Study Protocol Title:

Long term outcomes of COVID-19 Critical illness: cohort study of adult patients admitted to the Intensive Care Unit at Mater Dei hospital with COVID-19 infection.

Principal Investigator, Research Team, and Study Site:

Principal investigator: Dr Denise Mifsud Bonnici - denise.mifsud-bonnici@gov.mt

Co-Investigators: Dr Carl Tua - carl.tua@gov.mt

Research team and contact Information:

Dr Nicole Grech – nicole.grech@gov.mt

Dr Karen Torpiano – karen.sapiano@gov.mt

Dr Stephanie Santucci – stephanie.santucci@gov.mt

Dr Bernice Spiteri – bernice-sophie.spiteri@gov.mt

Dr Christabel Mizzi – christabel.a.mizzi@gov.mt

Dr Matthew Drake – matthew.drake@gov.mt

Dr Michael Buttigieg – michael.b.buttigieg@gov.mt

Dr Stephen Sciberras – stephen.sciberras@gov.mt

Study site:

Mater Dei Hospital, Malta

Research Synopsis

Study Title:

Long term outcomes of COVID-19 Critical illness: cohort study of adult patients admitted to the Intensive Care Unit at Mater Dei hospital with COVID-19 infection.

Study Population:

All patients admitted to the Intensive Care Unit with organ failure secondary to acute COVID-19 infection and successfully discharged from Mater Dei Hospital and surviving beyond 6 months after discharge, will be offered inclusion in the study.

Study Design:

An observational cohort study of patients discharged from the ICU following admission with COVID-19 infection.

Sample Size:

From the patients discharged from ITU over the months of September 2020 up until April 2021, we are predicting approximately 100 patients to have survived beyond 6 months after discharge from the unit. These will all be offered inclusion in the study.

Study Duration:

May 2021 to May 2022

Study Agent and Intervention Description (If applicable)

N/A

Study Aim:

To assess the long-term health outcomes of adult patients admitted to Mater Dei Hospital Intensive Care Unit with COVID-19 infection.

Background and Significance

The COVID-19 epidemic has placed an unprecedented strain on medical services worldwide. Throughout 2020 and early 2021, hospitals and their critical care services have been inundated with patients suffering from critical illness due to COVID-19, some of whom developed multi-organ failure and required a prolonged ICU stay. While the medical literature is now replete with publications and research on the acute phase of illness due to COVID-19, including critical illness, there is a paucity of studies detailing the long-term outcomes following COVID-19 critical illness.

While the negative long-term physical health, mental health and quality-of-life related effects of ARDS have been well documented, there has been very little long-term COVID-19 ARDS specific outcome studies published.

Objectives

Primary Objective:

To assess the long-term health outcomes of adult patients admitted to Mater Dei Hospital Intensive Care Unit with COVID-19 infection.

Secondary Objectives:

Specific objective 1:

Observation of the long-term organ failures and medical conditions as a sequalae of acute critical illness with COVID-19.

Specific objective 2:

Observation of the effect critical illness due to COVID-19 has on a patients' physical health, mental health and health related quality of life at 6 and 12 months after discharge from the ICU.

Specific objective 3:

Observation of how different severity of critical illness secondary to COVID-19 infection correlates with medium and long-term health related quality of life outcomes.

Study design/methodology

An observational cohort study of patients discharged from the ICU following admission with COVID-19 infection.

All patients discharged from the intensive care unit after a diagnosis of COVID-19 infection will be contacted by phone by one of the members of the research team listed below at six and twelve months after discharge. They will be asked to attend a follow-up appointment at the Pre-Operative Assessment Clinic in Mater Dei Hospital. They will be alone in the room with a researcher to protect their privacy, but they may request to have a person of their choosing such as a relative with them during the interview, if they so wish. For patients unable to attend the hospital appointment, an offer will be extended to perform the interview at their place of residence.

Participants will be asked a number of questions taken from validated questionnaires, namely the Hospital Anxiety and Depression Scale, the Barthel Index and the RAND 36-Item Health Survey. These questionnaires aim to establish the patient's own perception of his or her health, both physical and mental, his or her ability to perform daily activities alone or with help, and the patient's feelings about whether their health has changed since prior to their hospital admission and if so, in what way.

A physical examination will be offered to participants which includes examination of the heart and lungs by auscultation, and recording of height and weight as well as resting blood oxygen saturation via pulse oximetry.

Patients will also be asked to perform a six-minute walk test, if they feel they are able to. This essentially involves walking on a treadmill while clinical non-invasive monitoring such as ECG electrodes, a pulse oximeter and a blood pressure cuff are attached to monitor the vital signs during exercise. The test will be stopped if the patient requests this or if the researcher finds evidence that the patient is unfit to continue the test.

Pulmonary function testing will also be offered. This test would involve breathing through a specialised tube that calculates the flow rates that the patient is able to generate, both during normal breathing as well as during deep breathing. Once again, trained professionals will be performing this test and it will be stopped if the patient requests this or if the health professional deems the patient unfit to proceed with the test.

The participants' medical notes will also be reviewed to obtain retrospective medical history of the patients' initial admission to ICU.

Data collection will take place over a 1-year period between May 2021 and May 2022.

Study Population

All patients admitted to the Intensive Care Unit with organ failure secondary to acute COVID-19 infection and successfully discharged from Mater Dei Hospital and surviving beyond 6 months after discharge, will be offered inclusion in the study.

Inclusion /Exclusion Criteria:

A positive COVID PCR result before or during the patient's admission will be necessary for inclusion in the study. Participants will be over 18 years of age, with no restriction as regards race, ethnicity or gender.

Study Schedule:

Enrollment of participants and initiation of data collection is projected to start in May 2021. Participants will initially be included after 6 months from discharge from ITU, at which point they will be invited to attend for an interview, physical examination and pulmonary function tests. This will be repeated 12 months after discharge from ITU.

Data collection will take place over a 1-year period between May 2021 and May 2022. This will be followed by a period of data analysis with completion of the study by the end of 2022.

Analysis Plan:

Data analysis will initially be quantitative, regarding number of patients surviving beyond 6 months after discharge from ITU following their critical illness with COVID-19. Their residential arrangements following discharge will also be noted (care home or private residence).

Following this initial analysis, results of validated questionnaires which will be used to assess the patients, will be reviewed and this data will be compared to data from other studies regarding the general public of similar age groups as well as persons discharged from ITU after critical illness due to causes other than COVID-19. Their physical assessment (6 minute walk test) and pulmonary function test results will also be analyzed and compared to normal ranges for persons in their age group.

Informed Consent Process:

All patients who meet the criteria for enrollment in the study will be given both a verbal as well as written detailed explanation of what participation will entail. They will be spoken to in English or Maltese, depending on what their preferred language is and information letters will also be available in both languages. They will be asked to sign a consent form prior to enrollment in the study. Should they wish to ask any further questions or request clarification regarding their involvement in the study at any point during the study, one of the researchers will be available to provide the information they require.

Special Considerations for Persons who are Unable to Consent:

In the case of persons who are unable to provide informed consent, the legal carer will be approached for purposes of consent and will be asked to be present with the participant throughout the study session. Questions will be directed at the participant as much as possible but carers will be asked to provide information that participants cannot provide, should they feel comfortable doing so. Participants have a right to refuse to participate in any test or questionnaire that they do not wish to participate in, and carers also have the right to stop patients' participation in any test or questionnaire they feel is inappropriate for the person. In the case that the person regains their capacity to consent for themselves, they will be asked to confirm consent to participate in the study or have their data

removed, although this may not be possible for data that has been included in analysis and publication.

Refusal or Withdrawal of Data:

All participants and their carers are at liberty to refuse to participate in all or part of this research study. Participants and carers may refuse to answer any questions they are uncomfortable with, and may refuse to take any physical test that they do not wish to take. They may also ask to stop their participation in any questionnaire or physical test at any point in time. Participants or their carers may also ask for their data to be deleted after its collection, but should be aware that this may not be possible for data that has already been included in statistical analysis and publication. Refusal to participate in all or part of the study, or withdrawal of data after participation will not result in any loss of benefits and will not incur any penalties or liabilities. Participation is voluntary and any refusal to participate by the patient or guardian will not have any effect on the person's care pathway within the hospital.

Privacy and confidentiality:

Storage of Data:

All data collected in this study will be stored on MITA Sharepoint after anonymisation by use of a code. This is the official Mater Dei Hospital server for data storage and ensures security of the stored data. All data will be deleted after analysis of all gathered data is complete. A specific date for this cannot be given since the pandemic is an ongoing evolving situation.

Processing of Data:

Data will be analysed after collection is complete to extract statistical information about the long-term health effects of severe COVID-19 infection requiring intensive care admission. This data may be published in scientific journals at a later stage and shared with colleagues for instructional purposes. All data will be anonymised and no data which can lead to personal identification will be shared or published.

Data Accessibility:

The stored data will be accessible only to members of the research team whose names and email addresses are printed below.

Refusal or Withdrawal of Data: All participants are at liberty to refuse to participate in all or part of this research study. Participants may refuse to answer any questions they are uncomfortable with, and may refuse to take any physical test that they do not wish to take. They may also ask to stop their participation in any questionnaire or physical test at any point in time. Participants may also ask for their data to be deleted after its collection, but should be aware that this may not be possible for data that has already been included in statistical analysis and publication. Refusal to participate in all or part of the study, or withdrawal of data after participation will not result in any loss of benefits and will not incur any penalties or liabilities. Participation is voluntary and any refusal to participate will not have any effect on the person's care pathway within the hospital.

Risk/Benefit:

Risk to participants:

No risks to participants are foreseen as a direct result of this research study.

Benefits to Participants

The results of this research will contribute to a better understanding of the consequences of severe COVID-19 illness on patients several months after the resolution of their illness, and may help shape services to help these patients after their discharge from hospital.

Patients will benefit from referral to appropriate specialist outpatient clinics if our assessment reveals that they will benefit from this, and the participant is willing to attend.

Study Timeline:

Stage 1 - Screening and enrolment of participant - 1 month

Stage 2 - Data collection (interviews and physical assessment) – 1 year

Stage 3 - Data analysis – 3 months

Stage 4 - Presentation and publication

Conflict of Interest:

The investigators and researchers have no conflict of interest to declare.

References:

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COVID-19 on pulmonary function, functional capacity and quality of life. Eur Respir J 2021;