LETTER TO THE EDITOR

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The effect of curcumin on the risk of mortality in patients with COVID-19: A systematic review and meta-analysis of randomized trials

The coronavirus disease 2019 (COVID-19) pandemic is far from bygone, with the emergence of newer variations of concern of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While the worldwide vaccine rollout has progressed at a breakneck pace, the hunt for new safe, effective, and targeted treatments should continue in parallel due to the frequent occurrence of breakthrough cases. Curcumin is one such natural polyphenolic compound with multiple benefits, including antiviral, anti-inflammatory, anticoagulant, antiplatelet, and cytoprotective, which have been demonstrated to be advantageous in reducing the progression of several inflammatory illnesses (Rattis, Ramos, & Celes, 2021). The aforementioned effects have made curcumin one of the potential treatment options for patients with COVID-19. Since the pathophysiology of COVID-19 is known to involve life-threatening inflammatory reactions, cytokine storms, and coagulopathy, curcumin can be advantageous due to its anti-inflammatory effects via the inhibition of inflammasome formation (Yin et al., 2018). In addition, curcumin also demonstrates antiviral effects via its ability to bind to the viral primary protease (Mpro) enzyme of SARS-CoV-2, which is required for viral replication. Curcumin also prevents viral attachment and passage into the host cell with great potency (Dourado et al., 2021). The ability of curcumin in inhibiting the virus-receptor interaction is in two ways, according to modeling studies: it inhibits both the spike protein and the ACE2 receptor (Manoharan et al., 2020). Previously in this journal, the findings of the randomized trial reported by Hassaniazad et al. (2021) suggest that curcumin can accelerate the recovery of acute inflammatory phase in patients with COVID-19 by modulating inflammatory immune responses. Nevertheless, the mortality benefits of curcumin in patients with COVID-19 were not investigated in the aforementioned trial. Several controlled trials have been performed to validate the mortality benefits of curcumin in patients with COVID-19, and we aimed to summarize their overall efficacy in terms of mortality reduction in a systematic review and meta-analysis.

A systematic literature search with no language restriction was performed in multiple electronic databases, including PubMed, Cochrane Central Register of Controlled Trials, Google Scholar, Scopus, and pre-print servers (medRxiv, Research Square, SSRN) to identify eligible studies published from inception to January 20, 2022. Two investigators (CSK and DSR) independently performed the literature screening to identify eligible studies. We adopted the following search strategy: (curcumin OR curcuma OR diferuloylmethane OR turmeric) AND (COVID-19 OR SARS-CoV-2 OR coronavirus). In addition, the reference lists of relevant articles were also reviewed to search for additional studies. Studies eligible for inclusion were randomized controlled trials that compared the mortality outcomes between the use and nonuse of curcumin (at any dose and in any dosage form) in patients with COVID-19. We excluded single-arm trials, randomized trials that did not report mortality outcomes, and randomized trials with zero mortality events in the intervention and control arms.

The outcome of interest was all-cause mortality. Each included study was independently evaluated by two investigators (CSK and DSR), who also extracted the study characteristics. Study characteristics extracted included the first author's surname, year of publication, study design, the country where the trial was performed, mean/median age of patients, the regimen of curcumin, the regimen of comparative agents, number of deaths in the intervention arm, and number of deaths in the control arm. Two investigators (CSK and SSH) assessed the risk of bias of the randomized trials included with Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), which is a standardized method for assessing potential bias in reports of randomized interventions (Sterne et al., 2019). RoB 2 is structured into a fixed set of domains of bias, which includes "randomization", "deviations from intervention", "missing outcome data", "measurement of the outcome", and 'selection of the reported results. A proposed judgement about the risk of bias arising from each domain is generated by an algorithm, where judgment can be "Low" or "High" risk of bias or express 'Some concerns'. A random-effects model was used to estimate the pooled odds ratio for all-cause mortality with the use of curcumin relative to nonuse of curcumin, at 95% confidence intervals. We examined the heterogeneity between studies using the I^2 statistics and the χ^2 test, with 50% and significance at $p < .10$, respectively, indicating substantial heterogeneity. All analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Our literature search yielded 764 records. After deduplication and application of the eligibility criteria, five relevant articles were shortlisted for inclusion through full-text examination. Of these, two studies were excluded since they reported no mortality events. Eventually, three randomized trials (Pawar et al., 2021; Tahmasebi et al., 2021; Valizadeh et al., 2020) were included for this meta-analysis, with a total of 260 patients with COVID-19. Details of the included trials are depicted in Table 1.

TABLE 1 Characteristic of included studies

Study	Study design	Country	Age (median/mean)	Regimen of curcumin in the intervention group	Regimen of comparator intervention in the control group	Mortality events		Overall risk of bias[a]
						Curcumin users (n/N; %)	Noncurcumin users (n/N; %)	
Pawar et al. (2021)	Randomized, double-blind, controlled trial	India	N/A	Curcumin 525 mg twice daily for 14 days (plus piperine)	Probiotic	2/70; 2.9	11/70; 15.7	Low
Valizadeh et al. (2020)	Randomized, double-blind, placebo-controlled trial	Iran	Curcumin users = 53.3 Noncurcumin users = 51.4	Nano-curcumin 160 mg daily for 14 days (plus standard of care)	Placebo (plus standard of care which consisted of interferon beta-1b, bromhexine, and atorvastatin)	4/20; 20.0	8/20; 40.0	Low
Tahmasebi et al. (2021)	Randomized, double-blind, placebo-controlled trial	Iran	N/A	Nano-curcumin 80 mg twice daily for 21 days	Placebo	1/40; 2.5	6/40; 15.0	Low

[a]Risk of bias was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials.

The three included trials (Pawar et al., 2021; Tahmasebi et al., 2021; Valizadeh et al., 2020) which investigated the effect of the use of curcumin on the risk of mortality in patients with COVID-19 were randomized, double-blind, controlled trials. Two of the included trials (Tahmasebi et al., 2021; Valizadeh et al., 2020) were performed in Iran, whereas the remaining one trial (Pawar et al., 2021) was performed in India. The regimen of curcumin administered differed across the three trials: in the trials by Valizadeh et al. (2020) and Tahmasebi et al. (2021), curcumin was administered orally as nano-curcumin at a dose of 160 mg daily for 14 and 21 days, respectively, whereas, in the trial by Pawar et al. (2021), curcumin was administered orally at a dose of 525 mg twice daily for 14 days. The overall risk of bias as assessed by RoB 2 is presented in Table 1. All included trials (Pawar et al., 2021; Tahmasebi et al., 2021; Valizadeh et al., 2020) had an overall low risk of bias (low risk of bias in all the domains assessed).

The meta-analysis of three trials (Pawar et al., 2021; Tahmasebi et al., 2021; Valizadeh et al., 2020) revealed significantly reduced odds of mortality with the use of curcumin relative to the nonuse of curcumin in patients with COVID-19. The estimated effect indicates mortality benefits (Figure 1; pooled odds ratio = 0.23; 95% confidence interval 0.09 to 0.58, $I^2 = 0\%$, $p = .65$, $n = 260$), with adequate evidence to reject the model hypothesis of "no significant difference" at the current sample size.

To the best of the authors' knowledge, this is the first systematic review and meta-analysis that summarized the evidence from randomized trials regarding the effect of the use of curcumin on the risk of mortality in patients with COVID-19. Our findings indicate that oral curcumin administration as adjuvant therapy in patients with COVID-19 could significantly reduce their risk of mortality while hospitalized.

Indeed, few researchers have discussed the potential for curcumin to be repurposed as an innovative therapeutic agent for the treatment of COVID-19 (Soni et al., 2020; Zahedipour et al., 2020). As a prominent immune modulator, the mortality benefits of curcumin could stem primarily from its ability to suppress the expression of multiple pro-inflammatory cytokines in patients with COVID-19 via the inhibition of inflammasome formation. Indeed, in the trial by Valizadeh et al. (2020), the mRNA expression of interleukin-1β and interleukin-6 were dramatically decreased in patients with COVID-19 after the administration of nano-curcumin. Moreover, in the trial by Tahmasebi et al. (2021), the number of Th17 cells and gene expression and serum levels of Th17-mediated cytokines significantly reduced upon administration of nano-curcumin in patients with COVID-19 randomized to the intervention arm.

Nevertheless, when the included trials were analyzed individually, only the trial by Pawar et al. (2021) demonstrated significantly reduced risk of mortality with curcumin, which could be due to the coadministration of piperine which acts to improve the absorption of curcumin (Han, 2011). On the other hand, the antithrombotic effects of curcumin in patients with COVID-19, which could also contribute to the mortality benefits, should be investigated further, based on the findings in the trial by Pawar et al. (2021), which reported that patients in the intervention arm had near-normal INR, while patients in the control arm had values lower than the control.

FIGURE 1 Pooled odds ratio for all-cause mortality with the use of curcumin relative to nonuse of curcumin in patients with COVID-19
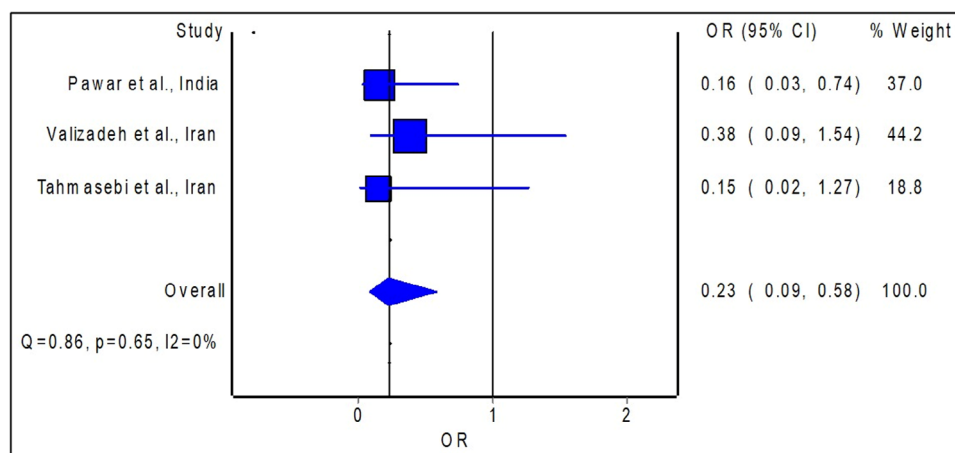
Several limitations should be considered while discussing the findings of our study. First, our systematic review and meta-analysis included only three trials with a small sample size. Further large-scale trials are needed to confirm our findings. Nevertheless, we believe it is important to disseminate our findings to stimulate more investigations on curcumin in patients with COVID-19. Second, all of the included trials were conducted in Asian countries, where dietary regimes habitually include curcuminoids, and thus the generalizability of our findings might be limited. It would be interesting to investigate the effects of curcumin in Western countries where the baseline dietary conditions might be different. Third, the mortality reduction with curcumin as reported in our meta-analysis may be exaggerated (relative risk reduction of 77%). Future trials investigating the efficacy of curcumin in COVID-19 should recruit more participants to produce more precise mortality estimates and also preferably adjust for covariates that could confound the mortality estimates.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

Chia Siang Kow[1,2] 🔟
Dinesh Sangarran Ramachandram[2]
Syed Shahzad Hasan[3,4]

[1]School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia
[2]School of Pharmacy, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia
[3]School of Applied Sciences, University of Huddersfield, Huddersfield, UK
[4]School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia

Correspondence
Chia Siang Kow, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia.
Email: chiasiang_93@hotmail.com

ORCID
Chia Siang Kow 🔟 https://orcid.org/0000-0002-8186-2926

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