Does Tocilizumab Influence the Outcome of Patients with COVID-19 Pneumonia Compared to the Standard Therapy? Retrospective Analysis of Data Obtained during Phase I COVID Pandemic

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Abstract

BACKGROUND: No gold standard therapy was approved globally for COVID-19 pneumonia to the date of this study. The pathophysiology of SARS-CoV-2 infection displayed the predominance of hyperinflammation and immune dysregulation in inducing multiorgan damage. Therefore, the potential benefits of both immune modulation and suppression in COVID-19 have been extensively discussed as a modality to control cytokine release syndrome (CRS). Abnormally high levels of interleukin-6 (IL-6) are a common finding in COVID-19 patients with pneumonia and acute respiratory distress syndrome, so the use of IL-6 antagonist was tested as a therapeutic option in controlling the disease. Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody that can specifically bind the membrane-bound IL-6 receptor and soluble IL-6 receptor, thereby inhibiting signal transduction. Tocilizumab is currently FDA approved for the management of rheumatoid arthritis, giant cell arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. This study is a retrospective analysis of data polled during Phase I of COVID pandemic, adopted by the isolation hospital of Kasr Al-Ainy Medical School, Cairo University, during the period from May to September 2020.

AIM: The aim of this study is to evaluate tocilizumab influence in the outcome; in terms of reducing the hospital stay, risk and duration of mechanical ventilation (invasive and noninvasive), mortality, and the incidence of complications related to drugs use (secondary bacterial infection and GIT bleeding) in patients with moderate-to-severe COVID-19.

METHODS: This retrospective, observational cohort study included adults (between 18 and 80 years) with moderate-to-severe COVID-19 pneumonia, who were admitted to isolation hospital of Kasr Al-Ainy Medical School, Cairo University, between May and September 2020. We segregated the patients into two groups: Group A: In addition to the standard care protocol according to the local guidelines of the Egyptian Ministry of Health and Population in that period (supplemental oxygen, steroids in a dose of 1–2 mg/kg methylprednisolone for 5–10 days, broad-spectrum antibiotics, vitamins, and prophylactic dose of anticoagulation with low-molecular-weight heparin, proton-pump inhibitor, and poly-vitamins), they received tocilizumab intravenously in a dose of 8 mg/kg bodyweight (up to a maximum of 800 mg per dose), divided in two shots 12–24 h apart. Group B: Those received the standard care protocol alone, noting that guidelines were adjusted later on according to the updated scientific publications and WHO recommendations. The primary endpoint was to evaluate the effect of different regimens in controlling the disease, the need for mechanical ventilation and its duration (either invasive or non-invasive), length of ICU stay, hospital stay, and in-hospital mortality. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney U-test. For comparison of serial measurements within each patient, the non-parametric Wilcoxon signed-rank test was used. For comparing categorical data, Chi-square (2) test was performed. Exact test was used instead when the expected frequency was <5. Correlations between quantitative variables were done using Spearman correlation coefficient.

RESULTS: During this period, 166 patients were admitted to ICU, suffering from severe hypoxemia with moderate to severe COVID-19 pneumonia, 10 of them were excluded (three were over 80 years old, other three had advanced stages of malignancy, two were on steroids therapy and non-invasive home ventilation due to chronic chest condition, and two were presented with MODs and deceased in <48 h from admission), thus, 156 were included in the study. Group A: Seventy-six patients (49%) received tocilizumab in addition to standard therapy, Group B: Eighty patients (51%) received standard therapy only. In Group A, the mean length of ICU stay was 8.96 days with mean length of hospital stay 13.76, compared to mean length of ICU stay 9 days in Group B (p = 0.57) and mean length of hospital stay 12.46 days (p = 0.117). In Group A, 35 patients (46%) needed non-invasive mechanical ventilation (MV),12 patients of the 35 needed invasive MV in later stage, compared to 26 patients (32%) in Group B, 14 patients of the 26 needed invasive MV in later stage (p = 0.16). In Group A, 14 patients (18.4%) needed invasive mechanical ventilation, compared to 19 patients (23.7%) in Group B (p = 0.213). In Group A, 6 (7.9%) of 76 patients died, compared to 13 (16.3%) of 80 in Group B p = 0.11. The incidence of secondary bacterial infection in Group A was 16 patients (21%) compared to 21 patients (26%) in Group B (p = 0.44).

CONCLUSION: In this study, we did not detect statistical difference in both groups of patients coming during CRS-associated COVID-19 pneumonia, regarding (ICU stay, need for and length of MV, the incidence of secondary bacterial infection, and in-hospital mortality) for COVID-19 moderate-to-severe pneumonia.

Introduction

During COVID-19 pandemic, respiratory manifestations were dominant in creating the majority of patients admitted to the hospital with varying degrees of hypoxemia and respiratory distress, especially dominant during the 2nd week of the start of symptoms (7–10 days) which characterized the COVID-19 pneumonia [1].

Various reports describe the disease process in three phases (viremia, cytokine release syndrome [CRS], and recovery), giving a special interest in the 2nd phase that is in a few cases may be severe enough to progress to acute respiratory distress syndrome (ARDS), rapid deterioration, increased oxygen need, and need for mechanical ventilation.

This had led to the theoretical idea of giving an immune modulatory therapy capable of reducing the hyperimmune response [2].

The current clinical approaches consider that the immune modulatory drugs have the potential to inhibit cytokines and treat the cytokine storm [3].

Steroids are still being used in pneumonia during recovery stage, and it is also recommended in ARDS [4]. Results from the RECOVERY trial showed that steroids reduce mortality among COVID-19 patients with severe respiratory complications [5], [6]. However, the doses used during the management of COVID-19 pneumonia were much different than the ones we use in the management of non-COVID pneumonia and ARDS (a dose of 1–2 mg/kg methylprednisolone for 5–10 days during CRS in COVID pneumonia) [7], [8].

Tocilizumab is a recombinant humanized monoclonal antibody of the IgG1 class, which is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor.

Tocilizumab is recommended for the treatment of severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and life-threatening CRS induced by chimeric antigen receptor T-cell therapy [9], [10].

The aim of this retrospective study was to evaluate two different regimens of immune modulatory therapy (combined therapy: Tocilizumab with steroids vs. steroids alone) in reducing the hospital stay, risk and duration of mechanical ventilation (invasive and non-invasive), mortality, and the incidence of complications related to drugs use (secondary bacterial infection and GIT bleeding) in patients with moderate-to-severe COVID-19 pneumonia who received the standard of care treatment.

Methods

Study design

This study is a retrospective, observational study, done on patients with moderate-to-severe COVID-19 pneumonia who were admitted to the isolation hospital of Kasr Al-Ainy Medical School, Cairo University, Egypt, between May and September 2020. The data were collected on baseline signs, symptoms, comorbidities, blood count, and biochemical markers.

The study population was adults (between 18 and 80 years) with COVID-19, confirmed by PCR on nasopharyngeal swab, who were admitted to ICU of isolation hospital of Kasr Al-Ainy Medical School between May 16, 2020, and September 24, 2020. Eligible patients had moderate-to-severe pneumonia, defined at least by one of the following:

Presence of a respiratory rate of 30 or more breaths per minute, peripheral blood oxygen saturation (SaO_2) of <93% in room air, a ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) of <300 mm Hg in room air, and lung infiltrates of more than 50%, according to Chinese management guidelines for COVID-19 (version 6.0) [2], [11].

Exclusion criteria

Patients who are <18 or more than 80 years, heart failure as predominant cause of acute respiratory failure, organ transplantation, history of chronic chest disease needed long-term oxygen therapy or home mechanical ventilation, pulmonary fibrosis, progressive neuromuscular disorders (e.g. Duchenne and ALS), dementia or decompensated psychiatric diseases, chronic use of immunosuppressive treatments for any cause, chronic use of corticosteroids, and pregnancy were excluded from the study.

Additional exclusion criteria for the use of tocilizumab were as follows: Coexistent infection other than COVID-19, history of severe allergic reactions to monoclonal antibodies, <500/μL neutrophils or <50 × 10^9 platelets, active diverticulitis, inflammatory bowel disease, or another symptomatic gastrointestinal tract condition that might predispose patients to bowel perforation, severe hematological, renal, or liver function impairment.

The study was approved by the Ethical Committee of Faculty of Medicine, Cairo University. All patients provided written informed consent.

Procedures

Patients were segregated into two groups:

Group A

In addition to receiving the standard of care protocol according to the local guidelines of the Egyptian Ministry of Health and Population in that period [12], patients in this group also received tocilizumab treatment. Patients were considered eligible for tocilizumab treatment if they showed SaO_2 of <93% and a PaO_2/FiO_2 ratio of <300 mm Hg in room air or a more than 30% decrease in their PaO_2/FiO_2 ratio in the previous 24 h during hospitalization, bilateral infiltrates in CT chest, in addition to elevated inflammatory markers (CRP, ferritin, LDH, and IL-6 levels) in the absence of any sign of secondary bacterial infection. Tocilizumab was administered by the intravenous route. Intravenous tocilizumab was administered in a dose of 8 mg/kg bodyweight (up to a maximum of 800 mg/dose) divided into two shots 12–24 h apart. The second dose was given as pharmacokinetic data suggested that adequate plasma levels of the drug could be obtained only after two doses, based on the results of pharmacokinetic models [13].

Group B

Those received the standard care protocol alone [12].

Standard of care treatment included oxygen supply to target SaO_2 reaching at least 92%, broad-spectrum antibiotic at the physician's discretion when suspecting a bacterial respiratory superinfection, methylprednisolone 1–2 mg/kg/day for 5–10 days, prophylactic doses of low-molecular-weight heparin according to bodyweight and renal function, proton-pump inhibitor, and poly-vitamins.

It is worth mentioning that the guidelines were adjusted later on according to the updated scientific publications and WHO recommendations.

The patients, full medical history, chronic comorbidities, demographic and epidemiological data, and baseline SaO_2 were obtained at hospital admission. Other treatments were recorded. The risk of multiorgan failure and mortality was assessed with Acute Physiology and Chronic Health Evaluation II (APACHE II) score [14], [15].

Clinical data, including symptoms, complete blood count, coagulation, inflammatory, and biochemical markers, were routinely registered in the patients' files according to local protocols of the hospital.

Outcome

The primary outcome of the study was to evaluate effect of both regimens on ICU stay, overall hospital stay, in-hospital mortality, need for mechanical ventilation (either invasive or non-invasive), and the incidence of complications related to the drugs as secondary bacterial infection and GIT bleeding.

Statistical analysis

We compared the baseline characteristics of the participants in both groups (Group A and Group B), including signs and symptoms, existing comorbidities, and blood count markers.

Key confounders were identified as age, medical comorbidities, and baseline APACHE II score which were the most probable causes of both treatment assignment and outcome risk.

We did a standard survival analysis, following up participants from the date of entry into clinics until discharge from hospital either with improvement or death. We compared the duration of ICU stay, overall hospital stay, need for mechanical ventilation (either invasive or non-invasive), and death in each treatment group. Also, the incidence of secondary bacterial infection in both groups was compared.

Data were coded and entered using the Statistical Package for the Social Sciences version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney U-test. For comparison of serial measurements within each patient, the non-parametric Wilcoxon signed-rank test was used. For comparing categorical data, Chi-square (2) test was performed. Exact test was used instead when the expected frequency is <5. Correlations between quantitative variables were done using Spearman correlation coefficient. $p < 0.05$ was considered as statistically significant [16], [17], [18].

Results

Of 166 patients admitted to the ICU with moderate-to-severe pneumonia, 10 (6%) patients were excluded (three of them were over 80 years old, three had advanced stages of malignancy, two were on steroids therapy and non-invasive home ventilation, and two presented with MODs and died within 12 h from admission), thus, 156 patients were included in our analysis with median age 56 (IQR 46–66).

Seventy-six patients (49%) received tocilizumab in addition to standard therapy including steroids (Group A) with median age 55 years (IQR 42–63) and 80 patients (51%) received standard therapy only including steroids (Group B) with median age 60 years (IQR 50–68), $p = 0.014$ (Table 1 and Figure 1).

Table 1: Age of patients in each group

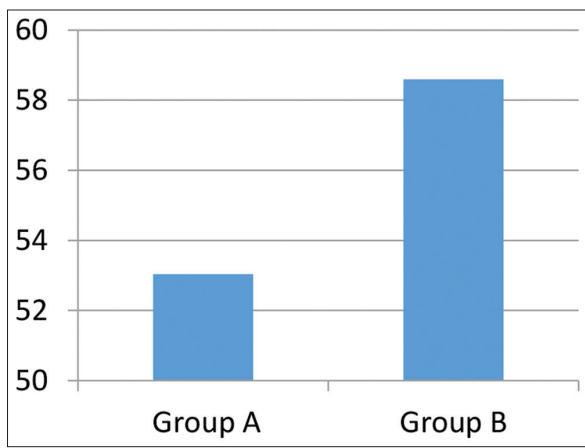| Age in groups	Group A			Group B			p value
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
Age	53.04 ± 12.05	55.00	29.00–74.00	58.59 ± 12.76	59.50	27.00–79.00	0.014

Figure 1: Age in groups

Overall, 118 out of 156 (75%) of the patients were male, 38 (25%) were female, in Group A, 64 out of 76 (84%) were male, 12 (16%) were female, in Group B, 54 (67%) out of 80 were male, 26 (33%) were female, p = 0.015 (Table 2 and Figure 2).

Table 2: Characteristics and comorbidities of patients in each group

Sex and comorbidities	Count (%)		p value
	Group A	Group B	
Sex			
Male	64 (84.2)	54 (67.5)	0.015
Female	12 (15.8)	26 (32.5)	
HTN			
Yes	34 (44.7)	42 (52.5)	0.332
No	42 (55.3)	38 (47.5)	
Diabetes			
Yes	36 (47.4)	35 (43.8)	0.650
No	40 (52.6)	45 (56.3)	
Cardiac history			
Yes	12 (15.8)	23 (28.7)	0.052
No	64 (84.2)	57 (71.3)	
Chronic respiratory problems			
Yes	9 (11.8)	8 (10.0)	0.712
No	67 (88.2)	72 (90.0)	
CKD			
Yes	1 (1.3)	10 (12.5)	0.006
No	75 (98.7)	70 (87.5)	
Chronic liver disease			
Yes	1 (1.3)	3 (3.8)	0.621
No	75 (98.7)	77 (96.3)	

Data for comorbidities among patients showed that Group A had a higher burden of diabetes; 36 (47%) out of 76 patients compared to 35 (44%) out of 80 in Group B (p = 0.65).
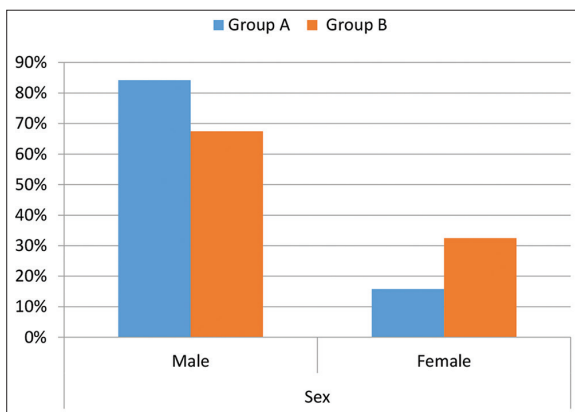

Figure 2: Demographic characters of groups (sex)

Hypertension was more prevalent in Group B, 42 (53%) out of 80 compared to 34 (45%) out of 76 in Group A (p = 0.33).
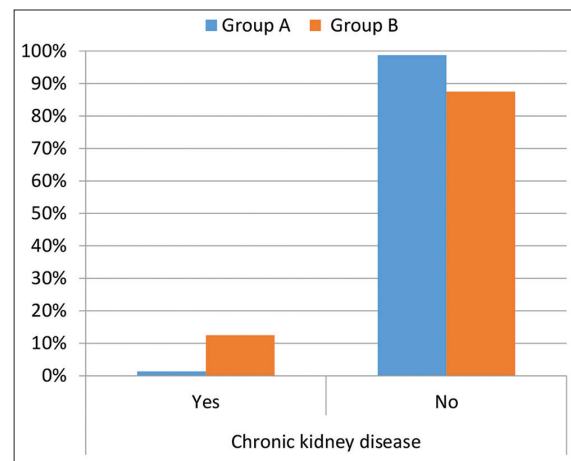

Figure 3: Comorbidities in groups (chronic kidney disease)

Chronic kidney disease was more frequent in Group B 10 (12.5%) patients compared to 1 (1.3%) patient in Group A, p = 0.006 (Table 2 and Figure 3).

Table 3: Laboratories and vital data on admission

Data on admission	Group A			Group B			p value
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
O$_2$ sat on admission (%)	83.47 ± 9.25	86.00	55.00–95.00	83.95 ± 9.07	86.00	45.00–93.00	0.653
Temperature (c)	38.97 ± 0.51	38.90	37.50–40.10	38.80 ± 0.38	38.80	37.00–40.00	0.098
TLC	7.41 ± 2.97	7.15	3.00–16.60	8.81 ± 4.93	7.95	1.60–28.00	0.154
Lymphocytes (%)	14.80 ± 8.90	13.00	2.70–47.00	15.59 ± 8.95	13.60	1.90–40.00	0.476
Ferritin	580.68 ± 366.22	439.00	44.00–1800.00	519.91 ± 360.96	413.50	9.00–2100.00	0.300
LDH	646.96 ± 293.63	590.50	176.00–1707.00	616.03 ± 271.96	578.00	255.00–1550.00	0.432
IL-6	108 ± 82.4	75	10–388	63 ± 102	19	2–390	0.001
CRP on admission	101.20 ± 60.24	86.50	13.40–242.00	116.20 ± 59.18	120.50	3.00–228.00	0.088
D-dimer	609.36 ± 1081.46	371.00	200.00–8750.00	672.96 ± 868.74	400.00	200.00–7227.00	0.109

Vital signs and biochemical markers, total leukocytic count, and inflammatory markers were compared between the two groups on admission, they did not show significant difference (Table 3), except for IL-6 level, which was significantly higher in Group A, with mean 108, median 75, compared to mean 63 and median 19 in Group B, p = 0.001 (Figure 4).
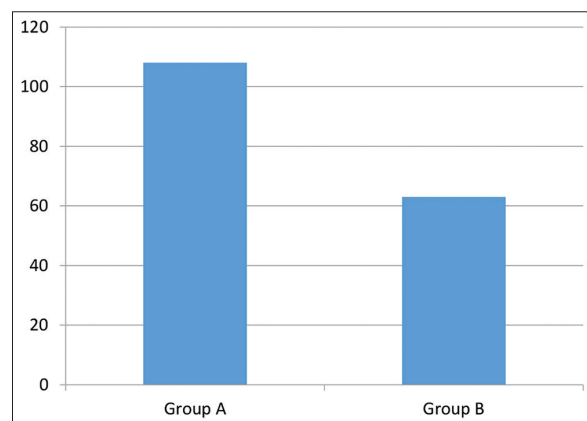

Figure 4: IL-6 level in groups on admission

Severity of symptoms and expected mortality in both groups were assessed and compared using APACHE II score.

Table 4: Acute Physiology and Chronic Health Evaluation II score in groups

Class	Count (%)		p value
	Group A	Group B	
II	7 (9.2)	16 (20.0)	0.11
III	20 (26.3)	12 (15.0)	
IV	34 (44.7)	24 (30.0)	
V	15 (19.7)	28 (35.0)	

APACHE II score mean in Group A was 13.1 with median 13 and SD 4.9, while in Group B, the mean was 15.3 with median 14 and SD 6.5 ($p = 0.093$).

Table 5: Evaluation of severity and expected mortality in groups

Severity on admission	Group A			Group B			p value
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
APACHE II score	13.14 ± 4.94	13.00	1.00–29.00	15.35 ± 6.50	14.00	5.00–34.00	0.093
Expected Mortality (%)	17.80 ± 11.35	15.00	4.00–55.00	22.48 ± 16.29	15.00	4.00–75.00	0.128

Mean expected mortality in Group A was 17.8% with median 15% and SD 11.35, mean expected mortality in Group B was 22.4%, with median 15% and SD 16.2, $p = 0.128$ (Tables 4 and 5, Figure 5).
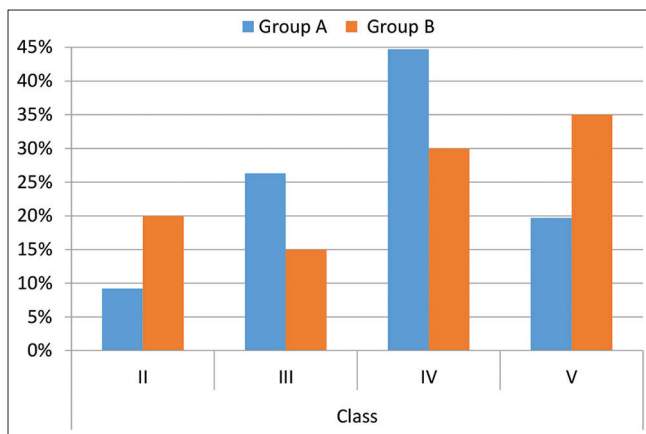

Figure 5: Distribution of patients according to APACHE II score in both groups

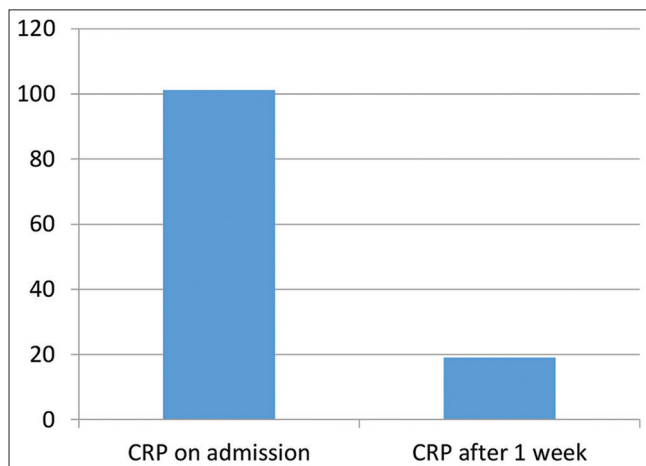Analysis of the results between the two groups showed significant laboratory decrease of inflammatory markers (CRP) in both groups within 1 week from starting treatment, which was more evident in Group A, on admission, CRP mean was 101, (median 86 and SD 60), compared to mean 19 (median 7.8, SD 25) after 1 week of treatment ($p = 0.001$). In Group B, mean on admission was 116, (median 120, SD 59), compared to mean 39 (median 18, SD 51) after 1 week with $p = 0.001$ (Figures 6 and 7).
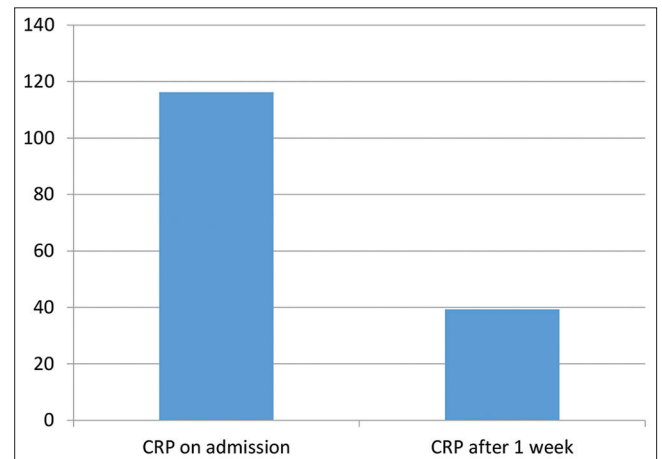

Figure 7: Change in CRP after 1 week of treatment in Group B

The comparison between the two groups showed that mean delta change in CRP in Group A was −79.5, with Median −87, SD −22, compared to mean delta change −64 in Group B, (median −80, SD −47) with $p = 0.006$. However, it is noted that change in CRP was not associated with clinical improvement of symptoms and signs of severe inflammatory response in all cases (Table 6 and Figure 8).

Table 6: CRP changes (on admission and after 1 week)

CRP changes	Group A			Group B			p value
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
CRP on admission	101.20 ± 60.24	86.50	13.40–242.00	116.20 ± 59.18	120.50	3.00–228.00	0.088
CRP after 1 week	19.11 ± 25.53	7.85	1.00–135.00	39.29 ± 51.92	18.00	0.60–220.00	0.003
CRP percentage change	−79.50 ± 22.70	−86.97	−99.44–9.65	−64.89 ± 47.20	−80.00	−98.84–170.18	0.006

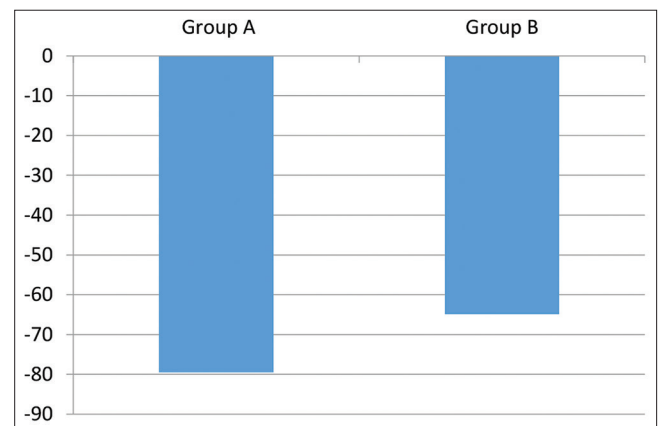There was no significant difference in both ICU duration of stay or overall hospital stay between two groups.

Figure 8: Delta change in CRP after 1 week in both groups

Figure 6: Change in CRP after 1 week of treatment in Group A

In Group A, mean duration of ICU stay was 8.9 days, (median 7 days, SD 5.7), compared to mean of 9 days in Group B (median 8 days, SD 5.6) (p-value 0.57).

Regarding the overall hospital stay in Group A, the mean was 13.7 days (median 12 days, SD 6.58), compared to mean of 12.4 days (median 11 days, SD 6.1) in Group B, p-value 0.117 (Table 7).

Table 7: Duration of intensive care unit stay, hospital stay, and mechanical ventilation in groups

Duration length	Group A			Group B			p value
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
Days of invasive MV	7.35 ± 3.6	7.00	0.00–12.00	7.38 ± 4.2	6.00	0.00–20.00	0.241
Days of non-invasive MV	5.08 ± 3.25	4.00	0.00–15.00	4.6 ± 4.07	3.00	0.00–18.00	0.098
ICU days	8.96 ± 5.70	7.00	3.00–30.00	9.00 ± 5.60	8.00	3.00–32.00	0.576
Hospital days	13.76 ± 6.58	12.00	3.00–34.00	12.46 ± 6.11	11.00	6.00–39.00	0.117

The two groups did not show significant difference in the need for mechanical ventilation (either invasive or non-invasive). Among 76 patients in Group A: 34 (45%) needed non-invasive MV, 12 of them needed invasive MV in later stage, as compared to 26 (32%) out of 80 in Group B, 14 of them needed invasive MV later (p-value 0.16) (Tables 7 and 8).

Table 8: Need for mechanical ventilation

Patients needed MV	Count (%)		p value
	Group A	Group B	
Patients needed invasive MV			
Yes	14 (18.4)	19 (23.8)	0.213
No	62 (81.6)	61 (76.3)	
Patients needed non invasive MV			
Yes	34 (45.4)	26 (32.5)	0.160
No	42 (54.6)	54 (67.5)	

Among the 34 patients who needed non-invasive MV in Group A, the mean for days spent under non-invasive MV was 5.08 day (median 4, SD 3.25), compared to mean of 4.6 days, (median 3, SD 4.07) among the 26 patients of Group B (p-value 0.098) (Tables 7 and 8).

The patients who needed invasive MV in Group A were 14 patients (18.5%) out of 76, while in Group B; 19 patients (23.8%) needed invasive MV (p-value 0.213) (Table 7).

Among the 14 patients who needed invasive MV in Group A, the mean for days spent under invasive MV was 7.35 days (median 7, SD 3.6), compared to mean of 47.38 days, (median 6, SD 4.2) in the 19 patients of Group B (p-value 0.24) (Table 7).

As for mortality, there was no difference between the two groups, 6 patients (8%) out of 76 in Group A died, while in Group B, 13 patients died (13%) out of 80 (p-value 0.111) (Table 9).

Table 9: Mortality in both groups

Outcome	Count (%)		p value
	Group A	Group B	
Improved	70 (92.1)	67 (83.8)	0.111
Died	6 (7.9)	13 (16.3)	

Sixteen patients (21%) in Group A developed secondary bacterial infection (mostly bacterial pneumonia and urinary tract infection) compared to 21 patients (26%) in Group B (p-value 0.446). However, it is worth mentioning that symptoms of secondary infection were frequently masked in patients of Group A as compared to the other group, thus were difficult to detect either clinically or even with the ordinary inflammatory markers. This may be due to depression of immune system after using the combination of tocilizumab with steroids (Table 10).

Table 10: Complications in both groups

Complications	Count (%)		p value
	Group A	Group B	
GIT bleeding			
Yes	2 (2.6)	4 (5.0)	0.682
No	74 (97.4)	76 (95.0)	
Secondary bacterial infection			
Yes	16 (21.1)	21 (26.3)	0.446
No	60 (78.9)	59 (73.8)	

Analysis of data showed significant relation between the incidence of secondary bacterial infection and mortality in both groups. Among the 37 patients who had secondary infection in both groups; 13 died (35%) (p-value 0.001).

Table 11: Relation between secondary bacterial infection and mortality in both groups

Outcome	Secondary bacterial infection in both groups, count (%)		p value
	Yes	No	
Died	13 (35.1)	6 (5.0)	<0.001
Improved	24 (64.9)	113 (95.0)	

Four patients died of the 16 (25%) who suffered from secondary bacterial infection in Group A (p-value 0.016). In Group B, nine patients died out of 21 (43%) after developing secondary bacterial infection (p-value 0.001) (Tables 11-13).

Table 12: Relation between secondary bacterial infection and mortality in Group A

Group A outcome	Secondary bacterial infection, count (%)		p value
	Yes	No	
Died	4 (25.0)	2 (3.3)	0.016
Improved	12 (75.0)	58 (96.7)	

Discussion

In many centers across world, off-label use of tocilizumab became standard of care for patients with COVID-19 in the presence of evidence of cytokine storm. However, practice patterns have varied from center to another.

Table 13: Relation between secondary bacterial infection and mortality in Group B

Group B outcome	Secondary bacterial infection, count (%)		p value
	Yes	No	
Died	9 (42.9)	4 (6.8)	<0.001
Improved	12 (57.1)	55 (93.2)	

The benefit from use of tocilizumab in controlling host immune response responsible for cytokine storm is still debatable. Many papers and trails claim no significant benefit from the use of tocilizumab

in COVID-19 patients. None of the tocilizumab randomized trials reported mortality benefits at 28 or 30 days [19], [20], [21], [22], [23].

On the other hand, both the RECOVERY trial, REMAP-CAP, and the CORIMUNO randomized clinical trial, also anticipate a beneficial effect of adding tocilizumab when compared with standard of care alone [20], [24], [25].

In this study, we are documenting our results retrospectively regarding the objective benefits of adding tocilizumab to the standard therapy.

However, being retrospective study, analysis of the results showed some limitations, heterogenicity was noted in the clinical characteristics and disease severity across intervention groups, most of older and sicker patients with multi-organ affection were in Group B which explains some of the selection bias when we choose who to receive tocilizumab, yet we found that there was no statistically significant difference in APACHE II SCORE between the two groups, denoting uniform selection of patients nullify the effect of added comorbidity in influencing the clinical course and mortality between the two groups.

Our results showed higher prevalence of males across both groups, overall, 118 out of 156 (75%) of the patients in both groups were male, p = 0.015 was considered.

This statistical difference may be related to the observation that gender has effect on the severity of symptoms and outcome in COVID-19, thus, the male sex is associated with increased severity of symptoms and higher rates of ICU admission. Hence, it is expected to have more males with critical condition than females [26].

The mean and median values of age were significantly higher in Group B, with mean of 58 years and median of 60 compared to 53 and 55 years as mean and median, respectively, in Group A (p = 0.014). Papers suggest that age is a risk factor for more severe form of the disease with increased expected mortality over 65 years. This correlates with the observation that patients of Group B who presented with more severe cases and multiorgan affection were generally older than the other group and that we were reluctant in using combined immune modulatory therapy among those older patients being sicker [27], [28].

Chronic kidney disease frequency was much higher in Group (B); 10 (12.5%) patients compared to one patient (1.3%) in Group A (p = 0.006). Papers suggest that chronic kidney disease is an independent risk factor for more severe COVID-19 disease [29].

IL-6 level was significantly higher in Group A; with values of 108 and 75 as mean and median, respectively, compared to 63 and 19 as mean and median values, respectively, in Group B (p = 0.001). This is due to the selection criteria used to choose patients who received tocilizumab (Group A), in which the elevated IL-6 was one of the laboratory markers of cytokine release syndrome.

The results showed significant decrease in inflammatory marker (CRP) in both groups after 1 week of using immune modulatory therapy, being even more evident in Group A. Comparison between the two groups showed that the mean delta change in CRP in Group A was −79.5 with median −87, SD −22, compared to mean delta change −64 in Group B, median −80, SD −47 with p = 0.006. However, the change in CRP was not associated with clinical improvement of symptoms and signs of severe inflammatory response in all cases.

Regarding the outcome, analysis of results did not show significant statistical difference that denoted the additional benefit of using tocilizumab in reducing mortality, despite earlier reports that suggested such benefits [20], [24], [25] which may be related to group of patients selected for this line of therapy, in other words, not all of them were in actual cytokine storm which may lead to some of dilution of the results.

Furthermore, duration of ICU stay, overall hospital stay, risk, and duration of mechanical ventilation (either invasive or non-invasive) did not show statistically significant difference between the two groups.

These results match with similar reports from other randomized double-blinded placebo-controlled trials, for example, REMDACTA trial and COVACTA trial [30], [31].

Even the incidence of complications associated with use of drugs (secondary bacterial infection and GIT bleeding) did not show significant difference between the two groups. Important observation to be mentioned that the detection of secondary infection was much more difficult in Group A, as symptoms were frequently masked in patients of Group A compared to the other group, thus were difficult to detect either clinically or even with ordinary inflammatory markers, this may be due to the effect of immune modulatory therapy.

Furthermore, despite the fact that the incidence of secondary bacterial infection was statistically insignificant between the two groups, yet there was direct relation between the incidence of secondary bacterial infection and the mortality in both groups.

However, our study has some limitations. First, it is not a randomized comparison, and therefore, unmeasured confounding cannot be ruled out (as seen in heterogenicity between two groups regarding age, severity of disease, and comorbidities). In addition, the results rely on the usual assumptions about the model being correctly specified.

Many questions remain open. The results must be considered in relation to different epidemiological settings. Tocilizumab use in severe COVID-19 pneumonia is still in its infancy period, and the best treatment strategies have yet to be developed.

Conclusion

Using tocilizumab in combination with steroids did not show additional benefit than that could be achieved using steroids alone regarding decreasing hospital mortality, need for mechanical ventilation (either invasive or non-invasive), duration of ICU stay, and overall hospital stay, also did not affect incidence of secondary bacterial infection in patients with moderate-to-severe COVID-19 pneumonia.

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