Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2024; 9(4): 702-711 Website: jnfs.ssu.ac.ir

Relationship between Diet-Related Inflammation and Hospitalization Risk and Disease Severity in Patients with COVID-19

Zahra Yari; PhD[*1], Samira Ebrahimof; PhD[1], Samira Soltanieh; MSc[2], Marieh Salavatizadeh; MSc[2], Sara Karimi; MSc[2], Sussan K. Ardestani; PhD[3], Mohammadreza Salehi; PhD[4], Soodeh Razeghi Jahromi; PhD[2], Tooba Ghazanfari; PhD[3] & Azita Hekmatdoost; MD, PhD[2]

[1] Department of Nutrition Research, National Nutrition and Food Technology Research Institute and Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2] Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology, Research Institute Shahid Beheshti University of Medical Science, Tehran, Iran; [3] Department of Immunology, Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran; [4] Department of Infectious Diseases, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

ORIGINAL ARTICLE

Article history:
Received: 7 Jan 2023
Revised: 26 Feb 2023
Accepted:29 Feb 2023

Corresponding author:
zahrayari_nut@yahoo.com
West Arghavan St. Farahzadi Blvd., Sharake Qods, Tehran, Iran.

Postal code: 1981619573
Tel: + 98 21 22357484

Keywords:
COVID-19; Inflammation; Diet; Infections; Biomarkers.

ABSTRACT

Background: Increased serum concentrations of inflammatory biomarkers in patients indicate a strong association between COVID-19 and inflammation. However, the association between diet-related inflammation and COVID-19 has been less investigated. The aim of this study is to investigate whether the inflammatory scores of the diet are associated with the severity of COVID-19 disease and the probability of hospitalization of patients. **Methods:** The authors conducted a cross-sectional study involving 141 patients with COVID-19. The empirical dietary inflammatory pattern (EDIP) and dietary inflammation scores (DIS) were calculated based on a 147-item semi-quantitative food frequency questionnaire. The association between serum levels of inflammatory biomarkers and diet-related inflammation was also investigated. **Results:** 74 inpatients and 87 outpatients participated in this study. Higher DIS scores were significantly associated with an increased risk of COVID-related hospitalization (Tertile3 vs. tertile1: OR = 3·62; 95 % CI 1·43 to 9·14, *P*=0·008 after fully adjustment). This association with EDIP was also observed, but it was not significant. **Conclusion:** The data from this provide evidence that a pro-inflammatory diet was associated with higher risk of hospitalization due to high severity of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19), a respiratory tract and systemic disease, was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. It was originally caused by the infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, although several new variants of SARS-CoV-2 have emerged since then (Chen *et al.*, 2020).

The presence of comorbidities, including obesity, type 2 diabetes, cardiovascular disease, hypertension, and chronic lung, kidney and liver

This paper should be cited as: Yari Z, Ebrahimof S, Soltanieh S, Salavatizadeh M, Karimi S, K. Ardestani S, Salehi MR, et al. ***Relationship between Diet-Related Inflammation and Hospitalization Risk and Disease Severity in Patients with COVID-19.*** *Journal of Nutrition and Food Security (JNFS)*, 2024; 9(4): 702-711.

[DOI: 10.18502/jnfs.v9i4.16899]

diseases exacerbates the severity of COVID-19 disease and its mortality (Yang *et al.*, 2020). In other words, these patients are not only likely to develop COVID-19 but also have a poor prognosis (Yang *et al.*, 2020). The etiology of these conditions mainly stems from poor nutrition and unhealthy lifestyle. Food insecurity has also been shown to approximately increase the risk of hospitalization due to COVID-19 by a factor of 4 (Ariya *et al.*, 2021). There is also no doubt that nutritional factors play a key role in both innate and adaptive immunity (Calder *et al.*, 2020). Among various factors promoting the inflammatory status of COVID-19, dietary components and intakes appear to play a substantial role, as they largely contribute to the onset of different chronic diseases (Terán, 2019). Induction of systemic inflammation and increase in inflammatory markers following an unhealthy diet (Casas *et al.*, 2014), on the one hand, and previous reports linking diet to COVID-19-like infectious diseases, such as influenza, on the other hand, support this hypothesis (Charland *et al.*, 2013).

Inflammation is an undeniable component of COVID-19 which is associated with increased synthesis and activation of inflammatory cytokines and acute phase reactants. The severity of the disease and lethality in COVID-19 are strongly associated with inflammation (Del Valle *et al.*, 2020). Interleukin-6 (IL-6) is one of the crucial elements in the pathogenesis of lung diseases that induces CRP expression in hepatocyte as a part of acute phase response (Del Valle *et al.*, 2020). Evidence has shown the association of pro-inflammatory and/or anti-inflammatory diets and dietary components with chronic diseases (Casas *et al.*, 2014). For example, it has been explicitly stated in studies that consumption of fish, vegetables , fruits, and green tea is associated with reduced inflammation, and consumption of simple sugars, and saturated and trans fats is associated with increased inflammation (Coe *et al.*, 2020). It is also reported that inflammatory markers are higher in African Americans than in white Americans, which may be due to differences in their dietary patterns (Bovell-Benjamin *et al.*, 2009). Correspondingly, it has been realized that compared to white Americans, COVID-19 has been found to be more prevalent in African Americans, and they suffer more from severe and lethal infections (Eiser, 2021).

On the basis of prior scientific evidence, two novel inflammatory indices, including empirical dietary inflammatory pattern (EDIP) and dietary inflammation scores (DIS), have been developed to evaluate the inflammation of dietary patterns (Byrd *et al.*, 2019, Tabung *et al.*, 2016). The goal of EDIP and DIS are to create an overall score to analyze the inflammatory potential of whole diets defined using food groups. Examining dietary patterns is more valuable than individual food components and can describe the usual consumption of foods in common diets (Willett and Stampfer, 2013).

Understanding the relationship between diet and COVID-19 can help emphasize the importance of nutrition in viral and infectious diseases. The current study aims to assess the association of DIS and EDIP with severity of COVID-19 and the risk of hospitalization due to disease.

Materials and Methods

Participants

The researchers carried out a COVID-19 case–control study on 74 inpatients and 87 outpatients evaluating the associations of diet-induced inflammation with the severity of COVID-19 and its risk of hospitalization. Hospitalized patients were enrolled via simple consecutive method from Imam Khomeini referral hospital in Tehran, Iran. Outpatients were enrolled from Simorgh clinical laboratory. The methodology of the sampling has been described comprehensively elsewhere (Ghazanfari *et al.*, 2021).

Testing positive PCR COVID-19 was the inclusion criteria, and patients with diabetes, hypertension, kidney disease, cancer, and cardiovascular diseases were excluded. Adherence to special diets over the past year, pregnancy, and lactation were also other exclusion criteria. Patients who were hospitalized, except in the Intensive Care Unit, and needed non- invasive

[DOI: 10.18502/jnfs.v9i4.16899]

respiratory support or receiving antibiotics concurrently with oxygen support were considered as inpatient group. Other patients with COVID-19 infection which was not severe enough to require hospitalization and were treated at home were included in the study as an outpatient group. Since this study was conducted at the beginning of COVID-19 pandemic, the patients only received normal saline, common cold medicines, and antibiotics. This study was part of project No. IR.NIMAD.REC.1399.041 from national institute for medical research development entitled "Immunological aspects of COVID-19 in selected provinces of Iran.

Dietary intake assessment

A valid and reliable 147-item semi-quantitative food frequency questionnaire (FFQ) was used to assess dietary intake of patients. The validity and reliability of FFQ were described in detail previously. Frequency of daily, weekly, and monthly consumption of each food items during the past year was collected through face-to-face interviews by a skilled nutritionist. In addition, the participants were all new cases; therefore, diet intake before the infection was assessed. After converting household measures of consumed foods to grams, the United States Department of Agriculture (USDA) food composition table (FCT) was used to calculate energy and nutrient contents. An Iranian FCT was also used for local food items.

Inflammatory scores calculation

Using dietary data derived from FFQ, empirical dietary inflammatory pattern (EDIP) and dietary inflammation scores (DIS) were determined based on previous studies (Byrd *et al.*, 2019, Tabung *et al.*, 2016). Higher total scores for each index indicated that the diet was more inflammatory.

Instead of 19 components, 18 food groups were used to calculate DIS because there was no information on supplementation intakes. These components included leafy green and cruciferous vegetables, refined grains, legumes, and starchy vegetables, tomatoes, apples and berries, deep yellow or orange vegetables and fruit, other vegetables, other fruits, and real fruit juices, added sugars, red and organ meats, processed meats, fish, poultry, high-fat dairy, low-fat dairy and tea, nuts, and other fats. Food groups were summed after standardization (to a mean of zero and SD of 1) to calculate DIS score.

To calculate EDIP, 15 food groups were used instead of 18 main components. One of the excluded components was alcoholic drinks. The exclusion of this group was due to religious considerations because the consumption of wine and beer is not common in Iran and maybe underreported. Also, low energy beverages were excluded from the questionnaire due to lack of access in Iran. Processed meat (sausage), red meat (beef, or lamb), organ meat (beef, calf, or chicken liver), other fish (canned tuna, or fish), refined grains (white bread, biscuit, white rice, pasta, or vermicelli), other vegetables (mixed vegetables, green pepper, cooked mushroom, eggplant, zucchini, or cucumber), high-energy and low-energy beverages (cola with sugar, carbonated beverages with sugar, fruit punch drinks), and tomatoes as pro-inflammatory group and tea, coffee, leafy green vegetables (cabbage, spinach, or lettuce), dark yellow vegetables (carrots, or squash), snacks (cracker, or potato chips), fruit juice (apple juice, cantaloupe juice, orange juice, or other fruit juice), and pizza as an anti-inflammatory group were considered in the EDIP calculation. After determining the daily intake of each food group, the values were multiplied by the proposed regression coefficients. After that, EDIP was calculated from all the weighted values. Finally, EDIP number was divided by 1000 to reduce the magnitude of the score.

Clinical parameters

A digital scale with an accuracy of 0.1 kg was used to measure weight and a mechanical, wall-mounted stadiometer, with an accuracy of 0.1 cm was used to measure height. Body mass index (BMI) was calculated by dividing weight (in kg) by height (m^2). Serum concentrations of interlukin-1 receptor antagonist (IL-1ra), interlukin-1 beta (IL-β), interlukin-6, C-reactive protein (CRP), white blood cells, and lymphocytes were

[DOI: 10.18502/jnfs.v9i4.16899]

measured.

Ethical considerations

The Ethical Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.NNFTRI.REC.1399.046) approved the study protocol in accordance with the Declaration of Helsinki. All the patients signed an informed consent form and the aims and procedures were explained to them.

Data analysis

Data analyses were conducted using the Statistical Package for Social Sciences (version 20.0; SPSS Inc., Chicago, IL). The level of statistical significance was considered $P<0.05$. Kolmogorov–Smirnov analysis was used to evaluate the normality of variables. For participants' baseline characteristics, mean±standard deviation or median (25–75) interquartile range (IQR) for continuous quantitative variables and percentage for qualitative variables were reported. Then, dietary intakes of DIS and EDIP components were compared across tertiles of DIS and EDIP using linear regression analysis. Logistic regression models were performed to estimate the odds ratio (ORs) and 95% confidence intervals (CIs) of COVID-related hospitalization risk across tertiles of the EDIP and DIS. The first tertile of each score was considered as the reference. The relationship between dietary inflammatory scores and the risk of hospitalization due to COVID-19 was evaluated as a crude model. Furthermore, potential confounders, including sex, age, BMI, and daily energy intake were adjusted in three separate models.

Results

Participants in the present study included 53% men and 47% women. The mean age of patients was 46.23±15.88 years, but hospitalized patients were significantly older than outpatients. The mean BMI of patients was 26.95±3.83 kg/m^2, and although BMI in hospitalized patients was higher than outpatients, this difference was not significant. Also, the median (IQR) of EDIP and DIS for all patients was 0.24 (0.08, 0.48) and 0.99 (-2.14, 3.34), respectively.

General characteristics, biochemical parameters, and dietary intakes of patients are summarized in **Table 1**. Compared with outpatients, inpatients had significantly lower intakes of energy and macronutrients. No significant difference was observed between the two groups in terms of biochemical parameters. Based on the median DIS and EDIP scores, outpatients had a healthier diet because DIS and EDIP scores were lower in outpatients compared to inpatients, although this difference was only statistically significant for DIS. **Table 2** presents the dietary intakes of EDIP and DIS components for study participants.

As shown in **Table 3**, about half of the patients in the third tertile (T3) of DIS were hospitalized, while in the first tertile (T1), only 19.6% were hospitalized, which was also statistically significant. However, similar results were not obtained for EDIP. The association of EDIP and DIS with the risk of hospitalization due to COVID-19 is shown in Table 3. First, this relationship was examined in a crude model that showed a higher odds of disease severity (hospitalization) in patients in the highest EDIP tertile (OR= 1.36; 95%CI: 0.56-3.13) and DIS tertile (OR= 3.62; 95%CI: 1.43-9.14) in comparison with those in the lowest tertile. But, P for trend was significant only for DIS (P=0.008) not for EDIP. In Model 3, after the adjustment of all potential confounding factors, the risk of disease severity in patients in the highest tertiles of DIS was 3.5 times higher than in patients in the lowest tertile. However, according to each of the three models, there was no statistically significant association between EDIP and risk of hospitalization due to COVID-19.

[DOI: 10.18502/jnfs.v9i4.16899]

Table 1. Basic characteristics of study participants based on COVID-19 severity.

Variable	In-patients (n=74) Moderate	Out-patients (n=87) Mild	P-value[a]
Sex			0.433
Male	30 (55)	45 (52)	
Female	24 (45)	42 (48)	
Age (y)	50.17 ± 15.45	43.91 ± 15.77	0.024
Weight (kg)	78.77 ± 13.45	76.59 ± 11.72	0.313
Height (cm)	1.68 ± 0.10	1.69 ± 0.10	0.567
Body mass index (kg/m^2)	27.66 ± 4.57	26.53 ± 3.26	0.089
Dietary intakes			
Energy (kcal/d)	1542.83 ± 592.03	1920.83 ± 648.07	0.001
Carbohydrate (g/day)	232.35 ± 95.30	290.16 ± 111.34	0.002
Protein (g/day)	51.50 ± 18.62	63.88 ± 23.29	0.001
Fat (g/day)	50.52 ± 25.94	63.71 ± 27.45	0.006
Biochemical Parameters			
WBC (10^3/µl)	6.34 ± 1.97	6.14 ± 2.24	0.638
Lymphocytes (%)	30.72 ± 10.44	32.62 ± 7.93	0.326
Neutrophils (%)	57.75 ± 11.11	50.09 ± 9.09	0.437
NLR	2.43 ± 2.07	1.96 ± 1.14	0.466
IL-1ra (pg/ml)	108.68 ± 413.54	52.45 ± 159.85	0.303
IL-1β (pg/ml)	11.55 ± 40.08	14.93 ± 52.89	0.728
IL-6 (pg/ml)	7.59 ± 15.22	11.38 ± 30.99	0.582
CRP (mg/l)	6.26 ± 7.53	4.96 ± 6.22	0.294
Inflammatory scores			
DIS	2.22 (-0.50, 4.00)	-0.4 (-3.87, 2.97)	0.002
EDIP	0.28 (0.09, 0.50)	0.19 (0.40, 0.45)	0.381

***WBC**: White blood cells; **NRL**: Neutrophil to lymphocyte ratio; **IL-1ra**: Interlukin-1 receptor antagonist; **IL-β**: Interlukin-1 beta; **IL-6**: Interlukin-6; **CRP**: C-reactive protein; **COVID IgM**: COVID immunoglobulin-M; **COVID IgG**: COVID immunoglobulin-G; **EDIP**: empirical dietary inflammatory pattern; **DIS**: dietary inflammation scores; [a:] Independent t-test and chi-square tests were used for quantitative and qualitative data, respectively. Data are presented as mean ± SD for continuous variable and number (percent) for categorical variables. EDIP and DIS are reported as median (IQR)*

Table 2. The intakes of empirical dietary inflammatory pattern and dietary inflammatory score components in the study population.

Variable	Tertiles			P-value
EDIP component	T1	T2	T3	
	0.04 (-0.03, 0.08)	0.23 (0.18, 0.3)	0.55 (0.46, 0.7)	
Processed meat (serving/d)	0 (0-0)	0 (0-01)	0 (0-2)	0.002
Red meat (serving/d)	0.04 (0.02-0.06)	0.04 (0.03-0.08)	0.05 (0.03-0.08)	0.370
Organ meat (serving/d)	0 (0-0.01)	0 (0-0.01)	0.01 (0-0.02)	0.192
Other fish (serving/d)	0.03 (0-0.08)	0.04 (0.02-0.07)	0.05 (0.03-0.13)	0.015
Other vegetables (serving/d)	0.89 (0.47-1.48)	1.85 (1.07-2.56)	2.94 (1.66-4.23)	<0.001
Refined grains (serving/d)	1.31 (0.86-1.79)	1.5 (1.07-2.27)	2.3 (1.1-5.16)	0.002
High-energy beverages (serving/d)	0 (0-0.03)	0.03 (0-0.07)	0.03 (0-0.23)	0.039
Tomatoes (serving/d)	0.32 (0.16-0.48)	0.48 (0.16-0.53)	1.14 (0.36-1.14)	<0.001
Tea (serving/d)	3.12 (2.08-5.2)	2.08 (1.04-3.12)	2.08 (1.04-3.12)	<0.001
Coffee (serving/d)	0 (0-0.04)	0 (0-0.2)	0 (0-0.2)	0.279
Dark yellow vegetables (serving/d)	0.09 (0.01-0.23)	0.2 (0.06-0.31)	0.15 (0.04-0.27)	0.137
Leafy green vegetables (serving/d)	0.42 (0.16-0.88)	0.38 (0.13-0.94)	0.43 (0.22-1.1)	0.706

[DOI: 10.18502/jnfs.v9i4.16899]

Snacks (serving/d)	0 (0-0.08)	0 (0-0.2)	0.05 (0-0.21)	0.197
Fruit juice (serving/d)	0 (0-0.04)	0 (0- 0)	0 (0-0.12)	0.205
Pizza (serving/d)	0.01 (0-0.03)	0.01 (0-0.03)	0.01 (0-0.02)	0.825
DIS component	-4.07 (-6.6, -2.15)	0.98 (-0.4, 2.17)	4.25 (3.3, 5.58)	
Leafy greens and Cruciferous vegetables (g/d)	51.64 (21.43-75.71)	20.19 (10.14-34.17)	9.43 (2.16-20.43)	<0.001
Tomatoes (g/d)	140 (60.45-140.15)	60 (30.28-140)	20 (9.33-50.28)	<0.001
Apples and berries (g/d)	200.21 (114.55-258.39)	192.57 (66.46-234.33)	58.74 (31.43-87.84)	<0.001
Deep yellow or orange Vegetables and fruit (g/d)	196.64 (88.28-285.68)	81.82 (21.8-126.88)	61.09 (34.33-123)	<0.001
Other fruits and real fruit juices (g/d)	560.64 (321.8-836.71)	357.84 (218.01-488.96)	268.02 (137.45-429.74)	<0.001
Other vegetables (g/d)	247.26 (187.68-315.03)	153.13 (109.2-214.47)	92.08 (66.91-142.93)	<0.001
Legumes (g/d)	17.19 (8.14-36.46)	10.68 (4.33-15.49)	6.36 (3.23-9)	<0.001
Fish (g/d)	6.87 (3.37-14.45)	3.37 (1.13-10.3)	3.37 (0-4.36)	0.018
Poultry (g/d)	24.28 (12.14-36.43)	24.29 (12.14-33.4)	24.2 (12.1 - 25)	0.022
Red and organ meats (g/d)	32.74 (26.7-51.9)	31.4 (21.9-40.4)	28.47 (20.3-37.5)	0.041
Processed meats (g/d)	0 (0-2.7)	0 (0-2)	0 (0-2)	0.409
Added sugars (g/d)	21.27 (13.27-62.66)	16 (5.31-57.47)	9.7 (2.02-27.5)	0.484
High-fat dairy (g/d)	12.03 (0.56-172.5)	1.5 (0-12.12)	1 (0-29.07)	0.007
Low-fat dairy (g/d)	117.14 (66.07-294.28)	238.67 (79.64-326.21)	131.07 (43.6-313.57)	0.674
Coffee and tea (g/d)	750 (390-1000)	535 (500-962.5)	500 (250-750)	0.096
Nuts (g/d)	10.82 (5.95-28.55)	3.55 (1.89-10.55)	3.55 (0.8-8.87)	<0.001
Other fats (g/d)	14.33 (9-32.8)	9.75 (6-27.73)	16.28 (7.23-37.14)	0.081
Refined grains and Starchy vegetables (g/d)	308.46 (207.38-365.87)	285.64 (187.81-346.73)	291.28 (187.38-363.11)	0.357

Data are presented as median (25–75 interquartile range); Linear regression analysis was used to test the trends of dietary components across tertiles of EDIP and DIS; ***EDIP****: empirical dietary inflammatory pattern;* ***DIS****: dietary inflammation scores.*

Table 3. Odds ratio (95% CI) COVID-19-associated hospitalization risk according to tertiles of inflammatory indices

Variable	Tertiles of scores			P_{trend}
	T1	T2	T3	
EDIP				
Median score	0.04 (-0.03, 0.08)	0.23 (0.18, 0.3)	0.55 (0.46, 0.7)	
In patients (%)	33.3	38.1	40.4	0.749
Model 1	1 (ref)	1.05 (0.46 – 2.42)	1.36 (0.56-3.13)	0.478
Model 2	1 (ref)	0.91 (0.38-2.16)	1.45 (0.60-3.5)	0.408
Model 3	1 (ref)	0.83 (0.33-2.25)	0.86 (0.32-2.25)	0.782
DIS				
Median score	-4.07 (-6.6, -2.15)	0.98 (-0.4, 2.17)	4.25 (3.3, 5.58)	
In patients (%)	19.6	40.8	46.8	0.009
Model 1	1 (ref)	1.04 (0.46-2.3)	3.62 (1.43-9.14)	0.008
Model 2	1 (ref)	1.18 (0.51-2.74)	4.93 (1.78-13.3)	0.002
Model 3	1 (ref)	1.1 (0.46-2.65)	3.52 (1.17-10.55)	0.033

EDIP*: Empirical dietary inflammatory pattern;* ***DIS****: Dietary inflammation scores;* ***Model 1****: Crude;* ***Model 2****: Adjustment for age, sex;* ***Model 3****: Adjustment for age, sex, BMI, energy intake; Logistic regression models were used to calculate the odds ratio (ORs) and 95% confidence intervals (CIs); P-value <0.05 was considered as significant.*

Discussion

In this cross-sectional study among patients with COVID-19 assessing the relationship between diet-induced inflammation and disease severity, the authors found that lower scores of DIS and EDIP were associated with lower risk of hospitalization due to COVID-19 infection. According to the findings of the present study, closer adherence to a

[DOI: 10.18502/jnfs.v9i4.16899]

pro-inflammatory diet with higher scores of DIS was associated with a higher risk of COVID-associated hospitalization, while no significant association was found between EDIP score and the risk of hospitalization due to COVID-19 infection. To the best of our knowledge, the association between DIS and EDIP and the risk of hospitalization due to COVID-19 infection has not been published previously.

Previously, DIS and EDIP have been shown to be associated with a reduced risk of nutrition-related diseases, including obesity, diabetes, and metabolic syndrome (Farhadnejad *et al.*, 2021, Teymoori *et al.*, 2021). On the other hand, a recent risk assessment study suggested that a 10% reduction in the prevalence of nutrition-related diseases such as obesity and type 2 diabetes prevented from about 11% hospitalization due to COVID-19 (O'hearn *et al.*, 2021).

Although a variety of factors such as genetic predisposition, obesity, and lifestyle determine one's inflammatory status, none is likely to be more important than the role of nutrition (Calder *et al.*, 2020). Diet plays a fundamental role in these poor metabolic health conditions, and accordingly, can affect the risk and severity of COVID-19. Therefore, the hypothesis of this study was that inflammatory score of diet is associated with the risk of hospitalization and the severity of COVID-19 disease.

DIS and EDIP are data-driven scores of dietary inflammation that represented the contribution of diet to being in an inflammatory state, and consequently, the development of diseases (Byrd *et al.*, 2019, Tabung *et al.*, 2016). These findings were in line with preliminary evidence showing that healthier diet was associated with a reduced burden of infectious diseases (Calder, 2020). In this regard, it was shown that adherence to a plant-based diet, which was considered an anti-inflammatory diet, was associated with a 73% and 59% lower risks of moderate-to-severe COVID-19-like infections, respectively (Kim *et al.*, 2021). Several studies suggested the role of healthy diet patterns in boosting the immune response, and thus, reducing the incidence or course of COVID-19 disease (Calder, 2020, Zabetakis *et al.*, 2020). However, despite extensive research into identifying nutritional strategies to reduce the risk of COVID-19 infection, no has not yet reported an association between dietary inflammatory pattern and COVID-19 severity.

EDIP focused primarily on that part of diet that appears to have the most positive correlation with inflammatory markers. The effect of the main anti-inflammatory contributors of the EDIP in this study was reduced due to religious considerations and under-reporting of alcohol consumption, and coffee consumption was also very low. Therefore, the participants were ranked in a narrow range of scores so the comparison of participants at different EDIP levels was limited. Unlike EDIP index, DIS showed a significant association with the risk of hospitalization. DIS is a dietary inflammatory index based on food groups that focuses on a wide range of dietary foods. Consequently, providing a more realistic assessment of usual dietary intake, the development of an inflammatory state might be correlated with pathogenesis of COVID-19. Inflammation was also recognized to be a determining factor in the severity of the infection in infected subjects. This condition was well characterized by increased levels of circulating inflammatory markers and increased acute phase reactants, including tumor necrosis factor-α, interleukins, and C-reactive protein. The role of IL-6 has already been demonstrated in the pathogenesis of lung diseases such as respiratory distress syndrome. IL-6 also complicated and exacerbated inflammatory status by inducing CRP expression in hepatocytes (Gudowska-Sawczuk *et al.*, 2018).

Part of the results of this study were in line with the study by Charland (Charland *et al.*, 2013). In this study, the relationship between low consumption of fruits and vegetables with more influenza hospitalization was pointed out. Interactions between nutrients and inflammation have been addressed in previous studies. Besides, the relationship between increasing the intake of fruits and vegetables with improving the inflammatory status was confirmed in various publications (Shivappa *et al.*, 2014, Wirth *et al.*,

[DOI: 10.18502/jnfs.v9i4.16899]

2016). Byrd et al also stated that diets containing higher inflammatory exposures, characterized by higher DIS scores, could be associated with increased diseases risk (Byrd *et al.*, 2019). In Moludi study (Moludi *et al.*, 2021) a significant association between Energy-Adjusted Dietary Inflammatory Index (E-DII) and incidence and the severity of COVID-19 was discovered. The findings of this study indicated that a higher score of the inflammatory diet was directly related to the severity of COVID-19 and greater risk of infection occurrence. This study found that higher E-DII (indicative of a pro-inflammatory diet) multifold the likelihood of contracting COVID-19 and its severity. So, compared to the patients in the first tertile, the risk of COVID-19 in the third tertile was 11.86 times higher. Furthermore, for each one unit increase in E-DII score, CRP and ESR levels increased by 1.40 and 1.02 units, respectively (Moludi *et al.*, 2021).

One of the potential mechanisms associated with diet and inflammation is the effects of diet on gut microbiome. The microbiome in turn affects the immune response, for instance, it can modify T-helper cell and T-regulatory cell (Singh *et al.*, 2017). Modulatory effects of certain dietary components such as micronutrients, antioxidants and essential fatty acids (α-linolenic acid, vitamins E, A and C; Zn, Se) on inflammation were also verified (Del Mar Bibiloni *et al.*, 2013). Another possible explanation could be epigenetic modifications in which diet affects the expression of immune-related genes, and therefore, can reduce or increase the severity of COVID-19 (Chlamydas *et al.*, 2021).

The findings should be interpreted in the light of several strengths and limitations. The main strengths were the following: it assessed the association of EDIP and DIS with the risk of COVID-19-related hospitalization for the first time. Moreover, dietary intakes were assessed by trained professionals using a valid and reliable food-frequency questionnaire during a face-to-face interview.

Several limitations of the current study should be noted. First, due to the cross-sectional design, the authors were not able to confirm the causal relationship between dietary inflammatory scores and COVID-19 severity or infer specific mechanisms. Second, it was not possible to modify all confounders due to unknown or unmeasured factors. Third, using FFQ was associated with measurement error as a potential bias. Fourth, three components of EDIP and one component of DIS were omitted in the calculation of scores. In addition, dietary inflammatory scores were not validated in Iranian population and its use is a potential concern. Using the USDA FCT rather than a complete Iranian FCT was the last limitation.

Conclusions

In conclusion, data provided evidence that diet-induced inflammation is associated with higher risk of hospitalization due to COVID-19 and more severe infection. To confirm and generalize these findings, further clinical research needs to be done on how dietary modification may impact the severity and duration of COVID-19 and immunity response.

Conflict of interests

The authors declared no conflict of interests.

Funding

No funding was received for this study.

Authors' contributions

Yari Z and Hekmatdoost A designed the research; Soltanieh S, Salavatizadeh M, kaimi S, Ardestani SK and Razeghi Jahromi S conducted the research; Yari Z and Ebrahimof S analyzed data; Yari Z and Ghazanfari T wrote the paper. Yari Z and Hekmatdoost A had primary responsibility for final content. All the authors read and approved the final manuscript.

Acknowledgements

This study is related to the project No. IR.NIMAD.REC.1399.041 from national institute for medical research development entitled “Immunological aspects of COVID-19 in selected provinces of Iran.

References

Ariya M, et al. 2021. Food insecurity arises the likelihood of hospitalization in patients with

[DOI: 10.18502/jnfs.v9i4.16899]

COVID-19. *Scientific reports.* **11 (1)**: 1-9.

Bovell-Benjamin AC, Dawkin N, Pace RD & Shikany JM 2009. Use of focus groups to understand African-Americans' dietary practices: Implications for modifying a food frequency questionnaire. *Preventive medicine.* **48 (6)**: 549-554.

Byrd DA, et al. 2019. Development and validation of novel dietary and lifestyle inflammation scores. *Journal of nutrition.* **149 (12)**: 2206-2218.

Calder PC 2020. Nutrition, immunity and COVID-19. *BMJ nutrition, prevention & health.* **3 (1)**: 74.

Calder PC, Carr AC, Gombart AF & Eggersdorfer M 2020. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. *Nutrients.* **12 (4)**: 1181.

Casas R, Sacanella E & Estruch R 2014. The immune protective effect of the Mediterranean diet against chronic low-grade inflammatory diseases. *Endocrine, metabolic & immune disorders-drug targets* **14 (4)**: 245-254.

Charland KM, et al. 2013. Relationship between community prevalence of obesity and associated behavioral factors and community rates of influenza-related hospitalizations in the United States. *Influenza and other respiratory viruses.* **7 (5)**: 718-728.

Chen Y, Liu Q & Guo D 2020. Emerging coronaviruses: genome structure, replication, and pathogenesis. *Journal of medical virology.* **92 (4)**: 418-423.

Chlamydas S, Papavassiliou AG & Piperi C 2021. Epigenetic mechanisms regulating COVID-19 infection. *Epigenetics.* **16 (3)**: 263-270.

Coe CL, et al. 2020. Cultural and life style practices associated with low inflammatory physiology in Japanese adults. *Brain, behavior, and immunity.* **90**: 385-392.

Del Mar Bibiloni M, Maffeis C, Llompart I, Pons A & Tur J 2013. Dietary factors associated with subclinical inflammation among girls. *European journal of clinical nutrition.* **67 (12)**: 1264-1270.

Del Valle DM, et al. 2020. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nature medicine.* **26 (10)**: 1636-1643.

Eiser AR 2021. Could dietary factors reduce COVID-19 mortality rates? Moderating the inflammatory state. *Journal of alternative and complementary medicine.* **27 (2)**: 176-178.

Farhadnejad H, Parastouei K, Rostami H, Mirmiran P & Azizi F 2021. Dietary and lifestyle inflammatory scores are associated with increased risk of metabolic syndrome in Iranian adults. *Diabetology & metabolic syndrome.* **13 (1)**: 1-10.

Ghazanfari T, et al. 2021. Interpretation of Hematological, Biochemical, and Immunological Findings of COVID-19 Disease: Biomarkers Associated with Severity and Mortality. *Iranian journal of allergy, asthma and immunology.* **20 (1)**: 46-66.

Gudowska-Sawczuk M, et al. 2018. Serum level of interleukin-6 (IL-6) and N-terminal propeptide of procollagen type I (PINP) in patients with liver diseases. *Scandinavian journal of clinical and laboratory investigation.* **78 (1-2)**: 125-130.

Kim H, et al. 2021. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case–control study in six countries. *BMJ nutrition, prevention & health.* bmjnph-2021-000272.

Moludi J, et al. 2021. The relationship between Dietary Inflammatory Index and disease severity and inflammatory status: a case–control study of COVID-19 patients. *British journal of nutrition.* 1-9.

O'hearn M, Liu J, Cudhea F, Micha R & Mozaffarian D 2021. Coronavirus disease 2019 hospitalizations attributable to cardiometabolic conditions in the United States: a comparative risk assessment analysis. *Journal of the American Heart Association.* **10 (5)**: e019259.

Shivappa N, et al. 2014. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public*

[DOI: 10.18502/jnfs.v9i4.16899]

health nutrition. **17 (8)**: 1825-1833.

Singh RK, et al. 2017. Influence of diet on the gut microbiome and implications for human health. *Journal of translational medicine.* **15 (1)**: 1-17.

Tabung FK, et al. 2016. Development and validation of an empirical dietary inflammatory index. *Journal of nutrition.* **146 (8)**: 1560-1570.

Terán G 2019. Relation between nutritional status, the outcome of infection and immune responses. Karolinska Institutet Sweden.

Teymoori F, et al. 2021. Dietary and lifestyle inflammatory scores and risk of incident diabetes: a prospective cohort among participants of Tehran lipid and glucose study. *BMC public health.* **21 (1)**: 1-12.

Willett WC & Stampfer MJ 2013. Current evidence on healthy eating. *Annual review of public health.* **34**: 77-95.

Wirth MD, et al. 2016. Anti-inflammatory Dietary Inflammatory Index scores are associated with healthier scores on other dietary indices. *Nutrition research.* **36 (3)**: 214-219.

Yang J, et al. 2020. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *International journal of infectious diseases.* **94**: 91-95.

Zabetakis I, Lordan R, Norton C & Tsoupras A 2020. COVID-19: the inflammation link and the role of nutrition in potential mitigation. *Nutrients.* **12 (5)**: 1466.

[DOI: 10.18502/jnfs.v9i4.16899]