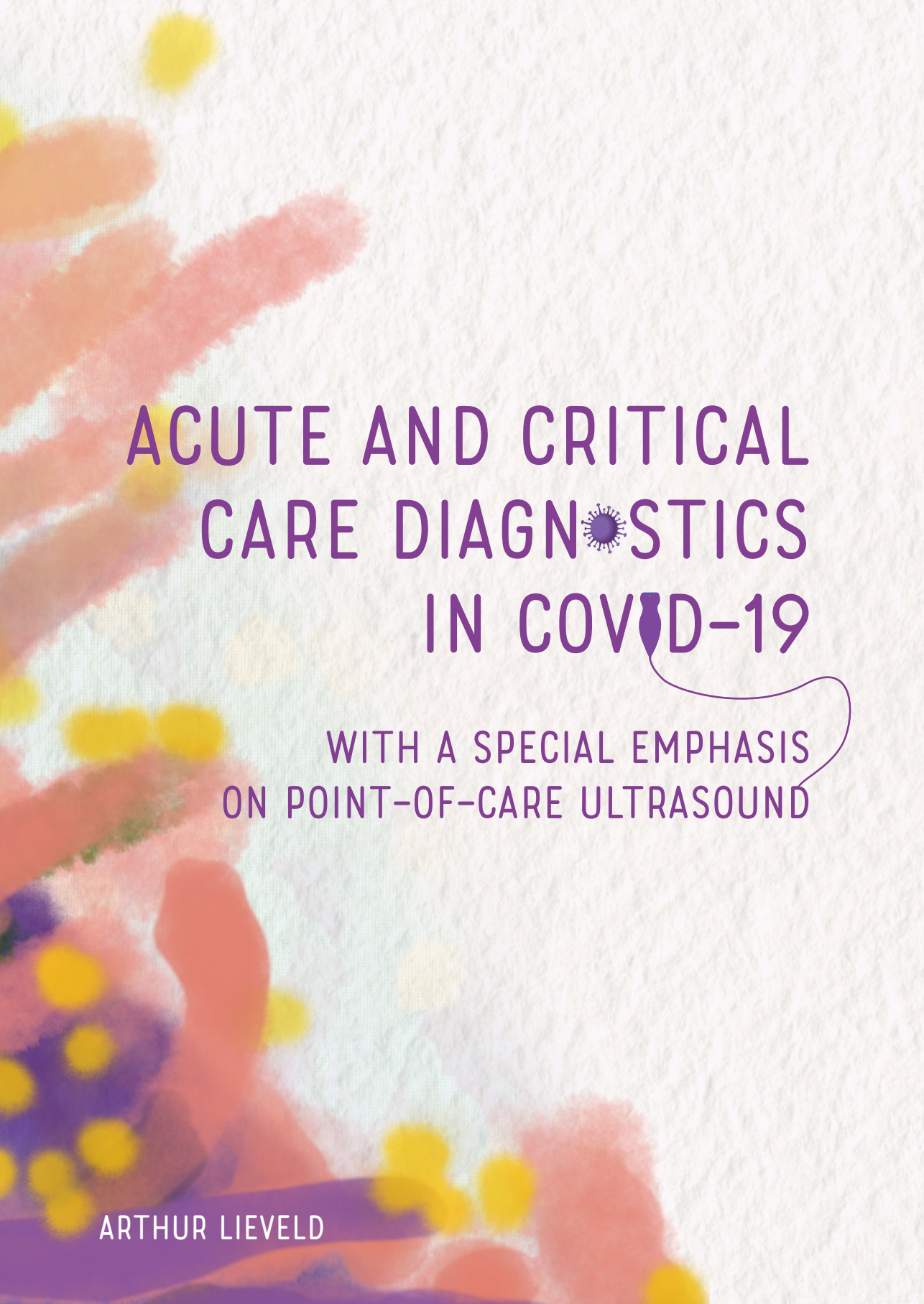


ACUTE AND CRITICAL CARE DIAGNOSTICS IN COVID-19

WITH A SPECIAL EMPHASIS ON POINT-OF-CARE ULTRASOUND

ARTHUR LIEVELD

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With a special emphasis on point-of-care ultrasound

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– Voor mijn ouders –

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1

General introduction and thesis outline

COVID-19 – a short history

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), which primarily manifests as a respiratory illness (i.e., dry cough, shortness of breath and fever). It belongs to a larger group of coronaviruses that causes health problems affecting the respiratory, gastrointestinal, liver and central nervous system of humans, bats, mice, livestock and wild animals. SARS-CoV-2 is the seventh coronavirus known to infect humans; HKU1, NL63, OC43 and 229E are associated with mild symptoms, while SARS-CoV, MERS-CoV and SARS-CoV-2 can cause severe disease.[1] COVID-19 is believed to be a zoonosis and emerged in December 2019 in Wuhan, Hubei province, China.[1,2] On 31 December 2019 the Wuhan Municipal Health Commission first put out a statement saying that there were signs of a pneumonia outbreak.[3]

There have been outbreaks with other coronaviruses in recent history; the SARS-CoV outbreak of 2002-2003 and the MERS outbreak of 2012. Similar to those coronaviruses SARS-CoV-2 spreads by inhalation of tiny droplets, contact of those droplets with eyes, nose or mouth (i.e., by someone coughing or sneezing, or after getting the virus on one's hands and then touching their face). But COVID-19 also has some distinctive traits.

Early modeling studies of COVID-19 case data found that the average time between a person being infected and that person infecting someone else was shorter than the average time between a person developing symptoms and the person they infected developing symptoms.[4] COVID-19 spread more rapidly than would be expected if transmission was restricted to the period of illness during which an individual was symptomatic, which is usually the case in viral infections. Approximately 35-50% of transmissions occurred through asymptomatic patients.[4,5] This meant COVID-19 could not be contained by symptom-based screening alone. Consequently, COVID-19 spread rapidly around the globe and was officially characterized as a pandemic on March 11, 2021.[6]

Early reports from China indicated that 15-20% of patients had to be hospitalized and up to 30% of admitted patients required prolonged intensive care unit (ICU) admission and organ support due to acute respiratory distress syndrome (ARDS).[7,8] As COVID-19 was a new disease, immunity against it was practically non-existent. As there were neither effective treatments nor vaccines available, health care systems around the world were faced with all but certain collapse under the looming number of patients they would have to facilitate. The optimal control of the pandemic thus depended on preventing transmission and this forced governments around the world to impose invasive measures to reduce transmission (i.e., lockdowns and social distancing).

The pandemic and those measures have had unprecedented effects on economies and societies all over the world, especially in low- and middle-income communities within and across countries.[9,10] As of 31 December 2021, exactly two years after the first report on COVID-19 was made public, there have been over 280 million cases worldwide, with more than 5 million dead.[11] Luckily, effective vaccines have been introduced at the end of 2020.[12,13] However, those have been distributed unequally with 67% of people in higher income countries having been vaccinated with at least one dose, but only 10% in low income countries.[14] Although the pandemic seems to be evolving to an endemic phase (at least in higher income countries), new (more contagious) COVID-19 variants could still emerge.

Point-of-care ultrasound (POCUS)

In 2019 I paused my internal medicine residency in Amsterdam to do a yearlong fellowship in acute medicine and point-of-care ultrasound (POCUS) at the Royal Berkshire Hospital in Reading, United Kingdom. My goal was to learn POCUS and bring my skills back to The Netherlands and teach others. I felt POCUS would give me extra tools to diagnose and manage my patients.

POCUS is defined as 'diagnostic or procedural guidance ultrasound that is performed by a clinician during a patient encounter to help guide the evaluation and management of the patient'.[15] It differs from consultative ultrasound in which a test is ordered by the clinician, performed by a technician and interpreted by a specialist who is not directly involved with the patient.[16]

For millennia – even dating back to Hippocrates and Charaka – inspection, percussion, and palpation have been the cornerstone of the physical exam.[17] The most recent addition has been auscultation by the invention of the stethoscope in 1816 by Rene Laënnec.[18] Although the usefulness of the traditional physical examination has been deemed indispensable, the evaluation of its accuracy and reliability has been limited and has not always not been subjected to the rigor of critical review that new diagnostics and treatments must undergo nowadays.[17,19] Indeed, the traditional physical examination often shows suboptimal performance, especially in cardiopulmonary diseases.[20–23]

POCUS adds information to the physical examination, while frequently obviating the need for further (more invasive) diagnostic testing.[17,20,23–25] Importantly, POCUS does not replace comprehensive examinations performed by radiologists or cardiologists, nor does it aim to. Its addition to the physical exam has been shown to be useful in many clinical situations,

particularly in the assessment and management of acutely and critically ill patients, where quick and accurate diagnosis and decision-making are of paramount importance.[16,24,26]

POCUS has demonstrated to reduce diagnostic uncertainty, provide prognostic information and allow monitoring of patients, while reducing costs, as well as time to diagnosis and treatment.[26–30] Moreover, POCUS is becoming increasingly portable, accessible and affordable, with systems the size of an electric razor that can be connected to a smartphone or tablet (Figure 1.1A-C). At the same time image quality is fast improving.[17,24] That is why POCUS is slowly, but steadily finding its way into clinical practice as well as the curricula of medical schools and specialty training programs.[24,26,31,32]



Figure 1.1: Different ultrasound machines.
A: Normal ultrasound machine: used in radiology and cardiology departments for comprehensive scans.
B: Mobile ultrasound machine: can be used in the hospital at the bedside.
C: Handheld ultrasound probe: can be plugged into a smartphone or tablet, which facilitates easy usage both in- and outside the hospital.

For me, the use of POCUS has transformed the way I practice medicine. It enables me to work more efficiently, make bedside diagnoses and real-time management decisions, while simultaneously involving the patient more in this process and strengthening the doctor-patient relationship.

My role during the pandemic

At the beginning of the pandemic in The Netherlands, our hospital processes were quickly reorganized to deal with the surge in COVID-19 patients. During the first wave, from March 2020 through August 2020, I was put on the acute care team that was charged with seeing, diagnosing, and treating COVID-19 patients at the emergency department (ED) and the medical wards. During the second wave, from September 2020 through December 2020, I was transferred to the ICU, where I was primarily charged with taking care of COVID-19 patients.

As waves of patients engulfed the ED, the wards and the ICU, questions quickly arose on how we could optimize the triage, diagnosis, and risk stratification of COVID-19 patients and allocate scarce medical resources efficiently. Almost naturally we also asked ourselves whether POCUS in particular could play a role in alleviating shortfalls in these areas.

Thesis outline

This thesis should be read as an almost chronological account of the clinical problems we faced and subsequently investigated while we were treating the waves of COVID-19 patients in real-time. It combines multiple original investigations, narrative reviews, book chapters and research letters concerning the diagnosis, risk stratification, monitoring and complications of COVID-19 patients in the acute and critical care setting during the emerging and developing pandemic, with a special emphasis on the role of POCUS.

The thesis is divided into three main parts:

- Part 1 – Conventional tests in COVID-19 patients presenting to the emergency department.
- Part 2 – Point-of-care ultrasound in COVID-19 patients in the acute care setting.
- Part 3 – Point-of-care ultrasound in COVID-19 patients in the critical care setting.

As the knowledge on COVID-19 rapidly developed, I have provided a short introduction for each chapter separately in the next section, in which the clinical problem we tried to

address as well as the medical literature on the subject at that particular point in time is summarized.

Part I | Conventional tests in COVID-19 patients presenting to the emergency department

The chapters in **Part 1** focus on the use of conventional tests in the diagnosis and prognosis of COVID-19, as well as its complications.

As no treatments or vaccines were available at the start of the pandemic, early detection was deemed crucial in containing the spread of COVID-19. Unfortunately, the SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) assay – which is the gold standard of COVID-19 diagnosis – was in short supply, had long turnaround times and limited sensitivity.[33] Rapid antigen tests were not available yet.[34] And importantly, chest X-rays (CXR) were found to have poor diagnostic accuracy for COVID-19 pneumonia.[35] To aid and expedite the diagnosis of COVID-19 (pneumonia) it was decided, early in the pandemic, that the majority of Dutch hospitals would perform a computed tomography (CT) of the chest in suspected COVID-19 patients at presentation to the ED.

These CTs were reported according to the COVID-19 Reporting and Data System (CO-RADS) introduced by the Radiology Society of the Netherlands (NVvR), based on recommendations of the Radiology Society of North America (RSNA).[36–38] In **Chapter 2** we report the prospective validation of the CO-RADS. We also assessed the association between the degree of affected lung tissue with hospital admission, ICU admission and 30-day mortality, using the corresponding CT severity score (CTSS), which is a semi-quantitative way of determining the extent of pulmonary involvement.

Bacterial coinfections are a feared complication of viral respiratory infections. In Influenza for instance bacterial coinfection rates range from 2-65%.[39] Unfortunately, it is difficult to distinguish between viral and bacterial respiratory infections on clinical grounds. Even though the bacterial coinfection rate in COVID-19 was found to be only 3.5% at presentation,[40] early reports showed that clinicians prescribed empirical antibiotics in the majority of COVID-19 patients.[39–41] Antibiotic overuse is the most preventable cause of antibiotic resistance. The United Nations (UN) put out a report in 2019 showing antimicrobial resistance will lead to progressively increasing morbidity and mortality – more than 10 million global deaths a year in 2050 – as well as economic damage due to higher health care expenditures and increased poverty and inequality.[42] It is therefore important to find tools that can help clinicians differentiate between viral and bacterial infections and in doing so help reduce antibiotic overuse. Biological markers such as procalcitonin (PCT) have been proposed but with conflicting results.[43–45] In **Chapter**

3 we therefore assessed whether PCT can help exclude bacterial (co)infection and thereby potentially reduce antibiotic overuse in patients that presented with respiratory symptoms to the ED of the Amsterdam UMC, location VUmc, in the winter seasons of 2019 and 2020.

As the pandemic spread over the globe, the scientific community investigated predictors of poor outcome in COVID-19 patients. As the number of diagnostic and prognostic prediction models rose, an early systematic review by Wynants et al. recommended against the use of any of them, as they had a high risk of bias, were poorly reported, overly optimistic, and not externally validated in the majority of cases.[46] In addition, most of those models were created on data of hospitalized patients with proven COVID-19, instead of (suspected) COVID-19 patients presenting to the ED. To be able to make a risk assessment immediately at the ED we investigated predictors for poor outcome in patients with (suspected) COVID-19 presenting to the EDs of both locations of the Amsterdam UMC. The prediction model that stemmed from this, was then externally validated in an Italian cohort. The results are presented in **Chapter 4**.

Part 2 | Point-of-care ultrasound in COVID-19 patients in the acute care setting

In the chapters grouped in **Part 2** we explore the use of POCUS for diagnosis, and prognostication of (suspected) COVID-19 patients in the ED and the medical ward. **Chapter 5** is a narrative review that serves as an introduction of the use of point-of-care lung ultrasound (LUS) in patients presenting with acute respiratory failure. As was mentioned in **Part 1** most hospitals in The Netherlands employed CT to help diagnose COVID-19 (pneumonia) due to shortcomings in microbiological tests and CXR diagnostic accuracy. **Chapter 5** shows that LUS has diagnostic properties that are better than CXR, and even equivalent to CT in diagnosing acute respiratory diseases. With the added advantage of being portable, affordable, and readily available (also in middle- and low-income countries). However, as the COVID-19 pandemic reached The Netherlands in March 2020, there were no prospective studies of diagnostic accuracy of LUS in COVID-19 yet. We therefore conducted a prospective, multicenter study that compared the diagnostic accuracy of 12-zone LUS and CT in diagnosing pneumonia in suspected COVID-19 patients at Radboudumc and both locations of the Amsterdam UMC. The results of which are presented in **Chapter 6**.

There are multiple LUS protocols in the literature, differing in the number of scan zones that are used; ranging from 6–14 zones. In search of the optimal balance between diagnostic accuracy and shortest possible scan time (and thus shortest exposure of a clinician to a possibly infected patient), we set out to compare the diagnostic accuracy of the most frequently used LUS protocols in diagnosing COVID-19 at the ED. The results

of this prospective, multicenter study, conducted in both locations of the Amsterdam UMC and Radboudumc, are presented in **Chapter 7**.

The degree of pulmonary involvement can be assessed by CT (**Chapter 2**), but also with LUS. This means LUS might also play a role in prognostication. In fact, in the late spring of 2020, the World Health Organization (WHO) recommended that the value of LUS regarding clinical outcomes and length of hospital outcomes should be further investigated.[47] In **Chapter 8** we therefore present the results of a prospective, multicenter study conducted in the same centers as **Chapter 6** and **Chapter 7**, which compared the association of the semi-quantitative lung ultrasound score (LUSS) – the most commonly used grading system of pulmonary involvement by LUS[48] – and CTSS with poor outcome (a composite end-point of ICU admission and mortality), and length of hospital stay. Additionally, we assessed the correlation between baseline LUSS and CTSS.

As the first COVID-19 wave spread across the world, reports of increased risk of venous thromboembolism (VTE) in COVID-19 emerged.[49–51] As it is well established that asymptomatic deep venous thrombosis (DVT) carries a high mortality risk,[52] this prompted us to conduct a cross-sectional study in which we used point-of-care compression ultrasound (CUS) of the deep leg veins – which has comparable diagnostic accuracy to a scan performed by a radiologist[53] – to screen for asymptomatic DVT in COVID-19 patients admitted to the medical ward. The results of this study, which was performed in four academic medical centers in The Netherlands, are described in **Chapter 9**.

Part 3 | Point-of-care ultrasound in COVID-19 patients in the critical care setting

Part 3 of this thesis addresses the use of POCUS in monitoring of the disease course and the diagnosis of its complications in critically ill COVID-19 patients.

Prone positioning is extensively used in critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS) to improve oxygenation.[54,55] Prolonged ventilation in prone position may hinder sequential monitoring, since existing scoring systems were validated in supine patients.[56,57] In **Chapter 10** we therefore report a single-center study exploring the agreement and measurement error of pulmonary involvement on LUS in both the supine and prone position. Analogous to **Chapter 7** we also investigated if pulmonary involvement could be monitored with a 6-zone instead of a 12-zone protocol, as this was previously suggested in ARDS literature.[58]

In extension of **Chapter 10** (and **Chapter 7**), and in response to the work of Volpicelli et al., and Mento et al.,[59,60] we debate the most optimal LUS protocol in monitoring pulmonary involvement in critically ill COVID-19 patients in a research letter presented in **Chapter 11**.

On the ICUs of the Amsterdam UMC, it was common practice to perform weekly CTs in critically ill COVID-19 patients whose condition deteriorated or recovery stagnated. These CTs were performed to quantify the degree of pulmonary involvement, and to diagnose a possible pulmonary embolism or coinfection. However, this policy is costly, places a large burden on health resources, while also carrying significant safety risks for patients.[61,62]

Moreover, it is neither clear if the degree of pulmonary involvement – as it changes over time – can differentiate between patients who will recover, or deteriorate and die. Nor if CT(SS) or LUS(S) are even capable of detecting clinically relevant changes. Literature on longitudinal monitoring of the disease course by CT and LUS, is limited to mostly small and retrospective case series, with often short follow-up time.[63–68] Furthermore, pleural line abnormalities and subpleural consolidations are currently not included in the LUSS, whilst they are often found in COVID-19 patients. Some have suggested that they should be incorporated in current grading systems as histologically they correlate with diffuse alveolar damage,[68–71] but such scores have not been validated.

Hence, in **Chapter 12** we report the results of an international multicenter study investigating if the degree of pulmonary involvement on LUS in the first week after intubation was associated with liberation from mechanical ventilation and poor outcome. In **Chapter 13** – instead of only taking baseline measurements of CTSS and LUSS into account – we compared the longitudinal correlation of weekly CT(SS) and LUS(S) in COVID-19 patients admitted to our ICU. We also investigated the reliability, measurement error and association with mortality of CTSS and LUSS. Additionally, in both **Chapter 12** & **Chapter 13**, we evaluated if the incorporation of pleural abnormalities improved the LUSS.

With regard to pulmonary embolisms, it has been suggested that multi-organ (lung, deep vein, and cardiac) POCUS might be useful in its diagnosis, but these studies were mostly conducted in non-ICU and non-COVID-19 settings.[72–74] In **Chapter 14** we therefore explore the diagnostic accuracy of multi-organ POCUS in the diagnosis of pulmonary embolisms in critically ill COVID-19 patients.

Lastly, as mechanical ventilation unloads the respiratory muscles, it can induce muscle atrophy and weakness even after a few days of mechanical ventilation. This impacts clinical outcomes such as duration of mechanical ventilation.[75–77] This is especially relevant for critically ill COVID-19 patients as they are subjected to extended periods of mechanical ventilation, and could thus find themselves in a vicious cycle of declining muscle thickness and strength and prolonged mechanical ventilation. However, it is unknown whether critically ill COVID-19 patients develop changes in respiratory muscle mass. Hence, we conducted a prospective, single-center study in consecutive patients to determine the

evolution of respiratory muscle thickness assessed by ultrasound as has been previously described in non-COVID-19 patients.[77] The results of which are presented in **Chapter 15**.

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PART 1

Conventional tests in COVID-19 patients presenting to the emergency department





2

Chest CT in COVID-19 at the ED: Validation of the COVID-19 Reporting and Data System (CO-RADS) and CT Severity Score

A prospective, multicenter, observational study

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Abstract

Background: CT is thought to play a key role in coronavirus disease 2019 (COVID-19) diagnostic workup. The possibility of comparing data across different settings depends on the systematic and reproducible manner in which the scans are analyzed and reported. The COVID-19 Reporting and Data System (CO-RADS) and the corresponding CT severity score (CTSS) introduced by the Radiological Society of the Netherlands (NVvR) attempt to do so. However, this system has not been externally validated. We aimed to prospectively validate the CO-RADS as a COVID-19 diagnostic tool at the ED and to evaluate whether the CTSS is associated with prognosis.

Methods: We conducted a prospective, observational study in two tertiary centers in The Netherlands, between March 19 and May 28, 2020. We consecutively included 741 adult patients at the ED with suspected COVID-19, who received a chest CT and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR). Diagnostic accuracy measures were calculated for CO-RADS, using PCR as reference. Logistic regression was performed for CTSS in relation to hospital admission, ICU admission, and 30-day mortality.

Results: 741 patients were included. We found an area under the curve (AUC) of 0.91 (95%CI 0.89-0.94) for CO-RADS using PCR as reference. The optimal CO-RADS cutoff was 4, with a sensitivity of 89.4% (95%CI 84.7-93.0) and specificity of 87.2% (95%CI 83.9-89.9). We found a significant association between CTSS and hospital admission, ICU admission and 30-day mortality; adjusted ORs per point increase in CTSS 1.19 (95%CI 1.09-1.28), 1.23 (95%CI 1.15-1.32), 1.14 (95%CI 1.07-1.22), respectively. Intraclass correlation coefficients for CO-RADS and CTSS were 0.94 (95%CI 0.91-0.96) and 0.82 (95%CI 0.70-0.90).

Conclusion: Our findings support the use of CO-RADS and CTSS in triage, diagnosis and management decisions for patients presenting with possible COVID-19 at the ED.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to put tremendous stress on health-care systems and societies worldwide. With second waves flaring up globally,[1,2] swift and accurate diagnosis is essential to profile patients and allocate scarce resources adequately. This is still hampered by limited sensitivity and availability of severe acute repiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR).[3–5] More importantly, PCR does not give any insight into pulmonary involvement, whereas pneumonia is the most common cause of severe morbidity and mortality in COVID-19.[6,7]

Chest imaging may play a key role in COVID-19 triage and diagnosis, as well as stratification of disease severity.[8–10] Conventional chest radiography (CXR) unfortunately has limited sensitivity for COVID-19 pneumonia. In retrospective studies sensitivity of chest computed tomography (CT) for COVID-19 is excellent and it may even be greater than that of PCR.[10–12] CTs are helpful in the diagnostic process at the ED because the results are available almost immediately and alternative diagnoses may be identified. In addition, using a semi-quantitative CT severity score (CTSS) is reported to correlate with disease severity, and might be used as a prognostic marker.[12–17]

Studies on using CT as an initial diagnostic modality are mostly retrospective in nature and from China, possibly reducing their generalizability to other regions. Although the CT characteristics of COVID-19 have been documented properly, no universal agreement exists on a systematic and reproducible way of evaluating and reporting CT abnormalities in patients with (suspected) COVID-19, which makes it difficult to compare data across different settings.[8,9,18–21]

The Radiological Society of the Netherlands (NVvR) recently introduced such a method, the COVID-19 Reporting and Data System (CO-RADS), which is largely based on the recommendations of the Radiological Society of North America (RSNA).[9,20,22] The CO-RADS is meant to be used for patients with moderate to severe symptoms of (suspected) COVID-19. It employs a scoring system from 0 to 5 to classify pulmonary involvement from very unlikely to very likely, respectively (e-Table 2.1). In 105 patients the NVvR found a very good performance for predicting COVID-19 (area under the curve [AUC] of 0.91 [95%CI 0.85-0.97]). In addition, interobserver agreement was substantial. Although these results are encouraging, a prospective external validation of the CO-RADS or any other CT classification system for COVID-19 is lacking.

In this observational study, we therefore set out to prospectively validate the CO-RADS system in two tertiary hospitals in The Netherlands. Furthermore, in accordance with

recent research recommendations from the WHO,[23] we analyzed whether the CTSS was associated with hospital admission, ICU admission and mortality.

Methods

Study design

This is a real-life, prospective, observational study. Patients were recruited consecutively from the EDs of the two university hospitals in Amsterdam, the Netherlands, between March 19 and May 28, 2020. The study was approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centers, location VUmc. An opt-out recruitment procedure was used to obtain consent for participation in the study.

All patients 18 years of age and older who visited the emergency department (ED) with suspected COVID-19 according to the WHO and Dutch Centre for Infectious Disease Control case definition (including either fever, malaise, respiratory symptoms, gastro-intestinal symptoms, or loss of taste and smell) were potentially eligible. Patients were

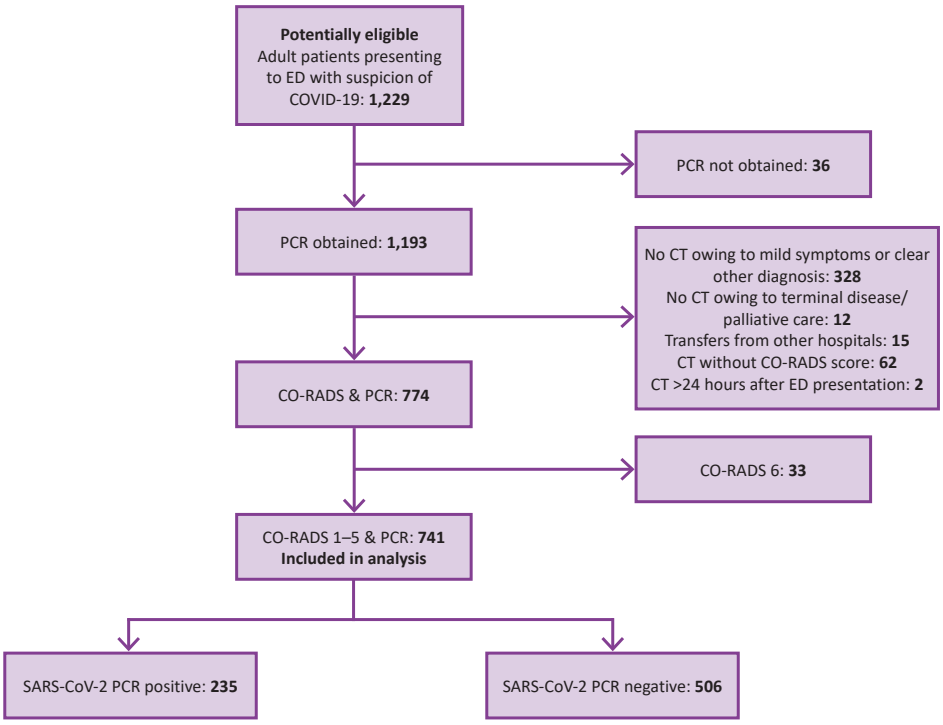


Figure 2.1: Flowchart of patient inclusion and exclusion.
Abbreviations: CO-RADS, COVID-19 Reporting and Data System; PCR, polymerase chain reaction; CT, computed tomography; SARS-CoV-2, severe acute repiratory syndrome coronavirus 2; ED, emergency department.

included if they received a PCR and chest CT with CO-RADS score. Exclusion criteria were age younger than 18 years, unwillingness to give verbal consent, or a CO-RADS 6 score (Figure 2.1).

Medical workup

All patients with suspected COVID-19 received a regular medical workup and a chest CT if deemed appropriate by the treating physician or according to local clinical protocol. Local protocol, based on Dutch Federation of Medical Specialists and WHO COVID-19 recommendations, dictated that physicians could perform a CT in a case of moderate to severe symptoms.[23,24] In a case with mild symptoms, physicians could forego additional imaging. Hospital admission criteria were saturation <94% or respiratory rate >20 breaths/min. ICU admission criteria were deterioration despite conventional respiratory support, patients requiring mechanical ventilation, or multi-organ failure. Admission decisions were not made based on CT data. All admitted patients with (suspected) COVID-19 were discussed daily in a multidisciplinary team (MDT), consisting of consultants in infectious disease, respiratory disease, and microbiology. The MDT decided on the final diagnosis, but it was not blinded for the CT results.

CT

The CTs were assessed by our local radiologists with varying degrees of experience. The radiologists had regular access to clinical information but did not have access to the PCR results, because CT scanning and reporting were done early after ED admission, before PCR results were available. The likelihood of COVID-19 pneumonia was reported according to the CO-RADS classification system (e-Table 2.1).[20,22]

CT scans were performed without the use of intravenous contrast agents in supine position at the end-inspiration level. Four different CT systems were used: GE Discovery CT750 HD (GE Healthcare, Waukesha, WI, USA), Siemens SOMATOM Drive, Siemens SOMATOM Force and Siemens SOMATOM Definition AS+ (Siemens Healthcare, Erlangen, Germany). If necessary, pitch was increased to reduce motion artifacts. Multiplanar CT images are reconstructed with a slice thickness of 0.625-3 mm.

To quantify pulmonary involvement, every CT with a CO-RADS of 3 or higher was graded according to the CTSS.[25] This is a visual assessment of the percentage of disease involvement in each lobe (e-Table 2.2). The total CTSS is the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement).

PCR

A naso- or oropharynx PCR was performed in all patients presenting to the ED, according to WHO standards. In case of a negative or inconclusive test result and high clinical suspicion of COVID-19, a nasopharynx or oropharynx PCR was repeated or sputum or bronchoalveolar lavage if available and possible, as indicated by the MDT.

Outcomes

As the primary outcome, sensitivity, specificity, predictive values, likelihood ratios, area under the receiver operating characteristic curve, and diagnostic accuracy were calculated for CO-RADS. For CTSS, we calculated the same measures, and ORs for hospital admission, ICU admission, and mortality.

Statistical analysis

Continuous variables were summarized by mean and SD, or by medians and interquartile range. Differences between groups were tested using the independent samples t-test, Mann-Whitney U test, χ^2 test or Fisher's exact test as appropriate. A two-sided significance level of 5% was used, and confidence intervals (95%CI) were reported for all analyses.

Discriminatory ability of CO-RADS and CTSS was determined by the area under the receiver operating characteristic curve. The optimal cutoff value was determined by the Youden's index. Diagnostic measures were subsequently calculated.For CTSS, we also employed a 'grey zone' approach. A grey zone represents a predictive test of poor accuracy, with a sensitivity and specificity <90%. Sensitivity and specificity were plotted as a function of the CTSS, to determine a grey zone for hospital admission, ICU admission, and mortality.

Logistic regression analysis was performed to test whether the CTSS score was associated with hospital admission, ICU admission, and 30-day mortality. Associations were quantified by ORs. We corrected for the following potential confounders: age, sex, and comorbidities (chronic obstructive pulmonary disease [COPD], asthma, cardiovascular disease, hypertension).[12–17]

Interobserver agreement was quantified between two acute radiologists, with 3 and 6 years of experience, and the initial assessing radiologist via the intraclass correlation coefficient (ICC). They independently assessed the CT images of 63 patients.

Cumulative sum control (CUSUM) charts were used to assess the learning curve for using CO-RADS for diagnosis of COVID-19. Two separate CUSUM charts were made – one for patients with a negative PCR (non-COVID) and one for patients with a positive PCR (COVID). In addition, CUSUM charts were made for overall accuracy including all patients.

Results

Study population

From March 19 until May 28, 2020, 1,229 patients with symptoms suggesting COVID-19 presented at the two EDs. Seven hundred forty-one patients fulfilled the inclusion criteria, of which 235 had a positive PCR result (see e-Table 2.3 for details on the excluded patients). In 56 of the PCR positive patients, the initial PCR was negative, and repeated PCR testing was needed to confirm COVID-19. Patients in the PCR positive group were on average more likely to require oxygen therapy, hospital admission, or ICU admission, and had a higher mortality rate. PCR positive patients were also more likely to have comorbidities such as cardiovascular disease, hypertension, and COPD (Table 2.1).

Table 2.1: Baseline characteristics

	All patients N=741	SARS-CoV-2 PCR positive N=235	SARS-CoV-2 PCR negative N=506	*p* value
Age, mean (SD)	62.1 (17.2)	62.5 (14.6)	61.9 (18.4)	**0.000**
Male, n (%)	417 (56.3)	136 (57.9)	281 (55.5)	0.209
Admission, n (%)	492 (66.4)	163 (69.4)	329 (65.0)	**0.000**
Admission IC, n (%)	84 (11.3)	44 (18.7)	40 (7.9)	**0.000**
30 days mortality, n (%)	74 (10.0)	33 (14.0)	41 (8.1)	**0.001**
In hospital mortality, n (%)	54 (7.3)	28 (11.9)	26 (5.1)	**0.000**
Duration of symptoms, days (SD)	6.7 (7.2)	7.9 (4.6)	6.0 (8.2)	**0.001**
Co-morbidities, n (%)				
Asthma	49 (6.6)	16 (6.8)	33 (6.5)	0.77
Chronic Cardiovascular Disease	197 (26.6)	50 (21.3)	147 (29.1)	**0.000**
COPD (GOLD >2) n (%)	128 (17.3)	27 (11.5)	101 (20.0)	**0.000**
Current malignancy	107 (14.4)	15 (6.4)	92 (18.2)	**0.000**
Diabetes Mellitus	189 (25.5)	69 (29.4)	120 (23.7)	**0.002**
Hypertension	292 (39.4)	107 (45.5)	185 (36.6)	**0.000**
Laboratory analysis on admission				
CRP (mg/L), median [IQR]	44.0 [86.5]	69.0 [86.0]	28.0 [79.3]	0.76
PCT	0.1 (0.28)	0.13 (0.22)	0.1 (0.35)	**0.002**
Positive blood culture, n (%)	36 (4.9)	1 (0.4)	35 (6.9)	**0.000**
Modified early warning score mean (SD)	2.86 (1.8)	3.0 (1.7)	2.8 (1.8)	0.076
Temperature (°C), mean (SD)	36.9 (1.3)	37.5 (1.1)	36.7 (1.3)	0.259
Respiratory rate, mean (SD)	22.7 (7.9)	24.9 (8.0)	21.7 (7.7)	0.070
Saturation levels (SD)	95.2 (5.6)	94.1 (6.1)	95.7 (5.3)	0.281
Oxygen therapy, n (%)	255 (34.9)	111 (47.8)	144 (28.9)	**0.002**
Intubation, n (%)	68 (9.2)	39 (16.6)	29 (5.7)	**0.000**

P values in bold are <0.05.

Abbreviations: SD, standard deviation; mg/L, milligrams per liter; CRP, C-reactive protein; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC, intensive care; IQR, interquartile range; PCR, polymerase chain reaction; PCT, procalcitonin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

CO-RADS

Figure 2.2 shows the distribution of PCR results with the CO-RADS score. We found that CO-RADS ≥4 was the optimal cutoff for discriminating between a positive and negative PCR, with an AUC of 0.91 (95%CI 0.89-0.94), with a sensitivity of 89.4% (95%CI 84.7-93.0), specificity of 87.2% (95%CI 83.9-89.9), negative predictive value (NPV) of 94.6% (95%CI 92.4-96.2) and positive predictive value (PPV) of 76.4% (95%CI 71.9-80.3) (Figure 2.3 & Table 2.2). The intraclass correlation coefficient was 0.94 (95%CI 0.91-0.96).

Using the MDT diagnosis as reference test instead of PCR did not change the optimal cutoff point. The ICC between radiologists we observed was 0.94 (95%CI 0.91-0.96).

Twenty-five patients had a false negative CT scan (CO-RADS ≤3, but positive PCR). Patients with a CO-RADS ≤2 had a significantly shorter duration of symptoms than those with a CO-RADS >2 (e-Table 2.4). Eleven (44%) of them had a symptom duration of less than 3 days. Eighteen patients (72%) were admitted, seven (28%) patients received oxygen, and only two (8%) patients needed ICU treatment. Sixty-five patients had a false positive CT scan (CO-RADS ≥4, but negative PCR), compared with PCR. Forty-six of those patients were still classified as having COVID-19 by the MDT; the remaining diagnoses are summarized in e-Table 2.5. The most common alternative diagnoses were bacterial pneumonia and decompensated heart failure (e-Table 2.6).

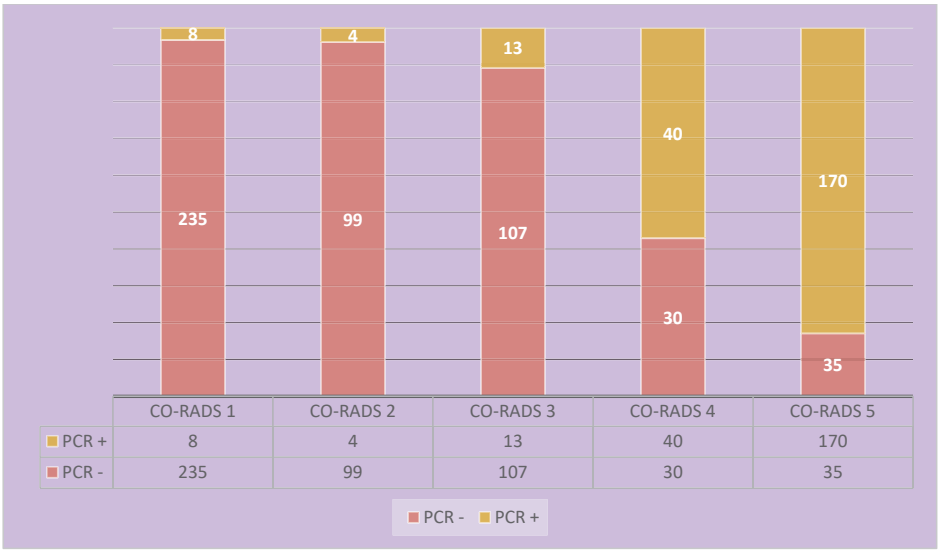
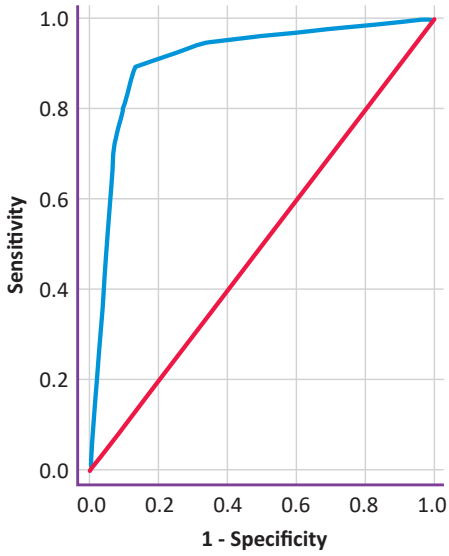


Figure 2.2: Distribution of PCR results and CO-RADS.
Abbreviations: CO-RADS, COVID-19 Reporting and Data System; PCR, polymerase chain reaction.



CO-RADS	Sensitivity	1-Specificity
1	100	100
2	96.6	53.6
3	94.9	34.0
4	89.4	12.8
5	72.3	6.9

Figure 2.3: ROC curve CO-RADS vs PCR results.
Red line: reference line.
Blue line: CO-RADS.
Abbreviations: AUC, area under the curve; CO-RADS, COVID-19 Reporting and Data System; PCR, polymerase chain reaction; ROC, receiver operating characteristic.

Table 2.2: Diagnostic accuracy measures

	CORADS 345 vs SARS-CoV-2 PCR	CORADS 45 vs SARS-CoV-2 PCR	CORADS 345 vs MDT diagnosis	CORADS 45 vs MDT diagnosis
Sensitivity % (95%CI)	95.1 (91.6-97.4)	89.4 (84.7-93.0)	94.2 (90.8-96.6)	87.7 (83.3-91.2)
Specificity % (95%CI)	66.0 (61.7-70.1)	87.2 (83.9-89.9)	73.3 (68.9-77.3)	95.8 (93.5-97.4)
Pos. Likelihood Ratio	2.8 (2.5-3.2)	6.96 (5.2-8.8)	3.52 (3.0-4.1)	20.7 (13.3-32.2)
Neg. Likelihood Ratio	0.07 (0.04-0.13)	0.12 (0.08-0.18)	0.08 (0.05-0.13)	0.13 (0.09-0.17)
Pos. Predictive Value % (95%CI)	57.5 (54.5-60.6)	76.4 (71.9-80.3)	69.6 (66.2-72.8)	93.1 (89.7-95.5)
Neg. Predictive Value % (95%CI)	96.5 (94.1-98.0)	94.6 (92.4-96.2)	95.1 (92.4-96.9)	92.3 (89.8-94.2)
Accuracy %	75.5 (72.3-78.5)	87.9 (82.3-90.1)	81.5 (78.5-84.2)	92.6 (90.5-94.4)

Abbreviations: CORADS, COVID-19 Reporting and Data System; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MDT, multidiscipinary team; CI, confidence interval.

The CUSUM plots in center 1 showed no strong upward or downward inflections, indicating a steady performance over time (e-Figure 2.2A). For center 2, an upward inflection was seen after the 80th COVID-negative patient was included (corresponding to the 161th consecutive patient included), showing a temporary increase in the false positive rate (e-Figure 2.2B).

CTSS

The CTSS was determined in 304 (41.0%) patients, who had a CO-RADS ≥3. Stratified according to three disease severity groups – 1) discharge home from ED, 2) hospital admission, or 3) ICU admission – we found a significant difference in mean CTSS; 5.5 (SD 3.6), 9.4 (SD 4.9), and 14.8 (SD 4.8), respectively.

Logistic regression showed a significant positive association between CTSS (per point increase) and hospital admission, ICU admission, and 30-day mortality (Table 2.3). These associations stayed significant after correcting for potential confounders age, sex, and the aforementioned comorbidities, with adjusted OR of 1.18 (95%CI 1.09-1.28); 1.23 (95%CI 1.15-1.32); and 1.14 (95%CI 1.07-1.22) respectively.

Table 2.3: CTSS Logistic regression

Association between CTSS and hospital admission				
	Crude analysis		Adjusted analysis*	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
CTSS	1.18 (1.09-1.27)	**0.000**	1.18 (1.09-1.28)	**0.000**
Association between CTSS and ICU admission				
	Crude analysis		Adjusted analysis*	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
CTSS	1.23 (1.16-1.32)	**0.000**	1.23 (1.15-1.32)	**0.000**
Association between CTSS and mortality				
	Crude analysis		Adjusted analysis*	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
CTSS	1.12 (1.05-1.19)	**0.001**	1.14 (1.07-1.22)	**0.000**

OR and CI of the association between CTSS and hospital ward, ICU admission and mortality per point increase in CTSS.

*Adjusted for age, sex, comorbidities (cardiovascular disease, COPD, asthma, high BP).

Abbreviations: BP, blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CTSS, computed tomography severity score; ICU, intensive care unit; OR, odds ratio.

For hospital admission, the optimal cutoff of the CTSS was 9, with an adequate AUC of 0.77 (95%CI 0.71-0.84), a sensitivity of 65.4% (95%CI 59.3-71.1), and specificity of 78.1% (95%CI 62.4-89.4). For ICU admission CTSS had a good AUC of 0.81 (95%CI 0.75-0.88) at a cutoff of 13, with a sensitivity of 72.6% (95%CI 58.3-84.1), and specificity of 79.8% (95%CI 74.4-84.6). For 30-day mortality, CTSS had a poor AUC of 0.63 (95%CI 0.53-0.73)

at a cutoff of 13, with a sensitivity of 72.2% (95%CI 58.3-84.1) and specificity of 79.8% (95%CI 74.4-84.6).

Grey zone analysis showed that a CTSS ≥10 was predictive of hospital admission with a specificity of ≥90%, whereas a score of ≤3 was ≥90% sensitive for ED discharge. A CTSS ≥15 was predictive of ICU admission with a specificity of ≥90%, and a score ≤9 excluded ICU admission with a sensitivity of ≥90%. A score of ≥17 was ≥90% specific for 30-day mortality, and a score ≤5 excluded 30-day mortality with a sensitivity of ≥90% (e-Figure 2.1A-C). The intraclass correlation coefficient for the CTSS was 0.82 (95%CI 0.7-0.9).

Discussion

To our knowledge, this is the first prospective multicenter study evaluating the diagnostic accuracy of chest CT in COVID-19 patients and externally validating a systematic CT reporting scheme. We found that: 1) CO-RADS discriminates excellently between a positive and negative PCR result, with an AUC of 0.91 (95%CI 0.89-0.94); 2) CTSS at ED presentation is associated with hospital admission, ICU admission, and 30-day mortality; 3) CUSUM analysis showed no significant learning curve; and 4) In combination with a high interobserver agreement, this indicates that the CO-RADS is easy to learn and use, even for less experienced radiologists.

CO-RADS in COVID-19 screening

The high NPV and low negative likelihood ratio (NLR) associated with a CO-RADS ≤3 indicate that these scores can aid in excluding the presence of COVID-19. A score of ≤3 could also aid in patient management, particularly patient isolation measures. Interestingly, we found that almost half of the false negative CTs were performed in patients with a short duration of symptoms (<3 days). Previous studies found that chest imaging might be negative in the earlier phases of the disease, because it has not involved the lung parenchyma yet.[11] Scanning too early in the disease course could falsely reassure clinicians.

CO-RADS in COVID-19 diagnosis

Our results indicate that a CO-RADS score ≥4 has a high positive likelihood ratio (PLR) and a corresponding good PPV in a high prevalence setting. As was argued before by Ai et al.[11] and Prokop et al.[20] the suboptimal clinical sensitivity of the gold standard PCR could result in a reduced specifity (and lower PPV and PLR) because this generates more false positive CTs.[3,5] This would mean that specificity of CO-RADS might actually be higher. In any case, a CO-RADS ≥4 seems to ascertain the diagnosis of COVID-19. A score of ≥4 can therefore be used to put a patient in isolation or self-quarantine.

When COVID-19 prevalence decreases, however, or the prevalence of similar diseases increases, the positive predictive value of a high CO-RADS will likely decrease. A recent Chinese/American study suggests that CT can distinguish COVID-19 from other viral pneumonias with moderate to high accuracy.[26] Further research is needed to assess whether CO-RADS is useful in a setting with a lower COVID-19 prevalence and a different case mix of other (viral) diseases that might produce similar abnormalities on CT.

CO-RADS summary

Our results externally validate CO-RADS as a reliable and reproducible tool in reporting pulmonary findings in patients suspected of COVID-19 in a pandemic setting. As stated in the RSNA Consensus statement, standardized reporting can provide guidance to radiologists, accelerate reporting during high demand, reduce reporting variability, enable care pathways, and facilitate a basis for data sharing, quality improvement and research.[9] CO-RADS can help achieve all those aims. Using CO-RADS could be especially helpful when PCR is not available and CT is conducted at the ED upon patient arrival as was the case in many Dutch hospitals during the pandemic. The Dutch Federation of Medical Specialists (FMS) has incorporated CO-RADS in the national COVID-19 care pathway recommendation.[24]

CTSS

Our results indicate that CTSS is positively associated with hospital and ICU admission, and also – albeit to a lesser extent – 30-day mortality even after correcting for confounders. The positive association of CTSS and hospital/ICU admission is greater than that of 30-day mortality. We also observed a smaller grey zone for hospital/ICU admission than 30-day mortality. This difference is probably explained because the time-to-event, in hospital/ICU admission is shorter than in 30-day mortality. Moreover, there are more complications of COVID-19 (i.e., pulmonary embolism) that also affect mortality and thus aren't captured by the CTSS.

However, although there are grey zones in each of these categories in which uncertainty remains, the upper and lower values can provide clinicians with a helpful tool to make faster and more adequate triage and management decisions, and to predict patient disease course. Especially because previous studies have shown that pulmonary involvement can predate worsening of severe respiratory symptoms,[13,14] the CTSS could be particularly helpful in patients that do not seem clinically ill (e.g., silent hypoxia), but based on the CTSS might deteriorate and thus benefit from admission and a higher level of monitoring.

Global perspective

Although these results are encouraging, debate continues about the place of CT in COVID-19 diagnostics. Dutch and Chinese guidelines include CT in their workup of COVID-19, but American and British guidelines are more reserved.[8,24,27] The recent Fleishner consensus statement concedes that the logistics surrounding the provision of CT services can be a daunting task in the face of this pandemic.[8] As second waves are flaring up this is of particular importance. CT is difficult to perform in unstable patients, and availability and costs can be an issue even in high-income countries. Risk of transmission during transport neccesitates stringent disinfection protocols and lead to prolonged CT down time. We have seen significant health disparities in COVID-19 outcome along geographic, socio-economic, ethnic, cultural and racial lines.[28–31] Portable imaging modalities like bedside lung ultrasound circumvent these issues, while showing better accuracy than CXR and similar accuracy to CT.[10,32–43] This may be considered as a viable alternative especially in low resource settings where CT might not be readily available.

Limitations/bias

Our study has some limitations. First, we stress that this study was conducted in a high-prevalence setting. Although CO-RADS was designed to be used in patients with moderate to severe symptoms in this pandemic, it is unclear how CO-RADS will function when the pandemic subsides, but it is reasonable to assume that the false positive rate will increase in such a situation. Conversely, negative predictive value is likely to increase when disease prevalence decreases. However, we argue that the need for quick and reliable triage is more pressing in a pandemic setting than in a situation in which prevalence is low and medical resources are not as overwhelmed.

Second, we assessed diagnostic accuracy of CO-RADS and CTSS in a population presenting to ED that were deemed to have moderate to severe symptoms, which justified additional imaging of the chest. Although this might reduce generalizibility to all patients in all settings, the diagnostic accuracy measures we report are reflective of daily practice in EDs all over the globe. After all, physicians will be more likely to perform additional tests and exclude alternative diagnoses in patients with more severe symptoms than when symptoms are milder and less threatening.

Whether CO-RADS would be applicable in asymptomatic or mildly symptomatic patients outside the ED is unclear, but the question is whether this would be desirable. We would argue against the use of CT in the general outpatient population, because the possible benefits (early diagnosis, fast triage), probably do not outweigh the possible harms (overuse of medical resources, health-care costs, radiation, increase of false negatives

because of less pulmonary involvement in this group). Third, we believe selection bias was minimal; the treating physicians were not aware of this study being undertaken, so they were not influenced in whether their patient got a CT or not. The chance of nonrandom selection of patients is therefore low. In addition, we consecutively included a very large consecutive sample of COVID-19 patients. Fourth, information bias was minimized because the PCR results were not known at the time the CT was done, and if they were, the results were excluded from the analysis. Fifth, the CO-RADS and CTSS were assessed by radiologists with varying levels of experience. However, CUSUM analysis did not show clear learning effects in the participating hospitals. Combined with a high agreement, this would suggest that both CO-RADS and CTSS are easy to use and reproduce.

Conclusion

CO-RADS is an easy-to-use tool to help radiologists and guide clinicians in diagnosis of COVID-19 in patients with moderate to severe symptoms presenting to the ED. Furthermore, the CTSS seems to be associated with hospital admission, ICU admission, and 30-day mortality, and therefore it might be used in management decisions. We encourage the international use of the CO-RADS and CTSS for patients with suspicion of COVID-19 at ED presentation, to provide a basis for further reporting, communication, and data sharing. We also suggest further studies to be conducted in other countries and care settings to increase the robustness of our findings.

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3

Optimal use of procalcitonin to rule out bacteremia in patients with possible viral infections

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Abstract

Background: During the winter, many patients visit the emergency department (ED) with a suspicion of respiratory infection, that could be either a viral or bacterial (co)infection. The aim of this study is to investigate whether the optimal cutoff of procalcitonin (PCT) is different in patients with and without proven viral infections to exclude bacterial (co) infection defined as bacteremia. We hypothesize that when a viral infection is confirmed, this lowers the probability of bacteremia and, therefore, influences the appropriate cutoff of procalcitonin.

Methods: This study was conducted in the emergency department of an academic medical center in The Netherlands in the winter of 2019 and 2020. Adults (>18 years) with suspected infection, in whom a blood culture and a rapid polymerase chain reaction (PCR) test for influenza (and in 2020 also SARS-CoV-2) was performed were included.

Results: A total of 546 patients were included of whom 47 (8.6%) had a positive blood culture. PCT had an area under the curve of 0.85, 95% confidence interval (95%CI) 0.80-0.91, for prediction of bacteremia. In patients with a proven viral infection (n=212) PCT <0.5 μg/L had a sensitivity of 100% (95%CI 63.1-100) and specificity of 81.2% (95%CI 75.1-86.3) to exclude bacteremia. In patients without a viral infection, the PCT cutoff point of <0.25 μg/L showed a sensitivity of 87.2% (95%CI 72.6-95.7) and specificity of 64.1% (95%CI 58.3-69.6).

Conclusion: In patients with a viral infection, our findings suggest that a PCT concentration of <0.50 μg/L makes bacteremia unlikely. However, this finding needs to be confirmed in a larger population of patients with viral infections, especially because the rate of bacterial (co)infection in our cohort was low.

Introduction

Annually more than 20% of adult emergency department (ED) visits occur due to severe infections.[1] The most frequent presenting symptoms are fever and respiratory complaints. It is difficult to distinguish between a viral and bacterial cause of these complaints based on clinical symptoms because the complaints in viral and bacterial disease show great overlap.[2,3] During the winter season in the Netherlands, this clinical dilemma is encountered more often as the incidence of viral infections rises. This is usually caused by the annual influenza epidemic; however, in 2020, this epidemic was supplanted by the coronavirus disease 2019 (COVID-19) pandemic. Rapid diagnosis of viral infections has become easier because of the wide availability of a rapid polymerase chain reaction (PCR) test.[4] However, despite a positive viral test, clinicians often prescribe antibiotics,[5,6] because viral infections predispose patients to bacterial (co)infection.[7–9] Particularly elderly patients are more susceptible to bacterial (co)infections and mortality in those cases is higher.

The rate of bacterial (co)infection in viral infections is highly variable. In influenza, bacterial (co)infection rates varying from 2% to 65% have been reported.[7] However, few studies have been conducted in the ED, and most of the available data stem from the intensive care unit (ICU). A recent meta-analysis reported a rate of bacterial (co)infection in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) at presentation of 3.5%, which might increase to 16% during the course of the disease.[10] Emerging literature shows that bacterial (co)infection in COVID-19 is also associated with a higher mortality risk.[11,12] The rate of bacterial (co)infections with other viruses such as rhinovirus or respiratory syncytial virus (RSV) has been mostly reported in ICU patients and as such it is hard to extrapolate to ED patients.[13]

Making this distinction is crucial in order to provide appropriate treatment, ensure patient safety, and reduce overuse of antibiotics. Estimated rates of unnecessary antibiotic use vary between 30-60%, rendering it the most preventable cause of antibiotic resistance.[14–17] Moreover, a recent report by the World Health Organization (WHO) found that antibiotic resistance could lead to a significant increase in economic costs, and 10 million annual deaths globally by 2050 without a sustained effort to contain it.[18–20]

To reduce antibiotic use and identify bacterial (co)infection more adequately, the use of biological markers such as procalcitonin (PCT) has been proposed, but with conflicting results.[21,22] One of the largest studies in the Cochrane meta-analysis of PCT[22] showed a high negative predictive value (NPV) of 91.9% for exclusion of a bacterial (co)infection in patients admitted to the ICU with influenza, despite a high prevalence of (co)infection.[23] A study by Riedel et al.[24] showed almost a similar NPV of 96.3% for a PCT cutoff of 0.1

µg/L in relation to positive blood cultures in patients at the ED, with a sensitivity of 75% and specificity of 76.6%. However, a retrospective study by Goodlet et al. raised concerns on using PCT as a rule-out tool, due to limited sensitivity.[25]

One of the explanations for the different results might be that PCT has been used with several cutoffs (<0.10 µg/L, <0.25 µg/L, <0.5 µg/L). In a review of PCT algorithms, it was advised to take the pre-test likelihood of bacterial infection into account to choose the appropriate cutoff.[25–28]

The aim of this study was to investigate if the PCT cutoff to exclude bacteremia should be different in patients with and without confirmed viral infections, presenting during a viral epidemic or pandemic. We hypothesized that if a viral infection was found, this lowered the probability of bacteremia and therefore influenced the appropriate cutoff of PCT.

Methods

Study design

The prospective observational study was approved by the local medical ethics committee, a waiver for informed consent was obtained. The PCT values were not used in clinical practice at the time, but only obtained for research purposes. The study was planned to run during 2 winter seasons, with the aim to use the influenza seasons. The first inclusion period was from January 2019 to April 2019, and the second inclusion period was from January 2020 until April 2020, coinciding with the start of the COVID-19 pandemic.

The Amsterdam University Medical Center (UMC) is a large teaching hospital with an estimated 30,000 ED presentations annually. It provides different training programs including emergency medicine residency training. Most patients seen in our ED were either referred by a general practitioner for acute review or are already undergoing other treatment at our facility.

All patients 18 years and older in whom a blood culture and a viral test were ordered in the ED were included. This was a consecutive sample of patients.

In our hospital, testing for influenza, was based on the case definition of the National Institute for Public Health and Environment, which includes fever and respiratory symptoms.[29] Testing for the novel SARS-CoV-2 was based on the clinical case definition of the National Institute for Public Health and Environment in March 2020. A blood culture was drawn when a bacterial (co)infection was suspected by the treating physician. In all included patients, PCT was determined in the blood sample that was drawn for other

biochemical tests. No additional sample was needed for this study. Patients were treated according to standard care. Patients were excluded if a blood culture, PCT, or viral test was not available.

Measurements

Bacteremia was defined as true positive blood cultures. All blood cultures are processed with the BACTEC system (Becton Dickinson). Culture results were reported in the electronic health system (EPIC). Positive blood culture results were routinely reviewed by a microbiologist. To establish true positivity, the student entering the patients' data in Castor checked if a microbiologist had written a comment on the culture result. In case no microbiologist assessment was available, contamination was assessed according to pre-established criteria (National Nosocomial Infection Surveillance parameters and surveillance criteria for bloodstream infection).[30] In the final data set, contaminated cultures were reclassified as negative cultures. PCT was measured using the Elecsys BRAHMS PCT assay. Viral testing was performed by Cepheid Xpert Flu A/B/RSV XC assay in 2019 and by the Cepheid Xpert SARS-CoV-2/Flu/RSV assay in 2020. If more extensive viral testing was deemed indicated by the treating physician, the result was used in our analysis. All patients with a positive viral test were considered to have a confirmed viral infection.

We identified eligible patients through the microbiology orders. The microbiology laboratory generated a list of patients for the research team in whom both a viral test and a blood culture was ordered in the ED, once a week. Baseline data of patients were then gathered from the electronic health record by trained students, using a script and predefined answer fields. These data were entered in a clinical data management platform, Castor EDC[31], in compliance with Good Clinical Practice regulations.

Outcome

The primary outcome was the diagnostic accuracy of PCT to exclude bacteremia at the predefined cutoffs of <0.10 µg/L, <0.25 µg/L, <0.5 µg/L, overall, and in subgroups based on results of viral testing. The diagnostic accuracy of PCT was defined as the sensitivity, specificity, positive/negative predictive values, likelihood ratios (LRs), and the area-under-the-curve (AUC) in excluding bacteremia.

Secondary outcomes were the difference between incidence of bacteremia in patients with and without viral infection and the use of antibiotics.

Statistical analysis

All data analyses were performed in SPSS version 26. Normally distributed continuous variables were expressed by their mean and SD. Continuous variables that were not normally distributed were expressed by their median and interquartile range [IQR]. Comparison of continuous values, not normally distributed was done with a non-parametric test (Mann-Whitney U). Analysis of proportions was done with χ^2 test (dichotomous variables). Receiver operating characteristic (ROC) curves were drawn to assess the overall diagnostic accuracy of PCT by calculating the AUC with 95% confidence intervals (95%CI). Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV), and the likelihood ratios (LRs) were calculated using MedCalc version 19.4 (MedCalc Software, Ostend, Belgium). Reporting was done in accordance with the guideline for Standards for Reporting diagnostic Accuracy (STARD) 2015.[32]

Sensitivity analysis

Due to the pandemic, SARS-CoV-2 infection heavily influenced the group of patients with a viral infection; 109 of the 212 patients with a viral infection had COVID-19. Therefore, we performed an additional analysis of the AUROC of PCT in the patients with a viral infection, excluding the patients with COVID-19.

Results

Study population

A total of 767 patients presented with suspected infection at the ED during the study period. Two hundred twenty-one patients were excluded because of missing data; they lacked either blood cultures, PCT, or both values (Figure 3.1).

The final study population included 546 patients. Patient demographics are described in Table 3.1. Forty-seven patients (8.6%) had a true positive blood culture. Fourteen blood cultures were classified as contaminated. Details of the contaminated cultures are described in e-Table 3.1. Of the 546 patients, 212 patients (38.8%) had a viral infection. Infection with SARS-CoV-2 was the most frequently diagnosed viral infection (n=109), followed by influenza A/B (n=62). More details of viral test results can be found in e-Table 3.2.

Overall diagnostic accuracy of PCT for bacteremia

The median PCT in the total study population (n=546) was 0.15 μg/L [IQR 0.06-0.57]. The area under the curve (AUC) was 0.86 (95%CI 0.81-0.91) and is displayed in Figure 3.2. The sensitivity, specificity, PPV and NPV, and LRs at the prespecified cutoffs are presented in Table 3.2.

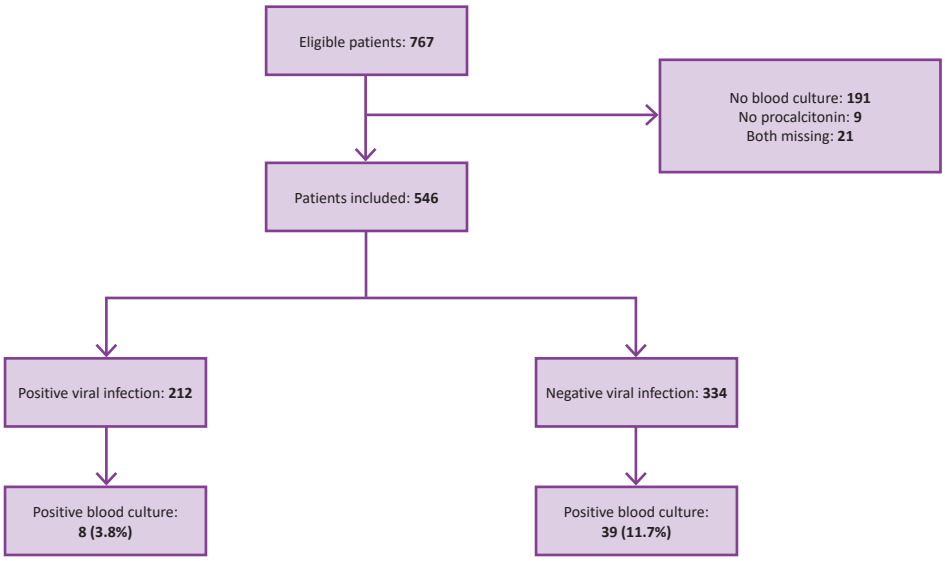


Figure 3.1: Flowchart of patient inclusion and exclusion.

Table 3.1: Baseline characteristics

General characteristics	Study population N=546
Gender	
Female, N (%)	245 (44.9)
Age, y, mean (SD)	64.0 (17.0)
Admission	
Hospital admission, n (%)	363 (66.5)
ICU admission, n (%)	45 (8.2)
Readmission (30 days), n (%)	47 (8.7)
Comorbidities	
Respiratory disease*, n (%)	89 (16.4)
Diabetes mellitus, n (%)	94 (17.3)
Vital parameters	
Respiratory rate, mean (SD)	21.7 (7.2)
Oxygen saturation levels, mean (SD)	95.3 (3.9)
Temperature °C, mean (SD)	37.4 (1.3)
MEWS score (median with IQR)	2.0 [2-4]
Laboratory tests (median with IQR)	
CRP (mg/L)	55.0 [17.0-115]
PCT (ng/mL)	0.15 [0.06-0.57]
Positive SARS-CoV-2 PCR (%)	109 (19.4)
Positive blood culture (%)	47 (8.6)
30-day mortality n (%)	63 (11.5)

*Emphysema, asthma, and chronic obstructive pulmonary disease.
Abbreviations: SD, standard deviation; CRP, C-reactive protein; IQR, interquartile range; MEWS, Modified Early Warning Score; PCR, polymerase chain reaction; PCT, procalcitonin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

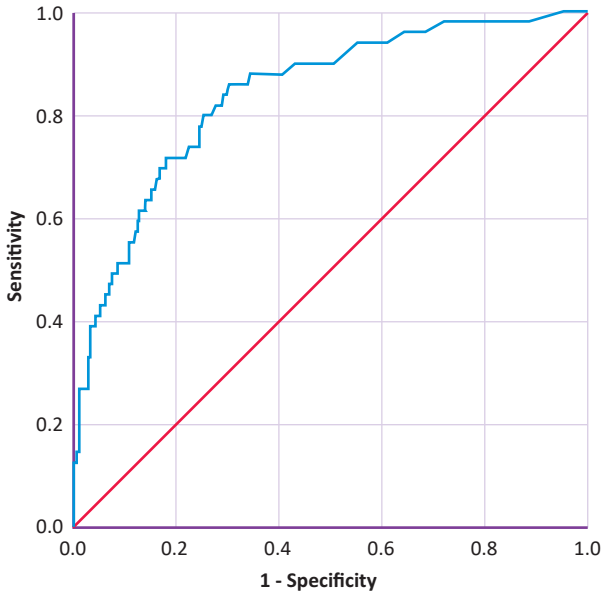


Figure 3.2: Overall ROC curve of procalcitonin versus bacteremia.
Abbreviation: ROC, receiver operating characteristic.

Eight of the 212 patients (3.8%) with a confirmed viral infection had bacteremia. In the patients without a viral infection, 39 of the 334 (11.7%) had bacteremia. This was a significant difference, *p* value 0.001 (χ^2 test).

PCT in patients with a proven viral infection

In patients with a viral infection (n=212), median PCT was 0.14 µg/L [IQR 0.07-0.34]. The AUC of PCT for prediction of bacteremia was 0.97 (95%CI 0.94-1.00). All 8 patients with a viral infection and bacteremia had a PCT value of ≥0.5 µg/L. The other diagnostic accuracy measures of PCT in patients with a positive viral test are presented in Table 3.3. In the group with a viral infection, the sensitivity was 100% (95%CI 63.1-100) and specificity was 81.2% (95%CI 75.1-86.3).

PCT in patients without proven viral infection

In patients without confirmed viral infection (n=334), the median PCT was 0.13 [IQR 0.05-0.48]. Of the 39 patients in this group with a positive blood culture, 28 had a PCT concentration of ≥0.5 µg/L. Of the other 11 patients with positive blood cultures, 2 had a PCT <0.10 µg/L. Three had a PCT ≥0.10 µg/L but <0.25 µg/L, and 6 had a PCT ≥0.25 µg/L but <0.5 µg/L. The AUC of PCT for the outcome of bacteremia was 0.83 (95%CI 0.76-0.88). The sensitivity, specificity, PPV and NPV, and LRs are presented in Table 3.4.

Table 3.2: Diagnostic accuracy PCT in predicting positive blood culture in total study population

Groups	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR- (95%CI)
PCT ≥ 0.10	95.7 (85.5-99.5)	38.9 (34.6-43.4)	12.9 (15.9-18.6)	99.0 (96.1-99.7)	1.57 (1.43-1.72)	0.11 (0.03-0.43)
PCT ≥ 0.25	89.4 (76.9-96.5)	65.7 (61.3-69.8)	25.7 (22.8-28.8)	97.90 (95.3-99.0)	2.61 (2.23-3.05)	0.16 (0.07-0.37)
PCT ≥ 0.50	76.6 (62.0-87.7)	77.6 (73.9-81.3)	24.5 (20.5-28.9)	97.2 (95.5-98.3)	3.44 (2.74-4.32)	0.30 (0.18-0.51)

All values are percentages, with the 95% confidence interval between brackets.
Abbreviations: CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.

Table 3.3: Diagnostic accuracy of PCT in predicting positive blood culture in study population with positive viral test (low pre-test probability)

Groups	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR- (95%CI)
PCT ≥ 0.10	100 (63.1-100)	34.0 (27.5-41.0)	5.65 (5.14-6.20)	100	1.51 (1.37-1.67)	0.00
PCT ≥ 0.25	100 (63.1-100)	68.0 (61.1-74.4)	11.0 (9.17-13.1)	100	3.12 (2.56-3.82)	0.00
PCT ≥ 0.50	100 (63.1-100)	81.2 (75.1-86.3)	17.4 (13.7-21.9)	100	5.21 (3.93-6.90)	0.00

Abbreviations: CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.

Table 3.4: Diagnostic accuracy of PCT in predicting positive blood culture in study population with negative viral test (high pre-test probability)

Groups	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR- (95%CI)
PCT ≥ 0.10	94.9 (82.7-99.4)	42.0 (36.4-48.0)	17.8 (16.1-19.6)	98.4 (94.1-99.6)	1.64 (1.45-1.85)	0.12 (0.03-0.47)
PCT ≥ 0.25	87.2 (72.6-95.7)	64.1 (58.3-69.6)	24.3 (21.0-28.3)	97.4 (94.3-98.9)	2.43 (2.00-2.96)	0.20 (0.09-0.45)
PCT ≥ 0.50	71.8 (55.1-85.0)	75.6 (70.3-80.4)	28.0 (22.7-34.0)	95.3 (92.4-97.1)	2.94 (2.22-3.90)	0.37 (0.23-0.62)

Abbreviations: CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.

False negatives

Eleven patients had a PCT <0.5 µg/L, but a true positive blood culture. None had a proven viral infection. The patient characteristics are summarized in e-Table 3.3. None of these patients died within 30 days of this episode. Five patients had bacteremia and a PCT <0.25 µg/L. The time between onset of complaints and the first laboratory measurement of PCT (Δ time) was less than 24 hours in all these patients.

Use of antibiotics

In total 288 of the 543 patients (53.0%) received antibiotics at the ED, including 37 patients with a positive blood culture. In patients with a confirmed viral infection, 107 of the 210 (50.9%) patients were treated with empirical antibiotics at the ED. Of these 107 patients, 74 (69.1%) had a PCT <0.5 µg/L. Of the patients without a viral infection (n=333), 180 (54.0%) patients were treated with empirical antibiotics in the ED. Of these patients, 71 (39.4%) had a PCT <0.25 µg/L. The most frequent administered antibiotic class were intravenous Cephalosporines (n=154, 51.8%). The median duration of a course of antibiotics was 6 [IQR 5-7] days.

Limitations

An important limitation is that this study focuses on bacteremia. Blood cultures are the gold standard for detecting for detecting bacteremia. However, a negative blood culture is no guarantee that there is no bacterial infection that has not reached the bloodstream (yet). Patients with pneumonia notoriously have low rates of bacteremia.[33] In addition, patients previously treated with antibiotics before presentation at the ED might have lower yield of blood cultures.[34] These might be explanations for why our study has a very low rate of bacterial (co)infection. Although the rate was comparable to what is found in COVID-19 literature it is less than what is found in influenza patients. The latter might be due to the fact that bacterial (co)infection in influenza literature has been defined in variable ways, which contributes to the large variation of (co)infection rates. In addition, most of the studies on influenza (co)infection have been performed in the ICU.[7] ICU and ED populations are not necessarily comparable. Therefore, it is important that the results of our study are confirmed in a larger sample of patients, with particular attention for the incidence of bacteremia in patients with influenza.

Another limitation is that our study was performed in a single tertiary center in the Netherlands. First, because of a strong primary care system, almost all patients in the Netherlands are seen first by a general practitioner, who does not refer uncomplicated cases of (viral) infection. Because of this selection, patients presenting to our ED probably represent a subgroup of patients with more severe illness. This is reflected in the high

number of admissions in our cohort (68%). Second, the population of our tertiary ED has a higher proportion of patients with malignancies and immunosuppressive treatments. This might influence the probability of bacteremia and limit generalizability.

Although all patients underwent influenza A/B/RSV testing (and SARS-CoV-2 testing when it became available in 2020), we did not limit our analysis to patients with influenza, RSV, and SARS-CoV-2. We pooled all viral infections that were found, because we expected any viral explanation for infectious complaints would make the chance of also having bacteremia smaller. The sensitivity analysis, excluding the SARS-CoV-2 patients, did not meaningfully change our results.

Discussion

Our study found that PCT performed better in patients with a viral infection, with a higher cutoff than in patients without viral infection. Previous publications have already advocated to vary the cutoff of PCT based on the likelihood of (severe) bacterial infection. Our insight in the low rate of bacteremia in patients with a confirmed viral infection can help us estimate this likelihood. In our study, PCT was ≥0.5 μg/L in all patients with a viral infection and bacteremia.

Until 2020, not many studies specifically reported the performance of PCT in the context of proven viral infection. A large observational study on influenza patients in the ICU found that low serum levels of PCT were an accurate predictor for excluding community acquired (co)infection during H1N1.[23] The authors reported that PCT is a promising tool, although its sensitivity at the cutoff of <0.50 ng/mL was only 78%. However, because this study was conducted in ICU patients it represented a much sicker population than our target population.

In the context of COVID-19, several studies have reported on PCT values and their relation to bacterial (co)infection. In most patients PCT was only mildly elevated, and higher levels were usually associated with bacterial (co)infections.[35,36] A meta-analysis of PCT in COVID-19 also noted this, but stressed the need for better data.[37] A few small studies have found favorable results on the use of PCT for antibiotic stewardship in COVID-19.[38–40] Our study seems to corroborate the findings in the aforementioned literature.

What this study adds to the current knowledge of PCT is that the results of (rapid) viral testing in the ED can be used to estimate the likelihood of bacteremia. If a viral infection is confirmed and the patient has PCT <0.5 μg/L, the chances of bacteremia might be very small. If we know that the patient has a very low chance of bacteremia, we might be able

to make better decisions on antibiotic use. In fact, if we had used PCT as guidance for antimicrobial therapy, antibiotic use could have been decreased from 50.9% to 21.9% in the patients with a viral infection. However, in the group without viral infection, a cutoff of <0.25 µg/L would have resulted in a much smaller reduction of 54% to 42%. In this group we would have missed 5 patients with positive blood cultures, all of whom had symptoms of less than 24 hours duration. This is a known pitfall of PCT. Earlier studies have shown that it can take 8-24 hours before PCT reaches high values.[24,25] Therefore, when patients present very soon after the onset of symptoms, PCT should be used with caution. In these cases, the PCT measurements should be repeated to ensure it is representative, in line with previous recommendations.[26]

Conclusion

Our results indicate that PCT is a promising tool to rule out bacteremia in patients with a viral infection. This finding needs to be confirmed in a larger population of patients with viral infections, especially because the rate of (co)infection in our cohort was low. In patients without a viral infection, PCT needs to be interpreted with caution, especially in patients with a short duration of symptoms.

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4

Predicting poor outcome in patients with suspected COVID-19 presenting to the Emergency Department (COVERED)
Development, internal and external validation of a prediction model

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Abstract

Background: A recent systematic review recommends against the use of any of the current COVID-19 prediction models in clinical practice. To enable clinicians to appropriately profile and treat suspected COVID-19 patients at the emergency department (ED), externally validated models that predict poor outcome are desperately needed. Our aims were to identify predictors of poor outcome, defined as mortality or intensive care unit (ICU) admission within 30 days, in patients presenting to the ED with a clinical suspicion of COVID-19, and to develop and externally validate a prediction model for poor outcome.

Methods: In this prospective, multicenter study, we enrolled suspected COVID-19 patients presenting at the EDs of two hospitals in the Netherlands. We used backward logistic regression to develop a prediction model. We used the area under the curve (AUC), Brier score and pseudo-R^2 to assess model performance. The model was externally validated in an Italian cohort.

Results: We included 1193 patients between March 12 and May 27, 2020, of whom 196 (16.4%) had a poor outcome. We identified 10 predictors of poor outcome: current malignancy (OR 2.774; 95%CI 1.682-4.576), systolic blood pressure (OR 0.981; 95%CI 0.964-0.998), heart rate (OR 1.001; 95%CI 0.97-1.028), respiratory rate (OR 1.078; 95%CI 1.046-1.111), oxygen saturation (OR 0.899; 95%CI 0.850-0.952), body temperature (OR 0.505; 95%CI 0.359-0.710), serum urea (OR 1.404; 95%CI 1.198-1.645), C-reactive protein (OR 1.013; 95%CI 1.001-1.024), lactate dehydrogenase (OR 1.007; 95%CI 1.002-1.013) and SARS-CoV-2 polymerase chain reaction result (OR 2.456; 95%CI 1.526-3.953).
The AUC was 0.86 (95%CI 0.83-0.89), with a Brier score of 0.32 and, and R^2 of 0.41. The AUC in the external validation cohort of 500 Italian patients was 0.70 (95%CI 0.65-0.75).

Conclusion: The COVERED risk score showed excellent discriminatory ability, also after external validation. It may aid clinical decision making, and improve triage at the ED in health care environments with high patient throughputs.

Introduction

The COVID-19 pandemic continues to put unprecedented pressure on health care systems and societies worldwide. Although some countries have started vaccination programs, the pandemic shows no signs of subsiding. It may take until the end of 2021 before we potentially see the effects of wide-scale vaccination and of herd immunity through infection.[1–3] Methods to quickly establish the correct diagnosis and prognosis in suspected COVID-19 patients at the emergency department (ED) remain of paramount importance to alleviate the strain on limited health care resources.

With approximately 20% of patients requiring admission and up to a third of admitted patients requiring (often prolonged) intensive care unit (ICU) treatment, research has focused on elucidating factors that can predict clinical deterioration and mortality.[4–7] Prediction of outcome is relevant, as SARS-CoV-2 polymerase chain reaction (PCR) results are often not readily available at ED presentation.[8–10] In some settings it may still take up to 48 hours for PCR results to be available, while triage and risk stratification decisions are preferably made promptly at the frontline.[11]

The most frequently reported predictors of severe prognosis in patients with COVID-19 include age, sex, comorbidities, elevated D-dimer, C-reactive protein (CRP), lymphocyte count and lactate dehydrogenase (LDH) levels, and features derived from computed tomography (CT) scans.[12–21]
Although a myriad of prognostic prediction models has entered the medical literature, a recent systematic review recommended against the use of any of these models in clinical practice.[12] The previous models were poorly reported, overly optimistic, and had a high risk of bias. Moreover, these studies were often limited to hospitalized patients with a proven COVID-19 infection, also intensive care unit admission was not regarded as a poor outcome.[12,22,23]
Widely accepted risk scores like the APACHE, Sepsis-Related Organ Failure Assessment (SOFA) and the quick SOFA (qSOFA), CURB-65 and Pneumonia Severity Index (PSI) scores provide a rough estimate of mortality risk. Their specificity and sensitivity, however, are limited in COVID-19 populations.[21,24–26]

The aim of this study was to identify predictors of poor outcome, and develop and externally validate a multivariable prediction model for patients presenting to the ED with suspected COVID-19. Secondly, we aimed to create an easy-to-use risk scoring system (the COVERED risk score) for poor outcome in order to support clinical decision making.

Methods

Study design

In this observational, prospective, multicenter cohort study, we enrolled all patients aged 18 years and over, visiting the ED with suspicion of COVID-19 infection. COVID-19 suspicion was based on the World Health Organization (WHO) and the Dutch National Institute for Public Health and the Environment (RIVM) criteria.[27] COVID-19 suspicion was defined as the patient having either fever, malaise, myalgia and respiratory symptoms, gastrointestinal symptoms, loss of smell or taste or unexplained delirium in the elderly. We used an opt-out recruitment procedure to obtain consent for participation in the study. The Medical Ethics Review Committee of the Amsterdam University Medical Centers, location VUmc approved the study (reference number: 2020.249). Details on the Dutch derivation and the Italian validation cohorts are provided below. Results were reported in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[28]

Data collection

Derivation cohort: Amsterdam, The Netherlands

Data for the derivation cohort of the COVERED risk score were collected at the EDs of two academic hospitals in Amsterdam, The Netherlands, between March 12 and May 27, 2020. This was done prospectively by reviewing the electronic health records of patients eligible for inclusion. Only variables collected at the moment of ED presentation were analyzed as possible risk predictor for poor outcome, including medical history, history of the presenting symptoms, vital signs, laboratory and radiology data. We defined poor outcome as ICU admission or all-cause mortality within 30 days after first presentation. We monitored outcomes until early July 2020.

External validation cohort: Brescia, Italy

The population used for external validation of the COVERED risk score included all patients older than 18 years visiting the emergency department of the Fondazione Poliambulanza Hospital in Lombardy, Italy with suspected COVID-19 infection between February and April, 2020. For this cohort, suspicion of COVID-19 was based on the WHO criteria as well. All patient data were collected from a prospectively fed electronic patient file system.

Statistical analysis

Normally distributed continuous variables are shown as mean with standard deviation (SD), whilst non-normally distributed continuous variables were shown as medians with

the interquartile range [IQR]. Continuous variables were compared using the independent samples t-test or Mann-Whitney U test, while the χ^2 or Fisher's exact tests were used to analyse categorical data, as appropriate. We defined statistical significance as a *p* value <0.05.

We selected variables potentially related to poor outcome based on existing evidence and expert opinion. These included demographic data, common clinical and laboratory tests, and parameters identified as relevant, following the process advocated by Wynants et al.[12] To avoid overfitting of the final model, we applied a minimum of 10-events-per-variable with the maximum number of predictors in multivariable analysis being set at one predictor per ten outcome cases. Variables missing in more than 30 percent of patients were not considered for inclusion in the multivariable model.

Linearity of the relation was assessed by using restricted cubic spline functions and plots and variables showing a non-linear relation with the outcome were included in the multivariable model using the restricted cubic spline format. We assessed multicollinearity through visual inspection of correlation matrices and Pearson's correlation coefficients. We used multiple imputations by chained equations with predictive mean matching to account for any missing data and generated m=50 imputed datasets because the average amount of missing data in the multivariable model was around 50%.[29]

We identified independent predictors of poor outcome using multivariable logistic regression with backward elimination based on the Wald statistic, with a threshold *p* value of 0.157.[28] We described variables included in the final model as odds ratio (OR) with their corresponding 95% confidence intervals (95%CI), and *p* value. We assessed the model's performance using the following metrics: The scaled Brier score was used to assess calibration and predictive accuracy. We used Nagelkerke pseudo-R^2 to quantify the explained variance in poor outcome by our model.

Finally, we employed the area under the curve (AUC) of the receiver operating characteristic (ROC) to assess the discrimination ability of our model, with ≤0.5 AUC <0.6 indicating no discriminatory performance; ≤0.6 AUC < 0.7 indicating poor discriminatory performance; ≤0.7 AUC <0.8 indicating good discriminatory performance; ≤0.8 AUC <0.9 indicating excellent discriminatory performance; and ≤0.9 AUC <1.0 indicating outstanding discriminatory performance.[30] We performed internal validation using 5-fold cross validation. We performed external validation on the Italian cohort, on the basis of a complete case analysis.

Details of statistical analysis, including internal and external validation, are shown in the e-Appendix. We conducted data analysis using SPSS software (IBM Corp., Armonk, N.Y.,

Table 4.1: Clinical characteristics of the enrolled patients with suspected COVID-19 (development cohort)

Characteristics	Missing values, %	Overall (N=1193)	Favourable outcome (N=997, 83.6%)	Poor outcome (N=196, 16.4%)	*p* value
Age, years	0	62 [48-74]	61 [46-73]	67 [58-75]	**<0.001**
Sex, n (%)					
Male	0	653 (54.7)	524 (52.6)	129 (65.8)	**0.001**
Female		540 (45.3)	473 (47.4)	67 (34.2)	
Presenting symptoms, n (%)					
Fever	0	511 (42.8)	436 (43.7)	75 (38.3)	0.157
Cough	0	637 (53.4)	548 (55.0)	89 (45.4)	**0.014**
Odynophagia	0	98 (8.2)	89 (8.9)	9 (4.6)	**0.043**
Rhinorrhea	0	77 (6.5)	72 (7.2)	5 (2.6)	**0.015**
Chest pain	0	211 (17.7)	195 (19.6)	16 (8.2)	**<0.001**
Myalgia	0	147 (12.3)	136 (13.6)	11 (5.6)	**0.002**
Joint pain	0	21 (1.8)	17 (1.7)	4 (2.0)	0.765
Fatigue	0	172 (14.4)	146 (14.6)	26 (13.3)	0.615
Dyspnea	0	637 (53.4)	505 (50.7)	132 (67.3)	**<0.001**
Headache	0	174 (14.6)	162 (16.2)	12 (6.1)	**<0.001**
Confusion	0	61 (5.1)	47 (4.7)	14 (7.1)	0.158
GI-symptoms	0	377 (31.6)	323 (32.4)	54 (27.6)	0.182
Comorbidities, n (%)					
Cardiovascular disease	0	275 (23.1)	226 (22.7)	49 (25.0)	0.479
Hypertension	0	414 (34.7)	331 (33.2)	83 (42.3)	**0.014**
Diabetes	0	255 (21.4)	205 (20.6)	50 (25.5)	0.122
Asthma	0	97 (8.1)	85 (8.5)	12 (6.1)	0.260
Malignancy	0	172 (14.4)	126 (12.6)	46 (23.5)	**<0.001**
Pulmonary disease	0	188 (15.8)	159 (15.9)	29 (14.8)	0.457
Obesity	38.8	287 (24.1)	225 (39.0)	62 (40.5)	0.780
History of smoking, n (%)					
No	22.8	451 (37.8)	386 (49.6)	65 (45.5)	0.363
Current		138 (11.6)	119 (15.3)	19 (13.3)	
Former		332 (27.8)	273 (35.1)	59 (41.3)	

Table 4.1: ***Continued***

Characteristics	Missing values, %	Overall (N=1193)	Favourable outcome (N=997, 83.6%)	Poor outcome (N=196, 16.4%)	*p* value
Vital parameters					
Systolic blood pressure, mmHg	3.6	132 [119-149]	133 [120-148]	131 [111-150]	0.107
Diastolic blood pressure, mmHg	3.9	80 [70-90]	80 [70-90]	79 [67-89]	0.059
Temperature, °C	9.3	36.8 [36.1-37.7]	36.7 [36.2-37.6]	37.0 [36.0-38.0]	0.325
Heart rate, beats/min.	2.0	90 [78-105]	89 [78-102]	99.29 (±24.54)	**<0.001**
Respiratory rate, breaths/min.	13.8	20 [16-25]	20 [16-24]	25 [20-31]	**<0.001**
Oxygen saturation level, %	2.8	97 [94-98]	97 [95-98]	95 [90-97]	**<0.001**
Oxygen therapy, n (%)	2.1	317 (26.6)	203 (20.7)	114 (60.3)	**<0.001**
MEWS	6.5				**<0.001**
<4, n (%)		833 (69.8)	753 (79.9)	80 (46.2)	
≥4, n (%)		282 (23.6)	189 (20.1)	93 (53.8)	
Consciousness (AVPU), n (%)					
A	3.3	1108 (92.9)	954 (97.9)	154 (85.6)	N/A
V		22 (1.8)	16 (1.6)	6 (3.3)	
P		10 (0.8)	3 (0.3)	7 (3.9)	
U		14 (1.2)	1 (0.1)	13 (7.2)	

Table 4.1 continues on next page.

Table 4.1: ***Continued***

Characteristics	Missing values, %	Overall (N=1193)	Favourable outcome (N=997, 83.6%)	Poor outcome (N=196, 16.4%)	*p* value
Laboratory findings					
White blood cell count	2.9	8.1 [5.8-11.3]	8.0 [5.8-11]	9.2 [5.9-14.0]	**0.004**
Lymphocyte count	16.6	1.12 [0.72-1.75]	1.17 [0.78-1.83]	0.80 [0.50-1.26]	**<0.001**
Platelet count	5.4	235 [178-303]	236 [179-306]	222 [169-284]	0.076
Urea	13.0	5.6 [4.0-8.5]	5.3 [3.9-7.6]	8.9 [5.6-13.6]	**<0.001**
Creatinine	4.4	80 [64-108]	77 [63-101]	95 [72-137]	**<0.001**
C-reactive protein	3.1	31.15 [5.73-90.23]	25 [4.3-77]	86 [30-164]	**<0.001**
Procalcitonin	59.3	0.09 [0.05-0.28]	0.08 [0.04-0.17]	0.29 [0.14-0.78]	**<0.001**
Alanine aminotransferase	12.2	26 [18-42]	25 [17-40]	35 [21-54]	**<0.001**
Aspartate aminotransferase	35.7	30 [22-50.5]	29 [21-46]	47 [28-75]	**<0.001**
Total bilirubin	13.3	8 [5-13]	8 [5-12]	9 [6-14]	0.087
Lactate dehydrogenase	28.7	248 [198-334]	233 [190-311]	334 [244-463]	**<0.001**
D-dimer	72.2	0.86 [0.39-1.87]	0.79 [0.37-1.59]	1.1 [0.65-3.27]	**0.003**
NT-pro-BNP	62.1	266 [78-1443]	221 [64-1108]	656 [159-2439]	**<0.001**
Troponin T	64.0	0.014 [0.006-0.030]	0.012 [0.005-0.022]	0.032 [0.013-0.065]	**<0.001**
Glucose	12.6	6.7 [5.7-8.5]	6.5 [5.6-8.2]	7.8 [6.3-10.9]	**<0.001**
Ferritin	98.4	518 [19-426]	427 [18-330]	1000 [236-N/A]	0.085
PCR Sars-COV-2, n (%)					
Positive	0	339 (28.4)	253 (25.4)	86 (43.9)	**<0.001**
Negative / not interpretable		854 (71.6)	744 (74.6)	110 (56.1)	
Radiological findings					
CT severity score	41.6	10 [6-13]	9 [5-12]	14±5	**<0.001**
Outcome, n (%)					
ICU admission	0	111 (9.3)	N/A	111 (56.6)	N/A
In hospital mortality	0	85 (7.1)	N/A	85 (43.3)	N/A
30-day mortality	0	113 (9.5)	N/A	113 (57.7)	N/A

Data is presented as percentages, median [IQR], mean ± SD or number (%). *P* values were calculated by independent samples t-test, Mann-Whitney U test, Pearson's χ^2 test or Fisher's exact test, as appropriate.

Abbreviations: min., minute; IQR, interquartile range; SD, standard deviation; ICU, intensive care unit; MEWS, Modified Early Warning Score; AVPU, Alert, Verbal, Pain, Unresponsive; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PCR, polymerase chain reaction; CT, computed tomography; N/A, not applicable

U.S.A.) version 26.0 and R (packages mice, rms and psfmi). We provided the final model equation in a Microsoft Excel (Microsoft Corp., Redmond, W.A., U.S.A.) file to enable easy usage of our model, while ensuring minimal loss of information. By filling in all the relevant variables in the Excel file, provided in e-Link 4.1, the probability of poor outcome can be quickly calculated.

Results

Study population

Derivation cohort

We collected data for 1193 patients who visited the ED with a suspected COVID-19 infection, between 12 March and 27 May, 2020 (Figure 4.1). Clinical characteristics and patient demographics are shown in Table 4.1.

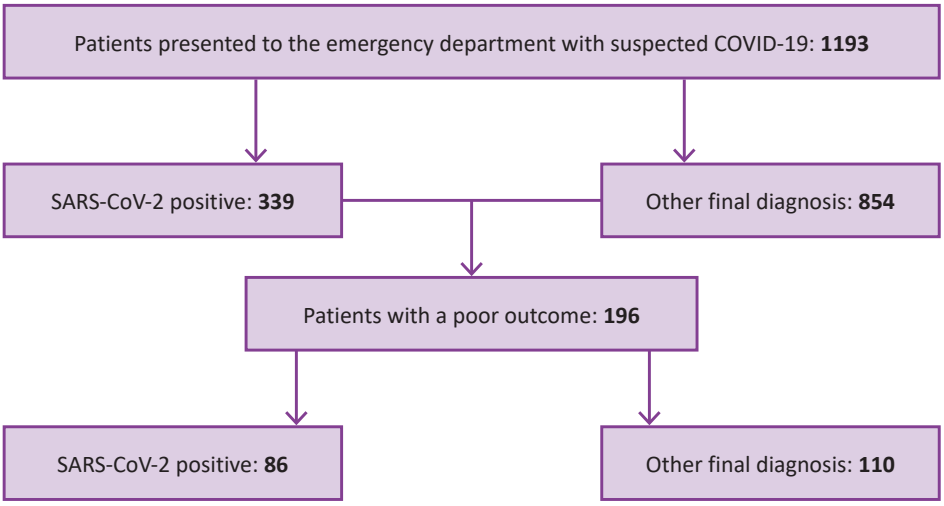


Figure 4.1: Flowchart of patient inclusion and exclusion.

The majority of patients was male (54.7%). Hypertension (34.7%) was the most common comorbidity, followed by cardiovascular disease (23.1%) and diabetes (21.4%). In total, 196 (16.4%) patients had a poor outcome. The poor outcome group consisted of older and more male patients. Hypertension and malignancy were more common in the poor outcome group and these patients were more likely to present with dyspnea, as well as a higher heart rate, higher respiratory rate and lower oxygen saturation. In addition, patients with poor outcome had significantly lower lymphocytes, higher white blood cell

count, serum creatinine, urea, CRP, procalcitonin, transaminases, LDH, glucose, cardiac enzymes, and a higher CT severity score. Patients with a poor outcome were also more likely to have a positive SARS-CoV-2 PCR. e-Table 4.1 summarizes the final diagnoses of the total group and the poor outcome group.

External validation cohort

The characteristics of the Italian validation cohort of 500 patients were different from the derivation cohort in various ways (Table 4.1 & e-Table 4.2). There were more men in the validation cohort than in the derivation cohort. The patients in the validation cohort were less likely to have a malignancy or chronic respiratory disease, but were more likely to have hypertension than patients in the derivation cohort. Patients in the validation cohort had higher LDH levels and were more likely to have a positive SARS-CoV-2 PCR than patients in the derivation cohort.

Model development

As advocated by Wynants et al., we selected potential predictors of poor outcome based on existing evidence and expert opinion.[12] Additionally, we only included readily available parameters to ensure easy applicability of the final COVERED risk score at the ED. Furthermore, we removed items with uncertain clinical credibility based on recent literature and counterintuitive results.[31] We excluded predictors with more than 30% of missing data from further analysis. Moreover, we included vital parameters separately instead of the whole Modified Early Warning Score (MEWS) to reduce loss of information.

Table 4.2: Final multivariable logistic regression model with independent predictors of poor outcome

Variable	Coefficient (SE)	OR (95%CI)	*p* value
Comorbidities			
Malignancy	1.020 (0.255)	2.774 (1.682-4.576)	**<0.001**
Vital parameters			
Systolic blood pressure, mmHg	-0.019 (0.009)	0.981 (0.964-0.998)	**0.029**
Heart rate, beats/min.	0.001 (0.014)	1.001 (0.974-1.028)	0.968
Respiratory rate, breaths/min.	0.075 (0.015)	1.078 (1.046-1.111)	**<0.001**
Oxygen saturation level, %	-0.106 (0.029)	0.899 (0.850-0.952)	**<0.001**
Temperature, °C	-0.683 (0.174)	0.505 (0.359-0.710)	**<0.001**
Laboratory findings			
Urea, mmol/L	0.338 (0.081)	1.404 (1.198-1.645)	**<0.001**
C-reactive protein, mg/L	0.013 (0.006)	1.013 (1.001-1.024)	**0.028**
Lactate dehydrogenase, U/L	0.007 (0.003)	1.007 (1.002-1.013)	**0.010**
SARS-CoV-2 PCR positive	0.898 (0.243)	2.456 (1.526-3.953)	**<0.001**
Intercept	28.450		

Multivariable logistic regression was performed using the backward elimination method.
Missing values were handled by multiple imputation.
Abbreviations: SE, standard error; PCR, polymerase chain reaction; min., minute; OR, odds ratio; CI, confidence interval; AVPU, Alert, Verbal, Pain, Unresponsive.

For comorbidities, we assumed that absence of recorded information implied absence of the item. Ultimately, 16 candidate variables remained and were analyzed as potential predictors for poor outcome (e-Table 4.3).

Backward logistic regression yielded a model with 10 predictors: malignancy, systolic blood pressure, respiratory rate, heart rate, oxygen saturation level, body temperature, urea, CRP, LDH and a PCR confirmed diagnosis of COVID-19 as predictors of poor outcome. Table 4.2 shows the coefficients and adjusted ORs for these variables.

Model evaluation

In the derivation cohort, the final prediction model had an AUC of 0.86 (95%CI 0.83-0.89), a scaled Brier score of 0.32 and a Nagelkerke's pseudo-R^2 of 0.41. We used 5-fold cross-validation to internally validate our model, the results of which are shown in Table 4.3 and Figure 4.2. After internal validation in the derivation cohort our model showed an AUC of 0.81 (95%CI 0.77-0.84), with a scaled Brier score of 0.21 and a Nagelkerke's pseudo-R^2 of 0.31.

Table 4.3: Internal validation by 5-fold cross validation

	Training set	Test set
AUC (discrimination)	0.859	0.809
Brier Score (calibration)	0.326	0.207
Pseudo-R^2 (explained variance)	0.412	0.308

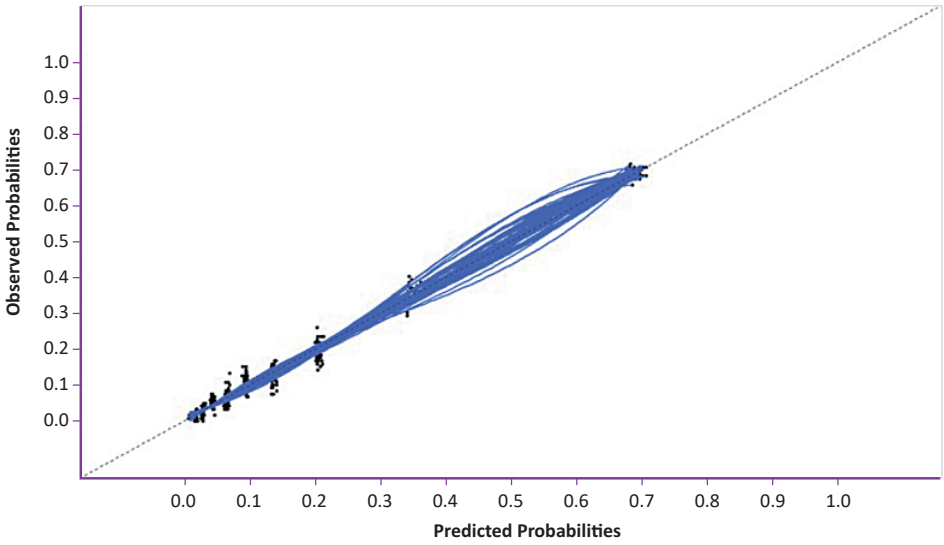


Figure 4.2: Calibration curve of the derivation cohort.

In the external validation cohort, the discriminatory power decreased slightly to an AUC of 0.70 (95%CI 0.65-0.75), with a Nagelkerke's pseudo-R^2 of 0.15 (Figure 4.3). The sensitivity and specificity for different cutoff points of the predicted risk are shown in Table 4.4.

The calibration curve in the external validation cohort showed that when the predicted risk was <50%, it coincided nicely with the observed risk. Whereas, predicted risks >50% tended to slightly overestimate observed risk. Nevertheless, 80% of the population had a predicted (and observed) risk <50% (Figure 4.3).

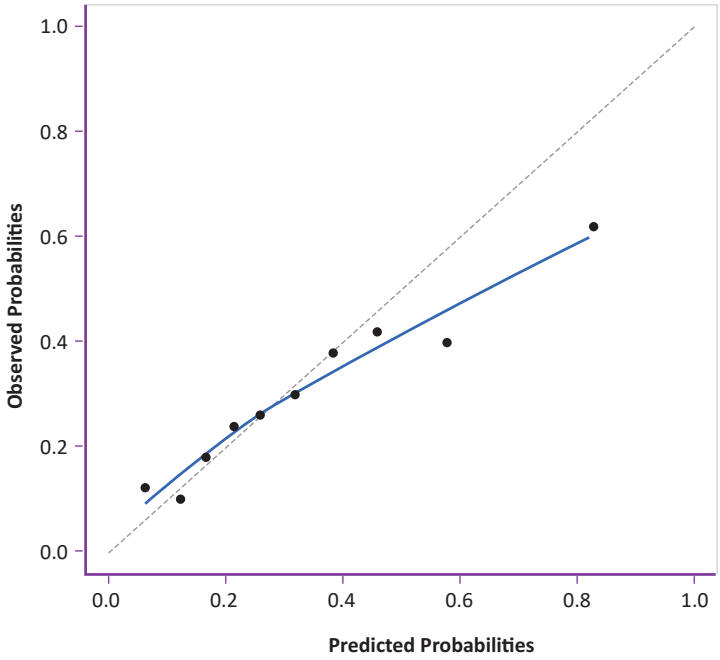


Figure 4.3: Calibration curve of the external validation cohort.

Table 4.4: Sensitivity analysis for different cutoff values of predicted risk of poor outcome

Predicted risk (%)	Sensitivity	Specificity
≥ 10	0.934	0.554
≥ 20	0.735	0.811
≥ 30	0.592	0.918
≥ 40	0.444	0.960
≥ 50	0.342	0.979
≥ 60	0.224	0.992
≥ 70	0.163	0.997
≥ 80	0.097	0.998
≥ 90	0.061	0.999

Discussion

To the best of our knowledge, this is the first study to develop and externally validate a risk scoring system which can be used at the ED to predict risk of poor outcome in patients presenting with suspected COVID-19. The final COVERED risk score model showed excellent discriminatory capacity in the derivation cohort with an AUC of 0.81. Although our model has been created to enhance clinical decision making at EDs in the Netherlands, it also shows potential for use in other countries with comparable health care resources. The discriminatory performance in the external validation cohort from Italy was still acceptable with an AUC of 0.70.

Evaluation of the COVERED risk score

The main strength of the COVERED risk score is that it is designed to be employed at the ED in suspected COVID-19 patients. This is relevant because SARS-CoV-2 PCR is often not readily available at EDs around the world, and triage decision will have to be made without a definite diagnosis of COVID-19.[8,11] The COVERED risk score gives the health care provider an extra tool to make the right triage and treatment decisions swiftly.

Most previous models were based on either population or admission data, had overoptimistically reported performance, a high risk of bias, and were developed in selected cohorts without external validation.[12,14–16,31,32] In contrast with most previous risk models, our risk score was developed in a multicenter setting with a large heterogenous sample size (n=1193) compared with previous models (sample sizes ranging from 26 to 577).[12] In addition, we also validated the COVERED risk score externally in an independent international cohort of 500 patients.

We did not categorize continuous variables, because this causes significant data loss, nor did we pool risk into prognostic risk groups (e.g., low, medium or high) because it introduces major problems in the analysis and interpretation of models such as ours.[33,34] Moreover, we feel that health care providers are better equipped with a risk score of poor outcome for the individual patient, and incorporating it with their clinical judgement and local and patient-specific conditions.

The reduction in AUC in the external validation cohort is mainly caused by differences in patient characteristics between the development and validation datasets, and thus of variables included in the final prediction model.[35] For example the amount of patients with malignancy was much higher in the derivation cohort than in the validation cohort. Conversely, PCR positives were much higher in the validation cohort. The difference in incidence of these strong predictors, may have caused a shift in predicted probabilities,

as well as an incorrect assignment of patients in risk categories at different outcome probability cutoff values on the ROC, resulting in a lower AUC value.

Calibration in the validation cohort was excellent in predicted risk up to 50%, which was seen in 80% of patients. In practice it is unlikely that the cutoff point upon which clinicians would change their management would be higher than 50%. Particularly because this would result in sensitivities below 35% in our case (Table 4.4). As such we argue that a minor reduction in calibration above this point is acceptable.

Comparison with other models

The predictors identified in our model are in line with the variables found in recently reported risk scores in proven COVID-19.[12,14,31] While the COVERED risk score has a few overlapping predictors with other risk scores, the differences can be accredited to differences in patient cohorts, health care systems, hospital environments, and life style habits. In addition, a wide variety of outcome measures (e.g., hospital admission, admission duration, mortality, ICU admission, and disease severity), and statistical methods were employed, among other factors. We want to stress that the COVERED risk score – like any other risk score – should be employed in conjunction with the clinical judgment of the health care provider.

Interestingly, neither male sex nor age were strong predictors in our cohort, although this has been the case in previous literature concerning COVID-19.[5,7,21] Comorbidities associated with age, such as malignancies or cardiovascular disease, rather than age itself, may contribute to prognosis severity.[21] Cardiovascular disease for instance was not included in a recent prognostic model, in which age was one of the main predictors.[31] However, our model did not find frequently identified comorbidities like hypertension, diabetes, chronic cardiovascular disease or chronic respiratory disease to be associated with poor outcome. The absence of chronic respiratory disease is in line with previous studies.[13,36] Current malignancy was the only comorbidity that was found to be associated with poor outcome. This association was found previously as well, and might be related to the fact that the included hospitals function as tertiary referral oncology centers.[17,32]

The association of vital sign abnormalities, inflammatory markers (e.g., CRP), kidney function markers (e.g., serum urea or creatinine), and cell injury markers (e.g., LDH) are in accordance with previously published literature on COVID-19 and other respiratory infections.[13,21] In addition, a recent study in patients who were being evaluated for COVID-19 found that PCR positivity was also associated with poor outcome.[21,37]

Missing values

Some variables could not be used due to a high number of missing cases. D-dimer levels for instance were not included in our model. However, emerging literature shows that SARS-CoV-2 can cause a hypercoagulable state which may lead to the intrapulmonary clot formation and microthrombi in the body. Furthermore, we did not include imaging studies in our model, although the presence of abnormalities on CT and lung ultrasound has been associated with poor prognosis.[38–40] However, as CT is not always used in the work up of suspected COVID-19 patients, we decided not to include CT abnormalities in our model, to make our score applicable to most settings.

Limitations/bias

Our study has some limitations. First, there is residual selection bias. We do believe that selection bias was minimized, due to incorporation of a large consecutive sample in two hospitals. Second, there could be misclassification of outcome. We feel that the risk of misclassification of the outcome was negligible due to a direct link between municipality, general practitioner and hospital mortality data. Third, the choice of common predictor variables was limited by data availability. However, the use of common parameters, which are readily available at ED presentation, greatly increases applicability and generalizability. In addition, complete case analysis would have led to exclusion of a significant proportion of our cohort, leading to inaccuracy and loss of power. Fourth, we only externally validated our study in one other cohort. Additional validation studies of the COVERED risk score could be performed in other settings. Variables in our model might require replacement with locally available equivalent measures, or recalibration might be needed to fit the local situation.[31] Fifth, we realize the criteria for ICU admission in the Netherlands might differ from criteria used in other countries. In the first wave, ICU admission criteria were quite stringent in the Netherlands. ICU admission – and even mortality – depends on the capacity of hospitals and ICUs to admit patients. Although the capacity to admit patients was different in our international external validation cohort, the discriminatory performance was still good (AUC of 0.70). We reiterate that the COVERED risk score will most likely need to be recalibrated with local data.

Conclusion

The COVERED risk score is an externally validated risk score which can offer health care providers at the ED a simple additional tool to quickly identify suspected COVID-19 patients with a potential poor outcome. It might give health care providers the means to triage patients more swiftly and to allocate scarce resources more effectively in health care environments with high patient throughput in an epidemic setting.

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PART 2

Point-of-care ultrasound in COVID-19 patients in the acute care setting





5

Lung ultrasound

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AWE Lieveld, A Walden

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Five key learning points

1. Bedside lung ultrasound has similar diagnostic properties as computed tomography in the diagnosis of acute respiratory failure
2. A scan can be performed in under 5 minutes, reducing time to diagnosis and treatment
3. It can be useful in monitoring lung aeration and guiding weaning of mechanical ventilation
4. It can help in assessing and draining pleural effusions
5. It can differentiate between pneumonia, acute respiratory syndrome and cardiac pulmonary oedema

Introduction

For many years it was felt that ultrasound was of no value in imaging the lung due to the low acoustic impedance of air. However, imaging of the pleura and the patterns of common artefacts found in lung ultrasound (LUS): A-lines (Figure 5.1 & e-Video 5.1) and B-lines (Figure 5.2-5.4 & e-Video 5.2-5.4), can be correlated with particular lung diseases. LUS diagnostic accuracy is better than physical examination and conventional radiograph (CXR), and comparable to chest computed tomography (CT) in diagnosing acute respiratory pathologies, ranging from heart failure to acute respiratory distress syndrome (ARDS).[1–5] Furthermore, it has a steep learning curve for physicians and other (para)medical personnel.[6–8] This chapter is an introduction on the role of ultrasound in imaging the lung.

Diagnosis of acute respiratory failure

In patients presenting with acute respiratory failure, LUS has a high diagnostic accuracy. Bedside LUS is a rapid, reproducible, dichotomous decision-making tool to come to a clear and reliable diagnosis. The most commonly used protocol is the Bedside Lung Ultrasound in Emergency (BLUE).[9] It uses an algorithmic approach, that employs three scan points per hemithorax, that can differentiate between causes of acute respiratory failure in under 5 minutes (e-Figure 5.1 & 5.2): The upper BLUE point is the yellow triangle, the lower BLUE point is the yellow square and the postero-lateral alveolar pleural syndrome (PLAPS) point is the yellow star.

The upper and lower BLUE points are identified and scanned looking for evidence of pleural sliding (e-Video 5.1). This is the lateral sideways movement of the pleura which is easily visualized. If it is absent (e-Video 5.5), we need to scan the entire hemithorax to see if there is still a point where the visceral and parietal pleura meet and lung sliding can be observed. This is the 'lung point' (e-Video 5.6) and its pathognomonic for pneumothorax. Once pleural sliding or 'lung pulse' (e-Video 5.7) has been confirmed and a pneumothorax has been excluded, the presence of A-lines and B-lines is determined. In the presence of bilateral A-lines, a two-point compression ultrasound (CUS) of the deep venous system of the lower limbs is performed to rule out venous thromboembolic disease and if this is negative, a scan of the postero-lateral alveolar pleural syndrome (PLAPS) point is made.

In the original study, the diagnostic accuracy was found to be over 90% for common causes of acute respiratory failure such as pneumonia, pulmonary embolism, chronic obstructive pulmonary disease and pneumothorax, even without considering history, clinical examination or lab results.[10] Other studies have shown it is reproducible in the

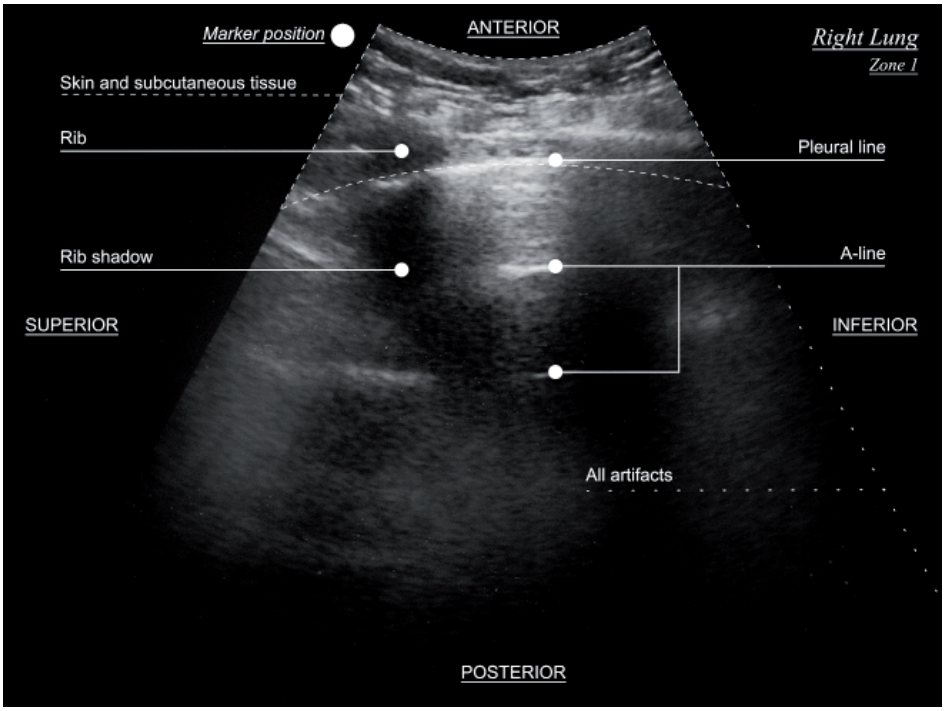


Figure 5.1: Normal lung.

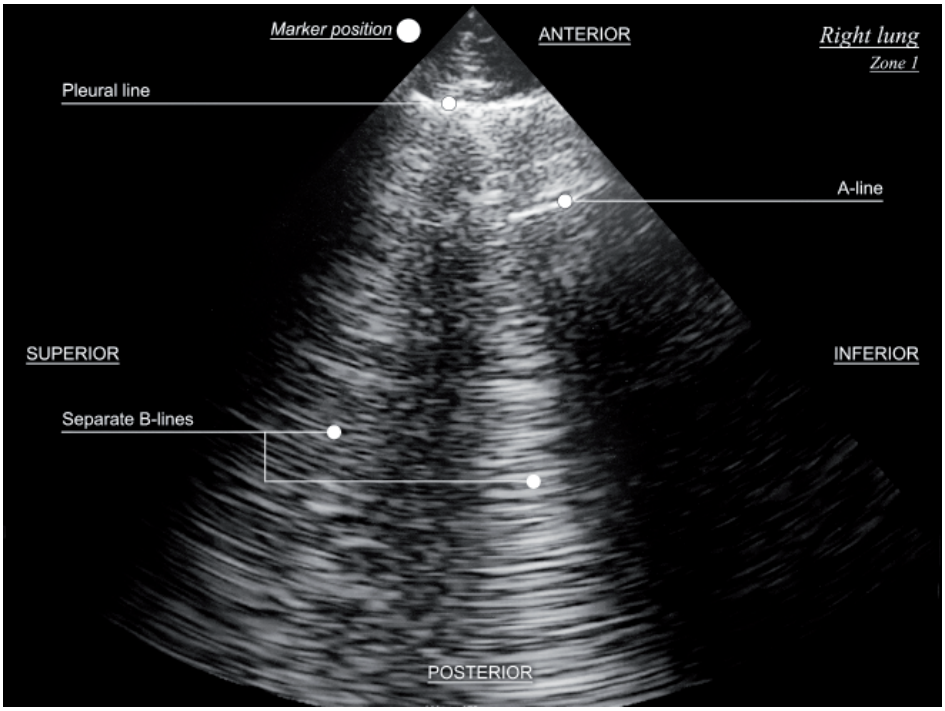


Figure 5.2: Discrete regularly spaced B-lines.

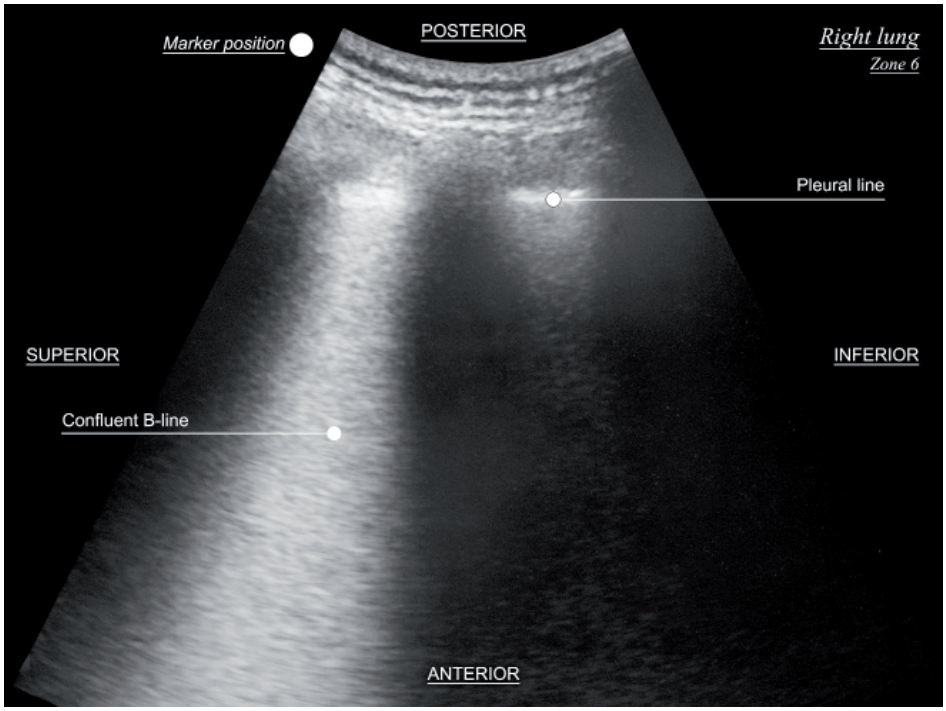


Figure 5.3: Confluent B-lines.

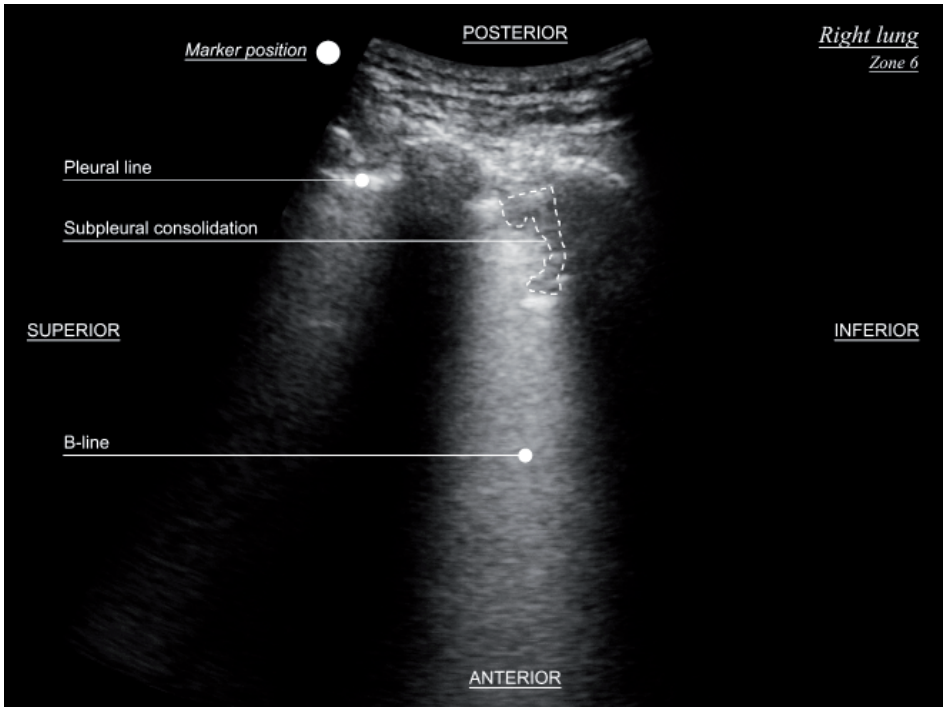


Figure 5.4: Subpleural consolidation with shred sign.

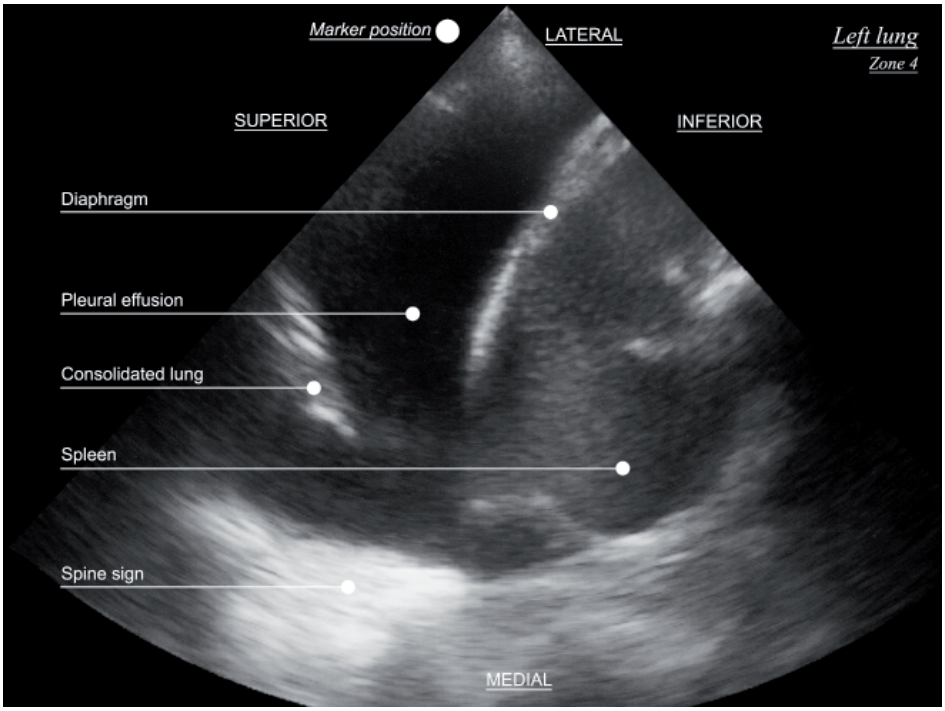


Figure 5.5: Uncomplicated effusion.

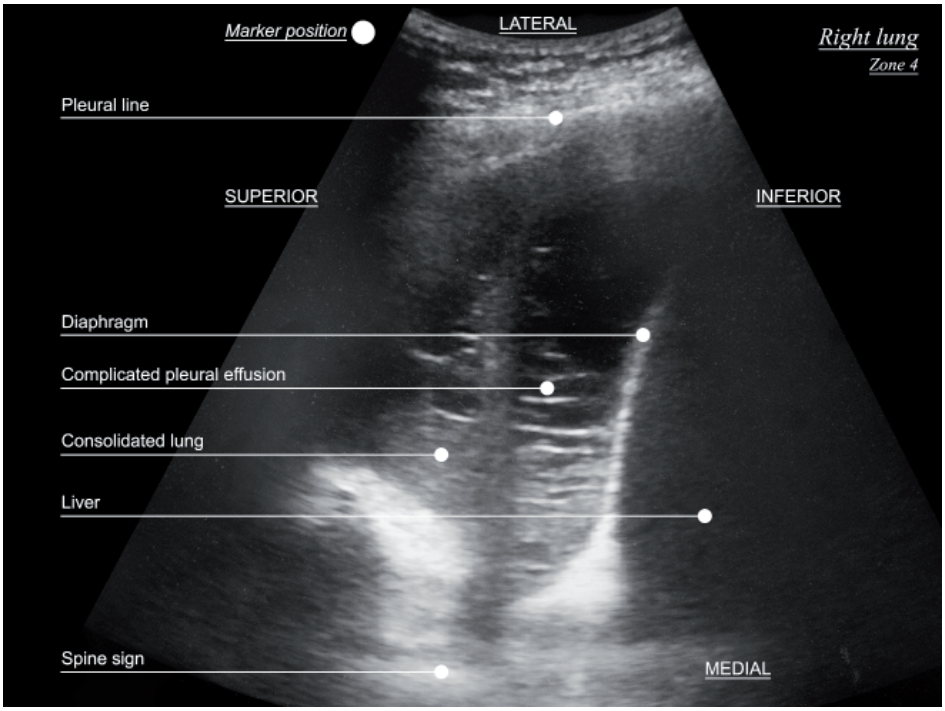


Figure 5.6: Complicated effusion.

emergency department as well,[11] and that LUS also reduces time to diagnosis and appropriate treatment.[4,12,13]

Ultrasound in the role of weaning from mechanical ventilation

Weaning and discontinuation of mechanical ventilation is a pivotal moment in the management of a critically ill patient. Failure to wean is the failure of a spontaneous breathing trial or reintubation 48 hours following discontinuation of mechanical ventilation. Up to 30% of patients fit these criteria with an associated increase in mortality and morbidity. In long stay patients the causes are multifaceted including respiratory, cardiac and neuromuscular factors. A structured approach is essential and ultrasound can be very helpful.[5]

Diaphragmatic function

There are two proposed diaphragm sonographic predictors of weaning outcome: the diaphragmatic excursion (DE), and the diaphragm thickening fraction (DTF). However, a recent meta-analysis does not support the use of DE in prediction of weaning outcome, and has shown that DTF is by itself a modest predictor of weaning outcome.[15]

Lung aeration

Conversely, by semi-quantifying lung aeration with the global lung aeration score, lung ultrasound can predict weaning outcome. It uses 12-zone scanning of the lung, apportioning a score of 0 (aerated lung) to 3 (consolidated) for each zone and adding the scores for a maximum of 36 (e-Table 5.1).[16] Zone 1, 2 and 6 are analogous to respectively the upper, and lower BLUE point and PLAPS point of the BLUE protocol (e-Figure 5.1). A dynamic re-aeration score based on the same four patterns can be computed before and after treatments aimed at improving lung aeration. Both scores can be used to determine the likely success of liberation from mechanical ventilation or extracorporeal membrane oxygenation (ECMO). It can also guide fluid resuscitation and re-aeration after ARDS or ventilator associated pneumonia (VAP).[5,16]

Pleural effusions

In case series, about 50% of patients on mechanical ventilation will develop pleural effusions (Figure 5.5 & e-Video 5.8) within the first 48 hours of their intensive care stay. Using ultrasound, both quantitative and qualitative considerations can be made about the need to drain the effusions.

Qualitatively, septations, loculations or even just non-anechoic pleural fluid should at the very least trigger a diagnostic pleural tap to look for evidence of infection or empyema (Figure 5.6 & e-Video 5.9). Flattening or inversion of the hemidiaphragm means it will be on an adverse portion of the length/tension curve and affect its function. Stimulation of stretch receptors in this situation is also likely to drive respiratory rate.

Quantitatively, the intrapleural distance (IPD) at the base of the lung can be correlated to effusion volume. With patient's supine, an IPD of 45 mm on the left or 50 mm on the right reliably predicts a volume of greater than 800 mL. If patients are supine and their trunk is in a 15 degree elevation, the formula for total fluid volume is as follows: pleural effusion volume (in milliliters) = (measured IPD in millimeters) x 20.[17] It is unclear at what volume the fluid should be drained, but it has been shown to be safe and lead to improvements in gas exchange.[18]

Distinguishing atelectasis from pneumonia

The characteristic features of consolidation due to obstruction, VAP or resorption atelectasis can be very similar as lung aeration is lost. It is especially important to be able to differentiate VAP from the rest. VAP develops in about 25% of mechanically ventilated patients, who are not on selective digestive tract decontamination. It increases the length of hospital stay by more than a week, adds costs, and it has about a 50% mortality rate that increases when adequate treatment is delayed.[5,16,19]

Interestingly, similar to CXR, we find (hemi)lobar infiltrates in all of the above mentioned diagnoses, these are therefore totally non-specific for VAP. Conversely, the small subpleural hypoechoic or tissue-like consolidations (Figure 5.4 & e-Video 5.3) or 'shred-sign' (e-Video 5.4) are very specific for VAP. Specificity increases if more regions are affected. Interestingly, these tend to occur anteriorly and upper laterally.

The most specific feature of VAP however are dynamic bronchograms (e-Video 5.10). Dynamic air bronchograms represent air in distal bronchi(oles) and are displayed as hyperechoic linear, or arborescent and mobile artefacts (>1 mm) within consolidations. They prove there's a patent airway and therefore exclude atelectasis. With re-aeration of atelectasis these will however reappear. Dynamic fluid bronchograms are hypoechoic linear or arborescent anechoic images, which represent fluid filled bronchi(oli) and are indicative of postobstructive pneumonia. Static air bronchograms can be seen in both resorption atelectasis and pneumonia and therefore cannot differentiate between the two.

In cases where consolidation is accompanied with an effusion, a complex effusion as well as a consolidation-to-pleural effusion ratio greater than one were more likely to be due to an infiltrative process, while a rhomboid shape consolidation increased the chance of compression atelectasis.[16] Preliminary evidence also suggests that color doppler might be of help in differentiating between atelectasis and infection.[20] Combining ultrasound with procalcitonin (PCT) has been suggested to increase specificity.[21] However current guidelines do not recommend the use of PCT in the diagnosis and treatment of VAP.

Ultrasound to distinguish ARDS from cardiac pulmonary oedema

Bedside LUS assessment has proven to be more accurate than physical examination, natriuretic peptide tests and CXR combined, in assessing patients with suspected acute cardiac pulmonary oedema (CPO).[4] Although both ARDS, pneumonia and CPO can produce a B-line pattern, the differentiation of the B-pattern can help further distinguish between several entities with often similar clinical pictures (e-Figure 5.2):

- A unilateral B-pattern suggests pneumonia.
- If homogeneous, bilateral and diffuse (i.e., at least 2 regions per hemithorax are affected) accompanied with a thin pleura (Figure 5.2 & e-Video 5.2) and (bi)lateral effusion (Figure 5.5 & e-Video 5.8) it orients to CPO.
- In contrast the B-pattern in ARDS and atypical or viral pneumonia is more heterogeneous, patchy and asymmetrical.
- ARDS is further characterized by a thickened, irregular pleura (e-Video 5.12) and small subpleural consolidations in gravity dependent areas (Figure 5.3-5.4 & e-Video 5.3).
- The C-profile, with its anterior consolidations also points towards ARDS (e-Video 5.4).

Bedside LUS has in fact been incorporated in the Kigali modification of the Berlin Definition of ARDS.[22] In a different population parenchymal lung disease (i.e., fibrosis, silicosis, sarcoidosis) exhibited a homogeneous B-pattern, but irregular and thickened pleura. Importantly, the ARDS pattern is also seen in COVID-19 pneumonia,[23,24] so LUS might play a role in diagnosis, risk stratification and monitoring in this pandemic.

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6

Diagnosing COVID-19 pneumonia in a pandemic setting: Lung Ultrasound versus CT (LUVCT)

A multicenter, prospective, observational study

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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 multicenter, 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 multidisciplinary team (MDT) diagnosis as reference. We also assessed agreement between LUS and CT, and between sonographers.

Results: 187 patients were included between March 19 and May 4, 2020. Area under the receiver operating characteristic (AUROC) was 0.81 (95%CI 0.75-0.88) for LUS and 0.89 (95%CI 0.84-0.94) for CT. Sensitivity and specificity for LUS were 91.9% (95%CI 84.0-96.7) and 71.0% (95%CI 61.1-79.6), versus 88.4% (95%CI 79.7-94.3) and 82.0% (95%CI 73.1-89.0) for CT. Negative likelihood ratio was 0.1 (95%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% (95%CI 69.9-87.9) compared to MDT diagnosis, with an AUROC of 0.85 (95%CI 0.79-0.91). Agreement between LUS and CT was 0.65. Interobserver agreement for LUS was good: 0.89 (95%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.

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 World Health Organization (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 analyzing and comparing diagnostic accuracy of LUS and CT in diagnosing pneumonia in patients with suspected COVID-19.

Methods

Study design

This is a pragmatic, multicenter, prospective, observational study. Patients were recruited from three academic hospitals in the Netherlands (Radboud University Medical Center, Nijmegen and both locations of the Amsterdam University Medical Centers) 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.

Medical workup

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 workup 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-Video 5.2-5.4) (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 e-Figure 5.1 for the lung ultrasound scan protocol. In this study the 12-zone scanning approach was used, in which the lungs were scanned in a lawn mower fashion.

In keeping with prespecified 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 (e-Table 6.1).[15–17,21,22] See e-Videos 5.2-5.4, 5.12 and 6.1 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 prespecified criteria (e-Table 2.1).[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 bronchoalveolar 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. Interobserver agreement was calculated between sonographers.

Statistical analysis

No sample size calculations were performed for this study. Normally distributed continuous variables are summarized by the mean and standard deviation (SD). Not normally distributed continuous variables are summarized 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 (95%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%CI for each cutoff. Agreement between LUS and chest CT was quantified with the Cohen's kappa statistic. Interobserver agreement between sonographers was measured with a weighted kappa via the intraclass 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 analyzed by AL, BK, FS, and KA using SPSS version 26.

Results

Study population

From March 19 until May 4, 2020, 187 patients were included (Figure 6.1). 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 intensive care unit (ICU) admission than PCR negative patients. See Table 6.1 for patient demographics and clinical characteristics.

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 6.2 & e-Table 6.2-6.3). 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%) (e-Table 6.4).

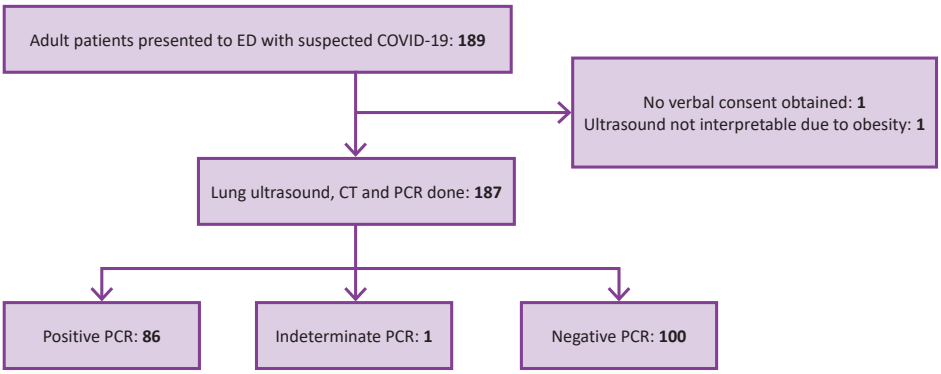


Figure 6.1: Flowchart of patient inclusion and exclusion.

Table 6.1: Baseline 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**
Comorbidities, 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 (°C), 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 emphasized in bold text.

Abbreviations: ED, emergency department; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; PCR, polymerase chain reaction; SD, standard deviation.

Diagnostic performance

For LUS we found a sensitivity of 91.9% (95%CI 84.0-96.7) and a specificity of 71.0% (95%CI 61.1-79.6) compared to PCR as a reference standard. AUROC was 0.81 (95%CI 0.75-0.88). The PLR and NLR were 3.2 (95%CI 2.3-4.3) and 0.1 (95%CI 0.06-0.24) respectively.

Comparing CT to PCR as a reference standard, we found a sensitivity of 88.4% (95%CI 79.7-94.3) and specificity of 82.0% (95%CI 73.1-89). AUROC was 0.89 (95%CI 0.84-0.94). The PLR and NLR were 4.9 (95%CI 3.2-7.5) and 0.14 (95%CI 0.08-0.26) respectively. See Table 6.2 and 6.3 for full results and e-Figure 6.1 for the ROC curve of both CT and LUS compared to PCR.

Table 6.2: Diagnostic results

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

Table 6.3: Diagnostic accuracy for COVID-19

	LUS vs PCR	CT vs PCR	LUS vs MDT 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)

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.
Abbreviations: LUS, lung ultrasound; MDT, multidisciplinary team; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

When we compared LUS to the MDT diagnosis, the AUROC increased to 0.85 (95%CI 0.79-0.91). Specificity increased to 80.0% (95%CI 69.9-87.9), PLR to 4.5 (95%CI 2.9-6.9), while the NLR remained similar 0.12 (95%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 (e-Table 6.5). The agreement between LUS and chest CT was substantial: 0.65. The interobserver agreement between scanning physicians was good: 0.89 (95%CI 0.83-0.93).

Discussion

To our knowledge this is the first study prospectively analyzing and comparing the diagnostic accuracy of LUS and chest CT in COVID-19 pneumonia. We found that: 1) LUS and CT have similarly good diagnostic accuracy for COVID-19 pneumonia, with an AUROC between 0.8 and 0.9; 2) there was substantial agreement between imaging modalities; and 3) there was good agreement between scanning physicians.

Screening test

The sensitivity, negative predictive value, and negative likelihood ratio found for LUS are promising. Only seven patients in our cohort had a false negative LUS compared to PCR (e-Table 6.3). 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 (95%CI 0.82-0.93).

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 self-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% (95%CI 61.1-79.6) and 82.0% (95%CI 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 negative 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 centers. 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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7

Comparing lung ultrasound: extensive versus short in COVID-19 (CLUES)

A multicenter, observational study at the emergency department

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Abstract

Background: Bedside lung ultrasound (LUS) is an affordable diagnostic tool that could contribute to identifying COVID-19 pneumonia. Different LUS protocols are currently used at the emergency department (ED) and there is a need to know their diagnostic accuracy.

Methods: This was a multicenter, prospective, observational study, to compare the diagnostic accuracy of three commonly used LUS protocols in identifying COVID-19 pneumonia at the ED. Adult patients with suspected COVID-19 at the ED, in whom we prospectively performed 12-zone LUS and SARS-CoV-2 polymerase chain reaction (PCR) were included. We assessed diagnostic accuracy for three different LUS protocols using both PCR and final diagnosis as a reference standard.

Results: Between March 19 and May 4, 2020, 202 patients were included. Sensitivity, specificity, and negative predictive value compared to PCR for the 12-zone LUS were 91.4% (95%CI 84.4-96.0), 83.5% (95%CI 74.6-90.3), and 90.0% (95%CI 82.7-94.4). For the 8-zone and 6-zone protocols these results were 79.7 (95%CI 69.9-87.6), 69.0% (95%CI 59.6-77.4), and 81.3% (95%CI 73.8-87.0) versus 89.9% (95%CI 81.7-95.3), 57.2% (95%CI 47.9-66.8), and 87.8% (95%CI 79.2-93.2). Negative likelihood ratios for 12-, 8-, and 6-zone protocols were 0.1, 0.3, and 0.2 respectively. Compared to the final diagnosis, specificity increased to 83.5% (95%CI 74.6-90.3), 78.4% (95%CI 68.8-86.1) and 65.0% (95%CI 54.6-74.4), while the negative likelihood ratios were 0.1, 0.2, and 0.16.

Conclusion: Identifying COVID-19 pneumonia at the ED can be aided by bedside LUS. The more efficient 6-zone protocol is an excellent screening tool whilst the 12-zone protocol is more specific and gives a general impression on lung involvement.

Introduction

The COVID-19 pandemic hotspot has moved to less affluent societies with more pronounced socio-economic disparities and limited medical resources.[1,2] Infected individuals need to be recognized and isolated to slow down the spread. The morbidity and mortality of COVID-19 is most frequently caused by pneumonia and acute respiratory failure with need for supportive medical care.[2,3]

SARS-CoV-2 reverse-transcription polymerase chain reaction (PCR) testing is the current gold standard for diagnosing COVID-19. However, PCR has limited sensitivity in daily practice, test capacity is often insufficient, and turnaround time too long to be useful in the emergency department (ED).[4] To overcome these limitations, imaging to detect lung involvement has been advocated since this is fast and widely available. Unfortunately, chest X-ray (CXR) has a poor negative predictive value.[5,6] Although chest computed tomography (CT) does have good diagnostic accuracy, it is not always available in resource constrained areas.[5–9] Moreover an extra risk of cross contamination of health care personnel and patients comes along with both radiologic techniques. Also, the necessary cleaning procedures are rather time consuming.[10]

Lung ultrasound (LUS) could contribute to identification of COVID-19 pneumonia and help guide patient management.[11–20] It has proven to reliably exclude COVID-19 pneumonia with equal accuracy to chest CT.[21–24] Its advantages include: speed, affordability, ease of use, availability in low resource situations (especially handheld devices), reducing the risk of transmission by minimizing the need for patient transport. And cleaning procedures are much easier particularly when handheld devices are used.[19,20,25]

Since the emergence of COVID-19 different LUS protocols have been used. The current protocols in COVID-19 scan 6,[19] 8,[23,26] 12,[17,18,24] or even 14[13,15] sites on the thoracic surface. It is unclear which of these protocols is best used in COVID-19.

The 12 and 14 site strategies can be performed within 10 minutes while the 6- and 8-site strategies take three minutes at the most. In an overcrowded ED scanning quickly is most desirable.

To our knowledge no studies comparing the diagnostic accuracy of different LUS protocols in pneumonia or any other etiology have been conducted. The literature on acute heart failure at the ED[27,28] and acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU)[29] have shown that utilizing less scan sites can be equally accurate.

In this real-life, multicenter, observational study we therefore assessed and compared the diagnostic accuracy of three commonly used bedside LUS protocols in identifying COVID-19 at the ED.

Methods

Study design

This multicenter, observational study was conducted at the EDs of three academic hospitals in the Netherlands (Radboud University Medical Center, Nijmegen, and both locations of the Amsterdam University Medical Centers) between March 19 and May 4, 2020. This study was registered with the Dutch Trial Registry (Trial NL8497). This study was approved by the Medical Ethical Committee (CMO region Arnhem-Nijmegen record 2020-6372). There were no patients or public involved in the study protocol.

All eligible patients were 18 years and older who visited the ED with suspected COVID-19. The COVID-19 case definition of the World Health Organization (WHO) and National Institute for Public Health and the Environment (RIVM) was used. This was initially defined as having either fever, malaise, myalgia, and respiratory symptoms, and subsequently included gastrointestinal symptoms, loss of smell or taste, and unexplained delirium in the elderly.

Inclusion criteria were a SARS-CoV-2 PCR and verbal informed consent. Exclusion criteria were age under 18 years, no verbal consent given.

All study participants received a regular medical workup (history, physical examination and routine laboratory tests) and a bedside LUS at the ED. If imaging of the thorax was deemed necessary by the treating physician a chest CT was performed which was in accordance with local clinical guidelines.

In patients with a high clinical suspicion but negative PCR a diagnosis of COVID-19 still could be made by a multidisciplinary team of experts (MDT) after excluding alternative diagnoses. In all three participating hospitals it was routine care that the admitted patients were discussed daily in this MDT consisting of consultants in infectious disease, respiratory disease and microbiology. This panel reviewed all available clinical, laboratory, microbiological, and CT data and decided on the final diagnosis. The expert panel was blinded for the LUS findings during the course of the study.

Ultrasound methods

Bedside LUS was performed at the ED as an extension of the physical exam. Scans were performed or supervised by acute internal medicine physicians who were certified in

point-of-care ultrasound and had entrustable professional activity (EPA) level of 4 (able to conduct and interpret a scan without supervision) or 5 (able to supervise others). All patients received a 12-zone ultrasound and the findings were classified for the different LUS protocols as described in the paragraphs below. The sonographers performing the LUS were blinded for the PCR and radiological results.

Handheld ultrasound systems (Iviz Sonosite® and Butterfly IQ®) were mostly used with a lung preset (i.e., settings amenable to the detection of B-line artefacts; see e-Video 5.2-5.4 for examples of B-lines). In case handheld systems were not available a cart-based system was used (Sonosite®) with an abdominal preset with tissue harmonic imaging switched off and dynamic range put at the lowest level.

Twelve-zone method

Scanning was done in a lawn mower fashion with 6 scanning sites on each hemithorax; two anteriorly, two laterally and two posteriorly. See e-Figure 5.1 for details on the scanning zones and technique. The ultrasound was assessed real-time as positive or negative for COVID-19. A scan was defined positive by the presence of sonographic abnormalities consistent with COVID-19 in two or more zones unilaterally, or one or more zones bilaterally (e-Table 6.1 shows typical sonographic findings in COVID-19 pneumonia).[18] See Figure 5.2-5.4, and e-Videos 5.2-5.4, 5.12 and 6.1 for examples of COVID-19 sonographic features.

Six-point method (BLUE protocol)

This protocol is an acronym for bedside lung ultrasound in emergency (BLUE) and categorizes the LUS findings into BLUE profiles (e-Figure 5.2).[30,31] Three sites on each hemithorax are scanned (e-Figure 5.1): the upper BLUE point (yellow triangle), the lower BLUE point (yellow square) and the postero-lateral alveolar pleural syndrome (PLAPS) point (yellow star). The BLUE profile was determined real-time. Based on the features and distribution of COVID-19 pneumonia, the following BLUE profiles were considered consistent with COVID-19 pneumonia:

- A-profile with bilateral PLAPS without pleural effusion;
- A/B-profile;
- B'-profile;
- C-profile.

Profiles that were deemed not in keeping with COVID-19 were:

- A-profile without PLAPS (asthma/COPD, pulmonary embolism, non-pulmonary conditions);

- A-profile with unilateral PLAPS (lobar pneumonia);
- A-profile with bilateral PLAPS due to pleural effusion (heart failure);
- B-profile (heart failure).

Eight-point method

The 8-point method only uses the anterior and lateral zones, excluding the posterior zones (e-Figure 5.1). A positive scan was defined by the presence of at least one of the artefacts described in e-Table 6.1 in one or more zones bilaterally or two or more zones unilaterally.

Outcome

Sensitivity, specificity, diagnostic accuracy, likelihood ratios and predictive values of three different LUS protocols in COVID-19 were assessed against two reference standards: (serial) PCR (gold standard) and the final diagnosis.

Statistical analysis

No sample size calculation was performed. Normally distributed continuous variables are summarized by their mean and standard deviation (SD). Continuous variables that are not normally distributed are summarized by their median and interquartile range [IQR]. Differences between patient groups were tested using the independent t-test for normally distributed outcomes and difference in means and 95% confidence interval (95%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 the different LUS protocols were compared using the McNemar test. Analyses were performed in SPSS version 26. Data were analyzed by the first four authors: BK, FS, AL, and KA.

Results

Study population

From March 19 until May 4 2020, 202 patients with a suspicion of COVID-19 were included in our study (e-Figure 7.1). There were neither missing data, nor adverse events. See Table 7.1 for patient demographics and clinical characteristics. The descriptive statistics of the LUS protocols are shown in Table 7.2 and Table 7.3.

Table 7.1: Baseline characteristics

Patient characteristics	All patients N=202	SARS-CoV-2 PCR positive N=89	SARS-CoV-2 PCR negative N=113	*p* value
Age, mean (SD)	62.4 (16.1)	62.6 (14.9)	62.3 (17.2)	0.281
Male, n (%)	117 (57.8)	53 (59.6)	64 (56.6)	0.336
Admission, n (%)	140 (69.3)	65 (73.0)	75 (66.4)	**0.000**
Admission IC, n (%)	10 (4.9)	8 (8.9)	2 (1.8)	**0.000**
30-day mortality, n (%)	15 (7.4)	6 (6.7)	9 (8.0)	0.467
In hospital mortality, n (%)	10 (4.9)	5 (5.6)	5 (4.4)	**0.018**
Duration of symptoms days (SD)	6.8 (5.6)	7.4 (4.1)	6.2 (6.5)	**0.001**
Comorbidities, n (%)				
Asthma	12 (5.9)	4 (4.5)	8 (7.1)	0.113
Chronic Cardiovascular Disease	44 (21.7)	18 (20.0)	26 (23.0)	0.301
COPD (GOLD >2) n (%)	31 (15.3)	12 (13.3)	19 (16.8)	0.170
Current Malignancy	42 (20.7)	9 (10.0)	33 (29.2)	**0.000**
Diabetes Mellitus	35 (17.3)	21 (23.6)	14 (12.4)	**0.000**
Laboratory analysis on admission				
Positive blood culture, n (%)	12 (5.9)	1 (1.1)	11 (9.7)	0.798
Modified early warning score mean (SD)	2.6 (1.9)	2.9 (1.9)	2.3 (1.8)	0.542
Temperature (°C), mean (SD)	37.5 (1.2)	37.8 (1.0)	37.2 (1.3)	0.105
Respiratory rate, mean (SD)	21.1 (7.0)	21.7 (7.4)	20.5 (6.6)	0.566
Saturation levels (SD)	95.8 (3.2)	94.9 (3.5)	96.5 (2.8)	0.120
Intubation, n (%)	10 (4.9)	8 (8.9)	2 (1.8)	**0.000**
Oxygen therapy, n (%)	59 (29.1)	35 (38.9)	24 (22)	**0.000**

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 7.2: Diagnostic accuracy measures of the three lung ultrasound protocols versus SARS-CoV-2 PCR

Diagnostic accuracy	6-point protocol vs SARS-CoV-2 PCR	8-point protocol vs SARS-CoV-2 PCR	12-zone protocol vs SARS-CoV-2 PCR
Sensitivity % (95%CI)	89.9 (81.7-95.3)	79.7 (69.9-87.6)	91.4 (84.4-96.0)
Specificity % (95%CI)	57.5 (47.9-66.8)	69.0 (59.6-77.4)	83.5 (74.6-90.3)
Positive likelihood ratio (95%CI)	2.1 (1.7-2.7)	2.6 (1.9-3.5)	5.5 (3.5-8.7)
Negative likelihood ratio (95%CI)	0.2 (0.1-0.3)	0.3 (0.2-0.5)	0.1 (0.05-0.2)
Positive predictive value % (95%CI)	62.5 (57.1-67.6)	67.0 (60.1-73.1)	85.7 (79.3-90.4)
Negative predictive value % (95%CI)	87.8 (79.2-93.2)	81.3 (73.8-87)	90.0 (82.7-94.4)
Accuracy % (95%CI)	71.8 (65.0-77.9)	73.8 (67.1-79.7)	87.6 (82.3-91.8)

Abbreviations: PCR, polymerase chain reaction; CI, confidence interval.

Table 7.3: Diagnostic accuracy measures of the three lung ultrasound protocols versus final diagnosis

Diagnostic accuracy	6-point protocol vs final diagnosis	8-point protocol vs final diagnosis	12-zone vs final diagnosis
Sensitivity % (95%CI)	89.5 (82.0-94.7)	81.0 (72.1-88.0)	91.4 (84.4-96.0)
Specificity % (95%CI)	65.0 (54.6-74.4)	78.4 (68.8-86.1)	83.5 (74.6-90.3)
Positive likelihood ratio (95%CI)	2.6 (1.9-3.4)	3.7 (2.5-5.5)	5.6 (3.6-8.8)
Negative likelihood ratio (95%CI)	0.16 (0.09-0.3)	0.2 (0.2-0.4)	0.1 (0.05-0.2)
Positive predictive value % (95%CI)	73.4 (67.7-78.5)	80.2 (73.3-85.7)	85.7 (79.2-90.4)
Negative predictive value % (95%CI)	85.1 (76.3-91.1)	79.2 (71.7-85.1)	90.0 (82.7-94.4)
Accuracy % (95%CI)	77.7 (71.4-83.3)	79.7 (73.5-85.0)	87.6 (82.3-91.8)

The following diagnostic measures for the different protocols compared to PCR were found: For 12-zone ultrasound we found a sensitivity 91.4% (95%CI 84.4-96.0), specificity of 83.5% (95%CI 74.6-90.3), negative predictive value of 90.0% (95%CI 82.7-94.4) and negative likelihood ratio of 0.1 (95%CI 0.05-0.2). For the 6-point protocol we found a sensitivity 89.9% (95%CI 81.7-95.3), specificity of 57.5% (95%CI 47.9-66.8), negative predictive value of 87.8% (95%CI 79.2-93.2), and negative likelihood ratio of 0.2 (95%CI 0.1-0.3). For the 8-point method we found a sensitivity 79.7% (95%CI 69.9-87.6), specificity of 69.0% (95%CI 59.6-77.4), negative predictive value of 81.3% (95%CI 73.8-87.0), and negative likelihood ratio of 0.3 (95%CI 0.2-0.5).

We also calculated diagnostic measures compared to the final diagnosis decided by the medical expert panel. 96 patients with a final diagnosis of COVID-19 had a positive 12-zone LUS. The statistical results were as follows:

The 12-zone LUS protocol had a sensitivity of 91.4% (95%CI 84.4-96.0), specificity of 83.5% (95%CI 74.6-90.3), negative predictive value of 90.0% (95%CI 82.7-94.4), and negative likelihood ratio of 0.1 (95%CI 0.05-0.2). The 6-point protocol had a sensitivity of 89.5 (95%CI 82.0-94.7), specificity of 65.0% (95%CI 54.6-74.4), negative predictive value of 85.1% (95%CI 76.3-91.1) and negative likelihood ratio of 0.16 (95%CI 0.09-0.3). The 8-point method had a sensitivity of 81.0% (95%CI 72.1-88.0), specificity of 78.4% (95%CI 68.8-86.1), negative predictive value of 79.2% (95%CI 71.7-85.1) and negative likelihood ratio of 0.2 (95%CI 0.2-0.4). Comprehensive results are shown in Table 7.2.

The interobserver reliability of 12-zone LUS was excellent, with an ICC of 0.88 (95%CI 0.77-0.95).

Six patients had false negative results in the 12-zone scan and thus also in the 6-point and 8-point protocol. In four of these patients' ultrasound abnormalities were seen in one zone only. Therefore, the results were not compatible with the prespecified criteria for a positive ultrasound scan. In the remaining two patients no abnormalities were seen at all.

Three patients had false negative results in the 6-point protocol. One of these was falsely negative in the 8-point protocol too. All three false negative ultrasounds had abnormalities visualized in one zone only. (e.g., BLUE profile A with unilateral PLAPS or only one site in the 8-point protocol). As such, they were not in keeping with COVID-19 pneumonia. However, if the 12-zone protocol was applied, all three ultrasounds were positive.

Eleven patients had a false negative ultrasound in the 8-point protocol but not in the 6-point or 12-zone protocol.

Twenty-nine patients had a false positive ultrasound in the 12-zone protocol. Further analysis of these 29 scans showed that 22 ultrasounds were falsely positive in all three protocols, 6 recordings in the 12-zone protocol and one other protocol (5/6 also in the 6-point protocol, 1/6 also in the 8-point protocol) and one false positive scan in the 12-zone protocol only.

Twenty-three patients had a false positive ultrasound in one or both of the 6-point and 8-point protocols but not in the 12-zone approach. Twelve scans were solely false positive in the 6-point method and two scans were false positive in the 8-point method only. The remaining nine false positive ultrasounds were considered as such in both the 6-point and 8-point protocols.

We found no significant difference in sensitivity between the 12-zone and 6-point protocol, but we did find a significant difference in sensitivity between those protocols and the 8-point protocol. In addition, there was no significant difference between the 12-zone and 8-point protocol specificity. But both were significantly more specific than the 6-point protocol. See e-Table 7.1A-B for full McNemar test results.

Discussion

Screening

The findings in our study show that the 6-point protocol and the 12-zone approach can reliably and safely rule out COVID-19 pneumonia. Our study also shows that one must convert to a complete 12-zone ultrasound in case any abnormalities are seen in the 6-point method. Application of this approach will minimize the chance of a false negative ultrasound in the 6-point protocol.

In our study the three false negatives in the 6-point protocol had the BLUE profile A with unilateral PLAPS which is suggestive of lobar pneumonia.[31,32] If the ultrasound examination was extended to a 12-zone scanning all three scans would have been ruled in. On the contrary, absence of any abnormality in the 6-point protocol safely rules out COVID-19 pneumonia. In our study this was shown by the excellent negative likelihood ratios of the 12-zone and 6-point protocols. Importantly, COVID-19 positive patients with false negative results in the 6-point protocol had no need for admission due to COVID-19 related symptoms.

Conversely, in our study the 8-point scanning method resulted in missing patients in whom supportive care was necessary. The lower sensitivity of this approach could be explained by the fact that scanning of the posterior chest is omitted. In COVID-19

pneumonia abnormalities tend to originate infero-posteriorly. Our results indicate that zone 6 (named PLAPS in the BLUE protocol) should be examined to have a high likelihood ratio. Although scanning this zone can sometimes be challenging in immobile, obese and bedridden patients, a supine patient can still be examined by adduction of the arm across the midline and thereby exposing the back of the chest.

Diagnosing

There seems to be a discernible rising trend in specificity when more zones were scanned (Table 7.3 & e-Table 7.1A-B). Although there was no significant difference between the 8-point and 12-zone protocols, their specificity was higher than the 6-point protocol. COVID-19 pneumonia has a patchy and irregular distribution. In the 6-point protocol too few zones are scanned to differentiate between diagnoses. Also, COVID-19 pneumonia tends to begin infero-posteriorly but this also holds true for pleural effusion and compression atelectasis. In the 8-point protocol there is no visualization of this area and thus valuable information which increases specificity is missed.

Still, the specificities of the LUS protocols in our study are substantially lower than found in literature on pneumonia.[31–36] This could be due to the fact that we are trying to differentiate between types of pneumonia. For example, findings which we considered suggestive of COVID-19 pneumonia could also be compatible with (bacterial) lobar pneumonia. Whereas in previous studies all types of pneumonia were aggregated. In addition, as we argued before, sonographic features of COVID-19 are not exclusive to COVID-19, but are also found in other etiologies of acute respiratory failure.[21] Sometimes we (mis)diagnosed a patient with COVID-19, while in fact they had heart failure, compression atelectasis, or progression of an intrapulmonary malignancy.

Perspectives

Bedside ultrasound could contribute to identifying COVID-19 pneumonia and guide patient management. Screening for signs of COVID-19 pneumonia will only take 3 minutes with an excellent negative predictive value, and when a 12-zone ultrasound is necessary this will take 10 minutes after which useful information to guide patient management is obtained. Also, this technique comes with less exposure of health care personnel and other patients to a patient with COVID-19 because of its use directly at the bedside. Most importantly, bedside LUS can be employed in resource constrained and remote areas, especially when handheld ultrasound devices are used.[21]

Limitations

This multicenter study has numerous limitations. As all patients were scanned using the 12-zone protocol, the diagnostic measures calculated in the 6-point protocol and 8-point protocol can be overrated. Because we applied a lawn mower technique more positive findings were seen in the 6-point protocol when compared to a strict adherence to the anatomical point described in this protocol. In our opinion, a too rigid adherence to exact anatomical points will result in a decrease in diagnostic accuracy especially in a disease with a patchy and irregular pattern like COVID-19 pneumonia. Only one physician performed the LUS per patient. Hospital protocol did not allow the same patient to be scanned by three separate physicians to minimize infection risk and to avoid unnecessary spending of scarce personal protection material. Since all the scanning was performed and recorded systematically in 12 separate images or clips, we consider the influence on the classification of the 6- and 8-point protocol as minimal. Moreover, the same methodology was used in research to compare different ultrasound protocols in heart failure and deep vein thrombosis.[27,28,37,38]

The diagnostic accuracy measures found in this study are subject to a possible attentional bias due to the high prevalence setting in which we performed our study. LUS has an excellent negative predictive value and sensitivity to screen for possible COVID-19. However, we advocate future research on this subject in low prevalence setting.

In this study we applied two reference standards for COVID-19: (serial) PCR (gold standard) and the final diagnosis. The latter was a positive decision made by an MDT based on clinical information, microbiological, SARS-COV-2 PCR and chest CT data. This approach reflects daily practice and has the advantages of detecting COVID-19 patients with false negative PCR results, and being applicable in circumstances where PCR data are not readily available. This approach is advocated by the World Health Organization (WHO). From a methodological viewpoint the comparison between a molecular diagnosis of COVID-19 (PCR) and imaging to detect COVID-19 pneumonia is incongruous. Still, pneumonia and its sequalae form the majority of COVID-19's morbidity and mortality so finding a way to screen for or diagnose pneumonia is important for real-life hospital care. For clarity reasons we reported the comparison between LUS and PCR, and the comparison between LUS and MDT decision separately. The results of both comparisons are respectively shown in Table 7.2 and Table 7.3. Importantly, regardless of the reference chosen the findings in our study remain the same. We have used various ultrasound systems (mostly handheld). Although this might introduce some heterogeneity, it does reflect daily clinical practice and thus adds to the generalizability of our findings.

Conclusion

Identifying COVID-19 at the ED can be aided by bedside lung ultrasound. A three minute scan of just 6 lung zones can safely rule out COVID-19 pneumonia. The 12-zone scanning protocol is the only protocol that seems specific enough to diagnose COVID-19 pneumonia at the ED in a high prevalence setting. We recommend further research be conducted in other settings to validate our findings.

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8

Assessing COVID-19 pneumonia – Clinical extension and risk with point-of-care ultrasound

A multicenter, prospective, observational study

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Abstract

Background: Assessing the extent of lung involvement is important for triage and care of COVID-19 pneumonia. We sought to determine the utility of point-of-care ultrasound (POCUS) for characterizing lung involvement and, thereby, clinical risk determination in COVID-19 pneumonia.

Methods: This multicenter, prospective, observational study included COVID-19 patients who received 12-zone lung ultrasound and chest computed tomography (CT) scanning in the emergency department (ED). We defined lung disease severity using the lung ultrasound score (LUSS) and chest CT severity score (CTSS). We assessed the association between the LUSS and poor outcome (ICU admission or 30-day all-cause mortality). We also assessed the association between LUSS and hospital length of stay. We examined the ability of the LUSS to differentiate between disease severity groups. Lastly, we estimated the correlation between the LUSS and CTSS, and the interrater agreement for the LUSS. We handled missing data by multiple imputation with chained equations and predictive mean matching.

Results: We included 114 patients treated between March 19 and May 4, 2020. A LUSS ≥12 was associated with a poor outcome within 30 days; hazard ratio (HR) 5.59 (95%CI 1.26-24.80), p=0.02. Admission duration was shorter in patients with a LUSS <12, adjusted HR 2.24 (95%CI 1.47-3.40), p<0.001. Mean LUSS differed between disease severity groups: no admission: 6.3 (standard deviation [SD] 4.4); hospital/ward: 13.1 (SD 6.4); and ICU: 18.0 (SD 5.0). The LUSS was able to discrimate between ED discharge and hospital admission excellently, with an area under the curve (AUC) of 0.83 (95%CI 0.75-0.91). Interrater agreement for the LUSS was strong; kappa 0.88 (95%CI 0.77-0.95). Correlation between the LUSS and CTSS was strong: kappa 0.60 (95%CI 0.48-0.71).

Conclusion: We showed that a baseline LUSS is associated with poor outcome, admission duration, and disease severity. The LUSS also correlates well with CTSS. Point-of-care lung ultrasound may aid risk stratification and triage of COVID-19 patients at the ED.

Introduction

The main cause of morbidity and mortality in COVID-19 is viral pneumonia, which can progress to acute respiratory distress syndrome (ARDS). Proper evaluation of pulmonary involvement is critical for appropriate triage, risk stratification, and efficient allocation of medical resources. This is especially important since new, more contagious genetic variants are emerging on multiple continents – some with the ability to generate more reinfections – which could put additional stress on already overwhelmed acute care pathways.[1]

Mounting evidence suggests that imaging studies like computed tomography (CT) are helpful in diagnosis of COVID-19 pneumonia. Findings on CT may precede clinical symptoms, and the degree of pulmonary involvement can help predict patient outcome.[2–8] However, CT is expensive and cumbersome. CT scans can be difficult to perform on unstable patients, operation of CT equipment requires extra personnel, and unavailability and high costs can be an issue, even in high income countries. Additionally, risk of COVID-19 transmission necessitates stringent desinfection protocols, and additionally cleaning of the radiology suite may lead to increased delays between uses.

Point-of-care ultrasound (POCUS) of the lung might circumvent these issues. Lung ultrasound has diagnostic accuracy comparable to CT – and superior to chest radiography (CXR) – in multiple aetiologies of respiratory failure, from pneumonia to ARDS.[9–15] Recent studies show that lung ultrasound also has better diagnostic accuracy than CXR in diagnosing COVID-19 pneumonia.[16,17] CXR is a poor diagnostic test in COVID-19 as it may miss up to 40% of confirmed cases.[18] Meanwhile, diagnostic accuracy of lung ultrasound approaches that of CT for COVID-19 pneumonia.[19,20] Lung ultrasound can safely exclude clinically relevant COVID-19 pneumonia and may aid COVID-19 diagnosis in high prevalence situations.[21]

The advantages of lung ultrasound over CT include: being fast to operate, simple to clean, portable, easily repeatable, and having low investment and operating costs. With proper personal protective equipment, lung ultrasound can be safely performed at the bedside within 10 minutes. Because of its usefulness in diagnosis and follow-up, lung ultrasound has become common practice, and even standard practice, in acute and critical care.[22,23]

The literature comparing the degree of pulmonary involvement between lung ultrasound and CT, along with literature detailing lung ultrasound's ability to stratify patients and predict outcomes, is limited to only single-center and/or retrospective studies.[22–25] In a recent meta-analysis, the World Health Organization (WHO) recommends that the value of lung ultrasound regarding both clinical outcomes and duration of hospital stay should

be investigated further due to inconclusive evidence.[26] To address this knowledge gap, we prospectively assessed the value of lung ultrasound during initial emergency department (ED) presentation in COVID-19 risk stratification and prognostication. In addition, we also evaluated the correlation between lung ultrasound and CT results in quantifying lung involvement in COVID-19 patients.

Methods

Study design

We performed a multicenter prospective, observational study. The study was registered with the Netherlands Trial Register and approved by the local Medical Ethical Committees. We conducted the study in 3 large university hospitals in The Netherlands: the Radboud University Medical Center in Nijmegen, the VU Medical Center in Amsterdam, and the Academic Medical Center in Amsterdam. They have 1065, 733 and 1002 beds, respectively. Each hospital has approximately 30,000 ED visits per years.

Patients were recruited between March 19 and May 4, 2020. Inclusion criteria were: presentation at the ED for acute internal medicine, presence of a certified sonographer, confirmed COVID-19, and lung ultrasound and chest CT performed within 24 hours of presentation. Exclusion criteria were either: no verbal consent and/or uninterpretable CT or lung ultrasound.

Per hospital procedure, all patients received a standard medical work-up (history, physical examination, common observations, and routine laboratory tests) and a SARS-CoV-2 polymerase chain reaction (PCR) test. Clinical criteria for ward admission were: oxygen saturation <94% (need for conventional supplemental oxygen), and/or respiratory rate >20/min. ICU admission criteria were either: deterioration despite conventional respiratory support or need for mechanical ventilation.

Lung ultrasound

Lung ultrasound was performed or supervised by acute internal medicine physicians who are both certified in POCUS and had an Entrustable Professional Activity (EPA) level of at least 4. The EPA concept has competency-based education targets to guarantee that all learners have a sufficient level of proficiency when they reach the required EPA level. Increasing levels of entrustment range from level 1 (not trusted to perform POCUS even under direct supervision) to level 4 (entrusted to use POCUS independently), and level 5 (engagement in POCUS education and research).[27]

We predominantly used handheld systems, with settings amenable to the detection of B-line artefacts.[28] The scanning physician was blinded for the PCR and CT results but not for the clinical picture. The lung ultrasound protocol consisted of a structured assessment of 6 zones of each hemithorax (e-Figure 5.1). Each zone was scored according to the same lung ultrasound score (LUSS) classification system used in intensive care, ARDS, and recent COVID-19 literature.[15,19,22,24,29,30] This system scores zones from 0 (well aerated) to 3 (consolidated) (e-Table 5.1). The total LUSS sums the scores from all 12 zones, creating a final score range from 0 (all regions are well aerated) to 36 (all regions are consolidated).

CT

Local radiologists assessed the chest CTs, using the COVID-19 Reporting and Data System (CO-RADS).[2,31–33] The CO-RADS uses a scale from 1 (very low) to 5 (very high), to indicate the likelihood of COVID-19 pneumonia. To quantify pulmonary involvement, every CT is graded according to the CT severity score (CTSS), when COVID-19 pneumonia is suspected (i.e., CO-RADS 3 and above).[34] The CTSS is a visual assessment of the percentage of disease involvement in each lobe (e-Table 2.2). The total CTSS is the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement). The radiologists were blinded for lung ultrasound and PCR results, but not for clinical information.

COVID-19 diagnosis

The diagnosis of COVID-19 was established by a positive PCR test result (from a nasopharyngeal, oropharyngeal, sputum or bronchoalveolar lavage sample) or by a clinician impression after alternative diagnoses were excluded. In patients with high clinical suspicion but negative PCR, a multidisciplinary team (MDT) of hospital clinicians determined the presence of COVID-19 on the basis of clinical, laboratory, microbiological, and/or CT data and only after excluding alternative diagnoses. Use of clinician impression as a reference is in line with WHO recommendations, due to suboptimal sensitivity of the PCR.[26] The MDT is comprised of specialists in infectious disease, respiratory disease, and microbiology, and discusses all admitted (suspected) COVID-19 cases in a daily plenary meeting. The team did not use lung ultrasound in the determination of COVID-19 presence.

Outcomes

The primary outcome was poor COVID-19 outcome, defined as the composite end-point of 30-day all-cause mortality or ICU admission. Secondary outcomes included hospital length of stay (days), disease severity groups (ED discharge, hospital ward admission, ICU admission).

Statistical analysis

We used Kaplan-Meier curves and Cox proportional hazards regression to assess the relationship between LUSS and time to poor outcome (a composite end-point of 30-day all-cause mortality or ICU admission), and admission duration. We dichotomized the LUSS using the median. We tested the proportional hazards assumption by checking that the Kaplan-Meier curves do not cross, and the log minus log curves run parallel. We assessed linearity for continuous variables by dividing them in tertiles and checking whether beta-coefficients systematically increase or decrease with increasing categories.

We reported hazard ratios (HR) (adjusted for any confounders if applicable) as effect size for the dichotomized LUSS used in the Kaplan-Meier curves, as well as for each per-point increase in LUSS seperately. We considered the following variables as potential confounders for relation between LUSS and outcome: duration of symptoms, age, sex, and comorbidities (chronic obstructive pulmonary disease, cardiovascular disease, hypertension, and diabetes mellitus).[2] We examined confounders separately to keep within the rule of 5-10 events-per-variable (EPV). We used a 10% change in LUSS beta-coefficient as confounder threshold.[35] We estimated a multivariate model, when allowed by the EPV rule, in which we adjusted for all confounders identified.

We compared differences between three disease severity grades; 1) mild: no admission/ED discharge; 2) moderate: hospital/ward admission; and 3) severe: ICU admission. We also compared means and proportions between these groups by one-way analysis of variance (ANOVA), χ^2 test, Fisher's exact test, or Kruskal-Wallis test, as appropriate. We used Tukey Honestly Significant Difference (HSD) post-hoc test to compare pairs of severity grades.

We determined the ability of LUSS to disriminate between disease severity by comparing receiver operating characteristic (ROC) curves. We determined the optimal cutoff with the Youden index. We also reported sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR).[36–38] A DOR of >10 is considered good.[39]

We also used a 'grey zone' approach.[40] This method allows the binary constraint of a 'black or white' decision to be avoided, which is often inappropriate for clinical or screening practice. Instead, our approach constructs a three-zone division for quantitative tests and purposefully includes a grey zone of inconclusive test results. In this case, we used a NLR of 0.1 and 0.2 and a PLR of 10 and 5 for the cutoffs of the grey zone. At these likelihood ratios, the approximate post-test change in probability is ~45% (large change) or ~30% (moderate change).[41]

We employed multiple imputation by chained equations (MICE) with predictive mean matching (PMM) to account for any missing data, assuming a missing at random (MAR) pattern. We pooled effect estimates from the imputation datasets using Rubin's rules. We generated m=10 imputed datasets, because of approximately 5-10% missing data.[42] We used all patient characteristics, laboratory values and radiological information mentioned in Table 8.1 and e-Table 8.1 with ≤30% missing data for imputation.

We compared descriptives (e.g., means and standard deviations) of the imputation model with the original data to make sure all imputed values are plausible. We conducted a sensitivity analysis by also performing a complete case analysis.[35]

We quantified the correlation between the LUSS and CTSS with Pearson's correlation coefficient. We assessed interobserver agreement for the LUSS by means of the intraclass correlation coefficient (ICC) with a two-way random effects model. Three sonographers with different levels of experience (EPA 3, 4, and 5) measured the LUSS in a random sample of 20 patients. We used a two-sided significance level of 5% for all analyses. We performed all analyses, as well as the multiple imputation in SPSS version 26.0.

Results

Study population

One hundred fourteen patients were included in the study, and data was collected between March 19 and May 4, 2020 (Figure 8.1). After initial intake at the ED, 24 patients were discharged home, 79 were admitted to the ward, and 12 required ICU admission (see Table 8.1 for patient demographics and clinical characteristics according to disease severity group.) A median of 12 lung ultrasound zones were recorded for each patient. 7 patients (6.1%) had missing zones, but all patients included had at least 6 zones scanned. CTSS data was missing for 5 patients (4.4%).

Associations between LUSS and patient outcomes

There were 17 poor outcome events (14.9%) within 30 days. Time to poor outcome was shorter in the group with a LUSS ≥12 compared to the group with a LUSS <12. None of the potential confounders altered the association between LUSS and poor outcome. We found a HR of 5.59 (95%CI 1.26-24.80), *p*=0.023 in the imputed dataset, with a comparable result in the complete case analysis (Table 8.2, Figure 8.2).

Hospital length of stay was longer among patients with LUSS ≥12 (Table 8.3, Figure 8.3). We found a crude HR of 1.98 (95%CI 1.34-2.93), *p*=0.001. Correcting for confounders

Table 8.1: Baseline characteristics

Patient characteristics	All patients: 114	No admission: 24	Ward admission: 78	ICU admission: 12	*p* value	Missing data (%)
Age, median [IQR]	63 [51.5-74]	57.5 [37-72]	67 [53-75]	61.5 [50.8-67]	**0.07**	0
Male, n (%)	67 (57.9)	16 (66.7)	41 (52.6)	9 (75)	0.24	0
30-day mortality, n (%)	7 (6.1)	0 (0)	5 (6.4)	2 (16.7)	0.14	0
90-day mortality, n (%)	11 (9.6)	0 (0)	7 (9)	4 (33.3)	**0.008**	0
Symptom days, median [IQR]	7 [6]	7 [5]	7 [7]	6.5 [3]	0.81	0
Length of stay, median [IQR]	7 [4]	0 [0]	5 [5]	33 [52]	**<0.001**	0
Symptoms, n (%)						
Fever	83 (71.9)	21 (87.5)	52 (66.7)	9 (75)	0.14	0
Cough	92 (79.8)	21 (87.5)	61 (78.2)	9 (75)	0.58	0
Dyspnea	75 (65.8)	13 (54.2)	52 (66.7)	10 (83.3)	0.23	0
Abdominal symptoms	45 (39.5)	10 (41.7)	30 (38.5)	5 (41.7)	0.96	0
Comorbidities, n (%)						
Cardiovascular disease	22 (19.3)	6 (25)	15 (19.2)	1 (8.3)	0.53	0
COPD	14 (12.3)	3 (12.5)	10 (12.8)	1 (8.3)	1.00	0
Hypertension	36 (31.6)	7 (29.2)	24 (30.8)	5 (41.7)	0.70	0
Diabetes mellitus	25 (21.9)	7 (29.2)	15 (19.2)	3 (25)	0.53	0
Obesity	35 (30.7)	7 (29.2)	23 (29.5)	5 (41.7)	0.94	0
Malignancy	13 (11.4)	4 (16.7)	7 (9)	2 (16.7)	0.33	0
Vital signs						
MEWS, median [IQR]	2 [1-4]	2 [0-2.8]	2.5 [1-3.3]	5.5 [4-6.8]	**<0.001**	0
Systolic blood pressure, mean (SD)	133 (19)	136 (22)	132 (18)	132 (22)	0.74	0.88
Heart rate, mean (SD)	88 (16)	91 (15)	86 (14)	98 (25)	**0.042**	0
Respiratory rate, mean (SD)	21 (7)	18 (5)	21 (6)	30 (10)	**<0.001**	3.5
Temperature, mean (SD)	37.7 (1.1)	37.6 (0.7)	37.8 (1.2)	37.5 (1.4)	0.64	0.88
Oxygen saturation, median [IQR]	96 [94-98]	97.5 [96-99]	95.5 [94-97]	92.5 [88.5-96]	**0.002**	0
Liters of oxygen, median [IQR]	0 [0-3]	0 [0-0]	0 [0-3]	4.5 [0.8-5]	**<0.001**	17.51

Table 8.1: ***Continued***

Patient characteristics	All patients: 114	No admission: 24	Ward admission: 78	ICU admission: 12	*p* value	Missing data (%)
Laboratory results						
Hemoglobin (mmol/l), mean (SD)	8.1 (1.1)	8.3 (1.3)	8.1 (1.0)	8.5 (1.6)	0.44	0.88
Neutrophils (x10^9/l), mean (SD)	4.7 (2.7)	3.4 (1.9)	5.0 (2.7)	6.1 (3.4)	**0.010**	7.02
Lymphocytes (x10^9/l), mean (SD)	0.97 (0.58)	0.98 (0.59)	0.95 (0.49)	1.1 (0.99)	0.80	7.02
Lactate dehydrogenase (U/L), mean (SD)	313 (104)	232 (60)	316 (90)	460 (106)	**<0.001**	9.65
CRP (mg/l), median [IQR]	60 [29-118]	26.4 [8.3-53.5]	60 [32-126]	102.5 [65-160.5]	**<0.001**	0.88
Creatinine (umol/l), median [IQR]	80 [60-100]	77 [66.8-102.5]	81 [58-100]	80.5 [66-126]	0.78	2.63
D-dimer (mg/l), median [IQR]	1.02 [0.75-1.82]	0.56 [0.46-0.86]	1.09 [1.01-4.6]	1.01 [0.81-1.47]	**0.03**	81.58
Hs Troponin T (ng/l), median [IQR]	0.015 [0.007-0.027]	0.015 [0.004-0.023]	0.016 [0.007-0.26]	0.045 [0.011-4.11]	0.24	58.77
Imaging scores						
LUSS, mean (SD)	12.2 (6.8)	6.3 (4.4)	13.1 (6.4)	18.0 (5.0)	**<0.001**	6.14
CT severity score, mean (SD)	9.3 (5.0)	4.8 (2.9)	9.9 (4.8)	13.3 (3.8)	**<0.001**	4.39

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; Hs, high-sensitivity; IQR, interquartile range; LUSS, lung ultrasound score; MEWS, Modified Early Warning Score; SD, standard deviation.

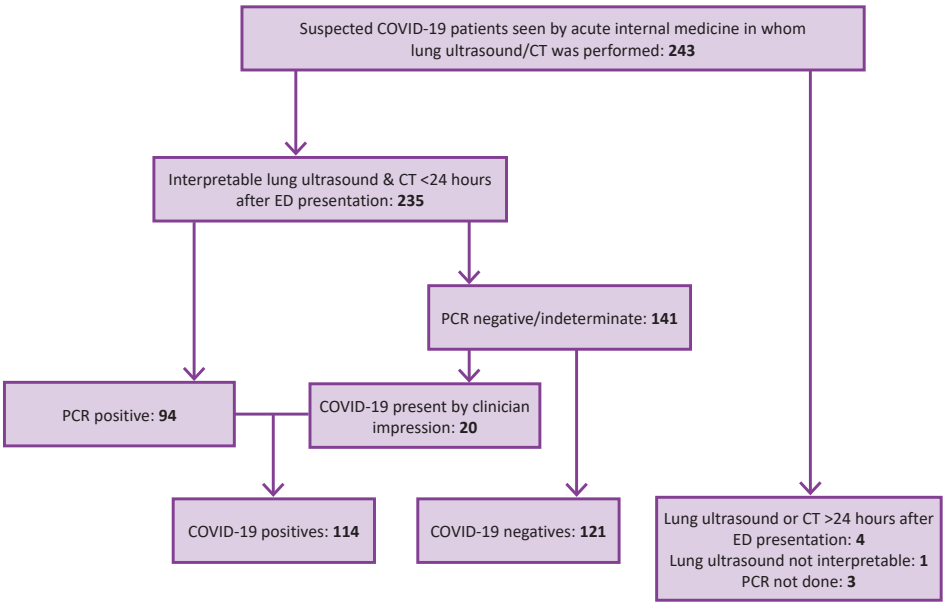


Figure 8.1: Flowchart of patient inclusion and exclusion.
Abbreviations: CT, computed tomography; ED, emergency department; PCR, polymerase chain reaction.

Table 8.2: Associations between lung ultrasound and poor COVID-19 patient outcomes

Model	HR (95%CI)	*p* value
LUSS – dichotomized at median: 12*		
Complete case	5.49 (1.24-24.34)	**0.03**
Imputed	5.59 (1.26-24.80)	**0.02**
LUSS – continuous**		
Complete case	1.11 (1.03-1.21)	**0.01**
Imputed	1.12 (1.04-1.21)	**0.004**

We reported crude (unadjusted) hazard ratios as no confounders were identified. Poor outcome defined as the composite end-point of 30-day all-cause mortality or ICU admission.
*LUSS <12 is the reference category.
**Hazard ratio for poor outcome per point increase in LUSS.
Abbreviations: CI, confidence interval; LUSS, lung ultrasound score; HR, hazard ratio.

lead to an increase in adjusted HR: 2.24 (95%CI 1.47-3.40), $p<0.001$. Analyses on imputed dataset and complete analysis yielded similar results.

Differences between disease severity groups

There was a statistically significant difference in mean LUSS between the disease severity grades (mild: no admission; moderate: ward admission; and severe: ICU admission), as determined by one-way ANOVA ($p<0.001$) (see end of Table 8.1). The mean LUSS were 6.3 (SD 4.4), 13.1 (SD 6.4), and 18.0 (SD 5.0) respectively. Tukey HSD post-hoc tests for pairwise comparisons revealed significant differences in mean LUSS for all pairs of groups.

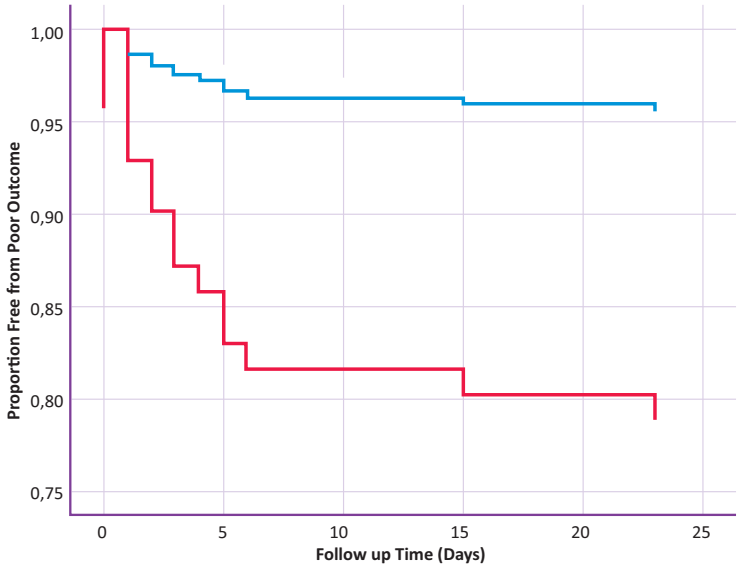


Figure 8.2: Kaplan-Meier curve for association between LUSS and poor COVID-19 outcomes.
Kaplan-Meier curves are based on complete case analysis. Poor outcome defined as intensive care unit admission or death at 30 days. The lung ultrasound score (LUSS) was dichotomized at the median of 12.
Red line: patients with a LUSS ≥12.
Blue line: patients with a LUSS <12.

Table 8.3: Associations between lung ultrasound and COVID-19 time to hospital discharge

Model	HR (95%CI)	*p* value
Lung ultrasound score – dichotomized at median: 12*		
Complete case (crude)	2.02 (1.35-3.00)	**0.001**
Complete case (adjusted)	2.46 (1.58-3.85)	**<0.001**
Imputed (crude)	1.98 (1.34-2.93)	**0.001**
Imputed (adjusted)	2.24 (1.47-3.40)	**<0.001**
Lung ultrasound score – continuous		
Complete case (crude)	1.06 (1.04-1.09)	**<0.001**
Complete case (adjusted)	1.07 (1.04-1.11)	**<0.001**
Imputed (crude)	1.05 (1.02-1.09)	**<0.001**
Imputed (adjusted)	1.06 (1.03-1.10)	**<0.001**

We reported crude and adjusted HR. Only duration of symptoms was a significant confounder.
*LUSS ≥12 is the reference category.
Abbreviations: CI, Confidence interval; LUSS, lung ultrasound score; HR, hazard ratio.

Discriminative ability

The AUC of the ROC curve that depicts the ability of the LUSS to discriminate between hospital admission (ward and ICU combined) and no admission was 0.83 (95%CI 0.75-0.91), which was almost identical to the CTSS. The optimal cutoff was 12, with a sensitivity of 70.2%, a specificity of 91.3%, and a diagnostic odds ratio of 24.8 (Figure 8.4).

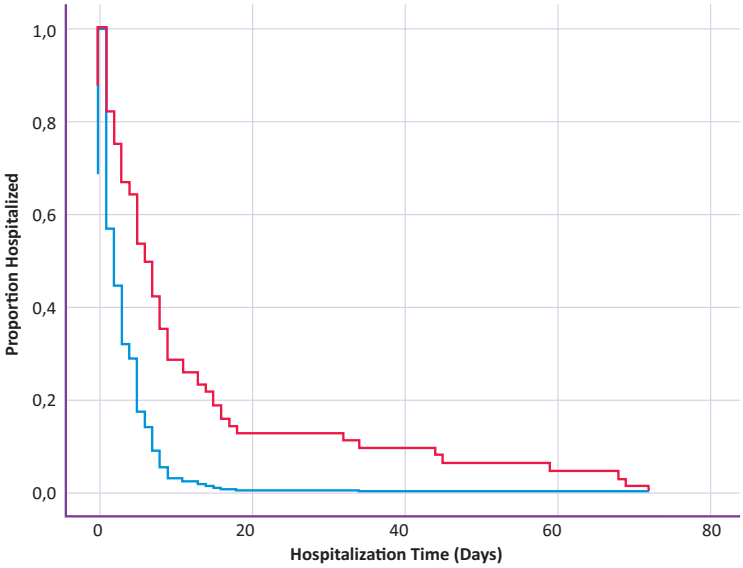


Figure 8.3: Kaplan-Meier curve for association between LUSS and time to discharge.
Kaplan-Meier curves are based on complete case analysis. The lung ultrasound score (LUSS) was dichotomized at the median of 12.
Red line: patients with a LUSS ≥12.
Blue line: patients with a LUSS <12.

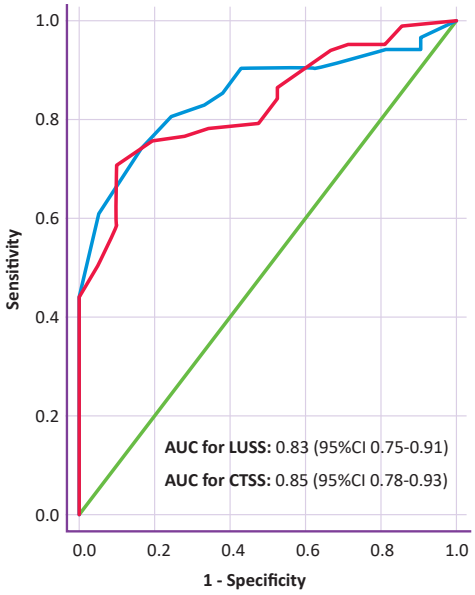


Figure 8.4: Receiver Operating Characteristics curves for associations between LUSS, CTSS and hospital admission.
Green line: reference line.
Red line: LUSS.
Blue line: CTSS.
Abbreviations: AUC, area under the curve; CTSS, computed tomography severity score; LUSS, lung ultrasound score.

Grey zone analysis with a high LR cutoff (i.e., NLR 0.1 and PLR 10) showed that patients with a LUSS ≤1 (that is, LUSS showing almost no signs of pulmonary involvement) could be discharged from ED. We found that patients with a LUSS ≥15 almost certainly required admission (Figure 8.5A). The grey zone (inconclusive test zone) contained 55.3% of patients. If we reduce the cutoff to a NLR of 0.2 and PLR of 5, the number of patients within the grey zone decreases to 30.7% (Figure 8.5B).

Patients with a LUSS ≥11 had a post-test increase in admission probability of 30%. Five patients were admitted for reasons not related to the COVID-19 diagnosis, including only one patient without any abnormalities on their LUSS and four patients without any CT abnormalities. In fact, all patients with a LUSS <3 did not require any supplemental oxygen.

Correlation between LUSS & CTSS

We found a strong positive association between the LUSS and CTSS, with a Pearson's correlation coefficient of 0.60 (95%CI 0.48-0.71). The interrater agreement for LUSS was excellent, with an ICC of 0.88 (95%CI 0.77-0.95).

Limitations/bias

Our study has several limitations. First, although we included consecutive patients when a certified sonographer was present, we could not include every positive COVID-19 patient. However, we have tried to enrol every eligible patient when a certified sonographer was present, therefore minimizing any possible selection bias. We therefore feel that these omissions have not influenced our results. We look forward to seeing these results corroborated in different settings. Second, the wide confidence intervals of the hazard ratios in the poor outcome analysis are an indication of the imprecision of the estimate. This is most likely due to the relatively small sample size. Our results should therefore be confirmed in a larger study. Third, we also included patients who were diagnosed on the basis of an MDT decision. However, results do not differ between the PCR positive and the MDT positive group. Fourth, we tried to minimise incorporation bias by blinding radiologists and scanning physicians for each other's results. However, they were aware of the patients' clinical parameters. While this may have caused an upward adjustment of LUSS and CTSS in sicker patients and vice versa in less sick patients, we would have expected this to apply to CT and LUSS to the same degree. Moreover, blinding them entirely from the patient's clinical information was not desirable as this does not reflect daily practice.

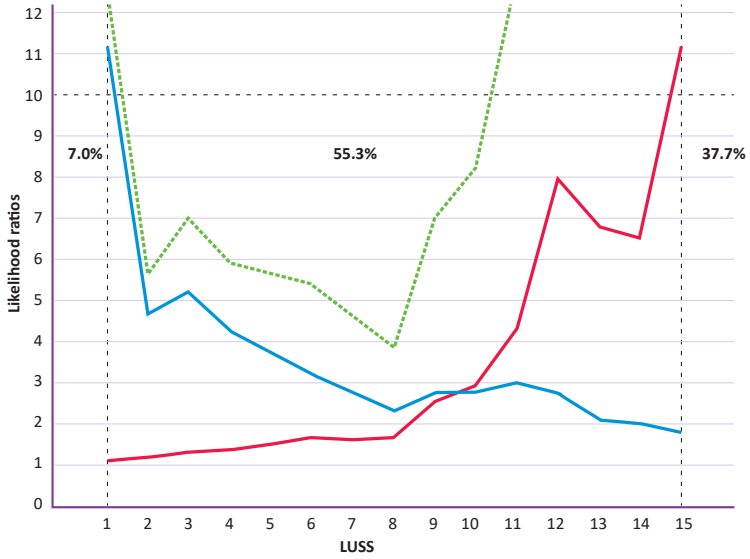


Figure 8.5A: Grey zone analysis – LUSS versus hospital admission – LR cutoff = 10.
Green line: DOR.
Red line: LR+.
Blue line: LR-.
Vertical dotted line: LR cutoff.
Abbreviations: LR+, positive likelihood ratio; LR-, negative likelihood ratio; LUSS, lung ultrasound score.

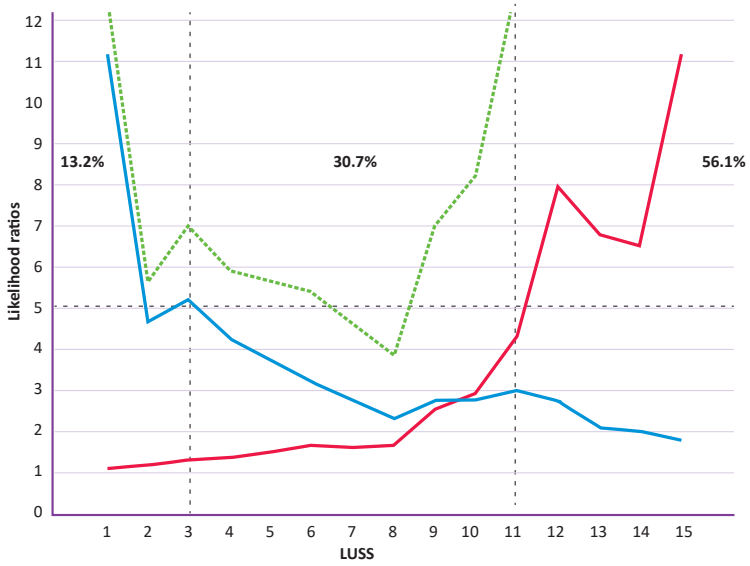


Figure 8.5B: Grey zone analysis – LUSS versus hospital admission – LR cutoff = 5.
Green line: DOR.
Red line: LR+.
Blue line: LR-.
Vertical dotted line: LR cutoff.
Abbreviations: LR+, positive likelihood ratio; LR-, negative likelihood ratio; LUSS, lung ultrasound score.

Discussion

To our knowledge, this is the first multicenter study to prospectively compare the correlation between the LUSS and CTSS in COVID-19, and assess the ability of LUSS in discriminating COVID-19 pneumonia disease severity and its association with prognosis.

Our results show that: 1) COVID-19 pulmonary involvement quantified by the semi-quantitative LUSS is strongly correlated with pulmonary involvement assessed by CT; and 2) Increasing LUSS is also positively associated with disease severity.

This is in keeping with other findings on viral pneumonias and ARDS,[15,30] as well as recent retrospective data in COVID-19.[22,24,43] The WHO and Fleischner Society agree that imaging studies should be considered in triage and management of patients, especially in resource constrained environments (e.g., no immediate PCR results) and in patients with at least moderate disease.[26,44] While CT is considered the gold standard to assess the degree of pulmonary involvement, our findings indicate that lung ultrasound could be a viable alternative to CT in the initial assessment of lung involvement in COVID-19.

Initially, it was believed that lung ultrasound would be less reliable than CT, because of its perceived inability to detect central lesions.[44] However, the peripheral distribution of COVID-19, makes lung ultrasound ideal for detection of these abnormalities.[19,45,46] In fact, lung ultrasound also serves as a reliable test in viral pneumonias that produce more central abnormalities such as influenza.[47–49] Incorporating lung ultrasound into routine COVID-19 diagnostics offers the potential of reducing stress on conventional radiological resources, decreasing the need of transporting ill, unstable patients to CT, and lowering the amount of health care personnel exposed to potentially contagious patients.[24,50]

Furthermore, the LUSS is able to excellently discriminate between patients who require admission and those who do not. Interestingly, the LUSS could do so just as well as the CTSS. Furthermore, the grey zone analysis indicates that the LUSS changes the post-test probability of admission moderately (~30%) in more than two-thirds of patients, and largely (~45%) in almost half of patients, which is also comparable to the CTSS.[2]

Previous studies found that chest imaging features can predate clinical symptoms or deterioration.[4,5] It has even been suggested that imaging findings might have additional value to clinical prognostic factors in selecting COVID-19 patients with high risk of poor outcome irrespective of clinical presentation or disease course.[51,52] Our findings show that baseline lung ultrasound is indeed a predictor of poor outcome at 30 days and prolonged admission. These results are in line with literature on CT in COVID-19 that shows that pulmonary involvement on CT might be independently associated with outcome.[2,4,5,53] Sensitivity

analysis shows no significant differences between the imputed and complete case data. Two recent retrospective single-center studies from Israel and the UK show a similar association between lung ultrasound and poor outcomes in COVID-19.[23,24] Our results add to accumulating evidence that a semi-quantitative LUSS, as a proxy for lung involvement, is predictive of a poor outcome in a range of other pathologies such as ARDS and heart failure.[15,54]

It is still unclear however, how lung ultrasound should be incorporated with other biomarkers and clinical information. Patients with a higher LUSS tend to be more ill, with increases in C-reactive protein (CRP), neutrophils, lactate dehydrogenase (LDH), and Modified Early Warning Score (MEWS) (Table 8.1). Combining lung ultrasound (and other POCUS modalities) with additional known prognostic factors for poor outcomes may enhance existing risk scores, as has been the case with CT findings.[51,52]

Time at the frontlines is of the essence; clinicians require tools that enable them to make quick and accurate diagnostic and management decisions. Reliability and speed are even more critical as waves of COVID-19 patients keep overwhelming EDs and clogging up acute (and regular) care pathways. Integrating POCUS into clinical decision making has shown to speed up diagnosis, improve patient triage, and time to treatment at the ED significantly.[12,55] Lung ultrasound in COVID-19 may be of particular additional value to the physical examination and sound clinical judgement in patients who do not present with overt symptoms (e.g., silent hypoxia, or desaturation only with exercise), but might still benefit from a higher level of monitoring based on a high LUSS. One could also speculate that serial point-of-care lung ultrasound, might be used to monitor pulmonary involvement, track the disease course, guide management, and determine response to treatment, without any radiation exposure. The LUSS might also be a welcome addition to laboratory markers, given the speed with which the results of POCUS are available. Lung ultrasound results can be obtained within 5-10 minutes, which is much faster than traditional laboratory or imaging results. Fortunately, POCUS is simple to learn for (para)medical personnel.[56,57] Furthermore, as an affordable and easy-to-use tool, POCUS could reduce obstacles to proper care, which is of particular importance given the ethnoracial, cultural, and socioeconomic disparities COVID-19 has laid bare worldwide.[58,59] Moreover, POCUS can be used in different care setting (e.g., ED, family practice, care homes, or rural medicine), further lowering barriers to adequate care during this pandemic.[60,61]

Future research should focus on the value of serial LUSS in monitoring and response to treatment, implementation of POCUS in different settings (e.g., nursing homes, outpatient clinics, community health centers, and general practitioner triage), and the development and validation of predictive models intergrating the LUSS with other prognostic factors.

Conclusion

In summary, we demonstrate that the LUSS correlates well with CTSS. Moreover, COVID-19 pulmonary involvement measured by lung ultrasound is significantly associated with poor outcome, disease severity and admission duration. Lung ultrasound may therefore help triage, risk stratification, and management of COVID-19 patients at the ED.

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9

Screening for asymptomatic proximal deep vein thrombosis in COVID-19 patients admitted to the medical ward
A cross-sectional study

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Abstract

Background: Patients with COVID-19 have an increased risk for venous thromboembolism (VTE), especially pulmonary embolism (PE). The exact prevalence of asymptomatic deep venous thrombosis (DVT) is not known, as is the usefulness of screening for DVT in patients admitted to ward with COVID-19. We therefore studied the prevalence of asymptomatic DVT in these patients.

Methods: We performed a cross-sectional observational multicenter study at four university medical centers in The Netherlands. All adult patients admitted with COVID-19 to a medical ward were eligible for inclusion, including patients who were transferred back from the intensive care unit (ICU) to the ward. The study protocol consisted of weekly cross-sectional rounds of extended compression ultrasound (ECUS).

Results: In total, 125 patients were included in the study. A significant proportion of patients (34; 27%) had developed a VTE during their admission for COVID-19 before the study ECUS was performed. In most VTE cases (27; 79%) this concerned pulmonary embolism. A new asymptomatic DVT was found in 5 of 125 patients (4.0%; 95%CI 1.3-9.1) (Table 9.2). Nine patients (7.2%; 95%CI 3.3-13.2) developed a VTE (all PE) diagnosed within 28 days after the screening ECUS was performed.

Conclusion: We found a low prevalence (4%) of newly discovered asymptomatic DVT outside the ICU setting in COVID-19 patients. Despite this low prevalence, nine patients developed PE (7%) within 28 days after the ECUS. This favors the hypothesis of local thrombus formation in the lungs. Based on our findings and literature, we do not recommend DVT ultrasound screening of asymptomatic patients with COVID-19 admitted to the ward.

Introduction

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged.[1] The clinical spectrum of this pathogen ranges from an asymptomatic infection and mild respiratory disease to severe viral pneumonia, collectively called coronavirus disease 2019 (COVID-19).[2] These latter patients have higher levels of D-dimer compared to non-severe cases. A high D-dimer reflects coagulopathy and disseminated intravascular coagulation (DIC) and is associated with an increased risk of death.[3] Studies on COVID-19 patients show a marked increase in the risk of venous thromboembolism (VTE). Pulmonary embolism (PE) occurred in 20.4% of French patients admitted to the intensive care unit (ICU) despite prophylactic antithrombotic treatment in almost all affected patients (20/22).[4] In a Dutch single-center cohort study, VTE was observed in 29 of 74 ICU patients despite thromboprophylaxis.[5] A multicenter study showed a 31% incidence of any thromboembolism (arterial and/or venous) in ICU patients despite standard prophylactic anticoagulation use, in most cases pulmonary embolism (81% of total thrombotic events).[6] These studies highlight the problem of thrombosis despite thromboprophylaxis in the ICU.

The incidence of (a)symptomatic deep vein thrombosis (DVT) outside the ICU is much lower. A study from Italy showed an incidence of VTE of 3.8% for patients admitted to the general ward, and half of them occurred within 24 hours of admission.[7] This is in line with the previously mentioned Dutch study, which showed an incidence of symptomatic DVT in 3% (4 of 124) of patients admitted to the ward, and asymptomatic DVT was only found in ICU patients.[5] However, data on asymptomatic VTE during ward admissions are scarce, as only 17 of these patients were screened with an ultrasound. It is unknown if PE comes from DVT or reflects a local pulmonary process of inflammation and coagulation in COVID-19. Whether early detection of asymptomatic DVT provides the opportunity to increase anticoagulation and prevent clinical deterioration due to PE in patients admitted to medical wards needs further research. Also, the optimal prophylactic anticoagulation dose for patients admitted to the ward with COVID-19 is a topic of ongoing debate.[8]

We conducted a study to determine the prevalence of asymptomatic DVT in COVID-19 patients admitted to medical wards. Our hypothesis is that COVID-19-related VTE is predominantly caused by local inflammation in the lungs and not the result of dislocating clots from DVT. As such, we expect a low prevalence of asymptomatic DVT.

Methods

Study design

We performed a cross-sectional observational multicenter study at four university medical centers in the Netherlands. All adult patients admitted with COVID-19 to a medical ward were eligible for inclusion, including patients who were transferred back from the ICU to the ward. The inclusion started the 27th of April 2020 and ended the 19th of June 2020 when the first wave of COVID-19 in the Netherlands ended. Patients were considered to have COVID-19 if this was confirmed with a positive polymerase chain reaction (PCR) test or when the treating (multidisciplinary) medical team concluded that it was clinically and radiographically highly suspected.

Ultrasound protocol

The study protocol consisted of weekly cross-sectional rounds of ultrasounds instead of examining every consecutive patient to save scarce personal protection equipment. Every patient was examined only once. Extended compression ultrasonography (ECUS) was performed on both legs with appreciation of the femoral vein and popliteal vein for at least five standardized points. From proximal to distal these include[9]:

- the common femoral vein;
- the common femoral vein at the entrance of the greater saphenous vein (e-Video 9.1: a compressible left common femoral vein: no DVT; e-Video 9.2: a noncompressible right common femoral vein: DVT);
- the femoral vein at the branching of the lateral perforator vein (e-Video 9.3: right femoral vein thrombosis);
- the distal femoral vein; and
- the popliteal vein (e-Video 9.4: a compressible left popliteal vein: no DVT; e-Video 9.5: a noncompressible right popliteal vein: DVT).

Distal DVT was not part of the diagnosis of DVT, as the clinical significance and need for anticoagulation in distal DVT is unsure.[10] Thrombosis was defined as the inability to completely compress the venous lumen (e-Video 9.1, 9.3 & 9.5). The ECUS exam was stored in the patient's record. When DVT was diagnosed, the treating physician was informed promptly. Subsequent treatment of (asymptomatic) VTE was not part of the research protocol and depended on local guidelines and/or as indicated by the treating physician.

Routine baseline characteristics were documented, including the use of anticoagulants (prophylactic and therapeutic dose) and previous VTE. The primary outcome was the finding of asymptomatic DVT.

Statistical analysis

Patient characteristics were analyzed with descriptive statistics. The proportion of VTE was assessed. Descriptive analysis was performed with SPSS 23.0. Based on a prevalence of asymptomatic DVT of 2.5% and a confidence interval of 0-5%, 150 patients would be needed for inclusion.

Results

Study population

In total, 144 patients were screened for eligibility; 17 patients were excluded because of lack of informed consent. Another two patients were already discharged before ECUS was possible. The remaining 125 patients were included in the study. Baseline characteristics are shown in Table 9.1. COVID-19 was proven with PCR in 122 of 125 patients (98%). A

Table 9.1: Baseline characteristics

	All patients (N=125)	Patients with DVT at ECUS screening (N=5)
No of hospitals	4	2
Male	89 (71)	4 (80)
Age	62 [53-70]	49 [37-67]
BMI	27.0 [24.0-30.7]	26.8 [23.9-31.1]
Positive PCR	122 (98)	5 (100)
Negative PCR, but clinically & radiographically highly suspected	3 (2)	0 (0)
History of DVT at admission	9 (7)	0 (0)
History of malignancy at admission	6 (5)	0 (0)
Use of thromboprophylaxis		
No	5 (4)	1 (17)
Low (prophylactic)	36 (29)	0 (0)
Intermediate	27 (22)	1 (17)
High (therapeutic)	57 (46)	3 (50)
At day of ECUS		
Days of COVID-19 symptoms	25 [13-38]	46 [24-75]
Days of admission	13 [5-28]	39 [10-58]
Prior ICU admission	64 (51)	4 (80)
Days of ICU admission	20 [12-29]	38 [18-48]
DVT related symptoms	0 (0)	0 (0)
VTE during current admission before ECUS	34 (27)	3 (60)
Pulmonary embolism	27 (22)	3 (60)
DVT leg	5 (4)	0 (0)
DVT arm	2 (2)	1 (20)

Data are presented as absolute numbers with (%) or interquartile range [IQR] as appropriate.
Abbreviations: BMI, body mass index; PCR, polymerase chain reaction; ECUS, extended compression ultrasound; ICU, intensive care unit; VTE, venous thromboembolism; DVT, deep vein thrombosis.

history of VTE before admission was present in nine patients (7%). Half of included patients had a prior ICU admission. A significant portion of patients (34; 27%) had developed a VTE during their admission for COVID-19 before the ECUS was performed, mostly pulmonary embolism (27 of 34; 79%). DVT of the arm and DVT of the leg were present in two and five patients respectively. The majority of patients received low molecular weight heparin (LMWH) when the screening ECUS was performed. This included a prophylactic dose in 63 patients (51%) and a high (therapeutic) dose in 57 patients (46%). Only five patients received no pharmacological thromboprophylaxis. In half of the patients, the ECUS was performed after intensive care admission, with a median ICU length of stay of 20 days. There were no patients with symptoms of DVT. The prevalence of asymptomatic DVT of the leg was still four of 64 patients (6.3%) in the subgroup of patients recovering from ICU admission (51%). One ward patient had a DVT without prior ICU admission (1.6%).

Asymptomatic DVT

A new asymptomatic DVT was found in five of 125 patients (4.0%; 95%CI 1.3-9.1) (Table 9.2). In only two patients (1.6%; 95%CI 0.2-5.7) therapeutic anticoagulant treatment was initiated. The remaining three patients were already therapeutically anticoagulated for a prior VTE. One patient received intermediate dose thromboprophylaxis, and the final patient had no anticoagulation. Nine patients (7.2%; 95%CI 3.3-13.2) had a VTE diagnosed within 28 days after the screening ECUS was performed with a median of three days [IQR 0.5-7.5]. In all cases, the VTE concerned PE, and no DVT was diagnosed. The overall 30-day mortality was 8.0% (95%CI 3.9-14.2) in all patients, and one out of five patients with an asymptomatic DVT died (20%).

Table 9.2: Prevalence of DVT

Outcome	All patients N=125 N (%; 95%CI)	Patients with previous VTE during admission N=34 N (%; 95%CI)	Patient without previous VTE during admission N=91 N (%; 95%CI)
Asymptomatic DVT found with ECUS screening	5 (4.0%; 1.3-9.1%)	3 (8.8%; 1.9-23.7%)	2 (2.2%; 0.3-7.7%)
VTE diagnosed within 28 days after study ECUS	9 (7.2%; 3.3-13.2%)	1 (2.9%; 0.1-15.3%)	8 (8.8%; 3.9-16.6%)
Pulmonary embolism	9 (7.2%; 3.3-13.2%)	1 (2.9%; 0.1-15.3%)	8 (8.8%; 3.9-16.6%)
DVT leg	0 (0.0%; 0.0-2.9%)	0 (0.0%; 0.0-10.3%)	0 (0.0%; 0.0-4.0%)
DVT arm	0 (0.0%; 0.0-2.9%)	0 (0.0%; 0.0-10.3%)	0 (0.0%; 0.0-4.0%)
Days after study ECUS – median [IQR]	3 [0.5-7.5]	0 [N/A]	3.5 [1.3-7.8]
30-day mortality	10 (8.0%; 3.9-14.2%)	1 (2.9%; 0.1-15.3%)	8 (8.8%; 3.9-16.6%)

Data are presented as absolute numbers with (%), interquartile range [IQR] or 95% confidence intervals (95%CI) as appropriate.
Abbreviations: CI, confidence interval; ECUS, extended compression ultrasound; VTE, venous thromboembolism; DVT, deep vein thrombosis.

Discussion

Prevalence of asymptomatic DVT

Our study shows a prevalence of 4% (95%CI 1.3-9.1) of asymptomatic proximal DVT in patients hospitalized with COVID-19 outside the ICU. Half of these patients were already treated with therapeutic dose anticoagulation because of previously diagnosed VTE during their admission. Finding an asymptomatic DVT in these patients had no clinical or therapeutic consequence. Despite a negative screening ECUS, nine of 125 (7.2%) patients developed PE after the ECUS exam (with a median of three days).

Our study is in line with findings in a previous Dutch study, as they showed a low incidence of symptomatic DVT (1.6%) and asymptomatic DVT (none of the 17 patients) of patients with COVID-19 on a general ward, in contrast to a cumulative incidence of 32% in ICU patients.[5] A study from Spain included 156 patients with COVID-19.[11] The ultrasound for asymptomatic DVT was positive in 23 patients (14.7%), but in 22 patients it only concerned a distal DVT. Also, they included patients with an elevated D-dimer (>1000 ng/mL) – these patients had to be hospitalized for at least 48h – and patients were excluded if therapeutic doses of anticoagulation were used, limiting the generalizability of their findings. No patient with a negative ultrasound developed PE at the time of the study's closure. An Italian study included 84 hospitalized COVID-19 patients and showed an overall proximal DVT incidence of 2.4%.[12] They were not able to report clinical outcomes of patients with (distal) DVT compared to patients without DVT. In another small study from Italy, 66 patients who were hospitalized for at least 5 days for COVID-19 underwent 2-points compressive ultrasonography in a single day.[13] The presence of an asymptomatic proximal DVT was confirmed in nine patients (13.6%), which was bilateral in three patients. Additional scanning in patients showed PE in five of them. Almost all patients received standard-dose thromboprophylaxis. Finally, a small retrospective French study of 42 patients reported a cumulative incidence of asymptomatic DVT of 19% (in eight of 42 patients).[14] However, in seven out of eight cases, it was only a distal DVT giving an incidence of proximal DVT of 2.3%. More recent studies confirm the low prevalence of asymptomatic proximal DVT.[15,16] In conclusion, all besides one study showed a low incidence of proximal DVT outside the ICU. Therefore, screening for asymptomatic DVT on a general ward does not seem useful.[17]

Underlying pathophysiology

The low prevalence of DVT in contrast to relatively high rates of PE, even after ICU discharge, may suggest local pulmonary thrombus formation and unique characteristics of COVID-19 coagulopathy. This theory is supported by several studies showing that multiple factors are involved in COVID-19-associated coagulopathy with high rates of venous

thromboembolism, although the exact mechanisms are yet to be elucidated.[18–20] The complex thromboinflammatory process in COVID-19 include endotheliopathy due to direct endothelial infection with SARS-COV-2 and indirect inflammation. The elevated levels of clotting factors and the loss of thromboprotective function with glycocalyx damage also contribute to the coagulopathy with local micro- and macro-vascular thrombosis.

Limitations

First, although ECUS is a full ultrasound exam of the deep venous system, it does not encompass (isolated) distal DVT (also known as calf DVT). These may have been missed and may progress to proximal DVT. However, it is unclear what the optimal treatment of distal DVT is, or if it should be treated at all. Second, we stopped the study after 125 inclusions, 25 patients short of our calculated sample size, due to a lack of COVID-19 patients in the summer of 2020. However, we do not think this had a large influence on our study results.

Furthermore, the majority already received intermediate dose or therapeutic anticoagulation. Lastly, we have only performed an ECUS once in each patient, and later development of asymptomatic DVT was not registered. However, no patient developed a symptomatic DVT within 28 days.

Conclusion

We have shown a low prevalence (4%) of newly discovered asymptomatic DVT outside the ICU setting in COVID-19 patients. Sixty percent of those patients were already treated with a therapeutic dose of anticoagulants because of a symptomatic thrombosis at another site. No patients developed a new DVT within 28 days after the ECUS, but nine patients did develop PE (7%). This may be explained by a local process of thrombus formation in the lungs instead of a dislocating thrombus from the extremities. Based on our findings and the extant literature, we do not recommend ECUS screening of asymptomatic patients with COVID-19 admitted to the ward.

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PART 3

Point-of-care ultrasound in COVID-19 patients in the critical care setting





10

Concise versus extended lung ultrasound score to monitor critically ill COVID-19 patients in supine and prone position

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Abstract

Background: Lung ultrasound (LUS) can be used to monitor critically ill patients with COVID-19, but the optimal number of examined lung zones is disputed.

Methods: This was a prospective observational study. The objective was to investigate whether concise (6 zones) and extended (12 zones) LUS scoring protocols are clinically equivalent in critically ill ICU patients with COVID-19. The primary outcome of this study was (statistical) agreement between concise and extended LUS score index (LUSI) evaluated in both supine and prone position. Agreement was determined using correlation coefficients and Bland-Altman plots to detect systematic differences between protocols. Secondary outcomes were difference between LUSI in supine and prone position using similar methods.

Results: We included 130 LUS examinations in 40 patients (mean age of 69±8.5, 75% male). Agreement between concise and extended LUSI had no clinically relevant constant or proportional bias and limits of agreement (LoA) below the smallest detectable change (SDC) of the scanning clinician.

Conclusion: Concise LUS was equally informative as extended LUS for monitoring critically ill patients with COVID-19 in supine or prone position. Clinicians can monitor patients undergoing position changes but must be wary that LUSI alterations may result from the position change itself rather than disease progression or clinical improvement.

Introduction

A significant portion of patients with COVID-19 develop acute respiratory syndrome (ARDS) and require admission to the intensive care unit (ICU), mechanical ventilation, and prone positioning.[1–3] Lung ultrasound (LUS) can be used as an alternative to chest computed tomography (CT) for diagnosing and monitoring COVID-19.[4–6]

Monitoring of pulmonary involvement, using the lung ultrasound score (LUSS), can be performed in supine and prone position. Various scan protocols of interest exist, but it is currently unclear which is most efficient.[7–9] The most widely used protocols, performed on 12 zones in supine position and prone position, have anatomical rationale but are time consuming and impractical in a setting where effective use of time and resources is crucial.[9–11] Two studies suggest that expeditious 6-zone examinations might be equally informative to their elaborate counterparts, but evidence in COVID-19 remains limited.[5,12] Moreover, prolonged ventilation in prone position may hinder sequential monitoring of pulmonary involvement, especially since position changes may alter LUSS as a result of recruitment and redistribution.[13,14]

The aim of this study was to investigate whether concise (6 zones) and extended (12 zones) LUS protocols are clinically equivalent for monitoring ICU patients with COVID-19.[15] We hypothesized that: 1) concise 6-zone LUS has strong agreement with an extended 12-zone LUS in supine and prone position, respectively; 2) LUS in supine position is correlated to LUS in prone position but may have large differences; and 3) LUS has high reproducibility.

Methods

Study design

This was a single-center prospective observational study. The study was performed in the ICU of a tertiary academic hospital (Amsterdam University Medical Center, location VUmc, Amsterdam, the Netherlands). LUS examinations are regularly performed in this ICU provided that a relevant clinical indication exists. The local institutional review board approved the study, and necessity for informed consent was waived (2020.011). The Standards of Reporting of Observational Studies in Epidemiology checklist was used in the drafting of this manuscript.[16]

Adult (>18 years) patients admitted to the ICU with a laboratory confirmed diagnosis of COVID-19 were eligible when invasive mechanical ventilation and prone positioning were required. Patients were included from November 11, 2020 until February 15, 2021. An

ultrasound examination was performed before and after positioning the patients from supine to prone (or vice versa), as shown in Figure 10.1.

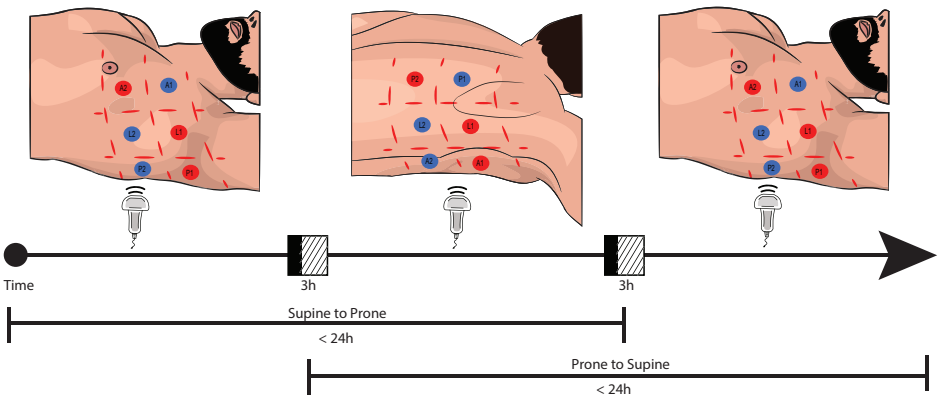


Figure 10.1: Inclusion and ultrasound protocol.
A before and after examination was performed within 24h from each other and at least 3h after position change. Each patient could be included during supine-to-prone positioning and prone-to-supine positioning. The middle examination could be 2 separate examinations or one examination depending on whether there was overlap in 24h time window. The collective dots represent the extended examination on each hemithorax, whereas the blue dots represent the concise examination. A1 and A2 are anterior; L1 and L2 are lateral; and P1 and P2 are posterior.

The agreement between concise and extended protocols was evaluated at the same time point with the same ultrasound transducer in either supine or prone position. Each patient required at least one prone and one supine examination to be included. The supine and prone examinations could not be >24h apart to allow comparison between protocols while minimizing changes related to disease course, fluid balance, and ventilator settings. In addition, the examination could only be performed if the patients had been in the same position for at least the previous 3h. This is because LUS detectable changes in aeration occur mostly during the first 3h after position change but not afterward.[11] The initial change reflects gravity-dependent shifts and redistribution of aeration. This study investigated agreement between protocols in steady state and not the immediate dynamic effects of prone positioning on LUS itself. Comparing protocols amid actively ongoing changes may interfere with assessment of protocol equivalence. Lastly, the protocol allowed 2 inclusions per patient, once for supine-to-prone positioning and once for prone-to-supine positioning (up to 4 examinations).

For example, a LUS examination is performed in supine position before position change. Then, a second LUS examination is performed in prone position at least 3h after position change but within 24h of the first examination. Last, a third examination is performed after resupination, at least 3h after position change and within 24h of the second examination.

The concise and extensive protocols can now be compared at individual examinations and across position changes (supine to prone as well as prone to supine).

Variables

Baseline characteristics and P_aO_2/F_iO_2 were collected and calculated closest to the time of ultrasound examination. Patients with a P_aO_2/F_iO_2 increase of ≥20mmHg after supine-to-prone position change were classified as responders, whereas those with a P_aO_2/F_iO_2 change <20mmHg were classified as non-responders.[3,17]

Ultrasound measurements

All examinations were performed or supervised by certified ultrasound physicians using a COVID-19 unit–restricted Sonosite Edge II ultrasound machine (Fujifilm Sonosite, Bothell, Washington). All measurements were performed using a 10-5 MHz linear transducer (Sonosite L38, Fujifilm Sonosite) or 5-3 MHz curvilinear transducer (Sonosite C60, Fujifilm Sonosite) with lung examination setting (multibeam imaging off and tissue harmonic imaging off) and depth until an adequately assessable video was obtained (at least >6cm).[10,18] Supine and prone examinations were conducted on 12 zones based on seminal LUS publications (e-Figure 5.1 & e-Table 5.1).[9,10] The 6-zone examination for supine and prone position, referred to as the concise examination, was a subgroup of zones selected based on the well-established BLUE protocol: A1, L2, and P2 for supine position; and P1, L2, and A2 for prone position (Figure 10.1). This zone distribution was selected because it can discern variations along both the anteroposterior and apical-basal axis. Regional subgroups (anterior, A1 and A2; lateral, L1 and L2; and posterior, P1 and P2) were also selected due to potential relevance of localization.[19]

Offline analyses of ultrasound images were performed by 2 investigators (MLAH and RSWS) blinded to patients' characteristics. The offline reviewers determined the LUSS per zone (e-Table 5.1): normal = 0 (e-Video 5.1); well-separated B-lines (>2) = 1 (e-Video 5.2); confluent B-lines, small subpleural consolidation = 2 (e-Video 5.3 & 5.12); large (lobar) consolidation with tissue-like pattern = 3 (e-Video 5.10 & 5.11). In order to adequately compare pulmonary involvement over different examinations, a LUS score index (LUSI), where LUS was expressed as a percentage of the total score achievable, was calculated and used for all analyses, as described previously.[5]

Statistical analysis

Statistical analyses were performed using SPSS version 26 (IBM, Armonk, New York) and R language for statistical computing (R Foundation for Statistical Computing, Vienna, Austria) with the tidyverse suite of packages (Posit, Boston, Massachusetts). Baseline

characteristics and outcome variables were presented as means ±SD, medians, and interquartile range or numbers and percentages when appropriate. Shapiro-Wilk test, visual inspection of histograms, and Q-Q plots were used to determine data distribution.

Primary outcome

Reliability between the concise and extended LUSI was tested in both supine and prone position using a Spearman correlation coefficient. Agreement (or measurement error) was visualized by Bland-Altman plots.[20,21] Agreement was considered clinically relevant when the Bland-Altman plots limits of agreement (LoA) were smaller than the smallest detectable change (SDC) for LUSI that is found between raters (see below). As this would indicate that the difference between concise and extended LUS examinations falls within typical LUSI measurement error.

Secondary outcome

The relation between supine and prone concise examinations was tested using a Spearman correlation coefficient. A Bland-Altman plot was created to further understand the agreement between these 2 examinations. The LoA were compared to the calculated SDC for LUSI.

Reproducibility

Interrater (MLAH vs RSWS) and intrarater (MLAH vs MLAH) agreement on interpretation of images after acquisition were estimated using a weighted kappa for ordinal data.[21] Based on previous literature, evaluation of 51 zones was required to reject the null hypothesis that agreement was moderate (kappa 0.5) when true agreement was very good (kappa 0.89).[6] The calculation was performed for a kappa agreement test assuming outcome frequency of 0.25, a of 0.05, and power of 0.80 and is likely an overestimation of sample size required for a weighted kappa test.[22] Ultimately, a distinct set of 52 zones were evaluated (3 extended supine and 1 extended prone full examinations selected at random) to ensure balanced anatomical zone representation. These data were also used to determine the SDC in supine and prone extended examination based on a previously published method.[21,23]

Sample size

For the sample size determination of the primary outcome, we performed a Monte Carlo simulation based on a linear regression model, as we expected a linear relationship between concise and extended protocols. We used an expected LUSI of 57.6±16.8 based on findings in previous literature.[5] We considered a constant error (bias) of ±5 with a regression coefficient of 0.9 (reflecting high association) and a normally distributed

standard error of 0.25. This would require 34 patients for an α of 0.05 and power of 0.90. We included until 40 patients to account for 20% potential data loss.

Results

Study population

A total of 40 out of 89 patients with COVID-19 admitted to the ICU during the study period were included. One hundred thirty examinations were included by 8 physician operators. Sixteen patients had 4 examinations; 18 patients had 3 examinations, and 6 patients had only 2 examinations; of these 6, 4 patients were only examined from supine to prone and 2 only from prone to supine. Ninety-two examinations (71%) were performed with the curvilinear transducer. Sixty-five (88%) of examinations across position change were performed with the same transducer.

The median times from ultrasound to position change and vice versa were 2.5 [7.75]h and 6.0 [5.75]h, respectively.

Table 10.1 shows the baseline characteristics of patients at the first supine ultrasound examination. Eighteen patients (45%) were responders to position change. As 2 patients did not have a supine-to-prone position change, they were classified based on their response to resupination.

Table 10.1: Baseline characteristics

	Patients (40)	Responders (18)	Non-responders (22)	*p* value
Age, years	69.1±8.5	69.8±8.0	68.6±9.1	0.717
Gender, male	30 (75%)	12 (66.7%)	18 (81.8%)	0.271
P_aO_2/F_iO_2 ratio	114.6±32.4	112.1±23.4	116.7±38.7	0.946
BMI (kg/m^2)	28.4±5.2	27.7±3.8	28.9±6.1	0.717
Time from ICU admission, days	4.9 [9.2]	5.3 [7.2]	4.6 [5.2]	0.737
Time between exams, hours	12.8±7.2	11.7±7.3	13.7±7.1	0.459
Extended supine LUSI	58.6±16.5	52.6±15.0	63.9±16.3	**0.021**
Extended prone LUSI	52.6±18.4	47.7±19.7	57.0±16.5	0.107

Responders are patients with an increase in P_aO_2/F_iO_2 ratio ≥20 after their first supine-to-prone position change (or prone-to-supine when the former is not available).
Abbreviations: ICU, intensive care unit; BMI, body mass index; LUSI, lung ultrasound score index; P_aO_2/F_iO_2 ratio, the ratio between arterial oxygen tension and fraction of oxygen in inspired air.

Table 10.2 shows the mean LUSI of total, regional, and concise LUS examinations. The mean LUSI was -5.9±13.1% after supine-to-prone positioning and +6.4±14.3% after prone-to-supine positioning.

Table 10.2: LUSI in extended, concise, and regional examinations across position changes

	Supine-to-prone (36)			Prone-to-supine (38)		
	Supine	Prone	Δ	Prone	Supine	Δ
Extended LUSI	58.6±16.5	52.6±18.4	-5.9±13.1	53.9±19.1	60.2±19.1	+6.4±14.3
Concise LUSI	60.5±16.5	53.1±18.8	-7.4±14.5	52.9±20.1	62.1±19.0	+9.2±16.2
Anterior LUSI	44.9±19.0	64.8±21.1	-19.9±20.7	68.6±21.6	53.5±20.2	-15.1±19.9
Lateral LUSI	55.1±21.2	48.8±20.7	-19.8±19.8	50.0±24.4	55.9±24.6	+5.9±20.0
Posterior LUSI	75.7±20.5	44.2±24.8	-31.5±23.0	43.0±25.1	71.3±22.6	+28.3±28.1

Abbreviations: LUSI, lung ultrasound score index; the total LUSI was comprised of 12 zones in supine position and of 16 zones in prone position; Δ, the difference before and after a turn.

Similarities: Concise and extended LUS

The Spearman correlation coefficient for concise and extended LUSI was 0.96 and 0.95 in supine and prone, respectively, indicating a very strong positive correlation in both positions.[24] Figure 10.2A depicts the Bland-Altman plot of the concise and extended LUSI in supine position. The systematic error (constant bias) was 1.9% with LoA ranging from 11.3% to -7.5%. There was no proportional bias (p=0.93). Figure 10.2B depicts the Bland-Altman plot of the concise and extended LUSI in prone position. The constant bias was -0.3% with LoA ranging from 10.8% to -11.3%. Again, we found no proportional bias (p=0.32).

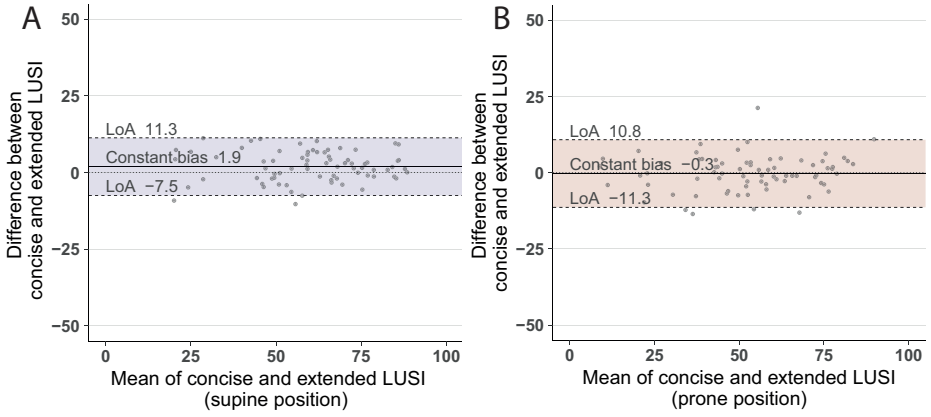


Figure 10.2A-B: Bland-Altman plots for 12-zone and 6-zone lung ultrasound score in supine (A) and prone (B) position.

Abbreviations: LUSI, lung ultrasound score index; LoA, limits of agreement (random error); Constant bias, (systematic error).

Differences: Supine and prone position LUS

The mean concise LUSI in supine position was 61.3±17.7%, and the mean concise LUSI in prone position was 53.0±19.3%. The Spearman correlation coefficient was 0.68, indicating a moderate positive correlation.[24] Figure 10.3A shows the Bland-Altman plot

for concise supine and prone examinations. The systematic error was +8.3% with LoA ranging from -21.7 to 38.3% and no proportional difference (p=0.33). Figure 10.3B shows a scatterplot depicting paired concise supine and prone examinations for responders and non-responders. Differences in LUSI between supine and prone position was not associated with oxygenation response (p=0.75).

Similar results were attained when comparing supine and prone position with extended protocols. In this case we found a systematic error of 6.2, no proportional bias, and LoA ranging from -20.7 to 33. The Spearman correlation coefficient was 0.65. The difference in LUSI between supine and prone position was not associated with oxygenation response (p>0.05).

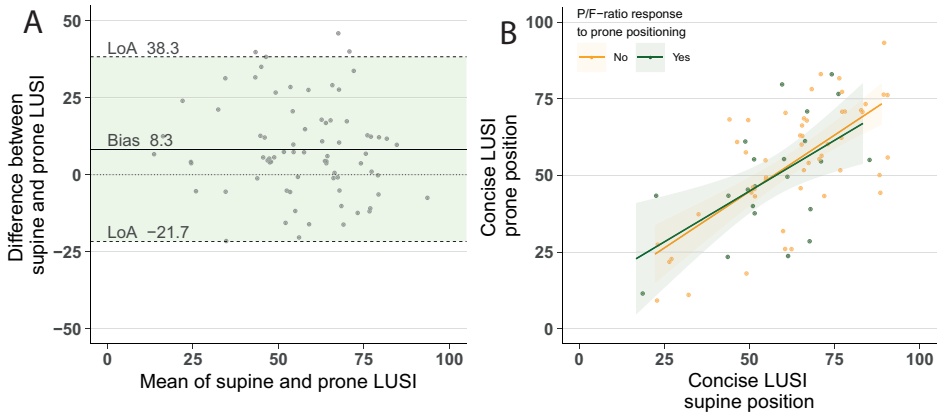


Figure 10.3A-B: Bland-Altman plot for the lung ultrasound score in supine and prone position (A) and scatterplot showing responder and non-responder groups for supine and prone position (B).
Abbreviation: LUSI, lung ultrasound score index.

Reproducibility: within and between raters

The weighted kappa for interrater and intrarater agreement were 0.81 and 0.88, respectively, indicating very good agreement.[25] The SDC between raters for both supine and prone LUSI were similar; 16.1% and 15.9%, respectively.

Consequently, the LoA for both concise and extended LUSI in either position (Figure 10.2A-B) fall within the measurement error. As such true changes between the two protocols cannot be reliably detected by raters, and the clinical advantage of using one protocol over the other is thus negligible.

Discussion

The main findings of this study on LUS methodology to monitor supine and prone critically ill patients with COVID-19 were: 1) concise and extended LUSI agree in both supine and prone position; no clinically relevant systematic differences were found between concise and extended LUSI protocols; 2) supine and prone LUS score index have a linear relationship, but prone LUSI is consistently 8% lower, and although true changes in LUSI across position changes occur they are not associated with oxygenation response; and 3) interrater and intrarater agreement were very good.

Monitoring of COVID-19 pneumonia using quantitative LUS provides important information about the progression of the disease and pulmonary involvement. This information can be used to predict clinical worsening, the need for mechanical ventilation, and weaning failure. It can also aid prognostication and optimize resource allocation.

Moreover, it may guide respiratory strategies that include PEEP titration and prone positioning.[26,27] The accepted standard chest CT scores (CTSS) are equivalent to LUS scores, but LUS is instantly accessible, suitable for routine use, and safer for patients and health care workers.[28,29] However, elaborate LUS monitoring scores, with varying configurations across different patient positions, are at odds with its clinical applicability. An extended examination (approximately 8-10 min) increases the amount of time spent at the bedside compared to a concise protocol (approximately 2-3 min).[30,31] Moreover, the time that is consumed after the examination also increases as extended examinations introduce complexity, necessity for recording forms, and may require transcription and reevaluation of more images and/or clips away from the bedside. This increases the threshold for LUS-based monitoring and impedes expeditious patient monitoring in settings that require efficient utilization of time and resources, such as the COVID-19 pandemic.

This study addresses these issues by demonstrating that for COVID-19 pneumonia – and perhaps ARDS from other causes by extrapolation – quantitative monitoring with a concise 6-zone ultrasound examination is as insightful as an extended LUS evaluation.[32,33] Thus, if a concise LUS protocol is deemed uninformative, the clinician should consider alternative diagnostic modalities rather than perform an extended LUS protocol. Lastly, in the absence of evidence, we should be cautious to overstate the ability of monitoring to directly affect patient outcomes.

The concise and extended LUS score index both in supine and prone position have a very strong correlation, a small constant bias, no proportional bias, and LoA fall within the measurement error (SDC) of the scanning clinicians. In other words, the measurement

errors associated with repeat measurements by different scanning clinicians produce larger differences in LUSI than using a concise examination over an extended examination. The acquisition of images and clips in this study was standardized. Repeat measurement error may be even greater when accounting for variation of image acquisition across different machines and probes.[34] Consequently, the difference between concise and extended LUSI is even more negligible.

Three other studies investigating the minimal number of required scan sites found similar results, further supporting the notion that scanning more zones is superfluous.[35–37] In this developing and methodologically heterogeneous field, it is crucial to compare protocols based on efficacy and efficiency rather than expanding it in the absence of rationale or evidence. This study offers the most comprehensive and multifaceted assessment of reproducibility (agreement and measurement error) of LUS protocols to date. Other protocol variations, both in number and distribution, exist (e.g., 4, 8, 14 or 28 zones) but were not investigated in the current study.[38–40]

There is a moderate correlation between LUSI in supine and prone positioning, signifying its virtue as a monitoring tool even across position changes. However, there are important position-related differences. Prone LUSI is lower (8%) than supine LUSI across the entire severity spectrum, and there are broad LoA. Clinicians monitoring patients with COVID-19 should be wary when monitoring a patient who has changed position. The differences in LUSI may result from the position change itself rather than disease progression or improvement during admission. A part of the differences in LUSI may result from lung (de)recruitment after position change, as a previous study has shown.[14] Consistent with previous studies, we found gravity-dependent redistribution of aeration loss from posterior to anterior zones (and vice versa).[13] However, we found no association between differences in LUSI and oxygenation after position change. Another potential explanation for the differences in LUSI between supine and prone positioning might come from the heterogeneous distribution of COVID-19, as scan sites of supine and prone do not have exact overlap.

Limitations

This study has several limitations. This was a single-center observational study. Eligible patients may have been missed because they did not undergo position changes, died or were discharged before inclusion, or if no investigator was available at the interval of potential inclusion. Consistent with previous studies, there is a selection bias for patients with P_aO_2/F_iO_2 <150mmHg as this is the accepted threshold for prone positioning. Patients were only evaluated 3h after prone positioning. During this time ventilator

settings might have been adjusted, a standard procedure during position change, and fluid balance might have changed; LUS and gas-exchange differences are, therefore, not solely the result of prone positioning but reflect the actual effects of prone positioning in the setting of conventional ICU care. This effect was likely minimal as the median time between examination and position change was within the time of an ICU shift (<8h). Moreover, changes in ventilator settings often accompany position changes in daily clinical practice. The comparison between concise and extended protocols was always derived using the same transducer. However, for comparison of supine and prone examination, ultrasound transducers with different frequency spectrums were occasionally used. The impact was likely minimal, as a large majority of examinations (88%) were performed using the same transducer.[34] As this investigation was focused on the number of zones, future examinations may consider the impact of other methodological variations in LUS such as protocol type, transducer type, and machine settings. Moreover, comparison was merely between concise and extended examinations of LUS, lacking the accepted standard chest CT. However, previous studies have already shown (near) equivalence between these modalities in COVID-19 monitoring.[5,41,42] Notably, this study investigated the methodology used for monitoring and not the effect of monitoring on clinical decision-making; this effect is addressed in previous studies.[43–45]

Strengths

This study has several strengths. Methodological investigations for LUS are needed as its heterogeneity has substantial impact on findings. This study presents robust, data-driven implications for LUS methodology.[41,46] Moreover, LUS assessment was performed by 2 separate investigators and highlights reproducibility and external validity of this method. Furthermore, the explicit inclusion protocol reflects conventional practice for patients with COVID-19 and patients with ARDS, further increasing its general applicability. Lastly, this study was adequately powered for its primary outcomes.

Conclusion

In both supine and prone position, a concise (6 zones) LUS scan protocol was equally as informative as the extensive (12 zones) scan protocol to monitor pulmonary involvement of critically ill patients with COVID-19. Clinicians can monitor patients undergoing position changes but must be wary that LUS alterations may result from the position change itself rather than disease progression or clinical improvement.

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11

Determining the optimal number of lung ultrasound zones to monitor COVID-19 patients
Can we keep it ultra-short and ultra-simple?

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Intensive Care Medicine 2021

Introduction

With much interest, we read the correspondence from Mento and colleagues, as well as the original study by Volpicelli and colleagues.[1,2] We would like to contribute original study results to move the discourse on optimal lung ultrasound (LUS) methodology forward. Although the work by Mento provides an interesting perspective, we believe that the method used to study agreement between lung ultrasound protocols may have inherently led to the presented conclusions. The authors compare the proportion of worst lung ultrasound scores (LUSS) across different protocols with a subjectively selected 14-zone protocol as reference standard.

First, whether the reference standard accurately represents total pulmonary involvement is uncertain. In fact, previous research has shown equivalence of both 6- or 12-zone protocols compared to gold standard chest computed tomography (CT).[3,4] Second, the 14-zone protocol's overrepresentation of posterior zones (43%) constitutes a scan-location bias, which is problematic when examining disease with gravity-dependent distribution. Consequently, comparing worst scores of predominantly posterior LUS protocols to worst scores of predominantly lateral or anterior LUS protocols inevitably leads to lower agreement. Third, exclusively evaluating worst LUSS disregards a plethora of particulars needed to assess true agreement between protocols. We present the results of a study with robust methods to comprehensively evaluate agreement between LUS protocols.

Methods

Study design

We performed a prospective observational study at the tertiary intensive care unit of the Amsterdam University Medical Centers, location VUmc. The study was approved by the local ethics board and need for informed consent was waived. A total of 191 examinations from 102 critically ill patients (81.4% male; mean age 64.9±11.4) affected by coronavirus disease 2019 (COVID-19) were examined and analyzed. Analyses were done in R statistical package

LUS protocols

All examinations were performed by five investigators using a COVID-19 unit-restricted SonoSite-Edge II ultrasound machine. All measurements were performed using a 10-5 MHz linear transducer or 5-3 MHz curvilinear transducer with lung examination setting and a depth of >6 centimeters.

The reference test was a 12-zone LUS protocol which has shown to have monitoring equivalence to CT and the index test was a 6-zone LUS protocol (Figure 11.1A).[4] The investigators scored the pulmonary involvement per zone from 0 (A-profile) to 3 (consolidation).[4–7] Please see e-Table 5.1 for the scoring system and corresponding examples in the e-Video section. In order to appropriately compare pulmonary involvement across protocols, a LUS index (LUSI = [total LUS / total LUS achievable] × 100) was calculated for both protocols.

Offline analyses of all ultrasound images of 191 examinations were performed by two investigators (MLAH and AWEL) blinded to the patient's baseline characteristics.

Reliability and measurement error

Protocols

Reliability was tested using Spearman's correlation coefficient for the two protocols. In addition, the measurement error was assessed by using the smallest detectable change (SDC) with accompanying 95% confidence intervals (95%CI). A Bland-Altman plot was used to visualize the systematic error (or constant bias) and random error (limits of agreement [LoA]) between the 6- and 12-zone protocols in accordance with previous literature.[8–10] Proportional bias was assessed by making a linear model of the difference (Bland-Altman plot Y axis) as a function of the mean (Bland-Altman plot X-axis) and assessing if the coefficient was significant (p<0.05).

The SDC represents the minimal change a score must show to ensure that the observed change is true and not a result of measurement error. Systematic and random error in measurements produce a difference in LUS that is not attributed to true changes in pulmonary involvement. These measurement errors can be quantified as the standard error of measurement (SEM). One can obtain a SEM by calculating a two-way mixed effects intraclass correlation coefficient model for agreement (ICC) and using the following formula:

$$SEM_{agreement} = \sigma \times \sqrt{1 - ICC_{agreement}}$$

The SEM can then be used to calculate the SDC, with the following formula:

$$SDC_{agreement} = 1.96 \times \sqrt{2} \times SEM_{agreement}$$

Raters

We used the ICC as a reliability measure for the raters and the SDC as a measurement error parameter. A power calculation was performed to determine the required sample size for the ICC between raters. A minimum acceptable reliability of 0.65, with an expected reliability of 0.89 based on previous research,[7] a power of 0.90, and a significance level of 0.05, resulted in a sample size of 27 examinations for two raters. Twenty-seven examinations were then selected from the total sample of 191 using a random number generator. These examinations were evaluated by both investigators (MLAH and AWEL).

Comparison

The comparison between the SDC of the raters and the SDC of the two protocols was estimated from 10,000 seeded bootstrapped comparisons in R language for statistical computing with the tidyverse suite of packages.

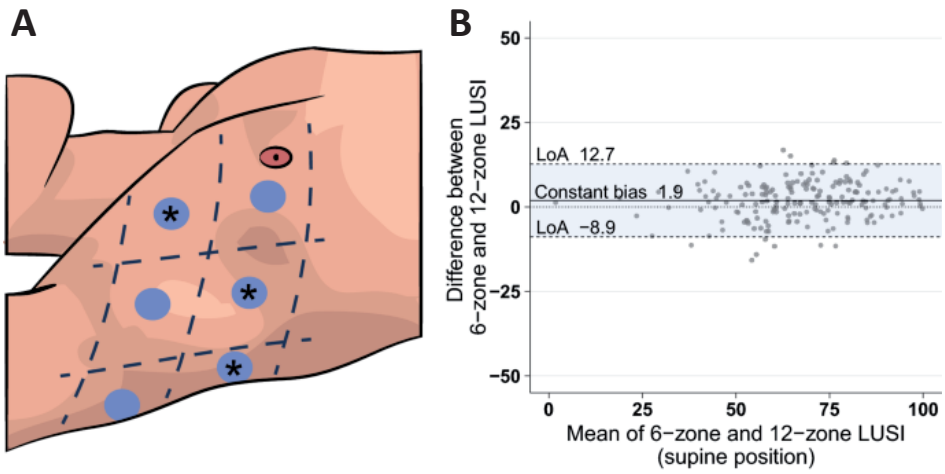


Figure 11.1: Lung ultrasound reference standard (blue) and index test (asterix) (A), and the Bland–Altman plot (B).
Each point represents agreement between the index and reference test in one examination in one patient. A jitter effect was added to improve visualization of data and avoid direct overlap of multiple examinations. Abbreviations: LoA, limits of agreement; LUSI, lung ultrasound score index—the lung ultrasound score expressed as a percentage of total score achievable.

Results

The Spearman's correlation coefficient was 0.94, indicating a strong correlation. The Bland–Altman plot of the two protocols exhibited a systematic error, indicating that 6-zone LUSI was consistently 1.9% (95%CI 1.1-2.7) higher than 12-zone LUSI (Figure 11.1B). No proportional bias was found, signifying that the two protocols agreed equally across disease severities. The SDC between protocols was 10.8% (95%CI 7.4-14.2).

The ICC of the investigators was 0.87, whereas the mean and standard deviation were 66.6±17.6. As a result, the SEM was 6.3, and the SDC proved to be 17.4% (95%CI 11.8-26.1). The SDC of the two protocols was significantly smaller than the investigators' SDC (p=0.019, derived from 10,000 bootstrapped comparisons). This showed that the differences between protocols were smaller than the true changes that are detectable by raters.

Conclusion

Monitoring COVID-19 with more than six zones does not appear to provide additional clinical information. This is important, because much of lung ultrasound's value is owed to its efficient bedside applicability, particularly in time and resource strained settings, such as the COVID-19 pandemic. Although these results need to be validated comprehensively, this study agrees with previous investigations concerning optimal number of lung ultrasound zones: less is more.[11]

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12

A lower global lung ultrasound score is associated with higher likelihood of successful extubation in invasively ventilated COVID-19 patients

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Abstract

Background: Lung ultrasound (LUS) can be used to assess loss of aeration, which is associated with outcome in patients with COVID-19 presenting to the emergency department (ED). We hypothesized that LUS scores are associated with outcome in critically ill COVID-19 patients receiving invasive ventilation.

Methods: This retrospective international multicenter study evaluated patients with COVID-19 related acute respiratory distress syndrome (ARDS) with at least one LUS study within 5 days after invasive mechanical ventilation initiation. The global lung ultrasound score (LUSS) was calculated by summing the 12 regional scores (range 0 to 36). Pleural line abnormalities and subpleural consolidations were also scored. The outcomes were successful liberation from the ventilator and intensive care mortality within 28 days, analyzed with multi-state, competing risk proportional hazard models.

Results: 137 patients with COVID-19 related ARDS were included in our study. The LUSS was associated with successful liberation from mechanical ventilation (hazard ratio (HR): 0.91 [95%CI 0.87-0.96]; p=0.0007), independently of the ARDS severity, but not with 28-day mortality (HR: 1.03 [95%CI 0.97-1.08]; p=0.36). Subpleural consolidation and pleural line abnormalities did not add to the prognostic value of the LUSS. Examinations within 24 hours of intubation showed no prognostic value.

Conclusion: To conclude, a lower LUSS 24 hours after invasive ventilation initiation is associated with increased probability of liberation from the mechanical ventilator COVID-19 ARDS patients, independently of the ARDS severity.

Introduction

Coronavirus disease 2019 (COVID-19) is responsible for hundreds of thousands of deaths worldwide, and this number is still rapidly increasing.[1] Respiratory failure is the most common and severe complication of COVID-19, and bilateral and multilobar infiltrates can progress rapidly over the first few days of illness.[2] Approximately 5% of hospitalized patients require admission to an intensive care unit (ICU), mainly for invasive mechanical ventilation.[3] There is a high variability in the reported mortality across invasively ventilated COVID-19 patients.[4–6] The severity of loss of aeration, typically assessed by chest computed tomography (CT) scan, has been related to outcomes in hospitalized COVID-19 patients,[7–9] but CT scan capacity is limited and CT may not even be available in settings with scant resources.

Lung ultrasound (LUS) is a bedside, radiation-free, low-cost diagnostic imaging tool that can be used for assessing lung aeration and parenchymal abnormalities.[10] The global lung ultrasound score (LUSS) quantifies lung aeration by translating LUS patterns into a numerical score across 12 lung regions and summing the results (e-Table 5.1).[11,12] Previous studies have shown a correlation between LUS and severity of acute respiratory distress syndrome (ARDS),[13] and with mortality in invasively ventilated critically ill patients.[14] LUS has previously been performed in a general population of COVID-19 patients outside the hospital,[15] presenting to the emergency department (ED),[16–18] and on the general wards[19–26] and has been found to be related to adverse outcomes including the need of invasive ventilation. Nevertheless, the role of LUS in evaluating the severity of patients after initiation of invasive ventilation is much less certain.[27] Evaluating lung disease severity with LUS may be important for ICU resource planning, especially in settings where resources are restricted, as well as for a more personalized ventilatory approach.[28]

The aim of this study is to assess the association between LUSS and outcome, specifically defined as liberation from the ventilator and survival in critically ill COVID-19 patients under invasive ventilation. We hypothesized the LUSS to have prognostic value in invasively ventilated COVID-19 patients independently of ARDS severity.

Methods

Study design

This is an international multicenter cohort study. We retrospectively reviewed patients with reverse transcriptase polymerase chain reaction (RT-PCR) confirmed COVID-19 under invasive ventilation in ICUs of four hospitals in three countries: the Brugmann University

Hospital Brussels (Brussel, Belgium), the Miulli Regional Hospital (Acquaviva delle Fonti, Italy) and the Amsterdam University Medical Centers, locations AMC and VUMC between February 2020 and 31 December 2020. LUS studies were performed as part of routine practice, and were executed by 10 experienced ultrasonographers who performed at least 50 systematic LUS exams before.

Ethical approval for this study was provided by the ethical committees of each hospital (Brugmann University Hospital N° CE 2020/136; Azienda Ospedaliero-Universitaria Policlinico di Bari 0030638/22/04/2020; Amsterdam UMC location AMC W18_311; Amsterdam UMC location VUMC 2020.011). Trial registration: Clinicaltrials.gov identifier: NCT04487769.

Patients were included if they received a LUS within the first 5 days after invasive ventilation initiation but before extubation. Patients who received a LUS while supported with extracorporeal membrane oxygenation (ECMO) were excluded. Only the first available examination of LUS was used for the analysis.

The following data was extracted from chart: demographic characteristics, APACHE II and SOFA score on admission, vital signs, and ventilator and blood gas parameters on the day of LUS examination.

LUS protocol

LUS examination was performed with the available equipment at the COVID ICUs of the participating hospitals. The following machines were available: MyLab™ Five ultrasound machine with a convex probe (Esaote Spa, Genova, Italy), a Vivid S5 with curvilinear probe (General Electric Healthcare, Chicago, USA), a LOGIQ E with a linear probe (GE Healthcare, Milwaukee, US) and a Sonosite Edge II (Fujifilm Sonosite, Bothell, Washington, United States).

The 12-zone protocol was used in all examinations in which ultrasound was performed on six areas on each side of the chest, i.e., two ventral regions, two lateral regions, and two posterior regions (e-Figure 5.1).[29] The aeration pattern observed in each region was scored from 0 to 3 according to the LUS aeration score as follows: '0', A-pattern with ≤2 B-lines; '1', more than 2 separated -— lines that cover ≤50% of the pleural line; '2', B-lines that cover >50% of the pleural line; or '3', lung consolidation (e-Table 5.1). In theory, the LUSS can range from from '0' (normal aeration in all regions) to '36' (severe abnormal aeration in all regions).[30] Presence of subpleural consolidations and abnormal pleural line was also assessed offline in each field using saved ultrasound clips.

Thickening and fragmentation of the pleural line and the finding of subpleural consolidations do not currently contribute to the LUSS aeration score but are often found in patients with COVID-19 infection. Therefore, we assessed the number of fields with

pleural line abnormalities and the number of fields with subpleural consolidations in a separate analysis. Pleural line abnormalities were defined as any deviation from the normally appearing thin, smooth and continuous hyperechoic line (compare e-Video 5.1: normal pleural line with e-Video 5.12: thickened/irregular pleural line).[29] Subpleural consolidations were defined as one or more echo poor regions juxtaposed to the pleural line (Figure 5.4 & e-Video 5.3), which were not large enough to be scored as a tissue-like pattern or 'lobar consolidation' in the lung aeration score (e-Video 5.10 & 5.11).[30]

Outcomes

The primary outcomes were the risks for successful liberation from invasive ventilation and intensive care mortality up to 28 days.

Statistical analysis

No formal power analysis was performed for this exploratory analysis. Rather, all patients that fulfilled the inclusion and exclusion criteria were included. Demographic, clinical, and outcome variables were presented as percentages for categorical variables and as means with standard deviations (SD) or medians with interquartile ranges [IQR] for continuous variables.

The association of LUSS with outcomes was analyzed with multi-state, competing risk proportional hazard models as described in the survival package via the compete function in R. Risks were estimated for successful extubation and mortality and compared to persistent intubation (reference category). Follow-up was censored after 28 days. Two sensitivity analysis were performed for the following predefined subgroups: (a) severity of ARDS according to P_aO_2/F_iO_2 based on cutoffs described in the Berlin definition[31] and (b) days of invasive ventilation before LUS examination (exam on day 0, day 1, day 2-3, day 4-5).

Receiver operating characteristic (ROC) curve analysis was used to derive the prognostic discriminatory performance of the LUSS in determining successful liberation from invasive ventilation and mortality at day 28. Based on the calculated area under the ROC curve (AUROCC) the prognostic accuracy was interpreted as follows: excellent between 0.9-1, good between 0.8-0.89, fair between 0.7-0.79, poor between 0.6-0.69 and very poor between 0.5-0.59.[32] AUROCCs were compared using the DeLong test. Two cutoffs were defined: one with a high sensitivity of above 80% for poor outcome (composite of persistent mechanical ventilation at day 28 or mortality; selecting for a good negative predictive value) and one with a high specificity of above 80% for poor outcome (selecting for a good positive predictive value). The analysis was repeated using the three categories resulting from these cutoffs. All analyses were performed in R through the R-studio interface (www.r-project.org, R version 3.3.1). A *p* value below 0.05 was considered significant.

Results

Study population

A total of 137 patients were studied. Patient characteristics are presented in Table 12.1. At day 28, 53 patients (38%) were successfully extubated, while 64 patients (47%) had died

Table 12.1: Baseline characterisics

	Successful liberation of mechanical ventilation and alive at 28 days	Still intubated or deceased at 28 days	*p* value
Number of patients	53	84	
Day of LUS	1 [0-2]	1 [0-2]	0.71
Demographics			
Age, years	61 [54-68]	71 [62-76]	**<0.01**
Sex, female	32 (61)	46 (54)	0.59
APACHE II	13 [12-17]	14 [12-22]	0.21
SOFA score	7 [5-8]	8 [5-10]	0.06
LUSS	18 [15-23]	21 [18-24]	**<0.01**
Subpleural consolidations, fields per patient	3 [1-5]	5 [2-6]	**0.01**
Pleural line abnormalities, fields per patient	3 [1-5]	3 [1-5]	0.91
Biology			
D-dimers, ng/ml	1440 [873-3875]	2326 [1720-4063]	**0.03**
CRP, µg/ml	77 [40-159]	108 [21-172]	0.81
Ventilation parameters			
Ventilation mode			
Volume controlled	20 (38)	36 (42)	0.59
Pressure controlled	17 (32)	30 (36)	0.71
Pressure support	16 (30)	18 (22)	0.31
Tidal volume, ml	425 [378-484]	418 [390-460]	0.71
Tidal volume, ml/kg PBW	6.3 [5.8-6.9]	6.3 [5.6-6.5]	0.75
PEEP set, cm H_2O	10 [8-12]	10 [8-12]	0.81
Pplat, cm H_2O	22 [19-26]	24 [20-27]	0.21
Driving Pressure	12 [11-17]	14 [10-17]	0.55
Static Compliance	35 [26-44]	31 [24-44]	0.55
SpO_2, %	94 [93-96]	95 [94-97]	0.83
F_iO_2	55 [50-70]	64 [55-80]	**<0.01**
P_aO_2/F_iO_2	148 [115-173]	113 [98-153]	**0.01**
Complications/procedures			
VAP	11(21)	59 (71)	**<0.01**
ECMO	0 (0)	4 (5)	0.15
Tracheostomy	5 (9)	19 (22)	0.06
Death (28 days)	0 (0)	64 (76)	

Data are presented as mean (± standard deviation) median [interquartile range] or number (%).
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; PBW, predicted body weight; PEEP, positive end–expiratory pressure; Pplat, plateau pressure; SpO_2, peripheral pulse oxymetric saturation; F_iO_2, fraction of inspired oxygen; P_aO_2, arterial oxygen tension; VAP, ventilator associated pneumonia; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LUSS, lung ultrasound score

and 20 patients (15%) were still receiving invasive mechanical ventilation. Compared to the patients who failed to be extubated within 28 days, patients who were successfully extubated had a higher P_aO_2/F_iO_2 of 148 mmHg [IQR 115-173] versus 113 mmHg ([IQR 98-153], *p*=0.013) and a lower LUSS of 18 [IQR 15-23] versus 21 points ([IQR 18-24], *p*=0.005).

Association between the LUSS and outcome

The LUSS was associated with successful liberation from invasive ventilation (hazard ratio (HR): 0.91 [95%CI 0.87-0.96]; *p*=0.0007) but not with 28-day mortality (HR: 1.03 [95%CI 0.97-1.08]; *p*=0.36) in competing risk analysis. However, the prognostic capacity of the LUSS for successful liberation from the ventilator at day 28 and mortality was poor (AUROCC of 0.65 [95%CI 0.54-0.74], AUROCC of 0.63 [95%CI 0.53-0.72], respectively). The optimal cutoff for >80% sensitivity for the combined endpoint of persistent mechanical ventilation or death at day 28 was 17, while it was 24 for >80% specificity (Table 12.3). The corresponding hazard ratios for the probability of being liberated from the ventilator compared to a score of 17 or below (low risk group, n=41), were 0.47 (95%CI 0.26-0.85; *p*=0.01) for the patients with LUS score 18-24 (intermediate risk group, n=71) and 0.37 (95%CI 0.17-0.79; *p*=0.01) for the patients with LUS above 24 (high risk group, n=25; Figure 12.1). Only patients with a LUSS of 24 and above had an increased probability of death (HR: 2.3; 95%CI 1.08-4.8; *p*=0.03) compared to a score of 17 or below. Adding subpleural consolidations or pleural line abnormalities did not improve the prognostic capacity for successful extubation or mortality at day 28 (Table 12.2).

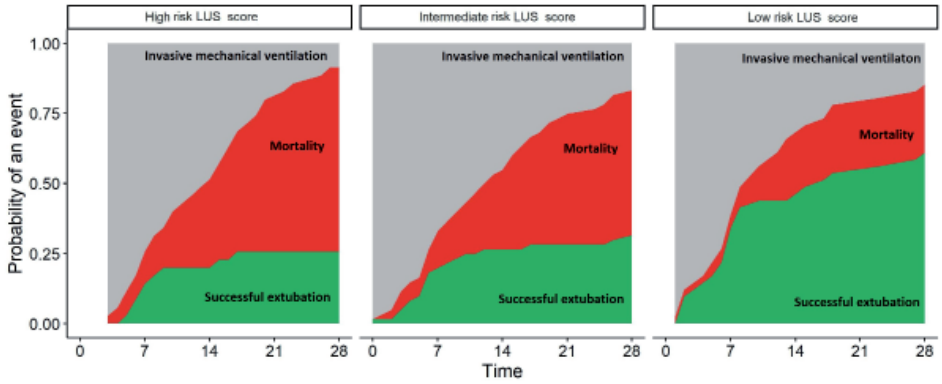


Figure 12.1: Three categories of LUSS and cumulative incidence of outcomes.
X-axis: days since intubations. Y-axis: probability of an event (extubation or death) in the population.
The three facets show the risk for patients with a high risk LUSS (left), intermediate risk (middle) and low risk LUSS (right). The red area shows the patients who died. The green area shows the patients who were successfully extubated.
Abbreviation: LUSS, lung ultrasound score.

Table 12.2: Prognostic values of LUSS alone and with the addition of number of areas with subpleural consolidations or pleural line abnormalities

Outcome	Score	AUROCC (95%CI)	Cutoff		Poor outcome	Good outcome
Successful liberation from mechanical ventilation while alive at day 28	LUSS	0.65 (0.54-0.74)	17	≥17	68	28
				<17	16	25
					Sensitivity: 81	Specificity: 47
			24	≥24	26	9
				<24	58	44
					Sensitivity: 31	Specificity: 83
	+ Subpleural consolidations	0.65 (0.55-0.75)	19	≥19	62	29
				<19	12	20
					Sensitivity: 84	Specificity: 41
			28	≥28	25	7
				<28	49	42
					Sensitivity: 32	Specificity: 86
	+ Pleural line abnormalities	0.61 (0.51-0.71)	18	≥18	61	32
				<18	13	17
					Sensitivity: 82	Specificity: 35
			28	≥28	13	17
				<28	53	40
					Sensitivity: 28	Specificity: 82
Outcome	Score	AUROCC (95%CI)	Cutoff		Poor outcome	Good outcome
Mortality at day 28	LUSS	0.63 (0.53-0.72)	17	≥17	54	42
				<17	10	31
					Sensitivity: 84	Specificity: 37
			24	≥24	23	12
				<24	41	61
					Sensitivity: 35	Specificity: 83
	+ Subpleural consolidations	0.61 (0.51-0.71)	19	≥19	46	45
				<19	10	22
					Sensitivity: 82	Specificity: 32
			28	≥28	19	13
				<28	37	54
					Sensitivity: 33	Specificity: 81
	+ Pleural line abnormalities	0.58 (0.47-0.68)	18	≥18	46	47
				<18	10	20
					Sensitivity: 82	Specificity: 30
			28	≥28	19	11
				<28	37	56
					Sensitivity: 33	Specificity: 83

Prognostic accuracy stratified for successful liberation from invasive ventilation and mortality at day 28. Areas under the receiver operating characteristic curve (AUROCC) with 95% confidence interval, optimal cutoff and corresponding sensitivity and specificity are shown for the global lung ultrasound score (LUSS) alone, and for the score in combination with subpleural consolidations and pleural line abnormalities. The *p* value indicates the difference between the LUSS and the score combined with either additional finding.

Subgroup analyses

When patients were classified according to ARDS severity, 11 patients (9%) had mild, 85 patients (68%) had moderate and 29 (23%) had severe ARDS. For twelve patients P_aO_2/F_iO_2 was missing. The LUSS was associated with the probability of being liberated from the ventilator while alive at 28 days after intubation independently of ARDS severity (Figure 12.2). There was no evidence for variation of LUSS association with outcome according to the categories of P_aO_2/F_iO_2 (no interaction; p=0.49).

The majority of the patients were examined within 24 hours after invasive ventilation initiation (61 patients, 44%) whereas 39 patients (28%) were examined between 24 and 48 hours, 24 patients (17%) between 48 and 96 hours and 13 patients (9%) between 96-120 hours after start of invasive ventilation. There was evidence of variation of LUSS according to the time of examination (interaction term, p=0.036). When the examination was performed within 24 hours after intubation, the LUSS was not associated with the probability of successful extubation in the first 28 days (Figure 12.2).

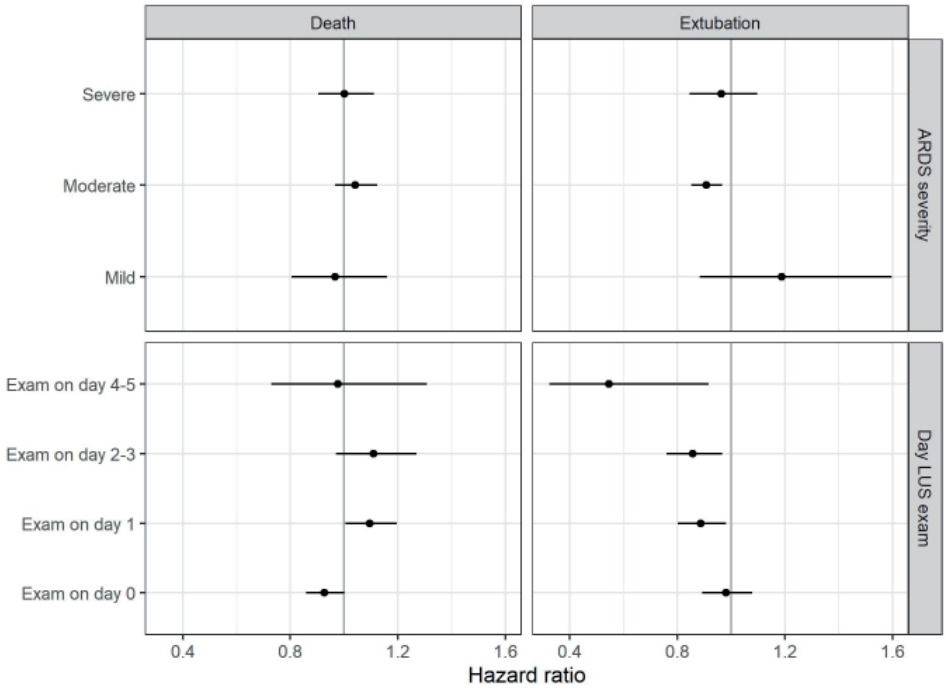


Figure 12.2: Forest plot of the LUSS association with probability of successful liberation of invasive ventilation and death at 28 days according to ARDS severity and the day of examination after start invasive ventilation.

X-axis: Hazard ratio for increase of the lung ultrasound score (LUSS) for mortality (left) and extubation (right) based on competing risk analysis. The dots provide the point estimate and the lines the 95% confidence interval for estimated associations, stratified for predefined subgroups.

Discussion

The results of this study can be summarized as follows: 1) an increasing LUSS is indicative of parenchymal damage and loss of aeration and associated with a lower likelihood of mechanical ventilation liberation during the first 28 days of invasive mechanical ventilation but not with mortality; 2) this association was independent from ARDS severity but not from timing of examination; and 3) additional LUS findings such as subpleural consolidations and pleural line abnormalities do not significantly improve the prognostic value.

LUS is an attractive method for evaluation the severity of COVID-19 patients, because ultrasound machines are widely available and thus the technique can be used even in resource-limited settings. Furthermore, LUS examination at the bedside can potentially decrease or eliminate the need for transport to the radiology department, which is helpful particularly in the context of invasively ventilated patients. Increasing LUSS was associated with a higher probability of requiring invasive ventilation for at least 28 days.

Severity assessment of severe COVID-19 early after invasive ventilation initiation is challenging as ventilator management can moderate the prognostic value of easily derived parameters such as the P_aO_2/F_iO_2.[33] Simultaneously, the compliance of the respiratory system is low in most of these patients and has little prognostic value.[34] In our study, patients who were successfully extubated had a similarly low respiratory system compliance compared to patients who were not successfully extubated. The loss of aeration estimation with LUS was associated with successful extubation independent of the P_aO_2/F_iO_2 categories that are used in clinical practice for ARDS severity assessment. Hence, based on these results we think LUS can be used as an additional tool to clinical and laboratory parameters for the appreciation of disease severity in invasively ventilated patients with COVID-19 ARDS.

We did not confirm the results of a previous study in non-COVID-19 related ARDS patients that showed that a LUSS of 16.5 was predictive for mortality.[35] As rapid extubation is predicted by less extensive parenchymal involvement, reflective of a lower degree of lung injury, we may speculate that mortality is mainly driven by the occurrence of ICU-acquired complications such as (co)infections, pulmonary embolism, ICU-acquired weakness, and the ability to endure prolonged duration of mechanical ventilation that is frequently needed for COVID-19 related ARDS. This finding is in line with a previous study that showed no association between decreased volume of well-aerated lung tissue as assessed by chest computed tomography and 30-day mortality in critically ill patients with COVID-19 ARDS.[36] Of note, that same study also showed that LUSS was a better predictor of outcome than the CT severity score (CTSS).

In non-COVID-19 related ARDS, the relationship between mortality rates and the amount of non-aerated areas in invasively ventilated patients is not clear either.[37–40] Even though the limited duration of follow-up of one month may have obscured associations with longer term mortality,[41] we conclude that the extent of parenchymal involvement is a poor predictor of outcome when applied to a cohort of critically ill patients requiring invasive mechanical ventilation.

We aimed to facilitate bedside estimation for the risk of adverse outcomes by identifying a cutoff for the LUSS that could predict mortality or liberation of invasive ventilation in COVID-19 related ARDS patients. In contrast to previous studies that evaluated patients who did not receive invasive mechanical ventilation,[17,19,23–25] we were unable to provide a single LUS value that was highly predictive of outcome. However, liberation of mechanical ventilation at 28 days was much more likely in patients with a LUSS lower than 17, while this was very unlikely in patients with a LUSS higher than 24. Importantly, these cutoffs are not to replace the continuous value and are arbitrary. We prespecified a sensitivity and specificity of 80% for successful extubation, but one could argue that higher certainties are needed for clinical decision making.

LUSS obtained from exams that were performed on the first day of invasive ventilation showed to have less prognostic value compared to LUS exams that were performed after the first day. We postulate that the association between global LUS scores and outcomes are influenced by the response to invasive mechanical ventilation and/or corticosteroid treatment. In our cohort, patients examined on the first day after invasive ventilation initiation had a median LUS score of 22. This score is consistent with the results of previous study in which patients with COVID-19 in the ED who required invasive ventilation had a median LUS score of 22.[19] Assessment of lung re-aeration by computed tomography in COVID-19 patients has shown conflicting results.[42,43] Assessment of the influence of ventilator management on association between the LUSS and outcomes should be a topic for future studies.

Subpleural consolidations and pleural line abnormalities are commonly used to distinguish ARDS from cardiogenic pulmonary oedema,[44] and are also frequently reported in patients with COVID-19 related ARDS.[45–48] In theory, both of these findings can be related to the severity of COVID-19 disease. Additionally, the presence of subpleural consolidations might also indicate a pulmonary embolism.[49] In terms of prognostication, both subpleural consolidations and pleural line abnormalities were found to be associated with the prognosis in COVID-19 patients outside[50] and inside the hospital.[19] We found more regions with subpleural consolidations in patients with a poor outcome, but not more pleural line abnormalities. Nevertheless, the extent of subpleural consolidations

or pleural line abnormalities were not quantitatively related to liberation of ventilation or mortality in the subset of COVID-19 patients who require intubation and mechanical ventilation. As the LUSS was associated with the extent of subpleural consolidations, we reason that subpleural consolidations are more related to the degree of lung aeration loss rather than to a distinct predictor of mortality or liberation of invasive ventilation.

Strengths & limitations

The main strength of this study is that the LUSS was assessed by an identical and systematic method by multiple investigators in patients that were treated in four different centers in three different countries. Moreover, we included only COVID-19 patients with severe respiratory failure undergoing invasive ventilation, a homogeneous group of patients that has been underrepresented in COVID-19 LUS cohorts. We accounted for competing risks and were able to distill an association with liberation of ventilation when accounting for the occurrence of mortality during the first 28 days of invasive ventilation. This study also has limitations. First, this is a retrospective study and the indication and time point for a LUS exam was not prescribed in a protocol. LUS exams were done as part of routine clinical practice and all performed within 5 days after start of invasive ventilation. Second, we could not assess the prognostic value of the changes in the LUS score over time as LUS exams were not performed repeatedly in the participating centers. Dynamic changes in LUS scores should be studied further as monitoring tool for re-aeration of lung tissue.[50] Additional studies should focus on LUS as it is an excellent technique to use in a resource-limited setting as alternative for chest radiography or chest CT.[28]

Conclusion

The LUSS is associated with successful liberation from invasive ventilation, but not with mortality during the first four weeks of invasive ventilation. In patients with a low LUSS, extubation can be expected in the first weeks of mechanical ventilation while this is uncommon in patients with a high LUSS. The extend of subpleural consolidations or pleural line abnormalities does not add prognostic value to the LUSS in invasively ventilated patients.

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13

Monitoring of pulmonary involvement in critically ill COVID-19 patients
Should lung ultrasound be preferred over CT?

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Abstract

Background: It is unclear if relevant changes in pulmonary involvement in critically ill COVID-19 patients can be reliably detected by the CT severity score (CTSS) and lung ultrasound score (LUSS), or if these changes have prognostic implications. In addition, it has been argued that adding pleural abnormalities to the LUSS could improve its prognostic value. The objective of this study was to compare LUSS and CTSS for the monitoring of COVID-19 pulmonary involvement through: 1) establishing the correlation of the LUSS (± pleural abnormalities) and CTSS throughout intensive care unit (ICU) admission; 2) assessing agreement and measurement error between raters for the LUSS, pleural abnormalities, and CTSS; 3) evaluating the association of the LUSS (± pleural abnormalities) and CTSS with mortality at different timepoints.

Methods: This is a prospective, observational study, conducted during the second COVID-19 wave at the AmsterdamUMC, location VUmc. Adult COVID-19 ICU patients were prospectively included when a CT or a 12-zone lung ultrasound (LUS) was performed at admission or at weekly intervals according to local protocol. Patients were followed 90 days or until death. We calculated: 1) The correlation of the LUSS (± pleural abnormalities) and CTSS throughout ICU admission with mixed models; 2) The intraclass correlation coefficients (ICCs) and smallest detectable changes (SDCs); 3) The association between the LUSS (± pleural abnormalities) and CTSS with mortality with mixed models.

Results: 82 consecutive patients were included. Correlation between LUSS and CTSS was 0.45 (95%CI 0.31-0.59). ICCs for LUSS, pleural abnormalities, and CTSS were 0.88 (95%CI 0.73-0.95), 0.94 (95%CI 0.90-0.96), and 0.84 (95%CI 0.65-0.93), with SDCs of 4.8, 1.4, and 3.9. The LUSS was associated with mortality in week 2, with a score difference between patients who survived or died greater than its SDC. Addition of pleural abnormalities was not beneficial. The CTSS was associated with mortality only in week 1, but with a score difference less than its SDC.

Conclusion: The LUSS outperformed CTSS in monitoring pulmonary involvement. Given the benefits of LUS over CT, it should be preferred as initial monitoring tool.

Introduction

Management of critically ill patients with Coronavirus Disease 2019 (COVID-19) requires accurate and appropriate clinical care while maintaining adequate infection control and minimizing patient harm. Chest computed tomography (CT) is the gold standard imaging modality to diagnose and monitor COVID-19 pneumonia.[1,2] However, CT requires patient transport to and from radiology. This carries considerable risks for critically ill patients, and healthcare workers, whilst laying claim to already stretched resources and personnel.[3,4] In contrast, point-of-care ultrasound (POCUS) offers the unique possibility to perform imaging studies at the bedside, obviating the need for transport. POCUS also has disadvantages: in untrained hands there is risk of interpretative error and the equipment may be microbially contaminated if not conscientiously used.[5]

Quantification of pulmonary involvement by lung ultrasound (LUS) has shown to be equivalent to CT.[6,7] Baseline lung ultrasound score (LUSS) is associated with intensive care unit (ICU) admission, hospital and ICU length of stay, ventilation duration, ARDS and even mortality (when included in a composite end-point).[6–11]

However, it is neither clear if clinically relevant changes in the degree of pulmonary involvement over time can be reliably detected by the LUSS and CT severity score (CTSS), nor if these changes have prognostic implications for mortality in critically ill COVID-19 patients. Literature on monitoring of the disease course by CT and LUS, is limited to mostly small and retrospective case series, with a short follow-up time.[12–17] In addition, hardly any studies investigated the reliability and measurement error of the CTSS and LUSS.[6,12,17] Furthermore, it has been argued that pleural line abnormalities and subpleural consolidations should be incorporated into the LUSS, since they are often found in patients with COVID-19 and correlate histologically with diffuse alveolar damage, and a such might have prognostic value.[10,11,17,18]

Our aim was to fill these knowledge gaps by comparing LUSS and CTSS for the monitoring of pulmonary involvement of critically ill COVID-19 patients during their ICU admission through: 1) establishing the correlation of LUSS (± pleural abnormalities) and CTSS to monitor pulmonary involvement throughout admission; 2) assessing agreement and measurement error between raters for LUSS, pleural abnormalities, and CTSS; 3) evaluating the association of the LUSS (± pleural abnormalities) and CTSS with mortality at different timepoints during ICU admission.

Methods

Study design

This is a prospective, observational study conducted at the academic ICU of the Amsterdam UMC, location VUmc between October 20, 2020 and February 20, 2021. The study was approved by the Medical Ethical Committee of the VUmc, along with a waiver of informed consent (2020.011). The trial was registered in the Dutch trial registry (NL8540).

Consecutive adult patients (≥18 years) with a laboratory confirmed diagnosis of COVID-19 were eligible for inclusion upon admission to ICU. Patients were included and followed when a chest CT or LUS were performed at admission or at one of the weekly intervals afterward. Patients were excluded when: COVID-19 was not the primary reason of admission (incidental finding), no CT or LUS was performed, or ≤6 lung zones were scanned. Start of follow-up was the first LUS or CT, whichever came first. Patients were followed up for 90 days by chart review or until death. Patient characteristics along with ventilator settings and laboratory values were collected from the electronic patient database at baseline and at the time of the CT.

ICU treatment protocol

Patients admitted to our ICU were treated with selective intestinal decontamination (Tobramycin 80 mg/Colistin 100 mg/Nystatin 2.000.000 IU) 10 ml suspension orally or via nasogastric tube(s) thrice daily, and 0.5 mg mouthpaste thrice daily for the duration mechanical ventilation. In addition, we prescribed intravenous Ceftriaxone 2 grams once daily for four days. We also treated patients with intravenous Dexamethasone 6 grams once daily for 7 days. The use of Tocilizumab was not yet protocol during this study.

Given the high incidence of the venous thromboembolism (VTE) reported in the literature from the first wave, the protocol in our ICU was to increase the dosing interval of prophylactic low molecular weight heparin (Fraxiparine), as described before.[19] Patients <100 kg received 2850 IE bidaily instead of once daily, while patients >100 kg received 5700 IE bidaily instead of once daily. With daily anti-factor Xa (anti-fXa) measurements every day, starting after the third dose, with a target level of 0.1-0.5 U/ml. When levels remained <0.1 U/ml, physicians could decide to increase the dose to get it within target range. When patients required therapeutic anticoagulation intravenous unfractionated heparin (UFH) was used, with a target activated partial thromboplastin time (aPTT) of 45-60. When no therapeutic aPTT levels of UFH were reached despite high doses (>25 IE/kg/hour), anti-fXa levels could be used to guide therapy, with a therapeutic target range of 0.3-0.7 IE/ml.

CT

It was standard practice for patients to receive a chest CT every week when their clinical condition did not improve or deteriorated. The CT was made to determine the amount of pulmonary involvement, and assess the presence of a possible superinfection or pulmonary embolism. CTs were evaluated by local radiologists with varying degrees of experience and access to clinical information – but not to the LUS examinations. A visual assessment of the percentage of pulmonary involvement in each lobe was summed for a total CTSS, used in the internationally validated COVID-19 Reporting and Data System (CO-RADS), ranging from 0 (no involvement) to 25 (maximum involvement), as described previously.[1] If a superinfection was suspected on CT, a trained and experienced pulmonologist would perform a bronchoalveolar lavage (BAL) at the location of the suspected superinfection. The decision to perform a CT (or a subsequent BAL) was made by the treating ICU consultant in consultation with a daily multidisciplinary team consisting of a consultant microbiologist, a consultant pulmonologist and at least five other ICU consultants.

LUS

LUS is a part of standard care on our ICU.[20] The examination was performed within 24 hours of the CT to minimize temporal influence on the correlation. The LUS operators were blinded for the CT result, but not for the clinical picture. A 12-zone scanning technique was used to calculate the LUSS (e-Figure 5.1). The LUSS has been extensively used in ARDS and COVID-19 studies.[6,21]

The LUSS has the following four progressive categories: 0 = normal aeration: A-lines or ≤2 B-lines (e-Video 5.1); 1 = moderate loss of aeration: three or more well-spaced B-lines (e-Video 5.2); 2 = severe loss of aeration: B-lines or subpleural consolidations in ≥50% of the zone (e-Video 5.3, 5.4 & 5.12); and 3 = complete loss of aeration: tissue-like pattern (e-Video 5.10-5.11). The total LUSS sums the scores from all 12 zones, creating a final score that ranges from 0 (all regions are well aerated) to 36 (all regions are consolidated) (e-Table 5.1).

As there is no standardization of pleural line abnormalities and subpleural consolidation, their classification is thus subjective.[22] Ji et al. suggested a qualitative scoring system of the pleural line, where a normal pleural line = 0, an 'irregular' pleural line = 1, and a 'blurred' pleural line = 2.[10] We tried to make a more reproducible, quantitative classification, with the following scores; a normal pleural line = 0 (e-Video 5.1 & 5.2); a thickened/irregular pleural line without clear subpleural consolidations = 1 (e-Video 5.12); subpleural consolidations <1 cm (e-Figure 13.1): 2; subpleural consolidations 1-2 cm = 3 (e-Video

5.3); subpleural consolidations 2-3 cm (e-Figure 13.2) = 4; subpleural consolidations ≥3 cm (e-Video 5.4), without progressing to tissue-like pattern or hepatization (see e-Video 5.10 & 5.11 for the latter) = 5.[11] The highest pleural abnormalities score was taken in each of the 12 zones.

Statistical analysis

Baseline characteristics and outcome variables were presented as means ± standard deviations (±SD), medians and interquartile range [IQR], or numbers (percentages %) where appropriate. Groups were compared with the independent t-test, ANOVA, χ^2-test, or Fisher's exact test. A Shapiro-Wilk test, visual inspection of histograms, and Q-Q plots were used to determine data distribution. A two-sided significance level of 5% was used for all analyses, 95% confidence intervals (95%CI) are reported. All mixed models analyses were done with the maximum likelihood method. Statistical analyses were performed using SPSS IBM version 24.0 (SPSS Inc., Chicago, IL, USA).

Correlation

Given the fact that we used repeated measurements over time, mixed models analysis was employed to calculate the correlation between the LUSS (± pleural abnormalities) and CTSS. We also assessed the correlation between the LUSS and CTSS on one hand, and arterial oxygen partial pressure to fractional inspired oxygen (P_aO_2/F_iO_2) ratio, and the alveolar dead space to tidal volume ratio according to Enghoff (V_d/V_t ratio) on the other.[23–25] A coefficient of 0-0.19 indicated a slight; 0.20-0.39 a fair; 0.40-0.59 a moderate; 0.60-0.79 a substantial; and 0.80-1.0 an almost perfect correlation.[26]

Agreement and measurement error between raters

We quantified reproducibility by assessing agreement and measurement error between raters for LUSS, pleural abnormalities, and CTSS by intraclass correlation coefficient (ICC) (two-way random effects model for agreement), and the smallest detectable change (SDC), respectively. The SDC represents the minimal change a score must show to ensure that the observed difference is a true change and not a product of measurement error (or imprecision) that may occur between raters. To visualize the SDC and corresponding limits of agreement (LoA) we also constructed Bland-Altman plots.[26] LUSS and pleural abnormalities were analyzed by AL and MHe, while the CTSS was analyzed by RvH and BT.

Mortality

We performed a linear mixed model analysis to assess if changes in pulmonary involvement – graded by either LUSS (± pleural abnormalities) or CTSS – are associated with mortality at different times during ICU admission. To do so, the development over time

for pulmonary involvement was compared between survivors and deceased patients. Therefore, the variables 'time' (treated as a categorical variable represented by dummy variables), 'deceased' (yes/no) and 'the interaction between time and deceased' were added to the linear mixed model.

Sample size

For the correlation between LUSS (± pleural abnormalities) and CTSS we consecutively included patients during the entire study period. However, taking into account a correlation of 0.67, alpha of 0.05 and beta of 0.20 at least 15 patients were needed.[7] For reproducibility between raters: both LUSS and CTSS previously described interrater agreement was excellent, albeit in the ED setting.[1,27] The required sample size for both LUSS and CTSS was calculated based on an expected agreement of 0.88, a precision 0.1, and alpha of 0.05 and beta of 0.20. This resulted in a sample size of 21 patients. For the classification of pleural abnormalities and subpleural consolidations, there are no known agreement or measurement error parameters. We expected an agreement of 0.8, with a precision of 0.1, an alpha and beta of 0.05 and 0.20. This resulted in a required sample size of 51 for two raters. To avoid scan-location bias we included 60.

Results

Of the 87 screened patients, 82 were included (Figure 13.1). Patient characteristics are shown in Table 13.1. Compared to survivors, patients in the deceased group were older, had more comorbidities, higher creatinine, C-reactive protein (CRP), cardiac enzymes, initial positive end-expiratory pressure (PEEP) settings, and longer ICU admission time. Although the difference in CRP and PEEP between the two groups is not clinically relevant. A superinfection was suspected in 27.8% of CTs. In 74% of those cases either the right or the left lower lobe was involved, and in the remaining cases the posterior parts of the upper lobes were predominantly involved.

Correlations

The correlation of CTSS with LUSS (without pleural abnormalities) was 0.45 (95%CI 0.31-0.59), while the correlation of CTSS with LUSS (including pleural abnormalities) 0.31 (95%CI 0.15-0.46). CTSS was not correlated with the P_aO_2/F_iO_2 ratio, whereas the LUSS was significantly negatively correlated. The LUSS was fairly correlated with the V_d/V_t ratio, and the CTSS was only slightly correlated with the V_d/V_t ratio (Table 13.2). Incorporation of pleural abnormalities to the LUSS did not lead to a significant improvement of the correlations.

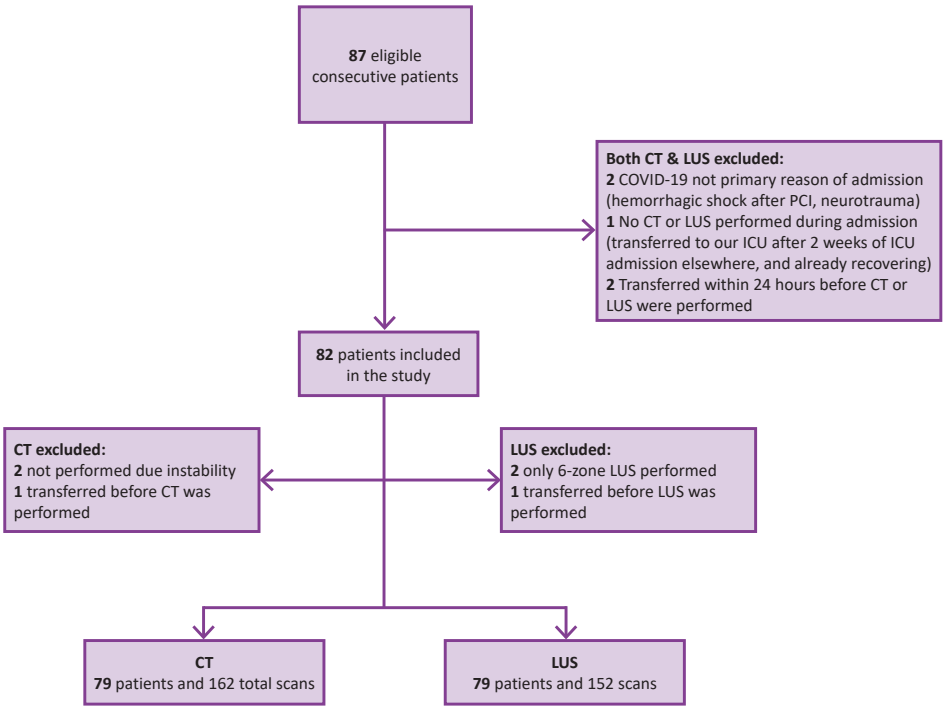


Figure 13.1: Flowchart of patient inclusion and exclusion.
Abbreviations: PCI, percutaneous coronary intervention; ICU, intensive care unit; CT, computed tomography; LUS, lung ultrasound.

Agreement and measurement error between raters

The ICC for LUSS was 0.88 (95%CI 0.73-0.95), while the SDC was 4.8. The ICC of pleural abnormalities was 0.94 (95%CI 0.90-0.96), while its SDC was 1.4. The ICC for CTSS was 0.84 (95%CI 0.65-0.93) and the SDC was 3.9. There was no proportional bias for LUSS or CTSS (Figure 13.2A-B).

However, for pleural abnormalities the measurement error is less on the extremes of the spectrum: (0) 'normal pleural line' and (4-5) 'subpleural consolidation ≥2 cm', compared to the categories in the middle (1) 'thickened/irregular pleura' to (3) 'subpleural consolidations <2 cm' (Figure 13.2C).

Mortality

In deceased patients a significant rise in LUSS was found compared to admission (Figure 13.3A). For survivors the difference compared to admission only became significant in week 3 for LUSS. However, the difference between survivors and deceased patients for LUSS was only significant after 2 weeks of admission; 5.62 (95%CI 2.44-3.99), which

Table 13.1: Baseline characteristics

	Total: 82	Alive: 50	Deceased: 32	*p* value
Demographics				
Age (years)	67 [59-74]	64 [57.8-70]	71.5 [65-76]	**<0.001**
Sex (male)	65 (79.3)	39 (78)	26 (81.3)	0.58
BMI (kg/m^2)	29.5 (6.1)	30.1 (5.5)	28.9 (6.6)	0.47
APACHE II	12 [10-13]	12 [10-12]	12 [10-13.3]	0.38
SOFA score	7.5 (2.9)	7.2 (2.9)	8.1 (2.9)	0.17
Charlson Comorbidity Index	3.2 (1.9)	2.8 (2.0)	3.8 (1.6)	**0.02**
Laboratory parameters				
Creatinine (umol/L)	80.5 [64.3-109.8]	70 [57.3-89.8]	103.5 [79.8-198.3]	**<0.001**
Leucocytes (x10^9/L)	10.2 (4.9)	9.8 (4.6)	10.8 (5.5)	0.43
CRP (mg/L)	139 [90-190]	128 [83-183]	159 [105.5-193.3]	**0.007**
Procalcitonin (ug/L)	0.35 [0.18-1.06]	0.27 [0.13-0.62]	0.75 [0.20-1.48]	0.42
LDH (U/L)	505 [398-643]	489 [398-618]	509 [392-730]	0.23
Hs Troponin T (ng/L)	24 [12.5-51.5]	18 [9.8-38]	39 [19-119]	**0.005**
NT-pro BNP (ng/L)	575 [237-1011]	472 [193-749]	756 [395-1658]	**<0.001**
aPTT (sec)	26 [23-30]	25 [23-30]	26 [23-29.5]	0.96
D-dimer (ng/ml)	1.65 [1.04-5.74]	1.42 [0.94-5.11]	2.96 [1.18-6.38]	0.87
Ventilation parameters				
PEEP (cm H_2O)	11 (3)	11 (2)	12 (3)	**0.04**
P_aO_2/F_iO_2 ratio	105 [75.8-147.5]	111.4 [75.8-147.5]	105 [75.6-154.6]	0.96
$etCO_2$ gap (kPa)	1.83 (0.96)	1.9 (1.1)	1.7 (0.8)	0.66
Initial imaging scores				
LUSS	21 (5)	21 (5)	21 (6)	0.55
Pleural abnormality score	13 (7.6)	12 (6)	15 (9.5)	0.14
CTSS	18 [16-22]	18 [16-21]	19 [15-23.5]	0.38
Outcomes				
ICU length of stay (days)	13 [6-28.5]	10 [6-40.5]	16 [8.3-20]	**<0.001**
28-day mortality	29 (35.4)	N/A	N/A	
90-day mortality	32 (39)	N/A	N/A	

Values are n (%), mean (±SD), or median [IQR] as appropriate. *P* values comparing patients are from χ^2-test, Fisher's exact test, ANOVA or Mann-Whitney U test, with α=0.05.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; aPTT, activated prothrombin time; BMI, body mass index; CRP, C-reactive protein; $etCO_2$, end-tidal carbon dioxide; Hs, high sensitivity; IQR, interquartile range; ICU, intensive care unit; IU, international units; kPa, kilopascal; L, liter; LDH, lactate dehydrogenase; LUSS, lung ultrasound score; NT-pro BNP, N-terminal pro b-type natriuretic peptide; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; P_aO_2/F_iO_2 ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; Pleural abnormality score, separate pleural abnormality score, so without inclusion in the LUSS; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

Table 13.2: Correlations of different scores of pulmonary involvement with respiratory parameters

	LUSS	LUSS + pleural abnormalities	CTSS
P_aO_2/F_iO_2 ratio	-0.31 *(-0.48 - -0.16)*	-0.20 *(-0.37 - -0.04)*	-0.11 *(-0.26 - 0.05)*
V_d/V_t	0.20 *(0.02 - 0.38)*	0.25 *(0.07 - 0.43)*	0.18 *(0.003 - 0.35)*

All values are given with their 95% confidence interval in italic.

Abbreviations: CTSS, computed tomography severity score; LUSS, lung ultrasound score; P_aO_2/F_iO_2 ratio, arterial oxygen partial pressure to fractional inspired oxygen ratio; V_d/V_t ratio, the alveolar dead space to tidal volume ratio.

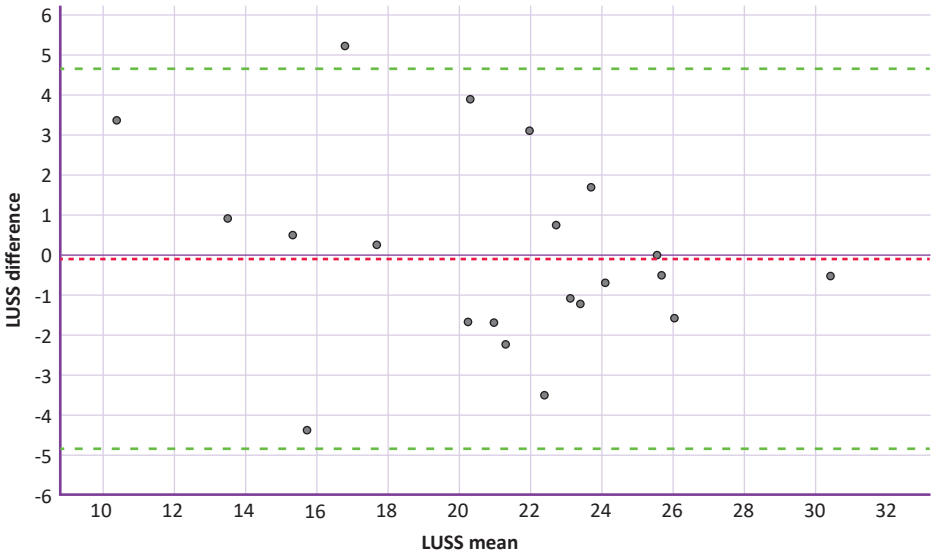


Figure 13.2A: Bland-Altman plot for LUSS.
Each point represents agreement between the two raters AL & MHe. A jitter effect was added to improve visualization of data and avoid direct overlap of multiple examinations.
Green dotted line: limits of agreement.
Red dotted line: mean systematic difference.
Abbreviation: LUSS, Lung ultrasound score.

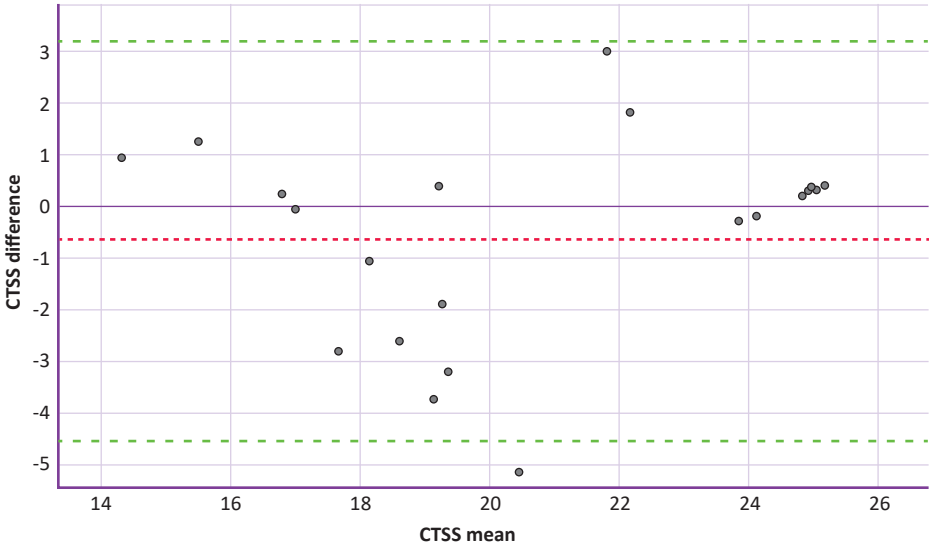


Figure 13.2B: Bland-Altman plot for CTSS.
Each point represents agreement between the two raters RvH & BT. A jitter effect was added to improve visualization of data and avoid direct overlap of multiple examinations.
Green dotted line: limits of agreement.
Red dotted line: mean systematic difference.
Abbreviation: CTSS, Computed tomography severity score.

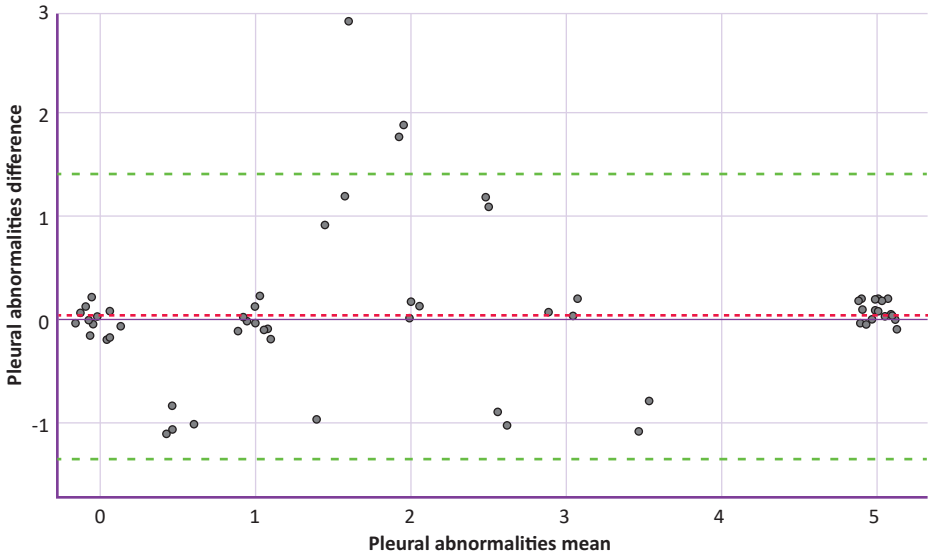


Figure 13.2C: Bland-Altman plot for pleural abnormalities on lung ultrasound.
A jitter effect was added to improve visualization of data and avoid direct overlap of multiple examinations.
Green dotted line: limits of agreement.
Red dotted line: mean systematic difference.

became insignificant afterward (e-Figure 13.3A). The addition of pleural abnormalities did not improve the association with mortality (e-Figure 13.3B).

In deceased patients CTSS rose significantly compared to baseline in the first week of admission, and remained stable afterwards (Figure 13.3B). In survivors there was a slower and smaller upward trend in CTSS until week 2 which also stabilized afterwards. The difference in CTSS between deceased patients and survivors was only significant after week 1; 3.0 (95%CI 0.38-5.62), but not afterwards (e-Figure 13.3C).

Discussion

The main findings of this prospective, observational study assessing the ability LUS and CT to monitor pulmonary involvement in COVID-19 ICU patients are: 1) LUSS has a moderate correlation with the CTSS for the quantification of pulmonary involvement, and a better correlation with the P_aO_2/F_iO_2 and V_d/V_t ratio than CTSS; 2) Serial LUSS is capable of detecting true changes in pulmonary involvement, whereas CTSS cannot; 3) Of the two scores, only a rise in LUSS after 2 weeks is significantly associated with mortality and detectable beyond measurement error. However, this association becomes insignificant

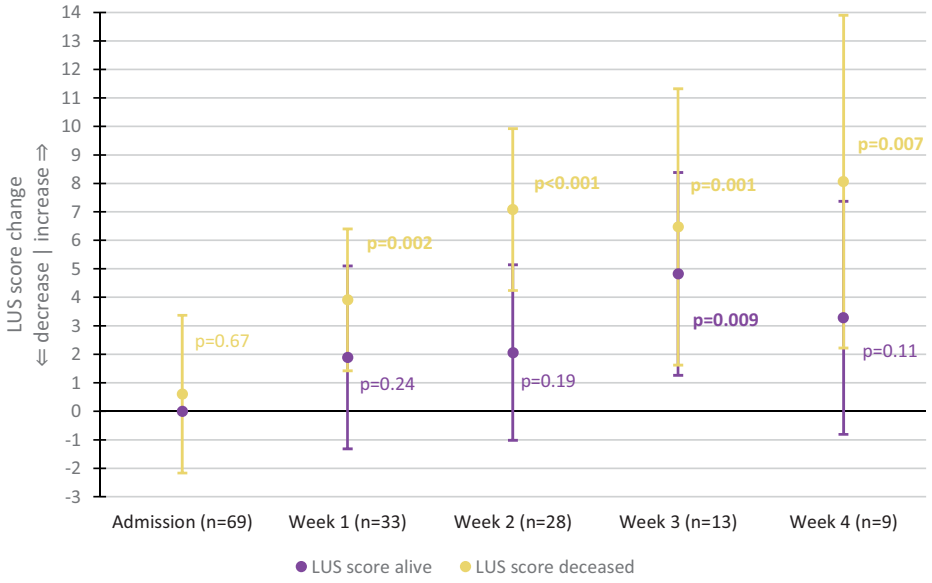


Figure 13.3A: LUSS changes over time compared to admission.
Each point represents the mean score change compared to admission with its 95% confidence interval.
Purple points: patients who survived.
Yellow points: patients who died.
P values should be interpreted as the significance of the change of that particular point compared to baseline. Significant *p* values are in bold. At admission, there was no difference between the LUSS of patients who survived until discharge or died during admission (*p*=0.67).
Abbreviation: LUSS, lung ultrasound score.

again in the weeks afterwards; 4) Addition of subpleural abnormalities did not lead to improvement of the existing LUSS.

Our results suggest LUS might be used as a substitute of chest CT for the monitoring of COVID-19 pneumonia severity in COVID-19 ICU patients. The correlation of the total LUSS and CTSS was moderate, which is comparable to previous studies.[6,7,17] Surprisingly, the CTSS didn't correlate with the P_aO_2/F_iO_2 ratio, and only correlated slightly with the V_d/V_t ratio. Even though the measurements were taken at time of CT. The LUSS correlated fairly with both. A worsening of the P_aO_2/F_iO_2 ratio over time would prompt a repeat CT in clinical practice to evaluate the progression of pulmonary involvement, but this thus seems redundant.

Although the degree of pulmonary involvement at presentation to the emergency department is associated with ICU admission and adverse events,[6–10] previous studies failed to show an association between LUSS or CTSS at ICU admission and mortality (without it being incorporated in a composite end-point).[1,7,8,17,28,29] The only other prospective study

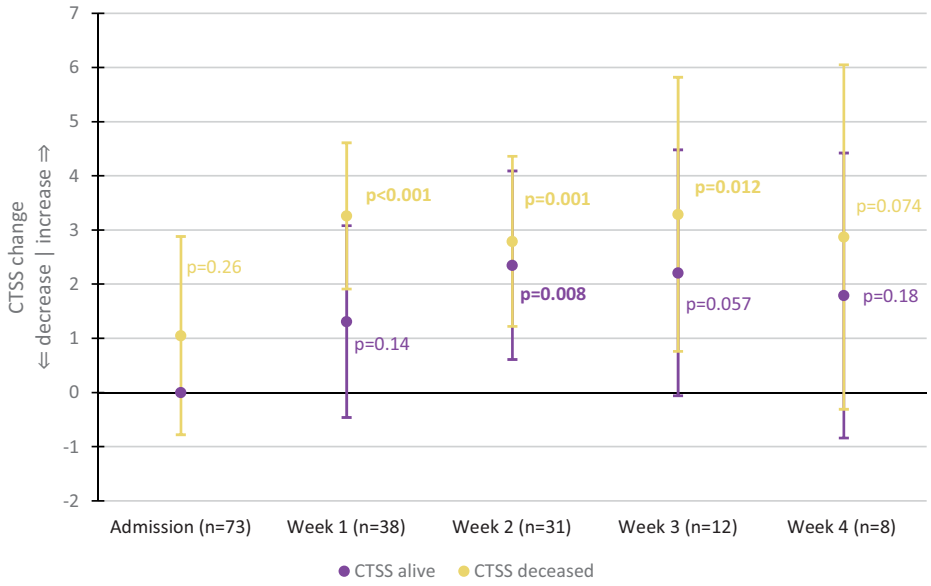


Figure 13.3B: CTSS changes over time compared to admission.
Each point represents the mean score change compared to admission with its 95% confidence interval.
Purple points: patients who survived.
Yellow points: patients who died.
P values should be interpreted as the significance of the change of that particular point compared to baseline. Significant *p* values are in bold. At admission, there was no difference between the CTSS of patients who survived until discharge or died during admission (*p*=0.26).
Abbreviation: CTSS, Computed tomography severity score.

assessing the prognostic value of serial LUS and CT, showed that the LUSS after 1 week did not differ significantly from the LUSS at admission, and did not show an association with mortality. However, our study showed that the LUSS might help differentiate between patients who survive or die if you follow them longer. Although the LUSS did not exceed the SDC (4.8) on a week-to-week basis, from week 2 onwards the LUSS exceeded the SDC, and was significantly higher compared to admission in deceased patients. The mean difference between deceased patients and survivors was significant and also exceeded the SDC in week 2. This wasn't the case in week 3 and 4, possibly owing to the small sample size, as results did show a trend. In patients who survived, both LUSS and CTSS showed no decrease over time, stressing the discrepancy between clinical recovery and lack of image resolution.[17]

Contrary to the LUSS, the CTSS seems not useful in monitoring ICU COVID-19 patients, which is at odds with the claims of the original CO-RADS protocol, which promoted the CTSS as a tool for follow-up.[30] Even though there was a statistically significant difference between patients who survived and those who died in week 1, it falls within the meas-

urement error. Indeed, the CTSS never changed more than its SDC (3.9); neither between admission and following weeks, nor between surviving and deceased patients. In other words, CTSS changes in these patients are more likely to be caused by measurement error than changes in disease severity.

This may be explained by the fact that the CTSS lacks responsiveness, suffers from ceiling effects, and employs categories that are too broad.[26,31] In addition, the CTSS only includes ground glass opacities, omitting consolidations and fibrosis which are present later in the disease.[14–17,30] Their incorporation might improve the CTSS. Other potential improvements may lie in increasing the number of categories of the CTSS, or using use of artificial intelligence (AI) to aid pulmonary involvement quantification.[32]

Although there are other reasons to perform a CT – i.e., suspicion of a pulmonary embolism, or of a superinfection – it could be argued that even for these indications CT does not have to be the first diagnostic step, and the number of CTs could at least be reduced. For instance, less invasive methods like routine screening of deep venous thrombosis (DVT) by POCUS could obviate the need for a CT pulmonary angiography (CTPA).[33–35] Furthermore, although there is some evidence in immunocompromised patients that CT-guided bronchoalveolar lavage (BAL) results in a higher yield,[36] BAL can also be performed without CT guidance.[37] In our cohort, a superinfection was suspected in 27.8% of CTs, which is comparable to what is reported in the most recent meta-analysis.[38] Since we found the posterior parts of the lungs were primarily involved when superinfection was suspected, we argue that a CT is not required to determine the optimal BAL location and these areas could be sampled empirically.

Some of the criticisms of the CTSS also apply to the LUSS, particularly the fact that its categories are too broad. However, we showed that including pleural abnormalities unfortunately did not improve the LUSS to a significant degree. Firstly, this might be due to the fact that the LUSS already incorporates pleural abnormalities and consolidations to some degree, so by adding them again you might be counting them twice.[21] Secondly, we found there is more measurement error in pleural abnormality categories 1-3, than categories 0 and 4-5. This is no surprise as there is no clear definition of a 'thickened', 'blurred', or 'irregular' pleural line, nor is it clear when an 'irregular' pleura is actually caused by clear subpleural consolidation(s). As such clinicians will interpret these constructs in different ways.[10,11] Moreover, it is unclear what the clinical relevance of pleural abnormalities of varying degrees is. As our results show they might not hold any additional value. In any case, universal standardization of these signs – as was done with other LUS signs – is paramount to facilitate comparison across studies.[22] All in all, we argue to keep using the existing LUSS – which has already been validated in multiple

settings – and that restraint should be exercised in creating new, more complex and/or unvalidated measurement instruments.[21,26]

Maybe in the future AI can help improve LUS quantification of pulmonary involvement, and elucidate which findings have additional prognostic value. It has shown promise in a few studies, but further innovation and research is required before it will be ready for use on a larger scale.[21,39–41] An important condition for AI-based quantification is that it should be directly applicable and useable at the bedside, so the benefits of the point-of-care nature of LUS are not lost.

In summary, we argue that if one would like to monitor ICU COVID-19 patients with an imaging modality, LUSS should be preferred over CTSS, at least as an initial step. Especially considering the cost, safety and time disadvantages associated with CT and the lack of its availability in many parts of the world.

Strengths & limitations

First, this was a single-center study with a relatively limited sample size. Still, this is the largest prospective study in consecutive COVID-19 ICU patients to investigate the ability of serial LUS and CT in monitoring and prognostication. Second, although we are a tertiary center, our case mix was reflective of the total ICU population since ICU patients were divided across the country according to a fair-share principle. Accordingly, we believe selection bias was therefore minimized. Third, time between LUS and CT was always below 24 hours, which limited imprecision of the correlations. Fourth, we only included patients who deteriorated or stagnated in their recovery, and did not perform a CT or LUS in patients that were recovering nor in patients in which the disease progressed to such a degree that further diagnostics and treatment were deemed no longer useful. Although, this does reflect daily practice, it would be interesting to include these groups in further research as well. Fifth, operators were blinded for CT results, reducing information bias to a minimum.

Conclusion

LUSS correlated with CTSS throughout ICU admission, but performed similar or better at agreement between raters and mortality prognostication. Incorporation of pleural abnormalities did not improve the LUSS. Given the benefits of LUS over CT, LUS should be preferred over CT as the initial monitoring tool in critically ill patients with COVID-19.

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14

Multi-organ point-of-care ultrasound for detection of pulmonary embolism in critically ill patients with COVID-19
A diagnostic accuracy study

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Abstract

Background: Critically ill patients with COVID-19 have an increased risk of developing pulmonary embolism (PE). Diagnosis of PE by point-of-care ultrasound (POCUS) might reduce the need for computed tomography pulmonary angiography (CTPA), while decreasing time-to-diagnosis.

Methods: This prospective, observational study included adult ICU patients with COVID-19. Multi-organ – lungs, deep vein, cardiac – POCUS was performed within 24 hours of CTPA, looking for subpleural consolidations, deep venous thrombosis (DVT), and right ventricular strain (RVS), respectively. We reported the scan time, and calculated diagnostic accuracy measures for these signs separately and in combination.

Results: 70 consecutive patients were included. 23 patients (32.8%) had a PE. Median scan time was 14 minutes [IQR 11-17]. Subpleural consolidations' diagnostic accuracy was: 42.9% (95%CI 34.1-52.0). DVT's and RVS' diagnostic accuracy was: 75.6% (95%CI 67.1-82.9) and 74.4% (95%CI 65.8-81.8). Their sensitivity was: 24.0% (95%CI 9.4-45.1), and 40.0% (95%CI 21.3-61.3), while their specificity was: 88.8% (95%CI 80.8-94.3), and: 83.0% (95%CI 74.2-89.8), respectively. Multi-organ POCUS sensitivity was: 87.5% (95%CI 67.6-97.3), and specificity was: 25% (95%CI 16.9-34.7).

Conclusion: Multi-organ POCUS – particularly combined deep vein and cardiac – rather than single-organ POCUS may be of aid in ruling out PE in critically ill patients with COVID-19 and help select patients for CTPA. In addition, finding RVS can make PE more likely in this setting, while a DVT would preclude the need for a CTPA.

Introduction

Clinical manifestations of Coronavirus Disease 2019 (COVID-19) extend beyond that of an upper respiratory tract infection or pneumonia.[1] Critically ill patients with COVID-19 have an increased risk of developing pulmonary embolism (PE), compared to hospitalized and intensive care unit (ICU) patients with other (respiratory) infections.[2–5] Computed tomography pulmonary angiography (CTPA) is the gold standard to diagnose PE. However, transport outside of the controlled ICU environment carries substantial risks for patients, while necessitating post-transport decontamination.[6,7] It also requires (scarce) personnel and reduces time that can be spent on patient care.

Point-of-care ultrasound (POCUS) might reduce the need for CTPAs in these patients – in already overwhelmed acute and critical health care systems worldwide – particularly in low- and middle-income regions.[8–10] Recent consensus statements recommend the use of POCUS as an initial test in critically ill COVID-19 patients.[3,5,11,12] However literature on POCUS for the detection of PE in these patients is still limited.

Studies in non-COVID-19 settings have shown that lung POCUS – by demonstrating subpleural consolidations – has good diagnostic accuracy for detecting PE.[13–15] However, since subpleural consolidations are also prominent sonographic features in COVID-19 and acute respiratory distress syndrome (ARDS), lung POCUS might be less accurate in detecting PE in critically ill COVID-19 patients.[16,17] To date, studies in COVID-19 patients are scarce, although a small case series showed promising results.[18]

Compression ultrasound of the deep veins of the lower extremities (deep vein POCUS) has demonstrated excellent accuracy in detecting deep venous thrombosis (DVT) – a proxy for PE – across a myriad of settings, including this pandemic.[19–22] Furthermore, cardiac POCUS may help identify PE indirectly by the detection of new right ventricular strain (RVS), which has high specificity for PE. Cardiac POCUS has been reported to be as reliable as formal echocardiography in detecting RVS.[23] However, RVS is found in 22-50% of patients with ARDS, which could limit its use in COVID-19.[19,24]

Combining different POCUS modalities (lung, deep vein, and cardiac) to detect pulmonary embolism has been advocated as well.[3,5,11,12,25] In the emergency department (ED) setting there are promising results of multi-organ POCUS in the detection of PE,[7,10,26] while others found no benefit.[27] However, there have been no studies in critically ill patients with (or without) COVID-19.

Therefore, our aim was to investigate the diagnostic accuracy of different POCUS modalities – lung, deep vein and cardiac – separately, and in combination (multi-organ POCUS) for the detection of PE in critically ill patients with COVID-19.

Methods

Study design

This is a prospective, observational study conducted at the academic adult ICU of the Amsterdam UMC, location VUmc, Amsterdam, The Netherlands, between October 20th 2020 and February 20th, 2021. Patients were followed up until May 20th, 2021. The study, and use of data gathered during routine ultrasound and CTPA, was approved by the Medical Ethical Committee of the VUmc, along with a waiver of informed consent (2020.011). The trial was registered in the Dutch trial registry (NL8540).

Consecutive adult patients (≥18 years) with a laboratory confirmed diagnosis of COVID-19 were eligible for inclusion upon admission to ICU. Patients were included when the multi-organ POCUS examination (index test) was performed within 24 hours of a CTPA (reference test). They could be included again if a CTPA was repeated. Patients were excluded if they were already on therapeutic anticoagulation, transferred to another hospital within 24 hours of CTPA, or died within 24 hours of CTPA. Baseline characteristics along with ventilator settings and laboratory values were collected from the electronic patient record closest to the time of CTPA.

Medical workup

As part of the departmental protocol, patients received a CT(PA) when their clinical condition did not improve or deteriorated approximately every 7 days to diagnose PE, to determine the extent of pulmonary involvement, and possible superinfection. If a PE was diagnosed, a CTPA was typically not repeated. A normal CT could still be repeated though to monitor the degree of pulmonary involvement or detect a possible superinfection. As commonly used clinical decision rules (i.e., WELLS, GENEVA or YEARS-criteria) are not validated in the ICU nor in the COVID-19 setting,[28–31] the decision to perform a CTPA was made by the treating ICU-consultant in consultation with a daily multidisciplinary team consisting of a consultant microbiologist, a consultant pulmonologist and at least three other ICU consultants.

Protocols

CT and CTPA protocol

Chest CT was performed on two multidetector CT scanners: Siemens Somatom Drive (Siemens Healthineers, Erlangen, Germany), and a GE Discovery 750 HD (GE Healthcare, Milwaukee, MI). All patients underwent CT scanning of the chest during end-inspiration. Slice thickness for all scanners was between 0.625-1.25 mm. CT Pulmonary angiography was performed by injecting of 50 mL contrast medium (Iomeron 300, Bracco Imaging, Germany) at 5 mL/s.

ICU treatment protocol

Patients admitted to our ICU were treated with selective intestinal decontamination (Tobramycin 80 mg/Colistin 100 mg/Nystatin 2.000.000 IU) 10 ml suspension orally or via nasogastric tube(s) thrice daily, and 0.5 mg mouthpaste thrice daily for the duration mechanical ventilation. In addition, we prescribed intravenous Ceftriaxone 2 grams once daily for four days. We also treated patients with intravenous Dexamethasone 6 grams once daily for 7 days. The use of Tocilizumab was not yet protocol.

Given the high incidence of the venous thromboembolism (VTE) reported in the literature from the first wave, the protocol in our ICU was to increase the dosing interval of prophylactic low molecular weight heparin (Fraxiparine). Patients <100 kg received 2850 IE bidaily instead of once daily, while patients >100 kg received 5700 IE bidaily instead of once daily. With daily anti-factor Xa (anti-fXa) measurements every day, starting after the third dose, with a target level of 0.1-0.5 U/ml. When levels remained <0.1 U/ml, physicians could decide to increase the dose to get it within target range. When patients required therapeutic anticoagulation intravenous unfractionated heparin (UFH) was used, with a target activated partial thromboplastin time (aPTT) of 45-60. When no therapeutic aPTT levels of UFH were reached despite high doses (>25 IE/kg/hour), anti-fXa levels could be used to guide therapy, with a therapeutic target range of 0.3-0.7 IE/ml.
All mechanically ventilated patients were treated with pressure control or pressure support, adhering to lung protective protocols advised by the Dutch Society of Intensive Care (NVIC), which are described elsewhere.[32]

Index test: POCUS

POCUS is part of the standard care on our ICU. All examinations were performed or supervised by experienced ultrasound physicians using a COVID-19 unit-restricted SonoSite-Edge II ultrasound machine.[33] They were blinded for CTPA result, but not for the clinical data. Lastly, the scan time was recorded for all investigations.

Lung POCUS: subpleural consolidations

Pulmonary embolism has been associated with subpleural consolidations on lung ultrasound.[13,34] A 10-5 MHz linear transducer or 5-3 MHz curvilinear transducer with lung examination setting was used. The lung ultrasound protocol consisted of a structured assessment of 6 zones of each hemithorax (e-Figure 5.1).[35] The recently modified criteria from Mathis et al. were used to diagnose PE in COVID-19 patients.[14,18] Likelihood of PE was determined to be:

- High (CON2): when two or more subpleural consolidations (≥1 cm) were detected (e-Video 14.1);
- Probable (CON1): when only one subpleural consolidation (≥1 cm) was detected (e-Figure 13.2 & e-Figure 14.1);
- Possible: when two (or more) subpleural consolidations (<1 cm) were detected (e-Figure 13.1 & e-Video 14.2);
- Low: when no consolidations were detected (e-Video 5.1 & 5.2).

Deep vein POCUS: DVT

A two-point compression ultrasound of the common femoral (e-Video 9.1) and popliteal vein (e-Video 9.4) was performed, using a 10-5 MHz linear transducer on venous setting following a previously described protocol.[36,37] If an indwelling central venous catheter (CVC) was present, it was also examined as far as possible after skin insertion. Deep venous thrombosis was defined as a non-compressible vein (e-Video 9.2 & 9.5).

Cardiac POCUS: RVS

Cardiac POCUS was performed using a 5-2 MHz phased array transducer on cardiac setting from as many cardiac windows as obtainable (i.e., ≥1 parasternal long axis [PLAX], parasternal short axis [PSAX], subcostal short axis [SSC], or apical 4 chamber [A4C]). See e-Video 14.3, 14.4, and 14.5 for clips of normal PLAX, PSAX, and 4AC views respectively. Right ventricular strain was determined by 'eye-balling' interventricular septum flattening/bowing into the left ventricle (see e-Video 14.6 for septal bowing in PLAX). In PSAX this is called: 'D-Sign' (e-Video 14.7). Or by assessing the right ventricle (RV) to left ventricle (LV) basal end diastolic diameter ratio, and/or McConnell's sign in 4AC (e-Video 14.8). A RV:LV ratio of ≥1 was deemed abnormal.[19,34,36,38] A visible RV thrombus was also deemed to be diagnostic.

Reference test: CTPA

CTPAs were evaluated by our local radiologists with varying degrees of experience, who did have access to the clinical information – but not the POCUS examinations. Pulmonary embolism was defined as a constant intravascular filling defect on CTPA. Location of a filling defect was registered for each lobe until most distal subsegmental levels. Right ventricular strain (RV:LV ratio ≥1) was also registered.

Statistical analysis

Baseline characteristics and outcome variables were presented as means ± standard deviations (±SD), medians and interquartile range [IQR], or numbers (percentages %) as appropriate.

We determined diagnostic accuracy measures; sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy for subpleural consolidations, RVS, and DVT separately and in different combinations. In addition, we determined a receiver operating characteristic (ROC) curve with corresponding area under the curve (AUC) for subpleural consolidations ≥1 cm. We established the optimal cutoff with the Youden index. Missing data were handled by pairwise deletion. McNemar tests were used to compare sensitivities and specificities of each single-organ modality with multi-organ POCUS. Missing data were handled by pairwise deletion. Statistical analyses were performed using SPSS IBM version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Study population

140 CTPAs were made in 70 consecutive patients, with a median of 2 scans per patient [IQR 1-3]. In 11 instances multi-organ POCUS data was missing because the scan was not conducted withing 24 hours of the CT scan. In 2 patients all of the POCUS scans were incomplete or could not performed, this was also the case for 1 additional lung POCUS, 4 deep vein POCUS and 2 cardiac POCUS (Figure 14.1). This was mainly due to the positioning of the patient (i.e., prone or lateral position). Patient baseline characteristics and outcomes are shown in Table 14.1. 62 Patients (88.6%) required mechanical ventilation during admission. 66 Patients (94.2%) developed moderate or severe ARDS. No patients had a previous history of RVS. 23 Patients (32.8%) had a PE, of which 12 (52.2%) were subsegmental. Median scan time of a full multi-organ POCUS exam was 14 minutes [IQR 11-17].

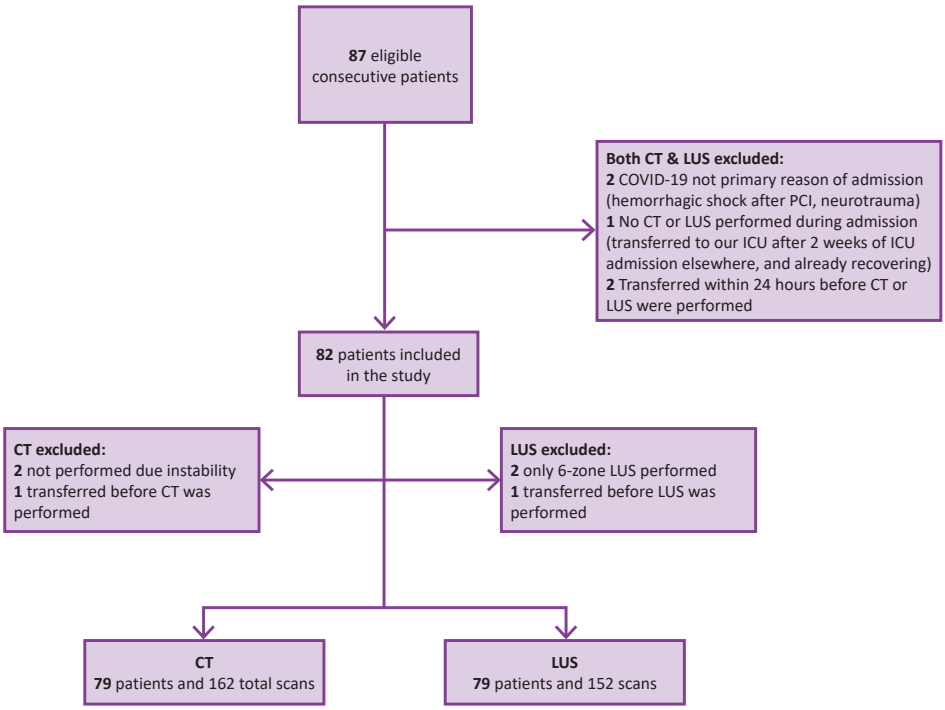


Figure 14.1: Flowchart of patient inclusion and exclusion.
Abbreviations: CT, computed tomography; ICU, intensive care unit; LUS, lung ultrasound; PCI, percutaneous coronary intervention.

Detection of pulmonary embolism

Single-organ POCUS

In Table 14.2 diagnostic accuracy measures are shown for the different POCUS signs of PE. For the high likelihood criterium for PE (≥2 subpleural consolidations of ≥1 cm) sensitivity was 70.8% (95%CI 48.9-87.4) and specificity 35.0% (95%CI 25.7-45.2). 82 patients (62.6%) had high PE likelihood criterium, of which 65 (79.2%) were falsely positive.

For the probable PE criterium (1 subpleural consolidation of ≥1 cm) sensitivity was 8.7% (95%CI 1.1-28.4), and specificity 78.6% (95%CI 69.5-86.1). Employing the possible or low likelihood criteria did not result in improved diagnostic accuracy measures.

The ROC curve for subpleural consolidations ≥1 cm showed an AUC of 0.58 (95%CI 0.45-0.72) with an optimal cutoff of 4 subpleural consolidations (Youden 0.29) (e-Figure 14.2). At this cutoff sensitivity was 60.9% and specificity 66.0%, with a PLR of 1.79 and NLR of 0.59.

Table 14.1: Baseline characteristics

	Patients
Demographics	
Age (years)	67.5 [60-75]
Sex (male)	56 (80)
BMI (kg/m^2)	28.6 (5.0)
APACHE II	12 [10-13]
SOFA score	7.6 (2.9)
Charlson Comorbidity Index	3 (1.8)
Laboratory parameters	
Creatinine (umol/L)	79 [64-104]
Leucocytes (x10^9/L)	10.5 (4.7)
CRP (mg/L)	128 [83-188]
Procalcitonin (ug/L)	0.35 [0.15-1.05]
LDH (U/L)	505 [399-648]
Hs Troponin T (ng/L)	23 [12.5-54]
NT-pro BNP (ng/L)	642 [272-903]
aPTT (sec)	25 [23-28]
D-dimer (ng/ml)	2.21 [1.18-6.30]
Ventilation parameters	
PEEP (cm H_2O)	11 (2.3)
P_aO_2/F_iO_2 ratio	106.3 [75.8-147.5]
$etCO_2$ gap (kPa)	1.76 (0.92)
Outcomes	
ICU length of stay (days)	14 [6-31.5]
Mechanical ventilation (days)	14.5 [6-31]
28-day mortality	25 (35.7)
90-day mortality	28 (40.0)

Values are n (%), mean (±SD), or median [IQR] as appropriate.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; aPTT, activated prothrombin time; BMI, body mass index; CRP, C-reactive protein; $etCO_2$, end-tidal carbon dioxide; F_iO_2, fraction of inspired oxygen; Hs, high sensitivity; IQR, interquartile range; ICU, intensive care unit; IU, international units; kPa, kilopascal; L, liter; LDH, lactate dehydrogenase; NT-pro BNP, N-terminal pro b-type natriuretic peptide; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; P_aO_2, partial pressure of arterial oxygen; P_aO_2/F_iO_2 (P/F) ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen); SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

DVT found by POCUS had a sensitivity of 24.0% (95%CI 9.4-45.1), but the highest specificity of all findings: 88.8% (95%CI 80.8-94.3). For RVS on cardiac POCUS sensitivity was 40.0% (95%CI 21.3-61.3) and a specificity 83.0% (95%CI 74.2-89.8). A visible RV thrombus was detected in 0% of cases.

Multi-organ POCUS

Signs of different POCUS modalities were combined to determine if this would increase diagnostic accuracy. For a positive multi-organ POCUS – so either a positive high PE likelihood criterium (CON2), DVT, or RVS – sensitivity was highest 87.5% (95%CI 67.6-97.3),

Table 14.2: 2x2 contingency tables & diagnostic accuracy measures for POCUS signs of pulmonary embolism

POCUS		CT PE +	PE -	Sensitivity % (95%CI)	Specificity % (95%CI)	NLR (95%CI)	PLR (95%CI)	NPV % (95%CI)	PPV % (95%CI)	Diagnostic Accuracy % (95%CI)
CON2	US+	17	65	70.8	36.3	0.80	1.11	84.1	20.7	42.9
	US-	7	37	(48.9-87.4)	(25.7-45.2)	(0.41-1.58)	(0.83-1.49)	(72.9-91.2)	(16.3-26.0)	(34.1-52.0)
CON1	US+	2	22	8.7	78.6	1.16	0.41	79.4	8.3	65.9
	US-	21	81	(1.1-28.4)	(69.5-86.1)	(0.99-1.36)	(0.10-1.61)	(76.7-81.9)	(2.3-26.5)	(56.9-74.1)
DVT	US+	6	11	24.0	88.8	0.86	2.14	82.1	35.3	75.6
	US-	19	87	(9.4-45.1)	(80.8-94.3)	(0.68-1.08)	(0.88-5.22)	(78.4-85.2)	(18.3-57.1)	(67.1-82.9)
RVS	US+	10	17	40.0	83.0	0.72	2.35	84.7	37.0	74.4
	US-	15	83	(21.3-61.3)	(74.2-89.8)	(0.52-1.01)	(1.23-4.49)	(79.9-88.5)	(23.6-52.9)	(65.8-81.8)
RVS or DVT	US+	14	26	56.0	73.5	0.60	2.11	86.8	35.0	69.9
	US-	11	72	(34.9-75.6)	(63.6-81.9)	(0.38-0.95)	(1.31-3.41)	(80.6-91.2)	(25.0-46.5)	(61.0-77.9)
RVS or DVT or CON2	US+	21	75	87.5	25.0	0.5	1.17	89.3	21.9	37.1
	US-	3	25	(67.6-97.3)	(16.9-34.7)	(0.16-1.52)	(0.97-1.41)	(73.3-96.2)	(18.8-25.3)	(28.6-46.2)
[RVS or DVT] & CON2	US+	10	16	43.5	83.3	0.68	2.62	86.0	38.5	75.6
	US-	13	80	(23.2-65.5)	(74.4-90.2)	(0.47-0.98)	(1.37-4.98)	(81.0-89.9)	(24.7-54.4)	(66.9-83.0)

Abbreviations: CI, confidence interval; CT, computed tomography; CON1, 1 subpleural consolidation of ≥1 cm (probable criterium); CON2, ≥2 subpleural consolidations of ≥1 cm (high likelihood criterium); DVT, deep venous thrombosis; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PE, pulmonary embolism; POCUS, point-of-care ultrasound; PPV, positive predictive value; RVS, right ventricular strain; US-, ultrasound negative; US+, ultrasound positive.

but specificity was lowest 25% (95%CI 16.9-34.7). A high PE likelihood criterium (CON2) combined with either a DVT or RVS resulted in the highest PPV and diagnostic accuracy. McNemar tests for sensitivity and specificity of all modalities compared to multi-organ POCUS are shown in e-Table 14.1. No combination of DVT or RVS with the probable likelihood criterium (CON1) improved diagnostic accuracy measures.

Discussion

The main findings of this prospective, observational study in adult critically ill patients with COVID-19 are that: 1) Single-organ POCUS modalities alone have low sensitivity (and poor NLR) and therefore are not helpful in ruling out PE; 2) Subpleural consolidations are hardly useful in the detection of PE; 3) DVT has good specificity for PE and its detection alone obviates the need for CTPA; 4) RVS has similar diagnostic accuracy to other settings, despite concomitant ARDS or mechanical ventilation, and may have a role in making PE more likely; 5) Multi-organ POCUS (particularly combined deep vein and cardiac POCUS) may have a role in ruling out PE.

Single-organ POCUS

Subpleural consolidations

We found rather poor diagnostic accuracy for subpleural consolidations in the detection of PE in critically ill COVID-19 patients, regardless of the criterium used or the number of subpleural consolidations. In contrast, the latest systematic reviews in the non-COVID-19 setting showed diagnostic accuracy of lung ultrasound was good in studies where the diagnostic threshold was at least one subpleural consolidation; with a sensitivity of 81.4-87%, and a specificity of 81.8-87.4%.[13,34] Studies using a diagnostic threshold of at least two subpleural consolidations had a worse sensitivity 44.2%, but better specificity 96.5%.[34] Most included studies were conducted in ambulatory patients,[15,34,39–41] and the authors noted a high potential of selection bias, limiting generalization of those results to critically ill COVID-19 patients.

Our results might be less remarkable when we revisit the pathophysiology of subpleural consolidations. Subpleural consolidations originate from the depletion of air in the lung. This may be caused by infarction, atelectasis or inflammation, and as such can be found in PE, COVID-19 pneumonia and ARDS.[15–17,42] This overlap is probably what caused the poor diagnostic accuracy in this particular setting. In addition, 52.2% of PEs found in our study were subsegmental. Outside the critically ill COVID-19 setting sensitivity of lung POCUS also drops from 89% – in central, lobar, and segmental PE – to 21% in subsegmental PE.[13]

Contrarily, in early reports, one group have argued that since thrombi are often located distally, and obscured by consolidation they often cannot be reliably visualized by CTPA, while lung POCUS actually does pick up those PEs.[18,43] The low specificity we found for subpleural consolidations and PE argues against this though. Furthermore, there is debate about what the clinical significance of such small emboli is, and if they should warrant detection or treatment.[44,45] PE – found by CTPA – has been associated with a higher mortality in COVID-19.[4] The REMAP-CAP trial showed no benefit of therapeutic anticoagulation in critically ill patients with COVID-19, while the majority of those patients will probably have subpleural consolidations.[46]

DVT

The prevalence of PE (32.8%) and DVT (21.4%) found in our study was comparable with the prevalence found in other screening studies in COVID-19 patients.[4,47,48] The pathophysiology of PE in COVID-19 is still not entirely clear. In contrast to 'classic' PE, it is probably multifactorial as COVID-19 patients exhibit all components of Virchow's triad: an immune-mediated hypercoagulable state, endothelial injury, and stasis/turbulence of blood flow (due to immobilization, hypoxemia induced vasoconstriction, and further exacerbated by the insertion of CVCs).[3,4,22,47–49] Indeed, PEs are associated with lower limb DVT in only 10-13.6% of COVID-19 patients, while this is 56-61% in undifferentiated cohorts, explaining the lower sensitivity.[7,50,51] Specificity is good though, indicating that finding a DVT can make the diagnosis of PE a little more likely, but its absence cannot rule it out.

On the other hand, detecting a DVT by POCUS would preclude the necessity of a CTPA, since therapeutic anticoagulation should be started regardless according to international guidelines.[34,52] Systematic DVT scanning by POCUS could save costs, time, and potentially lives given the increased mortality risk with concomitant VTE.[4] Meanwhile it would circumvent the downsides of having to take a potentially contagious and unstable patient to and from radiology for a CTPA or formal DVT scan. In line with current guidelines, we therefore advocate its use, as a DVT scan takes less than 2 minutes to perform, and results are just as reliable as a formal radiology exam.[3,4,19,21]

RVS

As is the case with subpleural consolidations, RVS is not a direct marker of PE. It is a proxy for clot burden and cardiopulmonary reserve.[19,23] The sensitivity and specificity found for RVS in our study are comparable to what is found for different features of RVS (i.e., RV:LV ratio ≥1, 'D-sign', and McConnell's sign) in the non-COVID-19 literature; 40% versus 24-54%, and 83% versus 87-98.6% respectively.[19,23,34] This supports the premise that RVS might help rule PE in (although the corresponding PLR only raises post-test probability

by approximately 15%), but cannot rule it out.[19,23,34,53] This could be explained by the fact that (COVID-19 related) ARDS itself can cause RVS.[19,24,54] Mechanical ventilation can also be of influence, but this was deemed less likely as we adhered to stringent lung protective mechanical ventilation protocols.[24,32] In order to discriminate between different causes of RVS – like PE or (COVID-19 related) ARDS – it might be prudent to perform scans at baseline and regular intervals. We hypothesize that a sudden increase in RV:LV ratio without changes in respiratory mechanics might be associated with PE, but further research is required before drawing definitive conclusions.

Multi-organ POCUS

The sensitivity found for multi-organ POCUS: 87.5% is similar to that in the non-COVID ED setting: 90%,[7,34,55] and combined lung and cardiac POCUS alone: 91%.[10] Our results suggest that multi-organ POCUS has a role in ruling out PE, or at least have the potential to reduce the amount of CTPA's (although the NLR is still very poor). The main driver of the good sensitivity seems to be subpleural consolidations, which as mentioned before seem to be ubiquitous in critically ill COVID-19 patients. The high likelihood PE criterium (CON2) was found in almost two-thirds of patients and was falsely positive in 80% of those patients. This causes specificity to drop well below the values found in a non-COVID-19 ED setting: 25% versus 86.2%, which leads to a poor NLR.

The sensitivity of combined deep vein and cardiac (without lung) POCUS was only 56% versus 87-89% in the non-COVID-19 setting.[7] This corresponds to a NLR of 0.6 (the lowest we found out of all combinations) which results in a reduction in posttest probability of PE of roughly 15%.[53] The specificity for combined deep vein and cardiac POCUS was comparable though: 73.5% versus 69-74%.[7,10] This results in a PLR of about 2 and thus an increase in posttest probability of PE approximately 15%.[53]

Global perspective

COVID-19 has laid bare health disparities along socio-economic, racial, cultural, and ethnic lines within and across regions and nations. CTPA is not always readily available in low- and middle-income countries, especially when resources are overwhelmed. POCUS is an affordable and easy-to-use tool, which could reduce barriers to timely adequate care.[10] Two descriptive studies suggest that POCUS could reduce >50% of CTPAs.[34] The emergence of handheld devices has made POCUS even more accessible. A complete multi-organ POCUS scan takes less than 15 minutes. Moreover, it is easy to learn for (para) medical personnel.[56,57] In our study, all POCUS scans were performed by ICU residents. Considering that non-specialist physicians see and treat the bulk of COVID-19 patients, this underscores the applicability of POCUS in a real-life setting.

Strengths & limitations

First, this was a single-center study with a relatively limited sample size. Still, this is the first and largest prospective study of consecutive COVID-19 patients to investigate the use of multi-organ POCUS in the detection of PE. Furthermore, our sample size was similar to those of most included studies in the aforementioned systematic reviews on VTE.[4,47,48] Second, although we are a tertiary center, our case mix was reflective of the Dutch COVID-19 ICU population since ICU patients were divided across the country according to a fair share principle. As such selection bias was minimal. Third, our way of assessing RVS combines the features most commonly reported in the literature.[34] We decided to use parameters that interpreters would be able to 'eye-ball' as we believed this is simpler, quicker and requires less skill than performing exact measurements (i.e., tricuspid annular plane systolic excursion [TAPSE], or measuring RV:LV ratio), while having similar diagnostic traits.[19,23,34] We thought our results would be applicable to a larger group of operators this way. Fourth, diagnostic accuracy studies on multi-organ POCUS in PE often suffer from suboptimal reporting.[34] Mainly information on the blinding of POCUS operators and the time interval between POCUS and the reference test are rarely reported. In our study, POCUS operators were always blinded from the CTPA results, which minimizes information bias. Time between POCUS and CT was always below 24 hours, so we believe any imprecision of the diagnostic accuracy measures was therefore curtailed. Additionally, our reference standard is the current gold standard in diagnosing PE. Our strict diagnostic protocol minimized the chance of missing any PEs, thereby reducing the risk of negatively influencing the diagnostic accuracy measures.

Future research

Future prospective investigations or randomized controlled trials should be conducted to analyze the impact of multi-organ POCUS in cost-effectiveness, reduced radiation exposure, and time to definitive diagnosis of PE. Further research should also focus on aspects that can help distinguish the different etiologies of consolidations like doppler and contrast enhanced ultrasonography.[18,58–61] Additionally, it would be interesting to see if POCUS signs could be used in concert with other parameters (i.e., $etCO_2$ gap or rapid D-dimer rise), or clinical decision rules.[62,63]

Conclusion

Multi-organ POCUS – particularly combined deep vein and cardiac – rather than single-organ POCUS may be of aid in ruling out PE in critically ill patients with COVID-19 and help select patients for CTPA. In addition, finding RVS can make PE more likely in this setting, while a DVT would preclude the need for a CTPA.

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15

Evolution of respiratory muscles thickness in mechanically ventilated patients with COVID-19

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Abstract

Background: Prolonged ventilation of patients with COVID-19 can cause atrophy and contractile weakness of respiratory muscle fibers. The aim of this study was to determine the evolution of respiratory muscle thickness assessed by ultrasound.

Methods: Adult (≥18 years old) patients admitted to the ICU who tested positive for SARS-CoV-2 and were ventilated for <24 hours were consecutively included. The first ultrasound examination (diaphragm, rectus abdominis, and lateral abdominal wall muscles) was performed within 24 hours of intubation and regarded as baseline measurement. After that, each following day an additional examination was performed, for a maximum of 8 examinations per patient.

Results: In total, 30 patients were included, of which 11 showed ≥10% decrease in diaphragm thickness from baseline; 10 showed <10% change, and 9 showed ≥10% increase from baseline. Symptom duration before intubation was highest in the decrease group: 12 days [IQR 11-14], p=0.03. Total time ventilated within the first week was lowest in the increase group: 156 hours [IQR 129-172], p=0.03. Median initial diaphragm thickness was 1.4 mm [IQR 1.1-1.6] and did not differ from final median thickness: 1.3 mm [IQR 1.1-1.5], p=0.54. The rectus abdominis did not show statistically significant changes, whereas lateral abdominal wall thickness decreased from 14 mm [IQR 10-16] at baseline to 11 mm [IQR 9-13] on the last day of mechanical ventilation (p=0.08). Mixed-effect linear regression demonstrated an association of atrophy and neuromuscular blocking agent (NMBA) use (p=0.01).

Conclusion: Overall, in ventilated patients with COVID-19, no change in diaphragm thickness was observed. Patients with decreased or unchanged thickness had a longer ventilation time than those with increased thickness. NMBA use was associated with decreased thickness. Rectus muscle thickness did not change over time, whereas lateral abdominal muscle thickness decreased, but this change was not statistically significant.

Introduction

Mechanical ventilation reduces the load placed on the respiratory muscles. This unloading can cause atrophy and contractile weakness of muscle fibers.[1–4] Studies have shown that loss of thickness of the respiratory muscles has important implications for clinical outcomes, including duration of mechanical ventilation.[3,4] Monitoring these changes is therefore of potential interest for clinicians. It could identify patients at risk for prolonged duration of ventilation and help adjust therapeutic goals accordingly.[5] This is particularly relevant in the current COVID-19 pandemic. Critically ill patients with COVID-19 may require mechanical ventilations for extended periods of time, creating conditions conducive to respiratory muscle weakness and dysfunction.[6,7] A recent histological study in deceased patients with COVID-19 demonstrated infiltration of the diaphragm by SARS-CoV-2 and development of muscle fibrosis.[8] Whether this also results in (additional) loss of muscle mass of the diaphragm and other respiratory muscles is unclear. Ultrasound is a low-cost, non-invasive tool that can been used to monitor respiratory muscle mass by measuring changes in thickness over time.[9–11] As such, the aim of this study was to determine the evolution of respiratory muscle thickness assessed by ultrasound as has been previously described in non-COVID-19 settings.[4,12]

Methods

Study design

This prospective observational study was conducted in an academic Intensive Care Unit (ICU) (Amsterdam UMC, location VUmc, Amsterdam, the Netherlands) with daily ultrasound examination being standard care. The protocol was approved by the local ethics board (Medisch Ethische Toetsings Commissie VUmc, study number: 2017.056) and registered in the Netherlands Trial Register (Registration ID: NL9053). The study was conducted in accordance with the Declaration of Helsinki and STROBE guidelines. Informed consent was obtained through an opt-out procedure. Patients were followed until death or 28 days after ICU discharge.

The study population consisted of adult (≥18 years old) patients admitted to the ICU, who tested positive for SARS-CoV-2 and were ventilated for <24 hours. Patients were consecutively included from November 2nd 2020 until January 21st 2021. Exclusion criteria were: past medical history of spinal cord injury or diaphragm paralysis. Even though patients were not specifically selected, no patients with significant chronic pulmonary pathology, neuromuscular disease, or mechanical ventilation for >48 hours in the past 3 months were included. If patients were extubated, transferred to a different medical

center or passed away within the first 72 hours of mechanical ventilation, they were excluded as well (Figure 15.1).

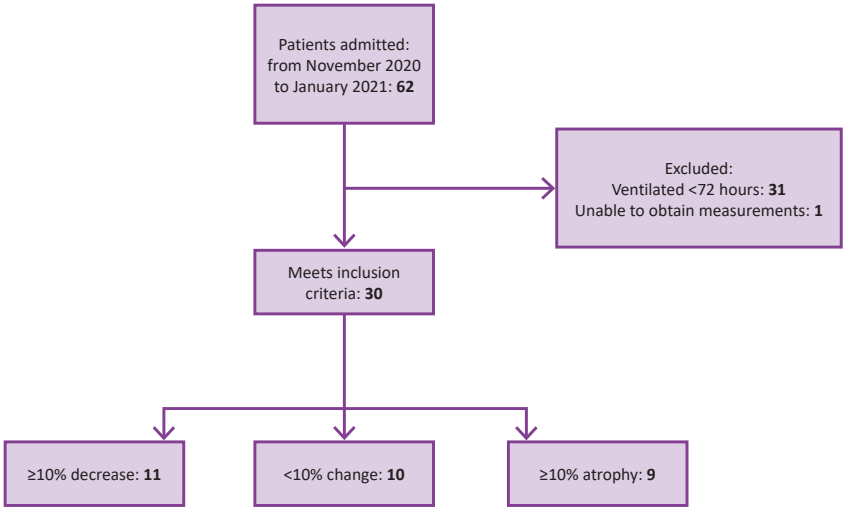


Figure 15.1: Flowchart of patient inclusion and exclusion.

The first ultrasound examination was performed within 24 hours of intubation and regarded as baseline measurement. After that, each following day an additional examination was performed for a maximum of 8 examinations per patient. We aimed to perform the measurements as closely to 24 hours apart as possible, but measurements within the same shift (day, evening, or night) were accepted. Baseline characteristics were recorded on the day of inclusion. At the time of each examination, clinical scores (Sequential Organ Failure Assessment [SOFA] and Acute Physiology And Chronic Health Evaluation II [APACHE II]), ventilator settings, sedatives- and neuromuscular blocking agents (NMBA) use were recorded. All patients were treated with Dexamethasone.[13] Treatment with monoclonal antibodies (i.e., Tocilizumab) was not yet introduced in our ICU.

Ultrasound examination

All ultrasound images were acquired by five well-trained researchers (MHa, JS, MHe, LV, AL) with extensive ultrasound experience (>2 years of almost daily ultrasound use) using a Sonosite Edge II ultrasound machine (Fujifilm Sonosite, Bothell, Washington). Of note, we did not investigate reproducibility measurements as they have been previously reported.[4,14,15]

Measurements were performed in the hospitals picture archiving and communication system after completion of the exam, to limit the time spent in the isolation unit. All images were acquired in supine position, or in case of the diaphragm sometimes in prone

position, with a 4-12 MHz high frequency linear transducer. Gain and depth settings were freely adjustable by the operator, but aimed to create ideal images for measurement (i.e., depth: just below the diaphragm so that it does not leave the window during respiration; and gain: to create contrast between the muscle tissue and pleural/peritoneal lines).[16] Clip length was adjusted to the patient's respiratory rate to capture at least 3 full breathing cycles.

Measurements included muscle thickness at end expiration (for the diaphragm), muscle thickness at end inspiration (for the rectus abdominis and lateral wall muscles), and were performed in at least 3 cycles. The average of these measurements was used as final value. During the first exam, the sites of examination were marked with a skin marker for the following examinations (Figure 15.2).

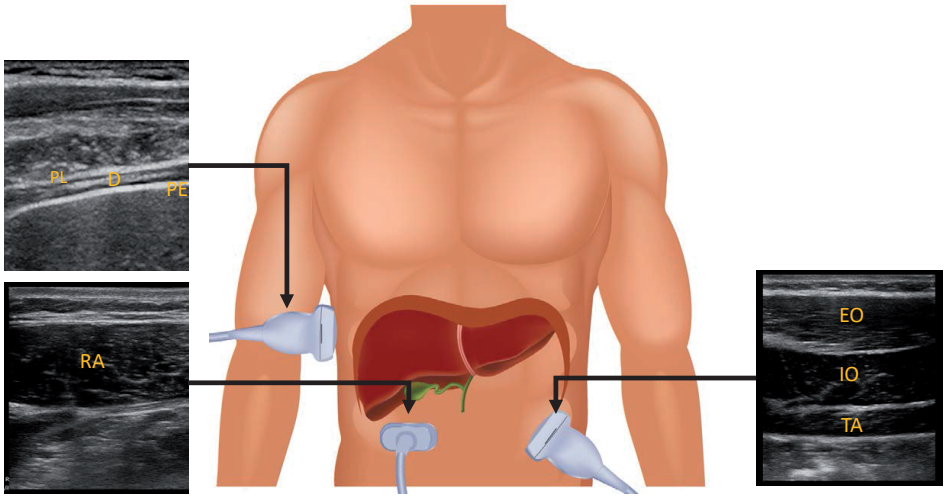


Figure 15.2: Transducer placement.
Abbreviations: PL, Pleura; D, Diaphragm; PE, Peritoneum; RA, Rectus Abdominis; EO, External Oblique; IO, Internal Oblique; TA, Transverse Abdominis.

Diaphragm

Images were acquired in the right zone of apposition between the 8th and 11th intercostal space perpendicular to the chest wall, so that three hyperechogenic lines (pleura, fibrous layer and peritoneum) were visible.[10,14,17] Calipers were placed between the 2 outer hyperechogenic layers.

Rectus abdominis

The rectus muscle was examined on the right side, perpendicular to the abdominal wall at its thickest portion in on the right side of the patient slightly supraumbilical.[18] Calipers

were placed between the fascia surrounding the muscle. During examination, only minimal pressure was applied to prevent compression of the muscle.

Lateral abdominal muscles

The lateral abdominal muscles were examined on the right side, perpendicular to the abdominal wall approximately at the midpoint between the arcus costalis and the ilium, with assessment of total thickness of the most ventral- and dorsal fascia in addition to measurement of individual muscle thickness.[4,19] Again, minimal pressure was applied to prevent compression of the muscle.

Statistical analysis

No sample size calculation was carried out for this pilot study as no previous data to base this calculation on exists in this patient group. At time of registration, we aimed to include 40 patients. However due to external factors such as lack of enough trained personnel for daily measurements and decreasing admissions of COVID-19 cases inclusion, was stopped at 30 patients. Analyses were performed on the entire cohort and comparisons were made between three predefined subgroups. These were based on previous literature by the percentage change from the muscle baseline thickness on day 7 (≥10% increase, ≥10% decrease and <10% change).[3] Missing data on muscle thickness during the study period were considered missing at random and were not imputed.

Baseline characteristics are presented for the entire cohort and per subgroup. They were tested for normality with the Shapiro-Wilk test, evaluation of histograms and Q-Q plots, and are presented as means ± standard deviations (SD), medians with interquartile range [IQR] or numbers (percentages) as appropriate. Differences in baseline characteristics between groups were tested with ANOVA, Kruskal-Wallis test, or χ^2 test as appropriate.

In addition, a mixed model regression analysis was performed to determine the presence of a statistically relevant association between variables hypothesized to impact loss of diaphragm thickness. To this end, independent variables (SOFA, APACHE-II, level of inspiratory support, level of positive end expiratory pressure [PEEP], $P_{0.1}$, hours of sedation and hours of NMBA use) were analyzed in a univariate analysis with percentual change of diaphragm thickness from baseline as dependent variable. The cutoff for inclusion in the multiple linear mixed effects model analysis was set at $p \leq 0.05$. A *p* value <0.05 was regarded as statistically significant.

Statistical analyses were performed using SPSS IBM version 22 (SPSS Inc., Chicago, IL, USA) and R statistical software version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Flow of patient inclusion is presented in Figure 15.1. Thirty patients were included, of which 11 showed ≥10% decrease in diaphragm thickness, 10 showed <10% change and 9 showed ≥10% increase compared to baseline. Of 212 examinations, images of the diaphragm could be acquired in 209 (99%) of cases, of the rectus abdominis in 142 (67%) and of the lateral abdominal muscles in 133 (62%). For the diaphragm, missing data was exclusively due to missed measurements. Whereas for abdominal muscles prone ventilation was the main reason for missing data; 151 missing data points, of which 142 (94%) were due to prone ventilation.

Regarding the clinical characteristics summarized in Table 15.1, a statistically significant difference was found in symptom duration before intubation between groups. The decrease

Table 15.1: Baseline characteristics

	Overall	10% decrease	<10% change	≥10% increase	*p* value
Number	30	11	10	9	
Age	69 [62-75]	68 [64-71]	74 [64-78]	66 [59-71]	0.138
Gender, Male	19	10 (91)	8 (80)	1 (11)	0.819
BMI, kg/m^2	28 [25-29]	28 [24-30]	27 [26-29]	29 [26-31]	0.588
Symptom duration, day 1	11 [7-13]	12 [11-14]	9 [5-12]	9 [7-11]	**0.026**
SOFA, day 1	7 [6-10]	7 [5-11]	7.5 [6-10]	8 [7-11]	0.832
APACHE II, day 1	23 [21-25]	23 [20-24]	24 [22-28]	22 [21-25]	0.440
Ventilator					
Total time ventilated during first week, hours	177 [153-186]	178 [136-188]	181 [178-187]	156 [129-172]	**0.026**
Average inspiratory support	11 [8-13]	11 [8-12]	12 [10-13]	9 [8-15]	0.675
Average PEEP	11 [10-13]	11 [10-12]	13 [12-13]	11 [10-13]	**0.047**
Average p0.1*	0.56 [0.11-1.24]	0.4 [0-1.54]	0.33 [0-0.79]	1.12 [0.42-1.26]	0.388
Average F_iO_2	53 [50-59]	53 [50-54]	55 [51-62]	50 [45-57]	0.271
Hours of sedation, until last ultrasound in hours	165 [133-180]	168 [133-181]	177 [165-182]	131 [105-157]	**0.004**
Hours of NMBA use, until last ultrasound in hours	59 [20-116]	106 [56-148]	68 [20-119]	22 [4-65]	0.093
Follow-up at day 28					0.167
Deceased	14	4	6	4	
Discharged	7	3	0	4	
Admitted at ICU	9	4	4	1	

Numbers are given as: mean ± standard deviation; median [interquartile range]; number (%).
*If no spontaneous respiratory activity was present it was denoted as zero.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; F_iO_2, fraction of inspired oxygen; NMBA, neuromuscular blocking agents; BMI, body mass index; SOFA, Sequential Organ Failure Assessement; PEEP, positive end expiratory pressure.

group had the longest duration of symptoms with 12 days [IQR 11-14], *p*=0.03. The total time spent on mechanical ventilation within the first week also differed significantly (*p*=0.03). In addition, a statistically significant difference was seen in hours of sedative use (*p*=0.004). Whereas duration of NMBA use was lower in the increase group, albeit without statistical significance (*p*=0.09). No difference was seen in clinical outcome on day 28. However, time spent on mechanical ventilation during the first week was lowest in the increase group (156 hours [IQR 129-172], *p*=0.03).

Table 15.2: Ultrasonographic characteristics first day and last day

	Overall	≥10% decrease	<10% change	≥10% increase	*p* value
Number	30	11	10	9	
Diaphragm thickness, in mm					
Baseline	1.4 [1.1-1.6]	1.6 [1.4-1.9]	1.3 [1.0-1.5]	1.2 [1.0-1.4]	**0.002***
Last day	1.3 [1.1-1.5]	1.2 [1.1-1.4]	1.3 [1.0-1.5]	1.5 [1.3-1.7]	0.086
Rectus abdominis thickness, in mm					
Baseline	6.9 [6.1-8.6]	7 [6-11.9]	7.3 [5.7-9.3]	6.3 [6.1-8.8]	0.885
Last day	7.6 [6.3-9.6]	7.7 [6.3-10.1]	6.9 [6.3-10.5]	6.5 [5.5-7.7]	0.294
Total lateral abdominal muscles thickness, in mm					
Baseline	13.8 [9.6-15.8]	15.2 [11.8-22.1]	12.8 [8.4-15.8]	12.8 [9.9-15.7]	0.404
Last day	10.7 [8.9-13]	10.7 [9.6-15.9]	11.4 [8-12.9]	9.8 [7.9-12.2]	0.398
External oblique, in mm					
Baseline	3.8 [2.6-4.6]	4.7 [3.2-6.6]	3.8 [2.2-4.4]	2.7 [2.5-3.9]	0.224
Last day	3.0 [2.2-3.6]	3 [2.4-4.2]	3.3 [1.7-3.7]	2.9 [2.1-3.2]	0.653
Internal oblique, in mm					
Baseline	4.8 [3.2-5.8]	5.8 [4.1-9.8]	4 [2.7-5.2]	4.8 [3.2-5.8]	0.312
Last day	3.4 [2.6-5]	3.6 [2.9-6.4]	3.3 [2.8-5.8]	2.6 [2-4.3]	0.221
Transverse abdominis, in mm					
Baseline	3 [2.3-3.5]	3.2 [2.5-4.2]	2.7 [1.7-3]	3.1 [2.2-3.6]	0.220
Last day	3 [2.6-3.8]	3 [2.7-4.6]	2.9 [2.3-4.9]	2.9 [1.8-3.4]	0.770

Numbers are given as: median [interquartile range].
**P* value is provided, however due to grouping by relative change from baseline, this value can be artificially significant.
Abbreviation: mm, millimeter.

Table 15.3: Muscle thickness at baseline versus the last day

Muscle	Thickness, baseline	Thickness, last day	*p* value
Diaphragm	1.4 [1.1-1.6]	1.3 [1.1-1.5]	0.544
Rectus abdominis	6.9 [6.1-8.6]	7.6 [6.3-9.6]	0.684
Lateral abdominal muscles	13.8 [9.6-15.8]	10.7 [8.9-13]	0.078
External oblique	3.8 [2.6-4.6]	3.0 [2.2-3.6]	0.107
Internal oblique	4.8 [3.2-5.8]	3.4 [2.6-5]	0.136
Transverse abdominis	3.0 [2.3-3.5]	3.0 [2.6-3.8]	0.663

Numbers are given as: median [interquartile range].

Values of ultrasound measurements of the respiratory muscles are depicted in Table 15.2 and Table 15.3. Changes of diaphragm thickness over time per group are depicted in Figure 15.3. Median initial diaphragm thickness was 1.4 mm [IQR 1.1-1.6] and did not differ from the final average thickness 1.3 mm [IQR 1.1-1.5], p=0.54. A trend towards a statistically significant difference on the last day was seen (p=0.09). The group with the highest initial thickness (1.6 mm [IQR 1.4-1.9]) also demonstrated the lowest thickness on the last day of ultrasound (1.2 mm [IQR 1.1-1.4]). The rectus abdominis did not show statistically significant changes, while lateral abdominal wall thickness decreased from 14 mm [IQR 10-16] at baseline to 11 mm [IQR 9-13] on the last day of mechanical ventilation (p=0.08). Of the latter, both external- and internal oblique muscles showed a decrease from first to last day, while the transverse abdominis did not, albeit all without statistical significance.

After backward stepwise exclusion of statistically nonsignificant variables, the final mixed-effect linear regression model contained hours of NMBA use (p=0.01) and PEEP (p=0.04). There were no missing data for the covariates. Three data points were excluded due to missing of the dependent variable.

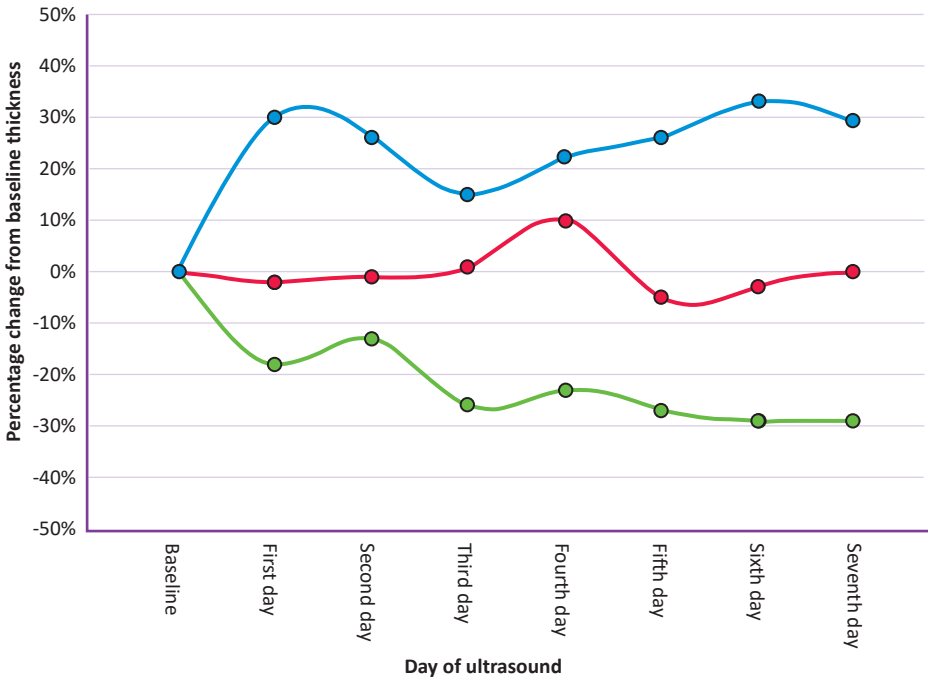


Figure 15.3: Evolution of diaphragm thickness over time per group.
Blue line: ≥10% gain from baseline.
Red line: 10% change from baseline.
Green line: ≥10% decrease from baseline.

Discussion

The findings of interest in this study in adult mechanically ventilated patients with COVID-19 that received daily ultrasound examination of the respiratory muscles are: 1) median diaphragm thickness did not change over time; 2) ventilation time was shortest in the increase group; 3) NMBA use was correlated with loss, whereas PEEP with gain of diaphragm thickness; and 4) lateral abdominal muscle thickness decreased but this change was not statistically significant.

The combination of viral expression in respiratory muscles, concomitant activation of fibrosis related gene expression, and prolonged ventilation in critically ill patients with COVID-19, led to the hypothesis that we would find a relevant decrease of overall diaphragm thickness in our cohort.[1,8,20] Surprisingly, this was not the case. As no histological data of muscle tissue are available, we can only speculate about the underlying reasons for this observation. First, inflammatory or increased respiratory effort induced changes during the course of the COVID-19 infection might lead to the formation of tissue oedema, masking the loss of muscle mass due to fibrosis. Although this might be a possible explanation, it should be noted that in a previous study the increases of respiratory muscle thickness originated from the fascia and membranes rather than muscle tissue itself.[4]

Second, patients were only examined during the first week of mechanical ventilation. A longer follow-up might be necessary to appreciate the full effect of these changes. This is supported by the fact that specimens in the histological studies were taken from patients that had passed away, with a median ventilation time of twelve days.[8] Third, we hypothesize that the relatively small sample size with a roughly equal distribution of patients with increase, no change and decrease of diaphragm thickness could have also resulted in a lack of measurable difference overall.

Intriguingly, the group of patients that did show >10% atrophy, also had the highest initial diaphragm thickness. While this is in line with a previous study, the underlying pathophysiology remains to be elucidated.[3] One hypothesis is that the respiratory muscles become hypertrophic due to a higher respiratory workload in the initial stages of the disease. But once mechanical ventilation is initiated – and the respiratory muscles are unloaded – those gains are lost again. However, the subacute time course of respiratory distress in both studies makes this unlikely.

The accumulation and loss of tissue oedema as described above seems like a more probable explanation. Nevertheless, these patients still showed a longer duration of mechanical ventilation during the first week than those with increased thickness,

highlighting the importance of monitoring these changes closely and elucidating the underlying causes.

Interestingly, our study found an association of decrease in diaphragm thickness with increased duration of NMBA use. Physiologically this is a very logical finding, as diaphragm inactivity has been shown to rapidly result in myofibrillar disuse.[1] Consequently, ventilation approaches that integrate diaphragm and lung protective ventilation – in other words, allowing sufficient respiratory activity to prevent respiratory muscle atrophy without harming those muscles or the lungs – pose an important challenge in this patient category.[5,9,21] Whether such an approach has impact on clinical outcomes is yet to be elucidated in future studies.[22]

In addition, PEEP was positively associated with change of diaphragm thickness. We hypothesize that this effect is not based on hypertrophy, but rather results from various confounding factors. For example, a lower resting position of the diaphragm at end expiration may result in increased end expiratory thickness due to passive shortening.[23]

Whereas overall thickness of the rectus abdominis muscle remained constant throughout the course of mechanical ventilation, the overall thickness of the lateral abdominal wall muscles did not, albeit without statistical significance. Interestingly, the decreased total thickness is most likely attributable to decreases of the internal and external oblique muscles, as the transverse abdominis thickness did not change over time. This needs to be corroborated in a larger study. The lack of statistically significant changes could be explained by the difference in rate of atrophy of the lateral abdominal muscles.[1,6,20] Nevertheless, these are interesting findings as they are in line with a previous study in the non-COVID-19 setting. This underlines the importance of not only considering the loss of diaphragmatic muscle mass but also that of the expiratory muscles.[4] Loss of thickness and potentially functionality could result in impaired airway clearance and longer hospital length of stay.[4]

Strengths & limitations

This study has some important limitations and strengths. First, an important limitation is that no sample size calculation was carried out and only 30 patients were included. Second, due to the frequent necessity for prone ventilation, measurements of the abdominal muscles could not always be performed resulting in missing data. For the diaphragm however, almost all attempted measurements were successful. Third, the cutoff at 10% change in thickness in either direction from baseline was derived from a previously published study.[3] While these categories had important clinical implications, they are not based on physiological or histological evidence for relevant atrophy or hypertrophy.

Nevertheless, a strength of this study was that patients were included consecutively, and only one patient meeting the inclusion criteria was excluded due to extreme body fat percentage hampering diaphragm visualization by ultrasound. In addition, measurements were performed daily without interruption, which is commonly not achieved. It should also be noted that results were comparable to a similar study in the non-COVID-19 setting.[12] This increases the probability that we included a representative sample.

Conclusion

Overall no change in diaphragm thickness was observed in ventilated patients with COVID-19. Patients with decreased or unchanged thickness had a longer ventilation time than those with increased thickness. NMBA use was associated with decreased thickness. Rectus muscle thickness did not change over time, whereas a trend was observed towards decreased lateral abdominal muscle thickness.

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PART 4

Synthesis





16

Discussion and future perspectives

Discussion

Part I | Conventional tests in COVID-19 patients presenting to the emergency department

Part 1 of this thesis focused on how conventional diagnostic tests could aid in the diagnosis and prognosis of (suspected) COVID-19, as well as its complications in patients presenting to the emergency department (ED).

At the start of the pandemic clinicians turned to computed tomography (CT) to aid rapid diagnosis, as well as risk stratification of suspected COVID-19 patients.[1–3] The main reason for this was that the capability and the resources to make a quick and accurate microbiological diagnosis of COVID-19 was lacking in those early days.[4,5] In addition, chest X-ray (CXR) proved to be inadequate in ruling COVID-19 pneumonia in or out.[6]

However, no universal agreement existed on a systematic and reproducible way of evaluating and reporting CT abnormalities in patients with (suspected) COVID-19.[2,7] In **Chapter 2** we reported the results of the largest study to date to prospectively and externally validate such a systematic reporting scheme: the COVID-19 Reporting and Data System (CO-RADS). The CO-RADS was introduced by the Radiology Society of the Netherlands (NVvR), based on recommendations of the Radiology Society of North America (RSNA).[1,7,8] The results of the multicenter study in **Chapter 2** showed that the CO-RADS is an excellent tool in differentiating between positive and negative COVID-19 patients at the ED. Furthermore, **Chapter 2** showed that the degree of pulmonary involvement at ED presentation – quantified by the CT severity score (CTSS) – had a significant positive association with hospital admission, intensive care unit (ICU) admission and 30-day mortality.

Bacterial (co)infection is a dreaded complication of viral respiratory infections. As it is difficult to differentiate between a viral respiratory infection and a bacterial one, antibiotics are often prescribed empirically to patients with a suspected respiratory infection to err on the side of caution. Inappropriate antibiotic prescription rates at the ED in non-COVID-19 settings range from 30 to 60%.[9,10] Although bacterial (co)infection rates in COVID-19 patients at ED presentation were found to be low (approximately 3%),[11] international literature showed that antibiotics were often still prescribed.[12] Since inappropriate prescription of antibiotics is the most important driver of antibiotic resistance, tools that can help make the distinction between a viral or bacterial infection are of paramount importance. Especially since the United Nations have shown that antibiotic resistance leads to an escalating increase in morbidity, health care costs and mortality worldwide.[13]

In **Chapter 3** we showed that procalcitonin (PCT) may aid in excluding a bacterial (co)infection in patients with respiratory symptoms presenting to ED. These results strengthen previous findings that have shown PCT as a promising tool to reduce the inappropriate prescription of antibiotics in multiple settings.[14–18] We also found that the PCT cutoff for a bacterial co(infection) can probably be raised to 0.5 in patients with a proven viral infection. This adds to a recently proposed PCT-based antibiotic algorithm for respiratory infections, where a more stringent cutoff of 0.25 was suggested.[19] Our results still suggest that when no viral infection is found, it is probably safer to use the lower cutoff of 0.25.

It is worth mentioning that PCT concentrations peak within the first 8-24 hours after a bacterial (co)infection, while they also decrease quickly after treatment (with a half-life of 22.5 hours).[19,20] So PCT might be low in patients with a bacterial (co)infection if they present shortly after developing symptoms.[21,22] To reduce the risk of inadvertently missing bacterial (co)infections, it may be helpful to repeat testing for PCT after 8-24 hours in patients with short duration of symptoms.[19,20] If PCT increases, clinicians can still consider initiating antibiotic treatment.

As the COVID-19 pandemic quickly overwhelmed health care systems all over the world, clinicians felt an urgent need to be able to swiftly and accurately triage and risk stratify suspected COVID-19 patients in order to allocate scarce resources more efficiently and optimize patient management. Although numerous prediction models quickly entered the literature during the first wave of the COVID-19 pandemic, they were considered to be of poor methodological quality and were rarely externally validated. The vast majority of them were indeed deemed hardly useful for clinical practice and were thought to do more harm than good.[23]

In **Chapter 4** we aimed to fill this knowledge gap by developing and externally validating a prognostication model that could predict poor outcome (ICU admission or 30-day mortality) in patients with suspected COVID-19 presenting to the ED: the COVERED risk score. Predictors of poor outcome were selected based on existing evidence and expert opinion. Following the process put forward by Wynants et al., we included readily available and easily obtainable demographic data, vital parameters and common laboratory tests.[23] The final COVERED risk score contained 10 such parameters and was developed on data of 1193 patients from the two locations of the Amsterdam UMC. The COVERED risk score was then externally validated in an Italian district general hospital cohort (Fondazione Poliambulanza, Brescia) of 500 patients. It showed good discrimination and calibration exemplifying that it could be employed in multiple settings and might be a welcome improvement over existing prediction models. The COVERED risk score equation is

provided in an easy-to-use Excel file, so individual risk can be easily calculated at the ED and patient management decision can be made accordingly (please see e-Link 4.1).

Part 2 | Point-of-care ultrasound in COVID-19 patients in the acute care setting

In **Part 2** we explored the use of point-of-care ultrasound (POCUS) for diagnosis and prognosis of (suspected) COVID-19 patients in the ED and the medical ward. Since most clinicians might be unfamiliar with the use of lung ultrasound (LUS) – and the most important sequalae of COVID-19 are pneumonia and acute respiratory distress syndrome (ARDS) – we provided an introduction to LUS in patients with acute respiratory symptoms in **Chapter 5**. LUS' diagnostic properties are better than CXR and physical examination combined, and almost equivalent to chest CT in diagnosing various acute respiratory pathologies including pneumonia and ARDS.[24–28] Importantly, 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.[29–32] We therefore hypothesized that LUS could be an interesting a viable alternative to CT in the COVID-19 setting.

In **Chapter 6-8** we reported the results of multiple prospective observational studies comparing LUS and CT in the diagnosis and prognosis of COVID-19 patients. The results of **Chapter 6** indeed showed that 12-zone LUS had a comparable excellent negative likelihood ratio (NLR) and only slightly lower positive likelihood ratio (PLR) than CT in diagnosing COVID-19 pneumonia. LUS proved to be safe in ruling out pulmonary involvement. As such it could aid in differentiating between patients that could be safely discharged and those who might require admission. An important reason for the lower PLR is that the sonographic features of COVID-19 are not exclusive to COVID-19. They are also observed in other etiologies of respiratory symptoms like other (viral or atypical) pneumonias, interstitial lung disease (ILD), ARDS, heart failure and atelectasis. However, this also holds true to a greater extent for CXR, and even for CT albeit to a lower degree.[1–3,33–35]

We were also interested in seeing if there was a difference in diagnostic accuracy between different LUS protocols. After all, if protocols involving less scan zones – particularly the 6-point Bedside Lung Ultrasound in Emergency (BLUE) protocol introduced by Lichtenstein et al.[24] and the 8-point protocol introduced by the group of Volpicelli et al.[36] – produced similar results, this would improve efficiency in overcrowded EDs.

The results of **Chapter 7** showed the 6-point protocol is an excellent screening tool due to its high NLR. It also revealed that it is important to scan the infero-posterior zones, which is unsurprising as COVID-19 associated abnormalities tend to originate there. The 8-point protocol does not and in doing so has a lower NLR. On the other hand, we found that

scanning less zones resulted in a worse PLR. So, more zones are needed to differentiate more accurately between different acute respiratory diseases.

It should be noted though, that the studies reported in **Chapter 6 & 7** were conducted in a high prevalence setting. When the prevalence of COVID-19 decreases and/or the prevalence of diseases which produce similar findings (e.g., ILD or influenza) increases, the PLR of LUS will probably decrease concomitantly. More research has to be done to assess whether LUS can distinguish COVID-19 from similar disease processes. Still the advantages of LUS over conventional radiological imaging mentioned above are such that LUS should be used as an extension of the physical examination, especially since a 6-point scan takes less than 3 minutes.

Risk stratification of COVID-19 patients can be done by quantifying the degree of pulmonary involvement with the CTSS (**Chapter 2**). Pulmonary involvement assessed by LUS has been shown to correlate well with extravascular lung water in dialysis, heart failure and ARDS, as well as associated CT scores.[37] As LUS seemed comparable to CT in diagnosis of COVID-19 (**Chapter 6 & 7**), we aimed to investigate whether LUS could be used in a similar way to CT in prognostication. In doing so we tried to address a knowledge gap the World Health Organization (WHO) had asserted, asking that the value of LUS regarding clinical outcomes should be further investigated.[35] After all, if this would be the case – also considering the practical advantages of LUS over CT – this could have large implications for clinical practice.

The findings presented in **Chapter 8** show that the semi-quantitative lung ultrasound score (LUSS) at initial ED presentation – analogous to the CTSS – is associated with poor outcome (ICU admission or 30-day all-cause mortality), admission duration and disease severity. The LUSS also correlated strongly with the CTSS. These results are in line with preliminary, retrospective studies on the utility of the LUSS in COVID-19,[38,39] and add to accumulating evidence that the degree of pulmonary involvement found on LUS can aid in grading disease severity in a range of different diseases, like the ones mentioned above.

As is reflected by **Chapters 2-8**, we were predominantly focused on the pulmonary parenchyma in the early stages of the pandemic. However as the first wave engulfed the globe, more and more reports emerged of an increased risk of venous thromboembolism (VTE) in COVID-19 patients.[40–42] Since asymptomatic deep venous thrombosis (DVT) carries an increased mortality risk outside the COVID-19 setting,[43] the hypothesis was that screening for DVTs might be warranted. In **Chapter 9** we reported the results of a multicenter cross-sectional study in which we screened COVID-19 patients admitted to the medical ward for asymptomatic proximal DVT with extended compression ultrasound

(ECUS). We found a low prevalence (4%) of asymptomatic DVT, while there was a high prevalence of pulmonary embolism (PE) (28.8%). These results were comparable to what is reported in the most recent systematic reviews.[40–42,44,45] The low prevalence of DVT, compared to the relatively high rates of PE, add to the theory that local clot formation is the underlying pathophysiological process, instead of a dislocating thrombus from the extremities.[46] Therefore systematic screening for asymptomatic DVTs in this setting does not seem helpful.

Part 3 | Point-of-care ultrasound in COVID-19 patients in the critical care setting

At the beginning of the second wave, I transferred to the ICU. The answers to the clinical dilemmas we encountered there will be discussed in **Part 3**. In **Part 3** we predominantly concentrated on the use of POCUS in monitoring the COVID-19 disease course, the association of LUS findings with prognosis, and the diagnosis of COVID-19 complications in the ICU (**Part 3**).

Chapter 10 had a dual aim. First, in line with **Chapter 7** and what has been previously suggested in the ARDS literature,[47] we set out to investigate if a 6-zone LUS could replace the more extensive 12-zone LUS in the monitoring of critically ill COVID-19 patients. Second, since prone positioning is extensively used in these patients, we also investigated the agreement and measurement error between extended (12-zone) and concise (6-zone) LUS in the supine and prone position.

The results outlined in **Chapter 10** showed excellent agreement between 6-zone and 12-zone scores in either position, with limits of agreement (LoA) that were smaller than the interrater smallest detectable change (SDC). This indicated that the already small measurement error between protocols is not even reliably detectable by raters and as such there is no argument for using the 12-zone instead of the 6-zone protocol.

Between positions the agreement was moderate with scores in prone position consistently lower (8%) than in supine position. Moreover, between positions the LoA were larger, indicating that the greater differences in scores between supine and prone position are actually not caused by real changes in pulmonary involvement, but are attributable to measurement error. Clinicians should therefore be cautious in comparing scores after position change. Moreover, the difference in LUSS between supine and prone position was not associated with oxygenation response.

Coincidentally, a recently published study by our group, which is not included in this thesis, found that a higher (anterior) LUSS before proning was associated with a worse

gas-exchange response to proning.[48] This is in line with previous literature, and might help select the appropriate ventilation strategy in patients with different ARDS phenotypes (i.e., advocating proning when the anterior zones are spared and aerated [focal ARDS], while favoring recruitment maneuvers when they are not [non-focal ARDS]).[49–51]

In the research letter presented in **Chapter 11**, we built on the findings of **Chapter 10** (as well as **Chapter 7**) and debated the optimal LUS protocol in assessing pulmonary involvement in response to the work of two Italian groups.[52,53] Where they proposed a 14-zone protocol, we showed that an adequate rationale and methodology for their claim was lacking, and consequently demonstrated that a 6-zone protocol was sufficient.

None of the studies reported in **Chapter 10 & 11** investigated the prognostic value of monitoring by an imaging modality. Indeed, it was not evident if the degree of pulmonary involvement – as it changed over time – was associated with hard endpoints. In addition, it was not clear if CT or LUS were even capable of detecting clinically relevant changes in critically ill COVID-19 patients. Nevertheless, it was common practice in the Amsterdam UMC to perform weekly CTs when these patients deteriorated or their recovery stagnated in order to: 1) quantify the degree of pulmonary involvement; 2) diagnose a possible PE; or 3) locate a possible superinfection and serve as a guide for subsequent broncoalveolar lavage (BAL). Apart from the high financial costs, this placed a large burden on already inundated resources, while also carrying significant safety risks for patients, without any clear evidence of its relevance.[54,55]

We therefore investigated if POCUS could be a viable alternative to CT in monitoring and prognostication (**Chapter 12 & 13**), diagnosis of PEs (**Chapter 14**) and if CT was necessary for the guidance of a BAL (**Chapter 13**).

In the retrospective multicenter observational study outlined in **Chapter 12**, we found that the LUSS within 24 hours of intubation was associated with successful liberation from mechanical ventilation, even independently from ARDS severity. Unfortunately we did not find an association with mortality. However, in **Chapter 12** we merely looked at the prognostic value of scans that were performed in the first 5 days and follow-up time was limited to only a month. We hypothesized that changes in pulmonary involvement later in the disease course might have (additional) prognostic value. And that patients should be followed up longer, since many critically ill COVID-19 patients were admitted to ICU longer than one month. The studies on monitoring of the disease course by CT and LUS, were hampered by the same issues as the study in **Chapter 12**: a short period of repeated scans, as well as insufficient follow-up time, while also being limited to mostly small and retrospective case series.[56–61]

In a single-center observational study involving a consecutive cohort of ICU patients, we assessed the longitudinal correlation of pulmonary involvement graded by weekly CT and LUS in COVID-19 patients admitted to our ICU. We included patients that underwent repeated scans up to 4 weeks of admission (**Chapter 13**). We also investigated reliability, measurement error and association with mortality of CTSS and LUSS, and reported the location of possible superinfections on CT, as they were used to guide BALs in our center. The longitudinal correlation of the LUSS and CTSS was slightly lower, but comparable to what we found in **Chapter 8**. The LUSS was correlated with respiratory parameters whereas the CTSS hardly was. And of the two scores, only a rise in LUSS after 2 weeks was significantly associated with mortality and detectable beyond measurement error. Although this association became statistically insignificant again in the weeks afterwards, a discernable trend did seem present. More importantly, the CTSS did not prove helpful in monitoring of critically ill COVID-19 patients, as it suffered from ceiling effects and lack of responsiveness. In our study we only included patients who deteriorated or stagnated in their recovery, and did not perform a CT or LUS in patients that were recovering, or in patients in which the disease progressed to such a degree that further diagnostics and treatment were deemed no longer useful. Although, this does reflect daily practice, it would be interesting to include these groups in further research as well.

Additionally, it was suggested that pleural line abnormalities and/or subpleural consolidations might improve existing LUS scores as they were shown in histological studies to be severe sequalae of COVID-19.[61,62] However, their incorporation into the LUSS did not lead to improvement of its prognostic value in both **Chapter 12 & 13**.

Furthermore, **Chapter 13** showed that possible superinfections on CT were almost exclusively located in the posterior lung fields. As such we argued that these fields could be sampled empirically by BAL instead of making a CT first. Hence, if an imaging modality is to be used to monitor the disease course at all, LUS should be preferred over CT at least initially.

Combining the results of **Chapter 3, 8, 12 & 13** we hypothesize that the degree of pulmonary involvement at initial ED presentation might help in risk stratification. But once a patient is admitted to the ICU their survival might be less dependent on the degree of pulmonary involvement than it is on other factors such as associated PEs, superinfections, ICU-acquired weakness and the (in)ability to endure prolonged periods of mechanical ventilation.[40,63] The limited prognostic value of pulmonary involvement assessment on the ICU is in line with other studies in the COVID-19 setting that failed to show a prognostic effect of assessment of pulmonary involvement at ICU admission on mortality – at least without it being incorporated in composite end-points with for instance

admission duration or mechanical ventilation duration.[39,64–67] The only other prospective study assessing the prognostic value of serial LUS and CT scanning, found similar results, stressing the discrepancy between clinical recovery and lack of image resolution.[61] Simply put: a high degree of pulmonary involvement might increase the risk of a patient requiring admission to ICU, and play a role in how long they stay there, but it does not seem to be a decisive factor in whether they live or die. This might sound pathophysiologically counterintuitive. But in non-COVID-19 ARDS, the relationship between mortality rates and the degree of pulmonary involvement is not clear either.[37,68]

Another reason to take a critically ill COVID-19 patient out of the protected environment of the ICU to radiology is to rule a PE in or out. As was highlighted in **Chapter 9**, PE prevalence in COVID-19 patients is high, especially in the ICU population. It has been suggested that lung, deep vein and cardiac POCUS – by detecting subpleural consolidations, DVT, and right ventricular strain (RVS) respectively – might be useful in the diagnosis of PE. But these studies were mostly conducted in non-ICU and non-COVID-19 settings.[30,69–71]

In **Chapter 14** we therefore reported the findings of a single-center, prospective diagnostic study, comparing the diagnostic accuracy of those different POCUS modalities – separately and in combination (multi-organ POCUS) – with CT pulmonary angiography (CTPA). The prevalence of DVT (21.4%) and PE (32.8%) was higher than we found in **Chapter 9** – probably due to the fact that this cohort consisted solely out of ICU patients and screening occurred on a weekly basis – but was comparable to the prevalence found in ICU literature.[40–42] We found that a combination of deep vein and cardiac POCUS – rather than any single modality alone – can be of aid in ruling out PE in critically ill COVID-19 patients. In addition, finding RVS can make PE more likely in this setting, while a DVT would preclude the need for a CTPA. Combined deep vein and cardiac POCUS specificity was found to be similar to other settings.[70–72] LUS was not found to be helpful in detecting PE, because of the overlap of the subpleural lesions associated with PEs with the subpleural consolidations caused by COVID-19.

Another potential complication of COVID-19 pertains to the effects of the treatment of the disease on the respiratory pump. Mechanical ventilation can lead to weakness of the respiratory muscles even within a few days, which might impact clinical outcomes.[73–75] This is especially relevant in critically ill COVID-19 patients as they are often submitted to prolonged bouts of mechanical ventilation and could thus be caught in a vicious cycle of increasing muscle weakness and protracted mechanical ventilation. In the last chapter (**Chapter 15**) we presented the results of a single-center prospective observational study to determine the evolution of respiratory muscle thickness assessed by POCUS as this had not been investigated previously in this setting.

Surprisingly no decrease in diaphragm thickness was observed. We could only speculate as to the reasons why: 1) inflammatory oedema formation might have masked the loss of muscle mass; 2) a longer follow-up time might have been necessary, although in the non-COVID-19 setting a decrease is observed in the first week; 3) we failed to show a decrease due to a small sample size. Interestingly, patients with decreased or unchanged thickness did have a longer ventilation time than those with increased thickness. Use of neuromuscular blocking agents (NMBA) was associated with loss, whereas PEEP was associated with gain of diaphragm thickness. The rectus abdominis muscle thickness did not change over time while a trend was observed towards decreased lateral abdominal muscle thickness. These findings are in line with a previous study in non-COVID-19 patients, stressing the importance of not only considering decline in diaphragmatic muscle mass, but also the expiratory muscles.[75]

Future perspectives

The enormous amount of medical knowledge about COVID-19 that was generated during the last three years has been nothing short of remarkable. With the swift development of antiviral treatments and more importantly vaccines, the pandemic seems to be gradually shifting to an endemic phase. The emergence of the Omicron variants – which although more contagious, generally cause less severe disease than previous variants – has probably helped as well.[76–81] Therefore it might be prudent to ponder what the future of POCUS is beyond the COVID-19 pandemic.

POCUS and diagnostic accuracy

The COVID-19 pandemic provided us with a unique opportunity to compare CT with POCUS. In a setting in which CTs are not routinely made, it is hard to envision diagnostic accuracy studies comparing POCUS with the gold standard CTs in the foreseeable future. The only exception would be studies investigating PE, since CTPAs are mandatory in this case. More importantly, there is an abundance of evidence which shows that POCUS approaches the diagnostic accuracy of CT for acute respiratory diagnoses in both the ED and ICU settings.[27,28,30,82,83] Similarly, the diagnostic accuracy of POCUS was good to excellent in basic abdominal ultrasound (including renal, bladder, abdominal aorta and biliary),[84–87] basic cardiac ultrasound (including global left ventricular function, RVS, pericardial effusion and inferior vena cava [IVC]),[86] extended focused sonography in trauma (eFAST: including pneumothorax, pericardial, pleural and intra-abdominal effusions),[88] DVT,[86,89,90] and in patients with undifferentiated shock.[91] Although more evidence is always welcome, there are more interesting avenues of potential research.

POCUS and outcomes

Although there has been some research on outcomes – like diagnostic and therapeutic impact,[31,92-99] time-to-diagnosis,[29,97,100] time-to-treatment,[100,101] time-to-discharge,[83,98,99] the use of additional (imaging) tests,[29,83,95,102-106] cost-effectiveness,[83,102,107,108] and patient reported outcome measures (PROMs)[109] – it has been rather limited to small and/or retrospective studies that mainly focus on the ED and ICU populations. Future research should focus on prospective – preferably randomized controlled – trials. These could for instance be cast in a flash mob design to accelerate the research process.[110] Furthermore they should include patients from different specialties and those who are already admitted to a normal ward. These studies should also include safety outcomes (e.g., inappropriately (un)treated patients, and the number of incidental or missed findings). Currently we are in the process of setting up such research for internal medicine patients with different (academic) hospitals in The Netherlands. Importantly, the effect of POCUS on 'hard' patient outcomes like morbidity and mortality will be challenging to study. It is not likely that POCUS – being a diagnostic modality – will be the primary determinant of such outcomes, hence we agree with Díaz-Gómez et al., that this will unlikely be a productive avenue of future research.[83] Moreover, we should be cautious to define the clinical relevance of POCUS based solely on its impact (or lack thereof) on clinical outcomes, as it can have an advantageous effect on other aspects of the diagnostic and therapeutic process.[99]

POCUS in different settings

Prehospital

Prehospital care providers form the initial step in patient triage and management. They have to make assessments with limited time and information, while they do not have immediate access to additional (imaging) tests to help them make adequate diagnoses and tailor the appropriate next step for their patients. Which is why – if they felt their patient needed such a test – they would have to refer the patient to hospital or a diagnostic center. It would be interesting to see if POCUS could be of aid in these situations. And if the studies done in other settings – either regarding diagnostic accuracy or outcomes – can be extrapolated to prehospital settings, like primary care, obstetric care, nursing homes, and emergency medical services (EMS).

In addition, the problem for clinicians taking referrals from the first line is that they cannot see the patient through a telephone. So, to err on the safe side of caution a clinician will often want to see a patient themselves. This is at odds with plans of keeping health care costs in check, and delivering the appropriate care at the appropriate time and place,

which is something policymakers, healthcare providers and governments are striving towards.[111–113]

Indeed, there is some evidence to suggest implementing POCUS increased diagnostic performance and outcomes, especially in trauma patients, however there is large heterogeneity between studies, and studies are limited to nonrandomized descriptive studies with high risk of bias.[114–117] Given the ad hoc applicability and ever increasing affordability and portability of POCUS it would be interesting to investigate if the integration of POCUS could optimize prehospital care pathways. For instance, EMS personnel could integrate POCUS not only in trauma, but also in the triage and immediate care of medical patients.[115] Furthermore, POCUS – with or without other point-of-care tests like C-reactive protein, PCT or D-dimer – could be incorporated in prehospital settings to diagnose (respiratory) infections, thoracic and abdominal free fluid, pneumothorax, (acute) abdominal aortic aneurysm, cardiac dysfunction, urinary retention, hydronephrosis, and DVTs. This would potentially obviate the need for further referral. Future research should also focus on the effect of (combinations of) point-of-care tests including POCUS and PCT in the prehospital setting on inappropriate antibiotic prescription (since most antibiotics are prescribing occurs in general practice),[118–121] referrals and ED presentations,[83] as well as the outcomes mentioned in the previous paragraph.

Telemedicine

Even when a prehospital care provider would have POCUS at their disposal, they could still feel the need to consult a specialist. With rapid developments in telemedicine, high-speed internet and cloud computing, one could envision that POCUS could also be combined with teleconsultations. Images and clips could be (in)directly assessed and supervised by the relevant clinician(s), even in real-time. Preliminary findings in remote areas have even shown that POCUS can be accurately performed even by (non-)physicians who are guided remotely.[83,115,122,123] Hence, POCUS might also lower barriers to proper diagnostics and adequate care in rural or austere areas, and middle- to low-income countries, thereby potentially reducing health care inequity and inequality. In these regions, the research on POCUS should be tailored to local needs. For instance, it could include the effects of obstetrical-, gynecological- and abdominal scanning on health outcomes.[115]

Technological advancements

POCUS is basically a logical evolution of Laennec's stethoscope, which is why some have dubbed it: 'the stethoscope of the 21st century'. But its current applications are only in its infancy. The holy grail would be a Star Trek-like tricorder which integrates different diagnostic modalities (and therapeutic functionalities) in one device, and would give you

a (differential) diagnosis and (best) treatment options instantaneously. Surely, we are not there yet. But the capabilities of systems are ever increasing. Technological advances in artificial intelligence (AI) are opening up medical imaging to automatic analysis. Already there are POCUS systems that can automatically quantify left ventricular ejection fraction, estimate the urinary bladder volume, and even interpret combined multi-organ POCUS exams. In addition, there are systems that actively guide the user to obtain the right views.[83] The implication of this would be that even less trained personnel could (eventually) also use POCUS. It would be interesting to investigate if the use of AI indeed has an impact to the outcomes mentioned in the previous paragraphs, and if it might reduce inter-rater variability and missed diagnoses.

Furthermore, in addition to color Doppler, most handheld systems now also have spectral Doppler capabilities. This means quantitative measurements can be made. Doppler might for instance be used to assess cardiac pressures, stroke volume, valvular abnormalities, and help guide fluid management.[124] The venous excess ultrasound score (VExUS), which utilizes POCUS of the IVC – in combination with spectral Doppler of the hepatic, portal and interlobar kidney veins – to assess fluid status, has shown predictive value for acute kidney injury in cardiac surgery patients on the ICU.[125] It would be interesting to investigate if it could do the same in other settings.

Additionally, contrast enhanced ultrasound (CEUS), which uses tiny intravascular microbubbles, is making its way into the POCUS arena. CEUS is not nephrotoxic, can greatly improve the visualization of cardiac structures, and has been shown to be better at diagnosing free fluid than conventional POCUS.[126,127] In one study, the improved image quality has been shown to lead to reduced resource use and costs. But further research is necessary to see if this holds up (for other indications).[128] CEUS might also be helpful in determining the site of active (abdominal) bleeding, visualize renal perfusion, and help improve visibility of the iliac veins and IVC in the case of suspected proximal DVT.

More research is also warranted to investigate if Doppler and CEUS have other applications in the POCUS setting. One of those areas would be to investigate if they can help differentiate between different etiologies of consolidations on LUS (e.g., PE, pneumonia, atelectasis or malignancy) in different settings.[129-133]

Learning and implementation

In recent years various medical societies have acknowledged the importance of POCUS and supported its use. As such, basic POCUS competencies have been formulated for various specialties, and POCUS is increasingly being incorporated in specialty training programs and medical curricula.[83,86,134-137] After all, since the quality of POCUS is highly

operator dependent, it is important operators are well trained and their competency is safeguarded. There are a plethora of (hands-on) courses and (online) teaching materials that can help students learn the basic skills. In fact, learning POCUS is fairly easy and in theory competency can be achieved quite quickly.[83,138-143] But there are important barriers in operators gaining the desired competency, which seem almost universal across countries and specialties; a lack of available equipment, time, skilled supervisors, available (handheld) ultrasound equipment, and quality assurance processes.[135,144] Progress in expanding POCUS has therefore been hampered.

We encourage the sharing of best practices by institutions where successful integration of POCUS training and supervision into daily practice has been achieved. However, we concede that in order to encourage broad faculty adoption, significant (system-level) behavioural and organizational change is likely required.[135,145] We therefore suggest further research should be undertaken to elucidate ways to achieve this.

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APPENDICES



e-Appendix

e-Table 2.1: CO-RADS score

Score	Level 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 LEVEL 3-5	• Tree-in-bud sign • Centrilobular nodular pattern • Lobar or segmental consolidation • Cavitation		• Bronchitis • Infectious bronchiolitis • Bronchopneumonia • Lobar pneumonia • Pulmonary abscess
3	Equivocal / unsure	• Equivocal for COVID-19 • Overlap with other pathology. • Findings have to be new or increased in magnitude	• Perihilar ground-glass • Ground-glass together with smooth interlobular septal thickening +/- pleural effusion • Extensive homogeneous ground-glass opacity • Small ground glass opacities, not centrilobular, 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

e-Table 2.1 continues on next page.

e-Table 2.1: ***Continued***

Score	Level of suspicion	Pulmonary findings	Obligatory features	Confirmatory patterns	Examples (of alternative diagnoses)
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 LEVEL 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			

Abbreviations: CO-RADS, COVID-19 Reporting and Data system; CT, computed tomography; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.

e-Table 2.2: CT severity score (CTSS): min 0 points – max 25 points

CTSS per lobe	Points
0%	0
1-5%	1
5-25%	2
25-50%	3
50-75%	4
>75%	5

e-Table 2.3: Patient characteristics excluded patients

	Excluded patients N=419	**SARS-CoV-2 PCR negative N=326**	**SARS-CoV-2 PCR positive N=83**	***p* value**
Age, mean (SD)	55.6 (17.8)	55.1 (17.9)	57.1 (16.3)	0.101
Male, n (%)	219 (52.3)	170 (52.1)	46 (55.4)	0.194
Admission, n (%)	150 (35.8)	103 (31.6)	45 (54.2)	**0.001**
Admission ICU, n (%)	22 (5.3)	14 (4.3)	8 (9.6)	**0.000**
30-day mortality, n (%)	30 (7.2)	21 (6.4)	9 (10.8)	**0.039**
In hospital mortality, n (%)	23 (5.5)	15 (4.6)	8 (9.6)	**0.000**
Duration of symptoms, days (SD)	7 (9.4)	6.3 (7.3)	8.2 (7.4)	0.181
Co-morbidities, n (%)				
Asthma	48 (11.5)	38 (11.7)	8 (9.6)	0.293
Chronic cardiovascular disease	71 (16.9)	57 (17.5)	12 (14.5)	0.178
COPD (GOLD >2)	57 (13.6)	47 (14.4)	10 (12.0)	0.258
Current malignancy	64 (15.3)	61 (18.7)	3 (3.6)	**0.000**
Diabetes Mellitus	55 (13.1)	45 (13.8)	8 (9.6)	**0.037**
Hypertension	105 (25.1)	80 (24.5)	21 (25.3)	0.777
Observations at presentation				
Modified early warning score mean (SD)	2.1 (1.6)	2.1 (1.6)	2.2 (1.6)	0.957
Temperature (Celsius), mean (SD)	37.7 (1.0)	36.7 (1.0)	37.1 (1.0)	**0.000**
Respiratory rate, mean (SD)	19.2 (5.9)	18.8 (5.6)	20.7 (6.6)	0.091
Saturation levels, mean (SD)	96.2 (4.6)	96.2 (4.7)	95.7 (4.2)	0.912
Oxygen therapy, n (%)	47 (11.2)	28 (8.8)	19 (23.8)	**0.000**
Intubation, n (%)	24 (5.7)	15 (4.6)	9 (10.8)	**0.000**

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PCR, polymerase chain reaction; SD, standard deviation.

e-Table 2.4: Duration of symptoms

CT	PCR + Days, mean (SD)	PCR - Days, mean (SD)
CO-RADS 1	2.7 (1.9)	5.8 (8.9)
CO-RADS 2	1.8 (1.0)	5.5 (6.7)
CO-RADS 3	6.1 (6.5)	5.7 (9.0)
CO-RADS 4	7.1 (4.6)	6.4 (5.6)
CO-RADS 5	8.5 (4.4)	9.7 (5.7)

Abbreviations: CO-RADS: COVID-19 Reporting and Data system, PCR: polymerase chain reaction, SD: standard deviation.

e-Table 2.5: False positive diagnoses

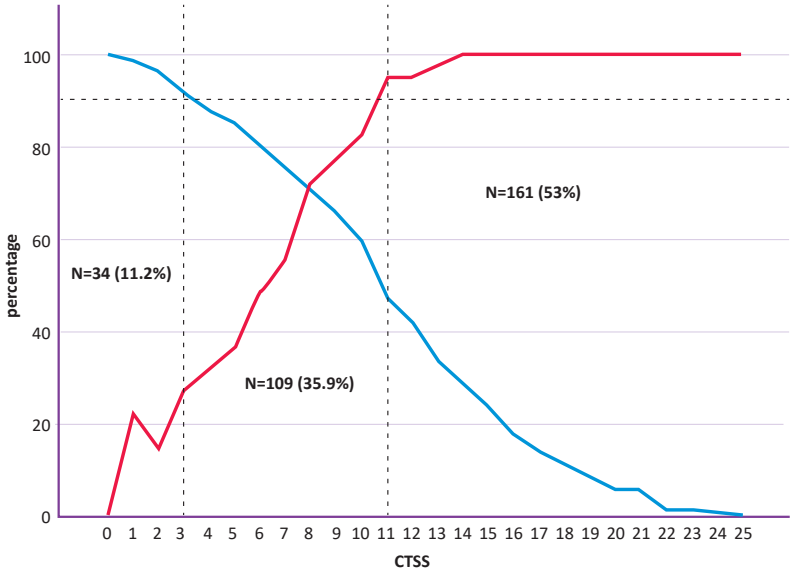
Diagnoses	N (%)
Bacterial pneumonia	7 (10.8)
Urosepsis	2 (3.1)
Exacerbation COPD	2 (3.1)
Malaise	2 (3.1)
Organ failure in acute decompensated liver cirrhosis	1 (1.5)
Taxol pneumonitis	1 (1.5)
Lymphoma	1 (1.5)
Cellulitis	1 (1.5)
Decompensated heart failure	1 (1.5)
Pericarditis	1 (1.5)

Abbreviations: COPD: chronic obstructive pulmonary disease.

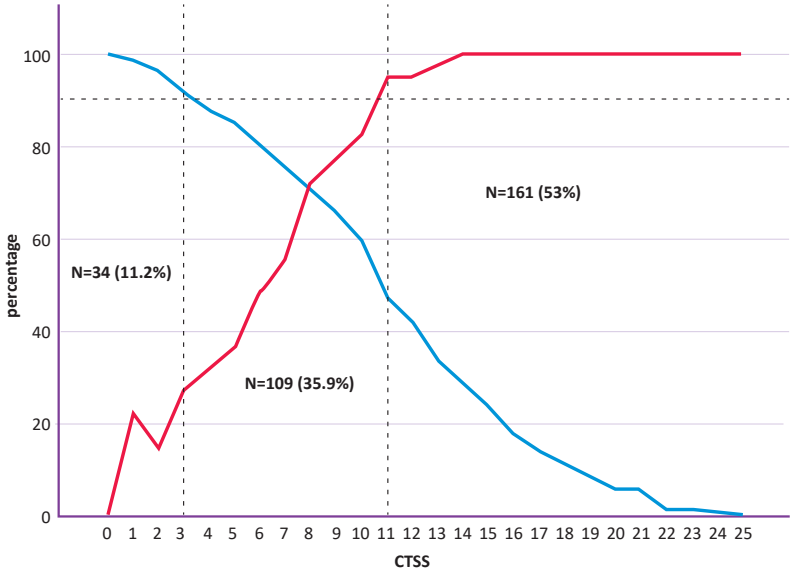
e-Table 2.6: Alternative diagnoses

Alternative diagnoses	Percentage (%)
Bacterial/aspiration pneumonia	25
Decompensated heart failure	12
Exacerbation COPD/asthma	10
Malignancy progression	8.5
Upper respiratory tract infection	7.6
Fever of unknown origin	4.0
Dyspnea of unknown origin	3.1
Pulmonary embolism	2.8
Malaise	2.7
Pericarditis	2.2
Sickle cell crisis	2.0
Neurological diseases*	2.0
Chronic cough	1.8
Gastrointestinal bleeding	1.3
Abdominal & gastrointestinal infections**	15

*Group consisting of a broad array of diagnoses: epilepsy, cerebrovascular accident, intracranial bleeding.
**Group consisting of a broad array of diagnoses: urinary tract infection, splenic abscess, abscess after low anterior resection, gastritis, liver cirrhosis, cholangitis, cholecystitis.
Abbreviations: COPD: chronic obstructive pulmonary disease.

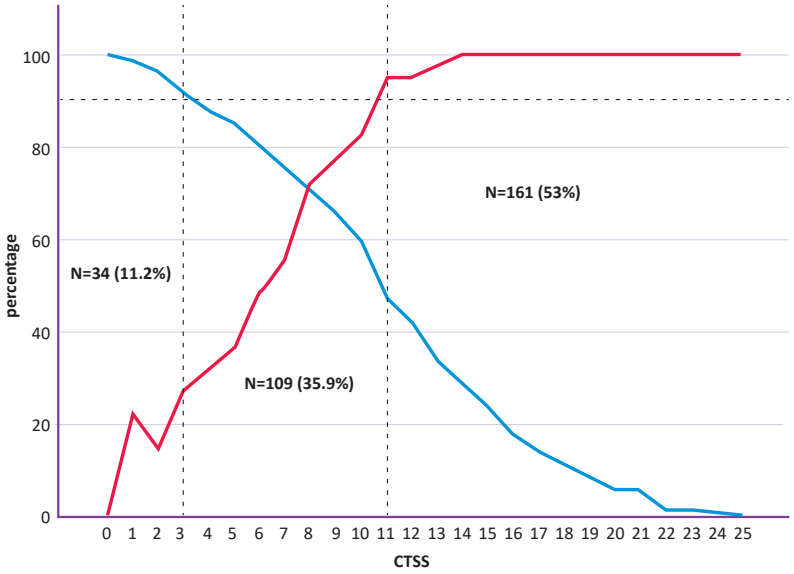


e-Figure 2.1A: Grey zone of CTSS vs hospital admission.
Red line: specificity.
Blue line: sensitivity.
Left vertical black line: 90% sensitivity cutoff.
Right vertical black line: 90% specificity cutoff.
Abbreviation: CTSS, computed tomography severity score.

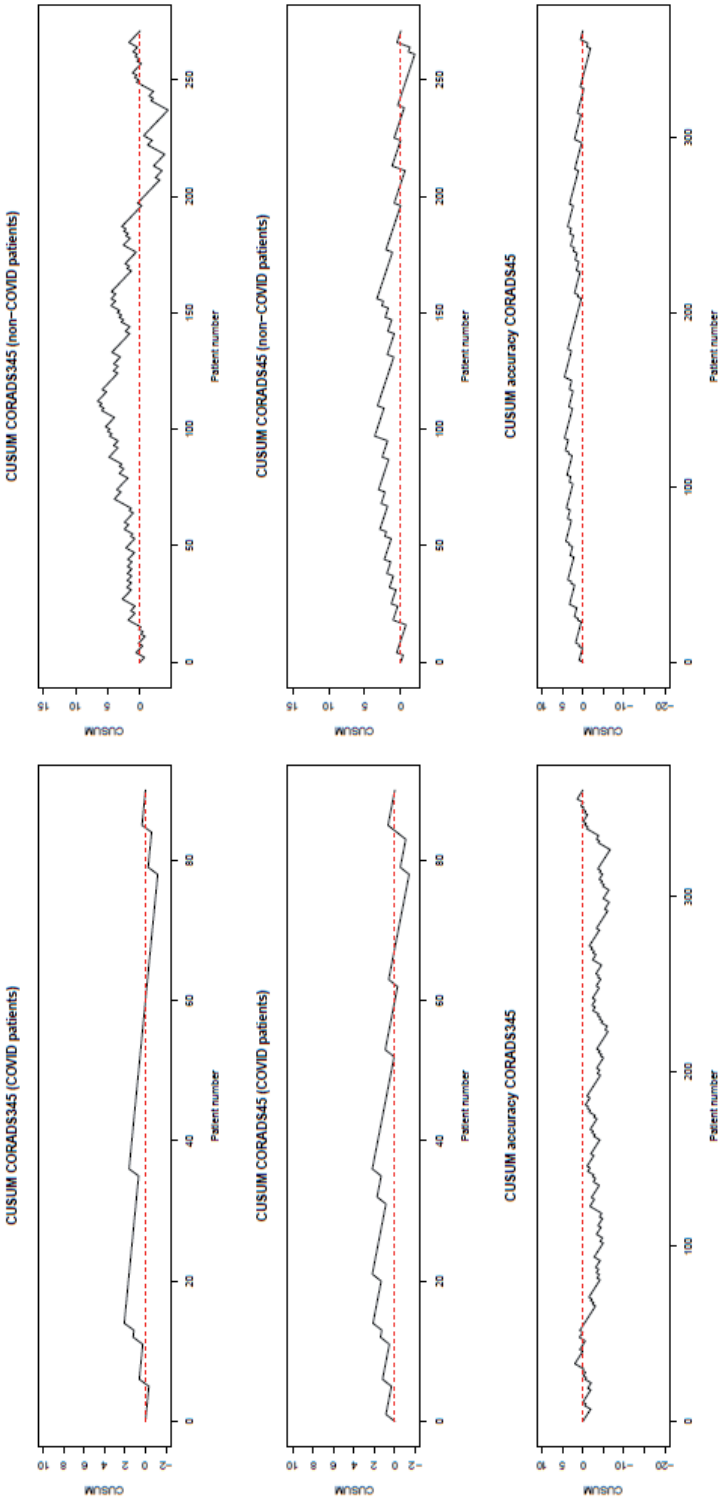


e-Figure 2.1B: Grey zone of CTSS vs ICU admission.
Red line: specificity.
Blue line: sensitivity.
Left vertical black line: 90% sensitivity cutoff.
Right vertical black line: 90% specificity cutoff.
Abbreviation: CTSS, computed tomography severity score; ICU, intensive care unit.

A

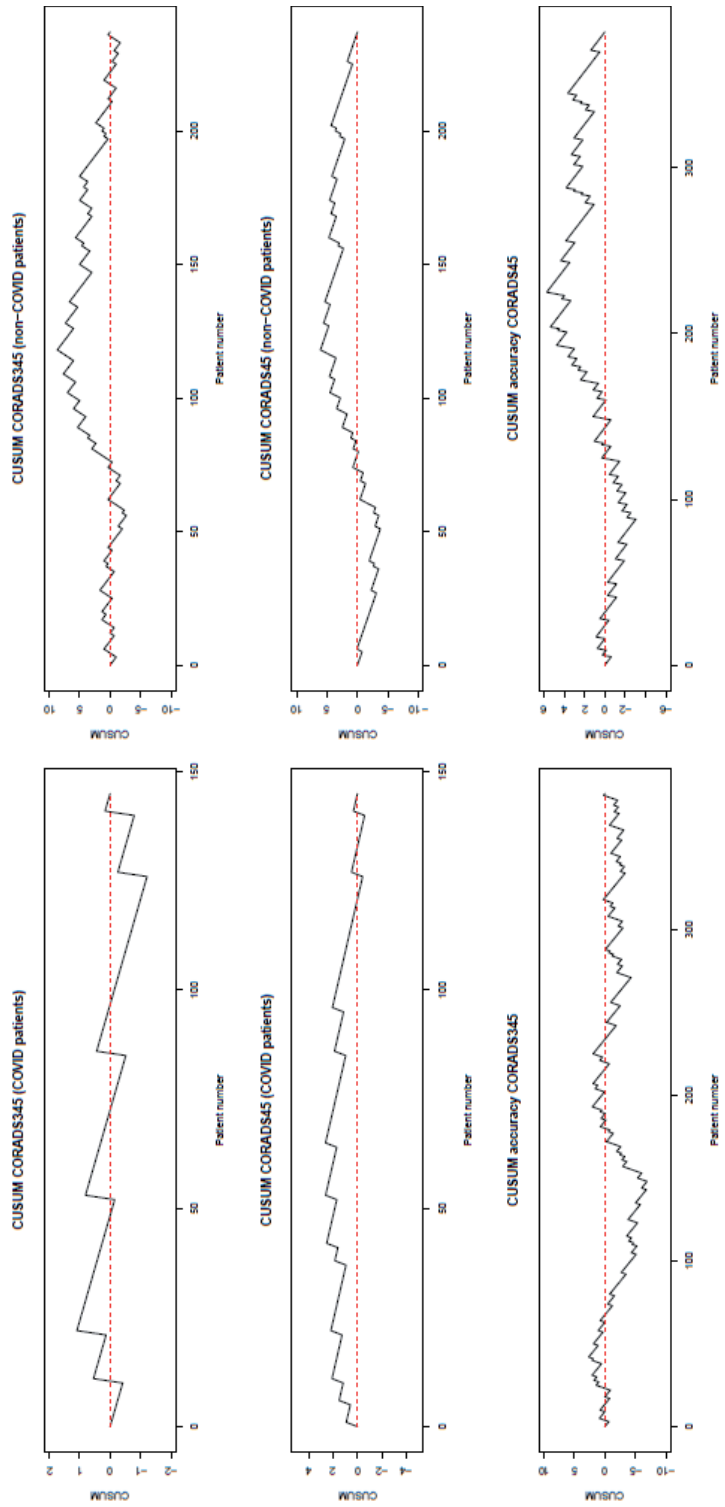


e-Figure 2.1C: Grey zone of CTSS vs 30-day mortality.
Red line: specificity.
Blue line: sensitivity.
Left vertical black line: 90% sensitivity cutoff.
Right vertical black line: 90% specificity cutoff.
Abbreviation: CTSS, computed tomography severity score.



e-Figure 2.2A: Cumulative sum (CUSUM) chart center 1.

A



e-Figure 2.2B: Cumulative sum (CUSUM) chart center 2.

Chapter 3

e-Table 3.1: Details of contaminated cultures

Bacterial pathogen found	PCT values (ng/L)
Rothia mucilaginosa (n=1)	0.62
Stahylococcus capitis (n=2)	0.02, 0.07
Staphylococcus pettenkoferi (n=2)	2.11, 0.06
Staphylococcus hominis (n=5)	1.89, 0.11, 2.15, 0.24, 0.17
Acinetobacter johnsonii and Chryseobacterium hominis (n=1)	0.04
Staphylococcus epidermidis and Kocuria species (n=1)	6.22
Streptococcus mitis (n=1)	0.03
Streptococcus oralis (n=1)	0.08

e-Table 3.2: Results of virology diagnostics

Viral diagnosis	Number of patients
Influenza A /B	62
SARS-CoV-2	109
Respiratory Syncytial Virus (RSV)	12
Human Metapneumovirus*	12
Coronavirus (not SARS-CoV-2)	6
Rhinovirus	4
Parainfluenza	3
Other (bocavirus, adenovirus, Epstein-Barr virus)	5

*In one patient both influenza B and Human Metapneumovirus was detected.

e-Table 3.3: Characteristics of patients with a positive blood culture and procalcitonin <0.5µg/L

BC result (N=11)	Δ time (hours)	PCT µg/L	CRP mg/l	MEWS	Blood pressure mmHg	Final diagnosis
E.coli	6-12 + 10*	0.09 26.7*	<2.5 22*	3	149/73	E. coli bacteremia
E.coli	6-12	0.07	9	2	100/60	Urosepsis
E.coli	12-18	0.12	39	1	105/60	Sepsis of unknown origin
E. faecalis	12-18	0.13	39	1	105/60	Fever unknown origin
F. nucleatum	12-18	0.17	11	2	62/47	Sepsis of unknown origin
Str. group G	12-18	0.25	15	1	139/67	Fever, probably due to infected leg ulcer
S. epidermidis	6-12	0.30	13	3	127/77	Catheter related blood stream infection
S. aureus	Unable to provide a history	0.32	273	4	142/82	S. aureus bacteremia due to osteomyelitis
Str. group G	24	0.39	63	0	143/92	Streptococcal bacteremia (immunocompromised)
Str. gallolyticus	>24	0.41	73	3	122/57	Infectious Endocarditis
Str. Group C	12-24	0.41	8	3	146/48	Bacteremia due to skin/ soft tissue infection

Δ time: the time between onset of complaints and the first procalcitonin measurement.
*A second measurement of procalcitonin was performed 10 hours after the first measurement, which showed a sharp increase in procalcitonin.
Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; MEWS, Modified Early Warning System; µg/L, microgram per liter; mg/l, milligram per liter.

Chapter 4

e-Table 4.1: Diagnostic categories, distribution in the total group and the poor outcome group

Diagnostic category	Number (%)
Total group	1193
Confirmed COVID-19	339 (28.4)
Respiratory tract infection	198 (16.6)
Suspected COVID-19	102 (8.5)
Exacerbation chronic pulmonary disease	62 (5.4)
Other infection	56 (4.6)
Intra-abdominal and gastrointestinal infection	50 (4.2)
Related to malignancy	49 (4.1)
Congestive heart failure	50 (4.2)
Urinary tract infection	49 (4.1)
Atypical thoracic pain	34 (2.8)
Acute cardiovascular disease	21 (1.8)
Neurological	21 (1.8)
Anxiety / hyperventilation	16 (1.4)
Pulmonary embolism	15 (1.3)
Dyspnea of unknown etiology	16 (1.3)
Sickle cell crisis	10 (0.8)
Out of hospital cardiac arrest	7 (0.6)
Severe self-poisoning	4 (0.3)
Other diagnosis	94 (7.9)
Poor outcome group	196
Confirmed COVID-19	86 (43.9)
Respiratory tract infection	22 (11.2)
Malignancy-related	20 (10.2)
Congestive heart failure	13 (6.6)
Intra-abdominal infection or bleeding	9 (4.6)
Out of hospital cardiac arrest	7 (3.6)
Exacerbation chronic pulmonary disease	7 (3.6)
Suspected COVID-19	6 (3.1)
Severe self-poisoning	4 (2.0)
Urinary tract infection	4 (2.0)
Neurological	3 (1.5)
Other diagnosis	15 (7.7)

e-Table 4.2: Clinical characteristics of the enrolled patients with suspected COVID-19 (validation cohort)

Characteristics	Overall (N=500)	Favourable outcome (N=349, 69.8%)	Poor outcome (N=151, 30.2%)	*p* value
Age, years	71 [61-79]	68 [59-77]	76 [69 -83]	**<0.001**
Sex, n (%)				
Male	337 (67.4)	226 (64.8)	111 (73.5)	0.062
Female	163 (32.6)	123 (35.2)	40 (26.5)	
Comorbidities, n (%)				
Cardiovascular disease	109 (21.8)	56 (16.0)	53 (35.1)	**<0.001**
Hypertension	221 (44.2)	138 (39.5)	83 (55.0)	**0.002**
Diabetes	97 (19.4)	61 (17.5)	36 (23.8)	0.110
Malignancy	27 (5.4)	18 (5.2)	9 (6.0)	0.673
Pulmonary disease (COPD)	2 (0.4)	2 (0.6)	0 (0.0)	1.000
History of smoking, n (%)	62 (12.4)	38 (19.4)	24 (30.4)	0.056
Vital parameters				
Systolic blood pressure, mmHg	129 [113-147]	130 [113-147]	126 [115-147]	0.585
Diastolic blood pressure, mmHg	75 [68-81]	76 [70-82]	71 [65-79]	**<0.001**
Temperature, °C	37.5 [36.8-38.2]	37.4 [36.8-38.2]	37.6 [36.8-38.4]	0.219
Heart rate, beats/min.	90 [80-102]	90 [81-104]	87 [75-100]	**0.018**
Respiratory rate, breaths/min.	18 [16-22]	18 [16-20]	20 [18-27]	**<0.001**
Oxygen saturation level, %	92 [88-95]	93 [90-95]	90 [81-93]	**<0.001**
Oxygen therapy, n (%)	233 (46.6)	150 (65.2)	83 (86.5)	**<0.001**
Consciousness (AVPU), n (%)				
A	470 (94.0)	335 (98.8)	135 (93.8)	N/A
V	8 (1.6)	3 (0.9)	5 (3.5)	
P	3 (0.6)	1 (0.3)	2 (1.4)	
U	2 (0.4)	0 (0.0)	2 (1.4)	
Laboratory findings				
White blood cell count	7.0 [5.2-9.4]	7.0 [5.2-9.1]	7.4 [5.1-9.8]	0.195
Lymphocyte count	0.98 [0.69-1.32]	1.07 [0.79-1.40]	0.73 [0.50-1.00]	**<0.001**
Urea	6.8 [4.8-10.0]	6.0 [4.3-8.3]	9.5 [6.8-14.5]	**<0.001**
C-reactive protein	94 [46-162]	79 [37-130]	146 [78-222]	**<0.001**
Lactate dehydrogenase	361 [280-482]	325 [264-429]	500 [363-647]	**<0.001**
PCR SARS-COV-2, n (%)				
Positive	420 (84.0)	283 (81.1)	137 (90.7)	**0.008**
Negative	80 (16.0)	66 (18.9)	14 (9.3)	
Outcome, n (%)				
ICU admission	52 (10.4)	N/A	52 (34.4%)	N/A
In hospital mortality	127 (25.4)	N/A	127 (84.1%)	N/A

Data is presented as median [IQR] or number (%). *P* values were calculated by Mann-Whitney U test, Pearson's Chi-square test or Fisher's exact test, as appropriate.

Abbreviations: COPD, chronic obstructive pulmonary disease; min., minute; IQR, interquartile range; ICU, intensive care unit; AVPU: Alert, Verbal, Pain, Unresponsive; PCR, polymerase chain reaction; N/A, not applicable.

e-Table 4.3: Candidate variables

Demographics
Sex
Age
Comorbidities
Chronic respiratory disease
Previous malignancy
Diabetes mellitus
Hypertension
Vital signs
Heart rate
Systolic blood pressure
Respiratory rate
Oxygen saturation
Temperature
Laboratory values
White blood cell count
Urea (mmol/l)
CRP (mg/l)
LDH (IU/l)
SARS-CoV-2 PCR result

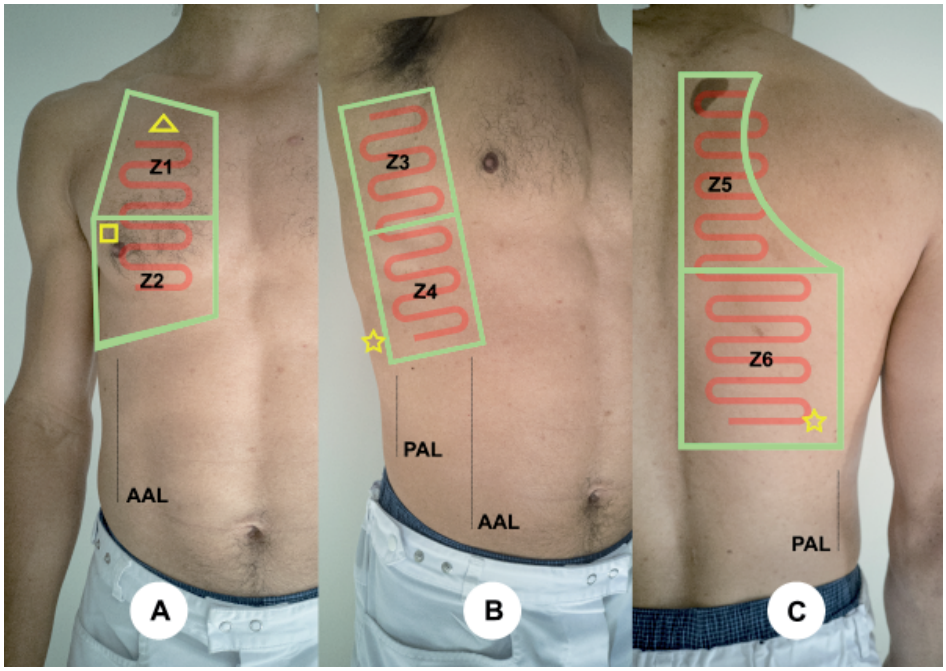
Abbreviations: LDH, lactate dehydrogenase; CRP, C-reactive protein; PCR, polymerase chain reaction; N/A, not applicable.

e-Link 4.1: Excel file with COVERED risk score formula.

Chapter 5

e-Table 5.1: Lung aeration score

No. points	Aeration	Description	Appearance
0	Normal	A-line pattern with <3 B-lines per zone	Figure 5.1 & e-Video 5.1: Normal lung ultrasound
1	Moderate loss	Multiple regularly spaced B-lines or confluent B-lines in less than 50% of the zone	Figure 5.2 & e-Video 5.2: Discrete regularly spaced B-lines e-Video 6.1: Patchy B-lines (COVID-19)
2	Severe loss	Confluent B-lines in more than 50% of the zone	Figure 5.3 & e-Video 5.3, 5.12: Confluent B-lines Figure 5.4 & e-Video 5.4: Subpleural consolidation with shred sign
3	Total loss	Lung consolidation or pleural effusion in more than 50% of the zone	Figure 5.5 & e-Video 5.8: Uncomplicated pleural effusion with consolidated lung Figure 5.6 & e-Video 5.9: Complicated pleural effusion with consolidated lung e-Video 5.11: Hepatization



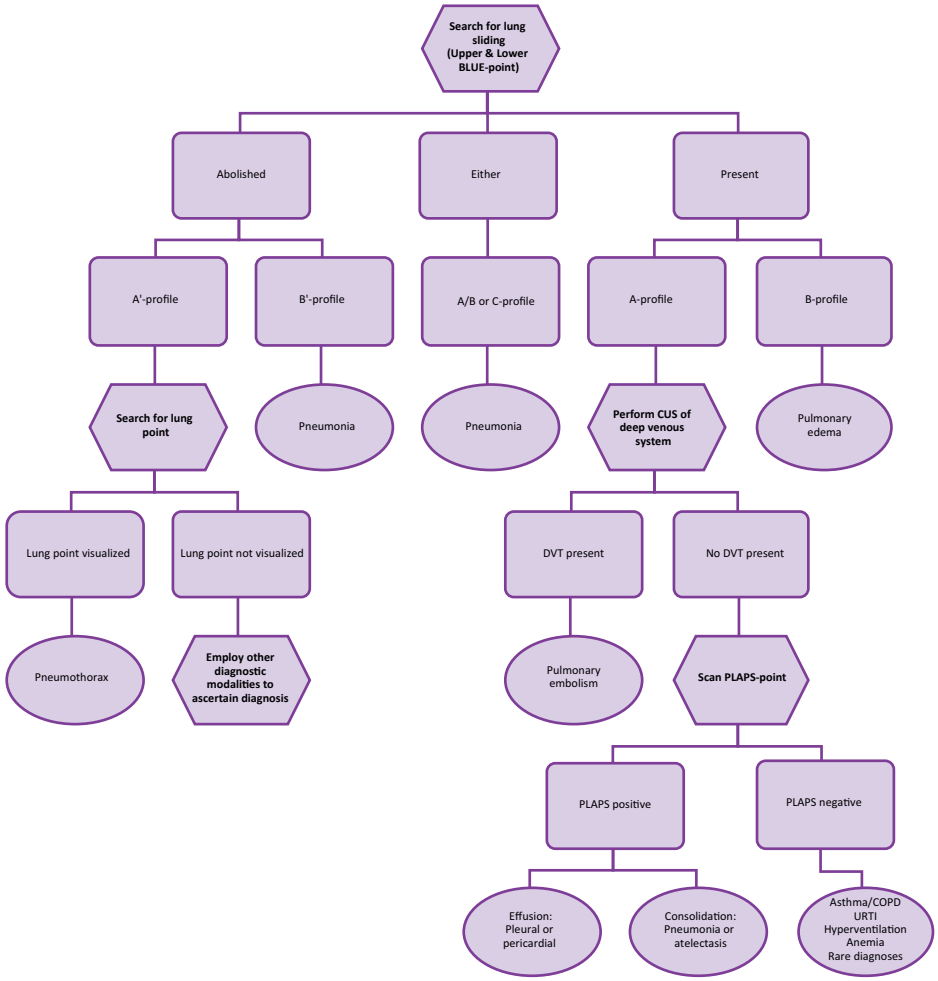
e-Figure 5.1: Lung ultrasound zones, BLUE points and different scan protocols.
This figure shows the six scan zones on the right hemi-thorax:

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.

A and B are divided by the AAL: anterior axillary line.
B and C are divided by the PAL: posterior axillary line.

- The 12-zone protocol: utilizes all 12-zones.
- The 8-point protocol: The 8-point method only uses the anterior and lateral zones, excluding the posterior zones.
- The 6-point protocol or Bedside Lung Ultrasound in Emergency (BLUE) protocol:
  - The upper BLUE point corresponds with Z1 or the yellow triangle;
  - The lower BLUE point corresponds with Z2 or the yellow square;
  - The postero-lateral alveolar pleural syndrome (PLAPS) point corresponds with Z6 or the yellow star.

Red line: illustrates the 'lawn mower' scanning technique. Each rib-space is evaluated, to minimize the risk of missing abnormalities.



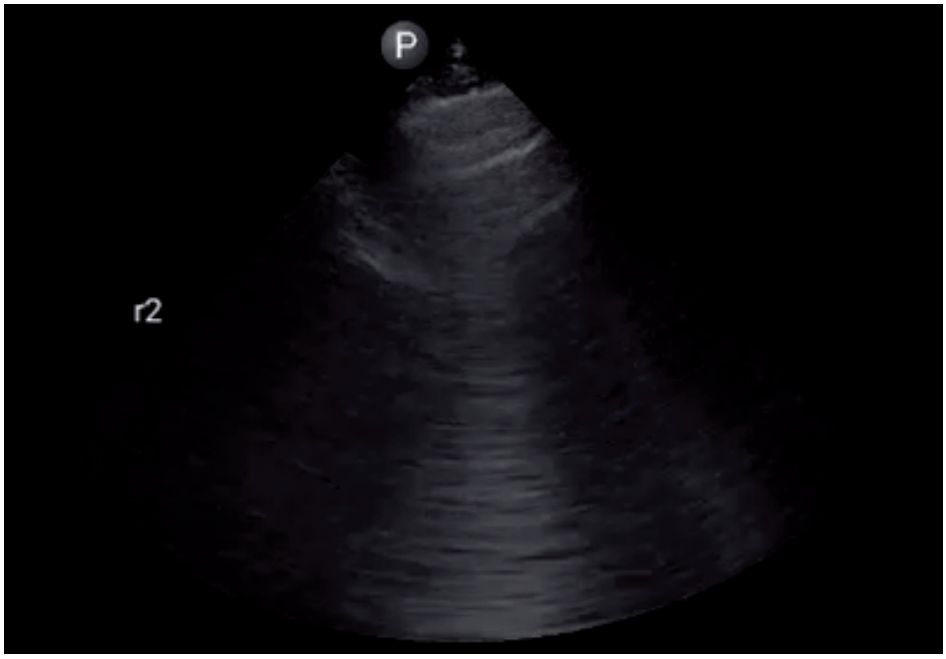
e-Figure 5.2: The BLUE protocol algorithm.
The Bedside Lung Ultrasound in Emergency (BLUE) protocol has utility for rapid assessment of acute dyspnea. This protocol assigns diagnoses according to specific patterns of ultrasound findings. Examples of these findings are presented in the e-Video section of this thesis.

- Boxes explanation:
  - Ovals: definitive diagnoses;
  - Rectangles: ultrasound finding or BLUE profile;
  - Hexagons: action to be performed by the clinician.
- BLUE profiles
  - A-profile, Lung sliding and A-lines present
  - A'-profile, No lung sliding, but with only A-lines present
  - B-profile, Lung sliding with bilateral B-lines
  - B'-profile, No lung sliding with B-lines
  - A/B-profile, Unilateral B-lines or bilateral alternating/patchy areas with B-lines
  - C-profile, Anterior consolidations

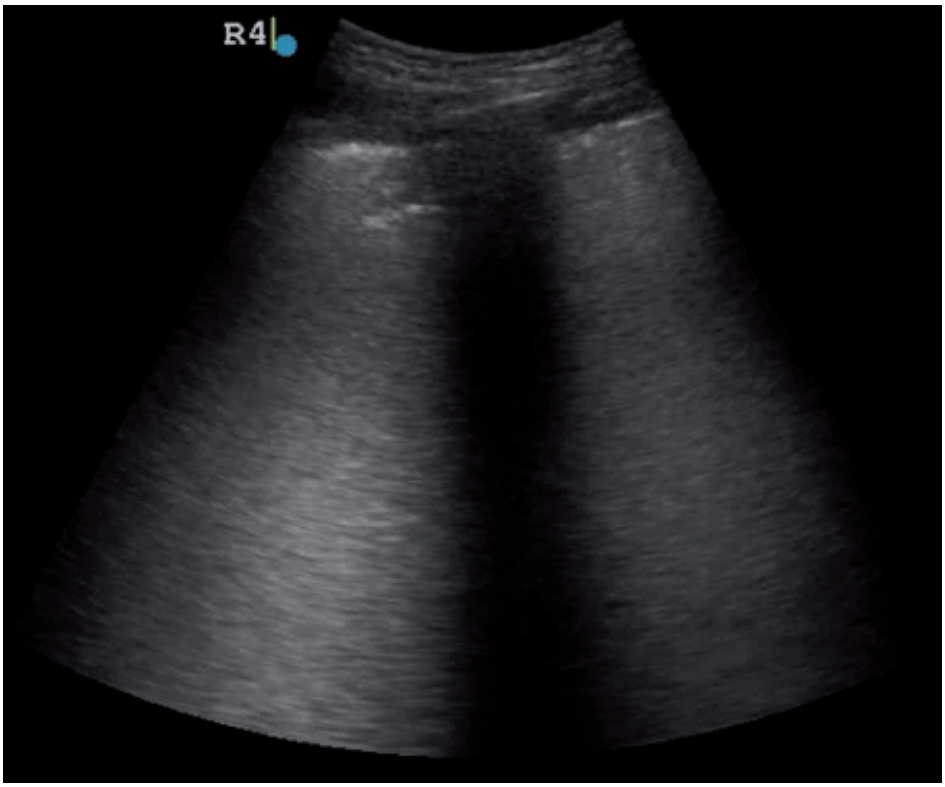
Abbreviations: COPD, chronic obstructive pulmonary disease; CUS, compression ultrasound; DVT, deep venous thrombosis; PLAPS, postero-lateral alveolar pleural syndrome; URTI, Upper respiratory tract infection; Rare diagnoses, neuromuscular disease, acute thoracic or abdominal aneurysm/dissection.



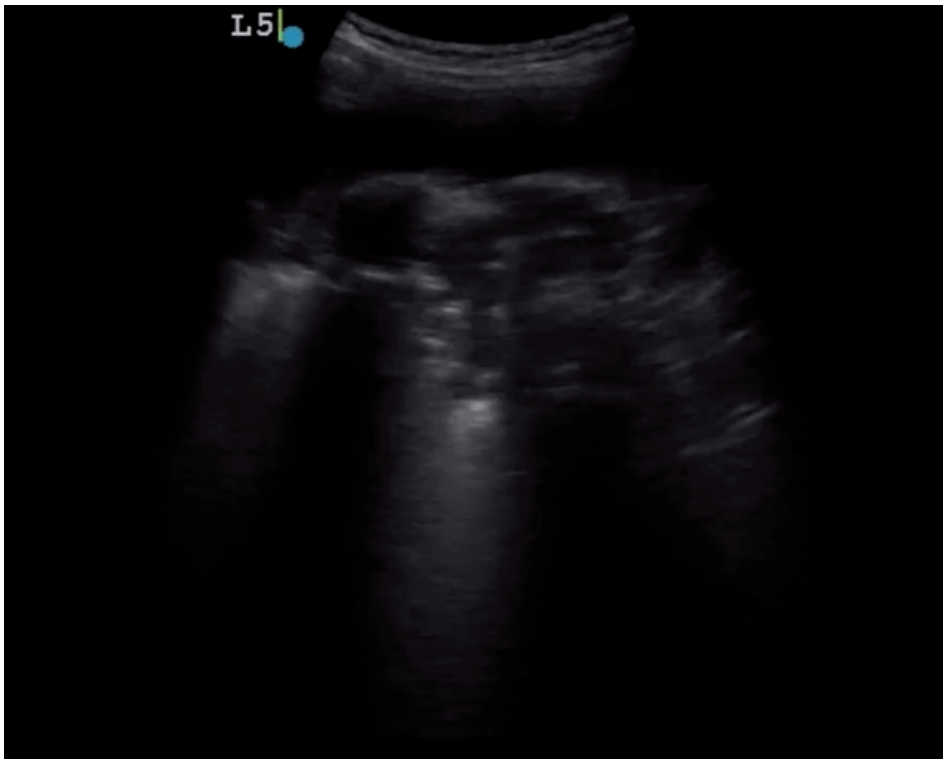
e-Video 5.1: Lung sliding & A-lines.



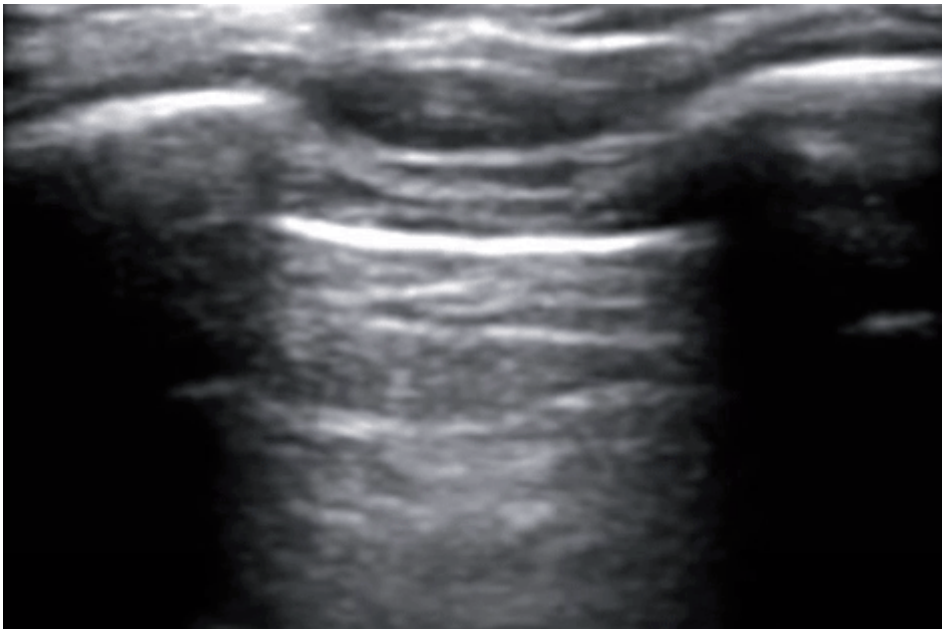
e-Video 5.2: Discrete regularly spaced B-lines.



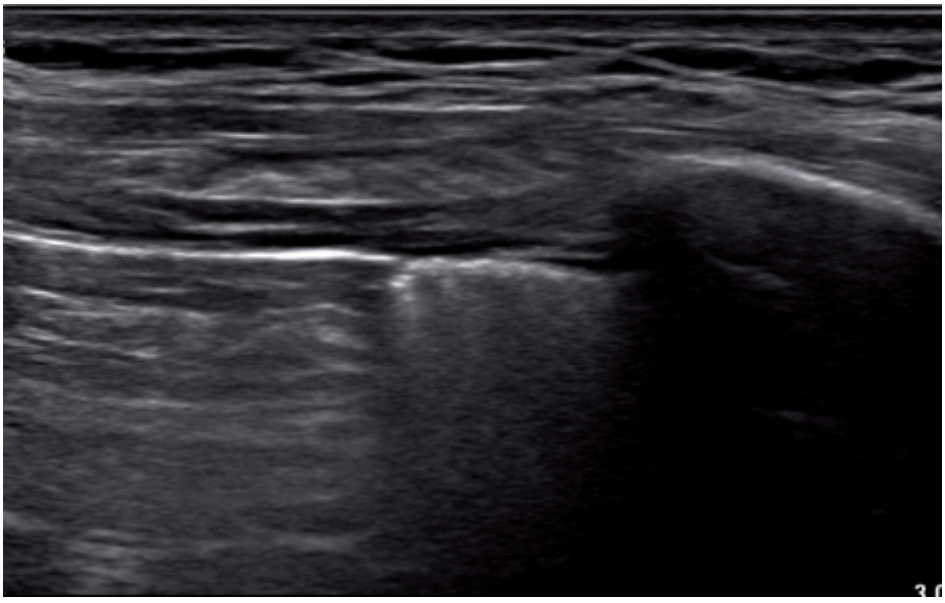
e-Video 5.3: Confluent B-lines with a small subpleural consolidation left of the rib shadow.



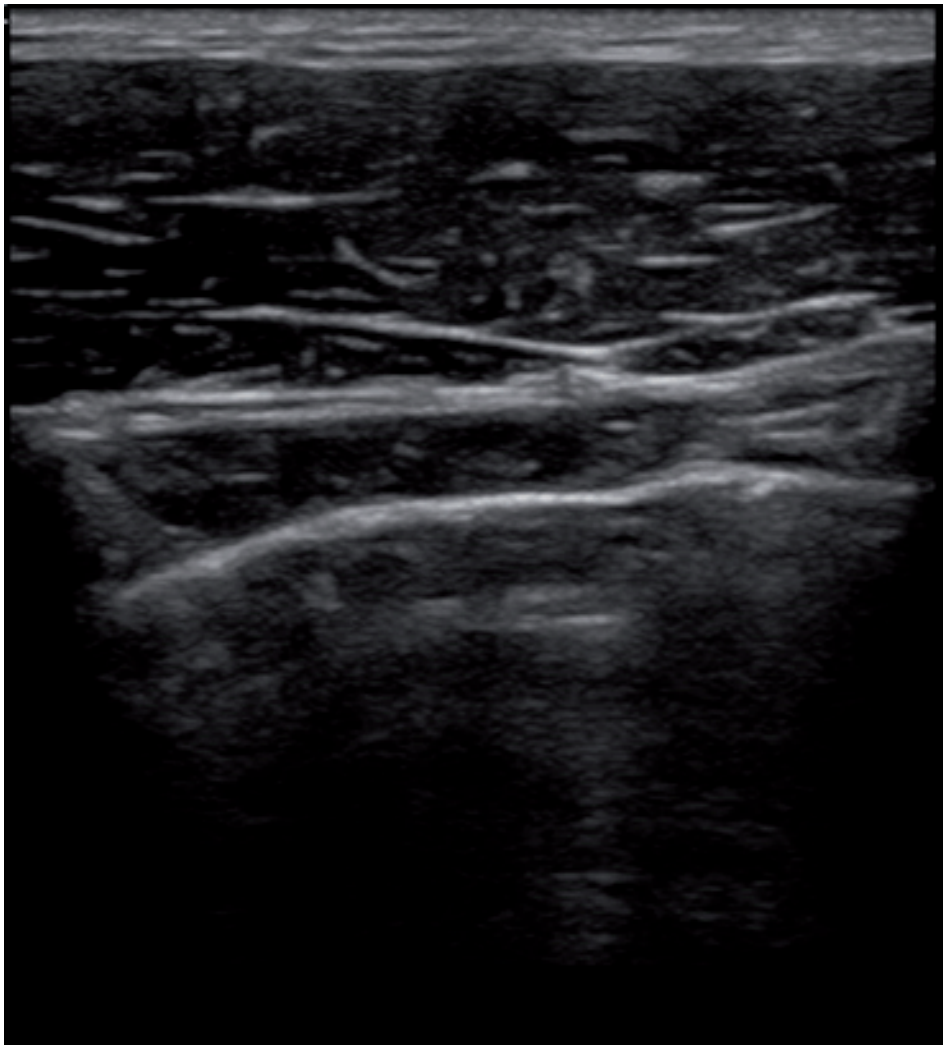
e-Video 5.4: Larger subpleural consolidation with shred sign.



e-Video 5.5: Absent lung sliding.



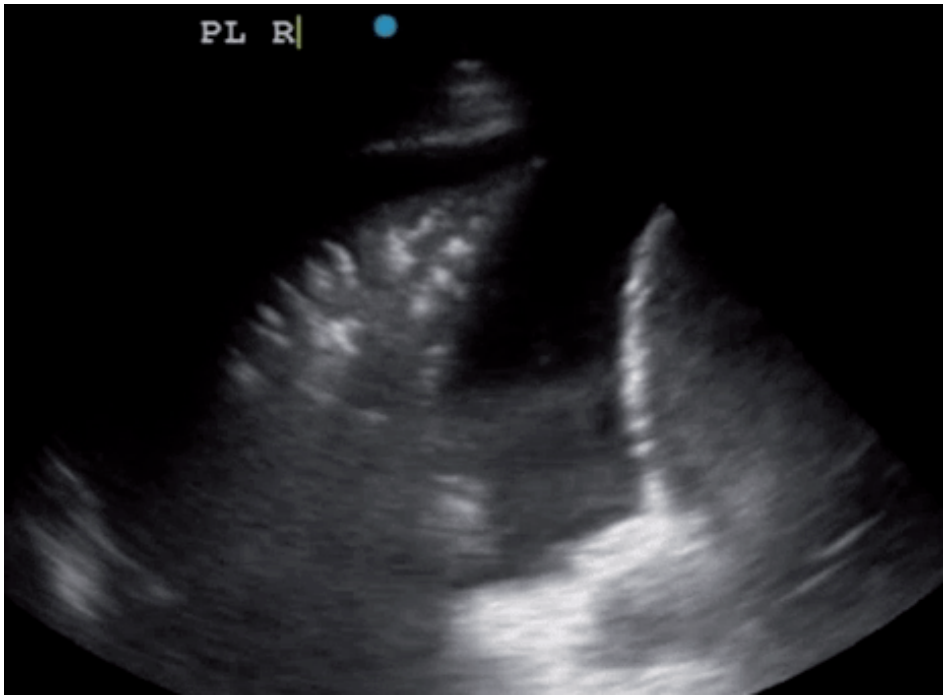
e-Video 5.6: Lung point.



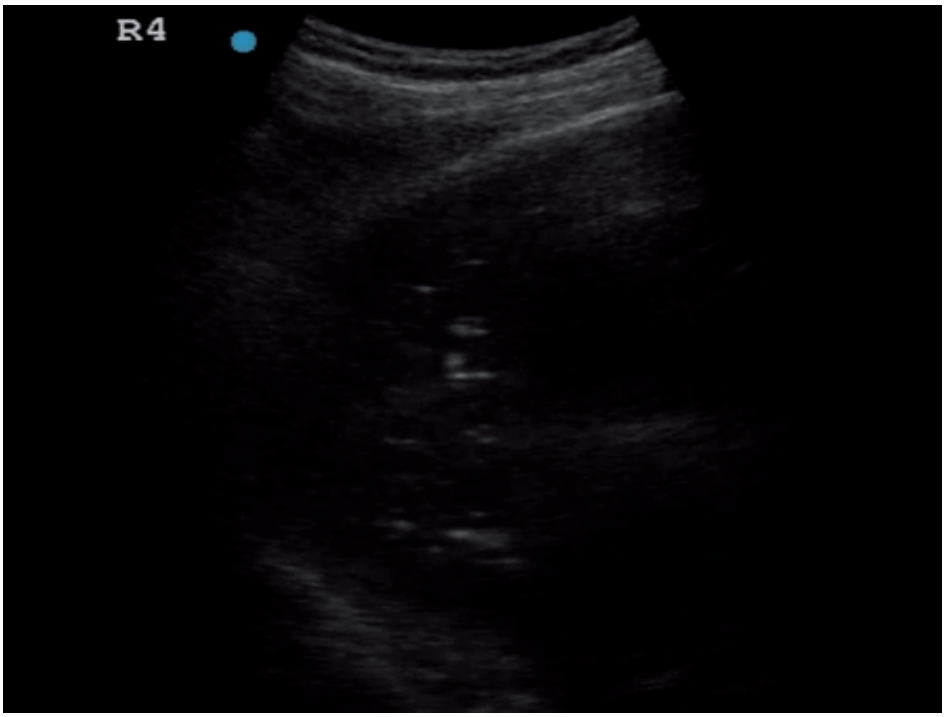
e-Video 5.7: Lung pulse.



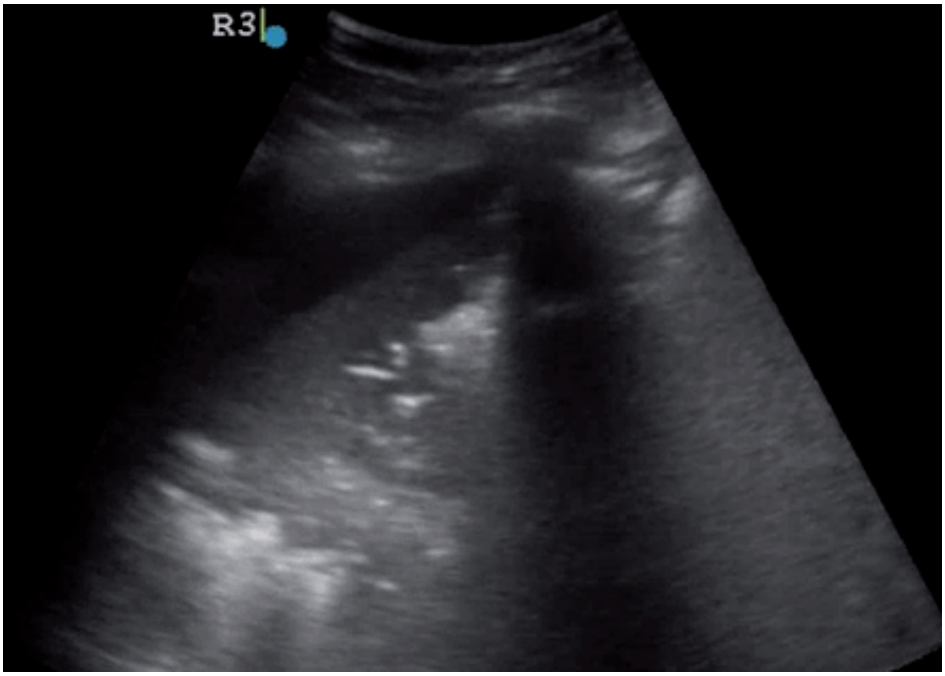
e-Video 5.8: Uncomplicated pleural effusion.



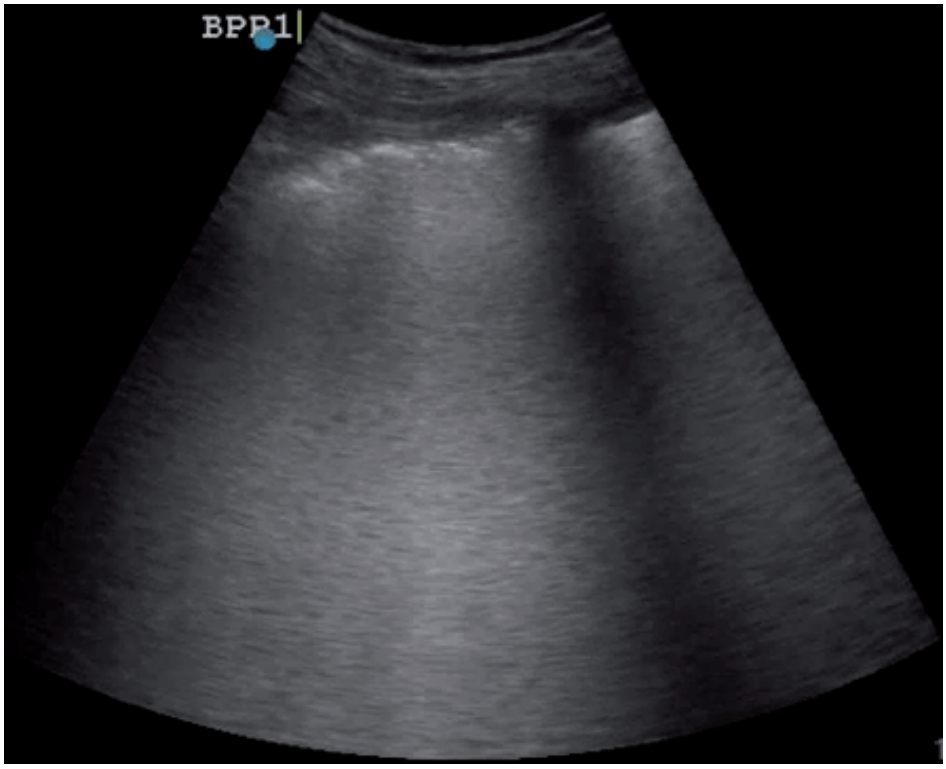
e-Video 5.9: Pleural effusion with hyperechoic speckles in the fluid indicating a possible complicated effusion or hemothorax.



e-Video 5.10: Dynamic air bronchogram.



e-Video 5.11: Hepatization.

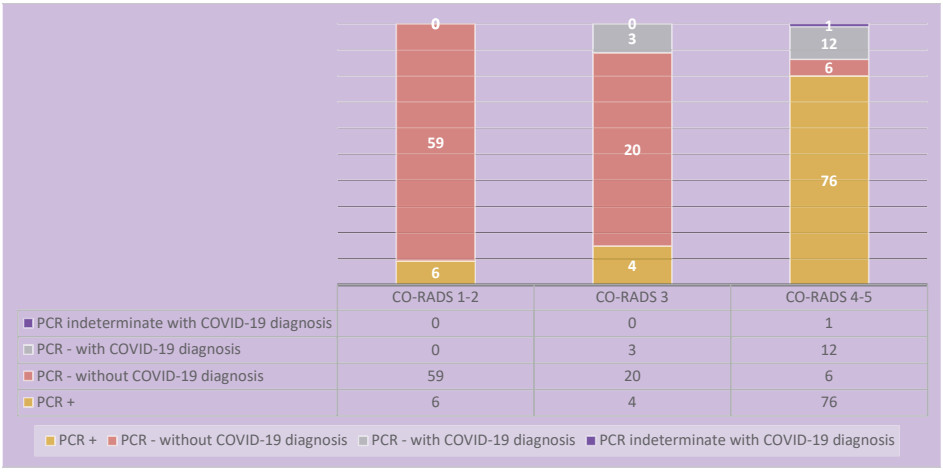


e-Video 5.12: Thickened/irregular pleural line with confluent B-lines.

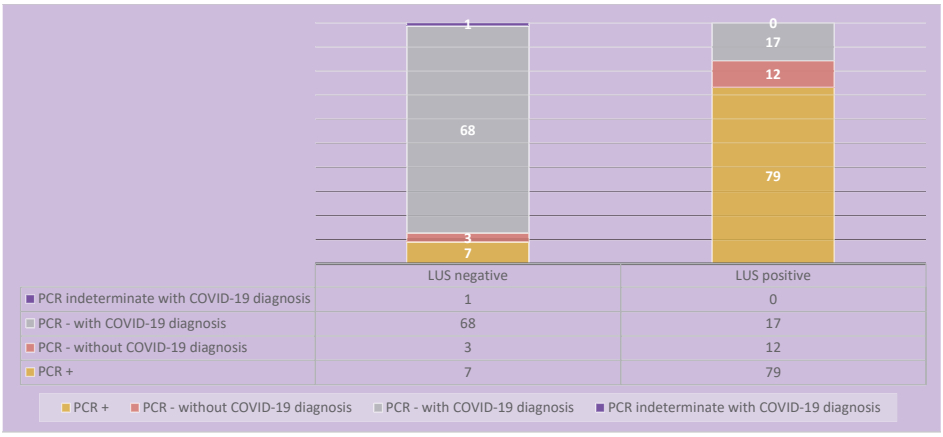
Chapter 6

e-Table 6.1: Sonographic features of COVID-19 pneumonia compared to CT findings

Lung ultrasound	Chest CT
Thickened & irregular pleural line (e-Video 5.12)	Thickened pleura
B-lines (discrete, multifocal or confluent) (e-Video 5.2)	Ground glass shadow and effusion
Confluent B-lines (e-Video 5.3 & 6.1)	Pulmonary infiltrating shadow
Subpleural consolidations or 'skip' lesions (e-Video 5.3)	Subpleural consolidation
Both non-translobar and translobar consolidation (e-Video 5.4)	Translobar consolidation
Rare pleural effusion (e-Video 5.8)	Rare pleural effusion
Multi-lobar, patchy distribution of abnormalities (e-Video 6.1)	More than two 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 e-Table 2.1 for a more detailed description.



e-Table 6.2: CT result versus PCR results and clinical diagnosis.
Abbreviations: CT, computed tomography; PCR, polymerase chain reaction.



e-Table 6.3: LUS result versus PCR results and clinical diagnosis.
Abbreviations: LUS, lung ultrasound; PCR, polymerase chain reaction.

e-Table 6.4: Alternative diagnoses in the PCR negative group

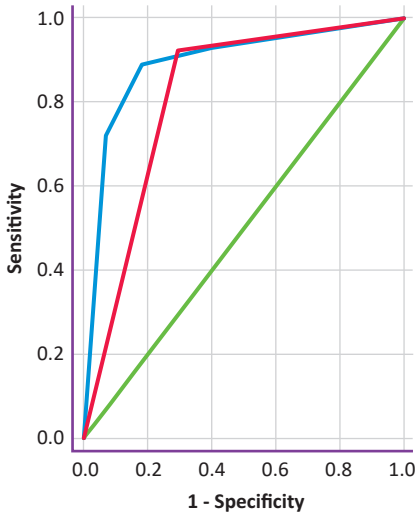
Alternative diagnoses	Number patients (%)
Exacerbation COPD/asthma	7 (7.0)
Bacterial/aspiration pneumonia	14 (14)
Upper respiratory tract infection (incl. bronchitis & bronchiolitis)	11 (11.0)
Malignancy progression	9 (9)
Decompensated heart failure	7 (7.0)
Fever of unknown origin	5 (5.0)
Pulmonary embolism	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: urinary tract infection, splenic abscess, abscess after low anterior resection, gastritis.
Abbreviations: COPD, chronic obstructive pulmonary disease.

e-Table 6.5: McNemar tests comparing sensitivity & specificity of LUS & CT

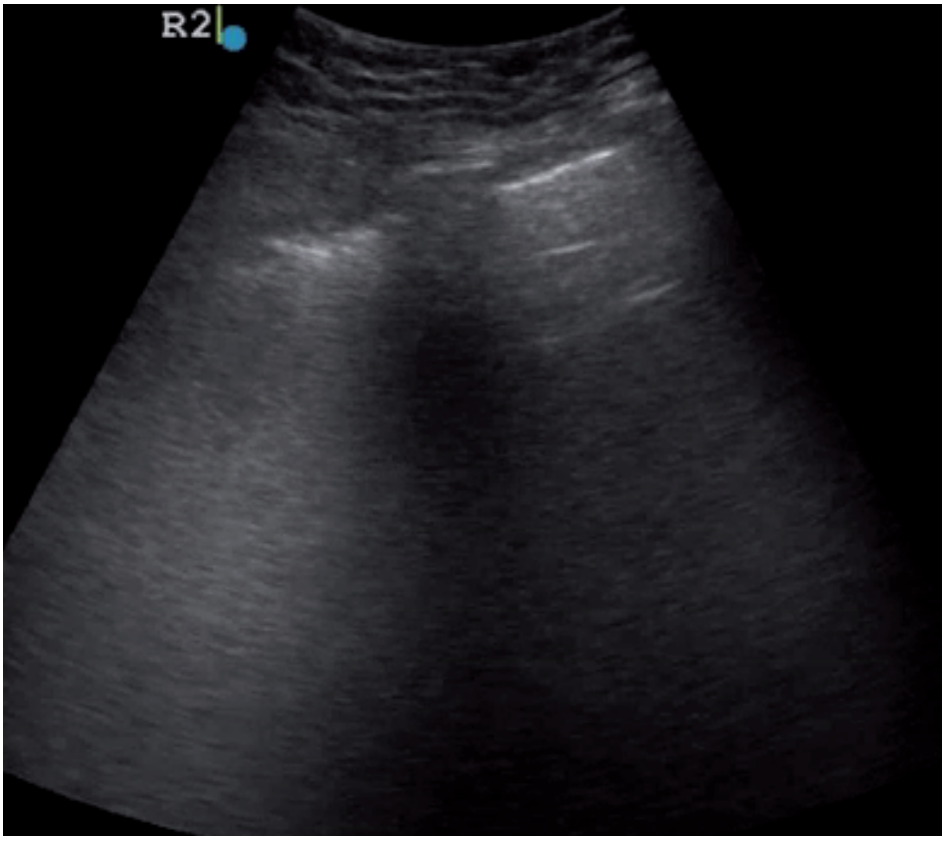
McNemar test	Sensitivity with PCR as reference	Specificity with PCR as reference	Sensitivity with MDT diagnosis as reference	Specificity with MDT diagnosis as reference
LUS vs CT	0.55	0.30	0.80	0.23

Abbreviations: CT, computed tomography; LUS, lung ultrasound; MDT, multidisciplinary team; PCR, polymerase chain reaction.



		Sensitivity	1 – Specificity
LUS (red line)	Negative	100%	100%
	Positive	91.9%	29.0%
CO-RADS (blue line)	1	100%	100%
	2	94.2%	54.0%
	3	93.0%	41.0%
	4	88.4%	18.0%
	5	72.1%	0.07%

e-Figure 6.1: ROC curve of lung ultrasound and computed tomography versus PCR.
Green line: reference line.
Red line: LUS.
Blue line: CO-RADS.
Abbreviations: CO-RADS, COVID-19 Reporting and Data System; LUS, lung ultrasound; PCR, polymerase chain reaction; ROC, receiver operating characteristic.



e-Video 6.1: Patchy distribution of B-lines (COVID-19).

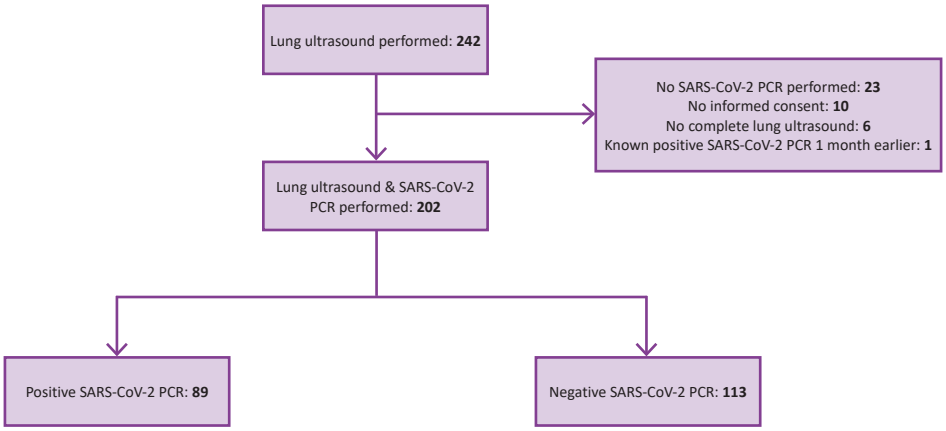
Chapter 7

e-Table 7.1A: McNemar test results with the polymerase chain reaction (PCR) as reference

McNemar test based on PCR results	12-zone vs 8-point	12-zone vs 6-point	8-point vs 6-point
Sensitivity	**0.000**	0.250	**0.022**
Specificity	0.238	**0.000**	**0.004**

e-Table 7.1B: McNemar test results with the final diagnosis as reference

McNemar test based on the final diagnosis	12-zone vs 8-point	12-zone vs 6-point	8-point vs 6-point
Sensitivity	**0.003**	0.625	**0.022**
Specificity	0.332	**0.000**	**0.004**



e-Figure 7.1: Flowchart of patient inclusion and exclusion.

A

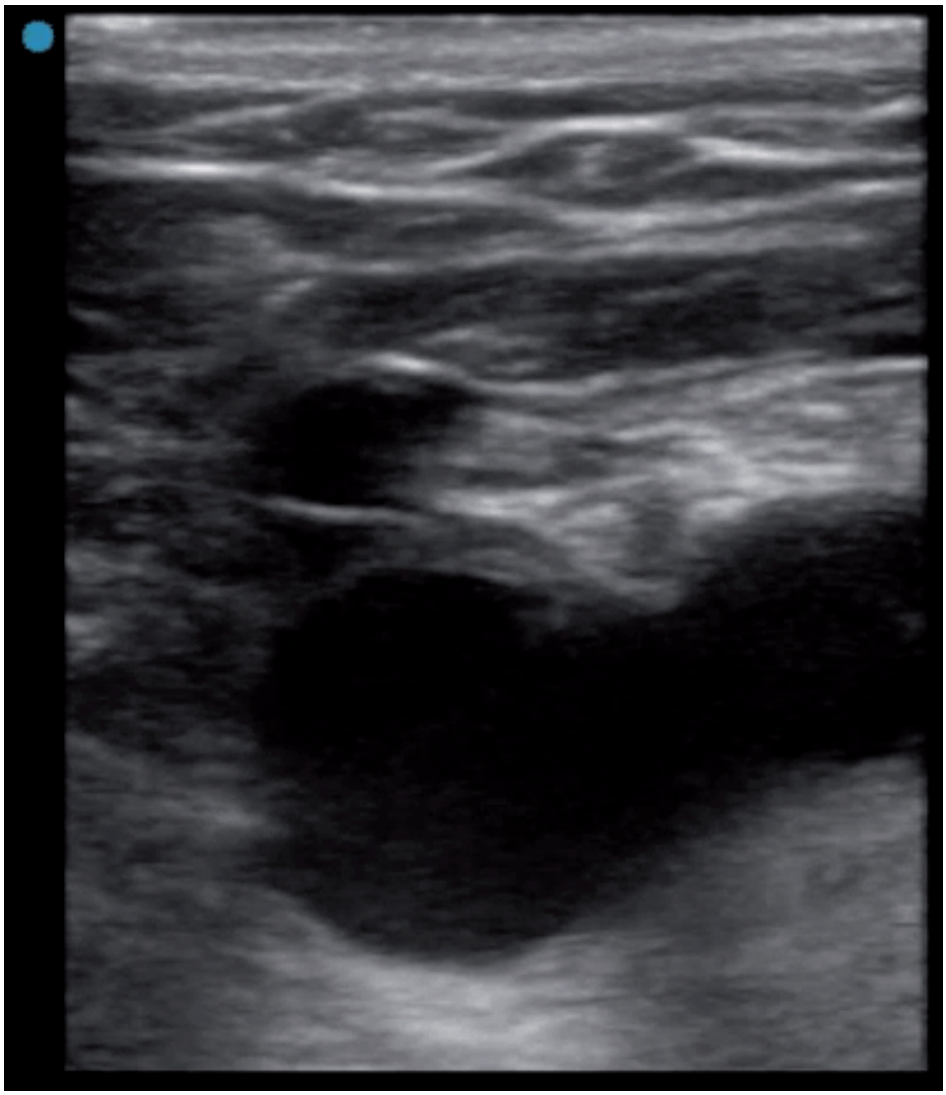
Chapter 8

e-Table 8.1: Additional imputation variables

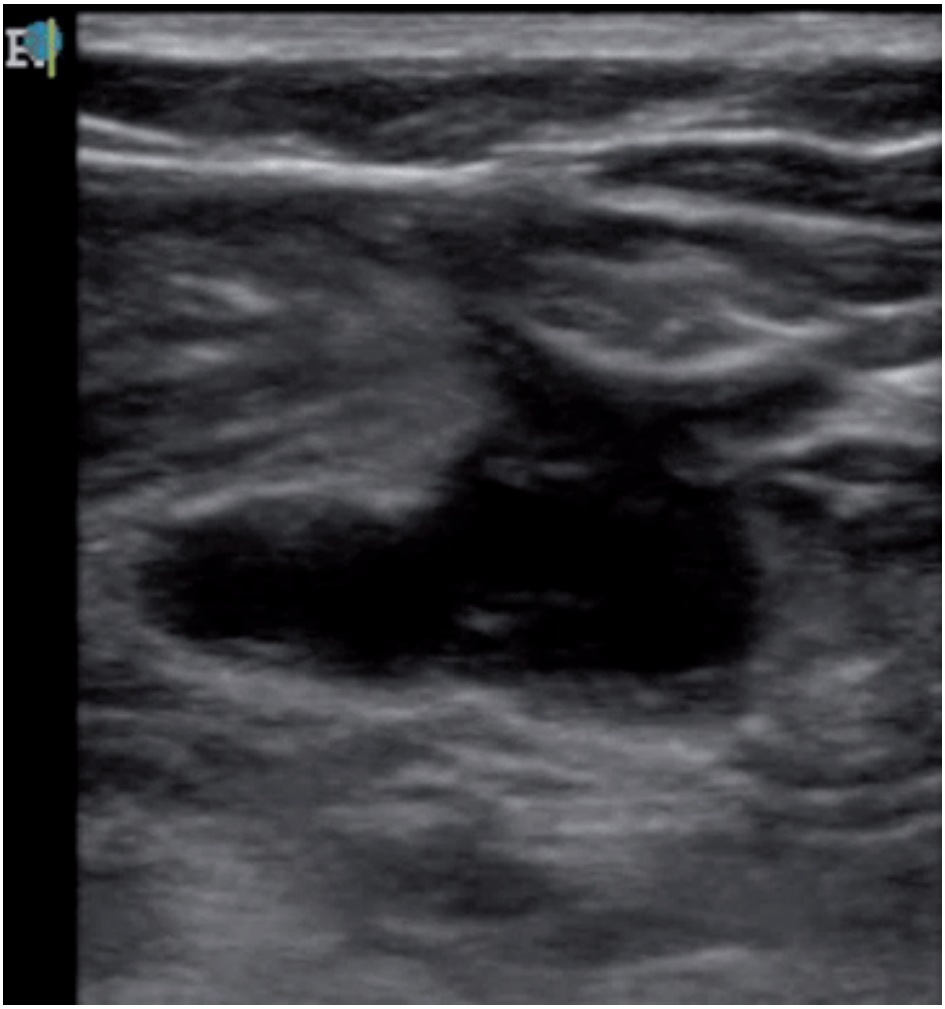
Additional imputation variable	Percentage of missing data
All symptom and sign variables*	0
All comorbidity variables**	0
Diastolic blood pressure	1.75
Urea	11.4
Sodium	4.39
Potassium	10.53
ASAT	23.68
ALAT	7.89
Bilirubin	7.02
Glucose	16.67
CO-RADS	0

*Wheezing, throat ache, chest pain, myalgia, joint pain, fatigue, rash, headache, lymphadenopathy.
**Immunodeficiency, asthma, chronic liver disease.
Abbreviations: CO-RADS, COVID-19 Reporting and Data System; ASAT, aspartate transferase; ALAT, alanine transferase.

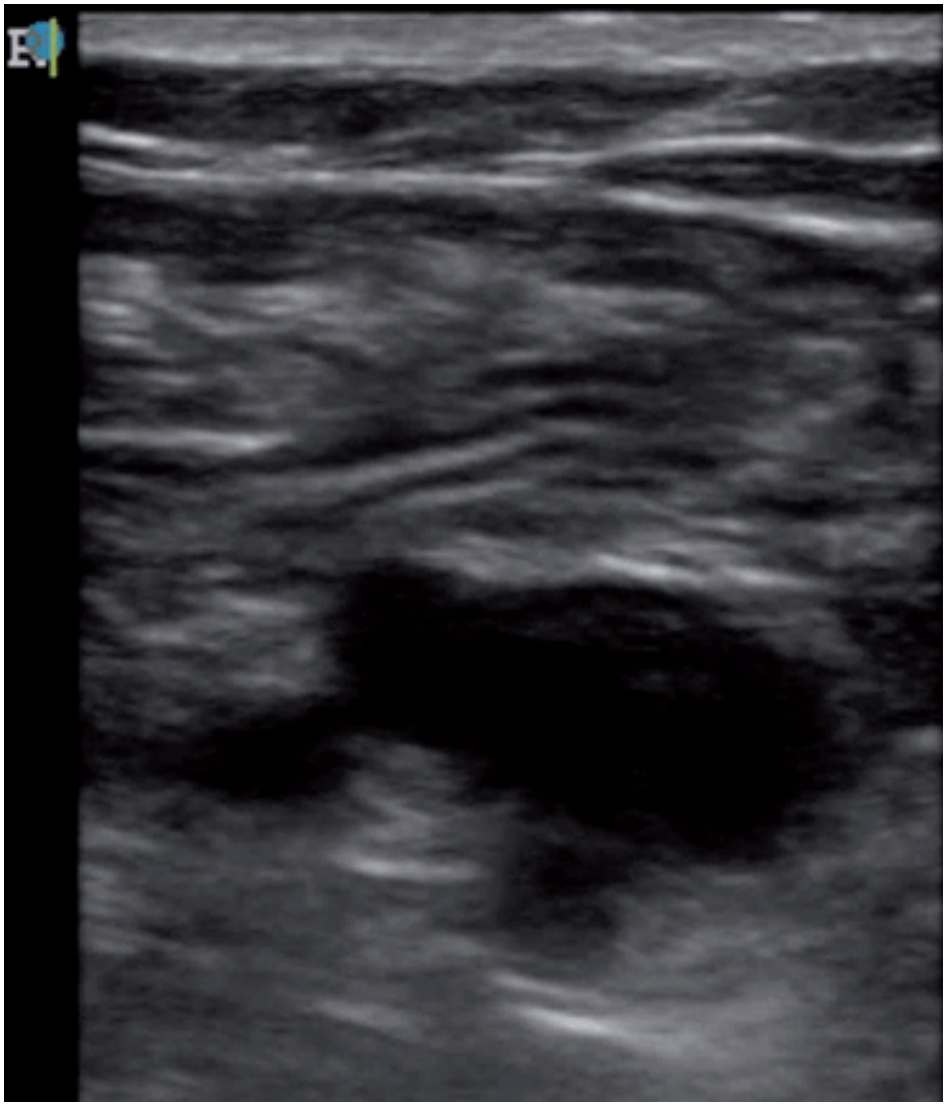
Chapter 9



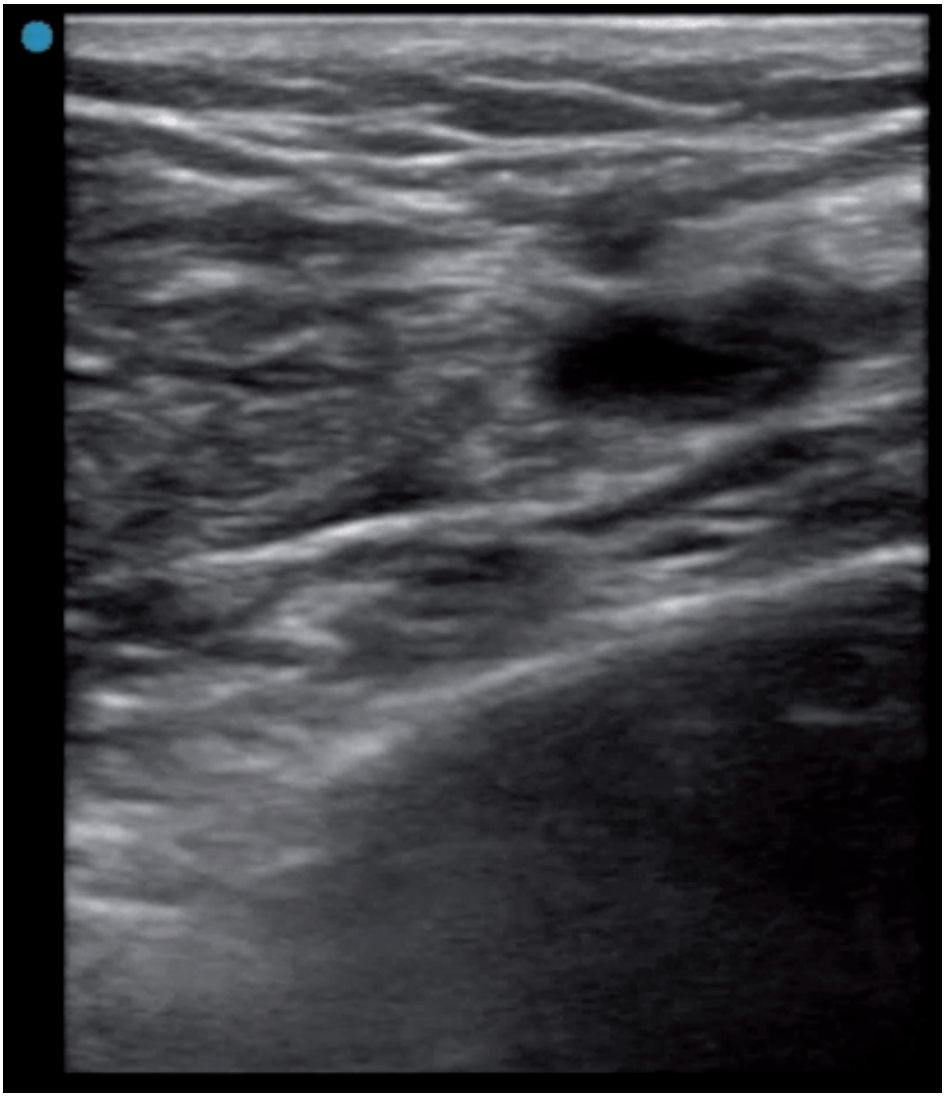
e-Video 9.1: Compressible left common femoral vein (no deep venous thrombosis).



e-Video 9.2: Right common femoral vein thrombosis.



e-Video 9.3: Right femoral vein thrombosis.

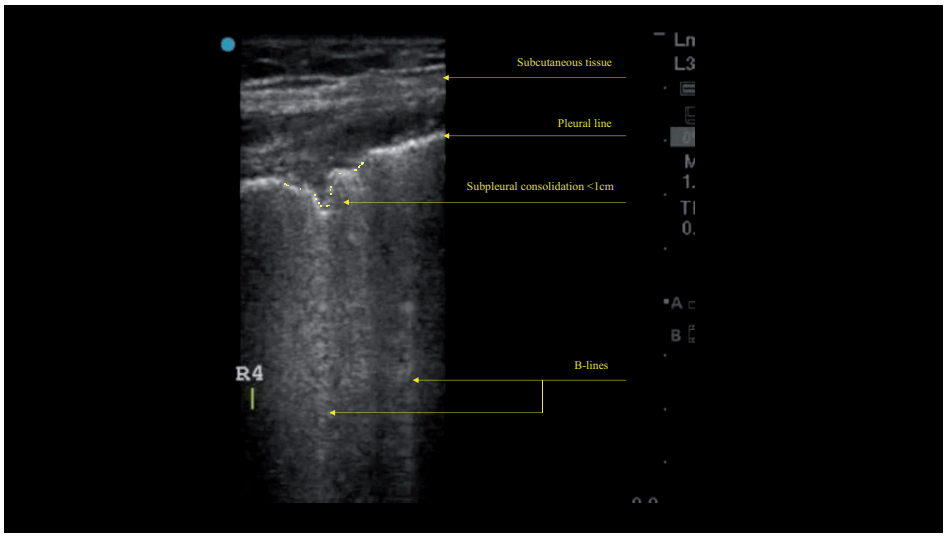


e-Video 9.4: Compressible left popliteal vein (no deep venous thrombosis).

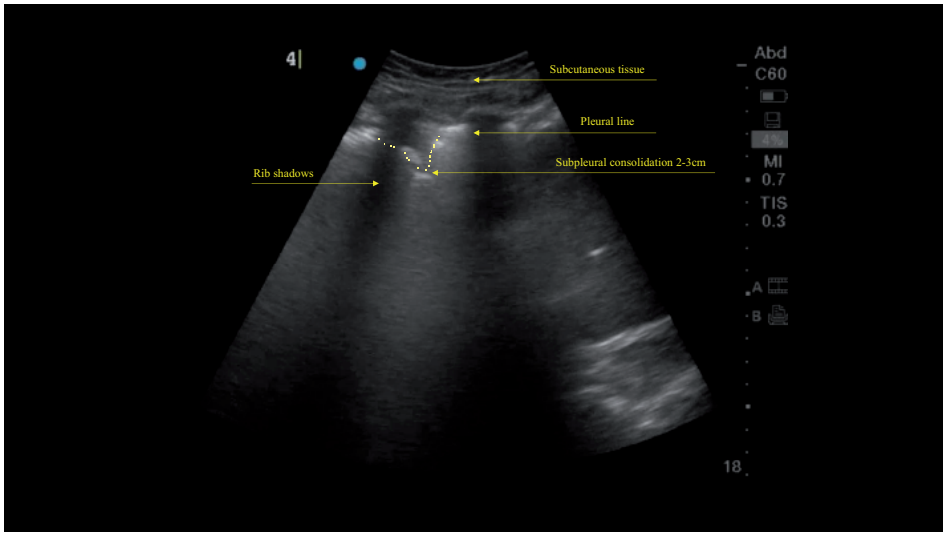


e-Video 9.5: Right popliteal vein thrombosis.

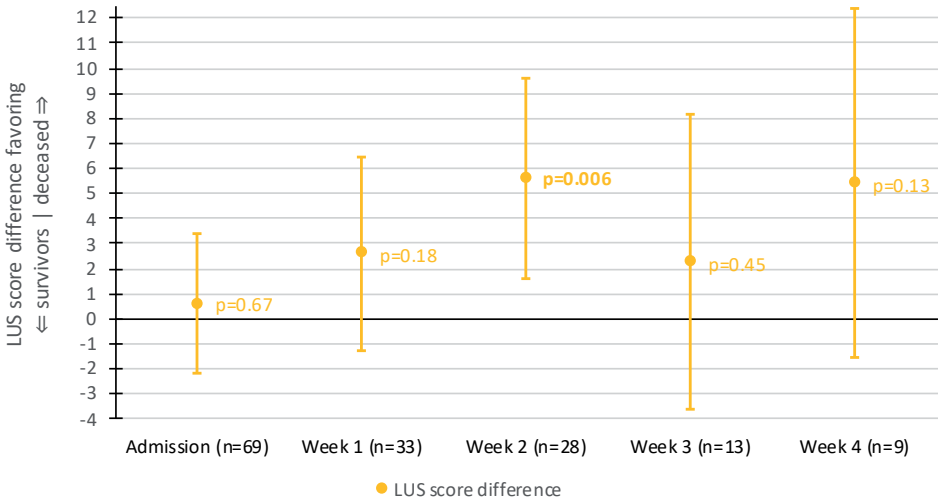
Chapter 13



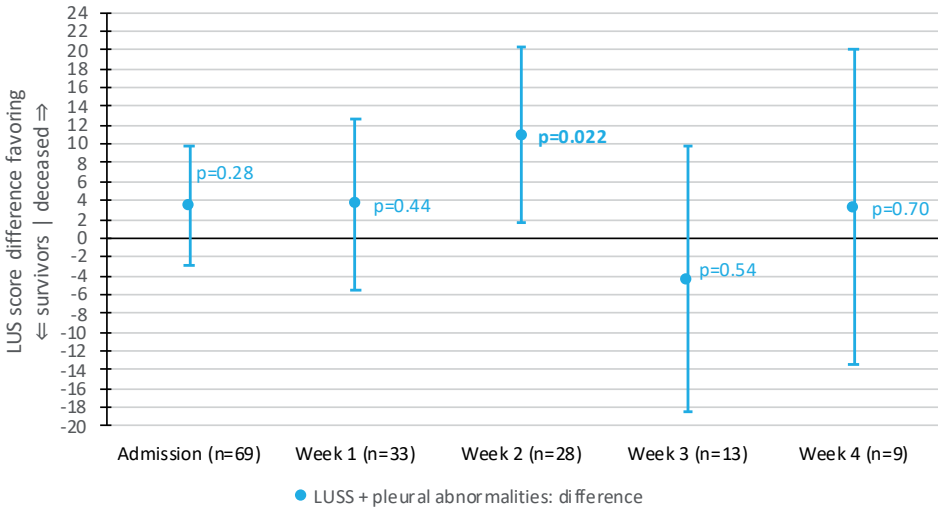
e-Figure 13.1: Small subpleural consolidation: <1cm.



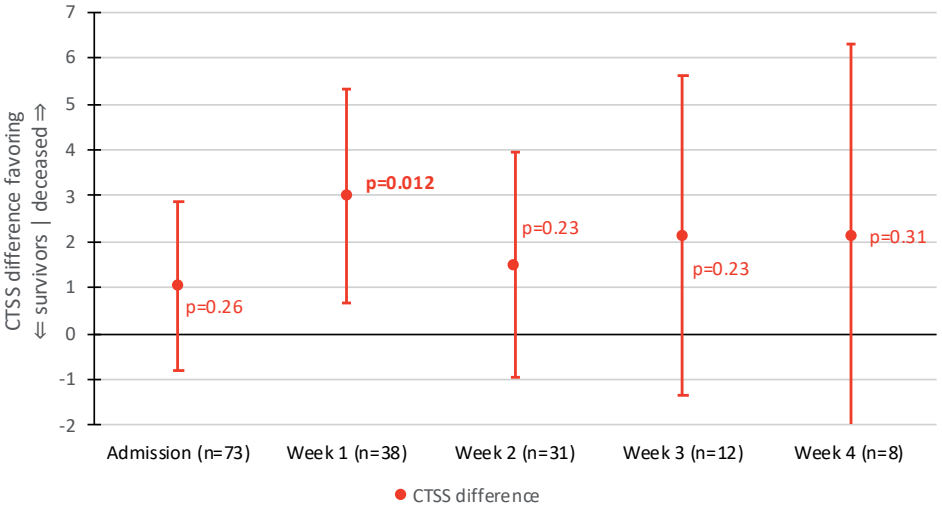
e-Figure 13.2: Larger subpleural consolidation: 2-3cm.



e-Figure 13.3A: Difference in LUSS: alive versus dead patients.
Each yellow point represents the mean score difference between alive and dead patients per week of admission with their 95% confidence interval. *P* values should be interpreted as the significance of the change of that particular point compared to baseline. Significant *p* values are in bold.
Abbreviations: LUSS, lung ultrasound score.



e-Figure 13.3B: Difference in LUSS + pleural abnormalities: alive versus dead patients.
Each blue point represents the mean score difference between alive and dead patients per week of admission with their 95% confidence interval. *P* values should be interpreted as the significance of the change of that particular point compared to baseline. Significant *p* values are in bold.
Abbreviations: LUSS, lung ultrasound score.



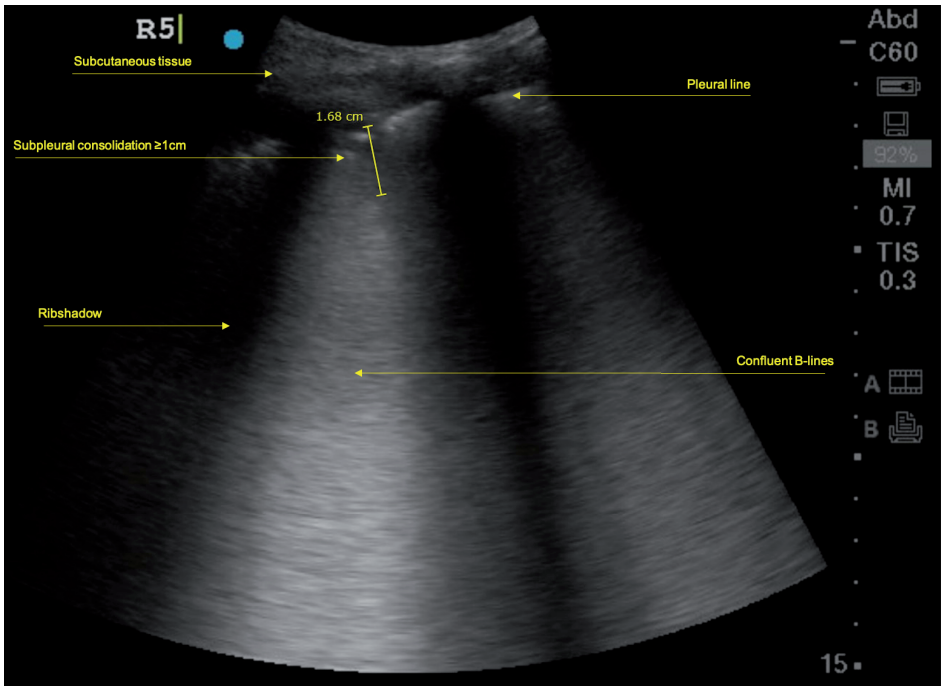
e-Figure 13.3C: Difference in CTSS: alive versus dead patients.
Each red point represents the mean score difference between alive and dead patients per week of admission with their 95% confidence interval. *P* values should be interpreted as the significance of the change of that particular point compared to baseline. Significant *p* values are in bold.
Abbreviations: CTSS: Computed tomography severity score.

Chapter 14

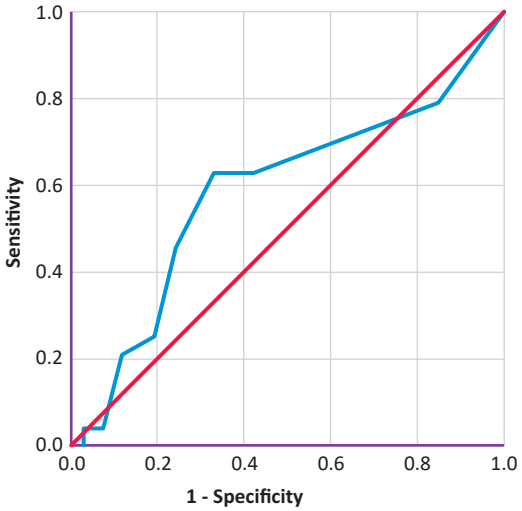
e-Table 14.1: McNemar tests of different POCUS modalities and combinations compared to multi-organ POCUS

POCUS signs	McNemar Sensitivity	McNemar Specificity
CON2	0.125	0.002
CON1	**<0.001**	<0.001
DVT	**<0.001**	<0.001
RVS	**0.001**	<0.001
RVS or DVT	**0.016**	<0.001
[RVS or DVT] & CON2	**0.002**	<0.001

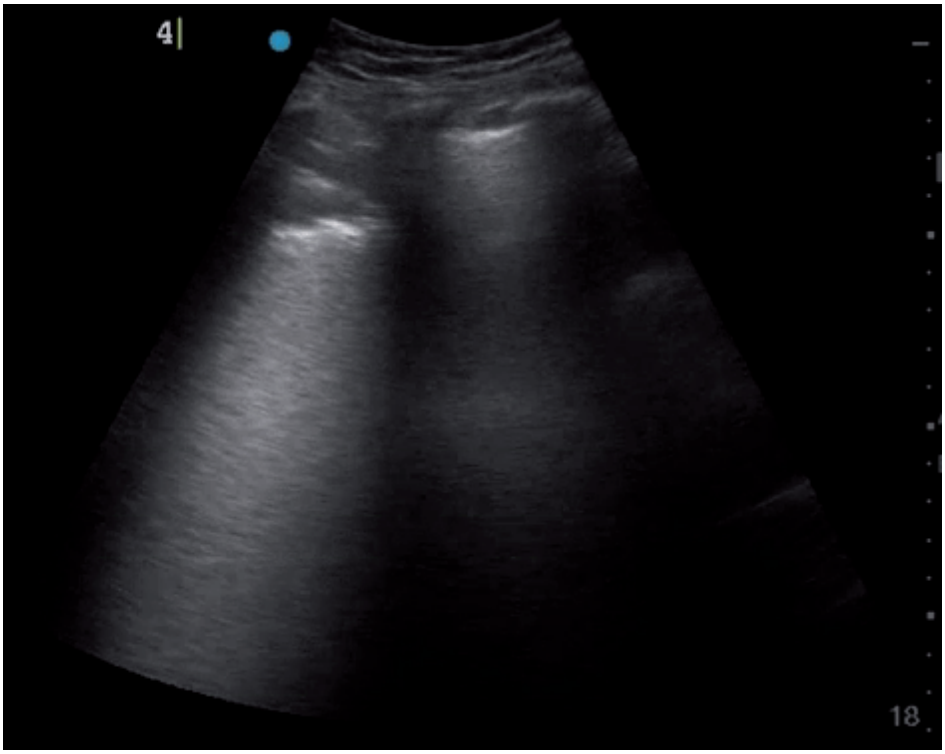
Values are **in bold** if multi-organ POCUS was higher, and underscored if multi-organ POCUS was lower.
Abbreviations: CON1, 1 subpleural consolidation of ≥1cm (probable criterium); CON2, ≥2 subpleural consolidations of ≥1cm (high likelihood criterium); DVT, deep venous thrombosis; RVS, right ventricular strain.



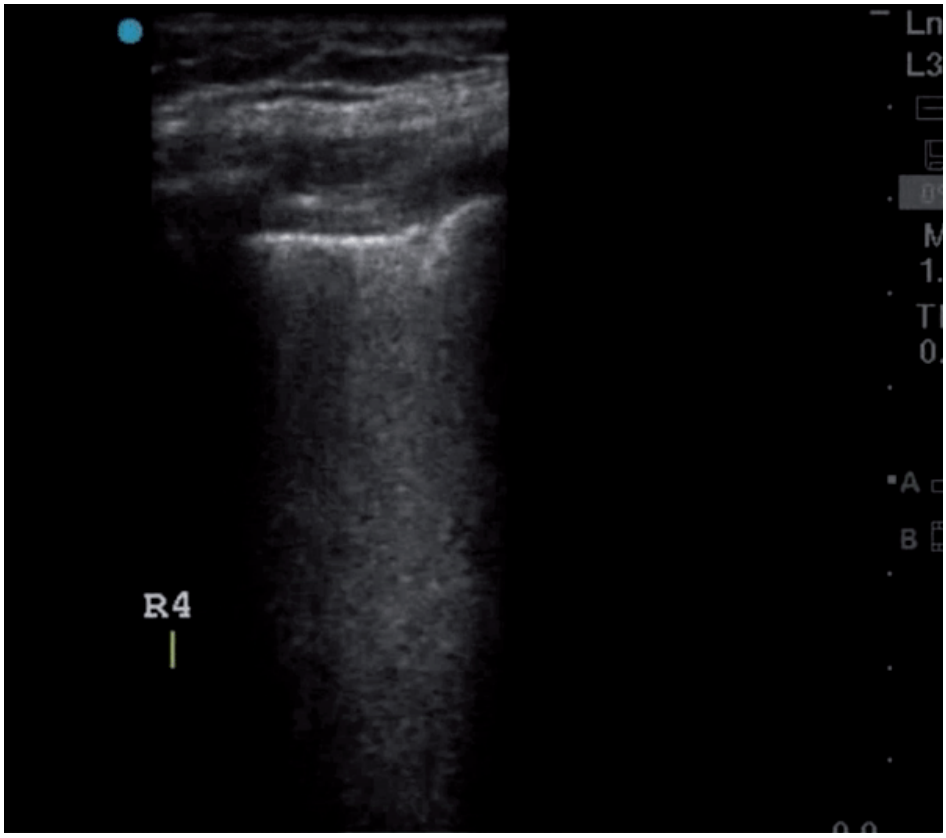
e-Figure 14.1: Subpleural consolidation ≥1cm with confluent B-lines.



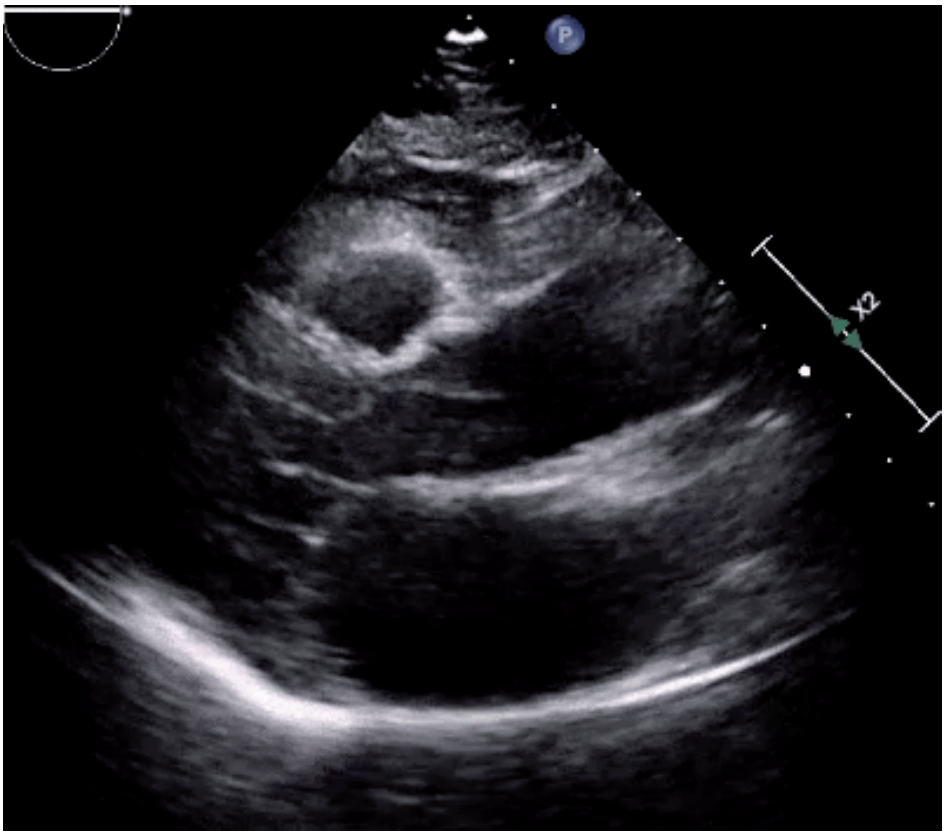
e-Figure 14.2: ROC curve of subpleural consolidations versus pulmonary embolism.
Red line: reference line.
Blue line: subpleural consolidations.
Abbreviations: ROC, receiver operating characteristic.



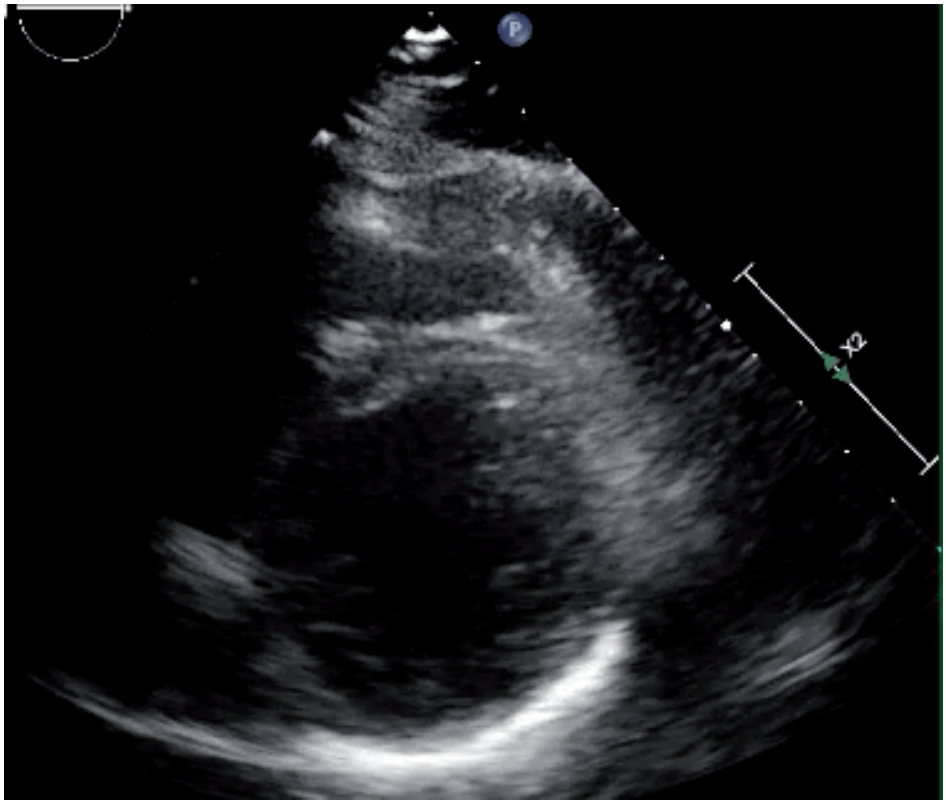
e-Video 14.1: Large subpleural consolidations ≥1cm.



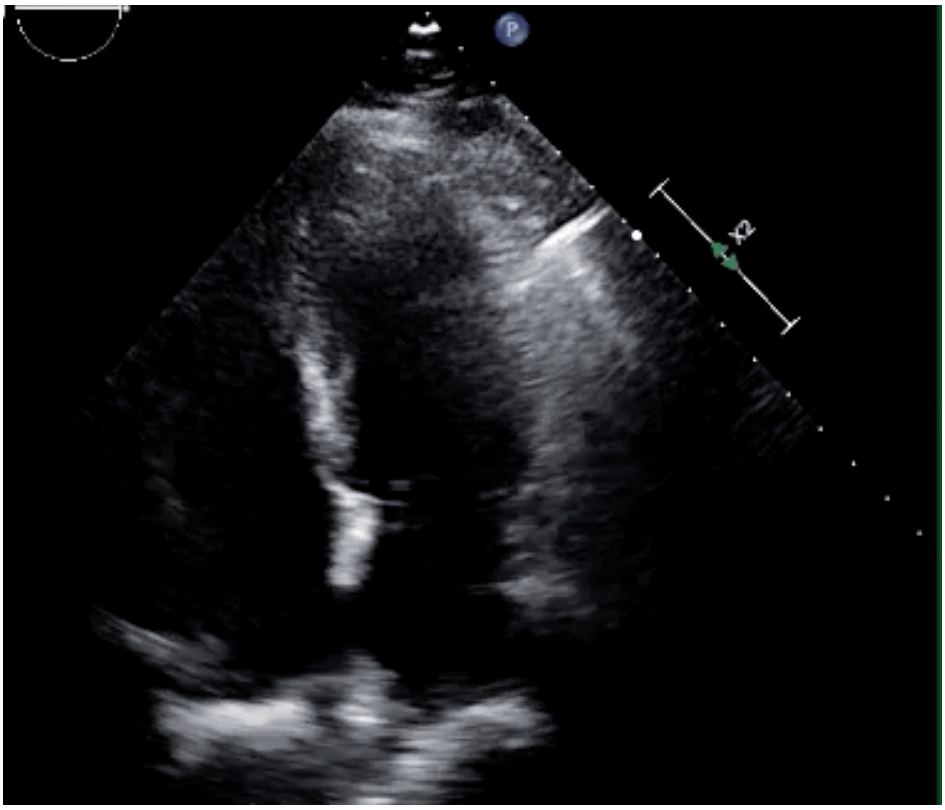
e-Video 14.2: Small subpleural consolidation <1cm.



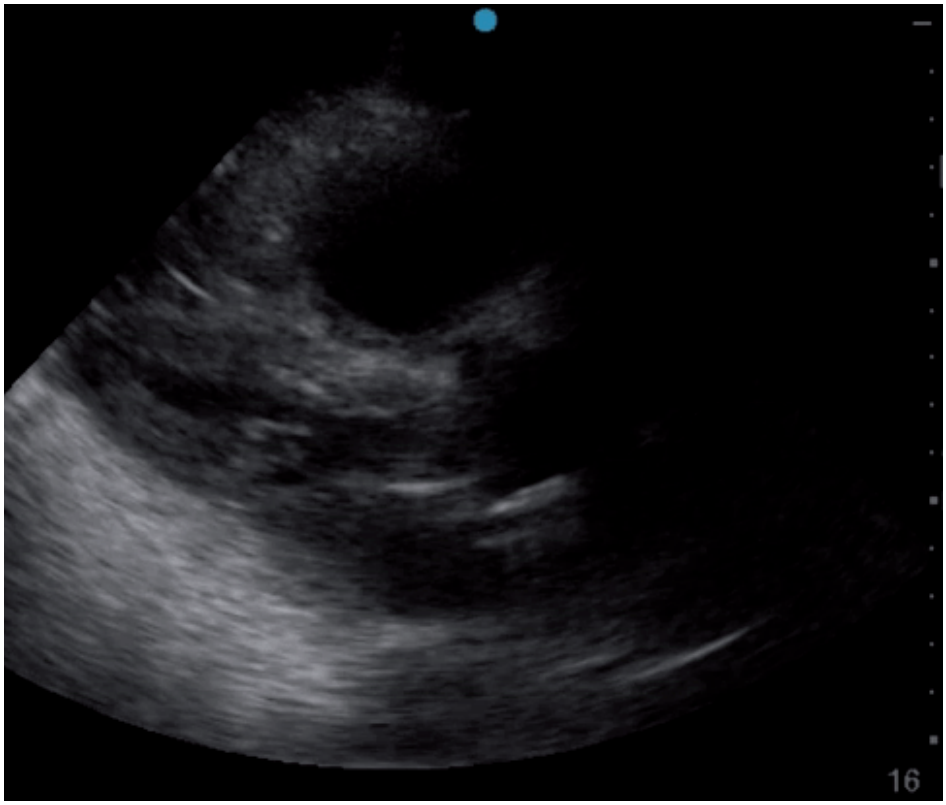
e-Video 14.3: Normal parasternal long axis (PLAX) view.



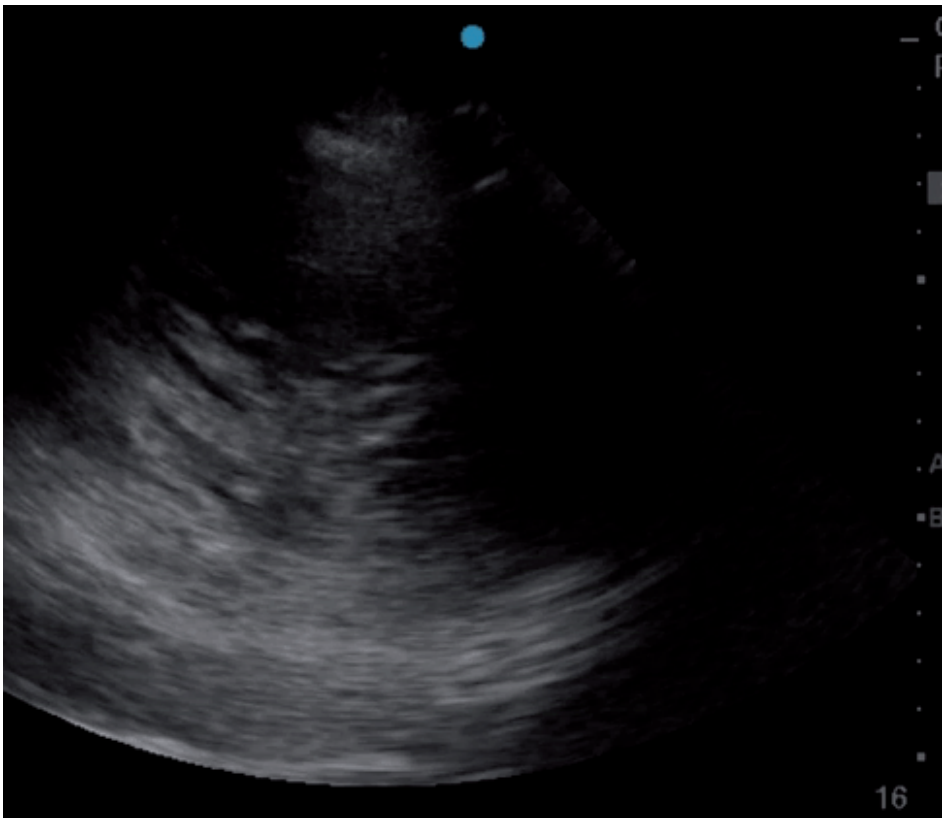
e-Video 14.4: Normal parasternal short axis (PSAX) view.



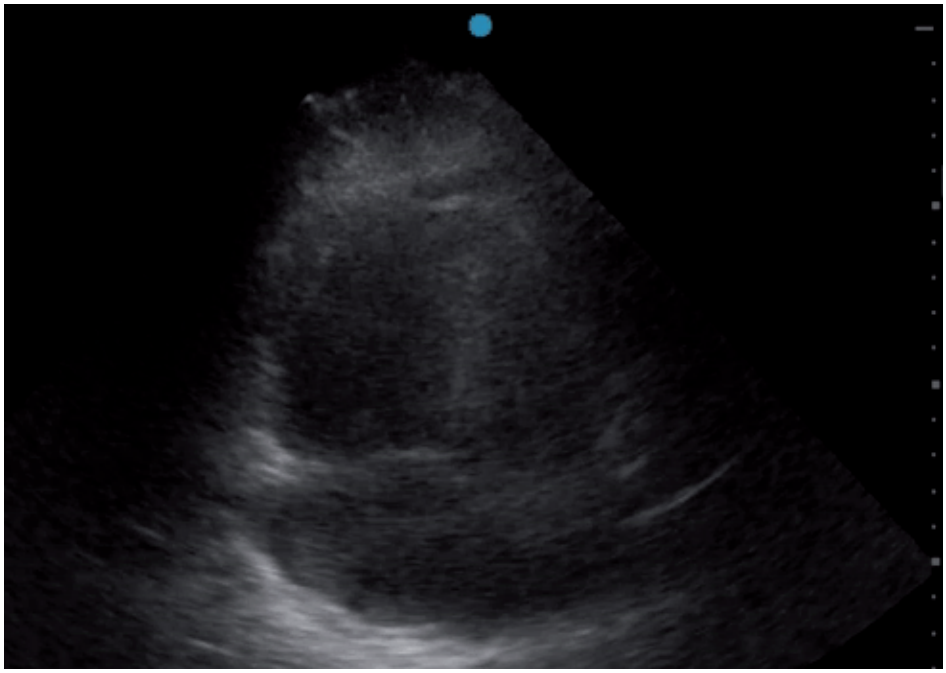
e-Video 14.5: Normal apical 4 chamber (A4C) view.



e-Video 14.6: Parasternal long axis view (PLAX) with right ventricular strain (septal bowing into left ventricle).



e-Video 14.7: Parasternal short axis (PSAX) view with right ventricular strain (D-sign).



e-Video 14.8: Apical 4 chamber (A4C) view with a right ventricle to left ventricle (RV:LV) ratio ≥1 and McConnell's sign.





List of publications

List of publications

Sorted by year of publication

1. Westland GJ, **Lieveld AWE**, Sohne M, Ten Wolde M. Massale longembolie. *A&I*. 2014;Jaargang 6(Editie 4).
2. Suurmond J, **Lieveld AWE**, van de Wetering M, Schouten-van Meeteren AYN. Towards culturally competent paediatric oncology care. A qualitative study from the perspective of care providers. *Eur J Cancer Care*. 2017;26(6):e12680. doi:10.1111/ecc.12680
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4. **Lieveld AWE**, Walden A. Chapter: Lung Ultrasound. In: Gilbert-Kawai E, Dutta D (Dev), Waldmann C, eds. *Intensive Care Medicine: The Essential Guide*. Cambridge University Press; Accepted for publication July 2020. Online ISBN: 9781108989060.
5. **Lieveld AWE***, Kok B*, Schuit FH*, et al. Diagnosing COVID-19 pneumonia in a pandemic setting: Lung Ultrasound versus CT (LUVCT) A multi-centre, prospective, observational study. *ERJ Open Research*. Published online September 30, 2020. doi:10. 1183/23120541.00539-2020
6. **Lieveld AWE***, Azijli K*, Teunissen BP, et al. Chest CT in COVID-19 at the ED: Validation of the COVID-19 Reporting and Data System (CO-RADS) and CT Severity Score. *Chest*. 2021;159(3):1126-1135. doi:10.1016/j.chest.2020.11.026
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10. Kok B*, Schuit FH*, **Lieveld AWE***, Azijli K, Nanayakkara PWB, Bosch FH. Comparing lung ultrasound: extensive versus short in COVID-19 (CLUES): a multicentre, observational study at the emergency department. *BMJ Open*. 2021;11(9):e048795. doi:10.1136/bmjopen-2021-048795

11. Heldeweg MLA, **Lieveld AWE**, de Grooth HJ, Heunks LMA, Tuinman PR. Determining the optimal number of lung ultrasound zones to monitor COVID-19 patients: can we keep it ultra-short and ultra-simple? *Intensive Care Med*. Published online June 26, 2021:1-3. doi:10.1007/s00134-021-06463-6
12. Pierrakos C, **Lieveld AWE**, Pisani L, et al. A Lower Global Lung Ultrasound Score Is Associated with Higher Likelihood of Successful Extubation in Invasively Ventilated COVID-19 Patients. *The American Journal of Tropical Medicine and Hygiene*. 2021; 1(aop). doi:10.4269/ajtmh.21-0545
13. Azijli K*, Minderhoud TC*, De Gans CJ, **Lieveld AWE**, Nanayakkara PWB. Optimal Use of Procalcitonin to Rule Out Bacteremia in Patients with Possible Viral Infections. *Journal of the American College of Emergency Physicians Open*. Published online 2022.
14. Olgers TJ, **Lieveld AWE**, Kok B, et al. Screening for asymptomatic proximal deep vein thrombosis in COVID-19 patients admitted to the medical ward: a cross-sectional study. *Journal of Ultrasound*. Published online May 2022.
15. Haaksma ME, Smit JM, Kramer R, Heldeweg MLA, Veldhuis LI, **Lieveld AWE**, et al. Evolution of respiratory muscles thickness in mechanically ventilated patients with COVID-19. *Respiratory Care*. Published online May 2022.
16. **Lieveld AWE***, Heldeweg MLA*, Smit JM, et al. Multi-organ point-of-care ultrasound for detection of pulmonary embolism in critically ill COVID-19 patients – A diagnostic accuracy study. *Journal of Critical Care*. 2022;69:153992. doi:10.1016/j.jcrc.2022.153992
17. Wesselius HM*, **Lieveld AWE***, van Dijk K, Hekker TAM, Peters EJG. Histoplasmose bij een patient met sarcoïdose. *Ned Tijdschr Geneeskd*. 2022;166:D6335.
18. Heldeweg MLA, Mousa A, van Ekeren J, **Lieveld AWE**, et al. Lung ultrasound to predict gas-exchange response to prone positioning in COVID-19 patients: A prospective study in pilot and confirmation cohorts. *J Crit Care*. 2023;73:154173. doi:10.1016/j.jcrc.2022.154173
19. Heldeweg MLA*, **Lieveld AWE***, Walburgh-Schmidt RS, et al. Concise Versus Extended Lung Ultrasound Score to Monitor Critically Ill Patients With COVID-19. *Respir Car*e. Published online January 17, 2023:respcare.10406. doi:10.4187/respcare.10406
20. **Lieveld AWE***, Heldeweg MLA*, Schouwenburg J, et al. Monitoring of pulmonary involvement in critically ill COVID-19 patients - should lung ultrasound be preferred over CT? *The Ultrasound Journal*. 2023;15(1):11. doi:10.1186/s13089-022-00299-x

**Shared first author; **Contributing author.*

A





Acknowledgements / Dankwoord

Acknowledgements / Dankwoord

If you made it this far, it means that you've almost finished reading my entire thesis. Or that you skipped the whole thing and just wanted read about the people that contributed to its creation. My heart hopes it's the former, although my mind realizes it's likely the latter. I can't really blame you and to be fair it doesn't matter! What's important is that this is the part where I get to thank the people that have been instrumental in making this thesis possible.

In 'On Airs, Waters, and Places' Hippocrates said that: 'man is the product of his environment'. The older I get (and yes, I am getting old), the more I realize how true that is. This thesis has been a case in point. It would never have come to fruition if I hadn't received the love, care and immeasurable support from the people around me. Consequently, this thesis is as at least as much their accomplishment as it is mine.

To begin, I would like to thank **all the patients, nursing staff, researchers, coauthors, consultants, fellows, registrars, and interns** that contributed to the studies presented in this thesis. Not only in the AmsterdamUMC, but in all the other participating hospitals in The Netherlands and the rest of Europe.

I also would like to extend my gratitude to my **reading committee** for taking the time out of their undoubtedly busy schedules to scrutinize my thesis.

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Lieve Cat, ik ben zo benieuwd naar wat de toekomst ons gaat brengen. Ik hou van je en ik kijk er ontzettend naar uit om samen met jou onze dochter groot te brengen. Maar misschien moeten we voor het zo ver is eerst eens beslissen hoe we haar gaan noemen.





About the author

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Arthur William Edward Lieveld was born on December 4, 1985, in Eindhoven, the Netherlands. He grew up in Nuenen, a small town near Eindhoven. After graduating from the Lorentz Casimir Lyceum in 2003, he spent the next year trying to become a tennis professional. Since you have never seen him at Wimbledon, it is fair to say that did not pan out. Unsure of what to do next, his tennis coach Mike Martin encouraged him to pursue a life helping people as a doctor. Inspired, he decided to go back to secondary school in 2004 to get the necessary subjects needed to get into medical school.

In 2005 Arthur enrolled at the University of Amsterdam (UvA). Driven by a fascination for the way the world works, he quit the honours program and put his internships on hold to get a master's degree in International Relations from the UvA.

When he resumed his internships in 2012, he quickly developed an interest in internal medicine. After he obtained his medical degree in 2014, he spent a year working at the internal medicine department of the Flevoziekenhuis in Almere. Subsequently, he got accepted to the internal medicine training program of the Vrije Universiteit (VU) of Amsterdam.

He spent the first three-and-a-half years of training at the OLVG Hospital in Amsterdam. During these years, he developed a love for teaching. He was nominated by interns for the award of best resident multiple times and won it twice.

Arthur also developed an interest in point-of-care ultrasound (POCUS). Driven by a desire to deepen his experience in POCUS, he put his training on hold in March 2019 and moved to Reading to do an acute medicine and POCUS fellowship at the Royal Berkshire Hospital, under the wing of dr. Andrew Walden. He quickly honed his skills and became an instructor at various basic and advanced ultrasound courses across Europe.

Arthur also received the Royal College of Radiology level 1 certification in gastrointestinal, urological and vascular ultrasound. And he became a member of the Ultrasound Taskforce of the Nederlandse Internisten Vereniging (NIV), and helped redesign the NIV POCUS course.

When he returned to finish his training at the VU, the COVID-19 pandemic hit. Which is when he was prompted to start the research that ultimately culminated in this thesis. He combined his research with clinical work at the emergency department, the medical wards and the intensive care unit. Simultaneously, he followed courses from the master's degree in clinical epidemiology from EpidM to become a registered Clinical Epidemiologist. He

also became the first internist (in training) certified in transthoracic echocardiography by the European Society of Cardiology/European Association of Cardiovascular Imaging after completing an echocardiography placement at the St. Antonius Hospital in Nieuwegein.

In June 2022 Arthur completed his training and started working as a consultant in acute internal medicine at the Maasstad Ziekenhuis in Rotterdam. He has an unwavering fascination for education, health care organization, and how novel techniques might improve the diagnosis and treatment of patients worldwide.

