ORIGINAL ARTICLE

IS TOCILIZUMAB AN EFFECTIVE THERAPY FOR SEVERE COVID-19: A SINGLE CENTER STUDY

Samreen Sarfaraz[1], Quratulain Shaikh[1], Sundus Iftikhar[2], Fivzia Farooq Herekar[1], Syed Ghazanfar Saleem[3], Fatima Kanani[4]

[1]Infectious Disease Department, The Indus Hospital and Health Network, Karachi, [2]Maternal and Child Health, Interactive Research and Development, Karachi, [3]Emergency Department, The Indus Hospital, Karachi

[4]Chemical Pathology Section, Department of Pathology, The Indus Hospital and Health Network, Karachi-Pakistan

Background: The quest for effective therapies in Covid-19 continues. We compared the outcome of severe COVID-19 patients treated with and without Tocilizumab, an IL-6 inhibitor. **Methods:** This is a prospective cohort study on the clinical characteristics and outcomes of patients with Covid-19 patients admitted at The Indus Hospital and Health Network, Karachi between 24th March and 19th June 2020. Adult patients who received TCZ were compared with respect to mortality and days of hospitalization with those who did not. **Results:** A total of 88 patients including 41 patients in the TCZ group and 47 in non-TCZ group were recruited. Baseline demographic characteristics were comparable. TCZ group patients presented with worse clinical features including median SpO2 82% vs 88%, $p<0.05$ and CRP 193 vs 133.9 mg/L, $p<0.05$. Approximately, 85.4% were admitted in ICU compared to 69.8% in non-TCZ group, $p>0.05$. Mortality was not different among the groups (46% in TCZ group vs 51.1% in non-TCZ group, $p>0.05$). Median length of hospital stays, days of intubation, use of inotropic agents, and use of invasive ventilation or in-hospital complications were similar between the groups. Sub-group analysis revealed that mortality within TCZ group was associated with high IL-6 levels (173 vs 69.66 pg/ml, $p<0.05$), ICU admission (100% vs 72%, $p<0.05$), need for mechanical ventilation (100% vs 13.6%, $p<0.05$) and higher incidence of in-hospital complications, $p<0.05$. **Conclusion:** TCZ failed to demonstrate any mortality benefit in our patients. Non-survivors within the TCZ group were more critical compared to survivors and developed more in hospital complications.

Keywords: COVID-19; Mortality; Tocilizumab

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) originated from Wuhan, China in December 2019. It was declared a pandemic by World Health Organization (WHO) in February 2020[1] and has infected more than 563,179,849 people till date leading to 63,771,48 deaths globally[2]. Approximately 10% of cases develop a severe pneumonia and progress to acute respiratory distress syndrome (ARDS).[3] Considerable mortality has been reported among hospitalized severe and critical COVID patients.[4,5] Similar to SARS and MERS infection, severe COVID-19 is characterized by both direct viral cytopathic damage and cytokine-mediated inflammatory injury, a phenomenon which was previously compared with the "cytokine release syndrome" (CRS) observed in patients on T cell immunotherapy.[6,7] Lung biopsies of fatal COVID-19 cases demonstrate severe alveolar oedema, proteinaceous exudate and dense lymphocytic infiltration.[8] Interleukin-6 (IL-6) is postulated to be a major player in the cytokine mediated destruction.[7] Inflammatory markers including C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin and D-dimer are raised in critical COVID pneumonia.[7] Tocilizumab (TCZ) is an IL-6 receptor antagonist approved by FDA for CRS in patients with chimeric antigen receptor (CAR) T-cell therapy.[9] Clinicians in China first used TCZ in severe COVID-19 patients with elevated IL-6 levels in an attempt to block the inflammatory pathway and halt disease progression.[10] Results of some published randomized controlled trials (RCTs) and observational studies evaluating the benefit of TCZ in COVID-19 seem promising.[11–14] However, some RCTs also contradict this evidence and fail to demonstrate any clinical or mortality benefit.[15–18]

Pakistan recorded its first case of COVID-19 on 26th February, 2020 and thereafter the infection rapidly spread across the country. The Indus Hospital and Health Network at its Karachi campus responded to the health emergency by establishing a dedicated 20-bedded COVID-19 facility on 19th March 2020 later expanding it to 60 beds. It was led by a team of infectious disease experts, pulmonologists and anaesthesiologists. TCZ was offered to severe COVID-19 patients on compassionate grounds after review of emerging literature. Later, TCZ was also incorporated in National COVID-19 management guidelines in Pakistan.[19] The aim of this paper is to compare the outcome of severe and critical COVID-19 patients who received TCZ with those who

did not, in the first wave of COVID-19 in Pakistan. Predictors of mortality in the TCZ subgroup were also assessed.

MATERIAL AND METHODS

This is a sub-study from a larger perspective cohort study[20] on (Nasopharyngeal RT-PCR positive) COVID-19 patients above 18 years of age admitted at The Indus Hospital and Health Network, Karachi between 24th March and 19th June 2020. All adult patients admitted to the COVID unit of the hospital were enrolled. The study received ethical approval under IRB approval number IRD_IRB_2020_04_002. For the purpose of this paper, we identified patients who received TCZ from our data and compared them with a group who did not receive TCZ in the COVID unit. Patients were classified according to national guidelines[19] as "severe COVID-19" if on admission they had respiratory rate higher than 30/min, SpO2 less than 90% on room air or Chest X-ray showing more than 50% of lung fields involved along with a positive nasopharyngeal PCR for COVID-19 and "Critical COVID-19" if along with the criteria for severe disease they manifested ARDS, Septic shock or multisystem organ failure (MSOF). TCZ was administered to severe and critical COVID-19 patients who demonstrated any of the following abnormalities as per the WHO guidelines.[21] Ferritin >2000 ng/ml or >1000 ng/ml and rising for 24 hours; lymphocyte percentage less than 20% and/or neutrophil to lymphocyte ratio (NLR) of more than 5 along with ferritin more than 700 ng/ml or LDH higher than 300 U/L or D-dimer higher than 1000 ng/ml or CRP higher than 70 mg/L. Most patients received a single intravenous dose of TCZ of 4–8 mg/kg (maximum 800 mg) and some critical patients exhibiting severe hyper-inflammation received 2 doses 12 hours apart. Factors determining the use of TCZ apart from clinical indications as mentioned above, were availability of the drug, presence of contra-indications (e.g., liver disease, kidney failure, presence of concomitant bacterial/ fungal infection) or physician's choice. Demographic information, clinical presentation, laboratory abnormalities and radiological imaging results were recorded. Patient's hospital course including management, in-hospital complications, need for ventilation, length of stay and final outcomes was also noted. The primary outcome was mortality in the two groups while we also compared length of stay, occurrence of in-hospital complications, use of inotropic support and use of mechanical ventilation. We performed a subgroup analysis based on mortality in the TCZ group. Data was recorded on a REDCap database and analyzed on SPSS v 24. Continuous variables were expressed as mean (SD) or median (IQR) as appropriate. Categorical variables were expressed as number (%). Student's t-test or Mann Whitney U test were used to compare continuous data. Chi square or Fischer's Exact test was used to compare categorical data. Length of hospital stay was compared using log-rank test and Kaplan Meir survival curves were made to show the survival function and p-value ≤0.05 was considered significant.

RESULTS

There were 41 patients in the TCZ group compared with 47 patients in the Non-TCZ group with a mean age of 57 years (Table-1). Most patients in the TCZ group (73%) were critical at presentation compared to non-TCZ group (53%), p=0.053. Clinical features at presentation were similar in both groups except that median oxygen saturation was 82% in the TCZ group vs 88% in the Non-TCZ group, p=0.012. Laboratory parameters were also comparable in both groups except for median absolute lymphocyte count (ALC) which was $1.02x10^9$ in TCZ group as opposed to $0.75x10^9$ in the non-TCZ group, p<0.05. Baseline median CRP in the TCZ group was 193 vs 133.9 mg/L in non-TCZ group, p<0.05. 9/41 patients received 2 doses of TCZ while 32/41 received a single dose. Most patients in the TCZ group showed bilateral radiographic findings including multi-lobar infiltrates (92% vs 31%) and consolidations (78% vs 31%) compared to the non-TCZ group, p<0.05. Clinical severity scores of SOFA and CURB 65 were comparable in the two groups but median MulBSTA score was 9 in the TCZ group and 11 in the non-TCZ group, p<0.05. Most patients in the TCZ group received non-invasive ventilation within the Emergency Department 75.6 % vs 35.6% in the Non-TCZ group, p<0.05. There was no statistical difference in ICU admissions, 85.4% in the TCZ vs 69.8% in the Non-TCZ group, p>0.05. Regarding other compassionate therapies, there was no difference in steroid use and use of Hydroxychloroquine, while 31.7% patients received IVIG in the TCZ group compared to 10.6% in the Non-TCZ group, p<0.05.

There were thirty-two patients who received one dose of TCZ and nine patients who received two doses. Due to the small number of patients in these groups, their characteristics could not be compared.

There was no difference in mortality; 46% in the TCZ group vs 51.1% in the non-TCZ group, p>0.05 (Table 2). Length of ICU stay was 9 days in the TCZ vs 8 days in the Non-TCZ, p>0.05. No significant differences were reported in the median length of hospital stay (10 days in TCZ group vs 8 days in Non-TCZ group days; p>0.05: Figure-1), median days of intubation (4.5 days in TCZ group vs 1 day in Non-TCZ group; p>0.05), use of ionotropic agents (43.9% in TCZ group vs 47.8% in Non-TCZ group; p>0.05) or use of invasive ventilation (53.7% in TCZ group vs 52.2% in Non-TCZ group; p>0.05). Cause of death was MSOF in 89.5% of patients in the TCZ group vs 47.4% in the Non-TCZ group, p>0.05. In-hospital complications including nosocomial infections, were also not significantly different in the two groups.

Sub-group analysis for mortality within the TCZ group showed that D-dimer, LDH, Ferritin, pro-calcitonin and IL-6 were significantly elevated among those who died after TCZ therapy, $p<0.05$ (Table-3). There was no difference in median CRP level at baseline (167.8 mg/L in survivors vs 219.4 mg/L in non-survivors; $p>0.05$) and the median maximum change in CRP level (baseline value - lowest post therapy value) after TCZ therapy in the two groups (26.05 in survivors vs 13.2 mg/L in non-survivor; $p>0.05$). Those who died had elevation of LDH after TCZ therapy as compared to survivors where levels decreased after therapy, $p=0.028$. Baseline serum albumin was significantly lower in fatal cases as compared to survivors, $p<0.05$. Although there was no statistical difference in disease category at presentation (severe/ critical), those who died had significantly higher mean SOFA scores (4.38 vs 5.39; $p<0.05$). All those who died (100%), needed ICU admission compared to 72.7% of those who survived ($p<0.05$). Need for invasive ventilation (13.6% in survivors vs 100% in non-survivors, $p<0.05$), median days of intubation (0 in survivors vs 7 in non-survivors, $p<0.05$) and use of inotropes (9.1% in survivors vs 84.2% in non-survivors, $p<0.05$) were higher in those who did not survive compared to those who survived. The survivors showed fewer in-hospital complications while fatal cases had more nosocomial infections, refractory shock and acute kidney injury ($p<0.05$). Repeat chest x-ray showed improvement in 95.5% of survivors compared to 52.2% of those who eventually died ($p<0.05$). Concomitant investigational therapies like intravenous immunoglobulin (IVIG), Azithromycin (AZT) and HCQ were associated with mortality ($p<0.05$). Therapeutic anticoagulation was also associated with mortality in our data ($p<0.05$).

Table-1: Baseline characteristics of the study participants by treatment group

	TCZ group (n=41)	**Non-TCZ group (n=47)**	***p*-value**
DEMOGRAPHIC FEATURES	**n (%)**	**n (%)**	
Age (years)[β]	57.09±11.92	57.94±12.19	0.743
Gender			
Male	36 (87.8)	36 (76.6)	0.174
Female	5 (12.2)	11 (23.4)	
Disease Severity			
Severe	11 (26.8)	22 (46.8)	0.053
Critical	30 (73.2)	25 (53.2)	
Comorbidities			
None	15 (36.6)	13 (27.7)	0.752
Hypertension	19 (46.3)	23 (48.9)	
Diabetes	19 (46.3)	21 (44.7)	
Chronic lung disease	1 (2.4)	2 (4.3)	
Renal disease	1 (2.4)	5 (10.6)	
Other	10 (24.4)	11 (23.4)	
CLINICAL FEATURES AT ADMISSION (Median (IQR))			
Heart rate per minute	107 (96-119)	107 (90-124)	0.933
Respiratory rate per minute	31 (26-37)	30 (24-36)	0.420
Temperature	98.6 (98-98.6)	98.6 (98-98.6)	0.606
Oxygen Saturation %	82 (70-89.5)	88 (82-93)	0.012*
GCS <15(n%)	0 (0)	2 (4.3)	0.496
=15(n%)	41 (100)	44 (95.7)	
PaO2/FiO2 Ratio	156 (82-230)	184 (126-255)	0.208
LABORATORY PARAMETERS AT ADMISSION (Median (IQR))			
Total WBC Count ($x10^9$/L)	10.8 (8.7-14.9)	11.48 (7.75-14.9)	0.572
Neutrophil to Lymphocyte Ratio	8.8 (6.73-12.4)	10.83 (5.43-18.79)	0.533
Absolute Lymphocyte Count ($x10^9$/L)	1.02 (0.73-1.45)	0.75 (0.53-1.3)	0.035*
Lymphocytes (%)	9.8 (7.15-12.25)	8.1 (4.9-14)	0.477
Neutrophils (%)	85.1 (82-88.9)	86.6 (76.6-91.1)	0.713
Hematocrit %	39.3 (36.05-42.15)	37.55 (33.95-40.35)	0.037*
Creatinine (mg/dl)	1.01 (0.81-1.33)	1.17 (0.98-1.51)	0.060
Sodium (mEq/L) [β]	136.22±4.53	134.72±6.18	0.204
Arterial lactate mmol/L	1.83 (1.45-3.07)	2.19 (1.7-3.31)	0.227
Serum Bicarbonate(mEq/L)	20 (18-22.5)	19 (16-21)	0.047*
INFLAMMATORY MARKERS AT ADMISSION (Median (IQR))			
D-dimer ng/ml	2032.5(602.75-8154.5)	4923 (1041.25-13448.75)	0.317
hs-Troponin I ng/L	12 (6-27)	10.5 (4.75-138.25)	0.510
CRP mg/L	193 (127.85-269.1)	133.9(76.1-243)	0.037*
Albumin g/dl	3.29 (3.06-3.49)	3.0 (2.73-3.45)	0.427
LDH U/L	522 (442.5-718)	53 1(380-738.5)	0.414
Ferritin ng/ml	1298.98 (718.62-1675.56)	983 (405.46-1675)	0.145
Pro-calcitonin ng/ml	0.33 (0.19-0.79)	0.57 (0.24-2.38)	0.054
IL-6 pg/ml	84.34 (28.25-185.03)	38.98 (17.26-98.9)	0.093
CHEST X-RAY FINDINGS			
Unilateral radiographic findings	1 (2.4)	3 (6.7)	0.000**
Bilateral radiographic findings	41 (100)	39 (86.7)	
Multi-lobar infiltrates	38 (92.7)	14 (31.1)	
Consolidation	32 (78)	14 (31.1)	
Pleural effusion	3 (7.3)	1 (2.2)	
Other	2 (4.9)	7 (15.6)	

ARDS at Admission	TCZ group (n=41)	Non-TCZ group (n=47)	*p*-value
No ARDS	4 (9.8)	5(10.6)	0.746
Mild	10(24.4)	16(34.0)	
Moderate	16(39.0)	17(36.2)	
Severe	11(26.8)	9(19.1)	
SEVERITY PREDICTING SCORES AT BASELINE (MEDIAN (IQR))			
SOFA	4.5(4-5)	5(4-8)	0.259
qSOFA score	1(1-1)	1(1-1)	0.760
CURB_65	1(0.5-2)	1(1-2)	0.159
MulBSTA	9(7-11)	11(9-13)	0.024*
MANAGEMENT STRATEGIES			
Use of noninvasive ventilation (in the ER)			
Yes	31 (75.6)	16 (35.6)	0.000**
No	10(24.4)	29 (64.4)	
Direct ICU admissions			
Yes	35(85.4)	30(69.8)	0.088
No	6(14.6)	13(30.2)	
Use of Methyl prednisolone			
Yes	37(90.2)	37(78.7)	0.141
No	4(9.8)	10(21.3)	
Use of IVIG			
Yes	13(31.7)	5(10.6)	0.015*
No	28(68.3)	42(89.4)	
Use of HCQ			
Yes	23(56.1)	34(72.3)	0.112
No	18(43.9)	13(27.7)	
Use of Azithromycin			
Yes	12(29.3)	24(51.1)	0.038*
No	29(70.7)	23(48.9)	
Use of HCQ and Azithromycin			
Yes	10(24.4)	21(44.7)	0.047*
No	31(75.6)	26(55.3)	

**p-value<0.0001, *p-value<0.05, [β] Mean±SD, ICU= Intensive care unit, GCS= Glasgow coma scale, hs= High sensitivity, ARDS= adult respiratory distress syndrome, ER= emergency room, IVIG= intravenous immunoglobulin, HCQ= Hydroxychloroquine

Table-2: Clinical Outcomes by treatment groups

	TCZ group (n=41)	Non-TCZ group (n=47)	*p*-value
	n (%)	n (%)	
Outcome			
Alive	22 (53.7)	23 (48.9)	0.658
Dead	19 (46.3)	24 (51.1)	
Length of hospital stay (days)[¥]	10 (7-16)	8 (5-16)	0.375
Length of ICU stay in days[¥]	9 (7-15)	8 (5-16)	0.231
Days of intubation[β]	4.5 (0-8)	1 (0-9.25)	0.323
Use of Inotropes			
Yes	18 (43.9)	22(47.8)	0.714
No	23 (56.1)	24 (52.2)	
Need for Mechanical ventilation			
Yes	22 (53.7)	24 (52.2)	0.890
No	19 (46.3)	22 (47.8)	
Cause of death			
ARDS	2 (10.5)	9 (47.4)	0.013*
Refractory shock	0 (0)	1 (5.3)	
Multi-system Organ Failure (MSOF)	17 (89.5)	9 (47.4)	
In-hospital complications			
None	14 (35.9)	15 (35.7)	0.124
Cardiac abnormalities	5 (12.8)	9 (21.4)	
Nosocomial infection	12 (30.8)	11 (26.2)	
Central nervous system abnormalities	0 (0)	2 (4.8)	
Septic shock	15 (38.5)	10 (23.8)	
Multi-organ dysfunction syndrome (MODS)	9 (23.1)	8 (19)	
Acute Kidney injury	18 (46.2)	17 (40.5)	
Thromboembolism	3 (7.7)	1 (2.4)	
Barotrauma	0 (0)	4 (9.5)	
Disseminated Intravascular Coagulation	6 (15.4)	0 (0)	
Severe hyper glycaemia	3 (7.7)	3 (7.1)	
Electrolyte abnormalities	3 (7.7)	4 (9.5)	
Other	11 (28.2)	9 (21.4)	

*p-value<0.05, [¥] Median (IQR), [β] Mean±SD, ICU= Intensive care unit

Table-3: Predictors of mortality in the TCZ group

	Survivors (n=22) N (%)	Non-survivors (n=19) N (%)	*p*-value
BASELINE LABORATORY PARAMETERS Median (IQR)			
Creatinine (mg/dl)	0.9 3(0.76-1.24)	1.15 (0.94-1.38)	0.060
D-dimer ng/ml	888 (499-2934)	5319 (1402-14547.7)	0.012*
LDH U/L	493 (404.75-628)	624.5 (470-845)	0.073
LDH U/L (maximum change) β©	23 (-16-314)	-163 (-419-65.5)	0.028*
Ferritin ng/ml	1015.9 (390.52-1589.2)	1675.56 (773.94-1675.56)	0.049*
Pro-calcitonin ng/ml	0.21 (0.12-0.3)	0.85 (0.42-2.3)	0.000**
IL-6 pg/ml	69.66 (27.08-136.8)	173.1 (35.09-403.4)	0.037*
CRP mg/L	167.85 (126.8-231)	219.4 (139.4-283.8)	0.210
CRP mg/L (maximum change) β©	26.05 (0-128)	13.2 (0-178.2)	0.848
Albumin g/dl β	3.36±0.34	3.11±0.44	0.084
CLINICAL PRESENTATION			
Disease severity			
Severe COVID-19	8 (36.4)	3 (15.8)	0.138
Critical COVID-19	14 (63.6)	16 (84.2)	
SOFA score β	4.38±0.59	5.89±2	0.005*
OUTCOMES			
ICU admission			
Yes	16 (72.7)	19 (100)	0.023*
No	6 (27.3)	0 (0.0)	
Length of ICU stay in days¥	7 (6.75-12.5)	8 (6.75-17)	0.562
Days of intubation¥	0 (0-2)	7 (5-9)	0.000**
Use of Inotropes			
Yes	2 (9.1)	16 (84.2)	0.000**
No	20 (90.9)	3 (15.8)	
Mechanical ventilation			
Yes	3 (13.6)	19 (100)	0.000**
No	19 (86.4)	0 (0)	
In-hospital complications			
None	13 (65)	1 (5.3)	0.000**
Cardiac abnormalities	1 (5.3)	4 (21.1)	
Nosocomial infection	3 (15)	9 (47.4)	
Refractory shock	1 (5)	14 (73.7)	
Multi-organ dysfunction syndrome (MODS)	0 (0)	9 (47.4)	
Acute Kidney injury	1 (5)	17 (89.5)	
Thromboembolism	0 (0)	3 (15.8)	
Disseminated Intravascular Coagulation	0 (0)	6 (31.6)	
Severe hyperglycemia	0 (0)	3 (15.8)	
Electrolyte abnormalities	0 (0)	3 (15.8)	
Other	3 (15.8)	7 (36.8)	
Chest X-ray 48 hours post TCZ			
Improved	21 (95.5)	10 (52.6)	0.004*
Static	1 (4.5)	7 (36.8)	
Deteriorated	0 (0.0)	2 (10.5)	
EFFECT OF OTHER COMPASSIONATE THERAPIES			
Methylprednisolone with TCZ			
Yes	20 (90.9)	17 (89.5)	1.00
No	2 (9.1)	2 (10.5)	
IVIG with TCZ			0.000**
Yes	1 (4.5)	12 (63.2)	
No	21 (95.5)	7 (36.8)	
HCQ with TCZ			
Yes	9 (40.9)	14 (73.7)	0.035*
No	13 (59.1)	5 (26.3)	
Azithromycin with TCZ			
Yes	3 (13.6)	9 (47.4)	0.018*
No	19 (86.4)	10 (52.6)	
HCQ and Azithromycin with TCZ			
Yes	2 (9.1)	8 (42.1)	0.014*
No	20 (90.9)	11 (57.9)	
Anticoagulation			
Therapeutic dose (0.5mg/kg)	7 (33.3)	15 (78.9)	0.004*
Prophylactic dose (1.0 mg/kg)	14 (66.7)	4 (21.1)	

**p-value<0.0001, *p-value<0.05, β Mean±SD,©calculated by the difference of baseline value and lowest post therapy value, ICU= Intensive care unit, GCS= Glasgow coma scale, ARDS= adult respiratory distress syndrome, ER= emergency room, IVIG= intravenous immunoglobulin, HCQ= Hydroxychloroquine)

DISCUSSION

In this study comparing outcomes of hospitalized severe and critical COVID-19 patients, there was no difference in in-hospital mortality (46.3% vs 51.1%, *p* 0.658) or duration of invasive ventilation, ICU or in-hospital stay in the TCZ group compared to the Non-TCZ group. The two groups were similar in their demographic features such as age and gender but those who received TCZ had significantly more severe disease with lower peripheral oxygen saturation, higher need for non-invasive ventilation (NIV) in Emergency room, florid radiological findings and higher CRP levels. Despite being a sicker group, the mortality in TCZ group is still comparable to that of a lesser severity Non-TCZ group, which may reflect a potential benefit due to the drug- a bigger sample size may have highlighted a statistical difference. The Recovery trial recruited 4116 COVID-19 patients on supplemental oxygen with CRP>75mg/L and the TCZ arm showed a statistically significant reduction in progression to mechanical ventilation and death as compared to the standard care arm (28 day mortality 31 versus 35 percent, relative risk 0.85, 95% CI 0.76–0.94), with subgroup analysis revealing those receiving concomitant dexamethasone (82%) more likely to benefit.[14] Similar results were echoed in the REMAPCAP trial and a meta-analysis of 8 RCTs.[13,22] Based on these results, National Institute of Health (NIH), Infectious Disease Society of America (IDSA) and National Health Service in the United Kingdom[23–25] now recommend adding TCZ as an adjunct to glucocorticoids in patients with increasing oxygen demand and raised inflammatory markers Conflicting evidence has, however emerged from several other RCTs, with no effect on disease progression, clinical or mortality benefit[16–18] with a trial from Brazil showing a trend toward higher 28-day mortality with TCZ (21 versus 9 percent, OR 2.7, 95% CI 0.97–8.35)[26]. The basis for variation in results is unclear with postulations that the trials which did not show benefit may have been under-powered or had not used concomitant glucocorticoids. Contradictory evidence has been reported in several published observational studies as well, with some highlighting significant survival advantage[27] and others noting no clinical benefit[28,29] Most of these observational studies lack comparison groups, have small sample sizes with varying diseases severity, used multiple compassionate therapies at different time frames and do not have data on confounders or side effects of drugs.[11,30]

Given that TCZ is expensive and has significant side effects, it is debatable if the small and conflicting data on mortality benefit justifies the cost and risks of therapy especially in the resource constrained situation prevailing in Pakistan. Moreover, given the high burden of Tuberculosis (TB) and multi drug resistant (MDR) bacterial infection in Pakistan, the formidable risk of acquiring either of them following immunosuppression with TCZ adds to its undesirability. Emily *et al* showed that nosocomial infections in critical COVID-19 patients were twice in TCZ group as compared to non-TCZ group.[30] Overall, there was no difference in incidence of nosocomial infections between the TCZ group and Non-TCZ group in our study but we saw 2 cases of candidemia and 3 cases of gram negative multidrug resistant organisms (MDRO) in the TCZ group. Modest reversible rise in liver enzymes was seen in some patients but severe hepatic injury was not seen. It is premature to comment on the risk of TB re-activation in survivors of COVID-19 treated with TCZ at this point in time.

Use of other compassionate therapies like Intravenous Immunoglobulins (IVIG) was significantly higher in the TCZ group. However, the use of Azithromycin (AZT) and AZT in combination with HCQ was higher in Non-TCZ group. Since this was a desperate situation for a novel infection in the first wave of COVID -19, physicians had a low threshold for administering any perceived potentially beneficial therapy.

In the sub-group analysis, we demonstrated important mortality predictors within the TCZ group. Non- survivors required ICU admission, mechanical ventilation and had significantly higher serum levels of D-dimer, ferritin, IL-6, pro-calcitonin and SOFA scores with lower serum albumin levels as compared to survivors. Wu et al found raised LDH and D-dimer to be risk factors for progression to ARDS and n.[7] Sara *et al* showed that non-survivors have twice normal D-dimers, higher median SOFA scores and more frequently need respiratory, inotropic and renal support.[31] High IL-6 levels secreted by pathogenic T cells and inflammatory monocytes are associated with impaired gas exchange, lung fibrosis, platelet aggregation and coagulopathy due to vascular endothelial injury and angiotensin II receptor microvascular dysfunction.[32,33] A meta-analysis reported mean IL-6 levels to be 2.9 times higher in patients with complicated COVID-19 disease compared to those with un complicated disease.[34] Similarly, Wu *et al* reported higher IL-6 levels of 6.05 in survivors vs 10.7 pg/ml among non-survivors, $p<0.05$.[7] Hence, IL-6 can be used as a guide to initiating therapy with TCZ.

The sub group analysis further demonstrated a sharp reduction in serum CRP levels post TCZ, consistent with other studies.[32,35] In contrast, serum LDH levels were seen to rise in non-survivors after

TCZ and may be used as an indicator of therapy failure. Radiological improvement after 48 hours of TCZ therapy was observed in 95.5% of survivors as compared to 52.6% of non-survivors, while 36.8% had no change on chest X-ray and 10.6% showed deterioration. It is worthy to note that despite radiological and CRP improvement, non-survivors showed clinical deterioration. Xu *et al* reported resolution of radiographic lesions following TCZ therapy in 19/21 (90%) of his patients[32]. Non-survivors had comparatively more complications like refractory shock, Acute Kidney Injury (AKI), nosocomial infections and thromboembolism.

Our study is unique in being among the few comparative reports of TCZ therapy in severe and critical COVID-19 patients. Prospectively collected data was used for this research and captured most confounders which can affect the response to TCZ therapy.

Limitations: Our study's main limitation is its small sample size, but declining number of cases towards the end of as the first wave, restricted the feasibility of further augmenting data. Due to the small sample size, the groups receiving 4 mg /k or 8 mg/k or those receiving either one and two doses of TCZ could not be compared. Moreover, as the study was observational, we were not able to randomly distribute confounders where a randomized controlled trial design would have worked best. Selection of groups was largely dependent on availability of drug or physician choice which may have introduced bias. It was not a registered RCT, and in the crisis's situation arising in the initial days of the pandemic, patients were being treated according to the evidence reflecting in literature and the availability of drugs. However, most baseline characteristics in our study groups are well balanced at presentation minimizing influence of various factors. Further application of advanced statistical methods to control for confounders would be desirable but is limited by sample size.

CONCLUSION

Our data did not show any significant mortality benefit of TCZ among severe COVID-19 patients at our center. We believe our TCZ group patients were sicker with extensive disease progression when the drug was offered to them. TCZ has shown benefit in some RCTs. Further well-structured RCT's are needed to delineate the sub group of patients who may derive maximum benefit from TCZ and also identify other effective therapeutic targets for the treatment of COVID-19 pneumonia.

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AUTHORS' CONTRIBUTION

SS: Concieved the study, ethical approval, data collection, manuscript writing. QS: Study design, ethical approval, data analyis, results, manuscript writing. SI: Data analysis and results writing. FFH: Concept of the study, data collection, manuscript writing. SGS: Ethical approval, data collection, manuscript writing. FK: Concept of the study, data collection, manuscript writing

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Address for Correspondence:

Fatima Kanani, Chemical Pathology Section, Department of Pathology, The Indus Hospital and Health Network, Karachi-Pakistan
Cell: +92 300 210 2283
Email: fatima.kanani@tih.org.pk