Advances in Pharmacology and Therapeutics Journal

Shahid Sadoughi University of Medical Sciences, Yazd, Iran

SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES

Original Article

Clinical Outcomes of Pentoxifylline Use in Hospitalized COVID-19 Patients Compared with Standard Therapy (2020–2021)

Running Title: Pentoxifylline Treatment in COVID-19 Patients

Zohreh Akhoundi Meybodi[1,2], Atoosa Hosseini[1], Faezesadat Heidari[1,2], Seyed Alireza Mousavi[1,2], Mohammad Reza Mirjalili[3], Akram Astani[2,4] *

[1] Department of Infectious Disease, Shahid Sadoughi General Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
[2] Infectious Disease Research Center, Shahid Sadoughi General Hospital. Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
[3] Departments of Internal Medicine, Shahid Sadoughi General Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
[4] Department of Microbiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

ARTICLEINFO

Received: 12/08/2025

Accepted: 06/08/2026

***Corresponding author**

Department of Microbiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Tel: +98- 9133408274

E-mail

akramastani@gmail.com

ORCID ID

0000-0002-6915-1320

Abstract

The COVID-19 pandemic, driven by SARS-CoV-2, has challenged global healthcare systems, necessitating exploration of adjunctive therapies to mitigate severe outcomes. This retrospective cross-sectional study, conducted at Shahid Sadoughi Hospital in Yazd, Iran, from 2020 to 2021, compared clinical outcomes in 200 patients with COVID-19, divided evenly between those receiving pentoxifylline (a phosphodiesterase inhibitor with anti-inflammatory properties) in addition to standard treatment and those receiving standard therapy alone (the control group). The outcomes assessed in the study included mortality rates, hospital stay duration, ICU admissions, and inflammatory markers (CRP, LDH, ESR, WBC, and lymphocyte percentage). The group treated with pentoxifylline experienced significantly higher mortality rates, with 30% compared to 11% in the control group ($P < 0.05$). Additionally, the average hospital stay was longer in the pentoxifylline recipient group (14.74 ± 8.645 days) than in the control group (6.29 ± 4.048 days; $P < 0.05$). There was also an increased rate of ICU admissions, with 30% in the pentoxifylline recipient group versus 6% in the control group ($P < 0.05$). Furthermore, elevated CRP and LDH levels and lymphopenia were associated with worse outcomes in the pentoxifylline recipient group ($P<0.05$). These findings contrast with prior studies suggesting that pentoxifylline may reduce inflammation and improve outcomes, highlighting the need for randomized controlled trials to clarify its role in COVID-19 management.

Keywords: COVID-19, Pentoxifylline, SARS-CoV-2, Inflammatory markers.

Citation: Akhoundi Meybodi Z, Hosseini A, Heidari F, Mousavi S.A, Mirjalili M.R, Astani A. Clinical Outcomes of Pentoxifylline Use in Hospitalized COVID-19 Patients Compared with Standard Therapy (2020–2021). Adv Pharmacol Ther J. 2025;5(4): 201-207.

Introduction

The novel coronavirus, SARS-CoV-2, emerged in December 2019 in Wuhan, China, and was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020 (1, 2). As a beta-coronavirus, SARS-CoV-2 causes a spectrum of clinical manifestations, from asymptomatic infections to severe acute respiratory distress syndrome (ARDS), multi-organ failure, and death (3-5). Severe cases often involve dysregulated inflammation, cytokine storm, hypercoagulability, myocardial injury, and thromboembolic complications. Despite the global vaccination rollout, no definitive antiviral agent has been identified to eliminate severe disease, prompting ongoing interest in repurposed drugs with anti-inflammatory or immunomodulatory effects. Pentoxifylline, a non-selective phosphodiesterase inhibitor, has shown promise in reducing pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6. It also inhibits platelet aggregation and improves microcirculatory flow. These characteristics suggest that pentoxifylline could help mitigate the inflammatory and thrombotic complications associated with COVID-19 (6-8). However, studies have reported mixed results: some indicate reduced inflammation and improved outcomes, while others have found no significant benefit (6, 7, 9). Furthermore, systematic evaluations have proposed pentoxifylline as a potential adjunct therapy due to its immunomodulatory and anti-fibrotic mechanisms (10). However, contemporary clinical findings remain inconsistent: some researchers report improved oxygenation and reduced inflammatory markers (11). Despite theoretical benefits, real-world clinical evidence on pentoxifylline remains limited and inconsistent, particularly in hospitalized populations.

This study, conducted at Shahid Sadoughi Hospital in Yazd, Iran, from 2020 to 2021, aimed to compare outcomes in COVID-19 patients treated with pentoxifylline in combination with standard treatment versus those receiving standard therapy alone (control). The primary objective was to assess the impact on mortality, hospital length of stay, ICU admission rates, and inflammatory markers. Additionally, the secondary objectives included evaluating the effects of age, gender, and specific inflammatory parameters (such as CRP, LDH, ESR, WBC, and lymphopenia) on these outcomes.

Methods

Study Design

This retrospective cohort study was conducted in 2022 and analyzed data from COVID-19 patients admitted to Shahid Sadoughi Hospital between 2020 and 2021. The patients were divided into two groups: one group received pentoxifylline (400 mg orally three times daily) in addition to standard treatment, while the control group received only standard treatment

Study Population

The study involved 200 adult patients with RT-PCR-confirmed SARS-CoV-2 infection, divided into two groups of 100 each. The inclusion criteria consisted of all hospitalized COVID-19 patients from 2020 to 2021 who received either pentoxifylline in addition to standard treatment or standard treatment alone. Patients

  DOI: https://doi.org/ 10.18502/aptj.v5i4.21759

under 18 years of age, those with incomplete medical records, or those missing data on key variables (such as inflammatory markers) were excluded from the study.

Data Collection

Data were extracted from hospital records, including demographic variables (age and gender), clinical outcomes (mortality, hospital stay duration, and ICU admissions), and laboratory parameters (CRP, LDH, ESR, WBC, and lymphocyte percentage). Standard treatment was administered according to the guidelines of Iran's Ministry of Health (version 8). This treatment included symptomatic therapies (e.g., acetaminophen, naproxen), antivirals (e.g., remdesivir, favipiravir), corticosteroids, and anticoagulants (e.g., heparin), tailored to the severity of the diseases (10, 12-15).

Statistical Analysis

The data were analyzed using SPSS version 25. Descriptive statistics, including frequencies, percentages, means, and standard deviations, were utilized to summarize the demographic and clinical characteristics. Continuous variables were compared using independent t-tests, while categorical variables were analyzed with chi-square tests. A P-value of less than 0.05 was deemed statistically significant.

Ethical Considerations

The study received approval from the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1402.043). Patient data were anonymized to maintain confidentiality.

Results

Demographic Characteristics

The study included 200 patients, with 100 in each group. **Table 1** summarizes the gender distribution.

Table 1. Gender Distribution across Study Groups

Treatment	Sex	Frequency Percentage	P-Value
Pentoxifylline treatment	Male	64%	> 0.05
	Female	36%	
Standard treatment	Male	60%	
	Female	40%	

In the pentoxifylline recipient group, 36 females (36%) and 64 males (64%) were included. In the control group, 40 females (40%) and 60 males (60%) were included. The distribution of gender between the two groups was not statistically different (χ^2 = 0.34, d.f. = 1, P = 0.56), suggesting that sex did not affect treatment outcomes (P > 0.05). The mean age of participants in the pentoxifylline recipient group was 59.41 ± 13.41 years, while in the control group, it was 55.70 ± 16.82 years. Based on **Table 2** age was found to be significantly associated with outcomes (P < 0.05).

Table 2. Mean Age of Participants by Treatment Group

Group	Mean age ± SD	p-value
Pentoxifylline	59.41 ± 13.41	< 0.05
Standard treatment	55.70 ± 16.82	

Inflammatory Markers

C-Reactive Protein (CRP): In the pentoxifylline recipient group, CRP was measured in 93 patients: 24 had negative CRP, 23 had CRP 1+, 30 had CRP 2+, 15 had CRP 3+, and 1 had CRP 4+. In the control group, 87 patients had CRP measured: 16 had a negative CRP, 16 had a CRP level of 1+, 29 had a CRP level of 2+, and 26 had a CRP level of 3+. (P<0.05) **(Table 3)**. Lactate Dehydrogenase (LDH): The mean LDH was 839.95 ± 30.427 IU/L in the pentoxifylline recipient group and 658.74 ± 198.779 IU/L in the control group (P<0.05).

Table 3. CRP Frequency by Treatment Group

Group	CRP Level	Frequency	Percentage Frequency	p-value
Pentoxifylline	0	24	25.8%	0.001
	1	23	24.7%	
	2	30	32.2%	
	3	15	16.1%	
	4	1	1.0%	
Standard treatment	0	16	18.3%	0.001
	1	16	18.3%	
	2	29	33.3%	
	3	26	27.9%	
	4	0	0.0%	

Erythrocyte Sedimentation Rate (ESR): The mean ESR was 45.67 ± 25.746 mm/h in the pentoxifylline recipient group and 46.28 ± 27.051 mm/h in the control group (P>0.05).

White Blood Cell Count (WBC): The mean WBC was 7534.7 ± 3735.97 cells/µL in the pentoxifylline recipient group and 6845.5 ± 3922.91 cells/µL in the control group (P>0.05).

Lymphocyte Percentage: According to **Table 4** the mean lymphocyte percentage was 14.3485 ± 8.15744% in the pentoxifylline recipient group and 20.7586 ± 11.12858% in the control group (P<0.05).

Table 4. Comparison of Parameters Between Treatment Groups

Parameter	Pentoxifylline + Standard (Mean ± SD)	Standard treatment (control) (Mean ± SD)	P-value
LDH (IU/L)	839.95 ± 30.43	658.74 ± 198.78	<0.05
ESR (mm/h)	45.67 ± 25.75	46.28 ± 27.05	
WBC (cells/µL)	7534.7 ± 3735.97	6845.5 ± 3922.91	
Lymphocyte (%)	14.34 ± 8.15	20.75 ± 11.12	

Clinical Outcomes

Hospital Stay Duration: The pentoxifylline recipient group had a mean hospital stay of 14.74 ± 8.645 days, significantly longer than the control group's 6.29 ± 4.048 days (P<0.05).

ICU Admission: Thirty patients (30%) in the pentoxifylline recipient group required ICU admission, compared to 6 (6%) in the control group (P<0.05).

Mortality: Mortality was significantly higher in the pentoxifylline recipient group (30% vs. 11%, P<0.05) **(Table 5).**

Table 5. Clinical Outcomes

Outcome	Pentoxifylline + Standard	Standard treatment only	P-value
Hospital Stay (days)	14.74 ± 8.645	6.29 ± 4.048	<0.05
ICU Admission (n, %)	30 (30%)	6 (6%)	
Mortality (n, %)	30 (30%)	11 (11%)	

Discussion

This study presents a detailed comparison of outcomes for COVID-19 patients treated with pentoxifylline in addition to standard treatment versus those receiving standard therapy alone (the control group). Contrary to expectations, pentoxifylline use was associated with poorer outcomes, including higher mortality (30% versus 11%), longer hospital stays (14.74 days versus 6.29 days), and increased ICU admissions (30% versus 6%). Additionally, elevated levels of CRP, LDH, and instances of lymphopenia were significantly linked to worse outcomes in the pentoxifylline recipient group. These findings challenge the hypothesis that

  DOI: https://doi.org/ 10.18502/aptj.v5i4.21759

pentoxifylline's anti-inflammatory properties would improve patient prognosis. Prior studies have suggested that pentoxifylline may reduce the severity of COVID-19 (16). Hendry et al. (2020) proposed pentoxifylline as a safe and affordable modulator of cytokines (17). Wall et al. (2021) reported a reduction in C-reactive protein (CRP) levels and a slightly lower mortality rate (24% in the pentoxifylline recipient group) (13).

In contrast, our study found higher mortality rates and worse inflammatory profiles among those treated with pentoxifylline. This may be attributed to the fact that pentoxifylline was administered to patients with more severe disease at baseline. Feret et al. (2021) observed increased lymphocyte counts and reduced lactate dehydrogenase (LDH) levels following pentoxifylline treatment; however, there was no significant impact on mortality or intubation rates. Their findings partially align with ours, but there are notable differences in clinical outcomes (15). Pentoxifylline's mechanisms include elevating cyclic AMP, reducing pro-inflammatory cytokines, and improving microcirculatory flow (18). These properties should, in theory, mitigate cytokine storms and thrombotic complications (15). However, our data suggest that these benefits may not translate in severe cases, where inflammatory cascades are advanced. The higher LDH and lymphopenia in the pentoxifylline recipient group may reflect greater disease severity rather than a direct drug effect (19). The renin-angiotensin-aldosterone system (RAS) hypothesis, where pentoxifylline modulates angiotensin II receptors to reduce lung injury (17), was not supported, consistent with studies showing no increased severity in patients on ACE inhibitors (20-23). The higher mortality and ICU admission rates in the pentoxifylline recipient group caution against its routine use in COVID-19 without further evidence (13, 24). The drug's anti-inflammatory effects may be insufficient in severe cases, and its administration to sicker patients could explain the observed outcomes (15, 23, 25). The more extended hospital stays may reflect delayed recovery or complications in this group.

Furthermore, recent mechanistic reviews suggest that although pentoxifylline may theoretically attenuate cytokine storm, its clinical effectiveness may depend heavily on timing, disease stage, and underlying comorbidities (24, 26). The retrospective design limits causality inferences. The retrospective design of this study limits the ability to infer causality, as treatment allocation and patient characteristics were not randomized. Furthermore, the sample size of 200 patients may limit statistical power and the generalizability of the findings to broader populations (26, 27). The presence of incomplete records and missing data (e.g., IL-6 and ferritin measurements) could introduce bias, particularly if the missingness is not random and differs systematically between patient groups (16, 28). Additionally, baseline differences in disease severity may have influenced the results, as the pentoxifylline recipient group might have included patients with more severe disease. Furthermore, the lack of long-term follow-up and evaluation of other complications, such as long COVID, limits the study's scope.

Conclusions

This study found that pentoxifylline, when used alongside standard treatment, was associated with higher mortality rates, longer hospital stays, and increased admissions to the ICU among COVID-19 patients at Shahid Sadoughi Hospital. Elevated levels of CRP and LDH, along with lymphopenia, were significantly linked to worse outcomes in the pentoxifylline recipient group. These findings contrast with previous studies and highlight the need for randomized controlled trials to clarify the role of pentoxifylline in the management of COVID-19.

Acknowledgment: None.

Conflict of interest: The authors declared no conflict of interest**.**

Funding: None.

Author's contribution: Z.A.M and F.H and A.A were responsible for designing of the study. A.H performed experiments. S.A.M and M.R.M analyzed and interpreted the results and A.A wrote the manuscript. All authors also contributed to the critical revision of the manuscript for important intellectual content, approved the final version, and are accountable for the integrity of its content.

Ethical considerations: The study received approval from the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1402.043). Patient data were anonymized to maintain confidentiality.

References

1. Yoo JH. On the Controversies Surrounding the Lab-Leak Theory of COVID-19. J Korean Med Sci. 2025;40(16):e153.
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. Jama. 2020;323(13):1239-42.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
4.Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
6. Jelodar MG, Hoseinzadeh F, Mirzaei S, Falahati Z, Saghafi F. Exploring pentoxifylline as an alternative treatment for dexamethasone in diabetic patients with COVID-19: a randomized controlled trial. European Journal of Medical Research. 2025;30(1):540.
7. Rahmanzade R, Rahmanzadeh R, Hashemian SM, Tabarsi P. Iran's Approach to COVID-19: Evolving Treatment Protocols and Ongoing Clinical Trials. Front Public Health. 2020;8:551889.
8. Seirafianpour F, Mozafarpoor S, Fattahi N, Sadeghzadeh-Bazargan A, Hanifiha M, Goodarzi A. Treatment of COVID-19 with pentoxifylline: Could it be a potential adjuvant therapy? Dermatol Ther. 2020;33(4):e13733.
9. seyedpour Sm, Akhlaghi SS, Fallahi S, Mozafari Komesh Tape P, Masrour H. Effectiveness of pentoxifylline in patients with moderate Covid-19. Health Biotechnology and Biopharma (HBB). 2024;8(2):63-79.
10. Lin Y, Xu Z, Zhou B, Ma K, Jiang M. Pentoxifylline Inhibits Pulmonary Fibrosis by Regulating Cellular Senescence in Mice. Frontiers in pharmacology. 2022;13:848263.
11. Oldman AH, Martin DS, Feelisch M, Grocott MPW, Cumpstey AF. Effects of perioperative oxygen concentration on oxidative stress in adult surgical patients: a systematic review. British journal of anaesthesia. 2021;126(3):622-32.
12. Assimakopoulos SF, Seintis F, Marangos M. Pentoxifylline and complicated COVID-19: A pathophysiologically based treatment proposal. Med Hypotheses. 2020;143:109926.
13. Wall GC, Smith HL, Trump MW, Mohr JD, DuMontier SP, Sabates BL, et al. Pentoxifylline or theophylline use in hospitalized COVID-19 patients requiring oxygen support. Clin Respir J. 2021;15(7):843-6.
14. Yu X, Pu H, Voss M. Overview of anti-inflammatory diets and their promising effects on non-communicable diseases. The British journal of nutrition. 2024;132(7):898-918.
15. Feret W, Nalewajska M, Wojczyński Ł, Witkiewicz W, Kłos P, Dziedziejko V, et al. Pentoxifylline as a Potential Adjuvant Therapy for COVID-19: Impeding the Burden of the Cytokine Storm. J Clin Med. 2021;10(22).

  DOI: https://doi.org/ 10.18502/aptj.v5i4.21759

16. Mostafa-Hedeab G, Al-Kuraishy HM, Al-Gareeb AI, Jeandet P, Saad HM, Batiha GE. A raising dawn of pentoxifylline in management of inflammatory disorders in Covid-19. Inflammopharmacology. 2022;30(3):799-809.
17. Hendry BM, Stafford N, Arnold AD, Sangwaiya A, Manglam V, Rosen SD, et al. Hypothesis: Pentoxifylline is a potential cytokine modulator therapeutic in COVID-19 patients. Pharmacology research & perspectives. 2020;8(4):e00631.
18. Ohshima N, Sato M. Effect of pentoxifylline on microvascular blood flow velocity. Angiology. 1981;32(11):752-63.
19. Maldonado V, Hernandez-Ramírez C, Oliva-Pérez EA, Sánchez-Martínez CO, Pimentel-González JF, Molina-Sánchez JR, et al. Pentoxifylline decreases serum LDH levels and increases lymphocyte count in COVID-19 patients: Results from an external pilot study. Int Immunopharmacol. 2021;90:107209.
20. Singh R, Rathore SS, Khan H, Bhurwal A, Sheraton M, Ghosh P, et al. Mortality and Severity in COVID-19 Patients on ACEIs and ARBs-A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. Frontiers in medicine. 2021;8:703661.
21. Zhang G, Wu Y, Xu R, Du X. Effects of renin-angiotensin-aldosterone system inhibitors on disease severity and mortality in patients with COVID-19: A meta-analysis. Journal of medical virology. 2021;93(4):2287-300.
22. RAAS inhibitors are not associated with mortality in COVID-19 patients: Findings from an observational multicenter study in Italy and a meta-analysis of 19 studies. Vascular pharmacology. 2020;135:106805.
23. DiNicolantonio JJ, Barroso-Aranda J. Harnessing adenosine A2A receptors as a strategy for suppressing the lung inflammation and thrombotic complications of COVID-19: Potential of pentoxifylline and dipyridamole. Med Hypotheses. 2020;143:110051.
24. Azizi H, Rouhani N, Shaki F, Karimpour-Razkenari E, Ghazaeian M, Salehifar E, et al. Pentoxifylline effects on hospitalized patients with COVID19: A randomized, double-blind clinical trial. Int Immunopharmacol. 2021;101(Pt B):108227.
25. Kreth S, Ledderose C, Luchting B, Weis F, Thiel M. Immunomodulatory properties of pentoxifylline are mediated via adenosine-dependent pathways. Shock (Augusta, Ga). 2010;34(1):10-6.
26. Ramzi A, Maya S, Balousha N, Amin M, Shiha MR. Pentoxifylline in COVID-19 and considerations for its research in long COVID. Inflammation research : official journal of the European Histamine Research Society [et al]. 2024;73(12):2057-68.
27. Sarhan RM, A EA, Essam Abou Warda A, Saied YM, Ibrahim HSG, Schaalan MF, et al. Pentoxifylline Effects on Hospitalized COVID-19 Patients with Cytokine Storm Syndrome: A Randomized Clinical Trial. Pharmaceuticals (Basel, Switzerland). 2023;16(4).
28. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of clinical epidemiology. 2008;61(4):344-9.