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The prognostic role of micronutrient status and supplements in COVID-19 outcomes: A systematic review

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A R T I C L E I N F O

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A B S T R A C T

Micronutrients constitute an adjuvant treatment for respiratory viral infections. Since there is no effective antiviral therapy for COVID-19 yet, adjuvant intervention for the survival of critically ill patients may be significant. Search of the PubMed, CINAHL and Cochrane databases was carried out to find human studies investigating the prognostic role of micronutrient status and the effects of micronutrient supplementation intervention in COVID-19 outcomes of adult patients. Patients with certain comorbidities (diabetes mellitus type 2, obesity, renal failure, liver dysfunction etc.) or pregnant women were excluded. 31 studies (27 observational studies and 4 clinical trials) spanning the years 2020–2021, pertaining to 8624 COVID-19 patients (mean age±SD, 61 ± 9 years) were included in this systematic review. Few studies provided direct evidence on the association of serum levels of vitamin D, calcium, zinc, magnesium, phosphorus and selenium to patients' survival or death. Vitamin D and calcium were the most studied micronutrients and those with a probable promising favorable impact on patients. This review highlights the importance of a balanced nutritional status for a favorable outcome in COVID-19. Micronutrients' deficiency on admission to hospital seems to be related to a high risk for ICU admission, intubation and even death. Nevertheless, evidence for intervention remains unclear.

1. Introduction

In December 2019, the Municipal Health Commission of Wuhan identified a large number of cases of viral pneumonia of unknown etiology. Soon, through sequence analysis, a new virus of the coronavirus family was identified and named SARS-CoV-2, while the resulting disease was named Corona Virus Induced Disease 2019 (COVID-19) (Zhu et al., 2020). By February 2020 the widespread transmission of the virus outside China became apparent, while on March 12, 2020, the World Health Organization (WHO) characterized the situation as a pandemic (WHO, 2020a). In early February 2021 the cases had exceeded 100 million worldwide, while over 2 million people had lost their lives due to COVID-19 (WHO, 2020b).

While SARS-CoV-2 seems to be accompanied by lower mortality rates than the previous corona viruses MERS and SARS-CoV-1, it is more contagious (Lu et al., 2020; Wang et al., 2020). Current estimates of mortality rates range from 0.5 to 3.5% overall (compared to 0.1% for seasonal flu) and are significantly higher in the elderly, people with comorbidities, or the immunosuppressed. Key risk factors are age over 65 years, coronary heart disease, heart failure, diabetes mellitus, chronic obstructive pulmonary disease, obesity and smoking (Guo et al., 2020; Huang et al., 2020a; Wang et al., 2020).

Vaccination has been proven a safe and efficient strategy against SARS-CoV-2 spread, the rapidity of which has substantially reduced the

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number of new COVID-19 cases and their severity in highly vaccinated countries, while microRNAs have been introduced as promising antiviral agents aside from their crucial use in vaccine technology (Abedi et al., 2021). However, antiviral treatment and evidence of other favorable interventions need further development (Tavilani et al., 2021; Whittaker et al., 2021). Regarding prognosis, risk factors have been clarified but recovery predictors are still under research (Abrahim et al., 2020; Alvarez-Esteban et al., 2021; Ny et al., 2021; Rydwik et al., 2021; Tolossa et al., 2021).

Recent reviews agree that micronutrients play a crucial role in COVID-19 progression, prognosis and survival, as in multiple other viral infections that primarily affect the respiratory tract (Cheng, 2020; Grant et al., 2020; Rozga et al., 2021; Zhang and Liu, 2020). The well-known essential role of vitamins, minerals, metalloids and other micronutrients in many biological, biochemical and molecular processes along with in vivo studies demonstrating a significant role of several micronutrients in COVID-19, led clinicians use micronutrients as a promising adjuvant therapy against SARS-CoV-2 severe pneumonia (Domingo and Marquès, 2021; Thakur et al., 2021). The already studied nutritional interventions for SARS-CoV and MERS-CoV infections and the underlying mechanism *via* which micronutrients inhibit these viruses are encouraging, as SARS-CoV-2 shares a 79.5% sequence identity with SARS-CoV and 50% with MERS-CoV (Jin et al., 2020; Jin et al., 2020; Zhu et al., 2020). Especially zinc and flavonoids have been proven to inhibit a special protease of the virus called 3C and improve survival (Jo et al., 2019, 2020; Keil et al., 2016; Lin et al., 2017; Ryu et al., 2010).

This systematic review summarizes and describes human studies investigating the prognostic role of micronutrient status and the effects of micronutrient supplementation intervention in COVID-19 outcomes of adult patients.

2. Materials and methods

2.1. Search strategy

The present systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic and comprehensive search of the PubMed, CINAHL and Cochrane databases was carried out for papers published from database inception until April 27, 2021. We used the following search algorithm: ("Wuhan coronavirus" or "Wuhan virus" or "novel coronavirus" or "nCoV" or "SARS-CoV-2″ or "SARS 2″ or "severe acute respiratory syndrome coronavirus 2″ or "COVID-19″ or "coronavirus disease 2019 virus" or "2019-nCoV" or "2019 novel coronavirus" or "severe acute respiratory syndrome coronavirus 2″ or "coronavirus" or "coronaviruses") AND ("Vitamin D″ or "vitamin D″ or "25-OH-calciferol" or "25 hydroxy calciferol " or "25-OH-vit D″ or "25-OH-vitamin d" or "25 hydroxy vitamin d" or Mg or zinc or "vitamin C″ or "ascorbate" or "ascorbic acid" or Ca or antioxidants or micronutrients) AND patients AND prognosis. The references of all eligible articles were also checked thoroughly.

2.2. Selection criteria

The eligibility criteria were based on the PICOS (Participants, Intervention, Comparison, Outcomes, Study design) acronym. Studies of COVID-19 inpatients, outpatients or both were included in the review, if they fulfilled the following criteria: (i) written in English language; (ii) investigated outcomes among SARS-CoV-2 infected adults according to specific micronutrients' blood levels; (iii) were prospective or retrospective cohort studies or cross-sectional studies or clinical trials; (iv) the study presented its final results; (v) there was a precise determination of the patients' levels of the studied micronutrient at the beginning and/or during the study protocol, so that objective evidence of the sufficiency or insufficiency of the studied micronutrient could be provided. Regarding the determination of prognosis, all studies looking for outcomes such as severe disease, need for mechanical ventilation (MV), intensive care unit (ICU) admission, mortality, end or duration of hospitalization, reduction of blood inflammatory markers and those estimating certain survival scores were included, to enclose only studies with specific or measurable outcomes. Studies were excluded if they focused only on patients with certain comorbidities (such as diabetes mellitus type 2, obesity, renal failure, liver dysfunction etc.) or pregnant women. These populations were excluded because their pre-comorbid conditions might had precluded potentially beneficial effects of vitamin supplements, whereas pregnant women might had already been taking nutrient supplements to maintain adequate micronutrient levels throughout gestation. Studies evaluating prognosis only throughout the improvement of symptoms were also excluded.

2.3. Quality assessment and data extraction

Titles and abstracts of studies were retrieved using the search strategy for all three databases and were extracted independently by three different authors (EP, DV and FB). These authors (EP, DV and FB) screened for eligibility the titles and abstracts of the retrieved papers and analyzed the full-text articles that met the eligibility criteria. Data extraction was performed as following: first author and year of publication, studied micronutrient, country, study design, demographic information (age, sex), sample size, COVID-19 test type for diagnosis, time of micronutrients laboratory evaluation, criteria for prognosis evaluation, results. Automation tools were not used in this process.

2.4. Compliance with ethics guidelines

This article is a review of previously conducted studies, in accordance with the PRISMA guidelines.

3. Results

3.1. Search results and selection of studies

Initial search yielded 186 studies. After excluding irrelevant papers and those matching to the research subject but not complying with the eligibility criteria, the final step of the screening process resulted in 31 studies (14 published in 2020 and 17 in 2021) spanning the years 2020–2021. Among included studies, 27 were observational studies (19 retrospective, 4 prospective, 4 cross-sectional) and 4 were clinical trials (2 double-blind placebo-controlled). The PRISMA flow diagram shows the selection and exclusion of studies (Fig. 1).

Fourteen studies focused on vitamin D (Vit D) levels as a key-micronutrient in prognosis, 12 on calcium (Ca), 4 on zinc (Zn), 4 on magnesium (Mg), 3 on phosphorus (P), 2 on vitamin C (Vit C), 2 on selenium (Se), 2 on folate while iron (Fe), vitamin B12 (Vit B12), vitamin E (Vit E), melatonin, N-acetylcysteine and pentoxifylline were also studied.

3.2. Study characteristics

This systematic review included 8624 COVID-19 patients with a mean age of 61 years. Among them 527 participated in clinical trials. Three studies (2 observational and 1 clinical trial) included COVID-19 patients who had been admitted to the ICU since their first hospitalization day (Chavarría et al., 2021; Vassiliou et al., 2020; Zheng et al., 2021).

As outcomes indicating prognosis most studies (21/31) used mortality or survival as primary or secondary outcomes (Alamdari et al., 2020; Bennouar et al., 2021; Capone et al., 2020; Carpagnano et al., 2021; Doaei et al., 2021; Entrenas Castillo et al., 2020; Ersoz and Yilmaz, 2021; Heller et al., 2021; Infante et al., 2021; Karahan and Katkat, 2021; Kashefizadeh et al., 2020; Lohia et al., 2021; Meisel et al., 2021; Moghaddam et al., 2020; Murai et al., 2021; Radujkovic et al., 2020; Sun

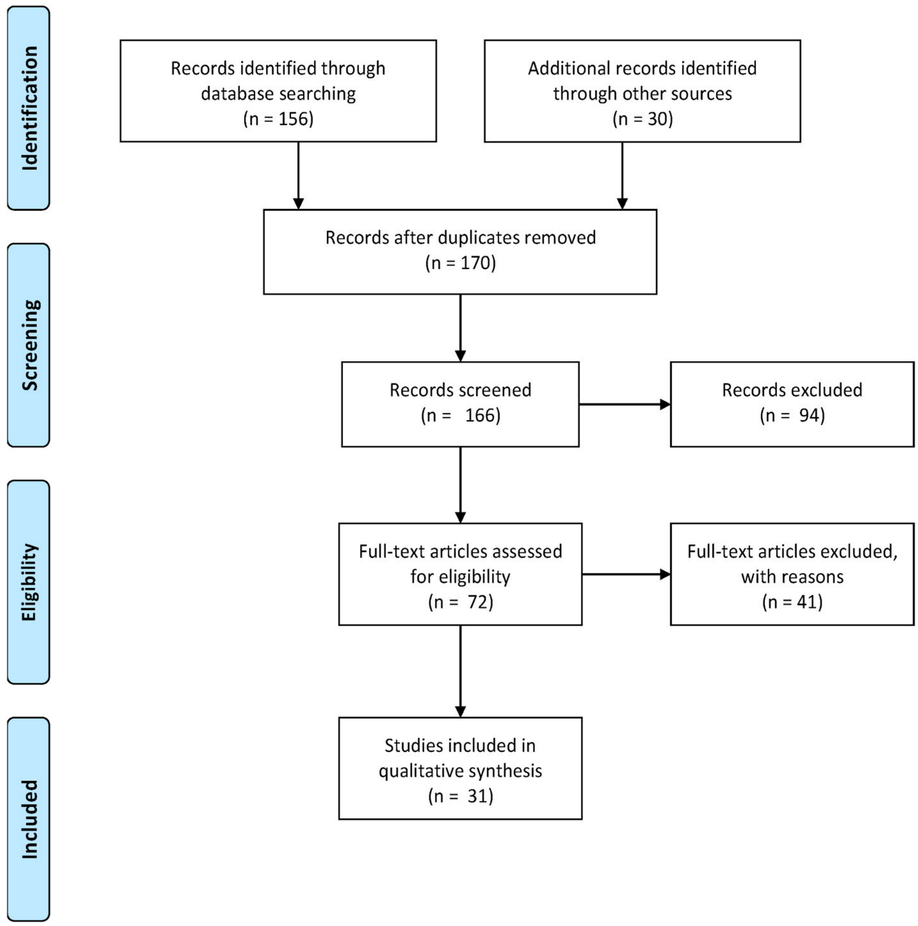

Fig. 1. PRISMA flow diagram of study selection.

et al., 2020; Tehrani et al., 2021; Tezcan et al., 2020; Vassiliou et al., 2020; Zheng et al., 2021). ICU admission or need for such admission was studied in 9/31 studies (Capone et al., 2020; Entrenas Castillo et al., 2020; Ersoz and Yilmaz, 2021; Lagier et al., 2020; Liu et al., 2020; Maghbooli et al., 2020; Murai et al., 2021; Tezcan et al., 2020; Yang et al., 2021), 9/31 studies used "length of hospitalization" (Capone et al., 2020; Entrenas Castillo et al., 2020; Ersoz and Yilmaz, 2021; Lagier et al., 2020; Liu et al., 2020; Maghbooli et al., 2020; Murai et al., 2021; Tezcan et al., 2020; Yang et al., 2021), MV was used by 5/31 (Liu et al., 2020; Murai et al., 2021; Radujkovic et al., 2020; Sun et al., 2020; Tezcan et al., 2020), blood levels of inflammatory markers were used by 8/31 (Carpagnano et al., 2021; Chavarría et al., 2021; Karahan and Katkat, 2021; Liu et al., 2020; Maghbooli et al., 2020; Radujkovic et al., 2020; Ricci et al., 2021; Yang et al., 2021) and 3/31 used already known weighted scores (Chavarría et al., 2021; Doaei et al., 2021; Ricci et al., 2021).

Almost all studies estimated blood levels of targeted micronutrients for all patients at least on admission. COVID-19 diagnosis was confirmed by polymerase chain reaction (PCR) test for all patients in all studies.

The main characteristics and results of the studies are presented in Tables 1 and 2, respectively.

3.3. Results on the prognostic role of each micronutrient

3.3.1. Vitamin D (Vit D)

Most studies in this systematic review focused on prognostic role of Vit D in COVID-19. Most observational studies presented Vit D blood levels on admission as prognostic factors given that in 5 studies survivors revealed higher levels on admission than non-survivors, while in 2 studies Vit D deficiency was related to higher mortality risk ratio (Bennouar et al., 2021; Carpagnano et al., 2021; Infante et al., 2021; Karahan and Katkat, 2021; Kashefizadeh et al., 2020; Radujkovic et al., 2020; Ricci et al., 2021; Tehrani et al., 2021; Vassiliou et al., 2020). MV was more common among patients with Vit D deficiency than patients with normal Vit D levels in a single study (Radujkovic et al., 2020). Inflammatory markers on admission were higher among patients with low Vit D levels than the rest or an inverse association between Vit D levels and inflammatory markers was detected (Carpagnano et al., 2021; Karahan and Katkat, 2021; Maghbooli et al., 2020; Radujkovic et al., 2020; Ricci et al., 2021). Finally, 4/14 studies concluded that Vit D was not associated to prognosis of COVID-19 patients (Allard et al., 2020; Ersoz and Yilmaz, 2021; Lohia et al., 2021; Murai et al., 2021), whereas one clinical trial targeting Vit D levels, reported significantly lower risk for ICU admission of the intervention group vs. controls, with only 1 patient receiving Vit D supplementation admitted to ICU (Entrenas Castillo et al., 2020).

3.3.2. Calcium (Ca)

Ca levels constituted a prognostic factor for COVID-19 patients. Survival was associated with normocalcemia and higher Ca levels (within normal limits) were related to higher survival rates (Bennouar et al., 2021; Kashefizadeh et al., 2020; J. Liu et al., 2020; Sun et al., 2020; Zheng et al., 2021). Low Ca levels were also a prognostic marker for the development of severe disease (Yang et al., 2021; Zhao et al., 2021). Duration of hospitalization and ICU admission were related to low admission Ca blood levels in some cases (Wu et al., 2020; Yang et al., 2021) whereas in 3 studies Ca was not a useful biomarker for prognosis (Alamdari et al., 2020; Allard et al., 2020; Tezcan et al., 2020).

Table 1
Main characteristics of included studies, study samples and micronutrients.

	First author, year	Micronutrient	Country	WHO region	Type of study	COVID-19 patients N	Age in years, mean (SD)	Females N (%)
1.	Chavarría et al., 2021	Vit C Vit E N-acetylcysteine Melatonin Pentoxifylline	Mexico	Americas	Clinical Trial (non-double-blind placebo-controlled)	110 in ICU	58 (13)	32 (29%)
2.	Ricci et al. (2021)	Vit D	Italy	Europe	Prospective	52 with lung involvement (22 Vit D deficient vs. 30 with normal Vit D)	77.5 (16) vs. 68.9 (18)	13 (59%) vs. 14 (47%)
3.	Infante et al. (2021)	Vit D	Italy	Europe	Retrospective	137 (78 survivors vs. 59 non-survivors)	65 (28) vs. 70 (29)	48 (35%)
4.	Ersoz and Yilmaz (2021)	Vit D Fe Vit B12 Folate	Turkey	Europe	Retrospective	310	57 (18)	149 (48)
5.	Kashefizadeh et al. (2020)	Ca Mg	Iran	Eastern Mediterranean	Retrospective	53	58 (13)	29 (55%)
6.	Zheng et al. (2021)	Ca	China	Western Pacific	Retrospective	180 in ICU	64	67 (37%)
7.	Karahan and Katkat (2021)	Vit D	Turkey	Europe	Retrospective	149	63 (15)	68 (46%)
8.	Bennouar et al. (2021)	Vit D Ca	Algeria	Africa	Prospective	120 critically ill	62 (18)	37 (31%)
9.	Lohia et al. (2021)	Vit D	USA	Americas	Retrospective	270 severely ill	64 (15)	153 (57%)
10.	Zhao et al. (2021)	Ca	China	Western Pacific	Retrospective	172 moderately ill (on admission)	65 (5)	90 (52%)
11.	Allard et al. (2020)	Zn Se Ca P Mg Vit D	France	Europe	Retrospective	108	62 (16)	44 (41%)
12.	Heller et al. (2021)	Zn Se	Germany	Europe	Cross-sectional	31	77 (5)	19 (54%)
13.	Maghbooli et al. (2020)	Vit D	Iran	Eastern Mediterranean	Cross-sectional	235	59 (15)	91 (39%)
14.	Radujkovic et al. (2020)	Vit D	Germany	Europe	Retrospective	185	60 (9)	90 (49%)
15.	Yang et al. (2021)	Ca P	China	Western Pacific	Retrospective	226 (104 confirmed patients and 122 suspected cases)	40 (4)	89 (39%)
16.	Jothimani et al. (2020)	Zn	India	South-East Asia	Prospective	47	34 (6)	18 (38%)
17.	Alamdari et al. (2020)	Ca Mg	Iran	Eastern Mediterranean	Cross-sectional	459	62 (12)	139 (30%)
18.	Tezcan et al. (2020)	Ca	Turkey	Europe	Retrospective	408	54 (16)	220 (54%)
19.	Entrenas Castillo et al. (2020)	Vit D	Spain	Europe	Clinical Trial (non-double-blind placebo-controlled)	76 inpatients	53 (10)	31 (41%)
20.	Capone et al. (2020)	Vit C Zn	USA	Americas	Retrospective	102	63 (3)	47 (46%)
21.	Carpagnano et al. (2021)	Vit D	Italy	Europe	Retrospective	42 (acute respiratory failure) inpatients to Respiratory Intermediate Care Unit	65 (13)	12 (29%)
22.	Moghaddam et al. (2020)	Se	Germany	Europe	Cross-sectional	33	77 (5)	19 (54%)
23.	Liu et al. (2020)	Ca	China	Western Pacific	Retrospective	107 severely ill	68 (2)	55 (51%)
24.	Lagier et al., 2020	Zn	France	Europe	Retrospective	3737	45 (17)	2033 (54%)
25.	Sun et al. (2020)	Ca Vit D	China	Western Pacific	Retrospective	241	65 (2)	129 (54%)
26.	Wu et al. (2020)	Ca	China	Western Pacific	Retrospective	125 discharged	55 (4)	59 (47)
27.	Meisel et al. (2021)	Folate	Israel	Europe	Retrospective	333	65 (3)	115 (35%)
28.	Doaei et al. (2021)	Omega-3 fatty acids	Iran	Eastern Mediterranean	Clinical Trial (double-blind placebo-controlled)	101 critically ill (28 intervention group *vs.* 73 control group)	66 (15) vs. 64 (14)	13 (46%) vs 28 (38%)
29.	Tehrani et al. (2021)	Vit D	Iran	Eastern Mediterranean	Retrospective	205 critically ill	60 (15)	79 (39%)
30.	Murai et al. (2021)	Vit D	Brazil	Americas	Clinical Trial (double-blind placebo-controlled)	240	56 (14)	104 (44%)
31.	Vassiliou et al. (2020)	Vit D	Greece	Europe	Prospective	30 in ICU	65 (11)	6 (20%)

Ca: calcium, COVID-19: Corona Virus Induced Disease 2019, Fe: iron, ICU: intensive care unit, Mg: magnesium, P: phosphorus, Se: selenium, Vit D: Vitamin D, Vit B12: Vitamin B12, Vit C: Vitamin C, Vit E: Vitamin E, Zn: zinc.

Table 2
Main results and protocols of included studies.

	First author, year	Micronutrients	Laboratory evaluations	Study protocol COVID-19 patient categories	Prognosis evaluation	Results
1.	Chavarría et al., 2021	Vit C Vit E N-acetylcysteine Melatonin Pentoxifylline	Baseline (day before treatment) and each day of treatment	• Per os or NG tube • 5 groups • Each group received pentoxifylline and 4/5 one of the other studied micronutrients • Treatment: every 12 h for 5 days	• SOFA, Apache II, SAPS II, Critical Illness Risk Score, COVIDGRAM and GCS scores •Inflammatory markers (CRP, IL-6, PCT)	IL-6 decreased in Vit C + Pentoxifylline, Vit E + Pentoxifylline, and NAC + Pentoxifylline treatments CRP decreased with all treatments PCT decreased in Vit C + Px, Vit E + Px and NAC + Px groups Antioxidant therapies improved all survival scores
2.	Ricci et al. (2021)	Vit D	Hospital admission	Vit D deficient (<10 ng/ml) or not	• SOFA, LIPI and TS scores • IL-6, hs-CRP, PCT	Higher IL-6 in Vit D deficient patients on admission Higher SOFA, LIPI and TS scores in patients with Vit D deficiency Higher mortality rate in Vit D deficient patients
3.	Infante et al., 2021	Vit D	Hospital admission	Survivors Non-survivors	Mortality	Higher Vit D in survivors *vs.* non-survivors Inverse association between Vit D and risk of in-hospital mortality
4.	Ersoz and Yilmaz (2021)	Vit D Fe Vit B12 Folate	Hospital admission	2 groups (ICU admission, intubation and death)	ICU admission Intubation Mortality	Higher Vit B12 in ICU or intubation patients and non-survivors Lower Fe in worse prognosis patients for all three factors Lower folate in patients in need for ICU admission
5.	Kashefizadeh et al. (2020)	Ca Mg	Hospital admission	Survivors Non-survivors	Length of hospitalization Mortality	Significantly lower Ca of non-survivors *vs.* survivors Insignificantly lower Mg on admission of survivors *vs.* non-survivors
6.	Zheng et al. (2021)	Ca	Every day	Survivors Non-survivors	Mortality	Significantly lower Ca on admission and on day of death of non-survivors *vs.* survivors
7.	Karahan and Katkat (2021)	Vit D	Hospital admission	Survivors Non-survivors	COVID-19 Severity Mortality Inflammatory markers including CRP	Lower Vit D in patients with severe-critical disease *vs.* moderate disease 93% of critically ill patients presented with Vit D insufficiency Vit D levels higher in survivors Vit D independently associated with mortality and negatively related to CRP
8.	Bennouar et al. (2021)	Vit D Ca	Hospital admission	Vit D: • deficient ≤20 ng/ml • insufficient 21–29 ng/ml • normal ≥30 ng/ml	In-hospital mortality within 28 days of admission	Significantly lower Ca and Vit D on admission of non-survivors *vs.* survivors Significant dose effect relation between both Vit D and Ca to mortality ratio (highest mortality ratio in patients with lowest levels for both micronutrients)
9.	Lohia et al. (2021)	Vit D	Hospital admission	Categorized according to each outcome separately	Mortality MV Thromboembolism (DVT, PE)	No association of Vit D with mortality, MV, ICU admission, thromboembolism
10.	Zhao et al. (2021)	Ca	Hospital admission	Categorized according to 2 outcomes	Critical illness or discharge with mild disease	Low Ca was a risk factor for severe disease Significantly lower Ca in severe *vs.* moderate disease
11.	Allard et al. (2020)	Zn Se Ca P Mg Vit D	Hospital admission	Categorized according to levels of each micronutrient separately	Severe COVID-19 pneumonia	Lower Zn, P and higher Mg in severe disease
12.	Heller et al. (2021)	Zn Se	Mean 5th (SD = 4) day of hospitalization	Survivors Non-survivors	Mortality	Most patients Zn deficient Zn significantly lower in non-survivors *vs.* survivors Zn increased consistently in both survivors and non-survivors throughout hospitalization Linear association between Zn and Se

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Table 2 (*continued*)

	First author, year	Micronutrients	Laboratory evaluations	Study protocol COVID-19 patient categories	Prognosis evaluation	Results
						Increasing Se day-by-day in survivors vs. stable Se in non-survivors
13.	Maghbooli et al. (2020)	Vit D	Hospital admission	Categorized according to Vit D cut-off: 30 ng/ml	Duration of Hospitalization ICU admission Severe disease (CDC criteria) CRP levels>40 mg/dl	Higher CRP in Vit D insufficient patients Vit D sufficiency independently associated with decreased disease severity No differences in hospitalization duration and ICU admissions between patients with or without Vit D sufficiency
14.	Radujkovic et al. (2020)	Vit D	Hospital admission	Inpatients Outpatients Median observation: 66 days	IMV Mortality IL-6 levels for inpatients	Vit D-deficient patients: • more commonly inpatients than outpatients • higher risk of IMV and/or death • higher median IL-6 at hospitalization
15.	Yang et al. (2021)	Ca P	Hospital admission ICU admission Discharge	Categorized according to each outcome independently	Disease severity (moderate vs. severe/critical) CT score ICU admission (+days of staying) Hospitalization days Inflammation markers	Significantly low P commonly detected in severe disease Low Ca in severe disease. Significantly more patients with low P and/or low Ca admitted to ICU *vs.* patients with normal levels Low Ca and P significantly correlated with low CT scores
16.	Jothimani et al. (2020)	Zn	6 h post- admission	Categorized according to Zn cut-off: 80 μg/dl All patients received multivitamins, including Vit C 500 mg bd and Zn 150 mg OD (after the test) as per standard care	Duration of hospitalization Disease severity	Zn deficient patients *vs.* patients with normal levels: • significantly more complications • significantly higher IL-6 • more hospitalization days • higher trend of death
17.	Alamdari et al. (2020)	Ca Mg	Hospital admission	Categorized according to studied outcome	Mortality	Survivors had significantly higher Mg on admission than those who died
18.	Tezcan et al. (2020)	Ca	Hospital admission	Categorized according to each studied outcome	ICU admission MV Duration of hospitalization Mortality	OR = 0.14 (NS) for mortality of hypocalcemic *vs.* normocalcemic patients on admission
19.	Entrenas Castillo et al. (2020)	Vit D	Hospital admission or day before treatment	Intervention group Control group (2:1 ratio) Intervention: oral calcifediol (0.532 mg) on admission (day 1) and 0.266 mg on day 3 and 7 and then the same dose once weekly until discharge or ICU admission	ICU admission Mortality	Significantly higher ICU admissions for control *vs.* intervention group Among patients receiving Vit D supplementation only 1 admitted to ICU
20.	Capone et al. (2020)	Vit C Zn	Hospital admission	73 received Vit C and Zn supplementation during treatment	Mortality ICU admission	Supplementation not associated with survival
21.	Carpagnano et al. (2021)	Vit D	12 h post-hospital admission	4 groups according to Vit D: • without hypovitaminosis ≥30 ng/mL • insufficient 20–30 ng/mL • moderately deficient 10–20 ng/ml • severely deficient <10 ng/ml	Morbidity Mortality Inflammatory markers (IL-6, CRP)	Tendency to higher IL-6 in patients with severe Vit D deficiency *vs.* all other groups Tendency to rapid unfavorable clinical evolution of patients with severe Vit D deficiency *vs.* all other groups 50% mortality risk in patients severely deficient *vs.* 5% in patients moderately deficient
22.	Moghaddam et al. (2020)	Se	Mean 5th (SD = 4) day of hospitalization	Survivors Non-survivors	Mortality	Significantly higher Se in survivors *vs.* non-survivors Se recovered with time in survivors but remained low or declined in non-survivors
23.	Liu et al. (2020)	Ca	Hospital admission	Categorized according to corrected serum Ca cut-off < 2.15 mmol/L	Inflammation markers (IL-6, PCT, CRP) Poor outcome: need for MV, ICU admission or death of any cause during admission	Negative correlation of Ca with all inflammatory markers Significantly lower Ca in patients with poor outcome Significantly lower Ca on admission in non survivors than the rest
24.	Lagier et al., 2020	Zn	Hospital admission	Poor outcome Favorable outcome	Poor outcome: ICU admission, death, hospitalization lasting ≥10 days	Low Zn significantly associated with poor outcomes

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Table 2 (*continued*)

	First author, year	Micronutrients	Laboratory evaluations	Study protocol COVID-19 patient categories	Prognosis evaluation	Results
25.	Sun et al. (2020)	Ca Vit D	Within 24 h of hospital admission all patients tested for Ca levels 26 patients tested for Vit D levels according to clinical needs	3 groups according to serum Ca: • ≤2.0 mmol/L • 2.0–2.2 mmol/L • >2.2 mmol/L All 26 patients had Vit D deficiency (mean = 10.2 ng/mL, SD = 0.7 ng/mL)	Septic shock Organ injury MODS 28-day mortality MV Continuous renal replacement therapy	Positive correlation between Ca and Vit D Higher 28-day mortality and organ injury incidence for patients with low Ca Lower Ca among non-survivors and patients with MODS, septic shock, organ injury, requiring MV or continuous renal replacement therapy
26.	Wu et al. (2020)	Ca	Hospital admission	Categorized according to total hospitalization stay	Duration of hospitalization (cut-off: 14 days)	Significantly lower Ca on admission in patients with hospitalization length >14 days *vs.*< 14 days
27.	Meisel et al. (2021)	Folate	At least once during hospitalization	Categorized according to folate levels (cut-off: 5.9 ng/mL = 13.37 nmol/L) for primary analysis and then divided into 4 groups • <7.4 ng/mL • 7.4–10.4 ng/mL • 10.4–14.8 ng/mL • >14.8 ng/mL	Mortality Invasive ventilatory support Length of hospital stay Acute kidney injury	No difference between patients with normal *vs.* decreased folate Decreased folate not associated with increased mortality risk or composite outcome of intubation and mortality risk Non-significant results after grouping patients according to folate level quartiles
28.	Doaei et al. (2021)	Omega-3 fatty acids	Baseline and 14 days of intervention	28 received fortified formula with n3-PUFA 73 controls 1 month observation	Apache II GCS Mortality	Significantly higher 1-month survival rate of intervention group
29.	Tehrani et al. (2021)	Vit D	Hospital admission	Categorized both according to disease severity (moderate = 162 *vs.* severe = 43) and Vit D status: • very low <10 ng/ml • insufficient 10–30 ng/ml • sufficient 30–100 ng/ml • toxic >100 ng/ml	Mortality	Significant difference in Vit D levels between improved and deceased patients only in severely ill patients
30.	Murai et al. (2021)	Vit D	Baseline	120 received single oral dose 200,000 IU Vit D *vs.* 120 received placebo	Hospitalization duration Mortality ICU admission MV	No significant differences in endpoints
31.	Vassiliou et al. (2020)	Vit D	ICU admission	2 groups: higher and lower than median value of the cohort (cut-off: 15.2 ng/mL)	28-day ICU mortality	All patients who died within 28 days belonged to the low Vit D group Low Vit D group had higher 28-day mortality probability Non-survivors critically ill patients had lower ICU admission Vit D *vs.* survivors

bd: twice a day, Ca: calcium, COVID-19: Corona Virus Induced Disease 2019, DVT: deep vein thrombosis, Fe: iron, GCS: Glasgow Coma Scale/Score, ICU: intensive care unit, IL-6:interleukin-6, IMV: invasive mechanical ventilation, LIPI: Lung Immune Prognostic Index, Mg: magnesium, MV: mechanical ventilation MODS: multiple organ dysfunction syndrome, OD: once a day, P: phosphorus, PE: pulmonary embolism, Se: selenium, SAPS: Simplified Acute Physiology Score, SOFA: Sequential Organ Failure assessment, TS: total score, Vit D: Vitamin D, Vit B12: Vitamin B12, Vit C: Vitamin C, Vit E: Vitamin E, Zn: zinc.

3.3.3. Zinc (Zn)

Low Zn blood levels were associated with the development of severe disease, more complications or longer hospitalization (Allard et al., 2020; Jothimani et al., 2020; Lagier et al., 2020). In some cases, survival was associated with high admission Zn levels (Heller et al., 2021; Lagier et al., 2020) but this was not verified in all studies (Capone et al., 2020).

3.3.4. Selenium (Se), Phosphate (P) and Magnesium (Mg)

Survival was associated with high blood levels of Se (Heller et al., 2021; Moghaddam et al., 2020), Mg (Alamdari et al., 2020; Kashefizadeh et al., 2020), P (Yang et al., 2021). Similarly, severe disease was inversely associated to P and Mg levels (Allard et al., 2020).

Several clinical trials suggested that micronutrients' supplementation was helpful in clinical improvement and survival of COVID-19 patients (Chavarría et al., 2021; Doaei et al., 2021; Entrenas Castillo et al., 2020; Murai et al., 2021).

4. Discussion

This review examines whether micronutrient status of COVID-19 patients is related to the course and outcome of the disease but even a year after the characterization of COVID-19 as a pandemic, direct evidence is still weak. Previous experience on the treatment of other SARS and viral infections suggests that nutrition may alter the outcome even in critically ill patients (Rowe et al., 2021). In addition, the activation of inflammation and development of an effective immune system are primarily associated to nutrition utilization (Marcos et al., 2003). The importance of inflammation in COVID-19 prognosis has been highlighted in survival analysis, as neutrophil-to-lymphocyte ratio and white blood cells have been introduced as one-month mortality predictors in COVID-19 (Vafadar Moradi et al., 2021). Nutrient deficiency alters cells regeneration and function, suppresses immune response, and contributes to diabetes mellitus type II, hypertension and coronary heart disease in the elderly (Bjorklund et al., 2020; Farrokhian et al., 2016;

Holmberg et al., 2017; Langley-Evans and Carrington, 2006).

COVID-19 has a multiplex pathophysiology and alters different metabolic pathways. Excess inflammation, endothelial damage, and the use of angiotensin converting enzyme 2 (ACE-2) as crucial cellular entrance for the virus, consist fundamental mechanisms of SARS-CoV-2 action. The suppression of the pathways involved in lung tissue destruction by specialized micromolecular agents such as Rho kinase inhibitors, along with the efficiency of multiple micronutrients targeting these processes, may promisingly result in boosting the immune response against the viral agent (Abedi et al., 2020).

Vit D has been proposed to have a special place on the cell protection mechanism by inhibiting the entrance of the virus in the cells *via* interaction of Vit D with its one receptor and ACE-2 (Glaab and Ostaszewski, 2020). Also, Vit D enablement is crucial for immune function as it participates to the pathways of function for normal T-cells, macrophages, dendritic cells and other immune cells (Aranow, 2011; Sigmundsdottir et al., 2007). Its role in the PLC-γ1 expression through a specific nuclear receptor is also mandatory for both the innate and adaptive immune systems (von Essen et al., 2010). Most human studies on COVID-19 patients agree that Vit D within normal limits on admission may assist in a favorable outcome. This finding strengthens the hypotheses that Vit D acts both as an immune booster and an antiviral agent. The molecular mechanism that may explain the benefit of Vit D supplementation in COVID-19 patients is its immunomodulatory effect on interleukin-6 (IL-6) production. Vit D reduces immune cell IL-6 production, and potentially reduces pro-inflammatory effects, but it does not specifically target IL-6 receptors, avoiding any negative impact on IL-6 anti-inflammatory actions (Silberstein, 2020). Furthermore, human studies have revealed a significant immunomodulatory capacity of Vit D to lower tumor necrosis factor (TNF) and interleukin-10 (IL-10) levels (Peterson and Heffernan, 2008; Schleithoff et al., 2006). Thus, multiple pathways are probably activated by Vit D and result in favorable immunoregulation against COVID-19, as IL-6, IL-10 and TNF are primarily involved in excess inflammation in COVID-19 severe illness (Pedersen and Ho, 2020). These findings, combined with the results of this systematic review, provide evidence for the use of Vit D as adjuvant factor targeting hyperinflammatory cytokines in COVID-19. Nevertheless, more clinical trials are needed to evaluate the action of Vit D supplements both in Vit D deficient patients and patients without insufficiency, along with its beneficial effects against the virus per se.

Calcium is along with Vit D the most studied molecule among critically ill COVID-19 patients. Hypocalcemia was a known abnormality accompanying multiple viral infections before the outbreak of COVID-19, thus low Ca levels among these patients were expected (Crespi and Alcock, 2021; Huang et al., 2020; Nathan et al., 2020). Although the exact pathophysiological mechanism causing this abnormality has not been clarified yet and multiple hypotheses including malnutrition of the elderlies, disturbed albumin binding and parathyroid hormone secretion caused by COVID-19 as well as the role of unsaturated fat elevation, have been proposed (Cappellini et al., 2020; Crespi and Alcock, 2021; Huang et al., 2020; Nathan et al., 2020; Torres et al., 2021). Two recent metanalyses studying hypocalcemia as a risk factor for critically illness and intubation, revealed that hypocalcemia was related to high D-dimer levels and thus a more inflammatory response to SARS-CoV-2 (Alemzadeh et al., 2021; Paliogiannis et al., 2020). Vice versa, our results indicate that normal Ca levels act protectively as they are related to survival. It is important to underline that SARS-CoV-2 cellular hypoxia leads to alteration of Ca cell signaling and results in great increase of intracellular Ca through two different processes: i) hijacking the Ca channels and pumps, thus intracellular Ca cannot get out of the cell and ii) enhancing the cellular entry of extracellular Ca obligatory for the translation of HIF-1α and HIF-2α, a process stimulated by hypoxia (Danta, 2020, 2021; Gusarova et al., 2011; Hui et al., 2006; Serebrovska et al., 2020). This pathophysiological process gives evidence that patients with normal serum Ca levels may not be attacked by SARS-CoV-2 in such a degree that cellular hypoxia has absorbed most of the extracellular Ca and that could explain why normocalcaemia on admission is related to survival. If this hypothesis works, Ca supplements cannot act as an adjuvant therapy targeting SARS-CoV-2 inflammatory cascade but only as a protective therapy to the crucial consequences of hypocalcemia itself.

Zinc belongs to minerals/metalloids and constitutes a co-factor for several enzymes participating in antioxidant reactions that assist the immune system (Black, 2003). Zn deficiency disturbs the development of immune cells and thus cell-mediated immunity but also humeral immunity (Maares and Haase, 2016; Skalny et al., 2020; Tuerk and Fazel, 2009). In clinical practice Zn deficiency has been related both to viral infections and severe pneumonia among the elderly and has been effective as a nutrient supplement in the recovery from common cold (Barnett et al., 2010; Mossad et al., 1996; Read et al., 2019). Zn has been found to participate in the molecular pathways of acute respiratory syndrome, as animal studies have proved that Zn deficiency results in significant increase in proinflammatory molecules along with lung epithelium remodeling and thus in increased permeability of proinflammatory markers that lead the cell to apoptosis (Bao and Knoell, 2006; Biaggio et al., 2010; Liu et al., 2014; St Croix et al., 2005). Zn deficiency may also participate in the inflammatory process that results in lung fibrosis (Biaggio et al., 2012). As for COVID-19, the aforementioned mechanisms may explain the clinical improvement of patients with normal Zn levels compared to those with Zn deficiency while a reverse association between Zn and IL-6 levels as well as Zn capability to inhibit SARS-CoV-2 RNA polymerase are described (Domingo and Marquès, 2021). In addition, in vitro experiments give indications that Zn may target and inhibit the SARS-CoV-2 agent itself (Iyigundogdu et al., 2017; Zhang and Liu, 2020). If we further consider the fact that Zn has worked as an adjuvant therapy in acute respiratory syndrome along with the results of the present review, Zn appears to be a promising nutrient supplement as an adjuvant treatment for COVID-19 patients (Haider et al., 2011; Skalny et al., 2020). Nevertheless, large scale clinical studies are needed to confirm this hypothesis.

This review indicates that other metalloids such as Se and Mg may relate to the prognosis of patients with SARS-CoV-2 infection. Mg is a crucial co-factor for multiple enzymatic reactions and low levels of Mg have been related to increased proinflammatory and inflammatory markers as well as molecules that disturb the normal endothelial function (Chacko et al., 2010). Selenium has been discussed as a crucial biomarker for the prognosis of multiple viral infections including influenza, coxsackie virus, cytomegalovirus and hepatitis C. Abnormal low levels of this molecule have been related to high pathogenicity of influenza and suppressed immune response against the agent (Chacko et al., 2010; Harthill, 2011; Steinbrenner et al., 2015). Domingo and Marquès reviewed the role of Se in regulating the host defense against SARS-CoV-2 and corroborate the immunomodulatory properties of this metalloid as well as the negative role of Se deficiency in COVID-19 patients (Domingo and Marquès, 2021). Phosphate participates in cell and tissue regeneration. Thus, high P levels may assist the cellular effort to maintain alive during the infection. However, neither animal nor in vivo studies have clarified the exact pathways and findings from human studies remain weak (Kumar et al., 2021). Other micronutrients that are discussed to act beneficially against SARS-CoV-2 but findings from human studies and clinical trials are not clear, are Vit C, Vit E, Fe, copper and other antioxidants (Cheng, 2020; Domingo and Marquès, 2021; Tavakol and Seifalian, 2021; Tojo et al., 2021).

5. Conclusion

The COVID-19 pandemic is a major threat to human life all over the world. The absence of an effective anti-SARS-CoV-2 treatment trace each possible favorable adjuvant therapy vital for the survival of critical and non-critical ill patients. This systematic review highlights the importance of a healthy micronutrient status for a favorable outcome in COVID-19. Vit D, Ca and Zn may make a significant difference if used as nutritional supplements on a primary point, but further clinical trials need to confirm it. In addition, micronutrients' deficiency on admission seems to be related with high risk for ICU admission, intubation and even death. Thus, it is important for individuals to maintain a healthy and balanced nutritional status to overcome a possible COVID-19 infection while further studies are required to evaluate if vitamin supplements would assist or not, a vaccinated or not individual, to actually contract SARS-CoV-2.

CRediT authorship contribution statement

Evmorfia Pechlivanidou: Project administration, Conceptualization, Investigation, Methodology, Writing – original draft. **Dimitrios Vlachakis:** Investigation, Methodology, Writing – original draft. **Konstantinos Tsarouhas:** Investigation, Writing – original draft. **Dimitris Panidis:** Visualization, Writing – original draft. **Christina Tsitsimpikou:** Visualization, Writing – original draft. **Christina Darviri:** Supervision, Writing – review & editing. **Dimitrios Kouretas:** Supervision, Writing – review & editing. **Flora Bacopoulou:** Project administration, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Glossary;Glossary

bd: twice a day
Ca: calcium
COVID-19: Corona Virus Induced Disease 2019
DVT: deep vein thrombosis
Fe: iron
GCS: Glasgow Coma Scale/Score
ICU: intensive care unit
IL-6: interleukin-6
L-10: interleukin-10
IMV: invasive mechanical ventilation
LIPI: Lung Immune Prognostic Index
Mg: magnesium
MV: mechanical ventilation
MODS: multiple organ dysfunction syndrome
OD: once a day
P: phosphorus
PCR: polymerase chain reaction
PE: pulmonary embolism
Se: selenium
SAPS: Simplified Acute Physiology Score
SOFA: Sequential Organ Failure assessment
TNF: tumor necrosis factor
TS: total score
Vit D: vitamin D
Vit B12: vitamin B12
Vit C: vitamin C
Vit E: vitamin E
WHO: World Health Organization
Zn: zinc