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CHEST

The Minimal Effect of Zinc on the Survival of Hospitalized Patients With COVID-19

An Observational Study

To the Editor:

Zinc is an investigational agent against coronavirus disease 2019 (COVID-19) and has known preventative and therapeutic roles in other infections.[1-3] Zinc deficiency is associated with lower survival among older patients with pneumonia and predisposes to other viral infections.[3] Established risk factors for critical COVID-19, including older age, diabetes mellitus, and cardiovascular disease, are also associated with zinc deficiency.[2]

The antiviral and immunomodulatory effects of zinc have made it a candidate against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection.[2-4] Zinc may decrease the activity of the angiotensin converting enzyme 2, the receptor for SARS-CoV-2. Zinc T-cell modulation may downregulate the cytokine storm associated with severe COVID-19.[2,4] These properties underlie the speculated efficacy of chloroquine, a zinc ionophore, and the derivative hydroxychloroquine, which are investigational agents in the worldwide World Health Organization SOLIDARITY trial.[2,5,6] Furthermore, chloroquine may increase cellular zinc uptake, suggesting therapeutic benefit from the combination of the two agents.[4]

Despite zinc's low risk of adverse effects, zinc's role in the management of COVID-19 must be supported by clinical data.[7] Therefore, we investigated the role of zinc among hospitalized patients with COVID-19.

Methods

In this single-institution retrospective study, we assessed the survival of hospitalized patients with COVID-19 treated with vs without zinc sulfate. This study was conducted in accordance with the amended Declaration of Helsinki. This study's protocol was approved and was granted a waiver of informed consent by the hospital board on April 15, 2020, based on its retrospective design and the lack of identifying information to be published, collected, or analyzed.

Data of all patients with COVID-19 (N = 242) admitted at the Hoboken University Medical Center until April 11, 2020, were retrospectively collected on April 21, 2020. COVID-19 was confirmed in all patients using quantitative real-time reverse transcription polymerase chain reaction for SARS-CoV-2 RNA. Clinical severity was stratified based on World Health Organization[8] guidelines according to clinical, radiographic, and laboratory information from the first 24 h of admission. The primary outcome was days from admission to in-hospital mortality. Data for patients who did not meet the primary outcome were censored on April 21, 2020.

Our primary analysis explored the causal association between zinc therapy and the survival of hospitalized patients with COVID-19. Inverse probability weighting (IPW) and a censorship model derived an effect estimate of zinc therapy on survival using the parameter defined as the average treatment effect on the treated (ATET). The lack of sufficient overlap or the positive probability of assignment to each treatment level precluded the estimation of the average treatment effect.

Multivariable logistic regression modeled the propensity to receive zinc by assigning weights to established predictors of mortality and to variables which may influence a physician's decision to administer zinc. These included the following: age, sex, race, the presence of heart disease or COPD, and clinical severity on admission.[9] Survival analysis with a Weibull censorship distribution model used covariates in the propensity model and potentially efficacious treatments with relevant between-group differences (lopinavir/ritonavir, systemic corticosteroids, IL-6 receptor inhibitors, and therapeutic anticoagulation). To explore the additive effect of zinc therapy on various therapies, we performed subgroup analyses among patients who received hydroxychloroquine, lopinavir/ritonavir, steroids, and IL-6 receptor inhibitors. The χ^2 test for balance assessed whether the distribution of covariates did not vary across treatment levels.

Secondary analysis using multivariable Cox regression with IPW for zinc therapy further assessed the association between zinc therapy and the primary outcome. Zinc therapy and nine other covariates were chosen to avoid overfitting the model (listed in Results section). Analyses (two-sided $\alpha = 0.05$) were performed using Stata/IC 16.1 (StataCorp).

Results

Of 242 patients, 81.0% received zinc sulfate at a total daily dose of 440 mg (100 mg elemental zinc). The median age of patients who received zinc was 65 years (interquartile range, 53-77), whereas that of the control group was 71 years (interquartile range, 58-84; $P = .07$); 86 (43.9%) were women in the zinc group compared with 18 (39.1%) among the control group ($P = .60$). In the zinc group, 40 (20.4%) had mild disease, 106 (54.1%) had severe disease, and 50 (25.5%) had critical disease.

TABLE 1] Baseline Clinical Characteristics of Patients With COVID-19 Who Received Zinc Sulfate Therapy vs Control Subjects

Variable	Zinc Sulfate Group (n = 196)	Control Group (n = 46)
Demographic characteristics		
Age, y	65 (53-77)	71 (58-84)
Female	86 (43.9)	18 (39.1)
BMI, kg/m^2	28.8 (25.4-32.1)	26.6 (22.2-29.4)
Clinical severity[a]		
Mild	40 (20.4)	14 (30.4)
Severe	106 (54.1)	21 (45.7)
Critical	50 (25.5)	11 (23.9)
Comorbidities		
None	40 (20.4)	8 (17.4)
Hypertension	98 (50.0)	29 (63.0)
Diabetes mellitus II	68 (34.7)	18 (39.1)
Cardiovascular disease	33 (16.8)	6 (13.0)
Hypercholesterolemia	68 (34.7)	15 (32.6)
Cancer	8 (4.1)	3 (6.5)
COPD	15 (7.7)	7 (15.2)
Chronic kidney disease	19 (9.7)	10 (21.7)
Asthma	23 (11.7)	5 (10.9)
Stroke	5 (2.6)	5 (10.9)
Clinical outcomes		
Discharged to home	75 (38.3)	17 (37.0)
ICU admission	58 (29.6)	7 (15.2)
Mortality	73 (37.2)	21 (45.7)
Vital signs in the first 24 h of admission		
Alert and oriented	156 (79.6)	34 (73.9)
Confused	40 (20.4)	12 (26.1)
Temperature, °C	38.0 (37.3-38.9)	37.4 (36.8-38.2)
Respiratory rate, breaths/min	22.0 (20.0-26.0)	20 (20.0-24.0)
Mean arterial pressure, mm Hg	79.0 (72.0-89.0)	78.5 (66.0-88.0)
Heart rate, beats/min	105 (93.8-115.0)	98 (88.0-111.5)
Spo_2 on room air	90.0 (84.0-94.0)	92.0 (85.0-95.0)
Therapies received		
Hydroxychloroquine	191 (97.4)	32 (69.6)
Antibacterial agents	191 (97.4)	44 (95.7)
Lopinavir/ritonavir	114 (58.1)	13 (28.3)
Systemic corticosteroids	56 (28.6)	6 (13.0)
IL-6 receptor inhibitor	71 (36.2)	9 (19.6)
Therapeutic anticoagulation	38 (19.4)	4 (8.7)

Values are No. of patients (%) or median (interquartile range). Spo_2 = oxygen saturation as measured by pulse oximetry.
[a]Clinical severity was stratified based on clinical, radiographic, and laboratory information from the first 24 h of admission. Patients with critical disease were those who developed ARDS, septic shock, or multiorgan failure, or those who required mechanical ventilation or ICU admission. Patients were classified as having severe disease if their Spo_2 on room air was ≤ 93%, if they required oxygen supplementation, or if their respiratory rate was ≥ 30 breaths/min without meeting any of the criteria for critical disease. Hospitalized patients were classified as having mild disease if their Spo_2 was ≥ 94% on room air or if they did not require oxygen supplementation, while not meeting any of the criteria for severe or critical disease.

TABLE 2] Inverse Probability Weighting With a Multivariate Logistic Regression Model for Treatment Propensity and Weibull Censorship Distribution Model for Survival

	Without Zinc Sulfate			With Zinc Sulfate		
Population	PO Mean	95% CI	*P* Value	ATET	95% CI	*P* Value
Entire cohort	5.87	3.94 to 7.81	< .001	0.84	−1.51 to 3.20	.48
Severe and critical patients	7.13	4.77 to 9.50	< .001	−1.18	−3.68 to 1.32	.35
Patients given hydroxychloroquine	7.11	5.01 to 9.21	< .001	−0.33	−2.85 to 2.19	.80
Patients given lopinavir/ritonavir	7.84	4.79 to 10.90	< .001	−0.42	−3.92 to 3.08	.82
Patients given steroids	5.07	3.03 to 7.11	< .001	2.03	−0.77 to 4.84	.16
Patients given IL-6 receptor inhibitors	8.20	5.57 to 10.82	< .001	−0.41	−3.67 to 2.85	.81

Inverse probability weighting with a multivariate logistic regression model was used to measure the propensity to receive treatment with the following covariates: age, sex (male vs female), race (white vs nonwhite), the presence of heart disease or COPD, and clinical severity on admission. A subsequent survival analysis with a Weibull censorship distribution model was performed with patient characteristics in the propensity model and lopinavir/ritonavir, systemic corticosteroids, IL-6 receptor inhibitors, and therapeutic anticoagulation as covariates. ATET = average treatment effect on the treated; PO = potential outcomes.

Among control subjects, 14 (30.4%), 21 (45.7%), and 11 (23.9%) had mild, severe, and critical disease, respectively ($P = .30$). Baseline clinical and treatment characteristics are summarized in Table 1.

In the zinc group, 73 patients (37.2%) met the primary outcome compared with 21 (45.7%) in the control group. In our primary analysis, the effect estimate of zinc therapy was an additional 0.84 days (ATET: 95% CI, −1.51 to 3.20; $P = .48$) (Table 2) of survival. However, this finding was imprecise. Subgroup analyses of severe and critical patients and of patients who received various therapies yielded results which were not statistically significant (Table 2). Postestimation χ^2 test for balance did not reject the null hypothesis that the IPW model balanced covariates between treatment levels ($P = .59$).

On multivariate Cox regression with IPW, zinc sulfate was not significantly associated with a change in risk of in-hospital mortality (adjusted hazard ratio, 0.66; 95% CI, 0.41 to 1.07; $P = .09$) (Table 3). Older age, male sex, and higher clinical severity were significantly associated with an increased risk of in-hospital mortality (Table 3). Use of IL-6 receptor inhibitors was associated with reduced mortality (Table 3).

Discussion

Our analyses demonstrate the lack of a causal association between zinc and the survival of hospitalized patients with COVID-19. Similarly, subgroup analyses stratified by severity or additional therapies did not yield significant causal associations. Given this study's

TABLE 3] Inverse Probability Weighting With Multivariate Cox Regression Defining aHRs of Mortality With Zinc Sulfate Therapy, Clinical Characteristics, and Therapies Received With Significant Between-Group Differences as Covariates

Clinical Characteristics and Therapies	aHR	95% CI	*P* Value
Zinc sulfate (yes vs no)	0.66	0.41 to 1.07	.09
Age	1.03	1.01 to 1.05	.001
Sex (male vs female)	1.72	1.00 to 2.97	.05
Heart disease (yes vs no)	0.94	0.43 to 2.07	.88
COPD (yes vs no)	0.86	0.30 to 2.46	.78
Clinical severity (vs mild)			
Severe disease	3.9	1.23 to 12.40	.02
Critical disease	39.61	11.96 to 131.44	< .001
Lopinavir/ritonavir (yes vs no)	1.00	0.63 to 1.58	.99
Steroids (yes vs no)	1.30	0.71 to 2.37	.40
IL-6 receptor inhibitors (yes vs no)	0.37	0.19 to 0.72	.004
Therapeutic anticoagulation (yes vs no)	0.86	0.44 to 1.70	.67

aHR = adjusted hazard ratio.

observational design, our findings must not be used to rule in or rule out the clinical benefit of zinc in the management of COVID-19. In addition, given the short period of observation, the effect estimate provides only a signal for a treatment effect, or the lack thereof, and must not be interpreted as the absolute number of days of survival among the treated.[10] Instead, our analyses may be used by prospective trials to determine the sample size necessary to assess survival benefit or may galvanize investigation using other outcomes of interest.

Our analyses may reduce the effects of confounders and selection bias in nonrandomized data.[10] Our findings showing an increased mortality risk among older patients, men, and those with higher admission severity are consistent with findings of prior literature and support the use of our methodology.[9] Future studies should look into the efficacy of IL-6 receptor inhibitors, which in this cohort was associated with lower in-hospital mortality.

This study is limited by its retrospective nature and the possibility of residual confounding. Given the single-center design, the sample size, and the larger proportion of patients given zinc sulfate, we are unable to rule out the possibility that the study was not powered to detect a small effect size––a limitation that motivated us to use ATET estimation to investigate the effect of zinc on COVID-19. Prospective randomized trials are needed to establish the utility of zinc in the management of COVID-19.

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