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The outcome of patients with Severe COVID 19 treated with tocilizumab:a Retrospective Cohort study

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ABSTRACT

BACKGROUND

Coronavirus disease 2019 triggers a cytokine storm resulting in high mortality. A key player in this cytokine storm has been considered as interleukin-6. Tocilizumab, a monoclonal antibody, is theorized to treat COVID-19 by inhibiting the interleukin-6 receptor. However, conflicting data supporting this hypothesis is available in the literature.

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METHODOLOGY

This retrospective cohort included 1001 severe COVID-19 patients from a tertiary care hospital, Pakistan, hospitalized from March 2020 to August 2021. Primary outcome was the proportion of patients expired. Beside proportion of patients discharged, requirements for assisted ventilation and ICU admission were other outcomes. We also saw the impact of tocilizumab on radiological findings, oxygenation, and inflammatory markers.

RESULTS

Of 100 patients in the toci group, 85(85%) patients were ultimately discharged, compared to only 57.9% patients in R-toci and 62.9% patients in SOC group were discharged ($p < 0.001$). Fifty-nine (38.8%) patients in R-toci group and one hundred ninety-six (26.2%) patients in SOC group were expired in comparison to toci group in which only eight (8%) of patients were expired ($p < 0.001$). Similarly need for invasive mechanical ventilation and ICU admission remained lowest in toci group. Improvement in radiological findings, oxygenation, and inflammatory markers was observed after using tocilizumab. Patients receiving standard of care had lowest survival. Among discharge patients, those who received standard of care had longest hospital stay.

CONCLUSION

Tocilizumab use in patients with severe COVID-19 is associated with a significant reduction in mortality, need for ICU admission and invasive mechanical ventilation.

KEYWORDS: Coronavirus disease 19, Assisted/invasive mechanical ventilation, Tocilizumab, Intensive care unit, mortality.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) has infected about 88 million people in 218 countries and territories, resulting in over 1.9 million deaths [1].

In Pakistan, the first case was discovered in February of 2020. By June, cases were on peak and then plummeted across the country by August. By mid-November, there had been over 350,000 confirmed cases and 7000 deaths [1]. Presentation of COVID-19 varies from mild asymptomatic to severe pneumonia, necessitating invasive mechanical ventilation or death [2-4]. The SARS-CoV-2 virus activates the immune system after infecting pneumocytes and other cells, resulting in a pro-inflammatory response. This progresses to the release of various chemokines and cytokines, like IL-6, tumor necrosis factor-α [5]. These cytokines stimulate a robust inflammatory response, progressing in respiratory failure, and death. The autopsy findings revealed extensive alveolar destruction, hyaline membrane development, and intra-alveolar edema in these patients [6].

Inter Leukin-6 plays a vital part in developing serious COVID-19 complications, among all released cytokines. Severe and critical COVID-19 patients have greater levels of IL-6 and poorer outcomes, according to a new meta-analysis. Severe COVID-19 patients had mean IL-6 levels about three times greater than those with non-severe illness (95 percent CI: 1.17–7.19) [7].

There is no approved treatment for COVID-19 pneumonia; a combination of immunomodulatory and antivirals has been used in clinical practice. In preliminary research, patients receiving lopinavir/ritonavir compared to usual therapy showed no benefit [8].

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Immunomodulatory drugs like selective cytokine inhibitors result in the inhibition of cytokine receptors or ligands [9].

These factors have led to an increase in tocilizumab (TCZ) use with varying results in COVID-19 [10]. The tocilizumab is approved for treating rheumatoid arthritis and for dampening the cytokine storm [11].

In a study from China [12] in patients at increased cytokine storm risk, tocilizumab proved significant clinical benefit. However, 80mg to 600mg doses were used. This research and other observations [13, 14] provide the chance for using off-label tocilizumab in severe COVID-19. By May 2020, tocilizumab was used for treating COVID-19 in a large number of studies [15, 16].

The purpose of this group was to see how effective tocilizumab was in treating severe COVID-19 than usual therapy.

MATERIALS AND METHODOLOGY

This Retrospective Cohort was conducted in a Karachi, Pakistan tertiary care facility. From March 2020 to August 2021, research participants were adults 18 and older with COVID-19 verified by PCR/Rapid Antigen Assay on a nasopharyngeal swab or radiological findings consistent with COVID-19.

Severe pneumonia was classified as having an oxygen saturation of less than 94 percent on room air and requiring oxygen or ventilation. Exclusion criteria for using tocilizumab were co-existing bacterial and fungal infections, history of a severe allergy to a monoclonal antibody, neutrophil Count <500, and platelet count < 50,000. The institutional clinical review committee gave its approval to the study (ERC).

We categorized patients as discharged irrespective they required supplemental oxygen at the time of discharge or released on room air (without supplemental oxygen). In addition, those who departed against medical advice (LAMA) were also classified as such.

PROCEDURE

At the time of admission, all patients were given COVID-19 standard of care treatment, which was done according to institutional guidelines and then according to Pakistani National Guidelines once policies were established. Standard of care included supplemental oxygen, low molecular weight heparin, and steroid, i.e., methylprednisolone 40 mg three times daily as a part of institutional protocol before the recommendation made by recovery trial and Dexamethasone 6 mg once daily after recovery trial).

Patients were also given tocilizumab if they had any of the following in the presence of severe or critical after receiving at least 24-48 hrs of steroids.

1. Ferritin more than 1000mcg/L in increasing or more than 2000mcg/L in patients requiring ventilation of high flow oxygen.
2. Lymphocytes less than 800/ml or less than 20%

and two of the following.

1. Ferritin more than 700mcg/L and rising
2. CRP greater than 70mg/L
3. D-Dimer greater than 1000ng/ml
4. LDH greater than 300IU

Tocilizumab was given as a single dose of 8 mg/kg body weight intravenously. Many patients could not receive tocilizumab in the initial days because of no clear-cut recommendations on the use of tocilizumab and global shortage later on. Remdesivir was given a 200mg loading dose, followed by 100mg once

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daily for four days if the patient presented within ten days of symptom onset. We divided patients in three groups; those who received tocilizumab and standard treatment (toci group), those who received tocilizumab along with remdesivir and standard treatment (R-toci group) and those who received only standard of treatment (SOC group). As addition of remdesivir in patients receiving tocilizumab might have affected the outcomes resulting in study bias; therefore, author decided to add R-toci group.

DATA COLLECTION

We compiled a complete list of patients hospitalized with a diagnosis of PCR-positive COVID-19 or based on their radiological results through electronic records. Twelve hundred and ninety-nine charts were examined, with 63 being eliminated due to missing medical records. One hundred twenty-seven were excluded because of mild and moderate symptoms of COVID-19. One hundred eight patients with severe pneumonia were excluded who were expired or intubated within 24 hours of admission. In contrast, 1001 patients were included in the study. We also manually reviewed the patient's charts to ensure accurate data capture. Through detailed chart review, extracted demographics, biochemical markers, laboratory parameters, and outcome of patients.

OUTCOME

The primary outcome of the interest was death. Simultaneously, discharge, the requirement for assisted ventilation and ICU admission were other outcomes of interest. We also assessed radiological findings, oxygenation, and inflammatory marker levels before and after use of tocilizumab.

STATISTICAL ANALYSIS

Participants' baseline characteristics were compared for laboratory parameters, existing comorbidities, and signs and symptoms. For continuous variables, the median and interquartile range were calculated. For categorical variables, we calculated frequencies and percentages and compared them using Fisher's exact test or Pearson's Chi-square test. We performed the Kruskal-Wallis test for computing the p-value of continuous variables. We did survival analysis from symptom onset until discharge, need for assisted ventilation, and death using Kaplan Meier Curve. We also compared the time from admission to death and invasive mechanical ventilation between groups using Cox regression analysis as a hazard ratio with 95% CI. Finally, Wilcoxon signed ranks test was performed for comparing the inflammatory markers before and after tocilizumab. The data were analysed with IBM SPSS Version 26, and a P-value <0.005 was judged statistically significant.

RESULTS

The study comprised a total of 1001 patients who met the inclusion criteria. Figure-1

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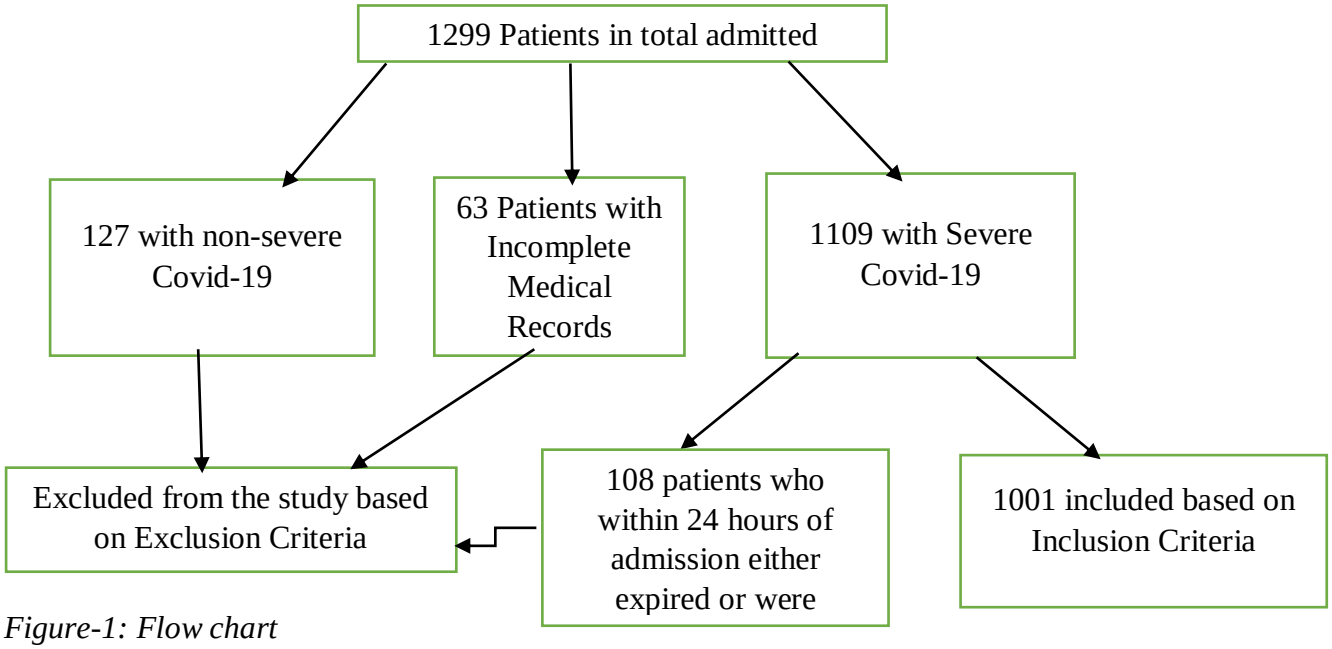

Figure-1: Flow chart

COVID-19; coronavirus disease 2019

Demographics and clinical characteristics are shown in table 1.

	Total	Tocilizumab	Tocilizumab and Remdesivir	Standard of Care	P-Value
Age (Mean and SD)		58.07±12.33	61.39±13.18	58.23±14.64	0.14
Gender					
Male	653 (65.2%)	61 (61%)	101 (66.4%)	491 (65.6%)	0.630
Female	348 (34.8%)	39 (39%)	51 (33.6%)	258 (74.1%)	
Diabetes mellitus	538 (53.7%)	60 (60%)	84 (55.3%)	394 (52.6%)	0.349
Hypertension	578 (57.7%)	47 (47%)	101 (66.4%)	430 (57.4%)	0.009
Asthma	64 (6.4%)	10 (10%)	11 (7.2%)	43 (5.7%)	0.236
Ischemic Heart Disease	181 (18.1%)	16 (16%)	26 (17.1%)	139 (18.6%)	0.777
End-Stage Renal Disease	44 (4.4%)	4 (4%)	10 (6.6%)	30 (4%)	0.362
Chronic Liver Disease	20 (2%)	5 (5%)	1 (0.7%)	14 (1.9%)	0.048

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Malignancy	20 (2%)	1 (1%)	1 (0.7%)	18 (2.4%)	0.282
Smoking	64 (6.4%)	11 (11%)	10 (6.6%)	43 (5.7%)	0.130
Symptoms					
Fever	841 (84%)	97 (97%)	132 (86.8%)	612 (81.7%)	<0.001
Cough	641 (64%)	87 (87%)	105 (69.1%)	449 (59.9%)	<0.001
Shortness of Breath	824 (82.3%)	97 (97%)	137 (90.1%)	590 (78.8%)	<0.001
Runny Nose	52 (5.2%)	17 (17%)	6 (3.9%)	29 (3.9%)	<0.001
Anorexia	147 (14.7%)	21 (21%)	13 (8.6%)	113 (15.1%)	0.020
Nausea	98 (9.8%)	13 (13%)	7 (4.6%)	78 (10.4%)	0.047
Vomiting	76 (7.6%)	4 (4%)	5 (3.3%)	67 (8.9%)	0.020
Diarrhea	97 (9.7%)	18 (18%)	9 (5.9%)	70 (9.3%)	0.005
Lethargy	449 (44.9%)	46 (46%)	63 (41.4%)	340 (45.4%)	0.652
Myalgia	272 (27.2%)	26 (26%)	41 (27%)	205 (27.4%)	0.957
Headache	59 (5.9%)	17 (17%)	8 (5.3%)	34 (4.5%)	0.001
Anosmia	136 (13.6%)	32 (32%)	14 (9.2%)	90 (12%)	<0.001
Altered Loss of Consciousness	123 (12.3%)	10 (10%)	16 (10.5%)	97 (13%)	0.541

Table 1: Demographic Characteristics
SD, Standard Deviation.

The toci group had 100 patients, R-toci group had 152 patients and the SOC group had 317. Six hundred fifty-three male and three hundred forty-eight female patients were there. The average age of patients in toci group, R-toci and SOC group was 58.07, 61.39 and 58.23, respectively.

Hypertension, ischemic heart disease, and diabetes were shown to be the most common concomitant conditions (P 0.009, P 0.349, P 0.777). Shortness of breath and fever were most typical presenting symptom found in 824 and 841 patients (P <0.001 in both). The second most prevalent symptom was cough, found in 641 patients (P <0.001 in both). Lethargy and Myalgia were other common presenting features (P 0.652; P 0.957). Baseline biochemical markers are shown in table 2.

	Tocilizumab	Tocilizumab + Remdesivir	Standard of Care	P-Value
	Median (IQR)	Median (IQR)	Median (IQR)	
Haemoglobin (g/dL)	12.45 (11-13.6)	12.5 (11.3-13.5)	12 .1(11-13.5)	0.936
White Blood Cells ($x10^9$/L)	10 (7-14.6)	10.7 (8-17)	10.5 (7.3-14.3)	0.202

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Neutrophils (%)	84 (77-90)	86 (80- 91.8)	83 (74-90)	0.021
Lymphocytes (%)	10 (5-16)	8 (4-14)	10 (5-17)	0.034
Platelets ($\times 10^9$/L)	261 (185.8-348.8)	228 (172.5-314)	239 (177-323)	0.028
ALT (U/L)	40 (30-78)	36 (20-58)	34 (23-59)	0.040
AST (U/L)	45 (31-58)	46 (31-77)	42 (29-70)	0.786
GGT (IU/L)	69 (40-110)	57 (28-102)	50 (28-93)	0.156
Urea	38 (27-57.8)	50 (35.3- 86.8)	40 (28-67)	<0.001
Creatinine	1 (1-1)	1.08 (.91- 1.9)	1.00 (.91-1.56)	0.001
D-dimer (ng/mL FEU)	1801 (688-4070)	1937 (790.5-11229)	1219.5 (632.5-4463.3)	0.220
LDH (U/L)	481.50 (369.5-649.50)	511 (385-650)	405 (296-571)	0.429
C-Reactive Protein (mg/L)	100 (26-176)	133 (87.3- 230.8)	97.2 (39.4-189.7)	0.001
Serum ferritin (ng/mL)	889 (583-1541)	854 (465.5- 1748)	724 (366-1455)	0.384
Procalcitonin	.53 (.32- 1)	.28(.12-1)	0.34 (.13- 1)	0.001

Table 2: Baseline Blood Counts and Biochemical Markers

IQR Interquartile range; FEU, Fibrinogen-equivalent units; ALT, alanine transaminase; AST, aspartate transaminase; GGT, Gamma-Glutamyl Transferase; LDH, lactate dehydrogenase.

Tocilizumab recipients had a significantly higher median haemoglobin count (12.45 g/dL vs. 12.5 g/dL vs. 12.1 g/dL, P 0.936) at presentation. Patients in R-toci group had higher median white cell count than toci and SOC group (10.7 $x10^9$/L vs. 10 $x10^9$/L vs. 10.5 $x10^9$/L, p 0.202), higher median neutrophil count (86% vs. 84% vs. 83%, p 0.021) and lower median lymphocyte count (8% vs. 10% vs. 10%, p 0.028). Higher levels of the inflammatory markers were found in groups receiving tocilizumab (toci and R-toci group) than SOC group.

Outcome	Total	Tocilizumab Given	Tocilizumab + Remdesivir	Standard of Care	P-Value
Discharged	644 (64.3%)	85 (85%)	88 (57.9%)	471 (62.9%)	<0.001
Expired	263 (26.3%)	8 (8%)	59 (38.8%)	196 (26.2%)	<0.001
LAMA	84 (8.4%)	7 (7%)	5 (3.3%)	72 (9.6%)	0.033
ICU	174	2 (2%)	46 (30.3%)	126 (16.8%)	<0.001

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Admission	(17.4%)				
Invasive Mechanical Ventilation (IMV)	92 (9.2%)	2 (2%)	18 (11.8%)	72 (9.6%)	0.022

Table 3: Outcome of Patients

LAMA; left against medical advice, O2; oxygen, ICU; intensive care unit

Of 100 patients in the toci group, 85(85%) patients were ultimately discharged, compared to only 57.9% patients in R-toci and 62.9% patients in SOC group were discharged ($p < 0.001$). Fifty-nine (38.8%) patients in R-toci group and one hundred ninety-six (26.2%) patients in SOC group were expired in comparison to toci group in which only eight (8%) of patients were expired ($p < 0.001$). Similarly need for invasive mechanical ventilation and ICU admission remained lowest in toci group (2% in each).

On Kaplan Meier analysis fig-2, patients who received standard of care had least survival when compared with either toci group or R-toci group (6 vs. 7 vs. 11 days; Log Rank p <0.001). Similarly, patient who received standard of care alone required mechanical ventilation earliest than the other groups (2.8 vs. 4.5 vs. 7.2 days; Log Rank p 0.003). Patients who received standard of care alone had prolonged hospital stay, while those receiving tocilizumab alone were release earliest of all (27 vs. 9.2 vs. 11 days; Log Rank p <0.001).

According to the Unadjusted Cox Regression Model, patients in toci group had a significantly lower risk of death (HR 0.510, 95 percent CI 0.379-0.687, p <0.001). Similarly, a significant reduction in risk of assisted ventilation was observed in the toci group (HR 0.430, 95 % CI 0.248-0.747, p 0.003).

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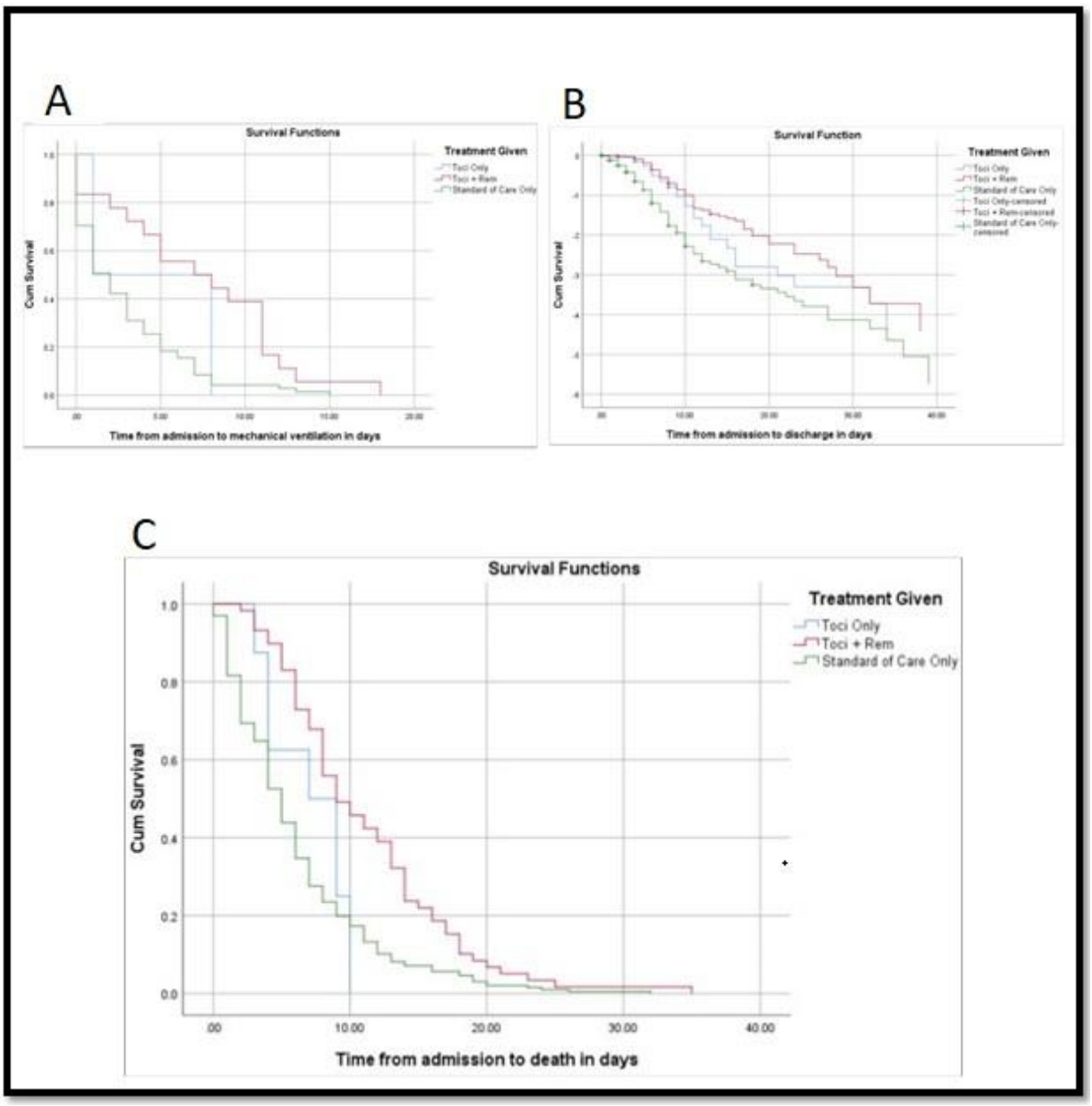

Figure-2: Kaplan-Meier curves (A) Time from Admission to Mechanical Ventilation in days; (B) Time from Admission to Discharge in days; (C) Time from Admission to Death in days.

Effect of Tocilizumab on oxygenation.

Patients who received tocilizumab either alone or in combination with remdesivir showed significant improvement in clinical symptoms and oxygenation.Fig-3 The majority of the patients reported some degree of general well-being in their symptoms, including improved shortness of breath and cough. On the clinical scale, 54.6% of patients had some degree of improvement in their oxygenation with a reduction in oxygen requirements or improvements in oxygenation on arterial blood gases analysis. Conversely, 29.2% of patients

reported worsening in oxygenation, and 16.2% reported no changes in oxygenation.

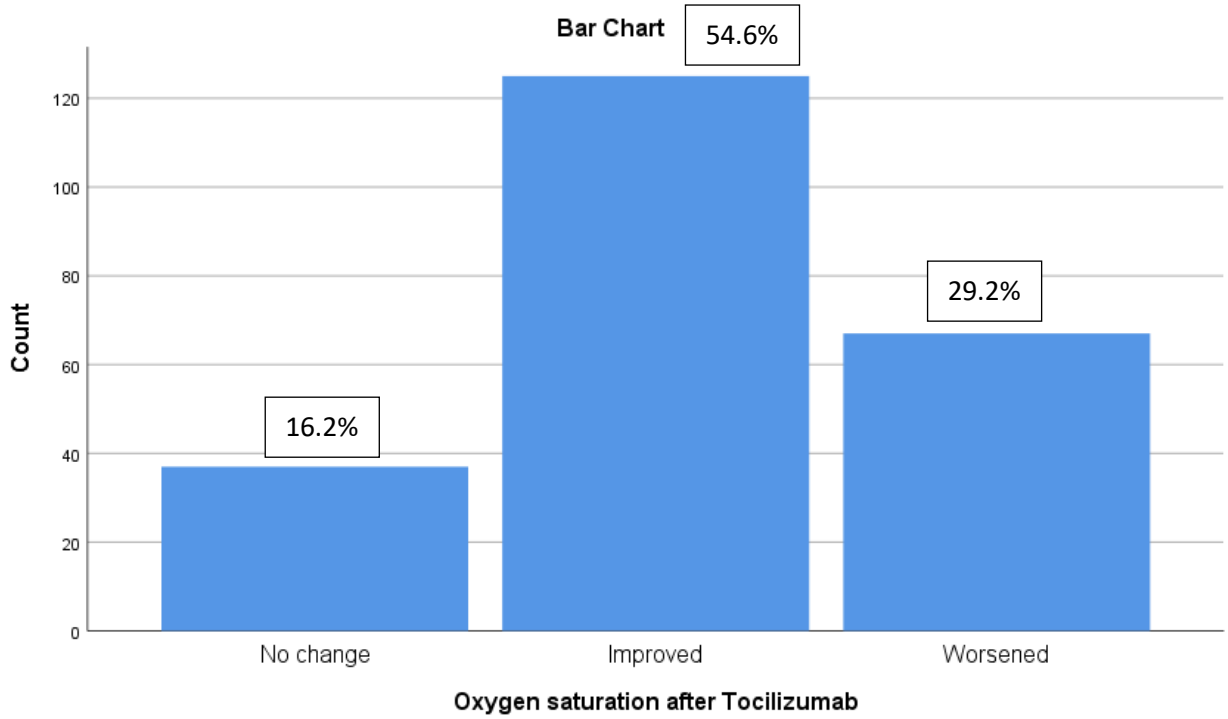

Figure-3 oxygenation of patients after tocilizumab

Effect of Tocilizumab on Radiological findings

Similarly, the patients who received tocilizumab showed improvements in radiological findings fig-4. 59.8% of patients had improvements in their chest x-rays after at least 24 hours of tocilizumab, 14% showed no change, while 26.2% showed worsening in radiological findings after tocilizumab use.

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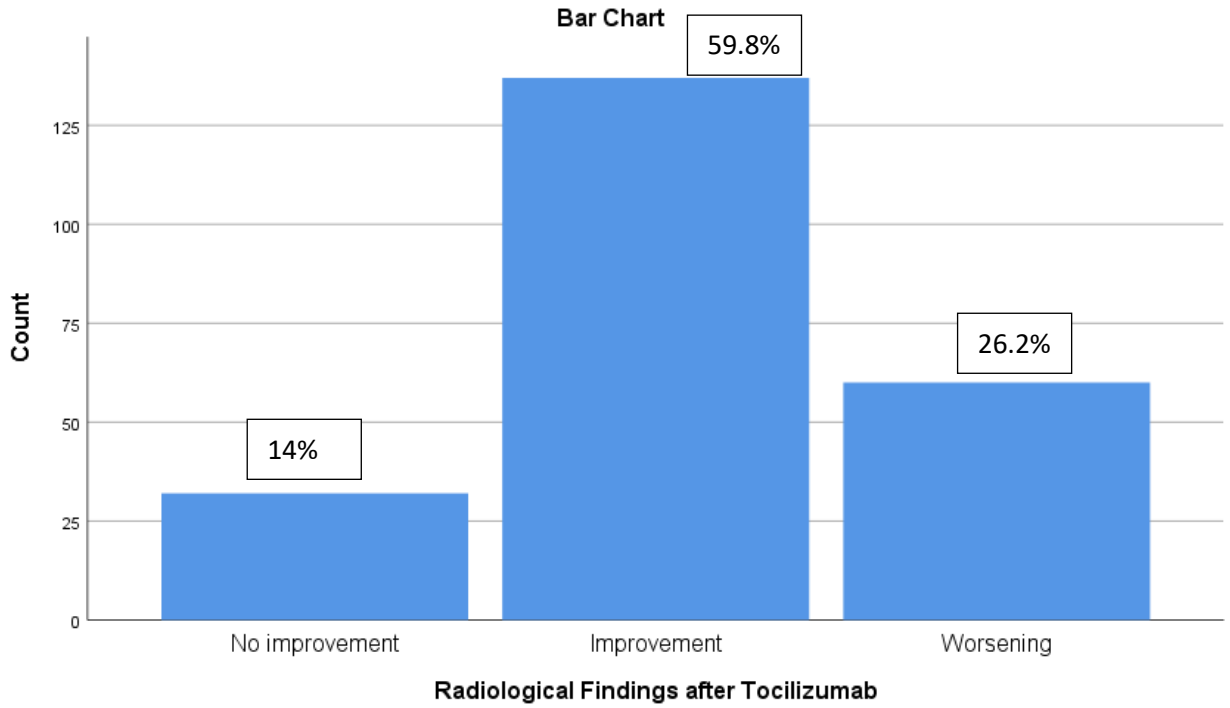

Figure-4 Radiological findings after tocilizumab

Tocilizumab effect on inflammatory markers

The use of tocilizumab in our patient population was associated with significant improvement in inflammatory markers within 24hours of use Table.5. D dimer declined to 1054, C-reactive protein to 19.65, serum ferritin reached 777, and lactate dehydrogenase went to a median value of 467.50 with statistical significance as (p <0.001 in each group).

	Markers before Tocilizumab	Markers after Tocilizumab	P value
	Median (IQR)	Median (IQR)	
D Dimer (ng/mL FEU)	1831 (854-6574)	1054 (621-3072)	<0.001
C-reactive protein (mg/L)	126.49 (55.87-222.31)	19.65 (8.83-47.13)	<0.001
Serum Ferritin (ng/mL)	846 (451-1617)	777 (469-1356)	<0.001
Lactate Dehydrogenase (U/L)	535.50 (408-756.50)	467.50 (341.75-566)	<0.001

Table-5 Inflammatory markers before and after tocilizumab
FEU Fibrinogen-equivalent units; IQR Interquartile range.

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DISCUSSION

COVID-19 may result in a hyper-inflammatory state leading to elevated IL-6 and other cytokines, contributing to lung injury, ARDS, and death [17-19]. IL-6 is a pleiotropic cytokine involved in inflammation and immune regulation. IL-6 also mediates systemic effects with fever and rise of acute phase reactants, local inflammation, and immunoregulation [20]. This defines the strategy for using inhibitors of IL-6 for treating COVID-19 [21].

This retrospective cohort is one of the most extensive reports comparing tocilizumab with the standard of care versus tocilizumab and remdesivir with standard of care vs standard of care alone from Pakistan. Here we reported the clinical outcome of these patients. This cohort's clinical data results show that radiological findings, clinical features, and oxygen requirements significantly improve after tocilizumab use, findings consistent with those reported by Xu X et al [22]. Symptomatic improvement and improvement in oxygenation have also been observed in several other retrospective studies [16, 22]. Similar findings were also reported from Spanish research by Sánchez-Rovira et al [23]. Significant reduction in inflammatory markers, improvement in oxygenation, and quicker fever resolution was also reported in few case series [24, 25]. However, improvement in oxygenation in patients who received tocilizumab was not written by Kewan T et al [26].

Ramaswamy et al., in their study, reported higher inflammatory markers and greater clinical instability in patients managed with tocilizumab compared to only standard of care; these findings are consistent with results seen in this cohort [27]. In this study although we found higher levels of inflammatory markers in patients receiving tocilizumab, the markers were found greater in R-toci group. Similarly, Quartuccio et al. discovered that patients who got tocilizumab had greater CRP and IL-6 levels [28]. In an open-labelled study, Sciascia et al. reported a significant reduction in inflammatory cytokines, including CRP, D-dimer, and serum ferritin [14]. Another research reported that; higher C-reactive proteins levels were significantly reduced in patients with tocilizumab; a similar reduction was also observed in the control group, which raised the question of whether the change was caused by tocilizumab or not [23]. Luo et al. found a decline in C-reactive protein by one week in their patient population after treatment with tocilizumab [29]. Similarly, Alattar et al. found a decline in C-reactive protein by one week [30]. All these findings favour the results of this cohort where we found significant reduction in risk inflammatory markers after the use of tocilizumab.

This cohort reports a significant reduction in mortality in the toci group, a finding consistent with that seen by Sanchez-Rovira et al [23]. A finding consistent with this cohort, although addition of remdesivir resulted in higher mortality which may be explainable by older age and higher number of hypertensive patients in this group. Patients who got tocilizumab had considerably lower mortality and the requirement for ICU hospitalization, according to a retrospective case-control study [15], another finding consistent with findings of this cohort. Need for ICU admission in our cohort was statistically significant and lower in toci group, a finding consistent with findings seen by Sanchez-Rovira et al. and Klopfenstein et al [15, 23]. Lower risk of death was also seen in a meta-

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analysis again a finding consistent with this study [31]. Reduced mortality was also reported in other meta-analysis studies, Rubio-Rivas et al [32], Khan et al [33] and Kotak et al [34], found RRs (95%CI) of 0.73 (0.57, 0.93), 0.83 (0.72, 0.96), and 0.56 (0.34, 0.92), respectively, and Sarfraz et al [35] and Zhao et al [36] found odds ratios (95%CI) of 0.42 (0.26, 0.69) and 0.44 (0.36, 0.55), respectively. Contrary to popular belief, one study demonstrated no difference in mortality between patients treated with tocilizumab and those treated with conventional therapy alone [37]. High mortality with tocilizumab was found in a retrospective cohort, where they reported 42% mortality in patients receiving tocilizumab [38].

Results of tocilizumab were found discouraging in a randomized trial; trial reported hazard ratio for death or intubation in tocilizumab group 0.83 (95% CI, 0.38-1.81; P 0.64) [39]; contrary to that this cohort found statistically significant hazard ratio for death and intubation. Lower mortality and requirement of assisted mechanical ventilation were also seen by Guaraldi et al. (HR 0.61, 95% CI 0.40-0.92; p 0.020) [40]. Roumier et al. study reported significant risk reduction in tocilizumab group assisted ventilation [41].

In a retrospective cohort from the United States, individuals who received tocilizumab had a four-day longer hospital stay than those who received standard therapy [26], a finding not consistent with this cohort where we found time from admission to discharge was lowest in toci group.

This study's main limitation is a retrospective design with a lack of randomized control group, single-centre experience, and dependence on electronic records rather than direct patient history. Potential confounding factors that can significantly influence the outcome are other significant limitations of this study. Unavailability of IL-6 level testing before and after use of tocilizumab would have been helpful. Another significant limitation of this cohort included using tocilizumab only in patients who deteriorated despite steroids, which resulted in selection bias. Adverse drug reactions, which include life-threatening infections linked to the use of tocilizumab, were not assessed in this cohort. Campochiaro et al. reported that 25% of patients experienced severe adverse events after tocilizumab, with 13% reporting bacteremia [42]. Morena et al. reported thrombocytopenia in 14%, bacteremia in 27%, and an increase in hepatic enzymes in 29% of patients treated with tocilizumab [43]. Finally, we did not assess the long-term follow-up of our patients.
A critical strength is that it validates the results from other studies, i.e., Xu X et al., Sanchez-Rovira et al., Abeer et al. The second necessary strength is a large sample size.

Tocilizumab use in patients with severe COVID-19 is associated with a significant reduction in mortality, need for ICU admission and invasive mechanical ventilation. However, well-controlled randomized trials are needed to clarify tocilizumab's role in treating patients with severe COVID-19.

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