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Early View

Original article

Diagnosing COVID-19 pneumonia in a pandemic setting: Lung Ultrasound *versus* CT (LUVCT) A multi-centre, prospective, observational study

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Diagnosing COVID-19 pneumonia in a pandemic setting:

Lung **U**ltrasound **v**ersus **CT (LUVCT)**

A multi-centre, prospective, observational study

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TAKE HOME MESSAGE

The #luvct study found that lung ultrasound (LUS) and CT have comparable diagnostic accuracy for COVID-19 pneumonia. LUS safely excludes COVID-19 pneumonia, and may aid diagnosis of COVID-19. This simple tool may prove especially useful in resource constrained settings!

ABSTRACT

Background: In this COVID-19 pandemic, fast and accurate testing is needed to profile patients at the emergency department (ED) and efficiently allocate resources. Chest imaging has been considered in COVID-19 workup, but evidence on lung ultrasound (LUS) is sparse. We therefore aimed to assess and compare the diagnostic accuracy of LUS and computed tomography (CT) in suspected COVID-19 patients.

Methods: This multi-centre, prospective, observational study included adult patients with suspected COVID-19 referred to internal medicine at the ED. We calculated diagnostic accuracy measures for LUS and CT using both PCR and multi-disciplinary team (MDT) diagnosis as reference. We also assessed agreement between LUS and CT, and between sonographers.

Results: Between March 19 and May 4, 2020, 187 patients were included. Area under the receiver operating characteristic (AUROC) was 0.81 (CI 0.75-0.88) for LUS and 0.89 (CI 0.84-0.94) for CT. Sensitivity and specificity for LUS were 91.9% (CI 84.0-96.7) and 71.0% (CI 61.1-79.6), versus 88.4% (CI 79.7-94.3) and 82.0% (CI 73.1-89.0) for CT. Negative likelihood ratio was 0.1 (CI 0.06-0.24) for LUS and 0.14 (0.08-0.3) for CT. No patient with a false negative LUS, required supplemental oxygen or admission. LUS specificity increased to 80% (CI 69.9-87.9) compared to MDT diagnosis, with an AUROC of 0.85 (CI 0.79-0.91). Agreement between LUS and CT was 0.65. Inter-observer agreement for LUS was good: 0.89 (CI 0.83-0.93).

Conclusion: LUS and CT have comparable diagnostic accuracy for COVID-19 pneumonia. LUS can safely exclude clinically relevant COVID-19 pneumonia and may aid COVID-19 diagnosis in high prevalence situations.

1. INTRODUCTION

COVID-19 is caused by the novel and rapidly spreading severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Cases continue to rise worldwide.[1, 2] With the pandemic hotspot moving to middle- and low-income regions such as Russia, India, Pakistan, Latin-America and Africa the consequences could be potentially catastrophic.[3] Since there is no effective treatment yet, early detection is crucial in halting COVID-19.

The SARS-CoV-2 reverse transcriptase polymerase chain reaction (PCR) assay is the gold standard for diagnosing COVID-19. Although it is highly specific, it has limited sensitivity, long turnaround time, and there is a worldwide shortage of test capacity. Serological tests are not useful in acute cases and reliable rapid antigen tests are unfortunately not available.[4, 5] This hampers immediate triage and decision-making. Moreover, microbiological tests do not give insight into lung involvement, while this is the main cause of morbidity and mortality.[6, 7] Correct assessment of lung involvement is thus crucial for appropriate triage, clinical management, and efficient allocation of scarce medical resources.

The WHO recently advocated chest imaging, especially when PCR results are not readily available, or the initial PCR is negative but clinical suspicion of COVID-19 remains high.[8] However, chest radiography (CXR) sensitivity is low [9, 10], and there are differences of opinion on the role of computed tomography (CT) in COVID-19.[9–12]

In view of the unmet clinical need for a fast and reliable test to diagnose or rule out COVID-19 pneumonia, bedside lung ultrasound (LUS) has attracted attention.[13–23] Although many clinicians might be unfamiliar with LUS, its diagnostic properties are better than CXR and physical examination combined, and equivalent to chest CT in diagnosing acute respiratory pathologies including pneumonia.[24–27] In addition, it has the advantage over CT of being portable, quick, radiation free, easy to disinfect, and low cost. Moreover, it integrates real-

time imaging into clinical decision making at the bedside, reducing time to diagnosis and treatment.[28–30]

Unfortunately, the literature on the use of LUS in COVID-19 is limited.[8] Therefore our objective was to investigate the role of LUS in suspected COVID-19 patients at the emergency department (ED). To our knowledge, this is the first prospective study analysing and comparing diagnostic accuracy of LUS and CT in diagnosing pneumonia in patients with suspected COVID-19.

2. METHODS

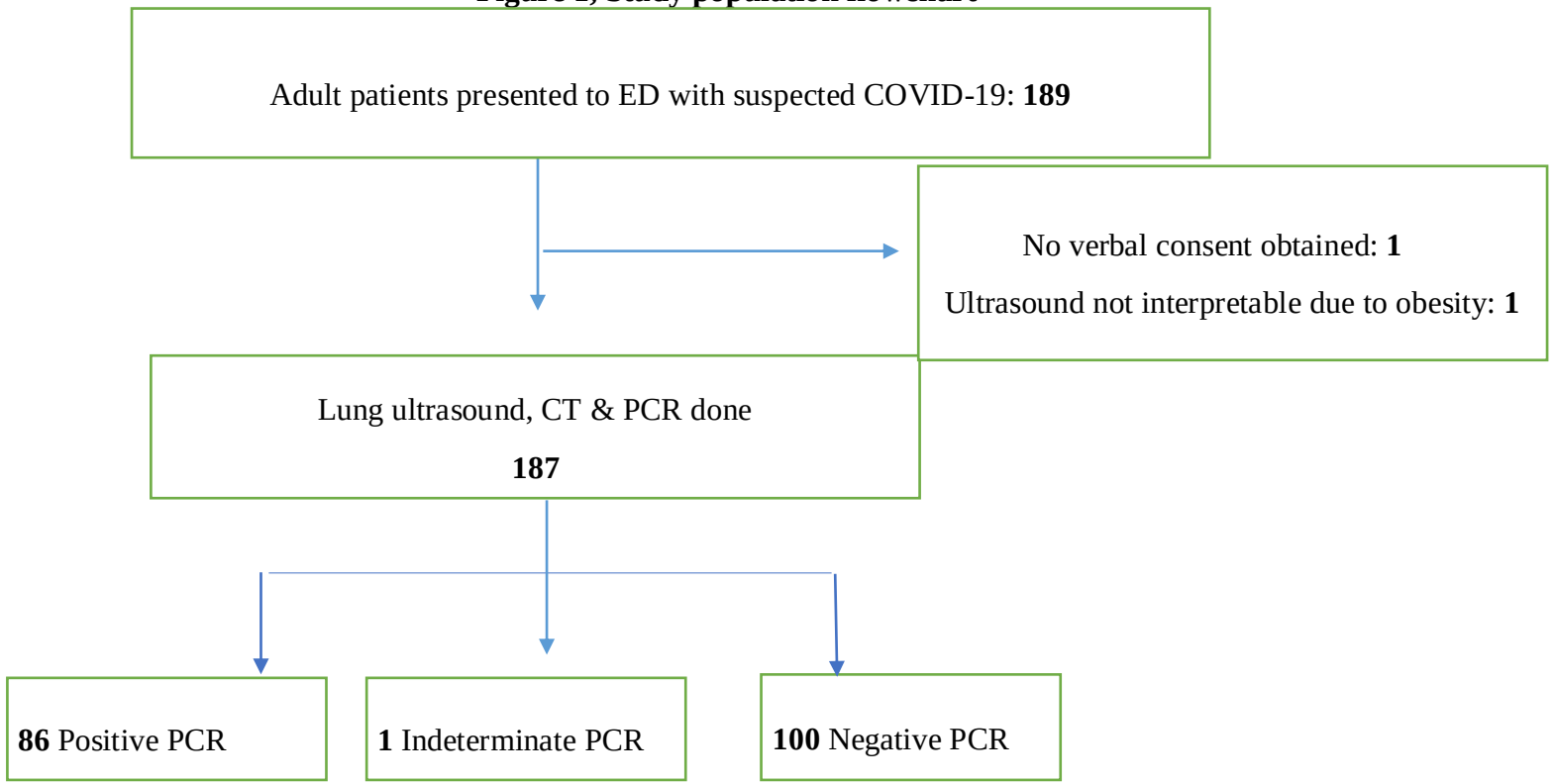
Study design and participants

This is a pragmatic, multi-centre, prospective, observational study. Patients were recruited from three academic hospitals in the Netherlands (Radboud University Medical Centre, Nijmegen and both locations of the Amsterdam University Medical Centres) between March 19 and May 4, 2020. On May 4 the percentage of positive PCRs in patients with suspected COVID-19 fell below 10%. This is used as the epidemic threshold by the Dutch Institute for Research and Healthcare (NIVEL) and National Institute for Public Health and the Environment (RIVM)).[31] The study was registered with the Netherlands Trial Register and approved by the Medical Ethical Committee (CMO region Arnhem-Nijmegen).

All patients 18 years and older who were referred to the ED for internal medicine with suspected COVID-19 were eligible. In our hospitals we adhered to the case definition of the RIVM and WHO. Suspected COVID-19 was initially defined as having either fever, malaise, myalgia and respiratory symptoms, but later also included gastrointestinal symptoms, loss of smell or taste and unexplained delirium in the elderly.

Patients were included when CT, LUS, and PCR were all performed. Exclusion criteria were: age under 18, no verbal consent, uninterpretable CT or LUS. The study protocol has been published and is available online.

Figure 1, Study population flowchart



Medical work up, admission & decision process

All patients received regular medical workup (history, physical examination and routine laboratory tests). In addition, they received a chest CT or/and PCR as indicated by local protocol. CXR was not routinely performed in the work-up of suspected COVID-19 in our hospitals. Clinical criteria for admission were: saturation <94%, and/or respiratory rate >20/min. It was standard practice in all participating hospitals that all admitted patients with suspected COVID-19 were discussed daily in a multidisciplinary team (MDT), consisting at least of consultants in infectious disease, respiratory disease and microbiology. In patients with a high clinical suspicion but negative PCR a diagnosis of COVID-19 could be made by this expert panel on the basis of clinical, laboratory, microbiological and CT data, after excluding alternative diagnoses. No clinical decisions were made based on LUS findings, the MDT was blinded for LUS results.

LUS

LUS was performed or supervised by internists (mostly registrars), who are certified in point-of-care ultrasound and have performed at least 20 supervised LUS. Both LUS and CT were done at presentation to ED or within 24 hours of admission. The majority of LUS were performed by the treating physician as an extension of the physical examination. As such, they were not blinded for the patient history or clinical picture. They were blinded for the PCR and CT result.

Handheld ultrasound systems were used with settings amenable to the detection of B-line artefacts (e.g. lung preset, or if this preset was not available; abdominal preset with tissue harmonic imaging switched off and dynamic range put at the lowest level).[16] See Online Supplementary Material Figure 1 for the scan protocol.

In keeping with pre-specified criteria in recent Chinese, Italian and British literature, LUS

was deemed positive if there were 3 or more B-lines and/or consolidation in two or more zones unilaterally or in one or more zones bilaterally. When COVID-19 features were not found or just in one zone unilaterally, the scan was deemed negative (see Online Supplementary Table 1).[15–17, 21, 22] See Online Supplementary Figure 2, and Videos for examples of COVID-19 sonographic features.

CT

The chest CTs were assessed by the local radiologists. The radiologists were blinded for LUS and PCR results, but not for clinical information. The likelihood of COVID-19 pneumonia was reported via the COVID-19 Reporting and Data System (CO-RADS), which uses a scale from 1 (very low) to 5 (very high), using pre-specified criteria (see Online Supplementary Material Table 2).[32] A CO-RADS score of 1 or 2 is regarded as negative, a score of 3 is equivocal, and a score of 4 or 5 is deemed positive. For the purpose of this study equivocal CTs were considered negative.

PCR

A PCR, obtained from the oropharynx or nasopharynx (or if available: sputum, feces, tracheal aspirate or broncho-alveolar lavage (BAL)), was performed in all patients according to WHO standards. The same PCR assay was used in all participating hospitals. In case of a negative or indeterminate test result but a high clinical suspicion, PCR was repeated. If a patient had an indeterminate test and no PCR was repeated, the PCR was considered negative.

Outcomes

Following WHO recommendations we used both (serial) PCR (gold standard), and clinical follow up (MDT diagnosis), to assess the sensitivity, specificity, diagnostic accuracy, area under the receiver operating characteristic (AUROC) curve, predictive values, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of LUS and CT. Agreement was

calculated between LUS and CT. Inter-observer agreement was calculated between sonographers.

Statistical analysis

No sample size calculations were performed for this study. Normally distributed continuous variables are summarised by the mean and standard deviation (SD). Not normally distributed continuous variables are summarised by the median and interquartile range (IQR). Differences between groups were tested using the independent t-test for normally distributed outcomes. Difference in means and 95% confidence interval (CI) were calculated. The widths of the intervals have not been adjusted for multiplicity, inferences drawn may therefore not be reproducible. Non-parametric Mann-Whitney U test was used to compare continuous outcomes that were not normally distributed between groups. Sensitivity and specificity of LUS and CT were compared using the McNemar test.

Discriminatory power of LUS and CT were determined by a receiver operating characteristic (ROC) curve and the corresponding AUROC with 95% confidence intervals (CI) for each cutoff.

Agreement between LUS and chest CT was quantified with the Cohen's kappa statistic. Inter-observer agreement between sonographers was measured with a weighted kappa via the intra-class correlation coefficient (ICC) with a two-way mixed effects model. Three sonographers independently assessed ultrasound recordings of 60 patients. This number was chosen as it allowed rejection of the null hypothesis that agreement was moderate (kappa 0.5) in case true agreement was good (kappa 0.8) with 80% power. The power-calculation was performed assuming proportions of negative and positive ratings of 40% and 60%. A two-sided significance level of 5% was used for all analyses. Data were analysed by AL, BK, FS, and KA using SPSS version 26.

3. RESULTS

From March 19 until May 4, 2020, 187 patients were included. There were neither missing data, nor adverse events. PCR positive patients on average had longer duration of symptoms, and more often required oxygen therapy and ICU admission than PCR negative patients. See Table 1 for patient demographics and clinical characteristics.

Study population

75 Patients had an initial positive PCR result, while 11 patients turned out positive after repeated testing. 15 Patients with negative PCR results were eventually diagnosed with COVID-19 (Table 2 and Online Supplementary Material Figure 3-4). The most common alternative diagnoses in the PCR negative group were bacterial/aspiration pneumonia (14%), upper respiratory tract infection (11%), progression of malignant disease (9%), exacerbation asthma/COPD (7%), and decompensated heart failure (7%) (Online Supplementary Table 3).

Diagnostic performance

For LUS we found a sensitivity of 91.9% (CI 84.0-96.7) and a specificity of 71.0% (CI 61.1-79.6) compared to PCR as a reference standard. AUROC was 0.81 (CI 0.75-0.88). The PLR and NLR were 3.2 (CI 2.3-4.3) and 0.1 (CI 0.06-0.24) respectively.

Comparing CT to PCR as a reference standard, we found a sensitivity of 88.4% (CI 79.7-94.3) and specificity of 82.0% (CI 73.1-89). AUROC was 0.89 (CI 0.84-0.94). The PLR and NLR were 4.9 (CI 3.2-7.5) and 0.14 (CI 0.08-0.26) respectively. See Table 2 and 3 for full results, Online Supplementary Material Figure 5-7 for ROC curves, and Online Supplementary Table 4 for details on false negative LUS and CT.

When we compared LUS to the MDT diagnosis, the AUROC increased to 0.85 (CI 0.79-0.91). Specificity increased to 80.0% (CI 69.9-87.9), PLR to 4.5 (CI 2.9-6.9), while the NLR

remained similar 0.12 (CI 0.07-0.2).

Using both PCR and the MDT diagnosis as a reference the McNemar test found no significant difference in sensitivity or specificity between LUS and CT (Online Supplementary Table 5). The agreement between LUS and chest CT was substantial: 0.65. The inter-observer agreement between scanning physicians was good: 0.89 (CI 0.83-0.93).

4. DISCUSSION

To our knowledge this is the first study prospectively analysing and comparing the diagnostic accuracy of LUS and chest CT in COVID-19 pneumonia. We found that LUS and CT have similarly good diagnostic accuracy for COVID-19 pneumonia, with AUROC between 0.8 and 0.9. In addition, we found substantial agreement between imaging modalities and good agreement between scanning physicians.

Screening test

The sensitivity, negative predictive value, and negative likelihood ratio found for LUS are promising (Table 3). Only seven patients in our cohort had a false negative LUS compared to PCR (Online Supplementary Material Table 4). Three of those patients also did not have a positive CT, indicating they did have COVID-19, but without pulmonary involvement. The reason for the lack of abnormalities could have been the short duration of symptoms (two days in these patients). Indeed, imaging studies have been shown to be negative in PCR positive patients in the first days of the disease.[32, 33] The four other patients had very mild abnormalities on CT, predominantly in the posterior and inferior zones, that hardly reached the pleura and therefore were (almost) undetectable via LUS. In keeping with what was observed in previous studies, it thus seems important that the inferior and posterior regions are examined. This can be challenging in obese or immobile patients as illustrated by the fact that one

of the false negative ultrasounds occurred in a patient in which the posterior fields could not be examined.

Interestingly, five of the seven 'false negative' patients actually did have sonographic COVID-19 features, but only in one unilateral zone, so we regarded those as negative. This might have been a sign of mild or early stage of COVID-19 pneumonia. If we would have regarded these patients as positive, the AUROC would have increased to 0.87 (CI 0.82-0.93) (Online Supplementary Material Figure 6).

Importantly, none of the patients that were missed on LUS required supplemental oxygen at any stage, nor did they need admission due to COVID-19 related symptoms. Our results demonstrate that LUS can be a safe screening tool for clinically relevant pulmonary involvement in COVID-19 patients who present at the ED.

However, when an alternative diagnosis is lacking, a high post-test probability of COVID-19 without pulmonary involvement may remain, especially when patients present early in the disease course. In those cases, patients should be instructed to home-quarantine and to seek medical help when symptoms worsen. With LUS as an extension of the physical examination, these decisions can be made within minutes of the patient presenting to ED without any further imaging.

Diagnostic test

Specificity for LUS was lower than CT; 71.0% (61.1-79.6) and 82.0% (73.1-89.0) respectively. The difference in specificity between CT and LUS of approximately 10% is consistent with what has previously been reported in the literature.[24, 26, 27]

One explanation for the low specificity of both modalities could be the lack of sensitivity of the PCR. This automatically generates more 'false positives'.[32, 33] We therefore also compared LUS with the MDT diagnosis. In our cohort 29 patients had a positive LUS and nega-

tive PCR. 12 Of them were eventually diagnosed with COVID-19 by the MDT. This led to a marked increase in specificity and PLR. Due to incorporation bias (incorporation of the CT results in the MDT diagnosis), CT should not be compared to the MDT diagnosis as this would overestimate accuracy.

Another reason for the lower specificity is that the sonographic features of COVID-19 are not exclusive to COVID-19. They are also observed in other etiologies like (viral or atypical) pneumonia, interstitial lung disease (ILD), acute respiratory distress syndrome (ARDS), heart failure and atelectasis. However, this is also the case for CT, albeit to a lesser extent.[9, 12, 32, 33] The most common diagnoses in patients with a false positive LUS were: pneumonia of another source (6), atelectasis in bedridden patients (5), and drug induced pneumonitis (3). There were no patients with underlying ILD in our cohort. When the prevalence of COVID-19 decreases and/or the prevalence of diseases which produce similar findings (e.g. ILD or influenza) increases, the positive predictive value of LUS will probably decrease concomitantly. More research has to be done to assess if LUS can distinguish COVID-19 from other similar disease processes.

Strengths

The results of this study are in line with the literature on diagnostic accuracy of LUS in acute respiratory failure caused by different etiologies ranging from pneumonia to ARDS.[24, 26, 27, 29, 30, 34, 35] Almost all LUS were performed by acute internal medicine registrars with modest LUS experience, which underscore the applicability of LUS in a real life-setting.

Advantages of LUS over CT include: ease of use, affordability, repeatability, and avoidance of radiation.[13, 14, 21–23] LUS can be used in (unstable) patients without the need to transport them. This reduces exposed health care personnel and equipment, which minimises wasting of scarce resources and potentially prevents nosocomial spread of infection.[9, 12, 18,

23] In addition, by integrating imaging into clinical decision making at the bedside, LUS can reduce time to diagnosis and treatment at the ED.[28, 30] One can also reduce diagnostic uncertainty by scanning other structures, such as the inferior vena cava, heart, and deep venous system of the lower extremities.[24, 28–30] If uncertainty still remains about the cause of respiratory symptoms or hypoxia, the treating physician can always employ additional conventional tests like CT.

COVID-19 has laid bare health disparities along socio-economic, racial, cultural, and ethnic lines across and within nations.[2, 3] CT is costly and might not be readily available, even in high-income countries.[8, 20] LUS is an affordable alternative, especially when handheld devices are used. It may be used in any care setting, further reducing barriers to adequate care.[17, 19] It has even been shown that it can be accurately performed by non-physicians who are guided remotely, so patients could be screened extramurally.[36] LUS has a steep learning curve, for physicians and other (para)medical personnel. The basics can be learned in under two hours.[37–39]

Limitations/bias

Our study has some important limitations. First, this was an observational study; no blinding, randomization or power calculation was performed. Second, our cohort was a convenience sample. We have tried to enrol every adult patient with suspected COVID-19 referred to internal medicine when a certified sonographer was present. We therefore feel that our cohort is random and representative and the chance of selection bias is minimal. Our cohort seems consistent with what is found in the literature in terms of mean duration of symptoms, comorbidity and mortality. We had a high number of patients with malignancies because all three hospitals are tertiary oncology centres. Third, the radiologists and the scanning physicians were aware of the patients' history and clinical pictures. While this may have led to some bias, clinical tests should preferably be guided by thorough clinical assessment. The integration of

imaging with clinical assessment in real-time is one of the main advantages of bedside ultrasound. Blinding sonographers for research purposes is therefore not desirable as the results would not be generalizable to daily practice.

Conclusion

Our study shows that the diagnostic accuracy of LUS is comparable to CT. We demonstrated that LUS can help in triage by excluding clinically relevant COVID-19 pneumonia at the ED and may aid in diagnosis of COVID-19 in a high prevalence setting. It may prove especially useful in situations where CT or PCR results are not readily available. We advocate the use of LUS as an extension of the physical examination and encourage setting up training programs worldwide so this tool can be used during and subsequent to the pandemic. We also suggest that further studies be conducted in different settings to validate our findings.

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6. TABLES

Table 1: Patient Characteristics

	All patients N = 187*	**PCR positive N=86**	**PCR negative N = 100**	**P value****
Age, mean (SD)	63.7 (15.7)	63.4(14.8)	64.1 (16.5)	0.668
Male, n (%)	108 (57.8)	50 (58.1)	58 (58.0)	0.97
Admission, n (%)	140 (74.9)	65 (75.6)	75 (75.0)	0.855
Admission ED to IC, n (%)	9 (4.8)	8 (9.3)	1 (1.0)	**0.000**
In hospital Mortality, n (%)	9 (4.8)	5 (5.8)	4 (4.0)	**0.001**
Obesity (based on clinical assessment)	52 (27.8)	27 (31.4)	25 (25)	0.676
Duration of symptoms days, (SD)	6.5 (5.1)	7.3 (4.1)	5.8 (5.8)	**0.007**
Co-morbidities, n (%)				
Asthma	10 (5.3)	3 (3.5)	7 (7.0)	0.033

Chronic Cardiovascular Disease	44 (23.5)	18 (20.9)	26 (26.0)	0.104
COPD (GOLD >2)	30 (5.3)	12 (14.0)	18 (18.0)	0.134
Current Malignancy	35 (18.7)	9 (10.5)	26 (26.0)	**0.000**
Diabetes Mellitus	36 (19.3)	21 (24.4)	15 (15.0)	**0.001**
Laboratory analysis on admission				
CRP (mg/L), median (IQR)	59 (81.5)	68 (83.8)	49.0 (80.8)	0.73
Procalcitonin (ng/mL), median (IQR)	0.1 (0.25)	0.12 (0.21)	0.1 (0.37)	**0.004**
Positive blood culture, n (%)	12 (6.4)	1 (1.2)	11 (11.0)	0.204
Positive influenza A/B, n (%)	0	0	0	0.593
Observations				
Modified early warning score (MEWS), mean (SD)	2.6 (1.8)	2.9 (1.6)	2.3 (1.8)	0.605

Temperature (Celsius), mean (SD)	37.5 (1.2)	37.8 (1.1)	37.2 (1.3)	0.174
Respiratory rate, mean (SD)	21.2 (6.9)	21.9 (7.2)	20.7 (6.7)	0.888
Oxygen saturation, mean (SD)	95.8 (3.2)	94.9(3.5)	96.4 (2.8)	0.165
Oxygen therapy, n (%)	58 (0.31)	34 (39.5)	24 (24.0)	**0.004**
Intubation	9 (4.8)	8 (9.3)	1 (1.0)	**0.000**

*One patient had an indeterminate PCR and no repeat PCR, that is why the total amount of patients of 187 differs from the sum of the PCR positives (86) and PCR negatives (100).

**Statistically significant differences between the PCR positive and PCR negative groups are emphasised in bold text.

Table 2: Diagnostic results

	PCR positive	PCR negative	Final diagnosis
Lung ultrasound: positive	79	29	91
Lung ultrasound: negative	7	71	10
CT: positive	76	18	
CT: negative	10	82	

Table 3: Diagnostic Accuracy for COVID-19

	Lung ultrasound vs PCR	**CT vs PCR**	**Lung ultrasound vs COVID-19 diagnosis***
Sensitivity % (95%CI)	91.9 (84.0-96.7)	88.4 (79.7-94.3)	90.1 (82.5-95.2)
Specificity % (95%CI)	71.0 (61.1-79.6)	82.0 (73.1-89.0)	80.0 (69.9-87.9)
Positive Likelihood ratio	3.2 (2.3-4.3)	4.9 (3.2-7.5)	4.5 (2.9-6.9)
Negative likelihood ratio	0.1 (0.06-0.24)	0.14 (0.08-0.26)	0.12 (0.07-0.2)
PPV % (95%CI)	73.2 (66.6-78.8)	80.9 (73.4-86.6)	84.2 (77.7-89.2)
NPV % (95%CI)	91.0 (83.1-95.4)	89.1 (82.0-93.7)	90.8 (81.7-95.6)
Accuracy % (95%CI)	80.7 (74.2-86.1)	85.0 (79.0-89.8)	82.8 (76.6-87.9)

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; CI, 95% confidence interval.

Outcomes for sensitivity, specificity, PPV and NPV are shown as percentage with the 95% confidence interval.

*According to multidisciplinary team COVID-19 is highly likely.

7. DATA SHARING STATEMENTS

Will individual participant data be available (including data dictionaries)?	yes
What data in particular will be shared?	Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices)
What other documents will be available?	Study protocol
When will data be available (start and end dates)?	Immediately following publication; no end date
With whom?	Investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose
For what types of analyses?	For individual participant data meta-analysis
By what mechanism will data be made available?	Proposals should be directed to p.nanayakkara@amsterdamumc.nl; to gain access, data requestors will need to sign a data access agreement

APPENDIX

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1. Collaborating investigators

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2. Tables

Appendix Table 1, Sonographic features of COVID-19 pneumonia compared to CT findings, after Peng et al, 2020[23]

Lung ultrasound	**Chest CT**
Thickened & irregular pleural line	Thickened pleura
B-lines (discrete, multifocal or confluent)	Ground glass opacities (GGOs)
Confluent B-lines	Pulmonary infiltrating shadow
Sub-pleural consolidations or 'skip' lesions	Sub-pleural consolidation
Both non-translobar and translobar consolidation	Translobar consolidation
Rare pleural effusion	Rare pleural effusion
Multi-zone, patchy distribution of abnormalities	Multiple lobes affected
Focal B-lines are the main feature in the early stage and in mild infection; alveolar interstitial syndrome is the main feature in the progressive stage and in critically ill patients; A-lines can be found in the convalescence; pleural line thickening with uneven B lines can be seen in patients with pulmonary fibrosis. Abnormalities are predominantly seen inferiorly and posteriorly	Negative or atypical in lung CT images in the super-early stage, followed by diffuse scattered or ground glass opacities, and with progression of the disease further lung consolidation. (See Appendix Table 2 for a more detailed description).

Score	CO-RADS of suspicion	Pulmonary findings	Obligatory features	Confirmatory patterns	Examples (of alternative diagnoses)
0	Not interpretable	• Incomplete depiction of the lung on CT OR • Technically insufficient for assigning a classification			Severe breathing or coughing artifacts
1	Very low	Normal chest CT	• Findings of unequivocal non-infectious etiology • Findings are stable compared to pathology on previous imaging		• Emphysema • (Known) interstitial pneumonitis • Nodules • Tumor • Interstitial edema
2	Low	• Findings typical of infectious etiology AND considered not compatible with COVID-19 AND • Absence of features of CO-RADS 3-5	• Tree-in-bud sign • Centri-lobular nodular pattern • Lobar or segmental consolidation • Cavitation		• Bronchitis • Infectious bronchiolitis • Bronchopneumonia • Lobar pneumonia • Pulmonary abscess

Appendix Table 2, CO-RADS, after Prokop et al, 2020[34]

3	Equivocal / unsure	• Equivocal for COVID-19 • Overlap with other pathology. • Findings have to be new or increased in magnitude	• Peri-hilar ground-glass • Ground-glass together with smooth interlobular septal thickening +/- pleural effusion • Extensive homogeneous ground-glass opacity • Small ground glass opacities, not centri-lobular, not located close to the visceral pleura • Consolidation compatible with organizing pneumonia without other typical findings of COVID-19		• Influenza • RSV or other viral pneumonias • Atypical alveolar edema • Pulmonary hemorrhage • Alternative infections combined with SARS-CoV-2
4	High	• Findings typical for pulmonary involvement of COVID-19 with additional non-typical features seen with other (viral) pneumonia • Findings have to be new or increased Findings similar to CO-RADS 5 *but:*	• Predominantly no contact with visceral pleura OR • Located strictly unilaterally OR • Predominant peri-bronchovascular distribution OR • Superimposed on severe diffuse pre-existing pulmonary abnormalities		

5	Very High	• Findings typical for pulmonary involvement of COVID-19 • Findings have to be new OR increased	• Ground-glass with or without consolidations close to visceral pleural surfaces, including fissures AND • Bilateral OR multifocal	• Ground glass: -**Unsharp demarcation**, (half) rounded shape. -**Sharp demarcation**, outlining multiple adjacent secondary pulmonary lobules. • Crazy paving. • Patterns compatible with **organizing pneumonia**, such as: -Reverse halo sign, -Extensive subpleural consolidations with air bronchograms -subpleural curvilinear bands -Ground glass with or without consolidation in an arching, tethered pattern with small connections to the pleura. • **Thickened vessels** within abnormalities	
6	PCR positive	Any pulmonary findings			

Appendix Table 3, Alternative diagnoses in the PCR negative group

Alternative diagnoses	**Number patients (%)**
Exacerbation COPD/asthma	7 (7.0)
Bacterial/aspiration pneumonia	14 (14)
Upper respiratory tract infection (incl. bronchitis & bronchiolitis)	11 (11.0)
Malignancy progression	9 (9)
Decompensated heart failure	7 (7.0)

Fever of unknown origin	5 (5.0)
Pulmonary embolism	4 (4.0)
Dyspnea of unknown origin	3 (3.0)
Acute Leukemia	3 (3.0)
Pulmonary hemorrhage	1 (1.0)
Chronic cough	1 (1.0)
Gastrointestinal bleeding	1 (1.0)
Acute onset stills Disease	1 (1.0)
Musculoskeletal	4 (4.0)
Abdominal & gastrointestinal infection*	17 (17)

*Group consisting of a broad array of diagnoses: UTI, splenic abscess, abscess after low anterior resection, gastritis

Appendix Table 4, False negative ultrasounds & CTs

4A. Both CT & LUS false negative

Sex + Age	False negative CT (CO-RADS)	False negative ultrasound	Diagnosis	Symptoms + days	Supplemental oxygen needed	Admission	Discharge
F, 74	2 (on CT only left lower lobe abnormalities)	R5-6, L5-6 not scanned due to immobility	1) Fall due to orthostatic hypotension and weakness due to Lewy-Body dementia; 2) Mild COVID-19	2 days: malaise, fall, fever, no resp symptoms; PMH/Orthostatic hypotension, Lewy-Body dementia	No	1 day due to fall, not COVID-19	Nursing home
F, 79	1 (normal)	No abnormalities	Mild COVID-19	2 days: fever, dry cough, headache; PMH/ Living with family due to poor condition, T2DM, ischemic heart disease, anemia, Guillain-Barre	No	no	Home
F, 75	3 (right upper lobe)	R5	1) Cellulitis; 2) COVID-19; 3) Recurrent delirium due to 1 and 2	unknown: delirium, fall, productive cough, neglected & dirty home, PMH/ HT, T2DM, 2x VTE: life-long anticoagulation, recent delirium after cellulitis, bedsores	No	2 days due to IV antibiotics for cellulitis, not COVID-19	Rehab

4B. Solely false negative CTs

4C. Solely false negative ultrasounds

Sex + Age	False negative CT (CO-RADS)	Lung ultrasound abnormalities	Diagnosis	Symptoms + days	Supplemental oxygen needed	Admission	Discharge
M, 63	3 (right upper & lower lobe, left lower lobe)	R4-6 & L 3-6	1) COVID-19 pneumonia with possible bacterial superinfection; 2) Hyperglycemic dysregulation; 3) AKI	unknown: respiratory insufficiency and hyperglycemic dysregulation; PMH/ T2DM	IC admission due to respiratory insufficiency	16 days	Rehab
F, 81	1 (normal)	L4-L6	1) Delirium due to 2) Herpes Zoster and COVID-19	7 days: herpes zoster & confusion; PMH/ HT, ischemic heart disease, hypothyroidism	No	3 days	Nursing home
M, 85	3 (right & left lower lobe)	R5-6 & L6	1) COVID-19; 2) Femur fracture right leg	1 day: fever, fall, confusion, dyspnea, with productive cough and nausea; PMH/ HT, atrial fibrillation, recent fall due to UTI with low energetic head trauma	1 evening due to fast AF and concomitant acute decompensated heart failure, afterwards no supplemental oxygen need	6 days due to femur fracture, not COVID-19	Rehab
M, 76	1 (dependent atelectasis)	R6 & L5-6	1) Low energetic trauma after fall; 2) COVID-19	5 days: PMH/ syndrome of Ledderhose, severe Parkinson's disease and Alzheimer's, lives in nursing home	1 evening	3 days due to fall	Back to nursing home
M, 74	1 (normal, with pancreatitis)	R6 & L6	1) Mild COVID-19; 2) Minor stroke with loss of function left hand 3) Pancreatitis	1 day: loss of function left hand, fever, running nose; PMH/ Bentall procedure due to aortic dissection, HT, atrial fibrillation with DDD-R pacemaker	No	3 days due to pancreatitis	Home
M, 70	3 (bronchopneumonia)	R1-6 & L1, L3-6	1) COVID-19 pneumonia with possible bacterial superinfection	2 days: malaise, fall, fever, no resp symptoms; PMH/Orthostatic hypotension, Lewy-Body dementia	Yes, 5 days	5 days	Nursing home
F, 72	1 (2nd CT 2 days later CO-RADS 4)	R1, R3-4, R6 & L1-4	1) COVID-19 pneumonia	1 day: running nose, malaise and fever; PMH/ adenocarcinoma sinus ethmoidalis, receiving palliative chemotherapy	no	17 days	Home

Sex + Age	CO-RADS	False negative ultrasound	Diagnosis	Symptoms + days	Supplemental oxygen needed	Admission	Discharge
F, 28	5 (left lower lobe)	L6	Mild COVID-19	7 days: fever, cough, running nose, malaise, nausea; PMH/ Peripheral T-cell lymphoma, mixed response to 5th line therapy (Bendamustine), therefore on list for allogenic stem cell transplant	No	no	Home
F, 57	4 (very mild, postero-inferior)	L3	1) Vasovagal collapse Mild COVID-19 gastroenteritis and pneumonia	7 days: predominantly fever, nausea, vomiting and diarrhea >5 times per day, presented with collapse. Also reported cough, dyspnea and headache, loss of taste; PMH/ sarcoidosis: on Prednisolone	No	1 day observation, due to collapse, not COVID-19	Home
F, 40	4 (right lower lobe)	L6	Mild COVID-19	1 day: fever, malaise, cough, dyspnea, chest pain; PMH/ Relapsing-remitting MS for which she recently had a autologous stem cell transplant	No	8 days because there wasn't enough care at home, not due to COVID-19	Home
M, 53	4 (all lobes, but not reaching the pleura)	No abnormalities	Mild COVID-19	5 days: cold symptoms, fever, dyspnea; PMH/ HT, pericarditis, pancreatitis	No	no	Home

PMH: previous medical history
HT: hypertension
OSAS: obstructive sleep apnea syndrome

T2DM: Type 2 Diabetes Mellitus
VTE: venous thromboembolism
UTI: urinary tract infection
DDD-R: dual-chamber pacemaker

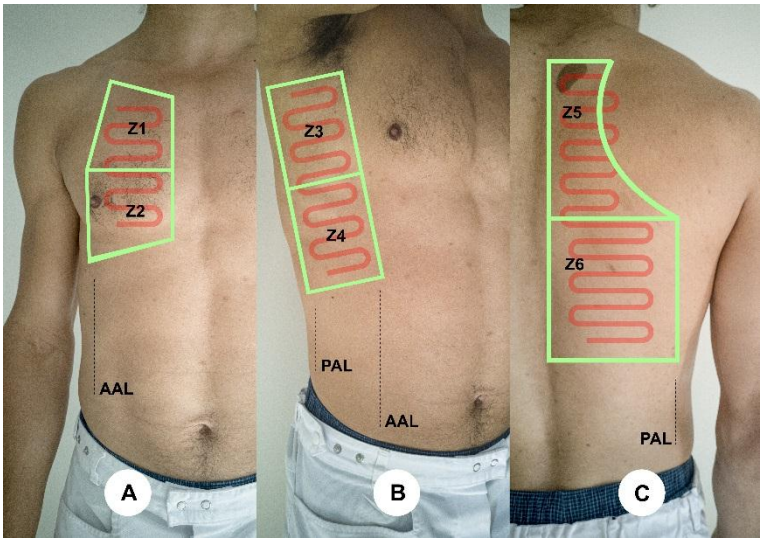
Appendix Table 5, McNemar test comparing sensitivity & specificity of LUS & CT

McNemar test[1]	Sensitivity with PCR as reference	Specificity with PCR as reference	Sensitivity with MDT diagnosis as reference	Specificity with MDT diagnosis as reference
LUS vs CT	0.55	0.30	0.80	0.23

[1]Exact Sig. (2-tailed), binomial distribution used

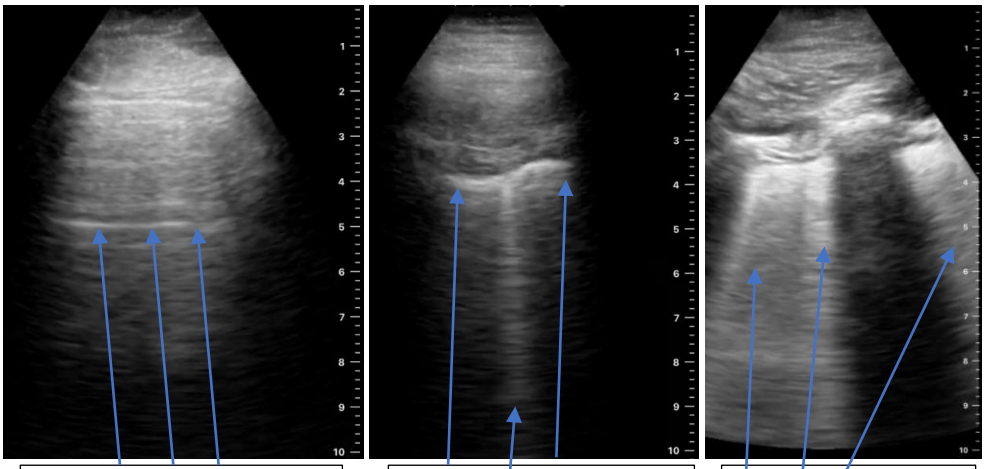
3. Figures

Appendix Figure 1, Scanning zones and technique



A twelve-zone scanning approach was used, in which the lungs were scanned in a lawn-mower fashion
This figure shows the six scan zones on the right hemi-thorax.
a) Anterior: Z1 anterior upper zone, Z2 anterior lower zone,
b) Lateral: Z3 lateral axilla zone, Z4 lateral lower zone
c) Posterior: Z5 posterior upper zone, Z6 posterior lower zone.
AAL: anterior axillary line
PAL: posterior axillary line
Red line: illustrates the 'lawn mower' scanning technique. Each rib-space is evaluated, to minimize the risk of missing abnormalities.

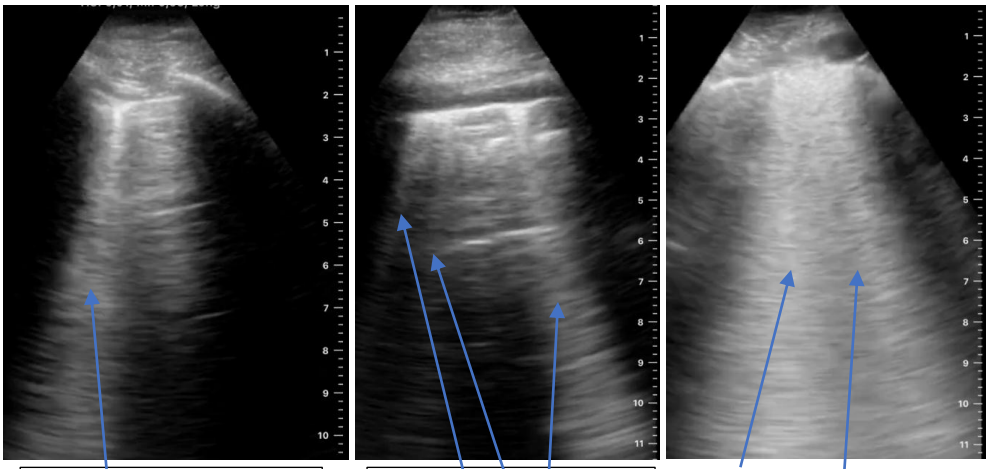
Appendix Figure 2, Sonographic features of COVID-19 pneumonia



Normal A-line pattern

Thickened pleural line, with 1 discrete B-line

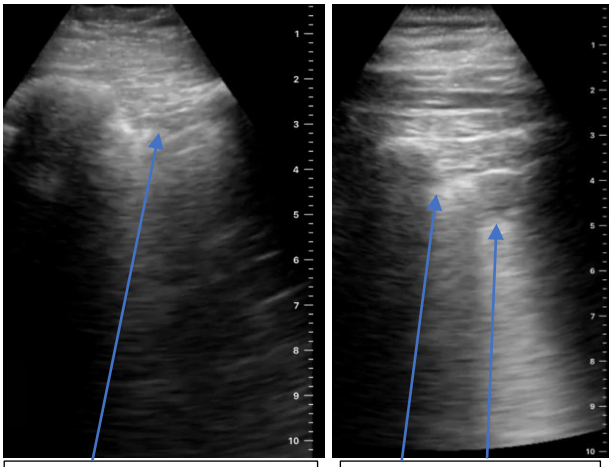
Thickened pleural line with confluent B-lines



Discrete B-line

Patchy or multifocal B-lines

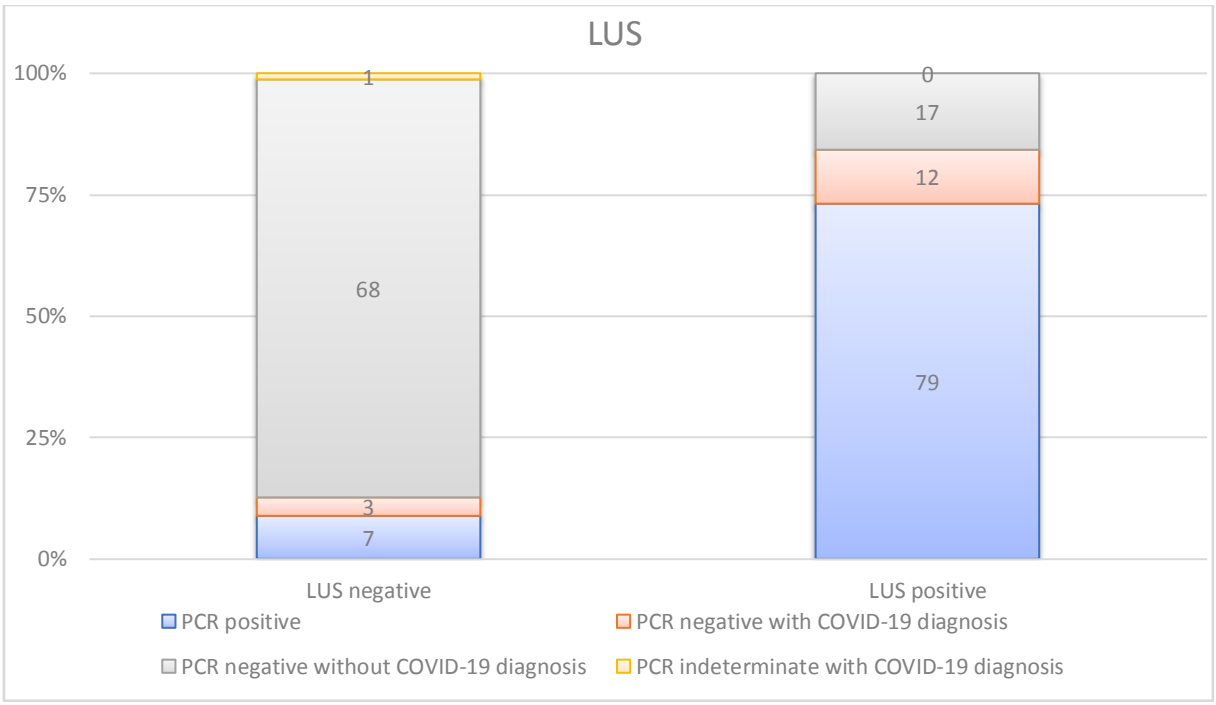
Confluent B-lines, 'waterfall sign'



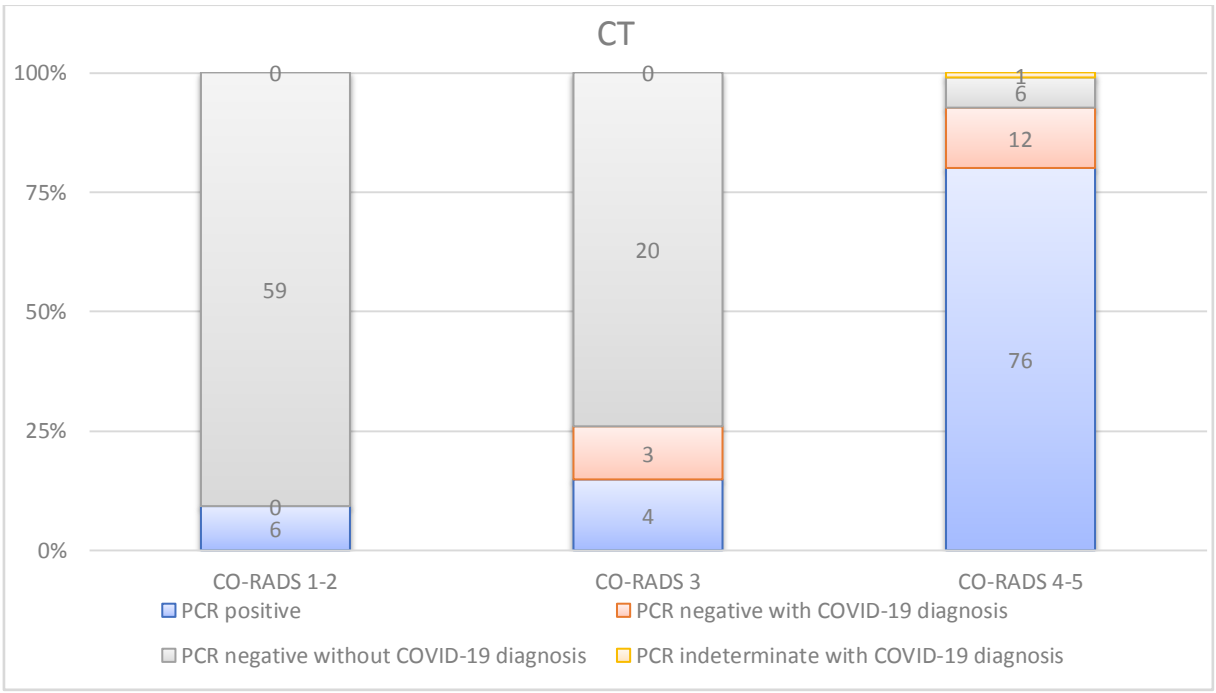
Small subpleural consolidation or 'skip' lesion

Large subpleural consolidation

Appendix Figure 3, LUS result vs PCR results and clinical diagnosis

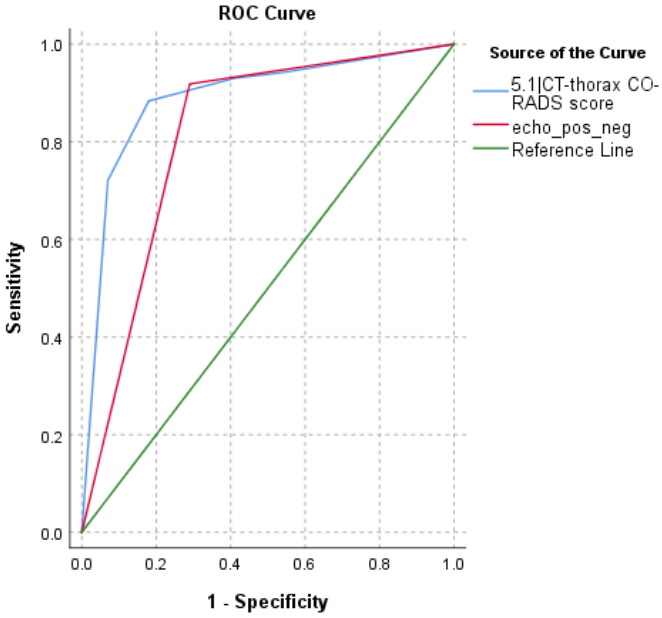


Appendix Figure 4, CT result vs PCR results and clinical diagnosis



Appendix Figure 5, ROC Curve: LUS & CT vs PCR

Area Under the ROC Curve



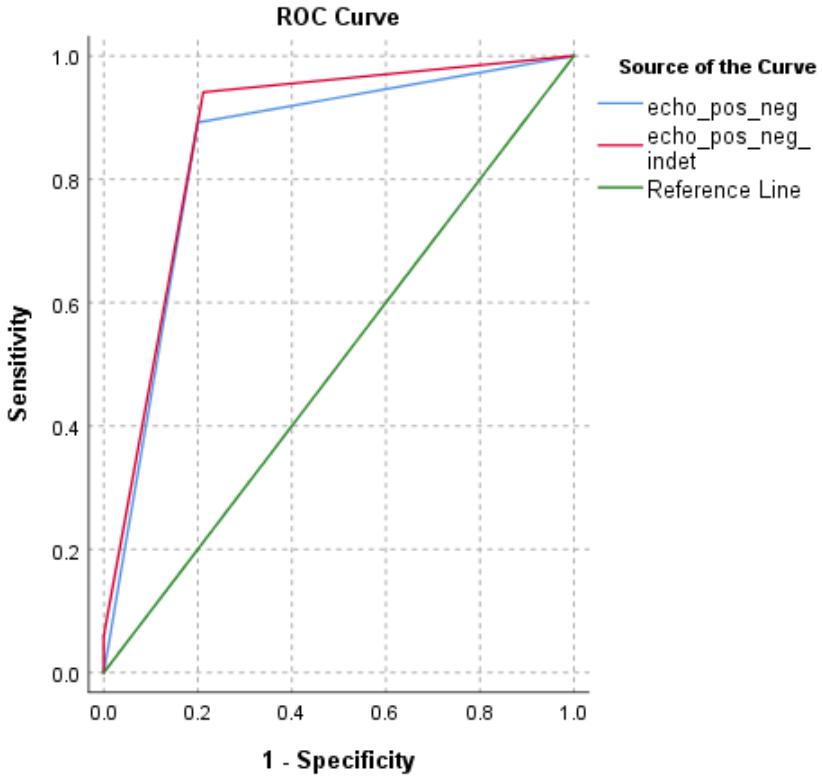
	Asymptotic 95% Confidence Interval	
ɔtic Sig.[b]	Lower Bound	Upper Bound
.000	.750	.878
.000	.839	.941

Coordinates of the ROC Curve

Test Result Variable(s)	Positive if Greater Than or Equal To[a]	Sensitivity	1 – Specificity
LUS (echo_pos_neg)	-1.00	1.000	1.000
	.50	.919	.290
	2.00	.000	.000
CT (CT Thorax CO-RADS score)	.00	1.000	1.000
	1.50	.942	.540
	2.50	.930	.410
	3.50	.884	.180
	4.50	.721	.070
	6.00	.000	.000

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

Appendix Figure 6, ROC Curve: LUS vs MDT diagnosis



Area Under the ROC Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
LUS (echo_pos_neg)	.846	.031	.000	.785	.907
LUS abnormalities in 1 zone regarded as positive (echo_pos_neg_indet)	.871	.028	.000	.815	.927

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Coordinates of the ROC Curve

Test Result Variable(s)	Positive if Greater Than or Equal To[a]	Sensitivity	1 – Specificity
LUS (echo_pos_neg)	-1.00	1.000	1.000
	.50	.892	.200
	2.00	.000	.000
LUS abnormalities in 1 zone regarded as positive (echo_pos_neg_indet)	-1.00	1.000	1.000
	.50	.941	.212
	1.50	.059	.000

	3.00	.000	.000

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

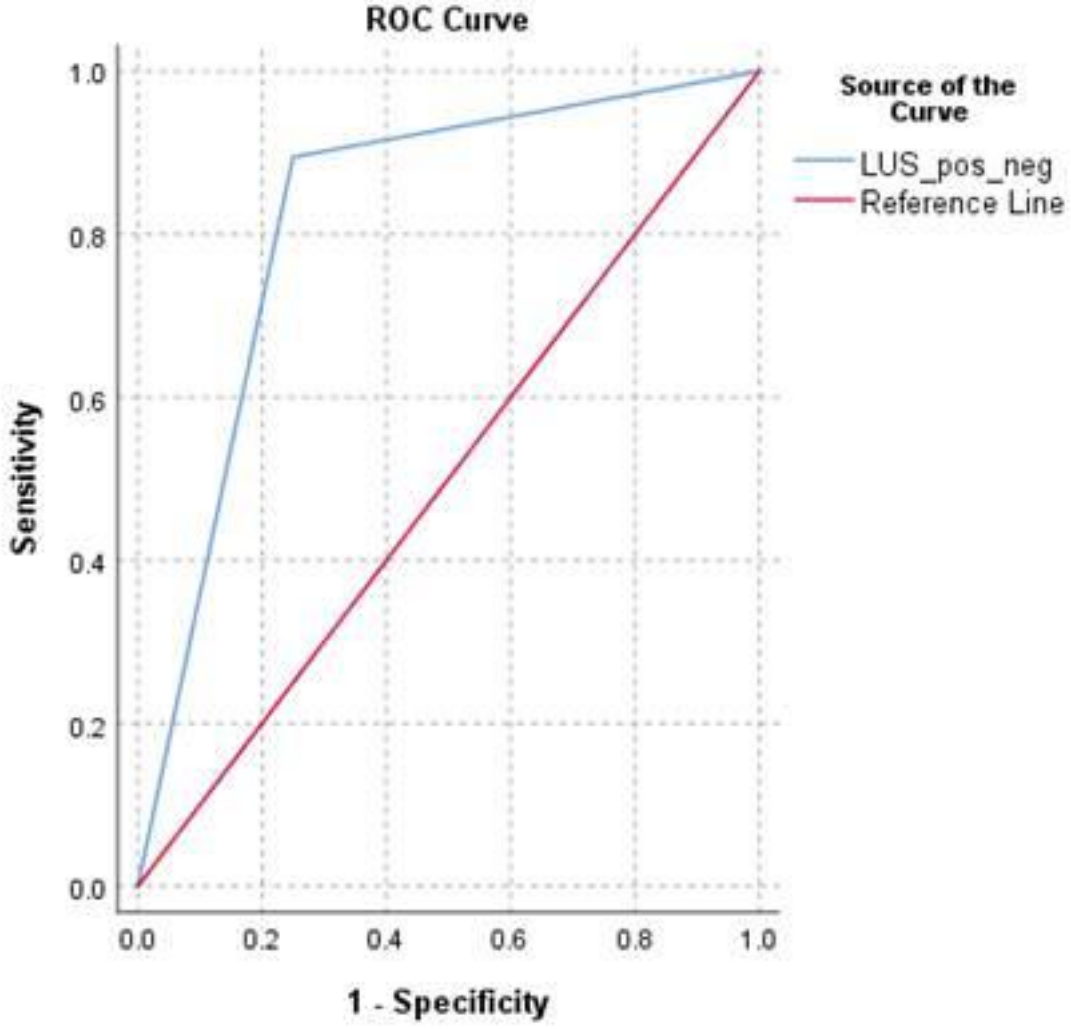
Appendix Figure 7, ROC Curve: LUS vs CT

Case Processing Summary

CORADS45	Valid N (listwise)
Positive[a]	95
Negative	92
Missing	0
Total	187

Larger values of the test result variable(s) indicate stronger evidence for a positive actual state.

a. The positive actual state is positive.



Area Under the ROC Curve

Test Result Variable(s): LUS_pos_neg

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.822	.032	.000	.759	.886

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Coordinates of the ROC Curve

Test Result Variable(s): LUS_pos_neg

Positive if Greater Than or	Sensitivity	1 - Specificity

Equal To[a]		
-1.00	1.000	1.000
.50	.895	.250
2.00	.000	.000

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

4. Videos


Normal A-line pattern.mp4


1 Thickened pleural line.mp4


2a discrete B-line.mp4


2b patchy B-lines.mp4


2c confluent B-lines.mp4


3a small subpleural consolidation.mp4


3b large subpleural consolidation.mp4