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Post-acute sequelae of SARS-CoV-2 infection (PASC): a protocol for a multidisciplinary prospective observational evaluation of a cohort of patients surviving hospitalisation in Sao Paulo, Brazil

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ABSTRACT

Introduction COVID-19 may lead to persistent and potentially incapacitating clinical manifestations (post-acute sequelae of SARS-CoV-2 infection (PASC)). Using easy-to-apply questionnaires and scales (often by telephone interviewing), several studies evaluated samples of COVID-19 inpatients from 4 weeks to several months after discharge. However, studies conducting systematic multidisciplinary assessments of PASC manifestations are scarce, with thorough in-person objective evaluations restricted to modestly sized subsamples presenting greatest disease severity.

Methods and analyses We will conduct a prospective observational study of surviving individuals (above 18 years of age) from a cohort of over 3000 subjects with laboratory-confirmed COVID-19 who were treated as inpatients at the largest academic health centre in Sao Paulo, Brazil (Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo). All eligible subjects will be consecutively invited to undergo a 1–2-day series of multidisciplinary assessments at 2 time-points, respectively, at 6–9 months and 12–15 months after discharge. Assessment schedules will include detailed multidomain questionnaires applied by medical research staff, self-report scales, objective evaluations of cardiopulmonary functioning, physical functionality and olfactory status, standardised neurological, psychiatric and cognitive examinations, as well as diagnostic laboratory, muscle ultrasound and chest imaging exams. Remaining material from blood tests will be incorporated by a local biobank for use in future investigations on inflammatory markers, genomics, transcriptomics, peptidomics and metabolomics.

Ethics and dissemination All components of this programme have been approved by local research ethics committees. We aim to provide insights into the frequency and severity of chronic/post-COVID multiorgan symptoms, as well as their interrelationships and associations with acute disease features, sociodemographic variables and

Strengths and limitations of this study

- We have four strengths: first, we will invite consecutively all subjects from a large COVID-19 sample who survived hospitalisation to participate of our systematic, prospective evaluation of multiorgan PASC manifestations.
- Second, the same detailed in-person assessments (surveys using standardised questionnaires/scales and objective assessments of functioning) will be applied to all individuals, rather than being partitioned among subsamples defined based on previous disease severity.
- Third, we will have access to baseline data regarding acute COVID-19 features and details of in-hospital stay that were recorded prospectively.
- Fourth, information regarding potential predictors of outcome will include both individual-level and neighborhood-level environmental variables, in addition to data on medical comorbidities.
- The limitations are that current re-infection will be ruled-out only by the absence of clinical signs and symptoms; and that subjects will be from one single hospital site (although large-sized and homogeneous in its administrative, diagnostic and treatment protocols).

environmental exposures. Findings will be disseminated in peer-reviewed journals and at scientific meetings. Additionally, we aim to provide a data repository to allow future pathophysiological investigations relating clinical PASC features to biomarker data extracted from blood samples.
Trial registration number RBR-8z7v5wc; Pre-results.

INTRODUCTION

COVID-19, caused by infection with the SARS-CoV-2, is a contagious disease with potentially severe and incapacitating manifestations. COVID-19 currently challenges scientific communities worldwide to rapidly produce findings to inform treatment and rehabilitation strategies for both its acute symptoms and possible long-term consequences, with an unprecedented need for multidisciplinary collaboration. Since the SARS-CoV-2 enters host cells via the ACE 2 receptor expressed in several tissues, complications of COVID-19 involving multiple organs are expected. There is emerging evidence that these symptoms may be persistent, characterising what is now being called post-acute sequelae of SARS-CoV-2 infection (PASC). A few reports have suggested that many patients display subacute, multiorgan symptoms 1 month to approximately 3 months from the onset of COVID-19 symptoms,[1–9] when replication-competent SARS-CoV-2 can no longer be isolated.[1] There is also a need for systematic studies to increase knowledge about longer-term PASC (or 'long COVID-19') manifestations, when abnormalities persist beyond 12 weeks of the onset of acute COVID-19 and cannot be explained by other diagnoses.[1 10] In a study that reassessed 1733 patients with COVID-19 after 6 months of in-hospital discharge (in China), 76% of patients reported at least 1 symptom.[11] Findings of multiple organ manifestations were detected, including pulmonary dysfunction, muscle weakness, kidney dysfunction, newly onset diabetes, venous thromboembolism, anxiety, depression and sleep disturbances. In another investigation of COVID-19 inpatients (n=478) conducted in France, persistent manifestations (including dyspnoea, fatigue and cognitive deficits) were also found frequently (in 51% of subjects) 4 months after discharge.[12]

Sao Paulo, Brazil, is one of the most densely populated and urbanised cities from low-income and middle-income countries (LMIC). During the 2020 COVID-19 outbreak, our largest public-funded academic health centre (Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo; HCFMUSP) undertook an operation that turned its main hospital into a fully dedicated inpatient facility for individuals presenting moderate to severe COVID-19.[13] A total of 900 beds were made available at this site, more than 300 of which in intensive care units (ICUs). Over 3500 inpatient admissions due to suspected SARS-CoV-2 infection took place from 30th March through August 2020.

This manuscript describes the methods for an observational prospective follow-up investigation of adult survivors from the above cohort, with two multidisciplinary evaluations planned to be conducted, respectively, at 6–9 months and 12–15 months after in-hospital discharge. Investigations of sequelae after recovery from acute COVID-19 in LMIC settings are relevant to confirm and extend findings of studies conducted elsewhere, and to assist in the planning of local rehabilitation programmes. Our main objectives are to describe the frequency and severity of multidomain symptoms and indices of disability using comprehensive assessment schedules; to investigate significant associations between persistent COVID-19 manifestations and variables related to the acute disease severity, lifestyle habits, COVID-related psychosocial stressors, sociodemographic status and urbanisation-related environmental risk factors; and to assess the potential for reversibility of PASC. Additionally, this multidisciplinary programme will create a data repository to allow further investigations on how different PASC subsyndromes may relate to each other, and future pathophysiological studies relating distinct clinical features of PASC to biomarker data extracted from blood samples obtained from the same subjects.

METHODS

The main components of the protocol were registered at the Brazilian Registry of Clinical Trials (https://ensaiosclinicos.gov.br/). Any relevant changes will be entered at that site.

Study design and setting

We will consecutively invite for the study all eligible adult individuals (≥18 years) who survived moderate or severe COVID-19 requiring hospital treatment for at least 24 hours, and who had their aetiological diagnosis confirmed by reverse-transcriptase PCR (RT-PCR) on swab-collected nasopharyngeal and/or oropharyngeal samples, or by ELISA to detect serum antibodies (in subjects for whom an RT-PCR test collected up to the 10th day of symptom onset was not available). From 3007 confirmed cases of COVID-19, a total of 1998 individuals required ICU care at any point during hospitalisation. Our survival rate immediately after in-hospital stay was over 60% from 30 March 2020 through August 2020, similarly to the figures reported for the Southeastern region of Brazil (where Sao Paulo is located) in retrospective nationwide analyses.[14] This provides a pool of over 1800 potential participants for the current investigation.

Rather than describing a single-study protocol, we summarise herein the methods of an aggregate of several longitudinal projects that were simultaneously proposed and ethically approved by individual research teams at HCFMUSP. These groups were joined together to collect data in an integrated fashion in order to: minimise patient inconvenience (concentrating several assessments on a single day); optimise use of resources; and maximise multidisciplinary interchange of experiences, fostering a comprehensive outlook on the individual health needs of study subjects.[1]

Invitations will begin as of 20 October 2020 and will continue until January 2022.

There are other ongoing research initiatives in the metropolitan region of Sao Paulo with assessments of large groups of individuals with laboratory-confirmed COVID-19 of different degrees of severity, also involving teams based at HCFMUSP.[15–17] Collaboration with these teams may allow us to compare results from our moderate to severe COVID-19 cohort with the findings obtained in demographically matched control groups of mild COVID-19 sufferers who recovered fully within 2–4 weeks after the disease onset. Conversely, we are not currently able to recruit an additional control group of patients admitted to hospital due to other infectious diseases such as community-acquired pneumonia (CAP) or dengue, as HCFMUSP admissions for such conditions have been substantially reduced during the ensuing COVID-19 pandemics.

All reports from this cohort study investigation will follow the principles of the Strengthening the Reporting of Observational Studies in Epidemiology statement.[18]

Patient and public involvement statement

There was no patient or public involvement in the design of this study.

Assessment schedules

A flow chart displaying the steps for the selection and multidisciplinary evaluation of potential participants at 6–9 months after in-hospital discharge is provided in figure 1.

A copy of all interview guides is provided as online supplemental material.

Semi-structured medical interviewing, vital sign and anthropometric measurements, physical and neurological examinations, and assessment of mental health status

A general interview will include selected items from the baseline interview of the Brazilian Longitudinal Study of Adult Health (ELSA-BRAZIL)[19] regarding sociodemographic characteristics, occupational history and retirement status (pre-COVID-19 and post-COVID-19), as well as lifestyle habits (food consumption and smoking) and self-rated health and medical history (with emphasis on previous and present comorbidities, cardiopulmonary symptoms and medication use). Additional questions will cover dermatological, endocrinological, gastrointestinal, haematological, nephrological, otorhinolaryngological and lower urinary tract symptoms, as well as episodes of re-infection and visits to emergency care and other hospital facilities since discharge. The questions in each medical domain were designed to allow self-rated assessments of: pre-COVID-19 symptoms; symptoms that emerged during acute COVID-19; and persistent symptoms since discharge. The interview also includes the Medical Research Council (MRC) Dyspnoea Scale,[20 21] the Clinical Frailty Scale,[22] the short form of the International Physical Exercise Questionnaire[23] and questions regarding current social support.

The interview will be divided in two consecutive subsessions, covering, respectively: its medical domains (conducted by a trained physician) and a brief systematic

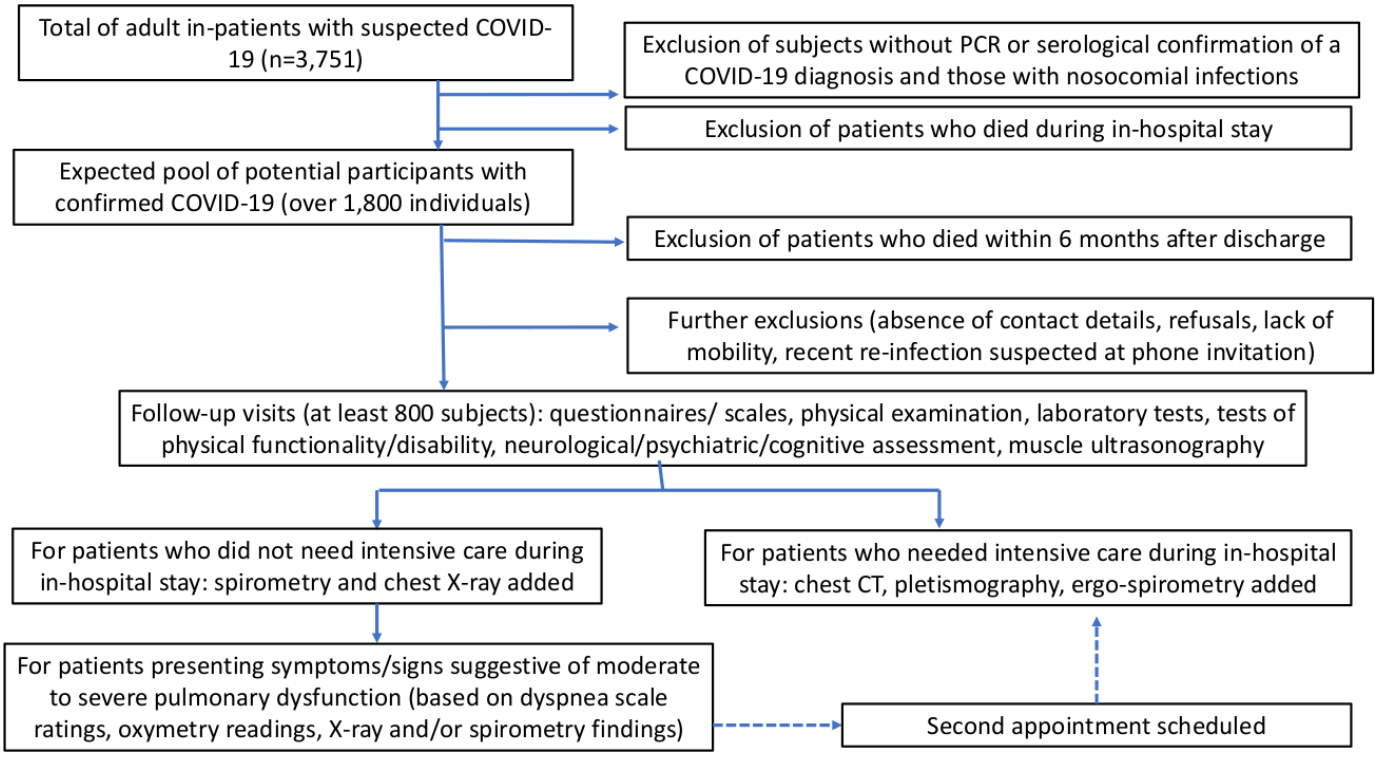

Figure 1 Flow chart and evaluation of potential participants at 6–9 months after in-hospital discharge.

physical examination, and the remaining items, conducted by trained non-medical research workers.

Digital electrocardiographic data will be acquired. Vital sign measurements will include resting arterial blood pressure and heart rate, pulse oxygen saturation, cardiac output, stroke volume, cardiac index, partial pressure of carbon dioxide and partial pressure of oxygen, all obtained with a fingertip device (MTX Cnoga) based on optical technology using colour image sensors.[24] Anthropometric measurements will include body mass index, waist circumference, arm circumference and calf perimeter.

For the neurological assessment, we adapted the WHO screening tool devised for neuroepidemiology investigations in LMIC.[25 26] This included a 15-item questionnaire adapted to account for COVID-related timing of symptoms and a 7-step screening for neurological signs, followed by a deeper, structured neurological examination in all cases, regardless of the results of the screening tool. Subjects will also be inquired about psychiatric manifestations in a comprehensive fashion, using structured instruments for the detection of common mental disorders, anxiety, depression and suicidal thinking,[27–30] post-traumatic stress disorder,[31] alcohol abuse[32] and psychotic symptoms.[33] The mental health assessment will also include questions regarding: the impact of COVID-19 on socioeconomic aspects of the subject's life; changes in patterns of substance use following COVID-19 (alcohol, tobacco, sedative drugs, opioids and others); and sexual dysfunction symptoms.

Laboratory testing and biobank storage of biological samples

Blood samples will be collected for serology COVID-19 testing and diagnostic laboratory tests. Urine samples will be collected for creatinine levels, urinalysis and assessment of kidney injury biomarkers. Remaining material from the samples collected for diagnostic tests will be incorporated by the biobank of the Tropical Medicine Institute (TMI) (which is also a part of HCFMUSP) for use in biomarker-based research investigations; DNA samples will be extracted from lymphocytes, and the PAXgene system will be used for RNA collection. Plasma samples will be extracted from blood collected using EDTA tubes, centrifuged and stored at −80° freezers. This biobank data will be used in future investigations evaluating relationships among PASC manifestations and data on inflammatory markers, genomics, transcriptomics, peptidomics and metabolomics.

Evaluation of disability, quality-of-life and physical functioning

Scales for the assessment of physical functioning, disability and quality-of-life (QOF) will include: the 5-level version of the EQ-5D scale to measure and value generic health;[34] the WHO Disability Assessment Schedule 2.0;[35] the Functional Independence Measure;[36] the Functional Oral Intake Scale;[37] the Post-COVID-19 Functional Status Scale;[38] the Functional Assessment of Chronic Illness Therapy-Fatigue Scale;[39] the Epworth Sleepiness Scale;[40] the Insomnia Severity Index;[41] and the Visual-Analogue Scale for pain.[42]

Structured physical tests will include: manual muscle testing using the MRC strength grading system;[43] the 10-m walk test;[44] the timed up and go test;[45] a measurement of hand grip strength[46] and the 1-minute sit-to-stand test.[47] Oximetry measurements and the Borg Dyspnoea Scale[48] will be undertaken immediately before and after the 1-minute sit-to-stand test, which will not be undertaken with subjects presenting resting pulse oximetry ratings lower than 90%.

Pulmonary function tests and chest imaging exams

Subjects who had been admitted to an ICU during the acute disease stage will undergo a whole-body plethysmography examination and an incremental cardiopulmonary exercise test (CPET), using methods described elsewhere.[49 50] These subjects will also undergo CT imaging of the chest using a 160-detector multi-slice equipment (Aquilion Prime, Canon Medical Systems Corporation, Japan) in the supine position, during end-inspiration and end-expiration without intravenous contrast. Reconstructed images (1-mm slice thickness an 1-mm interval with lung and soft tissue kernels) will be reviewed independently by two experienced thoracic radiologists and any disagreement will be resolved by consensus. The following findings suggestive of COVID-19-related lesions will be documented: ground-glass opacities, consolidation, reticulation, mosaic attenuation, parenchymal bands, atelectasis, architectural distortion, bronchiectasis and honeycomb.[51 52]

Subjects without a history of ICU admission during in-hospital stay will undergo: a frontal and lateral chest X-ray (searching for signs suggestive of COVID-related lesions such as ground-glass opacities, consolidation and linear and reticular opacities)[53]; and a conventional spirometry test using methods described elsewhere.[54] All individuals from this subgroup who fulfil any of the following five criteria will be invited for a second visit to undergo a plethysmography examination, a CPET and a CT scan of the chest: (a) a score on the MRC Dyspnoea Scale equal or greater than 2; (b) a resting pulse oximetry reading of 90% or above; (c) a decrement in the pulse oximetry reading of at least four points during the 1-minute sit-to-stand test; (d) the presence of forced vital capacity lower than 80% of predicted during the spirometry test and/or (e) the presence of pulmonary changes related to COVID-19 as assessed by conventional X-ray.

Muscle ultrasound

Using a 13-MHz GE Healthcare LOGIQe and a 13-MHz FujiFilm SonoSite M-Turbo probe and diagnostic ultrasonography equipment (Wuxi, China, and Bothell, Washington, USA, respectively), measurements of muscle thickness (MT) and echo intensity of the anterior rectus muscle and vastus medialis muscle will be obtained.[55] A strong correlation between conventional radiological

measurements (by MRI or CT) and ultrasound measurements of MT has been previously demonstrated.[56]

Olfactory tests

In addition to the otorhinolaryngological questions included in the interview described in the Semi-structured medical interviewing, vital sign and anthropometric measurements, physical and neurological examinations, and assessment of mental health status section (which will evaluate the presence of hearing loss, tinnitus, vestibulopathy disorders, nasal symptoms, olfactory and taste loss), subjects will undergo the objective 'u-Smell it olfactory test',[57] assisted by a physician. Subjects will be asked to scratch a total of five scents, smell each of them and choose one from five alternatives before moving forward to the next smell, until all five subtests are completed. On completion, a 0–5 smell score will be attributed to each subject. A set of Visual-Analogue Scales will also be applied assessing: the impact on QOF following COVID-related smell and taste loss; and the degree of chemosensitive recovery until the date of the interview.[58]

Cognitive test battery

All individuals will undergo a neuropsychological battery to identify impairments in different cognitive domains, including: the Trail Making Test–part A;[59] the digit-symbol test;[60] the temporo-spatial orientation subtest from the Mini-Mental State Examination[61] and the Consortium to Establish a Registry for Alzheimer's Disease battery.[62 63] Furthermore, we will assess the self-perceived memory status through the Memory Complaint Scale,[64] given both to the patient and a relative (if also present at the appointment).

Environmental exposures

Based on the permanent address of each individual, the following variables will be added to the database: neighbourhood socioeconomic conditions;[65] levels of air pollution and traffic density;[66] and residential greenness, distance to public green spaces and number of street trees.[67]

Procedures

Experienced research staff will make telephone invitations to subjects or close family members (in case of elderly individuals presenting some degree of dependence), followed by written messages using the freeware WhatsApp when no answer is obtained after two telephone attempts. Reasons for non-participation will be recorded.

The series of multidisciplinary assessments described in the Assessment schedules section will be concatenated to take 4–5 hours, with intervals for rest. Selected questions from the semi-structured interview described in subitem Semi-structured medical interviewing, vital sign and anthropometric measurements, physical and neurological examinations, and assessment of mental health status will be undertaken via teleconsultation ahead of the visit, whenever possible and convenient for study subjects and their relatives.

On the day preceding the actual visit of subjects to HCFMUSP, subjects will receive a telephone call during which they will be enquired regarding the sudden appearance of symptoms suggestive of SARS-CoV-2 re-infection. Symptomatic individuals will have their visit postponed, and they will be referred to the infectious disease outpatient clinic at HCFMUSP dedicated to the diagnosis and management of acute COVID-19. Subjects or relatives presenting fever on arrival for the scheduled multidisciplinary evaluations will be referred immediately to the same outpatient clinic. Additionally, all subjects will receive guidance at the end of their participation to seek out the infectious disease outpatient clinic in case of suspected re-infection.

Taking into account the long-lasting status of COVID-19 pandemics in Sao Paulo and in order to preserve the safety and social distancing of subjects and their relatives, three additional principles will be applied: (1) subjects will be asked to arrive using private transport, with expenses covered by the research programme; (2) rather than asking subjects and their relatives to circulate around several clinics for the multidisciplinary assessments, all evaluations (except the radiological exams) will be conducted at one single hospital sector, assembling a minimal number of researchers from each collaborating discipline to work on site; and (3) two separate facilities will be used simultaneously for the multidisciplinary assessments of different subjects. Those 2 sites will include: 1 temporary outpatient centre prepared to accommodate up to 8 visits per day of subjects without a history of ICU admission during in-hospital stay; and the clinical research centre of the Instituto do Coração at HCFMUSP, which accommodates up to 10 subjects who had been admitted to an ICU during acute COVID-19 to be evaluated daily. Both facilities are equipped to allow immediate action on any need for emergency interventions.

Data capture and management

Data from interviews, scales and complementary examinations will be captured and stored at real-time using web-based case report forms (CRFs) developed on a Research Electronic Data Capture (REDCap) system hosted at HCFMUSP.[68] A team of REDCap experts will manage the database and provide access for the different research groups to conduct interim and final statistical analyses.

Access to data collected prospectively during inpatient admissions due to acute COVID-19

A REDCap database of information for all cases with suspected COVID-19 during their admission as inpatients in the period between 30 March 2020 through August 2020 at HCFMUSP will be available for the current study. This database includes information on: address, age, sex and race; comorbidities and medications of regular use; acute COVID-19 symptom presentation; vital signs and

laboratory test results at admission; duration of symptoms; duration of hospital stay and treatment protocols used; and indices of disease severity and complications, including use of mechanical ventilation, admission to ICU, tracheostomy, use of vasoactive drugs, acute kidney injury and need for renal replacement therapy, delirium, stroke, pulmonary embolism and other thromboembolic events. Three different procedures were used to feed information in this database, including: automatic data extraction (comorbidities, vital signs, laboratory test results and prescriptions) from our electronic health record system; prospective manual entry of data by research teams during hospital stays; and retrospective extraction of data by a taskforce of researchers who re-evaluated both structured and non-structured fields of electronic CRFs.

Summarisation of clinical information and feedback to participants

Based on the assessments and scale cut-offs proposed by the research teams from the follow-up evaluations after in-hospital discharge, the data gathered will be summarised as short health reports to be used for the benefit of PASC sufferers in need of clinical care. Different specialised outpatient units at HCFMUSP are prepared to immediately provide care for subjects who are detected to display, for instance, significant signs of physical disability or persistent suicidal symptoms at the time of the research assessments. Potentially relevant clinical information will be fed back either directly to the subject and a significant relative via teleconsultation (followed by healthcare advice), or as a written report to be forwarded to the private or public health provider that will continue to care for the individual. A username and password will be provided to allow all individuals to have access to the laboratory and radiological test results in an electronic format.

Sample size estimation and planning for data analysis

Given both the paucity of previous COVID-19 investigations of the kind proposed herein and the continued restrictions imposed by the pandemics in Sao Paulo, Brazil, it is difficult to estimate the number of individuals who will agree to come to the follow-up visits. Given the large number of potential participants (above 1800) and the maximal daily work capacity of our research teams, we estimate that the sample size for the current study will be over 800 subjects (based on a rate of acceptance of at least 45%–50% of invited subjects), providing sufficient numbers to avoid an underpowered investigation. Planned analyses to fulfil the main aims of the study (as outlined at the introduction section of this paper) will include: descriptive statistics, multiple linear and ordinal regression models, and statistical comparisons of subgroups, with correction for multiple testing.

The cohort will be stratified into the three following groups: patients that did not require any oxygen support during in-hospital stay; patients who required supplementary oxygen; and patients who underwent invasive mechanical ventilation. In addition, given the heterogeneity of PASC phenotypes,[1] we will also run separate analyses for subgroups presenting specific types of sequelae (eg, pulmonary sequelae, renal sequelae and endocrine sequelae).

ETHICS AND DISSEMINATION

The Comissão de Ética para Análise de Projetos de Pesquisa (HCFMUSP's institutional review board) gave ethics approval for all protocol components for the study (approval numbers: 4.270.242, 4.502.334, 4.524.031, 4.302.745 and 4.391.560). Informed written consent will be obtained from participants (or their legal guardians) prior to study procedures. Informed written consent will also be given for remaining amounts of blood samples (collected for diagnostic tests) to be incorporated by the TMI biobank, and this has been ethically approved both by HCFMUSP's institutional review board and the Comissão Nacional de Ética em Pesquisa (approval number: B-016). Personal information of participants will be kept confidential.

DISCUSSION

There is a pressing need for observational studies documenting the presence of persistent symptoms and sequelae of COVID-19 after hospitalisation. However, thorough multidisciplinary investigations of large patient samples are still scarce. In a study of PASC that reassessed 1733 patients after 6 months of in-hospital discharge, assessments of multiorgan manifestations were restricted to a 12-item medical questionnaire, physical examination, a cerebrovascular/cardiovascular registration form, scales addressing QOL and dyspnoea, laboratory tests and a 6-minute walking test.[11] Objective assessments (including pulmonary function tests, ultrasonography of lower limb veins and abdomen, and CT of the chest) were conducted in a subsample of 390 patients, including only 76 ICU subjects.[11] In another study of 476 COVID-19 patients investigated 4 months after in-hospital discharge, symptom screening was undertaken by telephone; detailed in-person assessments were restricted to approximately one-third of the sample (those reporting relevant symptoms during the telephone interview and all ICU subjects), including laboratory tests, CT of the chest, cardiopulmonary tests, a 6-minute walking test, and cognitive and psychiatric assessments.[12]

In addition to the large size of our expected sample, one advantage of the study proposed herein is that we will conduct comprehensive symptom surveys and objective assessments of PASC manifestations in all individuals that agree to participate (rather than restricting more detailed schedules to a subsample with greater disease severity).[12] One other potential strength is that we will have access to baseline hospital data that were recorded prospectively. Moreover, rather than advertising the follow-up study

to potentially interested subjects, we will systematically search for individuals fulfilling inclusion criteria for the study. Conversely, one relevant limitation that should be acknowledged is the fact that we will rule out the presence of current re-infection only by the absence of clinical signs and symptoms, rather than by a negative RT-PCR test. Additionally, the fact that the study subjects will be all from one single hospital site might be taken as a further limitation. However, we should consider that HCFMUSP temporarily undertook a substantial multiplication of its capacity to treat cases of respiratory distress in 2020, thus allowing several hundreds of COVID-19 subjects from different city districts to be admitted to our hospital simultaneously. Over approximately 5 months, this setup led to numbers of treated COVID-19 cases comparable to the samples combining several medium-sized or large-sized hospitals included in studies conducted elsewhere. Moreover, our access to one large-sized, single-site sample implies that homogeneous in-stay protocols were used, thus potentially reducing inter-individual differences in outcome due to variations across hospitals regarding administrative, diagnostic and treatment routines.

Another relevant issue regards to the current impracticability to investigate long-term consequences and sequelae in concurrently assessed control groups of inpatients treated at HCFMUSP for other infectious diseases (such as CAP or dengue),[69 70] as stated in the Methods section. Such case–control comparison approach may not be needed for the evaluation of persistent symptoms and signs that are likely to be disproportionately prevalent in COVID-19 sufferers, such as olfactory manifestations.[58] However, the lack of such control groups is an important limitation for other investigations planned on our cohort, and this is a possible protocol change that will be introduced over the course of the study. Nevertheless, the lack of control groups will not jeopardise the validity of analyses investigating significant associations between risk factors and persistent manifestations of COVID-19, or analyses comparing patient subgroups divided according to specific disease features.

The individual interviews at the follow-up assessments will provide critical sociodemographic data that could not be obtained during in-hospital admissions, such as detailed information on educational background and current socioeconomic status. It has been demonstrated that individual-level and neighborhood-level variables provide complementary information about the contribution of socioeconomic conditions to health outcomes,[65] and both will be available to be tested as potentially significant factors associated with COVID-19 outcomes in our sample. The use of such variables should allow us to investigate the extent to which the vulnerability to more severe COVID-19 might be predicted not only by age, ethnicity and medical factors (eg, number of comorbidities)[71] but also socially determined factors such as poor housing conditions, unstable income and delayed access to health services.[72] Once our analyses will be carried out in a large urban LMIC setting, unique information may be gathered regarding the influence of disadvantaged socioeconomic status on specific long-term COVID-19 manifestations.[73]

As in other parts of the world, there is currently in Sao Paulo a commendable pressure from funding agencies, other research sponsors and public universities to ensure that scientific investigations will deliver, as much as possible, evidence-based data to inform real-time solutions to problems related to long-term consequences of COVID-19. Since the observational assessments will be carried out over several months, interim analyses of results may encourage our specialised research teams to plan for nested clinical trials testing the efficacy of short-term interventions targeting specific long-term COVID-19 manifestations. Additionally, we expect that the delivery of general care to the overall cohort will be facilitated by the procedure of summarisation of clinical information and follow-up contacts with participants and their care providers.

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