Supplementary Material S1: Protocol

"Vision Loss" and COVID-19 infection: A Systematic Review and Meta-Analysis"

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This study has been registered in PROSPERO (CRD42022339189). Deviations will be specified in the published manuscript for this systematic review and meta-analysis. This work is investigator-initiated and is not pending any specific funding.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a single-stranded RNA virus that belongs to the Coronaviridae family. [1]

The World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic on March 11, 2020, which led to a significant economic and healthcare burden. [2]

Current available diagnostic tests to detect COVID-19 include a triad of complementary approaches. The Polymerase chain reaction (PCR) is the most highly sensitive and specific molecular test to detect SARS-CoV-2 nucleic acids presence representing the gold standard technique because of its sensitivity and specificity. It uses primers matching a segment of the SARS-CoV-2 genetic material to detect COVID-19. [3]

After the exposure, the average incubation period may range from four to five days. [4] A wide range of symptoms has been associated with the SARS-CoV-2 infection, whose severity may vary from being asymptomatic to death. Although most patients either remain asymptomatic or experience common viral infection symptoms such as fever, cough, and fatigue, some patients may develop atypical symptoms such as neurological (headaches, loss of taste, smell), and ophthalmological symptoms (conjunctivitis, epiphora, and vision loss).[5]

Based on multiple cross-sectional studies, the incidence of ocular manifestation in COVID-19 patients might be as high as 30%.[6] At the pandemic beginning, many physicians reported eye redness and irritation in patients, describing 'conjunctival congestion' in Wuhan, China. In a recent systematic review and meta-analysis, Inomata et al. reported clinical and prodromal ocular symptoms in patients with COVID-19. The most common ocular findings among COVID-19 patients were conjunctivitis (86.4%), ocular pain (34.4%), dry eye (33.3%), and floaters (6.7%). [7]

"Visual loss" in COVID-19 patients was reported in a few articles. Nonetheless, it has

been observed that its onset may be due to viral neurotropism and indirect immunologic and neurovascular effects.

Furthermore, despite extensive research on sensory manifestations of COVID-19 since the start of the pandemic, only a few articles and no meta-analysis paper have assessed "vision loss" as a symptom during the SARS-CoV-2 infection. [8–36]

The present paper intends to systematically review current evidence regarding visual loss, caused by SARS-CoV-2, as well as determine the cumulative incidence of this symptom through a meta-analysis. In addition, we further aim to identify the characteristics of the "visual loss", thus evaluating factors that could contribute to understanding the association between COVID-19 and "visual loss".

Methods

This protocol was written with reference to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Ethical approval is not required as we will only conduct a secondary analysis of available data published in the literature. Our results will be submitted for peer-review publication and/or conference presentations.

Eligibility Criteria

Inclusion criteria:

1. Population: patients with "vision loss" developed during laboratory-confirmed Covid-19 infection.
2. Outcomes: cumulative incidence of "visual loss" in Covid-19 patients.
3. Study type: No studies restriction

Exclusion criteria:

1. Article not published in English language

2. All studies reporting patients with neither laboratory-confirmed Covid-19 infection nor Covid-19-related visual loss or studies reporting visual loss devolped after covid infection or vaccination.
3.

Information Sources

We will systematically search 3 databases (PubMed, Embase and Scopus). We will also hand-search the reference lists of the included articles and relevant reviews or journals, where applicable. We will attempt contact with the corresponding authors to obtain additional unpublished information.

Search Strategy

PubMed

Free Text
No limits applied

#	Search Term	No. Results
1	"vision"	
2	"loss"	
3	1 AND 2	
4	"blindness"	
5	3 OR 4	
6	" COVID-19" OR "SARS-CoV-2"	
7	5 AND 6	

Controlled Vocabulary: Medical Subject Headings (MeSH)
No limits applied

#	Search Term	No. of Results
1	("Vision Loss"[MeSH]) AND "COVID-19"[MeSH]	
2	("Blindness"[MeSH]) AND "COVID-19"[MeSH]	
3	("Loss of vision"[MeSH]) AND " COVID-19"[MeSH]	
4	("Poor Vision"[MeSH]) AND " COVID-19"[MeSH]	
5	("low vision"[MeSH]) AND " COVID-19"[MeSH]	

All MeSH search results had already been found in the free-text search.

Embase

Free Text
[embase]/lim, no other limits applied

Mapping options enabled:

- map to preferred term in Emtree
- search also as free text in all fields
- explode using narrower Emtree terms

search as broadly as possible

#	Search Term	No. of Results
1	(("vision") AND ("loss) OR ("blindness") AND (" COVID-19" OR "SARS-CoV-2")	

Scopus

Free Text

#	Search Term	No. of Results
1	TITLE-ABS-KEY("vision") AND TITLE-ABS-KEY ("loss") OR (TITLE-ABS-KEY (("blindness")) AND TITLE-ABS-KEY ("COVID-19" OR"SARS-CoV-2")	

Data Management

We will export the search results to Covidence systematic review software© (Veritas Health Innovation, Melbourne, Australia) available at www.covidence.org [37] to remove duplicates and manually screenthe records.

Selection Process

We will screen potentially eligible studies based on title and abstract, following which, wewill retrieve full texts for evaluation. This will be done by 2 independent reviewers.

Data Extraction & Data Items

We will extract the following data from each article: the first author, publication date, country, study design, sample size, study design, average age, gender, visual impairment description, "laterality", duration between the onset of COVID-19 symptoms and ocular symptoms, comorbidities, number of Covid-19 affected patients and diagnosis-

Two investigators will independently extract baseline and outcome data. If consensus is not be reached, two co-authors will be consulted for adjudication. Reasons for exclusion will be documented.

Risk of Bias

We plan to use the Newcastle-Ottawa Scale (NOS), to evaluate the risk of bias at the outcome level. As per the NOS grading in past reviews, we will grade studies as having a high (<5 stars), moderate (5-7 stars) or low risk of bias (≥8 star). For longitudinal studies, the NOS assigns a score out of 9 to each study (where 9 indicates that the study meets all9 criteria for quality assessments and 0 indicates that the study does not meet any of the criteria) based on potential domains of bias, such as selection, comparability, and outcome. For cross-sectional studies, the modified NOS assigns a score out of 10 to each study. Moreover, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports which consist of eight yes/no/unclear questions and the JBI critical appraisal checklist for case series was used for quality assessment of the case series will be used. [38]

Statistical Analysis

A random-effects meta-analysis of pooled prevalence and their 95% confidence intervals of Covid-19 affected patients who developed "visual loss" will be used based on the exact binomial distributions (i.e. number of "events" versus number of

"non-events" in a sample) with Freeman-Tukey double-arcsine transformation using the "metaprop" command in STATA (STATA corp, USA), version 17.0.

Keywords

Covid-19; visual impairment, poor vision

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