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The Efficacy of Colchicine IN Sepsis: The COLINS Randomized Clinical Trial

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Abstract

Background: Sepsis is a leading cause of mortality worldwide and is characterized by dysregulated inflammatory responses that contribute to multi-organ failure. Despite advances in supportive care, effective adjunctive anti-inflammatory therapies for sepsis remain limited. We aimed to determine whether colchicine, compared with placebo, improves inflammatory biomarkers and clinical outcomes in patients with sepsis.

Methods: The COLINS trial was a double-blind, randomized, placebo-controlled trial conducted in patients with sepsis. Patients were randomly assigned in a 1:1 ratio to receive colchicine (1 mg once daily) or a matched placebo for 10 days. Of 72 patients screened, 50 were randomized, and 44 completed the study. The primary outcome was the change in the IL-6 levels at day 4. Secondary outcomes included the change in procalcitonin at day 4, the SOFA score at days 4 and 10, 28-day mortality, the duration of mechanical ventilation, and the number of vasopressor-free days during study period.

Results: The mean age of patients was 48.4 years, and 18.2% were women. There was no significant difference in the IL-6 levels at day 4 between the colchicine group and the placebo group (P=0.42). Change in SOFA score at day 4 was significantly greater in the colchicine group than in the placebo group (P=0.02). Also, SOFA score at day 10 was significantly lower in the colchicine group (P<0.01). The number of ventilator-needed days was significantly lower in the colchicine group (P=0.04). We found no difference between colchicine and placebo in the procalcitonin level at day 4 (P=0.53), vasopressor-free days (P=0.13), or 28-day mortality (P=0.74).

Conclusion: In patients with sepsis, treatment with colchicine, significantly reduced the risk of multi-organ failure and increased ventilator-free days. However, there was no significant difference between two groups in the number of vasopressor-free days or mortality.

Keywords: Sepsis, Colchicine, COLINS trial, Anti-inflammatory, SOFA score

Introduction

Sepsis is a dysregulated response to infection that results in impaired tissue perfusion and oxygenation, leading to acute and potentially life-threatening organ failure.[1-5] Septic shock, a severe and critical form of sepsis with higher mortality, is characterized by persistent hypotension, tissue hypoxia, oliguria, and metabolic acidosis caused by vascular

vasodilation and increased capillary leak.[6] The incidence of sepsis is estimated at 250 to 500 cases per 100,000 people annually and accounts for about 6% of all hospital admissions.[7] The mortality rate for sepsis ranges from 20% to 30%, while septic shock has a significantly higher risk, between 34% and 70%, depending on patient demographics and healthcare settings.[7,8]

Current treatments for sepsis are fluid resuscitation, vasopressor agents, antimicrobial therapy, and organ support.[9] Despite the prompt use of these options, most patients with sepsis still develop multi-organ failure and death.[10] A dysregulated systemic inflammatory cascade plays a key role in the progression of sepsis and the disease's clinical course by causing veno-arterial vasodilation due to reduced vascular tone.[9] Therefore, anti-inflammatory agents may be helpful as adjunctive therapy during the inflammatory phase of sepsis.[10-12] Among these, corticosteroids have been widely studied, and clinical trials show that low-dose corticosteroids can lead to improved outcomes in patients with septic shock.[13] Based on the 2021 international guidelines for management of sepsis and septic shock, intravenous hydrocortisone at a dose of 50 mg every 6 hours can be considered for adults with septic shock who require ongoing vasopressor support.[14] Additionally, various drugs such as pentoxifylline, statins, intravenous immunoglobulin (IVIG), and ibuprofen have been evaluated in patients with sepsis for their potential to attenuate systemic inflammation.[15-18]

Colchicine, an alkaloid-based medication with anti-inflammatory properties, is approved by the US Food and Drug Administration (FDA) for the treatment of familial Mediterranean fever and gout, as well as for preventing stable ischemic heart disease.[19] It is also used off-label for conditions such as calcium pyrophosphate crystal arthritis, Behçet's syndrome, postpericardiotomy syndrome, pericarditis, Sweet syndrome, and vasculitis.[19-26] The proposed mechanisms for colchicine's anti-inflammatory effects include preventing the activation, degranulation, and migration of monocytes and neutrophils, as well as inhibiting nuclear factor-kappa B (NF-κB), tumor necrosis factor (TNF)-α, IL-6, and IL-1β.[19, 27] Recent experimental studies have shown that colchicine has beneficial effects in septic animal models. Liu et al. demonstrated that colchicine can significantly

reduce acute lung injury in septic mice by inhibiting the phosphorylation of signal transducer and activator of transcription-3 (STAT-3).[28] Additionally, the study by Kenig et al. found that low-dose colchicine alleviates sepsis-induced liver failure in mice.[29]

Based on the above evidence, the COLINS trial is the first study aimed to evaluate whether treatment with colchicine can improve clinical outcomes of patients with sepsis compared to a placebo.

Methods and design

Study ethics

The COLINS trial was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.PHARMACY.REC.1402.002). The registration number of this study at the International Clinical Trials Registry Platform is IRCT20231017059748N1. All patients or their caregivers completed and signed a consent form before the study enrollment. This trial was conducted in accordance with the Declaration of Helsinki and the later revisions of ethical principles for medical research.[30]

Study design and setting

The COLINS study was a double-blinded, placebo-controlled, randomized trial that investigated the efficacy of colchicine versus placebo in patients with sepsis from October 15, 2024, to June 30, 2025, at Imam-Reza Hospital, the largest northwest referral hospital affiliated with Tabriz University of Medical Sciences, Tabriz, Iran. The details of the trial protocol have been described previously.[31]

Study population

All patients aged 18 to 80 years admitted to the ICU with a suspected or proven infection as the main diagnosis for no more than 24 hours were enrolled in the trial. Exclusion criteria included hypersensitivity to colchicine, colchicine use within 4 weeks before the trial, pregnancy, lactation, malignancy, severe renal failure (eGFR <15 mL/min/1.73 m^2), end-stage renal disease, severe hepatic failure (Child-Pugh score B or C), and autoinflammatory disease.

Randomization and trial process

Eligible patients were randomly allocated in a 1:1 ratio to the colchicine or placebo groups using an online Web-based random allocation system with a blocked randomization method, employing block sizes of 4 and 6.[32] The sequentially numbered, opaque sealed envelopes (SNOSE) were used for allocation concealment.[33] All researchers of the trial and patients were blinded to the treatment procedure.

Patients in the intervention group received colchicine 1 mg daily for 10 days. In the control group, patients received a matching placebo tablet for 10 days. The placebo tablet was identical in appearance, color, and consistency to the colchicine tablet. All participants received standard treatments (volume resuscitation, vasopressors, and antibiotics) for their sepsis, as per local protocols. Colchicine was administered by gavage through a nasogastric tube in intubated patients. Baseline patients' demographic and clinical data were documented on a data collection form. Patients were evaluated at baseline, day 4, and day 10. Mortality was also assessed until day 28.

Study outcomes

The primary outcome was the change in IL-6 plasma levels from baseline to day 4, as assessed for each colchicine group as compared with placebo using a validated human cytokine ELISA kit. Secondary outcomes were the change in procalcitonin at day 4; the SOFA score, qSOFA score, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH) levels at days 4 and 10 compared to baseline; mortality at 28 days; and the need for mechanical ventilation and vasopressor-free days during the study period.

Safety outcomes, including gastrointestinal events (nausea, vomiting, and diarrhea) and serious adverse events (leukopenia, thrombocytopenia, hepatotoxicity, and rhabdomyolysis), were monitored during the trial period.

Sample size

The sample size was calculated for the IL-6 levels (primary outcome) by the G*power software. The sample size for the IL-6 levels, using the values of Karimi et al.'s study and considering a significance level of 0.05 and a power of 80%, was calculated to be 19

patients for each group and a total of 38 patients.[34] Considering a 15% dropout rate, at least 44 patients were needed.

Statistical analysis

The data analysis was done by SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Quantitative data and categorical data were reported as mean (standard deviation) and numbers and percentages (%), respectively. Between-groups differences were analyzed with an independent samples t-test. The paired t-tests or the Wilcoxon test were used for assessing within-group comparisons. Qualitative variables were compared between two groups using the chi-square test or Fisher's exact test. A mixed repeated measures analysis of variance (ANOVA) was performed for between- and within-group comparisons with Bonferroni's adjustment. The P-value of <0.05 was considered statistically significant.

Results

Patients

Between October 15, 2024, and June 30, 2025, a total of 72 patients were screened, of whom 50 patients were enrolled and underwent randomization in a 1:1 ratio to receive either colchicine or a matching placebo for 10 days. Ultimately, 44 patients completed the study (Figure 1). The baseline characteristics of the patients were balanced between the two treatment groups (Table 1). The mean age of patients was 48.4 years, and 18.2% were women. The mean Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score was 14.9. The mean SOFA score was 7.25 (7.1 in the colchicine group vs 7.4 in the placebo group).

Primary outcome

There was no significant difference in the IL-6 plasma levels at day 4 between the colchicine group and the placebo group (median, 88.4 pg/ml [IQR, 79.6 to 91.3 pg/ml] versus 90.79 pg/ml [IQR, 69.3 to 97.3 pg/ml], respectively; difference, -2.42 pg/ml [95% CI, -10.0 to 6.0; P = 0.42]) (Table 2).

Secondary outcomes

There were no statistically significant differences between the colchicine group and the placebo group in the procalcitonin level assessed at day 4 (median, 2.32 ng/mL [IQR, 1.96 to 2.48 ng/mL] versus 2.42 ng/mL [IQR, 2.11 to 2.86 ng/mL], respectively; difference, -0.10; 95% CI, -0.30 to 0.09; P=0.12) (Table 2).

We found no significant difference between the colchicine group and the placebo group in the LDH levels on day 4 (median, 697.0 U/L [IQR, 451 to 999] vs 728.0 U/L [IQR, 233 to 1409]; difference, -7.29; 95% CI, -194.85 to 150.96; P = 0.43) or day 10 (median, 633.0 U/L [IQR, 312 to 1153] vs 826.5.0 U/L [IQR, 342 to 1699]; difference, -46.32; 95% CI, --146.36 to 234.16; P = 0.31), and in the ESR levels on day 4 (median, 69.0 mm/hr [IQR, 14 to 108] vs 85.0 mm/hr [IQR, 40 to 115]; difference, -5.86; 95% CI, -25.71 to 11.71; P = 0.25) or day 10 (median, 50.0 mm/hr [IQR, 2 to 134] vs 65.0 mm/hr [IQR, 41 to 108]; difference, -11.72; 95% CI, -30.47 to 6.92; P = 0.13).

The median CRP level at day 4 was 76.0 mg/L [IQR, 20 to 232] in the colchicine group and 116.5 mg/L [IQR, 51 to 401] in the placebo group (median difference, -54.91; 95% CI, -107.85 to -7.68; P < 0.01). Also, CRP levels at day 10 were significantly lower in the colchicine group (median, 37.0 mg/L [IQR, 6 to 154] vs 82.5 mg/L [12 to 205]; difference, -42.27; 95% CI, -82.60 to -1.67; P = 0.02).

There was no significant difference in qSOFA scores between the colchicine and placebo groups on day 4 (mean, 1.3 vs 1.6 points respectively; difference, -0.21; 95% CI, -0.57 to 0.15; P = 0.05) or day 10 (mean, 1.1 vs 1.5 points respectively; difference, -0.39; 95% CI, -1.04 to 0.21; P = 0.05).

Change in mean SOFA scores from baseline to day 4 was significantly greater in the colchicine group (from 7.1 to 6.2 points) than in the placebo group (from 7.4 to 7.5 points); [difference, –1.27; 95% CI, –2.59 to 0.05; P = 0.02]. Also, mean SOFA scores at day 10 were significantly lower in the colchicine group (mean, 5.4 versus 7.0 points; difference, –1.61 [95% CI, –3.15 to 0.07]; P < 0.01).

The number of vasopressor-free days was 8.82 days in the colchicine group and 7.0 days in the placebo group (mean difference, 2.13 days; 95% CI, 0.21 to 4.26; P = 0.13).

The number of ventilator-needed days during the trial period was significantly lower in the colchicine group (mean, 7.0 days vs 9.0 days; between-groups difference, -2.5 days; 95% CI, -4.63 to -0.05; P = 0.04) (Table 2).

There were no significant differences in 28-day mortality between patients treated with colchicine or placebo (Figure 2). At 28 days, death occurred in 6 of 22 patients (27.3%) in the colchicine group and 7 of 22 patients (31.8%) in the placebo group (hazard ratio, 0.832; 95% CI, 0.28 to 2.48; P = 0.74).

Safety outcomes

Adverse events were reported for 3 patients (gastrointestinal event, diarrhea) in the colchicine group and 1 patient (diarrhea) in the placebo group. No serious adverse effects were reported.

Discussion

In this randomized, placebo-controlled clinical trial, treatment with colchicine at a dose of 1 mg daily was associated with a significant reduction in the SOFA score in patients with sepsis. This result is consistent with findings from previous studies evaluating anti-inflammatory drugs in sepsis. Staubach et al.'s study of pentoxifylline in 51 patients with sepsis found that the multiple organ dysfunction score decreased significantly in the pentoxifylline group compared with the placebo group on day 14 ($P < 0.05$).[15] Another randomized trial by Karimi et al. showed that 10 days of nanocurcumin treatment was associated with a significant reduction in the SOFA score on day 10 compared with placebo (mean, 6.1 points vs 6.7 points; P = 0.027).[34] In addition, patients assigned to the colchicine group had a shorter duration of mechanical ventilation than those receiving the placebo, a finding of our trial that is consistent with the results from the Karimi et al. trial[34] and the Rygård et al. meta-analyses[35].

Our trial showed that treatment with colchicine did not reduce mortality. This observation is concordant with findings from prior investigations of anti-inflammatory agents in sepsis, including corticosteroids, pentoxifylline, and nanocurcumin. [15, 29, 34] In contrast, meta-analyses of clinical trials evaluating polyclonal IVIG have suggested a mortality benefit

for preparations enriched with IgA or IgM; however, heterogeneity across studies included in these meta-analyses limits the interpretability of these findings.[36-38]

In the current trial, treatment with colchicine was not associated with an increase in vasopressor-free days as compared with placebo. This finding contrasts with results from recent meta-analyses of randomized trials evaluating corticosteroids in sepsis, which reported a reduction in the duration of shock and vasopressor requirements.[35]

However, numerous anti-inflammatory agents, including ibuprofen, statins, and deltibant, have failed to demonstrate clinical benefit in patients with sepsis.[16, 18, 39-41]

The rationale for evaluating colchicine in sepsis was supported by preclinical evidence demonstrating attenuation of organ injury in experimental models of sepsis. Liu et al. found that colchicine can significantly reduce acute lung injury in a septic model by hindering the phosphorylation of STAT-3.[28] Kenig et al.'s study demonstrated that low-dose colchicine alleviates sepsis-induced liver failure in mice by reducing pro-inflammatory cytokines.[29] In addition, colchicine has been investigated as a candidate drug for coronavirus disease 2019 (COVID-19), where an umbrella review of meta-analyses has suggested a mortality benefit in patients with mild to moderate COVID-19.[42, 43]

The progression of systemic inflammation can cause multiple organ failure in patients with sepsis and lead to increased mortality. The results of our trial showed that treatment with colchicine was associated with reduced multi-organ dysfunction, as reflected by a decrease in the SOFA score and the duration of mechanical ventilation. These findings suggest that early modulation of systemic inflammation, including reduction of CRP, may mitigate sepsis-related organ dysfunction without altering the downstream determinants of shock resolution or survival.

Study limitation

This study has some limitations. First, the study sample size was relatively small, which may limit the generalizability of our findings. Therefore, future studies with larger sample sizes are needed to confirm the results that we observed in the COLINS trial. Second, the trial was unable to assess patients' IL-6 and procalcitonin levels on day 10 due to cost limitations.

Conclusion

In patients with sepsis, treatment with colchicine, significantly reduces the risk of multi-organ failure and duration of mechanical ventilation without serious adverse events. However, the findings indicate that colchicine did not confer a significant benefit in terms of vasopressor-free days or mortality.

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Authors' contributions

Conceptualization: Hadi Hamishehkar, Ata Mahmoodpoor.

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Ethical Approval

This trial was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.PHARMACY.REC.1402.002). It has also been submitted to the Iranian Registry of Clinical Trials (IRCT20231017059748N1). We received consent forms from all patients.

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Availability of data and materials

The protocol is part of FP's Ph.D. thesis. All primary and secondary outcome data will be reported at the end of the trial. The participant-level information will be available through the corresponding author upon reasonable request.

Conflicts of interest

The authors declare that they have no competing interests.

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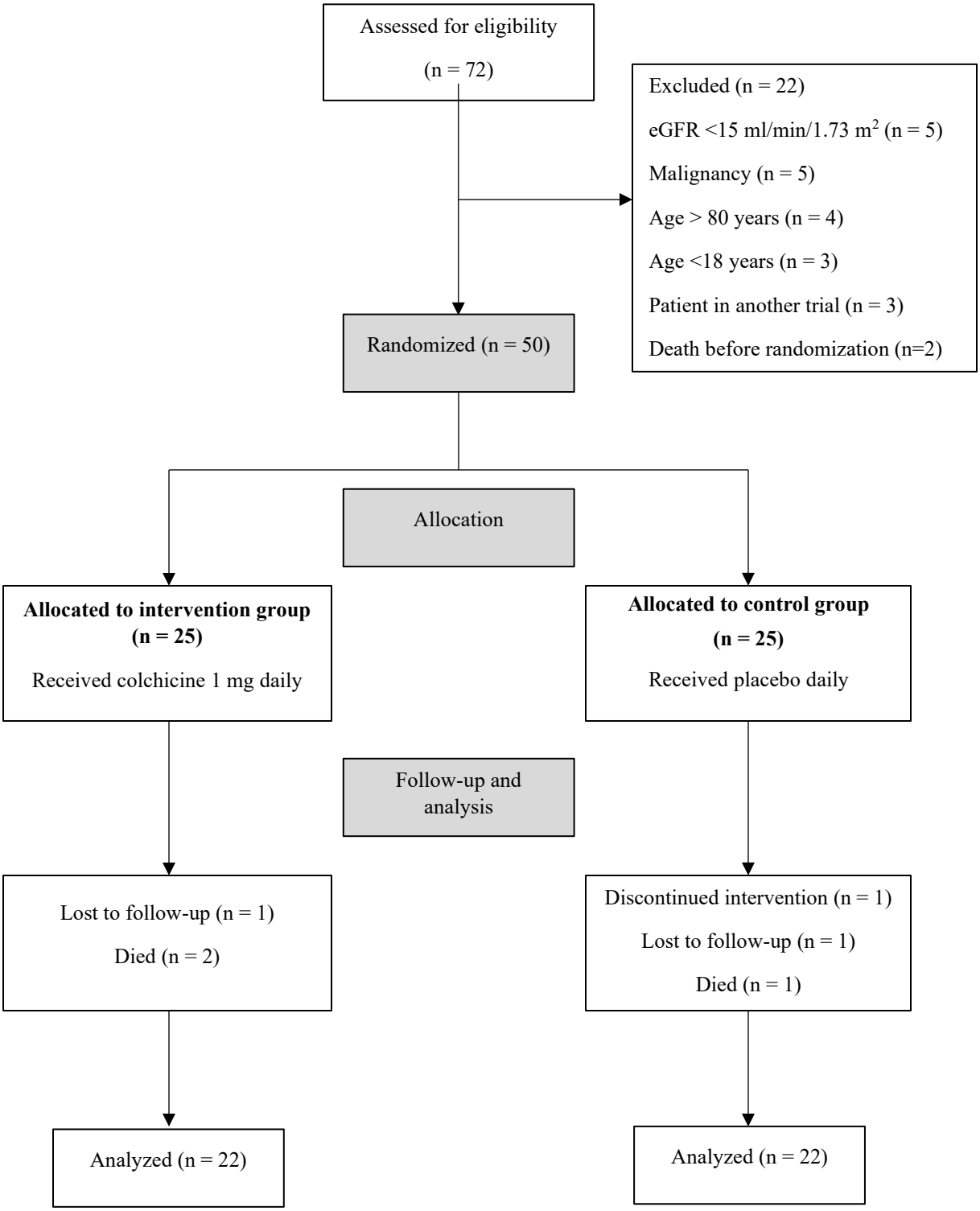

Figure 1. Enrollment, randomization, and follow-up of patients in the COLINS trial.

Table 1. Baseline characteristics of the patients in the COLINS trial			
Characteristic	**Colchicine group (N=22)**	**Placebo group (N=22)**	**P value**
Age-yr	46.9 ± 17.1	49.9 ± 15.8	0.55
Female sex – no. (%)	3 (13.6%)	5 (22.7%)	0.43
Body-mass index (kg/m^2)	26.1 ± 3.0	27.1 ± 5.4	0.72
APACHE II score⁋	14.8 ± 4.1	14.9 ± 4.3	0.64
Cause of admission – no. (%)			
Trauma	14 (63.6%)	12 (54.5%)	0.54
Medical	8 (36.4%)	10 (45.5%)	0.54
IL-6 (pg/mL)	89.2 ± 13.0	90.8 ± 19.0	0.86
Procalcitonin (ng/mL)	2.45 ± 0.27	2.39 ± 0.64	0.73
Temperature (°C)	37.7 ± 0.5	37.7 ± 0.8	0.53
Heart rate (beats/min)	88.3 ± 19.7	92.7 ± 14.7	0.41
Respiratory rate (breaths/min)	20.3 ± 4.2	20.1 ± 4.9	0.89
White blood cell count (10^3 /mm^3)	15.2 ± 4.5	15.3 ± 5.5	0.95
LDH (U/L)	706.2 ± 211.7	707.2 ± 247.8	0.99
ESR (mm/hr)	80.3 ± 35.1	72.2 ± 23.5	0.25
CRP (mg/L)	133.4 ± 74.6	139.9 ± 72.8	0.66
Sodium (mEq/L)	143.7 ± 7.8	144.8 ± 6.9	0.36
Potassium (mEq/L)	3.9 ± 0.4	4.1 ± 0.4	0.11
Magnesium (mg/dL)	1.9 ± 0.4	2.2 ± 0.4	0.10
qSOFA score╫	1.6 ± 0.6	1.5 ± 0.6	0.79
SOFA score∫∫	7.1 ± 1.5	7.4 ± 1.8	0.41
Systolic blood pressure (mmHg)	112.9 ± 16.9	116.3 ± 14.3	0.47
Diastolic blood pressure (mmHg)	68.6 ± 12.30	71.9 ± 13.3	0.40
Coexisting condition – no. (%)			
Hypertension	5 (22.7%)	6 (27.3%)	
Diabetes	4 (18.2%)	4 (18.2%)	
Cardiovascular disease	3 (13.6%)	1 (4.5%)	
COPD	1 (4.5%)	1 (4.5%)	
Hyperthyroid	1 (4.5%)	1 (4.5%)	
Dyslipidemia	1 (4.5%)	1 (4.5%)	
Source of infection – no. (%)**			
Pulmonary	18 (81.8%)	19 (86.3%)	
Blood	3 (13.6%)	3 (13.6%)	
CNS	1 (4.5%)	0	
Skin	1 (4.5%)	1 (4.5%)	
Urine	1 (4.5%)	1 (4.5%)	
Type of pathogen – no. (%)			
Klebsiella pneumonia	6 (27.3%)	9 (40.9%)	
Pseudomonas aeruginosa	7 (31.8%)	2 (9.1%)	
Acinetobacter baumanni	4 (18.2%)	4 (18.2%)	
Other	2 (9.1%)	4 (18.2%)	

Abbreviations: APACHE-II, Acute Physiology and Chronic Health Evaluation-II; IL-6, interleukin-6; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; qSOFA, Quick Sequential Organ Failure Assessment; SOFA, Sequential

Organ Failure Assessment; COPD, chronic obstructive pulmonary disease; CNS, central nervous system.

‖‖ Scores on the Acute Physiologic and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater disease severity and a higher risk of death.

╫ The qSOFA score is a modified version of the Sequential Organ Failure Assessment score. It consists of three components: systolic blood pressure ≤ 100 mmHg, change in mental status (Glasgow coma score < 15), and respiratory rate ≥ 22 breaths per minute, each of which is allocated one point. A qSOFA score of ≥ 2 points shows organ dysfunction.

∫∫ Scores on the Sequential Organ Failure Assessment (SOFA) were calculated by the sum of daily SOFA scores divided by the observation time. The SOFA score was calculated based on the assessment of six organ systems on the day of randomization (day 1). Scores range from 0 to 24, with higher scores indicating more severe organ dysfunction.

** Patients may have more than one site of infection.

Table 2. Primary and secondary outcomes.

Outcome	Median (IQR) or Mean (SD)		Difference (95% CI)	P value
	Colchicine (N=22)	Placebo (N=22)		

Primary				
IL-6 level (pg/mL)				
At baseline	91.92 (82.6-94.2)	87.89 (83.4-93.2)	4.03 (-3 to 11)	0.35
Day 4	88.38 (79.6-91.3)	90.79 (69.3-97.3)	-2.42 (-10 to 6)	0.42
Secondary				
Procalcitonin (ng/mL)				
At baseline	2.40 (2.29-2.60)	2.43 (2.14-2.53)	-0.02 (-0.22 to 0.18)	0.86
Day 4	2.32 (1.96-2.48)	2.42 (2.11-2.86)	-0.10 (-0.30 to 0.09)	0.12
LDH (U/L)				
At baseline	689.0 (452-1181)	768.0 (300-1229)	60.00 (-110.72 to 217.38)	0.99
Day 4	697.0 (451-999)	728.0 (233-1409)	-7.29 (-194.85 to 150.96)	0.43
Day 10	633.0 (312-1153)	826.5 (342-1699)	-46.32 (-146.36 to 234.16)	0.31
ESR (mm/hr)				
At baseline	87.0 (17-142)	81.0 (26-99)	6.44 (-11.37 to 26.25)	0.25
Day 4	69.0 (14-108)	85.0 (40-115)	-5.86 (-25.71 to 11.71)	0.25
Day 10	50.0 (2-134)	65.0 (41-108)	-11.72 (-30.47 to 6.92)	0.13
CRP (mg/L)				
At baseline	104.5 (45-300)	117.5 (54-280)	15.93 (-44.02 to 75.49)	0.66
Day 4	76.0 (20-232)	116.5 (51-401)	-54.91 (-107.85 to -7.68)	<0.01
Day 10	37.0 (6-154)	82.5 (12-205)	-42.27 (-82.60 to -1.67)	0.02
qSOFA score				
At baseline	1.6±0.6	1.5±0.6	-0.1 (-0.64 to 0.42)	0.79
Day 4	1.3±0.5	1.6±0.5	-0.21 (-0.57 to 0.15)	>0.05∫
Day 10	1.1±0.6	1.5±0.8	-0.39 (-1.04 to 0.21)	>0.05∫∫
SOFA score				
At baseline	7.1±1.5	7.4±1.8	-0.18 (-1.30 to 1.07)	0.41
Day 4	6.2±1.7	7.5±1.7	-1.27 (-2.59 to 0.049)	0.02
Day 10	5.4±2.4	7.0±2.1	-1.61 (-3.15 to 0.074)	<0.01∫∫∫
No. of free-vasopressor days	8.82±2.0	7.0±3.7	2.13 (0.21 to 4.26)	0.13
No. of mechanical ventilation days	7.0±3.8	9.0±2.1	-2.5 (-4.63 to -0.05)	0.04

Abbreviations: IL-6, interleukin-6; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; qSOFA, Quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment.

∫ The exact value of P was 0.052.

∫∫ The exact value of P was 0.054.

∫∫∫ The exact value of P was 0.008.

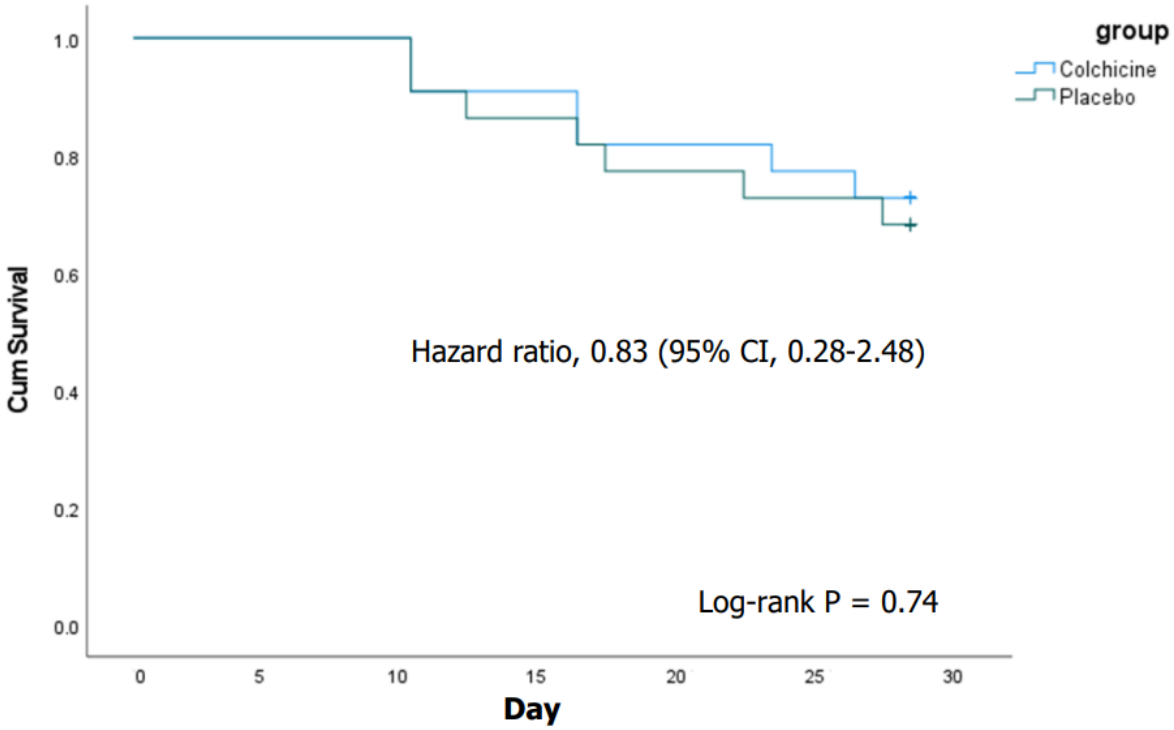

Figure 2. Kaplan-Meier curves for 28-day survival