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Syndemics of coronaviurs disease and aging: the interplay among nutrition, the immune system and health outcomes

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic revealed "many pandemics". Right from the beginning of the COVID pandemic and various intimidating waves of new variants seriously affected vulnerable populations, including the elderly. This scoping review aimed to summarize the available data on nutrition and immune response during aging and associations between the immune system and viral infections in the older population. The review particularly emphasizes micronutrients including vitamins C, D, zinc, and selenium and their relations to COVID-19 infection. We have summarized the available literature related to the nutritional management of COVID-19 infection to reduce adverse disease outcomes. The review found that the coexistence of micronutrient deficiencies, immune dysfunction, and high infection exposure increases the risk of mortality in older people with COVID-19. Most studies confirmed a positive association between vitamin D status or supplementation and its effect on COVID-19, whereas a few other studies reported a low zinc and selenium status in COVID-19 infected people. Immediate and adequate nutritional management could help tackle the adverse health consequences in elderly. Hence, the pandemic like this requires a comprehensive approach to understand all related aspects and needs further in-depth investigations related to micronutrient supplements to enhance immunity in COVID-19 infected older population.

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1. INTRODUCTION

Human coronaviruses were first described in the 1960s as being responsible for a substantial proportion of upper respiratory tract infections and severe respiratory diseases in the elderly [1]. The "Coronaviridae family," recognized as single-stranded positive-sense RNA viruses, includes severe acute respiratory syndrome (SARS) and the middle east respiratory syndrome (MERS) coronaviruses, which are associated with human respiratory diseases [2]. Since 2003, five new human coronaviruses have been discovered [1]. Nonetheless, this at-first novel coronavirus (SARS-CoV-2) as a causative agent of COVID-19 has shown substantial effects worldwide. In healthy adults, those with a coronavirus infection have reported symptoms of flu, malaise, and low-grade fever, whilst a prevalence of pneumonia is commonly found in elderly and immunocompromised patients. In the presence of other chronic diseases, COVID-19-derived systemic inflammation tended to make the respiratory symptoms of the infection more severe, leading to mortality [3].

The COVID-19 pandemic significantly affected the world in multiple ways and set out catastrophic consequences on the global economy. These effects have been felt at various levels: temporally as well as spatially. An already overwhelmed world were under new stressors due to more intimidating waves [4], especially of new variants such as Delta and Omicron. Starting from December 31, 2019, the virus in its various forms had infected nearly 450 million population within first two years at the global level [5]. Despite being a global pandemic, there were various specificities to its effects at various scales, particularly for some countries, communities, and individuals, due to the interplay among the pre-existing socio-cultural, economic, political and environmental conditions that result in unique human bodies that anthropologist Margaret Lock calls "local biologies" [6]. Because of these local biologies—a result of an interaction between biological processes and social contexts, certain populations and individuals were more vulnerable than others in the face of COVID-19, which is why medical anthropologists proposed syndemics theory and rejecting the notion of "global syndemics" [7]. The term "syndemics," created by critical medical anthropologist Merrill Singer, is a combination of "synergy" and "epidemics." This analytical "biosocial syndemics theory" considers the interplay among various bio-social factors and bridges "the critical knowledge gap" [8] in order to apply holistically produced evidence for infection prevention and care. This is an extension of our previous unpublished work focusing more on age-COVID-19 syndemic [9]. In this review article, we follow this theory to pay attention to what we call the "age-COVID-19 syndemic" with a focus on the associations among nutrition, age, immune systems, and COVID-19. As part of our research for this article, we reviewed the available published literature to evaluate the effects of nutrition on immunity among the elderly in relation to COVID-19. This scoping review aimed to summarize the available data on nutrition and immune response during aging and associations between the immune system and viral infections in the older population, however, the limited literature and evidence from case control or interventional studies warrants future studies.

2. METHOD

The proposed scoping review summarized the available literature by using search sources such as Google Scholar, PubMed, and Scopus databases to comply with our main objective focusing on nutrition and immunity in older population in relation to COVID-19 as shown in Figure 1. Since, this review is mainly narrative and does not include any systematic approach, however, the authors searched for a broader search term such as: i) COVID in older population; ii) COVID and immunity in older population; iii) COVID and malnutrition in older population; and iv) COVID mortality in older population to retrieve most appropriate data. The authors independently identified the most relevant English literature, including original papers, review articles, clinical trials, case studies, and series of letters (flow chart of study selection). Any grey literature, preprints, and articles other than English were excluded. We tried to accumulate relevant literature that seems appropriate for assessing our study objective and acquire a narrative approach focusing on our study objective. Since, it is scoping review of previous studies. Ethical approval or participants consent was not needed. By the time we conducted this review, the literature was still being produced, and studies were ongoing, continuously exploring and analyzing the effects and aftereffects of COVID-19 on different populations. Therefore, not all studies could be included in this review. Additionally, the rapid pace of emerging research posed challenges in maintaining a comprehensive overview of new findings. The final draft critically checked and discussed with all authors by resolving any discrepancies.

3. RESULTS AND DISCUSSION

The review found that the coexistence of micronutrient deficiencies, immune dysfunction, and high infection exposure increases the risk of mortality in older people with COVID-19. Most studies confirmed a positive association between vitamin D status or supplementation and it is effect on COVID-19, whereas a few other studies reported a low zinc and selenium status in COVID-19 infected people. The following sections provide such details.

3.1. Age-COVID-19 syndemics

The most severe consequences of coronavirus infection occurred in older populations, since people above 65 years of age were more likely to develop acute respiratory distress syndrome leading to death. For example, a comparative study from China and Italy reported a high mortality rate in the COVID-infected older populations compared to other age groups [10]. Age of infection, dose and route of infection, genetic susceptibility, and poor immune systems were a few important factors that in combination increased susceptibility to viral infections in older people [11]. Age-related physiological changes, tissue destruction, and the presence of concurrent infections, including urinary and gastrointestinal tract infections, also played a pivotal role in this regard. Other comorbidities like diabetes, hypertension, kidney, and cardiovascular diseases during aging also interrupted the normal homeostasis of innate and adaptive immunity, leading to adverse

disease outcomes in older COVID patients [12]. Concomitantly, the vicious cycle of malnutrition further reduced older individuals' capacities to fight against viral infection by compromising their immune systems. Simultaneously, age-related changes in both the innate and adaptive immune systems made older adults more prone to COVID-19 infections [13]. These comorbidities and situations synergistically affect each other showing a syndemic interaction among them.

An adaptive immune response against coronavirus requires stimulation of B and T cell epitopes [14]. However, COVID-19 related frailty, along with malnutrition, could pose adverse effects on regulatory T-cells and senescent natural killer cells, leading to adverse COVID-19 outcomes in the older population [15]. Recent studies have summarized the beneficial effects of micronutrients including vitamin C, D, zinc, and selenium for immune support and to reduce the risk of infection [16]. Antioxidant properties of these micronutrients containing enzymes such as superoxide dismutase, catalase, and glutathione peroxidase help to support the immune system [17]. Therefore, different treatment strategies, effective vaccines, and nutritional management of infected patients were under consideration as therapeutic measures against the evolving coronavirus. We emphasize these micronutrients and their relation to COVID-19- infected older people. Herein, we briefly summarize the available literature related to the nutritional management of a novel COVID-19 infection, which might help to boost the immune system and to prevent adverse outcomes in the older population. However, due to the dearth of clinical, interventional, and randomized controlled trials, the information provided may need to be updated in the future.

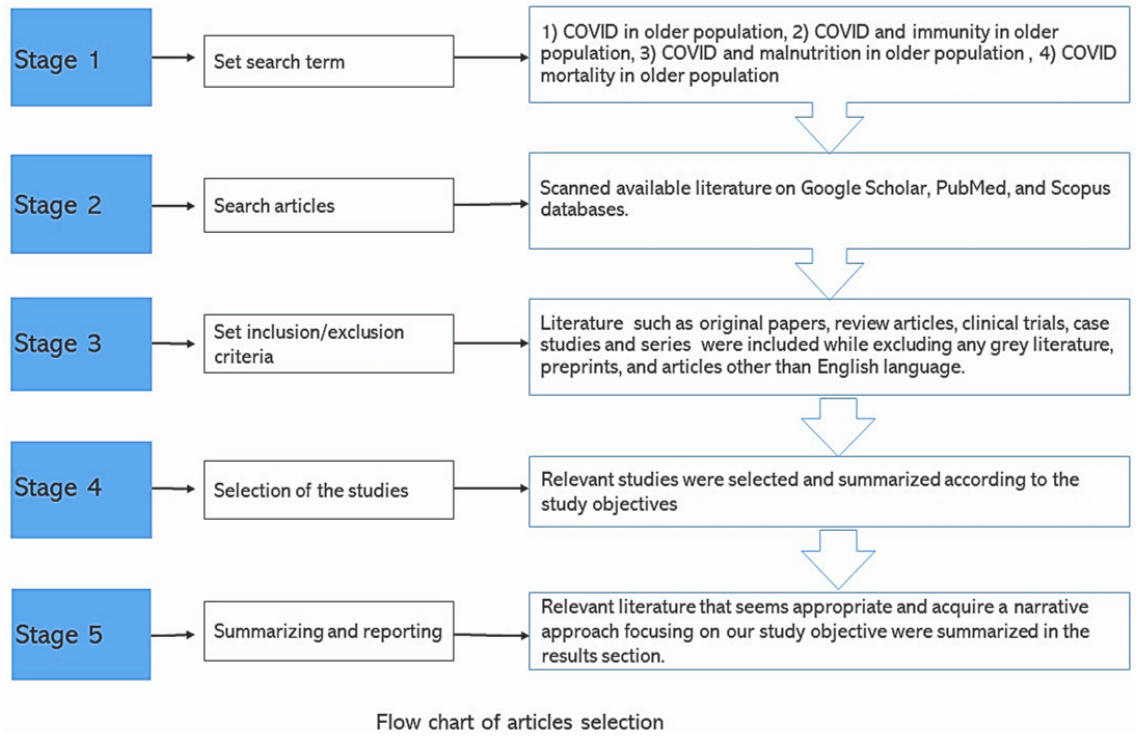

Figure 1. Flow chart of screening process

3.2. Viral infection and immune responses in the older population

Viral respiratory pathogens including influenza, respiratory syncytial virus, human metapneumovirus, and coronaviruses have been recognized as significant causes of hospitalizations in the older population [18]. A study of 195 countries has estimated 1,080,958 deaths in the older population due to lower respiratory infections [19]. A high burden of pneumonia, lower respiratory tract infections, and severe outcomes of respiratory syncytial virus infection are seen in elderly people. Correspondingly, in the United States, people aged 85 years or older have shown a 32 times higher death rate due to influenza-associated deaths than the younger population [20]. Both innate and adaptive immunity as a part of our immune systems helps to control viral infections. Macrophages, monocytes, and dendritic cells as parts of the innate immune system recognize the invading pathogens in the presence of pattern recognition receptors (PRRs) and microbe-associated molecular patterns (MAMPs). Furthermore, activation of B cells via viral antigen-specific helper T cells

produces antibodies to fight against the virus and to neutralize the infection. However, aging induces adverse effects on innate and adaptive immunity, resulting in impaired virus control and protective immunologic memory [21]. Moreover, the functioning and coordination of innate and adaptive immunity start to downregulate with age progression as shown in Figure 2 [16]. Owing to aging, several factors affect the normal functioning of the immune system: i) CD4+Th cells reduce the antigen response and increased differentiation into Th17 cells; ii) decline in the production of B cells leads to reduced antibody avidity and many responding cells; and iii) expansion of CD8+CD28−T cells impair the normal immune functions. Increased frequencies of CD28−T cells are directly or indirectly responsible for the immune dysfunctions in the elderly through compromising T cell homeostasis, thereby increasing the risk of viral infections. Similarly, changes in monocyte function (circulating innate immune cells) and phenotype due to aging increase the risk of age-related comorbidities [22].

Thus, the protective mechanisms against viral infection are seriously compromised in older people due to the interruption of immune responses. Immune senescence (changes in adaptive immunity mediated by T and B cells) due to old age reduce the resistance to new infectious agents and control of viral exposure. Furthermore, a low baseline of CD4/CD8 ratio, reduction of naïve T cells, and natural killer cells increase viral susceptibility in older people [23]. Additionally, due to decreased respiratory muscle strength, lung compliance, and cellular immunity, B cells fail to respond to new antigens and increased levels of inflammatory mediators in the older population [24]. Given that, older adults might not effectively switch from innate to adaptive immunity due to little or no antibody production, making them more susceptible to emerging infections [12].

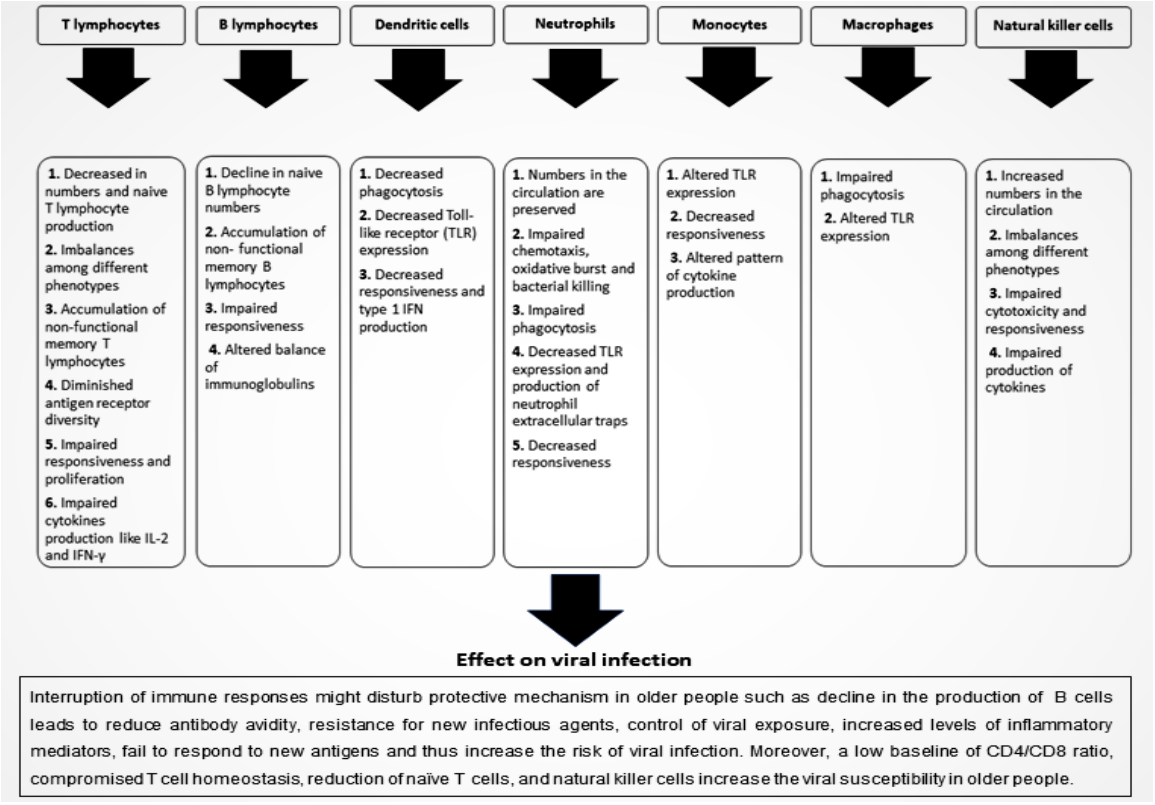

Figure 2. Age-related changes of the immune system and effects on viral infection in the older population

3.3. Nutrition and immune response in the older population

In older people, undernutrition instead of overnutrition is the main cause for concern due to low dietary intake, changes in metabolic demands, malabsorption of nutrients, and due to nutrient losses. Age-related malnutrition can further aggravate the general risk of viral infections and related comorbidities, including diarrhea, pneumonia, acute respiratory infections, higher hospital readmission rates, and mortality through suppressing the immune responses [25] as shown in Figure 3. This nutritional stress, along with viral infection, significantly increases oxidative stress and the formation of free radicals leading to cell death. Various micronutrients' synergistic roles in immunity are well established and recently reviewed. Different macro-and micronutrients influence the ability of the immune system to respond to infections. For example,

the immunoregulatory and anti-inflammatory properties of vitamin D regulate the growth and differentiation of multiple cell types involved in an innate and adaptive immune system (macrophages, dendritic cells, T cells and B cells) [26].

Similarly, vitamin C improves immune defense through supporting the cellular functions of both the innate and adaptive immune systems. Vitamin C is involved in apoptosis and clearance of spent neutrophils from infection sites by macrophages, thereby decreasing necrosis/NETosis and potential tissue damage [27]. Lack of other micronutrients such as zinc deficiency adversely affect T lymphocyte maturation, differentiation, cytokine production, B cell activation, and plasma cell differentiation, and alter the activities of monocytes, neutrophils, and natural killer cells. Therapeutic effects of zinc supplementation have been reported for viral diseases including respiratory tract infections, the common cold, and pneumonia [28]. Similarly, the establishment and progression of viral infections are influenced by the redox state of the host cell, and selenium regulates the cellular redox balance and results in both beneficial and detrimental effects on cellular immunity in the older population [29].

Both macro- and micronutrients have to mediate immunological effects on the host immune response through changes in gut microbes. In particular, fiber and fermented foods play crucial roles in maintaining healthy gut microbiota and in supporting the immune system's normal functioning. Equally, probiotics have been proposed to mediate acute upper respiratory tract infections by regulating the immune responses [30]. Essential amino acids and polyunsaturated fatty acids help to reduce inflammation and enhance immune protection for viral infections. Additionally, vitamins and trace elements, including vitamins A, B6, B12, C, D, E, zinc, iron, selenium, magnesium, copper, and omega-3 fatty acids, play essential and beneficial roles in the improvement of immune responses [31]. Vitamin A has been proven to be essential for the regulation of innate and cell-mediated immunity by growth and differentiation of B cells, natural killer cells, macrophages, and neutrophils [32]. Vitamin B-6 deficiency in the older population has been found to impair interleukin-2 production and peripheral blood lymphocyte proliferation to both T- and B-cell mitogens, while vitamin C intake appears to prevent respiratory and systemic infections by strengthening the immune system. In addition, zinc deficiency in elderly people due to low dietary zinc intake and intestinal malabsorption appears to impair the immune response, leading to degenerative diseases. It has been shown that low selenium status increases the risk of mortality by negatively affecting the immune system [33].

Figure 3. Determinants of risk of infection (COVID-19) in the older population

3.4. Micronutrients and COVID-19

Different studies discussed potential treatment strategies, including the interrelationship of COVID-19 and immune-building nutrition, to overcome the global threats of this pandemic [17]. Vitamins, trace elements and nutraceuticals in viral infections might play essential roles in the nutritional management of COVID-19+ elderly patients. Furthermore, several studies have demonstrated the associations between micronutrients and COVID 19; these as shown in Table 1 (see in Appendix). The studies found low zinc levels [16], [34]–[38] and selenium [39] in COVID infected patients. In contrast, the treatment of COVID-19 infected people with various or multiple micronutrient supplements appears to have beneficial effects and to reduce the risk of adverse disease outcomes [40], [41]. The therapeutic effects of zinc supplements on COVID-19 infections can be explained as due to modulation of antiviral and antibacterial immunity and by reducing inflammation and ventilator-induced lung injury [42]. Likewise, diarrhea is a frequently observed symptom in patients with COVID-19 [43], and the known beneficial effect of zinc supplements to treat acute and persistent diarrhea might help to reduce the disease morbidities [44]. A recent study found that selenium deficiency has been associated with COVID-19-related mortality due to reduced production of selenoprotein-P and glutathione peroxidase activity [45]. The initiation of adequate supplementation in high-risk areas and/or soon after the time of suspected infection with COVID-19 might help to reduce the adverse disease consequences [46]. In addition, immediate intervention with vitamin B3 might be beneficial during COVID-19 due to its lung-protective effects [14].

3.5. Association between vitamin D and COVID-19

There is a direct link between vitamin D supplements and severe clinical outcomes of patients infected with COVID-19. Studies found that vitamin D deficiency can aggravate acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections [47]. Thus, a dose of 10,000 IU/d of vitamin D3 through improving 25(OH)D concentrations has been suggested for people at risk of severe COVID-19 outcomes [48]. The most recent data confirm the positive association between vitamin D status or supplementation and its effect on COVID-19 as shown in Table 2 (see in Appendix). A study by Ling and colleagues found that cholecalciferol booster therapy, regardless of baseline serum 25(OH)D levels, appears to reduce the risk of mortality and adverse COVID-19 outcomes in acute COVID-19 infected people [49]. Similarly, another study showed that administration of a high dose of calcifediol or 25-hydroxyvitamin D significantly reduced the need for ICU treatment in COVID infected patients [50]. Additionally, several ongoing trials have been designed to evaluate the determined effects of vitamin D supplementation on COVID-19 disease progression and mortality risks. Other studies found that low vitamin D status in COVID-19 infected people led to adverse disease outcomes. Also, low vitamin D status was reported in COVID patients leading to adverse health outcomes and high mortality risks [51]–[59].

3.6. Nutritional recommendations for older population and COVID-19- infected patients

Given the interrelationship of malnutrition and immune response, restoration of deficient micronutrients is recommended to enhance immunity, thereby increasing resistance to infection and faster recovery in different life stages, including aging. For instance, vitamin D supplementation has shown strong beneficial effects on cell-mediated immunity in the older population. A daily dose of multivitamin or trace mineral supplements such as elemental zinc (120 mg/day), selenium (100 mg/day), and a daily dose of vitamin E supplements (200 mg/day) are recommended to reverse age-related immune dysfunction [60]. Similarly, a vitamin C intake of 100-200 mg/day is suggested to optimize cell and tissue levels and to ameliorate the severity of common cold infections [27].

The World Health Organization (WHO) recommended regular nutritional assessments, adequate protein intake, dietary counseling, and oral supplements, including adequate amounts of vitamins and minerals, to meet the older population's nutritional requirements. WHO and the Food and Agriculture Organization (FAO) provided the recommended nutrient intakes (RNIs) for vitamins and minerals in the older population as shown in Table 3. Additionally, carbohydrate, protein, and energy requirements are recommended to prevent weight loss, reduce the risk of COVID-19 complications, and promote disease recovery. WHO and FAO emphasize a well-balanced diet including fresh and unprocessed food, plenty of water to keep hydrated, a moderate number of oils and fat, and less salt and sugar intake to boost immune systems and to lower the risks of chronic illnesses and infectious diseases. The European Society for Clinical Nutrition and Metabolism (ESPEN) has provided a concise guide for the nutritional management of COVID-19 infected people, which includes malnutrition assessment, optimization of nutritional status, micronutrient supplements, regular physical activity, oral nutrition supplements-if required to meet patients' needs, and enteral nutrition for the patients whose nutritional requirements cannot be met orally.

Table 3. Recommended Nutrient Intakes (RNIs) in the older population

RNIs	Male (>65 years)	Female (>65 years)
Vitamin A[a]	300 µg RE/day	300 µg RE/day
Vitamin-D	15 µg/day or 600IU	15 µg/day or 600IU
Vitamin C	45 mg/day	45 mg/day
Calcium[b]	800 mg/day	800 mg/day
Vitamin K	65 µg/day	55 µg/day
Thiamine (19+ years)	1.2 mg/day	1.1 mg/day
Riboflavin (19+ years)	1.3 mg/day	1.1 mg/day
Niacin (19+ years)	16 mg NEs/day[c]	14 mg NEs/day[c]
Biotin (19+ years)	30 µg/day	30 µg/day
B6 (51+ years)	1.7 mg/day	1.5 mg/day
B12	2.4 µg/day	2.4 µg/day
Folic acid	400 µg/day	400 µg/day
Selenium	33 µg/day	25 µg/day
Magnesium	224 mg/day	190 mg/day
Zinc (Moderate bioavailability)	7 mg/day	4.9 mg/day

Adopted From WHO and FAO guidelines [61] [a]Estimated mean requirement: [b]Theoretical calcium allowance based on an animal protein intake of 20–40g: [c]niacin equivalents.

4. CONCLUSION

The older population with the underlying condition of malnutrition appeared to be at a higher risk of viral infection due to an interplay among various biosocial events, including malnutrition and an age that compromises immune responses to make particular populations vulnerable to be infected and affected by COVID-19. Most of the studies included in this review confirmed a positive association between vitamin D status or supplementation and its effect on COVID-19, while other studies reported a low zinc and selenium status in COVID-19-infected people. Further studies focusing on adequate nutrition management of elderly patients to reduce adverse disease outcomes are needed. Furthermore, immediate measures, including the planning and implementation of nutritional strategies to reduce age-related malnutrition, will help to minimize the risk of COVID-19-mediated adverse health effects, in future. Hence, similar critical situation will require a comprehensive approach for considering all relevant aspects to address the global health challenges imposed by any pandemic, especially for the elderly.

APPENDIX

Table 1. Characteristics of studies showing the association between micronutrients and COVID-19

Micronutrient	Ref.	Study design	Study aims	Number of participants	Intervention	Results	Conclusion
Zinc	[34]	A cross-sectional study	The study aimed to evaluate zinc status in COVID patients as compared to the control group	Total (n=171)	N/A	Zinc concentrations in COVID patients (mean±SD) Zn=717.4±246.2 µg/L Zinc concentrations in healthy subjects (mean± SD) Zn=975.7±294.0 µg/L	Zinc concentrations in COVID patients were low compared to healthy subjects.
Zinc and ascorbic acid	[35]	A randomized clinical trial	The study aimed to examine whether high-dose zinc and/or high-dose ascorbic acid reduce the severity or duration of disease symptoms compared with usual care among ambulatory patients with SARS-CoV-2 infection	Total (n=214) Allocated to and received standard of care (n=50) Allocated to and received ascorbic acid only (n=48) Allocated to and received zinc only (n=58) Allocated to and received ascorbic acid and zinc (n=58)	Patients were randomized in a 1:1:1:1 allocation ratio to receive either 10 days of i) zinc gluconate (50 mg), ii) ascorbic acid (8,000 mg), iii) both zinc and ascorbic acid, iv) standard of care.	Time to 50% reduction in symptoms (mean±SD) Usual care without supplementation= (6.7±4.4 days) Ascorbic acid group mean= (5.5±3.7 days) Zinc gluconate group= (5.9±4.9 days) Received both zinc and ascorbic acid= (5.5±3.4 days)	The study found that treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the 2 supplements did not significantly decrease the duration of symptoms compared with standard of care.
Zinc	[36]	An observational cohort study	The study investigated the association between serum zinc content and COVID-19 disease progression	Total (n=249)	N/A	Serum zinc content at admission (<50 µg/dL) and risk of in-hospital death OR 3.2 (95% CI, 1.01-10.12)	The study findings showed that low serum zinc levels are associated with adverse COVID-19 outcome

Table 1. Characteristics of studies showing the association between micronutrients and COVID-19 (*continued*)

Micronutrient	Ref.	Study design	Study aims	Number of participants	Intervention	Results	Conclusion
Zinc	[37]	A prospective study	The study aimed to evaluate the relationship between serum zinc in COVID-19 patients and its correlation with disease severity	COVID-19 patients (n=47) Healthy controls (n=45)	N/A	Zinc status in COVID patient's median (interquartile range) 74.5 (53.4–94.6) μg/dl Zinc status in control group median (interquartile range) 105 (95.65–120.90) μg/dl	The study reported that a significant number of COVID-19 patients were zinc deficient and zinc deficiency was associated with a prolonged hospital stay and increased mortality
Zinc	[38]	A retrospective observational study	This comparative study examined the outcomes among hospitalized COVID-19 patients who received hydroxychloroquine and azithromycin plus zinc sulphate versus hydroxychloroquine and azithromycin alone	Patients taking zinc sulphate in addition to hydroxychloroquine and azithromycin (n=411) Patients taking hydroxychloroquine and azithromycin alone (n=521)	Treatment group: patients were taking zinc sulphate (220 mg capsule containing 50 mg elemental zinc twice daily for 5 days) along with hydroxychloroquine (400 mg load followed by 200 mg twice daily for 5 days) and azithromycin (500 mg once daily) Control group: patients were taking hydroxychloroquine (400 mg load followed by 200 mg twice daily for five days) and azithromycin (500 mg once daily) alone	Zinc sulphate supplementation and frequency to discharge from hospital OR 1.53 (95% CI, 1.12–2.09) Zinc sulphate supplementation and reduction in mortality or transfer to hospice among patients who did not require ICU level care OR 0.449 (95% CI, 0.271–0.744)	The study findings showed that zinc sulphate appears to play a positive role in therapeutic management for COVID-19
Selenium	[39]	A cross-sectional study	The study aimed to analyze the blood serum selenium levels in COVID-19 patients compared to healthy controls to understand the correlation between selenium levels and COVID-19 viral infection	Total (n=60) COVID patient (n=30) Healthy controls (n=30)	N/A	Selenium levels of COVID patients (mean±SD) Se=69.2±8.7 ng/mL Selenium levels of control group (mean±SD) Se=79.1±10.9 ng/mL	The study found a low selenium status in patients with COVID-19 as compared to healthy controls
Vitamin C	[40]	A randomized controlled trial	The study aimed to assess the efficacy of adding high-dose intravenous vitamin C (HDIVC) to the regimens for patients with severe COVID-19 disease	Total (n=60) Supplementation group (n=30) Control group (n=30)	The treatment group were receiving 1.5 g vitamin C (IV) every 6 h for 5 days Control group included patients who did not receive vitamin C	Hospital length of stay (days), median (IQR) Treatment group=8.50 (7.0–12.0) days Control group =6.50 (4.0–12.0) days	The study did not find significantly better outcomes in the group who were treated with HDIVC in addition to the main treatment regimen at discharge
Vitamin D, magnesium, and vitamin B12	[41]	A cohort observational study	This study aimed to determine clinical outcomes of older patients with coronavirus (COVID-19) who received a combination of vitamin D, magnesium, and vitamin B12 (DMB) compared with those who did not receive the supplements	Total hospitalized patients >50 y of age (n=43) Received supplements (n=17) Not received supplements (n=26)	The supplementation (DMB) group were treated with a combination of 1000 IU/d oral vitamin D3, 150 mg/d oral magnesium, and 500 mcg/d oral vitamin B12	DMB exposure and oxygen therapy OR 0.13 (95% CI, 0.03–0.59) DMB exposure and intensive care support OR 0.20 (95% CI, 0.04–0.93)	A vitamin D/magnesium/vitamin B12 combination in older COVID-19 patients was associated with a significant reduction in intensive care support, requiring oxygen support, or both

Table 2. Characteristics of the studies showing an association between Vitamin D and COVID-19

Ref.	Study design	Study aim	Number of participants	Intervention	Results	Conclusion
[49]	A cross-sectional multicenter observational study	The study aimed to evaluate the association between serum 25-hydroxyvitamin D [25(OH)D] levels, vitamin D status, or cholecalciferol therapy, and its effect on predictors of COVID-19 mortality	Total (n=986) Treatment group (n=151)	Treatment with cholecalciferol using high-dose booster therapy (approximately ≥280,000 IU up to 7 weeks)	Booster cholecalciferol therapy and reduce risk of COVID-19 mortality OR 0.13 (95% CI, 0.05–0.35)	The study found that cholecalciferol booster therapy, regardless of baseline serum 25(OH)D levels, appears to reduce the risk of mortality in acute COVID-19 patients
[51]	A prospective multicenter observational study	The study investigated the association of vitamin D status and adverse COVID outcomes	Total (n=109)	N/A	Vitamin D status in COVID patients during hospitalization Vitamin D (<30 nmol/L)= 38% Vitamin D (30 –50 nmol/L) =27% Vitamin D (>50 nmol/L)=35% 9.2% of patients received vitamin D supplementation during hospitalization, but the initiation of supplementation was not related to disease severity. However, D-Dimer levels were moderately associated with 25(OH)D levels at disease onset (r=0.437, p<0.05)	Vitamin D deficiency was frequent among COVID-19 patients during hospitalization, but the study did not find any association of vitamin D status with adverse disease outcomes
[50]	A randomized double-masked clinical trial	The study evaluated the effect of calcifediol treatment on ICU admission and mortality rate among Spanish patients hospitalized for COVID-19	Total (n=76) Treated with cholecalciferol (n=50) No treatment (n=26)	Treatment group patients were given oral calcifediol (0.532 mg) at the day of admission, then oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission	Risk Estimate Odds Ratio for ICU admission in patients with calcifediol treatment vs without calcifediol treatment OR 0.03 (95% CI, 0.003 – 0.25)	The study found that administering a high dose of calcifediol or 25-hydroxyvitamin D, significantly reduced the need for ICU treatment in COVID-19 patients.
[52]	A retrospective observational study	The study aimed to evaluate the role of serum 25(OH) vitamin D status on COVID disease severity and related mortality	Total (n = 149)	N/A	Vitamin D deficiency and risk of in-hospital mortality OR 0.92 (95% CI, 0.87–0.98)	The study found that low serum 25(OH) vitamin D was associated with mortality in COVID-19 patients
[53]	A retrospective observational trial	The study determined the association between serum 25-hydroxyvitamin D 25(OH)D level on admission and radiologic stage and adverse COVID-19 outcomes	Total (n = 186)	N/A	Vitamin D deficiency (<20 ng/mL) and risk of mortality OR 3.87 (95% CI, 1.30–11.55)	The study found that low 25(OH)D levels in COVID patients on hospital admission are associated with COVID-19 disease stage and mortality
[54]	A prospective observational study	The study aimed to investigate that the association between 25-hydroxyvitaminD 25(OH)D levels and adverse outcomes of COVID-19 pneumonia	Total (n=30)	N/A	28-day ICU mortality in low vitamin D group (<15.2 ng/mL) n=5 28-Day ICU mortality in high vit D group (>15.2 ng/mL) n=0 Survival analysis showed that the low vitamin D group had a higher 28-day mortality risk (log-rank test, p=0.01)	The study findings showed that all COVID-19 patients who died within 28 days in ICU belonged to the low vitamin D group
[55]	An observational study	The study aimed to investigate 25OH-vitamin D serum concentrations with clinical parameters of lung involvement in elderly patients hospitalized for SARS-CoV-2 infection	Total (n=65)	N/A	A significantly lower vitamin D serum levels were found in the elderly COVID-19 patients who died during hospitalization compared to those who survived (median =3.0 vs. 8.4 ng/mL, p=0.046)	This study's findings showed that 25OH-vitamin D serum deficiency is associated with more severe lung involvement, longer disease duration, and risk of death in elderly COVID-19 patients
[56]	A multicenter, double-blind, randomized, placebo-controlled trial	The study aimed to investigate the effect of a single high dose of vitamin D3 on hospital length of stay in patients with COVID-19	Total (n=240) Treatment group (n=120) Placebo (n=120)	Treatment group received a single oral dose of 200000 IU of vitamin D3	Time to hospital stay median (interquartile range) Vitamin D3 group=7.0 (4.0-10.0) days Placebo group=7.0 (5.0-13.0) days Vitamin D3 group vs placebo group [between-group difference (95% CI) %] Risk of mortality 2.5 (95% CI, - 4.1–9.2)] Admission to the intensive care unit [-5.2 (95% CI, -15.1–4.7) %] Need for mechanical ventilation. [-6.8 (95% CI, -15.1–1.2) %]	The study found that a single high dose of vitamin D3, compared with placebo, did not significantly reduce hospital length of stay

Table 2. Characteristics of the studies showing an association between Vitamin D and COVID-19 (*continued*)

Ref.	Study design	Study aim	Number of participants	Intervention	Results	Conclusion
[57]	A retrospective, observational study	The study aimed to examine vitamin D levels in patients with acute respiratory failure due to COVID-19 and to assess any correlation of vitamin D status with disease severity and prognosis	Total (n=42)	N/A	A survival analysis highlighted that, after 10 days of hospitalization, severe COVID patients with vitamin D deficiency had a 50% mortality risk, while COVID patients with vitamin D (≥ 10 ng/mL) had a 5% mortality risk (p=0.019)	The study found that patients with severe vitamin D deficiency had a significantly higher mortality risk
[58]	A prospective, observational study	The study investigated the association between vitamin D deficiency and SARS-CoV-2 infection rate and mortality risk	Total (n=66,945)	N/A	An inverse correlation was observed between the mean level of 25(OH)D and SARS-CoV-2 infection rate (r=−0.43, p=0.02) and mortality rate (r=−0.42, p=0.02)	The study findings showed an association of vitamin D status with SARS-CoV-2 infection and related mortality
[59]	A prospective, observational study	The study aimed to examine the prevalence of vitamin D deficiency in hospitalized COVID patients and studied the association of baseline (25-OH)D levels with the severity of COVID-19 infection	Total (n=410) Treated with cholecalciferol (n=128)	Cholecalciferol (median dose of 60,000 IU)	25-OHD (ng/mL) status and disease severity in the older population OR 1.00 (95% CI, 0.99–1.002)	The study reported a high prevalence of vitamin D deficiency in COVID- 19 patients. However, there was no association between baseline serum (25-OH)D level and severe disease outcomes of COVID-19

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