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Micronutrients Levels in Covid-19 Patients - Systematic Review of Hospitalized Patients

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International Life Sciences Institute India

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Foreword

The world suffered from Covid-19 Pandemic which began towards the end of 2019 and is still continuing. Covid-19 had devastating effects on health, food and nutrition security as well as the economy. The pandemic will be remembered as one of the most disastrous occurrences in human history in the recent times. World still must recover from the unprecedented sufferings and huge devastation caused by Covid-19. However, the world reacted most remarkably in the fight against Covid-19. Sharing of information, resources, cooperation and collaboration in vaccines development and supply had positive impact on arresting the disease spread and bringing it under control.

Indian population also suffered from the adverse consequences of Covid-19. Concerned with the speed at which the infection was spreading and heaping untold miseries on people, ILSI India decided to look at the role of nutrition in prevention and management of infectious diseases like Covid-19. A Systematic Review was undertaken to study micronutrient levels in Covid-19 hospitalized patients. The objective of the Review was to learn some lessons and initiate action to reduce the sufferings.

The Review reveals that patients suffered from Hypovitaminosis as well as mineral deficiencies which adversely affected body's immunity and thus reduced body's ability to fight infections. Micronutrients deficiencies made Covid-19 patients more vulnerable to disease progression and severity outcomes. The presence of co-morbidities such as diabetes, hypertension etc. in Covid-19 patients further complicated the matter. Higher mortality, greater length of hospital stays, ICU admissions, and higher CRP levels were witnessed in such patients.

It is, therefore, recommended that Covid-19 patients should be checked for their micronutrient levels soon after admission to the hospital so as to integrate micronutrient supplementation into therapeutic management of Covid-19. This could be considered as an additional intervention to reduce disease severity.

This study further corroborates the role of nutrition in building health and immunity. It is hoped that the findings will be useful to policy makers, medical professionals, nutritionists, dieticians, researchers besides the other health care providers.



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ABSTRACT

Coronavirus Disease 2019 (Covid-19) pandemic has created a global health crisis. The present systematic review evaluated the impact of micronutrient status on the occurrence and prognosis of Covid-19. The review was done using PRISMA Statement. The main search engines used in the present research were PubMed, Google Scholar, Science Direct and Springer. The search explored all the relevant studies related to micronutrient status of hospitalized Covid-19 patients/critically ill Covid-19 patients, with or without comorbidities. The micronutrients studied were Vitamins A, B, C, D and K and Minerals - Zinc and Selenium. All study designs such as, Retrospective, Cohort, Prospective, Case-Control were included (All papers published till February, 2021). A total of 6944 articles were identified from the databases (PubMed- 657; Google Scholar- 1504, Science Direct-2840 and Springer-194) and screened by four reviewers. A total of **42** papers were included for the review. The present systematic review showed lower micronutrient levels among Covid-19 patients. Hypovitaminosis mainly Vitamin D and lower levels of minerals possibly impacted the immune system.

1. INTRODUCTION

Malnutrition in both forms undernutrition and overnutrition has an impact on immune response to infections. The availability of nutrients in the host's body determines and stimulates specific and non-specific defense mechanisms and immune responses towards the pathogen. 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. In any case, the nutritional state of the host plays an important role in susceptibility to infections and in recovery. The association between nutrition and the immune system is established, hence the role of nutrition in Covid-19 has been emphasized since the beginning of the pandemic (Butler et.al., 2021). Specific nutrients like Vitamins A, B Complex (Folic Acid, Vitamins B₆ and B₁₂), D, C, and the Minerals Fe, Se, Cu, and Zn, have been proven to enhance immune function (Richardson & Lovegrove, 2021). The relationship between nutrition and Covid-19 disease is becoming more distinct. It is imperative to monitor Covid-19 surviving patients for a long-term period to assess their anthropometric and biochemical parameters to ensure satisfactory recovery (Gröber & Holick., 2021).

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). Micronutrients like Vitamins A, B, C and D along with Zinc and Selenium have especially shown connections in critical illness with complications like 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. At present, most studies are based on small number of hospitalized patients, generating 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). This systematic review aims to examine the influence of micronutrient status of Covid-19 hospitalized patients on their clinical course and prognostic measures like hospital stay, mortality rates, respiratory distress etc. This would be beneficial for critical care physicians in management of the disease and adopting appropriate medical nutrition therapy, thereby improving patient outcomes.

2. METHODS

2.1 SEARCH STRATEGY AND SELECTION CRITERIA

This systematic review was carried out following the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement (Liberati et al., 2009). An extensive literature search was conducted by a team of four reviewers using four databases PubMed, Google Scholar, Science Direct and Springer. The search explored all the relevant studies related to micronutrient status of hospitalized Covid-19 patients/critically ill Covid-19 patients, with or without comorbidities like diabetes, hypertension, obesity, renal dysfunction, non-pregnant, non-lactating women population across the world. The micronutrients studied were Vitamins A, B, C, D and K and Minerals - Zinc and Selenium. Electronic health records of such hospitalized critically ill Covid-19 patients were also taken into account for literature search. 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 were included in the review. Only full-length research papers published in English were included. Due to the limited number of research studies conducted on Covid-19, all study designs such as, Retrospective, Cohort, Prospective, Case-Control were included. Owing to the heterogeneity in the selected studies, the collected data was not appropriate for meta-analysis. Therefore, the eligibility criteria of the included studies and study design was conducted according to the PICOS Model (Population, Intervention, Comparison,

Outcome, Study Design), to analyze the retrieved relevant articles and to carry out in depth processing of the collected data. A comprehensive search was made using the key words: (“vitamin” OR “micronutrient status”) AND (“Covid-19 hospitalized patients” OR “Covid-19 ICU patients”). Other methods were also employed for identifying relevant and additional studies like reference checking, hand searching or contacting experts in the field. The final result is shown with the PRISMA flow diagram (**Figure 1**).

A total of 6944 articles were identified from the databases (PubMed- 657; Google Scholar- 1504, Science Direct- 2840 and Springer- 194) and screened by four reviewers. After an initial screening for the micronutrients, an exclusive screening was undertaken as per the keywords, micronutrients status and title of the study. The assessment of the potentially relevant studies was screened independently by all the four reviewers. Subsequently, all the identified articles were further screened and grouped as accepted or rejected. The rejected papers were further categorized on the basis of 3 Criteria viz. Review Paper, Publication Date i.e., Papers Published after February, 2021 and for any ‘Other Reason’ like article not related to Covid-19, unavailability of full-length paper, not written in English language, letter to editor, patients aged less than 18 years, not hospitalized, etc. Lastly, all the accepted articles were further screened for any duplicates and any disagreement was resolved through a consensus of all four reviewers.

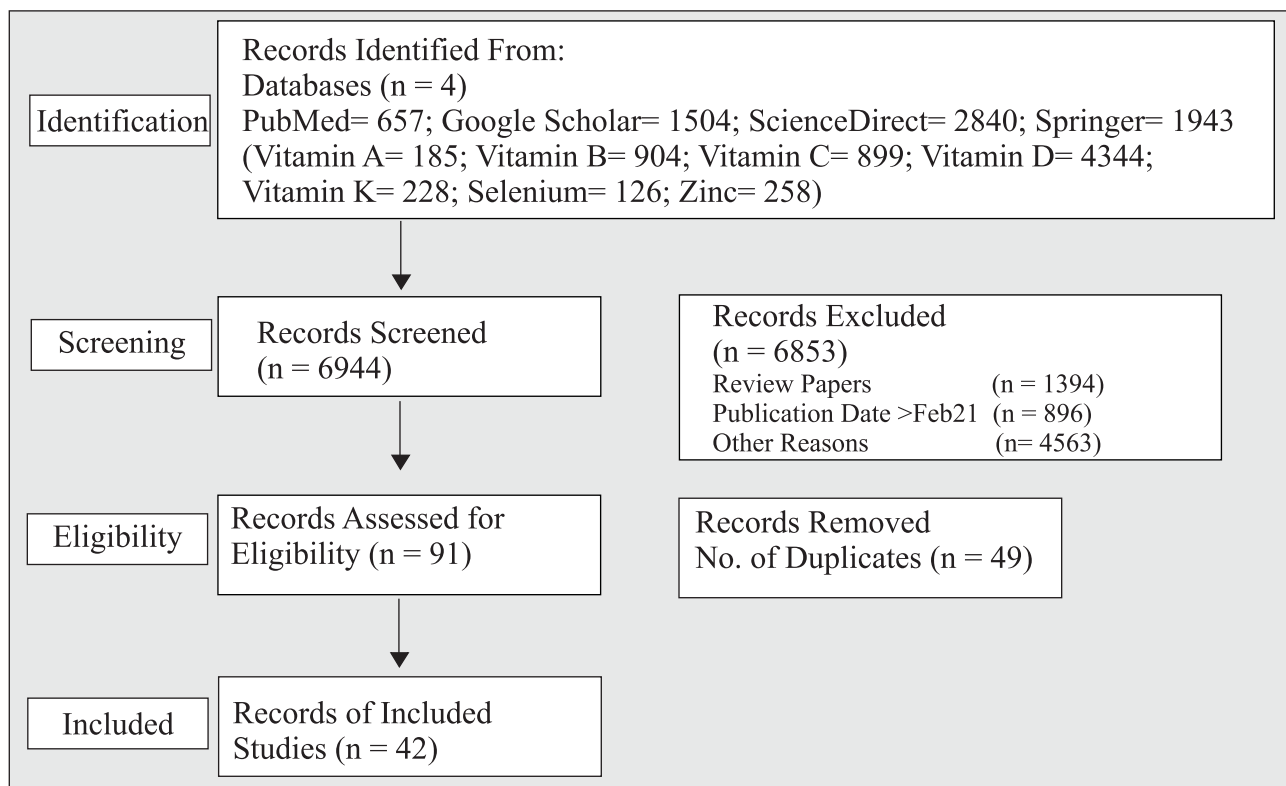


Figure 1. Flow Diagram of Study Selection Process According to PRISMA Guidelines

2.2 DATA EXTRACTION AND ANALYSIS

Descriptive findings from the selected studies were extracted to a spreadsheet and checked for accuracy by all the four reviewers. The following information was extracted from 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. This extracted information was further segregated and categorized as per the variable of interest viz micronutrient and its baseline level, micronutrient status and its

relationship with Covid-19 outcomes/severity, mortality, duration of hospital stay, ICU admission and inflammation. The analysis of the included studies was performed to evaluate and conclude the micronutrient status of Covid-19 hospitalized/critically ill ICU patients ≥ 18 years and its relation to various outcomes related to plasma/serum nutrient levels, length of hospital stay, survival rate to discharge, mortality rate, respiratory distress, etc.

3. RESULTS

3.1 KEY CHARACTERISTICS OF STUDIES INCLUDED

A total of **42** articles / published papers were included for the review. The key characteristics of the studies are presented in **Table 1**. Studies included both males and females hospitalized adults. Out of the 42 studies, 8 studies have been conducted in European Countries followed by 6 studies from Asian Countries and the rest were from North America, South America, and Africa. Different types of Observational Studies such as Cross-Sectional, Cohort, Matched Case-Control were included to assess the role of micronutrient status on Covid-19 in hospitalized patients. The sample size of these studies ranged from 21 to 646 patients.

The literature search showed a majority of the studies that assessed Serum Vitamin D Levels followed by studies on other Micronutrients such as Vitamin C, Vitamin K, Vitamins B₁, B₆, and B₁₂ and Minerals like Selenium and Zinc. No study was found to assess the Serum Vitamin A Levels among Covid-19 hospitalized patients. The Covid-19 outcomes assessed in each of the included studies covered mostly lung involvement, mortality, length of hospital stay, ventilation support, the severity of disease (ICU admission) to name a few.

Table 1. Key Characteristics of the Studies Included

S.No.	Author/ Year	Country	Population	Severity of Covid-19 Infection	Study Design	Sample Size (Covid-19 Cases)	Micronutrients
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	(Carpagnao 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
7	(Elibol & Baran, 2021)	Turkey	Adults, Male and Female	Hospitalized Patients	Cross Sectional Study	300	Vitamin D
8	(Ersöz & Yılmaz, 2021)	Turkey	Adults, Male and Female	Hospitalized Patients	Descriptive Observational Study, Retrospective Review of File	310	Vitamin B₁₂, Folate, Iron, Vitamin D
9	(Ferrari et al., 2020)	Italy	Adults, Male and Female	Hospitalized Patients	Retrospective Cohort Study.	347	Vitamin D
10	(Gonçalves et al., 2020)	Brazil	Adults, Male and Female	ICU Patients	Cross-Sectional Descriptive Study	176 Elderly Patients.	Vitamin D
11	(Hernández et al., 2021)	Spain	Adults, Male and Female	Hospitalized Patients	Retrospective Study	216 Covid Patients and 196 Control.	Vitamin D
12	(Infante et al., 2021)	Italy	Adults, Male and Female	Hospitalized Patients	Retrospective Study	137	Vitamin D
13	(Abdollahi et al., 2021)	Iran	Adults, Male and Female	Hospitalized Patients	Matched Case Control	201 Cases with Covid-19 and 201 Controls	Vitamin D
14	(Adami et al., 2021)	Italy	Adults, Male and Female	Hospitalized Patients	Retrospective Observational Study	61	Vitamin D
15	(Baktash et al., 2020)	UK	Older Patients Aged ≥ 65 Years	Hospitalized Patients	Prospective Cohort	105	Vitamin D
16	(De Smet et al., 2021)	Belgium	Whites of European Descent	Hospitalized Patients	Retrospective Observational	186	Vitamin D

17	(Kerget et al., 2020)	China	Adults	Hospitalized Patients	Case Control	108	Vitamin D
18	(Macaya et al., 2020)	Spain	Adults	Attending Emergency Department	Retrospective	80	Vitamin D
19	(Orchard et al., 2021)	UK	Adults	Admitted to ICU	Cohort Study	646 SARS-CoV-2 Positive Patients Hospitalized	Vitamin D
20	(Pizzini et al., 2020)	Austria	Predominantly Male Individuals (60%), Aged 58 ± 14 Years	Hospitalized Patients as well as Outpatients with Persistent Symptoms	Prospective Multicenter Observational Study	22 Hospitalized +87 Out Patients	Vitamin D
21	(Radujkovic et al., 2020)	Germany	Adults	Hospitalized as well as Outpatients	Prospective Non Interventional Register	185-93 Hospitalized, 92- Outpatients	Vitamin D
22	(Sulli et al., 2021)	Italy	Elderly	Hospitalized but not in ICU	Age and Sex-Matched Case-Control Study	65 Consecutive Covid-19 Patients (Mean Age \pm 13 Years) and 65 Sex-and Age- Matched Control Subjects (CNT) were Analyzed	Vitamin D

23	(Szeto et al., 2021)	USA	Adults	Covid Positive Hospitalized Patients	Retrospective Medical Record Review	700	Vitamin D
24	(Tehrani et al., 2021)	Iran	Adults	Hospitalized Patients	Descriptive Retrospective	205	Vitamin D
25	(Vassiliou et al., 2021)	Greece	Adults, Male and Female	ICU and Non-ICU Patients	Observational Single-Center Study	29 Covid-19 Patients in ICU and 10 Hospitalized Covid-19 Patients in Non-ICU	Vitamin D
26	(Vassiliou et al., 2020)	Greece	Adults, Male	Critically Ill ICU Patients	Observational Study	30	Vitamin D
27	(Ye et al., 2020)	China	Adults, Male and Female	Healthy Individuals Mild, Moderate, Severe/ Critically Ill Patients	Case-Control Study	80 Healthy Controls and 62 Patients Diagnosed with Covid-19	Vitamin D
28	(Cereda et al., 2021)	Italy	Adults, Male	Severe Pneumonia, ICU Patients	Cohort Study	129	Vitamin D
29	(Heller et al., 2021)	Germany	Adults, Male and Female	Covid-19 Infected Patients	Cross-Sectional Study	35	Zinc and Selenium
30	(Mardani et al., 2020)	Iran	Adults, Male and Female	Respiratory Difficulties and Lung Infection	Observational Study	123	Vitamin D
31	(Jothimani et al., 2020)	India	Adults, Male and Female	Acute Respiratory Distress	Observational Study	47	Zinc
32	(Karahan & Katkat, 2021)	Turkey	Adults, Female	Severe and Critical Covid-19	Retrospective Observational Study	149	Vitamin D

33	(Pinzon et al., 2020)	Indonesia	Adults, Male and Female	Covid-19 Infected Patients with Various Signs and Symptoms and Comorbidities	Case Series	10	Vitamin D
34	(Alguwaihes et al., 2020)	Saudi Arabia	Adults, Male and Female	Covid-19 Infected Patients with Diabetes Mellitus	Single-Center Retrospective Study	439	Vitamin D
35	(Alkattan et al., 2021)	Saudi Arabia	Adults, Male and Female	Patients Infected with SARS-CoV-2 and Diagnosed with Covid-19	Cross-Sectional Study	80 (Severe Cases, n=35, Non-Severe Cases, n=45)	Copper, Iron, Selenium, and Zinc
36	(Im et al., 2020)	South Korea	Adults, Male and Female	Covid-19 Infected Patients with Respiratory Distress	Observational Study	50	Vitamin B₁, B₆, B₁₂, Vitamin D (25 hydroxyvitamin D), Folate, Selenium, and Zinc
37	(Moghaddam et al., 2020)	Germany	Adults	Covid-19 Patients	Cross-Sectional Study	33	Selenium
38	(Hani et al 2021)	Indonesia	Adults, Male and Female	Hospitalized Patients	Cross-Sectional	50 Patients	Vitamin D
39	(Pizzini et al., 2020)	Austria	Adults	Hospitalized Patients	Prospective Multicentre Observational CoiLD Registry	87 Hospitalized Patients 18 out of these were in ICU	Vitamin D

40	Dofferhoff et al 2020	Netherlands	68± 12 Years, both Males and Females	Hospitalized Patients	Case-Control	135 Hospitalized Covid-19 Patients and 184 Historic Controls	Vitamin K
41	(Goncalves et al., 2021)	Brazil	Males and Females, 66-81 Years Old	Hospitalized Patients	Observational Study	269 Patients Admitted in the ICU Required Invasive Mechanical Ventilation	Zinc
42	(Vogel-González et al., 2021)	Spain	Males and Females, Median Age 65 (54 - 75 Years)	Hospitalized Patients	Observational Cohort Study	240 Hospitalized Patients	Zinc

Note : “Hospitalized Patients” denotes “Mild Cases and Mild Infections.”

3.2 MICRONUTRIENTS STATUS AND RELATIONSHIP WITH COVID-19 OUTCOMES / SEVERITY

3.2.1 Lung Involvement

The relationship of micronutrient status and the Covid-19 related outcomes specific to lung function is described in this section. Studies that assessed the role of micronutrient status with Covid-19 and associated lung involvement are presented in **Table 2**.

Table 2. Association of Micronutrients Status with Lung Involvement Among Hospitalized Covid-19 Patients

S.No.	Author/ Year	Micronutrients	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 ($\beta=0.10, P=0.004$).
2	(Barassi et al., n.d.)	Vitamin D	Vitamin D >30.0 ng/ml	Vitamin 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., 2020)	Vitamin D	NA	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	NA	Covid-19 Patients had Significantly Lower Serum Vitamin D Levels vs Controls. Higher Vitamin D Levels were Significantly Correlated with PaO₂ (p = 0.03), SO₂ (p = 0.05), PaO₂/FiO₂ (p = 0.02). A Negative Correlation was Observed Between Serum Vitamin D Levels and Severity of Radiologic Pulmonary Involvement.

6	(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 after Adjusting for Baseline Variables (OR, 15.4; 95% CI, 6.5-36.3; P<.001).
7	(Adami et al., 2021)	Vitamin D	NA	Patients with pO₂ <60 mmHg had Significantly Lower Levels of Serum 25 (OH) D Compared to Patients with pO₂ ≥ 60 mmHg (13.3 ng/mL vs 20.4 ng/mL Respectively, p=0.03).
8	(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 (Those Who were Later Diagnosed with Respiratory Distress/Pulse Oximeter Saturation ≤ 93% or PaO₂/FiO₂ <300 mmHg) Compared to Non-Severe Cases of Covid-19. No Significant Difference was Observed Between Zinc Levels of both Groups.
9	(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.
10	(Jothimani et al., 2020)	Zinc	Zinc Concentration was 80–120 mg/dl. 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.
11	(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 and At Follow Up were not Significantly Related to Lung Impairment.

Several studies have observed that lower Vitamin D levels may lead to lung impairment (Abrishami et al., 2021; Adami et al., 2021; Demir et al., 2021; Kerget et al., 2020; Pizzini et al., 2020; Sulli et al., 2021). Few studies have reported that lower Zinc levels may lead to acute respiratory distress (Gonçalves et al., 2021; Jothimani et al., 2020), while some have found no relationship (Alkattan et al., 2021). The results indicate a significant effect of the levels of Vitamin D on pulmonary function during Covid-19. To our knowledge, we provide evidence here that amongst all the micronutrients studied, it is Vitamin D that could have the most profound effect on lung function.

3.2.2 Mortality

Several studies have assessed the role of micronutrient status and Covid-19 associated mortality (**Table 3**). Majority of these studies reported that a lower micronutrient status (Vitamin D, Zinc, B₁₂, Vitamin C) resulted in higher mortality due to Covid-19. Out of the 19 Studies, 17 studies have shown that a deficient micronutrient status for Vitamins- B, C, D and Minerals - Zinc and Selenium has a direct effect on the survival rates of Covid-19 patients.

Table 3. Association of Micronutrients Status with Mortality Among Hospitalized Covid-19 Patients

S.No.	Author/Year	Micronutrients	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)	Vitamin C and Vitamin D	Vitamin C (17–154 µmol/L), Vitamin D ₂ and D ₃ (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	Vitamin D >78 nmol/l or >30 µg/l	The Lowest Mortality Rate was Observed Among the Group with Adequate 25(OH) D Levels (>78 nmol/l or 30 µg/l).
4	(Carpagnano et al., 2021)	Vitamin D	Vitamin D Insufficiency, Moderate and Severe 20–29, 10–19, and <10 ng/mL respectively	After 10 Days of Hospitalization, Severe Vitamin D Deficiency Patients had a 50% Mortality Risk, While those with Vitamin D ≥ 10 ng/mL had a 5% Mortality Risk.
5	(Ersöz & Yılmaz, 2021)	Vitamin B₁₂	NA	A Lower Level of Vitamin B₁₂ was Associated with Patient Mortality.

6	(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.
7	(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 Patients.
8	(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.
9	(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) D was Independently Associated with Mortality in Covid-19 Patients.
10	(Alguwaihes et al., 2020)	Vitamin D	25(OH)D (nmol/l) (75–250)	Severe Vitamin D Deficiency (Adjusted HR- 7, CI (2.7-28.2, p=0.007) was Associated with Death.
11	(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).
12	(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.

13	(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	C o n c e n t r a t i o n s (Combination of Serum Zn and Serum SELENOP) within the Reference Ranges Indicate High Chances for Survival.
14	(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 Mortality.
15	(Vassiliou et al., 2021)	Vitamin D	Vitamin D Deficient (19.9 ng/ml, N ¼ 32) and Vitamin D Insufficient (20-29.9 ng/ml, N ¼ 7)	No Difference was Observed Between Vitamin D Deficient and Insufficient Groups with Respect to Hospital Mortality or Disease Severity.
16	(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.
17	(Cereda et al., 2021)	Vitamin D	25(OH) 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) D Levels and In-Hospital Mortality was Observed.
18	(Jothimani et al., 2020)	Zinc	Zinc Concentration was 80–120 mg/dl. A Zinc Level<80 µg/dl was Defined as ‘Deficient’	Covid-19 Patients Showed Significantly Lower Zinc Levels when Compared to Healthy Controls Resulting in Increased Mortality.
19	(De Smet et al., 2021)	Vitamin D	Serum 25 (OH) D was 18.6 ng/ml	Vitamin D Deficiency on Admission after Adjusting for Confounders was Found to be Associated with Mortality (Odds Ratio [OR], 3.87; 95% Confidence Interval [CI], 1.30-11.55).

3.2.3 Duration of Hospital Stay

Few studies have assessed the role of micronutrient status and length of hospital stay among hospitalized Covid-19 patients as shown in **Table 4**.

Table 4 Association of Micronutrients Status with Duration of Hospital Stay Among Hospitalized Covid-19 Patients

S.No.	Author/Year	Micronutrients	Baseline Levels	Salient Findings
1	(Hernández et al., 2021)	Vitamin D	Serum 25(OH)D 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 25(OH)D Levels \geq 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	(Szeto et al., 2021)	Vitamin D	Vitamin D Deficiency (<20ng/ml) and Normal Vitamin D Levels (\geq 20ng/ml).	No Significant Relationship was Observed Between Pre Hospitalization Serum Vitamin D Status and Length of Stay .
4	(Jothimani et al., 2020)	Zinc	Zinc Level<80 μ g/dl was Defined as 'Deficient'	Covid-19 Patients with Significantly Lower Zinc Levels When Compared to Healthy Controls had Prolonged Hospital 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.

3.2.4 ICU Admission

A study by Baktash et al., (2020) conducted 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%, $p=0.042$). Another study found that lower Vitamin D levels were associated with ICU admission (Ersöz & Yılmaz, 2021). On the other hand, one study did not report any difference in Vitamin D levels among hospitalized patients and those admitted to the ICU (Orchard et al., 2021). Though, we found an effect of

the serum levels of micronutrients on mortality and hospital stay (**Table 3 and Table 4**), the results do not indicate conclusive evidence on the rate of ICU admissions of Covid-19 infected patients. Further, these studies only show the role of Vitamin D and signifies the importance of the optimal levels of this vitamin.

3.2.5 Inflammation

Five studies reported data on the relationship between serum Vitamin D levels and inflammation among hospitalized Covid 19 patients (Adami et al., 2021; Barassi et al., 2021; Demir et al., 2021; Pizzini et al., 2020; Sulli et al., 2021). The serum levels of 25(OH)D, the circulating metabolite of Vitamin D, are inversely correlated with inflammation. However, owing to the small number of studies and heterogeneity in the study designs included in the review, this warrants further investigation.

Table 5. Association of Micronutrients Status with Inflammation Among Hospitalized Covid-19 Patients

S.No.	Author/Year	Micronutrients	Baseline Levels/ Cut-Offs	Key Findings
1	(Barassi et al., 2021)	Vitamin D	Vitamin D >30.0 ng/mL	Negative Correlation Between Serum Vitamin D and C-Reactive Protein Levels.
2	(Sulli et al., 2021)	Vitamin D	NA	Statistically Significant Negative Correlation Observed Between Serum Vitamin D levels C-Reactive Protein (p =0.04).
3	(Demir et al., 2021)	Vitamin 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)	Vitamin D	NA	Patients with 25(OH)D Below 15 ng/mL were more likely to Show Increased Levels of CRP on Admission. Patients with 25 (OH) 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)	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 Inflammation or Severity of Disease.

3.2.6 Miscellaneous

Apart from the above results, some studies also assessed the prevalence of micronutrient deficiencies among patients with Covid-19. Other research articles focused on Hypovitaminosis among Covid-19 patients (Abdollahi et al., 2021; Gonçalves et al., 2020; Hani et al., 2020; Im et al., 2020; Macaya et al., 2020; Pinzon et al., 2020; Ye et al., 2021). An Observational Study conducted on hospitalized ICU patients (aged 66-81 years) observed a prevalence of 79.6% of Low Serum Zinc Levels (Gonçalves et al., 2021). 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 ($p < 0.001$).

It is interesting to note that there are a few studies with contradictory findings to what most studies present. A Retrospective Cohort Study conducted in Italy did not find any relationship between Vitamin D status and Covid-19 (Ferrari et al. 2020). Another Cross-Sectional Study conducted in Turkey did not find a statistically significant relationship between Low Vitamin D Levels and Dysgeusia among patients (Elibol & Baran, 2021). One Cross-Sectional study showed that Covid-19 cases had a significant elevation of Selenium (Alkattan et al., 2021), while another reported that many patients were deficient in Selenium (Im et al., 2020). There are limited number of published studies and heterogeneity in the study designs. We believe that these differences could have changed the outcomes.

4. Discussion

Coronavirus disease (Covid-19) is an infectious disease caused by SARS CoV-2. As of 10th December 2021, 267,865,289 confirmed Covid-19 cases and 5,285,888 deaths, have been reported by WHO globally. To curb this deadly virus a Universal Immunization Campaign is running in all parts of the world, wherein 8,158,815,265 vaccine shots have been administered as of 9th December 2021 (WHO, 2021). The unpredicted progression and severity of the infection diverted the objectives of treatment from curing to preventing the spread of infection. Maintenance of optimal nutrition status became a crucial aspect in controlling the infection spread. Optimal nutrition and dietary nutrient intake impact the immune system through gene expression, cell activation, and signaling molecules modification. In addition, various dietary ingredients are determinants of gut microbial composition and subsequently shape the immune responses in the body (Aslam et al., 2017).

This review sought to provide a comprehensive overview of literature investigating association between any micronutrient deficiency in mild and critically ill Covid-19 patients and Covid-19 disease progression with the associated outcomes. 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. A Retrospective Study on Spanish adults reported a higher prevalence of Vitamin D deficiency (82.2%) among covid-19 cases ($p=0.027$). Vitamin D has a potential role to act as a pluripotent hormone in different immunological mechanisms and may also have a role in the body's immune response to respiratory viruses (Hejazi et al., 2016). It's deficiency has also been associated with higher severity of pulmonary infection (Abrishami et al., 2021;

Barassi et al., 2021; Demir et al., 2021; Kerget et al., 2020; Sulli et al., 2021). Similar findings have been reported in our study, where 14 studies showed a significant association of poor Vitamin D stores along with a higher mortality rate among Covid-19 patients (**Table 3**), while significantly lower micronutrient level among patients determine their length of hospital stay and mortality rates (**Table 1 and Table 2**). 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). Studies have shown that Vitamin D deficient Covid-19 patients had a greater prevalence of longer length of hospital stay and higher chances of ICU admissions than those with lower serum 25(OH)D levels (Baktash et al., 2020; Demir et al., 2021; Ersöz & Yılmaz, 2021; Hernandez et al., 2014; Orchard et al., 2021; Szeto et al., 2021). The findings of our study are in accordance with this (**Table 4**). Vitamin D plays a crucial role in the regulation of the immune system via modulating the synthesis of inflammatory cytokines and impeding the proliferation of pro-inflammatory cells, which are important in the pathogenesis of many inflammatory diseases (Yin & Agrawal, 2014). The present review also reported a negative correlation between Vitamin D Levels and Inflammation (Adami et al., 2021; Barassi et al., 2021; Demir et al., 2021; Sulli et al., 2021). Nonetheless, this review only identified a single study that did not observe any relationship (Pizzini et al., 2020); while one study found that Vitamin D Levels were inversely related to D Dimer Levels (Hernández et al., 2021).

On similar aspects, the authors have found that Low Zinc Levels have shown associations with Lung Function, Mortality and Length of Hospital Stay (**Table 2 and Table 4**). Of relevance to the current review is the use of Zinc as an adjunct with the drug therapy in treating SARS-CoV2 infection. Zinc is another micronutrient that has been a part of preventive therapy against Covid-19 by diminishing inflammation, improving mucociliary clearance, reduced ventilator-induced lung injury. Zinc has gathered much interest due to its antiviral and antibacterial properties (Skalny et al., 2020). In a study conducted on the Indian population the researchers (Jothimani et al., 2020), reported that Lower Serum Zinc Levels (<80mg/dl) were associated with prolonged hospital stay (**Table 4**). Owing to the limited number of studies, 3 studies stating lung involvement, and 3 studies depicting the association with survival in Covid-19 patients these results warrant caution.

Selenium intensifies antioxidant enzymes and defensive proteins synthesis on the mucosal surface and assists in phagocytic action (Huang et al., 2012; Shi et al., 2020). With plenty of evidence based on animal studies, surprisingly there have been almost no trials of Selenium and Influenza or other respiratory infections. A very small number (9 Meta Analysis, Non-Covid-19) have investigated the impact of Selenium supplementation in critically ill patients in the ICU and reported an improvement with short term mortality (James et al., 2021). The present study show results on similar lines, where 2 studies by Heller et al., (2021) and Moghaddam et al., (2020) have shown a combination of Serum Zn and Serum SELENOP within the reference ranges indicating higher chances for survival among Covid-19 patients (**Table 3**). Vitamin B₁₂ has shown a similar role on Covid-19 mortality (Ersöz & Yilmaz, 2021) (**Table 3**). Old Age and Low Vitamin C Levels were co-dependent risk factors for mortality among Covid-19 patients (Arvinte et al., 2020). Elderly obese patients admitted to the ICU reported as high as 94% prevalence of Hypovitaminosis (Gonçalves et al., 2020).

The present review shows the impact of micronutrients on immunity and associated outcomes of the infections. Comparatively, existing reviews have mainly studied the supplemental effect of micronutrients on recovery of Covid-19 patients (Wang et al., 2021; James et al, 2021). In addition, we included only peer reviewed published papers and no pre-prints. 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 also exist in this review. As mentioned, the studies included in this review have varied study designs, owing to the limited number of original research studies on Covid-19. Thus, 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 is skewed towards Vitamin D, given the emphasis this micronutrient has received from most expert bodies and societies and hence the plethora of literature available on it. Given the abundance of micronutrients with beneficial roles in the immune system, more research is warranted on the other micronutrients as well, to examine their synergy to prevent disease progression in mild cases and more so in, critically ill Covid-19 patients. Most prominently, Vitamin D has been proven a vital nutrient in prevention and treatment of Covid-19 patients. Further studies are required to study the role of these micronutrients not only in treatment but prevention of this rapid spreading infection. While, there is extensive literature stating the role of Vitamin A as an antioxidant on improving immunity in infections, there is a dearth of research studies examining the association of Vitamin A status and Covid-19, hence no conclusive evidence on this micronutrient.

5. 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 Covid-19 patients and the associated occurrence of this disease. Hypovitaminosis particularly seen with Vitamin D and Lower Levels of Minerals pose a great impact on the body's immunity as re-instated and shown by this Systematic Review. This further combined with the presence of comorbidities like diabetes, hypertension etc. affect prognostic parameters, such as Mortality, Greater Length of Hospital Stay, ICU Admissions, and Higher CRP Levels among Covid-19 Patients. The knowledge of the 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. This review showed that micronutrients deficiencies made Covid-19 patients more vulnerable to disease progression and severity outcomes. 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 therapeutic management of Covid-19. This could be a non-pharmaceutical intervention to reduce disease severity in an unvaccinated population.

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