Long COVID: A Protocol for Systematic Review and Meta-analysis of Symptomatology and Treatment Approaches

Emmanuel Okechukwu Nna (e.nna@themping.org)
The Molecular Pathology Institute, Enugu https://orcid.org/0000-0001-6791-2336
Michael Abel Alao
University College Hospital Ibadan
Canice Anyachukwu
University of Nigeria Faculty of Health Sciences and Technology
Adanze Onyenonachi Asinobi
University College Hospital Ibadan
Babatunde Ogunbosi
University College Hospital Ibadan
Uchenna Okeke
Nigerian Navy Reference Hospital, Calabar
Damaris Osunkwo
National Hospital Abuja

Protocol

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Abstract

Background:

The burden of SAR COV-2 infection is not limited to the acute viraemia and its symptomatology but extends far beyond to include the long COVID, also known as post-COVID-19 syndrome,which may soon reach public health significance. We set out to produce a protocol for reliable and accurate systematic review and meta-analysis of the symptomatology and treatment approaches of long COVID globally.

Methods:

We developed a search strategy using MeSH terms, text words and entry terms. Nine databases will be searched: PubMed, Embase, CINAHL, AJOL, Google Scholar, Web of Science, Cochrane Library, Researchgate and Scopus. Only observational studies retrievable in the English Language will be included. The primary measurable outcome is the pooled prevalence of the symptoms of long COVID. The secondary outcomes include the summary effect sizes of the treatment approaches to the long COVID; the geographic, race, gender and age variations in symptomatology, and the quality of life of patients with long COVID. Identified studies will be screened, deduplicated, selected and data items extracted using DistillerSR software. All studies will be assessed for methodological, clinical and statistical heterogeneity. Assessment of meta-bias in the selected studies will be performed using the NIH Quality assessment tool for observational studies. Publication bias will be assessed using the funnel plot and Egger's regression intercept. The pooled prevalence will be expressed with SE and 95% CI. The strength of evidence from this analysis will be assessed using the NIH Quality Assessment for Systematic Reviews and Meta-analysis.

Discussion:

This analysis will map globally the symptoms of long COVID and its correlates, exploring the influences of geographic locations, race, age and gender, thereby enabling a severity index on a global scale. It will examine in detail the treatment approaches to the long COVID and their impacts on the quality of life of patients. The evidence from this study will inform health policies toward the management of post-COVID-19 syndrome. The outcome of this study will be published in peer-reviewed scientific journal.

Trial Registration Number:

This protocol is registered with PROSPERO, registration number CRD42021236457

Background

The term "Long COVID" was coined by a patient; Elisa Perego, an archaeologist at the University College London in May 2020 as a hashtag on twitter.[1, 2] Currently, there is no consensus on the terminologies for describing a conglomerate of long-term clinical signs and symptoms following COVID 19 infection.[3] This phenomenon has been given different terms including long COVID, chronic COVID syndrome (CCS),

Post-COVID-19 syndrome and Long Hauler to mention a few.[2-5] This further underscores the confusing nature and complexity of the COVID 19 infection and its devastating effects on the patients' quality of life. Long COVID refers to chronic COVID 19 symptoms extending beyond 12 weeks while the term 'post - acute COVID-19' is for symptoms extending beyond three weeks from the onset of first symptoms to 12 weeks.[5-8]

COVID 19 disease is a multi-systemic disorder capable of affecting virtually the entire human organ system. At the early days of the COVID pandemic, little did anyone know about the pending long term effect of the acute infection. Many patients who contracted SARS COV-2 infection recovered from the initial symptoms within a few weeks of on-set of the disease. But up to 20-80% in some series have been reported to experience symptoms long after the initial recovery.[9-12] These numbers appear to be increasing, almost reaching monumental public health significance.[13] Again, the persistence and pervasiveness of the long term symptomatology are devoid of the severity of the initial presentation.[14]

The symptomatogy of COVID 19 are protean ranging from mild symptoms such as malaise to crippling fatigue, breathlessness, enduring tiredness, reduced muscle function, impaired ability to perform daily tasks, cough, chest pain and mental health problems such as post-traumatic stress disorder, anxiety, loss of taste and smell, difficulty in sleeping, brain fog, gastrointestinal complaints and major depression.[4, 15] Consequent on severe primary injury to the heart, brain and lungs, are multiple medical conditions such as Alzheimer, strokes, Parkinson disease and heart failure to mention a few; thus the need to summarise these symptoms.[16, 17] Recently, complications such as poor glucose control in diabetic patients has been added to the list of the effects of long COVID.[18-20]

The mechanism of these clinical manifestations is not clear, but suggested pathways include the permanent damage to involved organs such as the lungs and heart. Besides, other postulation includes post-intensive care syndrome, post viral fatigue, the persistence of the virus due to a weak immune system, reinfection with another strain of the virus, persistence of inflammatory markers, an overwhelming immune response to the infection and post-traumatic stress [4]. Other risk factors include age, excess weight, disease condition like asthma, and having more than five symptoms in the first week of COVID-19 infection.[4, 8, 11, 21-23]

The occurrence of long COVID in paediatric age group infers that these symptoms are not age-dependent.[24, 25] However, symptoms appear to have gender variation in prevalence of the long COVID syndrome, likely in favour of the females compared with the males.[21]

Everyone infected with COVID-19 is at the risk of long COVID. Therefore, the hallmark to halting and preventing long COVID 19 disease largely rests on primary prevention and adoption of strict infection prevention and control measures.[26-29] A recent report on over a hundred thousand people who were vaccinated from December 2020 to January 2021 showed protection from COVID 19 infection, thus they were immuned against Long COVID.[30] However, it is too early to conclude on the potency, safety, effectiveness and immunogenicity of vaccines.[31-33]

The current approach to the treatment of long COVID is symptomatic rather than definitive. Many patients may recover spontaneously. However, some will require some specific therapeutic care in addition to rest and holistic support. The extent to which patients recover spontaneously and the need for monitoring of persistent sysmptoms are largely unknown.[34]

We set out to produce a protocol for reliable and accurate systematic review and meta-analysis of the symptomatology and treatment approaches of long COVID syndrome globally.

Methods And Design

Objective: The specific objectives of the study are:

1. To determine the pooled prevalence of the various symptoms of long COVID from primary studies.
2. To measure summary effect sizes of the treatment approaches to long COVID from primary studies.
3. To evaluate the influence of geographic variation, race, gender and age on symptomatology, treatment approaches and the quality of life of patients with long COVID.

Review Questions:

a. What is the pooled prevalence of various symptoms of long COVID?
b. What are the various reported treatment approaches to long COVID?
c. How do factors such as geographic location, race, age, social class and gender influence symptoms of and treatments to long COVID?

Study Characteristics:

Design

This is a protocol for systematic review and meta-analysis of symptoms and treatment approaches to long COVID. It focuses on observational studies published from 2019 to present time, that are retrievable in the English Language.

Inclusion Criteria:

A. Observational studies: Cohort studies, case controls, cross-sectional studies, historic cohort studies.
B. Studies must report the primary outcome: symptoms of long COVID
C. Study must be retrievable in the English language.

Exclusion criteria:

a. Reviews, editorials, interventional studies, commentaries, methodological articles, letters to editors, case reports
b. Duplicates/ replicates of studies.

c. Studies not retrievable in the English Language.

PICOS

Populations: patients suffering long COVID.

Intervention: Various treatment approaches

Comparator: No treatment

Outcomes: The primary outcome is the proportion of patients with various symptoms of long COVID. The effect size is prevalence.

The secondary outcome is the proportion of various treatment approaches to long COVID. The effect size is prevalence.

Information sources

The search will use sensitive topic-based strategies designed for each database. The search will be carried out in the following databases: PUBMED, EMBASE, CINAHL, RESEARCHGATE, AJOL, GOOGLE SCHOLAR, WEB OF SCIENCE, SCOPUS and COCHRANE LIBRARY. Only observational studies will be included, from 2019 to present time.

Search strategy

The search strategy includes text words and entry terms. Table 1 shows the search strategy for the long COVID as used in the Pubmed. The same search strategy will be used in other databases with slight modifications.

Data Extraction and Management

Data Extraction

Data will be managed in three main softwares: DistillerSR, CMA version 3 and Microsoft Excel.

a. Screening: Identified studies will be screened independently in pairs and blindly using the DistillerSR software at 6 different levels:

i. Level 1 will involve screening of identified studies for the study design. Only observational studies would be accepted

ii. Level 2 will involve screening of identified studies in the titles and abstracts using entry terms and keywords.

iii. Level 3 will involve further screening of the contents of articles by reading the full article using the same search strategy.

iv. Level 4 will involve snowballing of literature on references from eligible studies.

v. Level 5: Studies will be screened at outcome levels to select those that reported the primary outcome with or without secondary outcomes.

vi. Level 6 will involve grey literature that report primary outcome and or secondary outcomes.

Conflicts during screening will be resolved by a third independent reviewer who serves as a tie breaker.

b. Selection Process:

Screened studies will be selected based on study charateristics: study design, inclusion/exclusion criteria and agreement between two independent and blinded reviewers. Authors of included studies with missing data will be contacted via email and telephone. After selection, studies will be deduplicated. Data items will be extracted from selected studies into predefined forms in the DistillerSR.

c. Data Collection: Data items to be extracted from selected studies include:

i. Surname of first author and year of publication
ii. Symptoms of long COVID
iii. Treatment approaches to long COVID
iv. Socio-demographics: age, sex, race, geographic location and social class
v. Quality of life

Data items will be exported into predefined format in Microsoft Excel, to be imported into the CMA software for quantitative analysis.

Data Items/Measurable Outcomes

The key data items linked to measureable outcomes are i) various symptoms of long COVID, ii) various treatment types to long COVID, ii) socio-demographic variables, and iv) Quality of life for long COVID patients.

Risk of bias

The risk of bias (methodological quality) in the included studies will be assessed for the individual article using the National Institute of Health (NIH) Quality assessment tool for observational cohort and cross-sectional studies. The NIH Quality assessment tool has 14 questions. Studies that score 7 and above are considered good quality. This will be cross-checked with the Cochrane tool of risk of bias assessment (ROBINS-1). Publication bias in the selection of studies will be visually assessed using the funnel plot and associated variables such as trim and fill outcome, Egger’s regression intercept, Begg and Mazumdar's rank correlation and Orwin’s fail-safe N will be reported. Studies with extreme bias (NIH score

less than 5) will be subjected to sensitivity testing using the include/exclude function in the CMA Software.

Assessment of Meta-bias

Meta-bias will be assessed as follows:

i) Method of reporting long COVID at outcome level. It will consider the plurality of terms.

ii) Index of reporting outcomes in studies: Studies that were reported in different indices but similar in outcome and design will be converted to the primary effect size (prevalence) based on individual case evaluation.

iii) Heterogeneity will be assessed at the study level using the Q statistics, and its p-value, I^2, τ^2 (Tau squared). As a rule of thumb, I^2 values of less than 40% will be considered low heterogeneity while values > 40 but < 75 % will be considered moderate and values > 75% are high.

Data synthesis

Extacted data items will be used for both narrative synthesis and quantitative analysis.

The following criteria will be applied for analysis:

a. Studies that passed the methodological quality assessment using the NIH quality assessment tool will be cross-checked with the Cochrane Risk of Bias tool. The results will be presented in tabular format, indicating all the extractable data items as listed under data collection.
b. All studies with primary outcomes will be used for narrative synthesis.
c. All studies with good NIH quality scores that reported primary and or secondary outcomes will be used for quantitiative synthesis.
d. **Further Analysis:** Subgroup analysis will be performed using variables such as race, gender, socioenomic status, age and geographical location (country).

   Meta-regression will be performed on quantitative variables such as age, proportions of treatment approaches and quality of life as explanatory variables
e. Where heterogeneity is high, sensitivity testing using include/exclude functions in the CMA software will be performed.
f. The computational model for analysis is Random effect model since the several studies across the globe will be included.

Presentation and Reporting of Results

The study selection process will be summarised in a Prisma flow chart according to the PRISMA 2015 Statement and PRISMA-P Checklist. A table of the search strategy in various databases showing text

words and entry terms will be included. A list of eligible studies will be summarized in a table. Quantitative data such as prevalence of long COVID symptoms, 95 % CI, P values, and relative weights assigned to studies and heterogeneity tests will be reported in the forest plots. A table of quality scores and risk of bias of each eligible study will be included. Forest and regression plots to show sub-group analysis and meta-regression respectively will be included.

Discussion

This protocol will enable analysis to delineate the symptoms of long COVID and its correlates, exploring the influences of geographic locations, race, age and gender, thereby enabling a severity index on a global scale. It will examine in detail the treatment approaches to long COVID and their impacts on the quality of life of patients. The evidence from this study will inform health policies toward the management of post-COVID-19 syndrome. The outcome of this study will be published in peer-reviewed scientific journal.

GRADE: The quality of findings from this study will be assessed using the NIH Quality Assessment for Systematic Reviews and Meta-analysis.

List Of Abbreviations

GRADE: Grades of Recommendation, Assessment, Development and Evaluation.

PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-analyses Protocols

NIH: National Institute of Health

CMA: Comprehensive Meta-Analysis Software

Declarations

Acknowledgements:

We acknowledged the Molecular Pathology Institute for providing subscription for the DistillerSR software.

Availability of data and material:

Data and material from this study will be made available to the public unhindered.

Authors' contributions:

EN conceived the project. MA and EN designed the study; EN, MA, BO, DO, UO, AA and CA did searches on PubMed and other databases. MA started the early draft, EN expanded the draft fully and all authors corrected the manuscript and consented to publication. All the authors consented to the submission of manuscript.

Declaration of Conflicting Interests:

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Guarantor of the Review:

Dr. Emmanuel Nna

Ethical Approval/ Dissemination:

The study will use published data, thus, no ethical approval is required. The results obtained from this study will provide important information on pooled prevalence of symptoms and various treatment approaches to long COVID. The study will be published in a peer-reviewed scientific journal and made available to practitioners providing care to patients with long COVID.

Informed Consent:

Not applicable

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Table

Table 1: Search strategy for long COVID in PubMed

((Long-COVID OR long-haul COVID OR long COVID OR chronic COVID syndrome OR post-acute COVID19 syndrome OR long hauler COVID OR long haul COVID OR post-acute COVID syndrome))

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAPchecklistforLongCOVID.docx