1- TITLE

Prospective cohort of COVID-19 cases diagnose din Vall d'Hebron Hospital, Barcelona, during the 2020 outbreak.

Study protocol

Version: 1

Date: March 25, 2020

Infectious Diseases, Internal Medicine, Pneumology, Intensive Care, Emergency, Microbiology and Pharmacy Departments from Vall d'Hebron University Hospital Barcelona, Spain

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1- STUDY DETAILS

Study title	Prospective cohort of COVID-19 cases diagnosed in Vall d'Hebron Hospital, Barcelona, during the 2020 outbreak
Short title	COVID-19_HVH
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2- SUMMARY

Prospective cohort of COVID-19 cases diagnose din Vall d'Hebron Hospital, Barcelona, during the 2020 outbreak (COVID-19 HVH).

Introduction: Since the first cases diagnosed in late December 2019, COVID-19, the disease caused by the novel coronavirus SARS-CoV-2 has spread to all the continents causing more than 100,000 cases and 4,000 deaths worldwide. The first reports reflect a severe bilateral pneumonia, but the spectrum of the disease has proven to be wide, from asymptomatic cases to Severe Acute Respiratory Distress Syndrome, having a high lethality in those sick or old. Some drugs have been repositioned to treat COVID-19 with scarce data about their efficacy.

Objectives: The main objective of this study is to describe the clinical characteristics and outcomes of the COVID-19 cases diagnosed in adult patients in the Vall d'Hebron University Hospital. Secondary objectives include data about safety and efficacy of the off-label treatments used during the outbreak, corelate laboratory, clinical and microbiological data and perform an extended passive follow-up up to 12 months after the diagnosis.

Methods: This study is designed as a prospective cohort with no specific intervention and no control group. All patients older than 18 years with the diagnosed with a confirmed or probable COVID-19 willing to provide oral consent will be included. Confirmed ones are those with a PCR or serologic positive test for SARS-CoV-2. Probable cases are those that, lacking a confirmatory test have clinical, biochemical and radiological characteristics highly suggestive of COVID-19. Patients will be evaluated on a weekly basis during admission. Mortality and morbidity will be evaluated at 1, 2, 6 and 12 months after admission. Safety and tolerability will also be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Impact: This study will provide clinicians, laboratory staff and policymakers with an accurate picture of the performance of the Health System as a whole in this crisis. Debriefing our data will be important to learn, explain the gross differences seen when comparing different regions and settings and strengthen the surveillance and response systems.

3- INTRODUCTION

In December 2019, a cluster of cases with severe pneumonia of uncertain cause were detected in Wuhan, the capital city of Hubei province in China. In just three months, more than 100,000 cases and more than 4,000 deaths have been reported at 114 countries. (Jasarevic, WHO, 2020) The initial cases had in common the contact with a seafood market in the Chinese city. Just one week after the detection of these cases, a novel coronavirus, the SARS-CoV2, was found to be the most likely cause of the disease (COVID-19). SARS-CoV2 is a new betacoronavirus, different from the common cold coronaviruses (HKU1, 229E, NL63, OC43), the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) causing the outbreaks in 2002-2003 and 2012, respectively (Zhu, NEJM, 2020)

The disease caused by SARS-CoV2 appears to have a wide spectrum of severity, from asymptomatic infection to severe pneumonia with respiratory failure and death. (Huang, Lancet, 2020) In a retrospective cohort of 191 patients from two hospitals in Wuhan, fever and cough were the most common symptoms on admission. Almost all among those patients who developed respiratory insufficiency and required mechanical ventilation or extracorporeal membrane oxygenation finally died. In the multivariate analysis, with data from 171 patients (53 deaths), older age, higher SOFA score and a d-dimer higher than 1mcg/L at admission were associated with increased risk of death. (Zhou, Lancet, 2020)

Although zoonotic in origin, the virus soon proved to have a very efficient person-to person transmission, even when the person remains asymptomatic. The main transmission route are aerosol droplets from the respiratory tract, but the virus was also isolated from feces and even from fomites that have been in contact with infected persons; vertical transmission remains to be confirmed. (Han, 2020) In the cohort reported by Zhou and colleagues, the SARS-CoV2 RNA was detectable for a median of 20 days in survivors. (Zhou, lancet, 2020)

Despite being a brand-new virus, several pharmacological and non-pharmacological interventions have proved to have some efficacy in treating the disease and preventing its spread among communities, although information on mortality remains scarce. (CDC, Interim Clinical Guidance, 2020) The protease inhibitor lopinavir combined with ritonavir, used to treat the human immunodeficiency virus infection has shown some efficacy for the treatment of the SARS-CoV(Gronenberg, Lancet, 2005) and the MERS-CoV (Chan, JIDA, 2015). There are a few reports about its efficacy in COVID-19 patients. (Lim, J Korean Med Sci, 2020; Wang, Bio science trends, 2020) Remdesivir is a novel nucleotide analogue that has in vitro activity against several coronaviruses including the SARS-CoV2, SARS-CoV and MERS-CoV. (Sheahan, Science Trans Med, 2017). Chloroquine is another repurposed drug that has shown to be effective in vitro against a broad range of viruses. (Savarino, Lancet inf, 2006) During the SARS-CoV epidemic in 2002-2003, chloroquine was tested and found to have a good in-vitro activity when added to the cell culture either before or after exposure to the virus. (Vincent, Vir J, 2005) Remdesivir and chloroquine are highly effective in the control of SARS-CoV2 infection in vitro. (Wang, Cell Research, 2020). Hydroxychloroquine was been suggested to have higher activity for SARS-CoV-2 than chloroquine. (Xueting Yao, CID, 2020) There is also some evidence suggesting the usefulness of interferon and tocilizumab in the subgroup of patients with the most severe disease.

Most of these strategies are being used currently in our hospital, and we consider that it is important to thresh the information in order to be able to share objective information together with each one's experience in the care of these patients.

4- HYPOTHESYS

Although an outbreak situation implies ahigh burden of workload for the clinical staff, being able to prospectively collect the information of the cases managed in our center is of the utmost importance to provide real-time information about our performance as a health care point aiming to reach the highest care quality and, once the outbreak is over, to be able to debrief all actions and decisions taken during this public health emergency.

5- OBJECTIVES

5.1- Main objective

To describe the clinical characteristics and outcomes of the Covid-19 cases diagnosed in adult patients in the Vall d'Hebron Hospital, a University tertiary hospital in Barcelona, Spain. The main outcomes will be measured at one month after the diagnosis.

5.2- Secondary objectives

- Describe the safety profile of the off-label treatments used during the outbreak.
- Describe the efficacy outcomes differences between the different treatment combinations.
- Describe the risk factors for severe disease, need of ventilatory support, ICU admission and death.

- Describe the coinfections and superinfections diagnosed during the course of the Covd-19.
- Corelate clinical characteristics with the estimated viral load by means of semi-quantitative PCR.
- Correlate the outcomes with the estimated viral load by means of semi-quantitative PCR.
- Describe clinical outcomes at six months and twelve months after symptom onset.
- Describe the healthcare workers' incidence of the disease and relate it to exposure time.

6- METHODS

6.1- Study design

Prospective cohort of consecutive adults admitted to the Vall d'Hebron Hospital with confirmed or probable Covid-19 during the 2020 outbreak. The first patients will be included retrospectively up to the date of the Ethical Committee clearance.

6.2- Inclusion criteria

All patients 18 years of age or older diagnosed during the SARS-Cov-2 epidemic (February 1st, 2020 to the end of the outbreak as defined by the Spanish Epidemiologic Surveillance System) at Vall d'Hebron University Hospital in Barcelona, Spain.

6.3- Exclusion criteria

- The patient or a legal representative do not consent with the inclusion of the patient's data in the study.
- Oral consent from the patient or a legal representative is unavailable for the prospective cases.

6.4-Definitions

Cases:

- Confirmed case: all patients with a positive SARS-CoV-2 PCR test in a respiratory sample (nasopharyngeal swab, sputum, bronchoalveolar lavage or aspirate, tracheal aspirate).
- Probable case: all patients with respiratory symptoms (cough, dyspnoea, chest pain, rhinorrhoea) or fever and a chest imaging test with changes compatible with Covid-19.

Clinical Outcomes:

- Positive composite outcome: A patient will be considered to have a positive outcome if is alive and without oxygen therapy at each one of the pre-specified timepoints: hospital discharge, one month after hospital admission, 6 months after hospital admission and 12 months after hospital admission.
- Negative composite outcome: A patient will be considered to have a negative outcome if he/she is dead or still in need of supplementary oxygen at each one of the pre-specified timepoints: hospital discharge, one month after hospital admission, 6 months after hospital admission and 12 months after hospital admission.

- Positive simple outcome: A patient will be considered to have a positive outcome if is alive at each one of the pre-specified timepoints: hospital discharge, one month after hospital admission, 6 months after hospital admission and 12 months after hospital admission.
- Negative composite outcome: A patient will be considered to have a negative outcome if he/she is dead at each one of the pre-specified timepoints: hospital discharge, one month after hospital admission, 6 months after hospital admission and 12 months after hospital admission.
- Specific secondary outcomes: Acute Respiratory Distress Syndrome, Respiratory Insufficiency and its grade, Cardiac Insufficiency, acute myocardial injury, Septic Shock, Acute Kidney Injury and secondary infections. Please note that due to the high volume of admitted patients, arterial partial pressure of O2 cannot be recorded in all, and thus a proxy estimation of respiratory insufficiency can be used by means of oxygen saturation on pulse oximeter (SAFi). Presence or absence of these outcomes and date of onset. Used definitions are included in the variable list in Appendix I.

Safety Outcomes:

- Positive safety outcome: A patient will be considered to have a positive outcome if, during the treatment for SARS-CoV-2 or up to 14 days after the end of the treatment, he/she does not suffer any grade 3 or superior adverse event according to the definitions of the Common Terminology Criteria for Adverse Events (CTCAE) version 5 (Appendix II), OR any Serious Adverse Event (SAE) defined as:
    - Death of the subject.
    - Potentially lethal adverse reaction with the study drug. This refers to an event during which the subject was at an imminent risk of death; it does not refer to an event that could cause death shall this event be of a bigger intensity.
    - Hospitalization or prolongation of a previous hospitalization.
    - Disability that causes a significant functional impairment, temporarily or permanently.
    - Fetal malformation.
- Negative safety outcome: A patient will be considered to have a negative safety outcome if, during the treatment for SARS-CoV-2 or up to 14 days after the end of the treatment, he/she suffers any grade 3 or superior adverse event or any SAE.
- Positive tolerability outcome: A patient will be considered to have a positive tolerability outcome if, during the treatment for SARS-CoV-2 or up to 14 days after the end of the treatment, he/she does not suffer any adverse event.
- Negative tolerability outcome: A patient will be considered to have a positive tolerability outcome if, during the treatment for SARS-CoV-2 or up to 14 days after the end of the treatment, he/she suffers any adverse event.

Efficacy Outcomes:

This is not an interventional controlled group, so it is not its primary objective to provide information about the efficacy of the different treatments tested during the outbreak. Furthermore, the treatment recommendations change every few days as new evidence becomes available. On the other hand, resources are exhausted as the outbreak lasts longer and thus it is not possible to directly compare the treatment outcomes of the patients from different parts of the outbreak. Nevertheless, made to withdraw information about the influence of the different treatment regimens on the outcomes of COVID-19 patients, treatments will be stratified as follows:

- Hidroxicloroquine plus protease inhibitor

- Hidroxicloroquine plus azithromycin
- Lopinavir/ritonavir
- Darunavir/cobicistat
- Interferon
- Tocilizumab

The efficacy outcomes measured are listed below:

- Time in days to oxygen supplementation weaning.
- Time in days to fever resolution.
- Time in days to hospital discharge.
- ICU admission days.
- Mortality at 1, 6 and 12 months.

6.5- Sample size

This study will include a convenience sample size consisting of all patients diagnosed with a confirmed or probable Covid-19 during the study period.

6.6- Study schedule

Due to the emergency of the outbreak it is expected to start as soon as the clearance by the Ethical Committee is obtained.

A first preliminary report will be issued as soon as 500 patients are included in the database. The end of the study and the final report cannot be scheduled due to the unpredictable course of the current outbreak but will be delivered within 6 months after the outbreak end is declared in the autonomous community of Catalonia.

The cohort surveillance will be conducted in the facilities of Vall d'Hebron Hospital and by reviewing the Electronic Medical Charts and, if needed, by telephonic interview during the extended follow-up.

6.7- Data collection and variables

Data collection will be performed using a web-based electronic database created for the purposed of the study in the RedCAP platform (Vanderbilt University). The variables collected include sociodemographic characteristics, medical history, anthropometric characteristics and vital signs, physical examination and symptoms, concomitant medication, adverse events, blood tests, imaging studies, microbiological results, supportive measures needed, secondary specific outcomes and gross clinical outcomes. During admission the patients will be evaluated on admission, at 48h and on a weekly basis; after discharge, at month 1, 2, 6 and 12 after hospital admission. Table 1 summarizes the variables and the standard definitions used according to the current literature included in the database.

7- STATISTICAL CONSIDERATIONS

Descriptive statistics will be used for the proportions. A logistic univariate regression will be used to identify the candidate variables to enter in a multivariate logistic regression model to establish significant associations with the variables. Mortality and efficacy outcomes will be analyzed using Kaplan-Meier survival curves and Cox regression (analysis of factors associated with clinical outcomes). A propensity score test will be used to analyze the influence of the treatment regimens in clinical outcomes. A two tails p-value of 0.05 will be considered as the significance value. We have not planned an intermediate analysis.

8- ETHICAL CONSIDERATIONS

All participating subjects will be adequately informed orally. A written informed consent will not be collected because of both logistic and safety issues as the patients cannot touch materials that will be kept outside the isolation areas inside the hospital. Investigators will actively ask participants for the need of additional information, comments or doubts regarding the study.

Patient data will be treated in accordance with the current European and national regulations for the Protection of Personal Data. The personal data obtained will be the minimum amount to cover the purposes of the study. The data collected for the study will be identified by a code, and only investigators of the study, or personnel assigned by the investigators, will have access to the full dataset. The database will meet the most demanding security requirements and has an access log tracking accesses and modification. All patients have the right to revoke their participation in the study without prejudice to their medical care. Investigational Data will be kept at the institutions for the time legally required by regulations.

Covid-19 is a novel coronavirus with a high fatality rate among elderly and comorbid population. Healthcare worker are essential during the fight against an outbreak and should be carefully protected to ensure high quality patient care activity. Quarantine measures has been shown effective to curb hospital transmission, although high costs in terms loss of healthcare task force is paid. Infected healthcare workers should be kept in quarantine even for a longer time span, and it may pose a threat to their health with poor outcome derived from the SARS-Cov-2 infection. Finding a pharmaceutical intervention that can reduce the proportion of healthcare worker infected after a SARS-CoV-2 exposure will improve the sustainability of the health system during an outbreak. Additionally, it may be applied to household contacts to reduce the number of newly infected after an exposure with SARS-Cov-2 infected patient.

Appendix I. Study variables	
Description	**Observations**
Demographics	
Electronic Medical Record Number	
Date of birth	
Sex	
Gestation status	Yes/no.
Weeks of gestation	
Nationality	Where the patient was born.
Country of origin	If recent travel, where did the patient came from.
Date of arrival to Spain	If recent travel, date of arrival.
Medical history	
Smoking status	Active user, former user, never used.
Use of electronic tobacco products	Active user, former user, never used.
Alcoholic status	Daily alcohol intake ≥ 2 units of alcohol (1 unit of alcohol: 4% alcohol 250 ml (i.e. beer); 4.5% alcohol 218 ml (i.e. cider); 13% alcohol 76 ml (i.e. wine); 40% alcohol 25ml (i.e. whisky))
Current or previous use of intravenous illicit drugs	Yes/no.
Homeless status	Yes/no.
Psychiatric medical history	Yes/no.
Type of psychiatric medical history	Anxiety, psychotic, depressive, bipolar, other.
Cognitive impairment	Yes/no.
Barthel index at admission	
Eastern Cooperative Oncology Group (ECOG) performance scale	1-Completely active 2-Mild functional impairment 3-Autonomous for self-care; <50% of the time in bed 4-Autonomous for self-care; >50% of the time in bed 5-Nedds help for self-care 6-Death
Diabetic status	Type of treatment (none, oral, insulin); date and value of the last available glycated hemoglobin.
Immune suppression status	Yes/no.
Type of immune suppression	HIV; Solid Organ Transplantation; Bone Marrow Transplantation; Autoimmune/systemic disease; pharmacological; other (speciy).
HIV patients	Date and value of the last available CD4 T-cell count and viral load.
Solid neoplasm	Yes/no; status: active/no evidence of disease
Hematological neoplasm	Yes/no; status: active/no evidence of disease
Another hematological disease	Specify.

Arterial Hypertension	Yes/no.
Cardiac insufficiency	Yes/no.
Ischemic cardiomyopathy	Yes/no.
Atrial fibrillation	Yes/no.
Another cardiac disease	Specify.
Pneumopathy	Specify.
Spirometry before COVID-19	Value in mL and %, and date of the most recent FEV1 and CO diffusion (alveolar volume corrected).
Chronic kidney disease	Value and date of the last glomerular filtration rate (CKD-EPI formula); need for kidney replacement therapy.
Non-viral chronic liver disease	Yes/no.
Hepatitis B status	Yes/no.
Hepatitis C status	Yes/no.
Cirrhosis status	Yes/no.
Central Nervous System disease	Specify if vascular, autoimmune or degenerative
Obesity	Last known body mass index.
Concomitant medication	
Relevant chronic medication	ACEI, ARB, other anti-hypertension drugs, oral antidiabetics, insulin, anti-cholesterol drugs, anti-depressive drugs, anti-epileptic drugs, anxiolytic drugs, hydroxicloroquine, corticosteroids, conventional immune-suppressors, biologic immune-suppressors, other.
Biometric information	
Weight	
Height	
Body mass index	
Vital signs	
Systolic and diastolic blood pressure	
Temperature	
Cardiac rate	
Respiratory rate	
Oxygen saturation	(pulse-oximeter)
Oxygen therapy	Oxygen inspired fraction, flux and delivering device (nasal cannula, Venturi mask, reservoir mask, high flux nasal cannula, non-invasive mechanical ventilation, invasive mechanical ventilation)
Charlson index at the moment of diagnosis	
Outcome	
Final otcome	Discharged with negative PCR, discharged based on clinical judgement, hospitalized, adtmitted to the ICU, dead, lost to follow-up, transfered to other facility
Death related to COVID-19	Yes/no.
Blood tests (repeatable instrument with date of extraction)	

Hemoglobin	g/dL
Hematocrit	%
Mean corpuscular volume	
Leukocytes	X10^9/L
Neutrophils	%
Lymphocytes	%
Monocytes	%
Eosinophils	%
Platelets	X10^9/L
Thrombin time	%
Partial Thromboplastin Time	seconds
D-dimer	ng/mL
Fibrinogen	g/L
Glucose	mg/dL
Urea	mg/dL
Creatinine	mg/dL
Estimated glomerular filtration rate	CKD-EPI formula, insert 90 if eGFR >90
Urate	mg/dL
Sodium	mmol/L
Potassium	mmol/L
Calcium	mg/dL
Total bilirubin	mg/dL
Aspartate-aminotransferase	UI/L
Alanine-aminotransferase	UI/L
Alkaline phosphatase	UI/L
Gamma-glutaryl transferase	UI/L
Creatinine kinase	UI/L
Lactate-dehydrogenase	UI/L
Total cholesterol	mg/dL
Triglycerides	mg/dL
C reactive protein	mg/dL
Erythrocyte Sedimentation Rate	mm/h
Ferritin	ng/mL
Proteins	g/dL
Albumin	g/dL
High-sensitivity cardiac troponin	
Lactate	
Arterial partial O2 pressure	mmHg
Interleukin-6 (IL-6)	pg/mL
Interleukin-2 soluble receptor (srIL-2)	

Microbiology tests	
Nasopharyngeal swab	Result of the PCR test and date of extraction
Other samples	Type of sample (sputum, tracheal aspirate, bronchoalveolar lavage/aspirate), date of extraction, and PCR result
Pneumococcal antigen in urine	Positive/negative
Blood cultures	Dichotomic result and specifying isolated microorganism. Clinically significant?
Sputum culture	Dichotomic result and specifying isolated microorganism. Clinically significant?
Initial symptoms	
Onset date	Overall symptoms onset date, fever onset date and dyspnea onset date.
Symptom list	Fever, weight loss, general weakness, cough, dyspnea, expectoration, hemoptysis, pleuritic chest pain, night sweats, rhinorrhea, nasal congestion, anosmia, cachosmia, odynophagia, myalgia/arthralgia, nausea, vomiting, diarrhea, confusion, coma, asymptomatic, other symptoms.
Follow-up symptoms	
Overall patient evolution, according to clinical criteria	Stable, worsening, improvement.
Is the patient asymptomatic?	
Cough	Worse, stable, improvement, resolution, new onset, unknown.
Dyspnea	Worse, stable, improvement, resolution, new onset, unknown.
Expectoration	Worse, stable, improvement, resolution, new onset, unknown.
Diarrhea	Worse, stable, improvement, resolution, new onset, unknown.
Vomiting	Worse, stable, improvement, resolution, new onset, unknown.
Myalgia/arthralgia	Worse, stable, improvement, resolution, new onset, unknown.
General weakness	Worse, stable, improvement, resolution, new onset, unknown.
Hyporexia	Worse, stable, improvement, resolution, new onset, unknown.
Anosmia	Worse, stable, improvement, resolution, new onset, unknown.
Does the patient still have fever?	If no, specify date of resolution.
Physical exam	
General appearance	Good, regular, bad
Lung auscultation	Crackles, wheezes, ronchi, hypophonesis, other.
If crackles, lung fields affected	Unilateral/bilateral; basal, mid-third, upper-third, 2/3, global.
Imaging studies (repeatable instrument with date of performance)	

Chest X-ray	Acute lesion yes/no
If yes, type of lesion	Alveolar infiltrate, interstitial pneumonia, atelectasis, pleural effusion, other.
If yes, extension of the lesion	Unilateral/bilateral; <33%, 33-66%, >66%.
Chest CT scan	Acute lesion yes/no
If yes, type of lesion	Ground glass opacification; consolidation
If yes, extension of the lesion	Unilateral/bilateral; peripheral, posterior, multilobar, other.
If previous image study, how did it evolve?	Worse, stable, improvement, resolution, new onset, unknown.
Follow-up lung fucntion (repeatable instrument with date of performance)	
Spirometry after discharge	Value in mL and %, and date of the most recent FEV1 and CO diffusion (alveolar volume corrected).
6-minute walking test	Whether it was performed or not and date.
Treatment	
Department treating the patient	Infectious diseases, Internal Medicine, Intensive Care Unit, Other
Drug 1-9	Hydroxychloroquine, Lopinavir, Darunavir, Ceftriaxone, Azithromycin, Interferon beta, Tocilizumab, other. Drug1-9 start and stop dates.
Reason for drug 1-9 stop	Improvement, futility, toxicity, death, transfer to another facility, discharged home.
Corticosteroid use	Yes/no.
If corticosteroids were used, did the patient receive at least one high-dose bolus?	Yes/no. High-dose corticosteroid bolus is considered a single dose equivalent to 250mg of prednisone or superior.
If corticosteroids were used, specify	Drug (prednisone, metilprednisoloone, dexamethasone, hydrocortisone) and cumulated dose in prednisone equivalent miligrams.
Angiotensin Converting Enzyme Inhibitors	Use before hospital admission and whether they were withdrawn during the admission or not.
Angiotensin Receptor 2 blockers	Use before hospital admission and whether they were withdrawn during the admission or not.
Non-steroidal anti-inflammatory drugs	Use before hospital admission and whether they were withdrawn during the admission or not.
Adverse Events (AE, repeatable instrument for each adverse event)	
Did the patient present any AE?	Yes/no; name; onset and finishing dates.
Is it attributable to the medication used to treat COVID-19?	Yes/no.
Suspected drug	Name of the drug; start date, stop date.
Measures needed	No measures were needed; symptomatic treatment; temporary withdrawal of the suspected drug; permanent withdrawal of the suspected drug; temporal withdrawal of all drugs; permanent withdrawal of all drugs.
If symptomatic treatment was used	Specify
Grade of the AE	According to the CTCAE v5: mild (grade 1); moderate (grade 2-3); severe (grade 4-5)

Does the AE fulfill SAE criteria?	Yes/no. Serious Adverse Event: Death of the subject; Potentially lethal adverse reaction with the study drug; Hospitalization or prolongation of a previous hospitalization; Disability that causes a significant functional impairment, temporarily or permanently; Fetal malformation.
Needed hospital admission for management?	Yes/no
Outcome of the AE	Recovery without sequelae; recovery with sequelae; persistent signs or symptoms; death; unknown.
Intensive Care Unit (ICU) Admission	
The patient required ICU admission	Yes/no; date of admission and date of discharge.
Reason for ICU admission	Acute respiratory distress; septic shock; other (specify).
Ventilatory support	
The patient required ventilatory support	Yes/no.
Type of ventilatory support required	Multiple choice: Reservoir facial mask; high-flux nasal cannula; non-invasive mechanical ventilation; tracheal intubation and mechanical ventilation; extra-corporeal membrane oxygenation (ECMO).
Date of start and stop	Dates of start and stop for each category of ventilatory support.
Other support measures	
Vasoactive drugs	Starting and finishing date.
Renal Replacement Therapy	Excluding patients in hemodialysis before disease onset; starting and finishing date.
Secondary outcomes	
Acute Respiratory Distress Syndrome	Yes/no; date of onset. Berlin criteria: -Respiratory symptoms must have begun or worsened within one week of a known clinical insult. -Bilateral opacities on chest imaging that are not related to pleural effusion, atelectasis or nodules. -The respiratory insufficiency must not be completely explained by cardiac failure. -PaFi <200mmHg OR SAFI <235.
Acute Respiratory Insufficiency	Yes/no; date of onset. PaO2 <60mmHg; pulse-oximetry <90% on room air; PaFi <300 OR SAFI <315. -Mild: PaFi 299-200 -Moderate: PaFi 199-100 -Severe: PaFi 99 or less
Decompensated Cardiac Insufficiency	Yes/no; date of onset Combination of clinical signs/symptoms and echocardiographic findings.
Acute myocardial injury	Yes/no; date of onset. Acute elevation of cardiac troponin and/or acute change in echocardiographic or central catheter estimated cardiac function.
Septic shock	Yes/no; date of onset. Need of vasoactive drugs to maintain a mean arterial pressure of >65mmHg in absence of hypovolemia in the context of a suspected or confirmed systemic infection.

Acute Kidney Injury	Yes/no; date of onset. AKIN criteria: increase in serum creatinine of ≥0.3mg/dL or ≥50% within 48h OR urine output of <0.5mL/kg/h for >6 hours -Stage 1: Increase of serum creatinine ≥0.3mh or 150-200% of baseline OR urine output <0.5 mL/kg/h for 6-12h -Stage 2: Increase of serum creatinine to 200-300% of baseline OR urine output of <0.5mL/kg/h for 12-24h -Stage 3: increase of >300% OR increase of >0.5m/dL to ≥4mg/dL OR initiation of renal replacement therapy OR urine output <0.3mL7kg/h for >24h or anuria >12h
Secondary infection other than SARS-CoV-2	Yes/no; date of onset.
Data dictionary and instruments can be shared through REDCap on demand to the Principal Investigator.	