Chapter 22
Evaluation of Curcumin-Piperine Supplementation in COVID-19 Patients Admitted to the Intensive Care: A Double-Blind, Randomized Controlled Trial

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Abstract

Background

Curcumin is a traditional remedy for diseases associated with hyper-inflammatory responses and immune system impairment. Piperine, a bioactive compound in black pepper, has the potential to enhance curcumin bioavailability. 0This study aims to examine the effect of the curcumin-piperine co-supplementation in patients infected with SARS-CoV-2 and admitted to the intensive care unit (ICU).

Material and Methods

In this parallel randomized, double-blind, placebo-controlled trial, 40 patients with COVID-19 admitted to ICU were randomized to receive three capsules of curcumin (500 mg)-piperine (5 mg) or placebo for 7 days.

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Results
After 1 week of the intervention, serum aspartate aminotransferase (AST) ($p = 0.02$) and C-reactive protein (CRP) ($p = 0.03$) were significantly decreased, and hemoglobin was increased ($p = 0.03$) in the curcumin-piperine compared to the placebo group. However, compared with the placebo, curcumin-piperine had no significant effects on the other biochemical, hematological, and arterial blood gas and 28-day mortality rate was three patients in each group ($p = 0.99$).

Conclusion
The study results showed that short-term curcumin-piperine supplementation significantly decreased CRP, AST, and increased hemoglobin in COVID-19 patients admitted to the ICU. Based on these promising findings, curcumin appears to be a complementary treatment option for COVID-19 patients, although some parameters were not affected by the intervention.

Keywords Curcumin · Piperine · SARS-CoV-2 · COVID-19 · ICU · CRP

1 Introduction

The COVID-19 outbreak began in Wuhan, China, in December 2019 and spread quickly to other countries [1]. Based on its genome similarity of 79% to Coronaviruses, this new strain was called SARS-CoV-2 [2]. Many new SARS-CoV-2 variants have emerged since the first outbreak, despite isolation, lockdown, and other containment measures [3]. Recently, the WHO reported 600 million cases of confirmed COVID-19 and over 6.5 million deaths [4]. Even with rapid advances in public vaccination, the disease remains a major public health concern [5] and has negatively affected people's lives [6]. Despite early determination of the SARS-CoV-2 structure and the development of some effective treatments and vaccines [7], the virus continued to spread and the pathogenesis is still not entirely clear. However, it appears that a cytokine storm effect caused by alteration of the immune system

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plays a crucial role in disease effects [8]. The cytokine storm effect can lead to inflammatory responses and changes in hematologic parameters, leading to damaging effects such as severe lung damage, liver injury, and death in some cases [9–13].

A number of traditional compounds have shown some promise in curbing some of these effects and prove effective as well-tolerated alternate therapies for COVID-19 infection. Curcumin is a bioactive polyphenol with a multitude of pharmacological effects [14–21] and a number of recent studies have shown that this compound has beneficial effects on diseases associated with hyperinflammatory responses and immune system impairment, such as COVID-19 [8, 22–26]. Many preclinical and clinical studies have indicated the health benefits and safety (tolerated up to 12 g/day) benefits of this nutraceutical [27, 28]. Additionally, a wide range of pharmacological and biological activities have been attributed to its therapeutic mechanism of action, including immunomodulatory, anti-tumor, antimicrobial, antiviral, antioxidant, and anti-inflammatory properties [29–32]. However, the poor solubility in aqueous solutions, extensive metabolism in the liver and intestine, and rapid elimination of curcumin result in low bioavailability. To overcome this issue, compounds, such as piperine, a bioactive compound in black pepper, have been used to enhance curcumin absorption, inhibit metabolic enzymes, and limit curcumin clearance through the P glycoprotein efflux pump [33, 34]. Adding piperine to curcumin can significantly increase its bioavailability in humans [34]. Few studies have shown the benefits of curcumin in COVID-19 infection, but none have investigated the impact of curcumin-piperine supplementation in patients in intensive care units (ICUs). Thus, this study aims to examine the effect of the administration of curcumin-piperine supplementation on ICU patients infected with SARS-CoV-2.

2 Material and Methods

2.1 Study Design and Participants

This parallel randomized, double-blind, placebo-controlled trial assessing the efficacy of co-supplementation of curcumin-piperine on COVID-19 patients admitted to ICUs of Alzahra hospital, an academic hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, between June and September in 2021. The summary of the study protocol was published earlier [35]. The protocol was approved by the ethics committee of the Isfahan University of Medical Sciences (ethic code: IR.MUI.RESEARCH.REC.1400.057) and conducted based on the principles of the Declaration of Helsinki. The trial was also registered in the Iranian Registry of Clinical trials (IRCT) with ID: IRCT20121216011763N52. Before starting the study, the objectives and procedures of the trial were explained to patients or their caregivers, and written informed consent was obtained from all participants. Patients with a definitive diagnosis of COVID-19 confirmed via real-time polymerase chain reaction (RT-PCR), 30–70 years-old, and who were admitted to the ICUs, were

included. Exclusion criteria were as follows: unstable hemodynamic status, renal or liver disease, undergoing dialysis, cancer patients undergoing chemotherapy, and pregnancy. The other exclusion criteria included use of parenteral nutrition, taking anticoagulant drugs such as warfarin and having a history of sensitivity to herbal products such as turmeric and pepper. Patients were withdrawn from the trial if they were unwilling to continue or showed any adverse effects.

2.2 Randomization and Blinding

A total of 40 patients were randomized in a ratio of 1:1 into two groups. An independent statistician conducted the sequencing of the assignment using a table of random numbering and this was kept in opaque, sealed, numbered envelopes until the end of the assessment of the eligibility criteria. Curcumin-piperine and placebo capsules were provided in identical formats with the same shape, size, color, and odor. Participants, investigators, laboratory staff, outcome assessors, and data analyzers were blinded to treatment assignments until the completion of data analyses.

2.3 Intervention

Patients in the intervention group received three curcumin piperine capsules containing 500 mg curcumin and 5 mg piperine per capsule, amounting to a total of 1500 mg curcumin and 15 mg piperine in a day. Capsules were administered orally or with enteral nutrition (gavage) at 9 am, 3 pm, and 9 pm (6 h apart). The duration of the intervention was 7 days. Patients in the control group received three matched placebo capsules a day, each containing 505 mg maltodextrin (1515 mg maltodextrin/day). All capsules were provided by Sami-Sabinsa Group Limited (Bangalore, India). The intervention was started 24–48 h after admission to the ICU when hemodynamic resuscitation and stabilization were carried out and when patients received at least 70% of their energy requirements based on 25 kcal/kg body weight. All patients continued standard treatment as per the physician's prescriptions and were allowed to take their usual medications without any limitations.

2.4 Outcome Measures and Data Collection

Acute physiology and chronic health evaluation II (APACHE II) and NUTRIC score were calculated to assess COVID-19 disease severity and nutritional status of the patients, respectively, at the beginning of the study. Blood samples (5 mL) were obtained early in the morning after approximately 6 h fasting before and after the intervention. These were left for 60 min to allow clotting and centrifuged at room

temperature for 10 min to isolate serum, which was stored at −80 °C until use. The parameters measured were serum calcium (Ca), magnesium (Mg), sodium (Na), potassium (K), chloride (Cl), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin (ALB), C-reactive protein (CRP), complete blood count (CBC) including white blood cells (WBCs), red blood cells (RBCs), hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets (PLT), blood urea nitrogen (BUN), serum creatinine (Cr), prothrombin time (PT), and partial phromboplastin time (PTT). These parameters were assessed at baseline and end of the study at the laboratory center of Alzahra hospital using enzymatic methods and auto-analyzer with commercial kits (Pars Azmun, Karaj, Iran). Furthermore, arterial blood gas (ABG) was taken while the patient was breathing room air.

2.5 Statistical Analysis

The statistical package for the social sciences (SPSS) software version 16 (SPSS Inc., Chicago, IL, USA) was used to analyze data. Paired sample t and chi-squared tests were used to analyze within-group differences. The differences between the groups were assessed using independent student's t-test. Data were reported as mean ± standard deviation (SD) or frequency (percentage). Analysis of covariance (ANCOVA) was used to compare the mean values of continuous outcomes at the end of the study between two groups, considering adjustment for baseline values. Chi-squared or Fisher exact tests were used to compare qualitative outcomes between groups. A p-value less than 0.05 was considered statistically significant.

3 Results

A total of 94 patients were assessed for eligibility, 42 patients were excluded for not meeting inclusion criteria, and 12 persons refused to participate in the study (Fig. 22.1). After this, patients (19 men and 21 women) were randomized to receive the curcumin-piperine (n = 20) or maltodextrin (n = 20) capsules in three divided doses for 7 days. One subject in the curcumin piperine group and one subject in the control group died before the end of the study, and thus analyses were conducted on 38 patients (19 patients in the intervention and 19 samples in the control groups).

The baseline characteristics of patients were comparable between the groups. There was no significant difference between the groups in any of the baseline characteristics, including age, sex, APACHII, or NUTRIC scores (Table 22.1). The effects of curcumin-piperine supplementation on selected metabolic and biochemical parameters are shown in Table 22.2. The intra-group comparison showed a decreasing trend in serum AST in the curcumin-piperine group (p = 0.08) and a

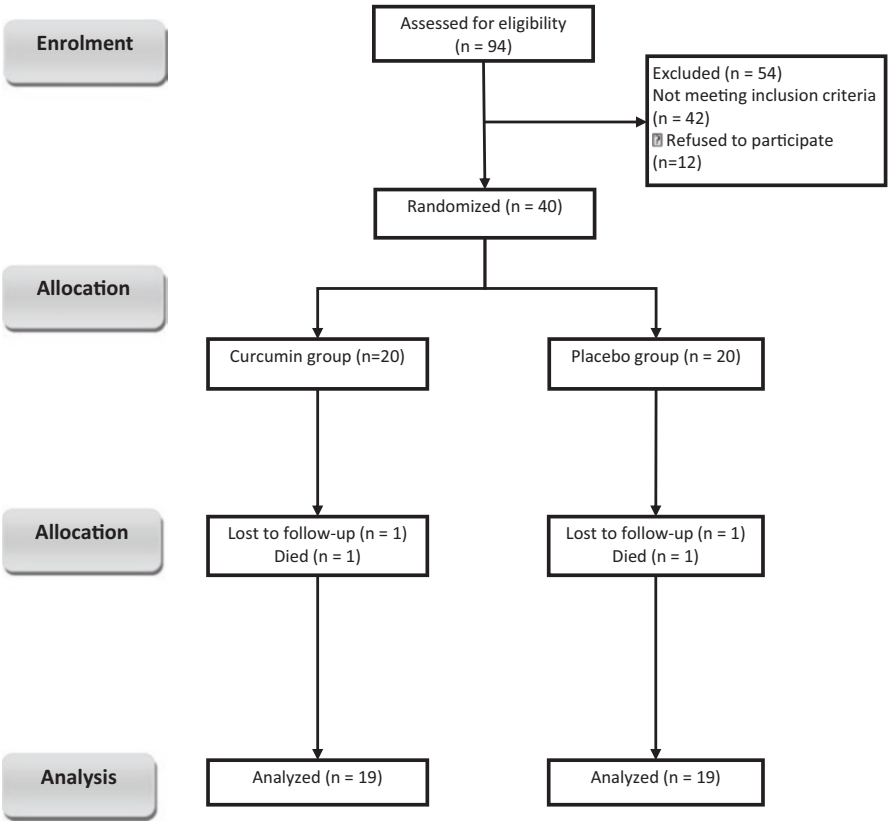

Fig. 22.1 Flowchart showing patient selection

Table 22.1 Summary of baseline characteristics of the patients

Variables	Intervention (20)	Placebo group (n = 20)	P-values
Age, y	50.26 ± 8.83	54.95 ± 12.58	0.513[a]
Sex (%men)	10(50)	9(45)	0.75[b]
APACH II	19.65 ± 5.51	17.30 ± 4.81	0.15[a]
NUTRIC	3.95 ± 1.50	3.70 ± 1.12	0.55[a]

Data are presented as mean ± SD or number (percent)
APACH acute physiology and chronic health evaluation
[a]Based on independent sample t-test
[b]Based on Pearson chi-squared test

significant increase in the level of AST in the placebo group (p = 0.03). Furthermore, compared to the baseline, after 7 days of intervention, a non-significant increase was found in the serum levels of BUN (p = 0.09), Cr (p = 0.07), ALT (p = 0.09) in the placebo and for ALP (p = 0.08) in the curcumin piperine group. Based on the inter-group comparisons, it was found that the AST (p = 0.02) and CRP (p = 0.03)

Table 22.2 Changes in metabolic and biochemical parameters during the study

	Curcumin-piperine group (n = 19)				Placebo group (n = 19)				
Variables	Baseline	Week one	MD ± SE[a]	P-value	Baseline	Week one	MD ± SE[a]	P-value[a]	P-value[b]
BUN (mg/dL)	23.3 ± 7.5	22.9 ± 9.4	−0.4 ± 1.8	0.86	30.0 ± 14.9	36.3 ± 26.5	6.3 ± 3.6	0.09	0.30
Cr (mg/dL)	1.0 ± 0.2	1.3 ± 1.6	0.3 ± 0.4	0.39	1.0 ± 0.3	1.4 ± 1.2	0.4 ± 0.2	0.07	0.77
ALT (IU/L)	58.7 ± 29.1	50.7 ± 43.0	−8.0 ± 10.7	0.46	31.4 ± 12.9	99.0 ± 171.2	67.6 ± 169.4	0.09	0.18
AST (IU/L)	42.7 ± 24.6	35.9 ± 19.3	−6.7 ± 3.6	0.08	29.9 ± 9.6	47.4 ± 33.0	17.5 ± 7.5	**0.03**	**0.02**
ALP (IU/L)	176.0 ± 62.9	206.1 ± 103.8	30.1 ± 16.3	0.08	221.1 ± 79.5	237.8 ± 85.9	16.7 ± 17.5	0.35	0.75
CRP (mg/L)	39.5 ± 35.1	27.8 ± 33.9	−11.6 ± 7.3	0.12	36.6 ± 33.2	49.5 ± 39.5	12.9 ± 8.7	0.15	**0.03**

Significant values ($p < 0.05$) shown in bold text

Data are expressed as means ± SD; p-value <0.05 is significant

MD mean differences, *SE* standard error, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *BUN* blood urea nitrogen, *Cr* creatinine, *CRP* C-reactive protein

[a]Based on paired t-test

[b]Based on analysis of covariance (ANCOVA)

levels significantly decreased in the intervention group in comparison to the placebo group. However, there were no significant differences regarding BUN, Cr, ALT, and ALP between groups.

The effects of curcumin-piperine supplementation on hematological parameters are presented in Table 22.3. Within-group comparisons indicated that one-week supplementation with curcumin piperine led to a significant increase in MCV ($p = 0.009$) and a significant decrease in platelets ($p = 0.02$), while there was no significant change regarding other variables. Also, in the placebo group, the lymphocyte count showed a significant increase ($p = 0.01$), while hemoglobin ($p = 0.07$) and MCHC ($p = 0.08$) showed a non-significant decrease. Between-group analysis showed that in comparison to the placebo, curcumin-piperine supplementation significantly increased the serum level of hemoglobin ($p = 0.03$). Minerals and ABG parameters and their changes are presented in Table 22.4. At the end of the intervention, we observed a significant increase in pCO_2 ($p = 0.02$) and a decrease in pH ($p = 0.01$) in the curcumin-piperine compared to the placebo group. The only significant finding in the placebo group was a decrease in Cl levels ($p = 0.02$). There was no significant difference in minerals and ABG gas parameters between the two groups (p for all > 0.05). Finally, the 28-day mortality rate was 3 (15%) patients in each group, with no statistical difference between the groups ($p = 0.99$).

4 Discussion

The results of this study suggest that curcumin-piperine consumption is efficacious and safe in COVID-19 patients. Recent studies revealed that this polyphenol could positively affect disease symptoms such as sore throat, cough, fever and weakness, O_2 saturation, and length of hospital stay [30, 36, 37]. The main findings of our study are that CRP and AST levels decreased, and hemoglobin concentration increased significantly with curcumin-piperine supplementation for 7 days in COVID-19 ICU patients.

A number of prior studies have obtained similar results regarding anti-inflammatory effects of curcumin in COVID-19. A previous randomized-controlled trial on 60 COVID-19 patients revealed that subjects receiving 160 mg of curcuminoids daily had reduced CRP levels than placebo [38], as we found here. It has also been shown that other inflammatory markers such as IL-6 and IL-1β are also reduced due to curcumin supplementation [22, 39, 40]. A systematic review performed in 2022 indicated that curcumin supplementation reduced not only pro-inflammatory cytokines but also was effective in increasing IL-10, IL-35, and TGF-a as anti-inflammatory cytokines [8]. These effects are most likely driven by the curcumin modulation of inflammatory signaling pathways such as the nuclear factor-κB (NF-kB), mitogen-activated protein kinase (MAPK), activator protein 1 (AP-1), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) transcription factors [24].

Table 22.3 Hematological analysis of blood samples and their changes in the intervention and placebo groups at baseline and at the end of the study

	Curcumin-piperine group (n = 19)				Placebo group (n = 19)				
Variables	Baseline	Week one	MD ± SE[a]	P-value[a]	Baseline	Week one	MD ± SE[a]	P-value[a]	P-value[b]
ALB (g/dL)	2.9 ± 0.3	3.0 ± 0.4	0.1 ± 0.1	0.23	2.9 ± 0.2	2.8 ± 0.4	−0.1 ± 0.1	0.15	0.06
WBC ($\times 10^9$/L)	18.1 ± 26.3	13.0 ± 4.7	−5.2 ± 5.5	0.36	13.0 ± 6.1	11.8 ± 5.6	−1.2 ± 1.2	0.33	0.70
Lym ($\times 10^9$/L)	6.9 ± 2.7	8.4 ± 5.4	1.5 ± 1.1	0.20	5.7 ± 2.6	7.6 ± 4.5	1.9 ± 0.7	**0.01**	0.72
NEUT ($\times 10^9$/L)	87.3 ± 4.3	85.6 ± 6.0	−1.8 ± 1.5	0.26	89.4 ± 5.2	86.9 ± 6.4	−2.5 ± 1.5	0.12	0.80
RBC ($\times 10^{12}$/L)	4.2 ± 0.7	4.2 ± 0.6	−0.02 ± 0.11	0.87	4.3 ± 0.8	4.1 ± 0.8	−0.2 ± 0.1	0.17	0.37
HB (g/dL)	11.9 ± 2.13	12.0 ± 1.8	0.2 ± 0.4	0.65	11.4 ± 1.6	10.9 ± 1.4	−0.5 ± 0.3	0.07	**0.03**
HCT (%)	34.9 ± 5.6	35.3 ± 4.9	0.4 ± 0.9	0.67	33.8 ± 4.4	33.2 ± 4.2	−0.6 ± 0.9	0.49	0.20
MCV (fL/cell)	83.0 ± 5.2	84.2 ± 4.3	1.23 ± 0.4	**0.009**	81.1 ± 8.6	78.6 ± 14.6	−2.5 ± 2.7	0.37	0.19
MCH (pg)	28.0 ± 2.9	28.1 ± 3.5	0.1 ± 0.4	0.83	27.6 ± 3.0	27.5 ± 3.5	−0.1 ± 0.5	0.93	0.84
MCHC (g/dL)	34.3 ± 1.9	34.1 ± 1.7	−0.2 ± 0.4	0.66	34.0 ± 0.9	33.2 ± 2.0	−0.8 ± 0.4	0.08	0.19
Platelets ($\times 10^9$/L)	198.4 ± 80.7	160.1 ± 68.3	38.3 ± 15.3	**0.02**	200.7 ± 90.3	178.2 ± 97.6	−22.5 ± 14.0	0.12	0.39
PT (s)	14.6 ± 7.6	12.1 ± 3.8	−2.5 ± 1.3	0.07	12.6 ± 1.3	12.6 ± 9.7	0.01 ± 2.3	0.99	0.64
PTT (s)	30.6 ± 4.4	34.1 ± 10.2	3.5 ± 2.5	0.18	31.8 ± 11.0	29.3 ± 7.9	−2.5 ± 3.4	0.47	0.14

Significant values ($p < 0.05$) shown in bold text

Data are expressed as means ± SD; p-value <0.05 is significant

MD mean differences, *SE* standard error, *ALB* albumin, *HB* hemoglobin, *Lym* lymphocytes, *HCT* hematocrit, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *NEUT* neutrophils, *PT* prothrombin time, *PTT* partial thromboplastin time, *RBC* red blood cells, *WBC* white blood cells

[a]Based on paired t-test

[b]Based on analysis of covariance (ANCOVA)

Table 22.4 Changes in some minerals and PH during the study

	Curcumin group (n = 19)				Placebo group (n = 19)				
Variable	Baseline	Week one	MD ± SE[a]	P-value[a]	Baseline	Week one	MD ± SE[a]	P-value[a]	P-value[b]
Na (mM)	137.3 ± 3.2	137.8 ± 3.1	0.5 ± 0.7	0.45	141.2 ± 5.6	140.0 ± 5.1	−1.2 ± 1.4	0.39	0.62
K (mM)	4.4 ± 0.4	4.6 ± 0.6	0.2 ± 0.1	0.18	4.6 ± 1.0	4.8 ± 0.7	0.2 ± 0.3	0.51	0.24
P (mg/dL)	3.2 ± 0.7	3.2 ± 0.7	0.02 ± 0.2	0.89	3.1 ± 0.5	3.3 ± 0.8	0.1 ± 0.2	0.48	0.66
Mg (mg/dL)	2.0 ± 0.2	2.0 ± 0.2	0.1 ± 0.1	0.42	2.1 ± 0.2	2.1 ± 0.2	0.01 ± 0.03	0.76	0.68
Cl (mEq/L)	105.4 ± 4.3	104.5 ± 4.6	−0.8 ± 0.9	0.33	107.1 ± 4.8	105.2 ± 3.8	−1.9 ± 0.8	**0.02**	0.66
Ca (mg/dL)	8.0 ± 0.7	8.2 ± 0.5	0.1 ± 0.2	0.42	8.0 ± 0.6	8.2 ± 0.6	0.2 ± 0.1	0.23	0.96
pH	7.5 ± 0.04	7.4 ± 0.1	−0.03 ± 0.01	**0.01**	7.2 ± 0.1	7.4 ± 0.1	−0.1 ± 0.02	0.09	0.23
$_{p}CO_2$ (mmHg)	39.5 ± 8.0	48.2 ± 15.6	8.7 ± 3.5	**0.02**	43.8 ± 10.3	48.8 ± 11.4	5.0 ± 3.1	0.12	0.82
HCO_3 (mEq/L)	26.3 ± 4.6	30.0 ± 9.8	3.7 ± 2.3	0.12	28.3 ± 7.7	28.1 ± 6.1	−0.2 ± 1.7	0.90	0.32

Significant values ($p < 0.05$) shown in bold text

Data are expressed as means ± SD; p-value <0.05 is significant

MD mean differences, *SE* standard error, *Na* sodium, *K* potassium, *Ca* calcium, *Cl* chlorine, *Mg* magnesium, *P* phosphorus

[a]Based on paired t-test

[b]Based on analysis of covariance (ANCOVA)

Higher levels of liver enzymes have been observed in many COVID-19 patients, which is related to the severity of the disease and mortality risk [41, 42]. It has been proposed that elevated levels of ALT and AST indicate a possibility of COVID-19 recurrence [43]. The lowering effects of curcumin on ALT and AST have been shown in some animal and human studies [44–47]. In the present clinical trial, the administration of curcumin-piperine combination reduced the levels of AST in COVID-19 patients compared to the placebo. In the intervention group, both ALT and AST levels decreased at the end of the study compared to the baseline, although these changes did not reach statistical significance. However, AST was significantly increased in the placebo group which may be an indicator of worsening severity. This could have been caused by uncontrolled inflammation, hypoxia, and potential hepatocyte damage caused by the viral infection and replication process in those patients receiving the placebo [48]. Although BUN and creatinine did not change significantly in the curcumin group, these markers increased in the placebo group compared to the baseline as a potential indicator of impaired renal function [49]. Increased BUN and creatinine levels also serve as risk factors for a more severe disease course and increased mortality [49, 50].

We also found that hemoglobin concentrations were significantly increased in individuals who received curcumin-piperine compared to those in the placebo group. Furthermore, hemoglobin concentrations and MCHC values showed non-significant decreases in the placebo group compared with the baseline values. This is consistent with a study by Huang et al. which found that approximately 38% of COVID-19 patients had decreased levels of hemoglobin [51]. In addition, Fouad et al. concluded that hemoglobin concentration is a helpful indicator of disease severity [52]. The effective transport of oxygen in the blood is directly influenced by the hemoglobin concentration and, when an infection occurs, the peripheral tissues require more oxygen, which may result in disease complications like hypoxia and ischemia [53]. This is also consistent with our finding in the curcumin-piperine group of a significant increase in MCV, which is an indicator of red blood cell volume.

Finally, there was no difference in the 28-day mortality rate between the intervention and control groups. This result is not in line with another study which showed that supplementation curcumin-piperine two times per day over 2 weeks reduced the mortality rate in COVID-19 patients [37]. However, it is possible that the larger sample size and longer treatment used in the above mentioned study accounts for this difference.

Our work has some limitations. First, the sample size was relatively small which may have impacted on our ability to detect some significant changes or differences between the groups. Second, the duration of this study was short, although it is common approach in trials of critically ill patients. Finally, the number of biomarkers and physiological parameters that we measured was small and could be expanded to include other inflammation-related analytes, such as cytokine arrays or multiplex immunoassay panels [54–57].

In conclusion, the results of the current randomized controlled trial revealed that short-term curcumin-piperine supplementation is well-tolerated and can significantly decrease CRP, AST, and increase hemoglobin levels in COVID-19 patients admitted to ICU. Based on these findings, further larger studies should be conducted

over both short and longer time periods to investigate the potential use of this compound as a novel therapeutic option for treatment of COVID-19 disease and potentially other respiratory virus infections.

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Competing Interests MM is the founder of Sami-Sabinsa group of companies.

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