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Serial measurements in COVID-19-induced acute respiratory disease to unravel heterogeneity of the disease course: design of the Maastricht Intensive Care COVID cohort (MaastrICCht)

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ABSTRACT

Introduction The course of the disease in SARS-CoV-2 infection in mechanically ventilated patients is unknown. To unravel the clinical heterogeneity of the SARS-CoV-2 infection in these patients, we designed the prospective observational Maastricht Intensive Care COVID cohort (MaastrICCht). We incorporated serial measurements that harbour aetiological, diagnostic and predictive information. The study aims to investigate the heterogeneity of the natural course of critically ill patients with a SARS-CoV-2 infection.

Methods and analysis Mechanically ventilated patients admitted to the intensive care with a SARS-CoV-2 infection will be included. We will collect clinical variables, vital parameters, laboratory variables, mechanical ventilator settings, chest electrical impedance tomography, ECGs, echocardiography as well as other imaging modalities to assess heterogeneity of the course of a SARS-CoV-2 infection in critically ill patients. The MaastrICCht is also designed to foster various other studies and registries and intends to create an open-source database for investigators. Therefore, a major part of the data collection is aligned with an existing national intensive care data registry and two international COVID-19 data collection initiatives. Additionally, we create a flexible design, so that additional measures can be added during the ongoing study based on new knowledge obtained from the rapidly growing body of evidence. The spread of the COVID-19 pandemic requires the swift implementation of observational research to unravel heterogeneity of the natural course of the disease of SARS-CoV-2 infection in mechanically ventilated patients. Our study design is expected to enhance aetiological, diagnostic and prognostic understanding of the disease. This paper describes the design of the MaastrICCht.

Ethics and dissemination Ethical approval has been obtained from the medical ethics committee (Medisch Ethische Toetsingscommissie 2020-1565/3 00 523) of the Maastricht University Medical Centre+ (Maastricht UMC+), which will be performed based on the Declaration of Helsinki. During the pandemic, the board of directors of Maastricht UMC+ adopted a policy to inform patients and ask their consent to use the collected data and to store serum samples for COVID-19 research purposes. All study

Strengths and limitations of this study

- ► Serial measurements are required that characterise the disease course of SARS-CoV-2 infection in mechanically ventilated patients.
- ► Data collection and analysis will be done according to a predefined protocol.
- ► Flexible, evolving design enabling the study of multiple aspects of SARS-CoV-2 infection in mechanically ventilated patients has been created.
- ► Single center, only intensive care unit patients, are included.

documentation will be stored securely for fifteen years after recruitment of the last patient. The results will be published in peer-reviewed academic journals, with a preference for open access journals, while particularly considering deposition of the manuscripts on a preprint server early.
Trial registration number The Netherlands Trial Register (NL8613).

INTRODUCTION

SARS-CoV-2 infection is highly heterogeneous in its presentation.[1–3] Approximately 40% of the patients show no clinical signs and 40% have a mild illness, whereas around 20% require hospitalisation, of whom 5%–10% develop a critical disease that requires mechanical ventilation.[4] The SARS-CoV-2 disease course in mechanically ventilated patients is unknown, while the COVID-19 pandemic, caused by SARS-CoV-2, stresses intensive care (IC) resources to maximum capacity in pandemic areas such as the Netherlands.[5] In contrast to other regions in the world,[6] we had time to plan, with the advantage to design a study that investigates heterogeneity of the disease course.

We hypothesise that a comprehensive characterisation of the heterogeneity of the natural course of critically ill patients with SARS-CoV-2 will enhance our aetiologic, diagnostic and prognostic understanding of the disease, which may help to guide IC resources and patient care. Therefore, we initiated the Maastricht Intensive Care COVID cohort (MaastrICCht). We intend to collect a broad set of clinical variables and biomarkers serially over time that precede the outcome in mechanically ventilated patients infected with SARS-CoV-2. Unfamiliarity with SARS-CoV-2 infection and its disease course raises many aetiologic diagnostic and prognostic questions in IC practice. For example, how does lung compliance develop over the course of the infection? How does multi-organ failure develop over the course of the disease for patients that survive versus those that do not? What are the cardiovascular complications that can be diagnosed early? Which patients develop thrombosis?[7] Is thrombotic risk driven by inflammation and affected by comorbidities, such as obesity, type 2 diabetes mellitus and the presence of cardiovascular disease?[3 7] Does immobilisation by a neuromuscular blockade, also, play a role?[8] Serial data to investigate such topics are scarce.[9 10]

The COVID-19 pandemic required swift implementation observational research activities to unravel the clinical changes in the course of the disease that precede favourable or poor outcome in mechanically ventilated patients with a SARS-CoV-2 infection admitted to the intensive care unit (ICU). We intend to use serial measurements to investigate the aetiology, diagnostic and prognostic value of respiratory variables (ie ventilator settings, prone positioning and chest electric impedance tomography (EIT)),[11–14] cardiovascular variables (laboratory variables, ECGs, echocardiograms and CT scans of the chest),[10] metabolic variables (kidney function, liver biochemistry and electrolytes) and thrombotic complications (laboratory variables and thrombotic events) among others as described below. We describe the design of the MaastrICCht in detail.

METHOD AND ANALYSIS

Participants

This prospective cohort study is conducted on the IC of the Maastricht University Medical Centre+ (Maastricht UMC+), a tertiary teaching hospital in the southern part of the Netherlands. Usually, our ICU has 27 beds, divided over three subunits to which all types of critically ill patients are admitted. However, to provide care for patients during the COVID-19 pandemic, our ICU underwent a rapid stepwise upgrade to a maximum of 64 beds, consisting of six subunits covering 52 beds for COVID-19 patients and two subunits covering twelve beds for IC patients without COVID-19.

We intend to include all patients admitted to one of our six COVID-19 IC subunits. Patients are intubated and mechanically ventilated and have a positive PCR for SARS-CoV-2 and/or a CT scan of the chest scored positive based on the COVID-19 Reporting and Data System (CO-RADS) Score of 4–5 by a radiologist.[15] Patients can be admitted via our emergency department, via non-ICU wards and by transportation from other ICUs either for tertiary care referral or due to lack of bed availability in the regional hospitals.

Patient and public involvement

The exceptional circumstance of COVID-19 pandemic did not allow to inquire for patient's priorities, experience and preferences, as patients were admitted in overwhelming numbers, stressing resources to a maximum capacity. Swift implementation of observational research activities to collect data felt as an ethical obligation to the society. There was no time/there were no resources available for patient involvement in the study design. However, as the exceptional circumstance for COVID-19 are retracting, we are now in contact with individual patients and patient organisations and they are involved into the conduct of future studies with our cohort and with collaborations. Dissemination of the study results takes place via the patient organisations and peer-reviewed publication. We intend to thank the patient's advice in the contributorship statement/acknowledgements of our published results in the future.

Registry and research questions

We developed a protocol for this prospective cohort that contains variables of interest, based on existing literature and based on variables of interest of study initiatives from other centres and study groups (please, see below).[16 17] Many cohort studies in patients with COVID-19 collect similar variables. We sought to collect all of these variables to be able to address a broad range of research questions. We established our list of variables to be retrieved (online supplemental table 1), which we intend to extend in the future. Furthermore, we developed a uniform protocol for patient charts during admission to allow for uniform collection of variables. Thus, we designed the cohort study to register a baseline set of clinical, biochemical and COVID-19-specific variables, and to collect all relevant

outcome variables. Additionally, we will record clinical data each day during ICU stay for patients included in the cohort.

A major advantage of this approach is that all variables collected for this cohort are part of routine clinical care but are now collected uniformly and reported in a predefined format. This prospective cohort will serve as an open-source database for other investigators to submit requests for the data. The cohort steering committee will consider all requests. To foster data sharing in the future, we chose to align a major part of data collection with an existing IC data registry and two international COVID-19 data collection initiatives (please, see below for details), in a way that is in line with the Findable, Accessible, Interoperable and Reusable (FAIR) data principle.[18] Our design thereby enables the contribution of data to other initiatives. A data-sharing agreement and plan, approved by the local institutional review board, will be necessary to share data of the MaastrICCht with other data collection initiatives. Also, the cohort is designed in such a way that additional measures can be added during the study period based on new knowledge obtained from the rapidly growing body of evidence. Approval by the local institutional review board will be necessary to add additional measurements that are not part of routine clinical care.

The first primary aim is to investigate the course of COVID-19 respiratory disease during mechanical ventilation. Therefore, we will, first, investigate the association between time (days after intubation) and variables that characterise ventilation. Next, we will compare how these variables develop over time for patients who survive or deceased. More specifically, we will use clinical respiratory variables, ventilator settings and chest EIT (described extensively in the supplemental material). Briefly, with regard to EIT, we will focus on dynamic compliance, percentage, collapse and percentage overdistension. Additionally, we intend to investigate the role of prone positioning in the course of the disease. The second primary aim will be to describe and investigate cardiovascular changes over time that determine incident thrombosis during mechanical ventilation of patients with COVID-19. Here, we will focus on cardiovascular biomarkers, such as biochemical markers of inflammation and coagulation, and markers of cardiac structure and function (i.e. ECG, echocardiography and CT scans of the chest). Third, we will investigate the development of multi-organ failure and compare its disease course for patients that survive versus deceased . Research questions are organised according to the type of research, e.g. aetiology, diagnostic and prognostic,.Examples are given in table 1.[5]

Data collection

The design and serial data collection enable aetiological, diagnostic and prognostic research, and we will first focus

Table 1 Research questions in COVID-19-induced respiratory disease in an intensive care population on mechanical ventilation

Research question	Aetiology
1	Is the development of dynamic compliance and chest EIT parameters more favourable in survivors as compared with non-survivors?
2	Is the development of multi-organ failure worse in non-survivors as compared with survivors?
3	Is an increase in d-dimer, fibrinogen, C reactive protein and ferritin plasma concentrations over time greater in patients with incident thrombosis?
	Diagnosis
4	Do ECG changes over time discriminate between incident thrombosis?
5	Does SOFA Score changes discriminate between survival or deceased?
6	Does prone, vs supine, positioning determine a favourable improvement in PaO2/FiO2 over time?
7	Does EIT, dynamic compliance, ARDS PEEP/FiO_2 or clinical opinion diagnose optimal PEEP best?
	Prognosis
8	Can conventional risk scores predict outcome in COVID-19 patients?
9	How do newly developed risk scores perform in our cohort?[43–47]
10	Can chest EIT predict prone positioning?
11	Can changes in PF ratio during the first 72 hours predict prone positioning?
12	Are serially measured coagulation tests able to predict adverse thromboembolic and mortality events during the course of the disease?
13	Does acute kidney injury burden predict mortality events during the course of the disease?[48]

ARDS, acute respiratory distress syndrome; EIT, electric impedance tomography; FiO_2, fractional inspired oxygen; PaO2
, Partial pressure of oxygen
; PEEP, Positive end-expiratory pressure; SOFA, sequential organ failure assessment.

on the topics of respiratory and cardiovascular disease and multi-organ failure. The flexible cohort design will allow us investigation of additional topics based on our extensive set of baseline and serial measurements (online supplemental table 1). All variables and measurements are predefined in our study protocol. Inclusion and collection of variables are performed by medical research interns and PhD candidates not involved in patient care. Data collection for this cohort has started on the 25th of March 2020 and will be continued without a predefined end date.

For the baseline characteristics, we will collect data that is aligned with the Dutch National Intensive Care Evaluation (NICE) registry and two international COVID-19 data collection initiatives. First, we will collect the minimal dataset of the NICE registry (https://www.stichting-nice.nl/), which includes data from each ICU across the Netherlands. The minimal dataset is the core registration that includes demographic, admission and discharge data of Dutch IC patients.[19] Second, we will collect data on the COVID-19 case report forms (CRF) of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and World Health Organization (WHO).[20] This ISARIC/WHO tool queries symptoms of clinical infection, comorbidities, pathogen testing, therapy and outcome variables. Third, we will collect data fostering the Cardiac complicAtions in Patients with SARS Corona vIrus 2 regisTrY, which is an extension of the COVID-19 CRF and of the WHO list that additionally queries cardiac history, diagnostics and occurrence of cardiovascular complications in COVID-19 patients.[21] Fourth, by collecting a vast number of additional variables (both from records and monitors) uniformly, we will be able to merge our cohort to address additional questions in collaboration with others.

Serial chest EIT

In our department, chest EIT is performed by specialist ventilation practitioners and is available if considered indicated to support clinical practice in patients with respiratory failure and thus is not performed in each patient each day.[14] EIT identifies a personalised positive end-expiratory pressure to guide an optimal ventilation distribution as shown in patients affected by the acute respiratory distress syndrome (ARDS).[22] During the upscaling of COVID-19 ICU subunits, the team of ventilation practitioners was extended with trained medical research interns and technical physicians to cover serial chest EIT measurements in each of the six COVID-19 IC subunits. Data collection on chest EIT was supervised by the specialist ventilation practitioners.

For the MaastrICCht, our specialist ventilation practitioner team will start the first chest EIT measurement in each admitted patient after intubation as soon as clinically and logistically possible. We intend to obtain measurements in every mechanically ventilated patient with COVID-19 with intervals of 2–3 days during their ICU admission, if feasible, and, in particular, after changing clinical conditions, that is, a change in ventilator settings,[23] clinical respiratory deterioration and changes in positioning (i.e., prone–supine and vice versa). If the patient stabilises and receives pressure support ventilation, chest EIT measurement frequency will decrease, and one to two measurements will be done during the further course of the disease, while on mechanical ventilation. Our chest EIT measurement protocol has been aligned with the chest EIT protocol of the Erasmus University Medical Centre, Rotterdam, the Netherlands, to enable pooling of chest EIT data in collaboration,[11–14 24] and is described in the online supplemental.

Serial clinical, physiological and laboratory measurements

We intend to collect daily clinical and physiological variables, laboratory variables, electrocardiography and medication use (please, see online supplemental table 1).[25 26] Consequently, a standard set of plasma and serum biomarkers will be measured daily. Also, for each serum blood sample, the leftover serum will be collected by our clinical chemistry department and stored for future biomarker studies (e.g., endothelial dysfunction markers and cytokines).[27] Similarly, citrated plasma will be used to study rotational thromboelastometry and thrombin generation. No samples for genetic analyses were obtained, however.

Additional measurements

We intend to collect data from echocardiography, chest X-rays and CT scans of the chest performed in daily care.[28] The latter will be performed for primary pulmonary assessment (acquired as non-contrast triage scans)[29] or for dedicated cardiovascular assessment (based on contrast-enhanced CT scans).

Outcome variables

We collect information on events and complications in all patients. We record the intubation and extubation date and time, need for extracorporeal membrane oxygenation[30] and need for renal replacement therapy, thromboembolic events and resuscitation.[31] We collect data from ICU admission until time of discharge. Data collection continues for patients who are readmitted to the ICU. In case a patient deceases, an intensivist will define the cause of death.[32 33]

Data management

A customised electronic CRF was developed and implemented for the current MaastriCCht, using CASTOR V.2020.18. Independent study monitoring of the organisation and the conduct of the study were in adherence to the Good Clinical Practice guidelines. All variables were considered in daily care and led to decisions on diagnostics and interventions.

Outline of the statistical analyses plan

All reports will be written following reporting guidelines appropriate for the type of study (i.e., Strengthening the Reporting of Observational Studies in Epidemiology for

observational studies, Standards for Reporting Diagnostic Accuracy (STARD) for diagnostic studies and Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) for prognostic studies; see the Enhancing the QUAlity and Transparency Of Health Research network at www.equator-network.org for detailed information). We will describe baseline characteristics of the study sample as means±SD, median and IQR, and percentages, as appropriate. Pvalues will be interpreted according to the American Statistical Association's Statement on Significance and P-Values.[34] All external researchers submitting a data request will be required to produce a statistical analysis plan that will be reviewed by the cohort steering committee. A summary of the statistical analysis plan for the currently planned research questions is summarised below.

In case of incomplete variables, data will be imputed if the proportion of incomplete patients is over 5%, excluding longitudinal measures that will be analysed using generalised linear mixed-effects regression. Multiple imputation will be used with the percentage of incomplete patients as the number of imputations. Predictive mean matching will be used to draw values to be imputed, as this is more robust to misspecification of the imputation model. If applicable, the results of multiply imputed data will be pooled using Rubin's rules. In other cases, results will be pooled using available pooling methods.

AetiologicalEtiological research questions

In order to use all serial data starting from intubation, for the primary analysis, we will use flexible longitudinal data analyses techniques such as generalised linear mixed-effects models. To fully investigate the respiratory disease course, we intend to use a 2-level generalised linear mixed-effects model (patients and days) to study the association between time and clinical respiratory/ventilator settings. In particular with regard to EIT, we intend to use a -3-level generalised linear mixed-effects model (patients, days and positive-end-expiratory pressure step) to study the association between time and dynamic compliance, percentage collapse and percentage overdistension. Where applicable, we will model longitudinal and time-to-event data simultaneously using a joint model in case of survival endpoints compared with binary endpoints. First, we will categorise the sample into groups of predefined outcomes, such as survivor versus non-survivors, responder versus non-responder to prone positioning and the presence versus the absence of thrombotic events. Then, we will model the preceding serial data over time for these categories. After reporting the crude results of the generalised linear mixed-effects models, the models will be extended with covariates to adjust for potential confounders. Confounders will be retained in the model according to the method of Rothman *et al*,[35] if they significantly contribute to the model, as quantified by the Akaike Information Criterion, or if they improve the precision of the estimated treatment effect. Effect modification will be examined for sex and based on pre-specified hypotheses. Results are reported as effect size with 95% CIs.

Diagnostic and prognostic research questions

Diagnostic and prognostic modelling will be performed with a minimum of ten events per variable that is regarded as a candidate diagnostic or prognostic variable. Variable selection will be performed using the Akaike Information Criterion to arrive at a more parsimonious model. Internal validation will be estimated using bootstrap resampling. In each bootstrap sample, the model fitting steps will be repeated. The bootstrap resampling yields a shrinkage factor that will be used to shrink the coefficients towards zero to compensate for overfitting (ie, the phenomenon that a model performs best on the data used to develop it). Also, the bootstrap internal validation will yield measures of performance adjusted for optimism (ie, it estimates measures of performance in future patients). Model performance will be quantified using estimates of model fit (i.e. Nagelkerke's R squared), of discriminative ability (the area under the receiver operating characteristic curve, including 95% CI) and of calibration, by visually inspecting a calibration plot. If applicable, the model outcome will be dichotomised and test characteristics, such as sensitivity, specificity, positive and negative likelihood ratio, will be computed.

In a pragmatic approach, with a world-wide requirement of understanding COVID-19 pathophysiology in mechanically ventilated patients, we chose a stepwise release of cohort data and locked the data collection for the first time on the 29th of April to release the first data as timely as possible. The results of this first data collection will be reported shortly.

Future perspectives

The data from this cohort will be released in a stepwise approach, so that in this acute phase, most pressing research questions can be addressed, but that the accumulation of data will produce ever-larger datasets for future research projects. If the same hypothesis will be tested over multiple data exports, we plan to correct for sequential testing.[36] We also aim to analyse the ECGs, echocardiography and CT imaging results that are acquired now for later analyses. In addition, the stored serum samples will be used for further biomarker research, which we aim to compare with biomarkers collected from patients affected by ARDS.[37] We will collect data on extracorporeal membrane oxygenation, which can support the Extracorporeal Life Support Organization's registry.[38] Also, we intend to analyse microbiology results as, for example, fast replication of RNA viruses is known to introduce mutations in viral replication. Replication mutations may introduce more or less virulent strains that infect humans. It remains unclear whether the most virulent SARS-CoV-2 strains of a total heterogeneous SARS-CoV-2 pool, in particular, are relevant for the course of the disease in infected patients who develop a critical illness.

Furthermore, the rapid spread of COVID-19 in the Netherlands required swift transfers of mechanically ventilated patients from smaller hospitals to our tertiary teaching hospital and from our hospital to Germany in several cases.[39 40] The study design includes a potential to address whether transferred patients' disease course and outcome differ from other admitted patients. Moreover, regional differences in outcome, both within our national as in comparison to Belgium and Germany can be explored and this collaboration is founded and funded.

In addition, we plan a long-term follow-up via outpatient clinic visits to evaluate the quality of life of survivors and will collaborate with rehabilitation medicine specialists.[41] Later, when the COVID-19 pandemic recedes, we will modify the ongoing cohort data collection to investigate and observe pathophysiological changes in other clinical variables and novel biomarkers of interest that precede favourable and poor outcome in patients without COVID-19 admitted to the IC.

Strengths and limitations

Our cohort study design has several strengths. First, the study is prospective by design and allows for many serial measurements in patients infected with SARS-CoV-2 over time. Second, systematic data collection is performed using a predefined protocol. Next, the data collection is in line with the FAIR data principle and combines a national IC data registry and two COVID-19 data collection initiatives. Another strength is the flexible design of the cohort and the organisation. This allows extending the variable list soon. Later, the ongoing cohort study's focus can easily be redefined to allow investigation of new pathophysiological concepts using new techniques or biomarkers in relation to outcome of IC patients. Our study is a cross-departmental joint approach throughout Maastricht UMC+ and in the region. A limitation of the study is the single centre approach and thereby a relatively small sample size, although the sample size of certain research questions is enlarged by merging our data with data from other research groups, as is anticipated. Furthermore, the growing body of evidence during the COVID-19 pandemic might amend therapy over time and this could affect studying the course of the disease. However, on the patient level, we intend to collect data on therapy daily and this will shed light on the course of therapeutic alterations within the cohort over time. Also, the stepwise data release might impair the power of the initial analyses. However, the fast spread of the SARS-CoV-2 virus affects patients worldwide and requires data to increase our understanding that may help to guide clinical decisions.[6] Another limitation is that we include only patients admitted to the ICU.[42] Observations made in our study may be generalised to critically ill patients, only. To shed some light on possible selection mechanisms for ICU admission, we intend to compare our cohort with hospitalised non-ICU patients with SARS-CoV-2 infection. However, no further exclusion criteria are determined. Hence, a heterogeneous sample of patients admitted to the ICU is expected. Our inclusion strategy thereby reduces the chance of selection bias, which contributes to the internal validity of the result for mechanically ventilated COVID-19 patients.

Collaborations

We have described the study design and data collection. Our approach aims to combine and compare the cohort data with the Dutch NICE registry, with other COVID-19 data collection initiatives such as the ISARIC and WHO data collections, with chest EIT data of COVID-19 from the IC of the Erasmus University Medical Centre, Rotterdam, the Netherlands, and interregional collaboration between Belgium and Germany among others.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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