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The Philippine *COVID-19 Outcomes: a Retrospective study Of Neurological* manifestations and *Associated* symptoms (The Philippine *CORONA* study): a protocol study

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ABSTRACT

Introduction The SARS-CoV-2, virus that caused the COVID-19 global pandemic, possesses a neuroinvasive potential. Patients with COVID-19 infection present with neurological signs and symptoms aside from the usual respiratory affectation. Moreover, COVID-19 is associated with several neurological diseases and complications, which may eventually affect clinical outcomes.

Objectives The Philippine COVID-19 Outcomes: a Retrospective study Of Neurological manifestations and Associated symptoms (The Philippine CORONA) study investigators will conduct a nationwide, multicentre study involving 37 institutions that aims to determine the neurological manifestations and factors associated with clinical outcomes in COVID-19 infection.

Methodology and analysis This is a retrospective cohort study (comparative between patients with and without neurological manifestations) via medical chart review involving adult patients with COVID-19 infection. Sample size was determined at 1342 patients. Demographic, clinical and neurological profiles will be obtained and summarised using descriptive statistics. Student's t-test for two independent samples and χ^2 test will be used to determine differences between distributions. HRs and 95% CI will be used as an outcome measure. Kaplan-Meier curves will be constructed to plot the time to onset of mortality (survival), respiratory failure, intensive care unit (ICU) admission, duration of ventilator dependence, length of ICU stay and length of hospital stay. The log-rank test will be employed to compare the Kaplan-Meier curves. Stratified analysis will be performed to identify confounders and effects modifiers. To compute for adjusted HR with 95% CI, crude HR of outcomes will be adjusted according to the prespecified possible confounders. Cox proportional regression models will be used to determine significant factors of outcomes. Testing for goodness of fit will also be done using Hosmer-Lemeshow test. Subgroup analysis will be performed for proven prespecified effect modifiers. The effects of missing data and outliers will also be evaluated in this study.

Ethics and dissemination This protocol was approved by the Single Joint Research Ethics Board of the Philippine Department of Health (SJREB-2020–24) and

Strengths and limitations of this study

► The Philippine COVID-19 Outcomes: a Retrospective study Of Neurological manifestations and Associated symptoms Study is a nationwide, multicentre, retrospective, cohort study with 37 Philippine sites.
► Full spectrum of neurological manifestations of COVID-19 will be collected.
► Retrospective gathering of data offers virtually no risk of COVID-19 infection to data collectors.
► Data from COVID-19 patients who did not go to the hospital are unobtainable.
► Recoding bias is inherent due to the retrospective nature of the study.

the institutional review board of the different study sites. The dissemination of results will be conducted through scientific/medical conferences and through journal publication. The lay versions of the results may be provided on request.

Trial registration number NCT04386083.

INTRODUCTION

The COVID-19 has been identified as the cause of an outbreak of respiratory illness in Wuhan, Hubei Province, China, in December 2019.[1] The COVID-19 pandemic has reached the Philippines with most of its cases found in the National Capital Region (NCR).[2] The major clinical features of COVID-19 include fever, cough, shortness of breath, myalgia, headache and diarrhoea.[3] The outcomes of this disease lead to prolonged hospital stay, intensive care unit (ICU) admission, dependence on invasive mechanical ventilation, respiratory failure and mortality.[4] The specific pathogen that causes this clinical syndrome has been named SARS-CoV-2, which is phylogenetically similar to SARS-CoV.[4] Like

the SARS-CoV strain, SARS-CoV-2 may possess a similar neuroinvasive potential.[5]

A study on cases with COVID-19 found that about 36.4% of patients displayed neurological manifestations of the central nervous system (CNS) and peripheral nervous system (PNS).[6] The associated spectrum of symptoms and signs were substantially broad such as altered mental status, headache, cognitive impairment, agitation, dysexecutive syndrome, seizures, corticospinal tract signs, dysgeusia, extraocular movement abnormalities and myalgia.[7–12] Several reports were published on neurological disorders associated with patients with COVID-19, including cerebrovascular disorders, encephalopathy, hypoxic brain injury, frequent convulsive seizures and inflammatory CNS syndromes like encephalitis, meningitis, acute disseminated encephalomyelitis and Guillain-Barre syndrome.[7–16] However, the estimates of the occurrences of these manifestations were based on studies with a relatively small sample size. Furthermore, the current description of COVID-19 neurological features are hampered to some extent by exceedingly variable reporting; thus, defining causality between this infection and certain neurological manifestations is crucial since this may lead to considerable complications.[17] An Italian observational study protocol on neurological manifestations has also been published to further document and corroborate these findings.[18]

Epidemiological data on the proportions and spectrum of non-respiratory symptoms and complications may be essential to increase the recognition of clinicians of the possibility of COVID-19 infection in the presence of other symptoms, particularly neurological manifestations. With this information, the probabilities of diagnosing COVID-19 disease may be strengthened depending on the presence of certain neurological manifestations. Furthermore, knowledge of other unrecognised symptoms and complications may allow early diagnosis that may permit early institution of personal protective equipment and proper contact precautions. Lastly, the presence of neurological manifestations may be used for estimating the risk of certain important clinical outcomes for better and well-informed clinical decisions in patients with COVID-19 disease.

To address this lack of important information in the overall management of patients with COVID-19, we organised a research study entitled 'The Philippine COVID-19 Outcomes: a Retrospective study Of Neurological manifestations and Associated symptoms (The Philippine CORONA Study)'.

Objectives
This quantitative, retrospective cohort, multicentre study aims: (1) to determine the demographic, clinical and neurological profile of patients with COVID-19 disease in the Philippines; (2) to determine the frequency of neurological symptoms and new-onset neurological disorders/complications in patients with COVID-19 disease; (3) to determine the neurological manifestations that are

significant factors of mortality, respiratory failure, duration of ventilator dependence, ICU admission, length of ICU stay and length of hospital stay among patients with COVID-19 disease; (4) to determine if there is significant difference between COVID-19 patients with neurological manifestations compared with those COVID-19 patients without neurological manifestations in terms of mortality, respiratory failure, duration of ventilator dependence, ICU admission, length of ICU stay and length of hospital stay; and (5) to determine the likelihood of mortality, respiratory failure and ICU admission, including the likelihood of longer duration of ventilator dependence and length of ICU and hospital stay in COVID-19 patients with neurological manifestations compared with those without neurological manifestations.

Scope, limitations and delimitations
The study will include confirmed cases of COVID-19 from the 37 participating institutions in the Philippines. Every country has its own healthcare system, whose level of development and strategies ultimately affect patient outcomes. Thus, the results of this study cannot be accurately generalised to other settings. In addition, patients with ages ≤18 years will be excluded in from this study. These younger patients may have different characteristics and outcomes; therefore, yielded estimates for adults in this study may not be applicable to this population subgroup. Moreover, this study will collect data from the patient records of patients with COVID-19; thus, data from patients with mild symptoms who did not go to the hospital and those who had spontaneous resolution of symptoms despite true infection with COVID-19 are unobtainable.

METHODOLOGY
To improve the quality of reporting of this study, the guidelines issued by the Strengthening the Reporting of Observational Studies in Epidemiology Initiative will be followed.[19]

Study design
The study will be conducted using a retrospective cohort (comparative) design (see figure 1).

Study sites and duration
We will conduct a nationwide, multicentre study involving 37 institutions in the Philippines (see figure 2). Most of these study sites can be found in the NCR, which remains to be the epicentre of the COVID-19 pandemic.[2] We will collect data for 6 months after institutional review board approval for every site.

Patient selection and cohort description
The cases will be identified using the designated COVID-19 censuses of all the participating centres. A total enumeration of patients with confirmed COVID-19 disease will be done in this study.

The cases identified should satisfy the following inclusion criteria: (A) adult patients at least 19 years of age;
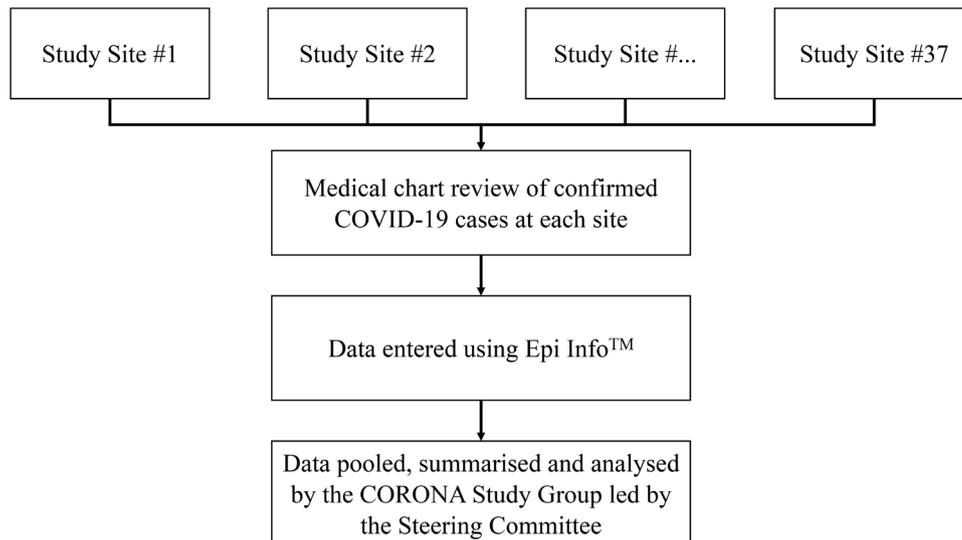
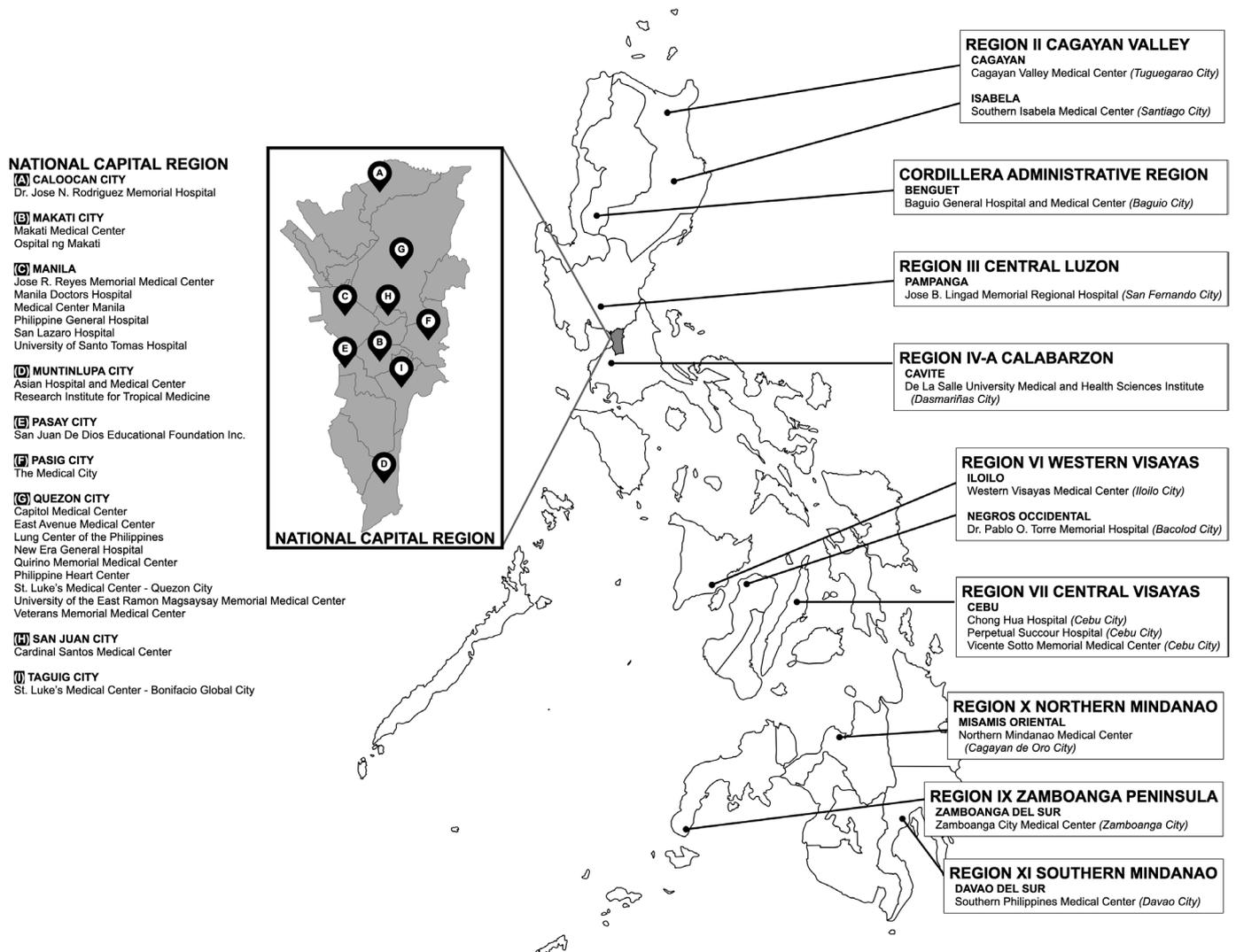**Figure 1** Schematic diagram of the study flow.

Figure 2 Location of 37 study sites of the Philippine CORONA study.

(B) cases confirmed by testing approved patient samples (ie, nasal swab, sputum and bronchoalveolar lavage fluid) employing real-time reverse transcription PCR (rRT-PCR)[20] from COVID-19 testing centres accredited by the Department of Health (DOH) of the Philippines, with clinical symptoms and signs attributable to COVID-19 disease (ie, respiratory as well as non-respiratory clinical signs and symptoms)[21]; and (C) cases with disposition (ie, discharged stable/recovered, home/discharged against medical advice, transferred to other hospital or died) at the end of the study period. Cases with conditions or diseases caused by other organisms (ie, bacteria, other viruses, fungi and so on) or caused by other pathologies unrelated to COVID-19 disease (ie, trauma) will be excluded.

The first cohort will involve patients with confirmed COVID-19 infection who presented with any neurological manifestation/s (ie, symptoms or complications/disorder). The comparator cohort will compose of patients with confirmed COVID-19 infection without neurological manifestation/s.

Sample size calculation

We looked into the mortality outcome measure for the purposes of sample size computation. Following the cohort study of Khaledifar et al,[22] the sample size was calculated using the following parameters: two-sided 95% significance level $(1 - \alpha)$; 80% power $(1 - \beta)$; unexposed/exposed ratio of 1; 5% of unexposed with outcome (case fatality rate from COVID19-Philippines Dashboard Tracker (PH)[23] as of 8 April 2020); and assumed risk ratio 2 (to see a two-fold increase in risk of mortality when neurological symptoms are present).

When these values were plugged in to the formula for cohort studies,[24] a minimum sample size of 1118 is required. To account for possible incomplete data, the sample was adjusted for 20% more. This means that the total sample size required is 1342 patients, which will be gathered from the participating centres.

Data collection

We formulated an electronic data collection form using Epi Info Software (V.7.2.2.16). The forms will be pilot-tested, and a formal data collection workshop will be conducted to ensure collection accuracy. The data will be obtained from the review of the medical records.

The following pertinent data will be obtained: (A) demographic data; (B) other clinical profile data/comorbidities; (C) neurological history; (D) date of illness onset; (E) respiratory and constitutional symptoms associated with COVID-19; (F) COVID-19 disease severity[25] at nadir; (G) data if neurological manifestation/s were present at onset prior to respiratory symptoms and the specific neurological manifestation/s present at onset; (H) neurological symptoms; (i) date of neurological symptom onset; (J) new-onset neurological disorders or complications; (K) date of new neurological disorder or complication onset; (L) imaging done; (M) cerebrospinal fluid analysis; (N) electrophysiological studies; (O) treatment given; (P) antibiotics given; (Q) neurological interventions given; (R) date of mortality and cause/s of mortality; (S) date of respiratory failure onset, date of mechanical ventilator cessation and cause/s of respiratory failure; (T) date of first day of ICU admission, date of discharge from ICU and indication/s for ICU admission; (U) other neurological outcomes at discharge; (V) date of hospital discharge; and (W) final disposition. See table 1 for the summary of the data to be collected for this study.

Main outcomes considered

The following patient outcomes will be considered for this study:

► Mortality (binary outcome): defined as the patients with confirmed COVID-19 who died.

► Respiratory failure (binary outcome): defined as the patients with confirmed COVID-19 who experienced clinical symptoms and signs of respiratory insufficiency. Clinically, this condition may manifest as tachypnoea/sign of increased work of breathing (ie, respiratory rate of ≥22), abnormal blood gases (ie, hypoxaemia as evidenced by partial pressure of oxygen (PaO_2) <60 or hypercapnia by partial pressure of carbon dioxide of >45), or requiring oxygen supplementation (ie, PaO_2 <60 or ratio of PaO_2/fraction of inspired oxygen (P/F ratio)) <300).

► Duration of ventilator dependence (continuous outcome): defined as the number of days from initiation of assisted ventilation to cessation of mechanical ventilator use.

► ICU admission (binary outcome): defined as the patients with confirmed COVID-19 admitted to an ICU or ICU-comparable setting.

► Length of ICU stay (continuous outcome): defined as the number of days admitted in the ICU or ICU-comparable setting.

► Length of hospital stay (continuous outcome): defined as the number of days from admission to discharge.

Data analysis plan

Statistical analysis will be performed using Stata V.7.2.2.16.

Demographic, clinical and neurological profiles will be summarised using descriptive statistics, in which categorical variables will be expressed as frequencies with corresponding percentages, and continuous variables will be pooled using means (SD).

Student's t-test for two independent samples and χ^2 test will be used to determine differences between distributions.

HRs and 95% CI will be used as an outcome measure. Kaplan-Meier curves will be constructed to plot the time to onset of mortality (survival), respiratory failure, ICU admission, duration of ventilator dependence (recategorised binary form), length of ICU stay (recategorised binary form) and length of hospital stay (recategorised binary form). Log-rank test will be employed to compare the Kaplan-Meier curves. Stratified analysis will be performed to identify confounders

Table 1 Data to be collected in this study

Data	Description
Demographic data and other clinical profile data	Age, sex, nationality, place of residence (city or province), weight, height, declared history of exposure (international travel, community or domestic travel and hospital), smoking status, healthcare worker status and pregnancy status.
Comorbidities	Hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic obstructive pulmonary disease, bronchial asthma, chronic kidney disease, chronic liver disease, obesity, malignancy, HIV and others.
Neurological history	Stroke/other cerebrovascular diseases, epilepsy, dementia, movement disorder, headache syndrome, CNS infection, PNS infection, central demyelinating syndrome, myelopathy, neuropathy, neuromuscular junction disorder, myopathy and others.
Respiratory and constitutional symptoms associated with COVID-19	Any respiratory/constitutional symptoms, cough, rhinorrhoea, sputum production, sore throat, haemoptysis, dyspnoea, fever, fatigue, arthralgia, diarrhoea and myalgia; date of illness onset.
COVID-19 disease severity at nadir	Mild: defined as presence of mild pneumonia or absence of pneumonia; severe disease: defined as the presence of dyspnoea, respiratory rate >30 breaths/minute, hypoxia (SpO_2 <93%) or >50% lung involvement on imaging within 24–48 hours; and critical disease: defined as the presence of respiratory failure, shock or multiorgan dysfunction.
Neurological symptoms	Any neurological symptom, headache, nausea, vomiting, seizure, altered sensorium, confusion, anosmia/hyposmia, blindness/decreased vision, eye pain, ophthalmoplegia/ophthalmoparesis, hearing loss/decreased hearing, dizziness, ageusia/dysgeusia, facial numbness, facial weakness, dysarthria, dysphonia, dysphagia, tongue weakness, neck weakness, extremity weakness, extremity numbness/paraesthesia, tremor, dystonia, choreoathetosis, bradykinaesia, ataxia, meningismus, myalgia and others; date of neurological symptom onset.
New-onset neurological disorders or complications	Any neurological complication, meningitis, encephalopathy, encephalitis, meningoencephalitis, anoxic/hypoxic brain syndrome, acute disseminated encephalomyelitis, acute necrotising haemorrhagic encephalopathy, any seizure disorder, acute symptomatic seizure, epilepsy, status epilepticus, any acute cerebrovascular disease (CVD), acute CVD (infarction), acute CVD (haemorrhagic), any movement disorder, movement disorders (hyperkinetic), movement disorders (hypokinetic), cerebellitis, optic neuritis, myelitis, sensory ganglionitis/dorsal radiculitis, anterior horn syndrome (polio-like syndrome)/ventral radiculitis, peripheral neuritis (GBS-like syndrome), peripheral neuritis (other than GBS-like syndrome), neuromuscular disorder, myositis and others; date of new neurological disorder or complication onset.
Imaging done	CT scan, MRI scan, affected portion/s of the neuroaxis in the imaging.
Cerebrospinal fluid (CSF) analysis	CSF total cell count, CSF neutrophil count, CSF lymphocyte count, CSF protein, CSF glucose, serum glucose, CSF COVID-19 test result and other CSF tests done.
Electrophysiological studies	Electroencephalography, and electromyography-nerve conduction studies tests, if done, and pertinent results.
Treatment given	Chloroquine, hydroxychloroquine, lopinavir+ritonavir, tocilizumab, remdesivir, systemic glucocorticoids, convalescent plasma and others; antibiotics given.
Neurological interventions	For example, antiplatelet, anticoagulant, antiepileptic drugs and others.
Mortality	Date of mortality and cause/s of mortality.
Respiratory failure	Date of respiratory failure onset, date of mechanical ventilator cessation and cause/s of respiratory failure.
ICU admission	Date of first day of ICU admission, date of discharge from ICU and indication/s for ICU admission.
Other neurological outcomes at discharge	Full neurological recovery: defined as patients with confirmed COVID-19 infection who had any neurological deficit during admission, who then had full neurological recovery with no noted neurological deficits at discharge; stable with improvement of neurological deficits: defined as patients with COVID-19 infection who had any neurological deficit during admission, who then had improvement but not complete resolution of the neurological deficits at discharge; stable with no improvement of neurological deficits: defined as the patients with COVID-19 infection who had any neurological deficit during admission, who then had no improvement of the neurological deficits at discharge

Table 1	Continued
Data	**Description**
Final disposition	Discharged stable/recovered, home against medical advice, transferred to other hospital, died/mortality; date of hospital discharge.

CNS, central nervous system; GBS, Guillain-Barre syndrome; ICU, intensive care unit; PNS, peripheral nervous system; SpO_2, peripheral capillary oxygen saturation.

and effects modifiers. To compute for adjusted HR with 95% CI, crude HR of outcomes at discrete time points will be adjusted for prespecified possible confounders such as age, history of cardiovascular or cerebrovascular disease, hypertension, diabetes mellitus, and respiratory disease, COVID-19 disease severity at nadir, and other significant confounding factors.

Cox proportional regression models will be used to determine significant factors of outcomes. Testing for goodness of fit will be done using Hosmer-Lemeshow test. Likelihood ratio tests and other information criteria (Akaike Information Criterion or Bayesian Information Criterion) will be used to refine the final model. Statistical significance will be considered if the 95% CI of HR or adjusted HR did not include the number one. A p value <0.05 (two tailed) is set for other analyses.

Subgroup analyses will be performed for proven prespecified effect modifiers. The following variables will be considered for subgroup analyses: age (19–64 years vs ≥65 years), sex, body mass index (<18.5 vs 18.5–22.9 vs ≥23 kg/m^2), with history of cardiovascular or cerebrovascular disease (presence or absence), hypertension (presence or absence), diabetes mellitus (presence or absence), respiratory disease (presence or absence), smoking status (smoker or non-smoker) and COVID-19 disease severity (mild, severe or critical disease).

The effects of missing data will be explored. All efforts will be exerted to minimise missing and spurious data. Validity of the submitted electronic data collection will be monitored and reviewed weekly to prevent missing or inaccurate input of data. Multiple imputations will be performed for missing data when possible. To check for robustness of results, analysis done for patients with complete data will be compared with the analysis with the imputed data.

The effects of outliers will also be assessed. Outliers will be assessed by z-score or boxplot. A cut-off of 3 SD from the mean can also be used. To check for robustness of results, analysis done with outliers will be compared with the analysis without the outliers.

Study organisational structure

A steering committee (AIE, MCCS, VMMA and RDGJ) was formed to direct and provide appropriate scientific, technical and methodological assistance to study site investigators and collaborators (see figure 3). Central administrative coordination, data management, administrative support, documentation of progress reports, data analyses and interpretation and journal publication are the main responsibilities of the steering committee. Study site investigators and collaborators are responsible for the proper collection and recording of data including the duty to maintain the confidentiality of information and the privacy of all identified patients for all the phases of the research processes.

This section is highlighted as part of the required formatting amendments by the Journal.

Ethics and dissemination

This research will adhere to the Philippine National Ethical Guidelines for Health and Health-related Research 2017.[26] This study is an observational, cohort study and will not allocate any type of intervention. The medical records of the identified patients will be reviewed retrospectively. To protect the privacy of the participant, the data collection forms will not contain any information (ie, names and institutional patient number) that could determine the identity of the patients. A sequential code will be recorded for each patient in the following format: AAA-BBB where AAA will pertain
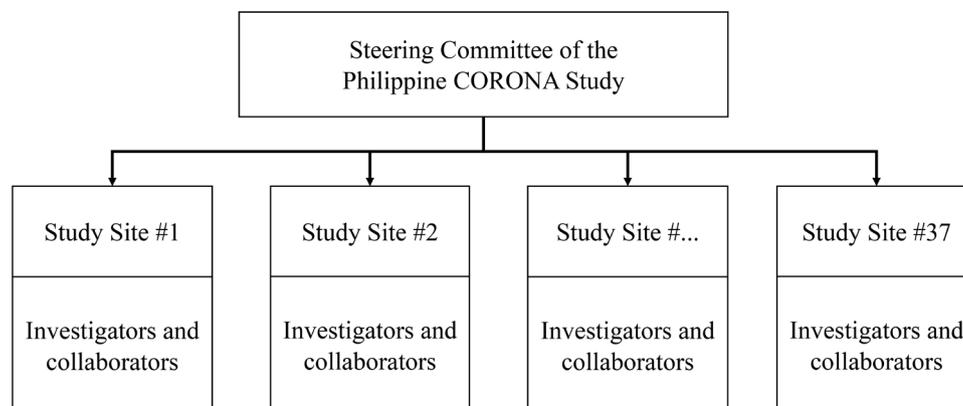

Figure 3 Organisational structure of oversight of the Philippine CORONA Study.

to the three-digit code randomly assigned to each study site; BBB will pertain to the sequential case number assigned by each study site. Each participating centre will designate a password-protected laptop for data collection; the password is known only to the study site.

This protocol was approved by the following institutional review boards: Single Joint Research Ethics Board of the DOH, Philippines (SJREB-2020-24); Asian Hospital and Medical Center, Muntinlupa City (2020- 010-A); Baguio General Hospital and Medical Center (BGHMC), Baguio City (BGHMC-ERC-2020-13); Cagayan Valley Medical Center (CVMC), Tuguegarao City; Capitol Medical Center, Quezon City; Cardinal Santos Medical Center (CSMC), San Juan City (CSMC REC 2020-020); Chong Hua Hospital, Cebu City (IRB 2420–04); De La Salle Medical and Health Sciences Institute (DLSMHSI), Cavite (2020-23-02-A); East Avenue Medical Center (EAMC), Quezon City (EAMC IERB 2020-38); Jose R. Reyes Memorial Medical Center, Manila; Jose B. Lingad Memorial Regional Hospital, San Fernando, Pampanga; Dr. Jose N. Rodriguez Memorial Hospital, Caloocan City; Lung Center of the Philippines (LCP), Quezon City (LCP-CT-010–2020); Manila Doctors Hospital, Manila (MDH IRB 2020-006); Makati Medical Center, Makati City (MMC IRB 2020–054); Manila Medical Center, Manila (MMERC 2020-09); Northern Mindanao Medical Center, Cagayan de Oro City (025-2020); Quirino Memorial Medical Center (QMMC), Quezon City (QMMC REB GCS 2020-28); Ospital ng Makati, Makati City; University of the Philippines – Philippine General Hospital (UP-PGH), Manila (2020-314-01 SJREB); Philippine Heart Center, Quezon City; Research Institute for Tropical Medicine, Muntinlupa City (RITM IRB 2020-16); San Lazaro Hospital, Manila; San Juan De Dios Educational Foundation Inc – Hospital, Pasay City (SJRIB 2020-0006); Southern Isabela Medical Center, Santiago City (2020-03); Southern Philippines Medical Center (SPMC), Davao City (P20062001); St. Luke's Medical Center, Quezon City (SL-20116); St. Luke's Medical Center, Bonifacio Global City, Taguig City (SL-20116); Southern Philippines Medical Center, Davao City; The Medical City, Pasig City; University of Santo Tomas Hospital, Manila (UST-REC-2020-04-071-MD); University of the East Ramon Magsaysay Memorial Medical Center, Inc, Quezon City (0835/E/2020/063); Veterans Memorial Medical Center (VMMC), Quezon City (VMMC-2020-025) and Vicente Sotto Memorial Medical Center, Cebu City (VSMMC-REC-O-2020–048).

The dissemination of results will be conducted through scientific/medical conferences and through journal publication. Only the aggregate results of the study shall be disseminated. The lay versions of the results may be provided on request.

Protocol registration and technical review approval

This protocol was registered in the ClinicalTrials.gov website. It has received technical review board approvals from the Department of Neurosciences, Philippine General Hospital and College of Medicine, University of the Philippines Manila, from the Cardinal Santos Medical Center (San Juan City) and from the Research Center for Clinical Epidemiology and Biostatistics, De La Salle Medical and Health Sciences Institute (Dasmariñas, Cavite).

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