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Efficacy of Persian barley water on clinical outcomes of hospitalized moderate-severity COVID-19 patients: a single-blind, add-on therapy, randomized controlled clinical trial

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Abstract. – OBJECTIVE: Coronavirus disease 2019 (COVID-19) is a debilitating disease with numerous medical and non-medical consequences. Our study aimed to evaluate the efficacy of Persian barley water in controlling the clinical outcomes of hospitalized COVID-19 patients.

PATIENTS AND METHODS: This was a single-blind, add-on therapy, randomized controlled clinical trial conducted in Shiraz, Iran, from January to March 2021. One hundred hospitalized COVID-19 patients with moderate disease severity were randomly allocated to receive routine treatment (per local protocols) with or without 250 ml of Persian barley water (PBW) daily for two weeks. Clinical outcomes and blood tests were recorded before and after the study period. Multivariable modeling was applied using Stata software for data analysis.

RESULTS: The PBW product passed our standardization and safety assessments. Length of hospital stay (LHS) was 4.5 days shorter in the intervention group than the control group regardless of history of cigarette smoking (95% confidence interval: -7.22, -1.79 days). Also, body temperature, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and creatinine significantly dropped in the intervention group compared to the control group. No adverse events related to PBW occurred.

CONCLUSIONS: This clinical trial demonstrated the efficacy of PBW in minimizing the LHS, fever, and levels of ESR, CRP, and creatinine among hospitalized COVID-19 patients with moderate disease severity. More robust trials can help find safe and effective herbal formulations as treatments for COVID-19.

Key Words:
COVID-19, SARS-CoV-2, Hospital stay, Barley, Persian medicine, Iran.

Introduction

The coronavirus disease 2019 (COVID-19), first identified in Wuhan City, China, was quickly declared by the World Health Organization (WHO) as a "Public Health Emergency of International Concern" on January 30, 2020, and, finally, as a pandemic on March 11, 2020[1]. It has had medical, educational, economic, and social consequences; with most students barred from attending school and university, many social activities halted, and the world economy severely damaged[2].

The fatality rate of COVID-19 is about 2-3%. The most important source of disease transmission are patients. Because asymptomatic persons can also transmit this disease, the entire population is susceptible to contracting the agent responsible for this disease – the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3-5]. The incubation period is 1 to 14 days[5,6], and the most important clinical symptoms are fatigue, dyspnea, fever, myalgia, and dry coughs. Laboratory findings show a decrease in lymphocytes and rise in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) that, in patients with severe COVID-19, is associated with increased levels of inflammatory factors such as tumor necrosis factor-α and interleukins 2, 7, and 10[7,8]. Length of hospital stay (LHS) is an important indicator for assessing the burden on the health system and related resources during the COVID-19 pandemic[9]. Longer admission in hospitals during such crises may result in a shortage of medical resources for new patients, blockade of medical

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facilities, increased morbidity and mortality, and decreased access to routine health services[10-12].

Prevention and treatment of this disease is still an urgent issue globally because there is currently no specific and approved cure for it[13,14]. Although potential therapeutic approaches such as eliminating and inhibiting viral replication, suppressing inflammatory processes, plasma therapy, vaccines, as well as the use of traditional, complementary, and integrative medicine (TCIM) have been identified based on research, there is no standard treatment and countries around the world act on their clinical experiences[14]. Persian medicine (PM) is one of the types of TCIM mentioned in the World Health Organization's global report on traditional and complementary medicine in 2019, with endorsements for preventive measures during respiratory pandemics[15,16]. To the best of our knowledge, no reports are yet available to show the positive effect of TCIM products on decreasing the LHS in patients with COVID-19.

One of the recommended treatments in PM for inflammatory conditions of the whole body, especially the respiratory system and consequential fever, is Persian barley water (PBW). This product is manufactured from *Hordeum vulgare* via a specific procedure described in detail in primary PM textbooks[17,18]. According to recent studies[19,20], barley is rich in constituents such as selenium, tocotrienols, phytic acid, catechin, lutein, vitamin E, and vitamin C; these compounds are responsible for its antioxidant and anti-inflammatory properties[19,20]. Barley grains also have immune-stimulating effects, antioxidant properties, protective effects on the liver and digestive system, anti-cancer effects, and act to reduce uric acid levels[21-25].

Due to the COVID-19 pandemic and the need to establish definitive or supportive treatments that reduce the LHS, improve clinical symptoms, or eliminate the disease and thus reduce further mortality, this randomized, controlled clinical trial was designed to evaluate the efficacy of PBW in controlling the clinical outcomes of hospitalized COVID-19 patients.

Patients and Methods

Study Design

This study was a single-center, double arm, parallel-group, single-blind, add-on therapy, randomized controlled clinical trial with a 1:1 allocation ratio conducted at Ali Asghar Hospital (the main hospital designated for COVID-19 patients in the city) affiliated to Shiraz University of Medical Sciences, Shiraz, Iran, from January to March 2021. No changes were made to the method after starting the trial.

Ethical Issues

This study was registered with the Iranian Registry of Clinical Trials prior to patient enrollment (IRCT20150830023823N3). The trial was performed in compliance with the Declaration of Helsinki (2013 revision), and was also reviewed, approved, and monitored by the Medical Ethics Committee of Shiraz University of Medical Sciences (reference number: IR.SUMS.REC.1399.216). All participants provided signed informed consent before participating in the trial.

Participants

Inclusion criteria for this study were patients with a definite diagnosis of COVID-19 pneumonia (pneumonitis) based on the National Guideline for 2019-nCoV[26], i.e., fever (oral temperature $\geq$ 37.8°C), polymerase chain reaction (PCR) confirmed-COVID-19, and at least one of the following: respiratory rate >24/min or O_2 saturation < 94% or PaO_2/FiO_2 ratio < 300 mmHg. Patients had to be hospitalized in the specified hospital due to COVID-19. They were not classified as patients with severe disease, did not need admission to the intensive care unit, and received no antiviral medications prior to enrollment. All participants were above 18 years old, and there were no limitations on gender. Additionally, voluntary signing of the informed consent form was required. Other exclusion criteria were pregnancy, lactation, history of any mental disorder, and history of hypersensitivity or allergy to barley.

Sample Size

Considering alpha=0.05 and power of study equal to 80%, we hypothesized that our intervention would show a 60% decrease in LHS. Thus, the sample size was determined as 45 patients in each group. Hence, assuming a 10% dropout rate, 50 cases were placed in each group.

Randomization and Blinding

Using the permutation block randomization method with block size 4 and based on the list from Random Allocation software, 100 eligible patients were randomly assigned to the interven-

tion group and the control group with a 1:1 allocation ratio[27]. We assigned two separate wards for the intervention and control groups, with two independent nurses caring for the allocated patients based on the study protocol. They were not aware of the patients' allocated treatment. The nurse assigned to provide treatment to the intervention group distributed PBW as a part of the patients' lunch packages. Outcome ascertainment was done by a research assistant who was also blinded about allocations.

Persian Barley Water Preparation

The standard protocol for the preparation of PBW included the following steps.

Preparing PBW

This study used peeled barley (*Hordeum vulgare*) whole grains produced in Beyza farm, south of Iran, with rain-fed irrigation.

Cleaning and Washing

The barley grains used to prepare PBW (on the same day as consumption as much as possible) were washed several times with Shiraz city tap water so that the milky color turned completely clear.

Boiling

To prepare each four glasses (about 250 ml per glass) of barley water, one cup (equivalent to 200 g or a glass with a French handle) of barley grains and 14 cups (of the same size) of water were poured into a pot then boiled with gentle heat. The foam formed on the water surface was removed and discarded during boiling until the barley grains were completely cooked and crushed. Once cooked, the barley grain shell could be separated in the form of a cheek wing from both sides and could easily be crushed with the fingers, and the resulting liquid had the color of onion skin. At this time, the stove flame was turned off. This stage took about one hour.

Filtration

About 3 minutes after the end of boiling, the resulting liquid was filtered through a mesh (No. 20), and its water (PBW) was separated. The PBW had a volume of about 1000 ml; in general, it can be consumed semi-hot or cold. This product was prepared daily in the hospital kitchen. For this purpose, a hospital chef was trained by the researcher before starting the project.

Study Procedure and Intervention

From the very beginning, the aim of the study, the procedure for conducting the study, and possible side effects of the drug were explained to each patient, and written informed consent was obtained. The data-gathering form was filled out by a nurse not involved in the trial for all enrolled patients to assess their clinical symptoms and to collect the laboratory data from electronic medical records. Finally, 100 eligible patients were randomly assigned to the intervention and control groups. Both groups received routine medication based on the "Iran National Guideline for 2019-nCoV"[26], but the intervention group also received a 250 ml PBW drink daily in the morning (11 am) for a period of 14 days by a special nurse with complete personal protection equipment. In order to eliminate the dose-confounding effect of the medications, only hospitalized patients with moderate COVID-19 severity and defined types and doses of COVID-19 medications (based on the abovementioned guideline) were included in the study.

Then, at the laboratory of Ali Asghar Hospital, blood samples were analyzed. For this purpose, a blood sample was drawn from the left arm of each patient by a nurse, according to the protocol approved by the Ethics Committee. The blood sample was tested on the same day. According to standard protocols, the samples were analyzed for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), creatinine (Cr), albumin, and neutrophil count in one laboratory using the BIO-LA-TEST kit (Delta Biologist Company, Italy) and SYSMEX SF-3000 hematology analyzer (Canada).

Outcome Measures

The primary outcome measure in this trial was the duration of hospitalization (the distance between the diagnosis and discharge) measured based on patient medical records. Secondary outcome measures were: (1) daily clinical symptoms (body temperature, respiratory rate, heart rate, dry coughs, body pain, chills, nausea, diarrhea) as evaluated by the "National Guideline for 2019-nCoV"[26]; (2) CRP, ESR, BUN, Cr, albumin, and neutrophil count after the intervention; (3) number of participants with any adverse events that were recorded in a diary during the treatment time.

Standardization and Safety Assessment

A. All of the enrolled participants were inquired about any adverse drug effects at daily follow-up visits. Any adverse effects were recorded in a diary.

B. Product quality control: To control the quality and ensure the uniformity of the product samples in each series of production, 100 grams of product per day were sampled and stored in the freezer until the date of testing.

C. Measuring the amount of dry matter: for this purpose, we poured 20 ml of the solution into a Petri dish and dried it in an oven. We measured and calculated the amount of dry matter obtained in each container for each day.

D. Total carbohydrate amount measurement: the total carbohydrate amount (TCA) was determined using the Phenol-Sulfuric Acid method according to the procedure described by DuBois et al[28]. The results were expressed as milligrams of carbohydrate in each ml of PBW or in its dry matter.

E. Determination of the total phenolic content: The total phenolic content (TPC) was determined using Folin-Ciocalteu reagent according to the procedure described by Hinneburg et al[29]. The results were expressed as milligrams of gallic acid equivalents per gram of dry matter (mg GA/g).

Statistical Analysis

Data were cleaned and prepared. Internal and external consistencies were identified and handled appropriately. Mean and standard deviation (SD) were used to describe continuous variables, and relative frequency (%) was calculated for categorical variables. The independent sample *t*-test was applied to compare continuous variables between the study groups at baseline. The chi-squared tests and Fisher's exact test were used for univariate analysis of the association of the study groups with the categorical variables. Panel data analysis was applied. Multivariable modeling was performed by applying a generalized estimating equation (GEE). The backward elimination technique was applied. Statistical interaction of the intervention with the smoking status was added in the modeling of the LHS; in this way, we analyzed if the effect of the study intervention differs in the presence of cigarette smoking. A *p*-value of 0.05 or less indicated statistical significance. Data analysis was done using Stata software (Release 11.2, College Station, TX: Stata Corp LLC).

Results

Out of 111 hospitalized patients evaluated, 100 were eligible to participate in the present study (Figure 1). These patients were randomly divided into the intervention and control groups. Demographic and clinical features of hospitalized patients are presented in Table I.

Each ml of PBW had 16 ± 6 mg of dry matter and contained 6.4 ± 2 mg of TCA. Also, the TPC was 72 ± 9 mg gallic acid equivalents in 100 gr of PBW dry matter or 0.011 ± 0.007 mg of gallic acid in each ml of the barley water.

According to the multivariable modeling, consumption of PBW in the intervention group significantly decreased the LHS by 4.5 days (95% CI: -7.22, -1.79 days) in comparison to the control group. The intervention and control groups stayed at the hospital for 3.41 (95% CI: 2.59, 4.23) and 4.84 (95% CI: 4.09, 5.58) days, respectively. This decrease was similar among patients who had or did not have a history of cigarette smoking. Also, PBW was significantly associated with a 2.50°C (95% CI: -4.87, -0.13 °C) decrease in body temperature (Table II).

The heart rate increased significantly in the intervention group by about 5.8 beats/min (95% CI: 3.33, 8.25/min) compared to the control group, though this difference was not clinically meaningful. The levels of inflammatory markers, including ESR and CRP, significantly decreased in the intervention group compared with the control group. The albumin concentration also fell significantly by 0.5 g/dL in the intervention group relative to the control group. In this period, BUN was elevated considerably (~3.3 mg/dL) in the intervention group compared to the control group, while this was inverse for creatinine with a 0.19 mg/dL decline. Other outcomes, including O_2 saturation, respiratory rate, cough, body pain, fatigue, and blood neutrophil count, did not show remarkable changes between groups using multivariable modeling. There were no intervention-related adverse events.

Discussion

The present study was a single-center, double-arm, parallel-group, single-blind, randomized controlled clinical trial on the clinical outcomes of 100 hospitalized COVID-19 patients. The re-

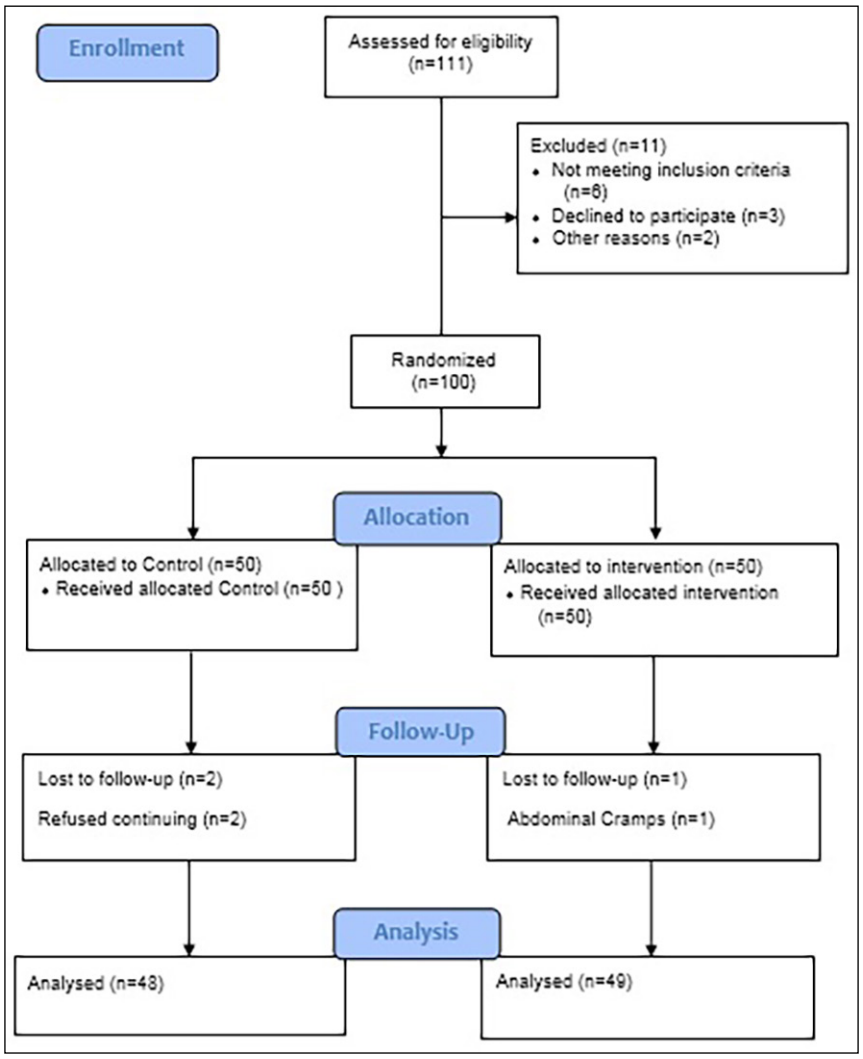

Figure 1. CONSORT Flowchart.

sults showed that PBW as an add-on to routine treatment could significantly decrease LHS, body temperature, BUN, and Cr of hospitalized COVID-19 patients.

The LHS due to COVID-19 is different in various countries, ranging from 4 to 53 days across 52 studies[11]. In this study, the LHS was in the middle of this range. Recent studies[8,30] have shown that female gender, fever, a history of chronic kidney or liver disease, glucocorticoid use, lymphopenia, and higher levels of Cr are associated with more extended hospitalization in COVID-19 patients. Multivariable regression analysis showed that PBW could significantly minimize two of these factors in our study, i.e., body temperature and level of blood Cr. The effectiveness of this traditional syrup in shortening the LHS might be attributed to these two outcomes.

Many researchers have discussed the anti-inflammatory effects of *Hordeum vulgare* as a mechanism for reducing fever[31]. Its combination of dietary fibers, mineral elements, unsaturated fatty acids, vitamins, and antioxidants could make barley effective in ameliorating inflammation and its consequences (e.g., fever). Moreover, barley polysaccharides enhanced the innate immune system in an experimental model[21]. Considering the thrombotic complications of COVID-19, the anti-atherosclerotic and platelet antagonist properties of barley should also be kept in mind[32-34]. The abovementioned structures and their special properties may explain the decrease in body temperature by about 2.5°C in the intervention group compared with the control group.

Since ancient times, barley grains have been used as a cough suppressant and remedy for common cold, bronchitis, and influenza-like symp-

Table I. Baseline demographic and clinical characteristics of the study participants. If not otherwise denoted, values are given as n (%).

Demographic/ Clinical characteristic	Control n = 50	Intervention n = 50	Clinical characteristic	Control n = 50	Intervention n = 50
Age (mean ± SD)	50.2 ± 13.8	56.8 ± 13.5	**Nausea**		
Education			**No**	24 (48.9)	36 (75.0)
Illiterate	10 (20.3)	14 (28.5)	**Mild**	17 (34.6)	11 (22.9)
Less than Diploma	13 (27.1)	13 (26.5)	**Moderate**	7 (14.2)	1 (2.0)
Diploma	7 (14.6)	7 (14.2)	**Severe**	1 (2.0)	0 (0)
Bsc	6 (12.5)	10 (20.5)	**Diarrhea**		
Msc	4 (8.3)	5 (10.3)	**No**	33 (68.7)	40 (83.3)
Gender			**Mild**	10 (20.8)	6 (12.5)
Male	29 (60.4)	37 (75.5)	**Moderate**	3 (6.2)	2 (4.1)
Female	19 (39.5)	12 (24.4)	**Severe**	2 (4.1)	0 (0)
Smoking			**Fever**		
Yes	5 (10.2)	9 (18.4)	**Yes**	29 (59.1)	15 (31.2)
No	44 (89.8)	40 (81.6)	**No**	20 (40.8)	33 (68.7)
Hx. of kidney and urinary system disease			**O_2 Saturation**		
Yes	2 (4)	1 (2)	**> 94%**	9 (18.3)	2 (4.1)
No	48 (96)	49 (98)	**90-94%**	37 (75.5)	39 (81.2)
Hx. of liver and biliary system disease			**< 90%**	3 (6.1)	7 (14.5)
Yes	1 (2)	0 (0)	**Fatigue**		
No	49 (98)	50 (100)	**No**	3 (6.1)	0(0)
Hx. of cardiovascular system disease			**Mild**	14 (28.5)	25 (52.0)
Yes	7 (14)	12 (24)	**Moderate**	25 (51.0)	21 (43.7)
No	43 (86)	38 (76)	**Severe**	7 (14.2)	2 (4.1)
Hx. of diabetes & endocrine system disease			**Chills**		
Yes	13 (36)	21 (42)	**No**	9 (18.3)	12 (26.0)
No	37 (74)	29 (58)	**Mild**	21 (42.8)	29 (63.0)
Hx. of hematology system disease			**Moderate**	16 (32.6)	5 (10.8)
Yes	1 (2)	0 (0)	**Severe**	3 (6.1)	0 (0)
No	49 (98)	50 (100)	**Dry Cough**		
Hx. of other organ diseases			**No**	2 (4.0)	0 (0)
Yes	2 (4)	0 (0)	**Mild**	14 (28.5)	19 (39.6)
No	48 (96)	50 (100)	**Moderate**	25 (50.0)	26 (54.1)
			Severe	8 (16.3)	3 (6.2)
			Respiratory rate/min		
			Less than 24	39 (81.2)	31 (63.3)
			24 to 30	9 (18.8)	17 (34.7)
			More than 30	0 (0.0)	1 (2.0)

toms in different traditional systems such as Ayurveda, Oriental medicine, traditional Chinese medicine, and PM[18,35,36]. There is also some evidence supporting the relieving effects of herbal medicines on different aspects of COVID-19 such as fever, respiratory symptoms, body pain, and so on in various traditional medicine systems[37-39]. Although the mechanisms of action are not yet completely clear, the immune-stimulating, anti-inflammatory, hepatoprotective, hypoglycemic, and antioxidant properties of *Hordeum vulgare* might play fundamental roles.

A history of chronic liver disease is an independent co-factor for longer hospitalization. A recent study[40] showed that more than one-third of hospitalized COVID-19 patients had abnormal liver function tests and prolonged LHS. This finding was in line with our results, which showed that PBW could significantly decrease the albumin level in COVID-19 patients. We also found a few values increasing significantly in the patients who consumed PBW compared with the control group, i.e., BUN (Δ=3.3 mg/dL) and heart rate (Δ=5.8 beats/minute). Still, it should be emphasized that these upsurges were not clinically meaningful.

There were no intervention-related adverse events in the COVID-19 patients participating in the trial, which supports the safety of PBW as an adjuvant remedy in moderately diseased hospitalized COVID-19 patients. Clinical trials of other treatment options for COVID-19 showed no acceptable efficacy and concomitant remarkable adverse events[41].

Table II. Effect of Persian barley water (PBW) on different clinical and biological characteristics of the COVID-19 patients.

Outcome	Crude Coefficient (95% CI)	Adjusted Coefficient* (95% CI)
Temperature (°C)	-1.47 (-3.62, 0.68)	-2.50 (-4.87, -0.13)
Respiratory Rate	-1.67 (-3.19, -0.15)	-1.03 (-2.25, 0.18)
Heart Rate	5.63 (3.28, 7.97)	5.79 (3.33, 8.25)
Body Pain	-0.12 (-0.66, 0.42)	-0.12 (-0.66, 0.42)
Exhaustion	-0.15 (-0.64, 0.33)	0.12 (-0.33, 0.57)
Cough	-0.17 (-0.61, 0.25)	-0.11 (-0.55, 0.31)
O2 Saturation (%)	-0.38 (-1.49, 0.70)	-0.39 (-1.51, 0.72)
ESR (mm/hr)	-4.33 (-6.75, -1.91)	-4.97 (-7.43, -2.51)
CRP (mg/L)	-0.69 (-1.26, -0.12)	-0.83 (-1.41, -0.24)
Albumin (g/dL)	-0.44 (-0.82, -0.07)	-0.50 (-0.88, -0.12)
Bun (mg/dL)	1.97 (0.42, 3.52)	3.30 (1.80, 4.80)
Cr (mg/dL)	-0.17 (-0.33, -0.02)	-0.19 (-0.36, -0.02)
Neutrophil Count (cells/μL)	16.89 (-22.32, 56.11)	16.89 (-22.32, 56.11)
Length of hospital stay (LHS) in days		
Among Cigarette Smokers	-0.96 (-1.24, -0.67)	-0.64 (-2.90, 1.62)
Among Non-smokers	-4.11 (-4.92, -3.30)	-3.84 (-6.71, -0.97)
Regardless of Smoking Status	-5.07 (-5.83, -4.31)	-4.50 (-7.22, -1.79)

*Adjusted effect of the study intervention on different outcome variables, estimated by applying generalized linear mixed-effects modeling (GLM) or generalized estimating equation (GEE). *Abbreviations:* CI: confidence interval; PBW: Persian barley water; ESR: erythrocyte sedimentation rate; mm/hr: millimeter per hour; CRP: c-reactive protein; mg/L: microgram per liter; BUN: blood urea nitrogen; mg/dL: microgram per deciliter; Cr: creatinine; cells/μL: cells per microliter; LHS: Length of hospital stay.

Of course, as the study participants were limited, it is essential to perform studies with larger sample sizes in the future. At the same time, the results of this current trial could be a suitable initiator of upcoming investigations. This study has several further limitations. Due to ethical concerns, it was impossible not to uphold standard treatment protocols, which could affect the trial's final results. Obligation to consume fresh PBW made it problematic to prepare a large amount of barley water as one batch for use throughout the study. Patients could not be blinded to group allocation, and no placebo intervention was available. Thus, at least some of the intervention's effects could be attributed to unspecific contextual factors.

Conclusions

This clinical trial revealed that add-on therapy with a PM formulation significantly decreased LHS, fever, and inflammatory indices (ESR, CRP) in hospitalized COVID-19 patients with moderate disease severity. Also, according to our findings, it might be helpful to decrease the Cr level as an independent factor. However, more studies with larger sample sizes are required to confirm the findings presented in the current trial.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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