Effect of Ivermectin in the Treatment of Coronavirus Disease 2019: A Trial Sequential Analysis Highlights the Requirement of Additional Randomized, Controlled Trials

To the Editor—We read with great interest the recent article by Roman et al [1] in which the authors explored the potential role of ivermectin in the treatment of coronavirus disease 2019 (COVID-19). They included 10 randomized, controlled trials (RCTs), totaling 1173 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–infected cases and investigated the effect of ivermectin on all-cause mortality, hospital length of stay, adverse events, and viral clearance.

The authors reported that additional ivermectin administration had no meaningful effect on reducing all-cause mortality, hospital length of stay, adverse event, or viral clearance in the COVID-19 patients.

We did not determine whether an adequate number of RCTs had been conducted before doing a data search or whether additional RCTs are required to conclude the role of ivermectin in the treatment of COVID-19, if any. We believe the research community would be very much interested in our search results.

Meta-analyses using a small number of trials or patients increase the chances of false-positive (type I error) or false-negative (type II error) results, leading to erroneous conclusions. In recent years, trial sequential analysis (TSA) has emerged as a promising statistical tool for addressing these challenges. The TSA uses various methodologies to determine the monitoring boundaries, required information size, and futility boundaries. The TSA outcome is more reliable than the usual meta-analysis results because the calculation of information size and threshold adjustment decreases early false-positive results. When the cumulative z curve reaches the required information size line or passes the monitoring or futility boundary, it indicates that enough trials have been done to derive a valid conclusion and that additional clinical
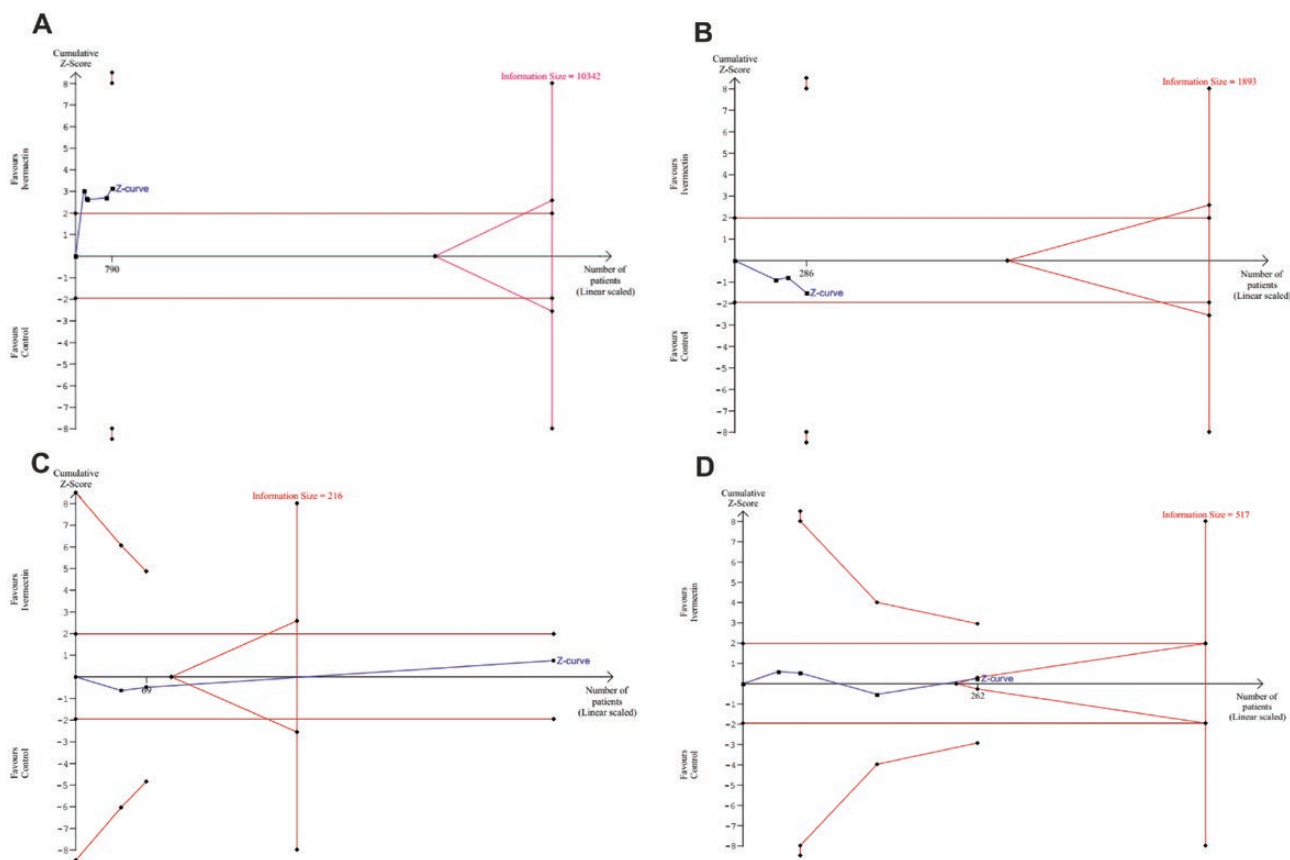

Figure 1. Trial sequential analysis for calculation of the required information size to accept or reject the possible role of ivermectin in coronavirus disease 2019: all-cause death *(A)*, duration of hospital stay *(B)*, adverse event *(C)*, and viral clearance *(D)*. On the left, the red, inward-sloping lines are the trial sequential monitoring boundaries. On the right, the red, outward-sloping lines are the futility region. The solid blue line is the cumulative z curve.

trials are unlikely to affect the inference [2–4].

We used the data from Roman et al [1] and performed TSA to study the efficacy of ivermectin on primary and secondary treatment outcomes in COVID-19 patients. We estimated the required information size to reject or support the role of ivermectin to be 33.33% relative risk reduction, maximum type I error of 1%, and maximum type II error of 10%, which yielded different required sample sizes for the studied outcome (all-cause mortality, n = 10342; hospital stay, n = 1893; adverse events, n = 216; viral clarence, n = 517; Figure 1). The cumulative z curve crossed the required information size predicted for adverse events (Figure 1C) and futility boundary for virus clearance (Figure 1D), which indicates that enough trials have already been conducted to conclude no role of ivermectin in improving adverse events or viral clarence. The cumulative z curve for all-cause mortality and length of hospital stay analyses did not cross the monitoring or futility boundaries, nor did it reach the required information size line, indicating that more trials are needed to reach a definitive conclusion for all-cause death (Figure 1A) and hospital stay outcome (Figure 1B). The present meta-analysis included 1173 COVID-19 cases; thus, additional RCTs in approximately 9170 COVID-19 cases (4585 patients in each intervention group) would be required to yield a conclusive finding. Based on the TSA results, we propose that more RCTs in different populations be conducted to reach the requisite event size for drawing a definitive conclusion about the importance of ivermectin in the treatment outcome of COVID-19.

Notes

Sunali Padhi, Abhijit Pati, and Aditya K. Panda

Department of Bioscience and Bioinformatics, Khallikote University, Berhampur, Odisha, India

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Correspondence: A. K. Panda, Department of Bioscience and Bioinformatics, Khallikote University, Sat-Chit-Ananda Vihar, Berhampur, Odisha, India, 761008 (adityarmrc@gmail.com, akpanda@khallikoteuniversity.ac.in).