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ORIGINAL ARTICLE

The effect of glutamine supplementation on serum levels of some inflammatory factors, oxidative stress, and appetite in COVID-19 patients: a case–control study

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Abstract

Background Malnutrition is seen in COVID-19 patients, and reducing malnutrition with appropriate therapies may improve these patients' health. This case–control study aimed to assess and compare serum levels of some inflammatory factors, oxidative stress, and appetite in COVID-19 patients with respiratory infections that receive glutamine treatment with a control group.

Methods In this study, patients who consented to use glutamine were considered as the case group and other patients who did not use glutamine were considered as a control group. Two hundred twenty-two COVID-19 patients (51.2 ± 6.7) using L-Glutamine and 230 COVID-19 patients (51.3 ± 8.2) with similar age, gender, and clinical status, as the control group, were included in the study. For 5 days, the case group consumed 10 g of glutamine supplement three times per day. At the end of the 5 days, blood samples were taken again to test for serum levels of IL1β, tumor necrosis factor-α, malondialdehyde, and total antioxidant capacity, then all data were analyzed.

Results Serum levels of β-1 interleukin, tumor necrosis factor-α and hs-CRP were significantly reduced with five days of glutamine supplementation ($p < 0.05$), and patients' appetite during 5 days of glutamine supplementation compared with the control group had a significant increase ($p < 0.05$).

Conclusion Glutamine supplementation in COVID-19 patients with respiratory infection significantly reduces serum levels of interleukin-1 β, hs-CRP, and tumor necrosis factor-α and significantly increases appetite, so glutamine supplementation may be useful for COVID-19 patients in the hospital.

Keywords Glutamine · COVID-19 · Appetite · Oxidative stress

Introduction

On March 11, 2020, the World Health Organization declared the COVID-19 as a pandemic (Daniel 2020). The main approach, especially in those with lower respiratory tract involvement, is focused on optimizing respiratory functions. In the elderly patients with low immune function, in individuals with nutritional deficiencies and people with chronic diseases, the morbidity and mortality of the COVID-19 are higher (Liu et al. 2020; Paladugu and Donato 2020). In COVID-19, the most common complication and problems are related to respiratory disease. Since the catabolic process continues (Berger 2020; Owen et al. 2021) in this disease, normal nutrition intake is not sufficient to support recovery. Decreasing the acute stress levels of specific amino acids such as glutamine enhances immunity in these patients (Naja and Hamadeh 2020). Various treatments are offered to improve respiratory infections. One of the supplements used is glutamine. Glutamine is the most abundant amino acid in plasma and skeletal muscle (Cruzat et al. 2018). This amino acid is a precursor to the synthesis of other amino acids, proteins, nucleotides, and many other biological molecules and is largely synthesized in muscle and used for

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gluconeogenesis in the liver (Cruzat et al. 2018; Shah et al. 2020). It is an important fuel for the cells of the immune system and may have stimulating effects on the immune system (Andersen et al. 2019). Glutamine also has antioxidant properties and increases the body's glutathione reserves that can increase the body's antioxidant capacity (Moura et al. 2017) and reduces oxidative stress and inflammatory factors. It has been shown that a daily dose of 0.5 g/kg of glutamine supplementation reduces nosocomial infections in hospitalized patients (Stehle et al. 2017). Some studies have shown that glutamine regulates the immune system in animals and humans (Cruzat et al. 2018). Another study showed that consumption of glutamine supplementation for 5 days can reduce the frequency of pneumonia, infection, and bacteremia in patients with multiple trauma (Stehle et al. 2017). Malnutrition in COVID-19 patients increases its complications. Malnutrition occurs in these patients during the disease due to decreased appetite. Some studies have shown that people with malnutrition experience more severe symptoms of COVID-19. As a result, it can be expected that the relationship between malnutrition and COVID-19 is a two-way relationship and a vicious cycle (Anker et al. 2020; Berger 2020; Owen et al. 2021). Malnutrition also exacerbates infection and increases mortality in COVID-19 by weakening the immune system. In some animal studies, it has been shown that infection reduces appetite, and eventually, the animal loses weight (Li et al. 2020a, b). Possible mechanisms of malnutrition in infectious patients include increased inflammatory factors such as elevated serum CRP levels (Derouiche 2020) and inflammatory interleukins such as IL1, IL6, and α-TNF. Numerous studies show that serum inflammatory factors (interleukins such as IL6, IL1β, and TNF-α) are elevated in these patients (Robinson et al. 2020). IL1β strongly promotes anorexia, increased energy expenditure, muscle protein loss, and leptin release (Rao et al. 2017). Oxidative stress also exacerbates malnutrition in these patients through changes in metabolism and energy (Hsieh et al. 2016). It has been reported that nutritional support can improve nutritional status and anthropometric factors in patients with respiratory infections (Baumgartner et al. 2021). On the other hand, it has been shown that glutamine can regulate appetite by affecting the secretion of Glucagon-like peptide 1 from the gastrointestinal tract (Andersson et al. 2018). Glucagon-like peptide 1 is a physiological regulator of energy intake and appetite (Adams et al. 2018). Glutamine is also involved in the formation of glutamate and GABA (Qureshi et al. 2020). Glutamate and GABA can stimulate appetite (Varela et al. 2021). Glutamine has the effect of reducing pro-inflammatory cytokines and may play a role in reducing mortality by controlling the infection (de Urbina et al. 2017). Only one study (Cengiz et al. 2020) investigated the glutamine supplementation effect on COVID-19 treatment and its result indicated that adding enteral L-glutamine to the normal nutrition in the early period of COVID-19 infection may lead to a shortened hospital stay and lead to less need for ICU, and until now there is no study about the glutamine supplementation effect on COVID-19 patients' serum levels of some inflammatory factors, oxidative stress, and appetite. Based on the COVID-19 treatment importance and reduction in mortality and morbidity, this case-control study aimed to assess and compare serum levels of some inflammatory factors, oxidative stress, and appetite in COVID-19 patients with respiratory infections that receive glutamine treatment with a control group.

Methods

Informed consent

This study was approved by the Ethics Committee of the Baku University of Medicine Sciences (ethical Number: 2020/4231) and Tehran University of Medical Science. Before the written consent, all patients were given complete information about the study protocol.

Study population

A total of 520 COVID-19 patients were screened and 452 patients who met the inclusion criteria were included in the study. Patients who applied to the COVID-19 outpatient clinics of the Hospital between Jan 28 and Mar 10, those who had lower respiratory tract involvement in computed thorax tomography (thorax CT), and positive real-time reverse-transcriptase-polymerase chain reaction (RT-PCR) test in the oro-nasopharyngeal swab, were included in the study. Glutamine supplementation is routinely ordered by a physician in the intensive care unit with the consent of the patient or his/her family and is purchased by the patient's family. In this study, patients who consented to use glutamine were considered as the case group and other patients who did not use glutamine were considered as the control group.

Patients with kidney and liver dysfunction, alcoholism, malignancy, connective tissue diseases, cardiovascular diseases, diabetes mellitus, neurological and psychiatric problems (Parkinson's disease, cerebrovascular disease, delirium, bipolar disorder, depression), and Patients whose weight and height could not be measured due to the severity of the disease and their inability to stand, etc. were excluded from the study. The Sequential Organ Failure Assessment (SOFA) scoring was performed on all patients for evaluating the severity of the disease before the beginning of the study. The patients who had a quick SOFA (qSOFA) value of >2 were also not included in the study. When a patient had malnutrition or was at risk of malnutrition at the beginning or in the following period of the hospital stay, we planned a

nutritional care plan and excluded them from the study. The patients whose clinical courses and laboratory parameters worsened through all given treatments were classified as severe sepsis according to the criteria of SOFA and excluded from the study. First, qSOFA was calculated with the blood pressure, respiratory rate, and mental status, if the qSOFA is 2 and/or bigger than 2, the patient was taken to the ICU and excluded from this study. SOFA measures individual or aggregate organ dysfunction in six organ systems (respiratory, coagulatory, liver, cardiovascular, renal, and neurologic) in the ICU and mostly predict hospital mortality.

Diagnosis of COVID-19

Thorax CT screenings of all patients were taken at the time of hospital admission. As stated in the guidelines, and the oropharyngeal sample was first taken with a swab, then a nasal sample was taken using the same swab, and placed in the same transport medium for diagnosis. Samples were tested by RT-PCR assay developed from the virus sequence.

Laboratory analysis

Before giving the supplement, 2 cc blood samples were taken from both groups. At the end of glutamine consumption, blood samples were taken again to assess serum levels of IL1β, tumor necrosis factor-α, malondialdehyde, and total antioxidant capacity, then all data were analyzed. COVID-19 patients with certain diseases, such as heart and liver disease, and those who were unwilling to cooperate were excluded from the study. To measure this cytokine, the sandwich ELISA method was used using the human ELISA kit manufactured by Diaclone Company with serial number 950.090.096.

To measure the total antioxidant capacity, RANDOX's RANSOM kit was used according to the recommended protocol by spectrophotometry using an Abbot autoanalyzer at 600 nm. The basis of this measurement is based on the incubation of a special substrate with peroxidase and hydrogen peroxide and the production of a radical substrate cation that produces a stable green-blue color that can be measured at a wavelength of 600 nm. The TAC value is in mmol/l.

To measure hs-CRP protein, Pars test diagnostic kit was used by immunoturbidimetric. According to the kit brochure, first 20 µl of serum with 200 µl of reagent 1 was placed at 37 °C for 5 min, then 200 µl of reagent 2 containing mouse monoclonal and goat polyclonal antibodies against human CRP antibody was added. Absorption was measured at 30 and 90 s with the Abbot autoanalyzer at 500 nm in mg/l.

Interleukins β_1 were measured by ELISA using Bender Med Systems kits (Vienna, Austria).

After discharging the patients before 5 days before the hospitalization period, according to the present project, the necessary recommendations regarding the use of supplements and placebo were provided to the parents and the patients were followed up to control them in terms of taking supplements.

Glutamine supplementation and nutritional status screening

The patient's nutritional status was investigated with the Nutritional Risk Screening (NRS-2002) at the hospital admission time. NRS-2002 has two levels such as impaired nutritional status and severity of disease (such as low, moderate, or severe for both of them), with an adjustment for age_70 years. The nutrition status as considering the first level of this screening was evaluated by the variables; Body Mass Index (BMI), weight loss in the last 3 months, and decreased food intake in the last week. The severity degrees of disease as considering the second level of NRS-2002 was defined as absent, mild, moderate, or severe that was converted to a numeric score between 1 and 3 according to recommendations. A total score under 3 suggested no nutritional risk. To obtain all information a data collection sheet was used.

All given meals for this study patients were prepared based on the appropriate guidelines in COVID-19 and consisted of equal protein and calorie contents. The case group consumed 10 g of glutamine powder three times per day for 5 days.

Appetite

In this study, a subjective index and an objective index for appetite measurement were considered. A visual analog scale (VAS) was used to quantify a subject's feelings on the desire to eat, hunger, prospective consumption, and fullness (for subjective parameters). To measure the food greasiness degree, food greasiness was added to the VAS. The scale 0–10 was adopted to evaluate the sensation before or after eating, and the higher the scale indicated the stronger the sensation. Based on their experience, the subjects were free to calibrate on each line that best matched how they were.

A sample size of $n = 210$ per group is required to provide 80% power to detect a difference in the mean levels with a significance of 0.05 (2-sided a).

Statistical analysis

The normal distribution of the data was tested using the one-sample Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as counts. The statistical comparisons were performed using the one-way ANOVA and SIDAK test. Categorical variables were compared using the Chi-square

test or Fisher exact test for small samples. Values of $p \leq 0.05$ were considered to be statistically significant. The statistical analysis was performed using SPSS 20.0 software (SPSS, Chicago, IL, USA) for Windows.

Results

Demographic characteristics of the study participants are given in Table 1. There was no significant difference in Age (p=0.114) and body mass index between control (Age 51.3 ± 8.2, BMI 29.1 ± 3.4) and case groups (Age 51.2 ± 6.7, BMI 29.4± 7.2). Symptoms, medications for COVID-19, and physical examination findings of the study groups are given in Table 2. There was no significant difference in all of the symptoms, medications, and physical examination findings between the study groups.

Necessity of intensive care unit, duration of hospitalization, and the number of mortality of the groups of study are given in Table 3. Duration of hospitalization was found as 14.3 ± 5.3 days in the control group and 10.5 ± 4.8 days in the intervention group (p=0.015). The number of the necessity of intensive care units was significantly higher in the control group (p = 0.008). There was a significant difference in mortality rates between the groups, 38 (3.47) deaths were observed in the control group. Laboratory and physical examination findings before and after the study are given in Table 4. In the case group, a significant decrease in total qSOFA score and respiratory rate was observed (p = 0.024). In the case group after glutamine supplementation, all of the stress oxidative factors were significantly decreased and all of the serum antioxidant factors were significantly increased (p<0.05). According to Table 6, the Chi-square test was used for appetite comparison before and after of study and the results showed that in the case group appetite increased significantly during the glutamine supplementation compared to the control group (p = 0.02). After study in the case group the TNF-α (p=0.004), hs-CRP (p=0.016), MDA (p=0.005), Interleukin 1 beta (p=0.021) decreased, and TAC (p=0.013) increased significantly, these factors did not change significantly after the study in control group patients. Based on one way ANOVA test, in the case group after comparison of variables related to before and after study, there was a significant difference in TNF-α (p=0.011), hs-CRP (p=0.023), MDA (p=0.011), Interleukin 1 beta (p=0.002), and TAC (p=0.020) (Table 5).

Table 1 Demographic characteristics of the study groups

Variables	Control group n=230	Case group n=222	P*
Age (years)	51.3 ± 8.2	51.2 ± 6.7	0.114
Gender			
Female	110 (47.82%)	112 (50.45)	0.387
Male	120(52.18%)	110 (49.55)	0.420
Body Mass Index (kg/m^2)	29.1 ± 3.4	29.4 ± 7.2	0.201
Smoking	43 (18.69)	41 (18.46)	0.744

*Based on independent T-test

Table 2 Symptoms, medication for COVID-19, and physical examination findings of the study groups

Symptoms	Control group n (%)	Case group n (%)	P*
Fever	202 (87.82)	205 (92.34)	0.428
Cough	230 (100)	220 (100)	0.314
Dispne	143 (62.17)	140 (63.06)	0.142
Fatigue	220 (95.65)	218(98.19)	0.480
Taste/smell abnormalities	82 (35.65)	80 (44.44)	0.105
Diarrhea	48(20.86)	50 (22.52)	0.238
Medications			
Hydroxychloroquine	230 (100)	222 (100)	0.808
Oseltamivir	230 (100)	222 (100)	0.619
Azithromycin	230 (100)	222(100)	0.616
Moxifloxacin	230 (100)	222 (100)	0.808
Lopinavir/Ritonavir	230 (100)	222(100)	0.611
Favipiravir	230 (100)	222 (100)	0.472
Other antibiotics	230(100)	222 (100)	0.148
Fever (C)	39.2 ± 0.6	39.6 ± 0.9	0.149
Systolic BP (mmHg)	107 ± 11	106 ± 12	0.439
Diastolic BP (mmHg)	78 ± 5	77 ± 4	0.204
Heart rate (/min.)	89.7 ± 6.4	89.1 ± 7.4	0.254
SO_2 (%)	92.6 ± 4.6	92.9 ± 2.9	0.179
Respiratory rate (/min.)	18.2 ± 4.3	18.4 ± 5.2	0.388
Pneumonia Severity Index	72.6 ± 10.33	71.8 ± 12.1	0.143
Pneumonia Severity Index Grade			
I	0	0 0.219	
II	230 (100)	222 (100)	
III	0	0	
IV	0	0	
V	0	0	

*Based on Chi-square test

Table 3 Duration of hospitalization, the necessity of intensive care unit, and mortality of the study groups after intervention

	Control group	Case group	p*
Duration of hospitalization	14.3 ± 5.3	10.5 ± 4.8	**0.015****
Necessity of intensive care unit (%)	123(53.47)	0	**0.008****
Mortality	38 (3.47)	0	**0.029****

*Based on independents t-test

**The significance level is less than 0.05

Table 4 Laboratory, physical examination findings and serum stress oxidative of the study groups

	Case group			Control group			P**
	Before glutamine	After glutamine	*p**	Before study	After study	*p**	
Physical examination findings							
Systolic BP(mmHg)	106 ± 12	105 ± 15	0.125	107 ± 11	106 ± 9	0.124	0.094
Diastolic BP(mmHg)	77 ± 4	76 ± 9	0.118	78 ± 5	77 ± 4	0.230	**0.152**
Heart rate (/min.)	89.1 ± 7.4	89.3 ± 8.8	0.403	89.7 ± 6.6	89.1 ± 7.6	0.103	0.147
SO_2 (%)	92.9 ± 2.9	92.7 ± 5.1	0.119	92.6 ± 4.6	92.6 ± 2.7	0.119	0.101
PaO_2 (mmHg)	72.1 ± 10.9	72.5 ± 13.9	0.247	72.8 ± 12.6	72.9 ± 9.6	0.507	0.116
Need for vasopressors	0	0		0	0		–
Quick SOFA (qSOFA) Scoring System							
Altered mental status							
Glasgow coma scale <	76 (37.83)	0	0.009	80 (34.78)	89(38.69)	0.051	0.004
Total Quick SOFA Score (qSOFA)							
1	74 (33.33)	0	0.024	68(29.62)	70(30.43)	0.085	0.002
2	0	0		0	0		
3	0	0		0	0		
TNF-α	6.72 ± 4.1	3.21 ± 1.4	0.004	5.49 ± 2.9	5.52 ± 3.2	0.204	0.001
Hs-CRP	19.14 ± 5.8	12.01 ± 4.9	0.016	19.64 ± 6.4	19.52 ± 3.2	0.119	0.003
MDA	5.8 ± 0.44	2.9 ± 0.82	0.005	5.1 ± 0.32	5.8 ± 0.23	0.401	0.042
TAC	0.42 ± 0.01	0.83 ± 0.06	0.013	0.39 ± 0.02	0.35 ± 0.03	0.625	0.030
Interleukin 1 beta (pg/ml)	3.83 ± 0.06	1.02 ± 0.01	0.021	3.69 ± 0.08	3.70 ± 0.02	0.231	0.001

**p* value is based on paired *T* test

***p* value is based on independent *T* test

Table 5 Comparison of laboratory, physical examination findings, and serum stress oxidative of the study groups based on Sidak's test

Variables	P_1 Control group Before study – after study	P_2 Case group Before study – after study	P_3 After study Case–control
Quick SOFA (qSOFA) scoring system	0.654	0.028**	0.031**
TNF-α	0.211	0.011**	0.042**
Hs-CRP	0.095	0.023**	0.001**
MDA	0.082	0.011**	0.022**
TAC	0.972	0.020**	0.014**
Interleukin 1 beta	0.0725	0.002**	0.001**

P1: Comparison of variables related to before study and after study in the control group

P2: Comparison of variables related to before study and after study in the case group

P3: Comparison of variables between control and case group after the study

**The significance level is less than 0.05

Discussion

This study is the first study that evaluated the effect of glutamine on serum antioxidants, TNF-α, CRP, MDA, interleukin-β_1, and the level of appetite in COVID-19 patients admitted to the intensive care unit. Decreased appetite has been reported in COVID-19 patients (Høier et al. 2021), this problem leads to immunity level reduction and as a result, the negative effects of the virus on the person. Therefore, improving the appetite level in COVID-19 patients is a very important issue and it is recommended to use glutamine to improve the appetite of these patients. Decreased appetite leads to a low intake of nutrients that are effective in immunity such as vitamin C,

Table6 Comparison of appetite after the intervention

Variables	Intervention group	Control group	*p**
Desire to eat	218	52	0.01
Satiety time after eating			
After eating a few tablespoons to a third of a plate	20	194	0.02
After eating half to all the food is served	200	36	
Rarely satiated	0	0	
Time of feel hungry			
Never	0	0	0.004
Low and sometimes	106	180	
The whole day	116	50	
Patients' opinions about the taste of food			
Bad and very bad	41	104	0.01
Moderate	10	101	
Good and very good	171	25	
No	0	0	

*Based on chi-square test

zinc, selenium, and protein, so the complications of this disease increase. The results of the present study showed that the amount of appetite during the 5 days of glutamine supplementation was significantly increased compared to the control group. Also in this present study results showed that the mean serum interleukin-1 β and tumor necrosis factor-α were significantly reduced by taking a five-day glutamine supplement. Increased levels of oxidative stress have been observed in patients with COVID-19 (Chernyak et al. 2020). Oxidative stress is responsible for the deterioration of these patients and cell damage (Laforge et al. 2020). Proper and healthy nutrition that is rich in antioxidants has a very important role in these patients' recovery (Iddir et al. 2020). Glutamine is a supplement that is used as an antioxidant in some intensive care units of hospitals for critically ill patients, especially those with respiratory infections (Cruzat et al. 2018). Skeletal muscle is the main reservoir of glutamine, and during infection the release of glutamine from the muscle doubles, so its serum level remains normal (Levitt and Levitt 2018). Cytokines and glucocorticoids increase the absorption of glutamine by the liver in infectious conditions (Cruzat et al. 2018). On the other hand, Cytokines regulate bowel movements and alter various brain signals involved in appetite (Vázquez-Frias et al. 2015). IL1β strongly promotes anorexia, increased energy expenditure, muscle protein loss, and leptin secretion (Peixoto da Silva et al. 2020), TNF-α also causes anorexia, muscle protein breakdown, inhibition of lipoprotein lipase, and reduction of lipid production (Patel and Patel 2017) and is associated with pathogenesis, development, and progression of various infections, autoimmune diseases, malignant diseases, etc. It has been shown that glutamine administration may play a role in improving the immune system (Cetinbas et al. 2010), reducing pneumonia (Rogero and dos Santos 2017), and ultimately in reducing mortality in patients. Consistent with the results of this study, a study by Fan et al. (2009) on animal models, showed that enteral and parenteral supplementation of glutamine significantly increased plasma and tissue glutamine concentrations and decreased TNF-α and IL1β plasma levels. Inconsistent with our result, the findings of the study by Delgado et al. showed that glutamine supplementation for 8 weeks did not affect inflammatory factors in the pulmonary sputum of cystic fibrosis patients that had a respiratory infection (Delgado 2013). This different result may be related to the different types of studies sample.

The results of the present study showed that the serum level of hs-CRP was significantly reduced with five days of glutamine supplementation. Glutamine is a dietary supplement that has antioxidant properties (Yuan et al. 2017). In COVID-19 patients, the level of hs-CRP in the blood increases (Li et al. 2020a, b). Animal studies have shown that glutamine can improve the antioxidant capacity of the body by increasing glutathione stores (Yeh et al. 2020). Consistent with the findings of our study, Faghihzadeh et al. (Faghihzadeh et al. 2014) in patients with non-alcoholic fatty liver disease, Tomé-Carneiro in patients with coronary artery disease (Tomé-Carneiro et al. 2013), and Bo et al. in smokers (Bo et al. 2013) showed that some dietary antioxidants consumption can reduce serum hs-CRP levels. The possible effect of glutamine in reducing serum hs-CRP may be due to its antioxidant properties, which can increase the activity of serum antioxidant enzymes (Tanha et al. 2012) and ultimately control serum hs-CRP levels. In the present study, the serum level of TAC, in COVID-19 patients with glutamine consumption, was significantly increased. In addition, the patients' serum MDA had significant changes after five glutamine supplementation. Increased oxidative stress is seen in patients with COVID-19, which may play a role in the pathogenesis of this disease. The end product of lipid peroxidation is active aldehydes such as malondialdehyde (MDA) (Tanha et al. 2012), which can be used as a marker of the oxidative stress level in the body. Oxidative stress occurs when free radical production is more than antioxidant capacity. Antioxidant enzymes and a variety of antioxidant compounds are produced in the body to counteract oxidative stress (Wang et al. 2019) to protect cells and ultimately tissues from damage caused by free radicals and ROS. There is a significant change in the level of TAC and MDA after the use of glutamine in COVID-19 with respiratory infection. Reducing the amount of TNF-α, hs-CRP, and IL B_1 can be useful to improve the inflammation in these patients.

The duration of the intervention, the problems of preparing laboratory kits, and the low cooperation of the COVID-19 patients' families were some of the limitations of this study. It is suggested that future studies be performed with more COVID-19 patients and with a longer intervention duration.

Conclusion

Daily consumption of 10 g of glutamine three times per day in COVID-19 patients with respiratory infection decreases the serum interleukin-β level, the level of alpha necrosis tumor factor, the serum hs-CRP level and increases the appetite of COVID-19 patients, so using this supplement can prevent malnutrition of COVID-19 patients with respiratory infectious diseases.

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Declarations

Conflict of interest The authors of this article have no conflict of interest.

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