Original Article

Use of Immune Modulating Agents to Regulate Hyperinflammation in Severe COVID 19: Assessment of Tocilizumab Use in Combination with Steroids

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ABSTRACT

Objective: In severe cases, COVID-19 can lead to a hyperinflammatory state, resulting in devastating outcomes. Immune modulation using steroids or other immune modulators can regulate the intensity of the inflammatory response; however, this theory has not been adequately assessed in practice. The current study aims to investigate the use of corticosteroids alone or in combination with tocilizumab to treat patients with severe COVID-19. **Methods:** This cross-sectional study was conducted on 166 Iranian patients with severe COVID-19 infection at Al-Zahra Hospital, who were treated with the standard treatment for severe COVID-19 infection, as per the 11th version of the Iranian guideline for COVID-19 treatment. Patients were categorized into three treatment groups based on the dose of corticosteroid treatment and tocilizumab therapy: (a) high-dose methylprednisolone (>1 mg/kg) alone, (b) low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg); and (c) high-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg). Mortality of patients as our primary outcome, laboratory parameters, length of hospitalization, intensive care unit (ICU) admission requirement, and drug-related adverse events were compared between groups. **Findings:** The second group showed significantly better outcomes, including shorter ICU stays, lower C-reactive protein and lactate dehydrogenase levels, and higher oxygen saturation and platelet counts than the other groups. Logistic regression revealed increased risks of mortality, nosocomial infection, and adverse effects, including hepatic and renal dysfunction and gastrointestinal bleeding, in Groups B and C compared with Group A. **Conclusion:** In all evaluated parameters, a low-dose steroid followed by tocilizumab was superior to a high-dose steroid alone or combined with tocilizumab. Although this combination treatment has been assessed worldwide, few studies have focused on its application in Iranian patients with severe COVID-19.

Keywords: *COVID-19, steroids, Tocilizumab*

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Introduction

COVID-19 emerged in Wuhan, China, in late December 2019. Soon, the world faced a global pandemic, with millions of individuals infected by the novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] COVID-19 induces a hyperinflammatory cytokine storm, with elevated interleukin-6 (IL-6), IL-2R, and tumor necrosis factor-alpha driving acute respiratory distress syndrome (ARDS), multiorgan failure, and severe disease progression. This inflammation also causes coagulation abnormalities, lymphopenia, and elevated C-reactive protein (CRP), ferritin, and D-dimer, correlating with

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higher mortality. Although most of the infected patients experienced asymptomatic to mild course of the disease limited to malaise, fever, cough, and flu-like symptoms, about 10% developed severe symptoms requiring hospitalization and intensive care unit (ICU) admission due to ARDS and multiorgan failure.[2-4] Initial treatments were supportive care, including fluid management, oxygen therapy, and mechanical ventilation. However, newer treatments targeting hyperinflammatory states characteristic of severe COVID-19 have emerged, such as steroids and other immunomodulatory agents.[5-7]

Previous experience with SARS and Middle East respiratory syndrome-led organizations such as the Infectious Diseases Society of America and the World Health Organization to caution against systemic corticosteroids due to risks such as delayed viral clearance and adverse events.[8,9] Nevertheless, some studies have shown promising outcomes with both high and low doses of systemic glucocorticoids in severe COVID-19 patients.[2,10-13] On the other hand, targeted immunomodulatory agents such as tocilizumab, a monoclonal antibody that blocks IL-6 receptors, are traditionally used in rheumatologic diseases. Tocilizumab reduces systemic inflammation by inhibiting IL-6 signaling, subsequently decreasing the need for mechanical ventilation and lowering mortality rates in critically ill patients.[14] Inconclusive but promising outcomes accompanied the use of this agent in COVID-19.[15-18]

Although the combination of corticosteroids and tocilizumab has been assessed in various global contexts, limited research has focused specifically on Iranian patients with severe COVID-19. This study addresses this gap by evaluating the combined use of corticosteroids and tocilizumab in this patient population.

Methods

This observational cross-sectional study was conducted on Iranian patients admitted to Al-Zahra Hospital, affiliated with Isfahan University of Medical Sciences, from April 2021 to March 2022. Patients or their legal guardians were informed about using their medical data for scientific research and provided written consent upon admission. Patients diagnosed with severe COVID-19 were included. The study protocol was designed according to the tenets of the Helsinki Declaration and approved by the Ethics Committee of Isfahan University of Medical Sciences. Inclusion criteria were: (1) positive COVID-19 polymerase chain reaction (PCR) test; (2) age ≥18 years; (3) patients diagnosed with severe COVID-19 infection or critically ill patients who did not respond to low-dose corticosteroid treatment only. Exclusion criteria were (1) pregnant patients; (2) immunocompromised patients; (3) patients with an absolute neutrophil count below 500 per microliter; (4) patients with serum platelet levels below 50,000 per microliter; (5) patients with a hospital stay of <5 days; (6) patients with more than 20% missing medical data.

A positive PCR test using a nasopharyngeal swab confirmed COVID-19 infection. Severe COVID-19 infection was defined by on-admission oxygen saturation <94%, PaO_2/FiO_2 <300, respiratory rate >30/min, and lung infiltration >50%.[19] Critically ill patients were identified as those with ARDS or septic shock requiring ICU admission.[20] All patients received an equal standard treatment according to the latest national guidelines for COVID-19 treatment.[21]

From April 1, 2021, to March 31, 2022, 314 patients met the inclusion criteria. However, 148 patients were excluded. The final sample size of the study was 166 patients with severe COVID-19 infection who were on a similar standard treatment.[20,21] Patients were equally divided into three groups based on their corticosteroid and tocilizumab therapy: (a) high-dose methylprednisolone (>1 mg/kg) alone; (b) low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg); and (c) high-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg).

Baseline demographic and laboratory information were collected, including age, sex, oxygen saturation, respiratory rate, and serum levels of CRP, lactate dehydrogenase (LDH), ferritin, and platelet count on the admission day. In addition, any history of comorbidities, such as diabetes mellitus, chronic kidney disease, end-stage renal disease (ESRD), hypertension, dyslipidemia, ischemic heart disease, atrial fibrillation, congestive heart failure, history of coronary artery bypass grafting (CABG), lung disease (asthma, chronic obstructive pulmonary disease, or interstitial lung disease), pulmonary thromboembolism (PTE), any history of hypothyroidism, dementia, Parkinson's disease, cerebrovascular accident, seizure, and malignancy with active chemotherapy, were collected.

The primary outcome was mortality among the groups. The secondary outcomes included: (1) total hospital admission duration (days); (2) length of ICU admission (days); (3) requirement for orotracheal intubation; (4) need for ICU admission; (5) nosocomial infections, gastrointestinal bleeding, and drug-related adverse effects, mainly hepatic and renal dysfunction; (6) change in oxygen saturation between the admission day

and discharge day; (7) change in respiratory rate from admission to discharge; and (8) change in laboratory parameters, such as CRP, LDH, ferritin, and platelet count, from admission to day 5 of hospitalization.

Two internal medicine resident physicians trained in the inclusion and exclusion criteria extracted data from the Hospital Information System. The extracted data were entered into the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 23. The qualitative data were presented as absolute numbers and percentages and the quantitative data as mean and standard deviation. Data distribution normality was assessed using the Kolmogorov–Smirnov test. The categorical data were compared using the Chi-square test. The continuous data were compared using analysis of variance (ANOVA); when significance was detected, *post hoc* tests were applied. Logistic regression analysis was performed using crude and adjusted models. Since clinical and laboratory parameters at admission were not significantly different between groups (except for platelet count), values collected on day 5 were compared rather than calculating the change from day 0 to day 5. An analysis of the covariance model was used to compare the platelet counts on day 5 between Groups A, B, and C, adjusting for the platelet count on admission day as a covariate. $P < 0.05$ was considered statistically significant.

Results

Baseline demographics, laboratory characteristics, and comorbidities of patients across the three treatment groups are summarized in Table 1. The mean age differed significantly between the groups ($P = 0.04$), with the reference group (A) having the highest mean age (61.93 ± 14.64 years) followed by Group B (55.29 ± 13.82 years) and Group C (57.77 ± 13.15 years). There was a significant difference between the prevalence of CABG among groups and the serum platelet count on the admission day ($P < 0.05$). None of the patients in any group had ESRD or PTE.

Treatment with low-dose methylprednisolone followed by a single dose of tocilizumab was associated with a significantly lower mortality rate (7.1%, odds ratio [OR]: 0.06) than the reference group (53.6%). In contrast, high-dose methylprednisolone followed by one dose of tocilizumab was associated with a higher mortality rate (69.9%) compared to the reference group (53.6%, OR: 1.85, $P = 0.12$). Logistic regression analyses conducted in crude and adjusted models (adjusting for age, CABG, and admission-day platelet count) confirmed these findings. Mortality remained significantly lower in Group B (OR: 0.06, $P < 0.001$) and higher in Group C (OR: 2.18, $P = 0.062$), though the latter did not reach statistical significance [Table 2, Figure 1a, b and Supplementary Table 1].

The orotracheal intubation requirement and the mean ICU stay were significantly lower in Group B ($P < 0.05$), whereas the total duration of hospital admission was not significantly different. Drug-related adverse effects such as renal dysfunction and nosocomial infection [Figure 2], respiratory rate, oxygen saturation, and laboratory parameters on the 5th day [Table 3 and Figure 3] were significantly improved in Group B ($P < 0.001$). The platelet count on day 5th was significantly higher in group B ($P = 0.007$, 95% confidence interval = 11.74–

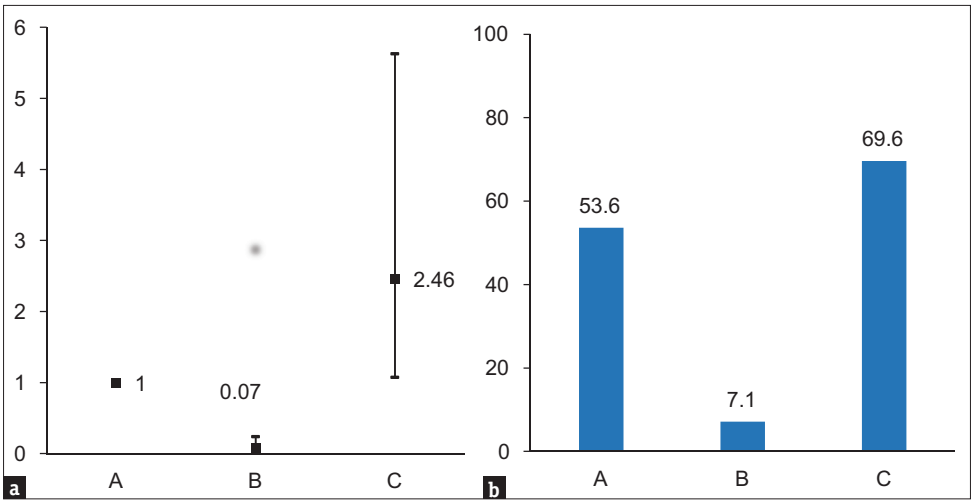

Figure 1: (a) Adjusted odd mortality ratio in the logistic regression model of Groups B (0.07 with 95% confidence interval of 0.02–0.24) and C (2.46 with 95% confidence interval of 1.07, 5.62) compared to Group A. (b) Mortality rate (%) between Groups A, B, and C. Group A: High-dose methylprednisolone alone (>1 mg/kg). Group B: Low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg). Group C: High-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg)

Table 1: Comparison of demographic data, laboratory tests, and comorbidities between groups

Variable	Group A	Group B	Group C	*P*
Total	56	56	56	-
Age (years)*	61.9±14.6	55.3±13.8	57.8±13.1	0.04
Male**	25 (44.6)	22 (39.3)	22 (39.3)	0.80
On admission				
Oxygen saturation*	84.5±5.0	84.7±4.1	82.3±10.2	0.14
RR* (per min)	27.0±5.4	26.7±5.1	27.8±5.5	0.53
CRP* (mg/dL)	88.8±14.0	93.8±10.6	89.8±13.8	0.10
LDH* (unit/L)	1206.5±406.3	1193.6±252.4	1181.1±370.8	0.93
Ferritin* (ng/mL)	1553±440	1619±373	1624±396	0.58
Platelet $\times 10^3$* (per µL)	191.9±68.3	169.2±54.9	160.5±53.5	0.02
DM**	17 (30.4)	15 (26.8)	13 (23.2)	0.69
CKD**	3 (5.4)	1 (1.8)	1 (1.8)	0.43
Lung disease**	2 (3.6)	3 (5.4)	3 (5.4)	0.87
Hypothyroidism**	6 (10.7)	9 (16.1)	3 (5.4)	0.18
Hyperlipidemia**	10 (17.9)	9 (16.1)	5 (8.9)	0.36
HTN**	24 (42.9)	19 (33.9)	17 (30.4)	0.36
IHD**	5 (8.9)	10 (17.9)	5 (8.9)	0.24
CHF**	2 (3.6)	1 (1.8)	0	0.36
CABG**	1 (1.8)	5 (8.9)	0	0.03
Arterial fibrillation**	2 (3.6)	1 (1.8)	0	0.36
PD**	2 (3.6)	0	0	0.13
Dementia**	0	1 (1.8)	0	0.36
Cerebrovascular event**	2 (3.6)	1 (1.8)	0	0.36
Seizure**	1 (1.8)	1 (1.8)	2 (3.6)	0.77
Malignancy**	0	1 (1.8)	0	0.36

*ANOVA, **Chi-square. As applicable, data are presented as mean±SD, or *n* (%). Group A=The reference group with high-dose methylprednisolone (>1 mg/kg) alone, Group B=Low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg). Group C=High-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), SD=Standard deviation, RR=Respiratory rate, CRP=C-reactive protein, LDH=Lactate dehydrogenase, DM=Diabetes mellitus, CKD=Chronic kidney disease, CABG=Coronary artery bypass grafting, ANOVA=Analysis of variance, IHD=Ischemic heart disease, CHF=Congestive heart failure, HTN=Hypertension, PD=Parkinson's disease

Table 2: Comparison of mortality rates between groups

Groups	Mortality rate	Crude model			Adjusted model*		
		OR	95% CI (minimum–maximum)	*P*	OR	95% CI (minimum–maximum)	*P*
Group A (%)	30/56 (53.6)	-	-	-	-	-	-
Group B (%)	4/56 (7.1)	0.07	0.02–0.21	0.00	0.07	0.02–0.24	0.00
Group C (%)	39/56 (69.6)	1.99	0.92–4.31	0.08	2.46	1.07–5.62	0.034

*Adjusted for age, history of CABG, and serum platelet count on admission day. Mortality rate (%) and OR in crude and adjusted logistic regression models between groups. Group A=The reference group with high-dose methylprednisolone (>1 mg/kg) alone, Group B=Low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), Group C=High-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), OR=Odds ratio, CI=Confidence interval, CABG=Coronary artery bypass grafting

72.39) and in Group C (P = 0.113). A summary of secondary outcomes is presented in Table 3 and Supplementary Table 2.

Discussion

Despite the progress made in managing COVID-19 through the development of various vaccines and therapeutic approaches, SARS-CoV-2 remains a persistent health concern, with the potential to reemerge as a significant public health challenge. Moreover, outpatient management of COVID-19 has significantly reduced the burden of mild and moderate disease. Yet, treating severe cases, particularly in critically ill patients, remains a topic of ongoing debate.[22,23] We evaluated the efficacy of three treatment regimens among these patients: High-dose corticosteroids alone and low-dose or high-dose corticosteroids in combination with tocilizumab. Our investigation revealed the combination of low-dose corticosteroids with tocilizumab was superior to the other two regimens, demonstrating a lower incidence of mortality, reduced ICU admission rates and lengths of stay, and improved clinical and laboratory

Table 3: Comparison of the secondary outcomes between groups

Secondary outcomes	Group A	Group B	Group C	*P*
Total admission (days)*	12.92±7.75	12.14±6.97	14.80±7.76	0.16
ICU admission (days)*	5.89±8.56	2.73±5.04	7.27±7.90	0.004
Intubation requirement**	30 (53.6)	8 (14.3)	42 (75)	<0.001
ICU admission requirement**	33 (58.9)	17 (30.4)	38 (67.9)	<0.001
Adverse effects				
Hepatic dysfunction**	28 (50)	29 (51.8)	31 (55.4)	0.84
Renal dysfunction**	29 (51.8)	10 (17.9)	25 (44.6)	0.001
GIB**	7 (12.5)	2 (3.6)	5 (8.9)	0.228
Nosocomial infection**	26 (46.4)	5 (8.9)	41 (73.2)	<0.001
Clinical parameters on day 5				
Oxygen saturation (%)*	81.37±9.85	89.37±5.11	75.94±10.94	<0.001
RR* (per min)	26.41±10.78	16.92±5.66	29.67±10.56	<0.001
Laboratory parameters on day 5				
CRP* (mg/dL)	44.35±35.39	17.17±20.24	50.50±36.08	<0.001
LDH* (unit/L)	1394±722	872±331	1565±751	<0.001
Ferritin* (ng/mL)	1815±125	1018±352	1653±518	0.367
Platelet $\times 10^3$* (per µL)	206.6±103.5	234.8±75.0	165.13±83.0	-

*ANOVA, **Chi-square. As applicable, data are presented as mean±SD, or *n* (%), Group A=The reference group with high-dose methylprednisolone (>1 mg/kg) alone, Group B=Low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), Group C=High-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), SD=Standard deviation, ICU=Intensive care unit, RR=Respiratory rate, CRP=C-reactive protein, LDH=Lactate dehydrogenase, ANOVA=Analysis of variance, GIB=Gastrointestinal bleeding

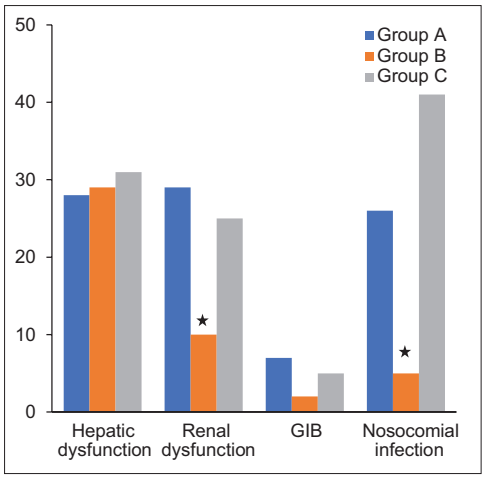

Figure 2: Incidence of drug-related adverse effects, including hepatic and renal dysfunction, nosocomial infection, and gastrointestinal bleeding in Groups A, B, and C. Renal dysfunction and nosocomial infection significantly decreased in Group B. Group A: High-dose methylprednisolone (>1 mg/kg) alone, Group B: Low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), and Group C: Reference group with high-dose methylprednisolone (>1 mg/kg) only followed by one dose of tocilizumab (8 mg/kg). ★: significantly lower ($P < 0.005$). GIB = Gastrointestinal bleeding

parameters after 5 days. Moreover, logistic regression analysis showed a significantly higher mortality risk in patients treated with high-dose corticosteroids alone or in combination with tocilizumab, compared with the low-dose corticosteroid plus tocilizumab regimen.

One of the lethal events following severe COVID-19 infection is a "cytokine storm," a severe inflammatory response driven by IL-6. Given the role of IL-6 in cytokine storms, researchers have explored immunomodulatory agents targeting cytokines, such as tocilizumab, a selective IL-6 receptor blocker. Early studies in the literature reported mixed outcomes with tocilizumab when used as monotherapy.[16,18,24,25] However, subsequent research demonstrated more promising results when tocilizumab was combined with corticosteroids, either concurrently or within a short interval (e.g., 48 h).

A large cohort study by Ruiz-Antorán *et al*. assessed the use of corticosteroids, tocilizumab, and their combination in severe COVID-19 cases. Their findings supported the superiority of combination therapy over monotherapy, with reduced adverse events and mortality.[26] Similarly, Mikulska *et al*. reported favorable outcomes with the use of methylprednisolone and tocilizumab, highlighting the efficacy of this combination in reducing adverse events and mortality; however, they did not directly compare this regimen to others. Their study concluded that tocilizumab alone, corticosteroids alone, and their combination provided better outcomes than standard care.[14] Van den Eynde *et al*. assessed tocilizumab combined with steroids versus steroids alone and reported that both approaches could effectively reduce the mortality rate; however, those receiving the combination therapy had a 25% lower mortality rate than the latter group.[15] Conversely, although dexamethasone alone or combined with tocilizumab significantly reduced mortality and intubation rates, neither approach

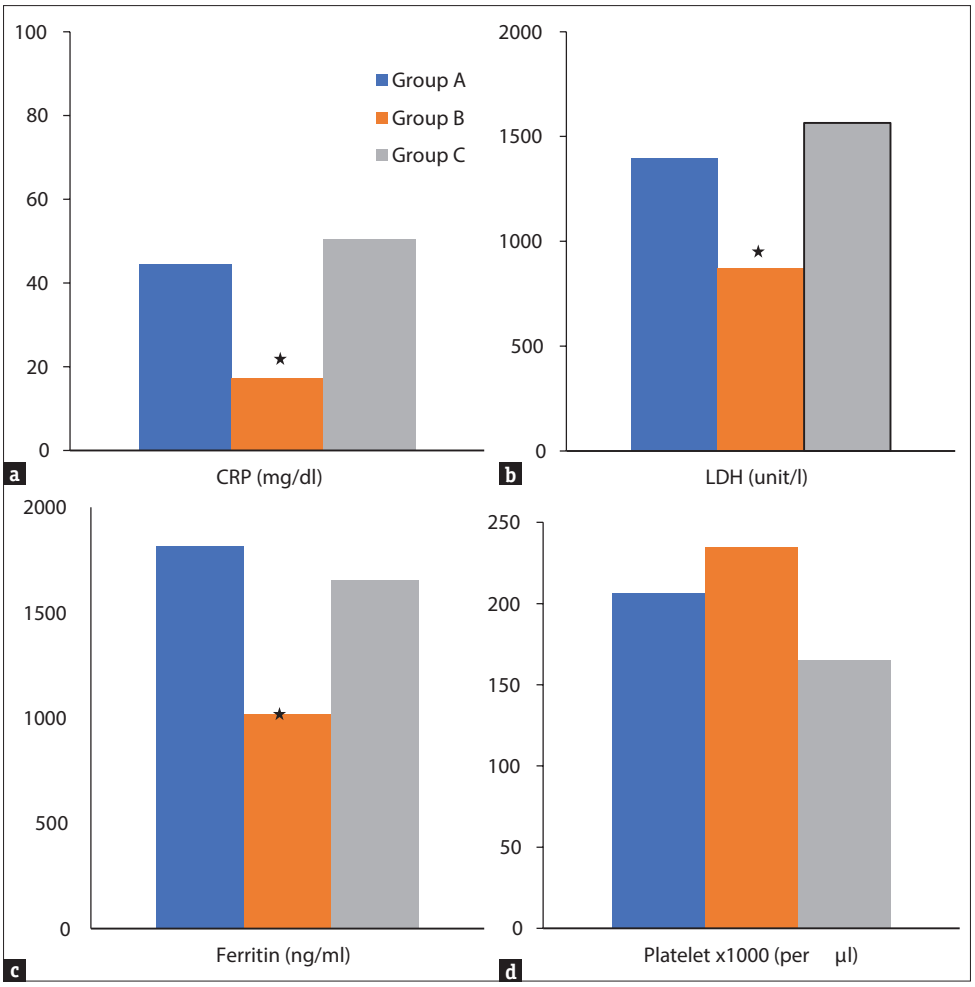

Figure 3: Laboratory parameters on day 5th in groups A, B, and C. (a) C-reactive protein (CRP, mg/dl); (b) lactate dehydrogenase (LDH, Unit/l); (c) Ferritin (ng/ml); (d) Serum platelet count (×1000/µL). CRP, LDH, and ferritin levels significantly decreased ($P < 0.001$) after treatment with low-dose methylprednisolone, followed by one dose of tocilizumab. In addition, plate count significantly increased in the same treatment group. Group A: The reference group with high-dose methylprednisolone (>1 mg/kg) alone. Group B: Low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg). Group C: High-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg). ★: Significantly different ($P < 0.005$). LDH = Lactate dehydrogenase, CRP = C-reactive protein

demonstrated clear superiority, given the negligible difference in adverse events between groups.[27]

A review of the literature shows that high-dose steroids, dexamethasone, or methylprednisolone could effectively lead to a reduced risk of intubation and mortality if applied appropriately.[23] The findings indicated that the steroids are most beneficial for those with severe COVID-19. Therefore, the use of steroids in individuals with milder or early-stage COVID-19 may result in a higher viral load due to increased viral shedding, which can trigger more significant inflammation and delay viral clearance.[28] The studies indicated that steroids in the low dose may be ineffective in adequately controlling the inflammatory storm.[14,29] Another survey by Ruiz-Antorán *et al*. in Spain found that tocilizumab reduced mortality more effectively when combined with lower doses of corticosteroids, likely due to a balanced immunomodulatory effect that mitigates hyperinflammation without excessive immunosuppression. High doses of corticosteroids alone may excessively suppress the immune response, increasing the risk of secondary infections and delaying viral clearance, whereas moderate doses preserve immune function while enhancing the effects of IL-6 blockade.[26] However, the study did not provide data on the need for intubation or ICU admission, the duration of ICU stays, or potential drug-related adverse effects, such as hepatic or renal dysfunction, secondary infections, or other complications associated with tocilizumab and corticosteroid use. Furthermore, the study population differs from ours in terms of baseline characteristics, severity of illness, and treatment protocols.

The study's cross-sectional design is the most significant limitation of the current report, as a randomized trial or a cohort design could lead to more reliable and conclusive outcomes.

Based on this study's findings, specifically among the Iranian population, the combination of low-dose corticosteroids with tocilizumab was superior to high-dose corticosteroids alone or in combination with tocilizumab in terms of key outcomes, including mortality rate, ICU admission rate, and duration, as well as the incidence of renal dysfunction and nosocomial infections. Further studies are recommended to confirm these findings and explore the underlying mechanisms and optimal dosing strategies for combination therapy.

Authors' Contribution

Each author contributed to the literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review.

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Conflicts of interest

There are no conflicts of interest.

References

1. Sadeghi S, Nasri P, Nasirian M, Mirenayat MS, Toghyani A, Khaksar M, *et al*. On admission hemoglobin and albumin, as the two novel factors associated with thrombosis in COVID-19 pneumonia. J Renal Inj Prev 2022;11:31957. [doi: 10.34172/jrip.2022.31957].
2. Sadeghi S, Arezoomandi N, Ardestani MM, Ardestani ME, Ghiasi F, Farajzadegan Z. Efficacy and safety comparison of two different doses of dexamethasone in hospitalized patients with COVID-19: A randomized clinical trial. J Res Pharm Pract 2022;11:136-43.
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;395:507-13.
4. Sadeghi A, Sadeghi S, Peikar MS, Yazdi M, Sharifi M, Ghafel S, *et al*. Efficacy of plasmapheresis in neutropenic patients suffering from cytokine storm because of severe COVID-19 infection. Blood Res 2023;58:91-8.
5. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, *et al*. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020;7:4.
6. Xu X, Han M, Li T, Sun W, Wang D, Fu B, *et al*. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 2020;117:10970-5.
7. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.
8. Bhimraj A, Morgan RL, Shumaker AH, Baden LR, Cheng VC, Edwards KM, *et al*. Infectious Diseases Society of America guidelines on the treatment and management of patients with coronavirus disease 2019 (COVID-19). Clin Infect Dis 2024;78:e250-e349. [doi: 10.1093/cid/ciac724].
9. World Health Organization. Clinical Management of Severe Acute Respiratory Infection (SARI) when COVID-19 Disease is Suspected: Interim Guidance. Paediatrics and Family Medicine, 2020;16:9-26.
10. Mirenayat MS, Sadeghi S, Fakharian A, Zahiri R, Mirtajani SB, Amraei Z, *et al*. The effect of short-term methylprednisolone on clinical outcome and lung CT scan in severe COVID-19: In-hospital and six weeks later follow-up. Int J Drug Res Clin 2023;1:e12-e.
11. RECOVERY Collaborative Group. Higher dose corticosteroids in hospitalised COVID-19 patients requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv 2022;2022.12.16.22283578.
12. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, *et al*. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 2020;324:1317-29.
13. Sirio-Libanes RP. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX randomized clinical trial. JAMA 2020;324:1307-16. [doi: 10.1001/jama.2020.17021].
14. Mikulska M, Nicolini LA, Signori A, Di Biagio A, Sepulcri C, Russo C, *et al*. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. Plos One 2020;15:e0237831.
15. Van den Eynde E, Gasch O, Oliva JC, Prieto E, Calzado S, Gomila A, *et al.* Corticosteroids and tocilizumab reduce in-hospital mortality in severe COVID-19 pneumonia: A retrospective study in a Spanish hospital. Infect Dis (Lond) 2021;53:291-302.
16. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, *et al.* Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med 2020;383:2333-44.
17. Jiménez-Brítez G, Ruiz P, Soler X. Tocilizumab plus glucocorticoids in severe and critically COVID-19 patients. A single center experience. Med Clin (Barc) 2020;155:410-1.
18. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, *et al*. Effect of tocilizumab versus standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. JAMA Intern Med 2021;181:24-31.
19. Wilfong EM, Lovly CM, Gillaspie EA, Huang LC, Shyr Y, Casey JD, *et al.* Severity of illness scores at presentation predict ICU admission and mortality in COVID-19. J Emerg Crit Care Med 2021;5:7.
20. Huang C, Soleimani J, Herasevich S, Pinevich Y, Pennington KM, Dong Y, *et al.* Clinical characteristics, treatment, and outcomes of critically ill patients with COVID-19: A scoping review. Mayo Clin Proc 2021;96:183-202.
21. 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.
22. Pinzón MA, Ortiz S, Holguín H, Betancur JF, Cardona Arango D, Laniado H, *et al.* Dexamethasone versus methylprednisolone high dose for COVID-19 pneumonia. PLoS One 2021;16:e0252057.
23. Lim PC, Wong KL, Rajah R, Chong MF, Chow TS, Subramaniam S, *et al*. Comparing the efficacy of tocilizumab with corticosteroid therapy in treating COVID-19 patients: A systematic review and meta-analysis. Daru 2022;30:211-28.
24. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS,

Melamed ML, *et al*. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med 2021;181:41-51.

25. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, *et al*. Effect of tocilizumab versus usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: A randomized clinical trial. JAMA Intern Med 2021;181:32-40.
26. Ruiz-Antorán B, Sancho-López A, Torres F, Moreno-Torres V, de Pablo-López I, García-López P, *et al*. Combination of tocilizumab and steroids to improve mortality in patients with severe COVID-19 infection: A Spanish, multicenter, cohort study. Infect Dis Ther 2021;10:347-62.
27. Hermine O, Mariette X, Porcher R, Djossou F, Nguyen Y, Arlet JB, *et al.* Tocilizumab plus dexamethasone versus dexamethasone in patients with moderate-to-severe COVID-19 pneumonia: A randomised clinical trial from the CORIMUNO-19 study group. EClinicalMedicine 2022;46:101362.
28. Li S, Hu Z, Song X. High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19. Clin Infect Dis 2021;72:1297-8.
29. Jeronimo CM, Farias ME, Val FF, Sampaio VS, Alexandre MA, Melo GC, *et al*. Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; METCOVID): A randomized, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2021;72:e373-81.

Supplementary Table 1: Mortality rate (%) and odd ratio in crude and adjusted logistic regression models between Groups B and C compared to group A

Groups	Crude model			Adjusted model*		
	OR	95% CI (minimum–maximum)	*P*	OR	95% CI (minimum–maximum)	*P*
Group A versus B	0.07	0.020.21	0.00	0.07	0.02–0.24	0.00
Group A versus C	1.99	0.92–4.31	0.08	2.46	1.07–5.62	0.034
Group B versus C	29.82	2.03–73.22	0.00	34.23	2.30–271.08	0.00

*Adjusted for age, history of CABG, and serum platelet count on admission day. Group A=The reference group with high-dose methylprednisolone (>1 mg/kg) alone, Group B=Low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), Group C=High-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), OR=Odds ratio, CI=Confidence interval, CABG=Coronary artery bypass grafting

Supplementary Table 2: Comparing the platelet count on day 5th between groups after adjusting for the platelet count on admission day

Change in platelet count	Adjusted 95% CI (minimum–maximum)	*P*
Group A versus C	−5.90–55.54	0.113
Group A versus B	11.74–72.39	0.007
Group B versus C	36.71–97.06	<0.001

Group A=The reference group with high-dose methylprednisolone (>1 mg/kg) alone, Group B=Low-dose methylprednisolone (<1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), Group C=High-dose methylprednisolone (>1 mg/kg) followed by one dose of tocilizumab (8 mg/kg), CI=Confidence interval