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Clinical outcomes of infliximab treatment in hospitalized patients with severe COVID-19; a parallel, double-blind, randomized controlled trial

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Abstract

Introduction: This study aims to assess the effectiveness and safety of infliximab in hospitalized patients with severe COVID-19.

Patients and Methods: This double blind, randomized controlled trial was conducted on 48 patients with COVID-19 at Hajar hospital in Shahrekord, Iran, from December 2020 to June 2021, to evaluate the efficacy and safety of infliximab in hospitalized patients with severe COVID-19. Eligible adults with confirmed severe COVID-19 were randomized to receive a single intravenous dose of infliximab (4 mg/kg) plus standard care (infliximab-treated group n = 24), or the control group (n = 24) received standard care alone. Data on demographics, clinical signs, radiologic findings, laboratory markers, and clinical outcomes were systematically collected at admission and during hospitalization. The primary outcomes included comparison of duration of hospital stay, mortality rate, mechanical ventilation requirement, and laboratory parameters between the two groups.

Results: The results indicate that infliximab treatment in patients was associated with better clinical outcomes, including reduced hospital stay, lower mortality rates, decreased need for mechanical ventilation, and experiencing of better oxygen saturation. Laboratory parameters showed that the infliximab group experienced improved immune cell profiles marked by increased lymphocytes and decreased neutrophils and white blood cells. Additionally, inflammatory and coagulation markers such as D-dimer, lactate dehydrogenase (LDH), and C-reactive protein (CRP) were more effectively reduced in the infliximab-treated group, reflecting better control of inflammation; however, infliximab treatment indicated no significant difference in platelet levels between groups.

Conclusion: Infliximab treatment in COVID-19 patients is associated with improved clinical outcomes, highlighting its potential as an effective immunomodulatory therapy.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20201229049873N1; https://irct.behdasht.gov.ir/trial/53791), and ethical code from Shahrekord University of Medical Sciences (IR.SKUMS.REC.1399.227; https://ethics.research.ac.ir/EthicsProposalView.php?id=169921).

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, was first identified in Wuhan, Hubei Province, China, in December 2019 (1,2). This novel virus was linked to a cluster of pneumonia cases associated with a seafood and live animal market in Wuhan (3). Following its discovery, SARS-CoV-2 rapidly spread both within China and globally, leading to a widespread pandemic recognized by the World Health Organization (WHO) in early 2020 (1,2). SARS-CoV-2 primarily targets the lower respiratory tract, leading to potentially life-threatening pneumonia; severe cases typically begin with an initial viral phase that progresses to an acute inflammatory phase characterized by infiltration of inflammatory cells, elevated pro-inflammatory cytokines and chemokines, and may culminate in acute respiratory distress syndrome (ARDS) (4-6).

The cytokine storm is the primary pathological mechanism driving ARDS in COVID-19 (7). It is characterized by the excessive release of cytokines, resulting in an uncontrolled systemic hyperinflammatory response; this immune dysregulation triggers acute-phase physiological changes, cytokine-mediated tissue damage, multi-organ failure, and can ultimately lead to death (8,9). Elevated levels of tumor necrosis factor-alpha (TNF-α), a key pro-inflammatory cytokine involved in regulating immune responses, have been shown to correlate

Key point

In a clinical trial study, we found that infliximab treatment in COVID-19 patients is linked to significantly better clinical outcomes, including reduced mortality, shorter hospital stays, and decreased need for mechanical ventilation, alongside improved oxygenation and decreased inflammation, highlighting its promise as a potent immunomodulatory therapy to enhance recovery.

with greater disease severity and higher mortality rates in COVID-19 (10). Levels of this cytokine have been significantly higher in patients who passed away from COVID-19 compared to those who survived (11). TNF-α, a key pro-inflammatory cytokine, plays a central role in driving the hyperinflammatory state and significantly contributes to the development and clinical manifestations of the cytokine storm; elevated levels of TNF-α can trigger various pathophysiological processes, including fever, increased vascular permeability, insulin resistance, and disseminated intravascular coagulation (12). Infliximab is an anti-TNF-α that binds with high affinity to TNF-α, forming stable complexes that effectively block the biological activity of this cytokine and prevent its interaction with cellular receptors (13,14). The previous studies have identified that infliximab binds to the E-F loop region of TNF-α, overlapping with the TNF-α-receptor interface and thereby inhibiting the downstream inflammatory cascade (13,15).

Infliximab has been investigated as an immunomodulatory therapy for COVID-19 patients with hyperinflammatory states, with large randomized controlled trials demonstrating significant mortality reduction. A major randomized controlled study involving 95 hospitals across the United States and Latin America found that while infliximab did not significantly improve time to recovery compared to placebo, it significantly reduced 28-day mortality from 14.5% to 10.1% (16). Recent retrospective studies have confirmed infliximab's effectiveness in reducing inflammatory markers like CXCL-10 (IP-10) and improving clinical outcomes in hospitalized COVID-19 patients (17), while the 2025 infectious diseases society of America guidelines have incorporated specific recommendations for infliximab use in hospitalized adults with severe or critical COVID-19 based on this evidence (18). Although infliximab therapy has shown some benefits, certain studies reported that it did not provide significant improvements over the standard of care in COVID-19 patients. Specifically, randomized clinical trials revealed no marked difference in time to recovery between infliximab and placebo groups among hospitalized patients, indicating limited added benefit in terms of recovery speed despite other potential positive outcomes (16). A retrospective study also found that infliximab therapy did not provide significant improvement over standard care in hospitalized patients with moderate to severe COVID-19 (19). Due to the presence of contradictory findings in earlier research, we conducted this clinical trial to thoroughly evaluate the impact of infliximab on clinical outcomes in patients affected by COVID-19.

Objectives

The objective of this study is to evaluate the efficacy and safety of infliximab, a TNF-α inhibitor, in improving clinical outcomes and survival rate in patients with severe COVID-19, by comparing hospital stay duration, mortality rate, need for mechanical ventilation, and laboratory parameters, including inflammatory and coagulation markers between the infliximab treatment plus standard care to standard care alone in a randomized controlled trial setting.

Patients and Methods

Study design and participants

This parallel, double-blind, randomized controlled trial study was conducted on 48 patients with severe COVID-19 at Hajar hospital in Shahrekord, Iran, from December 2020 to June 2021. The study aimed to evaluate the efficacy and safety of infliximab in improving clinical outcomes and survival rates in patients with severe COVID-19. Eligible hospitalized adult patients with severe COVID-19, confirmed by clinical presentation and radiologic findings, were randomly assigned to receive either infliximab plus standard care (intervention group [n = 24]) or standard care alone (control group [n = 24]).

Inclusion and exclusion criteria

Inclusion criteria for this study included hospitalized adult patients (18-60 years) diagnosed with severe COVID-19 confirmed by a positive test using reverse transcription polymerase chain reaction (RT-PCR) or computed tomography (CT) scan, peripheral oxygen saturation levels below 88%, respiratory rate >24 per minute, and elevated levels of inflammatory markers (high C-reactive protein [CRP], D-dimer, and ferritin levels) and Lymphopenia. Patients were required to provide informed consent and be eligible for infliximab treatment. Exclusion criteria comprised individuals with neurodegenerative diseases or conditions such as heart failure, uncontrolled hypertension, or active bacterial, viral, or parasitic infections other than COVID-19, use of biologic therapies contraindicating infliximab during the study period, unwilling to continue the study, and any medical conditions deemed by investigators to increase risk or interfere with study participation.

Sample size

The sample size calculation assumed a 28-day mortality rate of approximately 35%-50% in the control group receiving standard care alone, compared to an anticipated mortality reduction to 12-15% in the infliximab treatment group. Using a two-sided Fisher's exact test

with a significance level of α = 0.05 and targeting 80-95% statistical power to detect this clinically meaningful difference in primary mortality outcomes, the required sample size was calculated to be 20-22 patients per group. To account for potential dropouts, loss to follow-up, and protocol deviations commonly observed in COVID-19 clinical trials (approximately 10%-15%), the final sample size was established at 24 patients in each group (20,21).

Randomization/allocation

A computer-generated randomization sequence was created using permuted blocks of varying sizes to achieve 1:1 allocation between the infliximab and control groups. Allocation concealment was maintained through the use of sequentially numbered, sealed, opaque envelopes that were stored at each participating center and opened only after patient enrollment and informed consent. The randomization sequence generation and envelope preparation were performed by an independent statistician not involved in patient recruitment or clinical care.

Blinding

In this double-blind design, both the participants (patients) and the investigators (including clinicians, study staff, and outcome assessors) were blinded to the treatment allocation. This means they were unaware of which participants received the infliximab treatment and which were allocated to the control group.

Intervention

The intervention method in this study involved administering a single dose of infliximab (Remicade®; Janssen Biotech, USA) at 4 mg per kilogram of body weight intravenously over 2 hours by infusion to patients in the infliximab-treated group, in addition to the standard of care treatment for severe COVID-19. The control group received only the standard of care according to hospital protocols. The infliximab infusion was administered under clinical supervision, and patients were closely monitored for therapeutic response and any adverse events throughout the study period. The standard of care included supportive treatments such as oxygen therapy, antiviral medications, and corticosteroids as appropriate for each patient's clinical condition.

Data collection

Data collection for this study involved systematic and detailed recording of demographic characteristics, baseline clinical signs, radiologic findings, laboratory parameters, and clinical outcomes for all enrolled patients. Demographic and clinical baseline data, including age, body mass index (BMI), underlying diseases (such as diabetes mellitus, hypertension, and hyperlipidemia), and vital signs (respiratory rate, pulse rate, systolic blood pressure, and diastolic blood pressure), were collected at hospital admission. Radiologic assessments such as the presence of ground-glass opacity, consolidation, and crazy paving patterns on chest imaging, as well as oxygen therapy modalities including oxygen delivery by mask, nasal cannula, non-invasive ventilation, or high-flow devices, were recorded. Symptoms, including fever, cough, myalgia, fatigue, dyspnea, and diarrhea, were documented. Laboratory data, including oxygen saturation (O_2sat) levels, white blood cell counts (WBC), platelet counts, lymphocyte and neutrophil percentages, D-dimer, lactate dehydrogenase (LDH), and CRP levels, were measured on days 1, 7, and 14 of hospitalization. Clinical outcomes such as duration of hospitalization, mortality, and requirement for mechanical ventilation were tracked throughout the study. All data were collected using standardized forms, and quality control procedures were implemented to verify data integrity during the study period.

Outcome measurement

The primary outcome of this study is to compare the duration of hospital stay, mortality rate, need for mechanical ventilation, and changes in key laboratory parameters, such as inflammatory and coagulation markers, between patients treated with infliximab and those who did not receive infliximab. The secondary outcome includes the assessment of clinical recovery indicators like improvement in respiratory support, survival rate, safety, and adverse events, and the overall impact of infliximab on the severity and progression of COVID-19 in hospitalized patients.

Statistical analysis

Data analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 27 (IBM Corp., Armonk, NY, USA) software. Categorical data were presented as frequencies and percentages, while quantitative data were reported as mean and standard deviation (SD) for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. Levene's test was conducted to assess the equality of variances, and the Shapiro-Wilk test evaluated data normality. For group comparisons, the chi-square test was employed for categorical variables, the independent T-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables. The P value < 0.05 was considered significant for all statistical tests.

Results

At the beginning of the study, 61 individuals were assessed for eligibility. Of these, 13 were excluded; 9 did not meet the inclusion criteria, and 4 declined to participate. A total of 48 participants were then randomized, with 24 allocated to the infliximab-treated group, all of whom received the treatment, and 24 assigned to the control group, all of whom received a placebo. There were no participants lost to follow-up or excluded from analysis in either

group, resulting in 24 participants analyzed in each group (Figure 1).

The comparison between the infliximab-treated group and the control group revealed similar demographic characteristics and baseline clinical and radiologic findings. Both groups were comparable in terms of age, body mass index, and gender distribution, with similar proportions of males. The prevalence of underlying conditions such as diabetes mellitus, hypertension, and hyperlipidemia showed no significant differences between groups. Vital signs, including respiratory rate, pulse rate, systolic and diastolic blood pressure, were also similar in both groups. Radiologic findings demonstrated equivalence, along with similar needs for oxygen therapy. Presenting symptoms like fever, cough, myalgia, fatigue, dyspnea, and diarrhea occurred at comparable rates across both groups, indicating no statistically significant variation in clinical presentation or disease severity. Overall, the infliximab-treated and control groups were well matched in terms of baseline characteristics, clinical signs, radiologic findings, and symptomatology (Table 1).

Throughout the study duration, the infliximab-treated group demonstrated a pattern of improvement in O_2sat levels compared to the control group, with higher values observed at later time points. The WBC levels in the infliximab group showed a slight increase initially but tended to be lower than the control group by the study's end. Platelet counts varied between groups without a consistent significant difference. Notably, the percentage of lymphocytes increased over time in the infliximab group, contrasting with a decrease seen in the control group, while neutrophil percentages decreased in the infliximab group but remained higher in controls. Markers of coagulation and inflammation, such as D-dimer and LDH levels, decreased more in the infliximab-treated patients, indicating better control of inflammatory processes. Similarly, levels of CRP, a systemic inflammation marker, were significantly reduced in the infliximab group compared to controls during the course of treatment (Table 2).

The comparison of clinical outcomes between the infliximab-treated group and the control group demonstrated that those receiving infliximab experienced a shorter duration of hospitalization. Additionally, mortality rates were substantially lower in the infliximab-treated group compared to controls. The need for mechanical ventilation was also significantly reduced in the infliximab group, indicating better overall clinical outcomes (Table 3).

Discussion

Our findings demonstrated that the observed laboratory improvements in COVID-19 patients treated with

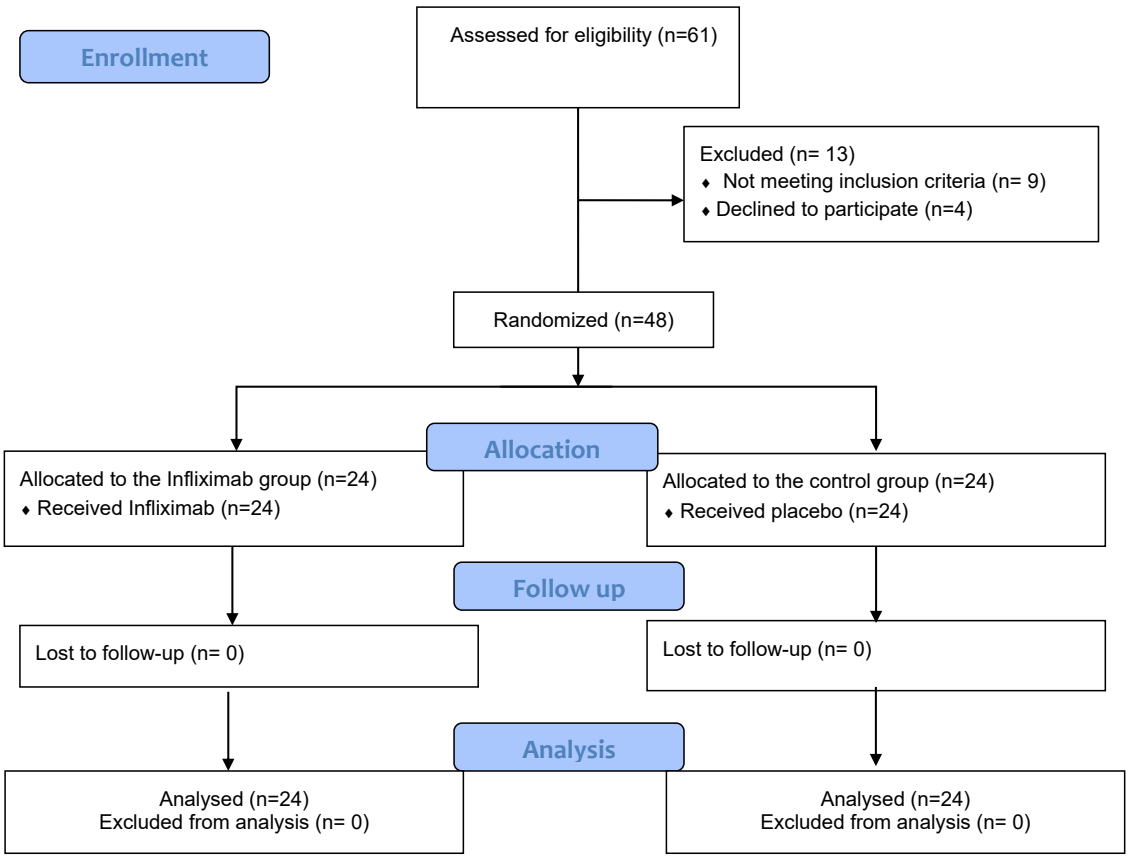

Figure 1. Participant flow diagram according to CONSORT guidelines.

Table 1. Comparison of demographic characteristics and baseline clinical and radiologic findings between the infliximab-treated and control groups

Characteristics		Group		*P* value
		Infliximab-treated (N = 24)	Control (N = 24)	
Demographic data & underlying disease	Age (years; Mean ± SD)	56.3 ± 12.7	55.5 ± 14.3	0.832*
	Body mass index (kg/m^2; Mean ± SD)	30.6 ± 6.1	28.7 ± 3.7	0.052*
	Male gender, N (%)	12 (50)	12 (50)	>0.99**
	Diabetes mellitus, N (%)	5 (20.8) [b]	11 (45.8)	0.066**
	Hypertension, N (%)	9 (37.5)	11(45.8)	0.561**
	Hyperlipidemia, N (%)	3 (12.5)	3 (12.5)	>0.99**
Vital signs	Respiratory rate (n/min; Mean ± SD)	30.7 ± 7.5	29.2 ± 5.7	0.432*
	Pulse rate (n/min; Mean ± SD)	95.6 ± 9.8	93 ± 16.2	0.518*
	SBP (mm Hg; Mean ± SD)	132.5 ± 21.9	125.5 ± 17.7	0.235*
	DBP (mm Hg; Mean ± SD)	76.5 ± 7.8	73.2 ± 13.1	0.293*
Radiologic findings & O_2 therapy	Ground-glass opacity, N (%)	24 (95.8)	24 (95.8)	>0.99**
	Consolidation, N (%)	15 (62.5)	15 (62.5)	>0.99**
	Crazy paving, N (%)	12 (50)	14 (58.3)	0.563**
	O_2 by mask or nasal, N (%)	9 (37.5)	10 (41.7)	0.825**
	O_2 by NIV or high flow, N (%)	15 (62.5)	14 (58.3)	0.761**
Symptoms	Fever, N (%)	21 (87.5)	20 (83.3)	0.925**
	Cough, N (%)	23 (95.8)	23 (95.8)	>0.99**
	Myalgia, N (%)	14 (58.3)	14 (58.3)	>0.99**
	Fatigue, N (%)	16 (66.7)	19 (79.2)	0.338**
	Dyspnea, N (%)	20 (83.3)	21 (91.3)	0.673**
	Diarrhea, N (%)	2 (8.3)	2 (8.3)	>0.99**

SD: Standard deviation, N: Number, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NIV; Non-invasive ventilation.
*Independent T-test, **Pearson Chi-square.

infliximab, including increased lymphocyte counts, decreased neutrophils and white blood cells, along with more effective reductions in inflammatory and coagulation markers such as D-dimer, LDH, and CRP, indicated enhanced regulation of the inflammatory response. These changes reflect better control of hyperinflammation, which is crucial in severe COVID-19, suggesting that infliximab may contribute to improved immune homeostasis and potentially better clinical outcomes, including a shorter duration of hospital stay, decreased mortality rates, and a reduced requirement for mechanical ventilation in this patient population. Our findings align with several previous studies that have investigated infliximab's impact on clinical outcomes in COVID-19 patients. For instance, a randomized placebo-controlled study reported significant mortality benefits and improved clinical status in hospitalized patients treated with infliximab, highlighting its potential to reduce severe disease progression (22). Additionally, combination therapy with infliximab and tocilizumab was shown to significantly shorten hospital stays, reduce mechanical ventilation needs, and lower mortality compared to standard care alone (23). However, some retrospective analyses and smaller studies have reported no statistically significant difference in mortality or recovery times when infliximab was added to the standard of care, with concerns also raised regarding increased secondary infections and liver enzyme elevations (16,19). Thus, while evidence points toward infliximab's beneficial role, heterogeneity in patient populations, timing of administration, and concomitant treatments may account for some discrepancies.

The growing body of evidence supports a potential immunomodulatory benefit of infliximab in managing severe COVID-19, likely due to its inhibition of TNF-α, a key cytokine in the hyperinflammatory cascade characteristic of severe disease (19,24,25). The immunological improvements observed, including restored lymphocyte counts and reductions in inflammatory markers, provide a plausible biological mechanism for the clinical benefits observed (19). Despite these promising findings, it is critical to balance these benefits against the risk of adverse effects, such as increased susceptibility to secondary infections and hepatotoxicity, which have been noted in several studies (16). Careful patient selection, focusing on those with marked hyperinflammation, and optimal timing of infliximab administration appear essential for maximizing therapeutic effects while minimizing harm. Further large, well-designed randomized trials are needed to clarify infliximab's precise role in COVID-19 management and integrate it effectively into treatment

Table 2. Comparative analysis of laboratory parameters and oxygen saturation levels in the infliximab-treated versus the control group throughout the study duration

Laboratory parameter	Time (day)	Treatment group		*P* value
		Infliximab-treated Mean ± SD/Median (IQR)	Control Mean ± SD/Median (IQR)	
O_2 sat (%)	1st	72.3 ± 8.5	75.7 ± 9.1	0.193*
	7th	85.7 ± 6.6	74.4 ± 12.7	0.041*
	14th	93 (90-95)	89 (85.5-93.5)	0.047**
WBC (10^3 /uL)	1st	9.5 ± 3.2	8 ± 2.7	0.088*
	7th	11.8 ± 2.9	13.1 ± 4	0.253*
	14th	10.2 (7.8-14.3)	13 (9.9-23.6)	0.049**
Platelet (10^3 /uL)	1st	218.6 ± 61.9	199.2 ± 79.8	0.352**
	7th	154.5 (122-227)	183 (126.5-237)	0.601**
	14th	197.3 ± 70.6	299.2 ± 126.6	0.342*
Lymphocyte (%)	1st	8.3 (4.9-13.8)	10 (7-14.3)	0.197*
	7th	12.3 ± 7.9	5.4 ± 3.9	< 0.001*
	14th	26 ± 14.7	11.4 ± 10.9	0.005*
Neutrophil (%)	1st	86.3 ± 6.6	82.2 ± 15.7	0.241*
	7th	82.3 ± 9.4	90.8 ± 5.2	< 0.001*
	14th	67.1 ± 16.5	82.8 ± 13.6	0.008*
D-dimer (ng/mL)	1st	907.5 (515.5-1719)	674 (472.2-834.5)	0.141**
	7th	619.5 (393-1727.7)	1894 (913.5-4705.5)	0.019**
	14th	312 (254-398)	839 (420.2-2602.7)	0.017**
LDH (U/L)	1st	636.2 ± 277.5	623.7 ± 310.1	0.884*
	7th	419.5 (331.5-493.5)	960 (701-1124.5)	< 0.001**
	14th	296 (267-328)	740 (363.5-1175)	0.009**
CRP (mg/L)	1st	2 (2-3)	2 (2-3)	0.973**
	7th	1.1 (0.7-1.3)	3 (2-3)	< 0.001**
	14th	0.8 (0.2-1.2)	2 (0.2-3)	0.004**

SD: Standard deviation, IQR: Interquartile range (Q1 - Q3), O_2sat: Oxygen saturation, WBC: White blood cell count, LDH: Lactate dehydrogenase, CRP: C-reactive protein.
*Independent T-test, **Mann Whitney U.

Table 3. Comparative analysis of clinical outcomes between the infliximab-treated and control groups throughout the study duration

Clinical outcome	Infliximab-treated	Control	*P* value
Hospitalization duration (days; Mean ± SD)	9.9 ± 4.6	12.6 ± 5.5	<0.001*
Mortality, N (%)	4 (16.7)	15 (62.5)	<0.001*
Mechanical ventilation, N (%)	4 (16.7)	15 (62.5)	0.001*

SD: Standard deviation, N: Number.
*Independent T-test, **Pearson Chi-square.

algorithms.

Overall, infliximab treatment in hospitalized COVID-19 patients shows promise in improving key clinical outcomes such as mortality, hospital stay duration, and ventilator requirements, consistent with the anti-inflammatory effects demonstrated in prior studies. However, clinical use must be cautiously implemented with attention to patient risk factors and monitoring for adverse events. The current evidence base, while encouraging, underscores the need for continued research to optimally define infliximab's efficacy, safety, and place in therapy within the broader context of COVID-19 immunomodulation strategies. These findings collectively suggest that infliximab could be a valuable adjunct to standard care in select patients suffering from severe COVID-19-associated hyperinflammation.

Conclusion

In conclusion, the study demonstrates that infliximab treatment in COVID-19 patients is associated with significantly improved clinical outcomes, including shorter hospital stays, reduced mortality, and a lower requirement for mechanical ventilation. These benefits are supported by laboratory findings showing better oxygenation, improved immune cell profiles, and more effective reduction of inflammation and coagulation markers in the infliximab group compared to controls. The results underscore

infliximab's potential as an effective therapeutic option to modulate immune response and improve recovery in patients, reflecting its capacity to control inflammation while enhancing clinical recovery.

Limitations of the study

The relatively small sample size of 48 patients may limit the generalizability of the findings and reduce statistical power to detect differences in some outcomes. The study was conducted at a single center, which may introduce selection bias and limit applicability to diverse populations or healthcare settings. The follow-up duration was limited to the hospitalization period, preventing assessment of long-term outcomes or late adverse effects of infliximab treatment. Furthermore, variations in the standard care protocol, including differences in supportive treatments such as antivirals and corticosteroids, could have influenced the results. Finally, certain exclusion criteria, such as the omission of patients with neurodegenerative diseases or heart failure, may restrict the applicability of the results to these patient subgroups. These limitations should be considered when interpreting the study outcomes and designing future research.

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Authors' contribution

Conceptualization: Akbar Soleymani Babadi and Jafar Majidi.
Data curation: Akbar Soleymani Babadi and Mohammad Mousavi.
Formal analysis: Soleiman Kheiri.
Investigation: Jafar Majidi and Mahdi Ghatrehsamani.
Methodology: Jafar Majidi and Soleiman Kheiri.
Project management: Mohammad Mousavi.
Resources: All authors.
Supervision: All authors.
Validation: Mohammad Mousavi and Mahdi Ghatrehsamani.
Writing–original draft: All authors.
Writing-review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Perplexity.ai and Grammarly.com) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The research was conducted in accordance with the principles outlined in the Declaration of Helsinki.. This study was conducted at Hajar hospital and derived from a research project (Registration number: 5642; Date: December 23, 2020), with the Ethical code (IR.SKUMS.REC.1399.227; https://ethics.research.ac.ir/EthicsProposalView.php?id=169921), approved by the Shahrekord University of Medical Sciences, Shahrekord, Iran. The study protocol was also registered as a clinical trial at the Iranian Registry of Clinical Trials (identifier: IRCT20201229049873N1; https://irct.behdasht.gov.ir/trial/53791). Accordingly, written informed consent was taken from all participants before any intervention. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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