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ORIGINAL ARTICLE

The Association between Body Mass Index and Probiotics Supplementation with Hospital Stay Duration and Symptoms among COVID-19 Iranian Patients

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ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) can cause a severe respiratory disease and systemic complications. The gut microbiota plays an important role in immune regulation, while obesity may worsen COVID-19 outcomes. This study investigated the interaction between body mass index (BMI) and probiotic supplementation on COVID-19 symptoms and length of hospital stay.

Methods: This cross-sectional study included 107 Iranian adults aged 20-60 years hospitalized with COVID-19 at Amir Alam Hospital, Tehran, Iran. Demographic characteristics, body composition, probiotic supplementation history, and COVID-19 symptoms were assessed using questionnaires and hospital records. Linear and binary logistic regression analyses were performed to evaluate associations and interactions.

Results: Probiotic consumption was negatively associated with lethargy (β=−3.09; 95%CI: −4.85, −1.32; p<0.01). BMI was positively associated with C-reactive protein (CRP) level (β=47.46; 95%CI: 5.24, 89.69; p=0.02). A correlation was observed between probiotic intake and lower BMI for duration of hospitalization (β=−3.28; 95%CI: −7.28, 0.00; p=0.05) and D-dimer level (β=−3.57; 95%CI: −31.35, 24.20; p=0.07). This association was also observed for diarrhea (OR=0.32; 95%CI: 0.01, 1.00; p=0.05) and stomachache (OR=0.43; 95%CI: 0.00, 1.45; p=0.09).

Conclusion: Probiotic consumption was associated with lower lethargy, while higher BMI was correlated with an increased CRP level. The observed interactions between probiotic intake and BMI for hospitalization duration, D-dimer, and gastrointestinal symptoms warrant further investigation in larger longitudinal and randomized controlled studies.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a recent coronavirus that was detected for the first time in Wuhan, China, in December 2019 (1). Iran was among the countries most severely affected by COVID-19, with approximately 6.7 million reported COVID-19 cases, ranking twelfth globally (2). The virus is associated with high rates of hospital admissions, respiratory failure, and mortality (1, 3). The most common symptoms of COVID-19 include fever, cough, tiredness, and loss of taste or smell, acute respiratory distress syndrome (ARDS), acute cardiac injury, acute renal injury and shock. Furthermore, the gastrointestinal symptoms including diarrhea, nausea and vomiting, have been frequently observed in COVID-19 patients (4).

Obesity impacts the immune system and may increase mortality from SARS-CoV-2 by exacerbating pneumonia and ARDS (5, 6). It was shown that obesity as a significant risk factor for severe COVID-19 progression, with higher body mass index (BMI) associated with increased rates of hospitalization, ICU admissions, and mortality. A systematic review and meta-analysis further confirmed that a BMI ≥30 kg/m^2 was associated with greater severity and prolonged duration of illness in COVID-19 patients. An imbalance in the intestinal microbial flora caused dysbiosis which was observed in some COVID-19 patients (7). ARDS may alter the intestinal microbiota. The gut serves as a central hub for immune function, containing approximately 70% of the body's immune cells (8). Probiotics, which are live microorganisms that provide health benefits when consumed in adequate amounts, play a key role in modulating the immune system including enhancing gut barrier integrity, increasing antimicrobial peptide production, and promoting the balance of beneficial microbes, while suppressing the growth of pathogenic bacteria. A growing body of research highlights the concept of the gut-lung axis, referring to the bidirectional interaction between gut microbiota and respiratory immune responses (9). Obesity alters gut microbiota composition which may increase endotoxemia and intestinal permeability. It can also elevate susceptibility to infections across mucosal surfaces by triggering pro-inflammatory immune reactions (10). A recent study in 2021, it was found that probiotic supplementation reduced upper respiratory tract infection symptoms in patients with a BMI ≥30 kg/m^2 (11).

While several studies have investigated the associations between BMI and COVID-19, probiotics supplementation and BMI and COVID-19 outcomes, no prior research has comprehensively examined the interaction between BMI and probiotic supplementation in relation to hospital stay duration (DH) and symptom severity among COVID-19 patients. This study aimed to fill this gap by evaluating the association between BMI and probiotics supplementation on COVID-19 DH and symptoms.

Materials and Methods

This cross-sectional study recruited 107 Iranian adults with COVID-19 who referred to Amir Alam Hospital in Tehran, Iran, between February and March 2020, using a random sampling method. The inclusion criteria were age between 20-60 years old, and the presence of COVID-19 symptoms including fever, chills, sore throat, tiredness, sneezing, hard breathing, chest pain and fatigue and other common symptoms. Data on symptoms were collected through a demographic questionnaire and verified against hospital records. COVID-19 infection was confirmed via reverse transcription polymerase chain reaction (RT-PCR) testing of nasopharyngeal and oropharyngeal samples, biochemical evaluation that included CRP and D-dimer.

As WHO interim guidance which is the Standard confirmation of acute SARS-CoV-2 infections, relies on the use of nucleic acid amplification tests (NAATs), including real-time reverse-transcription polymerase chain reaction (rRT-PCR), to identify distinct virus sequences, COVID-19 diagnosis was based on this guidance. The exclusion criteria were liver and kidney diseases, any rare viruses including HIV, and chemotherapy within the past month. DH was recorded as the number of days each participant stayed in the hospital. Criteria for discharge included clinical remission of respiratory symptoms, absence of fever for at least three days, significant improvement in both lungs on chest computed tomography (CT), and two consecutive negative throat-swab samples taken at least twenty-four hours apart. A well-trained nutritionist conducted all interviews and completed the questionnaires. The Ethical Committee of the Tehran University of Medical Sciences, Tehran, Iran approved this study (IR.TUMS.MEDICINE.REC.1399.433).

A questionnaire was used to collect data on age, sex, marital status, education, supplement intake history, family history of obesity, socioeconomic status, and job status. A Seca digital scale (Germany) with a precision of 0.1 kg was used to assess participants' body weight. Height was measured using a Seca 206 stadiometer (Germany) with a precision of 0.1 cm. BMI was also calculated as weight (kg) divided by height (m^2). The International Physical Activity Questionnaire (IPAQ) was used to assess

physical activity (PA) of participants. Discharge criteria included being medically stable, exhibiting improved respiratory symptoms, being afebrile for at least 24 hours without antipyretics medications (such as Tylenol, NSAIDs, etc.). Additionally, appropriate accommodations, transportation, and wrap-around services (including access to food, medications, clothing, toiletries, and basic necessities) were required to ensure safe isolation post discharge.

The data were analyzed using SPSS software (Version 21, Chicago, IL, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test (p>0.05). Continuous variables were reported as mean and standard deviation (SD) while categorical variables were presented as frequencies and percentages. Comparisons between groups were made using one-way ANOVA for continuous variables and chi-square tests for categorical variables. Analysis of covariance (ANCOVA) was used to adjust for potential confounders. Linear regression analysis was used to examine association between DH (days), recovery time (days), inflammatory markers including CRP (mg/mL) and D-dimer (ng/mL), and symptoms such as smell and taste, appetite and lethargy. Binary logistic regression analysis was used to assess association between smell, taste, appetite, and lethargy.

Generalized linear model (GLM) was conducted to assess the interaction between probiotics supplementation and BMI on DH, signs, and symptoms of COVID-19. Model 1 was adjusted for age, sex, educational level, BMI, and physical activity. Model 2 was adjusted for age, sex, educational level, BMI, physical activity, comorbidity, use of medication, and supplementation intake. In binary logistic regression; chest pain (No), headache (No), nose (No), vomiting (No), nausea (No), diarrhea (No), sore throat (No), stomach pain (No), joint pain (No), confusion (No), contusion (No), chills (NO), RDS (No) were considered as reference. For statistical analysis, confidence intervals (CIs) were calculated to provide a range of plausible values and to reflect the precision of the estimates. A p value <0.05 was considered statistically significant, and p values between 0.05 and 0.1 were interpreted as marginally significant.

Results

The study revealed that the mean (±SD) age, weight, and BMI were 46.21 (1.10) years, 86.75 (1.31) kg, and 29.36 (0.35) kg/m², respectively. The majority of participants were married (85%) and men (66%). The maximum duration of hospitalization was 17 days, and the maximum recovery time was 3 weeks. Probiotic supplementation was reported by 10 participants (9.5%). The association between BMI and COVID-19 signs, symptoms, and DH is presented in Table 1. There was a positive significant association between BMI and CRP (β=47.46; 95%CI=5.24, 89.69, p=0.02) in model 2 (after adjustment for age, sex, energy intake, BMI, physical activity, educational level, marital status, job status, underlying diseases, and medication use). Furthermore, a marginally significant positive association was observed between BMI and D-dimer levels (β=3.17; 95%CI=-4.12, 10.46, p=0.07).

Table 1: The association between BMI and hospitalization duration, COVID-19 signs and symptoms (N=107).

Variable		BMI	
		β (95% CI)	*P* value*
Hospitalization days			
DH (day)	Crude	0.24 (-0.98, 1.41)	0.68
	Model 1	0.28 (-0.88, 1.46)	0.63
	Model 2	0.02 (-1.15, 1.21)	0.96
Recovery time (day)	Crude	0.41 (-1.49, 2.32)	0.67
	Model 1	0.70 (-1.10, 2.51)	0.44
	Model 2	0.19 (-1.54, 1.92)	0.82
Signs			
CRP (mg/L)	Crude	39.60 (-2.79, 81.99)	0.06
	Model 1	42.43 (-0.21, 85.09)	0.05
	Model 2	47.46 (5.24, 89.69)	0.02
D-dimer (ng/mL)	Crude	1.78 (-5.13, 8.70)	0.61
	Model 1	2.83 (-4.45, 10.12)	0.44
	Model 2	3.17 (-4.12, 10.46)	0.07
Symptoms			
Smell	Crude	-0.94 (-2.36, 0.48)	0.19
	Model 1	-0.89 (-2.31, 0.52)	0.21
	Model 2	-0.85 (-2.27, 0.57)	0.24

Variable		BMI	
		β (95% CI)	*P* value*
Taste	Crude	-0.72 (2.14, 0.69)	0.31
	Model 1	-0.79 (-2.21, 0.62)	0.27
	Model 2	3.17 (-4.12, 10.46)	0.39
Appetite	Crude	-0.12 (-1.30, 1.05)	0.83
	Model 1	-0.19 (-1.36, 0.97)	0.74
	Model 2	-0.44 (-1.60, 0.71)	0.45
Lethargy	Crude	0.20 (-0.87, 1.28)	0.71
	Model 1	0.17 (-0.91, 1.25)	0.75
	Model 2	0.14 (-0.94, 1.23)	0.79
OR (95% CI)			
Chest pain	Crude	1.36 (0.78, 2.36)	0.26
	Model 1	0.61 (0.28, 1.36)	0.23
	Model 2	0.51 (0.22, 1.19)	0.12
Headache	Crude	0.70 (0.32,1.52)	0.37
	Model 1	0.77 (0.34,0.16)	0.51
	Model 2	0.95 (0.26,3.48)	0.95
Rhinitis	Crude	0.96 (0.44, 2.10)	0.93
	Model 1	0.99 (0.44, 2.23)	0.99
	Model 2	1.11 (0.46, 2.68)	0.80
Vomiting	Crude	0.01 (0.30, 3.33)	0.98
	Model 1	0.95 (0.26, 3.48)	0.94
	Model 2	0.95 (0.26, 0.34)	0.94
Nausea	Crude	0.89 (0.41, 1.93)	0.77
	Model 1	1.00 (0.44, 2.22)	0.99
	Model 2	0.83 (0.34, 2.05)	0.69
Diarrhea	Crude	0.63 (0.25, 1.58)	0.32
	Model 1	0.68 (0.26, 1.75)	0.42
	Model 2	0.44 (0.15, 1.33)	0.14
Sore throat	Crude	1.37 (0.60, 3.12)	0.44
	Model 1	1.32 (0.53, 63.11)	0.51
	Model 2	1.78 (0.70, 4.52)	0.22
Joint pain	Crude	0.44 (0.19, 1.00)	0.05
	Model 1	0.45 (0.19, 1.04)	0.06
	Model 2	0.44 (0.18, 1.06)	0.09
Stomachache	Crude	0.74 (0.26, 2.07)	0.57
	Model 1	0.77 (0.27, 2.19)	0.77
	Model 2	0.51 (0.22, 1.19)	0.12
Confusion	Crude	1.39 (0.60, 3.22)	0.43
	Model 1	1.36 (0.57, 3.22)	0.48
	Model 2	1.40 (0.57, 3.44)	0.46
Contusion	Crude	0.95 (0.44, 2.06)	0.91
	Model 1	1.02 (0.46, 2.24)	0.95
	Model 2	1.19 (0.51, 2.79)	0.67
Fever	Crude	1.12 (0.48, 2.65)	0.78
	Model 1	1.17 (0.49, 2.81)	0.71
	Model 2	1.03 (0.41, 2.62)	0.93
RDS	Crude	0.69 (0.27, 1.77)	0.44
	Model 1	0.72 (0.27, 1.91)	0.52
	Model 2	0.68 (0.25, 1.89)	0.46

BMI, Body mass index; DH, Duration of hospitalization; CI, Confidence interval; CRP, C-reactive protein; OR, Odds ratio; RDS, Respiratory distress syndrome. Model 1 was adjusted for age, sex, education level, BMI and physical activity. Model 2 was adjusted age, sex, education level, BMI, physical activity, comorbidity, use of medication, supplementation use. Biochemical factors (CRP) were reported as median. Data for continuous variables were obtained from linear regression and are presented as β and 95%CI. Data for categorical variables were obtained from binary regression and are reported as OR and 95%CI. Absence of signs and symptoms were considered as reference. Significant values are in bold. $p<0.05$ was considered statistically significant and $p=0.05$-0.07 was considered marginally significant.

Table 2 shows a significant negative association between probiotics and lethargy (β=-3.09; 95%CI=-4.85, -1.32; p<0.01) in model 2. However, no significant association was found between probiotic consumption and DH and recovery time (p>0.07). Furthermore, there was no significant association between supplement intake and levels of CRP and D-dimer (p>0.07). Table 3 demonstrates the correlation between probiotics supplementation and BMI for COVID-19 signs, symptoms, and DH. In model 2, a marginally significant negative interaction was found between probiotic intake and lower BMI for HD (β=-3.28; 95%CI=-7.28, 0.00; p=0.05) and D-dimer levels (β=-3.57; 95%CI=-31.35, 24.20; p=0.07). Additionally, a marginally significant interaction was noticed between probiotic intake and lower BMI for the reduced odds of diarrhea (OR=0.32; 95%CI=0.01, 1.00; p=0.05) and stomachache (OR=0.43; 95%CI=0.00, 1.45; p=0.09) in model 2.

Table 2: The association between probiotics intake and hospitalization duration, COVID-19 signs and symptoms (N=107).

Variable		Probiotics	
		β (95% CI)	***P* value***
Hospitalization days			
DH (day)	Crude	0.13 (-1.85, 2.12)	0.89
	Model 1	0.14 (-1.85, 2.14)	0.88
	Model 2	0.06 (-1.96, 2.10)	0.94
Recovery time (day)	Crude	-1.42 (-4.66, 1.81)	0.39
	Model 1	-1.42 (-4.48, 1.64)	0.36
	Model 2	-0.94 (-3.91, 2.01)	0.53
Signs			
CRP (mg/L)	Crude	-5.21 (-76.53, 66.10)	0.88
	Model 1	-8.37 (-77.60, 60.86)	0.81
	Model 2	15.62 (-53.62, 84.87)	0.65
D-dimer (ng/mL)	Crude	-1.57 (-13.69, 10.53)	0.79
	Model 1	-1.31 (-12.98, 10.34)	0.82
	Model 2	-3.40 (-15.51, 8.70)	0.58
Symptoms			
Smell	Crude	-0.48 (-2.93, 1.95)	0.69
	Model 1	-0.55 (-2.98, 1.87)	0.65
	Model 2	-0.04 (-2.49, 2.40)	0.96
Taste	Crude	0.03 (-2.39, 2.45)	0.98
	Model 1	-0.08 (-2.49, 2.33)	0.94
	Model 2	0.07 (-2.31, 2.46)	0.95
Appetite	Crude	-0.74 (-2.74, 1.25)	0.46
	Model 1	-0.73 (-2.71, 1.24)	0.46
	Model 2	-0.74 (-2.72, 1.23)	0.46
Lethargy	Crude	-2.82 (-4.59, -1.06)	<0.01
	Model 1	-2.82 (-4.58, -1.06)	<0.01
	Model 2	-3.09 (-4.85, -1.32)	<0.01
OR (95% CI)			
Chest pain	Crude	0.93 (0.25, 3.45)	0.92
	Model 1	0.87 (0.23, 3.31)	0.84
	Model 2	0.70 (0.17, 2.88)	0.62
Headache	Crude	0.93 (0.25, 3.45)	0.92
	Model 1	0.90 (0.23, 3.43)	0.88
	Model 2	0.51 (0.11, 2.29)	0.38
Rhinitis	Crude	1.43 (0.38, 5.29)	0.58
	Model 1	1.46 (0.38, 5.66)	0.57
	Model 2	1.23 (0.27, 5.54)	0.78
Vomiting	Crude	0.70 (0.08, 6.00)	0.74
	Model 1	0.88 (0.09, 8.21)	0.91
	Model 2	0.69 (0.06, 7.17)	0.75
Nausea	Crude	2.15 (0.57, 8.14)	0.25
	Model 1	2.46 (0.61, 9.83)	0.20
	Model 2	1.41 (0.30, 6.59)	0.65

Variable		Probiotics	
		β (95% CI)	*P* value*
Diarrhea	Crude	1.51 (0.35, 6.35)	0.57
	Model 1	1.74 (0.39, 7.77)	0.46
	Model 2	1.02 (0.20, 5.18)	0.97
Sore throat	Crude	0.88 (0.21, 3.65)	0.86
	Model 1	0.80 (0.18, 3.53)	0.77
	Model 2	0.87 (0.16, 4.49)	0.86
Joint pain	Crude	2.44 (0.49, 12.13)	0.27
	Model 1	2.53 (0.49, 12.85)	0.26
	Model 2	2.34 (0.43, 12.72)	0.32
Stomachache	Crude	0.00 (0.00, 0.00)	0.99
	Model 1	0.00 (0.00, 0.00)	0.99
	Model 2	0.00 (0.00, 0.00)	0.99
Confusion	Crude	0.00 (0.00, 0.00)	0.99
	Model 1	0.00 (0.00, 0.00)	0.99
	Model 2	0.00 (0.00, 0.00)	0.99
Contusion	Crude	2.01 (0.49, 8.25)	0.33
	Model 1	2.02 (0.48, 8.42)	0.33
	Model 2	1.91 (0.42, 8.71)	0.40
Fever	Crude	3.76 (0.45, 31.10)	0.21
	Model 1	3.85 (0.45, 32.41)	0.21
	Model 2	2.86 (0.30, 27.14)	0.35
RDS	Crude	0.88 (0.17, 4.46)	0.87
	Model 1	0.98 (0.18, 5.18)	0.98
	Model 2	0.77 (0.13, 4.30)	0.76

DH, Duration of hospitalization; CI, Confidence interval; CRP, C-reactive protein; OR, Odds ratio; RDS, Respiratory distress syndrome. Model 1 was adjusted for age, sex, education level, BMI, and physical activity. Model 2 was adjusted age, sex, education level, BMI, physical activity, comorbidity, use of medication, and supplementation use. Biochemical factors (CRP) were reported as median. Data for continuous variables were obtained from linear regression and are presented as β and 95%CI. Data for categorical variables were obtained from binary regression and are reported as OR and 95%CI. Not taking supplements and absence of signs and symptoms were considered as reference. Significant values are in bold. $p<0.05$ was considered statistically significant and $p=0.05$-0.07 was considered marginally significant.

Table 3. The interaction of BMI and probiotics intake with hospitalization duration, COVID-19 signs and symptoms (N=107).

Variables	Models	Probiotics intake * BMI	
		β (95% CI)	*P* value*
Hospitalization days			
DH (day)	Crude	-3.03 (-7.04, 0.96)	0.13
	Model 1	-3.14 (-7.18, 0.89)	0.12
	Model 2	-3.28 (-7.28, 0.00)	**0.05**
Recovery time (day)	Crude	-2.69 (-9.27, 3.87)	0.42
	Model 1	-2.53 (-8.66, 3.58)	0.41
	Model 2	-3.26 (-9.16, 2.63)	0.27
Signs			
CRP (mg/L)	Crude	56.83 (-86.34, 200.01)	0.43
	Model 1	61.17 (-84.26, 206.61)	0.41
	Model 2	56.13 (-86.09, 198.35)	0.43
D-dimer (ng/ml)	Crude	-4.89 (-32.46, 22.67)	0.72
	Model 1	-7.65 (-35.19, 19.88)	0.18
	Model 2	-3.57 (-31.35, 24.20)	**0.07**
Symptoms			
Smell	Crude	-0.74 (-5.68, 4.18)	0.76
	Model 1	-0.17 (-5.11, 4.77)	0.94
	Model 2	-0.58 (-5.50, 4.33)	0.81

Variables	Models	Probiotics intake * BMI	
		β (95% CI)	*P* value*
Taste	Crude	-3.00 (-7.89, 1.87)	0.22
	Model 1	-3.21 (-8.09, 1.66)	0.19
	Model 2	-3.58 (-8.32, 1.16)	0.14
Appetite	Crude	0.07 (-3.99, 4.14)	0.97
	Model 1	0.14 (-3.92, 4.20)	0.94
	Model 2	0.15 (-3.86, 4.17)	0.94
Lethargy	Crude	-0.94 (-4.52, 2.63)	0.60
	Model 1	-0.91 (-4.52, 2.69)	0.62
	Model 2	-0.70 (-4.25, 2.84)	0.69
		OR (95% CI)	
Chest pain	Crude	0.57 (0.04, 8.22)	0.68
	Model 1	0.42 (0.02, 6.74)	0.54
	Model 2	0.49 (0.02, 8.60)	0.62
Headache	Crude	0.68 (0.04, 9.74)	0.78
	Model 1	0.82 (0.05, 12.89)	0.89
	Model 2	1.03 (0.06, 16.67)	0.98
Rhinitis	Crude	1.05 (0.07, 15.03)	0.97
	Model 1	1.41 (0.08, 23.20)	0.80
	Model 2	1.60 (0.09, 27.00)	0.74
Vomiting	Crude	0.68 (0.00, 6.74)	0.77
	Model 1	0.24 (0.00, 2.47)	1.00
	Model 2	0.24 (0.00, 1.89)	0.87
Nausea	Crude	0.39 (0.02, 6.05)	0.50
	Model 1	0.43 (0.02, 7.40)	0.56
	Model 2	0.55 (0.03, 9.99)	0.69
Diarrhea	Crude	0.36 (0.01, 7.37)	**0.07**
	Model 1	0.30 (0.00, 0.98)	**0.05**
	Model 2	0.32 (0.01, 1.00)	**0.05**
Sore throat	Crude	0.91 (0.04, 17.65)	0.95
	Model 1	0.90 (0.03, 20.69)	0.95
	Model 2	0.88 (0.03, 23.97)	0.94
Joint pain	Crude	1.00 (0.00, 1.15)	1.00
	Model 1	1.00 (0.00, 1.25)	0.99
	Model 2	1.64 (0.00, 3.75)	0.98
Stomachache	Crude	0.77 (0.00, 2.44)	0.99
	Model 1	0.44 (0.00, 1.20)	1.00
	Model 2	0.43 (0.00, 1.45)	**0.09**
Confusion	Crude	1.50 (0.00, 5.68)	0.80
	Model 1	1.13 (0.00, 3.66)	1.00
	Model 2	1.17 (0.00, 5.78)	1.00
Contusion	Crude	1.44 (0.07, 27.32)	0.80
	Model 1	1.51 (0.07, 29.91)	0.78
	Model 2	1.84 (0.08, 39.38)	0.69
Fever	Crude	0.31 (0.00, 5.32)	0.99
	Model 1	0.34 (0.00, 7.33)	0.99
	Model 2	0.68 (0.00, 7.35)	0.99
RDS	Crude	1.18 (0.04, 31.12)	0.91
	Model 1	0.56 (0.01, 16.88)	0.74
	Model 2	2.06 (0.06, 61.50)	0.67

BMI, Body mass index; DH, Duration of hospitalization; CI, Confidence interval; CRP, C-reactive protein; OR, Odds ratio; RDS, Respiratory distress syndrome. Model 1 was adjusted for age, sex, education level, BMI, and physical activity. Model 2 was adjusted for age, sex, education level, BMI, physical activity, comorbidity, use of medication, and supplementation use. Biochemical factors (CRP) were reported as the median. Not taking supplements, BMI>median (29.384), and absence of signs and symptoms were considered as reference. Significant values are in bold. P<0.05 was considered statistically significant, and P=0.05-0.1 was considered marginally significant. Data for continuous variables were obtained from linear regression and are presented as β and 95% CI. Data for categorical variables were obtained from binary regression and are reported as OR and 95% CI. *The P values were obtained using the generalized linear models' method.

Discussion

This study examined the interaction between BMI and probiotic supplementation for COVID-19 symptoms and DH. Our findings showed a significant positive association between a higher BMI and elevated serum levels of CRP and D-dimer. Furthermore, probiotic supplementation within two weeks prior to the study was associated with reduced lethargy in COVID-19 patients. In addition, patients with lower BMI and probiotics supplementation intake had lower DH, D-dimer and lower odds of diarrhea and stomachache. These associations remained consistent after adjusting for potential confounders. Elevated CRP levels and D-dimer were shown to be indicators of increased inflammation and to be associated with COVID-19 outcomes. This aligns with a previous study that reported obesity contributed to systemic inflammation, respiratory dysfunction, and a pro-inflammatory state, which could exacerbate COVID-19 severity. This observational study found that obesity was associated with higher initial and peak levels of CRP and D-dimer, and COVID-19 severity in obese patients when compared to non-obese patients that is in line with our findings (12).

Furthermore, a systematic review concluded that inflammation is one of the contributing factors to the infection and COVID-19 disease. This study reported that obesity is a pro-inflammatory state, indicated by increased levels of CRP. Higher levels of inflammation are associated with increased disease severity in obese patients (13). Ameta-analysis study on COVID-19 patients in 2020 found that obesity and higher BMI were linked to disease complications including hospitalization, severe disease progression, and intensive care unit admission (14). In contrast, probiotics supplementation in the two weeks preceding the study was associated with reduced lethargy in COVID-19 patients. This finding highlights the potential of probiotics in alleviating fatigue and improving the overall well-being of COVID-19 patients. This finding was supported by previous studies indicating that probiotics can modulate immune responses, reduce excessive cytokine production, and exert anti-inflammatory effects which contribute to improved fatigue-related symptoms (12, 13).

Several mechanisms have been proposed to explain the link between obesity and COVID-19 outcomes. The existing evidence showed that obesity was associated with various respiratory system illnesses due to fat accumulation in the abdomen and mediastinum (15). Obese people are more likely to develop decreased respiratory system compliance and a decline in expiratory reserve volume due to reduced chest wall elasticity, limited truncal expansion, low respiratory muscle strength, and limited diaphragm excursion. These alterations increase the risk of cardiac stress, pulmonary hypertension, and pneumonia linked to hypoventilation (16). Obesity also induces a pro-inflammatory status which may be caused by adipocytes in hypoxic conditions that inappropriately secrete adipokines and cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and CRP. Existing evidence shows that IL-6 is an independent risk factor for severe COVID-19 (17, 18) which is positively linked to SARS-CoV-2 mortality rates (19).

Both abdominal and non-abdominal visceral fat contribute to a pro-inflammatory state, the release of inflammatory markers such as TNF-α and IL-6, activating immune pathways and leading to increased production of acute-phase reactants including procalcitonin (PCT) (20, 21) and CRP (22). IL-6 stimulates hepatic production of CRP, a non-specific acute-phase protein that is a sensitive indicator of tissue damage, infection, and inflammation which is associated with disease severity in COVID-19 patients (22). In addition, adipose tissue expresses high levels angiotensin-converting enzyme-2 (ACE-2) receptors, which have been recognized as a co-receptor for the virus that causes COVID-19 (23, 24).

It may help the virus propagate locally in visceral intrathoracic (lungs), epicardial (heart), and peri-renal (kidney) adipose tissue (25). Higher ACE2 receptor release from adipose tissue is linked to a higher likelihood of developing severe COVID-19. Furthermore, in obese COVID-19 patients, high levels of ACE-2 receptors in epicardial fat tissue may raise the risk of myocarditis (26). Obesity can exacerbate the pro-thrombotic effects of COVID-19 by promoting hypercoagulability through multiple pathways, including the upregulation of pro-coagulant factors, increased platelet activation, and impaired fibrinolysis (27). D-dimer is a soluble fibrin breakdown product is a marker of ongoing thrombotic and thrombolytic events such as pulmonary embolism (28). Following the initiation of coagulation and fibrinolysis, elevated levels of D-dimer have been observed in COVID-19 patients (29). Elevated D-dimer levels may be a predictor of outcome as they have been linked to higher in-hospital mortality rates and increased severity of COVID-19 (30).

Probiotics may exert beneficial effects through the gut-brain axis, which links gut microbiota and the central nervous system and influences mood, cognitive function, and energy levels (31, 32). The existing evidence shows that probiotics can improve mood, sleep quality, while reduce depression and

fatigue, which are common in COVID-19 patients (33). According to the gut-lung axis, respiratory infections and inflammation can cause gut microbiota imbalance, leading to dysbiosis (33). Previous researches have revealed a link between the gut microbiota and chronic fatigue syndrome, with probiotic supplementation showing promise in managing this condition (34, 35). Probiotics are live, non-pathogenic microorganisms that provide the host with a genuine health benefit (36).

Probiotics show several beneficial effects including mood and cognitive function improvement, fatigue reduction as well as anti-inflammatory, antioxidant, and immunomodulatory properties. Furthermore, probiotics regulate brain health via the gut-brain axis (37). Several studies demonstrated that probiotic supplements significantly improved mood and sleep quality; while reducing symptoms of depression and fatigue (38-40). Based on available evidences, probiotics may effectively mitigate both physical and mental fatigue, offering a promising approach for recovery and overall health improvement (38-40).

The combination of these two factors; BMI and probiotic supplementation; illustrates how obesity-related inflammation may exacerbate COVID-19 outcomes, while probiotics could offer a therapeutic strategy. This study examined both BMI and probiotics supplementation in relation to COVID-19 symptoms and DH. These findings provide novel insights into their potential interaction and suggest a need for further clinical trials to explore the efficacy of probiotics in overweight and obese patients with COVID-19. This study had several strengths. To the best of our knowledge, this is the first to examine the association between BMI, probiotics supplementation, and their impact on COVID-19 outcomes, focusing on DH and symptoms severity. Furthermore, several potential confounding variables were accounted in data analysis, ensuring a more accurate interpretation of the results by minimizing the influence of unrelated variables. However, this study had limitations that need to be taken into consideration. Firstly, the cross-sectional design limits the ability to establish causality. Secondly, reliance on self-reported anthropometric data may affect the accuracy of the results. Lastly, the relatively small sample size may limit the generalizability of the findings. As a result, larger, longitudinal, or experimental studies are needed to confirm these associations.

Conclusion

Our findings indicated a positive association between higher BMI and elevated CRP and D-dimer levels. Probiotic supplementation within the two weeks prior to the study was linked to reduced lethargy in COVID-19 patients. Overall, patients with lower BMI and probiotic use experienced lower DH, D-dimer levels, and reduced odds of diarrhea and stomachache. However, further researches, including longitudinal studies with larger sample sizes, control groups, and longitudinal designs, are essential to better understand the underlying mechanisms and to establish more robust evidence on the role of BMI and probiotics in the management of COVID-19.

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Authors' Contribution

AM1 contributed to the conception and design. FSH, ZZ, AM2, SN, SH, AZ, DKH, MS contributed to all experimental work and manuscript, FSH contributed to data and statistical analysis. AM1 and KhM, supervised the whole project. All authors performed editing and approving the final version of this paper for submission, also participated in the finalization of the manuscript and approved the final draft. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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