Focused lung ultrasound for diagnosing and risk-stratification of patients with COVID-19 symptoms

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Background

COVID-19 is defined as an infectious disease caused by SAR-CoV-2 virus. It results in pneumonia and sometimes respiratory failure. SARS-CoV-2 pandemic has led to massive strain on health care facilities. A large proportion of the population is at risk of COVID-19 and some estimates suggest that up to 15% will need hospitalization. Such number of patients strains the health care system to its maximum as capacity has limitations even in highly developed countries.

Early reports estimate that more than 80% of patients admitted to hospital with COVID-19 have abnormal findings on chest radiographs[1]. Thus, imaging seems to be an important part of the diagnostic work-up. In most hospitals however, access to CT-scanning of the thorax of all patients with COVID-19 or with suspicion of CODIV-19 is unrealistic due to restricted capacity. Chest radiographs are faster and easier to do, but may require transportation of the patient to the department of radiology which carries a risk of virus spreading in the hospital. On-site chest radiograph is often of such low quality that diagnosis or follow-up will be difficult.

Focused ultrasound examination of the lungs, FLUS, is a diagnostic tool that can show changes in the lung parenchyma due to pneumonia. FLUS is a bed-side examination performed by the physician which results in reduced risk of in-hospital virus contamination. Furthermore, results from FLUS are immediately available to the physician. This allows rapid decision-making which is essential in cases of high patient burdens as seen in the COVID-19 pandemic.

Furthermore, SARS-CoV-2 positive patients with pneumonia may be at higher risk of respiratory failure than those without pneumonia. Identifying patients at high risk can qualify decisions about monitoring level and organization of intensive care resources. Conversely, patient with COVID-19 symptoms but without pneumonic FLUS finding could likely be managed as out-patients. Such a risk-stratification may optimize the allocation of limited healthcare resources and reserve in-hospital capacity to those patients who needs it.

Hypothesis

FLUS can risk-stratify patients with COVID-19 symptoms.

FLUS can predict respiratory failure in patients with COVID-19 pneumonia.

FLUS can diagnose COVID-19 pneumonia with high sensitivity and specificity using PCR-test and chest radiograph as reference.

Aim

To study the ability of FLUS in COVID-19 to predictive respiratory failure.

To study the diagnostic capability of FLUS to find COVID-19 pneumonia.

To study risk-stratifying capability of FLUS in patients with COVID-19 symptoms.

Method

Design

Multicenter prospective cohort study with convenience sampling.

Setting

Emergency departments or internal medicine departments who admit patients with COVID-19 symptoms.

Participants

Patients who have COVID-19 symptoms and require diagnostic testing.

Patients who have a positive SAR-CoV-2 PCR-test and require admission to hospital.

Inclusion criteria

- Patients who are seen in COVID-clinics or emergency departments due to symptoms that require diagnostic work-up to COVID-19.
- Patients admitted to hospital with positive SARS-COV-2 PCR-test and in whom FLUS is performed less than 48 hours after admission.

Exclusion criteria

- Age less than 18 year.
- Former participation in this study.
- Pre-FLUS ventilator support.

Double inclusion

Inclusion in this study will not restrict patient from inclusion in other studies.

Recruitment

Participants are recruited at the local hospital. In Denmark the study is labelled quality assurance and the need for informed consent is thus waived. Local regulations are followed and it is the responsibility of each inclusion site to achieve appropriate regulatory permissions including need for approval from local ethical committees and healthcare authorities.

Variables

Ultrasound variables: FLUS are performed according to ERS guidelines and to Standard of Operating Procedure specific to this study. Film clips are recorded and saved for later evaluation. 14 zones are scanned. Film clips are marked with scanning position (L1, L2…etc.). If the patient in unable to sit, only anterior and lateral zones are scanned. FLUS findings are assessed on the film clips by an observer blinded to other variables. Finding are coded with 1/0 for presents of pneumonia. Moreover, a scoring system is applied:

FLUS findings	**Score**
Normal FLUS	0
Interstitial syndrome, defined as more than 3 B-lines in a single zone. Diverse B-lines or irregular pleura	1
interstitial syndrome, defined as more than 3 B-lines in a single zone. Confluent B-lines.	2
Consolidations (sub-pleurale, lobar, with or without air-bronchograms)	3

Data on FLUS operator: Level of medical degree. Years of experience with lung ultrasound. Completed training in FLUS.

From patient files the following data is extracted:

Patient demographic: Sex, age, height, weight, co-morbidities.

Clinical data on time of admission: Blood pressure, puls, peripheral saturation, respiratory frequency, temperature, length of illness, list of symptoms, limitation to treatment i.e. not suited or willing to intensive care treatment and intubation.

Data from radiographic diagnostics: Result of chest radiograph, CT or HRCT scanning, if done for clinical reasons. No further review of radiographic examinations is performed. Results given by local radiology department is used.

Microbiological data: Result of SARS-CoV-2 PCR-test form nasal/oral/laryngeal or tracheal samples.

Data from admission: Time of admission. Place of admission. Time of dismission. Admission to intensive care. Intubation. Time in ventilator. Death, survival. In hospital survival, 14- and 30-days survival.

Endpoints

Primary endpoint: FLUS (binary: positive/negative pneumonia) related to intubation (yes/no).

Secondary endpoints: Relationship between FLUS and SARS-CoV-2 PCR result.

Relationship between FLUS and radiographic findings.

Relationship between FLUS and admission to intensive care (not intubation).

Relationship between FLUS and re-admission (Patient returning to emergency department or COVID-clinic).

Scores of FLUS findings in different zones.

Data management

The study uses convenience sampling as FLUS may not be available at all times. FLUS is performed by the clinician such that only doctors with clinically relevant work are allowed to scan the patient. This minimizes the risk of disease transfer to doctors and reduces the use of protection equipment.

Ultrasound film clips are recorded according to standard operating procedure. Film clips are stored securely, according to local legal regulations. All variables extracted from patient files are stored in an eCRF using REDCap supplied by Aarhus University Hospital.

Every site will have access to enter data in data capture instruments. Access to REDCap is managed by the project steering committee at Aarhus University Hospital.

Data analysis

All data are analyzed in Stata.

Binary endpoints, including primary endpoint, are analyzed using Chi-2 test. Continuous data are assessed for parametric distribution and analyzed with Student´s T-test on logarithmic transformed data in case of non-parametric distribution.

Level of statistical significance is set to 5%.

A logistic prediction model will be developed. Dependent variable is intubation. Independent variables are age (continuous), FLUS result (Binary or ordinal), SARS-CoV-2 status (Binary) and peripheral oxygen saturation (continuous).

The data set will be divided in two. One is used for model development and one is used for validation of the model. Geographic external validity is tested. Internal validity is tested with bootstrapping method. Sensitivity, specificity and ROC AUC is calculated.

Sample size

No prior publications are available for sample size estimation.

For the prediction model we wish to include 10-15 events per independent variable, 50-75 events. From early estimations about 20% of admitted patients requiring intubation our estimate is 375-400 participants.

Inclusion period

An end date is set to May 15 2020. If COVID-19 pandemic in ongoing at this time point the study may extent.

Blinding

Ultrasound film clips are analyzed blinded to other variables.

Plan for publication

Data analysis is estimated to end July 1. 2020. Article submission is estimated to October, 2020.

Preliminary data analysis

Available data will be analyzed soon after 15. May.

Ethical considerations

FLUS is without any risk to patients. COVID-19 is an infectious disease and isolation is needed. Contamination during the study needs to be avoided. For this reason, FLUS is only performed by the physicians who are required to see the patient regardless of this study. The ultrasound equipment is cleaned after each examination in accordance with local guidelines.

Legal regulations

In Denmark the study is classified as a quality assurance project. Arrangements and permission to access to patient files in each site is required. According to guidance from the legal office at Region Midt a data management agreement in not needed.

International data agreements are required to data transfer from international sites to Denmark.

All international sites must adhere to local regulation. Responsibility of this is on the international site.

Publication

All results (negative, inconclusive or positive) are submitted to peer-reviewed medical journals. Qualification for authorship follows ICJME recommendations. A number of 50 patients included per site is set as the minimal limit of contribution required for authorship.

Group

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Perspective

The COVID-19 pandemic has had a tremendous impact on hospital resources. Optimal use of limited resources is essential when managing high level strain on health care systems.

Point-of-care FLUS allows for a rapid answer to the central question of whether the patient has pneumonia or not with the lowest possible use of resources. Demands on radiological resources will likely lead to long waiting time.

A large proportion of COVID-19 patients will need ventilatory support with intubation. Early identification of patients who are at high risk of respiratory failure will allow planning of intensive care resources. Conversely, patient without FLUS pathological findings may be managed safely as out-patients.

Results from this study will enhance our knowledge on COVID-19 related respiratory failure and give us an ability to manage large strains on health care resources.

Referencer

1. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020;NEJMoa2002032.

2. Laursen CB, Rahman NM, Volpicelli G, editors. Thoracic Ultrasound. Sheffield, United Kingdom: European Respiratory Society; 2018.