Clinical Infectious Diseases

RESEARCH ARTICLE

Twice daily oral zinc in the treatment of patients with Coronavirus Disease-19

A randomized double-blind controlled trial

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***Background*:** Zinc supplementation has been considered one of the potential therapies for coronavirus disease-19 (COVID-19). We aimed to examine zinc efficacy in adult patients with COVID-19 infection.

Methods: We conducted a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Patients tested positive for COVID-19 without end organ failure were randomized to oral zinc (n=231) or matching placebo (n=239) for 15 days. The primary combined outcome was death due to COVID-19 or ICU admission within 30 days after randomization. Secondary outcomes included length of hospital stay for inpatients and duration of COVID-19 symptoms with COVID-19 related hospitalization for outpatients.

***Findings*:** One hundred ninety patients (40.4%) were ambulatory and 280 patients (59.6%) were hospitalized. Mortality at 30-day was 6.5% in Zinc group and 9.2% in Placebo group [odds ratio (OR) 0.68 (0.34-1.35)]; ICU admission rate was respectively 5.2% and 11.3% [OR 0.43 (0.21-0.87)]. Combined outcome was lower in zinc group compared to placebo group [OR 0.58 (0.33-0.99)]. Consistent results were observed in prespecified subgroups of patients with age<65 years, those with comorbidity, and those who needed oxygen therapy at baseline. Length of hospital stay was shorter in zinc group compared to placebo group [difference 3.5 days, 95% CI (2.76-4.23)] in inpatients group; duration of COVID-19 symptoms decreased with zinc treatment compared to placebo in outpatients [difference 1.9 days, 95% CI (0.62-2.6)]. No severe adverse events were observed during the study.

***INTERPRETATION*:** Our results showed that in COVID-19 patients, oral zinc can decrease 30-day death and ICU admission rate and can shorten symptoms duration.

INTRODUCTION

Coronavirus disease-19 (COVID-19) pandemic has created a global health crisis since its first emergence in China late December 2019. Its high transmissibility and increased morbidity have made COVID-19 a serious public health threat and burden.[1] Various drugs were initially proclaimed effective against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the etiological agent of COVID-19; they were later disapproved.[2] Like in many other diseases, regulation of white blood cell production using immuno-nutrition is a novel concept that could be applied to COVID-19. Some molecules and nutrients such as zinc play central roles in keeping the function and integrity of the immune system.[3,4] It has been shown that serum zinc was inversely correlated with outcome in sepsis, highlighting the potential value of the zinc approach in COVID-

19 treatment.[5-8] Nevertheless, there is still limited evidence to support such a role of zinc in COVID-19, except from observational studies and few randomized clinical trials with small sample size.[9-11] The objective of the present trial was to evaluate the effect of zinc supplementation in non-critically ill COVID-19 patients. Our a priori hypothesis was that supplementation with zinc would reduce 30-day mortality and need to intensive care unit (ICU) admission.

METHODS

Study design

VIZIR was a prospective, randomized, double-blind, placebo-controlled, multicenter trial, conducted from 15 February 2022 to 4 May 2022. The protocol was approved by the institutional review board of all the participating centers. VIZIR study was carried out in Tunisia, in 3 referral Tunisian university hospitals (Fattouma Bourguiba Hospital Monastir, Sahloul Hospital Sousse, Farhat Hached Hospital Sousse) and 2 non-university hospitals (Ksar Hlel Hospital, Teboulba Hospital). Patients were firstly screened in the COVID-19 triage unit of each participating centers. Written informed consent was obtained from all patients before enrolment.

Study participants

Patients were eligible if they were 18 years or older, had a diagnosis of COVID-19. In all included patients, diagnosis of COVID-19 was performed by RT-PCR or rapid antigen test. Diagnostic imaging (CT-scan) is performed in patients who have negative first RT-PCR test results with concern for a false-negative RT-PCR (observer errors and by low viral RNA levels). In all cases, a diagnostic confirmation by repeated RT-PCR test was carried out.

Exclusion criteria

Patients were excluded if symptoms started beyond 7 days before inclusion. Patients under zinc treatment or known hypersensitivity to zinc, severe comorbid conditions including heart, liver, or renal failure (estimated glomerular filtration rate $\leq$30 mL/min/1.73 m^2), malignancies, unsuitability for oral administration, swallowing disorders; cognitive impairments or poor mental status and need for immediate ICU admission justified by the need for use of respiratory or cardiovascular organ support (oxygen delivered by high-flow nasal cannula, non-invasive or invasive mechanical ventilation, or the use of vasopressors or inotropes) were exclusion criteria. Refusal or inability to consent or to communicate were also exclusion criteria.

Randomization and interventions

For all included patients we collected the following data at the first medical visit: demographic and clinical data including age, gender, comorbidities, completed vaccination status (currently one, two or three doses of COVID-19 vaccine depending on the vaccine), symptoms, current treatment and physical examination findings, and severity grades [asymptomatic (grade I), symptomatic

without O_2 support (grade II), and symptomatic with O_2 support (grade III)]. Masked randomization was centralized and done electronically through an automated interactive web-response system (Dacima Software). Participants were randomly assigned (1:1) to either zinc treatment (Zinc group) or placebo (Placebo group). Allocation sequence was not stratified. Patients enrolled in Zinc group received 25mg of elemental zinc (Zinc plus®, Opalia Recordati, Tunisia) twice a day for 15 days. Patients enrolled in Placebo group received one capsule twice a day for 15 days. Zinc and placebo capsules were prepared, packed and specified by code numbers in similar shapes. The trial team, site staff, and patients were unaware of the randomized assignments. All patients received supportive care according to national guidelines. Standard of care background therapy included corticosteroids, prophylactic anti-coagulation, supplemental oxygen, and other treatments as clinically indicated. Trained research coordinators followed patients prospectively at home (outpatients were contacted via telephone calls) or in the hospital documenting compliance with study treatment and outcomes. For outpatients, we assessed at 15-day and 30-day follow-up the evolution of clinical symptoms, duration and appearance of new symptoms, the need for hospitalization, need for ICU admission and survival status. All outpatients were encouraged to report all adverse events and symptoms evolution during the study period. For inpatients, we recorded death and need for ICU admission, length of ICU and hospital stay at 30-day evaluation. The database was a validated electronic case report form (eCRF). All eCRF users were trained as per completion guidelines and the data entry was done directly by the study staff with the patients.

Outcome criteria

The primary outcomes measure was death rate, ICU admission rate, and combined outcome within 30 days after randomization. Secondary outcomes included length of stay in hospital and protocol treatment safety. In outpatients, secondary outcome included also duration of COVID-19 symptoms, need for hospitalization, and oxygen therapy. We assessed all the secondary outcomes through 30 days after randomization.

Statistical analysis,

Sample size calculation: Based on a projected combined event rate (death and ICU admission) at 30-day estimated at 30%, and using an alpha value of 0.05, a study of 460 patients will have 80% power to detect a 10% decrease in absolute risk in the zinc treatment group compared with the placebo group. The sample size was increased by 5% to compensate for the number of patients randomized but lost to follow-up, for a total sample size of 485 patients. We report mean and SD, median and IQR, frequency and percentages, depending on the nature and distribution of variables. We compared continuous variables with the Student's t test. We compared categorical variables using Fisher's exact test. We included Odds ratio(OR) and 95% confidence intervals (CIs) in the comparison of 30-day primary and secondary outcomes for each intervention, both overall and in prespecified subgroups, defined according to characteristics at randomization: age, gender, comorbidity (obesity, history of arterial hypertension, cardiac disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma, or kidney disease), and baseline clinical severity

grading.The differences in the distributions of the severity grades between the Zinc group and the Placebo group at 15 days and at 30 days were analyzed with the use of Wilcoxon–Mann–Whitney test generalized odds ratios. Frequency of adverse events and complications were compared with the χ^2 test. All analyses were done according to the intention-to-treat principle, without adjustment for multiple comparisons. Two-sided p values of less than 0·05 were considered to indicate statistical significance. All analyses were done using the Statistical Package for Social Sciences software (SPSS version 20.). This study is registered with ClinicalTrials.gov, number NCT05212480.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We screened 1200 patients; 513 were eligible, and 482 were enrolled (Figure 1). Twelve randomly assigned patients could not be evaluated, 8 withdrew consent and 4 because we could not ascertain their 30-day vital status; thus, there were 470 patients in the final intention-to-treat analysis. These patients were randomly assigned to either Zinc group (231 patients) or Placebo group (239 patients). Baseline characteristics of the included patients were summarized on table 1. One hundred ninety patients (40.4%) were treated as outpatients and 280 patients (59.6%) were hospitalized. The mean duration between the first COVID-19 symptom and inclusion in the study was 4.6±1.1 days. The mean age of patients was 54.2±17.3 years, 53% were men, and the mean BMI was 27.3±3.8 kg per m^2. The most frequent comorbidities were hypertension (23.4%) and diabetes (19.4%). About 20% of patients have a history of complete anti- COVID-19 vaccination (n=94) and 23% received at least one dose (n=108). Asthenia (56.4%), cough (47%) and fever (38.9%) were the most common signs at initial presentation; 38.9% of patients had oxygen saturation less than 92%. Adjunctive treatment included paracetamol (54.3%), steroids (37.7%), anticoagulants (48.3%) and oxygen via facial mask (42.9%). Patients did not receive any antivirals during the trial. There were no significant differences in baseline characteristics between the two groups. Specifically, distribution of severity grades in the two groups was similar; 5.6% and 5.9% of the Zinc and Placebo groups respectively were grade I, 34.2% and 35.1% were grade II, and 60.2% and 59% were grade III. Overall, 37 deaths were reported, 30 (81.1%) occurred in ICU, and 7 (18.9%) outside ICU. In Zinc group, 30-day mortality was 6.5% (95% CI, 3.3 - 9.6), ICU admission rate was 5.2% (95% CI, 2.3 - 8.0), and rate of combined outcome was 10.4% (95% CI, 6.4 - 14.3). In Placebo group, 30-day mortality was 9.2% (95% CI, 5.5 - 12.8), ICU admission rate was 11.3% (95% CI, 5.5 - 12.8), and rate of combined outcome was 16.7% (95% CI, 12.0 - 21.4) (Table 2). Combined outcome was reduced in Zinc group compared to Placebo group [OR 0.58

(0.33 - 0.99)] (Table 2); this difference was mainly related to the decrease of ICU admissions [OR 0.43 (0.21 - 0.87)] while death rate was not different between study groups [OR 0.68 (0.34-1.35)]. In prespecified subgroup analysis, there was evidence of a treatment positive effect with zinc, as compared with placebo in inpatients, patients aged >65 years, patients with comorbidity, and those requiring oxygen at baseline regarding combined primary outcome (Figure 2). In inpatients subgroup, the length of hospital stay was reduced in Zinc group compared to Placebo group (7.1±3.4 days versus 10.6±2.8 days; difference 3.5 days, 95% CI 2.76 - 4.23). In outpatients subgroup, duration of COVID-19 symptoms was shorter in Zinc group compared to Placebo group (9.6±4.1 days versus 12.8±6.7 days difference 1.9 days, 95% CI 0.62 - 2.6), whereas need for hospital admission rate was similar in both groups (1.2% vs 3.8% respectively) [OR 0.30 (0.03-2.8)]. The distributions of patients in the two groups on the basis of severity grade at baseline, at 15 and 30-day evaluation are shown in Figure 3. The percentage of grade I patients increased to 22.1% and 64.3% in Zinc group respectively at 15-day and 30-day compared to 9.7% [difference 12.7% (2.4 to 22.4)] and 49.6% in Placebo group [difference 15% (1.1 - 28.3)]. The percentage of grade III patients decreased to 46.8% (-13.4%) in Zinc group and increased to 60.5% (+1.5%) in Placebo group at 15-day [difference 14.9% (0.01 - 27.4)]; at 30-day the percentage of grade III patients decreased to 13.5% (-46.7%) in Zinc group and 23.1% (-35.9%) in Placebo group [difference 10.8% (-1.03 - 20.2)]. With regard to adverse events, there were no important between-group differences in the incidence of adverse events during the treatment period. Minor adverse events were observed in 9 patients (3.9%) of Zinc group and 17 patients (7.1%) of Placebo group [OR 0.52 0.23–1.12)]. Most of them were digestive symptoms. No treatment-related serious adverse events were reported in either treatment group.

DISCUSSION

In this multicenter, randomized, double blinded trial involving COVID-19 patients, a significant and clinically meaningful decrease of 30-day ICU admission rate and shorter COVID-19 symptoms was observed with oral zinc administered for 15 days. In our prespecified subgroup analyses, we found that this benefit was especially observed in aged patients and those with comorbid conditions or those who need oxygen.

Activity of zinc against infectious pathogens has been demonstrated in a variety of viral species.[12-16] However, there is very scant information available on the role and effect of zinc in coronavirus disease.[17-22] Jothimani et al[19] in a recently published study including of 47 COVID-19 patients, demonstrated that zinc deficiency was present in more than the half (57.4%) of their cohort and was associated with prolonged hospitalization and increased mortality compared to a control group. In four COVID-19 outpatients, Finzi et al reported that treatment with zinc reduced disease symptoms within 24 hours.[20] Several clinical trials are currently investigating the effects of

various doses of zinc either alone or with ionophores on the initiation and the progression of COVID-19 patients.

To our knowledge, this study is the first well powered, placebo-controlled clinical trial to report results of zinc for the treatment of patients with COVID-19. When administered orally to patients hospitalized with COVID-19 without end-organ failure, zinc demonstrated its efficacy to prevent ICU admission and to reduce hospital length of stay; for outpatients, zinc reduced symptom duration. Zinc should be considered for the treatment of patients with COVID-19. Major strengths of our trial include being a randomized controlled trial and the large sample size. Moreover, subgroup analyses showed a consistent result across both in low and high risk patients. For inpatients, although risk of death among patients receiving zinc and placebo was similar, the absolute risk reduction of ICU admission was approximately 10% and length of hospital stay was reduced by 3 days. These results suggest that, for survivors the disease trajectory is milder in zinc group patients, with reduced need for hospital care and organ support. In outpatients, zinc treatment was associated with reduction of COVID-19 symptoms duration by approximately 3 days besides there is a trend for less hospital admissions in patients in Zinc group but the difference was not significant with regard to the small sample size of this category of patients. Our results should be highlighted with regard to not only the magnitude of zinc positive effect but also to the fact that this product is readily available at a low price to a larger percentage of the population with minimal risk.

This trial has several limitations. First, generalizability is limited beyond patients with moderate clinical severity. Second, whether using zinc at higher doses than those prescribed in this trial would lead to different results is a question that needs to be investigated. Of note, the dose of zinc used in our study is within the range that is currently recommended[23]. Of relevance, 50 mg of zinc per day was found to be tolerable and unlikely to induce toxicity. Third, one could argue that longer treatment with zinc (>15 days) could add more clinical benefit. It is an important question, and we probably need specific data on long-term outcome and the possible preventive effect of zinc against long-COVID risk[24].The success of zinc treatment may be dependent on zinc serum levels; we did not assess serum zinc in the present study, and so we could not verify this relationship. Finally, although follow-up via telephone contact would not replace face to face visit, it was possible for us to assess outcomes in almost all of our included patients.

In summary, oral zinc treatment for 15 days is associated with a nearly 40% reduction of death and ICU admission with shortening of symptom duration in COVID-19 patients. Our results have very important clinical relevance in the absence of specific effective curative treatment.

Conflicts of interest: none declared.

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SARS-CoV-2, COVID-19, Zinc, outcome.

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Table1. Population characteristics at inclusion

	Zinc n=231	**Placebo n=239**
Age ;mean (SD)	54.6(17.4)	53.7(17.2)
Male gender; n (%)	121 (52.4)	128 (53.6)
BMI kg.m-2 ; mean (SD)	27.2(3.4)	27.4(4.2)
Active smoking; n (%)	36(15.6)	36(15.1)
Type 2 Diabetes; n (%)	37(16)	54(22.6)
Hypertension; n (%)	51(22.1)	59(24.7)
Coronary artery disease n (%)	5(2.2)	9(3.8)
COPD; n (%)	7(3)	4(1.7)
Asthma; n (%)	6(2.6)	5(2.1)
Renal failure; n (%)	4(1.7)	1(0.4)
Clinical signs, n (%)		

Asthenia	128(55.4)	137(57.3)
Cough	116(50.2)	105(43.9)
Fever	94(40.7)	89(37.2)
Polypnea	70(30.3)	73(30.5)
Headache	62(26.8)	72(30.1)
Chest Pain	33(14.3)	30(12.6)
Diarrhea	29(12.6)	33(13.8)
Joint pain	25(10.8)	16(6.7)
Anosmia	19(8.2)	28(11.7)
Vomiting	17(7.4)	17(7.1)
Taste Loss	13(5.6)	20(8.4)
Abdominal pain	10(4.3)	18(7.5)
Vital signs, mean (SD)		
Systolic blood pressure mmHg	114(41)	119(38)
Diastolic blood pressure mmHg	75(25)	76(22)
Respiratory rate c/min	22(4)	21(3)
Heart rate b/min	95(16)	94(15)
Pulse oxygen saturation %	92(5)	93(3)
Hospitalization, n (%)	146(63.2%)	134(56.1%)
Medication for COVID-19 other than the study drug, n (%)		
Dexamethasone or other steroids	87 (37.7)	90 (37.7)
Oxygen	106(45.9)	96(40.2)
Antibiotics	52(22.5)	45(18.8)
Paracetamol	132(57.1)	123(51.5)
Vitamin C	26(11.3)	26(10.9)
Anticoagulants	119(51.5)	108(45.2)

Abbreviations: COPD chronic obstructive pulmonary disease; BMI body mass index; SD Standard deviation

Table 2. 30-day primary outcome

	Zinc n= 231	Placebo n=239	P	OR [IC95%]
Death, n (%)	15 (6.5)	22 (9.2)	0.27	0.68 [0.34-1.35]
ICU admission, n (%)	12 (5.2)	27 (11.3)	0.01	0.43 [0.21-0.87]
Composite outcome, n (%)	24(10.4)	40 (16.7)	0.04	0.58 [0.33-0.99]

Abbreviation: ICU Intensive Care Unit

FIGURE LEGEND

Figure 1. Flow Diagram

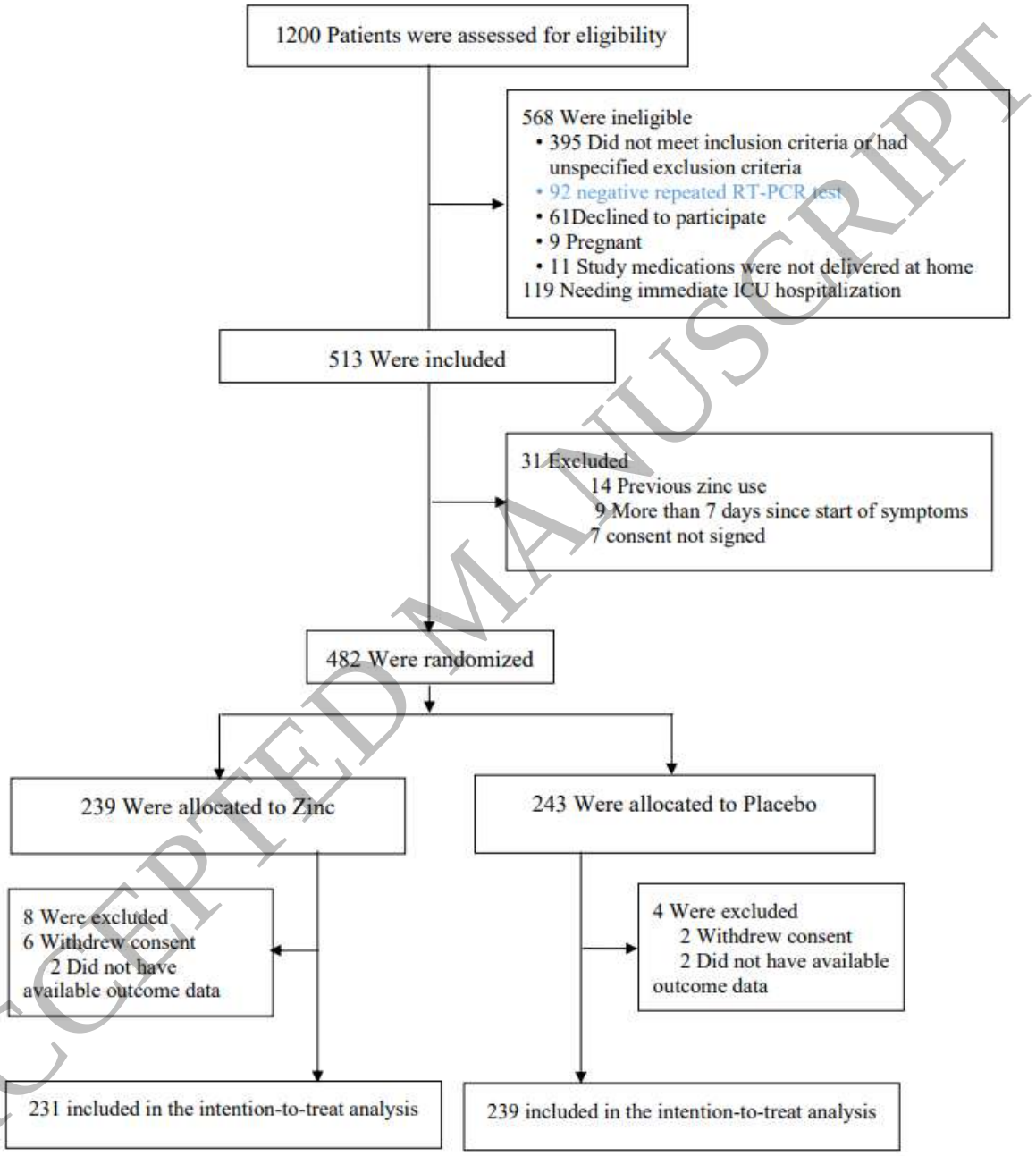

Figure 2. Forest plot of subgroup analysis of primary combined outcome including COVID-19-related death or intensive care unit admission at 30-day follow-up. Analyses of Zinc as compared with Placebo for the primary combined outcome including COVID-19-related death or intensive care unit admission at 30-day follow-up.

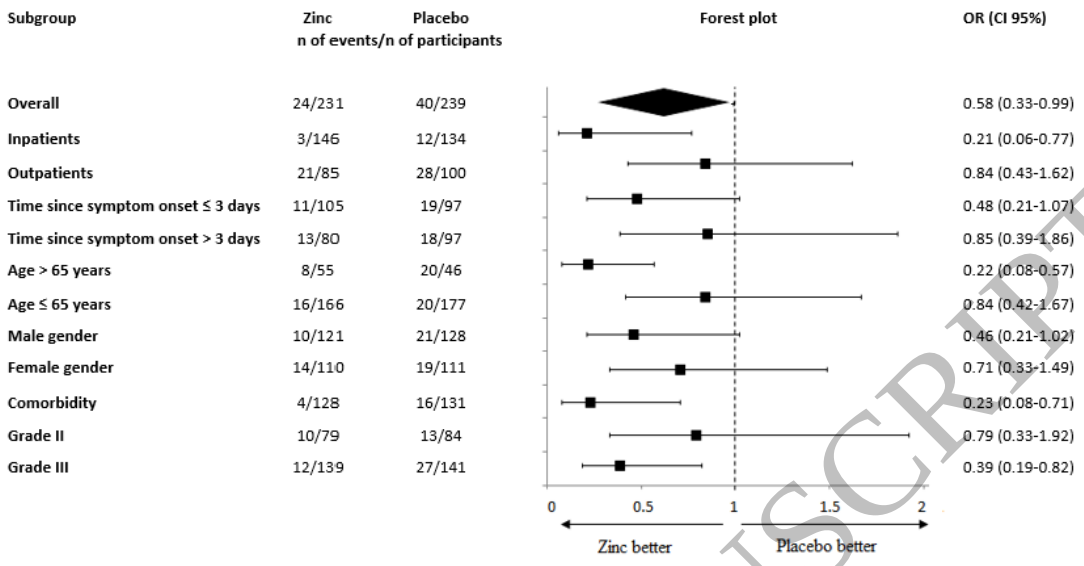

Figure 3. Shown is the distribution of severity grades in Zinc and Placebo groups at baseline, at day 15, and at day 30. The severity grades indicate the following: 1, no symptoms at all; 2, COVID-19 symptoms without oxygen requirement; 3, COVID-19 symptoms with oxygen requirement. At baseline, there was not a significant difference between the Zinc group and the Placebo group in the overall distribution of severity grades. At 15day, a significant difference between the study groups was observed (p=0.01). Distribution of severity grades at 30 day did not show significant difference between study groups.