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RESEARCH

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Evaluation of vitamin A and E deficiency with severity of SARS-COV-2 disease: a case–control study

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Abstract

Background Coronavirus disease 2019 can cause severe inflammation and damage to the lungs. Vitamins A and E are essential in the enhancement of immunity and they tend to decrease in cases with inflammation. Determination of serum levels of vitamins A and E in COVID-19 patients was the aim of the study.

Methods This case–control study was carried out on 30 ICU–admitted SARS-CoV-2–infected individuals (group A), 30 ward–admitted SARS-CoV-2–infected individuals (group B) and 30 healthy controls (group C). High-performance liquid chromatography was used to measure vitamin A and E levels.

Results Median levels of vitamin A in group A [0.16 (0.08–0.23) μg/ml] were significantly lower than those in group B [0.4 (0.15–0.65) μg/ml] and in group C [0.81 (0.70–1.16) μg/ml] with *P* value < 0.001, while there was no significant difference between groups concerning vitamin E levels (*P* value = 0.535). Vitamin A deficiency showed significant correlation with lower hemoglobin levels, lower platelet counts, higher total leucocyte counts, higher C- reactive protein levels, and higher D-dimer levels. ROC curve construction showed that vitamin A level with cut off < 0.65 μg/ml increases risk of acute respiratory distress syndrome (ARDS) development with sensitivity 90% and specificity 83.3%. Logistic regression analysis showed that cases with vitamin A levels < 0.65 μg/ml were more prone to develop ARDS (OR = 0.003 [0.000–0.036] *P* < 0.001).

Conclusion Levels of vitamin A were reduced in COVID-19 patients particularly in ICU–admitted cases. This ensures the association of decreased vitamin A with disease morbidity and the importance of vitamin A supplementation as part of disease management.

Trial registration Clinicaltrial.gov, NCT05946499. Registered 12 July 2023—Retrospectively registered.https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S000DGLS&selectaction=Edit&uid=U00070DC&ts=2&cx=gieusm.

Keywords COVID-19, SARS-CoV-2, Vitamin A, Vitamin E, HPLC

Introduction

Coronavirus disease 2019 (COVID-19) is a very infectious disease that manifests clinically by a wide variety of symptoms extending from asymptomatic to acute infection with severe pneumonia, respiratory failure, and death [1]. These clinical manifestations are initiated by an uncontrolled immune response that produces pro-inflammatory cytokines (cytokine storm), such as interleukin-6 (IL-6) [2]. Vitamin A is very

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important in infectious diseases, mainly pulmonary infections as it has a crucial role in normal lung tissue development and healing after infection-related injuries [3]. Vitamin A plays a regulatory role in the immune system and enhances the response of innate and adaptive immune cells. Consequently, it might be important for recovery following severe COVID-19 pneumonia [4, 5]. There is proof that the onset and severity of SARS-CoV-2 infection are significantly influenced by the overproduction of reactive oxygen species (ROS) [6]. As vitamin E is a strong antioxidant, it can protect the body from injury by free radicals and its deficiency can alter the reaction of the immune system and pathogenicity of viruses [7]. Studies dealing with vitamin A and E levels in COVID-19 patients are not sufficient. Thus, this study intended to evaluate vitamin A and E serum levels in COVID-19 patients.

Methods

Ethical considerations

The study has received approval from Cairo University's Faculty of Medicine's research ethics committee (approval number: MS-59–2020; date: 29/4/2020) and was conducted according to the guidelines of the Helsinki Declaration of 1975. Prior to clinical data and sample collection, informed consent was obtained from the patients.

Study design and data collection

This prospective case–control study was performed on 30 ICU–admitted SARS-CoV-2– infected individuals with ARDS or in need of oxygen supplementation (group A), 30 ward–admitted SARS-CoV-2–infected individuals not suffering from ARDS and not in need of oxygen supplementation (group B) and 30 sex and age–matched normal individuals as the control group (group C) in the period from September 2021 to April 2022. Cases were selected randomly from intensive care units (ICUs) and chest wards of Cairo University Hospitals while healthy controls were enrolled from the General Outpatient Clinic at Cairo University Hospitals. Patient selection bias was avoided by process of patient stratification into two groups according to the disease severity and the number of patients was equally distributed among the two groups. Diagnosis of SARS-CoV-2 infection was established by polymerase chain reaction testing of nasopharyngeal swab samples. Patients were grouped at the time of blood collection according to their status. Patients with immunodeficiency or other lung diseases were omitted from the study.

Analysis

For sample preparation, serum was obtained after centrifugation and kept at -20 °C until use for vitamin A/E assay. Samples, calibrators and 2 quality control levels were prepared under the same conditions in every run in agreement with the protocol afforded by the readymade kit purchased from Eureka (Chiaravalle, Italy; catalogue number: Z18610). From each sample, calibrator or control 100 µl were added to 200 µl of a deproteinization solution, and the mixture was then vortexed for 30 sec and centrifuged at 14,000 rpm for 5 min. Then, clear supernatant (200 µl) was pipetted into a glass vial to be ready for injection.

Vitamin A and E chromatographic separation was performed on high performance liquid chromatography (HPLC) Agilent 1260 platform (5301 Stevens Creek Blvd Santa Clara, California 95051, USA) with a photodiode array detector (DAD) set at 298 nm and a reversed–phase water column Cortex C18 (50 × 4.6 mm, 2.7 µ). To save the column, Javelin Col-filters (Chiaravalle, Italy; catalogue number: S90199511) were used. The methodology followed the protocol of the readymade kit. The run time was 6 min, the injection volume was 50 µl and the flow rate was 1 mL/min. The peaks of vitamin A, internal standard (ISD) and vitamin E had retention times (RTs) of 0.98, 2.2 and 3.4 min respectively (Fig. 1). Other laboratory tests as D-dimer, C-reactive protein (CRP) and complete blood count (CBC) were recruited from patients' files.

Statistical analysis

Version 28 of the SPSS (Statistical Package of Social Science) program (IBM Corp., Armonk, NY, USA) was used for data analysis. Mean and standard deviation express quantitative data (if parametric) or median and interquartile range (if non parametric), while frequencies and percentages express categorical variables. Comparisons between groups were performed using analysis of variance (ANOVA). Statistical significance was indicated when P values were < 0.05.

Results

Our study showed that the mean age in group A was 59.40 (± 13.04) years and in group B was 54.93 (± 15.70) years, while in the control group, the mean age was 53.43 (± 12.63) years. Regarding the sex distribution, 66.7% of the patients were female and 33.3% were male in group A. In group B 53.3% of the patients were female, and 46.7% were male. In group C, 53.3% of patients were female, and 46.7% were male (Table 1).

In our study, comorbidities were present in 29 patients in group A (96.7%), 23 patients in group B (76.7%) and

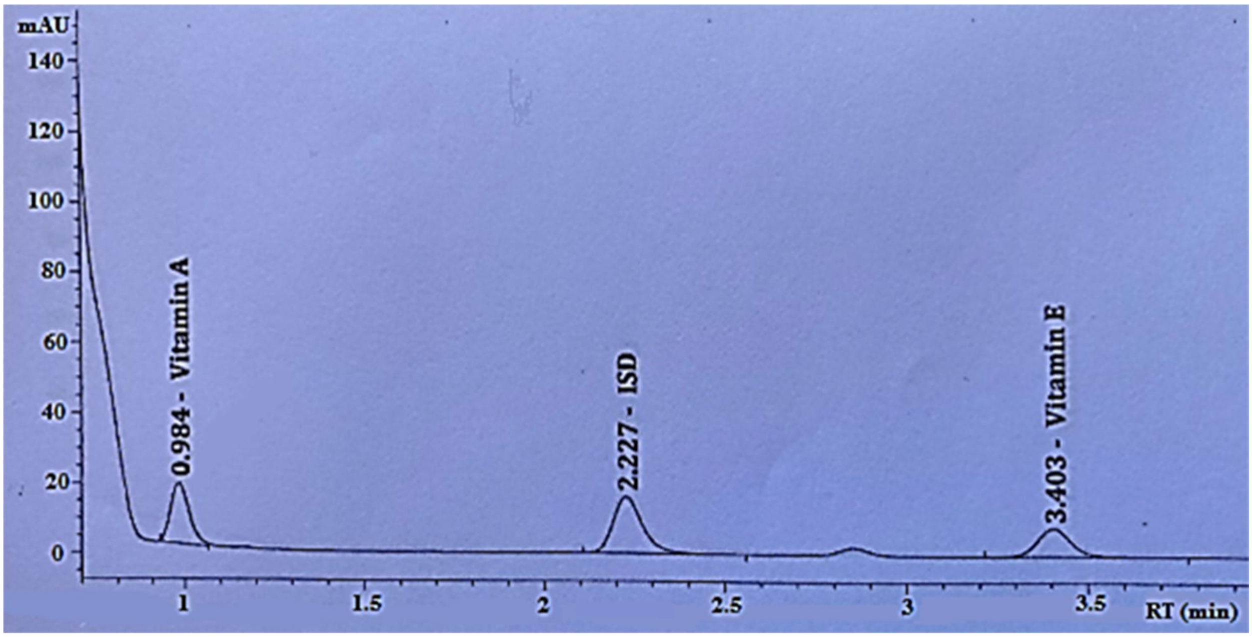

Fig. 1 The HPLC chromatographic peaks of vitamin A, internal standard (ISD) and vitamin E showed retention time (RT) of 0.98, 2.2 and 3.4 min respectively

Table 1 Demographic and clinical data of the study population

	Group A	Group B	Group C	*P* value
Age (years)†	59.40 (± 13.04)	54.93 (± 15.70)	53.43 (± 12.63)	0.228
Sex*				
Female	20 (66.7%)	16 (53.3%)	16 (53.3%)	0.483
Male	10 (33.3%)	14 (46.7%)	14 (46.7%)	
Co-morbidities*				
Yes	29 (96.7%)[a]	23 (76.7%)[a]	0 (0.0%)[b]	< 0.001
No	1 (3.3%)[a]	7 (23.3%)[a]	30 (100.0%)[b]	
Immunosuppressive drugs*				
Yes	11 (36.7%)[a]	17 (56.7%)[a]	0 (0.0%)[b]	< 0.001
No	19 (63.3%)[a]	13 (43.3%)[a]	30 (100.0%)[b]	

[a, b, c] Groups bearing same initials do not show statistical significant difference at *P* value < 0.05

[a, b, c] Groups bearing different initials show statistical significant difference at *P* value < 0.05

P value < 0.05 is considered statistically significant

† Data are presented as mean ± SD

* Data are presented as number (%)

none in group C, with no statistically significant difference between ICU and ward–admitted patients (Table 1). The incidence of comorbidities among cases was as follows: 23 patients had hypertension (38.3%), 22 patients had diabetes mellitus (36.6%) and 15 patients had cardiovascular diseases (25%). Additionally, there was no statistically significant difference in the use of immunosuppressive drugs between group A [11 patients (36.7%) and group B [17 patients (56.7%)] (*P* value > 0.05) (Table 1).

In the present study, the mean hemoglobin (Hb) level and platelet count were significantly lower in group A [10.64 (± 1.83) g/dl and 188.3 (± 71.81) $\times 10^9$/L respectively] and group B [11.74 (± 1.66) g/dl and 268.1 (± 96.53) $\times 10^9$/L respectively] than in group C [12.10 (± 1.40) g/dl and 313.6 (± 73.10) $\times 10^9$/L respectively] with *P* values 0.002 and < 0.001, respectively. However, the mean total leukocyte count (TLC) was higher in group A [14.77 (± 4.69) *10^3/cmm] than in group B [9.59 (± 3.44) *10^3/cmm] and in group C [6.9 (± 1.72) *10^3/cmm], showing statistical significance between different groups (*P* value < 0.001) (Table 2).

Median C-reactive protein (CRP) values were higher in severe cases admitted to the ICU [98.50 (66–140) mg/L], than in ward admitted patients [74.50 (48–121) mg/L] than in normal individuals [3.50 (1–6) mg/L], with statistically significant difference in the median values between different categories (*P* value < 0.001). Moreover, median D-dimer values were higher in group A [3.95 (1.90–10) mg/L] than in group B [0.9 (0.40–1.30) mg/L] and group C [0.15 (0–0.30) mg/L], showing a statistically significant difference among the 3 groups (*P* value < 0.001) (Table 2).

Our study revealed that median values for vitamin A were significantly lower in ICU–admitted cases [0.16 (0.08–0.23) µg/ml] than in ward–admitted cases [0.4 (0.15–0.65) µg/ml] and in normal individuals

Table 2 Laboratory findings among different groups

	Group A	Group B	Group C	*P* value
Hb (g/dl)†	10.64 (1.83)[a]	11.74 (1.66)[a]	12.10 (1.40)[b]	0.002
PLT (x 10^9/L)†	188.30 (71.81)[a]	268.07 (96.53)[a]	313.57 (73.10)[b]	< 0.001
TLC (*10^3/cmm)†	14.77 (4.69)[a]	9.59 (3.44)[b]	6.90 (1.72)[c]	< 0.001
CRP (mg/L) ‡	98.50 (66–140)[a]	74.50 (48–121)[b]	3.50 (1–6)[c]	< 0.001
D-dimer (mg/L) ‡	3.95 (1.9–10)[a]	0.90 (0.4–1.3)[b]	0.15 (0–3)[c]	< 0.001
Vitamin A (µg/ml) ‡	0.16 (0.08–0.23)[a]	0.40 (0.15–0.65)[b]	0.81 (0.70–1.16)[c]	< 0.001
Vitamin E (µg/ml) ‡	0.08 (0.08–14.3)	3.45 (0.08–8.30)	4.20 (0.09–7)	0.535

[a, b, c] Groups bearing same initials do not show statistical significant difference at *P* value < 0.05

[a, b, c] Groups bearing different initials show statistical significant difference at *P* value < 0.05

P value < 0.05 is considered statistically significant

† Data are presented as mean ± SD

‡ Data are presented as median (interquartile range)

[0.81 (0.70–1.16) µg/ml] (*P* value < 0.001). Although, the median value of vitamin E was lower in group A [0.08 (0.08–14.30) µg/ml] than in group B [3.45 (0.08–8.30) µg/ml] and group C [4.2 (0.09–7) µg/ml], no statistically significant difference was detected among the different groups (*P* value = 0.535) (Table 2).

Vitamin A deficiency showed statistically significant correlation with lower hemoglobin levels ($r = 0.222$, $P < 0.05$), lower platelet counts ($r = 0.485$, $P < 0.01$), higher TLC counts ($r = -0.444$, $P < 0.001$), higher CRP levels ($r = -0.551$, $P < 0.001$), and higher D-dimer levels ($r = -0.639$, $P < 0.001$) denoting severity of COVID-19 (Fig. 2).

In the present study, a receiver operating characteristic (ROC) curve was generated to predict the severity of COVID-19 using vitamin A level. A cut-off < 0.65 µg/ml vitamin A levels can predict ARDS development with a sensitivity of 90% and a specificity of 83.3%, an area under the curve (AUC) of 0.913, a 95% confidence interval of 0.857–0.970 and a *P* value < 0.001 (Fig. 3).

Additionally, logistic regression analysis showed a significant association of low levels of vitamin A with the development of ARDS (OR = 0.003 [0.000–0.036] *P* < 0.001) in COVID-19 patients who were hospitalized ($n = 60$).

Discussion

In the present study, vitamin A and E levels were assessed in ICU and ward admitted COVID-19 patients and compared to normal controls (age/sex matched). Additionally, the association of vitamin A levels with inflammatory markers and disease severity was analyzed.

Our study showed no statistically significant difference among severe cases (group A) and mild/moderate cases (group B) with regard to patients' comorbidities such as diabetes, hypertension, and cardiovascular diseases. Conversely, other studies have stated that the incidence of comorbidities such as hypertension, diabetes, and cardiovascular diseases was significantly higher in severely and critically ill patients than in ward–admitted patients [8, 9]. It was also reported that comorbidities were strongly associated with COVID-19 infection severity, and patients who had comorbidities develop severe symptoms and comparatively higher mortality rates [10].

In addition, this study showed no statistical significance between groups A and B regarding the use of immunosuppressive drugs. In an earlier study, it was reported that patients receiving steroids had reduced rates of mechanical ventilation, shortened ICU and hospital stays, and decreased mortality rates [11]. Additionally, treatment with tocilizumab in combination with steroids (methylprednisolone) was associated with a reduction in the mortality rate [12]. In contrast, other reports revealed unfavorable outcomes for steroid use. They found that the development of blood stream infection was independently associated with methylprednisolone use. Additionally, patients receiving steroids were unlikely to achieve clinical and radiological remission in 10 days when compared to patients not receiving steroids. Moreover, some patients treated with the dexamethasone and tocilizumab combination still need ICU admission, and other treatments are still needed [13].

This study also showed that median values of vitamin A were lower in group A than in group B than in group C in a statistically significant manner (*P* value < 0.001). Similarly, Tepasse et al. stated that vitamin A levels were significantly lower in hospitalized COVID-19 patients in different groups (mild, moderate, severe and critically ill) than in convalescent individuals (*P* < 0.01). Although they also found that the levels of vitamin A were lower in severe cases than in moderate cases, there was no statistically significant difference between the two groups

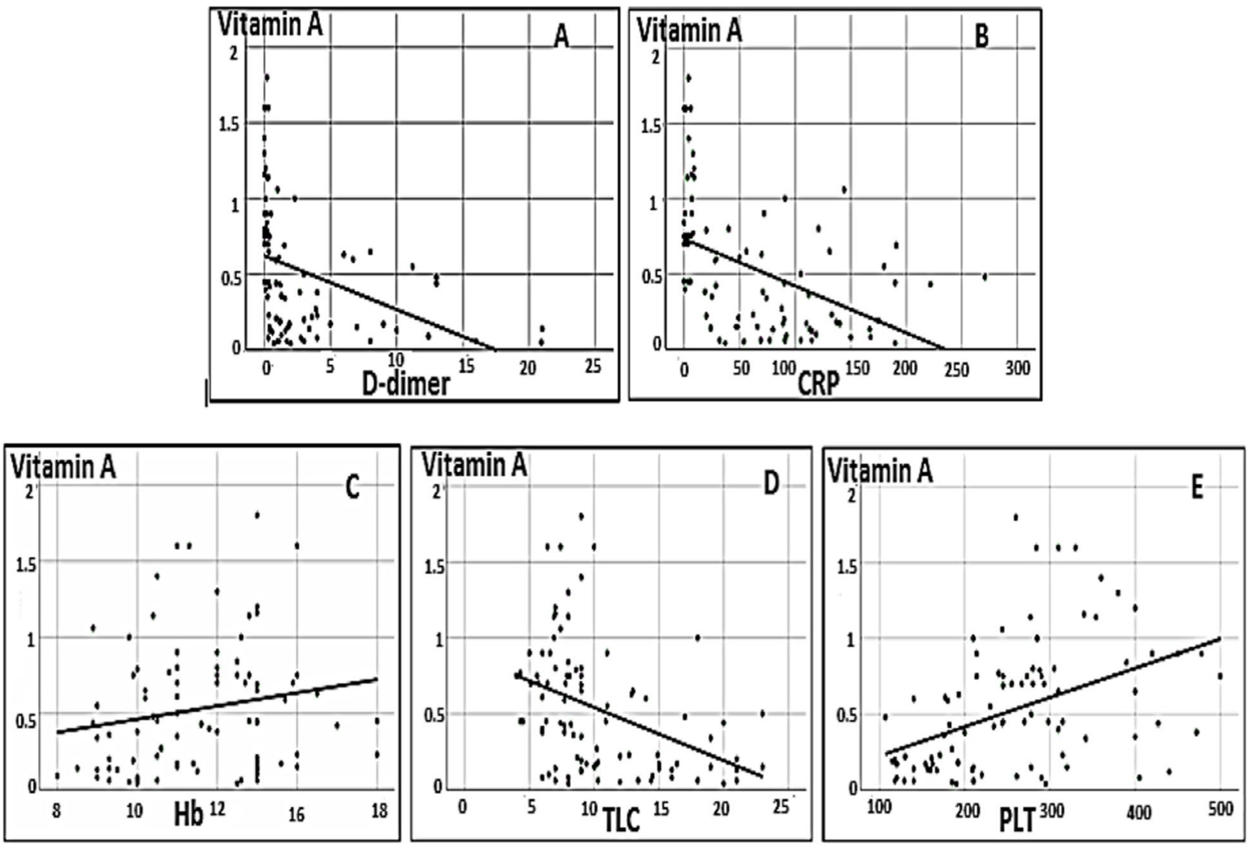

Fig. 2 Correlation between vitamin A and D-dimer (**A**), CRP (**B**), Hb (**C**), TLC (**D**) as well as PLT (**E**). Note: r, correlation coefficient. Vitamin A deficiency showed statistical significant correlation with lower hemoglobin levels ($r = 0.222$, $P < 0.05$), lower platelet count ($r = 0.485$, $P < 0.01$), higher TLC count ($r = -0.444$, $P < 0.001$), higher CRP levels ($r = -0.551$, $P < 0.001$), and higher D-dimer levels ($r = -0.639$, $P < 0.001$) denoting severity of COVID-19

[8]. Similarly, Tomasa-Irriguible et al. found that 71.1% of included patients had reduced vitamin A levels with a mean value of 0.17 (SD 0.06) μg/ml [14]. Another study performed by Berrocal et al. found that vitamin A deficiency was related to an increased risk for ICU admission [15]. Lower levels of vitamin A in severe cases (group A) support previously reported data that attribute the decrease in vitamin A to several mechanisms such as diminished intestinal absorption, decreased hepatic recruitment and renal loss caused by acute infections and inflammatory conditions [16–18]. Furthermore, it has been found that COVID-19 triggers an inflammatory response (cytokine storm), mostly affecting the lungs, liver, and kidneys, which increases the risk of vitamin A deficiency [19]. Vitamin A has an important role in lung function and development together with its critical role in the immune reaction against infections by promoting innate and adaptive immunity, thus preventing primary and secondary infections [20–22]. Moreover, vitamin A has been reported to minimize COVID-19 and medication-related induced complications [23]. Therefore, vitamin A supplementation can benefit SARS-COV -2–infected patients as reported by several studies [24–26]. This was also suggested in a previous study that reported that vitamin A could have a good pharmacological role in the treatment of SARS-COV-2–infected patients because of its antiviral and anti-inflammatory effects [14]. In addition, earlier studies exhibited that vitamin A supplements reduced manifestations of many infectious diseases in vitamin A deficient individuals caused by malnutrition [27, 28]. Moreover, it was reported that after receiving influenza vaccination, vitamin A supplementation can increase the humoral immunity of pediatric patients [29].

Our results showed that vitamin E levels were lower in the cases (groups A and B) than in the control group (group C), but no statistically significant difference existed. These results are in agreement with Hakamifard et al., who stated that no statistical significance was found regarding vitamin E levels when cases were

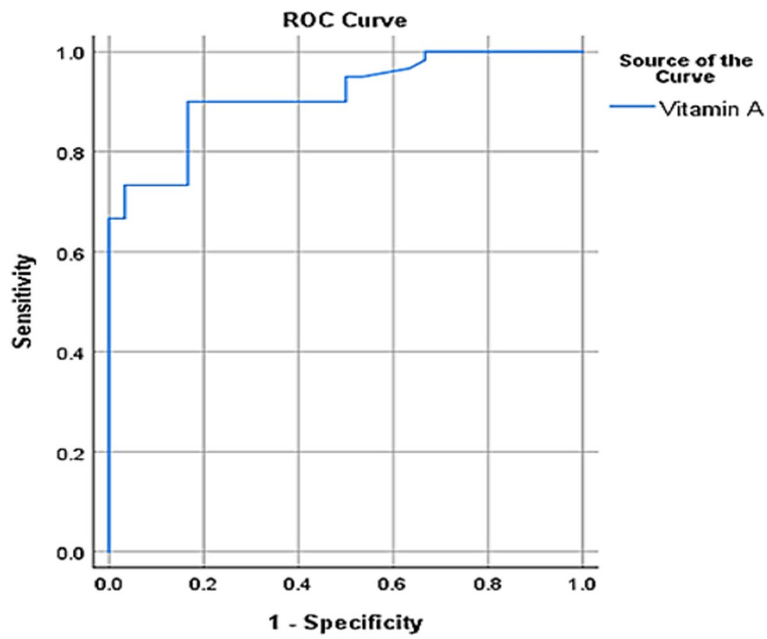

Fig. 3 Receiver operating characteristic (ROC) curve for prediction of Severity of COVID-19 using Vitamin A level. ROC curve construction revealed that a cutoff point < 0.65 µg/ml of vitamin A can predict COVID-19 disease severity and development of ARDS with sensitivity 90% and specificity 83.3%

compared with the control group; however, vitamin E supplementation shortened the duration of hospital stay [30]. Tomasa-Irriguible et al. also found that only 5.8% of COVID-19 patients had reduced vitamin E levels [14]. Conversely, a study reported that giving vitamin E to critically ill patients decreased their risk of developing ARDS and pneumonia and shortened their stay in the ICU [31]. Additionally, several animal and human reports have confirmed the direct and indirect roles of vitamin E in immune cells, mainly T cells [32]. The immunoregulatory and antioxidant effects of vitamin E have clinical significance by decreasing the host's vulnerability to viral infection, thus lowering the risk of respiratory illnesses including COVID-19 [33, 34]. Nutrients and food supplementation with anti-inflammatory, immunomodulatory and antioxidant activities can play significant defensive roles in the absence of well-known effective COVID-19 treatments. In this regard, supplementation with a nutrient such as vitamin E might be considered a crucial prospect in the treatment of SARS-CoV-2 infection although further research is needed to confirm its efficacy as a therapeutic approach for COVID-19 patients [35].

Furthermore, our study revealed that low vitamin A levels showed statistically significant correlation with lower hemoglobin levels, lower platelet counts, higher TLC counts, higher D-dimer levels and higher CRP levels, denoting the severity of COVID-19. Likewise, a report by Tepasse et al. revealed that high levels of CRP were significantly correlated with low vitamin A levels (r= -0.54, P < 0.001) which indicates a more severe disease course. They also assumed that reduced vitamin A levels in patients with COVID-19 rely on severity of the disease and that levels are decreased because of acute inflammation and infection rather than the presence of earlier malnutrition and vitamin A deficiency [8]. Additionally, Duncan et al. revealed that lower vitamin A is linked to increase of CRP [36].

Moreover, ROC curve construction revealed that a cut-off point < 0.65 µg/ml vitamin A can predict COVID-19 disease severity and the development of ARDS with sensitivity 90% and specificity 83.3%. In addition, logistic regression analysis showed that patients with vitamin A levels < 0.65 µg/ml were more prone to develop ARDS (OR = 0.003 [0.000–0.036] p < 0.001). In agreement with these results, it was reported that reduced vitamin A levels were significantly associated with the development of ARDS using logistic regression analysis (OR = 5.54 [1.01–30.26] p = 0.048) [8]. Similarly, Tomasa-Irriguible et al. found an association between the requirement for ICU admission and orotracheal intubation with decreased vitamin A levels [14]. Additionally, another study reported that respiratory tract infections and repeated respiratory tract infections were significantly related to reduction of serum levels of vitamin A [37].

Limitations

We included a relatively small number of participants in our study due to financial restrictions. Thus follow-up studies with larger sample sizes may help to ensure these results. Prospective clinical trials are needed to assess the ability of vitamin A supplementation to improve the outcome of COVID-19 patients.

Conclusions

Levels of vitamin A were decreased in SARS-CoV-2–infected patients, particularly in ICU–admitted cases. This ensures the association of low vitamin A with disease morbidity and the importance of vitamin A supplementation as part of disease management.

Abbreviations

ANOVA	Analysis of variance
ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus disease 2019
CBC	Complete blood count
CRP	C-reactive protein
DAD	Photodiode array detector
ICU	Intensive care unit
ISD	Internal standard
Hb	Hemoglobin
HPLC	High-performance liquid chromatography
IL-6	Interleukin-6
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPPS	Statistical Package of Social Science
TLC	Total leukocytic count

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Not applicable.

Authors' contributions
I.M. was involved in the conception and design of this work. S.H. and S.A. acquired the data. B.F. drafted the manuscript. H.H. and B.F. were involved in laboratory analysis and data interpretation. I.M., S.H. and B.F. revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Ethics approval and consent to participate
The study has received approval from Cairo University's Faculty of Medicine's research ethics committee (approval number: MS-59–2020; date: 29/4/2020). Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that there is no conflict of interests.

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