What is the recovery rate and risk of long-term consequences from COVID-19? - A harmonised, global observational study protocol

ISARIC COVID-19 Follow Up Working Group:

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Introduction

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, can lead to a diverse range of clinical manifestations, ranging from an asymptomatic viral shedding to an acute respiratory distress syndrome, and multiorgan failure with high risk of mortality. (1, 2) It is established that SARS-CoV-2 not only infects the respiratory tract but that ensuing viral replication and immune response also affect other organs which can lead to a risk of heart, renal, liver injury, in addition to an acute systemic inflammatory response and accompanying shock.(3-5) While most people have uncomplicated recoveries, some have prolonged illness even after recovery from the acute illness. (6-8) Identifying longer-term potential consequences and relationship with the acute illness is important for the management of patients, in particular, understanding how these interact and affect patients already living with other conditions such as cardiovascular disease and cancer will be paramount.

However, very little known about possible clinical sequelae that may persist after the resolution of acute infection. A recent longitudinal cohort of 143 patients followed after hospitalisation from COVID-19 in Italy, reported that 87% had at least one ongoing symptom, most (55%) with 3 or more symptoms at 60 day follow up, fatigue (53%), dyspnoea (43%), joint paint (27%) and chest pain (22%) being the most common. COVID-19 was associated with worsened quality of life among 44% of patients. (7) Prolonged course of illness has also been reported from people with mild Covid-19 who were not admitted to hospital. (6) A COVID-19 symptom tracking app, downloaded by 3.9 million people globally, reported that 10% of people using the app had symptoms at 25 days.(9)

Increasing evidence also suggests that infection with Sars-CoV-2 can cause neurological consequences, including altered mental status, comprising encephalopathy or encephalitis and primary psychiatric diagnoses. (10) While these symptoms arise acutely during the course of infection, less is known about the possible long-term consequences. Severely affected COVID-19 cases experience high levels of proinflammatory cytokines and acute respiratory dysfunction and often require assisted ventilation, factors suggested to cause cognitive decline. (3, 11).

Post-traumatic stress disorder (PTSD) and other consequences after intensive care (ICU) stay has been well documented previously. (12, 13) A systematic review of consequences after hospitalisation or ICU stay for severe acute respiratory infection and Middle East respiratory

syndrome coronavirus found consequences up to 6 months after discharge. Common consequences besides impaired diffusing capacity for carbon monoxide and reduced exercise capacity were PTSD (39%), depression (33%) and anxiety (30%). (14)

The emerging data and anecdotal evidence of long term recovery and persistent debilitating symptoms highlights the need for robust, standardised studies to assess the risk of and risk factors for consequences after COVID -19 infection. The purpose of this study is to establish a longitudinal cohort of patients with COVID -19 post-discharge, to characterize risk of long-term consequences and immune response over time in different populations globally. This will inform strategies to prevent risk of consequences; inform clinical management, rehabilitation and public health management strategies to reduce morbidity and improve outcomes.

Methods and analysis

This protocol has been developed by the International Severe Acute Respiratory and emerging infection consortium (ISARIC) COVID-19 follow up working group, and informed by a wide range of global stakeholders with expertise in clinical research, outbreak research, infectious disease, epidemiology, respiratory, critical care, rehabilitation, neurology, psychology, rheumatology, cardiology, oncology and public health medicine.

Study design

This is an international prospective, observational multi-site study to assess risk of and risk factors for longer term physical and psychosocial consequences of COVID-19 and immune response over time. The follow up module is developed as an open-access tool to be adapted by any site interested in following up patients with COVID-19, to facilitate standardized data collection globally which will enable combined analysis.

Population and setting

This protocol builds on the ISARIC/WHO COVID-19 clinical characterization protocol and tools already in operation. The initial follow up module (Tier 1) will be used for a sub-set of patients at participating sites, already included in the existing cohort of more than 85,973 individuals hospitalized with confirmed COVID-19 infection across 42 countries (as of 20 July 2020), using the ISARIC/WHO standardized Core- or RAPID Case Report Forms (CRFs). (15) These CRFs collect data on demographics, pre-existing comorbidities and risk factors, signs and symptoms experienced during the acute phase, and care and treatments received during hospitalization. This data will be linked to the follow up data. The Core- and RAPID CRFs can

be completed retrospectively for patients not yet included. Specific inclusion and exclusion criteria are as follows:

Inclusion criteria

- People aged 16 years and older
- Laboratory or physician confirmed COVID -19 infection
- More than 28 days since discharge from hospital with COVID -19 diagnosis
- Person (or family member/carer in patients with lack of capacity) consent to participate

Inclusion of vulnerable participants

The validated tools are designed for young people and adults of any age, including pregnant women, but not validated for children. A separate case report form will be developed for children.

Serial follow up

The follow up modules are designed in a tiered approach to be adapted depending on local resources and research needs. The Tier 1 case report form is designed to enable patient self-assessment, online or via paper forms, to allow easy distribution to all patients with laboratory confirmed or clinically diagnosed COVID-19 (Appendix 1). It can also be completed in-clinic at check-ups or for patients that are still hospitalized. The patient self-assessment form is developed to facilitate standardized, comparable data from multiple sites for independent and combined analysis.

Tier 1 is developed to be used for following up patients day 28 post-discharge, additionally at 3 to 6 months interval, with or without sampling (Figure 1). By being designed for patient self-completion to be administered via online link, by telephone or as a paper form, it allows wide distribution at low resource need. The module will collect data on demographics, hospital stay and re-admissions, all-cause and cause specific mortality (after the initial index event), specific consequences including; deep vein thrombosis (DVT), pulmonary embolism, recent febrile illness, new and persistent symptoms, quality of life (measured by EQ-5D-5L), dyspnoea (assessed using MRC dyspnoea scale), difficulties in functioning (UN/Washington disability score), lifestyle and socioeconomic data.

Sub-studies

The Tier 1 follow up module can be used to identify sub-set of patients experiencing specific symptomatology or syndromes for further follow up. The Tier 2 follow up module will be developed for in-clinic, in-depth follow up. By using a tiered approach, additional specialist

modules can be added for more complex follow up of emerging consequences in a flexible, adaptable way (Figure 2).

Biological samples

The CRF is to be used on its own for data collection or in a sub-set of patients in combination with sampling, for immunology, pathophysiology and other studies (16). It builds on the ISARIC/WHO Clinical Characterization Protocol (CCP).(16) The CCP is designed for any severe or potentially severe acute infection of public health interest, such as COVID-19. It is a standardized protocol for data and biological samples to be collected rapidly in a globally harmonised manner. The CCP can be used for the rapid, coordinated clinical investigation of confirmed cases of COVID-19. It is designed in a tiered approach to be adapted depending on resources and includes different level of sampling schedules (acute phase and follow up) that can be adapted depending on resources, to be combined with patient data collection using the acute phase CRFs and the follow up CRF.

Outcomes

The primary outcome of this study is to characterise physical and psychosocial consequences in patients post-COVID- 19 infection. Secondary outcomes include estimating the risk of and risk factors for post-COVID- 19 medical sequalae, psychosocial consequences and post-COVID-19 mortality. A subset of patients will have sampling to characterize longer term antibody and cell-mediated immune responses to SARS-CoV-2 and to evaluate risk of and risk factors for re-infection with future waves of COVID-19.

Data collection and entry

A standardized COVID-19 follow up CRF was developed through a series of virtual working group meetings and e-mail iterations. The CRF was piloted on patients in four settings and feedback incorporated into the final form (Appendix 1). The CRF is designed for patient self-assessment, via online link or paper form, or to be completed in-clinic or via telephone follow-up appointment.

The CRF will be available as open access on the ISARIC website, and for manual, online completion on the ISARIC hosted database.(17) The CRF will be set up to be distributed to patients via an online link, or for completion by clinical or research staff. Sites who wish to use the free, secure online database can contact: ncov@isaric.org. Individual sites retain ownership of the data entered onto the database. The data collected through the follow up

module will be linked with data on demographics, comorbidities, clinical characteristics, care and treatments collected using the ISARIC/WHO Core- or RAPID COVID-19 CRF (15).

Statistical analysis plan

Using the data, we will test for differences in outcomes across important demographic groups (age categories, sex, ethnicity, socioeconomic deprivation, comorbidities), specific exposures (severe COVID-19, critical care admission, ventilation) and initial clinical sequelae (who had complications on their index admission for COVID-19. We plan to use this platform to conduct timely analyses which coincide with public health or scientific need. Given these requirements, new questions we have not specified within this protocol may arise. Where this occurs, we will develop analysis plans prior to undertaking analyses, which will be made available on request. The plan below presents our guiding statistical framework.

Entered data will be summarised first by using simple statistics. Categorical data will be explored using frequencies and percentages, with differences in disease severity and treatment groups tested for using Chi-square tests or fisher's exact test where cell counts are under 5. For continuous data, distribution will be established using histograms and density plots. Data that are normally distributed will be summarised using group mean averages and standard deviation as a measure of central tendency. For non-parametric data, the median average will be used and presented alongside 25^{th} and 75^{th} centiles. Differences in normally distributed continuous data will be tested using Welch's two sample t-tests for 2 group data and ANOVA for 3 or more groups. Mann-Whitney U will be used to compare differences across 2 groups or Kruskall-Wallis tests for 3 or more groups, where continuous data follows a non-parametric distribution.

Outcomes will be expressed in three ways; 1) binary event data (for presence or absence of outcome of interest), 2) change over time (for continuous or ordinal data) or as 3) time to event data (for patients with serial measurements). We will calculate changes over time across symptom and outcome variables and use these changes over time to compare the effect of treatments or exposures on these outcomes. Time to event data will be captured for those who complete serial assessment forms. These data will be presented as Kaplan-Meier plots and differences tested for using log-rank tests. Competing risks (including death) will be accounted for using censoring.

To identify which patients are likely to develop persistent complications, functional impairment or reduced quality of life, we will use multilevel models to adjust for potential confounders. Level I fixed effects will include patient-level explanatory variables (i.e. age, sex) and level II

or III random effects will include site and country in the case where research questions require differences in country to be accounted for. Explanatory variables will be entered into models on the basis of clinical plausibility and final model selection guided by maximisation of the adjusted R^2 value and minimisation of the Akaike information criterion (AIC) or Bayesian information criterion (BIC). For binary event data, multilevel logistic regression will be used, and estimates presented as odds ratios alongside the corresponding 95% confidence interval. For continuous data, linear or generalised linear regression will be used and estimates presented as model coefficients, with 95% confidence intervals. Finally, time to event data will be presented as survival probability or hazard ratios, with 95% confidence intervals.

Statistical significance will be taken at the level of $P < 0.05$ *a-priori*. Analyses will be conducted in secure R (R Foundation for Statistical Computing, Vienna, AUT) or STATA (StataCorp LLC, TX, USA) environments.

Dissemination

The assessment of risk factors for longer term complication requires a longitudinal study linked to data on pre-existing conditions and patient data and care received during the acute phase. With this study we aim to characterize the risk of long-term consequences and immune response over time in patients following a diagnosis of COVID-19. We will collect data on wide range of outcomes including hospital stay and re-admissions, all-cause and cause specific mortality (after the initial index event), consequences e.g. DVT, pulmonary embolism, recent febrile illness, new, persistent symptoms, EQ-5D-5L, MRC dyspnea scale, UN/Washington disability score, lifestyle and employment status. Data from combined analysis will be disseminated through the ISARIC website and in open-access publications, under a group authorship.

There is a need for robust, standardised clinical data and research sample collection to characterise longer term consequences and wider impact of COVID-19 to inform clinical management, preventative and rehabilitation strategies in different at-risk population, to improve individual short- and longer-term outcomes during the ongoing pandemic globally. The follow up module is developed as an open-access tool to be adopted and adapted as appropriate by any site interested in following up patients with COVID-19 over time, to facilitate standardized data collection globally to enable combined analysis. The outcomes of this study will immediately inform strategies to prevent risk of consequences; clinical management, rehabilitation and public health management needs to reduce morbidity and improve outcomes.

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Figure 1. Schematic overview of the follow up data and sample timeframes

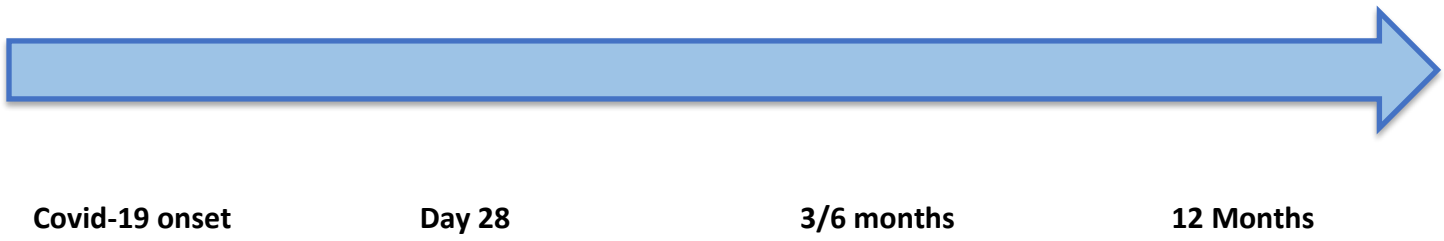

Figure 2. ISARIC's adaptable Covid-19 Follow-Up Protocol framework