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A Retrospective Cohort Study Comparing the Clinical Outcomes of Patients with Severe COVID-19 Treated with Different Regimens

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ABSTRACT

Background: This study evaluated the clinical effects of five treatment regimens, including tocilizumab plus baricitinib, tocilizumab plus co-trimoxazole, tocilizumab alone, high-dose corticosteroids alone, and high-dose corticosteroids plus baricitinib, on treatment outcomes of patients with severe COVID-19.
Materials & Methods: In this retrospective cohort study, 50 patients with severe COVID-19, who were admitted to the intensive care unit of Shafa hospital in Khorramabad (western Iran) from April to December 2021, were divided into five treatment groups: tocilizumab plus baricitinib, tocilizumab plus co-trimoxazole, tocilizumab alone, high-dose corticosteroids alone, and high-dose corticosteroids plus baricitinib. Patients were assessed based on vital signs, radiological imaging, clinical symptoms, and laboratory parameters recorded at baseline and throughout hospitalization.
Findings: The group receiving tocilizumab plus co-trimoxazole alongside standard therapy achieved the highest recovery rate (100%), whereas the group receiving tocilizumab plus baricitinib had the highest mortality rate (90%). These differences were statistically significant ($p< .05$). Mortality was also significantly associated with anemia; thrombocytopenia; elevated levels of CRP, ferritin, and LDH; and extensive pulmonary involvement ($p< .05$).
Conclusion: The findings indicated that regimens involving tocilizumab plus co-trimoxazole, corticosteroids plus baricitinib, or tocilizumab monotherapy were associated with lower mortality rates and improved recovery outcomes in patients with severe COVID-19. In contrast, the concurrent administration of tocilizumab and baricitinib was associated with higher mortality rates, possibly due to excessive immunosuppression. Elevated levels of CRP, ferritin, LDH, AST, and ALT, along with extensive lung involvement and anemia, were identified as significant predictors of mortality. Larger cohort studies are needed to confirm these findings.

Keywords: COVID-19, Tocilizumab, Baricitinib, Co-trimoxazole, High-dose corticosteroids

CITATION LINKS

[1] Yuki K, et al. COVID-19... [2] Li Q, Guan X, et al. Early transmission dynamics... [3] Zheng M, et al. Functional exhaustion of... [4] Ciotti M, et al. The COVID... [5] Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to... [6] Rabi FA, et al. SARS-CoV-2 and... [7] Cevik M, Bamford CG, Ho A. COVID-19 pandemic—a focused review for... [8] Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19... [9] Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms... [10] Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell... [11] Mao L, et al. Neurologic manifestations of... [12] Huang C, et al. Clinical features of... [13] Wang D, et al. Clinical characteristics of... [14] Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of... [15] Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of... [16] Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor... [17] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on... [18] Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike... [19] Millet JK, Whittaker GR. Host cell entry of Middle East respiratory syndrome... [20] Ou X, Liu Y, et al. Characterization of spike glycoprotein... [21] Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6... [22] Horby PW, Pessoa-Amorim G, Peto L, Brightling CE, Sarkar R, Thomas K, et al. Tocilizumab in... [23] Sunny S, Tran A, Lee J, Abdallah M, Chaudhry N, Quale J. Comparison of... [24] Cherian JJ, Eerike M, Bagepally BS, Das S, Panda S. Efficacy and safety of... [25] Choi SH, Choi JH, Lee JK, Eun BW, Song SH, Ahn B, et al. Clinical characteristics... [26] Adelborg K, Veres K, Horváth-Puhó E, Clouser M, Saad H, Sørensen HT. Risk and... [27] Ding Q, Xu W, Chen Y, Chang S, Zhang J. Correlation between...

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Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) emerged as a zoonotic pathogen that subsequently established sustained human-to-human transmission [1, 2], culminating in the World Health Organization (WHO)-declared COVID-19 (coronavirus disease 2019) pandemic across approximately 200 countries and territories [3]. As of April 2025, global surveillance data indicated approximately 777 million confirmed cases and 7.1 million associated deaths [4-7]. Meta-analytical evidence identifies fever (75–85%), cough (60–65%), fatigue (30–35%), and dyspnea (25–30%) as the predominant clinical manifestations [8], while anosmia and ageusia have been documented in over 40% of affected individuals [9, 10]. Additional frequently-reported symptoms include sputum production (20–25%), sore throat and headache (10–20% each) [11], and gastrointestinal manifestations such as nausea, vomiting, and diarrhea (5–15%) [12]. Patients with pre-existing comorbidities (including diabetes mellitus, hypertension, and cardiovascular or pulmonary diseases) as well as older adults exhibit heightened susceptibility to disease progression, encompassing respiratory failure, acute respiratory distress syndrome, and multiorgan dysfunction [12, 13].

Structurally, coronaviruses are enveloped, single-stranded RNA viruses comprising four structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) [14]. The S protein, organized into S1 and S2 subunits, mediates host-cell attachment and membrane fusion, respectively, with angiotensin-converting enzyme 2 (ACE2) serving as the principal functional receptor governing viral entry [14–16].

Severe COVID-19 is characterized by excessive inflammatory activation involving interleukin-6 (IL-6) and the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathways [17]. Tocilizumab inhibits IL-6 receptor signaling, while baricitinib suppresses downstream JAK-mediated inflammatory responses. Corticosteroids provide broad immunomodulatory effects, and co-trimoxazole may offer additional antimicrobial and anti-inflammatory benefits. Given the limited comparative evidence regarding these therapeutic strategies, this retrospective cohort study aimed to compare the clinical outcomes associated with different immunomodulatory treatment regimens in patients with severe COVID-19 [18–20].

Viral entry into host cells, including monocytes, macrophages, and dendritic cells, triggers the activation and secretion of IL-6 along with other proinflammatory cytokines. IL-6 exerts distinct proinflammatory effects and mediates inflammatory signaling through both cis- and trans-signaling pathways [9].

In the cis-signaling mechanism, IL-6 binds to the membrane-bound IL-6 receptor (mIL-6R), forming a complex with the membrane glycoprotein GP130. This complex subsequently activates downstream signaling cascades involving JAK and STAT proteins. Notably, GP130 is ubiquitously expressed, whereas mIL-6R expression is largely restricted to immune cells. Activation of the cis-signaling pathway induces diverse effects on both adaptive immune components (such as B and T lymphocytes) and innate immune cells (including neutrophils, macrophages, and natural killer cells), potentially contributing to the pathogenesis of cytokine release syndrome [9].

Within the trans-signaling pathway, elevated levels of circulating IL-6 interact with the soluble IL-6 receptor (sIL-6R), forming a complex with glycoprotein 130 (GP130) on the surface of various cell types. This IL-6–sIL-6R–JAK–STAT signaling complex enables the activation of cells lacking the membrane-bound IL-6 receptor (mIL-6R), including endothelial cells. Such activation triggers a systemic cytokine storm, characterized by the excessive release of vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), interleukin-8

(IL-8), and IL-6 itself, accompanied by the downregulation of E-cadherin expression in endothelial cells. Increased VEGF secretion, together with reduced E-cadherin levels, contributes to enhanced vascular permeability and leakage—mechanisms implicated in the pathogenesis of hypotension and pulmonary dysfunction observed in acute respiratory distress syndrome (ARDS) [21].

Given the inflammatory pathophysiology of COVID-19; the well-established anti-inflammatory and immunomodulatory effects of baricitinib, co-trimoxazole, tocilizumab, and methylprednisolone; as well as the lack of prior research directly comparing the clinical efficacy of combined treatment regimens—specifically tocilizumab with baricitinib, tocilizumab with co-trimoxazole, tocilizumab alone, high-dose corticosteroids alone, and high-dose corticosteroids with baricitinib—this retrospective cross-sectional study was conducted to assess and compare the therapeutic outcomes associated with these interventions in patients experiencing the cytokine storm phase of severe COVID-19.

Materials and Methods

Study population: The study population comprised all patients with severe COVID-19, who were admitted to the intensive care unit of Shafa hospital in Khorramabad from April to December 2021 and met the study inclusion criteria. Inclusion criteria included hospitalization due to suspected COVID-19 with a positive PCR test result or, in cases of a negative PCR, a strong clinical suspicion supported by typical radiographic findings suggestive of COVID-19, provided that the symptoms could not be attributed to other conditions (as determined by an infectious disease specialist). Patients were also required to present respiratory symptoms such as dyspnea, chest pain or pressure (with or without fever ≥ 38 °C), and an oxygen saturation (SpO_2) level below 90%. Eligible patients were classified as being in Phase 2 (severe) or Phase 3 (critical) of the disease and exhibited Stage 4 or 5 pulmonary involvement. Exclusion criteria included a history of hypersensitivity to cotrimoxazole, baricitinib, tocilizumab, or methylprednisolone; incomplete medical records; or pulmonary involvement below Stage 4. All eligible patients were included during the study period, employing a census approach; therefore, no additional sample size calculation was required.

Study groups and interventions: This retrospective cohort study examined patients with severe COVID-19, who were admitted to the intensive care unit of Shafa hospital in Khorramabad (western Iran) from April to December 2021. Five patient groups were analyzed: Group 1 received tocilizumab (400–800 mg daily) plus standard care; Group 2 received tocilizumab (400–800 mg daily) combined with cotrimoxazole (80/400–160/800 mg every 6–8 hours) plus standard care; Group 3 received tocilizumab (400–800 mg daily) combined with baricitinib (4 mg daily) plus standard care; Group 4 received methylprednisolone (250 mg daily) plus standard care; and Group 5 received methylprednisolone (250 mg daily) combined with baricitinib (4 mg daily) plus standard care.

Standard care included remdesivir (200 mg on day 1, followed by 100 mg daily for 7–14 days, depending on clinical condition) and dexamethasone (up to 8 mg daily), administered according to clinical judgment. Tocilizumab was administered as a single intravenous infusion (400–800 mg according to body weight and clinical status). Baricitinib was administered orally at a dose of 4 mg/day for up to 14 days or until discharge. High-dose corticosteroid therapy was defined as intravenous administration of methylprednisolone at a dose of 250 mg/day for three consecutive days. Co-trimoxazole was administered orally every 6–8 hours according to clinical status and renal function. Standard care consisted of remdesivir and dexamethasone according to institutional treatment protocols.

Data collection: Data were collected using a researcher-designed form encompassing demographic, clinical, and laboratory variables. Demographic data included age, sex, body mass index (BMI), and other relevant characteristics. Vital signs such as temperature, SpO_2, heart rate, and respiratory rate were recorded at baseline, throughout hospitalization, and at discharge. Additional data extracted from medical records included 28-day survival, recovery rate, mortality, daily SpO_2 and temperature, presence or absence of cough and dyspnea, daily respiratory rate, routine laboratory indices, length of hospital stay, discharge time, need for supplemental oxygen, frequency of oxygen administration, and requirement for non-invasive mechanical ventilation. Recovery was defined as survival until hospital discharge with documented clinical improvement and no need for acute inpatient care. Mortality was defined as all-cause in-hospital death occurring during the index hospitalization. Additionally, 28-day survival data were recorded where available.

Statistical analysis: The collected data were entered into SPSS software, Version 26.0. Descriptive statistics, including proportions, central tendency, and dispersion measures, were reported. Line graphs were used to visualize changes in mean indices over time. The inferential analyses employed included Chi-square test, one-way analysis of variance (ANOVA) or Kruskal-Wallis test (for non-normal data), independent samples t-test or Mann-Whitney U test, paired sample t-test, repeated measures ANOVA, and generalized estimating equations (GEE). Statistical significance was set at $p< .05$.

Findings

Participants: In this study, 50 eligible patients were included in the final analysis. The baseline characteristics of the study population are presented in Table 1.

Patient demographic and clinical data: Baseline demographic and clinical characteristics were compared between the five treatment groups, and no significant differences were found in age, sex distribution, BMI, smoking history, or comorbidities ($p> .05$; Table 1).

Clinical manifestations: Significant between-group differences were observed regarding muscle pain, fatigue, chest pain, decreased appetite, and sputum production ($p< .05$), whereas the remaining symptoms were similarly distributed across the treatment groups (Table 2).

Clinical parameters: The Kruskal-Wallis test results indicated a significant difference in lung CT scan status between the study groups ($p< .05$). Specifically, the second group had the highest proportion of patients with Stage 4 lung involvement (100%), while the third and fifth groups had the highest proportion of patients with Stage 5 lung involvement (100%) (Table 3). The Chi-square test results showed a significant difference in patient survival status between the groups ($p< .05$). Notably, the second group (patients treated with tocilizumab plus cotrimoxazole alongside the standard drug regimen) exhibited the highest recovery rate, whereas the third group (patients treated with tocilizumab plus baricitinib alongside the standard drug regimen) had the highest mortality rate (Table 3).

Laboratory parameters: At admission, ANOVA revealed significant intergroup differences in prothrombin time (PT), international normalized ratio (INR), C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), respiratory rate (RR), oxygen saturation (SpO_2), red blood cell count (RBC), hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), urea, alanine aminotransferase (ALT), and mean corpuscular hemoglobin (MCH) ($p< .05$). Although differences in prothrombin time, international normalized ratio, respiratory rate, mean corpuscular volume, and mean corpuscular hemoglobin were not clinically meaningful, other parameters showed no significant differences ($p> .05$). Group 2 consistently showed the most favorable in-

Table 1) Comparative summary of demographic and clinical data of patients in the study groups

Variable		First Group N (%)	Second Group N (%)	Third Group N (%)	Fourth Group N (%)	Fifth Group N (%)	*P* Value
Gender	Female	7 (63.60)	5 (55.60)	5 (50)	6 (60)	6 (60)	.977
	Male	4 (36.40)	4 (44.40)	5 (50)	4 (40)	4 (40)	
Tobacco use	Yes	0 (0)	1 (11.10)	2 (20)	1 (10)	1 (10)	.672
	No	11 (100)	8 (88.90)	8 (80)	9 (90)	9 (90)	
Underlying disease	Yes	5 (45.40)	5 (55.60)	8 (80)	6 (60)	6 (60)	.607
	No	6 (54.50)	4 (44.40)	2 (20)	4 (40)	4 (40)	
Blood pressure	Yes	4 (36.40)	3 (33.30)	6 (60)	6 (60)	5 (50)	.637
	No	7 (63.60)	6 (66.70)	4 (40)	4 (40)	5 (50)	
Diabetes	Yes	2 (18.20)	1 (11.10)	2 (20)	4 (40)	1 (10)	.464
	No	9 (81.80)	8 (88.90)	8 (80)	6 (60)	9 (90)	
Chronic heart disease	Yes	1 (9.10)	0 (0)	0 (0)	1 (10)	2 (20)	.451
	No	10 (90.90)	9 (100)	10 (100)	9 (90)	8 (80)	
Chronic kidney disease	Yes	1 (9.10)	0 (0)	0 (0)	1 (10)	0 (0)	.577
	No	10 (90.90)	9 (100)	10 (100)	9 (90)	10 (100)	
History of stroke	Yes	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	.395
	No	11 (100)	9 (100)	10 (100)	10 (100)	9 (90)	
History of heart attack	Yes	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	.395
	No	11 (100)	9 (100)	9 (90)	10 (100)	10 (100)	
Drug or food allergy	Yes	1 (9.10)	1 (11.10)	1 (10)	1 (10)	0 (0)	.892
	No	10 (90.90)	8 (88.90)	9 (90)	9 (90)	10 (100)	
Medication use in the past three months	Yes	7 (63.60)	5 (55.60)	7 (70)	7 (70)	6 (60)	.956
	No	4 (36.40)	4 (44.40)	3 (30)	3 (30)	4 (40)	

Variable		First Group N (%)	Second Group N (%)	Third Group N (%)	Fourth Group N (%)	Fifth Group N (%)	*P* Value
BMI	18.5>	1 (9.09)	1 (11.1)	0 (0)	1 (10)	2 (20)	.266
	18.5-24.9	1 (9.09)	5 (55.6)	0 (0)	2 (20)	3 (30)	
	25-29.9	6 (54.54)	2 (22.2)	6 (60)	5 (50)	4 (40)	
	30<	3 (27.27)	1 (11.1)	4 (40)	2 (20)	1 (10)	
Age (mean ±SD)	-	53.90±2.34	53.44±2.06	54.90±2.42	55.60±5.60	56.40±4	.354

flammatory and hematological profile (lowest levels of C-reactive protein, ferritin, and lactate dehydrogenase; and highest levels of oxygen saturation and red blood cell count), whereas Group 3 showed the lowest levels of oxygen saturation, red blood cell count, hemoglobin, and hematocrit, and Group 4 showed the highest levels of ferritin, lactate dehydrogenase, and hemoglobin, alongside the lowest levels of alanine aminotransferase (Table 4).

Variations in laboratory results in the study groups over time: Repeated measures analysis of variance demonstrated significant time-by-group interactions for white blood cell (WBC) count (p= .047) and platelet count (p= .008). WBC count changes over time were significant in the third and fourth groups, with the most pronounced increase from admission to the midpoint of hospitalization period (p= .006) observed in Group 4 relative to Group 2; no significant differences were found between the hospitalization midpoint and the discharge time (p= .683). Regarding platelet count, significant temporal changes were observed in all groups except Groups 2 and 3, with post hoc analysis showing significantly lower platelet counts in Group 5 compared to Groups 1 and 2 in the second and third time points. Hb levels declined significantly over time only in Group 4 (p= .002), with a statistically significant but clinically negligible time-by-group interaction (p= .027) driven by changes between the second and third time points. RBC counts decreased significantly in Groups 1 and 4, though the non-significant time-by-group interaction (p= .425) indicated no overall between-group difference. HCT levels changed significantly in Groups 2 and 3, and MCV levels changed significantly in Group 3 (p= .031), yet neither showed a significant overall between-group difference (p=.436 and p= .483, respectively). No significant within-group or between-group differences were observed for MCH, creatinine, aspartate aminotransferase (AST), urea, or lymphocyte, monocyte, and eosinophil counts (p> .05) (Table 5).

Variations in the average clinical indices of patients in the study groups over time: Changes in the average clinical indices of patients in the study groups over time were analyzed, and the results are shown in Figures 2-7. The scattered data points at the ends of the line graphs are attributed to the small sample size at the discharge time.

Generalized estimating equations (GEE) model: The GEE model was used to assess the impact of various drugs on clinical outcomes of patients with severe COVID-19, the findings indicated that the interaction effect of time within groups was not significant. Consequently, there were no significant differences in the average changes of pulse rate (PR), systolic blood pressure (SBP), diastol-

Table 2) Comparison of the frequency of COVID-19 symptoms among patients in the study groups

Factor		First Group N (%)	Second Group N (%)	Third Group N (%)	Fourth Group N (%)	Fifth Group N (%)	*P* Value
Fever	Yes	7 (63.60)	9 (100)	7 (70)	7 (70)	8 (80)	.46
	No	4 (36.40)	0 (0)	3 (30)	3 (30)	2 (20)	
Chills	Yes	8 (72.72)	7 (77.77)	5 (50)	7 (70)	5 (50)	.564
	No	3 (27.27)	2 (22.23)	5 (50)	3 (30)	5 (50)	
Runny nose	Yes	1 (9.10)	0 (0)	0 (0)	0 (0)	0 (0)	.46
	No	10 (90.90)	9 (100)	10 (100)	10 (100)	10 (100)	
Muscle pain	Yes	1 (9.10)	7 (77.77)	2 (20)	0 (0)	3 (30)	.001
	No	10 (90.90)	2 (22.23)	8 (80)	10 (100)	7 (70)	
Respiratory distress	Yes	8 (72.72)	8 (88.90)	9 (90)	8 (80)	9 (90)	.762
	No	3 (27.27)	1 (11.10)	1 (10)	2 (20)	1 (10)	
Decreased level of consciousness	Yes	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	.395
	No	11 (100)	9 (100)	9 (90)	10 (100)	10 (100)	
Headache	Yes	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	.395
	No	11 (100)	9 (100)	9 (90)	10 (100)	10 (100)	
Feeling tired	Yes	0 (0)	5 (55.60)	0 (0)	0 (0)	0 (0)	.001>
	No	11 (100)	4 (44.40)	10 (100)	10 (100)	10 (100)	
Chest pain	Yes	2 (18.20)	8 (88.90)	4 (40)	6 (60)	3 (30)	.017
	No	9 (81.80)	1 (11.10)	6 (60)	4 (40)	7 (70)	
General body weakness	Yes	5 (45.40)	6 (66.70)	5 (50)	4 (40)	6 (60)	.77
	No	6 (54.60)	3 (33.30)	5 (50)	6 (60)	4 (40)	
Nausea and vomiting	Yes	0 (0)	1 (11.10)	0 (0)	0 (0)	1 (10)	.491
	No	10 (100)	8 (88.90)	10 (100)	10 (100)	9 (90)	
Bellyache	Yes	0 (0)	0 (0)	2 (20)	0 (0)	1 (10)	.225
	No	11 (100)	9 (100)	8 (80)	10	9 (90)	
Decreased appetite	Yes	3 (27.27)	6 (66.67)	0 (0)	4 (40)	2 (20)	.026
	No	8 (72.72)	3 (33.33)	10 (100)	6 (60)	8 (80)	
Cough	Yes	7 (63.60)	8 (88.90)	7 (70)	7 (70)	6 (60)	.696
	No	4 (36.40)	1 (11.10)	3 (30)	3 (30)	4 (40)	
Phlegm	Yes	2 (18.20)	7 (77.77)	4 (40)	5 (50)	2 (20)	.047
	No	9 (81.80)	2 (22.23)	6 (60)	5 (50)	8 (80)	

ic blood pressure (DBP), and oxygen saturation (O_2) between the groups over time (p> .05). There was a notable difference in the trend of changes in average fever severity over time between the study groups; however, these changes were not clinically meaningful. The analysis results revealed a significant difference in the trend of changes in average respiratory rate (RR) over time between the study groups (p= .003). Further comparisons indicated that the average RR in Groups 1 and 2 was significantly higher than that in Group 5 on all days (p< .05). No significant differences were observed in the trend of changes in average RR over time between the other groups (p> .05).

Table 3) Status of lung involvement and survival in the patients studied

Variable	Condition	First Group N (%)	Second Group N (%)	Third Group N (%)	Fourth Group N (%)	Fifth Group N (%)	*P* Value
Status of lung involvement after CT scan	Stage 4 (51-75%)	8 (72.7)	9 (100)	0 (0)	3 (30)	0 (0)	.001
	Stage 5 (75-100%)	3 (27.3)	0 (0)	10 (100)	7 (70)	10 (100)	
Patient survival status	Recovery	7 (63.60)	9 (100)	1 (10)	3 (30)	4 (40)	.001
	Death	4 (36.40)	0 (0)	9 (90)	7 (70)	6 (60)	

Table 4) Comparison of mean clinical findings and laboratory indices of the studied patients at the time of admission

Variable	Group1 Mean ± SD Median (Interquartile Range)	Group 2 Mean ± SD Median (Interquartile Range)	Group 3 Mean ± SD Median (Interquartile Range)	Group 4 Mean ± SD Median (Interquartile Range)	Group 5 Mean ± SD Median (Interquartile Range)	*P* Value
PT	13.22±0.66 13 (00.00)	13.18±0.37 13 (0.38)	14.33±1.43 14 (0.50)	14.14±0.69 14 (1)	13.50±0.7 13 (1)	.001
INR	1.03±0.1 1 (00.00)	1.03±0.07 1 (0.08)	1.16±0.20 1.1 (0.05)	1.14±0.11 1.1 (0.20)	1.15±0.29 1 (0.2)	.008
PTT	33.77±5.09 32 (6.50)	37.12±2.10 37.50 (3)	36.22±3.52 35 (4)	36.57±1.51 37 (3)	35±2.87 35 (6)	.126
ESR	50.77±25.57 54 (51.50)	42.37±28.26 35 (44.75)	56.88±25.68 67 (50)	51.85±24.28 56 (51)	59.88±31.86 65 (41)	.459
CRP	2±0.86 2 (2)	1.62±0.51 2 (1)	2.11±1.05 2 (2)	2.14±0.37 2 (00.00)	2.77±0.66 3 (0)	.014
CPK	343.70±375.22 163 (405)	118.52±21.08 127.35 (40.13)	118.88±52.33 146 (80)	197.90±112.07 147.60 (176)	141.36±149.54 62 (153.20)	.358
Vit D	36.40±8.79 36.50 (15.70)	38.17±8.93 35.50 (17.05)	42.08±16.95 39.70 (29.6)	38.91±21.33 30.90 (30.5)	35.51±15.81 38.50 (10.90)	.95
Troponine	3.14±4.35 1.50 (2.15)	1.50±0.00 1.50 (0)	16.84±23.12 3.60 (33.70)	4.12±1.26 1.50 (26.30)	7.65±4.12 1.50 (5.05)	.061
D dimer	1622.77±1330.84 710 (267.50)	1111.87±679.92 984 (952.25)	1247.33±1393.95 508 (1537.50)	2785.70±3298.31 1767 (2056)	4502.11±4947.07 2718 (6613)	.254
Ferritin	464.11±436.43 345 (173)	104.87±20.72 96.50 (22.75)	613.66±532.90 376 (878)	621.14±605.54 314 (1269)	403.88±162.14 346 (251)	< .001
LDH	670.11±202.49 622 (277.50)	376.25±89.44 350.5 (165.75)	596.55±418.16 450 (251.50)	780.57±383.06 670 (283)	767.55±376.91 605 (443.50)	.001
T	37.50±0.40 37.7 (0.60)	37.56±0.26 37.60 (0.35)	37.5±0.48 37.80 (0.8)	37.62±0.33 37.70 (0.43)	37.90±0.76 37.90 (0.33)	.152

Variable	Group1 Mean ± SD Median (Interquartile Range)	Group 2 Mean ± SD Median (Interquartile Range)	Group 3 Mean ± SD Median (Interquartile Range)	Group 4 Mean ± SD Median (Interquartile Range)	Group 5 Mean ± SD Median (Interquartile Range)	*P* Value
PR	83.18±2.4 82 (3)	86.44±5.41 85 (7)	83.50±9.13 81.5 (7.5)	83.70±6.37 85 (6)	80.1±10.62 81.5 (6.75)	.179
RR	17.63±0.67 18 (1)	17.22±0.66 17 (1)	18±2.05 18 (2)	17.20±0.78 17 (1.25)	19.70±2.54 19 (5.25)	.033
Systolic BP	125.54±19.08 115 (35)	125.33±13.64 120 (21)	133.80±24.04 137.5 (25)	134.60±22.30 142.50 (38.75)	120.1±23.28 115 (42.50)	.453
Diastolic BP	77.54±9.95 80 (12)	82.22±5.93 84 (5)	79±14.47 83.50 (19.50)	82.20±8.61 84 (4)	76.80±10.60 75 (15.75)	.60
SpO2	82.63±5.23 85 (3)	85.94±1.74 86 (2)	74.80±10.11 77.50 (13.25)	83.50±3.50 83.5 (3.5)	80.30±4.37 81 (7.5)	.001
WBC	9.46±7.09 7 (6.6)	10.93±1.05 10.6 (1.95)	9.05±4.28 8.20 (3.90)	8.78±6.47 5.70 (9.25)	12.1±5.67 9.8 (10.53)	.123
RBC	4.65±0.56 4.58 (0.33)	4.69±0.17 4.81 (0.29)	3.88±0.82 3.93 (1.59)	4.69±0.54 4.68 (0.78)	4.63±1.08 4.86 (0.64)	.041
Hb	14.37±1.50 14.80 (2.10)	12.97±0.54 12.90 (0.65)	11.72±2.24 11.50 (4.05)	14.67±1.64 14.90 (3)	13.86±2.43 14.55 (2.55)	.016
HCT	42.98±5.58 42.2 (6)	38.2±1.20 39 (1.95)	35.48±6.86 34.6 (12.35)	42.18±3.87 42.75 (7.28)	41.66±8.20 43 (8.78)	.025
MCV	86.4±20.73 91.3 (10.40)	82.22±1.13 81.50 (2.15)	92.24±9.60 95.90 (5.40)	90.83±4.97 90.65 (8.88)	92.26±14.54 89.9 (14.70)	.005
MCH	31.27±1.84 31 (2.90)	27.50±1.16 27.1 (2)	30.61±3.47 31.60 (2.30)	31.42±1.78 31 (2.75)	30.62±4.78 29.45 (4.5)	.002
MCHC	35.42±4.82 33.80 (2.10)	33.23±0.91 32.9 (1.30)	33.03±0.54 33 (0.80)	33.91±0.93 34.05 (1.5)	33.38±1.89 33.95 (2.1)	.09
Platelet	156.36±76.53 125 (176)	178.55±36.99 167 (40.5)	143.22±86.31 135 (124.5)	152.12±32.85 141.5 (48.25)	164.37±57.33 156 (38)	.503
Poly	72.18±20.71 77 (10)	76.50±13.48 80 (10.25)	80.11±4.07 79 (6)	83.33±5.87 84 (8.75)	81.58±9.48 80.5 (16)	.266
Lymph	16.54±7.90 18 (12)	17.88±10.76 14 (7.5)	14.11±1.90 14 (3)	14.33±6.42 15.5 (11.25)	14.13±10.10 9 (17.75)	.861
Mono	2.63±1.43 2 (2)	2.22±0.66 2 (00.00)	2.55±0.88 2 (1.5)	1.91±0.72 2 (0.75)	1.67±0.70 1.70 (1)	.068
Eos	1.63±0.67 2 (1)	1.44±0.52 1 (1)	2±0.86 2 (0.5)	2±1.69 1.5 (1)	2.33±2.29 1 (4)	.768

Variable	Group1 Mean ± SD Median (Interquartile Range)	Group 2 Mean ± SD Median (Interquartile Range)	Group 3 Mean ± SD Median (Interquartile Range)	Group 4 Mean ± SD Median (Interquartile Range)	Group 5 Mean ± SD Median (Interquartile Range)	*P* Value
Urea	41±8.47 43 (9.5)	49±16.57 49 (29.75)	67.55±41.21 54 (48.5)	62.57±24.82 59 (35)	74.33±37.59 79 (69)	.044
Creatinine	1.14±0.16 1.1 (0.31)	1.35±0.51 1.35 (0.96)	1.19±0.31 1.11 (0.48)	1.24±0.37 1.10 (0.38)	1.20±0.33 1.06 (0.69)	.984
AST	67.44±25.44 79 (51.5)	43.25±8.24 41.5 (10.50)	104.33±181.01 45 (45)	54.42±26.45 45 (46)	45.66±21.02 41 (31.5)	.443
ALT	74.66±30.18 69 (45.50)	34.75±17.80 35.50 (36.75)	61.88±62.84 39 (44)	51.14±27.17 47 (59)	45.77±16.47 42 (23.5)	.038

Table 5) Comparison of changes in mean laboratory indices of patients in the study groups over time (at admission, during hospitalization, at discharge)

Variable	Group	At Admission Mean ± SD Median (Interquartile Range)	During Hospitalization Mean ± SD Median (Interquartile Range)	At Discharge Mean ± SD Median (Interquartile Range)	*P* Intragroup	*P* Intergroup
WBC 10^3 (cu.mm)	First group	9.46±7.09 7 (6.6)	11.25±6.94 9.80 (4.98)	10.87±7.03 8.60 (5.10)	.421	.047
	Second group	10.93±1.05 10.6 (1.95)	9.34±2.23 8.45 (3.53)	7.67±5.73 5 (4.95)	.15	
	Third group	9.05±4.28 8.20 (3.90)	10.69±4.13 9.23 (5.12)	10.08±4.67 10.40 (7.30)	.029	
	Fourth group	8.78±6.47 5.70 (9.25)	15.15±11.12 11.43 (18.07)	16.40±9.64 14.35 (17.70)	.013	
	Fifth group	12.1±5.67 9.8 (10.53)	12.67±3.61 11.65 (6.01)	12.90±8.11 9.60 (15.03)	.741	
RBC (ul)	First group	4.65±0.56 4.58 (0.33)	4.42±0.41 4.41 (0.53)	4.41±0.53 4.30 (0.80)	.034	.425
	Second group	4.69±0.17 4.81 (0.29)	4.57±0.17 4.59 (0.35)	4.77±0.35 4.95 (0.60)	.151	
	Third group	3.88±0.82 3.93 (1.59)	3.71±0.78 3.46 (1.27)	3.69±0.73 3.52 (1.12)	.282	
	Fourth group	4.69±0.54 4.68 (0.78)	4.52±0.78 4.74 (1.17)	4.34±0.90 4.54 (1.44)	.037	
	Fifth group	4.63±1.08 4.86 (0.64)	4.32±0.65 4.23 (0.96)	4.35±0.70 4.12 (1.2)	.42	
Hb (g / dl)	First group	14.37±1.50 14.80 (2.10)	14.2±1.32 14 (2)	14.28±1.56 13.80 (2.70)	.856	.027
	Second group	12.97±0.54 12.90 (0.65)	13.12±0.81 13.32 (1.30)	13.54±1.01 13.60 (0.55)	.112	
	Third group	11.72±2.24 11.50 (4.05)	11.24±2.50 10.10 (3.73)	10.94±2.66 10.10 (4.2)	.274	
	Fourth group	14.67±1.64 14.90 (3)	13.78±1.97 14.11 (2.46)	12.80±1.99 12.95 (2.28)	.002	
	Fifth group	13.86±2.43 14.55 (2.55)	13.40±2.39 12.83 (3.19)	13.03±2.95 12.85 (3.23)	.502	

Variable	Group	At Admission Mean ± SD Median (Interquartile Range)	During Hospitalization Mean ± SD Median (Interquartile Range)	At Discharge Mean ± SD Median (Interquartile Range)	*P* Intragroup	*P* Intergroup
HCT (%)	First group	42.98±5.58 42.2 (6)	42.49±3.49 41.4 (5.05)	41.64±4.75 40.4 (8.10)	.575	.436
	Second group	38.2±1.20 39 (1.95)	38.13±1.12 38.26 (1.41)	39.08±2.09 39.2 (2.35)	.033	
	Third group	35.48±6.86 34.6 (12.35)	33.01±6.95 32.77 (13.11)	32.57±8.38 31 (12.05)	.028	
	Fourth group	42.18±3.87 42.75 (7.28)	40.24±4.97 41.30 (7.09)	39.07±5.44 40.50 (7.73)	.058	
	Fifth group	41.66±8.20 43 (8.78)	39.66±7.09 38.6 (9.45)	40.66±8.69 38.90 (11.68)	.252	
MCV (FL)	First group	86.4±20.73 91.3 (10.40)	96.13±4.38 94.85 (5.20)	94.70±6.12 96.50 (5.60)	.174	.483
	Second group	82.22±1.13 81.50 (2.15)	83.52±2.18 82.1 (4.28)	84.4±2.74 83.40 (5.30)	.031	
	Third group	92.24±9.60 95.90 (5.40)	93.08±8.58 95.92 (9.27)	91.4±12.76 93.5 (12.80)	.56	
	Fourth group	90.83±4.97 90.65 (8.88)	91.98±4.09 92.79 (5.97)	91.85±9.50 94.05 (13.75)	.269	
	Fifth group	92.26±14.54 89.9 (14.70)	91.24±4.34 90.25 (8.58)	90.65±8.62 90.15 (17.43)	.837	
MCH (Pg)	First group	31.27±1.84 31 (2.90)	32.52±1.77 31.78 (1.91)	32.39±1.97 32.10 (1.90)	.192	.12
	Second group	27.50±1.16 27.1 (2)	27.83±1.26 27.53 (2.09)	28.96±1.89 28.9 (2.1)	.054	
	Third group	30.61±3.47 31.60 (2.30)	30.63±2.64 31.26 (30.06)	30.33±3.61 31.2 (4.4)	.809	
	Fourth group	31.42±1.78 31 (2.75)	31.43±1.59 31.22 (1.79)	29.96±2.52 30.05 (2.68)	.069	
	Fifth group	30.62±4.78 29.45 (4.5)	30.80±1.78 30.35 (3.52)	30.57±2.52 29.85 (5.03)	.989	
MCHC (g/dL)	First group	35.42±4.82 33.80 (2.10)	33.45±0.72 33.43 (1.12)	34.10±0.87 34.2 (1.40)	.138	.008
	Second group	33.23±0.91 32.9 (1.30)	33.63±0.79 33.38 (1.41)	34.22±0.79 34.5 (0.75)	.058	
	Third group	33.03±0.54 33 (0.80)	33.31±1.21 33.81 (1.31)	33.64±1.56 33.20 (2.6)	.366	
	Fourth group	33.91±0.93 34.05 (1.5)	33.68±0.81 33.52 (1.49)	32.53±2.10 32.6 (3.35)	.093	
	Fifth group	33.38±1.89 33.95 (2.1)	33.35±0.71 33.41 (1.18)	32.46±1.11 32.3 (1.70)	.456	
Platelet (ul)	First group	156.36±76.53 125 (176)	197.42±93.7 182.5 (177.58)	191.72±93.51 200 (142)	.026	.008
	Second group	178.55±36.99 167 (40.5)	185.96±33.21 181.63 (35.27)	193.22±36.72 181 (51.5)	.339	
	Third group	143.22±86.31 135 (124.5)	153.40±86.59 144.16 (155.5)	108.11±64.59 141 (128.5)	.067	
	Fourth group	152.12±32.85 141.5 (48.25)	206.32±65.05 187.62 (70.99)	168.87±89.88 133.5 (148.25)	.036	
	Fifth group	164.37±57.33 156 (38)	119.63±51.70 120.31 (57.35)	100.37±74.23 94.50 (91)	.076	

Variable	Group	At Admission Mean ± SD Median (Interquartile Range)	During Hospitalization Mean ± SD Median (Interquartile Range)	At Discharge Mean ± SD Median (Interquartile Range)	*P* Intragroup	*P* Intergroup
Poly (%)	First group	72.18±20.71 77 (10)	-	74±21.54 78 (12)	.048	.33
	Second group	76.50±13.48 80 (10.25)	-	82.48±4.16 83.4 (7)	.149	
	Third group	80.11±4.07 79 (6)	-	83.66±3.31 84 (5)	.079	
	Fourth group	83.33±5.87 84 (8.75)	-	82.77±7.87 86 (12.75)	.744	
	Fifth group	81.58±9.48 80.5 (16)	-	84.12±2.94 84 (5.75)	.592	
Lymph (%)	First group	16.54±7.90 18 (12)	-	15.72±6.88 15 (13)	.582	.713
	Second group	17.88±10.76 14 (7.5)	-	16.66±11.2 13 (8)	.43	
	Third group	14.11±1.90 14 (3)	-	14.11±4.16 13 (3.5)	.941	
	Fourth group	14.33±6.42 15.5 (11.25)	-	12.61±5.79 12.5 (8.5)	.186	
	Fifth group	14.13±10.10 9 (17.75)	-	10.87±3.90 9.5 (7.5)	.171	
Mono (%)	First group	2.63±1.43 2 (2)	-	2.45±1.50 2 (3)	.341	.135
	Second group	2.22±0.66 2 (00.00)	-	2 ±1 2 (1.5)	.347	
	Third group	2.55±0.88 2 (1.5)	-	2.11±0.78 2 (1.5)	.168	
	Fourth group	1.91±0.72 2 (0.75)	-	2.41±0.96 2.05 (1)	.164	
	Fifth group	1.67±0.70 1.70 (1)	-	1.78±0.72 2 (1.23)	.743	
Eos (%)	First group	1.63±0.67 2 (1)	-	1.81±1.40 1 (1)	.676	.854
	Second group	1.44±0.52 1 (1)	-	1.44±0.72 1 (1)	.99	
	Third group	2±0.86 2 (0.5)	-	1.55±0.52 2 (1)	.225	
	Fourth group	2±1.69 1.5 (1)	-	1.78±1.46 1 (2.25)	.645	
	Fifth group	2.33±2.29 1 (4)	-	1.87±0.64 2 (0.75)	.636	
Urea (Mg/dl)	First group	41±8.47 43 (9.5)	63.13±42.08 47 (35.33)	53.25±35.51 40 (14.85)	.193	.051
	Second group	49±16.57 49 (29.75)	38.39±9.53 38.33±14.63)	31.75±11.63 30.5 (18)	.19	
	Third group	67.55±41.21 54 (48.5)	78.68±33.47 72.80 (61.94)	105±44.13 112 (76.5)	.165	
	Fourth group	62.57±24.82 59 (35)	79.09±33.63 73.5 (30)	98.71±58.79 75 (108)	.067	
	Fifth group	74.33±37.59 79 (69)	71.66±30.60 66.50 (53.81)	91.55±65.28 89 (92.5)	.515	

Variable	Group	At Admission Mean ± SD Median (Interquartile Range)	During Hospitalization Mean ± SD Median (Interquartile Range)	At Discharge Mean ± SD Median (Interquartile Range)	*P* Intragroup	*P* Intergroup
Creatinine (mg/ dl)	First group	1.14±0.16 1.1 (0.31)	1.35±0.57 1.22 (0.59)	1.18±2.25 0.95 (0.48)	.663	.502
	Second group	1.35±0.51 1.35 (0.96)	1.11±0.29 1.05 (0.28)	0.91±0.10 0.88 (0.18)	.416	
	Third group	1.19±0.31 1.11 (0.48)	1.05±0.24 0.97 (0.39)	1.46±0.69 1.31 (1.08)	.236	
	Fourth group	1.24±0.37 1.10 (0.38)	1.26±0.30 1.29 (0.44)	1.25±0.42 1.1 (0.54)	.623	
	Fifth group	1.20±0.33 1.06 (0.69)	1.14±0.31 1.1 (0.59)	1.15±0.39 1.1 (0.8)	.55	
AST (U/L)	First group	67.44±25.44 79 (51.5)	57.67±22.10 57 (39.13)	143.88±259.22 58 (72.50)	.209	.123
	Second group	43.25±8.24 41.5 (10.50)	46.65±4.68 47.5 (7.69)	44.75±6.58 45.50 (11)	.478	
	Third group	104.33±181.01 45 (45)	123.59±213.82 34 (57.44)	178.55±292.93 70 (137)	.174	
	Fourth group	54.42±26.45 45 (46)	67.92±34.10 59.14 (62.50)	85.48±13.56 68 (2791)	.388	
	Fifth group	45.66±21.02 41 (31.5)	43.76±11.16 44 (21.31)	53.11±17.70 54 (34.50)	.149	
ALT (U/L)	First group	74.66±30.18 69 (45.50)	61.97±28.40 55.60 (42.48)	138.66±224.92 49 (80)	.278	.136
	Second group	34.75±17.80 35.50 (36.75)	39.03±21.32 40.50±30.75	31±12.25 29 (18.25)	.406	
	Third group	61.88±62.84 39 (44)	81.51±89.89 62 (52.15)	142.88±167.56 65 (177.50)	.165	
	Fourth group	51.14±27.17 47 (59)	53.82±14.27 59 (25.87)	675.28±1055.33 72 (2166)	.284	
	Fifth group	45.77±16.47 42 (23.5)	42.08±14.24 32 (26.63)	51.33±22.66 49 (40)	.276	

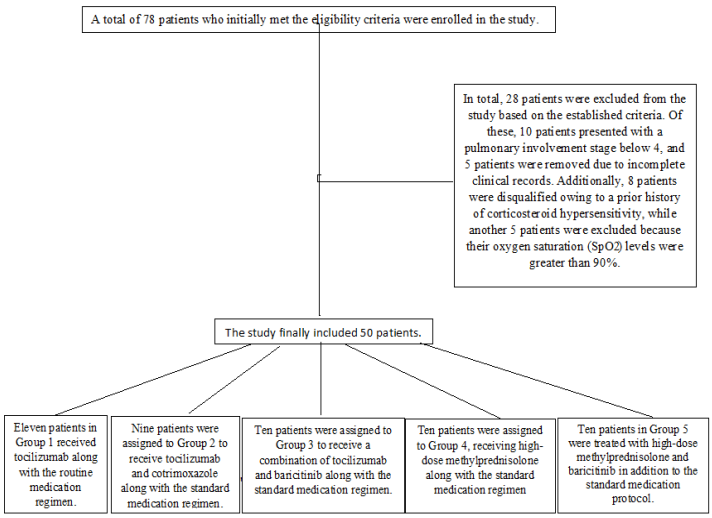


Figure 1) Sampling method used in the current investigation

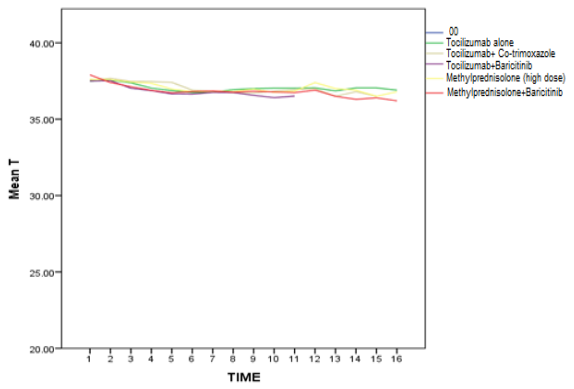


Figure 2) Comparison of changes in mean fever over time among patients with severe COVID19- in the study groups

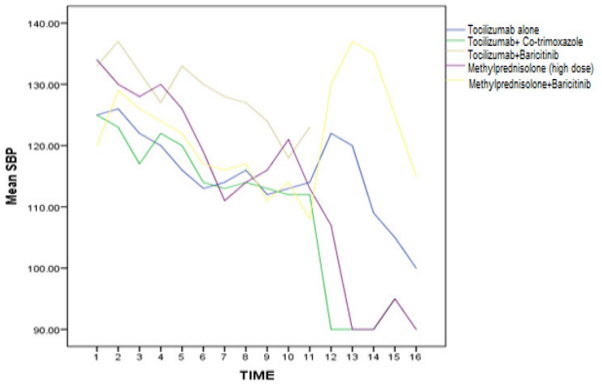


Figure 5) Comparison of changes in mean SBP over time among patients with severe COVID19- in the study groups

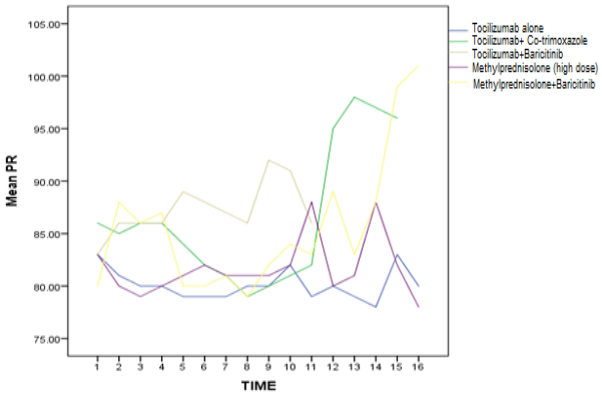


Figure 3) Comparison of changes in mean PR over time among patients with severe COVID19- in the study groups

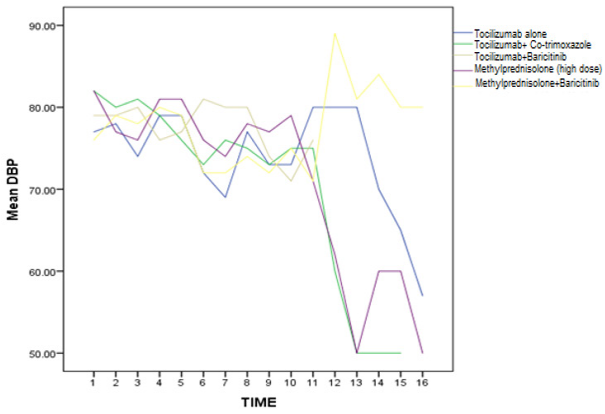


Figure 6) Comparison of changes in mean DBP over time among patients with severe COVID19- in the study groups

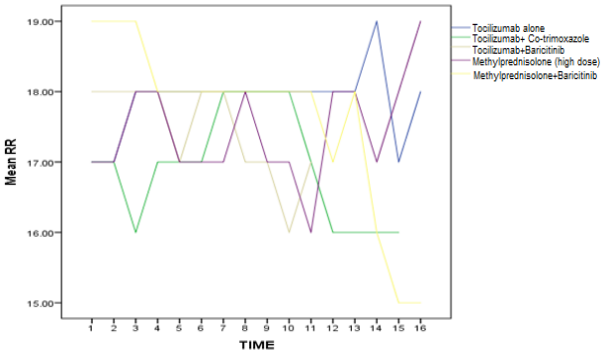


Figure 4) Comparison of changes in mean RR over time among patients with severe COVID19- in the study groups

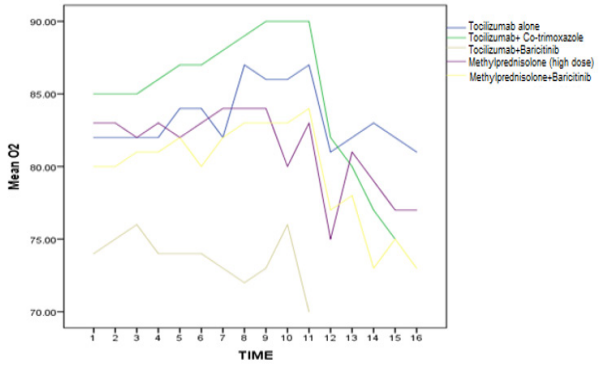


Figure 7) Comparison of changes in mean O2 over time among patients with severe COVID19- in the study groups

Discussion

The present investigation demonstrated heterogeneous outcomes associated with different therapeutic regimens administered to patients admitted to the ICU with severe COVID-19. In our cohort, tocilizumab monotherapy was associated with a mortality rate of 36.4%, a figure that falls within the wide range reported in previous randomized controlled trials (RCTs). For instance, Horby et al. (2021) [22] reported a modest but significant reduction in mortality rate following the administration of tocilizumab combined with standard corticosteroid therapy, while

other RCTs and meta-analyses have yielded less consistent results, suggesting that the efficacy of IL-6 receptor blockade may be strongly dependent on patient selection, timing of administration, and concomitant therapies. In striking contrast to the partial benefits of tocilizumab alone, the combination of tocilizumab and cotrimoxazole in this study was associated with a 0% mortality rate, an outcome that appears considerably more favorable than those reported in most existing trials. Although limited evidence from small randomized and observational studies suggests that cotrimoxazole may confer antibacterial protection, reduce secondary infections, and improve clinical outcomes in severe COVID-19, the magnitude of benefit observed in our cohort was likely influenced by factors such as baseline disease severity, supportive care, or unmeasured confounders. Hence, although the findings support the hypothesis that cotrimoxazole could provide adjunctive benefit, these results should be interpreted with caution and require validation in larger, controlled clinical trials.

The results of administering the combination of tocilizumab with baricitinib diverged even more markedly from global evidence. In our cohort, this treatment regimen was associated with a mortality rate of 90%, despite the fact that several large randomized controlled trials (RCTs), including Sunny et al. (2023) [23] and Cherian et al. (2022) [24], consistently have demonstrated that baricitinib, particularly when used alongside corticosteroids, significantly reduces mortality, decreases the need for intensive care, and improves recovery time. This discrepancy could likely be explained with confounding by indication, as the patients who received tocilizumab plus baricitinib represented the most critically-ill subgroup, characterized by extensive Stage-5 pulmonary involvement, severe anemia, and thrombocytopenia. In such cases, excessive immunosuppression may also increase vulnerability to secondary infections, thereby contributing to poor outcomes. Conversely, the addition of baricitinib to high-dose methylprednisolone in another subgroup of the current study reduced mortality from 70 to 60%, suggesting a potential survival benefit consistent with the synergistic anti-inflammatory effect previously reported in the literature. Together, these findings illustrate the complexity of immunomodulatory therapy in COVID-19 patients and underscore the importance of adjusting for baseline disease severity when comparing treatment effects in observational cohorts.

The strong prognostic value of laboratory and clinical biomarkers observed in the present study aligns closely with international evidence. It was found that anemia, thrombocytopenia, and elevated levels of markers such as LDH, CRP, ferritin, AST, and ALT were consistently associated with worse outcomes, including higher mortality rates. These findings reinforce those of prior meta-analyses, demonstrating that patients with LDH levels above reference thresholds face a significantly increased risk of progression to severe disease and death, while elevated CRP and ferritin levels serve as robust predictors of systemic inflammation and poor prognosis [25]. Similarly, the association of anemia and thrombocytopenia with adverse outcomes has been well documented in large Chinese and European cohorts, where decreased hemoglobin and platelet count independently predicted disease severity and mortality [26, 27]. The convergence of the present study results with these findings not only strengthens the validity of the results but also underscores the necessity of comprehensive biomarker monitoring in managing critically-ill COVID-19 patients. In summary, although the results suggest potential survival benefits associated with certain therapeutic strategies—particularly tocilizumab combined with cotrimoxazole and baricitinib combined with corticosteroids—they also highlight the risk of detrimental effects arising from inappropriate combinations of immunomodulators, as indicated

by the poor outcomes observed with tocilizumab plus baricitinib. The divergence between the present study findings and those of large randomized trials underscores the limitations of retrospective single-center studies, especially the risks of indication bias and limited sample sizes. Nonetheless, the alignment of biomarker analysis results with those from global scientific literature strongly corroborates the predictive role of these laboratory parameters in clinical outcomes. Future studies involving larger populations, rigorous adjustment for baseline disease severity, and randomized designs will be necessary to clarify the true benefit–risk profile of specific immunomodulatory combinations in the treatment of severe COVID-19.

Conclusion

The present study results indicated that treatment protocols incorporating tocilizumab combined with co-trimoxazole, corticosteroids combined with baricitinib, as well as tocilizumab monotherapy were associated with lower mortality rates and improved recovery outcomes in patients with severe COVID-19. Conversely, the concurrent administration of tocilizumab and baricitinib was associated with a higher mortality rate, potentially due to the induction of profound immunosuppression. Furthermore, elevated levels of CRP, ferritin, LDH, AST, and ALT, along with extensive pulmonary involvement and anemia, were identified as significant risk factors for patient mortality. Nevertheless, additional investigations involving larger cohorts are warranted to validate these findings.

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References

1. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215:108427.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199-207.
3. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol. 2020;17(5):533-5.
4. Ciotti M, Ciccozzi M, Terrinoni A, Jiang WC, Wang CB, Bernardini S. The COVID-19 pandemic. Crit Rev Clin Lab Sci. 2020;57(6):365-88.
5. Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. Immunol Res. 2014;59(1):118-28.
6. Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and coronavirus disease 2019: What we know so far. Pathogens. 2020;9(3):231.
7. Cevik M, Bamford CG, Ho A. COVID-19 pandemic—a focused review for clinicians. Clin Microbiol Infect. 2020;26(7):842-7.
8. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021;19(3):141-54.
9. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel

coronavirus (SARS-CoV-2): A systematic review and meta-analysis of 148 studies. PLoS One. 2020;15(6):e0234765.
10. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and taste dysfunction in patients with COVID-19: A systematic review and meta-analysis. Mayo Clin Proc. 2020;95(8):1621-31.
11. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-90.
12. 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.
13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
14. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. Biochem Biophys Res Commun. 2020;525(1):135-40.
15. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181(2):281-92.
16. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5(4):562-9.
17. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185-92.
18. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci. 2009;106(14):5871-6.
19. Millet JK, Whittaker GR. Host cell entry of Middle East respiratory syndrome coronavirus after two-step, furin-mediated activation of the spike protein. Proc Natl Acad Sci. 2014;111(42):15214-9.
20. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020;11(1):1620.
21. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8(8):959-70.
22. Horby PW, Pessoa-Amorim G, Peto L, Brightling CE, Sarkar R, Thomas K, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): Preliminary results of a randomized, controlled, open-label, platform trial. medRxiv. 2021.
23. Sunny S, Tran A, Lee J, Abdallah M, Chaudhry N, Quale J. Comparison of tocilizumab vs baricitinib in clinical outcomes among hospitalized patients with COVID-19: Experience from a public hospital system in New York city. Open Forum Infect Dis. 2023;10(8):ofad426.
24. Cherian JJ, Eerike M, Bagepally BS, Das S, Panda S. Efficacy and safety of baricitinib and tocilizumab in hospitalized patients with COVID-19: A comparison using systematic review and meta-analysis. Front Pharmacol. 2022;13:1004308.
25. Choi SH, Choi JH, Lee JK, Eun BW, Song SH, Ahn B, et al. Clinical characteristics and outcomes of children with SARS-CoV-2 infection during the Delta and Omicron variant-dominant periods in Korea. J Korean Med Sci. 2023;38(9):e70.
26. Adelborg K, Veres K, Horváth-Puhó E, Clouser M, Saad H, Sørensen HT. Risk and adverse clinical outcomes of thrombocytopenia among patients with solid tumors: A Danish population-based cohort study. Br J Cancer. 2024;130(9):1485-92.
27. Ding Q, Xu W, Chen Y, Chang S, Zhang J. Correlation between thrombocytopenia and adverse outcomes in patients with atrial fibrillation: A systematic review and meta-analysis. Front Cardiovasc Med. 2024;11:1383470.