



# Higher Adherence to the Mediterranean Dietary Pattern Is Inversely Associated With Severity of COVID-19 and Related Symptoms: A Cross-Sectional Study

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**Background and Aims:** Adherence to the Mediterranean diet (MD) has been associated with a decreased risk of developing a variety of chronic diseases that are comorbidities in COVID-19 patients. However, its association to the severity and symptoms of COVID-19 are still unknown. This study aimed to examine the association between adherence to the MD pattern and COVID-19 severity and symptoms in Iranian hospitalized patients.

**Methods:** In this cross-sectional study, 250 COVID-19 patients aged 18 to 65 were examined. We employed a food frequency questionnaire (FFQ) to obtain data on dietary intake of participants in the year prior to their COVID-19 diagnosis. COVID-19 severity was determined using the National Institutes of Health's Coronavirus Disease 2019 report. Additionally, symptoms associated with COVID-19, inflammatory markers, and other variables were evaluated. The scoring method proposed by Trichopoulos et al. was used to assess adherence to the MD.

**Results:** The participants' mean age was  $44.1 \pm 12.1$  years, and 46% of them had severe COVID-19. Patients who adhered more closely to the MD had lower serum C-reactive protein levels (7.80 vs. 37.36 mg/l) and erythrocyte sedimentation rate (14.08 vs. 42.65 mm/h). Those with the highest MD score were 77% less likely to have severe COVID-19 after controlling for confounding variables. The MD score was also found to be inversely associated with COVID-19 symptoms, including dyspnea, cough, fever, chills, weakness, myalgia, nausea and vomiting, and sore throat.

**Conclusion:** Higher adherence to the MD was associated with a decreased likelihood of COVID-19 severity and symptoms, as well as a shorter duration of hospitalization and convalescence, and inflammatory biomarkers.

**Keywords:** COVID-19, dietary pattern, severe disease, infectious disease, Mediterranean diet

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), a viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a global health concern, resulting in over six million deaths worldwide by the end of March 2022 (1). It is no surprise that this has become the pandemic the most impacting pandemic of this century (2, 3). The COVID-19 pandemic has profoundly affected numerous facets of global life, including health care systems and the economy (4, 5). COVID-19, in addition to causing significant global management disorders, can result in aggressive sequelae and death as a result of a harmful link between the immune, respiratory, and cardiovascular systems (6–8). Besides advanced pharmacological treatments, non-pharmacological interventions have gained attention to assist in combating primary and secondary events of COVID-19 (9, 10). In this regard, dietary habits are critical due to their long-term physiological necessity (11).

While COVID-19 is a disease with a strong inflammatory stimulus that manifests primarily in moderate to severe conditions, resulting in a “cytokine storm” as a result of an excessive immune response (12, 13), numerous nutraceutical agents (e.g., herbal medicines), personalized vitamin and mineral dosing regimens, and dietary patterns all have anti-inflammatory properties that appear to reduce the production and action of inflammatory molecules and pathways (14–16). Recent randomized clinical trials (RCTs) showed that nutrient supplementation alone has no discernible effect on the management of COVID-19 and should be used only as a supplement to correct a diagnosed nutritional deficiency (17, 18). Dietary patterns and COVID-19 have received less attention, with most studies on dietary patterns focusing on dietary changes caused by the pandemic or lockdown (19). Interestingly, following plant-based diets were associated with a decreased risk of moderate-to-severe COVID-19 infection in a population-based case-control study involving 2,884 participants from six countries (20). In addition, an observational study of 509 COVID-19 patients suggested an inverse association between adherence to a vegetarian diet and severity of COVID-19 symptoms as well as an increased risk for non-vegetarians (21).

The Mediterranean diet (MD) is a widespread dietary pattern associated with anti-inflammatory properties due to its high consumption of olive oil, nuts, seeds, vegetables, fruits, whole grains, low-fat dairy, and low intake of meats and dairy products (22–25). The MD is a healthy dietary approach that promotes overall well-being (26) and is associated with risk reduction of the common comorbidities observed in COVID-19 patients (27). Indeed, MD patterns have a preventive effect on cardiovascular diseases and diabetes, which are risk factors for severe COVID-19 infection and its associated complications (28). Thus, the present study aimed to investigate the association between adherence to the MD pattern and the severity of COVID-19 and related symptoms in a sample of adult Iranian hospitalized patients.

## METHODS

### Participants

We conducted a retrospective cross-sectional study on 250 patients aged 18–65 who had recovered from COVID-19. Using a convenience sampling method, participants were drawn from Shahid Beheshti Hospital in Kashan, Iran. This research was conducted between June and September 2021. The Kashan University of Medical Sciences Ethics Committee reviewed and approved the study's protocol (Registration No. IR.KAUMS.MEDNT.REC.1400.048). Informed consent was obtained from study participants prior to enrollment in the study.

At first, we examined the medical records of 600 COVID-19 patients with available medical data from Shahid Beheshti Hospital who had been diagnosed within the previous 3 months were included. We excluded 350 patients after considering the following items as the exclusion criteria: any comorbidities or diseases other than COVID-19, such as diabetes, cardiovascular disease, or diseases that affect COVID-19 severity; a body mass index (BMI) >40 kg/m<sup>2</sup>; current pregnancy or breastfeeding; active smoking; consuming dietary supplements more than twice a week prior to the COVID-19 diagnosis; being on any special diets; taking any medications that affect respiratory tract function, such as fluticasone, flunisolide, and so on; and incomplete medical records. In addition, all enrolled patients were not vaccinated because public vaccination had not yet begun in Iran at the time of the study.

### Assessment of Dietary Intakes

Dietary intakes were assessed using a web-based 168-item food frequency questionnaire (FFQ) to collect data on dietary intakes of participants during a year preceding their COVID-19 diagnosis. The reliability and validity of the FFQ have previously been evaluated (29). We utilized the FFQ to assess dietary intakes because the patients in this study were hospitalized and their diets may have changed due to the disease and its consequences. This questionnaire allowed participants to report their dietary intakes daily, monthly, or annually. Then, using ‘household measures,’ the dietary intakes were converted to grams per day (g/d). Nutritionist IV software was used to calculate the dietary intakes of micronutrients and macronutrients.

Adherence to the MD was used following the method introduced by Trichopoulou et al. (30). The adherence was quantitated by calculating the MD score. To accomplish this, nine components were taken into account: vegetables, fruits, nuts, legumes, fish, whole grains, the ratio of monounsaturated fatty acids (MUFAs) to saturated fatty acids (SFAs), meats (red meat, poultry, and processed meats), and dairy. Participants who were above the median intakes of vegetables, fruits, nuts, legumes, fish, whole grains, and the highest MUFA to SFA ratio and those who were below the median intakes of meats and dairy received a score of 1. In contrast, individuals at the top median intakes of meat and dairy products as well as those at the bottom median intakes of whole grains, fruits, vegetables, fish, nuts, and legumes received a score of 0. These scores were summed up to calculate the overall MD score.

## Measurement of COVID-19 Severity

The severity of COVID-19 was described and classified using the National Institute of Health's Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, updated on October 19, 2021 (31). This guideline defines patients with severe illness as those who have SpO<sub>2</sub> <94% on room air at sea level, arterial partial oxygen pressure/fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) <300 mmHg, respiratory rate (RR) >30 breaths/min, or lung infiltrates >50%, and a cluster of respiratory failure, septic shock, and/or multiple organ dysfunction.

## Measurement of COVID-19 Symptoms

Patients were asked to fill out a questionnaire including questions about the presence of common COVID-19 manifestations, i.e., fever, chilling, dyspnea, cough, weakness, muscle pain, sore throat, nausea, and vomiting.

## Assessment of Inflammatory Markers

The first available measures of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were obtained from medical records during patients' hospitalization.

## Assessment of Other Variables

A general questionnaire was used to collect information about each patient's demographics, physical activity, convalescence duration, administration of supplement, corticosteroid, and antiviral drug intake, and participants' height and weight.

## Statistical Analysis

We divided participants into tertile groups based on their MD score. To determine normality, we used the Kolmogorov-Smirnov test. Means and standard deviations for continuous variables and percentages for categorical variables were reported to describe the general characteristics of participants across tertiles of MD score. The general characteristics of study participants were compared using one-way analysis of variance (ANOVA) for continuous and chi-square tests for quantitative variables across tertiles of MD score. The inflammatory biomarkers were compared using covariance analysis (ANCOVA) across the MD score tertiles, after adjustment for age, gender, BMI, and physical activity. The association between the MD score and severe COVID-19, as well as its symptoms was assessed using binary logistic regression in multiple models. At the first model findings were adjusted for age (continuous), gender (male/female), and energy intake/BMR (continuous). In the second model, additional adjustments were made for (sedentary/moderate/intense), supplementation (yes/no), corticosteroid use (yes/no), and antiviral medication use (yes/no). In the third model, there was an additional adjustment for the BMI (continuous). The Statistical Package for the Social Sciences (SPSS Inc., version 25) was used in the current study. Statistical significance was defined as *P*-values <0.05.

**TABLE 1** | General characteristics of participants across tertiles of Mediterranean diet.

	Tertiles of MD score			<i>P</i> <sup>*</sup>
	T1 <i>n</i> = 80	T2 <i>n</i> = 81	T3 <i>n</i> = 89	
Age (years)	44.7 ± 12.6	41.9 ± 12.0	45.7 ± 11.7	0.12
Female (%)	61.3	50.6	46.1	0.13
Body mass index (kg/m <sup>2</sup> )	29.3 ± 3.7	26.1 ± 3.5	25.7 ± 3.0	<0.001
Physical activity				
Sedentary	18.8	7.4	11.2	0.12
Moderate	73.8	88.9	79.8	
Intense	7.5	3.7	9.0	
Overweight or obese (%)	88.8	61.7	52.8	<0.001
Supplements intake (%)	98.8	91.4	94.4	0.10
Corticosteroids use (%)	97.5	87.7	91.0	0.06
Antiviral Drugs use (%)	97.5	87.7	91.0	0.06
Duration of hospitalization (d)	8.1 ± 3.2	5.7 ± 2.4	5.9 ± 2.6	<0.001
Convalescence duration (d)	10.8 ± 3.8	9.5 ± 4.1	8.2 ± 2.9	<0.001

<sup>\*</sup>Obtained from ANOVA or Chi-square test, where appropriate.

## RESULTS

The general characteristics of study participants across tertiles of MD score are summarized in **Table 1**. The mean age and gender distribution were not significantly different across the MD score tertiles. Participants at the highest tertile of MD score had a lower BMI and were less likely to be overweight or obese. Furthermore, they had a significantly shorter length of hospitalization and convalescence than those in the lowest tertile.

**Table 2** depicts dietary intakes of selected food groups and nutrients across tertiles of the MD score. Compared to the lowest tertile, participants at the top tertile of the MD score had higher intakes of protein, carbohydrate, dietary fiber, n-3 fatty acids, vitamins B1, B2, B6, B12, folate, calcium potassium, magnesium intakes when compared to those at the lowest tertile. These participants also had lower daily energy, fat, SFAs, MUFAs, vitamin B3, and vitamin D intakes. It is worth noting that those at the highest tertile of the MD score significantly consumed more fruits, vegetables, legumes, nuts, whole grains, and fish and lower meats than those at the.

**Table 3** illustrates serum levels of inflammatory biomarkers across the MD score tertiles. After controlling for age, gender, BMI, and physical activity, participants in the top tertile had significantly lower CRP (7.80 ± 1.87 vs. 37.36 ± 2.05 mg/l) and ESR (14.08 ± 2.17 vs. 42.65 ± 2.37 mm/hr.) than those in the bottom tertile (*P* < 0.001).

Crude and multivariable-adjusted odds ratios (OR), with 95% confidence intervals (CIs), for severe COVID-19 according to tertiles of MD score are presented in **Table 4**. Patients in the top tertile of the MD score had lower odds of having severe COVID-19 than patients in the bottom tertile, in the crude model (OR: 0.15; 95% CI: 0.08, 0.30, *P* < 0.001). After

**TABLE 2** | Selected food groups and nutrients intakes of participants across tertiles of Mediterranean diet score.

	Tertiles of MD score			<i>P</i> <sup>a</sup>
	T1 <i>n</i> = 80	T2 <i>n</i> = 81	T3 <i>n</i> = 89	
<b>Nutrients</b>				
Energy (kcal/d)	2,811.4 ± 552.7	2,638.3 ± 470.3	2,788.6 ± 351.2	0.04
Protein (g/d)	101.3 ± 15.7	108.1 ± 19.1	114.2 ± 14.0	<0.001
Fat (g/d)	109.8 ± 33.1	97.0 ± 26.3	96.3 ± 15.9	0.005
Carbohydrate (g/d)	416.6 ± 58.9	393.0 ± 55.3	419.6 ± 43.5	0.002
Cholesterol (mg/d)	432.5 ± 146.7	450.8 ± 160.1	448.2 ± 161.0	0.72
Dietary fiber (g/d)	18.7 ± 2.7	23.2 ± 4.0	27.1 ± 2.9	<0.001
SFAs (g/d)	34.2 ± 11.6	27.3 ± 9.5	25.0 ± 4.9	<0.001
MUFAs (g/d)	34.3 ± 11.3	27.5 ± 8.7	27.7 ± 6.1	<0.001
n-3 Fatty acids (g/d)	0.33 ± 0.11	0.34 ± 0.16	0.52 ± 0.15	<0.001
Vitamin B1 (mg/d)	2.5 ± 0.3	2.4 ± 0.4	2.6 ± 0.3	0.001
Vitamin B2 (mg/d)	1.8 ± 0.3	2.0 ± 0.4	2.1 ± 0.3	<0.001
Vitamin B3 (mg/d)	28.2 ± 4.4	26.5 ± 4.5	27.5 ± 3.4	0.04
Vitamin B6 (mg/d)	1.5 ± 0.3	1.7 ± 0.3	1.9 ± 0.2	<0.001
Folate (μg/d)	337.5 ± 61.7	427.6 ± 80.1	476.6 ± 65.7	<0.001
Vitamin B12 (μg/d)	3.6 ± 0.9	4.0 ± 1.4	4.9 ± 1.1	<0.001
Vitamin D (μg/d)	2.53 ± 0.90	2.21 ± 0.68	2.11 ± 0.56	0.003
Calcium (mg/d)	843.8 ± 125.9	917.6 ± 140.0	961.5 ± 106.8	<0.001
Potassium (mg/d)	3,274.3 ± 488.1	3,703.4 ± 520.8	4,136.0 ± 425.9	<0.001
Magnesium (mg/d)	292.0 ± 43.3	326.5 ± 49.6	364.3 ± 39.1	<0.001
<b>Food groups</b>				
Fruits (g/d)	241.0 ± 66.7	368.4 ± 109.1	448.0 ± 69.7	<0.001
Vegetables (g/d)	196.8 ± 46.0	286.8 ± 92.1	342.0 ± 79.6	<0.001
Whole grains (g/d)	49.4 ± 61.4	116.2 ± 84.3	81.8 ± 76.1	<0.001
Legumes (g/d)	92.6 ± 22.0	143.2 ± 37.1	163.3 ± 32.6	<0.001
Nuts (g/d)	19.9 ± 9.8	30.8 ± 13.0	39.5 ± 10.3	<0.001
Fish (g/d)	12.8 ± 6.1	20.6 ± 11.9	34.2 ± 10.7	<0.001
Dairy (g/d)	278.3 ± 82.9	295.0 ± 69.7	291.9 ± 48.2	0.35
Meats and meat products (g/d)	119.4 ± 34.4	106.5 ± 29.8	96.9 ± 30.8	<0.001

MUFAs, monounsaturated fatty acids; SFAs, saturated fatty acids.

Data are presented as mean ± SD.

<sup>a</sup>Obtained from ANOVA.

controlling for potential confounding factors, participants with the highest MD score were 84% less likely to have severe COVID-19 than those with the lowest score (OR: 0.16; 95% CI: 0.08, 0.32,  $P < 0.001$ ). Additional adjustment for BMI attenuated, but did not eliminate, the association (OR: 0.23; 95% CI: 0.11, 0.50,  $P < 0.001$ ). When the analyses were done individually based on BMI status, surprisingly the association was significant only among overweight or obese patients; implying an 86% decreased probability of having severe COVID-19 (OR: 0.14; 95% CI: 0.06, 0.36,  $P < 0.001$ ). However, there was no association among normal weight patients (OR: 0.35; 95% CI: 0.07, 1.77,  $P = 0.22$ ) (**Supplementary Table 1**). Concerning the different components of the MD pattern, we found a significant inverse association between odds of severe COVID-19 and consumption of vegetables (OR: 0.31; 95% CI: 0.15, 0.64,  $P = 0.002$ ), fruits (OR: 0.35; 95% CI: 0.17, 0.74,  $P = 0.006$ ), legumes (OR: 0.35; 95% CI: 0.17, 0.71,  $P = 0.004$ ), nuts (OR: 0.35; 95%

CI: 0.16, 0.74,  $P = 0.006$ ), whole grains (OR: 0.39; 95% CI: 0.19, 0.80,  $P = 0.01$ ), and fish (OR: 0.31; 95% CI: 0.15, 0.64,  $P = 0.002$ ). There were no additional significant association between other MD components and severity of COVID-19 (**Supplementary Table 2**).

**Table 5** outlines the crude and multivariable-adjusted OR for COVID-19 symptoms according to tertiles of the MD score. After controlling for potential confounders, there was a significant inverse relationship between the MD score and the likelihood of experiencing COVID-19 symptoms such as dyspnea (OR: 0.32; 95% CI: 0.13, 0.76,  $P = 0.03$ ), cough (OR: 0.11; 95% CI: 0.05, 0.26,  $P < 0.001$ ), fever (OR: 0.11; 95% CI: 0.03, 0.37,  $P < 0.001$ ), chilling (OR 0.06; 95% CI: 0.01, 0.26,  $P < 0.001$ ), weakness (OR: 0.34; 95% CI: 0.15, 0.76,  $P = 0.01$ ), myalgia (OR: 0.34; 95% CI: 0.16, 0.72,  $P = 0.005$ ), nausea and vomiting (OR: 0.06; 95% CI: 0.01, 0.30,  $P < 0.001$ ), and sore throat (OR: 0.08; 95% CI: 0.03, 0.21,  $P < 0.001$ ).

**TABLE 3 |** Inflammatory biomarkers across tertiles of Mediterranean diet.

	Tertiles of MD score			P*
	T1 n = 80	T2 n = 81	T3 n = 89	
CRP (mg/l)	37.36 ± 2.05	15.18 ± 1.90	7.80 ± 1.87	<0.001
ESR (mm/hr)	42.65 ± 2.37	19.29 ± 2.21	14.08 ± 2.17	<0.001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Data are presented as mean ± SE.

\*Values were adjusted for age, sex, BMI, and physical activity using ANCOVA.

**TABLE 4 |** Odds ratio (95% CI) of severe disease according to tertiles of Mediterranean diet.

	Tertiles of MD score			P*
	T1 n = 80	T2 n = 81	T3 n = 89	
Crude	1.00	0.17 (0.08, 0.33)	0.15 (0.08, 0.30)	<0.001
Model 1	1.00	0.17 (0.09, 0.35)	0.17 (0.08, 0.33)	<0.001
Model 2	1.00	0.18 (0.08, 0.37)	0.16 (0.08, 0.32)	<0.001
Model 3	1.00	0.24 (0.11, 0.51)	0.23 (0.11, 0.50)	<0.001

BMR, Basal Metabolic Rate; BMI, body mass index.

Model 1: Adjusted for age, sex, and energy intake/BMR.

Model 2: Further adjusted for physical activity, supplement use, corticosteroids use, and antiviral drugs use.

Model 3: Further adjusted for BMI.

\*Obtained from Binary logistic regression.

## DISCUSSION

This study found an inverse association between a higher MD score and odds of having severe COVID-19 as well as a shorter duration of hospitalization and convalescence. Even though there was little difference in total energy intake among the participants, those in the upper tertile of MD scores had significantly lower levels of inflammatory biomarkers such as CRP ( $7.80 \pm 1.87$  vs.  $37.36 \pm 2.05$  mg/l) and ESR ( $14.08 \pm 2.17$  vs.  $42.65 \pm 2.37$ ) than those in the lowest tertile. Both CRP and ESR are widely used as systemic inflammatory biomarkers (32). The ESR may reveal the presence of inflammation in the body because it measures the rate at which red blood cells drop or settle in the plasma of a randomly selected anticoagulated blood sample, and inflammation can result in cell clumping (32). On the other hand, CRP is an unspecific acute-phase reactant that is produced and synthesized in the liver in response to a variety of pro-inflammatory cytokines (32).

Taking this comparison into account, those in the upper tertile of the MD consumed more protein, carbohydrates, fiber, n-3 fatty acids, vitamin B complex (B1, B2, B6, B12, folate), calcium, potassium, and magnesium, while consuming less total fat, primarily saturated fat. This is an expected result, as individuals with the highest MD scores consumed significantly more fruits, vegetables, legumes, nuts, whole grains, fish, and lean meats, all of which contain functional elements

**TABLE 5 |** Odds ratio (95% CI) for symptoms of COVID-19 according to tertiles of Mediterranean diet.

	Tertiles of MD score			P*
	T1 n = 80	T2 n = 81	T3 n = 89	
<b>Dyspnea</b>				
Crude	1.00	0.13 (0.06, 0.28)	0.18 (0.08, 0.40)	<0.001
Model 1	1.00	0.13 (0.06, 0.29)	0.20 (0.09, 0.45)	<0.001
Model 2	1.00	0.16 (0.07, 0.36)	0.22 (0.10, 0.50)	<0.001
Model 3	1.00	0.20 (0.08, 0.47)	0.32 (0.13, 0.76)	0.03
<b>Cough</b>				
Crude	1.00	0.18 (0.08, 0.40)	0.07 (0.03, 0.16)	<0.001
Model 1	1.00	0.18 (0.08, 0.40)	0.08 (0.03, 0.17)	<0.001
Model 2	1.00	0.18 (0.08, 0.42)	0.07 (0.03, 0.17)	<0.001
Model 3	1.00	0.25 (0.11, 0.59)	0.11 (0.05, 0.26)	<0.001
<b>Fever</b>				
Crude	1.00	0.12 (0.04, 0.38)	0.09 (0.03, 0.27)	<0.001
Model 1	1.00	0.13 (0.04, 0.39)	0.09 (0.03, 0.28)	<0.001
Model 2	1.00	0.12 (0.04, 0.39)	0.10 (0.03, 0.29)	<0.001
Model 3	1.00	0.15 (0.05, 0.47)	0.11 (0.03, 0.37)	<0.001
<b>Chilling</b>				
Crude	1.00	0.06 (0.01, 0.25)	0.04 (0.01, 0.19)	<0.001
Model 1	1.00	0.06 (0.01, 0.26)	0.04 (0.01, 0.20)	<0.001
Model 2	1.00	0.06 (0.01, 0.26)	0.05 (0.01, 0.21)	<0.001
Model 3	1.00	0.07 (0.01, 0.31)	0.06 (0.01, 0.26)	<0.001
<b>Weakness</b>				
Crude	1.00	0.39 (0.20, 0.75)	0.26 (0.13, 0.52)	<0.001
Model 1	1.00	0.42 (0.21, 0.84)	0.26 (0.12, 0.53)	<0.001
Model 2	1.00	0.41 (0.20, 0.82)	0.25 (0.12, 0.53)	<0.001
Model 3	1.00	0.51 (0.24, 1.08)	0.34 (0.15, 0.76)	0.01
<b>Myalgia</b>				
Crude	1.00	0.46 (0.24, 0.86)	0.26 (0.14, 0.49)	<0.001
Model 1	1.00	0.50 (0.26, 0.96)	0.26 (0.13, 0.51)	<0.001
Model 2	1.00	0.51 (0.26, 0.99)	0.26 (0.13, 0.52)	<0.001
Model 3	1.00	0.64 (0.32, 1.30)	0.34 (0.16, 0.72)	0.005
<b>Nausea and vomiting</b>				
Crude	1.00	0.27 (0.11, 0.65)	0.06 (0.01, 0.25)	<0.001
Model 1	1.00	0.26 (0.10, 0.63)	0.05 (0.01, 0.22)	<0.001
Model 2	1.00	0.33 (0.13, 0.81)	0.05 (0.01, 0.25)	<0.001
Model 3	1.00	0.36 (0.13, 0.94)	0.06 (0.01, 0.30)	<0.001
<b>Sore throat</b>				
Crude	1.00	0.43 (0.23, 0.81)	0.07 (0.03, 0.18)	<0.001
Model 1	1.00	0.44 (0.23, 0.84)	0.06 (0.02, 0.16)	<0.001
Model 2	1.00	0.41 (0.21, 0.81)	0.06 (0.02, 0.15)	<0.001
Model 3	1.00	0.50 (0.24, 1.02)	0.08 (0.03, 0.21)	<0.001

BMR, Basal Metabolic Rate; BMI, body mass index.

Model 1: Adjusted for age, sex, and energy intake/BMR.

Model 2: Further adjusted for physical activity, supplement use, corticosteroids use, and antiviral drugs use.

Model 3: Further adjusted for BMI.

\*Obtained from Binary logistic regression.

that may help mitigate COVID-related inflammation. COVID-19 causes a cytokine storm (e.g., interferon-alpha, interferon-gamma, interleukin (IL)-1, IL-6, IL-12, IL-18, IL-33, tumor

necrosis factor-alpha (TNF- $\alpha$ ), and transforming growth factor- $\beta$ , a central tenet that exacerbates the severity of COVID-19 (33). RCTs demonstrated the beneficial effects of the MD on the inflammatory status and primary events. In an RCT involving 372 participants over 3 months, adequate consumption of cereals and fruits, combined with a higher intake of nuts and olive oil, was associated with lower levels of IL-6, CRP, and other inflammatory biomarkers such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (34, 35). Most importantly, the Prevención con Dieta Mediterránea (PREDIMED) trial, a multicenter study involving 7,447 patients at high risk of cardiovascular disease, demonstrated that the MD has long-term benefits by reducing the incidence of major cardiovascular events compared to a low-fat diet after a mean follow-up of 5 years (36–40). Concerning polyphenols, a sub-study of the PREDIMED trial involving 1,170 elderly participants showed a significant inverse association between polyphenol intake as measured by the urinary biomarker total polyphenol excretion and inflammatory markers, with a significant decrease in plasma concentrations of VCAM-1, ICAM-1, IL-6, TNF- $\alpha$ , and monocyte chemoattractant protein (41). The favorable effects of the MD pattern on platelet-activating factor-induced platelet aggregation is another potential against COVID-19, as the platelet-activating factor is a critical molecule in the pathogenesis of this ailment (42). The phytochemical mixture across the MD diet may be more efficient than individual food substances (43). Indeed, complex natural products target many facets involved in inflammation and thrombosis in a synergistic manner (43–45).

Apart from increased intake of functional nutrients, the lower intake of saturated fatty acids observed in the upper tertile of the MD score may contribute to a less inflammatory state, as this type of fat stimulates the production of CRP and TNF- $\alpha$ , as well as signaling pathways involving toll-like receptor-4 (46, 47). In light of this, replacing SFAs with the increase in MUFAs or PUFA found in nuts is a strong recommendation (47–50). In our study, the upper tertiles of the MD score not only had a lower intake of saturated fat but also MUFA consumption, which is an odd result given that the MD is high in MUFA due to the high consumption of olive oil. Nonetheless, this result is explicable by the fact that this research was conducted in Iran, a country whose population consumes a significant amount of nuts, primarily walnuts, which are a recognized source of PUFA (51–53). The consumption of nuts by participants in the upper tertile of the MD score was within the range associated with a sustained decline in low-grade inflammation. For example, acute and chronic studies demonstrated that nut consumption of between 20 and 90 g/day might reduce pro-inflammatory cytokines and improves associated outcomes (e.g., cardiovascular parameters and visceral fat) (54–56). Much of these benefits can be explained by high content of antioxidants, vitamins, and minerals such as selenium and alpha-tocopherol across nuts (57).

## Strengths and Limitations

As for strengths, this study shed lights on a nutritional strategy that could be used in place of isolate supplements

in the fight against the COVID-19 pandemic. Such a result is significant when considering the global population. On the other hand, because our study was conducted on a single population (Iranians), we encourage additional multicenter research to confirm our findings. Due to the cross-sectional design of this study, which is a common limitation in nutrition and medical research, this study cannot infer causation, and thus recommendations cannot be affirmed. Despite extensive adjustment for potential confounding variables, the possibility of residual confounding cannot be completely ruled out. It should be noted that the sample size and all participants were drawn from a single-center, so generalizability to the general public should be approached with caution. Additionally, the FFQs rely on interviewees' memory, and despite our efforts to accurately measure their estimated nutrient intake over a year in grams, the memory bias inherent in this type of questionnaire cannot be ignored, particularly in relation to overweight and obese individuals, who are more likely to underreport their energy intake (58). To overcome this, we controlled for the proportion of energy intake to basal metabolic rate (BMR) in the analyses, which was calculated using Schofield equation (59). MD score calculation method is limited as it is based on the relationship between each participant's food consumption and depends on whether or not the population has a high or low rate of adherence to the MD. This study examined the effect of a dietary pattern on COVID-19 in a population with no pre-existing conditions and a low-risk profile (such as diabetes, cardiovascular disease, smoking, morbid obesity). Those who are at greater risk may experience a different response to the dietary items. Therefore, it would be prudent for future research to evaluate high-risk groups. We have no specific information on the type of dietary supplements consumed, hence we evaluate them all in a similar way. We also did not assess hospital nutrition or nutritional risk. To the extent that recent research shows that customized hospital diets have been used for COVID-19 patients (60), this merits further attention.

Finally, we did not assess a robust laboratory panel for the inflammatory status, such as the whole inflammatory signaling cascade of CRP, which includes at least IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (61). Insufficient data on the use of nonsteroidal anti-inflammatory drugs (NSAIDs), monoclonal antibodies, IL-6 inhibitors, and blood pressure medications was another limitation. Furthermore, we did not assess the level of antioxidants and polyphenols in urine or blood. Therefore, additional research is necessary to better understand the metabolic pathways involved in this process.

## CONCLUSION

Following a MD pattern can result in a favorable profile against COVID-19, as we observed that a higher MD score was associated with shorter length of hospital stay, convalescence, symptoms, as well as reduced severity and inflammatory status (low CRP and ESR levels) in patients with COVID-19. However,

RCTs are necessary in order to provide recommendations for any population.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kashan University of Medical Sciences, IR.KAUMS.MEDNT.REC.1400.048. The patients/participants provided their written informed consent to participate in this study.

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## AUTHOR CONTRIBUTIONS

NZ and SM: conceptualization, formal analysis, writing original draft, and writing review and editing. AE, MT, HK, and CA: data collection. AM: supervision, conceptualization, methodology, investigation, funding acquisition, formal analysis, writing original draft, and writing review and editing. HS, FT, HC, and KV: writing review and editing. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2022.911273/full#supplementary-material>

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