Efficacy of tocilizumab in treatment of COVID-19 pneumonia: A case-control study from a tertiary care hospital

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ABSTRACT

Background and Objective: Coronavirus disease 2019 (COVID-19) is a viral infectious disease caused by the severe acute respiratory syndrome virus, which has affected billions of people across the globe. The pathogenesis of respiratory inflammation involves elevated concentration of interleukin-6; hence, interventions targeting interleukin-6 receptor, such as tocilizumab (TCZ), have been investigated as potential treatment amidst the dilemma of COVID-19 management. The aim of the study is to analyse the efficacy and safety of TCZ and record the outcome in COVID-19 patients.

Materials and Methods: A retrospective case–control study of 80 patients in each group (N = 160) was carried out in a tertiary care hospital in Vadodara, Gujarat. Non-pregnant COVID-19–positive patients above 12 years of age were included in the study and were divided into case (those given TCZ) and control (those given standard treatment) groups after collecting their history and related data. From each group, further data was collected in the form of general and systemic examination, investigations and calculation of inflammatory and Sequential Organ Failure Assessment (SOFA) scores.

Results: Overall mortality was less in the case group compared to the control group. Patients with moderate to severe disease, age <55 years, patients having no comorbidity and patients with higher oxygen demand had lower deaths when given TCZ. Inflammatory score <3 and SOFA score <6 were associated with reduced mortality in the case group. Additionally, the study found significant results by simultaneously analysing two parameters in combination, which has not been done in any other study to the best of our knowledge.

Conclusions: Adjuvant TCZ therapy had overall mortality benefit compared to standard treatment, with specific benefit observed in those with increasing disease severity, young to middle-age group, absence of comorbidity, higher oxygen requirements and lower inflammatory and SOFA scores.

KEY WORDS: Adjuvant Tocilizumab, COVID-19 pneumonia, inflammatory score, moderate to severe disease, retrospective case–control study, SOFA score

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral infectious disease caused by the severe acute respiratory syndrome (SARS-CoV-2) virus, which has affected billions of people across the globe and was first detected in the city of Wuhan.

The severity of the infection is widely variable. Most of the patients develop mild to moderate respiratory illness and recover without requiring any specific treatment. However, some develop serious disease in the form of breathlessness, chest pain, persistent high-grade fever and hypoxia, requiring urgent medical attention.[6] Elderly population, especially those with comorbid conditions (diabetes, hypertension, immunocompromised states, cancer, etc.), are more prone to develop serious illness.

The pathogenesis of respiratory inflammation involves elevated concentrations of inflammatory markers such as procalcitonin, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin and D-dimer, which have been the key factors in COVID-19 host immune impairment, by stimulating a vigorous proinflammatory response, leading to cytokine storm. Measurement of these markers might assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.[2] Additionally, Sequential Organ Failure Assessment (SOFA) scores may be an independent risk factor for hospital death and can be used well to assess the severity and prognosis of COVID-19.[3] Therefore, immunomodulatory interventions targeting these markers have been investigated as potential treatments to counterbalance the host immune dysregulation.

Tocilizumab (TCZ) is a recombinant humanised monoclonal antibody that was used during the COVID-19 pandemic as an interleukin-6 (IL-6) receptor antagonist. Amidst the dilemma of COVID-19 management, it proved to be beneficial in terms of its safety and efficacy profile and gave positive outcomes like reduced mortality, reduced risk of admission into intensive care unit (ICU) admission and lesser need for mechanical ventilation.[4] Some evidence suggest that TCZ may help to avoid the progression of severe COVID-19 disease.

Therefore, the aim of this retrospective case–control study is to analyse the efficacy and safety of TCZ in patients with COVID-19 acute respiratory distress syndrome (ARDS), record the outcome, monitor various changes in serum markers and to find out those parameters which should be considered before administration of TCZ to gain maximum benefit from the drug.

MATERIALS AND METHODS

After getting permission from the Institutional Ethics Committee for Human Research-PG research, this study has been carried out at SSG Hospital, a tertiary care hospital at Vadodara, Gujarat, from the time period of April–December 2020. It was a retrospective case–control type of study comprising 80 cases and controls each (N = 160).

The patients involved in the study were confirmed COVID positive (by reverse transcriptase-polymerase chain reaction [RT-PCR]/rapid antigen test) requiring medical attention (difficulty in breathing, high-grade fever, severe cough >5 days, with comorbid conditions).[9] Pregnant females and those under 12 years of age were excluded from the study. Data regarding personal history including biodata, treatment history, mode of ventilation and comorbid conditions were collected after taking consent from the patients.

A total of 160 patients were divided into case and control groups, in which 80 patients who were given TCZ (8 mg/kg to a maximum dose of 800 mg intravenous) were part of the case group (group A) and 80 patients who were not given TCZ (on standard treatment based on the guidelines of the Government of India) were part of the control group (group B). Thereafter, clinical information (general and systemic examination) and laboratory findings were collected including calculation of the inflammatory score[5] and SOFA score, as mentioned in Tables 1 and 2.

Outcome of the study was analysed for various parameters, such as age, disease severity, comorbidities, mode of ventilation, inflammatory score, SOFA score and combinations of any two of the above parameters, in the form of death and discharge for each group. The statistical methods used were Chi-square test, P value (P) and odds ratio (OR) with 95% confidence interval (www.socscistatistic.com).

RESULTS

Here, we have compared the clinical outcome of patients who were given TCZ (group A) to that of patients who were not given TCZ (group B).

In group A, out of 80 cases, 43 (53.75%) patients died and 37 (46.25%) were discharged, whereas in group B, out of 80 controls, 65 (81.25%) patients died and 15 (18.75%) were discharged. There was a significant difference in the mortality between case and control groups (P=0.000205). Group B had 3.73 times more mortality compared to group A (OR = 3.71).

| Table 1: Inflammatory markers scoring system |
|---------------------------------------------|
| Inflammatory marker | Score 0 (normal) | Score 1 (abnormal) |
| NLR             | 1–3             | >3             |
| CRP (mg/dL)     | <5              | >5             |
| Ferritin (mg/dL)| <300            | >300           |
| LDH (U/L)       | <460            | >460           |
| IL-6 (pg/mL)    | <7              | >7             |
| D-dimer (μg/mL) | <0.5            | >0.5           |

CRP = C-reactive protein, IL-6 = interleukin-6, LDH = lactate dehydrogenase, NLR = neutrophil lymphocyte ratio
Disease severity
As shown in Table 3, there was a significant association between mortality and administration of TCZ in moderate to severe disease, where higher mortality was seen in the control group B compared to case group A ($P=0.022243$, OR = 4.89 and $P=0.004532$, OR = 4.24 for moderate and severe disease, respectively). This finding suggests that TCZ could be effective in reducing mortality in those with moderate to severe disease.

Age
The age of participants ranged from 26 to 76 years, with the mean age being 56.8 years. In both groups A and B, there were 29 patients below the age of 55 years and 51 patients above the age of 55 years. In group A, among the patients aged below 55 years, seven (8.75%) patients died and 29 (27.5%) patients were discharged. In group B, amongst the patients aged below 55 years, 20 (25%) patients died and six (7.5%) patients were discharged ($P=0.000621$). For patients below 55 years of age, the mortality was 6.98 times higher in group B compared to group A (OR = 6.98). This significant association suggests that TCZ is effective in reducing death in young and middle-aged population, especially those below the age of 55 years. However, no such association was seen in those above 55 years of age.

Comorbidities
In each of the groups A and B, patients were grouped according to the number of comorbidities they were suffering from, such as patients with no comorbidities ($n=25$), with one comorbidity ($n=31$), with two comorbidities ($n=18$) and with three or more comorbidities ($n=6$).

Among the patients with no comorbidities, in group A, 10 (12.5%) patients died and 15 (18.75%) patients were discharged and in group B, 19 (23.75%) patients died and six (7.5%) patients were discharged ($P=0.009914$, OR = 0.21). This result suggests that there were significantly lower deaths in group A compared to group B.

However, in patients with comorbidities, no significant difference was observed in mortality when both groups were compared. As per this result, it could be concluded that in patients with no comorbidities, those receiving TCZ showed 0.21 times lower death rate compared to those who did not receive it. Moreover, administration of TCZ did not lower deaths in patients with comorbidities in each group, suggesting that presence of comorbid conditions led to higher mortality irrespective of TCZ administration.

Mode of ventilation
When data was analysed with respect to mode of ventilation at the time of admission, it showed the

Table 2: Sequential (sepsis-related) Organ Failure Assessment score

| SOFA score | 0 | 1 | 2 | 3 | 4 |
|------------|---|---|---|---|---|
| Respiration PaO$_2$/FiO$_2$ (kPa/mmHg) | >400=5.3 | 301–400 | 201–300 | 101–200 | ≤100 |
| (4.1–5.3) | | (2.8–4.0) | (1.4–2.7) | | (≤3) |
| Coagulation | >150 | 101–150 | 51–100 | 21–50 | ≤20 |
| Platelets ($\times 10^9$ mm$^3$) | <1.2 | 1.2–1.9 | 2–5.9 | 6–11.9 | ≥12 |
| Liver | | | | | |
| Bilirubin (mg/dL) | | | | | |
| CNS (GCS) | No hypotension MAP<70 mmHg Dopamine≤5 or dobutamine any dose Dopamine>5 Dopamine>15 | | | | |
| Renal | <1.2 | 1.2–1.9 | 2.0–3.4 | 3.5–4.9 | >5 |
| Creatinine (mg/dL) | | | | | |

PaO$_2$=arterial oxygen pressure, FiO$_2$=fraction of inspired oxygen, MAP=mean arterial pressure, GCS=glasgow coma scale, CNS=central nervous system, CVS=cardiovascular system, SOFA=sequential organ failure assessment

Table 3: Efficacy of tocilizumab in reducing mortality according to the severity of disease in the case and control groups

| Severity of disease | Died | Discharged | Row total |
|---------------------|------|------------|-----------|
| Group A (case)      | 5 (6.25%) | 8 (10%) | 13 | $P=0.1576$ (not significant) |
| Group B (control)   | 6 (7.5%) | 7 (8.75%) | 13 |
| Column total        | 11 | 15 | 26 |

| Severity of disease | Died | Discharged | Row total |
|---------------------|------|------------|-----------|
| Group A (case)      | 9 (11.25%) | 11 (13.75%) | 20 | $P=0.022243$ (significant) |
| Group B (control)   | 16 (20%) | 4 (5%) | 20 |
| Column total        | 25 | 15 | 40 |

| Severity of disease | Died | Discharged | Row total |
|---------------------|------|------------|-----------|
| Group A (case)      | 29 (36.25%) | 18 (22.5%) | 47 | $P=0.004532$ (significant) |
| Group B (control)   | 41 (51.25%) | 6 (7.5%) | 47 |
| Column total        | 70 | 24 | 94 |
following results. In group A, nine out of 19 patients on room air (47.37%), five out of 14 patients on high-flow nasal oxygen (HFNO; 35.71%) and 14 out of 23 patients on non-rebreather mask (NRBM; 60.87%) died. In group B, five out of 11 patients on room air (45.45%), 12 out of 16 patients on HFNO (75%) and 27 out of 31 patients on NRBM (87%) died. This finding suggests that patients with high oxygen demand were benefitted by administration of TCZ when compared to their counterparts, in the form of lower death rate. However, statistical calculations failed to establish any significance for the above finding.

Among the patients on bilevel positive airway pressure (BiPAP), 12 (57.13%) died and nine (42.85%) were discharged out of 21 patients in group A. In group B, out of 16 patients, 15 (93.75%) died and only one patient was discharged. Statistically significant difference was observed in the death rates of the two groups (P = 0.034824 with Yates correction, OR = 0.09). All three patients on intermittent positive pressure ventilation (IPPV) in group A and four out of five patients on IPPV in group B died. The sample size of IPPV patients was very small to derive any conclusion about the efficacy of TCZ in reducing mortality in such patients.

The above analysed data suggests that patients in the control group with higher oxygen requirements showed higher deaths than those in the case group (OR = 11.25), showing the efficacy of TCZ in reducing mortality in such patients.

**Disease severity and number of comorbid conditions**

In each group of the study, patients were divided according to the severity of disease, such as mild (n = 13), moderate (n = 20) and severe (n = 47). They were further divided into two subgroups according to the number of comorbidities, such as patients with no or one comorbidities and patients with two or more comorbidities.

Use of TCZ did not show any significant association with reducing mortality in mild COVID-19 disease with or without comorbidities.

Seventeen out of 20 patients with moderate disease and 30 out of 47 patients with severe disease had no or one comorbid condition.

Out of 17 patients with moderate disease in each group, eight (47.1%) died and nine (52.9%) were discharged in group A and 15 (88.24%) died and two (11.76%) were discharged in group B. There was significantly lower death in the case group compared to the control group in moderately affected patients with no or one comorbidity (P = 0.010284 with Yates correction, OR = 0.12).

Similarly, out of 30 severely ill patients with no/one comorbidity in each group, 17 (56.67%) died and 13 (43.33%) were discharged in group A and 25 (83.33%) died and five (16.67%) were discharged in group B (P = 0.034212 with Yates correction, OR = 0.26). This result suggests that among severely ill patients with no/one comorbidity, those who received TCZ had 0.26 times lower mortality compared to those who did not receive it.

Moderate to severely ill patients with two or more comorbidities did not show any association of TCZ use and reduced mortality.

From the above analysis, it could be concluded that use of TCZ is more effective in reducing mortality in patients of moderate to severe disease with no/one comorbidity than in those with mild disease or in those suffering from multiple comorbidities.

**Age and disease severity**

In mild, moderate and severe disease groups, patients were further subdivided according to age: age less than 55 years and age more than 55 years.

For those who were less than 55 years of age, no significant effect was observed between age and mortality in patients with mild disease. However, out of five patients with moderate disease in each group, one (20%) died and four (80%) were discharged in the case group and four (80%) died and one (20%) was discharged in the control group. Although no statistical significance was obtained for the above finding, larger sample size is needed for proper analysis of the efficacy of TCZ in such groups.

Among patients with age less than 55 years suffering from a severe form of COVID-19 disease, in group A, six (37.5%) patients died and 10 (62.5%) patients were discharged. In group B, 14 (87.5%) patients died and two (12.5%) patients were discharged. There was a significant difference in the deaths of severely ill patients less than 55 years of age who were given TCZ compared to those who were not given TCZ (P = 0.010587 with Yates correction, OR = 0.09).

The above result suggests that use of TCZ in moderate to severely ill patients of age less than 55 years seems to reduce mortality.

Patients older than 55 years of age, irrespective of severity of disease, were not benefitted by the use of TCZ in terms of mortality.

**Age and additional comorbid conditions**

Among patients aged less than 55 years and suffering from no other comorbidity conditions, in group A, six (46.15%) patients died and seven (53.85%) patients were discharged. In group B, 11 (84.62%) patients died and two (15.38%) patients were discharged (OR = 0.16). This suggests 0.16 times lower deaths of patients who were given TCZ compared to those who were not given TCZ, among patients aged less than 55 years who were suffering from no comorbidity condition.

Among those in a similar age group suffering from any one comorbid condition, in group A, two (15.38%) patients...
died and 11 (84.62%) patients were discharged. In group B, eight (61.54%) patients died and five (38.46%) patients were discharged. There was a significant difference in the case and control groups in patients younger than 55 years suffering from one comorbid condition (P=0.043846 with Yates correction, OR = 0.11).

Among patients aged less than 55 years and suffering from two or more comorbid conditions, in group A, one patient died and three patients were discharged. In group B, all four died. However, no significance could be obtained for this finding due to very small sample size.

All the patients who were older than 55 years of age, irrespective of the number of comorbid conditions, were not benefitted by the use of TCZ in terms of mortality.

**Inflammatory score**
In group A, a total of 35 patients had an inflammatory score of less than 3, and in group B, 40 patients had an inflammatory score of less than 3. Of these, in group A, 15 patients died and 20 patients were discharged. In group B, 28 patients died and 12 patients were discharged. A statistically significant difference was obtained in deaths between groups A and B (P=0.017738, OR = 0.32, relative risk [RR] = 0.61).

However, no significant association was obtained between the use of TCZ and deaths in the case and control groups for the patients with an inflammatory score of more than 3. This suggests the efficacy of TCZ in reducing mortality in those with a low inflammatory score. Thus, the inflammatory score could be used to predict the outcome of patients receiving TCZ, making it a deciding tool for potential candidates who can be administered TCZ.

**SOFA score**
In group A, a total of 28 patients had a SOFA score of less than 6, and in group B, 33 patients had a SOFA score of less than 6. Of these, in group A, 11 patients died and 17 patients were discharged. In group B, 21 patients died and 12 patients were discharged (OR = 0.37, RR = 0.62). This result suggests 0.37 times lower deaths in the case group compared to the control group in those who had a SOFA score of less than 6.

In patients with a SOFA score of more than 6, no statistically significant difference was found in the case and control groups.

This finding also suggests the efficacy of TCZ in reducing mortality in those with a low SOFA score, similar to the inflammatory score.

**DISCUSSION**
TCZ emerged as the potential treatment for COVID-19 during the outbreak in Wuhan.[8-7] A case–control study and meta-analysis by Jiang et al.[14] observed a lower mortality rate in the TCZ treatment group than in the standard treatment group (9.47% vs. 16.84%, P = 0.134), but the results were not statistically significant. However, in our study, we found a similar result in terms of mortality with statistical significance, where mortality was 53.75% in the case group compared to 81.25% in the control group (P=0.000205, OR = 3.71). Additionally, our study also showed that TCZ was effective in the moderate to severe form of COVID-19, with a significant increase in discharge rates (P=0.02223 and P=0.0044532 for moderate and severe disease, respectively).

A single-centre retrospective study by Radulescu et al.[9] reported the association of mortality with advancing age, disease severity, lung damage, ICU admission, cardiovascular comorbidities and IL-6 > 100 pg/mL on TCZ administration. Similarly, in our study, higher mortality was observed in those who were older than 55 years. But the contrasting feature in our study was statistically significant lower mortality in the case group compared to the control group in those less than 55 years of age (P=0.000621). Our study found results similar to those obtained by Radulescu et al. in terms of mortality in comorbid patients. In our study, those who were not suffering from any comorbid condition were benefitted by TCZ compared to those who received standard treatment (P=0.009914).

Gokhale et al.[10] observed in randomized controlled trials that the use of TCZ as rescue therapy in patients of severe COVID-19 pneumonia with hypoxia gave significant survival benefit (P=0.013) in our study, we similarly found the efficacy of TCZ in reducing mortality in those with higher oxygen requirement, such as those on HFNO, NRBM and BiPAP (P=0.034824).

We have intrinsically analyzed the relation of several parameters with each other and found statistically significant results. This has not been performed in any other study so far, to the best of our knowledge. The significant results obtained were lower deaths in those with moderate to severe disease and no/one comorbidity (P=0.010284, P=0.034212), in those less than 55 years of age with moderate to severe disease (P=0.010587) and in those less than 55 years of age with no/one comorbidity (P=0.043846).

There was an increase in the inflammatory markers due to the COVID-19 pathology[11-12] and its pretreatment level was found to be of prognostic importance. According to the study by Broman et al.,[13] IL-6 and CRP are the strongest predictors of COVID-19 outcome. In another retrospective study by Olewicz-Gawlik et al.,[14] it was found that more than 50% patients who survived and were given TCZ had lower levels of LDH, IL-6 and white blood cells (WBC) on 7 and 14 days after the drug therapy. IL-6 and LDH were found to have an effect on predicting the outcome. Our study predicted the outcome with the inflammatory score (mentioned above) used by Shastri and Raval,[15] where we found that those with a score less than 3 showed lower deaths on administration of TCZ.
compared to those in the control group ($P=0.017738$). However, those with a score more than 3 had no benefit from the use of TCZ.

The SOFA score has been used to predict the clinical outcomes of patients with multiple organ failure requiring intensive care. A retrospective, observational cohort study by Guaraldi et al. observed that after adjustment of SOFA score, TCZ treatment was associated with a reduced risk of invasive mechanical ventilation or death ($P = 0.020$). In our study, we further observed that those with a SOFA score of less than 6 who received TCZ showed lower deaths compared to those who did not receive TCZ (OR = 0.37). However, no such result was obtained for those with a SOFA score of more than 6 in both groups.

**CONCLUSION**

This study showed that adjuvant therapy with TCZ had an overall mortality benefit in patients who were administered TCZ compared to that in patients who were not administered TCZ. A significant statistical association was seen in terms of a reduced mortality in the case group compared to the control group for parameters such as moderate to severe disease, age less than 55 years, having no comorbidity and having higher oxygen demand as in those who were on artificial mode of ventilation (HFNO, NRBM, BiPAP).

When two parameters were analyzed in combination, statistically significant additional mortality benefit was seen in those who were given TCZ compared to those who received standard treatment in the following groups: moderate to severely ill patients with no/one comorbidity, those less than 55 years of age with moderate to severe disease and those less than 55 years of age with no/one comorbidity.

Therefore, it could be concluded from the study that TCZ is effective in lowering deaths and should be considered in patients with moderate to severely disease, young and middle-aged population, patients with no comorbidity and patients with higher oxygen requirements.

Decreased death rates were seen with adjuvant TCZ therapy in patients who had an inflammatory score of less than 3 and in patients with a SOFA score of less than 6, making these scores as a predicting as well as a deciding tool for administration of TCZ.

No significant mortality benefit was seen when TCZ was administered in the patients aged above 55 years or suffering from mild form of COVID-19 disease, or with comorbidities, or who were either on room air or IPPV on admission, or who had an inflammatory score of more than 3 or a SOFA score of more than 6. In our study, we also found that the subgroups not benefitted by adjuvant TCZ treatment are patients with mild disease with either age less than 55 years or with/without comorbidity, moderate to severely ill patients with two or more comorbidities, and age more than 55 years with irrespective of either disease severity or presence/absence of comorbid conditions. These parameters could be helpful for the treating physician to decide the course of treatment with TCZ and to predict the outcome in such patients.

To sum up, from our study, we found the efficacy of TCZ in reducing mortality in COVID-19 patients. The study also helped us to derive the parameters to be considered before administration of TCZ to gain maximum benefit of the drug and to exclude patients who would achieve no mortality benefit from treatment with the adjuvant TCZ.

**Ethical committee approval number**  
IECBHR/188-2020

**Declaration of patient consent**  
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**  
There are no conflicts of interest.

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