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The Post-COVID Era - Advances and Challenges in Pharmacology

Effects of L-carnitine supplementation in patients with mild-to-moderate COVID-19 disease: a pilot study

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Abstract

Background The present single-center clinical trial was designed to evaluate the potential benefits of L-carnitine supplementation in patients with COVID-19 disease.

Methods and patients The study was conducted on 75 patients with mild-to-moderate COVID-19 hospitalized in Shahid Beheshti Hospital-Hamadan, IRAN. The participants were randomly divided into intervention ($n=32$) and control groups ($n=43$). The control group received their standard hospital treatment only. In addition to standard medications, the intervention group received 3000 mg oral L-carnitine daily in three divided doses for five days. The blood samples were collected and para-clinical parameters were measured at the beginning and end of the treatment. Clinical outcomes were also recorded, and data were analyzed using χ^2 and *t*-tests.

Results Higher means of O2 saturation were observed in the intervention rather than in the control group. Mean erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were significantly lower in the intervention group. Furthermore, mean alkaline phosphatase (ALP) activity and lactate dehydrogenase (LDH) were lower in the intervention group. Also, lower mean serum creatine phosphokinase (CPK) was observed in the intervention group. No significant differences were observed in terms of clinical symptoms; however, six patients (14%) in the control group died due to the complications of COVID-19, while all patients in the intervention group survived.

Conclusion Taken together, L-carnitine can be considered as a drug supplement in patients with COVID-19.

Keywords COVID-19 · L-carnitine · C-reactive protein · Para-clinical examination · Clinical outcome

Introduction

COVID-19 was identified as a worldwide concern by the World Health Organization (WHO) after an outbreak in Wuhan, China [1]. This disease led to higher levels of infection in crowded areas [2]. It has also affected economics, especially in developed countries. The scientists were confronted with a severe lack of data about this disease and trying to gather more knowledge on its control, prevention and treatment. This shortcoming prompted researchers to gather a large amount of data about the disease. In addition, high levels of morbidity and mortality [3] had harmful consequences on human life [4], presented healthcare professionals with pressing challenges, and exposed the weaknesses of national health systems worldwide.

Coronavirus is an enveloped single-stranded-RNA positive-sense virus that includes four subgroups called alpha, beta, delta, and gamma, of which beta type is responsible for

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COVID-19. This virus uses angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptors to enter cells is finding in the cardiopulmonary tissue, lymphocytes, macrophages, etc. [5].

Clinical features range from asymptomatic to acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. Common clinical features include fever, persistent cough, sore throat, headache, fatigue, myalgia and shortness of breath, which in most cases resolve spontaneously. However, in some cases, it progresses and causes complications, such as organ failure (mainly in the liver and kidney) [6], septic shock, pulmonary edema, severe pneumonia, and ARDS, which eventually may lead to death [7].

Morbidity and mortality are more common in the elderly and people with underlying diseases [8]. There is currently no effective treatment for COVID-19. The first-line treatment is to relieve the symptoms with painkiller drugs, such as acetaminophen and naproxen, and other medicines like diphenhydramine, etc. In severe cases, oxygen therapy is required. In some patients, anti-influenza drugs, such as oseltamivir and other drugs, such as hydroxychloroquine and doxycycline, are prescribed [9]. Due to the effect of the virus on T lymphocytes and consequent disruption of the immune system, infected patients may become susceptible to bacterial infections; therefore, antibiotic therapy may also be necessary [7].

Studies have not yet fully elucidated the pathophysiology of this disease [10]. In COVID-19 patients, an increase in inflammatory cytokines, such as interleukin 6 (IL-6), IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (GCSF), interferon γ-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1-alpha (MIP1A), and tumor necrosis factor α (TNF-α), is observed which is called "cytokine storm" [5]. The release of cytokines, which are effective regulators of inflammatory responses, stimulates the secretion of many glycoproteins, such as C-reactive protein, from the liver. This protein, in turn, controls and regulates the inflammatory processes [11]. Therefore, it seems that the reduction of serum CRP levels in affected patients can probably be promising in reducing some complications of the disease, such as cardiovascular risks.

Despite the development of several vaccines for COVID-19, there are doubts about the complete eradication of the disease because of the genetic changes that occur in the virus's genome. In October 2022 FDA has approved Remdesivir for the treatment of COVID-19, besides, some medications such as Molnupiravir are in advanced stages of approval. Due to the nature of COVID-19, which is an infectious and inflammatory disease, L-carnitine may be considered a suitable therapeutic supplement as it has shown promising results in some viral infections related to the respiratory system [12]. However, there is little evidence for the effect of this compound in COVID-19 patients.

L-carnitine (beta-hydroxy-gamma *N*-trimethyl aminobutyric acid) is a cofactor for transporting fatty acids from the mitochondrial membrane to the matrix and plays an important role in fatty acids metabolism. L-carnitine reduces the production of ketone bodies by reducing the level of fatty acids and their lower entry into hepatocytes, decreasing oxidative stress and inflammation [13]. 75% of L-carnitine reaches the body through food, and the rest is made from the lysine and methionine amino acids in the liver and kidneys. About 95% of L-carnitine is stored in skeletal muscle, and a small amount is accumulated in the brain, heart, and sperm [14]. L-carnitine is also used in treating heart disease, including irregular heartbeat, myocardial infarction (cardiomyopathy), angina, and ischemia [15]. Taking high doses of L-carnitine stimulates immune system function and improves neutrophil and macrophage function. This improvement in function is due to the effect of L-carnitine on glucose 6-phosphate dehydrogenase and the production of macrophage inhibitory factor-1 (MIF1) in neutrophils [16]. This supplement reduces leukotriene synthesis by inactivating the lipoxygenase process and reducing lung tissue inflammation [17]. L-carnitine is thought to reduce muscle cell damage and ultimately reduce the production of inflammatory proteins in patients and athletes by increasing intracellular membrane stability [13]. Recently, it has been reported that the carnitine level of the body is negatively correlated with COVID-19 susceptibility and severity. So, an increase in the carnitine amount was associated with lower vulnerability to COVID-19 [18]. Also, another study used a combined metabolic activators regimen that included l-carnitine, and results showed that treating patients with this regimen accelerate the recovery period of COVID-19 [19].

In the present study, we investigate the effect of L-carnitine supplementation alone on the level of inflammatory parameters in patients with COVID-19. The primary objective of the study is to evaluate the extent of changes in inflammatory factors, such as CRP and ESR, following L-carnitine supplementation.

Materials and methods

Participation

This clinical trial was performed on hospitalized COVID-19 patients in Shahid Beheshti Hospital, Hamadan (IRAN). The target population was patients whose diagnosis of COVID-19 was confirmed based on Iranian ministry of health guidelines and hospitalized with mild-to-moderate disease. This study was approved by the ethics committee of Hamadan University of Medical Sciences with IR.UMSHA.

REC.1399.650 ethics code and registered in the Iranian Registry of Clinical Trials (IRCT20200921048794N1).

Inclusion criteria included: age above 18 and below 60 years, positive polymerase chain reaction (PCR) test, hospitalization, infection with coronavirus, and mild-to-moderate disease severity (according to the ministry of health guidelines). Exclusion criteria included: Pregnancy, lactation, severe cardiovascular disease, having other infections such as human immunodeficiency virus (HIV), history of taking L-carnitine supplement in the last month, requires intensive care units (ICU), patients with high and critical disease severity, taking anti-inflammatory drugs out of the patient's medication regimen and the patient's unwillingness to continue cooperating with investigators.

Study design

This is a single-center, prospective, randomized, double-blind, and pilot clinical trial evaluating L-carnitine effect in patients with mild-to-moderate COVID-19 hospitalized in Shahid Beheshti Hospital, (Hamadan, IRAN). After diagnosis by the relevant specialist physician and obtaining informed consent, the patient's characteristics including demographic characteristics (age, sex), marital status and underlying diseases were registered.

The patients were randomly divided into intervention and control groups after providing informed written consent. Assignment of patients into control or intervention groups was random block; briefly we put three A sheets (control) and two B sheets (intervention) in an envelope and each time we randomly picked one of the sheets and assigned the patient to the control or intervention groups, respectively. The removed sheet was not returned to the envelope until the other sheets in the envelope were finished. After pulling out all five sheets randomly, all sheets were returned to the drawer and this procedure was continued for the next five patients until the desired sample size was reached.

The control group received only their routine hospital treatment, including remdesivir, beta-interferon, and dexamethasone. In addition to the routine medication, the intervention group received 1000 mg oral L-carnitine tablet (Karen pharmaceutical Company, Iran) every 8 h for five days (3 gr daily).

At the start of the study (before receiving the drug) and at the end of the study (five days after receiving the drug), 7 ml blood samples were taken from patients in the hospital and transferred to the laboratory. The level of inflammatory factors and other serum factors, such as CRP, ESR, white blood cell (WBC) count, neutrophil, lymphocyte, monocyte, platelet, hemoglobin, hematocrit (HCT), alanine transaminase (ALT), aspartate transaminase, ALP, LDH, urea, creatinine, sodium, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and CPK, were measured in blood tests. O2 saturation level was also measured with a pulse oximeter in the hospital. Clinical outcomes including fever, cough, and death were also recorded.

Statistical analysis

Qualitative data were presented as frequency (and percentage), and compared using a χ^2 test. Quantitative data were presented as mean ± standard deviation (SD), and a two-sided *T*-test was used to compare the means between the intervention and control groups. The analyses were performed by SPSS 24 software at a 95% confidence interval level (CI).

Results

Demographics and patient's characteristics

Figure 1 illustrates a flow chart of the trial process. During the study period, 221 patients were screened for eligibility. Of the 114 patients who were eligible for inclusion in the study, 38 patients were excluded according to our study exclusion criteria, and 76 patients participated in the study, including 43 individuals assigned to the control and 33 to the intervention group (Fig. 1). The mean age of patients in the control and intervention groups was 45.04 ± 14.19 and 43.40 ± 8.42 years, respectively. The mean body weight was 74.34 ± 10.43 kg in the control and 80.28 ± 14.33 kg in the intervention group ($p = 0.121$, by *T*-test).

The patient's characteristics are listed in Table 1. Twenty-five (58.1%) patients in the control group and 18 (56.3%) patients in the intervention group were males, and there was no significant difference between the groups in terms of sex ($p = 0.184$; χ^2 test). Six (14%) patients in the control group and 4 (12.5%) patients in the intervention group had university degrees, and a significant difference regarding education level ($p = 0.029$; χ^2 test) between the two groups was observed. In the control and intervention groups, 43 (95.3%) and 29 (90.6%) patients were married, respectively ($p = 0.260$; χ^2 test). Additionally, 21 (48.8%) patients in the control group and 19 (59.4%) patients in the intervention group had no underlying diseases. In contrast, others suffered from conditions, such as diabetes, hypertension (HTN), hypothyroidism, hyperthyroidism, multiple sclerosis (MS), rheumatoid arthritis (RA), Hodgkin lymphoma, seizure, cancer, and other diseases ($p = 0.008$; χ^2 test) (Table 1).

Para-clinical test result

The results of the para-clinical examination are listed in Table 2. O2 saturation, ESR, WBC count, HCT, LDH,

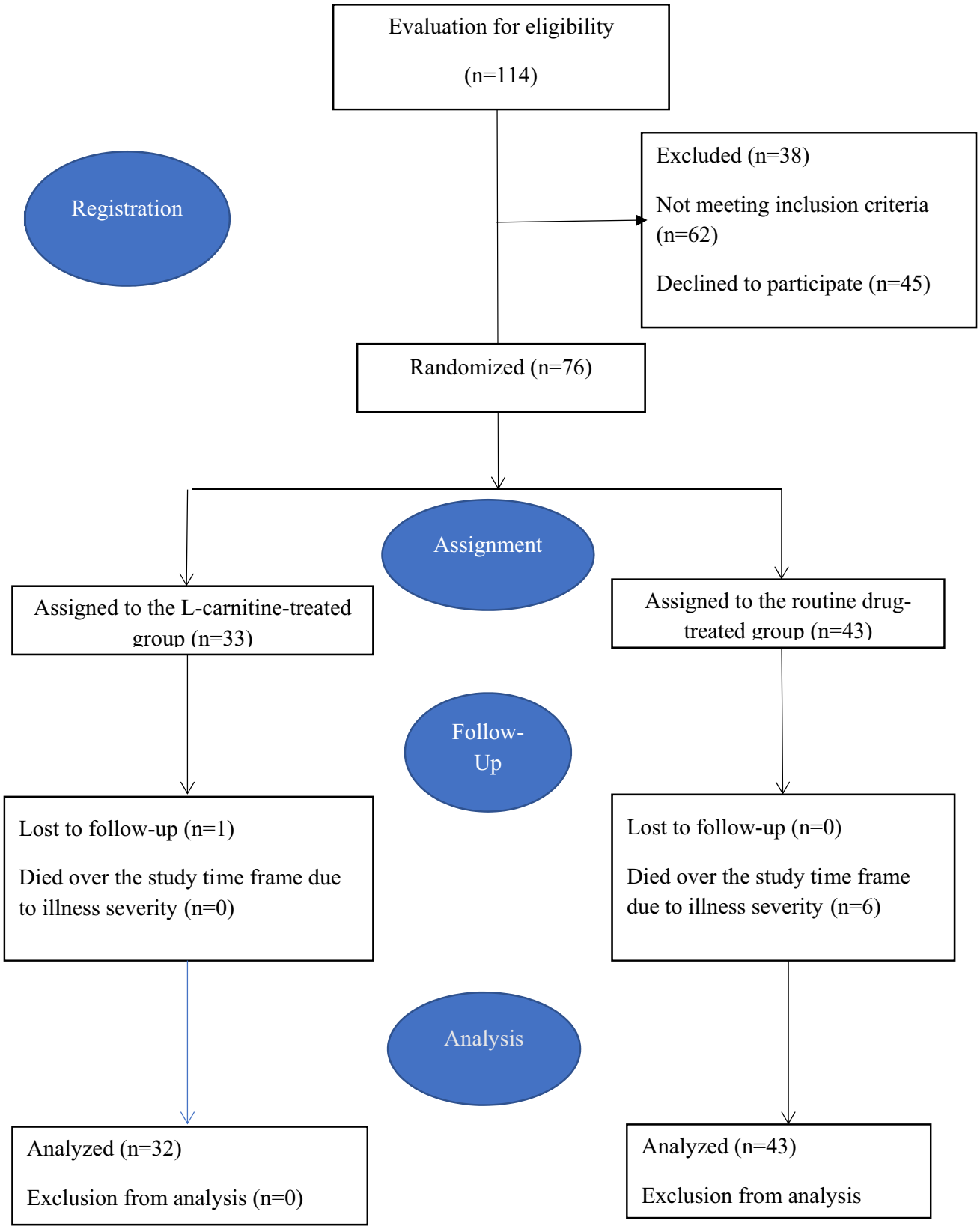

Fig. 1 The study flow diagram

Table 1 Patient's characteristics in control and intervention groups

Variable	Control *N* (%)	Intervention *N* (%)	χ^2	*p**	Sample size
Sex					
Male	25 (58.1%)	18 (56.2%)	0.027	0.184	75
Female	18 (41.9%)	14 (43.8%)			
Education					
No	11 (25.6%)	2 (6.3%)	5.836	0.029*	75
None-college educated	26 (60.4%)	26 (81.3%)			
Collage educated	6 (14%)	4 (12.4%)			
Marital status					
Single	2 (4.7%)	3 (9.4%)	0.658	0.260	75
Married	41 (95.3%)	29 (90.6%)			
Underlying disease					
No	21 (48.8%)	19 (59.3%)	7.685	0.008*	75
Hypertension	2 (4.7%)	3 (9.4%)			
Diabetes	2 (4.7%)	1 (3.1%)			
Hypothyroidism	1 (2.3%)	2 (6.3%)			
Hyperthyroidism	0 (0%)	1 (3.1%)			
MS	1 (2.3%)	0 (0%)			
RA	3 (7%)	1 (3.1%)			
Hodgkin lymphoma	2 (4.7%)	0 (0%)			
Seizure	1 (2.3%)	0 (0%)			
Cancer	1 (2.3%)	0 (0%)			
Hypertension and Diabetes	5 (11.6%)	3 (9.4%)			
Others	4 (9.3%)	2 (6.3%)			

*χ^2

urea, creatinine, and PTT were different between the two control and intervention groups at the beginning of the study ($p < 0.05$; two-sided *T*-test) while other parameters including CRP, ferritin, neutrophil count, lymphocyte count, monocyte count, platelet, Hb, ALT, AST, ALP, Sodium, PT, INR, and CPK were the same with no statistical differences ($p > 0.05$; two-sided *T*-test). After the treatment, significant changes in some para-clinical parameters were seen. A higher mean of O2 saturation (Adjusted *p* value = 0.039; two-sided *T*-test) was observed in the intervention rather than in the control group. In addition, mean ESR and CRP, as indicators of inflammation, were significantly lower in the intervention group compared to the control ($p = 0.021$ and $p = 0.009$, respectively; two-sided *T*-test). Furthermore, a significant slight decrease in mean Hb was observed in the intervention rather than in the control group after treatment ($p = 0.026$; two-sided *T*-test). Also, mean ALP and LDH activity were lower in the intervention compared to the control group significantly ($p = 0.010$ and $p = 0.002$, respectively; two-sided *T*-test). Additionally, lower mean CPK was also observed in the intervention group, which was statistically significant ($p = 0.019$; two-sided *T*-test). However, there were insignificant differences in the other para-clinical parameters between the control and intervention groups ($p > 0.05$; two-sided *T*-test) (Table 2).

Clinical outcomes

The frequencies of primary outcomes, including fever, cough, and death are listed in Table 3. Twenty-five (58.1%) patients in the control and 19 (59.4%) patients in the intervention group had fever. Cough was seen in 28 patients in the control group (65.1%) and 19 patients in the intervention group (59.4%), in which differences were insignificant and no differences in patients clinical symptoms were observed during the five days of the study. As a result, in the entire population we studied, 47 (62.6%) patients had cough and 44 (58.6%) patients had fever, which are common symptoms of this disease. Finally, 6 (14%) patients in the control group died due to the complications of COVID-19, while all the patients in the intervention group survived ($p = 0.030$; χ^2 test) (Table 3).

Table 2 Clinical examination results

Parameter	Group	Before treatment							After treatment							Adjusted *p* value
		n	Mean	SD	Mean diff	*p*	*t* value	df	*n*	Mean	SD	Mean diff	*p*	*t* value	df	
O2 saturation	Control	43	90.4186	4.03103	− 2.33140	0.000	− 2.936	73	43	92.2791	2.41351	− 1.65843	0.000	− 3.525	73	0.039*
	Intervention	32	92.7500	2.28600	− 2.33140				32	93.9375	1.29359	− 1.65843				
CRP	Control	43	1.8837	1.11717	0.28997	0.779	1.143	73	43	1.6233	2.15548	1.31076	0.021*	3.358	73	
	Intervention	32	1.5938	1.04293	0.28997				32	0.3125	.53506	1.31076				
ESR	Control	43	54.1512	30.70027	20.68241	0.002	3.370	73	43	43.0349	30.74674	23.09738	0.000	4.124	73	0.009*
	Intervention	32	33.4688	18.71688	20.68241				32	19.9375	8.63951	23.09738				
Ferritin	Control	11	381.6364	304.88203	− 3.59441	0.064	− 0.036	22	10	338.4000	192.51620	− 40.21538	0.772	− 0.517	21	
	Intervention	13	385.2308	169.50327	− 3.59441				13	378.6154	179.14033	− 40.21538				
WBC count	Control	43	7397.6744	5722.6987	1869.5494	0.021	1.744	73	43	8060.4651	5057.1562	660.46512	0.163	0.670	73	
	Intervention	32	5528.1250	2302.6260	1869.5494				32	7400.0000	2713.4076	660.46512				
Neutrophil	Control	43	75.2791	11.37735	6.09157	0.544	2.308	73	43	79.7674	11.19489	11.14244	0.861	4.283	73	
	Intervention	32	69.1875	11.20322	6.09157				32	68.6250	11.07089	11.14244				
Lymphocyte	Control	43	20.3488	10.46282	− 6.52616	0.463	− 2.719	73	43	16.8372	10.30703	− 10.78779	0.287	− 4.671	73	
	Intervention	32	26.8750	10.03140	− 6.52616				32	27.6250	9.30054	− 10.78779				
Monocyte	Control	43	2.8605	1.72629	0.17297	0.629	0.467	73	43	2.3953	1.57570	− 0.26090	0.566	− 0.636	73	
	Intervention	32	2.6875	1.37811	0.17297				32	2.6563	1.97744	− 0.26090				
Platelet	Control	43	193.2558	89.50874	2.56831	0.697	0.134	73	43	218.6744	81.95170	− 4.26308	0.611	− 0.232	73	
	Intervention	32	190.6875	71.63908	2.56831				32	222.9375	74.03484	− 4.26308				
Hb	Control	43	12.9000	2.44316	− 1.46250	0.083	− 2.861	73	43	12.5884	2.47658	− 1.58975	0.026*	− 3.124	73	
	Intervention	32	14.3625	1.78845	− 1.46250				32	14.1781	1.69682	− 1.58975				
HCT	Control	43	38.9930	6.49213	− 4.39448	0.021	− 3.321	73	43	38.1233	6.21985	− 4.85799	0.248	− 3.653	73	0.124
	Intervention	32	43.3875	4.30632	− 4.39448				32	42.9813	4.90006	− 4.85799				
ALT	Control	42	39.9286	29.04697	1.52232	0.682	0.228	72	43	67.5814	39.27027	− 1.60610	0.804	− 0.174	73	
	Intervention	32	38.4063	27.55272	1.52232				32	69.1875	39.74470	− 1.60610				
AST	Control	43	33.0000	19.67837	1.28125	0.893	0.280	73	43	43.7209	21.20122	0.81468	0.407	0.140	73	
	Intervention	32	31.7188	19.48073	1.28125				32	42.9063	29.37341	0.81468				
ALP	Control	40	180.7750	93.51662	− 7.52500	0.273	− .0374	68	40	193.5750	98.69401	6.24167	0.010	0.326	68	
	Intervention	30	188.3000	67.24641	− 7.52500				30	187.3333	40.96789	6.24167				
LDH	Control	37	676.2703	247.77528	169.60360	0.005	2.889	56	39	664.1282	386.49560	242.65201	0.003	2.819	58	0.002**
	Intervention	21	506.6667	137.14785	169.60360				21	421.4762	97.25462	242.65201				
Urea	Control	43	35.8140	20.07635	11.25145	0.000	3.073	73	43	38.0930	16.75000	8.15552	0.002	2.550	73	0.547
	Intervention	32	24.5625	5.74140	11.25145				32	29.9375	7.85324	8.15552				
Creatinine	Control	43	1.0491	0.41734	0.11188	0.006	1.438	73	43	0.9244	0.21085	− 0.05621	0.050	− 1.294	73	
	Intervention	32	0.9372	0.16005	0.11188				32	0.9806	0.14607	− 0.05621				
Sodium	Control	43	137.3953	6.00848	0.33285	0.209	0.293	73	43	137.2558	5.03366	− 0.99419	0.206	− 1.021	73	
	Intervention	32	137.0625	2.61432	0.33285				32	138.2500	2.57782	− 0.99419				

Table 2 (continued)

Parameter	Group	Before treatment						After treatment						Adjusted *p* value
		n	Mean	SD	Mean diff	*p*	*t* value	df	*n*	Mean	SD	Mean diff	*p*	*t* value	df	
PT	Control	43	12.2767	2.95642	0.56737	0.064	1.037	73	43	12.4674	1.69449	0.06119	0.021*	0.192	73	
	Intervention	32	11.7094	1.04491	0.56737				32	12.4063	0.71389	0.06119				
PTT	Control	43	25.6442	4.08320	0.41919	0.032	0.546	73	43	25.6860	5.16654	− 0.37958	0.477	− 0.396	73	
	Intervention	32	25.2250	1.69401	0.41919				32	26.0656	1.85483	− 0.37958				
INR	Control	43	1.1258	0.31020	0.06485	0.107	1.101	72	43	1.1088	0.16681	− 0.03536	0.635	− 0.952	72	
	Intervention	31	1.0610	0.12300	0.06485				31	1.1442	0.14366	− 0.03536				
CPK	Control	9	133.4444	135.43459	72.44444	0.156	1.411	15	6	343.0000	612.50992	284.00000	0.019*	1.328	12	
	Intervention	8	61.0000	54.47411	72.44444				8	59.0000	31.65890	284.00000				

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *ALP* alkaline phosphatase activity, *LDH* lactate dehydrogenase, *CPK* serum creatine phosphokinase, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalized ratio, *WBC* white blood cell, *HCT* hematocrit

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

Table 3 The primary outcomes of patient's in control and intervention groups

Outcome	Control *N* (%)	Intervention *N* (%)	χ^2	*p**	Sample size
Fever					
No	18 (41.9%)	13 (40.6%)	0.012	0.186	75
Yes	25 (58.1%)	19 (59.4%)			
Cough					
No	15 (34.9%)	13 (40.6%)	0.258	0.167	75
Yes	28 (65.1%)	19 (59.4%)			
Death					
No	37 (86%)	32 (100%)	4.853	0.030*	75
Yes	6 (14%)	0 (0%)			

*χ^2

Discussion

In the current study, the potential benefits of L-carnitine supplementation in patients with COVID-19 disease have been evaluated. Statistical analyses revealed that L-carnitine supplementation can decrease inflammation caused by infection, increase oxygen saturation levels and decrease liver enzymes levels. The results of this study showed that the administration of L-carnitine significantly improves blood oxygen saturation in COVID-19 patients. As a result, the need for the ventilator decreased in patients. Following the spread of infection from the upper respiratory tract to the lungs, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infects the lung cells through a specific ACE2 receptor, which destroys these cells, leading to decreased oxygen saturation. It has been reported that a higher carnitine level was causally associated with decreased susceptibility and severity of COVID-19. Increased percentage of oxygen saturation as a result of L-carnitine supplementation in patients can accelerate the recovery of symptoms. This improved oxygen saturation may be due to decreased ACE2 expression and thus inhibition of virus binding to lung cells [18]. In this regard, Bellamine et al. showed that L-carnitine can reduce the expression of ACE2 in human pulmonary epithelial cells in vitro as well as in clinical conditions in animal models and humans [20]. The effect of L-carnitine on reducing ACE2 expression is through its effect on increasing hepatocyte nuclear factor 4 alpha (HNF4-α) level [21]. HNF4-α play a direct role in lowering ACE2 expression [22]. The results of another study using a lamb model with increased pulmonary blood flow showed that chronic l-carnitine treatment alleviates changes in lung carnitine homeostasis, reduces associated oxidative stress, and improves pulmonary mitochondrial function, NO signaling and eventually endothelial function [23].

In the present study, considerable increase in inflammatory factors, such as CRP and ESR, has been observed during infection and inflammation caused by COVID-19. On the other hand, according to the obtained results, the mean CRP and ESR levels in patients receiving L-carnitine were significantly reduced. As a result, reducing these factors can be indicated an improvement in the disease process. In this regard, Liu et al. by examining 78 patients admitted to Wuhan Hospital in China, showed an increased CRP level in patients with COVID-19 [24]. Similar results were observed in a study by Mardani et al. on COVID-19 patients in Iran [25]. In addition, some studies show the role of L-carnitine supplementation in reducing inflammation and thus reducing CRP and ESR in hemodialysis patients [14]. Bellamine et al. showed that L-carnitine reduces serum CRP levels in rodents infected with the SARS-CoV2 virus and in patients with COVID-19 [20]. L-carnitine increases ACE1 and decreases ACE2 in lung and muscle tissue, thereby reducing inflammation by converting angiotensin I to angiotensin II, which plays an anti-inflammatory role [26]. However, L-carnitine and its active form, acetyl-carnitine, are involved in the systemic reduction of inflammation by reducing inflammatory factors and cytokines, such as CRP, IL-6, and TNF-α [27]. Since cytokine storms cause the progression of COVID-19 disease, the use of L-carnitine can prevent the progress of infections [28]. It should also be noted that L-carnitine inhibits lipid peroxidation, reduces oxidative stress, such as ROS, improves mitochondrial function, and thus plays a pivotal role in reducing inflammation [29]. Additionally, L-carnitine is thought to be a booster of the immune system (such as increasing the function of macrophages), which is involved in reducing infection and inflammation [30].

In this study, we found that L-carnitine did not change the mean levels of liver enzymes, including ALT and AST, but prevented the excessive increase in ALP levels. However, some studies have shown increased levels of liver enzymes during COVID-19 [31]. Numerous studies have demonstrated the role of L-carnitine in lowering liver damage by reducing the levels of liver enzymes, such as ALT, AST and ALP [32]. In addition, regenerative glutathione synthesis in the liver is reduced during liver injury. L-Carnitine has antioxidant properties and reduces glutathione by reducing thiol groups [33].

Our study showed that L-carnitine decreases urea and creatinine levels in patients, although only a significant difference in urea levels was observed between the two groups. Some studies have shown that urea is increased in patients with COVID-19 [11]. L-carnitine is considered a therapeutic supplement in patients with kidney disease, and those who need hemodialysis. The administration of L-carnitine in renal patients is associated with a decrease in urea and creatinine, which is due to the improvement of the body's overall metabolism in patients and a reduction in protein catabolism [34].

The results of our study showed that L-carnitine supplementation reduced PT time, although it did not alter PTT and INR. Increased PT is an essential feature of COVID-19 and is a risk factor for disease severity and poor prognosis. High PT is caused by defects in the coagulation system and thrombocytopenia [35]. Previous studies have also shown that L-carnitine reduces PT time in liver patients such as those with encephalopathy [36]. The effect of L-carnitine in reducing PT time is due to its antioxidant properties in the liver, which protects liver cells from damage [37].

Our results showed that L-carnitine significantly reduces the mean CPK and LDH in patients compared to the control group. CPK is found mainly in skeletal muscle and brain, and its increase indicates damage to these tissues. LDH is also found in abundance in all body cells and plays a direct role in energy metabolism. Any increase in the levels of these enzymes indicates the presence of a defect in one of the body's organs. In some patients with COVID-19, damage to organs such as muscles has been reported, resulting in increased CPK and LDH enzymes. Some studies have shown that L-carnitine reduces damage to muscles and organs of the body, such as the kidneys and reduces CPK and LDH levels in patients [38].

Looking for a comparison between the control and intervention groups, we found that the frequency of patients who had cough or fever after the treatment did not significantly differ. However, death was not observed in any patients receiving L-carnitine. First, the reduction in death from disease can be due to an increase in the level of saturated oxygen in the blood, which facilitates oxygen delivery and thus stops the progression of the disease. Second, L-carnitine may reduce the inflammatory processes, prevent the virus from attaching to the host cell by reducing ACE2, and regulate energy metabolism, thereby preventing patient mortality. However, for definitive conclusions, more studies with larger sample sizes are needed.

L-Carnitine acts as a cofactor and vitamin-like and can regulate metabolic pathways. This compound is naturally present in all body cells, albeit small. However, in some people, especially elderly patients and people who are not adequately nourished, this factor may decrease. Therefore, the use of L-carnitine as a supplement can play an important role in the recovery of such patients. In our study, death due to complications of COVID-19 was not observed in the group receiving L-carnitine, although 40.6% of patients in the intervention group had underlying diseases, such as hypertension and diabetes. In line with our study, Rothkopf et al. also showed that a combination supplement containing multivitamins, zinc, thiamine, ergocalciferol, pyridoxine, and, carnitine helped improve the treatment of elderly patients with COVID-19 [39].

A limitation of our study was the short duration of L-carnitine administration; so the treatment was performed for five days. Also, treatment in patients hospitalized in Iran is based on the administration of remdesivir or favipiravir and it was impossible to investigate the interaction between L-carnitine and these antiviral drugs. Additionally, the study was a single-center investigation.

Conclusion

The results obtained in the present study indicate the use of L-carnitine in patients with COVID-19, could contribute to the reduction of inflammation caused by infection, oxygen delivery improvement by increasing oxygen saturation levels, normalization of elevated liver enzymes, regulation of the body's energy metabolism, and ultimately reduce clinical mortality through multiple metabolic pathways. As a result, L-carnitine can be suggested as a pharmacological supplement in patients with COVID-19, but further research and clinical studies with larger sample sizes are needed to confirm and extend the results of this study.

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Author contributions SST was involved in patient registering, data acquisition, Conceptualization and final checking of the manuscript. MG carried out the data acquisition and drafting. MEE participated and involved in interpretation of data, and final check of the draft and helped to revise the manuscript. YM involved in doing statistical analysis and revising. RH the supervisor of the study, was involved in concept, design, support of study, drafting and final checking of the manuscript. All authors read and approved the final manuscript.

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Data availability Some data generated or analyzed during this study are included in supplementary information files. All datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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