Review

Vitamin A Nutritional Status and Clinical Outcomes in COVID-19: A Systematic Review

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Summary The role of vitamin A in the pathophysiological context of coronavirus disease 2019 (COVID-19) represents a current challenge, given the major impact of COVID-19 on morbidity and mortality and the importance of retinol in pulmonary and immunomodulatory functions. The aim of this review is to assess the relationship between vitamin A nutritional status and clinical outcomes in people with COVID-19. The PubMed, Web of Science, Scopus and ScienceDirect databases were used to search for observational studies that assessed retinol levels in hospitalized individuals with COVID-19, following the PRISMA recommendations. A total of 1,912 articles were identified and seven met the inclusion criteria. Four studies showed borderline or deficient retinol blood levels (retinol <0.20 mg/L or <0.70 mol/L) in people with COVID-19, associated with worsened clinical outcomes. In the other three studies lower mean values of this vitamin were identified in COVID-19 symptomatic groups compared to asymptomatic or convalescent groups that showed worse clinical outcomes. The results suggest a possible association between retinol and COVID-19 outcomes. However, there is a clear need to develop clinical trials to elucidate the role of vitamin A in the pathophysiological process of COVID-19.

Key Words vitamin A, retinol, retinoic acid, COVID-19, SARS-CoV-2, hospitalization

Coronavirus disease 2019 (COVID-19) is an infectious pathology caused by the SARS-CoV-2 virus (*1*). Global data from the World Health Organization (WHO) indicate that by august 2023, 770,085,713 confirmed cases of COVID-19 have been reported, including 6,956,173 deaths; of these most of the reported cases occurred in Europe (35.9%), Asia and Oceania (26.7%) followed by the American continent (25.2%) (*2*). The morbimortality caused by this disease is having a major health impact.

Among the leading causes of death in people with COVID-19 are those related to the impact of SARS-CoV-2 on the lung. The virus promotes severe acute respiratory syndrome, an inflammatory condition associated with extensive pulmonary fibrosis, caused by enhancement of the transition from lipofibroblast to myofibroblast (*3*, *4*). In this severe inflammatory context, efficient immune response is essential and adequate nutrition becomes imperative to keep the installed infection under control (*5*). Furthermore, the pulmonary and immunomodulatory roles of vitamin A are uncovered, since retinol has a broad effect in modulating the immune system, promoting epithelial integrity with formation, keratinization, stratification, differentiation and functional maturation of epithelial cells (*6*, *7*).

Lipofibroblasts depend on retinoids to initiate, coordinate, and regulate alveolar septum eruption and alveologenesis. Therefore, the loss of retinoids during the virus-induced lipofibroblast-myofibroblast transition may impair the lung's ability to repair damaged epithelial surfaces, potentially leading to long-lasting injury, lasting scarring, lung fibrosis and reduced lung capacity, which could manifest in a 'long COVID-19' effect. In addition, it is suggested that SARS-CoV2 may lead to systemic vitamin A deficiency through a combination of increased urinary losses, reduced intake and absorption, and increased utilization of this vitamin (*4*), not yet fully clarified.

In view of the above, clarifying the role of vitamin A in the pathophysiological context of COVID-19 represents a current challenge and has instigating researchers, considering its presumed protective effect against the worsening of the disease. Thus, the present literature review analyzed the immunological properties of retinol and to evaluate the relationship between vitamin A nutritional status and clinical outcomes in people with COVID-19.

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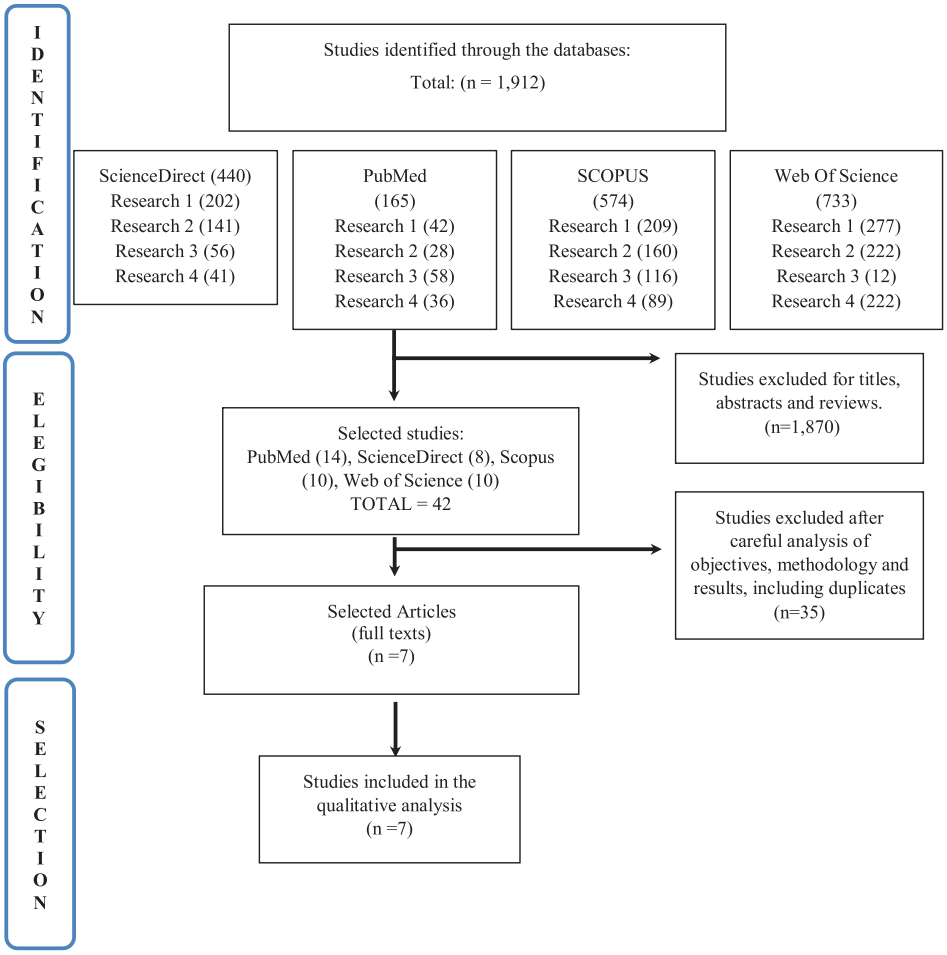

Fig. 1. Flowchart of the search results in the consulted databases, screening, eligibility and inclusion of articles in the systematic review. Research 1: Vitamin A AND COVID-19 AND hospitalization; Research 2: Vitamin A AND SARS-CoV-2 AND hospitalization; Research 3: Vitamin A OR Retinol AND COVID-19 AND hospitalization; Research 4: Vitamin A OR Retinol AND SARS-CoV-2 AND hospitalization. Source: Collected data.

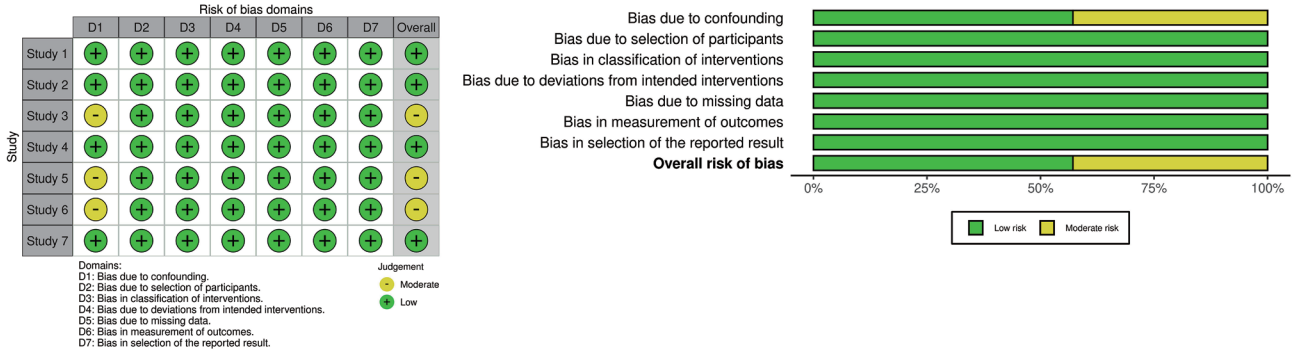

Fig. 2. Cochrane risk of bias in non-randomized studies of interventions (ROBINS-I) for the included studies.

Methods

Eligibility criteria. Clinical trials on the relationship between COVID-19 and vitamin A are rare because it is a subject that is currently being discussed, so only observational studies (cross-sectional and cohort) developed in humans with COVID-19 and aged over 18 y, without restriction of gender and ethnicity were included. The search had no publication year limit. Studies that did not assess retinol levels, were not available in full, reviews and articles in languages other than English, Portuguese and Spanish were excluded.

Search and selection strategies. The studies were selected through the electronic databases PubMed, Scopus, Web of Science and ScienceDirect in December 2022 by two reviewers (IKFO and VCC) independently and without restrictions on period and language. The following Medical Subject Headings (MeSH) descriptors were used: Vitamin A/Retinol/Retinoic Acid/COVID-19/

Sars-Cov-2/Hospitalization. The Boolean operators "AND" and "OR" were used as follows: (vitamin A OR Retinol OR Retinoic Acid) AND (COVID-19 OR Sars-CoV-2) AND Hospitalization. In case of disagreement during selection, a careful analysis of the study was carried out, so that a consensus could be reached between the evaluators regarding the selection or exclusion of articles.

Data extraction. After reading the titles and abstracts in the databases, the articles were exported to *EndNote Web* software (Thomson Research Software, Carlsbad, CA, USA) for complete study reading. A data extraction form was developed using Excel (version 16.47), where reviewers recorded the relevant data that were extracted from the studies. Discrepancies in data extraction were resolved by discussion or arbitration by a third reviewer (GSS) if there was no consensus.

Bias risk assessment. The risk of bias was assessed using the ROBINS-I (Risk Of Bias In Non-Randomized Studies - of Interventions) tool from the Cochrane platform. The tool assessed seven domains: (I) Confounding bias, (II) Participant selection bias, (III) Intervention classification bias, (IV) Intervention deviation bias, (V) Data loss bias, (VI) Outcome measurement bias, and (VII) Outcome reporting bias. After analyzing the domains, classification according to risk (low, moderate, severe, critical) was performed (*8*).

Results

The literature search according to the pre-established strategy resulted in 1,912 articles. Of these, 574 were from Scopus, 165 from PubMed, 733 from Web of Science, and 440 from ScienceDirect. After the selection and extraction process, 7 articles were included for this review. Figure 1 shows the flowchart with the results of the search in the databases, according to the PRISMA protocol.

Figure 2 shows the results of the Cochrane ROBINS-I assessment of the quality of the trials included in the review. Low to moderate risk of bias is observed, thus characterizing studies with a good methodological design.

Table 1 presents information from the included articles, highlighting their respective results and most important findings.

The selected studies indicate a decrease in retinol levels in COVID-19 patients, with more significant decreases observed in severe cases, as shown in the studies by Voelkle et al., Vollenberg et al., Sarohan et al., and Al-Saleh et al. (*9–12*).

Studies by Tepasse et al., Tomasa-Irriguible et al., Beigmohammadi et al., and Al-Saleh et al. (*12–15*) reported an increase in inflammatory activity and its possible correlation with adverse clinical outcomes such as acute respiratory distress syndrome, orotracheal intubation, and mortality. These findings suggest the involvement of inflammation in the relationship between the severity of COVID-19 and vitamin A levels.

Discussion

This literature review aimed to investigate the relationship between vitamin A-related nutritional status and the severity of clinical outcomes in COVID-19, focusing on blood retinol levels. Seven studies were selected that evaluated 608 adult and elderly individuals of both sexes, aged over 40 y in six different countries, published between 2020 and 2022.

Based on the international guidelines for vitamin A deficiency—VAD (*16*, *17*), it was observed that in four of the selected studies, the mean blood concentrations of retinol were borderline or deficient (retinol <0.20 mg/L or <0.70 μmol/L) in people with COVID-19 (*9*, *10*, *13*, *14*). In addition, worsening clinical outcomes were reported when retinol concentrations were <0.20 mg/L (need for hospitalization and intensive care unit (ICU) admission, use of mechanical ventilation, intubation, acute respiratory distress syndrome, and mortality). In the other three studies (*11*, *12*), although retinol levels <0.20 mg/L were not observed, lower mean retinol concentrations were found in the COVID-19 groups compared to controls, which was associated with worse clinical outcomes.

Four studies evaluated inflammatory markers in participants. Found them to be elevated, as well as related to vitamin A status and worsening outcomes in COVID-19, reporting retinol deficiency, reduced antioxidant enzymes, increased disease severity, and higher mortality. Such clinical manifestations may result from a hyperinflammatory state with production of various pro-inflammatory cytokines (TNF-α, IL-6, IL-2, IL-17, MCP-1, MIP-1α, CRP, IFN-γ, IP-10). These cytokines are known to cause significant changes in various components of the immune system, such as a decrease in T lymphocytes and natural killer (NK) cells, as well as reduced levels of IgM and IgG immunoglobulins (*18–21*). These data support the hypothesis that elevated levels of pro-inflammatory cytokines and concomitant immunocompromised status, coupled with low vitamin A-levels, are associated with worse prognosis in COVID-19 (*10–13*). In fact, over the past three years, COVID-19 has shown a wide range of clinical manifestations in infected individuals, from asymptomatic infection to acute respiratory distress syndrome (ARDS) and multiple organ failure leading to death. These clinical variations have been studied extensively, but it is already known that they may be related to characteristics such as age, history of pre-existing chronic diseases, nutritional status, and nutrient deficiencies (*22*), including presumably vitamin A because of its potential protective role in respiratory and infectious diseases.

It is in this scenario that the relationship between VAD and worsening prognostic indicators in COVID-19 has attracted the attention of the scientific community. Vitamin A has a well-known role on primary immune defense through the alteration of several pathways of cellular and humoral immune reconstitution. It is also essential to highlight the importance of vitamin A in maintaining epithelial integrity, through its active metabolite all-trans retinoic acid, which regulates the

Table 1. Retinol levels in patients with COVID-19.

Author/Year/ Country	Type of study	Sample (*n*) and mean age	Sex (*n*)	Groups	Outcomes assessed (objectives)	Results
Sarohan et al. (2022) (*11*) Turkey	Observational (cross-sectional)	50 63.2 y	F: 29 M: 21	•COVID-19 severe—Intensive Care Unit—ICU (27) •Control—asymptomatic (23)	Serum retinol levels in critically ill patients with COVID-19 and their relationship with the disease pathogenesis.	Serum retinol levels in the severe COVID-19 group was 0.37 mg/L and in the control group 0.52 mg/L. There was a significant reduction in retinol in the COVID-19 group compared to the control group.
Tepasse et al. (2021) (*13*) Germany	Observational (cross-sectional)	87 54 y	F: 5 M: 82	•Convalescent (47) •COVID-19 (40) •Critical (22) •Severe (9) •Moderate (9)	Association between plasma levels of vitamin A and both the severity of COVID-19 (as measured through inflammatory parameters and the incidence of Acute Respiratory Distress Syndrome—ARDS) and the outcome of the disease (mortality).	Vitamin A deficiency was 41% in the COVID-19 critical, 11% severe, and 11% moderate group. Plasma vitamin A levels <0.2 mg/L were associated with increased: Acute Respiratory Distress Syndrome, mortality, disease severity and inflammatory markers.
Beigmohammadi,et al. (2021) (*15*) Iran	Observational (cross-sectional)	60 53.5 y	F: 21 M: 39	•COVID-19: mild to moderate (n=40) •COVID-19: severe (n=20)	Serum levels of micronutrients, such as retinol, folic acid (B9), cyanocobalamin (B12), ascorbic acid, tocopherol, vitamin D, magnesium, zinc, and iron, were assessed in relation to expected normal values. The association between these levels and inflammatory markers (erythrocyte sedimentation rate, CRP, IFN-γ, TNF-α, and IL-6) and disease severity assessed using the Acute Physiological Assessment and Chronic Health Assessment (APACHE) score was explored. A score of APACHE ≥25 indicates severe COVID-19.	The serum vitamin A levels of the sample was 0.25 mg/L. Reduced vitamin A levels associated with increased levels of inflammatory markers and micronutrient deficiency were associated with greater severity and mortality from COVID-19.
Al-Saleh et al. (2022) (*12*) Saudi Arabia	Observational (cross-sectional)	155 50 y	F: 78 M: 77	•Asymptomatic (16) •Light (49) •Moderate (68) •Severe (22)	Association between essential metal states (copper, zinc, and selenium), retinol, tocopherol, vitamin D, and antioxidant enzyme activity (Superoxide dismutase—SOD and Total Antioxidant Capacity) in COVID-19 patients.	Retinol levels in the total sample were <0.343 mg/L[1] and in the severe group <0.166 mg/L. The prevalence of vitamin A deficiency was 37% overall and 23% severe group. Reduced superoxide dismutase activity was related to increased activity of inflammatory markers.
Tomasa-Irriguible et al. (2021) (*14*) Spain	Observational (cross-sectional)	120 58.7 y	F: 43 M: 77	•COVID-19 severe (presence of Acute Respiratory Distress Syndrome—ARDS)	Association between the levels of micronutrients retinol, pyridoxine (B6), ascorbic acid, vitamin D, tocopherol and zinc in patients with severe COVID-19 and their clinical outcome (admission to the Intensive Care Unit—ICU, orotracheal intubation and mortality).	Average retinol levels were 0.17 mg/L, and 71.7% of the population was considered vitamin A deficient. Lower retinol levels (<0.2 mg/L) were associated with a greater need for ICU admission (62.1%), orotracheal intubation (92.3%) and higher levels of C-reactive protein (86%), interleukin-6 (78%) and D-DIMER (68%).

Table 1. Continued

Author/Year/ Country	Type of study	Sample (*n*) and mean age	Sex (*n*)	Groups	Outcomes assessed (objectives)	Results
Voelkle M et al. (2022) (*9*) Switzerland	Observational cohort (prospective)	57 67 y	F: 23 M: 34	Micronutrient deficiency •No deficiency (12) •A deficiency (10) •Two deficiencies (16) •Multiple deficiencies (19)	Association between levels of micronutrients retinol, cyanocobalamin (B12), folic acid (B9), vitamin D, tocopherol, zinc and selenium and disease progression (hospital mortality and/or admission to the ICU—Intensive Care Unit).	The mean serum retinol levels in the total sample were 0.34 mg/L, being 0.42 mg/L in the mild status group and 0.19 mg/L in the severe status group.[2] The prevalence of vitamin A deficiency in the total sample was 39%, with 73% of the individuals in the severe status group having deficiency. Retinol levels <0.2 mg/L were associated with longer hospital stay, increased need for Intensive Care Unit and mechanical ventilation, and a higher risk of in-hospital mortality.
Vollenberg et al. (2022) (*10*) Germany	Observational, prospective, multicenter (cross-sectional)	79 58 y	F: 14 M: 65	•Convalescent (20); COVID-19 (59): •Critical—Acute Respiratory Distress Syndrome—ARDS (19) •Severe—with oxygen disturbance (20) •Moderate—no oxygenation disturbance (20)	Plasma levels of vitamin A and RBP4 in COVID-19 patients and their correlation with disease severity and progression.	Serum vitamin A levels were: COVID-19 (0.34 mg/L); Critical (0.26 mg/mL); Severe and Moderate (0.37 mg/L). The RBP4 levels in the COVID-19 group was17.02 mg/L. Reduced plasma levels of RBP4 were associated with liver dysfunction and increased inflammatory markers.

[1] Low level classification according to KFSH&RCVA.

[2] Values correspond, respectively, in: (general—1.2 μmol/L; mild—1.5 μmol/L; and severe—0.7 μmol/L). F: female; M: male; VA: vitamin A; %DVA: prevalence of vitamin A deficiency; ARDS: acute respiratory distress syndrome; SOD: superoxide dismutase; ICU: Intensive Care Unit; CRP: C-reactive protein; IFN-γ: interferon gamma; TNF-α: tumour necrosis factor alpha; IL-6: interleukin-6; RBP4: retinol-binding protein 4.

production of mucin, an important component in the physical barrier of defense against pathogens. Thus, when retinol concentrations are low, this function is compromised, rendering the cells more vulnerable to infectious processes (*23–25*).

Specifically, three studies found a higher incidence of orotracheal intubation, mechanical ventilation, and development of acute respiratory distress syndrome (ARDS). In these studies, retinol concentrations were found to be less than 0.20 mg/L, providing support for the hypothesis that vitamin A deficiency heightens susceptibility to respiratory complications in individuals suffering from COVID-19 due to alterations in respiratory epithelium integrity, heightened inflammatory response, and compromised immune activity (*4*, *26*).

One mechanism linked to pulmonary involvement in COVID-19 is the SARS-CoV-2 virus's high affinity for binding to angiotensin-converting enzyme-2 (ACE-2), which enters the tissues and damages surfactant-producing alveolar type 2 cells. This damage is caused by stimulated production of inflammatory cytokines (IL-1, IL-6, and IL-10) and tumor necrosis factors (*27*). This leads to increased capillary permeability and impaired gas exchange, causing symptoms such as shortness of breath, hypoxia and hypoxemia (*28*).

It is crucial to note that the acute inflammatory process, high viral load, and associated catabolic changes of COVID-19 are contributing factors to decreased levels of vitamin A in the blood. Reduced blood concentrations of retinol are also observed due to other mechanisms, including increased urinary loss, hindered mobilization of hepatic deposits (via the inhibition of cytochrome-oxidase enzymes), and decreased intestinal absorption, which are common occurrences during infections and acute inflammatory conditions (*29–33*).

Conclusion

The analysis of the included study results suggests a correlation between retinol levels and COVID-19 outcomes. Vitamin A plays a crucial role in the activation of the immune response, but its deficiency (VAD) worsens the clinical status of patients and increases the risk of mortality.

However, it is noteworthy that the studies analyzed in this review were observational and lacked a healthy control group, which makes it challenging to grasp the correlation between vitamin A status and severe COVID-19 complications. It is unclear whether VAD is a pre-existing condition or a result of viral infection. Randomized controlled clinical trials are necessary to determine the role of vitamin A in the pathophysiology of COVID-19 and to confirm if retinol concentration is a significant prognostic biomarker for both the active and severe phases of the disease.

Authorship

The drafting and design of the systematic review was carried out by IKFO, VCC, GSS, AAP, NVNM and MAFA. IKFO, VCC and GSS were responsible for the database search. Data interpretation was carried out by IKFO, VCC, CHRL and AAP. The manuscript was written by IKFO, VCC, EMMN, MCCM, LAL, PHCR and AAP, respecting the conventional structure and clear, objective language.

Disclosure of state of COI

The authors declare that they have no conflicts of interest.

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