OPINION ARTICLE

COVID-19 and blood groups – there is an elephant in the room, but who cares? Do we need additional rules for preprints? [version 1; peer review: 2 approved]

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) not only can cause very severe disease but, less obviously, the virus can also infect science in unpredicted ways. It seems that during these times some basic rules of science will lose validity and we do not know if they will come back. Though not necessarily always being the case, problems can arise from messages that make their way to public media straight from preprints. An impressive example is a recent study on an association between ABO blood groups and the severity of COVID-19. The study was first published as a preprint which almost immediately gathered an enormous amount of public interest though major drawbacks of the study had been identified by members of the scientific community. One of the major advantages of preprints is to present data, even if still incomplete, to the scientific community for an early discussion. It does not serve the quality of science if possible critical considerations are not addressed adequately until these preliminary studies go public and are submitted for publication in classical journals. Accordingly, clear additional rules for handling data derived from preprints are advocated herein. Speed does not have an advantage on its own.

Keywords

COVID-19, disease severity, blood group, preprints

This article is included in the **Emerging Diseases** and **Outbreaks** gateway.

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In general, associations between blood groups and infectious diseases are well known. They may be either related to the probability of becoming infected or to a more or less severe course of the disease. Recently, associations of ABO blood groups and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) have attracted a lot of scientific interest, due to a number of studies where such associations have been investigated. One such study has generated enormous public interest.

As to SARS-COV-2 and blood types, initial interest in the field was stimulated by a preprint by Zhao *et al.*, which was initially published on March 16, 2020¹. Based on their results, individuals with blood group A had a significantly higher risk for acquiring COVID-19 compared with non-A blood groups, whereas individuals with blood group O were found to be at a significantly lower risk for the infection. Less than one month later, another preprint appeared also addressing a possible link between COVID-19 and blood groups, but did not find any significant associations between blood groups and intubation or death². Again one month later, the first report on a genome-wide association study (GWAS), carried out by a European consortium, appeared as a preprint³, which was followed by a press release. This was then published as a *New England Journal of Medicine (NEJM)* paper⁴, again accompanied by a corresponding press release, and apparently all based on the same group of COVID-19 patients receiving oxygen and a control group. The critical considerations outlined herein mainly relate to the preprint by the European consortium, the paper published in *NEJM*, and the two press releases. The message of all four was that people with blood group A have a much higher risk for respiratory failure during the course of COVID-19 than those with B or O. This caused a huge public reaction (Table 1), resulting in a lot of anxiousness due to headlines being published in the media, such as “People with blood type A more likely to suffer severe coronavirus symptoms, research finds” (Telegraph, UK, 4th June 2020⁵) and TV reports (e.g. News9 India of June 5, 2020⁶). Both the high public interest, as well as possible clinical applications of the findings, warrant a critical analysis of the methods and data applied.

The preprint and its weakness

The European consortium (with K. Ellinghaus and F. Degenhardt from Kiel, Germany, as shared first authors and A. Franke, Kiel, and T. H. Karlsen, Oslo, Norway, as corresponding authors) published the results of a GWAS with COVID-19 patients from Spain and Italy who all received oxygen during the course of the disease³. One of two significant association signals was located at chromosomal band 9q34, corresponding to the ABO blood group locus. It was claimed that the ABO blood groups thus are associated with COVID-19 induced respiratory failure “with higher risk for A-positive individuals and a protective effect for blood group O”. Shortly after the

preprint’s appearance the headlines and news went viral (Table 1).

In a few media articles, the message was overreached, for example by Medscape, Germany, who stated that an association between COVID-19 **mortality** and blood groups has been found (12th June 2020⁷). In particular in German-speaking countries, interest in the results of the study was also stimulated by a tweet from Karl Lauterbach⁸, professor of Health Economics and Clinical Epidemiology at the University of Cologne and member of the Deutscher Bundestag, which was frequently cited in public media (Figure 1).

Despite this wide-spread interest, the value of the study suffers from its control group, which comprises a total of 2,381 individuals. According to the preprint, the control group, among others, included “998 randomly selected blood donors at Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan with no evidence of Covid-19 who were genotyped for the purpose of the present study.”³. Two further control panels with genotype data derived from previous studies using the same genotyping array were included as well (from Italy n=396 and from Spain n=987). Due to the selection of the control group, the findings do not allow for the conclusion that ABO blood types influence the severity of symptoms, since no comparison has been made between people receiving oxygen versus those mildly affected (e.g. non-hospitalized) as a control group. Accordingly, similar results have to be expected, if blood groups affect one’s chance getting infected at all. This problem was pinpointed early on by some in the public media, for example by The Scientist Magazine (“Ideally, a GWAS analysis would analyze the genomes of people with COVID-19 and compare those who didn’t get very sick to those who experienced severe symptoms, instead of using population-based controls whose exposure to the virus is unknown, says Priya Duggal, a genetic epidemiologist at the Johns Hopkins Bloomberg School of Public Health who did not participate in the study.”; 8th June 2020⁹) and the German *Sueddeutsche Zeitung* (15th June 2020¹⁰).

Already at this time, at least one of the authors of this study apparently was well aware of this major shortcoming: “The study was not perfect. Ideally there would be another full group of patients for comparison who were infected but who did not develop the severe disease. This was one reason, said

¹<https://www.telegraph.co.uk/global-health/science-and-disease/people-blood-type-likely-suffer-severe-coronavirus-symptoms/>

²<https://www.youtube.com/watch?v=OfRQ-DYCV6s>.

³https://deutsch.medscape.com/artikelansicht/4908983?faf=1&src=soc_fb_200701_mscpmrk_de_single_covid

⁴<https://www.hsph.harvard.edu/voices/events/karl-lauterbach-professor-of-health-economics-and-clinical-epidemiology-university-of-cologne-member-of-the-deutsche-bundestag/>

⁵<https://www.the-scientist.com/news-opinion/two-genetic-regions-linked-with-severe-covid-19-67619>

⁶<https://www.sueddeutsche.de/wissen/genetik-covid-19-coronavirus-krankheit-verlauf-1.4934939?reduced=true>

Table 1. Examples of public media addressing the study in its preprint stage with their headlines.

Headline	Appeared in	Date	Link
Blood type A associated with higher risk of COVID-19	Report, Azerbaijan	June 3, 2020	https://report.az/en/health/blood-type-a-associated-with-higher-risk-of-covid-19/
Genes May Leave Some People More Vulnerable to Severe Covid-19	The New York Times, USA	June 3, 2020	https://www.nytimes.com/2020/06/03/health/coronavirus-blood-type-genetics.html
People with blood type A more likely to suffer severe coronavirus symptoms, research finds	Telegraph, UK, June 4	June 4, 2020	https://www.telegraph.co.uk/global-health/science-and-disease/people-blood-type-likely-suffer-severe-coronavirus-symptoms/
C'est dans le SANG: la génétique pourrait faire en sorte que certaines personnes soient affectées PIRE par Covid-19, selon une étude [It's in the BLOOD: Genetics could make some people worst affected by Covid-19, study finds]	News 24, France	June 4, 2020	https://news-24.fr/cest-dans-le-sang-la-genetique-pourrait-faire-en-sortes-que-certaines-personnes-soient-affectees-pire-par-covid-19-selon-une-etude/
Study links respiratory illness during Covid to blood groups	Hindustan Times, India,	June 4, 2020	https://www.hindustantimes.com/india-news/study-links-respiratory-illness-during-covid-to-blood-groups/story-uejN9ZIDB6h4UGnyCABel.html
COVID-19 patients with blood group 'A+' more likely to need oxygen support: Study	India TV, India	June 5, 2020	https://www.indiatvnews.com/science/coronavirus-study-patients-with-blood-group-a-at-higher-risk-covid-19-treatment-623551
Scientists find link between COVID-19 severity and genetics -Patients with blood type A were linked to a 50% increase in the likelihood in needing to get oxygen or go on a ventilator	Jerusalem Post, Israel	June 7, 2020	https://www.jpost.com/international/scientists-find-link-between-covid-19-severity-and-genetics-630413
El grupo sanguíneo es determinante para el desarrollo de una infección con coronavirus [Blood group decides the development of a coronavirus infection]	El Comercio, Spain	June 8, 2020	https://www.elcomercio.es/internacional/corresponsales-8-junio-20200608083029-ntrc.html
Blutgruppe könnte Krankheitsverlauf von Covid-19 beeinflussen [Blood type could influence the course of Covid-19 disease]	Spiegel, Germany	June 9, 2020	https://www.spiegel.de/wissenschaft/medizin/coronavirus-beeinfluusst-die-blutgruppe-den-krankheitsverlauf-a-818f0aac-a788-4b5a-b203-e8196d747ae2
Coronavirus, il gruppo sanguigno O protegge davvero di più? [Coronavirus, is blood type O really more protective?]	Corriere della Sera, Italy	June 10, 2020	https://www.corriere.it/salute/cardiologia/20_giugno_10/gruppo-sanguigno-coronavirus-0-protegge-dawero-piu-466d72ba-ab14-11ea-ab2d-35b3b77b559f.shtml
Bloody hell. How your blood type could increase your risk of dying from coronavirus – and how to find out yours	The Sun, UK	June 12, 2020	https://www.thesun.co.uk/news/11845115/blood-type-increase-risk-dying-coronavirus-how-to-find-yours/
Your blood type could worsen virus risk	The Australian	June 12, 2020	https://www.theaustralian.com.au/world/the-times/coronavirus-blood-type-puts-you-at-worse-risk-of-virus-susceptibility-and-severity/news-story/bb0e6fc15ce75b15a23521e7adfd6696

Headline	Appeared in	Date	Link
Appearance of New England Journal of Medicine paper (June 17, 2020)			
<i>Study ties blood type to COVID-19 risk; O may help, A hurt</i>	U.S. News	June 17, 2020	https://www.usnews.com/news/world/articles/2020-06-17/study-ties-blood-type-to-covid-19-risk-o-may-help-a-hurt
<i>More evidence your BLOOD may help determine your coronavirus risks: Study of thousands of Europeans finds people with Type O are less likely to catch the virus and those with Type A get sicker</i>	Daily Mail, UK	June 17, 2020	https://www.dailymail.co.uk/health/article-8434167/Study-ties-blood-type-COVID-19-risk-O-help-A-hurt.html
<i>Blood Type, Genetics Could Impact Odds for Severe COVID-19: Study</i>	U.S. News	June 18, 2020	https://www.usnews.com/news/health-news/articles/2020-06-18/blood-type-genetics-could-impact-odds-for-severe-covid-19-study
<i>Blood types and COVID-19 risk confirmed</i>	News Medical Life Sciences, USA	June 18, 2020	https://www.news-medical.net/news/20200618/Blood-types-and-COVID-19-risk-confirmed.aspx
<i>Blood type, genes tied to risk of severe COVID-19: European study</i>	Reuters, USA	June 18, 2020	https://www.reuters.com/article/us-health-coronavirus-genes/blood-type-genes-tied-to-risk-of-severe-covid-19-european-study-idUSKBN23P38C
<i>Studie: Blutgruppe beeinflusst Schwere von Covid-19-Verlauf</i> [Study: blood group influences severity of Covid-19 course]	Zeit, Germany	June 18, 2020	https://www.zeit.de/news/2020-06/18/studie-blutgruppe-beeinfluusst-schwere-von-covid-19-verlauf

Figure 1. Tweet by German health professional and politician Karl Lauterbach addressing the preprint. [A very remarkable result shown in a robust study. Blood group A about 50% higher risk for severe course of COVID-19. Risk twice as high as with blood group O. Blood group B in between. Because immune response depends on the blood group it makes sense]. (https://twitter.com/Karl_Lauterbach/status/1268522737573728257, translated from German). Permission to reproduce this tweet was obtained from Karl Lauterbach's office.

Professor Franke, that he could not be confident of the exact risk increase linked to blood type: “It may be 20 per cent, it may be 30 per cent, it may be 50 per cent.” (as quoted in The Australian, 12th June 2020^e). Nevertheless, a press release^h by the lead author’s own institution (Universitätsklinikum Schleswig-Holstein) on 10th June 2020 revealed that according to their results “people with blood group A have a roughly 50% elevated risk for a severe course of COVID-19 than people with other blood groups. Vice versa, people with blood group O were protected against severe disease by nearly 50%” (translated from German).

The study received accolade, but doubt remains

On 17th June 2020, the paper was published in the *New England Journal of Medicine*⁴, and the study received recognition. Unfortunately, the problem with the control group became even more complicated because the description was changed from the preprint: “We recruited 998 randomly selected blood donors at Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, who underwent genotyping for the purpose of the present study. A total of 40 of these participants had evidence of the development of anti-SARS-CoV-2 antibodies, all of whom had mild or no Covid-19 symptoms.”⁴

In contrast, according to the preprint³, all 998 blood donors did not show evidence of COVID-19. Also, it is unclear if

all had been tested for antibodies and by which test. What was the control group then? A pre-COVID-19 population? Apparently not, but maybe in part. Patients infected, but with mild or absent symptoms of COVID-19 constituting part of the controls, make interpretation of the data even more difficult if not impossible. Despite this, a second press releaseⁱ by the lead author’s institution was published on 18th June 2020, which unequivocally concludes: “The study had shown that people with blood group A have an approximately 50 percent higher risk of severe Covid-19 progression than people with other blood groups. In contrast, people with type O blood groups were almost 50 percent better protected against serious covid-19 disease.”. The appearance of the now peer-reviewed paper caused a second wave of headlines (see Table 1). Nevertheless, most notably a large part of the media coverage was gained in the two-week period when only the preprint was available (Figure 2).

The enormous attention is also reflected by the preprint and article metrics, e.g. compared to a paper by Latz *et al.*⁵ also addressing a possible association between blood groups and the severity of COVID-19, but which came to an opposite conclusion (Figure 3). Simultaneously, the publication caused an enormous level of public interest and anxiety as witnessed by the coverage gained in public media (Table 1).

Are additional rules for preprints needed?

How could it happen that, to say the least, a misleading message spread so rapidly and at a preprint stage? What makes the story so appealing for public recognition? It’s not the association with an anonymous gene. Instead, people know about blood groups and many even know about their own. Besides

^e<https://www.theaustralian.com.au/world/the-times/coronavirus-blood-type-puts-you-at-worse-risk-of-virus-susceptibility-and-severity/news-story/bb0e6fc15ce75b15a23521e7addf6696>

^hhttps://www.uksh.de/Service/Presse/Presseinformationen/2020/Weltweit+erste+gro%C3%9F+genomweite+Studie+_+Kieler+Forschungsteam+findet+Genvarianten+f%C3%BCr+schweren+Verlauf+von+Covid_19-p-184658.html

ⁱ<https://idw-online.de/de/news?print=1&id=749683>

Figure 2. Timeline showing dates of preprint, press releases, and publication of the paper in New England Journal of Medicine. NEJM: New England Journal of Medicine. UKSH: Universitätsklinikum Schleswig-Holstein, Germany.

Figure 3. Article metrics for the preprint by Ellinghaus *et al.*³ (number of abstract and preprint views), the *Annals of Hematology* paper by Latz *et al.*⁵ (number of accesses), and the *New England Journal of Medicine* paper by Ellinghaus *et al.*⁴ (number of views). Metrics for 5 and 14 days after publication are given.

genetic association there is obviously a direct interest in personal risk. Can we thus blame the hunger of the public for intriguing messages on COVID-19 that might affect people personally? At least this is not the only factor explaining the high public interest in this case. It seems reasonable to speculate that a scientifically more correct interpretation of the limits of the study at the preprint stage and in the press releases might have led to a drastically decreased level of interest by public media, but the message of the study has been made more fascinating by the authors themselves – with their press releases and the preprint. Should thus the preprint system of publishing a piece of work without peer review be blamed?

One of the main arguments in favour of sharing work in its preliminary preprint form is that articles are improved by

feedback from a wider group of readers instead of only formal peer review by few experts, and that science works faster if results are made available sooner after being completed⁶. Basically, both principles have worked here. As for the speed, the preprint was published some two weeks earlier than the paper in *NEJM*. However, it could be said that there was no such need for speed, and more important was the opportunity to gather feedback from a larger community, which has worked nearly perfectly. Currently, there are 39 comments for the preprint by Ellinghaus and coworkers³. Of these, some comment on the issues faced with the controls⁷, and this problem was also

⁷<https://www.medrxiv.org/content/10.1101/2020.05.31.20114991v1>

pinpointed very early on by experts in the public media and, curiously enough, even at least by one of the authors (see above). Moreover, there were also contradictory findings, which were neither appropriately mentioned in the preprint nor in the *NEJM* paper, e.g. the preprint by Zietz and Tatonetti² that appeared earlier on the same server (medRxiv).

One of the main advantages of a preprint, i.e. the chance to have it critically considered by a larger group of peers, has evaporated here due to the short time between the preprint and appearance of the paper, giving the authors no chance to consider comments and criticism. Of note, even now the preprint has not been corrected, though the control group is apparently not correctly described given that the description in the *NEJM* is correct.

There is a low level of control until preprints go public, which clearly increases the author's responsibilities. Aimed at the benefit for the scientific community, preprints have to balance a possible need for speed with "suitable safeguards to protect the public"⁶ as well. The case presented here illustrates the adverse effects associated with a loss of such balance and clearly advocates additional rules for preprints. To put it simply, authors should not leave the room while the elephant is still in it. Whenever submitting a manuscript which corresponds to a preprint, a time of some weeks should be given to the extended group of peers to comment on and vice versa, authors should communicate possible comments along with the manuscript and they should declare that they have read and considered all these comments carefully. During that time, there should not be any press releases from the authors. In a comment on their study⁵

investigating possible associations between the severity of COVID-19 and ABO blood groups, Latz *et al.* made the rigorous statement that they are confident their principle finding "will help debunk the kinds of clinically unfounded rumours and misinformation that can readily gain traction in the midst of a pandemic, and in some cases become part of accepted medical practice"^k. Certainly, we as scientists have a direct responsibility to avoid this type of misinformation.

And what on the actual news on COVID-19 severity and blood groups? "Risk does not depend (much) on blood type" stated The New York Times on 15th July 2020^l. The Latz *et al.*⁵ study, based on 1,289 COV+ individuals, concluded that blood type was not associated with intubation or mortality in COVID-19 patients. Similarly, the recently published second version of the preprint by Zietz and Tatonetti⁷ even revealed a significantly lesser risk for intubation for individuals with blood group A.

Data availability

No data is associated with this article.

^k<https://hms.harvard.edu/news/covid-19-blood-type>

^l<https://www.nytimes.com/2020/07/15/science/coronavirus-blood-type.html>

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[Reference Source](#)

Open Peer Review

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This article highlights the conundrum that preprint servers can play in bypassing the formal publication peer review process. The particular case study focuses on two papers listed on medical preprint servers that asserted an association between ABO blood groups and CoV-SARS-2 incidence and/or morbidity. The conclusions from these two papers (and an online study by 23andme) were widely discussed in the lay press, often with dramatic tabloid headlines (see Table 1). The “Elephant in the Room” is the author’s increased scientific and public responsibility for the information on the preprint server—even after manuscript acceptance. The subsequent formal peer review and later studies subsequently disclosed problems with the control groups (blood donors and not COVID patients).

Comments:

Bullerdiel raised several issues that arose from institutional press announcements regarding a paper that was listed on preprint server but not formally accepted. The author’s institution also bears responsibility for the public perception the preprint was a peer-reviewed, accepted findings. It sadly demonstrates the need for public institutions to aggressively “market” science discoveries in the lay press.

It is surprising that scientific journals have not pushed back at the listing of manuscripts on preprint servers. In these two instances, the preprint server acted to undermine the regular peer review process. All journals require that authors state that the submitted manuscript is NOT under consideration by other journals. In the cited example, the authors effectively had a dual submission to NEJM and the preprint server because of public interest, which was driven by institutional marketing. As Bullerdiel exposed, the time between preprint listing and NEJM acceptance was a mere two weeks. This obviated any insight or useful criticism from a preprint listing.

I have personal insight into these two papers and was contacted by multiple scientific and lay press organizations. In addition, I received emails from scared citizens for weeks, wondering if they needed to have their blood typed. Although I refused to comment on the articles as

preprints, I did offer some opinions and skepticism once the European GWAS article was accepted by NEJM. My skepticism was based on the control groups, as well as the US experience, in which COVID19 appeared worse among African Americans, who have a higher incidence of group O than whites. As noted by Bullerdiek, subsequent US studies found no association between ABO and COVID19.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Transfusion Medicine, Immunohematology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 25 September 2020

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In this article, Bullerdiek makes some cogent criticisms of the rapid publication of preprints, with specific reference to a recent publication on the association between ABO blood groups, SARS-CoV-2 infection and the resulting disease, COVID-19. He concludes by proposing that additional rules should be observed by the authors of preprints. Specifically, three rules are suggested:

1. A time of some weeks should be given to the extended group of peers to comment on and vice versa;
2. authors should communicate possible comments along with the manuscript and they should declare that they have read and considered all these comments carefully; and

3. during that time, there should not be any press releases from the authors.

Comments

1. The main purposes of publishing a preprint are to make findings widely known without delay; to solicit responses and critical appraisal; and to establish the authors' priority in a competitive field. There is little logic, on any of these grounds, in publishing a preprint a very short time (two weeks, as in the present instance) before the print version. I concur with Bullerdiek on this principle.
2. The publication of a preprint increases the normal responsibilities on the authors to be accurate and, in particular, to respond appropriately to criticism both in the final 'print' version and also in revised preprints if serious issues are identified or if there will be a long delay before the print version is published.
3. It is impossible to foresee, and still less to prevent, the distortion or misinterpretation that may follow the publication of a scientific paper. However, in circumstances of exceptionally wide and intense public interest, such as in the present coronavirus pandemic, it is proportionally more important to make public announcements such as press releases that are worded cautiously, in such a way as to minimize the chance of exaggeration or misinterpretation by others, especially in the popular press.
4. Genetic association studies, by definition, can identify associations but cannot identify the mechanism of any observed association. In the present case of the preprint on ABO blood groups and SARS-CoV-2 infection by Ellinghaus, Degenhardt *et al.*, there is a stark difference between two potential causes of the observed association. That is, ABO blood group might influence either the risk of acquiring SARS-CoV-2 infection, or the severity of a resulting illness, COVID-19; these are not mutually exclusive possibilities, and both might be true. The broad conclusion of the Ellinghaus, Degenhardt *et al* preprint, that ABO blood group influences the risk of COVID-19, is consistent with recent publications from several other groups, but it is not yet certain whether the association is due to an effect on acquisition of infection or on the pathogenesis of the resulting disease. The recently revised preprint by Zietz and Tatonetti, cited by Bullerdiek, favours the notion that the primary effect of ABO blood group in SARS-CoV-2 infection is on the risk of acquisition of the infection, not on disease severity. Further studies are needed to identify potential mechanisms, in particular of the apparent protective effect of blood group O.

What, then, of the proposed additional rules for the publication of preprints, listed above? I believe that the first two should be strongly recommended, but it is difficult and inappropriate to mandate strict numerical limit on the time between preprint and final publication of a peer-reviewed paper. However, I believe that press releases should not be forbidden: the authors remain responsible for the decision whether it is appropriate and helpful to make a press release, and for the content and style of any release.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology, immunology, genetics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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