Mousavi *et al. BMC Nutrition* (2024) 10:168
https://doi.org/10.1186/s40795-024-00983-2

BMC Nutrition

RESEARCH Open Access

# The relationship between healthy eating index and Mediterranean diet adherence score with inflammatory indices and disease severity: a case-control study of hospitalized COVID-19 patients

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**Abstract**

**Background** Recent studies have focused on the connection between nutrition, inflammation, and infectious diseases. This study was conducted to investigate the relationship between the Mediterranean diet adherence score (MDS) and the healthy eating index (HEI) with some clinical findings of patients with COVID-19.

**Methods** This case–control study was conducted in 29 Bahman hospital of Tabriz, Iran, from June to December 2022. Totally, 300 individuals (150 patients with COVID-19 as cases and 150 subjects who had not affected by COVID-19 as controls) was selected using convenience random sampling method to participate in the study. The 138-items food frequency questionnaire-derived dietary data were applied to compute HEI and MDS. Serum levels of BUN, creatinine and inflammatory markers including the Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured.

**Results** Both the HEI and MDS of case group was significantly lower than control group ($p < 0.001$). The MDS was negatively associated with hospitalization duration ($R$=-0.209, $P < 0.001$) and serum ESR level ($R$=-0.420, $P < 0.001$). A negative relationship was also seen between ESR level and HEI ($R$=-0.13, $P = 0.017$).

**Conclusion** It is concluded that higher MDS and HEI contribute to lower inflammatory markers and then diminished risk of covid-19 infection.

**Keywords** COVID-19, Mediterranean diet, Healthy eating, Inflammation

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## Introduction

The Coronavirus disease 2019 (COVID-19) pandemic, which was started in December 2019, has emerged as a significant danger to global public health [1], resulting in millions of deaths. The symptoms of coronavirus infection can differ among various host species [2]. In humans, coronavirus infections can range from no symptoms to experiencing fever, cough, and difficulty breathing [3]. World Health Organization continuously updating testing standards to ensure accurate diagnosis and detection [2]. Hospitalized patients with COVID-19 commonly experience complications such as pneumonia, acute respiratory distress syndrome, liver injury, and shock. These complications are identified through various tests and markers including RT-PCR for viral genetic material, radiological tests, and serological tests that detect abnormalities like low lymphocyte count, elevated inflammatory markers, and abnormal coagulation parameters [4]. Since there are no proven treatments available, the approach to treatment focuses on relieving symptoms. Current clinical management involves implementing measures to prevent and control infections, along with providing supportive care [5]. The focus of treatment for COVID-19 is on relieving symptoms, as there are currently no proven treatments available. Clinical management involves preventing and controlling infections and providing supportive care. Patients with COVID-19 often have higher levels of inflammatory cytokines and serologic indicators of inflammation, which can lead to lymphocytopenia and contribute to the pathogenesis of the virus [6]. However, this hyperinflammatory response can also be used to identify patients at high risk of severe disease and respiratory complications, allowing for more aggressive treatment and monitoring. Targeting the hyperinflammatory response with drugs that inhibit specific cytokines, such as IL-6 inhibitors, has shown promising results in clinical trials. Overall, understanding and addressing the hyperinflammatory response in COVID-19 patients may improve treatment outcomes [7, 8]. The connection between nutrition, immunity, and infectious diseases has been studied, with various nutrients known to be essential for immune function, and it is believed that subclinical immune dysfunction caused by micronutrient deficiencies may affect the progression of COVID-19 in humans [9]. Previous research on the anti-inflammatory effects of the Mediterranean diet has mostly looked at adults, but the findings have been inconclusive [10]. The Mediterranean diet consists a variety of plant-based foods and is rich in antioxidants, dietary fiber, unsaturated fats, omega-3 fatty acids, vitamins, minerals, and phytochemicals. Then, it has anti-inflammatory, potentially antimicrobial, and immunomodulatory properties that can enhance the immune system and prevent the infectious diseases [11, 12]. Recent studies have indicated that dietary inflammatory index was potentially correlated with serum inflammatory markers including C-reactive protein (CRP), interleukin-1 (IL-1), IL-12, TNF-alpha, and erythrocyte sedimentation rate (ESR) [35, 36].

Research conducted in 2023 demonstrated that following a Mediterranean diet was associated with reduced symptoms of COVID-19 and lower levels of inflammation in affected individuals. This suggests that adopting a high-quality dietary pattern, such as the Mediterranean diet, may offer protection against COVID-19 [13]. Barrea et al. (2022) emphasized the inclusion of olives, olive oil, fruits, and vegetables in this diet, as these components play a role in the recovery process of Covid-19 patients [14]. Recent studies have shown that following the Healthy Eating Index (HEI) is associated with a lower risk of hospitalization and shorter hospital stays for patients with COVID-19 [15]. The HEI-2015 includes two groupings : Adequacy components that include nine types of food that should be consumed in sufficient quantity (total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy products, total protein, seafood and plant protein, and fatty acids) and moderation components that include food groups that should be consumed in a limited manner (refined grains, sodium, added sugars, and saturated fat) [16]. According to literature, it is essential to accurately estimate long-term habitual food intake. The Food Frequency Questionnaire (FFQ) is commonly utilized in nutritional epidemiological studies to evaluate an individual's typical dietary intake. This tool is particularly useful for examining the connection between diet and health outcomes [16, 17]. Finally, considering the severe complications and economic burden of COVID-19 disease, this study was conducted with the aim of investigating the relationship between the healthy dietary indices including HEI and Mediterranean diet adherence score (MDS) with disease severity, hospitalization duration, and some inflammatory markers among the hospitalized patients with covid-19.

## Methods and materials

### Study design

The present case-control study was carried out at Bahman Hospital in Tabriz, Iran, from June to December 2022. The study protocol was approved by the Medical Ethics Committee of the Sabzevar University of Medical Sciences, according to the Declaration of Helsinki (approval number (IR.MEDSAB.REC.1401.001). All participants provided signed informed consent.

### Sample size

The G*Power software was utilized to calculate the sample size for the study. Assuming $\alpha = 0.05$, study power of 80%, and a dropout rate = 20%, the estimated sample size required for each group was determined to be 150 cases. Totally, 300 individuals (150 patients with COVID-19 as cases and 150 subjects who had not affected by COVID-19 as controls) was selected using convenience random sampling method to participate in the study.

### Participants

The study included individuals aged between 18 and 40 years who were admitted to an intensive care unit (ICU) with a confirmed diagnosis of COVID-19 through a PCR test. As for controls, 150 patients who were admitted in the same hospital were selected. The control group comprised individuals who tested negative for COVID-19 and exhibited no symptoms. They were referred to the hospital for different medical issues. Subjects who were following specific diets, such as vegetarian diets or weight loss diets, people who have followed a diet with a daily calorie of more than 3500 Kcal or lower than 1000 Kcal, individuals with previously diagnosed malignancy or inflammatory diseases, and participants unwilling to adhere to the study protocol were excluded from the study. If they were unable to answer the question impartially, we sought assistance from the immediate family members of the patients to ensure the completion of the questionnaires by the participants.

### Disease severity

The COVID-19's severity in hospitalized patients is classified into three stages. Stage I, known as the early stages of infection, is characterized by stable vital signs such as blood pressure, pulse, and respiration rate. The oxygen saturation level (SpO2) is equal to or greater than 93% at this stage. Stage II, known as the respiratory phase, is further divided into severe and moderate phases. In the moderate respiratory phase, the SpO2 level ranges from 90 to 93%. The severe respiratory phase is marked by a rapid progression of respiratory symptoms, including worsened dyspnea, tachypnea (pulse rate (RR) > 30), SpO2 levels below 90%, partial pressure of oxygen in arterial blood (PaO2) /fraction of inspired oxygen ≤ 300 mmHg, an increase in the alveolar-arterial gradient, and over 50% lung involvement observed in computed tomography (CT) scans. Stage III, referred to as the exacerbation phase of inflammation, is critical. At this stage, patients experience multiorgan failure, symptoms of shock, and respiratory failure (SpO2 ≤ 88%) despite non-invasive oxygen therapy.

### Outcomes assessment

Baseline questionnaires, which consisted of information on disease severity, chest CT findings, medical history, laboratory tests, demographic details, and duration of hospitalization, were completed and obtained from files and documents. Blood samples and CT scans were taken within 24 h of admission. Relevant information was collected and extracted from files and documents. Patients' contact information was also obtained from the files. Upon admission, the patients' height and weight were measured. The body mass index (BMI) was determined by dividing the body weight (in kilograms) by the square of the height (in square meters).

### Dietary intake

The participants' typical dietary intake was evaluated using a 138-item semi-quantitative FFQ administered via telephone by a dietitian. The FFQ included a detailed list of food items commonly consumed by Iranians, along with standard serving sizes for each item. Participants were requested to indicate the frequency of their consumption of a specific food item over the previous year, selecting from options such as monthly, weekly, or daily. Using standard household measures, the portion sizes of the consumed foods were computed in grams. For the Iranian population, this questionnaire has already been validated (31). Dietary data derived from the FFQ were used to calculate the adherence to Mediterranean Diet Score (MDS) and the Healthy Eating Index (HEI).

### HEI

The HEI consisted of twelve components in two principal categories; moderation and adequacy. There were nine components of adequacy, which included sea food and plant proteins, total protein foods, dairy, total vegetables, greens and beans, whole fruits, total fruits, whole grains, and fatty acids [polyunsaturated fatty acid (PUFA) + monounsaturated fatty acid (MUFA)/saturated fatty acid (SFA)]. Additionally, there were three components of moderation, which included empty calories, sodium, and refined grains. The HEI scoring standard was adjusted for energy (per 1000 kcal) for various food categories including sodium, refined grains, whole grains, plant proteins, seafood, meat, dairy products, peas, beans, all vegetables, total fruits, and whole fruits. Empty calories, which included added sugars and solid fats, were computed as a percentage of the total calorie intake. The point value for each component in the adequacy category ranged from 5 to 10, while those in the moderation category ranged from 10 to 20. In the category of adequacy, a higher intake led to a higher score. If no food from a specific component was consumed, that component was assigned a value of zero. Maximum points were awarded if the recommended amount or more was consumed. In the category of moderation, the maximum points were achieved by consuming the recommended quantity or less [32].

**Table 1** Demographic and anthropometric characteristics of study participants

| Variable | Case (*n* = 150) | Control (*n* = 150) | *p*. value |
|---|---|---|---|
| Age (years) | 46.07 ± 8.25 | 46.90 ± 7.86 | 0.375 |
| Gender* | | | |
| Male | 79 (52.7) | 74 (49.3) | 0.729 |
| Female | 71 (47.3) | 76 (50.7) | |
| Education (years) | 8.17 ± 4.51 | 8.17 ± 4.82 | 0.998 |
| Weight (Kg) | 74.89 ± 12.69 | 75.89 ± 13.66 | 0.512 |
| Height (cm) | 162.75 ± 9.54 | 162.95 ± 9.58 | 0.861 |
| BMI (kg/m2) | 28.24 ± 3.97 | 28.53 ± 4.17 | 0.536 |
| Hospitalization duration (day) | 8.50 ± 5.41 | 5.40 ± 0.83 | **< 0.001** |
| Disease severity* | | | |
| 1 | 96 (64.0) | - | - |
| 2 | 26 (17.3) | - | |
| 3 | 28 (18.7) | - | |

P.values based on Independent sample T-test

* P.values based on K-2 test

**Table 2** Biochemical variables of study participants

| Variable | Case (*n* = 150) | Control (*n* = 150) | *p*.value |
|---|---|---|---|
| CRP (mg/l)* | 7.15<br>4.00–84.00 | 6.00<br>1.70–9.60 | **< 0.001** |
| ESR (mm/h)* | Median: 38.50<br>Range: 4.00–84.00 | 9.00<br>2.00–16.00 | **< 0.001** |

P.values based on Independent sample T-test

* P.values based on Mann-Whitney

**Table 3** Dietary indices of study participants

| | Case (*n* = 150) | Control (*n* = 150) | *p*.value |
|---|---|---|---|
| Adequacy | | | |
| Fruits | 8.60 ± 3.43 | 8.52 ± 1.98 | 0.805 |
| Vegetables | 6.41 ± 3.22 | 8.67 ± 1.88 | < 0.001 |
| Grains | 7.32 ± 3.03 | 8.74 ± 1.78 | < 0.001 |
| Dairy | 5.61 ± 3.12 | 8.31 ± 2.36 | < 0.001 |
| Protein foods | 8.67 ± 3.41 | 8.85 ± 2.56 | 0.606 |
| Fats | 14.06 ± 5.71 | 13.17 ± 6.72 | 0.219 |
| Moderation | | | |
| Refined grains | 6.37 ± 4.77 | 9.01 ± 2.79 | < 0.001 |
| Sodium | 9.26 ± 5.12 | 10.15 ± 1.75 | 0.046 |
| Empty calories | 3.04 ± 1.85 | 3.71 ± 1.11 | 0.148 |
| HEI | 69.47 ± 15.54 | 79.13 ± 11.18 | < 0.001 |
| MDS | 3.91 ± 2.25 | 5.59 ± 1.65 | < 0.001 |

P.values based on Independent sample T-test

### MDS

The MDS index was calculated on a scale of 55 points. We considered ten key components of the Mediterranean diet, including full-fat dairy products, poultry, red meat, fish, olive oil, legumes, potatoes, vegetables, fruits, and unrefined cereals. Participants were assigned scores of 5, 4, 3, 2, 1, or 0 based on their reported daily consumption, weekly consumption, very frequent consumption, frequent consumption, rare consumption, and no consumption, respectively. Conversely, for foods that are not typically part of this diet, we assigned scores on a reverse scale [33].

### Biochemical variables

After a 12-hour fasting period, blood samples were taken from the antecubital vein to assess the concentration of C-reactive protein (CRP) using immunoturbidimetry. Also, the erythrocyte sedimentation rate (ESR) was tested.

### Statistical analysis

All analyses were conducted using version 20 of the SPSS software. At first, the Kolmogorov-Smirnov test was employed to assess the normality of the numerical data. The quantitative and normal data were reported as mean ± standard deviation (SD). Further, qualitative and categorical variables were shown as frequency (percent). The variables between the control and case groups were compared using the chi-square, Mann-Whitney, and independent sample T-test. The Spearman correlation test was used to assess the relationship between study variables and dietary indices. Age, sex, education level, weight, and BMI were consider as the confounders in the analysis. The significance level for all analyzes was considered $p < 0.05$.

## Results

The current case-control study was conducted on 150 hospitalized patients with covid-19 (case) and 150 individuals without the history of covid-19 (control). Demographic and anthropometric characteristics of the study participants were shown in Table 1. As seen, the mean ± SD of the participants' age in the case and control groups were 46.07 ± 8.25 and 46.90 ± 7.86 years that had not any significant differences. Further, the BMI was not significantly differed among two study groups. Most of the case participants (64.0%) were in the first level of disease severity. The hospitalization duration of case individuals was significantly higher than control group ($p < 0.001$). Serum levels of inflammatory markers were shown in Table 2. The inflammatory markers including CRP and ESR levels had significant differences between the groups ($p < 0.001$), as case group had higher levels of ESR and CRP. The HEI and MDS indices are shown in Table 3. Furthermore, the adequacy and moderation factors are separately expressed in Table 3. Both the HEI and MDS of case group was significantly lower than control group ($p < 0.001$). Table 4 has shown the CRP and ESR levels according to the various categories of HEI and MDS. As shown, in all the categories both the inflammatory markers were significantly higher in case compared to the control group ($P < 0.001$).

**Table 4** Serum inflammatory indices in HEI and MDS categories among study participants

| Variables | HEI | | | | | | MDS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | < 61 | | 62–80 | | > 81 | | < 3 | | 4–6 | | > 7 | |
| | Case (*n* = 38) | Control (*n* = 9) | Case (*n* = 76) | Control (*n* = 72) | Case (*n* = 36) | Control (*n* = 69) | Case (*n* = 86) | Control (*n* = 4) | Case (*n* = 34) | Control (*n* = 85) | Case (*n* = 30) | Control (*n* = 61) |
| CRP | 6.59 ± 2.01 | 5.02 ± 2.06 | 6.66 ± 1.39 | 5.51 ± 1.91 | 6.51 ± 1.69 | 5.84 ± 1.90 | 6.55 ± 1.57 | 4.30 ± 1.96 | 6.81 ± 1.40 | 5.69 ± 2.00 | 6.55 ± 2.03 | 5.64 ± 1.78 |
| ESR | 33.31 ± 24.22 | 7.89 ± 5.18 | 41.30 ± 25.60 | 8.43 ± 4.33 | 41.36 ± 22.60 | 9.38 ± 4.54 | 45.20 ± 24.57 | 9.72 ± 4.60 | 31.38 ± 22.02 | 9.72 ± 4.60 | 31.33 ± 23.66 | 7.72 ± 4.12 |

Both the CRP and ESR levels were significantly differed between case and control groups ($P < 0.001$)

There was a moderate negatively relationship between MDS and hospitalization duration ($R$=-0.209, $p<0.001$) and serum ESR level ($R$=-0.420, $P<0.001$). Further, hospitalization duration was associated with HEI levels ($R$=-0.124, $P<0.05$). A weak negative relationship was also seen between ESR level and HEI ($R$=-0.13, $P$=0.017). A weak negative relationship was shown between moderation and CRP ($R$=-0.158, $P$=0.006) (Table 5).

## Discussion

The results of this study showed that both the HEI and MDS in COVID-19 patients were significantly lower than control group. Further, serum inflammatory markers including CRP and ESR levels were significantly higher in case than control group. There was a weak negatively association between ESR and both HEI and MDS. Furthermore, higher MDS and HEI were correlated with lower hospitalization duration. The diet moderation was weakly correlated with ESR and CRP.

Higher dietary indices reflect consuming of more healthy food items including vegetables, fruits, fish, and whole grains have many phytochemical substances that can improve immune responses, and also may reduce the progression of respiratory infection symptoms that were seen among patients with COVID-19 [21–23]. Nguyen et al. (2021) showed that persons with higher Healthy Eating Score (HES) levels or being physically active were at a lower risk of COVID 19 infection in comparison to those with low HES or physical inactivity [20]. Previous studies expressed that special nutrients such as micro nutrients (iron, zinc, copper, selenium), vitamins (A, B6, B12, C, D, and E, and folate), amino acids, omega-3 fatty acids (EPA and DHA) and phytochemical substances such as polyphenols have important roles in the functioning of the immune system against bacteria and virus and release of cytokines. Diets based on plants are rich in whole grains, legumes, vegetables, fruits, seeds and low in meat intake. Therefore, these foods have a high dose of nutrients and it may explain some of these effects [24–26]. Also, plant foods have protease inhibitors like trypsin and trypsin-chymotrypsin inhibitors, which are able to prevent SARS-CoV- 2 from binding to human cells [27]. Also, fish is excellent source of omega-3 fatty acids such as EPA and DHA and vitamin D and selenium. It seems that fish is effective in preventing and treating COVID-19 due to the presence of omega-3 fatty acids and vitamins A and D. In a research by Shiri et al., the combined effect of omega-9 fatty acid, vitamins A and D on the immune system of mice showed that the combination of these three nutrients significantly increases the secretion of inflammatory cytokines. In addition, protein D1, which is a lipid mediator derived from omega-3, it can significantly reduce the multiplication of the influenza virus [28–31].

**Table 5** Association of MDS, HEI, Moderation, and adequacy of the diet with study variables

| | MDS | | HEI | | Moderation | | Adequacy | |
|---|---|---|---|---|---|---|---|---|
| Variable | R | *P* | R | *P* | R | *P* | R | *P* |
| Hospitalization duration | -0.209 | **< 0.001** | -0.124 | **0.031** | -0.038 | 0.511 | -0.116 | **0.045** |
| Disease severity | 0.034 | 0.676 | 0.033 | 0.688 | 0.086 | 0.297 | -0.017 | 0.841 |
| ESR | -0.420 | **< 0.001** | -0.138 | **0.017** | -0.190 | **0.001** | -0.060 | 0.300 |
| CRP | -0.112 | 0.052 | -0.086 | 0.136 | -0.158 | **0.006** | -0.020 | 0.735 |

Age, sex, education level, weight, and BMI were consider as the confounders in the analysis

Although there was not any association between dietary scores and disease severity in this study, MDS and HEI were negatively correlated with hospitalization duration. Merino et al. (2021) showed that healthy plant foods were correlated with less risk of infection and severity of COVID-19 [18]. Hegazy et al. (2023) demonstrated that healthier nutrition and physical activity correlated with reduced COVID-19 disease severity [19]. The result of the studies indicated that healthy diets by numerous mechanisms involved in reduction of the risk of COVID-19 infection and hospitalization such as improving the immune system by promoting of antibody production, proliferation of lymphocytes and decreasing of oxidative stress [29].

There was a negatively association between ESR and both HEI and MDS. Previous studies have also shown an inverse relationship between healthy diets and inflammatory indicators [36, 37]. Mediterranean diet has high amounts of trace elements such as Fe, Cu, Zn, Ca, and Mg that are contributed to lower inflammatory response. Furthermore, salt content of this diet is lower than unhealthy diets such as western diets that causes hyperosmotic stress and induce the release of proinflammatory cytokines. The anti-inflammation effects of polyphenols that are high in healthy diets are another cause of lower inflammatory markers [34]. The polyphenols have diverse biochemical structures and are considered as the functional foods. Recent studies have shown that some of the polyphenol compounds are associated with higher secretion of adiponectin and AMPK activation, as well as inhibition of NF-κB activation that results to diminished adipogenesis and adipose inflammation [34].

Finally, it appears that healthy eating habits is a main factor related to increasing immune-protective and immune-regulatory activity against to COVID-19 disease severity.

The strength of this case-control study was its appropriate sample size. Further, the study had some limitation that should be noted. First, the social, psychological, and physical activity indices of the patients were not measured. Second, there was a small sample size in second and third groups of disease severity. Third, the other inflammatory factors were not measured due to the budget constraints. Future studies with a higher sample size and a wider range of COVID-19 severity may provide more accurate results.

## Conclusions

It is concluded that patients with COVD-19 have experienced more inflammatory diets compared to control group, which were assessed by lower MDS and HEI among them. A healthy diet with high levels of HEI and MDS were correlated with lower serum ESR status and hospitalization duration among patients with COVID-19.

**Acknowledgements**

This study was supported by Sabzevar University of Medical sciences, Sabzevar, Iran. The authors thank the staff of 29 Bahman Hospital in Tabriz city for their valuable assistance; the authors also gratefully acknowledge the co-operation of the participating patients, without whom this investigation would not have been possible.

**Author contributions**

RM: Data collection, manuscript writing. SR: Data collection, manuscript writing. SSY: Data analysis. AK: Project development, manuscript writing. EF: Data analysis, manuscript editing.

**Funding**

This research was funded by Sabzevar University of Medical Sciences.

**Data availability**

The data that support the findings of this study will be available following a reasonable request from corresponding author.

## Declarations

**Ethics approval and consent to participate**

The study protocol was approved by the Medical Ethics Committee of the Sabzevar University of Medical Sciences, according to the Declaration of Helsinki (approval number (IR.MEDSAB.REC.1401.001). All participants provided signed informed consent.

**Competing interests**

The authors declare no competing interests.

Received: 14 June 2024 / Accepted: 17 December 2024
Published online: 30 December 2024

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