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Study Protocol

Registry for Clinical Presentation and Management of Patients with Coronavirus Disease 2019 in the Emergency Room - ReCovER

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2. Introduction

In December 2019 emerged the novel *severe acute respiratory coronavirus 2* (SARS-CoV-2), which causes a highly contagious pulmonary disease (COVID-19). The clinical picture of COVID-19 varies from asymptomatic or mild to severe or critical cases of viral pneumonia and acute respiratory distress syndrome (ARDS)[1]. SARS-CoV-2 causes infections of clustering onset especially among patients with comorbidities[2,3]. Factors associated with high susceptibility include older age and male sex[4].

Since the first described cases in Wuhan, China, COVID-19 has developed into a global pandemic with approximately 900,000 confirmed cases worldwide by April 2020[5].

Our understanding of the disease is evolving and mainly derives from experiences in China, Iran, USA, Italy and Spain. While many aspects of COVID-19 are yet to be clarified, it has confronted healthcare systems worldwide with enormous challenges.

The number of seriously or critically ill patients in the hardest struck regions (e.g. Lombardy, Italy) exceeded local hospital and ICU-capacities by far. This has prompted unusual political decisions such as nation-wide and week-long lockdowns in order to „flatten the curve“ of the rate of new infections[6].

Emergency departments (ED) play a central role in managing the influx and initial management of patients into a hospital. Their major objective is to triage patients according to the severity of injury or illness and to initiate diagnostics and first therapeutic steps.

Great numbers of patients reporting to the Emergency Department at the same time - a characteristic during pandemics - exert an enormous pressure on healthcare professionals. The lack of appropriate capacities in the hospitals requires rapid decision-making on who has to be admitted and who can be discharged from the ED and safely managed at home. In the case of COVID-19 there is additional insecurity because of the high risk of infection for nurses and doctors.

The contagiousness of COVID-19 requires early spatial separation of presumably infected individuals from other patients and increases the burden of working under personal protective equipment (PPE).

3. Study Rationale

Patients with COVID-19 usually present in the ED and receive their initial medical check-up here. It is the ED where crucial diagnostic and therapeutic steps are taken and where the decision for admission or discharge is made. As of now, the effectiveness and value of these initial measures and decisions are unclear. With still raising numbers of infections despite regulatory constraints in place, there is an urgent need to develop valid decision trees on how to treat patients suspected with COVID-19 in the ED.

Apart from the already described risk factors little is known about if and to which degree an infection with COVID-19 itself predisposes to other acute conditions (e.g. myocarditis, myocardial infarction or stroke). We will try to gather information of comorbidities and other conditions at the time of presentation of COVID-19 patients to the ED.

Not all patients seek medical consultation at the very beginning of symptoms. The course of the disease prior to admission as well as the momentary health status at presentation to the ED are of interest because they influence risk stratification and decision-making of treating physicians. For example: an immunocompromised patient who presents with mild symptoms at a very early stage of COVID-19 would probably be deemed more at risk than the same patient who reports mild symptoms without progression for a duration of several weeks.

The ratio of patients with mild or moderate to severe symptoms will help to calculate the need for hospital beds including beds on Intensive Care Units (ICU) and Intermediate Care Units (IMC), as well as the need for other hospital resources. It will also help to identify the need for capacities in ambulatory care. COVID-19 Patients with mild or moderate symptoms can remain in quarantine at home. This would not only disburden hospitals but would also lower the risk for previously uninfected patients otherwise having to share rooms and wards with them.

Confirming the diagnosis

There is uncertainty with regard to the best initial diagnostic in COVID-19 patients. Diagnostic tool of choice is a low-dose CT-scan of the thorax, which will detect typical radiologic signs of COVID-19 (ground-glass-opacities, bilateral consolidations and

„crazy paving“) with a high sensitivity, and in some cases even before onset of clinical symptoms[7]. However, these features are also seen in other viral pneumonias and specificity reaches only 25%[8]. Moreover, a CT-scan might not be available 24/7 in all hospitals, is time-consuming and exposes radiologic personnel to the risk of infection. Additionally, as is described later, many patients present with severe hypoxemia, a situation in which they might not be able to lie in a supine position in the CT-scanner. The role of lung ultrasound (LUS) in detection of COVID-19 has not been examined properly so far.

Testing for COVID-19 usually is done using an oral swab (or expectorated sputum) and real-time PCR (RT-PCR) after a clinical suspicion based on different parameters and/or after visits of the patient to regions with high prevalence of SARS-CoV-2[9]. The sensitivity of this method has not been systematically evaluated, however, false-positive, as well as false-negative results have been reported[10,11]. Moreover, there are sometimes contradictory results of RT-PCR and CT-scan[12]. The registry will be used to collect and compare diagnostic data from radiological exams as well as RT-PCR-testing.

Many COVID-19 patients present with shortness of breath and hypoxemia. Physicians have used different therapeutic approaches including high-flow oxygen (HFNC), non-invasive ventilation or intubation and mechanical ventilation. While a trial with non-invasive methods is deemed safe and adequate by most experts[13,14], others have raised concerns and advocate early intubation and invasive ventilation in COVID-19[15]. Participants of the registry will be asked to state the method of oxygenation/ventilatory support that was initiated in the ED.

Admission vs. discharge

As has already been laid out, patients with COVID-19 exhibit symptoms of different severity. It is neither possible nor would it be reasonable to hospitalize every patient in which the condition is suspected or confirmed. Unfortunately, there are no diagnostic markers or laboratory cut-offs that help decide if a COVID-19 patient who presents to the ED has to be hospitalized or can be safely managed in ambulatory care. Our goal is to gather information of outcomes in both hospitalized and discharged patients and to compare this data with epidemiological, clinical, laboratory and radiologic data from the date of their visit to the ED.

The ED is the first contact to a hospital. Diagnostic and therapeutic measures from patients who are hospitalized due to the severity of their disease will be analyzed as well as complications or death during hospitalization. The duration of hospitalization will be analyzed and compared to the initial clinical picture.

4. Objectives

The objective of this registry is to identify predicting factors in the clinical picture of COVID-19 patients presenting to the ED. The rationale is to differentiate patients at risk for progression to serious illness from those who can be managed in ambulatory care. This will improve our ability to allocate available resources correctly and to meet the needs of as many patients as possible. Specific objectives are:

4.1 Primary objective

- In patients with confirmed SARS-CoV-2 infection: Identification of clinical and diagnostic parameters as well as risk factors that facilitate distinguishing patients who should be hospitalized from patients who can be discharged from the ED safely.

4.2 Secondary objectives

- In patients with suspicion of SARS-CoV-2 infection: Identification of clinical and diagnostic parameters as well as risk factors that facilitate distinguishing patients who should be hospitalized from patients who can be discharged from the ED safely.
- Identification of clinical and diagnostic characteristics (other than direct confirmation of SARS-CoV-2 infection by e.g. qPCR) that distinguish patients with and without COVID-19.
- Identification of individual clinical or diagnostic characteristics encountered on presentation in the ED that are associated with the clinical course of COVID-19 (mild, moderate, severe).
- Comparison and validation of diagnostic strategies (e.g. lung ultrasound, low-dose CT scan).

- Comparison of effectiveness of different early treatment strategies against hypoxemia (e.g. non-invasive vs. invasive ventilation) in severe COVID-19.
- Comparison of methods of risk stratification and allocation of hospital capacities.
- Description of diagnostic (including all results) and therapeutic management (including specific therapy for COVID-19) during hospitalization.
- In patients that were discharged from the ED: Descriptive analysis of complications, re-hospitalization rate, death, time to recovery at home.
- In patients ≥65 years of age: impact of Clinical Frailty Scale on outcome.

Precise data concerning the effectiveness and / or safety of off-label-used antiviral therapeutics to treat COVID-19 will not be documented and determined.

5. Study Period

Start date of recruitment: Immediately after vote of the ethics committee
End date: not determined

6. Patient Population

6.1 Inclusion criteria

- Clinical suspicion or evidence of SARS-CoV-2-infection on presentation in the ED

6.2 Exclusion criteria

- none

The main interest of this cohort study is to evaluate clinical signs and symptoms of COVID-19-positive patients. In addition, the inclusion of patients with clinical suspicion of COVID-19 but who are then tested negative for the virus provides the opportunity to

evaluate the usefulness of scores or factors (composed from both clinical features as well as further findings) that facilitate identification of SARS-CoV-2-infection on clinical grounds. Using a 1:1 case-control-design, an equal number of patients with and without confirmed SARS-CoV-2 infection that present consecutively to the ED in the same time frame are going to be enrolled. In practice, all patients with confirmed infection will be enrolled first. Afterwards, for each enrolled COVID-19 patient (index), one patient with signs and symptoms of COVID-19 but with a negative virus testing that has presented to the ED on the same day (and the same hour) as the index patients will be enrolled. If more than one potential control patient exists than the one that was admitted the closest to the index patient will be enrolled. Thus, a possible selection bias which certainly has to be taken into account, will be prevented. Since no interventions are performed in this study and no data other than reported in the medical records file, no observer bias is anticipated.

Participating study sites

ReCovER is a freely accessible, worldwide registry aiming to include as many cases of SARS-CoV-2 cases as possible to decipher the impact of SARS-CoV-2 and its implications on management in the ED in the current pandemic. For that reason, the number and type of participating study sites cannot be determined at the current situation of the pandemic.

Since *ReCovER* is an anonymous registry, study-logs that would allow re-identification of patients will not be recorded.

7. Case Report Form

The electronic Case Report (eCRF) will be established using the survey software EFS Survey™ (Questback), which is broadly used by international research groups for epidemiological and sociological research projects. ClinicalSurveys.net is hosted by QuestBack, Oslo, Norway on servers in Cologne, Germany as part of a software-as-a-service agreement. Data entry is carried out via an interactive macro created by the

survey software, which can be accessed via any internet browser using encrypted communication via TLS 1.2 with an AES 256 GCM bit key and ECDHE RSA key exchange certificate provided by COMODO RSA Domain Validation Server. The eCRF will be accessible through the General Data Protection Regulation (GDPR)-compliant platform ClinicalSurveys.net. All documented data are automatically collected in the database. Data protection from loss and unauthorized access is ensured by regular back-up of data, hierarchized management of rights, rigid firewall configuration and authentication protocols. All Good Epidemiological Practice (GEP) requirements are met by the survey software EFS Survey™ (Questback)[16].

The study protocol, the ethics committee's approval, the full eCRF as portable document file (PDF) and the access to the eCRF itself will be available under the following website:

https://www.clinicalsurveys.net/uc/main/2890/loft/front.php?controller=website&pid=260&page=list_patients&sub_pid=6389&old_template=survey_list&SES=9f279910609eb6a32b25a8c66a59e197

Participants, who wish to contribute cases, will receive account-details for login following request via E-mail. Full name, institution and E-mail address have to be supplied.

The following core data set will be collected:

1. Epidemiological data: country, institution and level of care of the institution, exposure area
2. Demographic data: age-group, gender, ethnicity, weight, height, smoking
3. Data of SARS-CoV-2-infection: year of infection, virus species, co-infections with other pathogens, clinical characteristics upon diagnosis
4. Data of concomitant diseases: diagnosis, duration of diagnosis, current status of treatment
5. Diagnostic measures and findings: cultural, serological and molecular diagnosis, medical examination, clinical assessment scores, laboratory results of blood and urine, ultrasound, CT, MRI, x-ray
6. Course of disease: presentation to the ED, discharge to ambulatory care, admission to ward/ intensive care unit (ICU), development of acute respiratory

distress syndrome (ARDS), cardiac arrhythmia, renal failure, major bleeding event / disseminated intravascular coagulation and sepsis, respectively

7. Treatment approaches: Oxygen supply (nasal prong, mask, HFNC), Non-invasive ventilation, invasive ventilation, extracorporeal membrane oxygenation (ECMO) (duration). Antiviral and antibiotic therapy (drug, duration, frequency), sedation, therapy with catecholamines, diuretic therapy (drug, duration, frequency), dialysis (mode of dialysis, duration, frequency), side effects.
8. Treatment response, development of chronic diseases, duration of hospitalization, further information on clinical course as documented in medical records
9. Cause of death, autopsy results if applicable

Further clinical information may be extracted from the medical report files and captured in the data base if deemed appropriate.

8. Data Analysis

Data will be analyzed employing descriptive statistical methods.

9. Ethical Considerations and Data Privacy Protection

In the current study, ethical consideration and data privacy protection have to be taken into account with regard to the retrospective design of the Registry for Clinical Presentation and Management of Patients with Coronavirus Disease 2019 in the Emergency Room - *ReCovER* including a one-stage documentation of clinical data. Only clinical data created during the standard medical care will be collected and documented into the eCRF. As there is no interventional aspect to this study, there are neither associated risks nor benefits for the participating patient.

Digital documentation of clinical data will be performed in an anonymized manner without entering of any identifiable data, such as name or date of birth, into the database. Additionally, there will be no pseudonyms of cases, which would enable a re-

identification of patients retrospectively. As collected clinical data refers to common medical conditions and treatment approaches in medical care, retrospective re-identification of patients on basis of these clinical data will not be possible. Therefore, we consider an informed consent is not necessary under the given circumstances of *ReCovER*.

Data protection from unauthorized access and loss is ensured by regular back up of data, hierarchized management of rights, rigid firewall configuration and authentication protocols. Contributors to *ReCovER* log into the system with username and password including numbers, letters and symbols and they can only view the cases submitted by themselves. All data transmissions are encrypted. Clinical data are documented in an anonymized manner with no directly identifying data other than the investigator names and sites being stored on QuestBack servers. Ownership and responsibility for data and the eCRF are regulated by contracts between the University Hospital of Cologne and QuestBack. Administration of the eCRF is restricted to selected and named administrators at the University Hospital of Cologne.

All clinical data fall under medical confidentiality. All study procedures of *ReCovER* fulfill the Good Epidemiological Practice (GEP) requirements of German and European legislation[16].

10. Authorship policy

Authorship will be restricted to the centers that contribute clinical data to *ReCovER*. For each participating center there will be authorship positions available.

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Cologne, 28.05.2020
Place, Date

Signature

12. References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020.
3. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335-7.
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
5. COVID-19 Situation Report. 2020. at https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf?sfvrsn=5ae25bc7_2.)
6. Lazzerini M, Putoto G. COVID-19 in Italy: momentous decisions and many uncertainties. Lancet Glob Health 2020.
7. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425-34.
8. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020:200642.
9. Patel A, Jernigan DB, nCo VCDCRT. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak - United States, December 31, 2019-February 4, 2020. MMWR Morb Mortal Wkly Rep 2020;69:140-6.
10. Yu F, Yan L, Wang N, et al. Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. Clin Infect Dis 2020.
11. Winichakoon P, Chaiwarith R, Liwsrisakun C, et al. Negative Nasopharyngeal and Oropharyngeal Swab Does Not Rule Out COVID-19. J Clin Microbiol 2020.
12. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. Radiology 2020:200343.
13. Clinical management of severe acute respiratory infection when COVID-19 is suspected. Interim guidance. World Health Organisation (WHO), 2020. at https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.)
14. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med 2020.
15. Kluge S, Janssens U, Welte T, Weber-Carstens S, Marx G, Karagiannidis C. [Recommendations for critically ill patients with COVID-19]. Med Klin Intensivmed Notfmed 2020.
16. Hoffmann W, Latza U, Baumeister SE, et al. Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): a guideline developed by the German Society for Epidemiology. European journal of epidemiology 2019;34:301-17.