Reply to Padhi et al

To the Editor—Coronavirus disease 2019 (COVID-19) is characterized by endotheliitis and vasculitis [1, 2], which has been repeatedly reported to be associated with the intercellular adhesion molecule 1 (ICAM-1) K469E polymorphism, as in coronary artery disease [3], type 1 diabetes [4], and inflammatory bowel disease [5]. In their letter [6], Padhi et al report that ICAM-1 K469E polymorphism was positively correlated with a higher possibility of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and related mortality rate, thus concluding that ICAM-1 variants may play a role in susceptibility to SARS-CoV-2 infections and increased chances of death.

However, it is necessary to interpret this conclusion prudently. Aside from the genetic polymorphism, the uneven infection rate could be influenced by imbalances in the government management ability to deal with public health emergencies (emergency response ability of primary health institutions, information level, international cooperation, implementation of effective isolation measures) [7], the supply of SARS-CoV-2 testing reagents, the willingness of the public for screening, and the scope of vaccination. Similarly, in addition to genetic factors, the diverse mortality rates may be affected by many factors, such as unequal healthcare systems [8], different methods of calculating mortality rates (deaths directly or indirectly related to SARS-CoV-2 infection), preexisting diseases [9], virus variants, and demographic characteristics (male sex and older age are associated with higher mortality rates) [10].

Therefore, based on the considerations above, the study by Padhi et al provides only preliminary assumptions regarding the correlation among ICAM-1 K469E polymorphism, susceptibility to SARS-CoV-2 infection, and related mortality rates. Thus, as the authors noted, a successful case-control study is necessary to explore the associations.

Notes

Financial support. This work was supported by the Key Research and Development Program of Hunan Province (grant 2020SK3011).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Ming Tong,1 Qing Zheng,2 Fang Chen,2 and Yimin Zhu2

1Department of Infectious Diseases, The First Affiliated Hospital of Hunan Normal University (Hunan Provincial People’s Hospital), Changsha, Hunan, China, 2Institute of Emergency Medicine, Hunan Provincial Key Laboratory of Emergency and Critical Care Metabolomics, The First Affiliated Hospital of Hunan Normal University (Hunan Provincial People’s Hospital), Changsha, Hunan, China, and 3Department of Geriatrics, The First Affiliated Hospital of Hunan Normal University (Hunan Provincial People’s Hospital), Changsha, Hunan, China.

References

1. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020; 41:3038–44.
2. Fox SE, Lameira FS, Rinker EB, Vander Heide RS. Cardiac endotheliitis and multisystem inflammatory syndrome after COVID-19. Ann Intern Med 2020; 173:1025–7.
3. Li D, Qu C, Dong P. The ICAM-1 K469E polymorphism is associated with the risk of coronary artery disease: a meta-analysis. Coron Artery Dis 2014; 25:665–70.
4. Kristiansen OP, Nolsøe RL, Holst H, et al; Danish Study Group of IDDM in Childhood. The intercellular adhesion molecule-1 K469E polymorphism in type 1 diabetes. Immunogenetics 2000; 52:107–11.
5. Matsuzawa J, Sugimura K, Matsuda Y, et al. Association between K469E allele of intercellular adhesion molecule 1 gene and inflammatory bowel disease in a Japanese population. Gut 2003; 52:75–8.
6. Padhi S, Sahu S, Pati A, Mohanty A, Panda A. Minor allele of intercellular adhesion molecule-1 (ICAM-1) polymorphism (rs5498 1462A>G) is associated with SARS-CoV-2 infection and related mortality. J Infect Dis 2021.
7. Pradhan D, Biswasroy P, Kumar Naik P, Ghosh G, Rath G. A review of current interventions for COVID-19 prevention. Arch Med Res 2020; 51:363–74.
8. Lawal Y. Africa’s low COVID-19 mortality rate: a paradox? Int J Infect Dis 2021; 102:118–22.
9. Liu H, Chen S, Liu M, Nie H, Lu H. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: a systematic review and meta-analysis. Aging Dis 2020; 11:668–78.
10. Grasselli G, Greco M, Zanella A, et al; COVID-19 Lombardy ICU Network. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med 2020; 180:1345–55.

Received 18 May 2021; editorial decision 18 May 2021; accepted 29 June 2021; published online June 30, 2021. Correspondence: Yimin Zhu, Institute of Emergency Medicine, Hunan Provincial Key Laboratory of Emergency and Critical Care Metabolomics, The First Affiliated Hospital of Hunan Normal University (Hunan Provincial People’s Hospital), Changsha, Hunan 410005, China (cszhyumin@163.com).

The Journal of Infectious Diseases® 2021;224:735
© The Author(s) 2021. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/infdis/jiaz280

Regarding “The Clinical and Economic Burden of Norovirus Gastroenteritis in the United States”

To the Editor—In their recent article, Bartsch et al report the calculated economic costs of rotavirus infection in the United States using a Monte Carlo simulation model [1]. This study importantly
concludes that rotavirus infection produces a heavy economic burden on the healthcare system in the United States. The authors’ Monte Carlo simulation decision tree (Figure 1) evaluates several parameters from established data sources and estimates the cost of norovirus illness through the model. Included in their analysis is productivity loss for both time of illness and if death occurs.

After reviewing the decision tree, we are concerned that an error occurred in either the decision tree figure, the Monte Carlo simulation calculations, or possibly both. Our specific point of concern involves the branch point where a patient lives in the algorithm. In 5 of the 6 times where this branchpoint occurs, the figure indicates that survival is associated with lifetime productivity losses for the patient (labeled 1–5). We believe that death would be associated with lifetime productivity losses and that the figure is incorrect. However, in 1 of the 6 times where this branchpoint occurred, it is death that is associated with lifetime productivity losses (labeled 6). These discrepancies lead us to be concerned that 1 or more of the Monte Carlo simulation calculations could have been run in error.

We think it would be prudent for the authors to reevaluate the decision tree figure and recheck the underlying equations used for their Monte Carlo simulation to clarify if any errors occurred.

Notes

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
hours for the in vivo parasite clearance half-life.

This observation is consistent with numerous laboratory studies showing that artemisinin resistance in *P. falciparum* is associated with loss of ring-stage susceptibility [3–6]. Indeed, this clinical study can be considered as a rather laborious in vivo ring-stage survival assay [4]. The “viability” effect measure is derived from the subsequent ex vivo growth of malaria parasites following different drug exposures. The reduction in viability reflects the damage done by the drug exposure in vivo, and any parasite sequestered antimalarial drug in the ex vivo culture, and the continued effects of that damage. This was compared with the serial parasite densities at the time of blood sampling, which are used to provide a parasite clearance rate [7].

The serial quantitative polymerase chain reaction derived parasitemia profiles shown by Rebelo et al [1], fig 3 strongly suggest continued input into the circulation from ongoing schizogony [2, 8]. This explains why parasite densities in blood do not fall for approximately 8 hours. The most commonly used parasite clearance rate estimator explicitly accounts for this lag-phase [7]. In contrast, the viability estimates use blood samples containing circulating parasites and high artesunate concentrations, and much of the effect is observed by the first sampling time point (2 hours). Taking a blood sample and diluting out the antimalarial drug does not instantly stop it working. Parasites take time to die, so it is not surprising that the ex vivo assessment over days suggests greater “killing” than the densities of parasites in the blood at the time of sampling would suggest, but to conclude that “parasite resistance to artemisinins may have a more profound effect on in vivo drug efficacy than previously appreciated” is not warranted. If this means that parasite killing by artemisinins has been underestimated, then it is not compatible with clinical trial observations of the relationship between dosing, duration of treatment, and outcome [9].

The title of the article, “Parasite viability as a superior measure of antimalarial drug activity in humans” [1], suggests a significant advance, but it is not clear why or how it would be used to assess antimalarial drugs. It is stated that “the use of parasite clearance to measure drug activity and to inform decisions about drug development should be reconsidered in view of these new insights.” It is unclear what these insights are and whether these difficult and laborious serial in vivo studies would offer any advantage over the currently used, simple ring-stage in vitro tests [4, 6], which identify the loss of ring-stage activity in artemisinin-resistant parasites very well.

The meaning and predictive value of the estimated half-life from the viability studies are also unclear. The observed log-linear decline in parasite densities in blood after artemisinin treatment provides a clearance half-life of about 3.5 hours, which, if continued, would result in an approximately 16 000-fold decrease per life-cycle. This predicts that ≥5 days of artemisinin monotherapy (regardless of dosing frequency) are needed to clear an infection with a biomass of $10^{15}$ parasites. This matches clinical observations [9]. But what is the meaning or utility of the half-life estimated from the viability study? Interpreted literally, a continued half-life of 0.75 hours would kill all the infecting malaria parasites within a day, which clearly does not match clinical observations.

As for dose finding, the results presented in [1] fig 3 suggest that the fits to the serial viability log-linear declines are poor and, thus, the derived viability half-lives are imprecise in comparison with the parasite clearance profiles. Indeed, it is unclear whether declines are exponential and, therefore, whether the model is appropriate. This does not give confidence that a concentration-effect (dose-response) estimate derived from these