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The effectiveness of high-dose intravenous vitamin C for patients with coronavirus disease 2019: A systematic review and meta-analysis

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ABSTRACT

Objectives: Vitamin C has anti-inflammatory effects. This review aimed to investigate the therapeutic effect of high-dose intravenous vitamin C (HDIVC) in patients with coronavirus disease 2019 (COVID-19).
Methods: The following key phrases were searched for article inclusion: "Vitamin C OR ascorbic acid" AND "COVID-19 OR coronavirus disease 2019 OR severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2". Articles that utilized HDIVC for the management of patients with COVID-19 were included, whereas review articles and case reports were excluded from this review. Moreover, we performed a meta-analysis to evaluate whether HDIVC can reduce the length of hospital stay and in-hospital mortality rate of patients with severe COVID-19.
Results: In total, eight articles were included in this review, and five studies were included in the meta-analysis. The length of hospital stay was not significantly different between the HDIVC and control groups. Also, although our meta-analysis showed a tendency for HDIVC to reduce the in-hospital mortality rate in patients with severe COVID-19, the in-hospital mortality rate was not significantly different between patients treated with HDIVC and those who did not receive HDIVC.
Conclusions: Evidence supporting the therapeutic use of HDICV in COVID-19 patients is lacking. Further studies are required for drawing a clear conclusion on this topic.

1. Introduction

Since the first confirmed case of the coronavirus disease 2019 (COVID-19) in late 2019, COVID-19 has rapidly spread worldwide in just 2–3 months and eventually became a global health issue.[1] Majority of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have mild symptoms, such as cough, sore throat, runny nose, headache, body ache, and loss of taste, and do not require hospitalization.[2,3] However, pneumonia is a potential complication of COVID-19, and 10–20% of patients suffer from severe pneumonia and acute respiratory distress syndrome, which can lead to sepsis or multiple organ failure.[4] Patients with mild to moderate COVID-19 require proper management to prevent disease aggravation. Those with severe symptoms or systemic complications need intensive care to reduce the risk of mortality. Thus far, despite much effort, effective therapeutic medications have not been developed and the main management for COVID-19 patients is supportive treatment.

In severe COVID-19 patients, pro-inflammatory cytokines are assumed to be activated.[5] It is suggested that chronic inflammation is the main risk factor for increased COVID-19 morbidity and mortality.[5] Vitamin C has a number of beneficial anti-inflammatory effects by modulating nuclear transcription factor kappa B, inhibiting proinflammatory cytokine production, neutralizing reactive oxygen species, and assisting immunomodulation as a cofactor of various biosynthetic pathways in the immune system.[6–8] In addition, vitamin C protects neutrophils and phagocytes avoiding damage after oxidative burst and activates a caspase-dependent cascade that facilitates programmed apoptosis and inhibits necrosis.[9,10]

During the infectious state, especially lung infection or a critically ill state after the infection, oxidative stress becomes prominent.[11,12] Vitamin C has antioxidant properties that increases in patients with infection, which frequently reduces vitamin C levels, and in patients with pneumonia or critical illness, it suppresses inflammation and improves immunoregulatory function.[13–15] In addition, vitamin C can

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shorten the duration of infection in the respiratory tract and regulate disease severity.[16,17] Several studies have recommended the use of vitamin C in patients with respiratory tract infections or critical illnesses for its therapeutic advantages,[18,19] in particular, high-dose intravenous vitamin C (HDIVC) that can reduce the severity of patients' symptoms, shorten the length of hospitalization and duration of mechanical ventilation, and result in vasopressor sparing and reduction of in-hospital mortality rate.[20–23]

Vitamin C can be supplied via oral or intravenous (IV) routes. However, the use of oral vitamin C is limited because of its low absorption rate.[24,25] Majority of orally administered vitamin C is flushed out of the body without being used, and its peak plasma concentration is very low,[26] making it difficult to achieve its therapeutic plasma level. In contrast, the IV administration of vitamin C can reach the therapeutic level quickly with 30–70 times higher peak plasma concentration compared with that of oral vitamin C by bypassing the limits of intestinal transporters.[27]

HDIVC has also been administered in patients with COVID-19 in many previous studies that evaluated the effectiveness of HDIVC in patients with COVID-19 in different settings with various clinical findings and results.[28–36] In 2021, Zhang et al.[34] conducted a randomized controlled trial pilot study comparing the effects of HDIVC with placebo to determine whether HDIVC infusion was effective against severe COVID-19. HDIVC was not effective in reducing in-hospital mortality and improving invasive mechanical ventilation-free days in 28 days. However, HDIVC was effective in improving the arterial partial pressure of O2/fraction of inspired O2 ratio, suggesting that HDIVC can have an oxygenation benefit in patients with severe COVID-19. In addition, a meta-analysis protocol to investigate the therapeutic effect of vitamin C on COVID-19 has been published. According to a meta-analysis protocol by Huang et al. in 2021,[36] vitamin C reduces the duration of ICU hospitalization in pneumonia patients by an average of 8% and shortens the duration of mechanical ventilation. Therefore, it was reported that HDIVC could be successfully applied to the treatment of patients with COVID-19-related pneumonia. Previous studies have yielded not only similar findings but also contradictory findings, and thus the therapeutic effects of HDIVC in COVID-19 patients remain unclear. This review aims to present the findings from recent studies on the possible role of high-dose vitamin C in the management of patients with COVID-19.

2. Methods

2.1. Search strategy

In this study, the PICO (population, intervention, comparison, outcome) model for establishing the search strategy was set as follows: (1) patients or population, patients with severe COVID-19; (2) Intervention, HDIVC; (3) Comparison, placebo or usual care; (4) Outcome, in-hospital mortality rate and length of hospital stay. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Articles published between January 1, 2019, and July 29, 2021, were searched in the PubMed, Cochrane, Embase, and Web of Science databases using the following key phrases: "Vitamin C OR ascorbic acid" AND "COVID-19 OR coronavirus disease 2019 OR severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2."

2.2. Inclusion and exclusion criteria

The following studies were included in this study: (1) studies in which HDIVC (daily total dose ≥2 g) was administered to patients with severe COVID-19, (2) studies evaluating in-hospital mortality rate or length of hospital stay, (3) studies comparing HDIVC to placebo or control groups, (4) studies written in English. The exclusion criteria were as follows: (1) review articles, case report, protocol, and conference presentation.

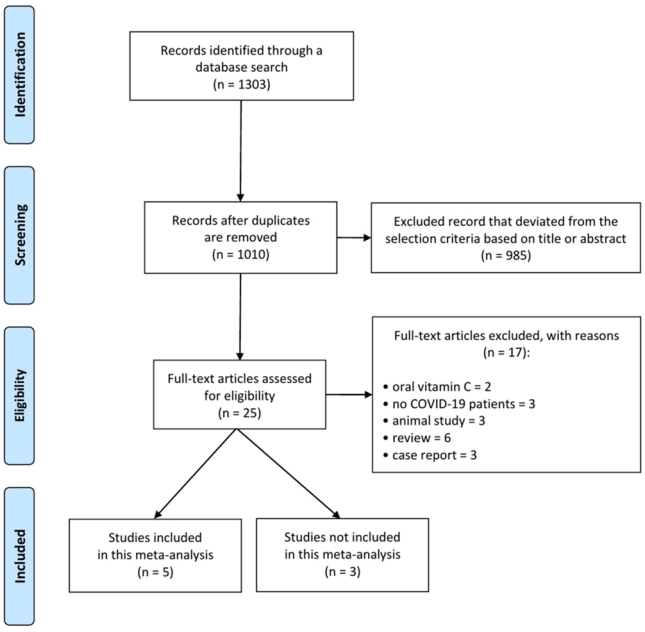

Fig. 1. Flowchart showing the search results.

2.3. Data extraction

Data for meta-analysis were independently investigated by two researchers (M.C.C and Y.J.C). Duplicate studies were excluded, and studies that met the eligibility criteria were selected. Studies were evaluated for eligibility by reviewing the title and abstract. After reading the full text, studies were finally selected for inclusion in the meta-analysis, and discrepancies were resolved through discussion.

2.4. Quality assessment

Quality assessment for randomized trials was conducted using the Cochrane Collaboration tool and for retrospective studies, using the Newcastle-Ottawa quality assessment scale (study quality: low (0−3), moderate (4−6), high (7−9)).[37,38]

2.5. Statistical analysis

The extracted data were analyzed using Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, NJ, USA). A heterogeneity test was conducted using the I^2 statistic to evaluate the extent of inconsistency in the obtained results. If the I^2 value was $> 50\%$, data were considered to have substantial heterogeneity, and a random-effects model was used for data analysis. In contrast, if the I^2 value was $\leq 50\%$, then the pooled data were considered homogeneous, and a fixed-effects model was applied for data analysis. We analyzed the odds ratio (OR) for in-hospital mortality rate (with 95% confidence interval [CI]) and the standard mean difference (SMD) (with 95% CI) for length of hospital stay. Statistical significance was set at $p < 0.05$.

2.6. Publication bias

Funnel plot and Egger's test were used to confirm publication bias of studies included in meta-analysis. A funnel plot is a graph that shows the relationship between the sample size and the effect size, and it is easy to visually check whether the distribution is symmetrical with respect to the pooled estimate. Egger's test was performed to test whether the funnel plot is symmetric. The Comprehensive Meta-Analysis version 2 was used for funnel plot and Egger's test. In the result of Egger's test, when the p-value was > 0.05, it was considered that there was no

Table 1
Key published studies on the role of high-dose vitamin C in the treatment of COVID-19.

First author, year	Study design	Number of patients (E/C)	HDIVC protocol	Treatment other than HDIVC	Outcome measurement	Summary of outcome	Number of death case (E/C)
Gao, 2021 (27)[a]	Retrospective	46/30	12 g/day for 1st day, 6 g/day for the 2nd to 5th days, for a total of 5 days	Antibiotics, corticosteroids, immunomodulators and other antivirals (e.g., Lopinavir/Ritonavir, Ribavirin)	Mortality rate, oxygen support status	Reduced mortality rate in severe COVID-19 patients after HDIVC. Improved oxygen support status after HDIVC	1/5
JamaliMoghadamSiahkali, 2021 (28)[a]	RCT	30/30	6 g/day(1.5 g every 6 h) for 5 days	Lopinavir/Ritonavir 400/100 mg twice daily and single dose of oral hydroxychloroquine (400 mg) on the first day of hospitalization	Mortality rate, length of hospital stay, length of ICU stay, oxygen saturation	Longer hospital stay in the control group, and no significant difference in mortality rate, length of ICU stay, and oxygen saturation	3/3
Kumari, 2020 (29)[a]	RCT	75/75	50 mg/kg/day; treatment duration was not described	Dexamethasone and prophylactic antibiotics	Mortality rate, length of hospital stay, need for mechanical ventilator	Shorter length of hospital stay in the HDIVC group; no difference in mortality rate and need for mechanical ventilator	7/11
Li, 2021 (30)[a]	Retrospective	8/24	9 g/day (1.5 g every 6 h) for 4 days	Hydrocortisone 50 mg every 6 h and thiamine 200 mg every 12 h for a total course of 4 days	Mortality rate, length of hospital stay, length of ICU stay	Higher mortality rate in the HDIVC group; no difference in length of hospital stay and ICU stay	7/19
Suna, 2021 (31)	Retrospective	153/170	2 g/day; treatment duration was not described	No information	Mortality rate, length of hospital stay, readmission rate, ICU admission, and advanced oxygen support	No significant difference	17/24
Thomas, 2021 (32)	RCT	48 (HDIVC)/58 (zinc)/58 (HDIVC+zinc)/ 50 (control)	8 g/day (divided over 2–3 times a day) for 10 days	If necessary, glucocorticoid	Symptoms related to COVID-19, mortality rate, hospitalization rate	No significant difference	1(HDIVC)/0 (zinc) 2 (HDIVC+zinc)/ 0 (control)
Zhang, 2021 (33)[a]	RCT	27/29	12 g/day for 7 days	Oseltamivir + azithromycin (if necessary, Piperacillin/tazobactam or hydrocortisone (1 mg/kg/day))	Mortality rate, length of hospital stay, length of ICU stay	No significant difference	6/11
Zhao, 2021 (34)	Retrospective	55/55	100 mg/kg for 7 days	Antiviral therapy (if necessary, glucocorticoid)	Rate of transition to severe state, duration of systematic inflammatory response	Lower rate of transition to severe state and shorter duration of systematic inflammatory response in the HDIVC group	No information

E, experimental group; C, control group; HDIVC, high-dose intravenous vitamin C; COVID-19, coronavirus disease 2019; ICU, intensive care unit; RCT, randomized controlled trial

[a] Studies that included for meta-analysis

publication bias.

3. Results

3.1. Study selection and characteristics

A total of 1303 articles were identified as potentially relevant articles in the primary literature search (Fig. 1). After reviewing the titles and abstracts and assessing their eligibility based on the full text, eight articles were included in this review (Table 1) (randomized controlled trials [RCT], 4[29,30,33,34]; retrospective studies, 4[28,31,32,35]). Of the included articles, five were used for meta-analysis. In the five studies included in the meta-analysis, 186 participants were included in the HDIVC group and 188 participants were included in the control group. In three studies not included in the meta-analysis, 256 participants in the HDIVC group and 275 participants in the control group were included. In all studies, the dose of HDIVC administered to patients with COVID-19 was 50 mg or more per day.

3.2. Results of the meta-analysis

In the meta-analysis to analyze the effectiveness of HDIVC in patients

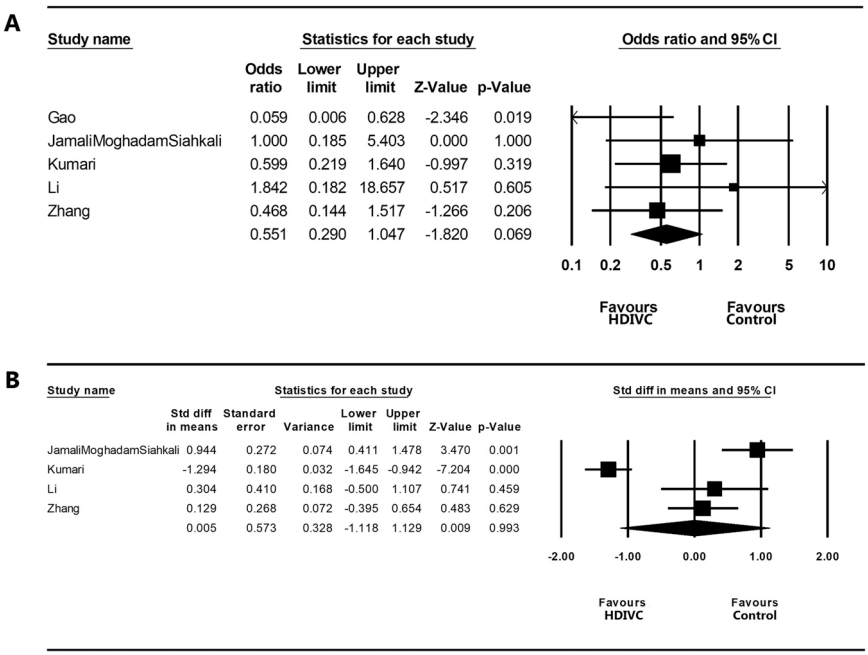

Fig. 2. Results of the meta-analysis on the difference of (A) in-hospital mortality rate and (B) length of hospital stay between the high-dose intravenous vitamin C (HDIVC) group and control group. Meta-analysis was performed with Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, NJ, USA).

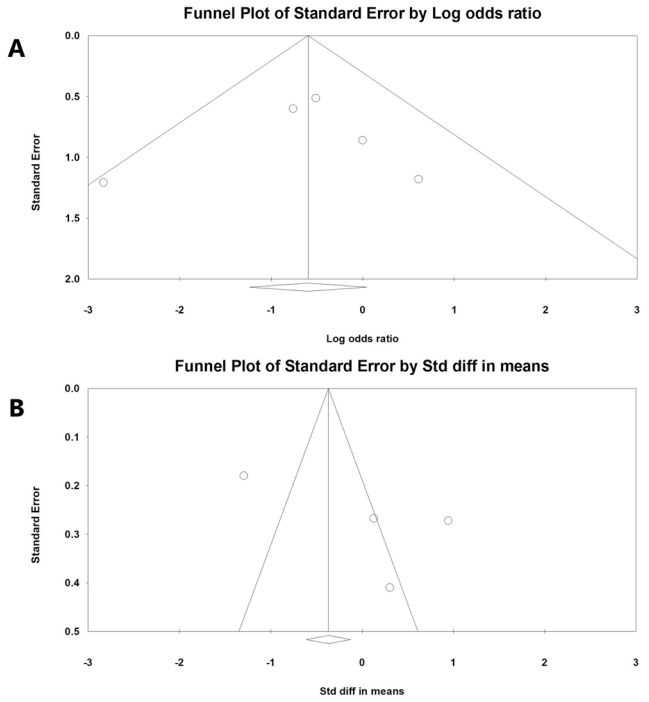

Fig. 3. Graphic funnel plots of the included studies. Comparison of (A) in-hospital mortality rate and (B) length of hospital stay between the high-dose intravenous vitamin C (HDIVC) and control groups.

with severe COVID-19, 186 patients who received treatment with HDIVC and 184 patients who received standard care only without HDIVC were recruited from five studies (three RCTs[29,30,34] and two retrospective studies[28,31]). For the meta-analysis of in-hospital mortality rate, a fixed-effects model was adopted (I^2 = 20.877) (Fig. 2A). In-hospital mortality rate was not significantly different between the HDIVC and control groups (OR = 0.551 [95% CI = 0.290–1.047], p = 0.069). However, the in-hospital mortality rate of patients treated with HDIVC tended to be lower than that of patients who did not receive HDIVC. In the meta-analysis of the length of hospital stay, a random-effects model was used (I^2 = 94.638) (Fig. 2B). The length of hospital stay was not significantly different between the HDIVC and control groups (SMD = 0.005 [95% CI = −1.118 to 1.129], p = 0.993). The risk of publication bias was determined using a funnel plot and Egger's test. Funnel plots of the in-hospital mortality rate and length of hospital stay were visually symmetrical (Fig. 3). In Egger's test, p-values were 0.404 and 0.118 in the analyses of in-hospital mortality rate and length of hospital stay, respectively. Therefore, a significant publication bias was unlikely to occur.

3.3. Review of the studies that were not included in the meta-analysis

Summarizing the results of three studies that were not included in the meta-analysis, two studies (Thomas et al. and Suna et al.'s studies) evaluated the effectiveness of HDIVC in COVID-19 patients without considering disease severity.[32,33] In-hospital mortality and length of hospital stay (hospitalization rates) were not significantly improved after the treatment with HDIVC. The other study (Zhao et al.'s study) analyzed the effectiveness of HDIVC in patients with moderate COVID-19.[35] Fifty-five patients treated with HDIVC showed significantly shorter duration and lower occurrence of systemic inflammatory response syndrome compared to that of 55 patients in the control group.

3.4. Adverse effects

In all eight included studies,[28–35] the rate of occurrence of adverse effects after the treatment of COVID-19 between the HDIVC and control groups was not significantly different. In addition, specific adverse events related to HDIVC treatment, such as headache, nausea, bloating, or abdominal discomfort, have not been reported.

3.5. Assessment of the study quality

In the assessment of quality of included studies, of four RCTs,[29,30,33,34] all studies were rated as having a low risk of bias in the random sequence, incomplete outcome data, and selective reporting domains

Table 2
Results of the quality assessment using of the Cochrane Collaboration tool (A) and the Newcastle-Ottawa quality assessment scale (B).

Randomized trials (A)	Quality criteria	Selection bias		Performance bias		Detection bias	Attrition bias	Reporting bias		
		Random sequence generation	Allocation concealment	Blinding of participants and personnel		Blinding of outcome assessment	Incomplete outcome data	Selective reporting		
	JamaliMoghadamSiahkali, 2021 (28)	Low risk	Unclear	High risk		High risk	Low risk	Low risk		
	Kumari, 2020 (29)	Low risk	Unclear	Unclear		High risk	Low risk	Low risk		
	Thomas,2021 (32)	Low risk	Unclear	Unclear		High risk	Low risk	Low risk		
	Zhang, 2021 (33)	Low risk	Low risk	Low risk		Low risk	Low risk	Low risk		
Retrospective studies (B)	Quality criteria	Selection				Comparability	Exposure			Total (9)
		Is case definition adequate? (1)	Representativeness of the cases (1)	Selection of controls (1)	Definition of controls (1)	Comparability on basis of design or analysis (2)	Ascertainment of exposure (1)	Same method of ascertainment for cases and controls (1)	Nonresponse rate (1)	
	Gao, 2021 (27)	★	★	★	★	★★	★	★	★	9
	Li, 2021 (30)	★	★	★	★	★★	★	★	★	9
	Suna, 2021 (31)	★	★	★	★	★★	★	★	★	9
	Zhao, 2021 (34)	★	★	★		★★	★	★		9

(Table 2). However, only one RCT (Zhang et al.'s study[34]) was rated as having a low risk of bias in the domains of allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. All four retrospective studies[28,31,32,35] were rated as nine stars, which are considered of high quality.

4. Discussion

Although theoretical evidence supporting the use of HDIVC in patients with infectious disease is sufficient and some previous studies showed positive therapeutic effect of HDIVC, in our review, we hardly found the prominent effectiveness of HDIVC in COVID-19 patients.

In the meta-analysis, although the in-hospital mortality rate tended to be reduced after HDIVC in severe COVID-19 patients, the in-hospital mortality rate was not significantly different between patients treated with HDIVC and those who did not receive HDIVC. Also, the length of hospital stay was not significantly different between the HDIVC and control groups. In addition, the studies that were conducted without considering disease severity showed no better prognosis after the treatment with HDIVC. Although Zhao et al. showed the positive therapeutic effect in moderate COVID-19 after the treatment with HDIVC, its reliability is low due to lack of studies that showed positive therapeutic effect of HDIVC.

In patients with moderate to severe COVID-19, pro-inflammatory cytokines and systemic inflammation are largely increased, which damages the alveolar capillaries and multiple organs.[39,40] It was reported that the anti-inflammatory effect of HDIVC might reduce inflammation in the body of COVID-19 patients and might prevent the transition to a severe state or death.[6–8] Despite some positive therapeutic findings in COVID-19 patients, the main conclusion of our review including that of our meta-analysis is that the use of HDIVC is not helpful for treating patients with COVID-19. Conversely, combinatorial use of steroids or tocilizumab with HDIVC can help to modulate inflammation in patients with COVID-19.[41]

5. Conclusions

Currently, there is no evidence to support the role of high-dose intravenous vitamin C in the management of patients with COVID-19 due to infection with SARS-CoV-2. There have been few controlled studies on this topic. With the recent developments in vaccines to prevent COVID-19 and the ongoing clinical trials to investigate specific antiviral therapies, it is unclear whether there will be future controlled clinical studies on the therapeutic role of high-dose intravenous vitamin C in COVID-19. To reach an accurate conclusion on this issue, further clinical trials with large sample sizes should be performed. In addition, our review of the literature indicates that heterogeneous doses of vitamin C can affect the results after the treatment. Thus, studies to evaluate the most appropriate dose for patients with COVID-19 should be conducted. Furthermore, the term "severe COVID-19" was not clearly defined in the; therefore, the severity of COVID-19 cases included in our analysis is heterogeneous. Severity of COVID-19 cases may change the effectiveness of HDIVC; hence, this variable should also be evaluated in the future.

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CRediT authorship contribution statement

Sang Gyu Kwak: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing – original draft, Writing – review & editing, **Yoo Jin Choo:** Project

administration, Visualization, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing – original draft, Writing – review & editing, **Min Cheol Chang:** Supervision, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing – original draft, Writing – review & editing.

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Declaration of Competing Interest

The authors report no declarations of interest.

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