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Study protocol: The Philippine **C**OVID-19 **O**utcomes: a **R**etrospective study **O**f **N**eurological manifestations and **A**ssociated symptoms (The Philippine **CORONA** Study)

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ABSTRACT

Introduction:
The SARS-CoV-2, virus which caused the coronavirus disease (COVID-19) global pandemic, may possess a neuroinvasive potential. It is hypothesized that patients with COVID-19 disease may also present with neurological signs and symptoms aside from the usual respiratory affectation. Moreover, it appears that COVID-19 may be associated with several neurological diseases and complications, which may eventually affect clinical outcomes.

Objectives:
The Philippine CORONA study investigators will conduct a nationwide, multicenter study involving 31 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 1,342 patients. Demographic, clinical and neurological profiles will be obtained and summarized using descriptive statistics. Student's t-test for two independent samples and chi-squared test will be used to determine differences between distributions. Hazard ratios (HR) and 95% confidence interval 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, 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.

Ethical consideration:
This protocol was approved by the Single Joint Research Ethics Board of the Philippine Department of Health (SJREB-2020-24) and the institutional review board of the different study sites.

Registration number: NCT04386083

Keywords: COVID-19, Neurologic manifestations; Outcomes; Cohort study

ARTICLE SUMMARY

Strengths and limitations:

- CORONA is a nationwide, multicenter, retrospective, cohort study with 31 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.

INTRODUCTION

The coronavirus disease (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 diarrhea [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 severe acute respiratory syndrome coronavirus 2 (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]. This virus utilizes angiotensin converting enzyme 2 (ACE2) receptor to gain entry into cells which is present in multiple organs of the body including glial cells and neurons [5,6]. Modes of transmission by these viral pathogens may involve transcellular, paracellular and retrograde axonal transport along sensory and olfactory nerves, and through hematogenous spread or viremia [7].

A study on cases with COVID-19 found that about 36.4% of patients displayed neurologic manifestations of the central nervous system (CNS) and peripheral nervous system (PNS) [8]. These estimates, however, were based on studies with small number of patients. Some reports have been recently published on neurologic disorders associated with COVID-19 patients including frequent convulsive seizures, Guillain-Barre syndrome (GBS), meningitis and acute hemorrhagic necrotizing encephalopathy [9–12].

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 unrecognized symptoms and complications may allow early diagnosis which may permit early institution of personal protective equipment and proper contact precautions. Lastly, the presence of neurological manifestations may be utilized 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 COVID-19 patients, we organized 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, multicenter 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 to 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, length of ICU and hospital stay in COVID-19 patients with neurological manifestations compared to those without neurological manifestations.

Scope, limitations and delimitations

The study will include confirmed cases of COVID-19 from the 31 participating institutions in the Philippines. Every country has its own health care system, whose level of development and strategies ultimately affect patient outcomes. Thus, the results of this study cannot be accurately generalized to other settings. In addition, patients with ages $\leq$ 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 COVID-19 patients; 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 (STROBE) Initiative will be followed [13].

Study design

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

Study sites and duration

We will conduct a nationwide, multicenter study involving 31 institutions in the Philippines (see Fig 2). Most of these study sites can be found in the NCR, which remains to be the epicenter 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 centers. 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; (b) cases confirmed by testing approved patient samples (i.e. nasal swab, sputum, bronchoalveolar lavage fluid) employing real-time reverse transcription polymerase chain reaction (rRT-PCR) [14] from COVID-19 testing centers accredited by the Department of Health (DOH) of the Philippines, with clinical symptoms and signs attributable to COVID-19 disease (i.e. respiratory as well as non-respiratory clinical signs and symptoms) [15]; (c) cases with disposition (i.e., 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 (i.e. bacteria, other viruses, fungi, etc.) or caused by other pathologies unrelated to COVID-19 disease (i.e., trauma) will be excluded.

The first cohort will involve patients with confirmed COVID-19 infection who presented with any neurological manifestation/s (i.e., symptoms or complications/ disorder). The comparator cohort will comprise 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. [16]. 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-PH [17] as of 8 April 2020); Assumed risk ratio 2 (to see a two-fold increase in risk of mortality when neurologic symptoms are present).

When these values were plugged-in to the formula for cohort studies [18], a minimum sample size of 1,118 is required. To account for possible incomplete data, the sample was adjusted for 20% more. This means that the total sample size required is 1,342 patients which will be gathered from the participating centers.

Data collection

We formulated an electronic data collection form using Epi Info™ Software (Version 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 and other clinical profile data (b) comorbidities; (c) past neurological history; (d) date of illness onset; (e) respiratory and constitutional symptoms associated with COVID-19; (f) COVID-19 disease severity [19] 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 (CSF) fluid analysis; (n) electrophysiologic studies; (o) treatment given; (p) antibiotics given; (q) neurological interventions given; (r) date of mortality, cause/s of mortality; (s) date of respiratory failure onset, date of mechanical ventilator cessation, cause/s of respiratory failure; (t) date of first day of ICU admission, date of discharge from ICU, indication/s for ICU admission; (u) other neurological outcomes at discharge; (v) date of hospital discharge; (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 tachypnea, abnormal blood gases (hypoxemia or hypercapnia), signs of increased work of breathing, and requiring oxygen supplementation [20];
- Duration of ventilator dependence (continuous outcome) – defined as the number of days from initiation of assisted ventilation to cessation of mechanical ventilator use;

Table 1. Data to be collected in this study.

Data	Description
Demographic data and other clinical profile data	Age, sex, nationality, and place of residence (city or province), weight, height, declared history of exposure (international travel, community or domestic travel, 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
Past 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, rhinorrhea, sputum production, sore throat, hemoptysis, dyspnea, fever, fatigue, arthralgia, diarrhea, 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 dyspnea, respiratory rate > 30 breaths/ minute, hypoxia (SpO_2 <93%), or > 50% lung involvement on imaging within 24 to 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/ paresthesia, tremor, dystonia, choreoathetosis, bradykinesia, 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 necrotizing hemorrhagic encephalopathy, any seizure disorder, acute symptomatic seizure, epilepsy, status epilepticus, any acute cerebrovascular disease (CVD), acute CVD (infarction), acute CVD (hemorrhagic), 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	Computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, affected portion/s of the neuroaxis in the imaging
Cerebrospinal (CSF) fluid analysis	CSF total cell count, CSF neutrophil count, CSF lymphocyte count, CSF protein, CSF glucose, serum glucose, CSF COVID-19 test result, other CSF tests done
Electrophysiologic studies	Electroencephalography (EEG), and electromyography-nerve conduction studies (EMG-NCS) tests, if done, and pertinent results
Treatment given	Chloroquine, hydroxychloroquine, lopinavir + ritonavir, tocilizumab, remdesivir, systemic glucocorticoids, convalescent plasma, and others; Antibiotics given
Neurological interventions	E.g., Antiplatelet, anticoagulant, antiepileptic drugs, and others
Mortality	Date of mortality, cause/s of mortality
Respiratory failure	Date of respiratory failure onset, date of mechanical ventilator cessation, cause/s of respiratory failure
ICU admission	Date of first day of ICU admission, date of discharge from ICU, 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
Final disposition	Discharged stable/recovered, home against medical advice, transferred to other hospital, died/mortality); date of hospital discharge

- Intensive care unit (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®, Version 7.2.2.16 (College Station, TX: StataCorp LP).

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

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

Hazard ratios (HR) and 95% confidence interval 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 (recategorized binary form), length of ICU stay (recategorized binary form), length of hospital stay (recategorized binary form). 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 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% confidence interval 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 to 64 years vs $\geq$ 65 years), sex, body-mass index (<18.5 vs 18.5 to 22.9 vs $\geq$ 23 kg/m^2), with past 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 nonsmoker), and COVID-19 disease severity (mild, severe or critical disease).

The effects of missing data will be explored. All efforts will be exerted to minimize 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 to 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 standard deviations from the mean can also be used. To check for robustness of results, analysis done with outliers will be compared to the analysis without the outliers.

Study organizational structure

A steering committee (AIE, MCS, VMA, and RDJ) was formed to direct and provide appropriate scientific, technical, and methodological assistance to study site investigators and collaborators (see Fig 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.

Ethical considerations

This research will adhere to the Philippine *National Ethical Guidelines for Health and Health-related Research (NEGHHRR) 2017* [21]. 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 (i.e., names, 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 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 center will designate a password-protected laptop for data collection; the password is known only to the study site.

This protocol has been approved by the following institutional review boards: Single Joint Research Ethics Board of the DOH, Philippines (SJREB-2020-24); Cardinal Santos Medical

Center, San Juan City (CSMC REC 2020-020); East Avenue Medical Center (EAMC), Quezon City (EAMC IERB 2020-38); Jose B. Lingad Memorial Regional Hospital, San Fernando, Pampanga; Manila Doctors Hospital, Manila City (MDH IRB 2020-006); Makati Medical Center, Makati City (MMC IRB 2020-054); Philippine Heart Center, Quezon City; Research Institute for Tropical Medicine, Muntinlupa City (RITM IRB 2020-16); Southern Philippines Medical Center, Davao City; The Medical City, Pasig City; and University of Santo Tomas Hospital, Manila City (UST-REC-2020-04-071-MD).

SUMMARY

The Philippine CORONA Study, a nationwide multicenter study involving 31 institutions, is designed to address the large knowledge gap of the neurological manifestations and factors leading to clinical outcomes in COVID-19 infection. The evidence that will be gleaned from this collaborative work will serve as a benchmark information to aid physicians to better recognize the full neurological spectrum of its clinical presentations. Furthermore, the results that will be obtained from this study may contribute to the risk estimation of important clinical outcomes, essential to the overall care of COVID-19 patients.

Protocol registration and technical review approval

This protocol was registered in the ClinicalTrials.gov website (Identifier: NCT04386083). It has received a technical review board approval from the Department of Neurosciences, Philippine General Hospital and College of Medicine, University of the Philippines Manila and from the Cardinal Santos Medical Center, San Juan City, Philippines.

Funding source

The Philippine Neurological Association (PNA), the accredited national professional society of neurologists in the Philippines, is the major study sponsor. The study will also receive funding from the Philippine General Hospital – Expanded Hospital Research Office, University of the Philippines Manila.

Our funding sources had no role in the design of the protocol, and will not be involved during the methodological execution, data analyses and interpretation, and decision to submit or to publish the study results.

Authors' contribution

AIE, MCS, VMA, and RDJ conceived the idea and wrote the initial drafts and revisions of the protocol. All authors made substantial contributions in this protocol for intellectual content.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

We would like to thank Almira Abigail Doreen O. Apor, MD of the Department of Neurosciences, Philippine General Hospital, Philippines for illustrating Fig 2 for this publication.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

REFERENCES

1 Adhikari SP, Meng S, Wu Y-J, *et al.* Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty* 2020;**9**:29. doi:10.1186/s40249-020-00646-x

2 Department of Health. COVID-19 case tracker. 2020.https://www.doh.gov.ph/covid-19/case-tracker (accessed 10 May 2020).

3 Philippine Society for Microbiology and Infectious Diseases. Interim guidelines on the clinical management of adult patients with suspected or confirmed COVID-19 infection. 2020.

4 Guan W, Ni Z, Hu Y, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;:NEJMoa2002032. doi:10.1056/NEJMoa2002032

5 Li Y, Bai W, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J Med Virol* 2020;**92**:552–5. doi:10.1002/jmv.25728

6 Baig AM, Khaleeq A, Ali U, *et al.* Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci* 2020;**11**:995–8. doi:10.1021/acschemneuro.0c00122

7 Robinson CP, Busl KM. Neurologic manifestations of severe respiratory viral contagions. *Crit Care Explor* 2020;**2**:e0107. doi:10.1097/CCE.0000000000000107

8 Mao L, Jin H, Wang M, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;:e201127. doi:10.1001/jamaneurol.2020.1127

9 Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: A case report. *Iran Red Crescent Med J* 2020;**22**. doi:10.5812/ircmj.102828

10 Poyiadji N, Shahin G, Noujaim D, *et al.* COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020;:201187. doi:10.1148/radiol.2020201187

11 Zhao H, Shen D, Zhou H, *et al.* Guillain-Barré syndrome associated with SARS-CoV-2 infection: Causality or coincidence? *Lancet Neurol* Published Online First: April 2020. doi:10.1016/S1474-4422(20)30109-5

12 Moriguchi T, Harii N, Goto J, *et al.* A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* Published Online First: April 2020. doi:10.1016/j.ijid.2020.03.062

13 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**:344–9. doi:10.1016/j.jclinepi.2007.11.008

14 Lu R, Zhao X, Li J, *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* 2020;**395**:565–74. doi:10.1016/S0140-6736(20)30251-8

15 Centers for Disease Control and Prevention. Evaluating and testing persons for coronavirus disease 2019 (COVID-19). 2020.https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html (accessed 7 Apr 2020).

16 Khaledifar A, Hashemzadeh M, Solati K, *et al.* The protocol of a population-based prospective cohort study in southwest of Iran to analyze common non-communicable

diseases: Shahrekord cohort study. *BMC Public Health* 2018;**18**:660. doi:10.1186/s12889-018-5364-2

17 Haw J, Uy J. COVID-19 cases and deaths in the Philippines dashboard. 2020.https://public.tableau.com/profile/jason.haw#!/vizhome/COVID-19CasesandDeathsinthePhilippines/Dashboard?publish=yes (accessed 8 Apr 2020).

18 Fleiss JL. *Statistical methods for rates and proportions*. 1st Ed. London: : John Wiley & Sons 1981.

19 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA* Published Online First: 24 February 2020. doi:10.1001/jama.2020.2648

20 Tulaimat A, Patel A, Wisniewski M, *et al.* The validity and reliability of the clinical assessment of increased work of breathing in acutely ill patients. *J Crit Care* 2016;**34**:111–5. doi:10.1016/j.jcrc.2016.04.013

21 Philippine Research Ethics Board. *National ethical guidelines for health and health-related research*. Taguig City: : Philippine Council for Health Research and Development Department of Science and Technology 2017.

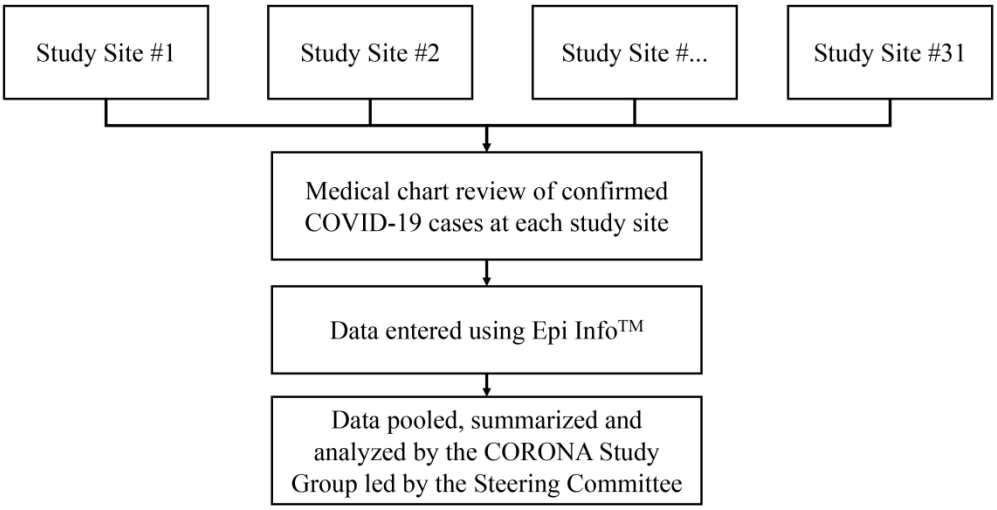

Fig 1. Schematic diagram of the study flow.

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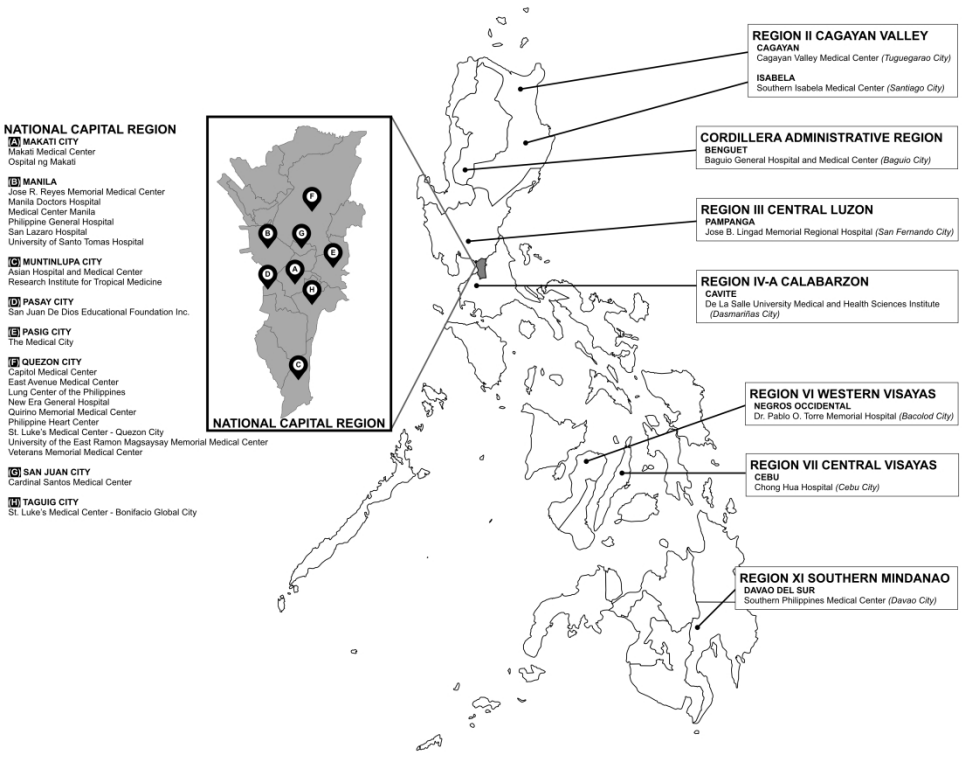

Fig 2. Location of study sites of the Philippine CORONA Study.

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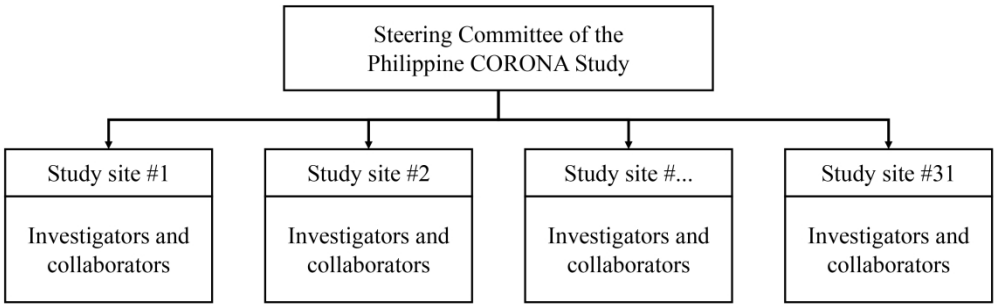

Fig 3. Organizational structure of oversight of the Philippine CORONA Study.

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BMJ Open

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

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Study protocol: The Philippine **C**OVID-19 **O**utcomes: a **R**etrospective study **O**f **N**eurological manifestations and **A**ssociated symptoms (The Philippine **CORONA** Study)

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ABSTRACT

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

Objectives:
The Philippine CORONA study investigators will conduct a nationwide, multicenter 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 1,342 patients. Demographic, clinical and neurological profiles will be obtained and summarized using descriptive statistics. Student's t-test for two independent samples and chi-squared test will be used to determine differences between distributions. Hazard ratios (HR) and 95% confidence interval 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, 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 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 upon request.

Registration number: NCT04386083

Keywords: COVID-19, Neurologic manifestations; Outcomes; Cohort study

ARTICLE SUMMARY

Strengths and limitations:

- CORONA is a nationwide, multicenter, 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.

INTRODUCTION

The coronavirus disease (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 diarrhea [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 severe acute respiratory syndrome coronavirus 2 (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 neurologic 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 neurologic disorders associated with COVID-19 patients, including cerebrovascular disorders, encephalopathy, hypoxic brain injury, frequent convulsive seizures, inflammatory CNS syndromes like encephalitis, meningitis, acute disseminated encephalomyelitis, and Guillain-Barre syndrome (GBS) [7–10,12–17]. 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 [18]. An Italian observational study protocol on neurological manifestations has also been published to further document and corroborate these findings [19].

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 unrecognized symptoms and complications may allow early diagnosis which may permit early institution of personal protective equipment and proper contact precautions. Lastly, the presence of neurological manifestations may be utilized 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 COVID-19 patients, we organized 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, multicenter 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 to 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, length of ICU and hospital stay in COVID-19 patients with neurological manifestations compared to 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 health care system, whose level of development and strategies ultimately affect patient outcomes. Thus, the results of this study cannot be accurately generalized to other settings. In addition, patients with ages $\leq$ 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 COVID-19 patients; 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 (STROBE) Initiative will be followed [20].

Study design

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

Study sites and duration

We will conduct a nationwide, multicenter study involving 37 institutions in the Philippines (see Fig 2). Most of these study sites can be found in the NCR, which remains to be the epicenter 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 centers. 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; (b) cases confirmed by testing approved patient samples (i.e. nasal swab, sputum, bronchoalveolar lavage fluid) employing real-time reverse transcription polymerase chain reaction (rRT-PCR) [21] from COVID-19 testing centers accredited by the Department of Health (DOH) of the Philippines, with clinical symptoms and signs attributable to COVID-19 disease (i.e. respiratory as well as non-respiratory clinical signs and symptoms) [22]; (c) cases with disposition (i.e., 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 (i.e. bacteria, other viruses, fungi, etc.) or caused by other pathologies unrelated to COVID-19 disease (i.e., trauma) will be excluded.

The first cohort will involve patients with confirmed COVID-19 infection who presented with any neurological manifestation/s (i.e., symptoms or complications/ disorder). The comparator cohort will comprise 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. [23]. 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-PH [24] as of 8 April 2020); Assumed risk ratio 2 (to see a two-fold increase in risk of mortality when neurologic symptoms are present).

When these values were plugged-in to the formula for cohort studies [25], a minimum sample size of 1,118 is required. To account for possible incomplete data, the sample was adjusted for 20% more. This means that the total sample size required is 1,342 patients which will be gathered from the participating centers.

Data collection

We formulated an electronic data collection form using Epi Info™ Software (Version 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 and other clinical profile data (b) comorbidities; (c) past neurological history; (d) date of illness onset; (e) respiratory and constitutional symptoms associated with COVID-19; (f) COVID-19 disease severity [26] 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 (CSF) fluid analysis; (n) electrophysiologic studies; (o) treatment given; (p) antibiotics given; (q) neurological interventions given; (r) date of mortality, cause/s of mortality; (s) date of respiratory failure onset, date of mechanical ventilator cessation, cause/s of respiratory failure; (t) date of first day of ICU admission, date of discharge from ICU, indication/s for ICU admission; (u) other neurological outcomes at discharge; (v) date of hospital discharge; (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 tachypnea/sign of increased work of breathing (i.e., respiratory rate of $\geq$ 22), abnormal blood gases (i.e., hypoxemia as evidenced by partial pressure of oxygen (PaO2) < 60 or hypercapnia by partial pressure of carbon dioxide ($PaCO_2$) of

Table 1. Data to be collected in this study.

Data	Description
Demographic data and other clinical profile data	Age, sex, nationality, and place of residence (city or province), weight, height, declared history of exposure (international travel, community or domestic travel, 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
Past 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, rhinorrhea, sputum production, sore throat, hemoptysis, dyspnea, fever, fatigue, arthralgia, diarrhea, 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 dyspnea, respiratory rate > 30 breaths/ minute, hypoxia (SpO_2 <93%), or > 50% lung involvement on imaging within 24 to 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/ paresthesia, tremor, dystonia, choreoathetosis, bradykinesia, 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 necrotizing hemorrhagic encephalopathy, any seizure disorder, acute symptomatic seizure, epilepsy, status epilepticus, any acute cerebrovascular disease (CVD), acute CVD (infarction), acute CVD (hemorrhagic), 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	Computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, affected portion/s of the neuroaxis in the imaging
Cerebrospinal (CSF) fluid analysis	CSF total cell count, CSF neutrophil count, CSF lymphocyte count, CSF protein, CSF glucose, serum glucose, CSF COVID-19 test result, other CSF tests done
Electrophysiologic studies	Electroencephalography (EEG), and electromyography-nerve conduction studies (EMG-NCS) tests, if done, and pertinent results
Treatment given	Chloroquine, hydroxychloroquine, lopinavir + ritonavir, tocilizumab, remdesivir, systemic glucocorticoids, convalescent plasma, and others; Antibiotics given
Neurological interventions	E.g., Antiplatelet, anticoagulant, antiepileptic drugs, and others
Mortality	Date of mortality, cause/s of mortality
Respiratory failure	Date of respiratory failure onset, date of mechanical ventilator cessation, cause/s of respiratory failure
ICU admission	Date of first day of ICU admission, date of discharge from ICU, 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
Final disposition	Discharged stable/recovered, home against medical advice, transferred to other hospital, died/mortality); date of hospital discharge

> 45), or requiring oxygen supplementation (i.e., PaO_2 < 60 or ratio of PaO_2/fraction of inspired oxygen (FiO_2) [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;
- Intensive care unit (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®, Version 7.2.2.16 (College Station, TX: StataCorp LP).

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

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

Hazard ratios (HR) and 95% confidence interval 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 (recategorized binary form), length of ICU stay (recategorized binary form), length of hospital stay (recategorized binary form). 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 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% confidence interval 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 to 64 years vs $\geq$ 65 years), sex, body-mass index ($<$18.5 vs 18.5 to 22.9 vs $\geq$ 23 kg/m^2), with past 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 nonsmoker), and COVID-19 disease severity (mild, severe or critical disease).

The effects of missing data will be explored. All efforts will be exerted to minimize 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 to 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 standard deviations from the mean can also be used. To check for robustness of results, analysis done with outliers will be compared to the analysis without the outliers.

Study organizational structure

A steering committee (AIE, MCS, VMA, and RDJ) was formed to direct and provide appropriate scientific, technical, and methodological assistance to study site investigators and collaborators (see Fig 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 (NEGHHRR) 2017* [27]. 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 (i.e., names, 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 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 center 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 (AHMC), Muntinlupa City (2020-010-A); Baguio General Hospital and Medical Center (BGHMC), Baguio City (BGHMC-ERC-2020-13); Capitol Medical Center (CMC), Quezon City; Cardinal Santos Medical Center (CSMC), San Juan City (CSMC REC 2020-020); Chong Hua Hospital (CHH), Cebu City (IRB 2420-04); East Avenue Medical Center (EAMC), Quezon City (EAMC IERB 2020-38); Jose R. Reyes Memorial Medical Center (JRRMMC), Manila; Jose B. Lingad Memorial Regional Hospital, San Fernando, Pampanga; Dr. Jose N. Rodriguez Memorial Hospital (Tala Leprosarium), Caloocan City; Lung Center of the Philippines (LCP), Quezon City (LCP-CT-010-2020); Manila Doctors Hospital, Manila City (MDH IRB 2020-006); Makati Medical Center, Makati City (MMC IRB 2020-054); Manila Medical Center (ManilaMed), 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 (OsMak), Makati City; Philippine General Hospital, Manila; Philippine Heart Center (PHC), Quezon City; Research Institute for Tropical Medicine, Muntinlupa City (RITM IRB 2020-16); San Lazaro Hospital, Manila; San Juan De Dios Educational Foundation Inc. (SJDEFI) – Hospital, Pasay City (SJRIB 2020-0006); Southern Isabela Medical Center (SIMC), Santiago City (2020-03); St. Luke's Medical Center, Quezon City (SL-20116); St. Luke's Medical Center, Bonifacio Global City (SLMC-GC), Taguig City

(SL-20116); Southern Philippines Medical Center (SPMC), Davao City; The Medical City (TMC), Pasig City; University of Santo Tomas Hospital, Manila City (UST-REC-2020-04-071-MD); University of the East Ramon Magsaysay Memorial Medical Center (UERMMMC), Inc., Quezon City (0835/E/2020/063) 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 upon request.

Protocol registration and technical review approval

This protocol was registered in the ClinicalTrials.gov website (Identifier: NCT04386083). 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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- Expanded Hospital Research Office (EHRO), Philippine General Hospital (PGH) (Grant/Award Number: N/A).

Role of funding sources

Our funding sources had no role in the design of the protocol, and will not be involved during the methodological execution, data analyses and interpretation, and decision to submit or to publish the study results.

Authors' contribution

AIE, MCS, VMA, and RDJ conceived the idea and wrote the initial drafts and revisions of the protocol. All authors made substantial contributions in this protocol for intellectual content.

Conflict of interest

The authors declare no conflict of interest.

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Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

REFERENCES

1 Adhikari SP, Meng S, Wu Y-J, *et al.* Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty* 2020;**9**:29. doi:10.1186/s40249-020-00646-x

2 Department of Health. COVID-19 case tracker. 2020.https://www.doh.gov.ph/covid-19/case-tracker (accessed 10 May 2020).

3 Philippine Society for Microbiology and Infectious Diseases. Interim guidelines on the clinical management of adult patients with suspected or confirmed COVID-19 infection. 2020.

4 Guan W, Ni Z, Hu Y, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;:NEJMoa2002032. doi:10.1056/NEJMoa2002032

5 Li Y, Bai W, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J Med Virol* 2020;**92**:552–5. doi:10.1002/jmv.25728

6 Mao L, Jin H, Wang M, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;:e201127. doi:10.1001/jamaneurol.2020.1127

7 Paterson RW, Brown RL, Benjamin L, *et al.* The emerging spectrum of COVID-19 neurology: Clinical, radiological and laboratory findings. *Brain* Published Online First: 8 July 2020. doi:10.1093/brain/awaa240

8 Pinna P, Grewal P, Hall JP, *et al.* Neurological manifestations and COVID-19: Experiences from a tertiary care center at the frontline. *J Neurol Sci* 2020;**415**:116969.

doi:10.1016/j.jns.2020.116969

9 Varatharaj A, Thomas N, Ellul MA, *et al.* Neurological and neuropsychiatric complications of COVID-19 in 153 patients: A UK-wide surveillance study. *The Lancet Psychiatry* Published Online First: June 2020. doi:10.1016/S2215-0366(20)30287-X

10 Mahammedi A, Saba L, Vagal A, *et al.* Imaging in neurological disease of hospitalized COVID-19 patients: An Italian multicenter retrospective observational study. *Radiology* 2020;:201933. doi:10.1148/radiol.2020201933

11 Collantes ME, Espiritu A, Sy MC, *et al.* Neurological manifestations in COVID-19 infection: A systematic review and meta-analysis. *Can J Neurol Sci / J Can des Sci Neurol* 2020;:1–26. doi:10.1017/cjn.2020.146

12 Helms J, Kremer S, Merdji H, *et al.* Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020;:NEJMc2008597. doi:10.1056/NEJMc2008597

13 Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: A case report. *Iran Red Crescent Med J* 2020;**22**. doi:10.5812/ircmj.102828

14 Poyiadji N, Shahin G, Noujaim D, *et al.* COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020;:201187. doi:10.1148/radiol.2020201187

15 Zhao H, Shen D, Zhou H, *et al.* Guillain-Barré syndrome associated with SARS-CoV-2 infection: Causality or coincidence? *Lancet Neurol* Published Online First: April 2020. doi:10.1016/S1474-4422(20)30109-5

16 Moriguchi T, Harii N, Goto J, *et al.* A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* Published Online First: April 2020.

doi:10.1016/j.ijid.2020.03.062

17 Collantes ME V., Espiritu AI, Sy MCC, *et al.* Neurological manifestations in COVID-19 infection: A systematic review and meta-analysis. *Can J Neurol Sci / J Can des Sci Neurol* 2020;:1–26. doi:10.1017/cjn.2020.146

18 Ellul M, Varatharaj A, Nicholson TR, *et al.* Defining causality in COVID-19 and neurological disorders. *J Neurol Neurosurg Psychiatry* 2020;**91**:811–2. doi:10.1136/jnnp-2020-323667

19 Ferrarese C, Silani V, Priori A, *et al.* An Italian multicenter retrospective-prospective observational study on neurological manifestations of COVID-19 (NEUROCOVID). *Neurol Sci* 2020;**41**:1355–9. doi:10.1007/s10072-020-04450-1

20 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**:344–9. doi:10.1016/j.jclinepi.2007.11.008

21 Lu R, Zhao X, Li J, *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* 2020;**395**:565–74. doi:10.1016/S0140-6736(20)30251-8

22 Centers for Disease Control and Prevention. Evaluating and testing persons for coronavirus disease 2019 (COVID-19). 2020.https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html (accessed 7 Apr 2020).

23 Khaledifar A, Hashemzadeh M, Solati K, *et al.* The protocol of a population-based prospective cohort study in southwest of Iran to analyze common non-communicable diseases: Shahrekord cohort study. *BMC Public Health* 2018;**18**:660. doi:10.1186/s12889-018-5364-2

24 Haw J, Uy J. COVID-19 cases and deaths in the Philippines dashboard. 2020.https://public.tableau.com/profile/jason.haw#!/vizhome/COVID-19CasesandDeathsinthePhilippines/Dashboard?publish=yes (accessed 8 Apr 2020).

25 Fleiss JL. *Statistical methods for rates and proportions*. 1st Ed. London: : John Wiley & Sons 1981.

26 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA* Published Online First: 24 February 2020. doi:10.1001/jama.2020.2648

27 Philippine Research Ethics Board. *National ethical guidelines for health and health-related research*. Taguig City: : Philippine Council for Health Research and Development Department of Science and Technology 2017.

FIGURE CAPTIONS

Fig 1. Schematic diagram of the study flow.

Fig 2. Location of 37 study sites of the Philippine CORONA Study.

Fig 3. Organizational structure of oversight of the Philippine CORONA Study

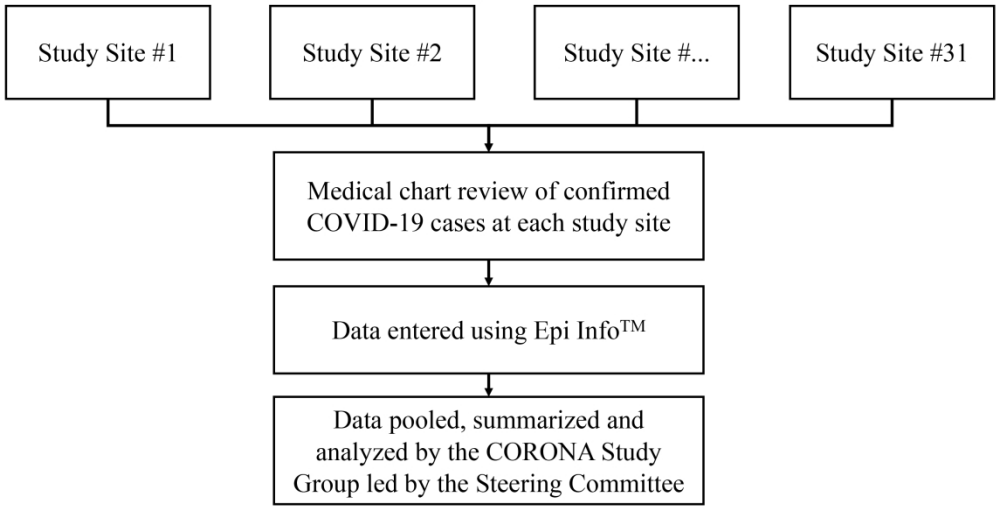

Fig 1. Schematic diagram of the study flow.

1015x520mm (72 x 72 DPI)

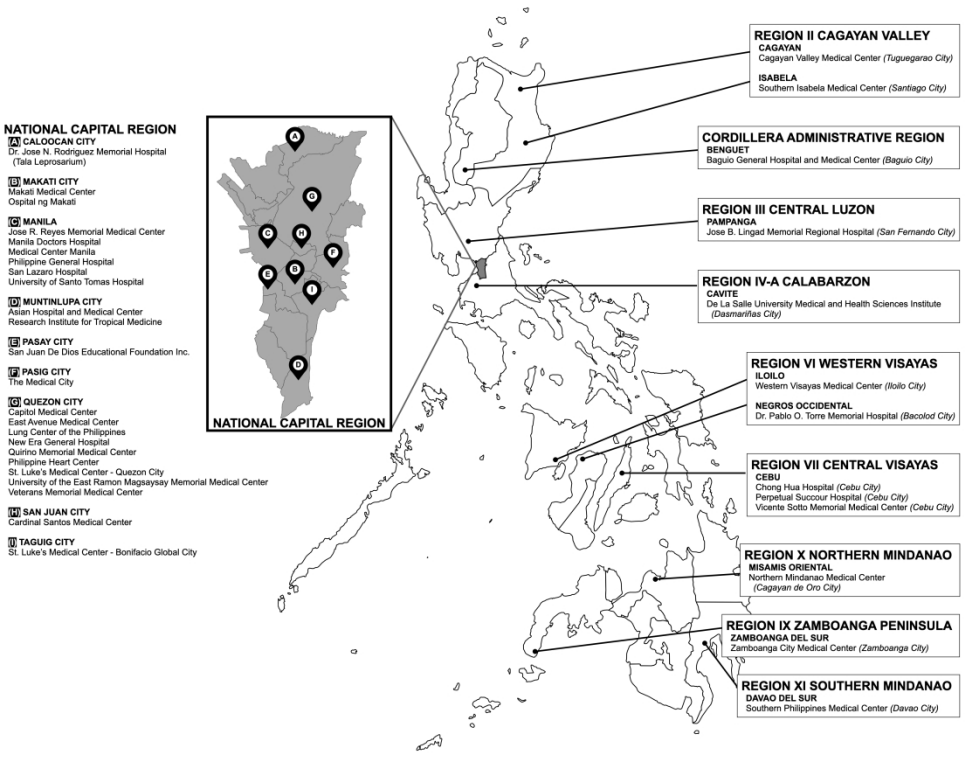

Fig 2. Location of 37 study sites of the Philippine CORONA Study

1411x1058mm (72 x 72 DPI)

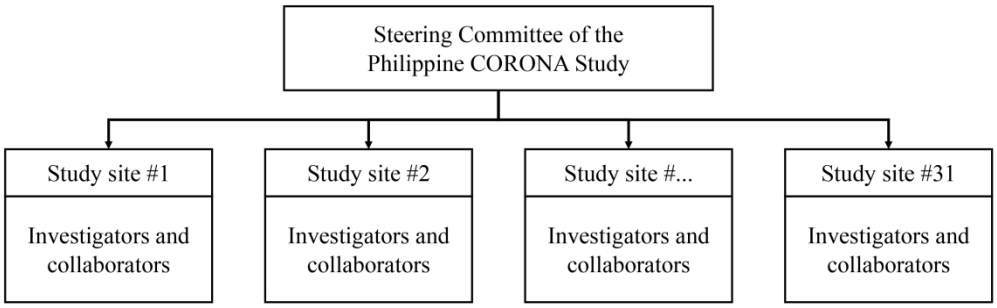

Fig 3. Organizational structure of oversight of the Philippine CORONA Study.

1120x346mm (72 x 72 DPI)