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LETTER

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Response: Epileptic discharges in acutely ill patients investigated for SARS-CoV-2/COVID-19 and the absence of evidence

We appreciate the interest of Drs Rai, Gogia, and Tremont-Lukats in our preliminary report and their attempt to re-evaluate our findings using the Bayesian binomial statistics.[1] Their conclusion that more observations are needed is in close agreement with our manuscript's discussion and conclusions. One reason we published this work as a "preliminary report" was the low sample size of our case series and particularly of the COVID-19-negative group (n = 6), given that our study was done during the peak of COVID-19 pandemic in our region.[2] Along with this limitation, we were also cautious in our manuscript to highlight a number of other possible confounders that should be considered in future studies on the subject, among them false-negative rates of SARS-CoV-2/COVID-19 testing and associated pre-existing and clinical data, as outlined also in the subsequent paragraphs.

Whether one chooses the Bayesian or frequentist statistics, confidence upon their statistical outputs is strongly dependent on the sample sizes. A simple thought experiment is shown in Figure 1, using the same dataset that the authors used from our manuscript, that is, the rate of epileptiform discharges (EDs) in the COVID-19-negative (1/6, Group 1 or prior) and COVID-19-positive (9/22, Group 2 or posterior) cohorts. By merely increasing the sample size of the prior tenfold, while maintaining the same proportion of subjects with EDs over the total size (ie, from 1/6 to 10/60), and leaving the posterior (COVID-19-positive) dataset unchanged, both the simple sequential (SS) Bayesian A/B test and Fisher's exact test provide some level of statistical significance.

However, extrapolating findings from small-sample exploratory studies of new patient populations, like our study, to larger populations without collecting real data is hard to recommend. Careful selection of the prior distributions needs to be done to incorporate in the hypothesis factors that may be important in positively or negatively controlling the likelihood of occurrence of a tested outcome. As shown in our cohort, acutely ill patients investigated for COVID-19-suspected presentations have multiple clinical confounders that can either increase or decrease the likelihood of appearance of EDs on their EEG, as shown in table 1 of our report.[2] These include comorbid conditions, such as hypoxia/hypoxemia or respiratory failure, metabolic or electrolyte abnormalities, the underlying inflammatory/infectious processes, prior history of epilepsy, and new acute neurological insults, any of which may potentially increase the risk of EDs. In contrast, as discussed in our report, the administration of antiseizure and/or sedative medications was often done in advance of an EEG study, following best clinical practice, and may have reduced the likelihood of observing seizures or EDs in the EEGs. The multitude of all of these confounding factors cannot be modeled with a sample size of 6 or 22, that is a key reason we advocated for further larger-scale studies to expand our preliminary observations and learn the true impact of SARS-CoV-2/COVID-19 infection on potentially activating epileptiform abnormalities.

Our study was the first published case series describing the EEG findings in acutely ill patients who were admitted and investigated for COVID-19, and we reported this not only to increase awareness about the potential impact of the virus on EEG and epileptiform abnormalities but also to encourage more studies on the subject. Subsequent to our report, case series of COVID-19-positive patients with EEG studies (n = 13-111 each) have been published by independent groups; yet, none has incorporated COVID-19-negative patient populations exhibiting similar presentations. Among COVID-19-positive patients, the reported rates of EDs in these recently published studies varied between 0% and 38%[3-10]; our reported 40.9% rate falls at the higher end of the spectrum. Such a spread of rates of epileptiform EEGs among small- or moderate-scale case series from different institutions exemplifies how differences in inclusion criteria, study design, patient enrollment and demographics, and clinical history may alter outcomes. In addition to the clinical confounders discussed earlier, known factors that may contribute to this broad range of rates of epileptiform EEGs among these studies of acutely ill COVID-19-positive patients include the type of EEGs (mostly brief routine EEGs or longer records), the inclusion criteria with regard to indications for EEGs, or the severity of COVID-19 illness. Similar

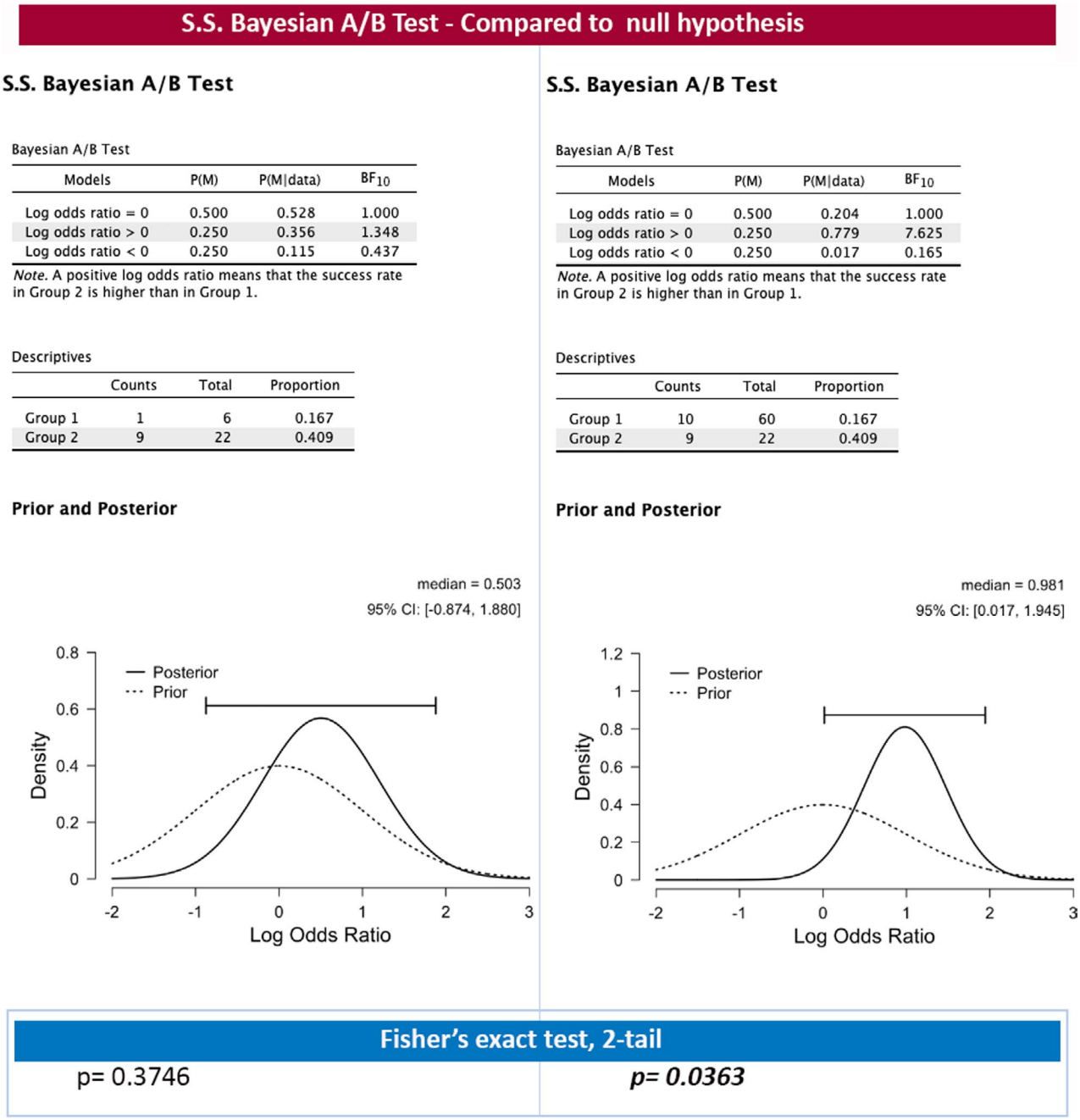

FIGURE 1 Effect of sample size on outputs of the simple sequential (SS) Bayesian (A/B test) vs frequentist (Fisher's exact test) statistics. Re-evaluation of the statistical significance of the difference in the rates of epileptiform discharges (EDs) observed in the EEGs of acutely ill COVID-19-negative (Group 1, 16.7%) vs COVID-19-positive (Group 2, 40.9%) patients, considering different sample sizes of the prior (Group 1) distribution. Our original data[2] (n = 6, Group 1) do not yield statistical significance when examined by either the Bayesian A/B test or a frequentist statistical method, Fisher's exact test. Increasing the sample size of the prior to n = 60 produces significant evidence, with both the Bayesian and Fisher's exact tests, favoring the alternate hypothesis, that the rates of epileptiform EEGs are higher in COVID-19-positive patients than in COVID-19-negative patients. The Bayesian A/B test was done using the JASP software (https://jasp-stats.org) and Fisher's exact test using JMP version 10.0.0 (SAS Institute Inc, Cary NC, USA)

to our study, many of these studies also acknowledged the high percentage of patients on sedatives and/or antiseizure medications at the time of EEG that may decrease the yield of EDs. As also discussed in our report, adequately powered and controlled studies are needed to validate our findings, factoring all the plausible variables, to obtain a more accurate depiction of the likelihood for new EDs in the setting of acute COVID-19 illness. Certainly, the larger sample sizes that are likely to be achieved in the near future, for both COVID-19-positive and COVID-19-negative patients, will offer a true depiction of the likelihood for new epileptiform EEG abnormalities in the setting of COVID-19 acute illness.

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CONFLICT OF INTEREST

We have no conflicts of interest to declare in regard to this response. AS Galanopoulou is co-editor in Chief of *Epilepsia Open* and has received royalties for publications from Elsevier and Morgan & Claypool publishers. SR Haut serves on the editorial board of *Epilepsy and Behavior*. SL Moshé is serving as associate editor of *Neurobiology of Disease* and serves on the editorial board of *Brain and Development, Pediatric Neurology, and Physiological Research*. He receives from Elsevier an annual compensation for his work as associate editor in *Neurobiology of Disease* and royalties from two books he co-edited. He has received consultant's fees from UCB and Pfizer. AB Boro is site PI for clinical trials sponsored by Biogen, SK Life Science, Neurelis, and UCB. He receives no salary support for other reimbursement for these projects. All funds go to the institution. None of the other authors have conflicts to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Aristea S. Galanopoulou[1,2,3,4,5]
David L. McArthur[6]
Victor Ferastraoaru[2,3]
Daniel J. Correa[2,3]
Koshi Cherian[1,2,3]
Susan Duberstein[1,2,3]
Jonathan Gursky[2,3]
Rajani Hanumanthu[2,3]
Christine Hung[2,3]
Isaac Molinero[1,2,3]
Olga Khodakivska[2,3]
Alan D. Legatt[2,3,5]
Puja Patel[1,2,3]
Jillian Rosengard[2,3]
Elayna Rubens[2,3]
William Sugrue[2,3]
Elissa Yozawitz[1,2,3]
Mark F. Mehler[2,5,7]
Karen Ballaban-Gil[1,2,3]
Sheryl R. Haut[2,3]
Rishi Malhotra[2,9]
Solomon L. Moshé[1,2,3,4,5,8]
Alexis Boro[2,3]

[1]*Isabelle Rapin Division of Child Neurology, Albert Einstein College of Medicine, Bronx, NY, USA*
[2]*Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA*
[3]*Comprehensive Einstein/Montefiore Epilepsy Center, Albert Einstein College of Medicine, Bronx, NY, USA*
[4]*Laboratory of Developmental Epilepsy, Albert Einstein College of Medicine, Bronx, NY, USA*
[5]*Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA*
[6]*Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*
[7]*Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY, USA*
[8]*Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY, USA*
[9]*Department of Medicine and Leo M Davidoff Department of Neurological Surgery, Albert Einstein College of Medicine*

[Correction added on November 11, 2020, after first online publication: Rishi Malhotra has been added as an author.]

Correspondence
Aristea S. Galanopoulou MD PhD, Saul R. Korey Department of Neurology, Dominick P. Purpura Department of Neuroscience, Isabelle Rapin Division of Child Neurology, Albert Einstein College of Medicine, 1410 Pelham Parkway South, Kennedy Center Rm 306, Bronx NY 10461, USA.
Email: aristea.galanopoulou@einsteinmed.org

ORCID

Aristea S. Galanopoulou https://orcid.org/0000-0002-0472-2903
David L. McArthur https://orcid.org/0000-0003-3385-1314
Victor Ferastraoaru https://orcid.org/0000-0003-4180-3558
Daniel J. Correa https://orcid.org/0000-0002-6490-9331
Jonathan Gursky https://orcid.org/0000-0002-1632-6107
Isaac Molinero https://orcid.org/0000-0003-1595-546X
Puja Patel https://orcid.org/0000-0002-5895-3926
Jillian Rosengard https://orcid.org/0000-0001-7349-7474
Elissa Yozawitz https://orcid.org/0000-0001-8230-8364
Solomon L. Moshé https://orcid.org/0000-0001-9427-9476

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