Micronutrient status of COVID-19 hospitalized patients- A systematic review

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THE 1918 SPANISH FLU

WORLD ECONOMIC FORUM

PANDEMIC DECLARED

9 NEWS

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Millions have died from #COVID19 since the start of this pandemic and 15000 are still dying each week.

15000 mothers, daughters, fathers, sons, brothers, sisters, friends... people we love.

I know we are tired, but when did this become acceptable?

A short thread...

Figure 2. COVID-19 cases per 100 000 population reported by countries, territories and areas, 8 - 14 August 2022*
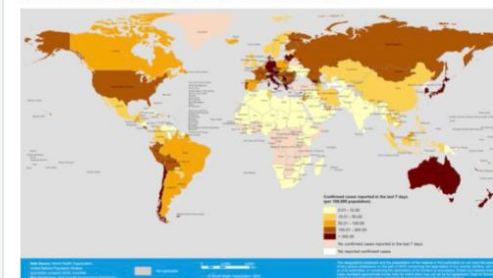
INTRODUCTION

- A novel coronavirus (SARS-CoV-2), causing serious respiratory illness like pneumonia and lung failure was first reported in Wuhan city, China at the end of 2019. It rapidly spread resulting in a global pandemic.

- Globally, as of 29 September 2022, there have been 613,942,561 confirmed cases of COVID-19, including 6,520,263 deaths, reported to WHO. As of 27 September 2022, a total of 12,677,499,928 vaccine doses have been administered.
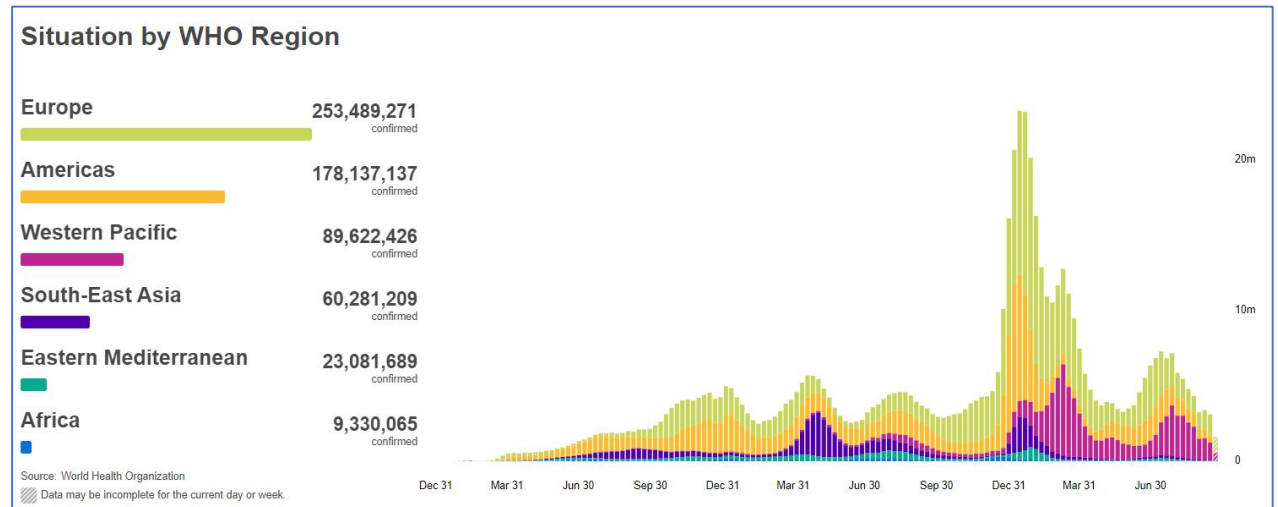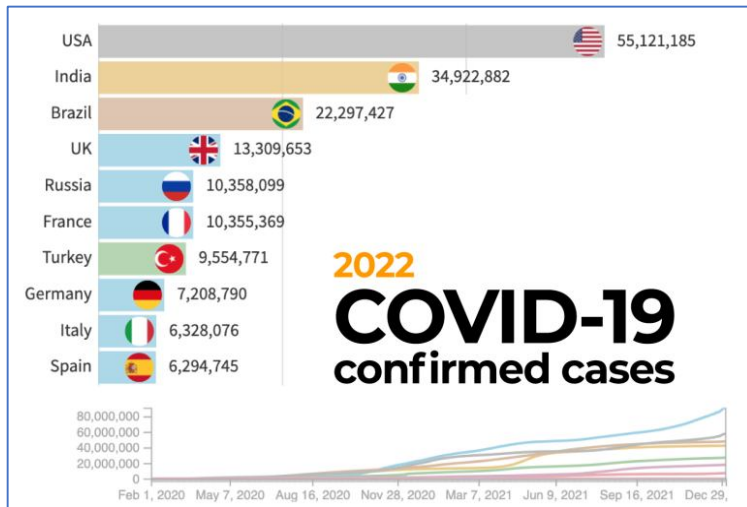
- The role of nutrition in COVID-19 has been emphasized since the beginning of the pandemic (Butler et.al., 2021).

- The way it manifests is a vicious cycle, and thus whether the deficiencies and alterations are predisposing factor to infectious diseases or vice versa is unimportant.
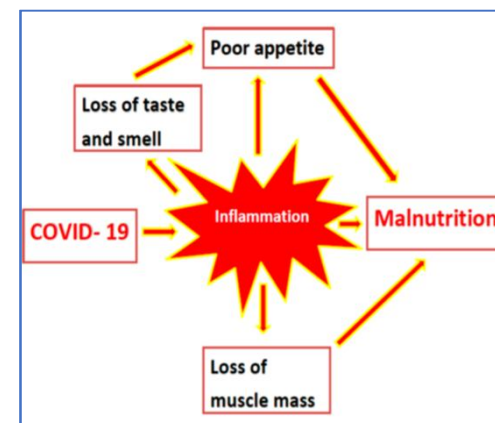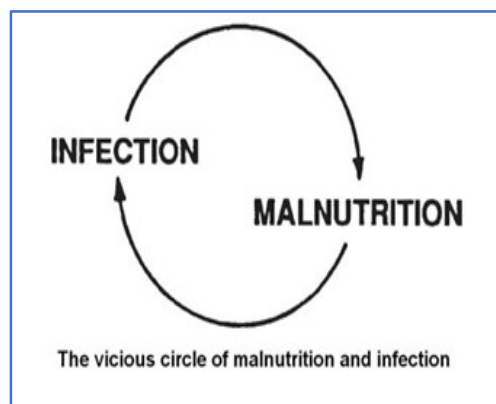
Risk factors for malnutrition that are related to the novel severe acute respiratory syndrome coronavirus (COVID-19).

- In any case, the nutritional state of the host plays an important role in susceptibility to infections and in recovery (Calder et al., 2020).

- An acute infectious state induces hyper catabolism in the body, subsequently causing further loss and depletion of body nutrient stores along with increased nutrient demands.

Evidence that maintaining optimal nutrition status for a well-functioning immune system might promote recovery for mild COVID-19 patients

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Abstract

COVID-19 is a viral infectious disease caused by SARS-COV2. Its clinical signs and symptoms are on a broad spectrum ranging from asymptomatic to severe complications like multi-organ failure, thromboembolism, and severe pneumonia with respiratory failure. Worse outcomes and higher mortality rates have been reported in the elderly, people with co-morbidities, and malnourished individuals. Nutrition is fundamental to good health and immune function. It forms an integral component of treatment modalities for various acute and chronic diseases, especially

Recent research has shown that a sub-optimal micronutrient status may support the onset of COVID-19 and augment its severity
(Wei et al.,2020; Carr 2020; Alzaben et al.,2020, Im et al., 2020).

Micronutrients like vitamins A, B, C and D along with zinc and selenium have especially shown connections in critical illness with complications :
- respiratory infections
- lung function
- duration of hospital stay etc.

(Szeto et al.,2020; Marik et al.,2020).

It is important to consider that differences in susceptibility and severity of COVID-19 could be partly due to insufficient micronutrient levels for adequate immune and organ function.

Most studies were based on small number of hospitalized patients
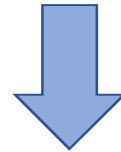
STRONG EVIDENCE on altered micronutrient status in SEVERE/CRITICAL CASES OF COVID -19

(Abrishami et al.,2020; Arvinte et al.,2020; Ye et al.,2020, Heller et al.,2021).

SYSTEMATIC REVIEW

Influence of micronutrient status of COVID-19 hospitalized patients

ON their clinical course and outcomes like hospital stay, mortality rates, respiratory distress etc.

Better Management of the disease and appropriate nutrition therapy

METHODS

Search strategy and selection criteria   Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement.

INCLUSION

- Extensive literature search : Electronic health records (Jan 2020-Feb 2021)

- Studies with COVID-19 associated complications as outcomes i.e. plasma/serum nutrient levels,

  length of hospital stay,

  survival rate to discharge,

   mortality rate,

   respiratory distress,

   any other micronutrient specific measure

- Only full-length peer reviewed research papers (no pre-prints), published in English.

- All study designs such as retrospective, cohort, prospective, case-control were included.

- key words: ("vitamin" OR "micronutrient status") AND ("COVID-19 hospitalized patients" OR "COVID-19 ICU patients").

Identification

Records identified from:
Databases (n = 4)
PubMed= 657; Google Scholar= 1504; ScienceDirect= 2840; Springer= 1943
(Vitamin A= 185; Vitamin B= 904; Vitamin C= 899; Vitamin D= 4344; Vitamin K= 228; Selenium= 126; Zinc= 258)

Screening

Records screened
(n = 6944)

Records excluded
(n = 6853)
Review papers   (n = 1394)
Publication date >Feb21 (n = 896)
Other reasons   (n= 4563)

Eligibility

Records assessed for eligibility (n = 91)

Records Removed
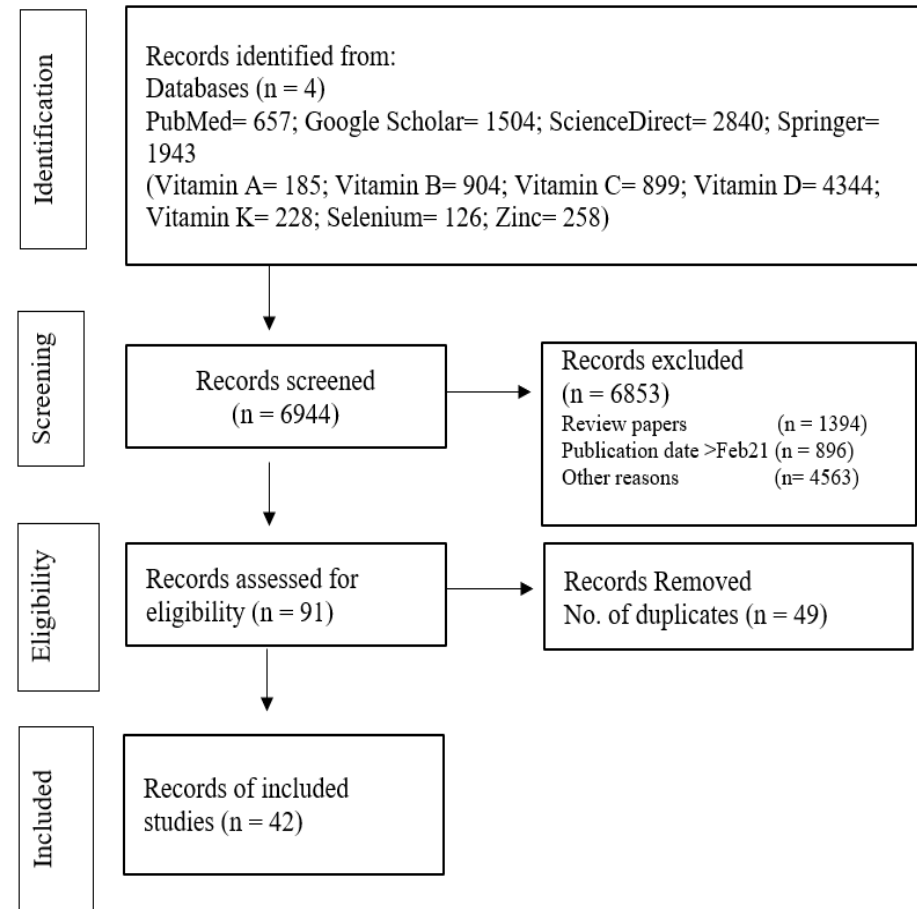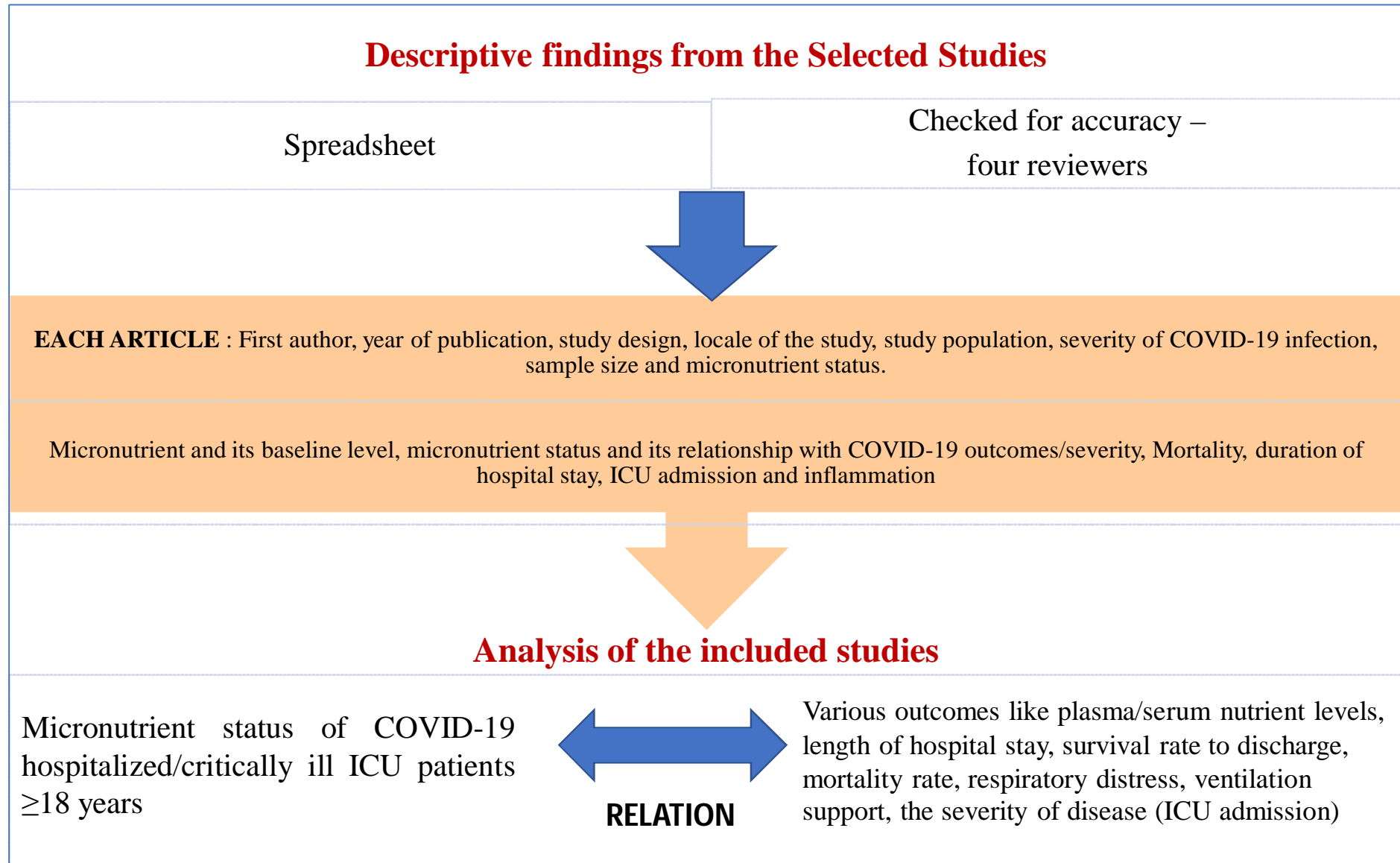No. of duplicates (n = 49)

Included

Records of included studies (n = 42)

Figure 1. Flow diagram of study selection process according to PRISMA guidelines

Data extraction and analysis

Descriptive findings from the Selected Studies

Spreadsheet	Checked for accuracy – four reviewers

EACH ARTICLE : First author, year of publication, study design, locale of the study, study population, severity of COVID-19 infection, sample size and micronutrient status.

Micronutrient and its baseline level, micronutrient status and its relationship with COVID-19 outcomes/severity, Mortality, duration of hospital stay, ICU admission and inflammation

Analysis of the included studies

Micronutrient status of COVID-19 hospitalized/critically ill ICU patients ≥18 years

RELATION

Various outcomes like plasma/serum nutrient levels, length of hospital stay, survival rate to discharge, mortality rate, respiratory distress, ventilation support, the severity of disease (ICU admission)

RESULTS

Key characteristics of studies included

42 research studies

Males and females hospitalized adults

- 8 European countries, 6 Asian countries , rest from North America, South America, and Africa

Different types of Observational study designs

Cross-sectional, cohort, matched case-control

- Sample size – 21- 646 patients

- Lung involvement, mortality, length of hospital stay, ventilation support, the severity of disease (ICU admission)

**Literature Search**

| Serum Vitamin D | Vitamin C, Vitamin K, Vitamins B1, B6, and B12 | Selenium and Zinc | **Vitamin A** |

S. No.	Author year	Country	Population	Severity of covid infection	Study design	Sample size (COVID Cases)	Micronutrient
1	(Abrishami et al., 2021)	Iran	Adults, male and female	Lung involvement	Retrospective study	73	Vitamin D
2	(Arvinte et al., 2020)	USA	Adults, male and female	Critically ill	Cross-sectional, pilot study	21	Vitamin C and Vitamin D
3	(Barassi et al., n.d.)	Italy	Adults, male and female	Hospitalized patients	Cross sectional study	118	Vitamin D
4	(Bennouar et al., 2021)	Algeria	Adults, male and female	Severe hospitalized patients	Cohort, prospective, single-center study	120	Vitamin D
5	(Carpagnano et al., 2021)	Italy	Adults, male and female	Acute respiratory failure due to COVID-19	Retrospective, observational study	42	Vitamin D
6	(Demir et al., 2021)	Turkey	Adults, male and female	Hospitalized patients	Retrospective cohort study	COVID-19 (227) and non-COVID-19 patients (260)	Vitamin D

MICRONUTRIENT STATUS AND RELATIONSHIP WITH COVID 19 OUTCOMES/SEVERITY

Lung Involvement	Mortality	Duration of hospital stay

ICU Admission	Inflammation
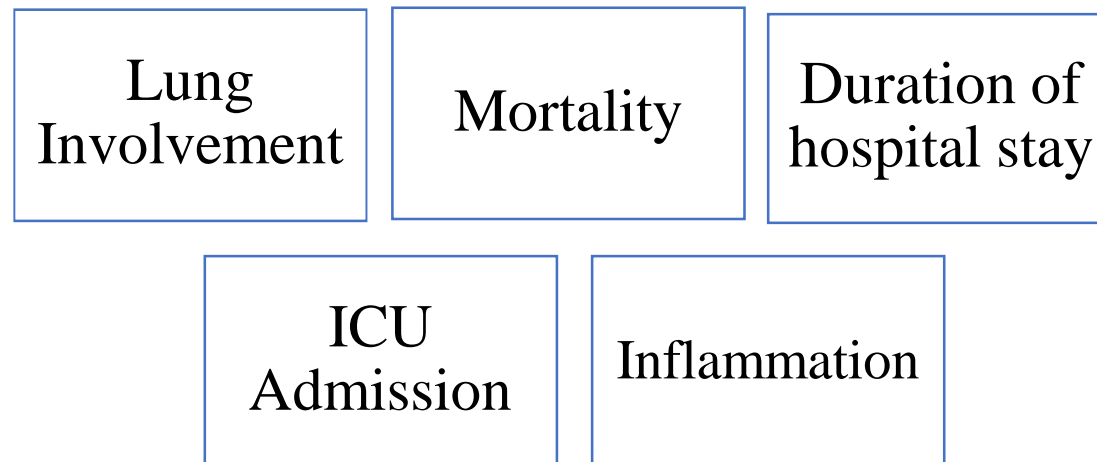
Association of Micronutrient Status with <u>Lung Involvement</u> among Hospitalized Covid-19 Patients

11 studies : Vitamin D, Zinc, Selenium

Vitamin D

S.No.	Author year	Micronutrient	Measurement of baseline levels	Key findings
1	(Abrishami et al., 2021)	Vitamin D	25(OH)D concentration < 25 ng/mL	Higher levels of 25(OH)D were associated with significantly less extent of total lung involvement (β=− 0.10, P=0.004).
2	(Barassi et al., n.d.)	Vitamin D	Vit D >30.0 ng/mL	Vit D levels in O2 support patients were significantly higher among patients than those on continuous airway pressure devices and non-invasive mechanical ventilation
3	(Demir et al., 2021)	Vitamin D	vitamin D > 30 ng/ml	Patients with serum vitamin D levels > 30ng/ml had lower lung involvement
4	(Kerget et al., n.d.)	Vitamin D	-	Vitamin D levels were lower in Covid-19 patients vs controls (p=0.004) Patients who developed acute respiratory distress and macrophage acute syndrome had significantly lower vitamin D levels than controls (p=0.001)
5	(Sulli et al., 2021)	Vitamin D	-	Covid-19 patients had significantly lower serum vitamin D serum levels vs controls Higher vitamin D levels were significantly correlated with PaO2 (p = 0.03), SO2 (p = 0.05), PaO2/FiO2 (p = 0.02)
6	(Adami et al., 2021)	Vitamin D	-	Patients with pO2 <60 mmHg had significantly lower levels of serum 25-OH-vitamin D compared to patients with pO2 ≥60 mmHg (13.3 ng/mL vs 20.4 ng/mL respectively, p=0.03)
7	(Orchard et al., 2021)	Vitamin D	Normal vitamin D level (>50 nmol/L) and vitamin-D deficiency (<50 nmol/L)	No significant differences in invasive and non-invasive mechanical ventilation between patients with low and normal vitamin-D levels
8	(Pizzini et al., 2020)	Vitamin D	25 (OH)D- 30-50 nmol/L insufficient, above 100 nmol/l- normal	Low vitamin D levels at the onset of disease at follow up were not significantly related to lung impairment

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Zinc and Selenium

1	(Gonçalves et al., 2021)	Zinc	Serum zinc <70ug/dL - low zinc levels	Low serum zinc levels were statistically significantly associated with severe acute respiratory distress syndrome.
2	(Jothimani et al., 2020)	Zinc	Zinc concentration was 80–120 mg/dl. n. A zinc level<80 mg/dl was defined as 'deficient'	COVID-19 patients with significantly lower zinc levels were found to have higher rates of complications, acute respiratory distress syndrome when compared to controls
3	(Alkattan et al., 2021)	Selenium and zinc	Selenium (mcg/L)- 138, Zinc (mcg/dl)- 121.78	There was a significant elevation of selenium and iron serum levels among severe cases.

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Association of Micronutrient Status with <u>Mortality</u> among Hospitalized Covid-19 Patients

14 studies : Vitamin D

Vitamin C and Vitamin D

S.No.	Author	Micronutrient	Baseline levels	Findings
1	(Abrishami et al., 2021)	Vitamin D	25(OH)D concentration < 25 ng/mL	Vitamin D deficiency was associated with a significant increase in the risk of mortality
2	(Arvinte et al., 2020)	Vit C and Vit D	vitamin C (17–154 μmol/L), vitamin D2 and D3 (30–100 ng/mL)	Older age and low vitamin C levels were co-dependent risk factors for mortality.
3	(Bennouar et al., 2021)	Vitamin D	Vit D >78 nmol/1 or >30 μg/1	The lowest mortality rate was observed among the group with adequate 25(OH) D levels (>78 nmol/1 or 30 μg/1)
4	(Carpagnano et al., 2021)	Vitamin D	Vitamin D insufficiency, moderate and severe - 20–29, 10–19, and < 10 ng/mL respectively	Severe vitamin D deficiency patients had a 50% mortality risk, while those with vitamin D ≥ 10 ng/mL had a 5% mortality risk.
5	(Infante et al., 2021)	Vitamin D	serum 25(OH)D levels <30 ng/mL	Serum 25(OH)D levels at admission were significantly higher in survivors than non-survivors. Serum 25(OH)D levels were significantly inversely associated with the risk of COVID-19-related in-hospital mortality
6	(Radujkovic et al., 2020)	Vitamin D	16.6 (12.4–22.5) ng/ml	Vitamin D deficiency was associated with severity/mortality of COVID-19
7	(Tehrani et al., 2021)	Vitamin D	The mean level of vitamin D was 33.86 ± 26.42 in the moderate group and 35.41 ± 21.25 in the severe group	Vitamin D deficiency was associated with a significant increase in the risk of mortality

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8	(Karahan & Katkat, 2021)	Vitamin D	vitamin D groups; Normal (Serum 25(OH) vitamin D level >30 ng/mL), Vitamin D insufficiency (21-29 ng/mL), and deficiency (<20 ng/mL)	Serum 25(OH) vitamin D was independently associated with mortality in COVID-19 patients.
9	(Alguwaihes et al., 2020)	Vitamin D	25(OH)D (nmol/l) (75–250)	Severe vitamin D deficiency (p=0.007) was associated with death
10	(Vassiliou et al., 2020)	Vitamin D	25(OH)D levels, patients were stratified in two groups: higher and lower than the median value of the cohort (15.2 ng/mL).	Low vitamin D group (lower than 15.2ng/ml) had an increased risk of 28-day mortality
11	(Cereda et al., 2021)	Vitamin D	25(OH)Vitamin D serum levels: insufficient (<30 -20 ng/mL), moderately deficient (<20 -10 ng/mL), severely deficient (<10 ng/mL).	A significant positive association between increasing 25(OH)vitamin D levels and in-hospital mortality was observed
12	(De Smet et al., 2021)	Vitamin D	Serum 25-OH-vitamin D was 18.6 ng/ml	Vitamin D deficiency on admission after adjusting for confounders was found to be associated with mortality

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13	(Szeto et al., 2021)	Vitamin D	Vitamin D deficiency (<20ng/ml) and normal vitamin D levels (>=20ng/ml)	No significant relationship was observed between pre hospitalisation serum vitamin D status and mortality
14	(Vassiliou et al., 2021)	Vitamin D	vitamin D deficient (19.9 ng/ml) and vitamin D insufficient (20-29.9 ng/ml).	No difference was observed between Vitamin D deficient and insufficient groups with respect to hospital mortality or disease severity

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Vitamin B12, Zinc and Selenium

S.No.	Author	Micronutrient	Baseline levels	Findings
1	(Ersöz & Yılmaz, 2021)	Vitamin B 12	NA	A lower level of vit B12 was associated with patient mortality
2	(Vogel-González et al., 2021)	Zinc	Zinc <50ug/dL- low zinc levels	Serum zinc levels lower than 50 µg/dL at admission correlated with worse clinical presentation, longer time to reach stability, and higher mortality. Serum zinc concentration at admission was significantly higher among individuals who survived (62 µg/dL (52–72)) compared to those who died (49 µg/dL (42–53); p < 0.001)
3	(Moghaddam et al., 2020)	Selenium	SELENOP quantification ELISA, total serum Se, and Glutathione peroxidase activity	Selenium status was significantly higher among survivors than non-survivors
4	(Heller et al., 2021)	Zinc and Selenium	The lower limit (Zn deficiency) at <642.5 µg/L is represented by the bottom 2.5% of Zn values. Serum Zn below 638.7 µg/L and serum SELENOP below 2.56 mg/L	Concentrations (combination of serum Zn and serum SELENOP) within the reference ranges indicate high chances for survival
5	(Jothimani et al., 2020)	Zinc	Zinc concentration was 80–120 mg/dl. n. A zinc level<80 mg/dl was defined as 'deficient'.	COVID-19 patients showed significantly lower zinc levels when compared to healthy controls resulting in increased mortality

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Association of Micronutrient Status with <u>Duration of Hospital Stay</u> among Hospitalized Covid-19 Patients

5 studies : Vitamin D and Zinc

Vitamin D and Zinc

S.No.	Author	Micronutrient	Baseline Levels	Salient Findings
1	(Hernández et al., 2021)	Vitamin D	Serum 25OHD levels <20 ng/mL (50 nmol/L)	Vitamin D-deficient COVID-19 patients had a greater prevalence of longer length of hospital stay than those with serum 25OHD levels ≥20 ng/mL.
2	(Demir et al., 2021)	Vitamin D	vitamin D > 30 ng/ml	Patients with vitamin D levels of >30 ng/ml had significantly shorter hospital stays
3	(Jothimani et al., 2020)	Zinc	Zinc level<80 mg/dl was defined as 'deficient'.	COVID-19 patients with significantly lower zinc levels when compared to healthy controls had prolonged hospital stay
4	(Szeto et al., 2021)	Vitamin D	Vitamin D deficiency (<20ng/ml) and normal vitamin D levels (>=20ng/ml)	No significant relationship was observed between pre hospitalization serum vitamin D status and length of stay
5	(Orchard et al., 2021)	Vitamin D	Normal vitamin D levels (>50 nmol/L) and vitamin-D deficiency (<50 nmol/L)	No significant differences in the number of hospital days between patients with low and normal vitamin-D levels.

ASSOCIATION

NO ASSOCIATION

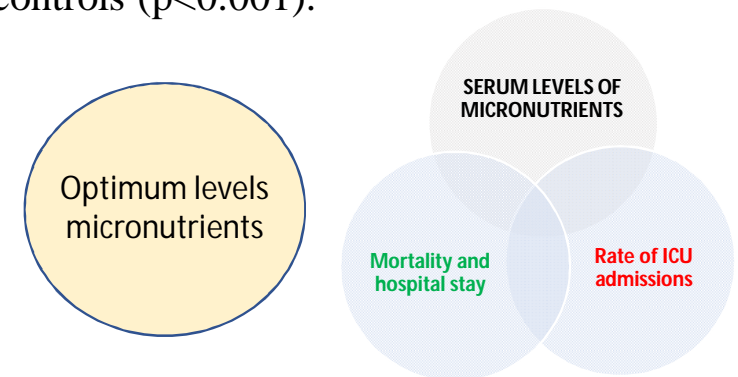**Association of Micronutrient Status with <u>ICU admission</u> among Hospitalized Covid-19 Patients**

Baktash et al (2020) on older hospitalized patients of United Kingdom aged 65 years and above reported that vitamin D deficient patients had a high dependency unit admission (30.77 % vs 9.68%, p=0.042).

Ersöz & Yılmaz (2021) found that lower vitamin D levels were associated with ICU admission

Orchard et al (2021) did not report any difference in vitamin D levels among hospitalized patients and those admitted to the ICU.

Miscellaneous

A case-control study by Dofferhoff et al. (2020) on Dutch hospitalized adults reported an insufficiency of extrahepatic Vitamin K since dp-ucMGP was increased in COVID-19 patients compared to controls (p<0.001).

SERUM LEVELS OF
MICRONUTRIENTS

Optimum levels
micronutrients

Mortality and
hospital stay

Rate of ICU
admissions

Association of Micronutrient Status with Inflammation among Hospitalized Covid-19 Patients

S.No.	Reference	Micronutrient	Baseline levels/cut-offs	Key Findings
1	(Barassi et al., n.d.)	Vit D	Vit D >30.0 ng/mL	Negative correlation between serum vitamin D and C-reactive protein levels
2	(Sulli et al., 2021)	Vit D	-	Statistically significant negative correlation observed between serum vitamin D levels C-reactive protein (p = 0.04)
3	(Demir et al., 2021)	Vit D	vitamin D > 30 ng/ml	Patients with vitamin D levels of >30 ng/ml had significantly lower D-dimer and C-reactive protein (CRP) levels
4	(Adami et al., 2021)	Vit D	serum 25-OH-vitamin D	Patients with 25-OH-vitamin D below 15 ng/mL were more likely to show increased levels of CRP on admission. Patients with 25-OH-vitamin D below 20 ng/mL had a 3-fold higher risk of having CRP above 50 mg/L (n=28, 63.8%) compared to patients with normal vitamin D.
5	(Pizzini et al., 2020)	Vit D	25 (OH)D-30-50 nmol/L insufficient, above 100 nmol/l-normal	Low vitamin D levels at the onset of disease at follow up were not significantly related to inflammation or severity of disease

ASSOCIATION

NO ASSOCIATION

DISCUSSION

- In the current review of **42** published studies, we found out that **micronutrients do play an important role in the progression of the COVID-19 disease.**

- **Vitamin D** was the most studied micronutrient in this review.

- Supplementation with Vitamin D to prevent or treat COVID-19 however, remains subject to more research (Diabetes, T.L. ,2021; National Institute for Health and Care Excellence, 2020).

- Envisaging the length of the hospital stay for COVID-19 infected patients could help health care authorities to better manage the health care facilities (Vekaria et al.,2021).

  Impact of micronutrient status ⟶ associated outcomes of the infections

  Supplemental effect of micronutrients ⟶ recovery of COVID-19 patients

  (Wang et al.,2021; James et al,2021).

- The included studies were from different countries of the world including Asian countries. This increases the external validity of the outcomes across regions.

- The main strength of this systematic review is that it examines the level of serum micronutrients and their association with outcomes of adult patients with COVID-19. The literature taken from other viral infections are far from consistent and this review attempts to ensure that people have an adequate dietary intake is critical.

LIMITATIONS

- Varied study designs , owing to the limited number of original research studies on COVID-19

More robust evidence is required to generalize these findings of micronutrient serum levels for dosage and regimen to prevent coronavirus episodes.

- Also, the spectrum of micronutrients investigated becomes skewed towards vitamin D (more literature available)

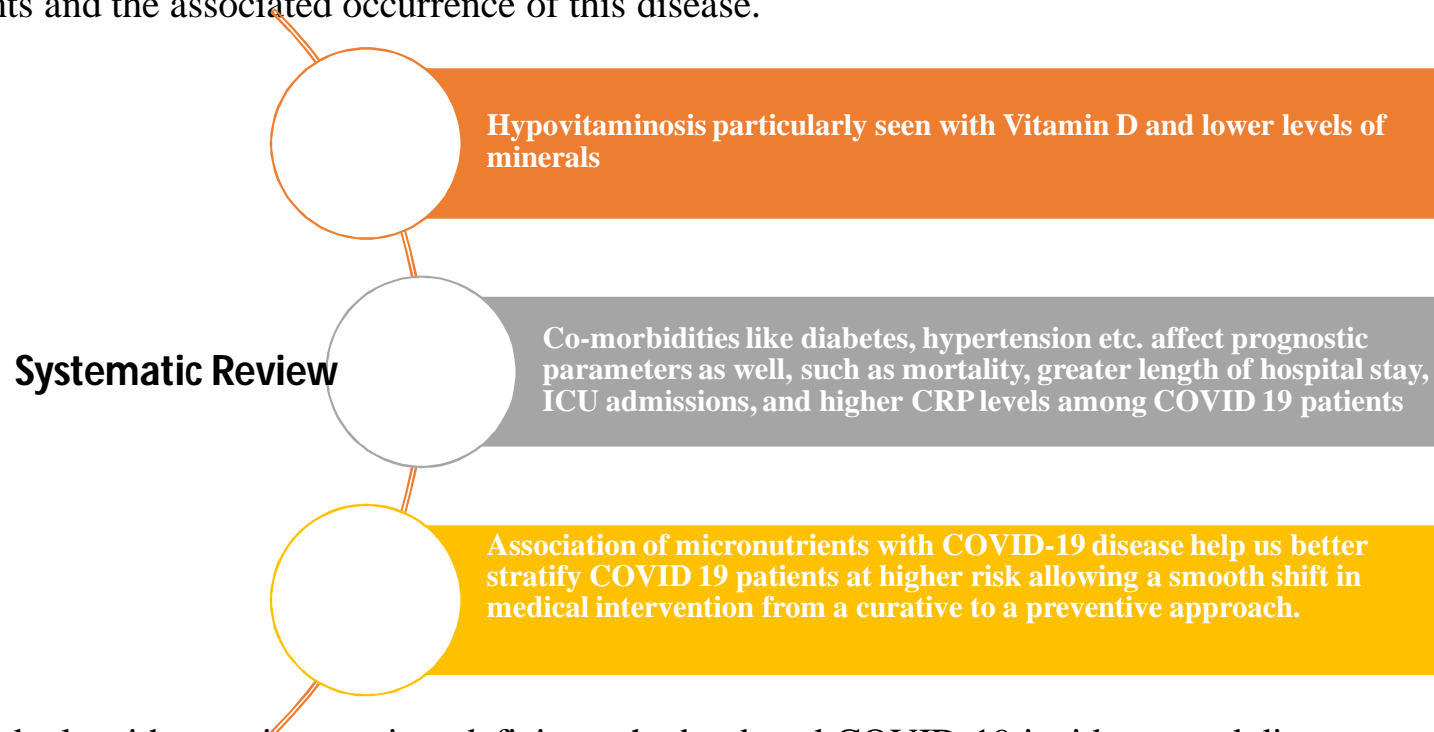 More research is warranted → other micronutrients

  Dearth of research studies on vitamin A status → COVID-19

CONCLUSION

- Optimum nutrition has been one of the most researched aspects during this pandemic among researchers and the general public. The present systematic review depicts the presence of lower micronutrient levels among COVID19 patients and the associated occurrence of this disease.

Systematic Review

Hypovitaminosis particularly seen with Vitamin D and lower levels of minerals

Co-morbidities like diabetes, hypertension etc. affect prognostic parameters as well, such as mortality, greater length of hospital stay, ICU admissions, and higher CRP levels among COVID 19 patients

Association of micronutrients with COVID-19 disease help us better stratify COVID 19 patients at higher risk allowing a smooth shift in medical intervention from a curative to a preventive approach.

- Individuals without micronutrient deficiency had reduced COVID-19 incidence and disease severity.

- This review suggests that COVID-19 patients should be checked for their micronutrient levels soon after admission to the hospital so as to integrate micronutrient supplementation into the prevention and therapeutic management of COVID-19.

WARRANTS further research

- Relationship of Micronutrient status with duration of hospital stay/ ICU admission.

- Effect of Vitamin A and C on COVID-19 outcomes/severity of illness

"Every time you eat or drink, you are either feeding disease or fighting it."

Heather Morgan