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PREDICTORS OF INTRAHOSPITAL MORTALITY IN PATIENTS WITH CORONAVIRUS DISEASE 2019 AND CEREBROVASCULAR DISEASES: RAPID SYSTEMATIC REVIEW AND META-ANALYSIS PROTOCOL

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Abstract

Background: The coronavirus disease 2019 (COVID19) is a novel pandemic disease caused by the β-coronavirus SARS-CoV-2. This disease affects primarily the respiratory organs, but it may also affect the vascular system. COVID19 may lead to either coagulopathies or hemorrhagic disorders involving the central nervous system. Risk factors for a fatal outcome have been suggested but not completely elucidated.

Objectives: This systematic review protocol aims to identify clinical, imaging, and laboratory variables associated with intra-hospital mortality in patients with COVID19 and cerebrovascular disease. **Materials and Methods**: Studies will be retrieved from Web of Science, MEDLINE, Scopus, EBSCOhost, Ovid, Rayyan's COVID-19 Open Research Dataset, and Google Scholar. Inclusion criteria will be observational studies or clinical trials describing patients with both COVID19 and cerebrovascular disease. Exclusion criteria will be studies whose patients remained hospitalized with no defined outcome (intrahospital mortality or discharge), studies written in languages different from English, published before 2019 or in case the full text could not be retrieved. All demographic, laboratory and imaging variables will be extracted. Data synthesis will be presented in graphs, figures, and summary of findings tables. A global mortality rate will be calculated. A narrative synthesis will be included. A meta-analysis will be performed. For mortality rate and statistical synthesis, only studies reporting the main outcome (intra-hospital mortality or discharge) will be considered. Quality of the evidence will be assessed using the JBI Critical Appraisal tools. This protocol received no funding and is registered in PROSPERO.

Keywords: *Coronavirus, Stroke, Hemorrhage, Outcome, Predictor, SARS-CoV-2.*

Introduction

The coronavirus disease 2019 (COVID19) is a novel pandemic disease caused by the β-coronavirus SARS-CoV-2 [1]. Due to its recent appearance, research on its prevention, treatment and outcomes is still ongoing. The infection may lead to either symptomatic or asymptomatic cases [2]. These latter group may represent 17% of all cases, including children [3].

About 80% of COVID19 patients may receive ambulatory treatment [4]. Nonetheless, the disease has challenged the Emergency Services [5]. Risk factors for a fatal outcome have been suggested but not completely elucidated; those factors include having cancer, organ transplantation, hypertension, diabetes, heart disease, or chronic kidney disease, among other comorbidities [6].

The disease affects primarily the respiratory organs, but the vascular system may also be compromised. This might occur since the angiotensin converting enzyme 2 (ACE2) receptor, where the virus binds to enter the cells, is expressed in the vascular endothelium [4]. It seems that COVID19 leads to a hypercoagulable state that increases thrombotic events[1]. The inflammatory response to the virus may be responsible for this phenomenon [7], as occurs in sepsis [8]. Interestingly, hemorrhagic disorders may also occur during the disease[1]. Additionally, COVID19 may lead to multi-organ failure [2].

Those conditions may affect the nervous system and yield long-term sequelae [7, 9]. Both central and peripheral nervous systems may be affected [2]. This is not surprising since its predecessor virus SARS-CoV, and the related virus MERS-CoV, were also associated with neurological disorders, such as ischemic stroke and Guillain-Barré syndrome [2, 7].

Some studies estimate that 35-82% of COVID19 patients (especially the severe cases) may show neurological symptoms[10, 11]; loss of smell and taste are some examples, but other cases may be more severe[2]. Intracerebral hemorrhage and meningoencephalitis after COVID19 have been described in a 36-year-old patient without additional relevant medical history [12].

A large multicenter cohort study identified the following neurological manifestations in COVID19 patients: headache, anosmia, ageusia, syncope, acute encephalopathy, stroke (all types), coma, seizures, dysautonomia, meningitis, myelopathy, paralysis, aphasia, movement abnormalities, abnormal tone, abnormal brainstem reflexes, and sensory abnormalities[11]. Mental clouding may also be present [13]. The incidence of those signs and symptoms may be related to both age and gender [11]. Some neurological symptoms may occur even in the absence of respiratory manifestations [3].

It is considered that SARS-CoV-2 virus shows tropism for nervous system cells, since neurons, glia[8, 9], oligodendrocytes, and microvascular endothelial cells[7], may express the ACE2 receptor, which is the virus target[2]. The virus might invade the brain by retrograde axonal transport through the olfactory nerve[7]; once within the brain, it may be further distributed trans-synaptically[7]. The virus RNA has been detected in cerebrospinal fluid from a COVID19 patient[10], although complete viral particles have not been found in the central nervous system [3].

Either respiratory or neurological symptoms may appear first in COVID19 [4], although a respiratory onset is more common[1]. The latter group may show a more severe course[1], although discrepant results have been published [8]. Their mortality rate is 29-44%[1, 9] but it might be underestimated[9]. Cerebrovascular diseases increase more than two-fold mortality risk in COVID19 patients (RR 2.38) [8], but some studies have found no association [11, 14].

Stroke may appear in a median of 10 days after symptom onset [4]. It has been estimated that the incidence of stroke in COVID19 patients is 28% (for hemorrhagic stroke) and 71% (for ischemic stroke) [1]. However, incidence as low as 0.4-2.7% has been reported [9, 15]. Those discrepancies may be related to the inclusion of different patient populations.

Past neurological disorders are a risk factor for developing neurological manifestations after COVID19 [11]. Up to 55% of COVID19 patients who had a history of cerebrovascular disease may have a fatal outcome[16]. The odds ratio for mortality in those patients has been estimated at 4.7[16]. A meta-analysis of three studies has shown the cerebrovascular disease is associated with severe COVID19 (patients requiring mechanical ventilation, vital life support, intensive care unit admission, death)[17], but other studies are not completely consistent with that result [16].

According to some systematic reviews, stroke in the general population is 33% more frequent in males than in females[18]. Incidence for other types of cerebrovascular disease (such as intracerebral or subarachnoid hemorrhage) is also 60-84% higher in men[18]. However, cardioembolic stroke is more common in women[18]; also, stroke severity and lethality may be greater in this gender [18].

Associated risk factors for ischemic stroke during COVID19 are hypertension, diabetes mellitus, obesity, smoking, dyslipidemia, coronary artery disease [9], and D-dimer levels[8], among others. However, most of those variables are risk factors for an ischemic attack or for COVID19 *per se* [14], and it is not clear if they could predict mortality in the concurrent cases [9]. Indeed, a previous meta-analysis has found that a poor outcome in COVID19 patients with cerebrovascular diseases is not associated with either hypertension, diabetes, or cardiovascular disease[8].

Some studies have reported that neurological manifestations as headache, anosmia, ageusia, and syncope are associated with a reduced mortality risk, although this result might be underestimated [11]. Also, some studies have suggested that large-vessel clotting may occur in patients with no risk factors for stroke [8]. Some authors consider that "it is required to clarify the association of the cerebrovascular disease with the risk of mortality in COVID-19 patients by using a systematically quantitative meta-analysis" [16].

Thus, it has been suggested that COVID19 increases the risk for developing cerebrovascular disease [9] but it is not clear if cerebrovascular disease may, in turn, increase the mortality risk for COVID19 patients. The co-occurrence of these diseases is a challenge for medical practice both for patients' outcome and for physicians' own safety [4]. Some surgical procedures that involve a high risk for contagion are endotracheal intubation or extubation, surgeries exposing respiratory or digestive tracts, the use of instruments producing aerosolization, and contaminated tissues [3]. The American Heart Association has provided some guidance for the care of stroke patients during this pandemic [4].

The primary objective for this review protocol is to identify which clinical, imaging and laboratory variables are associated with intra-hospital mortality in adult patients with COVID19 and cerebrovascular disease.

Study rationale

A previous meta-analysis has studied the risk for mortality in COVID19 patients with either ischemic or hemorrhagic stroke[1], but other cerebrovascular diseases were not considered. Otrher systematic review and meta-analysis have described the clinical characteristics and mortality rate of patients with COVID19 and stroke, but predictors for this outcome were not described [19]. The present protocol includes a comprehensive search strategy compared to recent systematic reviews and meta-analyses[1, 9, 16, 17], with more databases, search terms, diseases, study types, and predictors included. The present protocol will analyze the mortality risk for comorbid COVID19 and a wide group of cerebrovascular diseases. Since the pandemic is rapidly evolving, continuous updates are needed.

Methods

Protocol development

We used an online tool to determine the appropriate type of review article for our research questions and objectives as previously reported [20] and the result was "rapid review of prognostic studies with meta-analysis, if appropriate" (available at https://whatreviewisrightforyou.knowledgetranslation.net/map/results?id=6830&code=IQiNlrTqwy).

The International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/), the JBI Clinical On-line Network of Evidence for Care and Therapeutics (JBI COnNECT+, https://connect.jbiconnectplus.org/), and the Open Science Framework (OSF, https://osf.io/) databases were consulted to identify ongoing protocols for systematic reviews related to our research questions, but no similar studies were retrieved (Aug. 11th, 2021).

The protocol for this systematic review complies with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020 [21]), complemented with the PRISMA extensions for abstracts (PRISMA-A [22]), protocols (PRISMA-P [23]), the Cochrane guidelines for rapid reviews [24], the JBI Manual for Evidence Synthesis [25] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE [26]). Those guidelines were applied as much as suitable for a rapid systematic review and meta-analysis protocol.

Our protocol was drafted by the research team and revised as necessary. Supporting materials are made publicly available through the Open Science Framework (https://osf.io/m5c8f/?view_only=42cd92c2c62343b7add191885d3e60f6) as previously reported [27] (registration date Oct 11th, 2021; last update March 7th, 2022). Our research team is comprised of clinical, preclinical, and socio-medical researchers.

Objectives

The primary objective for this review protocol is to Identify which clinical, imaging and laboratory variables are associated with intra-hospital mortality in adult patients with COVID19 and cerebrovascular disease.

Secondary objectives are as follows:

- To identify the clinical features associated with intra-hospital

mortality in adult patients with COVID19 and cerebrovascular disease.
- To identify the laboratory parameters associated with intra-hospital mortality in adult patients with COVID19 and cerebrovascular disease.
- To identify the imaging findings associated with intra-hospital mortality in adult patients with COVID19 and cerebrovascular disease.
- To determine the intra-hospital mortality rate in adult patients with COVID19 and cerebrovascular disease.

Research questions [28–30] for this review are described in Table 1.

Search strategy and screening

Search strategy was elaborated by a trained researcher, is reported according with PRISMA-S [31] and was peer-reviewed using PRESS [32]. Published studies (all publication types) will be retrieved from Web of Science (WoS, Clarivate), MEDLINE (PubMed), Scopus, EBSCOhost (Academic Search Ultimate), and Ovid, from database inception to present. Also, Rayyan's COVID19 Open Research Dataset (CORD-19, https://rayyan.qcri.org/) and the first 100 results from Google Scholar (sorted by relevance without citations), will be retrieved [27]. Author's collections will also be considered. Researchers will be contacted if necessary. No other sources will be consulted.

Table 1. Research questions for this systematic review.

Question type	Framework	Description
Primary research question	**MIP** (Methodology, Issues, Participants)	What clinical, imaging, and laboratory variables (**M**) are associated with intra-hospital mortality (**I**) in adult patients with COVID19 and cerebrovascular disease (**P**)?
Secondary research question 1	**CoCoPop** (Condition, Context, Population)	What are the clinical features (**Co**) associated with mortality (**Co**) in adult patients with COVID19 and cerebrovascular disease (**Pop**)?
Secondary research question 2	**CoCoPop** (Condition, Context, Population)	What are the laboratory parameters (**Co**) associated with mortality (**Co**) in adult patients with COVID19 and cerebrovascular disease (**Pop**)?
Secondary research question 3	**CoCoPop** (Condition, Context, Population)	What are the imaging findings (**Co**) associated with mortality (**Co**) in adult patients with COVID19 and cerebrovascular disease (**Pop**)?
Secondary research question 4	**ProPheT** (Problem, Phenomenon of interest, Timing)	In adult patients with COVID19 and cerebrovascular disease (**Pro**), what is their mortality rate (**Phe**) during hospitalization (**T**)?

Databases, their providers and coverage dates (if available) are listed in Appendix A (available at https://osf.io/m5c8f/?view_only=42cd92c2c62343b7add191885d3e60f6). Search algorithms were elaborated using an online tool (except that for EBSCOhost, which was adapted from other algorithms), and are publicly available (https://app.2dsearch.com/new-query/6121111257675200049767c4). Those algorithms were adjusted as necessary during the line-by-line analysis, which is described on Appendix B (available at https://osf.io/m5c8f/?view_only=42cd92c2c62343b7add191885d3e60f6). Some search terms were taken from a previous protocol [33].

Articles written in languages different than English will not be considered [24]. Default EBSCOhost configuration (Limiters - Hidden NetLibrary Holdings; Expanders - Apply equivalent subjects; Search modes - Boolean/Phrase) will be used, no other filters or limits will be applied. Gray literature will be consulted through the Conference Proceedings Citation Index-Science (Web of Science), OpenDissertations (EBSCOhost), and Google Scholar. Retrieved references will be de-duplicated using Rayyan QCRI default algorithm, complemented with Zotero and Endnote [34]. Identified duplicates will be manually revised to confirm duplicated publications and will be eliminated [34].

Two independent researchers will assess all references for eligibility using Sysrev [35] according to predefined criteria; discrepancies will be resolved with a third independent

researcher's decision. Two screening stages (Title/Abstract, and Full-text) will be performed [25]. Agreement between reviewers will be assessed using Sysrev concordance tools [35]. The screening process will be pilot-tested using a random sample of 25-50 studies [24, 25].

Studies selected for inclusion will be retrieved using the Retraction Watch database (http://retractiondatabase.org/) to identify retracted studies, which will be eliminated. The search strategy will be rerun after twelve months or before the final analysis to identify more recent studies for possible inclusion in further updates of this review. Results from the search strategy will be described in a PRISMA flow diagram using an online tool [36].

Eligibility criteria

Inclusion criteria

- Observational studies (cross-sectional studies, cohort studies, case-control studies, case reports, case series [25]) describing adult patients (>18 years old, independently of sex/gender) with both COVID19 (confirmed by nasopharyngeal swab or bronchoalveolar lavage PCR test [37]) and any cerebrovascular disease.
- Clinical trials (randomized, quasi-randomized or non-randomized) describing adult patients (>18 years old, independently of sex/gender) with both COVID19 (confirmed by nasopharyngeal swab or bronchoalveolar lavage PCR test [37]) and any cerebrovascular disease.
- No specific diagnostic criteria for cerebrovascular disorders will be considered if the studies describe their population as presenting the condition, as previously reported [38].
- Either descriptive, analytic, prospective, or retrospective study designs, are eligible.
- Experimental models may be considered for a narrative synthesis only.

Exclusion criteria

- Pediatric patient populations
- Patients that remain hospitalized by the publication of the corresponding studies.
- Studies written in languages different than English, as recommended for rapid reviews [24].
- Articles published before 2019 (not likely related to COVID19).
- Studies whose full text could not be retrieved.

These criteria may be adjusted during the screening process, as previously reported [27]. Adjustments will be applied to all studies and reported accordingly.

Data extraction

Variables to be extracted include, but are not limited to, the following: age, sex/gender, symptoms at onset (neurologic or respiratory), history of cerebrovascular disease, sample size, diabetes, hypertension, obesity, medical intervention (surgical, non-surgical), smoking history, chronic obstructive pulmonary disease, cancer, chronic liver disease, immunosuppression status, chronic renal disease, fever, dyspnea, and headache. All laboratory and imaging results will be extracted.

Cerebrovascular diseases will be classified as hemorrhagic, ischemic, venous, or other. These categories are not mutually exclusive. Outcome will be defined as intra-hospital mortality or discharge, as previously reported [39]. No specific criteria for diagnosis of cerebrovascular diseases will be applied, if the studies describe their patients as having the condition, as previously reported [38].

Data will be extracted by independent researchers using Sysrev [35], discrepancies will be solved by a third researcher. This process will be pilot-tested using a random sample of 25-50 studies [24, 25]. No data will be extracted from figures. Review articles are not eligible for these data extracting methods to avoid possible duplication with the original studies. Experimental models are not eligible for these extracting methods. Unclear information will not be considered. No imputation method will be applied for missing data. Units of measure will be converted to the most frequently reported.

Quality of evidence

Quality of evidence for the studies selected for inclusion will be assessed by two independent researchers [25] using the JBI critical appraisal tools for cross-sectional studies, case-control studies, case reports, case series, cohort studies, quasi-experimental studies, randomized clinical trials [40], and systematic reviews [41]. Inter-rater reliability will be calculated using Sysrev concordance tool [35]. Discrepancies will be solved by a third researcher [25]. This process will be pilot-tested using a random sample of 25-50 studies [24, 25]. Studies will not be excluded based on these ratings, but quality of the evidence will be reported in tabular form, as previously reported [40].

Data synthesis

Data summaries will be presented in graphs, figures, and summary of findings tables. A narrative synthesis will be included. All studies are eligible for these synthesis methods. The global mortality rate (M) will be calculated with the following formula: M=100*D/T, where "D" is the number of deceased cases and "T" is the total number of cases included in the analysis [1].

This will be reported as percentage. Only studies reporting the main outcome (intra-hospital mortality or discharge) will be considered for mortality rate calculation and statistical synthesis (meta-analysis). If patients are not explicitly described as adults of if their age is not mentioned their information will be included in the narrative synthesis only. A subgroup analysis by cerebrovascular disease type (hemorrhagic, ischemic, venous, or other) will be performed. If sample size is large enough a meta-regression including all variables will be conducted.

Statistical synthesis

A fixed effect and random effects (RE) frequentist and a Bayesian meta-analysis will be conducted based on adjusted odds ratio estimates and their standard errors (or confidence interval in its absence). As a sensitivity analysis, a simple model using a non-adjusted ratio will be conducted. The inverse variance method will be used for pooling, a restricted maximum-likelihood estimator (REML) for $\tau 2$, and a Q-profile method for confidence interval of $\tau 2$ and τ. The packages meta::metagen and metafor::rma.uni will be used to fit the frequentist models. A Bias-corrected (BC) Bayesian RE 42 model will be fitted, which uses a mixture of two random effects distributions that represent a model of interest and a model of bias. The BC Bayesian RE model will be allowed to include the internal validity bias associated with experimental design in the meta-analysis, which provides robust estimations avoiding model misspecification.

The function metafor::replmiss will be used to calculate the standard errors when in the original studies only the confidence interval was provided assuming normality. The heterogeneity will be evaluated using I2 statistic and prediction intervals (which reflects the uncertainty we expect in the summary effect if a new study is incorporated in the analysis).

The meta-regression will be conducted in case exist enough studies per predictor, to explore the effect under the risk and the heterogeneities measures.

The preferred estimates for the risk will be odd ratio (OR), in case to find other measures of risk like Hazard ratio (HR), we will make the assumption that is equal to OR (assuming that the prevalence of CA events is low which makes then equivalent). Publication bias will be explored with formal tests if the number of studies is large enough (at least 10).

Strengths and limitations of the present protocol

This protocol allows a comprehensive analysis of possible predictors for intrahospital mortality in several cerebrovascular diseases. The multidisciplinary research group provides complementary perspectives from several profiles. An effort will be made to include experimental models (if available) within the narrative synthesis. As the rapid review will only include studies published in English, we are likely to miss studies that were published exclusively in non-English languages. This study will not evaluate specific causes for death, nor long term outcomes.

Authors' contributions

I.P.N. provided methodological expertise and contributed with the original idea, designed protocol's methodology (including the search strategy), coordinated co-author's participation and activities, drafted the protocol, will document and implement protocol amendments, and is the guarantor of the review. C.E.D.C. contributed with the original idea, preliminar searches and analyses, revised and approved the protocol. P.T. provided methodological expertise, contributed designing the methodology, drafted and approved the protocol. H.S. provided methodological expertise, contributed designing the methodology, performed the search strategy peer-review, drafted, revised, and approved the protocol. V.L.C.G. contributed elaborating and framing research questions, drafted, revised and approved the protocol. B.C. provided topic expertise, contributed designing the methodology, revised, and approved the protocol. C.R. provided topic expertise and contributed with supervising the reviewer team, revised and approved the protocol. A.K.S., E.J.B.U., and C.A.C.daC. revised and approved the protocol.

Disclosure of interest

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Data availability statement

This protocol is publicly available through PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022285364) and Open Science Framework (https://osf.io/m5c8f/?view_only=42cd92c2c62343b7add191885d3e60f6,

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