# A Prospective International Lung Ultrasound Analysis Study in Tertiary Maternity Wards During the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic

*To the Editor*: During the coronavirus disease 2019 (COVID-19) outbreak, all patient categories have been affected, including one of the most fragile groups: pregnant women. Although experts provided general suggestions on the best treatment of pregnant women with suspicion of or confirmed COVID-19, these considerations were mainly based on retrospective studies or case series.[1–8] No prospective study is currently available about the treatment of patients with suspicion of or confirmed COVID-19 during pregnancy. Moreover, no data are reported on the treatment of asymptomatic pregnant patients testing positive for COVID-19 or pregnant patients admitted to delivery rooms.

The current reference standard for the etiologic diagnosis of severe acute respiratory syndrome coronavirus 2 infection is an analysis of respiratory tract specimens on a (real-time) reverse transcription polymerase chain reaction (PCR). However, this test has a high false-negative rate, due to both a nasopharyngeal swab sampling error, which often requires repeated sampling, and a low viral burden.[9] Currently, high-resolution computed tomography (CT) is the main tool for the primary diagnosis and evaluation of respiratory disease severity in patients with COVID-19.[10–12] Computed tomography of the chest has higher specificity than nasal/pharyngeal swabs for diagnosis.[13] Therefore, several clinicians are now routinely using CT as a screening tool.

In pregnant patients, lung ultrasound (LUS) could be a valid alternative imaging tool instead of thoracic CT to guarantee appropriate care for these patients. Symptomatic patients with a low risk of developing serious disease may be possibly reassured and could leave the hospital soon after delivery. On the other hand, LUS could possibly indicate patients at a higher risk for a future need of oxygen or ventilation support and who might need more careful monitoring and longer hospitalization. In view of the wide availability in delivery suites, the low cost, and easy bedside application, LUS examinations could also be readily repeated during patient follow-up as needed. Indeed, LUS has recently been suggested by the Chinese Critical Care Ultrasound Study Group[14] and the Italian Academy of Thoracic Ultrasound as an accurate tool to detect lung involvement during COVID-19.[15–17] Lung ultrasound is also a practical approach that can be used by obstetricians-gynecologists.[18]

## Study Aims

The primary objective of this study is to assess the predictive value of LUS for the clinical status of patients 1 week after admission. Secondary objectives are as follows: (1) to investigate the possibility of reducing the number of scanning planes without losing accuracy; all patients will be scanned in 14 different areas, but it might result in the finding that some areas are more commonly involved, which will be assessed at the end of the study; (2) to compare LUS with PCR testing to predict the clinical status 1 week after admission; (3) to describe LUS features of COVID19-positive pregnant women and their changes in a 1-week follow-up; (4) to compare symptoms and laboratory results with the LUS features; (5) to calculate the number of avoided CT scans in symptomatic pregnant patients; and (6) to collect clips and images for artificial intelligence research.

## Study Design and Setting

### *Study Design*

This work is an international multicenter exploratory prospective observational study. All included investigators have already attended a fast LUS teaching program.

### *Sample Size*

The study will include a total estimated number of 1850 patients in 1 month from 7 different centers. The prevalence of COVID-19 will vary greatly (from <5% to almost 50%). We estimate that an overall 10% to 20% of patients may test COVID-19 positive. The number of patients who will need oxygen or ventilation support was not known at the start of the study.

***Patients***

The study will include all consecutive pregnant patients who are admitted to the hospital during pregnancy or for delivery, with at least a 1-night stay. Inclusion criteria are pregnant patients admitted during the COVID-19 pandemic: (1) patients with confirmed COVID-19 infection (see below); (2) symptomatic patients with suspicion of COVID-19 infection (swab taken on admission); and (3) patients asymptomatic for COVID-19 with other fetal-maternal diseases or who come for delivery or cesarean delivery. Exclusion criteria are as follows: (1) maternal preexisting lung disease; (2) maternal cardiac problems; and (3) severely ill patients in an unstable condition requiring immediate life-saving procedures.

Definition of a suspected case (World Health Organization and International Society of Ultrasound in Obstetrics and Gynecology guideline)[6]: (1) a patient with acute respiratory illness (fever and at least 1 sign/symptom of respiratory disease [eg, cough or shortness of breath]) and with no other etiology that fully explains the clinical presentation and a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 infection during the 14 days before symptom onset; or (2) a patient with any acute respiratory illness and who has been in contact with a confirmed or probable case of COVID-19 infection in the 14 days before onset of symptoms; or (3) a patient with severe acute respiratory infection (fever and at least 1 sign/symptom of respiratory disease [eg, cough or shortness of breath]) and who requires hospitalization and who has no other etiology that fully explains the clinical presentation.

## Data Collection

***General Procedures***

Given the situation of isolation, patients will provide verbal informed consent. Informed consent will be acquired in front of 2 independent witnesses, who will sign the consent at the end of the information process.

Data collection is done through Web-based clinical data miner (CDM) software. Data are stored on a secure server. For patients without COVID-19, data will be entered into the CDM at admission and after 1 week; if they are still hospitalized or in case of discharge before 1 week, the patient's status will be assessed by a phone call. For patients with symptoms or with a positive diagnosis based on PCR or thoracic CT, information will be entered into the CDM on admission, after 24 and 72 hours, and after 1 week.

Information on treatment of the patient, including the type of treatment, oxygen supplementation, continuous positive airway pressure, or invasive ventilation, will be recorded. For patients giving birth during the week of follow-up, neonatal data will be collected.

***Clinical Information***

*Type of Hospital*

To describe the study population, information on the type of hospital (local public hospital, regional public hospital, or university hospital) will be recorded.

*Patients*

Epidemiologic data will include age, ethnicity, nationality, region of residence in the last 14 days, parity, singleton or multiple pregnancies, interval days from symptom onset, and type of symptoms at onset.

*Personal History: Previous or Ongoing Maternal Disease and Indication for Admission*

The clinical assessment will include body temperature, respiratory rate, resting oxygen saturation, maternal heartbeat, oxygen support, endotracheal intubation, admission to an intensive care unit, and type of treatment.

*Laboratory Evaluation*

The laboratory evaluation will include the white blood cells count, lymphocyte count (absolute number and percentage), C-reactive protein, platelet count, liver enzymes, lactate dehydrogenase, and RNA PCR for COVID-19 on a throat swab.

***Lung Ultrasound Examination***

The hardware used for LUS is noted, its operator, and the type of professional (physician, midwife, or sonographer), specialization (eg, gynecologist, pediatrician, radiologist, or anesthesiologist), and experience with ultrasound (US) examinations (years). All US examiners must have attended the fast-teaching

program (see https://covid19.disi.unitn.it/iclusdb/login), and they must have passed the posttest.

### *Method*

Images pertaining to this document are available at https://onlinelibrary.wiley.com/doi/abs/10.1002/jum.15285. For each patient, 14 areas will be scanned (3 posterior, 2 lateral, and 2 anterior). Each of the 14 areas will receive a COVID LUS score:

- Score 0 (normal pattern). The pleural line is continuous and regular. Horizontal artifacts (A-lines) are present.
- Score 1 (pattern of mild disease). The pleural line is not continuous, and below the points of discontinuity, vertical white lines (B-lines) are visible.
- Score 2 (pattern of moderate disease). The pleural line is broken (interrupted), and below the points of discontinuity, small-to-large consolidated areas (hypoechoic areas) with associated white areas (white lung) are visible.
- Score 3 (pattern of severe disease). Dense white lung with or without larger consolidations is visible.

At the end of the procedure, the clinician will write the highest score obtained for each area (eg, quadrant 1, score 2; quadrant 10, score 1; and so on).

Classification of LUS results:

- Lung US negative (group A), score 0 in all 14 areas or score 1 in areas on one side (right or left) (this means that score 1 is pathologic only when present bilaterally).
- Lung US positive (both groups B and C have to be considered positive), group B (mild disease), score 1 in at least 2 areas localized bilaterally and no areas with score higher than 1; group C (moderate/severe disease), score higher than 2 in at least 2 areas localized bilaterally.

During the intercostal US examination, a 10-second video clip for each examined area (14 videoclips in total), as well as anonymized US images and volumes, will be recorded for subsequent digital analysis. These will be sent to Katholieke Universiteit Leuven, Department of Development and Regeneration, University College London, Center for Medical Imaging and Computing–Translational Imaging Group, University of Trento, Ultrasound Laboratory Trento, Department of Information Engineering and Computer Science, for artificial intelligence analysis. Centers will state whether they will be taking part by sending clips, images, and volumes.

### *Time Points*

For patients with COVID-19 patients (patients with symptoms or a positive diagnosis at recruitment),

The first evaluation (within 6 hours from admission) will include epidemiologic data, a personal history, clinical, laboratory, and obstetric parameters, and an LUS examination. The second evaluation (after 24–30 hours) will included clinical, laboratory (swab test repetition if the first test result is negative), and LUS examinations. The third evaluation (after 72 hours) will include clinical, laboratory, and LUS examinations. The fourth evaluation (after 1 week) will include clinical, laboratory, and LUS examinations. Additional time point examinations can be planned in cases in which clinical conditions worsen or whenever a new COVID therapy is included.

For asymptomatic patients, the first evaluation (within 6 hours from admission) will include epidemiologic data, a personal history, clinical, laboratory, and obstetric parameters, and an LUS examination. After 1 week, clinical data will be gathered, eventually via telephone if the patient is at home.

### *Outcome Measures (Patient's Status)*

For the outcome at 1 week from admission, a good outcome will include discharge or inpatient breathing in free air; a poor outcome will include patients with oxygen support, patients with continuous positive airway pressure/a high-oxygen flow cannula, or patients with endotracheal intubation during the week. For patients giving birth during this time frame, we will also collect neonatal data (delivery [vaginal or cesarean and gestational age], neonate [male of female], birth weight, Apgar score, and vertical transmission in a case in which the mother is confirmed COVID-19 positive (yes, no, or not tested]).

### *Clinical Management*

According to the clinical decision of each institution, any treatment including pharmacologic assistance, a clinical procedure, or both will be recorded.

## Statistical Analysis

***Population Analysis***

We discerned the following population analysis: (1) all patients recruited in all centers will constitute the full-analysis (FA) group; (2) all patients recruited at centers that test everyone (with PCR) for COVID-19 will constitute the testing-all group; and (3) all patients who were symptomatic (but not yet confirmed COVID-19 positive) will be considered symptomatic patients. The primary end point will be s the diagnostic performance in terms of the area under the receiver operating characteristic curve (also known as the *c* statistic) and sensitivity and specificity relating to the prediction of a poor outcome (see definition above).

***Statistical Methods***

All methods can be subject to change, depending on unforeseen data-related issues or the incidence of a poor outcome. For example, if few patients have a poor outcome, a logistic regression analyses may not be reasonable.

Primary objective (FA): (1) area under the curve of LUS to predict a good outcome; (2) sensitivity and specificity of positive LUS results to predict a good outcome; and (3) logistic regression of a good outcome on the LUS score and COVID-19 status at recruitment (symptomatic/confirmed versus asymptomatic) and their interaction. Secondary objectives: demographic, clinical (eg, comorbidities and symptoms of COVID-19), and LUS features will be described for the FA and relevant subgroups.

To study whether some scanning planes for the LUS score are irrelevant, we will describe the score for each of the 14 planes to assess the distribution and variability in the score. In addition, we will perform stepwise selection with the area under the curve as the criterion. This will be done with data in the FA group.

To compare LUS with PCR testing to predict the patient status at 1 week, we will calculate the sensitivity and specificity and differences therein between tests using 95% confidence intervals. We will perform a logistic regression analysis of a poor outcome on LUS and PCR results. This will be done on the testing-all group to avoid a selection bias (some centers only test symptomatic cases, whereas other centers test everyone). Using the symptomatic patients, we plan to do the same for the symptomatic patients only. On stored US images, clips, and volumes, artificial intelligence techniques will be applied for automated detection of abnormal signal patterns, eventually compatible with pathologic clinical findings.

## Sample Size Estimation

No reasonable sample size estimation could be done. We anticipate that the recruitment of 1850 patients from 7 sites in Italy, the United Kingdom, and Belgium would lead to inclusion of 185 to 370 patients with a diagnosis of COVID-19. Over the course of the study, the prevalence might vary.

## Data Handling and Management

Only persons officially registered as study investigators receive a user login to access the CDM Web platform and enter data. The users of the CDM Web platform will be sorted by center and department. Each investigator has access to the data that he or she has personally entered but also to the data of investigators working within the same department. Users with data manager privileges have access to the data entered by all investigators. All transmission of data between computers of the investigators and users ("clients") and the CDM Web server is encrypted. Access to the platform requires a user login and is regulated by the registration of users by the center or department and the use of data manager privileges, as described above. Safety is one of the requirements that have been pursued when developing the CDM.

## Ethics and Regulatory Approvals

The multicenter project has been approved by the Ethics Committee of the Fondazione Policlinico Agostino Gemelli, Istituto di Ricovero e Cura a Carattere Scientifico, and Research Ethics Committee Universitair Ziekenhuis/Katholieke Universiteit Leuven (ECD S63988). The study will be performed in accordance with the terms of the protocol and the

generally accepted standards of good clinical practice, and the investigators will adhere to all applicable laws and regulations governing the conduct of clinical trials, including but not limited to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki.

The participating site will obtain an informed consent (considering the context, oral consent is acceptable during the COVID-19 pandemic, although the written consent might be requested depending on the applicable local legislation and local Ethics Committee requirements) for all patients before their enrollment and participation in the study in compliance with all applicable laws and regulations and the approval of the (local) Ethics Committee.

The investigator will treat all information and data relating to the study as confidential and shall not disclose such information to any third parties or use of such information for any purpose other than the performance of the study. The collection, processing, and disclosure of encoded personal data, such as patient health and medical information, is subject to compliance with applicable personal data protection and the processing of personal data (directive 95/46/EC and for Leuven, the Belgian law of December 8, 1992, on the Protection of the Privacy in Relation to the Processing of Personal Data) and the privacy laws applicable to the participating site's location). The study is registered on clinicaltrials.gov (ClinicalTrials.gov identifier NCT04353141).

## Expected Results and Clinical Impact

During the current COVID-19 outbreak, the possibility of assessing the lungs of pregnant women by means of radiation-free diagnostic imaging methods would be of the utmost importance if this would prove to be a reliable test to predict the outcome after 1 week, as has also been shown in children.[19] Moreover, LUS allows a lung assessment to be performed at the bedside. With this study, we essentially expect to confirm the clinical utility of LUS to determine COVID-19 pneumonia in pregnant women on a large multicenter and multinational cohort, as we previously showed in a pilot cohort.[20] In addition, we expect to evaluate the ability of gynecologists in performing this procedure after specific training.[21] Importantly, in case we confirm the feasibility by gynecologists, our study would have the indirect benefit of allowing women affected by gynecologic and obstetric conditions with possible lung involvement (pneumonias and cancers) to be assessed with this noninvasive procedure.

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