ORIGINAL ARTICLE | COVID-19 OUTCOMES

Correlation Between Plasma Vitamin C Concentration and COVID-19 Outcomes among Patients Seen at a Major Hospital in the United Arab Emirates

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ABSTRACT

Background and Objective: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a newly emerged coronavirus that causes coronavirus disease-2019 (COVID-19) with varying degrees of disease manifestations. Vitamin C is an essential water-soluble vitamin with anti-inflammatory, antioxidant, antiviral, and immunomodulatory functions. The study aimed to investigate the association between serum vitamin C concentration and outcomes of COVID-19 among adults in the United Arab Emirates (UAE).

Methods: This retrospective observational study included 67 COVID-19 patients aged 30-59 years old. Measurement of vitamin C levels was performed at the National Reference Laboratory, UAE using liquid chromatography-tandem mass spectrometry (LC/MS-MS). The cut-off value was 0.4 mg/dl; plasma levels that ranged from 0.4 to 2 mg/dl were defined as sufficient. Values above 2 mg/dl were recognized as high and values less than 0.4 mg/dl are considered low or deficient.

Results: Among the included patients, 58.2% suffered from vitamin C deficiency. We found a statistically significant correlation between the concentration of serum vitamin C and age (p=0.03), the presence of hypertension (p=0.013), diabetes (p=0.01), and the development of pneumonia (p=0.012). There was no significant correlation between the concentration of serum vitamin C and the need for mechanical ventilation, Intensive Care Unit (ICU) admission, COVID-19 severity, or mortality. The risk of COVID-19 severity decreased in patients with sufficient vitamin C levels by 52% compared to patients with vitamin C deficiency (p=0.177). There was a statistically significant correlation between vitamin C sufficiency and low lactate dehydrogenase, C-reactive protein (CRP), and fibrinogen. However, the odds of vitamin C sufficiency in COVID-19 patients were significantly associated with lowering CRP levels (OR=0.99, 95% CI: (0.98-1.00), p=0.024).

Conclusion and Global Health Implications: Low serum vitamin C concentrations were associated with several demographic characteristics of patients, the presence of pneumonia, and inflammation. Furthermore, improving our social determinants, such as how we live, eat, drink, and vitamin C supplementation could positively impact the future health of the individual, community, and population.

Keywords: • Vitamin C • COVID-19 • SARS-CoV-2 • Inflammation • Pneumonia • United Arab Emirates • Global Health

1. Introduction

1.1. Background of the Study

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a new coronavirus that emerged in Wuhan, China, in December 2019; the virus caused a pneumonia disease named Coronavirus Disease-2019 (COVID-19).[1] COVID-19 leads to varying degrees of manifestations ranging from cough and fever to multi-organ damage and death.[2] Previous reports suggested that the pathophysiological mechanism of severe disease outcomes depends on the aggravated immune response or virus-activated cytokine release storm.[3] During this phase, there is a marked increase in several inflammatory markers, including interleukin (IL)-1b, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), interferon γ, ferritin, C-reactive protein (CRP), and D-dimer.[3–6]

Vitamin C, or ascorbic acid, is an essential water-soluble vitamin. It has anti-inflammatory, antioxidant, antiviral, and immunomodulatory properties and has a role in regulating innate and adaptive immune responses.[7–9] Vitamin C is involved in the development and maturation of T lymphocytes, acts as a chemotactic agent, and has an antioxidant function mediated by reducing dehydroascorbic acid to ascorbic acid in phagocytes.[10,11] In a pilot study by Arvinte et al., vitamins C and D were lower among critically ill COVID-19 patients. Increased age and vitamin C deficiency were codependent risk factors for mortality among COVID-19 patients. These findings highlight the importance of vitamin C assessment and supplementation among COVID-19 patients.[12] Krishnan et al. observed that COVID-19 patients admitted to the intensive care unit (ICU) and who needed mechanical ventilation supplemented with vitamin C showed a decreased risk of mortality (p= 0.0066).[13]

There are various social determinants of health issues, such as how we live, eat, and drink, as well as age, which can influence vitamin C concentrations and, as a result, the outcome of COVID-19, demonstrating how this can affect an individual's, community's, and population's health. Attempting to gain a thorough grasp of how various social and clinical elements influence human health, this study was meant to provide new insights into one simple probable factor influencing global health shortly.

Few studies have examined the relationship between vitamin C concentration and COVID-19 outcomes. Tomasa-Irriguible et al. investigated the impact of vitamin C deficiency among critically ill COVID-19 patients.[14] They observed that up to 82% of them suffered from vitamin C deficiency. However, this was a single-center study including only critically ill patients. Additionally, they did not assess the associations between vitamin C levels and disease outcomes or consider confounding factors.[14] Undetectable levels of vitamin C were also observed in more than 90% of COVID-19 patients with ARDS; however, the study included a limited number of patients, and the correlation between ARDS and vitamin C levels was not evaluated.[15] The correlation with the whole spectrum of COVID-19 also lacked some gaps, considering the potential effect of associated comorbidities, pathophysiological hyperinflammation, clinical presentations, presence of pneumonia, severity, and mortality. Additionally, studying this link in a multiethnic population could be more significant. Previous studies have highlighted that vitamin C status may vary according to ethnicity, which might be attributed to dietary habits or cooking practices.[16] Because the United Arab Emirates (UAE) has a multiethnic population, this was a nice spot to apply our study to investigate the role of ethnicity in the pathophysiology of COVID-19.

1.2. Objectives of the Study

The study objective was to determine the association between serum vitamin C concentration and outcomes of COVID-19. Specifically, clinical presentation, the need for mechanical ventilation, ICU admission, COVID-19-caused severity, and mortality.

2. Methods

2.1. Study Design and Population

This retrospective, noninterventional study enrolled 67 COVID-19 patients treated at NMC Royal Hospital, Khalifa City, Abu Dhabi, UAE, between April 8, 2020 and June 30, 2020. COVID-19 diagnosis was confirmed by real-time reverse transcriptase-polymerase chain reaction (RT−PCR)

assay of nasopharyngeal swab specimens. Solgent's 2019-nCoV RT–PCR Kit and the Bio-Rad Cycler PCR, USA, were used for RT–PCR analysis per the manufacturer's instructions. Detection was performed using a CFX96 plate reader from Bio-Rad (Bio-Rad Laboratories, Inc. California, USA). A positive SARS-CoV-2 sample was defined by a cycle threshold (CT) value. To protect patients' privacy, all patient identities were deleted throughout data processing. This study was conducted according to the Declaration of Helsinki. The study was reviewed and approved by the NMC Central scientific committee approval (NMCHC\CSC\2021\0001), NMC Regional Research Ethics Committee, Abu Dhabi approval number (NMC\PREC\AUC\2021\0006), and Abu Dhabi Health COVID-19 Research Ethics Committee (DOH/CVDC/2021/738).

2.2. Data Collection

Data were collected from all patients' medical reports: demographic and clinical characteristics, laboratory findings, radiography, treatment, and outcomes. According to clinical evaluation, all patients underwent chest X-ray and/or computed tomography (CT) at admission and at different times. The severity of COVID-19 was determined based on COVID-19 Severity guidelines by the World Health Organization (WHO).

2.3. Vitamin C Analysis

Measurement of serum vitamin C levels was performed at the National Reference Laboratory (UAE) under order code 001805; the test was performed using liquid chromatography-tandem mass spectrometry (LC/MS-MS). The cut-off value was 0.4 mg/dl, plasma levels that ranged from 0.4 to 2 mg/dl were defined sufficient. Values above 2 mg/dl were recognized as high and values less than 0.4 mg/dl are considered low or deficient. The test was developed by LabCorp (Burlington, NC, USA).

2.4. Data Management and Statistical Analysis

After data collection and verification, all data were entered for statistical analysis using R Software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) - "Eggshell Igloo," and the appropriate statistical tests were carried out. Quantitative data with a normal distribution are summarized as the mean ± standard deviation (SD) and range or as the median and interquartile range when the data were not normally distributed. Qualitative data were summarized as frequency (n) and percentage (%). The Shapiro test was used to verify the normality of distribution, while logarithmic transformation was applied when applicable. The chi-square test was used for comparative analysis to determine the correlation between serum vitamin C levels and severity, mortality, ICU admission, and need for mechanical ventilation among COVID-19 patients.

The logistic regression model was performed to determine the independent association of vitamin C sufficiency with the severity of COVID-19, mortality, and significant factors in the univariate analysis. The linear regression model was conducted to estimate the correlation between serum vitamin C levels and immune-inflammatory response biochemical markers using the Spearman correlation coefficient (r). The Kruskal–Wallis test was used for comparative analysis of the association between serum vitamin C concentration and immune-inflammatory response markers. The confidence interval was set to 95%, and the accepted error margin was 5%. Therefore, the p-value was considered significant as follows: $p > 0.05$: nonsignificant (NS), $p < 0.05$: significant (S), and $p < 0.01$: highly significant (HS).

3. Results

3.1. Demographic and Clinical Characteristics of the Study Population

The current study included 67 patients with COVID-19 treated at NMC Royal Hospital. There were 53 (75%) males among the study population aged between 30 and 59 years. Nearly 72% of the study cohort was Asian. There were 39 (58.2%) patients suffering from vitamin C deficiency. At clinical presentation, 76.6% of patients experienced shortness of breath, 86.4% had a fever, and 70.1% developed pneumonia, but their O_2 saturation (74.6%) was above 95% (Table 1).

Table 1: Characteristics of COVID-19 patients according to disease severity and mortality

Demographics			
Age category (years)	0-29	10	14.9%
	30-59	51	76.1%
	≥ 60	6	9.0%
Sex	Female	14	20.9%
	Male	53	79.1%
Race/Ethnicity	Asian	48	71.6%
	Black	3	4.5%
	White	16	23.9%
Clinical Presentation			
Vitamin C Level (mg/dl)	Deficient	39	58.2%
	Sufficient	28	41.8%
Hypertension	No	47	82.5%
	Yes	10	17.5%
Diabetes mellitus	No	47	77.0%
	Yes	14	23.0%
Cardiovascular diseases	No	64	97.0%
	Yes	2	3.0%
Shortness of Breath	No	15	23.4%
	Yes	49	76.6%
Fever	No	9	13.6%
	Yes	57	86.4%
O_2 saturation	< = 85	4	6.0%
	86-94	13	19.4%
	95-100	50	74.6%
Radiology	Normal	20	29.9%
	Pneumonia	47	70.1%
Biochemical Characteristics			
WBC (×10⁹/L)	Mean±SD	7.1	3.2
Hemoglobin (g/dl)	Mean±SD	14.2	4.1
Platelet Count (×10⁹/L)	Mean±SD	337.6	149.0
CRP (mg/L)	Mean±SD	76.4	100.6
D-Dimer (µg/mL)	Mean±SD	2.0	5.4
IL-6 (pg/ml)	Mean±SD	124.5	263.2
LDH (U/L)	Mean±SD	365.2	295.7
ALT (u/l)	Mean±SD	52.3	39.2
AST (u/l)	Mean±SD	52.1	36.7
Creatinine (µmol/L)	Mean±SD	2.1	9.7
Neutrophil Count (×10⁹/L)	Mean±SD	62.2	15.7
Lymphocyte Count(×10⁹/L)	Mean±SD	27.9	13.3
Neutrophil-to-Lymphocyte Ratio (NLR)	Mean±SD	4.0	5.2

(Contd...)

Table 1: *(Continued)*

Biochemical Characteristics			
RDW.CV	Mean±SD	13.7	2.6
Fibrinogen (mg/dL)	Mean±SD	540.6	221.9
Ferritin (ng/mL)	Mean±SD	823.1	1368.3
Prothrombin Time (PT)	Mean±SD	14.3	1.3
International Normalized Ratio (INR)	Mean±SD	1.0	0.1
Troponin. I	Mean±SD	0.0	0.0
Procalcitonin	Mean±SD	0.2	0.5
Glutamate	Mean±SD	6.6	2.6

(Data are presented as a range, mean±SD for continuous variables, and n and % for categorical variables)

3.2. Correlation Between Vitamin C Levels and Patient Characteristics

We observed that vitamin C-deficient COVID-19 patients were older than those with sufficient vitamin C levels (p=0.03). Ninety percent and 85.7% of hypertensive and diabetic COVID-19 patients, respectively, were suffering from a deficiency of vitamin C (p=0.013, p=0.01, respectively). Among the patients who developed pneumonia, 68.1% showed significantly deficient levels of vitamin C compared to COVID-19 patients with normal chest X-ray findings (p=0.012). There was no significant difference between sufficient or deficient vitamin C levels and other disease outcomes in COVID-19 patients, including severity, mortality, ICU admission, and the need for mechanical ventilation (Table 2).

3.3. Association Between Vitamin C Sufficiency, Patient Characteristics and Disease Severity, and Mortality

According to the logistic regression model, the risk of disease severity and mortality increased significantly by 1.11 (OR=1.11, 95% CI: 1.05-1.19, p=0.001) and 1.09 (OR=1.09, 95% CI: 1.01-1.19, p=0.026) fold, respectively, for each one-year increase in the patient's age. The presence of diabetes mellitus was also significantly associated with increased disease severity by 4.24-fold (OR=4.24, 95% CI: 1.24-16.04, p=0.024). Patients who presented with shortness of breath were at increased risk of disease severity by approximately 11.4-fold shortness of breath (OR=11.41, 95% CI: 2.04-214.77, p=0.023). On

Table 2: Comparative analysis of the association between plasma vitamin C levels and patient demographics, clinical presentation, severity, mortality, ventilation, and ICU admission

Patient characteristics		Deficient	Sufficient	P value
Demographics				
Age (years)	Mean±SD	44.4±14.3	37.6±8.4	0.03
Sex	Female	7 (50.0%)	7 (50.0%)	0.484
	Male	32 (60.4%)	21 (39.6%)	
Race/Ethnicity	Asian	29 (60.4%)	19 (39.6%)	0.643
	Black	1 (33.3%)	2 (66.7%)	
	White	9 (56.2%)	7 (43.8%)	
Clinical Presentation				
Hypertension	No	22 (46.8%)	25 (53.2%)	0.013
	Yes	9 (90.0%)	1 (10.0%)	
Diabetes Mellitus	No	22 (46.8%)	25 (53.2%)	0.01
	Yes	12 (85.7%)	2 (14.3%)	
Cardiovascular Diseases	No	36 (56.2%)	28 (43.8%)	0.218
	Yes	2 (100.0%)	0 (0.0%)	
O_2 Saturation	< = 85	3 (75.0%)	1 (25.0%)	0.209
	86-94	10 (76.9%)	3 (23.1%)	
	95-100	26 (52.0%)	24 (48.0%)	
Shortness of Breath	No	8 (53.3%)	7 (46.7%)	0.688
	Yes	29 (59.2%)	20 (40.8%)	
Fever	No	5 (55.6%)	4 (44.4%)	0.895
	Yes	33 (57.9%)	24 (42.1%)	
Radiology	Normal	7 (35.0%)	13 (65.0%)	0.012
	Pneumonia	32 (68.1%)	15 (31.9%)	
Disease Severity	Non-Severe	23 (52.3%)	21 (47.7%)	0.173
	Severe	16 (69.6%)	7 (30.4%)	
Mortality	Discharged	36 (56.2%)	28 (43.8%)	0.133
	Died	3 (100.0%)	0 (0.0%)	
Ventilation	No	25 (54.3%)	21 (45.7%)	0.399
	Invasive	3 (100.0%)	0 (0.0%)	
	Low flow O2	8 (66.7%)	4 (33.3%)	
	Non-Invasive	3 (50.0%)	3 (50.0%)	
ICU Admission	No	35 (58.3%)	25 (41.7%)	0.952
	Yes	4 (57.1%)	3 (42.9%)	

(Data are presented as n and %)

the other hand, COVID-19 severity and mortality decreased significantly by 46% (OR=0.54, 95% CI: 0.34-0.72, p=0.001) and 29% (OR=0.71, 95% CI: 0.47-0.89, p=0.025), respectively, for each one-unit increase in O_2 saturation level. Furthermore, it was observed that the risk of COVID-19 severity decreased in patients with sufficient vitamin C levels by approximately 52% compared to patients with deficient vitamin C levels, but the p-value was 0.177. After adjusting for the effect of other patients' demographic and clinical characteristics in the multivariate logistic regression model, it was shown that the adjusted odds of severity for those factors were nonsignificant, proving the absence of any potential confounders (Tables 3 and 4).

3.4. Association Between Plasma Vitamin C Levels and Biochemical Markers

There was a significant association between sufficient vitamin C levels and decreased serum levels of CRP, lactate dehydrogenase (LDH), and fibrinogen according to the Spearman correlation coefficient (r). In contrast, there was no association between sufficient vitamin C levels and platelet and lymphocyte counts, ferritin, or D-dimer levels. Univariate logistic regression analysis showed that the odds of vitamin C sufficiency in COVID-19 patients were significantly associated with the lowering of CRP levels (OR=0.99, 95% CI: 0.98-1.00, p=0.024) (Tables 5 and 6).

4. Discussion

This observational study demonstrated a strong correlation between vitamin C deficiency and pneumonia among COVID-19 patients. In contrast, there was no statistically significant association between serum vitamin C levels and other disease outcomes, including disease severity, ICU admission, need for mechanical ventilation, and mortality.

To the best of our knowledge, this study is considered the first in the UAE and among one of the first reports describing vitamin C status among COVID-19 patients globally. In our study, 58.2% of COVID-19 patients had deficient vitamin C levels, whereas Irritguible and Bielsa-Berrocal observed

Table 3: Predictors for COVID-19 severity using univariate and multivariate logistic regression analysis

		Non-Severe	Severe	Crude OR (95%CI)	Adjusted OR (95%CI)
Demographics					
Age (years)	Mean (SD)	37.3 (9.6)	49.7 (13.8)	1.11 (1.05-1.19, p=0.001)	23480.44 (0.00-Inf, p=0.999)
Sex	Female	11 (25.0)	3 (13.0)	-	-
	Male	33 (75.0)	20 (87.0)	2.22 (0.61-10.70, p=0.261)	Inf (0.00-Inf, p=1.000)
Race/Ethnicity	Asian	30 (68.2)	18 (78.3)	-	-
	Black	3 (6.8)	0 (0.0)	0.00 (NA-Inf, p=0.991)	0.00 (0.00-Inf, p=0.999)
	White	11 (25.0)	5 (21.7)	0.76 (0.21-2.45, p=0.652)	0.00 (0.00-Inf, p=0.999)
Clinical Presentation					
Hypertension	No	34 (89.5)	13 (68.4)	-	-
	Yes	4 (10.5)	6 (31.6)	3.92 (0.97-17.58, p=0.059)	0.00 (0.00-Inf, p=1.000)
Diabetes Mellitus	No	33 (86.8)	14 (60.9)	-	-
	Yes	5 (13.2)	9 (39.1)	4.24 (1.24-16.04, p=0.024)	0.00 (0.00-Inf, p=1.000)
Cardiovascular Diseases	No	43 (97.7)	21 (95.5)	-	-
	Yes	1 (2.3)	1 (4.5)	2.05 (0.08-53.51, p=0.618)	Inf (0.00-Inf, p=1.000)
Shortness of Breath	No	14 (34.1)	1 (4.3)	-	-
	Yes	27 (65.9)	22 (95.7)	11.41 (2.04-214.77, p=0.023)	Inf (0.00-Inf, p=1.000)
Fever	No	8 (18.6)	1 (4.3)	-	-
	Yes	35 (81.4)	22 (95.7)	5.03 (0.84-96.59, p=0.140)	0.00 (0.00-Inf, p=1.000)
O_2 Saturation	Mean (SD)	98.3 (1.3)	90.1 (6.0)	0.54 (0.34-0.72, p=0.001)	0.00 (0.00-Inf, p=0.999)
Radiology	Normal	20 (45.5)	0 (0.0)	-	-
	Pneumonia	24 (54.5)	23 (100.0)	Inf (0.00-NA, p=0.990)	Inf (0.00-Inf, p=1.000)
Vitamin C Levels	Deficient	23 (52.3)	16 (69.6)	-	-
	Sufficient	21 (47.7)	7 (30.4)	0.48 (0.16-1.36, p=0.177)	0.00 (0.00-Inf, p=1.000)
ICU Admission	No	44 (100.0)	16 (69.6)	-	-
	Yes	0 (0.0)	7 (30.4)	Inf (0.00-NA, p=0.990)	0.00 (0.00-Inf, p=1.000)

(Data are presented as a range, mean±SD for continuous variables, and n and % for categorical variables)

Table 4: Predictors for COVID-19 mortality using univariate and multivariate logistic regression analysis

		Discharged	Died	Crude OR (95%CI)	Adjusted OR (95%CI)
Demographics					
Age (years)	Mean (SD)	40.7 (11.7)	60.7 (19.3)	1.09 (1.01-1.19, p=0.026)	0.17 (NA-Inf, p=1.000)
Sex	Female	14 (21.9)	0 (0.0)	-	-
	Male	50 (78.1)	3 (100.0)	Inf (0.00-NA, p=0.995)	0.00 (0.00-Inf, p=1.000)
Race/Ethnicity	Asian	47 (73.4)	1 (33.3)	-	-
	Black	3 (4.7)	0 (0.0)	0.00 (NA-Inf, p=0.997)	Inf (0.00-Inf, p=1.000)
	White	14 (21.9)	2 (66.7)	6.71 (0.60-150.97, p=0.131)	Inf (0.00-Inf, p=1.000)
Clinical Presentation					
Hypertension	No	47 (87.0)	0 (0.0)	-	-
	Yes	7 (13.0)	3 (100.0)	Inf (0.00-NA, p=0.996)	69.61 (0.00-Inf, p=1.000)
Diabetes Mellitus	No	46 (79.3)	1 (33.3)	-	-
	Yes	12 (20.7)	2 (66.7)	7.67 (0.68-173.42, p=0.108)	Inf (0.00-Inf, p=1.000)
Shortness of Breath	No	15 (24.6)	0 (0.0)	-	-
	Yes	46 (75.4)	3 (100.0)	Inf (0.00-NA, p=0.995)	0.00 (0.00-Inf, p=1.000)
Fever	No	9 (14.3)	0 (0.0)	-	-
	Yes	54 (85.7)	3 (100.0)	Inf (0.00-NA, p=0.996)	Inf (0.00-Inf, p=1.000)
O_2 Saturation	Mean (SD)	96.0 (4.8)	84.7 (6.4)	0.71 (0.47-0.89, p=0.025)	1.80 (NA-Inf, p=1.000)
Radiology	Normal	20 (31.2)	0 (0.0)	-	-
	Pneumonia	44 (68.8)	3 (100.0)	Inf (0.00-NA, p=0.994)	Inf (0.00-Inf, p=1.000)
Vitamin C Levels	Deficient	36 (56.2)	3 (100.0)	-	-
	Sufficient	28 (43.8)	0 (0.0)	0.00 (NA-Inf, p=0.996)	0.00 (0.00-Inf, p=1.000)
ICU Admission	No	60 (93.8)	0 (0.0)	-	-
	Yes	4 (6.2)	3 (100.0)	Inf (0.00-NA, p=0.996)	Inf (0.00-Inf, p=1.000)

(Data are presented as a range and mean±SD for continuous variables and n and % for categorical variables)

Table 5: Univariate linear regression models of the association between serum vitamin C levels and immune-inflammatory response biochemical markers

Immune-Inflammatory Response Markers		Coefficient (95%CI)	Spearman coefficient (r)
Platelet Count(×10⁹/L)	[125,719]	-0.00 (-0.00 to 0.00, p=0.488)	-0.138
Lymphocyte Count(×10⁹/L)	[2.8,52.8]	0.01 (-0.00 to 0.01, p=0.051)	0.237
CRP (mg/L)	[0.04,478]	-0.00 (-0.00 to -0.00, p=0.002)	-0.397
Ferritin (ng/mL)	[4.4,8894]	-0.00 (-0.00 to 0.00, p=0.471)	-0.215
LDH (U/L)	[4.1,1886]	-0.00 (-0.00 to -0.00, p=0.015)	-0.433
Fibrinogen (mg/dL)	[234,1178]	-0.00 (-0.00 to -0.00, p=0.012)	-0.338
D-Dimer (μg/mL)	[0.08,33.2]	-0.02 (-0.03 to 0.00, p=0.085)	-0.295

(Data are presented as a range)

that 82% of the patients were suffering from vitamin C deficiency.[14] Another study reported undetectable vitamin C levels among 94.4% of COVID-19 patients.[15] These variations among studies could be attributed to the measurement technique, food intake, the nature of vitamin C, such as light sensitivity and rapid oxidation, different patient characteristics, and the small sample size of all studies, decreasing generalizability. The exact mechanism by which vitamin C decreases during viral infections remains unclear. However, several hypotheses explain the possible mechanisms involved, such as increased

Table 6: Comparative analysis of the association between serum vitamin C levels and immune-inflammatory response markers

Immune-Inflammatory Response Markers		Deficient	Sufficient	OR (95%CI)
Platelet Count(×10⁹/L)	Mean (SD)	341.6 (146.5)	332.1 (154.9)	1.00 (1.00-1.00, p=0.796)
Lymphocyte Count(×10⁹/L)	Mean (SD)	27.1 (13.6)	29.0 (13.0)	1.01 (0.97-1.05, p=0.561)
CRP (mg/L)	Mean (SD)	101.3 (114.2)	40.6 (63.2)	0.99 (0.98-1.00, p=0.024)
Ferritin (ng/mL)	Mean (SD)	847.3 (1099.2)	789.3 (1695.3)	1.00 (1.00-1.00, p=0.863)
LDH (U/L)	Mean (SD)	428.5 (356.0)	277.0 (146.7)	1.00 (0.99-1.00, p=0.056)
Fibrinogen (mg/dL)	Mean (SD)	577.7 (241.4)	488.9 (183.3)	1.00 (1.00-1.00, p=0.109)
D-Dimer (µg/mL)	Mean (SD)	2.9 (6.8)	0.7 (1.5)	0.83 (0.51-1.00, p=0.227)

production of reactive oxygen species, decreased recycling and absorption, increased metabolic consumption, and increased glomerular filtration.[15,17] We found that COVID-19 patients with pneumonia had significantly lower vitamin C levels than patients with normal X-ray findings (p=0.012). Corkovic et al. also showed marked vitamin C deficiency among acute pneumonia and chronic obstructive pulmonary disease with exacerbation patients; the authors also demonstrated a negative correlation between decreased vitamin C and inflammatory markers.[18]

Old age and diabetes or hypertension among COVID-19 patients were significantly associated with vitamin C deficiency. These observations are consistent with other reports. McCall et al. reported that the risk of vitamin C deficiency increases by 2% per year-unit increase at age.[19] Wilson et al. reported a higher proportion of vitamin C deficiency among patients with type 2 diabetes mellitus than among those with normal glucose levels. Additionally, they showed that fasting glucose could be considered an independent indicator of the serum concentration of vitamin C.[20] This could be attributed to competitive inhibition for uptake between blood glucose and dehydroascorbic acid, which is the oxidized form of the vitamin for glucose transporters (GLUTs).[21] A recent meta-analysis showed lower vitamin C concentrations among hypertensive patients than among normotensive subjects; there was also an inverse association between diastolic and systolic blood pressure and vitamin C concentrations.[22]

We could not determine the association between vitamin C concentration and COVID-19-related mortality due to the limited sample size and the limited number of deaths observed in our study population during the study period, which underestimated the real association between vitamin C levels and mortality due to COVID-19. The risk of severe COVID-19 outcomes decreased by 52% among patients with sufficient vitamin C concentrations compared to those with deficient concentrations. However, this reduction in disease severity was not statistically significant but could also be attributed to the small sample size.

Our findings showed that vitamin C sufficiency is strongly associated with lowering inflammatory markers, such as CRP, LDH, and fibrinogen. The mechanisms by which vitamin C could ameliorate the immune system, in addition to its antioxidant activity, include, first, downregulation of several proinflammatory cytokines, including TNF-α, IL-1β, and NF-κB[23,24]; second, upregulation of interferon production[25]; third, abolishment of upregulated angiotensin-converting enzyme 2 (ACE2), which is a SARS-CoV-2 entry receptor induced by IL-7[26]; fourth, increasing the production of cortisol and promoting the protective effect of corticosteroids; and fifth, enhancing the function of the lung epithelial barrier.[27]

The beneficial effect of supplementary vitamin C for COVID-19 patients is still controversial. In a randomized double-blinded clinical trial conducted by Mahmoodpoor and colleagues, high-dose administration of vitamin C (60 mg/kg/day) was associated with a significant decrease in the need for mechanical ventilation and inflammation, in addition to an insignificant reduction in mortality among critically ill COVID-19 patients with pneumonia.[28] In contrast, Seet and colleagues, in an open-label

parallel randomized clinical trial, showed that either oral hydroxychloroquine or povidone-iodine throat spray was better than vitamin C in reducing SARS-CoV-2 infection among men living in a region with high exposure rates or closed.[29] Thomas et al. found that outpatient treatment of COVID-19 with either zinc, vitamin C, or their combination had no beneficial effect on the reduction of SARS-CoV-2 symptoms when compared to the standard of care.[30] Several social determinants, such as how we live, eat, and drink, in addition to the safe therapeutic window of vitamin C supplements, can affect vitamin C concentrations and therefore influence the outcome of COVID-19. This should be brought to the attention of the social and community in general, as it may have future effects on the health of the individual, community, and population.

4.1. Strengths and Limitations of the study

Even though there is inadequate evidence to advocate for or against the use of vitamin C for the treatment of COVID-19 patients, vitamin C-rich foods as well as vitamin C supplementation, could be recommended for COVID-19 cases due to the wide therapeutic window of vitamin C supplementation. To provide more advice on the role of vitamin C in the prevention and treatment of COVID-19, the results from appropriately powered, well-designed, and well-conducted clinical trials are needed. Our study has certain limitations, such as the limited sample size and the fact that it is a retrospective analysis, which could lessen the significance of our findings. In addition, we did not investigate whether the consumption of vitamin C supplements had an impact on the overall outcomes. In addition, the patients who participated in the research were taking a variety of other medications simultaneously, which may also have impacted the results.

5. Conclusion and Global Health Implications

In this observational study, low serum vitamin C concentrations were associated with several demographic characteristics of patients, the presence of pneumonia, and inflammation. Patients with adequate vitamin C levels had a lower risk of COVID-19 severity, but the difference was not statistically significant.

This study recommends conducting more extensive controlled clinical trials with a sufficient sample size to examine the efficacy of vitamin C among patients with COVID-19 and examine the beneficial role of vitamin C supplementation as an adjuvant during treatment or prophylaxis of SARS-CoV-2 infection. We also brought to the attention of the social community in general that addressing social determinants, such as how we live, eat, and drink, as well as vitamin C supplementation, could have a good impact on the future health of the individual, community, and population.

Compliance with Ethical Standards

Key Messages

► Serum vitamin C concentrations were associated with various patient characteristics, such as age, hypertension, and diabetes mellitus, as well as the development of pneumonia and increased inflammation.

► Compared to patients with vitamin C deficiency, the likelihood of COVID-19 severity decreased non-significantly, and vitamin C sufficiency was associated with lower lactate dehydrogenase, C-reactive protein (CRP), and fibrinogen levels.

► Improving our socioeconomic determinants, such as how we live, eat, and drink, as well as vitamin C supplementation, may positively impact the individual, community, and population's future health.

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