



# Does Peer Reviewing for COVID-19-Related Papers Still Work?

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## OPEN ACCESS

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### Specialty section:

This article was submitted to  
Scholarly Communication,  
a section of the journal  
Frontiers in Research Metrics and  
Analytics

Received: 16 June 2020

Accepted: 22 September 2020

Published: 08 October 2020

### Citation:

Orellana-Serradell O, Díaz MC, González MF, Gutiérrez M, Herrera D, Jara D, Maureira D, Ruiz-Fuentes JL, Sanhueza S and Leyton L (2020) Does Peer Reviewing for COVID-19-Related Papers Still Work? *Front. Res. Metr. Anal.* 5:571886. doi: 10.3389/fma.2020.571886

**Keywords:** coronavirus, severe acute respiratory syndrome, SARS-CoV-2, infectious disease, pandemic, scientific rigor, research funds

## INTRODUCTION

In this article, we aimed to analyze whether coronavirus disease 2019 (COVID-19)-associated articles were being subjected to the same standards of peer-review as non-COVID-19 articles. In order to do this, we taught eight PhD students manuscript reviewing skills and analyzed eight papers published in valued journals, five of them on COVID-19. Each selected publication was reviewed by at least two graduate students from a Scientific English class and two scientists in charge of the course at the Faculty of Medicine, Universidad de Chile. Several shortcomings were identified in the revised studies, particularly on those related to COVID-19, which led us to conclude that the emergency imposed by the COVID-19 has endangered the quality of the accepted studies.

The COVID-19 pandemic caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has rapidly spread throughout the world. This virus is killing many people, and taking a massive physical, as well as mental toll, on the lives of all those that have been infected (Yi et al., 2020). The COVID-19 pandemic has severely depressed every country's economy because governments have been obliged to apply quarantine measures to control the disease. Thus, the impact has not only been on people's health, but also on their lifestyle and economic situation (Nicola et al., 2020). For these same reasons, many people, including politicians and leaders from different countries, have turned to the scientific community for answers regarding actions that need to be taken to control and treat the disease. Nevertheless, many scientific studies published these days concerning the COVID-19 virus, even those reported by important journals, fall short on experimental evidence to support their conclusions. It is clear that great pressure exists to rapidly know more about this virus and how to stop the pandemic. Notwithstanding, we believe that this is leading editors and reviewers to accept manuscripts that would have never been considered for publication under different circumstances. It is not bad science, it is just not the complete story; the story that the good, high impact journals would normally ask for, when peer reviewing manuscripts for publication.

**TABLE 1 |** Criteria used to evaluate the work performed by the students. Peer reviewing was performed as suggested by published literature (Benos et al., 2003; McPeck et al., 2009; Lippi, 2018).

#### Comprehension and articulation of the summary

Objective and accurate summary of author's main points (Introduction)

Summary includes the author's main points, including evidence provided to support his/her arguments

#### Critique

Reference to the structure of the article is provided (logical, well supported arguments)

Evaluation and critical judgment of the data collection, techniques are provided

Evaluation and critical judgment of how the data were analyzed are provided

Evaluation and critical judgment of how the data were interpreted by the authors are provided

Evaluation and critical judgment of how successful the authors were at making their point

Arguments to support your agreement or disagreement are provided

A general evaluation of the article is provided at the end

#### Format and style

Arguments are backed-up with appropriate references

Citations are complete (author, Journal, etc.)

Correct grammar, spelling, and punctuation

Writing is clear, logical and easy to follow

Use of paragraphing, devices to join sentences and ideas are appropriate

## ARTICLE ANALYSIS

In a Scientific English course for postgraduate students, we taught them how to review a manuscript and gave them several scientific papers on COVID-19 published in prestigious journals. Their task was to elaborate a critique, according to the instructions given by the professors. Additionally, non-COVID-19 articles (but of related subtopics) from similar journals were reviewed by the students as controls. All papers were evaluated by at least two students and reviewed by the two scientists in charge of the course.

Considering that: i) journals have received a wealth of manuscripts on COVID-19 and therefore, accelerated the publication reviewing process to allow faster publication, and dissemination of information (pandemic publishing) (Kwon, 2020); ii) the worldwide daily confirmed peak of COVID-19 deaths was at the middle of April 2020 (<https://ourworldindata.org/grapher/daily-covid-deaths-region>), and started rising in December 2019; and iii) data published in a middle-to-high impact journal (IF > 9; 2019) can cause more damage to the public because it is easier to consider the information as reliable and valid (Kwon, 2020), the papers were selected based on the following criteria: i) paper main topic was on COVID-19; ii) publication date was between January–June 2020; iii) articles were mainly brief reports; only one research article was selected; iv) papers were published by journals with an IF > 9.4 (2019). Additionally, as controls, we selected three papers meeting the same criteria, except they did not cover COVID-19.

To perform the critique, we used the criteria described under the sub-item “Critique” in **Table 1**. These criteria included: structure of the paper, data collection, appropriate methods and controls to gather the evidence, analysis and interpretation of evidence lead the reader to similar conclusions than the authors.

A paper written by Emmie de Wit and colleagues and published by *PNAS* in February 2020 (de Wit et al., 2020) was reviewed by all students. In this paper, the authors reported that prophylactic treatment with the antiviral drug Remdesivir prevented clinical manifestations in the lungs of *Rhesus*

*macaques* infected with MERS-CoV, and provided a clear clinical benefit when the drug was administered post infection. They suggest that Remdesivir could be useful in the treatment of other coronaviruses such as SARS-CoV-2, the virus responsible for COVID-19. Although the article is well backed up, there were a number of important concerns. First, the number of animals in each group of the study was very small (six), which led to a considerable variation in the results observed, making the reported therapeutic effect of Remdesivir questionable. In addition, although the authors had two different types of vehicle control groups (three animals/group), the results were treated as if these two groups were the same. Furthermore, the study lacked a control group without viral inoculation. Additionally, only male animals were used, despite the evidence indicating that adverse effects may vary between male and female animals (Klein, 2012). Finally, important clinical details about the macaques, such as their age—which is known to influence MERS-CoV infection outcome (Garbati et al., 2016)—weight, physical activity, presence of chronic diseases, etc., should have been indicated. Yet another limitation of this publication was the absence of toxicity assays. Measurements of renal clearance, liver or renal damage, and determinations of Remdesivir side effects, such as nausea, should have been included. Similar concerns were raised in the rest of the articles analyzed.

In another report by Giamarellos-Bourboulis and colleagues published in *Cell Host & Microbe* in April 2020 (Giamarellos-Bourboulis et al., 2020), the authors describe a unique signature of the immune response, different from that induced by bacterial community-acquired pneumonia sepsis or H1N1 influenza, which precedes severe respiratory failure in COVID-19 patients. The common critique to this study was the lack of healthy controls in some of the experiments, which appeared in only a few of the comparisons performed throughout the article. Healthy controls should have been included in all the analyses, and their clinical data, provided. Additionally, some of the conclusions were drawn using data that appears as non-significant in the corresponding graphs. For example, Figure 2E shows no statistically significant differences between

B lymphocyte counts, when comparing immune dysregulated patient samples and intermediate state patients or healthy controls. Therefore, the authors should not have drawn the conclusion of lymphopenia as a characteristic of COVID-19 patients with immune dysregulation. Moreover, many of the figures have high data dispersion, and some of them even show outliers. Statistical outcomes obtained using data sets that include outliers can often be misleading and compromise the generalizability of the research findings (Salgado et al., 2016).

Another example is the study by Hoffmann and colleagues published in *Molecular Cell* in April 2020 (Hoffmann et al., 2020). The authors demonstrate the importance of a multibasic site in the SARS-CoV-2 spike protein, for proteolytic cleavage. They identify the endo protease Furin as a potential target for therapeutic intervention, since this protease cleaves the S protein, which is a key step for viral entry into lung cells. However, the quantitative densitometric analyses of the immunoblots showing cleavage comparison were not provided, making it hard to extrapolate their conclusions to the actual COVID-19 condition. Furthermore, this study lacked physiologically relevant models, such as a primary lung cell line or an *in vivo* system, in order to test the different mutations of the multibasic site. The use of a more appropriate model would have permitted a rigorous evaluation of how these mutations affect viral infection. In addition, an *in vivo* approach would also have been useful to test the effects of the Furin inhibitor, a shortcoming the authors themselves acknowledge in the discussion section, considering that the drug may exert toxic effects. Thus, suggesting Furin as a COVID-19 therapeutic target seemed rather premature.

The brief communication published in *Nature Medicine* in April 2020 by Leung et al. (2020) discusses the efficacy of face masks in preventing transmission of three different viruses, including COVID-19. A major concern here was that the authors did not clearly describe the masks used in the experiments, particularly, in terms of the submicron-sized filter or the mask certification. This information is highly relevant because differences have been reported between different face masks and their ability to filter aerosols (Oberg and Brosseau, 2008). Moreover, differences between aerosols and droplet transmission were not discussed and although the authors concluded that for all studied viruses shedding is higher in nasal swabs than in throat swabs, they did not provide a statistical analysis of these results. Another important problem was the small size of the population analyzed for coronavirus (only 17 patients) and the fact that this sample included patients with chronic medical conditions (five patients) and one smoker. These conditions may cause changes in the respiratory rate and other symptoms that might not be a direct consequence of viral infection but of the underlying condition (Martin et al., 2016; Britto et al., 2017). As an outcome, the number of viral copies in exhaled breath could be altered and might not reflect the real values of most patients. Furthermore, swab samples were taken from all 17 patients; however, in the droplet vs. aerosol experiments, the number of patients was reduced to 10 (without mask) and 9 (with mask), respectively. This limited sample size is insufficient to draw significant conclusions.

The last report on COVID-19 reviewed was the one published in *Science* by Rockx et al. (2020) in April 2020. Here, the authors studied the pathogenesis of infection produced by SARS-CoV-2 and compared it with that of SARS-CoV and MERS-CoV, using a non-human primate infection model. A common critique here was that the information provided about the studied subjects was incomplete, considering that the main goal of the article was to describe an appropriate animal model for COVID-19 trials. No information concerning the macaques, such as physical status or health condition was provided, although these are parameters that can affect the severity of respiratory diseases. Moreover, the authors did not provide information concerning the exact age of macaques in both MERS and SARS groups, nor did they mention specific details about the inoculation doses used in the experiments. Moreover, the data showed high variability and no statistical analyses were provided.

The first article reviewed as a control was published in *Cell Host & Microbe* by Di Luccia and colleagues, on June 2020 (Di Luccia et al., 2020). The authors studied the effect that undernutrition and microbiota can have on the immune response to oral vaccination in a gnotobiotic mouse model. In this article, we observed that sample collection and clinical data from the donors, the methodology regarding the mouse model, controls and statistics were well detailed. Nevertheless, a common critique found was that the study included only fecal samples from one child donor for each group of study (supplement-responsive and supplement-hyposresponsive).

Another article we used as a control was published in *PNAS* by Wang and colleagues, on June 2020 (Wang et al., 2020). Here, the authors compared the capacity to lower the viral load of wild-type anti-HIV-1 immunoglobulin G1, using an Fc Null variant of the same antibody in both a humanized mouse model and in *R. macaques*. The article was well written, the methodology was explained with enough detail, and the controls and sample sizes used were appropriate. The only critique made was that the confirmation of the results using different antibodies were performed using distinct virus strains.

Our last article reviewed as a control was published in *Nature Medicine*, in March 2020. Here, Colby and colleagues provide evidence for the safety, immunogenicity, and viral rebound dynamics of a heterologous Ad26, MVA vaccine regimen in antiretroviral therapy-suppressed HIV patients (Colby et al., 2020). The major criticism found here was that the authors did not perform power calculations to obtain an optimal sample size, which they mention was due to the number of available subjects. Furthermore, they used the Wilcoxon test (which compares two related samples) for statistical significance even though their graphs show the comparison of multiple populations. Additionally, they only studied Asian males, which confers, gender and ethnic biases to their results.

Therefore, major criticisms that were common to most of the reports on COVID-19 were: i) high variability of the results, or no statistical analysis provided, or results with non-significant differences; ii) lack of appropriate controls; iii) models were not described in detail, incomplete patient information, insufficient information about the experimental design, exact

**TABLE 2** | Summary of selected articles, indicating the journal and its impact factor, along with the number of days to final acceptance, and the article type, i.e., short (green) vs. long (orange) articles.

Paper on COVID-19?	Journal (IF 2019)	Dates of reception/acceptance	Number of days	Article type
Yes	<i>Molecular Cell</i> (15, 5)	Received March 15, 2020; accepted April 17, 2020	33	Short article
Yes	<i>Nature Medicine</i> (36)	Received February 3, 2020; accepted February 20, 2020	17	Brief communication
Yes	<i>Cell Host &amp; Microbe</i> (15, 9)	Received March 19, 2020; accepted April 9, 2020	21	Report
Yes	<i>Science</i> (40)	Received March 15, 2020; accepted April 15, 2020	31	Report
Yes	<i>PNAS</i> (9, 41)	Received December 16, 2019; accepted February 7, 2020	56	Research article
No	<i>Nature Medicine</i> (36)	Received May 6, 2019; accepted January 24, 2020	262	Brief communication
No	<i>PNAS</i> (9, 41)	Received April 27, 2020; accepted June 17, 2020	51	Research article
No	<i>Cell Host &amp; Microbe</i> (15, 9)	Received February 14, 2020; accepted April 8, 2020	54	Short article

age or lack of information related to doses inoculated, etc.; iv) small sample size; v) no indication of toxicity assays; vi) insufficient evidence provided to claim clinical relevance; vii) a more physiologically relevant model would have been necessary to draw the conclusions. All of the aforementioned elements are crucial requisites that should not be bypassed in the peer reviewing process. Nevertheless, we did notice a greater number of these issues in COVID-19 related papers than in control papers. Additionally, the students also noted that non-COVID-19 articles were more prone to discussing the limitations of the studies and less prone to overselling their results in comparison to COVID-19 related ones. Importantly, a more extended reviewing process was evident for the control articles (>50 days) when compared to the COVID-19 papers (mean = 31 days) (Table 2).

## DISCUSSION

Scientific rigor is a must no matter the circumstances. Thus, researchers and scientific journals should not take advantage of the pandemic contingency to publish papers that do not present enough evidence to support the conclusions claimed by the authors. Particularly, in these times when people turn to scientists in search of answers to calm their fears and concerns. The peer review process should assist the scientific community in “assuring the quality of research before it is published and before it can be examined and used by a wider audience” (Cargill and O’Connor, 2013). Therefore, peer reviewing should be carried out thoroughly and meticulously to guarantee that carefully conducted scientific studies are being published in these emergency times.

In addition, because the situation is critical and it will inevitably affect the economy worldwide, significant financial cuts are foreseen in every field and discipline, and science is not an exception. However, this is a typical catch-twenty-two situation. Science, research, and experimentation is needed to learn about all these microbes, viruses, and other microorganisms that can cause severe damage to human health, yet funds are being cut in order to provide money for other more immediate needs. What all the relevant players need to learn from this experience, is that science should always be an action rather than a reaction, which is what we are now learning from these articles that have been peer reviewed using less than rigorous criteria. Likewise, while fear of running out of funds and

the urgent need for a treatment for this deadly disease may be pressuring from all angles to publish at any cost, ethics and rigor are core scientific values that need to be met to draw meaningful conclusions.

Interestingly, when the students were asked to review additional non-COVID-19 articles as controls for this Opinion, they rapidly noticed the apparent differences in the details between COVID-19 and non-COVID-19 articles with respect to the methodology used and other significant issues analyzed during this study (see Table 1). Thus, the question as to whether COVID-19 articles, given the current pandemic, are being reviewed with a less critical eye is supported here by the comparison performed with the non-COVID-19 article reviews. Until now, other authors have also remarked on this issue (Bagdasarian et al., 2020; Kwon, 2020). However, it is noteworthy to point out that peer reviewing is a complex task that involves human judgment and interpretation of someone else’s experimental design and findings, and as such, it is not free of error (e.g. see <http://retractionwatch.com/>).

## AUTHOR CONTRIBUTIONS

The authors confirm to have contributed to this work and have all approved it for publication.

## FUNDING

LL was funded by the Agencia Nacional de Investigación y Desarrollo (ANID) grant (FCYT1200836), OO was funded by the Millennium Nucleus of Ion Channel-Associated Diseases (MiNICAD), and the PhD students by ANID fellowships [Beca Doctorado Nacional 21190214 (DJ); 21170292 (MFG); 21201941 (DM); 21191668 (DH); 21190725 (JR); 21191341 (MD), and tuition fee/stipend grant for Doctoral Studies 2020, from the Faculty of Medicine, Universidad de Chile (MG, SS)].

## ACKNOWLEDGMENTS

The authors would like to thank Andrew Quest for insightful discussions regarding the topic and Ana María Avalos for her editing/proofreading contribution.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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