all the information needed to triage patients in need for hospitalisation within minutes. Despite other biomarkers [10, 11] shown to correlate with clinical outcomes, most of these are not suitable for rapid screening because they are time consuming. Our approach takes < 10 min to select patients in true need for hospitalisation.

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 $S_{pO_2} \geq 93\%$ may not require hospitalisation. Severe pneumonia is defined as fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths·min⁻¹; severe respiratory distress; or $S_{pO_2} \leq 93\%$ on room air. In the present study, however, only seven out of 41 patients who were in need for hospitalisation had a $S_{pO_2} < 93\%$ and fulfilled the WHO criteria. All other patients turned out to be more seriously ill than estimated based on S_{pO_2} alone. Since S_{pO_2} merely reflects tissue oxygenation, in our view, additional blood gas analysis is mandatory in all dyspnoeic patients. Moreover, ABG analysis is easy to perform and provides, next to arterial oxygen tension, information on ventilatory drive (arterial carbon dioxide tension) and allows the A-a gradient to be calculated. 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 hospitalisation could have been made based on NEWS. In conclusion, based on our findings, we suggest that a 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 gradient < 36.4 mmHg or an age-adjusted A-a gradient ≤ 19.5 mmHg, respectively.

Data availability: Data are available upon reasonable request.

Conflict of interest: M.P. de Roos has nothing to disclose. I.D. Kilsdonk has nothing to disclose. P-P.W. Hekking has nothing to disclose. J. Peringa has nothing to disclose. N.G. Dijkstra has nothing to disclose. P.W.A. Kunst has nothing to disclose. P. Bresser has nothing to disclose. H.J. Reesink has nothing to disclose.

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