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**Point-of-care ultrasonography for risk stratification of COVID-19 patients (POCUSCO): a study protocol of an international study**

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TITLE: Point-of-care ultrasonography for risk stratification of COVID-19 patients (POCUSCO): a study protocol of an international study

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ABSTRACT

Introduction

In the context of the COVID-19 pandemic, early identification of patients who are likely to get worse is a major concern. Severity mainly depends on the development of acute respiratory distress syndrome (ARDS) with a predominance of subpleural lesions. Lung point-of-care ultrasonography (LUS-POCUS) is highly effective in detecting pulmonary peripheral patterns and may be appropriate for examining COVID-19 patients. We suggest that LUS-POCUS performed during the initial examination may identify COVID-19 patients who are at a high-risk of complicated treatment or unfavourable evolution.

Methods and analysis

The study is a prospective, multicentre study. Adult patients visiting the emergency department (ED) of participating centres for suspected or confirmed COVID-19 are assessed for inclusion. Included patients have LUS-POCUS performed within 48 hours following ED admission. The severity of lung damage is assessed using the LUS-POCUS score based on 36 points for ARDS. Apart from the LUS-POCUS score assessment, patients are treated as standard. If a CT scan is performed, its result is collected. For hospitalised patients, a second LUS-POCUS is performed at day 5 +/- 3. A follow-up is carried out on day 14 and the patient’s status according to the Ordinal Scale for Clinical Improvement for COVID-19 from the World Health Organization is recorded.

The primary outcome is the rate of patients requiring intubation with mechanical ventilation or who dead from any cause during the 14 days following inclusion. We will determine the area under the ROC curve of LUS-POCUS.

Ethics and dissemination

The protocol has been approved by the French and Belgian Ethics Committees and is carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study is funding by a grant from the French Health Ministry and its findings will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number: NCT04338100
STRENGTHS AND LIMITATIONS OF THIS STUDY

- Lung ultrasound (LUS-POCUS) is a simple and non-invasive tool, currently used in everyday clinical practice, that may be an alternative to CT scan as a prognostic tool in patients with suspected or confirmed COVID-19.

- POCUSCO is a prospective cohort study aimed to assess the value of LUS-POCUS to identify patients who are at a high-risk of adverse clinical outcomes.

- The study will focus on the initial exam of patients with suspected or confirmed mild-to moderate COVID-19.

- The primary outcome, a composite of death or intubation within 14 days after inclusion, is clinical and consensual.

- POCUSCO is, in our knowledge, the first prospective study on this specific topic but its results should be confirmed in a formal implementation trial.
BACKGROUND

The COVID-19 pandemic has developed worldwide in less than 4 months [1,2]. While most patients have a mild or uncomplicated form of the disease (80%), approximately 15% need hospital care and 5% intensive care [3]. Severe cases are characterised by pulmonary involvement which may progress to acute respiratory distress syndrome (ARDS), usually between day 7 and day 10 [4]. Early identification of patients who are likely to get worse is therefore a major concern.

While chest X-ray has poor diagnostic performances [4], pulmonary computed tomography (CT scan) appears to be very sensitive (97%) and quite specific to COVID-19 in patients with clinical suspicion of COVID-19, provided that it is not performed within the first four days after symptom onset [5,6]. A subpleural bilateral ground-glass pattern can precede the positivity of RT-PCR for SARS-CoV-2 [7]. In retrospective studies, quantitative CT scan analysis, using a CT scoring method, seems to accurately assess the severity and predict mortality of COVID-19 patients [11] [12]. Therefore, CT scan is now considered as the best imaging test to assess COVID-19 patients and is recommended as a first-line diagnostic tool by national societies of radiology [8–10]. However, performing CT scans for all or many patients with suspected COVID-19 may result in radiology departments being overwhelmed, especially considering bio-cleaning between patients. Moreover, CT scans may lead to adverse effects including induced cancer due to the cumulative diagnostic irradiation.

Chest ultrasonography may be an alternative to CT scans as a prognosis tool. It is simple, non-invasive, non-irradiating, inexpensive and available at the point of care (POCUS). Most emergency physicians and many other specialists (pneumologists, infectious disease and intensive care physicians) are trained to perform lung-POCUS (LUS-POCUS) and use it in their everyday practice. Multiple studies have demonstrated its superiority to chest X-ray in detecting pneumonia [13]. In ARDS, a scoring system has been developed and has shown good correlation with mortality [14,15]. LUS-POCUS is highly effective in detecting peripheral patterns and seems appropriate to examine COVID-19 patients.
Aims and hypothesis

Our main hypothesis is that LUS-POCUS performed during the initial examination may identify high-risk COVID-19 patients and lead to close monitoring of those patients. The key secondary aim is to evaluate the risk of unfavourable outcome over time and whether LUS-POCUS performances vary depending on time. The other secondary aim is to determine risk stratification threshold values and classify three levels of risk: low-risk, intermediate-risk and high-risk patients. We will compare this to CT scan risk stratification performances and the type of lesions. The final secondary aim is to evaluate if adding value of LUS-POCUS score to previous risk stratification clinical rules (qSOFA, CRB65 and CURB 65) that have been developed in order to predict death of adult patients with COVID-19 [16], making it possible to identify more precisely high-risk patients.

METHODS/DESIGN

Study Design

Point-of-care ultrasonography for risk stratification of COVID-19 patients (POCUSCO) is a non-interventional, prospective, multicentre study conducted by Angers University Hospital (France) and led in 11 participating centres across France and Belgium. The study was registered with ClinicalTrials.gov on 4 April 2020.

Study settings and population

Participation in the study is proposed to patients referred to or hospitalised in one of the 11 participating centres from France and Belgium. Patients are screened, and if the patients fulfil all inclusion criteria and none of the study’s non-inclusion criteria, written information is given, and non-opposition consent is collected. Patients are treated as standard. A systematic lung ultrasonography exam is performed on every study patient and a LUS-POCUS score ranging from 0 to 36 points is given. If a chest CT scan is performed, the result is collected in addition to, in particular, the quantification of the extent of pulmonary lesions in percentage from 0% to 100%, carried out according to the recommendations of the French Society of Radiology [8]. Patient then either returns home or is hospitalised. For hospitalised patients, if possible, a second chest ultrasonography is performed on day 5 +/- 3 days. The extent of lung damage is assessed by the LUS-POCUS score. A follow-up is carried out on day 14 and the patient’s status according to the Ordinal Scale for Clinical Improvement for COVID-19 from the WHO is recorded [17].
**Inclusion criteria**

For this study, adult patients (\(\geq 18\) years old) with COVID-19 that is confirmed by positive SARS-CoV-2 RT-PCR, suggested by typical CT scan lesions or considered as probable by the in-charge physician are recruited. Patients should not require respiratory assistance and/or other intensive care and should not be subject to a limitation of treatments. Patients must also be beneficiaries of a social security scheme in order to be included.

**Non-inclusion criteria**

Exclusion criteria include refusal to participate, inability to follow up at day 14 and any conditions making lung ultrasonography impossible (body mass index \(> 35\) kg/m\(^2\), history of pneumonectomy, etc.).

**Lung point-of-care ultrasonography (LUS-POCUS)**

Lung POCUS is performed by trained practitioners with ultrasound scanners using the following parameters: low frequency (2-5 MHz) transductors, convex (abdominal transductors) or small linear (cardiac transductors) type probes that optimally explore at the thoracic depth from 6 cm to 10 cm. This includes patient LUS-POCUS performed within 48 hours following admission to the emergency department. Considering the COVID-19 pandemic, special protective precautions are respected to limit the risk of contamination between the patient and the operator (disposable single-use personal protective equipment, single-use ultrasound probe protection covers, cleaning and anti-viral disinfection before and after each use). LUS-POCUS is performed using the BLUE-PLUS Protocol 12 regions method [15] investigated in a semi-recumbent or supine position (figure 1, panel A). All intercostal spaces of the upper and lower parts of the anterior, lateral and posterior regions of the left and right chest walls were examined, resulting in 12 areas of investigation. Four ultrasound aeration patterns are defined [14,18] (figure 1, panel B): *profile 0 or normal aeration*: line sliding sign associated with respiratory movement or less than 3 B lines; *profile 1 or moderate loss of lung aeration*: a clear number of multiple visible B lines with horizontal spacing between adjacent B lines \(\leq 7\) mm (B1 lines); *profile 2 or severe loss of lung aeration*: multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines \(\leq 3\) mm, including “white lung”; and *profile 3 or pulmonary consolidation*: hyperechoic lung tissue, accompanied by dynamic air bronchogram. The LUS-POCUS score is determined by allocating 0, 1, 2 or 3 points to profiles 0, 1, 2 or 3 respectively in every area. Each of the 12 lung areas is examined and the final LUS-POCUS score of the patient is the sum of each regional ultrasound score (ranging from 0 to 36 points). We also determine the presence of pleural effusion, or absence thereof, for each hemithorax.
Primary outcome

The primary outcome is the occurrence of death, regardless of cause, or the use of intubation or invasive ventilation within the 14 days (day 14) following inclusion. The ability of POCUS to detect the primary outcome occurrence will be evaluated by determining the 95% confidence interval of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. LUS-POCUS prognostic value will be considered as clinically relevant if the lower bound of the 95% confidence interval is equal or greater than 0.7.

Secondary outcomes

The secondary outcomes include the following parameters:

- The risk of unfavourable outcome (occurrence of death or the use of intubation or invasive ventilation) over time – i.e. the LUS-POCUS performances according to the delay of outcome assessment. This involves evaluating, in patients with a confirmed or probable SARS-CoV-2 infection, whether LUS-POCUS score performances vary depending on time, between day 1 and day 14, and, if so, until which time horizon its performances are clinically relevant. For this purpose, we will determine the period for which the lower limit of the 95% confidence interval of the AUC of the LUS-POCUS score ROC curve is at least 0.7.

- The risk stratification threshold values of LUS-POCUS score defining three risk groups: low-risk patients, intermediate-risk patients, and high-risk patients. For this purpose, we will determine two threshold values on the inflection points of the ROC curve: first maximising the specificity for a sensitivity of at least 95%, second maximising the sensitivity for a specificity of at least 95%.

- Effect of adding LUS-POCUS score value to previous several risk stratification clinical rules for pulmonary infection or sepsis: qSOFA, CRB 65 and CURB 65. For this purpose, we will attribute 0, 1 or 2 points to LUS-POCUS score according to the two predefined threshold values and will assess: sensitivities of qSOFA with and without addition of LUS-POCUS score result; specificities of qSOFA with and without addition of LUS-POCUS score result; sensitivities of CRB 65 with and without addition of LUS-POCUS score result; specificities of CRB 65 with and without addition of LUS-POCUS score result; sensitivities of CRB 65 with and without addition of LUS-POCUS score result; specificities of CRB 65 with and without addition of LUS-POCUS score result.

- The capacity of the initial LUS-POCUS score to predict clinical status using the World Health Organization (WHO) nine-point Ordinal Scale for Clinical Improvement for COVID-19 [17] depending
on time. A linear mixed model will be performed evaluating the WHO clinical status by t0 LUS-POCUS score and time. A random effect variable corresponding to the individual level will be included in such a model.

- The correlation between LUS-POCUS and CT scan assessment of lung damage. For this purpose, we will determine the intra-class correlation coefficient between LUS-POCUS assessment according to the number of affected areas from a total of 12 and CT scan assessment according to the quantification proposed by the French Society of Radiology: 0 - normal; 1 - minor (< 10%), 2 - moderate (10%-25%), 3 - significant (25%-50%), 4 - severe (50%-75%), 5 - critical (> 75%) [19,20].

- The comparison of LUS-POCUS performances with that of chest computed tomography to identify patients with an unfavourable outcome. For this purpose, we will compare the AUC of the ROC curves of LUS-POCUS score and CT scan quantification of lung damage to identify patients with an unfavourable outcome (need for intubation and mechanical ventilation or death) at day 14.

- LUS-POCUS score evolution performances in the subgroup of hospitalised patients having a second chest ultrasonography at day 5 +/- 3 days of inclusion. We will assess the performances of the LUS-POCUS score evolution between the first and the second assessment in identifying patients with unfavourable outcome (intubation and mechanical ventilation requirement or death). For this purpose, we will calculate the delta between the first and second LUS-POCUS score and determine the AUC of the ROC curve and its 95% confidence interval.

- LUS-POCUS score performances ability to predict the risk of unfavourable outcome in the subgroup of patients with positive SARS-CoV-2 RT-PCR results.

*Participant timeline*

Study participation duration for a participant is 14 days.

*Sample size*

To study diagnostic performances of lung ultrasound to identify high-risk patients, we will determine the 95% confidence interval of the AUC of the ROC curve and consider LUS-POCUS capacity as clinically relevant if the lower limit of the 95% confidence interval is at least 0.7. This is assuming that the observed AUC will be 0.8. Based on data from COVID-19 in China, the rate of death or need for tracheal intubation is estimated at 20% in high-risk patients. As severely ill critical patients are excluded of our study, we estimate that this rate will be around 10%. Therefore, a headcount of 286 patients must be studied to demonstrate, under a bilateral hypothesis, a significant AUC of 0.80 with
an alpha risk of 5% and a power of 80%. Taking into consideration patients lost to follow up and those who cannot be evaluated (estimated at 5%), it is necessary to include 300 patients in total.

**Recruitment**

Inclusions started on 10 April 2020 in Angers University Hospital and 11 centres had included at least one patient by 18 April 2020. Taking into account the number of participating centres (11) and the evolution of COVID-19, the estimated duration of inclusion is 3 months.

**Data collection, management, and analysis**

**Data collection and management**

All data related to this study are collected using a standardised electronic case report form (eCRF) and based on valid documents (patient medical record). In the eCRF and follow-up calls, patients can be identified by a unique number composed of the centre number and the patient number at the centre. The confidentiality of patients and their personal health information is always maintained by restricting access to patient records and eCRF.

**Statistical analysis**

Many different data sets are described in this study. Quantitative data is described using means and standard deviations and compared with Student t-test. Qualitative data are described using numbers and percentages and compared with $X^2$ Pearson-test. LUS-POCUS properties to predict unfavourable outcome over time is estimated by calculating the area under the curve (AUC) and its 95% confidence interval. In cases of significant properties to predict worsening (lower limit of the AUC greater than or equal to 0.7), two thresholds will be calculated. The first will maximise specificity with a sensitivity greater than or equal to 95% and the second will maximise sensitivity with a specificity greater than or equal to 95%. Sensitivity and specificity will be estimated by the 632+ bootstrap method. Other diagnostic parameters will also be estimated by AUCs. Dynamic changes of LUS-POCUS diagnostic properties will be realised depending on the time AUC and also its 95% confidence interval. Comparison of quantitative estimates of pulmonary damage between CT scan and LUS-POCUS methods will be assessed using intra-class correlation coefficient and its 95% intra-class coefficient. The association between the LUS-POCUS score at day 0, time and the clinical status of patients at day 14 according to the WHO Ordinal Scale for Clinical Improvement for COVID-19 patients will be assessed by using linear mixed models including t0 and time LUS-POCUS score as fixed effects and patients as random effect. AUCs and correlation coefficients will be interpreted in cases of...
sufficiently precise estimates (size of the 95% interval confidence greater than or equal to 0.3). To study the impact of adding the result of LUS-POCUS evaluation to several risk stratification clinical rules for pulmonary infection or sepsis (qSOFA, CRB 65 and CURB 65), AUCs will be compared with or without its component with a DeLong test.

Ethics and dissemination

Legal obligations and approval

The sponsor of the study is CHU d’Angers (Angers University Hospital). The sponsor obtained prior approval from the Comité de Protection des Personnes (CPP) du Sud-Ouest et Outre-Mer 2 (n°ID-RCB: 2020-A00782-37 / 2-20-025 id7566, 3 April 2020) and the Belgian Comité d’Ethique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc (2020/14AVR/223, 15 April 2020). The Declaration of Helsinki and the Good Clinical Practice guidelines will be respected by the study. The coordinating investigator can make an amendment after submission to the sponsor, and approval from the CPP. After complying with these different stages, the amendment will be implemented.

Dissemination of results

Considering the ongoing COVID-19 pandemic, the main result of the study regarding the lung ultrasound performances to predict unfavourable development will be deposited on a preprint server and presented in a peer-reviewed journal as soon as possible. The full results of the study will be presented in national and international meetings and in peer-reviewed journals.

Trial status

Inclusions started on 10 April 2020.
DISCUSSION

This study protocol describes, to our knowledge, the first prospective, multi-centre study evaluating point-of-care ultrasonography for risk stratification of COVID-19 patients.

While the usefulness of ultrasound for standard organ examinations has been shown and unanimously accepted for a long time, the lung ultrasound has traditionally been excluded from this repertoire [21]. Ultrasound techniques have expanded, and their usefulness has been gradually demonstrated and democratised worldwide by the works of Lichtenstein et al. [15,18] and Volpicelli et al. [22,23].

Many articles have been published on this topic in the context of the COVID-19 pandemic but mostly based on expert opinion without evidence based data [24–27]. Buonsenso et al. even suggest that lung ultrasounds could replace stethoscopes in the ongoing COVID-19 pandemic, which could possibly reduce the risk of exposure of healthcare workers [28]. Its main advantages for COVID-19 can be seen [25] in the following stages: 1. triage (pneumonia/non-pneumonia) of symptomatic patients at home as well as in the prehospital phase; 2. diagnostic suspicion and awareness in the emergency department setting; 3. treatment of intensive care unit patients with regard to ventilation and weaning. Therefore, as highlighted by Soldati et al. [25], studies aimed at clarifying the diagnostic and prognostic role of lung POCUS in COVID-19 are urgently needed. This is the principal aim of our study.

CT scan is considered as the best imaging test to assess COVID-19 patients but is expensive, time consuming and may lead to several adverse effects [8–10]. POCUSCO will allow assessment of the correlation between LUS-POCUS and lung CT scan results and comparison of their performances.

Lung ultrasound will also likely make it possible to monitor the clinical course of COVID-19 patients and the effects of therapeutic measures [29]. This is the reason why we designed our study by integrating a monitoring ultrasound at day 5 +/- 3.

The potential advantages of LUS-POCUS are important, especially versus lung CT scan. However, the scientific community warns us about its limitations and pitfalls [30,31], meaning that we need an adequately designed study to determine the limits and advantages of this tool. POCUSCO may likely provide part of the expected answers.

The POCUSCO study results are particularly anticipated and after the protocol was reviewed and approved by French and Belgian Ethics Committee, recruitment began on 10 April 2020. The results are anticipated for the end of June 2020.
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FOOTNOTES

Authors’ contributions: FM, PMR, VD, JFH and DD conceived and designed the study. All authors participated in the design of POCUSCO and contributed to revisions of the original manuscript. JFH performed the statistical plan and sample size calculation. All authors edited the manuscript and read and approved the final manuscript.

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Panel A. Lung Point Of Care Ultrasonography Method

A. Twelve chest areas of investigation following BLUE-PLUS Protocol: zone 1: upper anterior chest wall; zone 2: lower anterior chest wall; zone 3: upper lateral chest wall; zone 4: lower lateral chest wall; zone 5: upper posterolateral chest wall; zone 6: lower posterolateral chest wall

B. LUS-POCUS score grid: Four ultrasound aeration profiles are searched in each zones and points are affected to them according to their severity. Profile 0 or normal aeration (0 point): line sliding sign associated with respiratory movement or less than 3 B lines; Profile 1 or moderate loss of lung aeration (1 point): a clear number of multiple visible B-lines with horizontal spacing between adjacent B lines ≤ 7 mm (B1 lines); Profile 2 or severe loss of lung aeration (2 points): multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines ≤ 3 mm, including “white lung”; and Profile 3 or pulmonary consolidation (3 points): hyperechoic lung tissue, accompanied by dynamic air bronchogram

Panel B. Examples of four ultrasound aeration profiles

a. Profile 0 or normal aeration b. Profile 1 or moderate loss of lung aeration ; c. Profile 2 or severe loss of lung aeration; d. Profile 3 or pulmonary consolidation.

338x190mm (300 x 300 DPI)
# Point-of-care ultrasonography for risk stratification of non-critical COVID-19 patients on admission (POCUSCO): a study protocol of an international study

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TITLE: Point-of-care ultrasonography for risk stratification of non-critical COVID-19 patients on admission (POCUSCO): a study protocol of an international study

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ABSTRACT

Introduction

In the context of the COVID-19 pandemic, early identification of patients who are likely to get worse is a major concern. Severity mainly depends on the development of acute respiratory distress syndrome (ARDS) with a predominance of subpleural lesions. Lung point-of-care ultrasonography (L-POCUS) is highly effective in detecting pulmonary peripheral patterns and may be appropriate for examining COVID-19 patients. We suggest that L-POCUS performed during the initial examination may identify COVID-19 patients who are at a high-risk of complicated treatment or unfavourable evolution.

Methods and analysis

POCUSCO is a prospective, multicentre study. Adult patients visiting the emergency department (ED) of participating centres for suspected or confirmed COVID-19 are assessed for inclusion. Included patients have L-POCUS performed within 48 hours following ED admission. The severity of lung damage is assessed using the L-POCUS score based on 36 points for ARDS. Apart from the L-POCUS score assessment, patients are treated as recommended by the World Health Organization (WHO). If a CT scan is performed, its result is collected. For hospitalised patients, a second L-POCUS is performed at day 5 +/- 3. A follow-up is carried out on day 14 and the patient’s status according to the Ordinal Scale for Clinical Improvement for COVID-19 from the WHO is recorded.

The primary outcome is the rate of patients requiring intubation or who dead from any cause during the 14 days following inclusion. We will determine the area under the ROC curve of L-POCUS.

Ethics and dissemination

The protocol has been approved by the French and Belgian Ethics Committees and is carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study is funding by a grant from the French Health Ministry and its findings will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number: NCT04338100
STRENGTHS AND LIMITATIONS OF THIS STUDY

- Lung ultrasound (L-POCUS) is a simple and non-invasive tool, currently used in everyday clinical practice, that may be an alternative to CT scan as a prognostic tool in patients with suspected or confirmed COVID-19.

- POCUSCO is a prospective cohort study aimed to assess the value of L-POCUS to identify patients who are at a high-risk of adverse clinical outcomes.

- The study will focus on the initial exam of patients with suspected or confirmed mild-to moderate COVID-19.

- The primary outcome, a composite of death or intubation within 14 days after inclusion, is clinical and consensual.

- POCUSCO is, in our knowledge, the first prospective study on this specific topic but its results should be confirmed in a formal implementation trial.
BACKGROUND

The COVID-19 pandemic has developed worldwide in less than 4 months [1,2]. While most patients have a mild or uncomplicated form of the disease (80%), approximately 15% need hospital care and 5% intensive care [3]. Severe cases are characterised by pulmonary involvement which may progress to acute respiratory distress syndrome (ARDS), usually between day 7 and day 10 [4]. Early identification of patients who are likely to get worse is therefore a major concern.

While chest X-ray has poor diagnostic performances [4], pulmonary computed tomography (CT scan) appears to be very sensitive (97%) and quite specific to COVID-19 in patients with clinical suspicion of COVID-19, provided that it is not performed within the first four days after symptom onset [5,6]. A subpleural bilateral ground-glass pattern can precede the positivity of RT-PCR for SARS-CoV-2 [7]. In retrospective studies, quantitative CT scan analysis, using a CT scoring method, seems to accurately assess the severity and predict mortality of COVID-19 patients [8] [9]. Therefore, CT scan is now considered as the best imaging test to assess COVID-19 patients and is recommended as a first-line diagnostic tool by national societies of radiology [10–12]. However, performing CT scans for all or many patients with suspected COVID-19 may result in radiology departments being overwhelmed, especially considering bio-cleaning between patients. Moreover, CT scans may lead to adverse effects including induced cancer due to the cumulative diagnostic irradiation.

Chest ultrasonography may be an alternative to CT scans as a prognosis tool. It is simple, non-invasive, non-irradiating, inexpensive and available at the point of care (POCUS). Most emergency physicians and many other specialists (pneumologists, infectious disease and intensive care physicians) are trained to perform lung-POCUS (L-POCUS) and use it in their everyday practice. Multiple studies have demonstrated its superiority to chest X-ray in detecting pneumonia [13]. In ARDS, a scoring system has been developed and has shown good correlation with mortality [14,15]. L-POCUS is highly effective in detecting peripheral patterns and pleural abnormalities and seems appropriate to examine COVID-19 patients [16]. A recent review confirms that most of patients with COVID-19 have L-POCUS abnormalities in correlation with CT findings and highlights its potential value in help-decision making for triage or follow-up [17]. However, the performances of L-POCUS to predict an unfavourable outcome still unclear and remain to be confirmed in a large prospective study.
Aims and hypothesis

Our main hypothesis is that L-POCUS performed during the initial examination may identify high-risk COVID-19 patients and lead to close monitoring of those patients. The key secondary aim is to evaluate the risk of unfavourable outcome over time and whether L-POCUS performances vary depending on time. The other secondary aim is to determine risk stratification threshold values and classify three levels of risk: low-risk, intermediate-risk and high-risk patients. We will compare this to CT scan risk stratification performances and the type of lesions. The final secondary aim is to evaluate if adding value of L-POCUS score to previous risk stratification clinical rules (qSOFA, CRB65 and CURB 65) that have been developed in order to predict death of adult patients with COVID-19 [18], making it possible to identify more precisely high-risk patients.

METHODS/DESIGN

Study Design

Point-of-care ultrasonography for risk stratification of COVID-19 patients (POCUSCO) is a non-interventional, prospective, multicentre study conducted by Angers University Hospital (France) and led in 11 participating centres across France and Belgium. The study was registered with ClinicalTrials.gov on 4 April 2020.

Study settings and population

Participation in the study is proposed to patients referred to or hospitalised in one of the 11 participating centres from France and Belgium. Patients are screened, and if the patients fulfil all inclusion criteria and none of the study’s non-inclusion criteria, written information is given, and non-opposition consent is collected. A systematic lung ultrasonography exam is performed on every study patient and a L-POCUS score ranging from 0 to 36 points is given. If a chest CT scan is performed, the result is collected in addition to, in particular, the quantification of the extent of pulmonary lesions in percentage from 0% to 100%, carried out according to the recommendations of the French Society of Radiology [10]. Apart from the L-POCUS score assessment, patients are treated as usual according to local procedures in participating hospitals[19]. Patient then either returns home or is hospitalised. For hospitalised patients, if possible, a second chest ultrasonography is performed on day 5 +/- 3 days. The extent of lung damage is assessed by the L-POCUS score. A follow-up is carried out on day 14 and the patient’s status according to the Ordinal Scale for Clinical Improvement for COVID-19 from the WHO is recorded (Table 1) [20].
**Table 1: Organization Scale of Clinical Improvement (OSCI) of the World Health Organization (WHO)**

| Patient state                  | Descriptor                                      | Score |
|-------------------------------|-------------------------------------------------|-------|
| Uninfected                    | No clinical or virological evidence of infection | 0     |
| Ambulatory                    | No limitation of activities                      | 1     |
|                               | Limitation of activities                         | 2     |
| Hospitalized Mild Disease     | Hospitalized, no oxygen therapy                  | 3     |
|                               | Oxygen by mask or nasal prongs                   | 4     |
| Hospitalized Severe Disease   | Non-invasive ventilation or high-flow oxygen      | 5     |
|                               | Intubation and mechanical ventilation            | 6     |
|                               | Ventilation + additional organ support: pressors, renal replacement therapy, ECMO... | 7     |
| Dead                          | Death                                           | 8     |

**Inclusion criteria**

For this study, adult patients (≥ 18 years old) with COVID-19 that is confirmed by positive SARS-CoV-2 RT-PCR, suggested by typical CT scan lesions or considered as probable by the in-charge physician are recruited. Patients should not require respiratory assistance and/or other intensive care and should not be subject to a limitation of treatments. Patients must also be beneficiaries of a social security scheme in order to be included.

**Non-inclusion criteria**

Exclusion criteria include refusal to participate, inability to follow up at day 14 and any conditions making lung ultrasonography impossible (body mass index > 35 kg/m², history of pneumonectomy, etc.).
Lung point-of-care ultrasonography (L-POCUS)

Lung POCUS is performed by trained practitioners with ultrasound scanners using the following parameters: low frequency (2-5 MHz) transducers, convex (abdominal transducers) or small linear (cardiac transducers) type probes that optimally explore at the thoracic depth from 6 cm to 10 cm. This includes patient L-POCUS performed within 48 hours following admission to the emergency department. Considering the COVID-19 pandemic, special protective precautions are respected to limit the risk of contamination between the patient and the operator (disposable single-use personal protective equipment, single-use ultrasound probe protection covers, cleaning and anti-viral disinfection before and after each use). L-POCUS is performed using the BLUE-PLUS Protocol 12 regions method [15] investigated in a semi-recumbent or supine position (figure 1, panel A). All intercostal spaces of the upper and lower parts of the anterior, lateral and posterior regions of the left and right chest walls were examined, resulting in 12 areas of investigation. Four ultrasound aeration stages are defined [14,21] (figure 1, panel B): stage 0 or normal aeration: line sliding sign associated with respiratory movement or less than 3 B lines; stage 1 or moderate loss of lung aeration: a clear number of multiple visible B lines with horizontal spacing between adjacent B lines ≤ 7 mm (B1 lines); stage 2 or severe loss of lung aeration: multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines ≤ 3 mm, including “white lung”; and stage 3 or pulmonary consolidation: hyperechoic lung tissue, accompanied by dynamic air bronchogram. The L-POCUS score is determined by allocating 0, 1, 2 or 3 points to parenchymal aeration stages 0, 1, 2 or 3 respectively in every area. Each of the 12 lung areas is examined and the final L-POCUS aeration score, ranging from 0 to 36 points, is the sum of each regional ultrasound score. We also determine the presence of pleural effusion, or absence thereof, for each hemithorax.

Trial outcomes

Primary outcome

The primary outcome is the occurrence of death, regardless of cause, or the use of intubation or invasive ventilation within the 14 days (day 14) following inclusion. The ability of POCUS to detect the primary outcome occurrence will be evaluated by determining the 95% confidence interval of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. L-POCUS prognostic value will be considered as clinically relevant if the lower bound of the 95% confidence interval is equal or greater than 0.7.
Secondary outcomes

The secondary outcomes include the following parameters:

- The risk of unfavourable outcome (occurrence of death or the use of intubation or invasive ventilation) over time – i.e. the L-POCUS performances according to the delay of outcome assessment. This involves evaluating, in patients with a confirmed or probable SARS-CoV-2 infection, whether L-POCUS score performances vary depending on time, between day 1 and day 14, and, if so, until which time horizon its performances are clinically relevant. For this purpose, we will determine the period for which the lower limit of the 95% confidence interval of the AUC of the L-POCUS score ROC curve is at least 0.7.

- The risk stratification threshold values of L-POCUS score defining three risk groups: low-risk patients, intermediate-risk patients, and high-risk patients. For this purpose, we will determine two threshold values on the inflection points of the ROC curve: first maximising the specificity for a sensitivity of at least 95%, second maximising the sensitivity for a specificity of at least 95%.

- Effect of adding L-POCUS score value to previous several risk stratification clinical rules for pulmonary infection or sepsis: qSOFA, CRB 65 and CURB 65. For this purpose, we will attribute 0, 1 or 2 points to L-POCUS score according to the two predefined threshold values and will assess: sensitivities of qSOFA with and without addition of L-POCUS score result; specificities of qSOFA with and without addition of L-POCUS score result; sensitivities of CRB 65 with and without addition of L-POCUS score result; specificities of CRB 65 with and without addition of L-POCUS score result; sensitivities of CRB 65 with and without addition of L-POCUS score result; specificities of CRB 65 with and without addition of L-POCUS score result.

- The capacity of the initial L-POCUS score to predict clinical status using the World Health Organization (WHO) nine-point Ordinal Scale for Clinical Improvement for COVID-19 [20] depending on time. A linear mixed model will be performed evaluating the WHO clinical status by t 0 L-POCUS score and time. A random effect variable corresponding to the individual level will be included in such a model.

- The correlation between L-POCUS and CT scan assessment of lung damage. For this purpose, we will assess the number of affected areas among the 12 studied with L-POCUS and will classify the extent of lung damage as normal, minor, moderate, significant, severe and critical, for zero, 1 to 2, 3 to 5, 6 to 8, 9 to 10, and 11 to 12 affected areas, respectively.
We will compare this quantification to those observed with CT scan according to the scale proposed by the French Society of Radiology: 0 - normal; 1 - minor (< 10%), 2 - moderate (10%-25%), 3 - significant (25%-50%), 4 - severe (50%-75%), 5 - critical (> 75%)[22,23].

- The comparison of L-POCUS performances with that of chest computed tomography to identify patients with an unfavourable outcome. For this purpose, we will compare the AUC of the ROC curves of L-POCUS score and CT scan quantification of lung damage to identify patients with an unfavourable outcome (need for intubation and mechanical ventilation or death) at day 14.

- L-POCUS score evolution performances in the subgroup of hospitalised patients having a second chest ultrasonography at day 5 +/- 3 days of inclusion. We will assess the performances of the L-POCUS score evolution between the first and the second assessment in identifying patients with unfavourable outcome (intubation and mechanical ventilation requirement or death). For this purpose, we will calculate the delta between the first and second L-POCUS score and determine the AUC of the ROC curve and its 95% confidence interval.

- L-POCUS score performances ability to predict the risk of unfavourable outcome in the subgroup of patients with positive SARS-CoV-2 RT-PCR results.

**Participant timeline**

Study participation duration for a participant is 14 days.

**Sample size**

To study diagnostic performances of lung ultrasound to identify high-risk patients, we will determine the 95% confidence interval of the AUC of the ROC curve and consider L-POCUS capacity as clinically relevant if the lower limit of the 95% confidence interval is at least 0.7. This is assuming that the observed AUC will be 0.8. Based on data from COVID-19 in China, the rate of death or need for tracheal intubation is estimated at 20% in high-risk patients. As severely ill critical patients are excluded of our study, we estimate that this rate will be around 10%. Therefore, a headcount of 286 patients must be studied to demonstrate, under a bilateral hypothesis, a significant AUC of 0.80 with an alpha risk of 5% and a power of 80%. Taking into consideration patients lost to follow up and those who cannot be evaluated (estimated at 5%), it is necessary to include 300 patients in total.
Recruitment

Inclusions started on 10 April 2020 in Angers University Hospital and 11 centres had included at least one patient by 18 April 2020. Taking into account the number of participating centres (11) and the evolution of COVID-19, the estimated duration of inclusion is 3 months.

Patient and Public Involvement:

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Data collection, management, and analysis

Data collection and management

All data related to this study are collected using a standardised electronic case report form (eCRF) and based on valid documents (patient medical record). In the eCRF and follow-up calls, patients can be identified by a unique number composed of the centre number and the patient number at the centre. The confidentiality of patients and their personal health information is always maintained by restricting access to patient records and eCRF.

Statistical analysis

Many different data sets are described in this study. Quantitative data is described using means and standard deviations. Qualitative data are described using numbers and percentages and compared, for proportions of each OSCI status as a function of L-POCUS aeration score or RT-PCR status, with $X^2$ Pearson-test, but no conclusion will be drawn from them. L-POCUS properties to predict unfavourable outcome over time is estimated by calculating the area under the curve (AUC) and its 95% confidence interval. In cases of significant properties to predict worsening (lower limit of the AUC greater than or equal to 0.7), two thresholds will be calculated. The first will maximise specificity with a sensitivity greater than or equal to 95% and the second will maximise sensitivity with a specificity greater than or equal to 95%. Sensitivity and specificity will be estimated by the 632+ bootstrap method. A calibration have also been done, with a comparison of the proportion of patients identified as “at risk of unfavourable outcomes”, and the proportion of patients who actually experienced unfavourable outcomes has been added in the manuscript. Other diagnostic parameters
will also be estimated by AUCs. Dynamic changes of L-POCUS diagnostic properties will be realised depending on the time AUC and also its 95% confidence interval. Comparison of quantitative estimates of pulmonary damage between CT scan and L-POCUS methods will be assessed using intra-class correlation coefficient and its 95% intra-class coefficient. The thresholds for identifying levels of correlations are described follow: < 0.50: poor correlation; 0.50 to 0.75: moderate; 0.75 to 0.90: good and > 0.90: excellent. The association between the L-POCUS score at day 0, time and the clinical status of patients at day 14 according to the WHO Ordinal Scale for Clinical Improvement for COVID-19 patients will be assessed by using linear mixed models including to and time L-POCUS score as fixed effects and patients as random effect. To study the impact of adding the result of L-POCUS evaluation to several risk stratification clinical rules for pulmonary infection or sepsis (qSOFA, CRB 65 and CURB 65), AUCs will be compared with or without its component with a DeLong test.

Ethics and dissemination

Legal obligations and approval

The sponsor of the study is CHU d’Angers (Angers University Hospital). The sponsor obtained prior approval from the Comité de Protection des Personnes (CPP) du Sud-Ouest et Outre-Mer 2 (n° ID-RCB: 2020-A00782-37 / 2-20-025 id7566, 3 April 2020) and the Belgian Comité d’Ethique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc (2020/14AVR/223, 15 April 2020). The Declaration of Helsinki and the Good Clinical Practice guidelines will be respected by the study. The coordinating investigator can make an amendment after submission to the sponsor, and approval from the CPP. After complying with these different stages, the amendment will be implemented.

Dissemination of results

Considering the ongoing COVID-19 pandemic, the main result of the study regarding the lung ultrasound performances to predict unfavourable development will be deposited on a preprint server and presented in a peer-reviewed journal as soon as possible. This study adhere to TRIPOD guidelines, by verifying the 22 items of TRIPOD checklist during the conception of this protocol [24]. The STROBE statement will be used before submitting the manuscript to a journal [25].

The full results of the study will be presented in national and international meetings and in peer-reviewed journals.
Trial status

Inclusions started on 10 April 2020.

DISCUSSION

This study protocol describes a prospective and multi-centre study evaluating point-of-care ultrasonography for risk stratification of COVID-19 patients.

While the usefulness of ultrasound for standard organ examinations has been shown and unanimously accepted for a long time, the lung ultrasound has traditionally been excluded from this repertoire [26]. Ultrasound techniques have expanded, and their usefulness has been gradually demonstrated and democratised worldwide by the works of Lichtenstein et al. [15,21] and Volpicelli et al. [27,28].

Many articles have been published on this topic in the context of the COVID-19 pandemic but mostly based on expert opinion without evidence based data [29–32]. Buonsenso et al. even suggest that lung ultrasounds could replace stethoscopes in the ongoing COVID-19 pandemic, which could possibly reduce the risk of exposure of healthcare workers [33]. Its main advantages for COVID-19 can be seen [30] in the following stages: 1. triage (pneumonia/non-pneumonia) of symptomatic patients at home as well as in the prehospital phase; 2. diagnostic suspicion and awareness in the emergency department setting; 3. treatment of intensive care unit patients with regard to ventilation and weaning. Therefore, as highlighted by Soldati et al. [30], studies aimed at clarifying the diagnostic and prognostic role of lung POCUS in COVID-19 are urgently needed. This is the principal aim of our study.

CT scan is considered as the best imaging test to assess COVID-19 patients but is expensive, time consuming and may lead to several adverse effects [10–12]. POCUSCO will allow assessment of the correlation between L-POCUS and lung CT scan results and comparison of their performances.

Lung ultrasound will also likely make it possible to monitor the clinical course of COVID-19 patients and the effects of therapeutic measures [34]. This is the reason why we designed our study by integrating a monitoring ultrasound at day 5 +/- 3.

The potential advantages of L-POCUS are important, especially versus lung CT scan. However, the scientific community warns us about its limitations and pitfalls [35,36], meaning that we need an adequately designed study to determine the limits and advantages of this tool. POCUSCO may likely provide part of the expected answers.
There are some limitations in the conception of this study. Firstly, at the time we wrote the protocol and on the basis of the first observational studies in China, the expected rate of mortality or intubation and invasive ventilation request was set to 10% [18]. However, recent data have demonstrated mortality rates lower than those observed in the early phases of the epidemic in Wuhan [1,37]. Moreover, the efficacy of some treatments as corticosteroids has been recently proved in COVID-19. [38]. As a result, the rate of our primary outcome may be lower than expected, impairing the powerful of our trial and enlarging the 95% confidence intervals of our estimates. Secondly, as only patients with a mild to moderate COVID-19 will be included, most of them may be discharged home without the possibility to perform a second L-POCUS at day 5 +/- 3 following the inclusion. Therefore, the assessment of the performances of the L-POCUS score evolution may be limited. A final limitation is related to POCUS itself, all operators not having the same level of experience in POCUS realisation and all hospitals not using the same devices [39]. The inter-individual variability in the L-POCUS score grading may then be increase. The L-POCUS performances may be under-evaluated as compared within an expert centre, but our results will show the performances that should be expected in real life care.

The POCUSCO study results are particularly anticipated and after the protocol was reviewed and approved by French and Belgian Ethics Committee, recruitment began on 10 April 2020. The results are anticipated for the end of June 2020.
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FOOTNOTES

**Authors’ contributions:** FM, PMR, VD, JFH and DD conceived and designed the study. FM, PMR, VD, DD, JFH, JR, FD, DS, JRI and CA participated in the design of POCUSCO and contributed to revisions of the original manuscript. JFH, FM and JRI performed the statistical plan and sample size calculation. FM, DD, FD, DS, VD and PMR realized acquisition of data. JFH and FM performed data analysis and interpretation. All authors edited the manuscript and read and approved the final manuscript.

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Figure 1 legend:

Panel A. Lung Point Of Care Ultrasonography Method (L-POCUS)

A. Twelve chest areas of investigation following BLUE-PLUS Protocol: zone 1: upper anterior chest wall; zone 2: lower anterior chest wall; zone 3: upper lateral chest wall; zone 4: lower lateral chest wall; zone 5: upper posterolateral chest wall; zone 6: lower posterolateral chest wall

B. L-POCUS score grid: Four ultrasound parenchymal aeration stages are searched in each zones and points are affected to them according to their severity. Stage 0 or normal aeration (0 point): line sliding sign associated with respiratory movement or less than 3 B lines; Stage 1 or moderate loss of lung aeration (1 point): a clear number of multiple visible B-lines with horizontal spacing between adjacent B lines ≤ 7 mm (B1 lines); Stage 2 or severe loss of lung aeration (2 points): multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines ≤ 3 mm, including “white lung”; and Stage 3 or pulmonary consolidation (3 points): hyperechoic lung tissue, accompanied by dynamic air bronchogram

Panel B. Examples of four ultrasound aeration stages

a. Stage 0 or normal aeration b. Stage 1 or moderate loss of lung aeration; c. Stage 2 or severe loss of lung aeration; d. Stage 3 or pulmonary consolidation.
Figure 1 legend:

Panel A. Lung Point Of Care Ultrasonography Method (L-POCUS)
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## Point-of-care ultrasonography for risk stratification of non-critical COVID-19 patients on admission (POCUSCO): a study protocol of an international study

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TITLE: Point-of-care ultrasonography for risk stratification of non-critical COVID-19 patients on admission (POCUSCO): a study protocol of an international study

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ABSTRACT

Introduction

In the context of the COVID-19 pandemic, early identification of patients who are likely to get worse is a major concern. Severity mainly depends on the development of acute respiratory distress syndrome (ARDS) with a predominance of subpleural lesions. Lung point-of-care ultrasonography (L-POCUS) is highly effective in detecting pulmonary peripheral patterns and may be appropriate for examining COVID-19 patients. We suggest that L-POCUS performed during the initial examination may identify COVID-19 patients who are at a high-risk of complicated treatment or unfavourable evolution.

Methods and analysis

POCUSCO is a prospective, multicentre study. Adult patients visiting the emergency department (ED) of participating centres for suspected or confirmed COVID-19 are assessed for inclusion. Included patients have L-POCUS performed within 48 hours following ED admission. The severity of lung damage is assessed using the L-POCUS score based on 36 points for ARDS. Apart from the L-POCUS score assessment, patients are treated as recommended by the World Health Organization (WHO). For hospitalised patients, a second L-POCUS is performed at day 5 +/- 3. A follow-up is carried out on day 14 and the patient’s status according to the Ordinal Scale for Clinical Improvement for COVID-19 from the WHO is recorded.

The primary outcome is the rate of patients requiring intubation or who dead from any cause during the 14 days following inclusion. We will determine the area under the ROC curve of L-POCUS.

Ethics and dissemination

The protocol has been approved by the French and Belgian Ethics Committees and is carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study is funding by a grant from the French Health Ministry and its findings will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number: NCT04338100
STRENGTHS AND LIMITATIONS OF THIS STUDY

- Lung ultrasound (L-POCUS) is a simple and non-invasive tool, currently used in everyday clinical practice, that may be an alternative to CT scan as a prognostic tool in patients with suspected or confirmed COVID-19.

- POCUSCO is a prospective cohort study aimed to assess the value of L-POCUS to identify patients who are at a high-risk of adverse clinical outcomes.

- The study will focus on the initial exam of patients with suspected or confirmed mild-to-moderate COVID-19.

- The primary outcome, a composite of death or intubation within 14 days after inclusion, is clinical and consensual.

- POCUSCO is, in our knowledge, the first prospective study on this specific topic but its results should be confirmed in a formal implementation trial.
BACKGROUND

The COVID-19 pandemic has developed worldwide in less than 4 months [1,2]. While most patients have a mild or uncomplicated form of the disease (80%), approximately 15% need hospital care and 5% intensive care [3]. Severe cases are characterised by pulmonary involvement which may progress to acute respiratory distress syndrome (ARDS), usually between day 7 and day 10 [4]. Early identification of patients who are likely to get worse is therefore a major concern.

While chest X-ray has poor diagnostic performances [4], pulmonary computed tomography (CT scan) appears to be very sensitive (97%) and quite specific to COVID-19 in patients with clinical suspicion of COVID-19, provided that it is not performed within the first four days after symptom onset [5,6]. A subpleural bilateral ground-glass pattern can precede the positivity of RT-PCR for SARS-CoV-2 [7]. In retrospective studies, quantitative CT scan analysis, using a CT scoring method, seems to accurately assess the severity and predict mortality of COVID-19 patients [8,9]. Therefore, CT scan is now considered as the best imaging test to assess COVID-19 patients and is recommended as a first-line diagnostic tool by national societies of radiology [10–12]. However, performing CT scans for all or many patients with suspected COVID-19 may result in radiology departments being overwhelmed, especially considering bio-cleaning between patients. Moreover, CT scans may lead to adverse effects including induced cancer due to the cumulative diagnostic irradiation.

Chest ultrasonography may be an alternative to CT scans as a prognosis tool. It is simple, non-invasive, non-irradiating, inexpensive and available at the point of care (POCUS). Most emergency physicians and many other specialists (pneumologists, infectious disease and intensive care physicians) are trained to perform lung-POCUS (L-POCUS) and use it in their everyday practice. Multiple studies have demonstrated its superiority to chest X-ray in detecting pneumonia [13]. In ARDS, a scoring system has been developed and has shown good correlation with mortality [14,15]. L-POCUS is highly effective in detecting peripheral patterns and pleural abnormalities and seems appropriate to examine COVID-19 patients [16]. A recent review confirms that most of patients with COVID-19 have L-POCUS abnormalities in correlation with CT findings and highlights its potential value in help-decision making for triage or follow-up [17]. However, the performances of L-POCUS to predict an unfavourable outcome still unclear and remain to be confirmed in a large prospective study.
Aims and hypothesis

Our main hypothesis is that L-POCUS performed during the initial examination may identify high-risk COVID-19 patients and lead to close monitoring of those patients. The key secondary aim is to evaluate the risk of unfavourable outcome over time and whether L-POCUS performances vary depending on time. The other secondary aim is to determine risk stratification threshold values and classify three levels of risk: low-risk, intermediate-risk and high-risk patients. The final secondary aim is to evaluate if adding value of L-POCUS score to previous risk stratification clinical rules (qSOFA, CRB65 and CURB 65) that have been developed in order to predict death of adult patients with COVID-19 [18], making it possible to identify more precisely high-risk patients.

METHODS/DESIGN

Study Design

Point-of-care ultrasonography for risk stratification of COVID-19 patients (POCUSCO) is a non-interventional, prospective, multicentre study conducted by Angers University Hospital (France) and led in 11 participating centres across France and Belgium. The study was registered with ClinicalTrials.gov on 4 April 2020.

Study settings and population

Participation in the study is proposed to patients referred to or hospitalised in one of the 11 participating centres from France and Belgium. Patients are screened, and if the patients fulfil all inclusion criteria and none of the study’s non-inclusion criteria, written information is given, and non-opposition consent is collected. A systematic lung ultrasonography exam is performed on every study patient and a L-POCUS score ranging from 0 to 36 points is given. Apart from the L-POCUS score assessment, patients are treated as usual according to local procedures in participating hospitals[19]. Patient then either returns home or is hospitalised. For hospitalised patients, if possible, a second chest ultrasonography is performed on day 5 +/- 3 days. The extent of lung damage is assessed by the L-POCUS score. A follow-up is carried out on day 14 and the patient’s status according to the Ordinal Scale for Clinical Improvement for COVID-19 from the WHO is recorded (Table 1) [20].
Table 1: Organization Scale of Clinical Improvement (OSCI) of the World Health Organization (WHO)

| Patient state               | Descriptor                                           | Score |
|-----------------------------|------------------------------------------------------|-------|
| Uninfected                  | No clinical or virological evidence of infection     | 0     |
| Ambulatory                  | No limitation of activities                          | 1     |
|                             | Limitation of activities                             | 2     |
| Hospitalized Mild Disease   | Hospitalized, no oxygen therapy                      | 3     |
|                             | Oxygen by mask or nasal prongs                       | 4     |
| Hospitalized Severe Disease | Non-invasive ventilation or high-flow oxygen          | 5     |
|                             | Intubation and mechanical ventilation                | 6     |
|                             | Ventilation + additional organ support: pressors, renal replacement therapy, ECMO... | 7     |
| Dead                        | Death                                                | 8     |

Inclusion criteria

For this study, adult patients (≥ 18 years old) with COVID-19 that is confirmed by positive SARS-CoV-2 RT-PCR, suggested by typical CT scan lesions or considered as probable by the in-charge physician are recruited. Patients should not require respiratory assistance and/or other intensive care and should not be subject to a limitation of treatments. Patients must also be beneficiaries of a social security scheme in order to be included.

Non-inclusion criteria

Exclusion criteria include refusal to participate, inability to follow up at day 14 and any conditions making lung ultrasonography impossible (body mass index > 35 kg/m², history of pneumonectomy, etc.).
Lung point-of-care ultrasonography (L-POCUS)

Lung POCUS is performed by trained practitioners with ultrasound scanners using the following parameters: low frequency (2-5 MHz) transducers, convex (abdominal transductors) or small linear (cardiac transductors) type probes that optimally explore at the thoracic depth from 6 cm to 10 cm. This includes patient L-POCUS performed within 48 hours following admission to the emergency department. Considering the COVID-19 pandemic, special protective precautions are respected to limit the risk of contamination between the patient and the operator (disposable single-use personal protective equipment, single-use ultrasound probe protection covers, cleaning and anti-viral disinfection before and after each use). L-POCUS is performed using the BLUE-PLUS Protocol 12 regions method [15] investigated in a semi-recumbent or supine position (figure 1, panel A). All intercostal spaces of the upper and lower parts of the anterior, lateral and posterior regions of the left and right chest walls were examined, resulting in 12 areas of investigation. Four ultrasound aeration stages are defined [14,21] (figure 1, panel B): stage 0 or normal aeration: line sliding sign associated with respiratory movement or less than 3 B lines; stage 1 or moderate loss of lung aeration: a clear number of multiple visible B lines with horizontal spacing between adjacent B lines ≤ 7 mm (B1 lines); stage 2 or severe loss of lung aeration: multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines ≤ 3 mm, including “white lung”; and stage 3 or pulmonary consolidation: hyperechoic lung tissue, accompanied by dynamic air bronchogram. The L-POCUS score is determined by allocating 0, 1, 2 or 3 points to parenchymal aeration stages 0, 1, 2 or 3 respectively in every area. Each of the 12 lung areas is examined and the final L-POCUS aeration score, ranging from 0 to 36 points, is the sum of each regional ultrasound score. We also determine the presence of pleural effusion, or absence thereof, for each hemithorax.

Trial outcomes

Primary outcome

The primary outcome is the occurrence of death, regardless of cause, or the use of intubation or invasive ventilation within the 14 days (day 14) following inclusion. The ability of POCUS to detect the primary outcome occurrence will be evaluated by determining the 95% confidence interval of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. L-POCUS prognostic value will be considered as clinically relevant if the lower bound of the 95% confidence interval is equal or greater than 0.7.

A sensitivity analysis is performed with the 14-day all-cause mortality rate as outcome.
**Secondary outcomes**

The secondary outcomes include the following parameters:

- The risk of unfavourable outcome (occurrence of death or the use of intubation or invasive ventilation) over time – i.e. the L-POCUS performances according to the delay of outcome assessment. This involves evaluating, in patients with a confirmed or probable SARS-CoV-2 infection, whether L-POCUS score performances vary depending on time, between day 1 and day 14, and, if so, until which time horizon its performances are clinically relevant. For this purpose, we will determine the period for which the lower limit of the 95% confidence interval of the AUC of the L-POCUS score ROC curve is at least 0.7.

- The risk stratification threshold values of L-POCUS score defining three risk groups: low-risk patients, intermediate-risk patients, and high-risk patients. For this purpose, we will determine two threshold values: first maximising the specificity for a sensitivity of at least 95%, second maximising the sensitivity for a specificity of at least 95%.

- Effect of adding L-POCUS score value to previous several risk stratification clinical rules for pulmonary infection or sepsis: qSOFA, CRB 65 and CURB 65. For this purpose, we will attribute 0, 1 or 2 points to L-POCUS score according to the two predefined threshold values and will assess the AUCs of qSOFA, CRB 65 and CURB 65 with and without addition of L-POCUS score result.

- The capacity of the initial L-POCUS score to predict clinical status using the World Health Organization (WHO) nine-point Ordinal Scale for Clinical Improvement for COVID-19 at Day 14 [20].

- L-POCUS score evolution performances in the subgroup of hospitalised patients having a second chest ultrasonography at day 5 +/- 3 days of inclusion. We will assess the performances of the L-POCUS score evolution between the first and the second assessment in identifying patients with unfavourable outcome (intubation and mechanical ventilation requirement or death). For this purpose, we will calculate the delta between the first and second L-POCUS score and determine the AUC of the ROC curve and its 95% confidence interval.

- L-POCUS score performances ability to predict the risk of unfavourable outcome in the subgroup of patients with positive SARS-CoV-2 RT-PCR results.

**Participant timeline**

Study participation duration for a participant is 14 days.

**Sample size**
To study diagnostic performances of lung ultrasound to identify high-risk patients, we will determine the 95% confidence interval of the AUC of the ROC curve and consider L-POCUS capacity as clinically relevant if the lower limit of the 95% confidence interval is at least 0.7. This is assuming that the observed AUC will be 0.8. Based on data from COVID-19 in China, the rate of death or need for tracheal intubation is estimated at 20% in high-risk patients. As severely ill critical patients are excluded from our study, we estimate that this rate will be around 10%. Therefore, assuming a rate of death or tracheal intubation requirement of 10%, and expecting an AUC of 0.8, the number of patients required to achieve a lower limit of the 95% confidence interval upper than 0.7 was estimated to 286. Taking into consideration patients lost to follow up and those who cannot be evaluated (estimated at 5%), it is necessary to include 300 patients in total.

Recruitment

Inclusions started on 10 April 2020 in Angers University Hospital and 11 centres had included at least one patient by 18 April 2020. Taking into account the number of participating centres (11) and the evolution of COVID-19, the estimated duration of inclusion is 3 months.

Patient and Public Involvement:

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Data collection, management, and analysis

Data collection and management

All data related to this study are collected using a standardised electronic case report form (eCRF) and based on valid documents (patient medical record). In the eCRF and follow-up calls, patients can be identified by a unique number composed of the centre number and the patient number at the centre. The confidentiality of patients and their personal health information is always maintained by restricting access to patient records and eCRF.

Statistical analysis

Many different data sets are described in this study. Quantitative data is described using means and standard deviations. Qualitative data are described using numbers, percentages and 95% confidence
intervals. L-POCUS properties to predict unfavourable outcome over time is estimated by calculating the area under the curve (AUC) and its 95% confidence interval. In cases of significant properties to predict worsening (lower limit of the AUC greater than or equal to 0.7), two thresholds will be calculated. The first will maximise specificity with a sensitivity greater than or equal to 95% and the second will maximise sensitivity with a specificity greater than or equal to 95%. Sensitivity and specificity will be estimated by the 632+ bootstrap method. Calibration will be assessed with the Hosmer-Lemeshow goodness-of-fit statistic. A Brier score will be also reported, summarizing the magnitude of error in the probability forecasts between 0.0 and 1.0, where a perfectly calibrated model would score 0.0. Other diagnostic parameters will also be estimated by AUCs. Dynamic changes of L-POCUS diagnostic properties will be realised depending on the time AUC and also its 95% confidence interval. The association between the L-POCUS score at day 0 and the clinical status of patients at day 14 according to the WHO Ordinal Scale for Clinical Improvement for COVID-19 patients will be assessed by using the Spearman rank’s correlation coefficient. To study the impact of adding the result of L-POCUS evaluation to several risk stratification clinical rules for pulmonary infection or sepsis (qSOFA, CRB 65 and CURB 65), AUCs will be compared with or without its component with a DeLong test.

**Ethics and dissemination**

**Legal obligations and approval**

The sponsor of the study is CHU d’Angers (Angers University Hospital). The sponsor obtained prior approval from the Comité de Protection des Personnes (CPP) du Sud-Ouest et Outre-Mer 2 (n°ID-RCB: 2020-A00782-37 / 2-20-025 id7566, 3 April 2020) and the Belgian Comité d’Ethique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc (2020/14AVR/223, 15 April 2020). The Declaration of Helsinki and the Good Clinical Practice guidelines will be respected by the study. The coordinating investigator can make an amendment after submission to the sponsor, and approval from the CPP. After complying with these different stages, the amendment will be implemented.

**Dissemination of results**

Considering the ongoing COVID-19 pandemic, the main result of the study regarding the lung ultrasound performances to predict unfavourable development will be deposited on a preprint server and presented in a peer-reviewed journal as soon as possible. This study adhere to TRIPOD guidelines, by verifying the 22 items of TRIPOD checklist during the conception of this protocol[22]. The STROBE statement will be used before submitting the manuscript to a journal [23].
The full results of the study will be presented in national and international meetings and in peer-reviewed journals.

**Trial status**

Inclusions started on 10 April 2020.

**DISCUSSION**

This study protocol describes a prospective and multi-centre study evaluating point-of-care ultrasonography for risk stratification of COVID-19 patients.

While the usefulness of ultrasound for standard organ examinations has been shown and unanimously accepted for a long time, the lung ultrasound has traditionally been excluded from this repertoire [24]. Ultrasound techniques have expanded, and their usefulness has been gradually demonstrated and democratised worldwide by the works of Lichtenstein et al. [15,21] and Volpicelli et al. [25,26].

Many articles have been published on this topic in the context of the COVID-19 pandemic but mostly based on expert opinion without evidence based data [27–30]. Buonsenso et al. even suggest that lung ultrasounds could replace stethoscopes in the ongoing COVID-19 pandemic, which could possibly reduce the risk of exposure of healthcare workers [31]. Its main advantages for COVID-19 can be seen [28] in the following stages: 1. triage (pneumonia/non-pneumonia) of symptomatic patients at home as well as in the prehospital phase; 2. diagnostic suspicion and awareness in the emergency department setting; 3. treatment of intensive care unit patients with regard to ventilation and weaning. Therefore, as highlighted by Soldati et al. [28], studies aimed at clarifying the diagnostic and prognostic role of lung POCUS in COVID-19 are urgently needed. This is the principal aim of our study.

Lung ultrasound will also likely make it possible to monitor the clinical course of COVID-19 patients and the effects of therapeutic measures [32]. This is the reason why we designed our study by integrating a monitoring ultrasound at day 5 +/- 3.

The potential advantages of L-POCUS are important, especially versus lung CT scan. However, the scientific community warns us about its limitations and pitfalls [33,34], meaning that we need an adequately designed study to determine the limits and advantages of this tool. POCUSCO may likely provide part of the expected answers.
There are some limitations in the conception of this study. Firstly, at the time we wrote the protocol and on the basis of the first observational studies in China, the expected rate of mortality or intubation and invasive ventilation request was set to 10% [18]. However, recent data have demonstrated mortality rates lower than those observed in the early phases of the epidemic in Wuhan [1,35]. Moreover, the efficacy of some treatments as corticosteroids has been recently proved in COVID-19 [36]. As a result, the rate of our primary outcome may be lower than expected, impairing the powerful of our trial and enlarging the 95% confidence intervals of our estimates.

Secondly, as only patients with a mild to moderate COVID-19 will be included, most of them may be discharged home without the possibility to perform a second L-POCUS at day 5 +/- 3 following the inclusion. Therefore, the assessment of the performances of the L-POCUS score evolution may be limited. A final limitation is related to POCUS itself, all operators not having the same level of experience in POCUS realisation and all hospitals not using the same devices [37]. The inter-individual variability in the L-POCUS score grading may then be increase. The L-POCUS performances may be under-evaluated as compared within an expert centre, but our results will show the performances that should be expected in real life care.

The POCUSCO study results are particularly anticipated and after the protocol was reviewed and approved by French and Belgian Ethics Committee, recruitment began on 10 April 2020. The results are anticipated for the end of June 2020.
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FOOTNOTES

Authors’ contributions: FM, PMR, VD, JFH and DD conceived and designed the study. FM, PMR, VD, DD, JFH, JR, FD, DS, JRI and CA participated in the design of POCUSCO and contributed to revisions of the original manuscript. JFH, FM and JRI performed the statistical plan and sample size calculation. FM, DD, FD, DS, VD and PMR realized acquisition of data. JFH and FM performed data analysis and interpretation. All authors edited the manuscript and read and approved the final manuscript.

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Fig. 1: *A. Lung Point Of Care Ultrasonography Method (L-POCUS)*

- **Twelve chest areas of investigation following BLUE-PLUS Protocol:** *zone 1*: upper anterior chest wall; *zone 2*: lower anterior chest wall; *zone 3*: upper lateral chest wall; *zone 4*: lower lateral chest wall; *zone 5*: upper posterolateral chest wall; *zone 6*: lower posterolateral chest wall

- **L-POCUS score grid:** Four ultrasound parenchymal aeration stages are searched in each zones and points are affected to them according to their severity. *Stage 0 or normal aeration (0 point):* line sliding sign associated with respiratory movement or less than 3 B lines; *Stage 1 or moderate loss of lung aeration (1 point):* a clear number of multiple visible B-lines with horizontal spacing between adjacent B lines ≤ 7 mm (B1 lines); *Stage 2 or severe loss of lung aeration (2 points):* multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines ≤ 3 mm, including “white lung”; and *Stage 3 or pulmonary consolidation (3 points):* hyperechoic lung tissue, accompanied by dynamic air bronchogram

*Panel B. Examples of four ultrasound aeration stages*

- **Stage 0 or normal aeration**
- **Stage 1 or moderate loss of lung aeration**
- **Stage 2 or severe loss of lung aeration**
- **Stage 3 or pulmonary consolidation**
Figure 1 legend:

Panel A. Lung Point Of Care Ultrasonography Method (L-POCUS)
A. Twelve chest areas of investigation following BLUE-PLUS Protocol: zone 1: upper anterior chest wall; zone 2: lower anterior chest wall; zone 3: upper lateral chest wall; zone 4: lower lateral chest wall; zone 5: upper posterolateral chest wall; zone 6: lower posterolateral chest wall
B. L-POCUS score grid: Four ultrasound parenchymal aeration stages are searched in each zones and points are affected to them according to their severity. Stage 0 or normal aeration (0 point): line sliding sign associated with respiratory movement or less than 3 B lines; Stage 1 or moderate loss of lung aeration (1 point): a clear number of multiple visible B-lines with horizontal spacing between adjacent B lines ≤ 7 mm (B1 lines); Stage 2 or severe loss of lung aeration (2 points): multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines ≤ 3 mm, including "white lung"; and Stage 3 or pulmonary consolidation (3 points): hyperechoic lung tissue, accompanied by dynamic air bronchogram

Panel B. Examples of four ultrasound aeration stages
a. Stage 0 or normal aeration b. Stage 1 or moderate loss of lung aeration ; c. Stage 2 or severe loss of lung aeration; d. Stage 3 or pulmonary consolidation.
# Point-of-care ultrasonography for risk stratification of non-critical COVID-19 patients on admission (POCUSCO): a study protocol of an international study

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TITLE: Point-of-care ultrasonography for risk stratification of non-critical COVID-19 patients on admission (POCUSCO): a study protocol of an international study

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ABSTRACT

Introduction

In the context of the COVID-19 pandemic, early identification of patients who are likely to get worse is a major concern. Severity mainly depends on the development of acute respiratory distress syndrome (ARDS) with a predominance of subpleural lesions. Lung point-of-care ultrasonography (L-POCUS) is highly effective in detecting pulmonary peripheral patterns and may be appropriate for examining COVID-19 patients. We suggest that L-POCUS performed during the initial examination may identify COVID-19 patients who are at a high-risk of complicated treatment or unfavourable evolution.

Methods and analysis

POCUSCO is a prospective, multicentre study. Adult patients visiting the emergency department (ED) of participating centres for suspected or confirmed COVID-19 are assessed for inclusion. Included patients have L-POCUS performed within 48 hours following ED admission. The severity of lung damage is assessed using the L-POCUS score based on 36 points for ARDS. Apart from the L-POCUS score assessment, patients are treated as recommended by the World Health Organization (WHO). For hospitalised patients, a second L-POCUS is performed at day 5 +/- 3. A follow-up is carried out on day 14 and the patient’s status according to the Ordinal Scale for Clinical Improvement for COVID-19 from the WHO is recorded.

The primary outcome is the rate of patients requiring intubation or who dead from any cause during the 14 days following inclusion. We will determine the area under the ROC curve of L-POCUS.

Ethics and dissemination

The protocol has been approved by the French and Belgian Ethics Committees and is carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study is funding by a grant from the French Health Ministry and its findings will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number: NCT04338100
STRENGTHS AND LIMITATIONS OF THIS STUDY

- Lung ultrasound (L-POCUS) is a simple and non-invasive tool, currently used in everyday clinical practice, that may be an alternative to CT scan as a prognostic tool in patients with suspected or confirmed COVID-19.

- POCUSCO is a prospective cohort study aimed to assess the value of L-POCUS to identify patients who are at a high-risk of adverse clinical outcomes.

- The study will focus on the initial exam of patients with suspected or confirmed mild-to moderate COVID-19.

- The primary outcome, a composite of death or intubation within 14 days after inclusion, is clinical and consensual.

- POCUSCO is, in our knowledge, the first prospective study on this specific topic but its results should be confirmed in a formal implementation trial.
BACKGROUND

The COVID-19 pandemic has developed worldwide in less than 4 months [1,2]. While most patients have a mild or uncomplicated form of the disease (80%), approximately 15% need hospital care and 5% intensive care [3]. Severe cases are characterised by pulmonary involvement which may progress to acute respiratory distress syndrome (ARDS), usually between day 7 and day 10 [4]. Early identification of patients who are likely to get worse is therefore a major concern.

While chest X-ray has poor diagnostic performances [4], pulmonary computed tomography (CT scan) appears to be very sensitive (97%) and quite specific to COVID-19 in patients with clinical suspicion of COVID-19, provided that it is not performed within the first four days after symptom onset [5,6]. A subpleural bilateral ground-glass pattern can precede the positivity of RT-PCR for SARS-CoV-2 [7]. In retrospective studies, quantitative CT scan analysis, using a CT scoring method, seems to accurately assess the severity and predict mortality of COVID-19 patients [8,9]. Therefore, CT scan is now considered as the best imaging test to assess COVID-19 patients and is recommended as a first-line diagnostic tool by national societies of radiology [10–12]. However, performing CT scans for all or many patients with suspected COVID-19 may result in radiology departments being overwhelmed, especially considering bio-cleaning between patients. Moreover, CT scans may lead to adverse effects including induced cancer due to the cumulative diagnostic irradiation.

Chest ultrasonography may be an alternative to CT scans as a prognosis tool. It is simple, non-invasive, non-irradiating, inexpensive and available at the point of care (POCUS). Most emergency physicians and many other specialists (pneumologists, infectious disease and intensive care physicians) are trained to perform lung-POCUS (L-POCUS) and use it in their everyday practice. Multiple studies have demonstrated its superiority to chest X-ray in detecting pneumonia [13]. In ARDS, a scoring system has been developed and has shown good correlation with mortality [14,15]. L-POCUS is highly effective in detecting peripheral patterns and pleural abnormalities and seems appropriate to examine COVID-19 patients [16]. A recent review confirms that most of patients with COVID-19 have L-POCUS abnormalities in correlation with CT findings and highlights its potential value in help-decision making for triage or follow-up [17]. However, the performances of L-POCUS to predict an unfavourable outcome still unclear and remain to be confirmed in a large prospective study.
Aims and hypothesis

Our main hypothesis is that L-POCUS performed during the initial examination may identify high-risk COVID-19 patients and lead to close monitoring of those patients. The key secondary aim is to evaluate the risk of unfavourable outcome over time and whether L-POCUS performances vary depending on time. The other secondary aim is to determine risk stratification threshold values and classify three levels of risk: low-risk, intermediate-risk and high-risk patients. The final secondary aim is to evaluate if adding value of L-POCUS score to previous risk stratification clinical rules (qSOFA, CRB65 and CURB 65) that have been developed in order to predict death of adult patients with COVID-19 [18], making it possible to identify more precisely high-risk patients.

METHODS/DESIGN

Study Design

Point-of-care ultrasonography for risk stratification of COVID-19 patients (POCUSCO) is a non-interventional, prospective, multicentre study conducted by Angers University Hospital (France) and led in 11 participating centres across France and Belgium. The study was registered with ClinicalTrials.gov on 4 April 2020.

Study settings and population

Participation in the study is proposed to patients referred to or hospitalised in one of the 11 participating centres from France and Belgium. Patients are screened, and if the patients fulfil all inclusion criteria and none of the study’s non-inclusion criteria, written information is given, and non-opposition consent is collected. A systematic lung ultrasonography exam is performed on every study patient and a L-POCUS score ranging from 0 to 36 points is given. Apart from the L-POCUS score assessment, patients are treated as usual according to local procedures in participating hospitals[19]. Patient then either returns home or is hospitalised. For hospitalised patients, if possible, a second chest ultrasonography is performed on day 5 +/- 3 days. The extent of lung damage is assessed by the L-POCUS score. A follow-up is carried out on day 14 and the patient’s status according to the Ordinal Scale for Clinical Improvement for COVID-19 from the WHO is recorded (Table 1) [20].
Table 1: Organization Scale of Clinical Improvement (OSCI) of the World Health Organization (WHO)

| Patient state            | Descriptor                                      | Score |
|--------------------------|-------------------------------------------------|-------|
| Uninfected               | No clinical or virological evidence of infection | 0     |
| Ambulatory               | No limitation of activities                      | 1     |
|                          | Limitation of activities                         | 2     |
| Hospitalized Mild Disease| Hospitalized, no oxygen therapy                  | 3     |
|                          | Oxygen by mask or nasal prongs                   | 4     |
| Hospitalized Severe Disease| Non-invasive ventilation or high-flow oxygen   | 5     |
|                          | Intubation and mechanical ventilation            | 6     |
|                          | Ventilation + additional organ support: pressors, renal replacement therapy, ECMO... | 7     |
| Dead                     | Death                                           | 8     |

Inclusion criteria

For this study, adult patients (≥ 18 years old) with COVID-19 that is confirmed by positive SARS-CoV-2 RT-PCR, suggested by typical CT scan lesions or considered as probable by the in-charge physician are recruited. Patients should not require respiratory assistance and/or other intensive care and should not be subject to a limitation of treatments. Patients must also be beneficiaries of a social security scheme in order to be included.

Non-inclusion criteria

Exclusion criteria include refusal to participate, inability to follow up at day 14 and any conditions making lung ultrasonography impossible (body mass index > 35 kg/m², history of pneumonectomy, etc.).
Lung point-of-care ultrasonography (L-POCUS)

Lung POCUS is performed by trained practitioners with ultrasound scanners using the following parameters: low frequency (2-5 MHz) transductors, convex (abdominal transductors) or small linear (cardiac transductors) type probes that optimally explore at the thoracic depth from 6 cm to 10 cm. This includes patient L-POCUS performed within 48 hours following admission to the emergency department. Considering the COVID-19 pandemic, special protective precautions are respected to limit the risk of contamination between the patient and the operator (disposable single-use personal protective equipment, single-use ultrasound probe protection covers, cleaning and anti-viral disinfection before and after each use). L-POCUS is performed using the BLUE-PLUS Protocol 12 regions method [15] investigated in a semi-recumbent or supine position (figure 1, panel A). All intercostal spaces of the upper and lower parts of the anterior, lateral and posterior regions of the left and right chest walls were examined, resulting in 12 areas of investigation. Four ultrasound aeration stages are defined [14,21] (figure 1, panel B): stage 0 or normal aeration: line sliding sign associated with respiratory movement or less than 3 B lines; stage 1 or moderate loss of lung aeration: a clear number of multiple visible B lines with horizontal spacing between adjacent B lines ≤ 7 mm (B1 lines); stage 2 or severe loss of lung aeration: multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines ≤ 3 mm, including “white lung”; and stage 3 or pulmonary consolidation: hyperechoic lung tissue, accompanied by dynamic air bronchogram. The L-POCUS score is determined by allocating 0, 1, 2 or 3 points to parenchymal aeration stages 0, 1, 2 or 3 respectively in every area. Each of the 12 lung areas is examined and the final L-POCUS aeration score, ranging from 0 to 36 points, is the sum of each regional ultrasound score. We also determine the presence of pleural effusion, or absence thereof, for each hemithorax.

Trial outcomes

Primary outcome

The primary outcome is the occurrence of death, regardless of cause, or the use of intubation or invasive ventilation within the 14 days (day 14) following inclusion. The ability of POCUS to detect the primary outcome occurrence will be evaluated by determining the 95% confidence interval of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. L-POCUS prognostic value will be considered as clinically relevant if the lower bound of the 95% confidence interval is equal or greater than 0.7.

A sensitivity analysis is performed with the 14-day all-cause mortality rate as outcome.
Secondary outcomes

The secondary outcomes include the following parameters:

- The risk of unfavourable outcome (occurrence of death or the use of intubation or invasive ventilation) over time – i.e. the L-POCUS performances according to the delay of outcome assessment. This involves evaluating, in patients with a confirmed or probable SARS-CoV-2 infection, whether L-POCUS score performances vary depending on time, between day 1 and day 14, and, if so, until which time horizon its performances are clinically relevant. For this purpose, we will determine the period for which the lower limit of the 95% confidence interval of the AUC of the L-POCUS score ROC curve is at least 0.7.

- The risk stratification threshold values of L-POCUS score defining three risk groups: low-risk patients, intermediate-risk patients, and high-risk patients. For this purpose, we will determine two threshold values: first maximising the specificity for a sensitivity of at least 95%, second maximising the sensitivity for a specificity of at least 95%.

- Effect of adding L-POCUS score value to previous several risk stratification clinical rules for pulmonary infection or sepsis: qSOFA, CRB 65 and CURB 65. For this purpose, we will attribute 0, 1 or 2 points to L-POCUS score according to the two predefined threshold values and will assess the AUCs of qSOFA, CRB 65 and CURB 65 with and without addition of L-POCUS score result.

- L-POCUS score evolution performances in the subgroup of hospitalised patients having a second chest ultrasonography at day 5 +/- 3 days of inclusion. We will assess the performances of the L-POCUS score evolution between the first and the second assessment in identifying patients with unfavourable outcome (intubation and mechanical ventilation requirement or death). For this purpose, we will calculate the delta between the first and second L-POCUS score and determine the AUC of the ROC curve and its 95% confidence interval.

- L-POCUS score performances ability to predict the risk of unfavourable outcome in the subgroup of patients with positive SARS-CoV-2 RT-PCR results.

Participant timeline

Study participation duration for a participant is 14 days.

Sample size

To study diagnostic performances of lung ultrasound to identify high-risk patients, we will determine the 95% confidence interval of the AUC of the ROC curve and consider L-POCUS capacity as clinically
relevant if the lower limit of the 95% confidence interval is at least 0.7. This is assuming that the observed AUC will be 0.8. Based on data from COVID-19 in China, the rate of death or need for tracheal intubation is estimated at 20% in high-risk patients. As severely ill critical patients are excluded of our study, we estimate that this rate will be around 10%. Therefore, assuming a rate of death or tracheal intubation requirement of 10%, and expecting an AUC of 0.8, the number of patients required to achieve a lower limit of the 95% confidence interval upper than 0.7 was estimated to 286. Taking into consideration patients lost to follow up and those who cannot be evaluated (estimated at 5%), it is necessary to include 300 patients in total.

**Recruitment**

Inclusions started on 10 April 2020 in Angers University Hospital and 11 centres had included at least one patient by 18 April 2020. Taking into account the number of participating centres (11) and the evolution of COVID-19, the estimated duration of inclusion is 3 months.

**Patient and Public Involvement:**

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

**Data collection, management, and analysis**

**Data collection and management**

All data related to this study are collected using a standardised electronic case report form (eCRF) and based on valid documents (patient medical record). In the eCRF and follow-up calls, patients can be identified by a unique number composed of the centre number and the patient number at the centre. The confidentiality of patients and their personal health information is always maintained by restricting access to patient records and eCRF.

**Statistical analysis**

Many different data sets are described in this study. Quantitative data is described using means and standard deviations. Qualitative data are described using numbers, percentages and 95% confidence intervals. L-POCUS properties to predict unfavourable outcome over time is estimated by calculating the area under the curve (AUC) and its 95% confidence interval. Sensitivity and specificity will be
estimated by the 632+ bootstrap method. Calibration will be assessed with the calibration slope and the calibration intercept. A flexible calibration curve will be provided. A Brier score will be also reported, summarizing the magnitude of error in the probability forecasts between 0.0 and 1.0, where a perfectly calibrated model would score 0.0. Two thresholds will be calculated. The first will maximise specificity with a sensitivity greater than or equal to 95% and the second will maximise sensitivity with a specificity greater than or equal to 95%. For these threshold values, we will present sensitivity, specificity, predictive values and likelihood ratios. Dynamic changes of L-POCUS diagnostic properties will be realised depending on the time AUC and also its 95% confidence interval. To study the impact of adding the result of L-POCUS evaluation to several risk stratification clinical rules for pulmonary infection or sepsis (qSOFA, CRB 65 and CURB 65), AUCs will be compared with or without its component with a DeLong test. In this purpose, we will attribute 0, 1, or 2 points to L-POCUS result as low, moderate or high risk according to the predefined thresholds values and assessed the AUC of the risk-stratification rules with and without adding the L-POCUS result value. Calibration of these rules will also be assessed with the calibration slope and calibration intercept.

Ethics and dissemination

Legal obligations and approval

The sponsor of the study is CHU d’Angers (Angers University Hospital). The sponsor obtained prior approval from the Comité de Protection des Personnes (CPP) du Sud-Ouest et Outre-Mer 2 (n°ID-RCB: 2020-A00782-37 / 2-20-025 id7566, 3 April 2020) and the Belgian Comité d’Ethique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc (2020/14AVR/223, 15 April 2020). The Declaration of Helsinki and the Good Clinical Practice guidelines will be respected by the study. The coordinating investigator can make an amendment after submission to the sponsor, and approval from the CPP. After complying with these different stages, the amendment will be implemented.

Dissemination of results

Considering the ongoing COVID-19 pandemic, the main result of the study regarding the lung ultrasound performances to predict unfavourable development will be deposited on a preprint server and presented in a peer-reviewed journal as soon as possible. This study adhere to TRIPOD guidelines, by verifying the 22 items of TRIPOD checklist during the conception of this protocol[22]. The STROBE statement will be used before submitting the manuscript to a journal [23].

The full results of the study will be presented in national and international meetings and in peer-reviewed journals.
DISCUSSION

This study protocol describes a prospective and multi-centre study evaluating point-of-care ultrasonography for risk stratification of COVID-19 patients.

While the usefulness of ultrasound for standard organ examinations has been shown and unanimously accepted for a long time, the lung ultrasound has traditionally been excluded from this repertoire [24]. Ultrasound techniques have expanded, and their usefulness has been gradually demonstrated and democratised worldwide by the works of Lichtenstein et al. [15,21] and Volpicelli et al. [25,26].

Many articles have been published on this topic in the context of the COVID-19 pandemic but mostly based on expert opinion without evidence based data [27–30]. Buonsenso et al. even suggest that lung ultrasounds could replace stethoscopes in the ongoing COVID-19 pandemic, which could possibly reduce the risk of exposure of healthcare workers [31]. Its main advantages for COVID-19 can be seen [28] in the following stages: 1. triage (pneumonia/non-pneumonia) of symptomatic patients at home as well as in the prehospital phase; 2. diagnostic suspicion and awareness in the emergency department setting; 3. treatment of intensive care unit patients with regard to ventilation and weaning. Therefore, as highlighted by Soldati et al. [28], studies aimed at clarifying the diagnostic and prognostic role of lung POCUS in COVID-19 are urgently needed. This is the principal aim of our study.

Lung ultrasound will also likely make it possible to monitor the clinical course of COVID-19 patients and the effects of therapeutic measures [32]. This is the reason why we designed our study by integrating a monitoring ultrasound at day 5 +/- 3.

The potential advantages of L-POCUS are important, especially versus lung CT scan. However, the scientific community warns us about its limitations and pitfalls [33,34], meaning that we need an adequately designed study to determine the limits and advantages of this tool. POCUSCO may likely provide part of the expected answers.

There are some limitations in the conception of this study. Firstly, at the time we wrote the protocol and on the basis of the first observational studies in China, the expected rate of mortality or
intubation and invasive ventilation request was set to 10% [18]. However, recent data have demonstrated mortality rates lower than those observed in the early phases of the epidemic in Wuhan [1,35]. Moreover, the efficacy of some treatments as corticosteroids has been recently proved in COVID-19. [36]. As a result, the rate of our primary outcome may be lower than expected, impairing the powerful of our trial and enlarging the 95% confidence intervals of our estimates. Secondly, as only patients with a mild to moderate COVID-19 will be included, most of them may be discharged home without the possibility to perform a second L-POCUS at day 5 +/- 3 following the inclusion. Therefore, the assessment of the performances of the L-POCUS score evolution may be limited. A final limitation is related to POCUS itself, all operators not having the same level of experience in POCUS realisation and all hospitals not using the same devices [37]. The inter-individual variability in the L-POCUS score grading may then be increase. The L-POCUS performances may be under-evaluated as compared within an expert centre, but our results will show the performances that should be expected in real life care.

The POCUSCO study results are particularly anticipated and after the protocol was reviewed and approved by French and Belgian Ethics Committee, recruitment began on 10 April 2020. The results are anticipated for the end of June 2020.
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FOOTNOTES

Authors’ contributions: FM, PMR, VD, JFH and DD conceived and designed the study. FM, PMR, VD, DD, JFH, JR, FD, DS, JRI and CA participated in the design of POCUSCO and contributed to revisions of the original manuscript. JFH, FM and JRI performed the statistical plan and sample size calculation. FM, DD, FD, DS, VD and PMR realized acquisition of data. JFH and FM performed data analysis and interpretation. All authors edited the manuscript and read and approved the final manuscript.

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Competing interests’ statement: none declared

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Figure 1 legend:

Panel A. Lung Point Of Care Ultrasonography Method (L-POCUS)

A. Twelve chest areas of investigation following BLUE-PLUS Protocol: zone 1: upper anterior chest wall; zone 2: lower anterior chest wall; zone 3: upper lateral chest wall; zone 4: lower lateral chest wall; zone 5: upper posterolateral chest wall; zone 6: lower posterolateral chest wall

B. L-POCUS score grid: Four ultrasound parenchymal aeration stages are searched in each zones and points are affected to them according to their severity. Stage 0 or normal aeration (0 point): line sliding sign associated with respiratory movement or less than 3 B lines; Stage 1 or moderate loss of lung aeration (1 point): a clear number of multiple visible B-lines with horizontal spacing between adjacent B lines ≤ 7 mm (B1 lines); Stage 2 or severe loss of lung aeration (2 points): multiple B lines fused together that were difficult to count with horizontal spacing between adjacent B lines ≤ 3 mm, including “white lung”; and Stage 3 or pulmonary consolidation (3 points): hyperechoic lung tissue, accompanied by dynamic air bronchogram

Panel B. Examples of four ultrasound aeration stages

a. Stage 0 or normal aeration b. Stage 1 or moderate loss of lung aeration; c. Stage 2 or severe loss of lung aeration; d. Stage 3 or pulmonary consolidation.
Figure 1 legend:

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