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Systematic Review

Impact of Zinc Supplementation on Mortality and ICU Stay in COVID-19 Patients: A Systematic Review and Meta-analysis

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Abstract

Background: The COVID-19 pandemic has affected healthcare globally. Vitamins supplementation has gained attention for adjunctive therapy. In particular, zinc has been known for its antiviral and immunomodulatory properties, making it a potential therapeutic option for COVID-19. Therefore, this systematic review aimed to evaluate the impact of zinc supplementation on clinical outcomes in ICU COVID-19 patients, namely mortality rates, intensive care unit (ICU) admission rate, and the length hospital stays. **Methods**: This review followed the PRISMA and the Cochrane Handbook guidelines. Eligible studies were published in English from December 2019 onward, while studies on other supplements, or involving children or pregnant women were excluded. A systematic search across PubMed, ScienceDirect, and Web of Science identified relevant studies. Study quality was assessed using the revised version of Cochrane risk of bias (RoB-2) tool for randomized clinical trials (RCTs), and the modified version of Newcastle for observational studies. **Results**: The search results yielded 1442 findings, out of them, eight studies were included. The reviewed studies included 2185 participants, primarily males aged 18–72. The primary outcomes showed that zinc supplementation significantly reduced mortality, with a pooled odds ratio of 0.57 (95% CI: 0.41–0.79, P = 0.0006), indicating a 43% lower mortality risk. There was no heterogeneity across the studies (I^2 = 0). Secondary outcomes showed reduced hospital stays and symptom duration in some studies but inconsistent effects on hospitalization rates, ventilation need, or ICU care. **Conclusions**: This review concluded that zinc supplementation significantly reduced mortality in COVID-19 patients. While zinc showed some benefits in reducing hospital stays and improving inflammatory markers, its effects on ICU admissions, ventilation, and overall recovery were inconsistent. Further research is needed to determine its optimal use and long-term clinical significance.

Keywords: COVID-19; zinc; Intensive care unit; mortality, systematic review.

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Introduction

COVID-19 pandemic has affected societies, economies, and healthcare systems worldwide [1]. It has placed burden on intensive care units (ICUs) globally [2]. Critically ill patients face several challenges, including the need for effective treatments. Advanced treatment approaches such as precision medicine are found to be hindered by issues like multi-morbidity and the need for timely interventions [3]. Therefore, several factors play a role in patient therapy, and adjunctive treatment may possess a beneficial therapeutic outcome .

Zinc is an essential trace element crucial for immune function that has a vital role in both innate and adaptive immunity [4]. First of all, it is integral to immune cell development, activation, and maturation, affecting neutrophils, natural killer cells, T and B lymphocytes, and macrophages [5]. Conditions such as zinc deficiency impairs various immune functions, including phagocytosis, cytokine production, and antibody synthesis, leading to increased susceptibility to infections [6]. Conversely, zinc supplementation can enhance immune responses, especially in the elderly with low zinc levels [7]. In addition, zinc also exhibits direct antiviral properties against viruses through different mechanism [4]. Zinc concentrations, either higher or lower than normal ranges negatively affect the immune function [8].

It is worth noting that Zinc has emerged as a therapeutic agent in the fight against COVID-19 due to its antiviral and immunomodulatory properties. Studies suggest that zinc can inhibit SARS-CoV-2 RNA polymerase, reducing viral replication [9]. Zinc supplementation may enhance antiviral immunity, restore immune cell function, and act synergistically with standard antiviral therapies [10]. Additionally, zinc's role in maintaining mucociliary clearance and respiratory epithelial barrier function may help pre-vent bacterial co-infections [9].

Studies that tested the effect of zinc supplementation among COVID-19 patients has resulted in mixed findings [10]. Recent meta-analyses suggest that zinc supplementation may have beneficial effects for COVID-19 patients [11]. Two studies found that zinc supplementation was associated with significantly lower mortality rates in COVID-19 patients [11, 12]. However, one meta-analysis reported no beneficial impact on survival to hospital discharge or in-hospital mortality and observed longer hospital and ICU stays in the zinc-supplemented group [13]. The conflicting results indicate that further research is needed to establish accurate conclusions regarding the efficacy of zinc supplementation in COVID-19 management.

There is an urgent need to synthesize evidence regarding the impact of zinc supplementation in critically ill COVID-19 patients, especially those in ICUs, where treatment strategies can significantly influence outcomes. Although prior studies have explored zinc's immunomodulatory and antiviral properties, their findings on its clinical benefits, such as reducing mortality rates and shortening ICU or hospital stays, remain inconsistent and inconclusive. These discrepancies highlight the necessity to synthesize existing evidence and clarify zinc's role in improving the prognosis of severely ill COVID-19 patients.

This systematic review aimed to evaluate the impact of zinc supplementation on key outcomes in COVID-19 ICU patients including mortality rates, admission rates and the length of ICU or hospital stays.

Materials and Methods

This systematic review was conducted in accordance with the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane

Handbook for Systematic Reviews of Interventions, ensuring methodological rigor and transparency throughout the process [14]. The review focused on Randomized Controlled Trials (RCTs), as they represent the gold standard for assessing the effectiveness of interventions, and observational studies that have focused on the same out-come measures.

Eligibility Criteria

The inclusion criteria for this review were studies that assessed the effect of zinc supplementation on ICU COVID-19 patients aged 18 years and older. The intervention being evaluated was zinc supplementation, compared to a placebo group receiving no supplementation. Studies that included zinc doses between 25 mg and 75 mg daily (oral) or up to 0.5 mg/kg/day (intravenous) were included. Eligible studies must have reported on key outcomes including mortality rate, admission rate, length of hospital or ICU stay, overall hospital stay, immune function, and dependence on ventilation. PICO criteria presented in Table 1.

Only studies published in English from December 2019 onwards were included in the review. Exclusion criteria included studies that do not specifically assess the effect of zinc supplementation or focus on other types of supplementations. Studies that involved populations such as pregnant women or children were excluded. Additionally, case reports, reviews, editorials, and letters to the editor were excluded due to their limited methodological rigor and lack of data for systematic analysis.

Search Strategy

A comprehensive search was conducted in major electronic databases, including PubMed, ScienceDirect, and Web of Science. The study used the search strategy outlined in the supplementary material. Reference lists of included studies and relevant reviews were hand-searched for additional studies that may meet the inclusion criteria.

Table 1. PICO Criteria for the current review.

Criteria	Description
Population (P)	ICU patients diagnosed with COVID-19 > 18 years.
Intervention (I)	Zinc supplementation
Comparator (C)	No supplementation
Outcomes (O)	Primary outcome: Mortality rate. Secondary outcome: Hospital stay, admission rate, length of ICU stays, survival to hospital discharge, immune function and ventilation dependency.

Study Selection

Titles and abstracts of identified studies were screened independently by three re-viewers. Full-text articles were retrieved for studies meeting the initial inclusion criteria. Discrepancies were resolved through discussion, and, if necessary, a fourth reviewer will arbitrate. A PRISMA flow diagram was used to document the number of studies identified, screened, included, and excluded, along with reasons for exclusion at each stage.

Data Extraction:

Data from the included studies were extracted using a pre-designed data extraction form. Extracted information included details on study design, participant characteristics, interventions, outcomes, and results (Table 2).

Risk of Bias Assessment (ROB)

Two tools were considered for the evaluation of studies risk of bias. The risk of bias (ROB) in individual studies was assessed using the Cochrane Risk of Bias Tool (RoB-2) for RCTs [15, 16]. This tool evaluated bias across various domains, including randomization, allocation concealment, blinding, incomplete outcome data, and selective outcome re-porting. Each study was rated as "low," "high," or "unclear" risk of bias. Discrepancies between reviewers were resolved through discussion. In addition,

Newcastle–Ottawa scale was used for the observational studies [17]. Each study was evaluated by two re-viewers independently.

Statistical Analysis

Meta-analysis was conducted using RevMan Web 5.4 which estimated the pooled effect size of mortality rate among the studies. In this review, ($P < 0.05$) was considered as statistically significant and 95% confidence interval (95% CI) was regarded as effective size in the analysis. For assessing heterogeneity, I^2 and Chi-square tests were done. I2 was categorized as low (0–50%), moderate (51–75%) or high (> 75%) for assess heterogeneity.

Results

The search strategy yielded 1442 studies, out of which 80 were duplicates. The remaining 1362 studies underwent screening of their titles and abstracts, and 1327 records were excluded. The full texts of the remaining 35 studies were obtained and assessed for eligibility. Out of them, eight studies, including six RCTs were finally included in the review [18-25]. Figure 1 shows the PRISMA flow chart which details the selection process of the included studies.

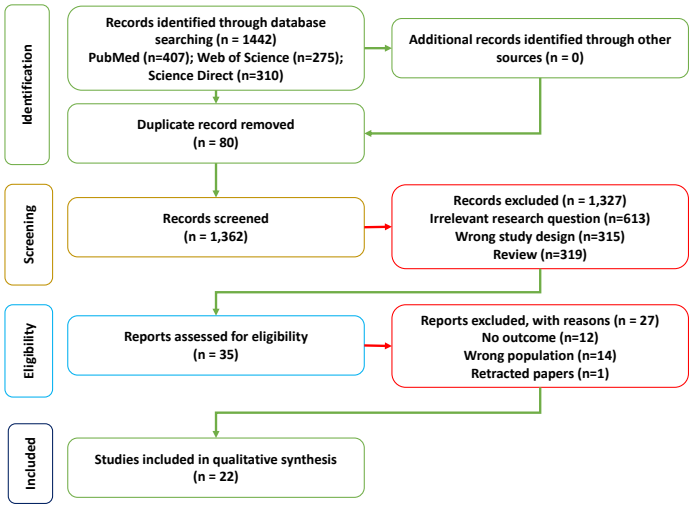

Figure 1. PRISMA Flowchart of the selection process.

Characteristics and Outcomes of the Included Studies

All the included studies were double-blinded RCTs conducted across various countries, including Saudi Arabia [20], Egypt [23], India [22], Tunisia [21], and the United States [18, 19, 24, 25]. The studies investigated the effects of zinc supplementation on COVID-19-related outcomes such as time to symptom resolution, hospital stay duration, need for assisted ventilation, all-cause mortality, and blood biomarker concentrations. Sample sizes varied, ranging from 19 to 932, encompassing diverse populations including patients with comorbidities (Table 2).

The review included a total of 2185 participants with an approximate age range between 18 and 72 years. Across these studies, the rate of males was more prevalent than females. In the intervention group, males' rates were reported in five studies as follows: (53%, 73.3%, 56.1, 64.3, 54.2%) [18, 21, 23, 25]. Only one study reported a higher rate of females [19], while one study had an equal gender distribution [22]. The

prevalence of common conditions varied, reflecting different patient populations. Overall, hypertension was the most prevalent condition across the studies, while diabetes was also a significant concern in several studies, particularly in two studies [19, 21]. COVID-19 severity ranged from mild to moderate in most studies. Smoking history was potentially contributing to more severe COVID-19 symptoms [19].

The zinc supplementation doses, and delivery methods varied across the studies. One study administered 25 mg of zinc twice daily (50 mg/day) as oral capsules [21]. Similarly, Partap et al.

provided 40 mg daily via oral tablets [22]. In critically ill patients, Sulaiman et al. used 220 mg daily (50 mg elemental zinc) through enteral tablets [20]. Patel et al. employed a high-dose regimen, delivering 0.5 mg/kg/day of elemental zinc intravenously, diluted in 250 mL of normal saline infused over 3 hours [18]. Thomas et al., administered 50 mg/day using oral zinc gluconate [19]. Two studies used the same regimen of 220 mg of zinc sulfate twice daily (440 mg/day, 100 mg elemental zinc) ad-ministered orally [23, 24]. Carlucci et al., 2020 [25], also utilized 220 mg twice daily. All placebo groups received substances that were identical in appearance and taste to the active treatment, ensuring a double-blind design. The characteristics of the included studies are shown in Table 2.

Table 2. Characteristics and outcomes of the included studies.

Author, year, country	Sample size	Sample characteristics	Intervention	Primary outcome	Secondary outcome	Summary of finding
Abdallah et al., 2023, Tunisia [21]	470	Age: Mean: 54.2 ± 17.3 years. Gender: Overall: 53% male. Body Mass Index (BMI): Overall: Mean 27.3 ± 3.8 kg/m^2. Among them, 40.4% were outpatients, and 59.6% were inpatients; Oxygen saturation levels below 92%: 38.9% Comorbidities: Hypertension: 23.4% Diabetes: 19.4% History of coronary artery disease, COPD, asthma, and renal failure were less frequent.	Zinc group: Received 25 mg twice daily for 15 days. Placebo group: Received identical capsules without active ingredients. Follow-up lasted 30 days to assess symptoms, mortality rates, or ICU admission.	Death and ICU admission rates at 30 days; Composite outcome combining death and ICU admission.	Length of hospital stay (inpatients); Symptom duration and need for hospitalization (outpatients); Treatment safety and adverse events.	Mortality: 6.5% in the zinc vs. 9.2% in the placebo group (NS). ICU admission: 5.2% zinc vs. 11.3% placebo (statistically significant). Length of Hospital Stay: 7.1 days in zinc vs. 10.6 days in placebo. Symptom duration for outpatients: 9.6 days in zinc vs. 12.8 days in placebo. Serious Side effects: None reported. Hospitalization Rate (Outpatients): No significant
Partap et al.,2023, India [22]	181	Adults from Mumbai and Pune, India, with mild to moderate COVID-19, evenly split by gender, mostly over 30 years old, 47% with chronic conditions, 47% Vitamin D deficient, 12% zinc deficient, and over half vaccinated with at least one dose.	Group 1: Vitamin D3 (180,000 IU bolus + 2,000 IU daily). Group 2: Zinc (40 mg daily). Group 3: Vitamin D3 + Zinc. Group 4: Placebo. Duration: 8 weeks.	Time to resolution of fever, cough, and shortness of breath.	Duration of individual symptoms, hospitalization rates, need for assisted ventilation, all-cause mortality, changes in blood biomarkers (e.g., vitamin D, zinc, inflammatory markers).	Vitamin D: 3 days (95% CI: 2–5) vs. placebo: 3 days (95% CI: 2–4), HR: 0.92, P = 0.650. Zinc: 3 days (95% CI: 2–4) vs. placebo: 3 days (95% CI: 2–4), HR: 0.94, (P = 0.745). No significant changes in secondary outcomes or biomarkers.
Sulaiman et al., 2021, Saudi Arabia [20]	164	The patients were critically ill with COVID-19, aged 18 years or older, and admitted to the ICU in two tertiary hospitals in Saudi Arabia between March 2020 and March 2021. They were classified based on whether they received zinc sulfate as adjunctive therapy during their ICU stay.	Zinc sulfate (220 mg daily, equivalent to 50 mg elemental zinc). compared to control group Route: Administered via enteral tablets. Timing: Initiated during ICU stay. Duration: Median of 11 days (range: 6–15 days). Decision: Based on physician's clinical judgment.	30-day mortality.	In-hospital mortality, ICU and hospital length of stay, ventilator-free days within 30 days, and complications during the ICU stay (acute kidney injury, liver injury, and thrombosis/infraction).	4.30-Day Mortality: Significantly reduced in the zinc group (23.2% vs. 38.8%, P = 0.03). ICU and Hospital Stay: NS (p > 0.46). vs control group. Inflammatory Markers: Significant reduction in D-dimer and fibrinogen in zinc group (p < 0.001). Ventilation and Immune Complications: NS
Patel et al., 2021, United states [18]	33	Average age of 59-63 years, 73.3% of whom were males, and comorbidities including hypertension (46.7%-	- Participants were randomized into two groups: High-Dose Intravenous Zinc (HDIVZn) group and Placebo group.	Serum Zinc Levels. Oxygenation Requirement (in non-ventilated patients).	Safety and Feasibility: Monitoring for any adverse events associated with HDIVZn administration.	High-dose intravenous zinc corrected zinc deficiency by day 6 safely Mortality is 7.7% by day 7 and 14.3% by day 28 in the

		50%) and diabetes (16.7%-20%). Zinc levels were below the deficiency threshold (10.7 µmol/L)	- The dose administered was 0.5 mg/kg/day of elemental zinc (equivalent to 0.24 mg/kg/day elemental concentration). - Zinc was diluted in 250 mL of normal saline and infused via peripheral intravenous access over a period of 3 hours. Treatment duration: Maximum of 7 days, or Until hospital discharge or death. A total of 94 HDIVZn administrations were performed during the study. -Participants in the placebo group received 250 mL of normal saline, infused similarly to the intervention group.	PaO_2/FiO_2 Ratio (in ventilated patients).	Clinical Outcomes: Improvement in clinical status, assessed using an eight-level ordinal scale at multiple time points (Day 1, Day 7, Day 14, and Day 28). Other Laboratory Measures: Changes in levels of trace metals (copper, calcium, magnesium) and inflammatory markers like C-reactive protein (CRP).	zinc group vs. 16.7% in placebo group At Day 28: HDIVZn group with 2 deaths reported (14.3%) vs. 3 deaths (16.7%) in the Control group. length of stay or survival rates is NS.
Thomas et al., 2021, United States [19]	214	Age: Mean 45.2 years (SD = 14.6). Gender: 61.7% were women (n = 132). Geographic location: Participants were from outpatient care settings in Ohio and Florida. Race/Ethnicity: White: 71.7% (n = 152). Black: 23.8% (n = 51). Other/Not reported: 4.2% (n = 11). Smoking history: 31.8% (n = 68) were current or former smokers. Baseline symptom severity (12-point scale): Mean symptom score was 4.3 (SD = 1.9). The mean Body Mass Index (BMI) 30.0, interquartile range (IQR) 26.2–36.6. Diabetes: 13.6% (n = 29) Hypertension: 32.7% (n = 70) Dyslipidemia: 26.2% (n = 56) Asthma: 15.4% (n = 33) Anxiety: 18.2% (n = 39) Depression: 15.4% (n = 33)	Participants received one of the following for 10 days after a confirmed SARS-CoV-2 diagnosis: Ascorbic acid only: 8000 mg/day, divided over 2–3 doses with meals. Zinc gluconate only: 50 mg/day at bedtime. Combination of ascorbic acid and zinc gluconate. Standard care: No supplements provided.	Number of days to reach a 50% reduction in symptoms (fever, cough, shortness of breath, and fatigue),	Time to reach a total symptom severity score of 0. Cumulative symptom severity score at day 5. Hospitalizations and deaths during the study period. Adverse effects from the supplements. Additional medications required during the study.	Time to 50% reduction in symptoms is NS between groups. Overall p-value = 0.45 Symptom severity score at day 5: NS across groups. Hospitalizations: 17 patients (7.9%) were hospitalized; NS. Deaths: 3 patients (1.4%) died, NS. Adverse effects: Mild side effects (e.g., nausea, diarrhea) in the ascorbic acid group.
Yao et al., 2020, USA [24]	242	Age (Median, IQR): Zinc group: 65 (53–77) Control group: 71 (58–84) years Sex (Female): Zinc group: (43.9%) Control group: (39.1\%) Clinical Severity: Mild: Zinc 20.4% Control 30.4% Severe: Zinc: 54.1% Control: 45.7% Critical: Zinc: 25.5% Control 23.9% Mortality: Zinc group: (37.2%)	Treatment Group: Zinc sulfate at a daily dose of 440 mg (100 mg elemental zinc) + standard care. Control Group: Standard care without zinc sulfate	Survival (days from admission to in-hospital mortality).	ICU admission; Discharge to home	Mortality: Zinc group: 73/196 (37.2%) vs. control group: 21/46 (45.7%) ICU admission: Zinc 58/196(29.6%) and 58/196(29.6%) vs. 7/46 (15.2%)7/46(15.2%) in control group Discharge to home: Zinc 75/196 (38.3%) and 75/196(38.3%) vs. control group 17/46 (37.0%)17/46(37.0%) There was no significant survival benefit observed after adjustments.

		Control group: (45.7%)				
Carlucci et al., 2020, USA [25]	932	Age (mean ± SD): Zinc group: 63.19 ± 15.18 Non-zinc group: 61.83 ± 15.97 Sex (female) Zinc group: (35.7%) No zinc group: (38.6%) History Hypertension: Zinc = 37.5% No zinc 39.9% Diabetes: Zinc= 25.5% No zinc= 25% Cardiovascular conditions: Zinc= 44.3% No zinc = 47.6%	Treatment Group: Hydroxychloroquine, azithromycin, and zinc sulfate (220 mg PO BID). Control Group: Hydroxychloroquine and azithromycin alone.	Mortality or transfer to hospice.	Discharge destination (home vs. other).; Need for intensive care unit (ICU) admission; Need for mechanical ventilation; Length of hospitalization; ICU duration	Primary Outcome: Addition of zinc sulfate decreased mortality or transfer to hospice among non-ICU patients (adjusted OR 0.449, 95% CI 0.271–0.744, p=0.002). Secondary Outcomes: Increased discharge home (adjusted OR 1.53, 95% CI 1.12–2.09, p=0.008). Decreased need for ICU care and invasive ventilation in unadjusted analyses; these associations were not significant after adjustment. Hospital stay length, ICU duration, or oxygen requirements: NS.
Abd-Elsalam et al., 2020, Egypt [23]	191	Age (Mean ± SD): Zinc group: 43.48±14.62 No zinc group: 43.64±13. Gender: Male: Zinc (54.2%) No zinc (67.4%) Female: Zinc (45.8%) No zinc: (32.6%) Clinical Severity: Mild: Zinc 9.4% No zinc 12.6% Moderate: Zinc: 60.4% No zinc: 57.9% Severe: Zinc = 18.8% No zinc = 21.1% Critical: Zinc = 11.6% No zinc = 8.4%	Treatment Group: Hydroxychloroquine (400 mg BID on Day 1, then 200 mg BID for 5 days) + Zinc sulfate (220 mg BID, containing 50 mg elemental zinc). Control Group: Hydroxychloroquine only.	Recovery within 28 days, need for mechanical ventilation, and mortality.	Duration of hospital stay.	(non-significant findings were observed among outcomes) Recovery after 28 days: Zinc group: 76/96 (79.2%) No zinc group: 74/95 (77.9%) Need for mechanical ventilation: Zinc group: 4/96 (4.2%) No zinc group: 6/95 (6.3%) Mortality: Zinc group: 5/96 (5.2%) No zinc group: 5/95 (5.3%) Duration of hospital stay: Zinc group: 13.51±5.34 days No zinc group: 14.01±6.26 days

Note: BID, twice a day, COPD, Chronic Obstructive Pulmonary Disease, ICU, Intensive Care Units, NS, Not Significant, PO, by orally.

Primary Outcomes

The effect of Zinc supplementation on mortality event rate

Five studies were conducted to assess the effect of Zinc supplementation on mortality event [18, 20, 23-25]. The findings showed that zinc has significantly reduced mortality compared to placebo, as evidenced by a pooled odds ratio of 0.57 (95% CI: 0.41–0.79, P = 0.0006), indicating a 43% reduction in mortality risk. In the zinc supplementation group, 125 events occurred among 762 participants, compared to 118 events among 680 participants in the placebo group. The analysis showed no heterogeneity among the included studies (I^2=0) demonstrating consistent findings across studies (Figure 2).

Secondary outcomes

In terms of secondary outcomes, one study reported a reduction in hospital stays for inpatients (7.1 days vs. 10.6 days) and a shortening of symptom duration for outpatients (9.6 vs. 12.8 days), indicating that zinc may have a beneficial effect on recovery time [21]. However, another study found no significant differences in hospitalization rates or symptom resolution [22]. In regard to ventilation need, two studies found no significant differences between zinc and control groups [20, 22]. Furthermore, two studies reported no significant effect on length of hospital stay [18, 25]. However, Carlucci et al. did report an increase in home discharge in non-ICU patients

receiving zinc sulfate (adjusted OR = 1.53, P=0.008). Zinc supplementation also showed improvements on inflammatory markers such as D-dimer and fibrinogen in the study by Sulaiman et al. although there were no corresponding changes in ICU care or ventilation dependency [20]. Finally, no significant adverse effects were reported in the zinc groups in the reviewed studies.

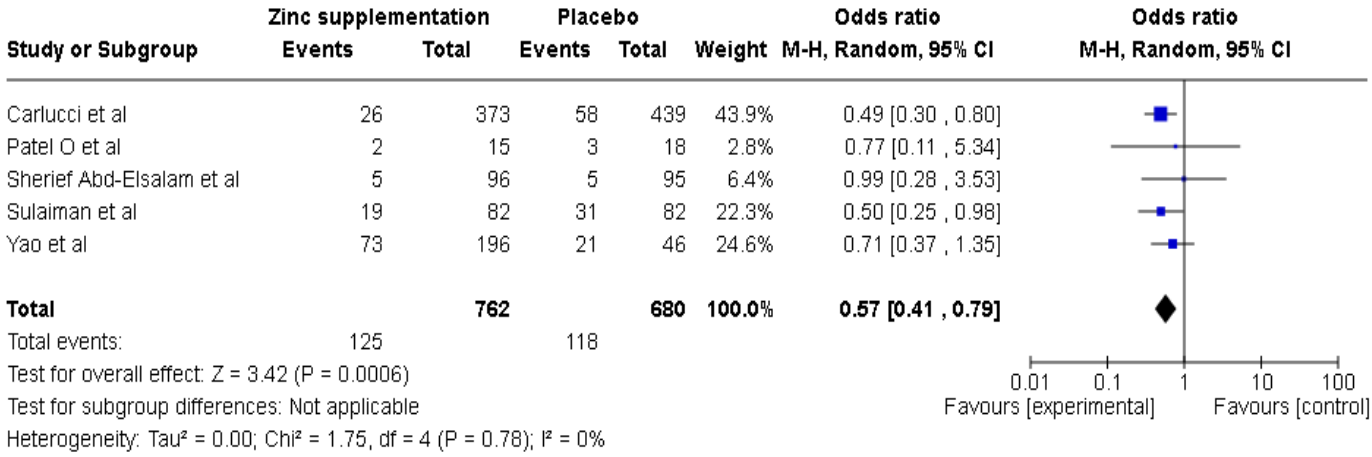

Figure 2. Forest plot of odd ratio for the effect of zinc supplementation on mortality rate. CI, confidence interval, ICU, intensive care unit.

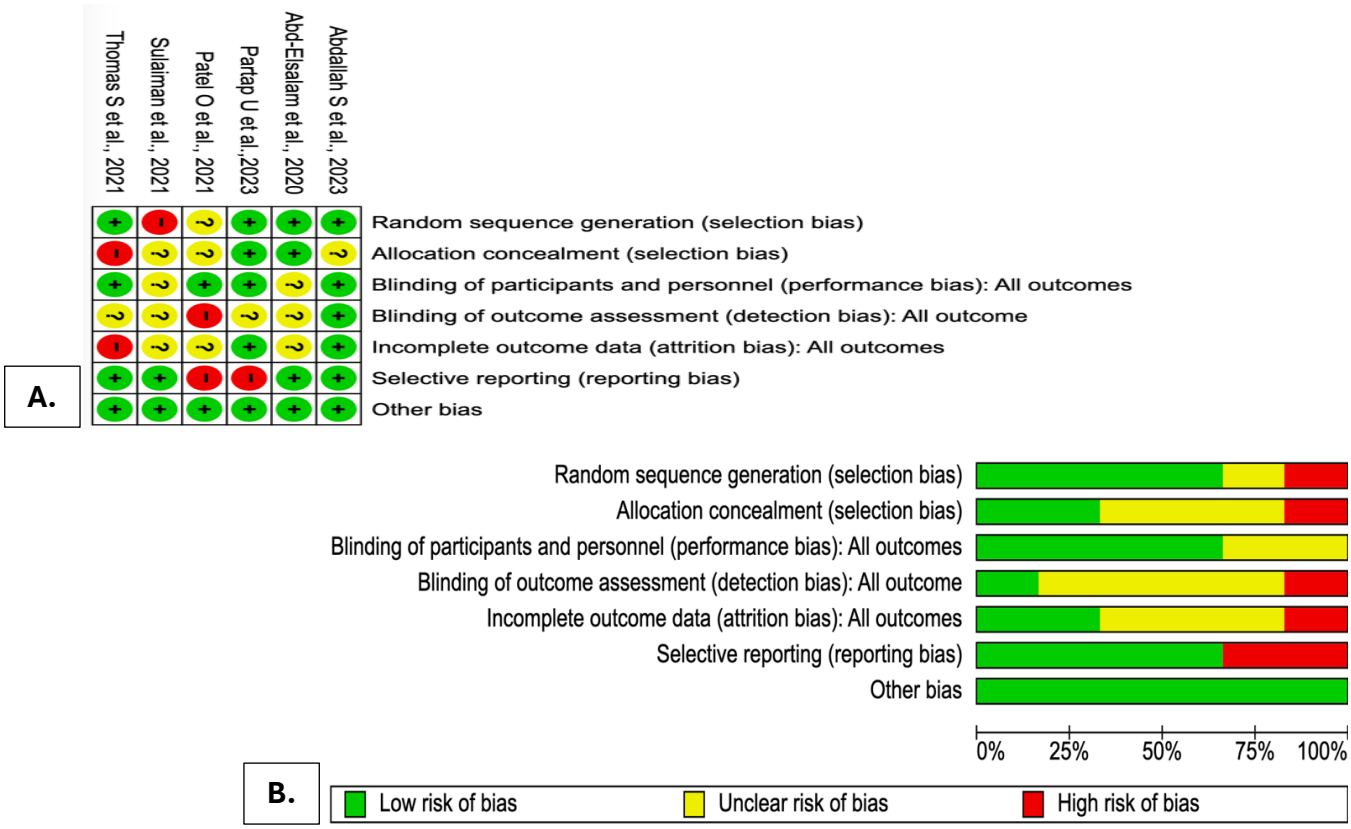

Figure 3. Risk of bias assessment for RCT studies: (a) Risk of bias summary; (b) Risk of bias assessment.

Regarding ICU admission, Abdallah et al. reported a statistically significant re-duction in ICU admission for patients receiving zinc (5.2% vs. 11.3% with placebo) [21]. In contrast, Partap et al. found no significant difference in ICU admissions [22]. Sulaiman et al. showed no significant differences were found in ICU stay or ventilation dependency [20]. Similarly, Patel et al. did not observe any significant effect of high-dose intravenous zinc administration on oxygenation, PaO_2/FiO_2 ratios [18]. Similarly, Abd-Elsalam et al. found no significant differences in recovery at 28 days (79.2% with zinc vs. 77.9% without) and mechanical ventilation needs [23].

Risk of bias assessment (ROB)

The ROB assessment revealed notable differences across studies. Random sequence generation indicated high and unclear risks in Al Sulaiman et al. (2021) [20] and Patel et al. (2021) [18]. Allocation concealment and participant blinding were appropriately ad-dressed in some studies [22, 23]. Incomplete outcome data posed a significant risk in Thomas et al [19], while selective reporting biases were evident in Patel et al. (2021) [18], Partap et al. (2023) [22]. These findings underscored the need for standardized method-ologies to enhance the reliability and comparability of future research (Figure 3 a, b). Studies that have done by Yao et al. [24] and Carlucci et al. [25] were found to have good quality based on the modified Newcastle-Ottawa Scale by the researcher's judgement.

Discussion

This systematic review included eight studies, six were RCTs and two were observational studies. All included studies aimed to evaluate the effects of zinc supple-mentation on COVID-19 patients, in terms of mortality rate, admission rate, and hospital length of stay, survival to hospital discharge, immune function and ventilation de-pendency.

The review found that zinc supplementation may reduce mortality rates in COVID-19 patients. The results of this review demonstrated a significant reduction in mortality with zinc supplementation, with a 43% reduction in mortality risk compared to placebo (OR = 0.57, 95% CI: 0.41–0.79, P = 0.0006). This finding highlighted the potential role of zinc in improving survival outcomes. However, to fully understand the implications, it is necessary to consider several factors, including the type and dose of zinc de-livered, differences in study populations, and sample size variations.

This finding is aligned with another study in the literature, which indicated that zinc's immune-boosting and anti-inflammatory properties could help reduce complications and death in severely ill patients [11]. This benefit may be attributed to zinc's role in immune function, including its ability to reduce inflammation and enhance antiviral immunity. Zinc has been shown to inhibit viral replication and to reduce levels of inflammatory cytokines like IL-6 and IL-1, which are elevated in severe COVID-19 conditions [26].

The effect of zinc on mortality could vary depending on the form of zinc supple-mentation and the dose administered. Some studies included in the review used high-dose intravenous zinc (HDIVZn), while others used oral zinc salts, which could impact bioavailability and efficacy. Intravenous administration may provide higher serum zinc levels rapidly, potentially leading to more pronounced therapeutic effects in critically ill patients.

In contrast, the rest of the included studies did not indicate significant difference in mortality rates between the intervention and placebo groups. This is aligned with another study which

showed that the evidence on whether zinc as an adjunct treatment to covid-19 patients reduced complications and death in COVID-19 patients is still inconclusive [5].

A reduction in hospital stays and symptom duration was observed in one study. Abdallah et al. [21] reported shorter hospital stays for inpatients (7.1 days vs. 10.6 days) and faster symptom resolution for outpatients (9.6 days vs. 12.8 days) in the zinc group, suggesting potential benefits in recovery time. In contrast, other studies, including those by Patel et al. [18], Carlucci et al. [25], and Partap et al. [22], found no significant improvements in hospitalization rates or duration, indicating that the effect of zinc supplementation on these outcomes may vary based on patient characteristics or study set-tings. However, Carlucci et al. [25] did report an increased rate of home discharges among non-ICU patients receiving zinc sulfate (adjusted OR = 1.53, P = 0.008), which highlights a potential role for zinc in facilitating recovery in less severely ill patients.

The effect of zinc supplementation on ICU admissions and ventilation needs was inconsistent across studies. Abdallah et al. [21] found a significant reduction in ICU admission rates (5.2% vs. 11.3%), suggesting a protective role for zinc in preventing severe progression. However, Sulaiman et al. [20], Partap et al. [22], and Patel et al. [18] reported no significant differences in ICU stay, ventilation dependency, or oxygenation parameters, such as PaO_2/FiO_2 ratios. These findings suggest that zinc effect on respiratory outcomes and critical care requirements may be limited, particularly in severe cases.

Improvements in inflammatory markers, such as reductions in D-dimer and fibrinogen levels, were observed, which may indicate zinc's potential to modulate inflammation [20]. However, these biochemical improvements did not translate into significant clinical benefits, such as reduced ICU care or ventilation dependency.

Mixed outcomes were reported regarding symptom resolution and overall recovery. Abd-Elsalam et al. [23] found no significant differences in recovery rates at 28 days (79.2% with zinc vs. 77.9% with placebo). Similarly, Partap et al. [22] found no significant differences in symptom resolution. This suggests that while zinc may improve certain secondary outcomes, its overall impact on recovery and survival remains limited.

The results of this review hold broader relevance for societal health and future re-search. The mixed findings on zinc supplementation, particularly its benefits for critically ill patients, can inform targeted interventions in healthcare settings. For instance, prioritizing zinc supplementation in resource-limited regions with higher prevalence of zinc deficiency could enhance outcomes for severe cases. In addition, the absence of significant benefits in mild cases suggests that public health recommendations should focus on severe cases rather than broad supplementation for all COVID-19 patients. Findings that zinc may reduce ICU admission rates and mortality in severe cases could justify its inclusion in treatment protocols, reducing healthcare burdens during pandemics or similar crises .

To enhance outcomes in COVID-19 management, policymakers should develop targeted zinc supplementation programs for high-risk groups and promote nutritional education to address deficiencies, specifically in resource-limited settings. Practitioners are advised to use zinc supplementation selectively for critically ill patients, monitor for adverse effects, and personalize treatment based on individual needs. Researchers should prioritize studies on specific subpopulations, optimize

supplementation protocols, investigate zinc's mechanisms of action, and explore its broader applications in managing critical illnesses. Standardizing study designs and outcome measures will further improve the reliability of findings, enabling policymakers and healthcare professionals to make evidence-based decisions.

This review acknowledges several limitations that affected the robustness and generalizability of its findings. Heterogeneity among studies, including differences in patient populations, disease severity, zinc dosages, and treatment protocols, contributed to inconsistent results. Small sample sizes in several trials reduced statistical power, while variations in methodological approaches, such as inclusion criteria and outcome measures, complicated direct comparisons. The absence of subgroup analyses, particularly for patients with zinc deficiency or distinct comorbidities, limited insights into specific populations that might benefit most. Short study durations hindered the assessment of long-term outcomes, and reports of mild adverse effects highlighted the need for data on the safety and efficacy of high-dose zinc. Confounding factors, such as concurrent therapies, further obscured zinc's isolated effects.

Conclusions

This systematic review synthesized evidence from eight studies to assess the impact of zinc supplementation on mortality rates and ICU stay in COVID-19 patients. The findings showed the significant impact of zinc supplementation in reducing mortality, with a 43% lower risk compared to placebo. While zinc demonstrated some benefits in secondary outcomes, such as reducing hospital stays, shortening symptom duration, and improving inflammatory markers, its effects on ICU admissions, ventilation needs, and overall recovery were inconsistent. The intervention was well-tolerated with no significant adverse effects reported. These findings suggest that zinc supplementation may play a supportive role in improving outcomes, though further research is needed to determine its optimal use and long-term clinical significance.

Abbreviations

ICU	Intensive Care Units
RCTs	Randomized Controlled Trials
ROB	Risk of Bias assessment
PICO	Population, Intervention, Comparator and outcomes
PRISMA	The Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SARS-Cov-2 RNA	Severe Acute Respiratory Syndrome Coronavirus 2 Ribonucleic acid
COVID-19	Coronavirus Disease of 2019
CRP	C-Reactive Protein

Supplementary Information

Supplementary Table S1

Declarations

Author Contributions: "Conceptualization, I.B. and N.A.; methodology, I.B. , N.A., A.A. and M.A.; software, N.A., A.A. and M.A.; validation, I.B. and N.A.; formal analysis, N.A., A.A. and M.A.; investigation, I.B., N.A., A.A. and M.A.; resources, I.B.; data curation, N.A., A.A. and M.A.; writing—original draft preparation, I.B., N.A, A.A and M.A; writing—review and editing, I.B. and N.A.; visualization, I.B.; supervision, I.B.; project administration, I.B. All authors have read and agreed to the published version of the manuscript."

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