Concept Article

Critical analysis of methodological and conceptual aspects of "c19study"

Análise crítica de aspectos metodológicos e conceituais do "c19study"

Rafael Leite Pacheco[1]
Ana Luiza Cabrera Martimbianco[2]
Raphael Einsfeld[3]
Rachel Riera[4]

[1]Corresponding author. Centro Universitário São Camilo (São Paulo). São Paulo, Brazil. rleitepacheco@hotmail.com
[2]Centro Universitário São Camilo (São Paulo), Universidade Metropolitana de Santos (Santos). São Paulo, Brazil. analuizacabrera@hotmail.com
[3]Centro Universitário São Camilo (São Paulo). São Paulo, Brazil. raphael.einsfeld@saocamilo-sp.br
[4]Hospital Sírio-Libanês, Universidade Federal de São Paulo (São Paulo). São Paulo, Brazil. rachelriera@hotmail.com

KEYWORDS: Systematic reviews. Evidence Synthesis. Hydroxychloroquine. COVID-19.

Main text

Since the beginning of the current pandemic, an increasing amount of scientific and non-scientific information about COVID-19 has been available in a short period. Approximately 80,000 studies related to COVID-19 have been indexed in MEDLINE until the date of this article. This context – a backlog of a huge volume of information - has made more evident the importance of studies, such as systematic reviews, which synthesize and critically evaluate the evidence to guide healthcare decision making.

The "c19study" initiative[1] proposed to elaborate some of these summaries and to publish their results on a website (https://c19study.com). For this purpose, the effects of interventions for COVID-19, such as hydroxychloroquine, ivermectin, vitamin D, zinc, and remdesivir have been evaluated throughout the pandemic. The theoretical goal proposed advocated by "c19study" is valid and should be recognized if not for its important methodological and conceptual constraints.

The "c19study" is an example of a case that teaches us why we should not only ask ourselves "where is the scientific evidence", but also "how much we can trust the scientific evidence".

The "c19study" has declared on its website that 173 studies have been cataloged and categorized so far that evaluated the effects of hydroxychloroquine to treat patients with COVID-19. Indeed, this seems to be a great catalog of primary studies that could count for a good synthesis of evidence.

From then on, the next phases of a systematic review would be the critical evaluation of this initial body of studies (identification of biases and estimation of their impact on results) and the analysis of their results employing qualitative or quantitative syntheses (meta-analysis). And what are the appropriate tools and methodological approaches to conducting these phases to respond with less uncertainty and more confidence to decision-makers?

Submitted 12/02/2020, Accepted 12/05/2020, Published 12/08/2020
J. Évid-Based Healthc., Salvador, 2020 December;2(2):131-134
http://dx.doi.org/10.17267/2675-021Xevidence.v2i2.3449
ISSN: 2675-021X

How to cite this article: Pacheco RL, Martimbianco ALC, Einsfeld R, Riera R. Critical analysis of methodological and conceptual aspects of "c19study". J Évid-Based Healthc. 2020;2(2):131-134. http://dx.doi.org/10.17267/2675-021Xevidence.v2i2.3449

The approach adopted by "c19study" is problematic and leads to misinterpretations and precipitations about the real certainty we have in the set of evidence about the effects of referred interventions. We will discuss point by point the weaknesses of the "c19study" synthesis method to exemplify errors that should be avoided in future health evidence summaries (see Box 1). The discussion will focus on the synthesis of hydroxychloroquine, which presents the largest volume of information. However, the points discussed can be generalized to the other interventions considered by "c19study".

Box 1. Main methodological and conceptual constraints adopted by the "c19study"

1. Lack of eligibility criteria and methods of identification and selection of primary studies.
2. No prior definition of the outcomes considered.
3. Failure to assess and report bias of the included studies.
4. Establishment of the "counting of votes" method for the quantitative overview.
5. Misguided model was adopted to estimate the number of "deaths that could be avoided" with the use of hydroxychloroquine.
6. Spurious perception of "open science".
7. Anonymity of authors and failure to disclose conflicts of interest.

1. Lack of eligibility criteria and methods of identification and selection of primary studies

To trust the results of an evidence synthesis on healthcare, it is necessary to understand how the search strategy for studies was carried out (terms and filters used, bases researched, etc.), if it was sensitive and broad enough to retrieve all existing studies that meet the eligibility criteria and if they were included in the synthesis. The "c19study" does not define eligibility criteria and does not present how the search for new primary studies is being performed.

A great heterogeneity of "included studies" is observed. For example, a newspaper article published in 1889 reporting an experience in the use of quinine for the treatment of respiratory infections[2] was included. However, the authors (anonymous) of "c19study" affirm that newspaper articles were not considered in the evaluation of the hydroxychloroquine effect, which raises even more doubts about the adequacy of the methodological approach adopted.

2. No prior definition of the outcomes considered

The outcomes considered in an evidence synthesis should be chosen based on their clinical relevance (to the patient and the decision-maker), as "mortality" is more relevant than "time to viral load negativity".

Clinical studies evaluate more than one outcome, and final conclusions need to be based on the totality of results presented, which may be inconsistent between different outcomes. A well-planned synthesis identifies in advance which outcomes will be considered, giving priority to those that will impact the clinical care of patients.

The "c19study" did not define the outcomes of interest for any of its summaries and grouped the results of different outcomes into a unique analysis concluding at the end, through a single decision, whether the intervention was "favorable" or "unfavorable".

A synthesis that does not pre-define outcomes of interest presents a vague conclusion. If the conclusion is that hydroxychloroquine has a beneficial effect, one must define "benefit". What is the benefit of hydroxychloroquine? In the "c19study" synthesis, most of the studies included evaluated serological, surrogate, and clinically limited outcomes, and yet their results were added to clinically relevant outcomes such as mortality.

3. Failure to assess and report bias of the included studies

Methodological approaches adopted in the planning, conducting, and reporting phases of a study may increase the risk of bias, driving its results out from the real effect of the evaluated intervention[3,4]. The risk of bias of the included studies in a synthesis of evidence should be assessed through specific and valid tools for each study design, such as the Cochrane Risk of Bias Table for randomized clinical trials[5].

The "c19study" neglects the assessment of the risk of bias underlying the considered primary studies. We can expect that most of the included studies have limitations in at least one domain of the risk of bias, which would reduce the certainty of the results observed. In a synthesis, especially when many studies exist, we need to ask ourselves: "which included studies can we trust the most"? In the “c19 study”, under the absence of the risk of bias assessment, the studies were considered to have the same ability to find the real effect of hydroxychloroquine, which is certainly not true.

4. Establishment of the "vote-counting" method for quantitative synthesis

One of the advantages of a systematic review is the possibility to perform a quantitative synthesis (meta-analysis) of the identified primary study data. When the studies are sufficiently homogeneous, and their data are available in an appropriate way, it is possible to conduct a meta-analysis of the individual weighted estimates of the studies (each study weights by contributing to the final result), generating a single estimate of the effect of the intervention on that assessed outcome.

The synthesis method used by "c19study" is outdated and known as "vote-counting based on statistical significance"[6,7]. The authors "categorize" a study as "positive" or "negative", according to the identification or not of benefit with the use of the intervention, and perform the count of the number of studies in each category (votes). In the end, the category with the highest number of studies "wins the vote", indicating the final conclusion of the synthesis.

The method has issues that have led to the abandonment of its use and the adoption of more reproducible, objective, transparent, and reliable approaches. In the "vote-counting" method, the studies have the same weight, i.e., a large clinical trial with low risk of bias that evaluated mortality "is counted as a vote" - the same as a small study with a high risk of bias that evaluated a laboratory outcome.

Another uncertain element is the decision of "positive" or "negative". As mentioned above, the same study can evaluate several outcomes that may be inconsistent between them. Besides, the decision should not be based solely on the statistical significance of the outcomes, which seems to have been done in "c19study". The proper interpretation of the outcome results in clinical studies should be based on the size of the effect of the intervention and on the clinical relevance that this effect may have on the health condition of patients.

5. The misguided model adopted to estimate the number of "deaths that could be avoided" with the use of the hydroxychloroquine

In a parallel publication (not peer-reviewed), the authors of the "c19study" performed a random-effects meta-analysis combining the relative risk estimates of different outcomes from included studies. In the end, the result of the meta-analysis for those studies that evaluated the "early treatment" with hydroxychloroquine showed a relative risk of 0.37 (95% confidence interval = 0.29 to 0.49).

Based on this result, the authors of the "c19study" concluded a "63% improvement" using hydroxychloroquine. However, it is not possible to interpret this estimate, as several outcomes contributed to this value. The "63% improvement" includes data on viral load, hospitalization, mortality, and other outcomes that were combined in a single estimate and without considering the quality of the data (originating from different studies, with different risks of bias).

On its website, the authors of the "c19study" also developed a dynamic model that estimates the number of deaths that could be avoided using hydroxychloroquine, considering the "63% improvement". However, even if this estimation of relative risk exclusively evaluated the mortality reduction and the certainty of this evidence was high, the implementation of the model would be erroneous since mortality in different populations depends on a variety of factors, including the adoption of multiple interventions, health services infrastructure and population behaviors. It is not possible to attribute the reduction in the absolute number of deaths exclusively to an individual factor, in this case, the use of hydroxychloroquine.

6. Spurious perception of "open science"

The "c19study" has invited the scientific community and the general population to contribute with its results and presents in a visual format the included primary studies and the decisions made by the authors. These approaches may give the spurious perception of "open science". Definitely, "c19study" is not a model of transparency in research, it does not present all the methods used to achieve the results presented, and when it does, it uses obsolete, subjective, and imprecise methods. There is no "open science" without transparency in the methods and presentation of results.

7. The anonymity of authors and failure to disclose conflicts of interest

The authorship of "c19study" is unknown. According to the website, the authors are "Ph.D. students, researchers, and professors, who want to make a contribution even if small" and the justification for the anonymity is the "fear of receiving death threats". Thus, it is not possible to identify if there are sources of funding for the initiative and if there is any conflict of interest of the authors that could impact the results presented.

Conclusion

The "c19study" presents evidence summaries with significant underlying methodological and conceptual limitations. Its conclusions, estimates, and predictions should not be used for individual or population decision making. Other evidence syntheses with high methodological quality are available for the same technologies and should be prioritized.

Author contributions

Riera R and Pacheco RL participated in the design. Pacheco RL, Martimbianco ALC, and Riera R participated in the data acquisition. Pacheco RL, Einsfeld R, Martimbianco ALC wrote the first version of the manuscript. Riera R revised the manuscript. All authors approved the final version.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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