Tocilizumab improves survival in severe COVID-19 pneumonia with persistent hypoxia: A retrospective cohort study with follow-up from Mumbai, India

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Research article

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Abstract

**Background:** Cytokine storm triggered by Severe Corona Virus Disease 2019 (COVID-19) is associated with high mortality. With high 'Interlukin -6' (IL-6) levels reported in COVID-19 related deaths in China\(^1\), IL-6 is considered to be the key player in COVID-19 cytokine storm. Tocilizumab, a monoclonal antibody against IL-6 receptor, is used on compassionate grounds for treatment of COVID-19 cytokine storm. The aim of this study was to assess effect of tocilizumab on mortality due to COVID-19 cytokine storm.

**Method:** This retrospective, observational study included patients of severe COVID-19 pneumonia with persistent hypoxia (defined as saturation 94% or less on supplemental Oxygen of 15 L per minute through non-rebreathing mask or PaO2/FiO2 ratio of less than 200) who were admitted to a tertiary care center in Mumbai, India, between 31\(^{st}\) March to 5\(^{th}\) July 2020. In addition to standard care, single Inj. Tocilizumab 400mg was given intravenously to 151 consecutive COVID-19 patients with persistent hypoxia, from 13\(^{th}\) May to 5\(^{th}\) July 2020. These 151 patients were retrospectively analysed and compared with historic controls, i.e consecutive COVID-19 patients with persistent hypoxia, defined as stated above (N=118, from our first COVID-19 admission on 31\(^{st}\) March to 12\(^{th}\) May 2020 i.e, till tocilizumab was available in hospital). Univariate and multivariate Cox regression analysis was performed for identifying predictors of survival. Statistical analysis was performed using IBM SPSS version 26.

**Results:** On multivariate Cox regression analysis, independent predictors of survival were use of tocilizumab (HR 0.621, 95% CI 0.427-0.903, P 0.013) and higher oxygen saturation.

**Conclusion:** Tocilizumab improved survival in severe COVID-19 pneumonia with persistent hypoxia

**Background**

In December 2019, a newly discovered corona virus, SARS-CoV-2 caused the novel corona virus disease (COVID-19), that spread rapidly to become a pandemic. Though around 80% patients have a mild course and overall mortality is 2-3% only, around 20% need hospitalization (14% have severe disease and 5% are critical)\(^2\). Mortality is high in those with severe acute lung injury. With absence of specific antiviral drugs, treatment is essentially empirical, supportive and symptomatic, with

- antiviral - Lopinavir/ Ritonavir\(^3\), Remdesivir\(^4\), Favipiravir, Oseltamavir, Interferons, Ivermectin\(^5\) (in vitro reduction in viral load)
- Convalescent plasma with passive antiviral antibodies transfer,
- drugs to reduce virus induced inflammatory response including Methyl Prednisolone and IL-6 blockade with Tocilizumab\(^6,7,8,9\), JAK-inhibitors\(^10\)
- conventional or Low Molecular Weight Heparin (LMWH) for virus induced coagulopathy\(^11,12\)
- Hydroxychloroquin and Azithromycin
• supportive – Oxygen therapy/ high flow nasal cannula, non-invasive ventilation, mechanical ventilator, extracorporeal membrane oxygenation, antibiotics (to treat secondary infection), inotropic support and renal replacement.

Autopsy studies from deaths due to corona virus infection suggested that aberrant host immune response results in a lethal inflammatory cytokine storm.\textsuperscript{13} Increased alveolar exudates caused by aberrant host immune response and inflammatory cytokine storm probably impedes alveolar gas exchange and contributes to the mortality of severe COVID-19 patients. IL-6 is one of the most important cytokines involved in COVID-19 cytokine storm. Therefore tocilizumab, a humanized monoclonal antibody against IL-6 receptor (IL-6R) is investigated in treatment of seriously ill COVID-19 patients with cytokine storm. Untreated cytokine storm can progress from respiratory failure, to cardiovascular collapse, multiorgan dysfunction, and death.

**Methods**

Study design and participants: This is a retrospective, observational study done at a single tertiary care center in Mumbai, India. The study population included adults of age more than 18 years with a positive nasopharyngeal swab for COVID-19 by RT-PCR, admitted from 31\textsuperscript{st} March-5\textsuperscript{th} July 2020.

Inclusion criteria were:

• persistent hypoxia (defined as saturation 94\% or less on supplemental Oxygen of 15 L per minute through non-rebreathing mask or PaO2/FiO2 ratio of less than 200),
• bilateral pulmonary infiltrates on chest x-ray and
• raised inflammatory markers (C-Reactive Protein, Lactose Dehydrogenase, Ferritin)

Tocilizumab was available to us (free through the Municipal Corporation of Greater Mumbai) from 13\textsuperscript{th} May onwards and was used in patients satisfying inclusion criteria from 13\textsuperscript{th} May to 5\textsuperscript{th} July. Although all three inclusion criteria were mandatory in tocilizumab group, in the historic control group the only two mandatory inclusion criteria applied were persistent hypoxia as defined above and presence of bilateral alveolar shadows. High C-reactive Protein could not be applied as inclusion criterion in the historic control group due to non availability of this test in our institute at that time, with prevalent financial constraints at that time.

Exclusion Criteria were:

• altered sensorium
• hypotension requiring multiple inotropic agents or multisystem organ failure (MSOF)
• patients suffering from terminal malignancy
• cardiomyopathy with ejection fraction less than 20%

Clinical features, co-morbidities, laboratory investigations and treatment details of all patients satisfying inclusion criteria were recorded. We have follow up of 55 days after last patient enrolment. Historic control group consisted of patients with COVID-19 infection satisfying inclusion criteria, from 31st March to 12th May (i.e, from first COVID-19 admission to our hospital till tocilizumab became available). Their data was obtained from indoor papers medical records. The study was approved by the Institutional Ethical Committee. Written consent for compassionate use of tocilizumab was obtained from patient or relative, and a consent waiver was permitted by institutional ethics committee for this retrospective study.

Procedures:

All patients received standard treatment consisting of antibiotics (Piperacilin-Tzobactum or Meropenem/Vancomycin in view of critical condition), hydroxychloroquine 400 mg once daily, ivermectin 12 mg once daily, oseltamivir 75 mg twice daily, low molecular weight heparin 1 mg/ kg subcutaneously once daily (twice daily if D-dimer >3000 ng/mL), methylprednisolone 125-500 mg intravenously once daily, and other supportive care as needed (Oxygen through non-rebreathing mask, High Flow Nasal Canula, Noninvasive or invasive ventilator support, inotropic support, renal replacement therapy). In addition to standard treatment, tocilizumab group received single intravenous dose of 400mg tocilizumab.

Outcomes: Primary outcome was death or recovery.

Statistical analysis: Comparison of the characteristics of the patients who received tocilizumab versus the control group, and comparison of characteristics of patients who survived versus those who died was performed. For comparison of categorical data, chi square test was used while for ordinal or continuous data, independent samples Mann Whitney U test was used. A p value of less than 0.05 was considered as significant.

Univariate and multivariate Cox regression analysis and logistic regression were performed for identifying predictors of survival. Log rank test was used to compare survival between patients who received tocilizumab versus the control group. Survival time was calculated from the date of giving tocilizumab to avoid immortal time bias. Statistical analysis was performed using IBM SPSS version 26.

Results

From 31st March to 5th July 2020, a total of 2183 COVID-19 patients were admitted under Medicine department. Three hundred and ninety seven had persistent hypoxia (defined as saturation 94% or less on supplemental Oxygen of 15 L per minute through non-rebreathing mask or PaO2/FiO2 ratio of less than 200); of them 128 died within 24 hours of admission and were not included in the study. A total of 269
patients with persistent hypoxia were included in the study. One fifty one received single intravenous infusion of tocilizumab 400mg and 118 who did not, were historic controls.

Their characteristics are shown in table 1. Tocilizumab group was younger (53 years v/s 55 years), but had lower mean Oxygen saturation of 86 % (82-92%) v/s 91% (88-93%) in the control group. In tocilizumab group 63.6 % had at least one co-morbidity and 36.4% were without any co-morbidity, whereas in the control group 74.6% had at least one co-morbidity and 25.4% were without any comorbidity. Tocilizumab group had more patients with obesity and less proportion of patients with hypertension than the control group.

Non invasive ventilation was used in 56/151 patients from tocilizumab group (15 of them later required invasive ventilation) but in none from control group (as a rule, it was avoided initially due to fear of aerosolization with increased risk to health care workers). Overall, 30 patients required invasive ventilation (22 from tocilizumab group and 8 from control group). Inotropic support was required in 11 patients from tocilizumab group and 7 patients from control group. In tocilizumab group, 79 out of 151 died (52.3 % mortality) and in control group 74 out of 118 died (62.7%). Figure 1 depicts effect of tocilizumab on overall survival. (The median survival in the tocilizumab group was significantly longer than in the control group; 18 days (95% CI: 11.3 to 24.7) versus 9 days (95% CI: 5.7 to 12.3); log rank p 0.007). From tocilizumab group 72 out of 151 patients (47.7%) were discharged, whereas from the control group 44 out of 118 (37.3%) were discharged. Tocilizumab was well tolerated and no adverse drug reactions were noted.

Table 2 shows comparison of the demographic and laboratory parameters in ‘overall’ survived versus non-survived groups (including both control and tocilizumab groups). Those who survived were significantly younger (52 v/s 55 years, p= 0.029) and had significantly higher Oxygen saturation (91% v/s 88%, p= 0.002), lower respiratory rate (30 v/s 36 breaths per min, p=0.001) and lower serum creatinine (1mg/dl v/s 1.3mg/dl, p=0.001). The higher average serum creatinine in the non-survived group probably reflected some degree of hypotension with prerenal element.

Our patients, on the whole, did not have significant leucopenia (white blood cells less than 4000), lymphopenia or thrombocytopenia.

D-dimer level was higher in the 'not-survived' group, ( mean 1411 ng / ml, range of 1000-5000 ng/ ml) than in those who survived ( mean 1000 ng / ml, range of 1000-1927 ng / ml), but the difference was not statistically significant (P 0.079).
Total 38 radiological scans (High Resolution CT chest: 26, CT-Pulmonary Angiography: 9, CT-brain: 3) were done in 28 out of 151 patients receiving Tocilizumab. Of these 28 patients, 21 were not on any form of advanced respiratory support at any time. Seven patients had radiological scans done early in the disease and ultimately required advanced respiratory support (HFNC/ NIV/ ventilator). Only 7 out of 68 patients who were on advanced respiratory support (HFNC/ NIV/ Ventilator) had radiological scans done before getting switched to the same. In the 28 patients with radio-imaging available 11 patients expired and 17 were discharged. The CT severity scores were similar in the two groups (median of 21 versus 24; p value of 0.343). The median CORAD score was also 6 in both groups (p 1.000).

Table 3 depicts univariate and multivariate Cox regression analysis. Data on CRP, SGOT, SGPT, LDH, IL-6, WBC and differential count, platelet count, ferritin and d-dimer was not available in all patients in the control group. Data on respiratory rate was available only for 142 patients and d-dimer data was available for 78 patients. Hence these parameters were not included in the multivariate analysis. On multivariate analysis, ‘older age’ was not detected to be a risk factor for death. Survival was not different in those with or without any co-morbidity.

The independent predictors of survival were use of tocilizumab (HR 0.621, 95% CI 0.427-0.903, P 0.013), higher oxygen saturation (HR 0.969, 95% CI 0.950-0.989, p 0.002) and use of invasive ventilation (HR 2.31, 95% CI: 1.442-3.701, p 0.001) on multivariate analysis.

Table 4 depicts comparison of the characteristics of the patients who survived (N=72) versus those who did not (N=79), in the tocilizumab group. Tocilizumab was administered on 2nd to 5th day of admission (average 3rd day) in both groups. Those who ‘survived’ had higher Oxygen saturation than ‘non-survived group’ (mean 88% with a range of 85-93% v/s mean 85% and range of 79-90%- p=0.014) and were less tachypnic than ‘non-survived group’(respiratory rate 30 v/s 36 breaths per min, p=0.002),at the time of enrolment for tocilizumab. Obesity and raised serum creatinine, on the other hand, had adverse effect on survival, p=0.039 and 0.001 respectively. Blood levels of inflammatory markers were comparable in both groups. D-dimer was higher in those who did not survive than in those who survived, but the difference was not statistically significant. Proportion of patients who required invasive ventilation was significantly more amongst patients who died as compared to those who survived (26.6% versus 1.4%, p 0.001).

Discussion

We found a significant reduction in risk of death in severe COVID-19 pneumonia with persistent hypoxia receiving a single dose of intravenous tocilizumab 400mg, compared with those treated with standard care alone. The hazards of dying in the tocilizumab group were 0.621 times of that in the control group. We reported 47.1% mortality in our first 70 patients of severe COVID-19 pneumonia with persistent
hypoxia treated with tocilizumab till 5th June 2020, compared with 67% mortality in 90 controls (three weeks prior to availability of tocilizumab) with persistent hypoxia due to severe COVID pneumonia. At three weeks follow-up 11 / 151 (15.7%) patients were still hospitalized. Two of them died later, increasing mortality to 50% in tocilizumab group. In a retrospective observational study in COVID 19 patients treated in ICU in New Jersey, Noa et al reported 49% mortality in 210 patients treated with tocilizumab and 61% mortality in 420 patients who did not receive tocilizumab. In present study, 60 out of our 151 patients from tocilizumab group were managed in COVID ICU. Due to non-availability of COVID ICU beds, 15 patients received non-invasive ventilation (NIV) in covid wards, and 7 patients received oxygen through high flow nasal canula (HFNC) in covid wards. Non invasive ventilation was used in 56 patients from tocilizumab group (15 of them later required invasive ventilation) but in none from control group (it was avoided initially due to fear of aerosolization causing increased risk to health care workers). Overall, 30 patients required invasive ventilation (22 from tocilizumab group and 8 from control group. Many investigators, for example Kewan, Nicola have used early Tocilizumab in Covid 19 treatment. Nicola et al used tocilizumab in patients with peripheral Oxygen saturation 93% on room air or PaO2/FiO2 less than 300mm of Hg, and documented reduction in mortality from 50% to 7.7%. With early use of tocilizumab, Nicola et al could reduce risk of death by 94%. Although more than 70% of our admitted patients were hypoxic (Oxygen saturation less than 95% on ambient air) during hospital stay, the limited availability of tocilizumab made it mandatory for us to formulate strict inclusion criteria for tocilizumab administration. These criteria were formulated by consensus of department members and approved by institutional ethics committee. (saturation 94% or less on 15L per min supplemental Oxygen through non-rebreathing mask or PaO2/FiO2 less than 200). Depending upon inclusion criteria for use of tocilizumab in severe Covid19 pneumonia, severity of disease at the time of intervention and primary outcomes various outcomes are reported. Guaraldi et al reported mortality in tocilizumab versus standard care group to be 7% and 20% respectively (P<.0001), with inclusion criteria being respiratory rate more than or equal to 30 per min, Oxygen saturation less than or equal to 93% on room air or PaO2/FiO2 ratio being 300 or less, and bilateral lung infiltrates more than 50% being present within 24 to 48 of admission. Average PaO2/FiO2 ratio in their study was 169 in tocilizumab group as against 277 in standard care group. They also reported the effect of tocilizumab was at least two times higher in people with a baseline PaO2/FiO2 ratio of less than 150 mm Hg, implying that the benefit of tocilizumab could be greater in patients with a greater risk of death or mechanical ventilation. Rossotti et al reported tocilizumab use to be associated with a better overall survival (HR 0.499 [95% CI 0.262-0.952], p=0.035) as compared to control, their inclusion criteria being respiratory rate more than or equal to 30 per min, Oxygen saturation less than or equal to 93% on room air or PaO2/FiO2 ratio being 300 or less. In STOP-COVID trial (large multicenter observational comparative study from USA, in ICU admitted Covid-19 patients receiving tolicizumab within 48 hours of ICU admission versus non-tocilizumab cohort, with 419 and 3492 patients respectively after inverse probability weighting to match baseline characteristics and severity of illness, retrospectively analyzed), Gupta et al, reported 28.9% mortality in those treated with tocilizumab and 40.6% in not treated with tocilizumab. During a median follow-up of 27 days, patients treated with tocilizumab were reported to have a lower risk of death compared with those not treated with...
tocilizumab (HR, 0.71; 95%CI, 0.56-0.92), and on stratification as per severity of hypoxaemia as PaO2/FiO2 ratio on ICU admission (HRs, 0.88 [95% CI, 0.58-1.35] for \( \geq 200 \) mm Hg or no mechanical ventilation and 0.59 [95% CI, 0.43-0.81] for <200 mmHg and mechanical ventilation. The recently published Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial\textsuperscript{18} found that dexamethasone reduces mortality in hospitalized patients with COVID-19. The beneficial effect of dexamethasone was particularly pronounced in patients receiving invasive mechanical ventilation. These early data suggest that medications targeting dysregulated inflammation may be a promising therapeutic strategy among critically ill patients with COVID-19. But in published randomized control trials on tocilizumab in Covid19, the effect of tocilizumab on mortality are discordant with the results of observational studies. Possible reasons could be study design, different study population, severity of illness and timing of administration of tocilizumab.

So far 5 RCTs are completed\textsuperscript{19,20,21,22}, four of them are published and 1 press release\textsuperscript{23} given by investigators. In BACC (randomized, double-blind, placebo-controlled) trial\textsuperscript{19}, 16% patients did not require supplemental O2, 80% required less than 6L per min O2. Though average saturation and PaO2/FiO2 ratio is not mentioned, over 90% patients had mild disease severity. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; \( P=0.64 \)). Authors have not ruled out possibility of some benefit or harm due to wide CI, though tocilizumab was not effective for preventing intubation or death. In the sample size calculations for this trial, the authors assumed an event rate for the primary outcome of 30% in the placebo group and 15% in the tocilizumab group. However, only 27 patients (11.2%) had a primary-outcome event (19 [7.8%] were intubated and 8 [3.3%] died without having been intubated). This represents an event rate that was lower than anticipated for both groups, which is likely to have limited the ability to discern a treatment effect.\textsuperscript{24}

In CORIMUNO-TOCI-19 (open label RCT) by Hermine et al\textsuperscript{20}, patients with PaO2/FiO2 200-300 were included, whereas those from ICU/ on HFNC/NIV/MV (mechanical ventilator) were excluded, on day 14 12% reduction in need for MV or death was reported, but no reduction in death on day 28. In RCT-TCZ-COVID-19 by Salvarani et al\textsuperscript{21} included patients with PaO2/FiO2 200-300, average being 264, with average CRP 8.2, there was no benefit in achieving primary outcome (death/ MV/ PaO2:Fio2<150) with tocilizumab. In this study among the 17 patients reaching one primary endpoint (PaO2/FiO2 <150) in the standard care group, 14 received tocilizumab as a rescue therapy (as per protocol). At 30 days, the incidence of intubation and death was comparable between the 2 groups. One can infer that the early administration of tocilizumab does not provide any significant advantage in reduction of intubation or mortality over a deferred administration at PaO2/FiO2 ratio less than 150mmHg. In COVACTA trial\textsuperscript{22} (randomized, double-blind, placebo-controlled), which reported no mortality benefits on 28 day with tocilizumab, eligibility criteria were broad, viz. patients with saturation less than 94% on room air, which also enrolled 37% patients on MV.

Regarding EMPACTA\textsuperscript{23}, yet to be published, details obtained from clinicaltrials.gov\textsuperscript{25} and press release from Roche\textsuperscript{23}. It included patients with saturation less than 94% at room air. Whereas EMPACTA trial, with
similar inclusion criteria was conducted in minority groups (blacks, Hispanics, Asians), who have higher risk of death, 44% reduction in need for mechanical ventilator or death was reported.

In a meta-analysis by Tleyhej et al\textsuperscript{26} which included 5 completed RCTs (1325 patients) and 18 cohort studies (9850 patients), authors report Cumulative moderate-certainty evidence shows that tocilizumab reduces the risk of mechanical ventilation in hospitalized COVID-19 patients. While RCTs showed that tocilizumab did not reduce short-term mortality, low-certainty evidence from cohort studies suggests an association between tocilizumab and lower mortality. The authors state that the sample size required for an RCT to detect an RR of 0.73 for mortality with tocilizumab (with 80% power and \( \alpha \) 0.05) is 4506 patients (2253 in each arm). The total number of patients in the five RCTs is 772 patients in the tocilizumab group and 553 patients in the control group.

Press release from ongoing REMAP-CAP trial\textsuperscript{27} on 19\textsuperscript{th} November stated tocilizumab was 99 per cent more likely to reduce deaths and time spent in intensive care among critically ill patients with severe COVID-19, compared to patients who did not receive the treatment. REMAP-CAP trial inclusion criteria are patients admitted to ICU with severe pneumonia requiring respiratory support such as high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation and COVID-19 infection confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis). On 25\textsuperscript{th} November, Interim position statement\textsuperscript{28} given by NHS England is, ’until the full data from the REMAP-CAP and RECOVERY trials are available, the off-label use of tocilizumab within critical care should follow the criteria and information described in this interim clinical position. The trial Data and Safety Monitoring Board (DSMB) has determined that it is ethically imperative to withdraw the standard-of-care control arm of the immune modulator domain of the REMAP-CAP trial.’

In the current study, clinical response in terms of reduction in Oxygen requirements and respiratory rate was observed within 24-72 hours of tocilizumab infusion in those who responded. C-reactive Protein improved by day 3 to 4. Amongst patients who received tocilizumab, D-dimer levels were higher in ‘non-survived’ group than in ‘survived’ group. Although this difference was not statistically significant, suspicion of terminal pulmonary thromboembolic event was high on clinical grounds in the non-survived group. Zhou et al\textsuperscript{29} reported D-dimer more than 1000 nanogram/ml to be a risk factor for mortality. A Chinese group\textsuperscript{30} and BACC supplementary data\textsuperscript{19} have reported that coagulation abnormalities probably did not improve with tocilizumab. Our clinical impression is that patients in whom clinical improvement in terms of reduced Oxygen requirement did not occur had either extensive lung involvement or high D-dimer or pulmonary thrombi on CT-Pulmonary angiography (imaging could not be performed in all patients due to logistics issues in patients on High Flow Nasal Canula or on non-invasive or mechanical ventilators). In 26 patients HRCT chest could be performed, all had CO-RAD score\textsuperscript{31} 6 (1 lowest to 6 highest suspicion) and average CT-severity score\textsuperscript{32} was 21 out of 25. A study from Wuhan\textsuperscript{33} reported maximum CT score higher than 11 was associated with development of severe illness. CT-pulmonary angiography was performed in 9 patients, and documented pulmonary thrombi in 3 patients. CT-brain
was performed in 3 patients and documented brain infarcts in all. One patient with pulmonary thrombus developed two large infarcts in brain despite full dose heparin and streptokinase for pulmonary thrombus. Radiological imaging was not possible in more severely affected patients due to them being on advanced respiratory support.

The possibility of secondary infection due to immunosuppressants (steroids and tocilizumab), contributing to morbidity, also has to be considered in both Tocilizumab and control groups, though higher antibiotics like Piperacillin Tazobactum or Meropenem / Vancomycin were used in all critically ill patients. Procalcitonin levels could not be done due to cost constraints. Presence or absence of any co-morbidity did not affect primary outcome in the current study.

**Conclusion**

Use of tocilizumab confers a significant survival benefit in COVID19 patients with persistent hypoxia despite optimal supportive care.

One of the limitations of this study was that tocilizumab group was overall younger, but this factor was likely to have been offset by lower average Oxygen saturation level in tocilizumab group, though propensity matching was not done.

These preliminary results are encouraging. Randomised controlled trials on use of tocilizumab as rescue therapy in patients of severe COVID-19 pneumonia with hypoxia (PaO2/FiO2 less than 200) due to hyperinflammatory state, are warranted.

**Abbreviations**

1. COVID 19 : Corona Virus Disease 2019
2. IL-6 : Interleukin 6
3. NIV: Non-invasive ventilation
4. HFNC: High Flow nasal canula
5. MV: Mechanical ventilator
6. JAK: Janus kinase
7. RT-PCR: Real time polymerase chain reaction
8. CRP: C-reactive protein
9. SGOT: Serum glutamic-oxaloacetic transaminase.
10. SGPT: Serum glutamic-pyruvic transaminase
11. LDH: Lactose dehydrogenase
12. WBC: White blood Corpuscle
13. CO-RADS: Coronavirus disease 2019 (COVID-19) Reporting and Data System
14. CTPA: Computerised tomography pulmonary angiography
15. HRCT: High resolution computerised tomography

Declarations

- **Ethics approval and consent to participate:** We confirm that our study was submitted to and approved by our institutional ethics committee.

Full name of the Ethics committee- Institutional Ethics Committee Human Research, Lokmanya Tilak Municipal Medical College and General Hospital, Registration Number-ECR/266/Lokmanya/Inst/MH/2013RR-16

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- **Consent to publish:** Not Applicable

- **Availability of data and materials:** raw data available upon reasonable request from the corresponding author.

- **Competing interests:** Authors have 'No competing interests’ to declare

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Tables
Table 1
Comparison of the characteristics of the patients who received tocilizumab versus those who did not.

| Variable                  | Tocilizumab (n = 151) | Control (n = 118) | P value |
|---------------------------|------------------------|-------------------|---------|
| Age                       | 53 (44–60)             | 55 (47–64)        | 0.007   |
| Male sex                  | 107 (70.9)             | 69 (58.5)         | 0.034   |
| Hypertension              | 40 (26.5)              | 53 (44.9)         | 0.002   |
| Diabetes                  | 78 (51.7)              | 59 (50)           | 0.788   |
| Obesity                   | 14 (9.3)               | 0 (0)             | 0.001   |
| Other comorbidities       | 5 (3.3)                | 13 (11)           | 0.012   |
| Number of comorbidities   | 1 (0–1)                | 1 (1–2)           | 0.031   |
| No comorbidities          | 55 (36.4)              | 28 (23.7)         | 0.035   |
| Category*                 | 125 (82.8)             | 108 (91.5)        | 0.036   |
| E                         | 26 (17.2)              | 10 (8.5)          |         |
| F                         |                       |                   |         |
| Oxygen saturation         | 86 (82–92)             | 91 (88–93)        | 0.001   |
| Respiratory rate          | 34 (30–40)             | 30 (27–38)        | 0.137   |
| Serum creatinine          | 1 (1–1.9)              | 1.3 (1–1.7)       | 0.002   |
| Non-invasive ventilation  | 56 (37.1)              | 0 (0)             | 0.001   |
| Invasive ventilation      | 22 (14.6)              | 8 (6.8)           | 0.044   |
| Deaths                    | 79 (52.3)              | 74 (62.7)         | 0.088   |

*Revised guidelines on clinical management of COVID-19. Ministry of health & family welfare, directorate general of health services, government of India, (2020). https://www.mohfw.gov.in/pdf/Revised National Clinical Management Guideline for COVID1931032020.pdf
Table 2
Comparison of the characteristics of the patients who survived versus those who did not (both tocilizumab and control groups)

| Variable                  | Survived (n = 116) | Died (n = 153) | P value |
|---------------------------|--------------------|----------------|---------|
| Age                       | 52 (44–60)         | 55 (47–62)     | 0.029   |
| Male sex                  | 71 (61.2)          | 105 (68.6)     | 0.205   |
| Hypertension              | 37 (31.9)          | 56 (36.6)      | 0.422   |
| Diabetes                  | 55 (47.4)          | 82 (53.6)      | 0.315   |
| Obesity                   | 3 (2.6)            | 11 (7.2)       | 0.092   |
| Other comorbidities       | 8 (6.9)            | 10 (6.5)       | 0.907   |
| Number of comorbidities   | 1 (0–1)            | 1 (0–2)        | 0.074   |
| Category                  | 105 (90.5)         | 128 (83.7)     | 0.10    |
| E                         | 11 (9.5)           | 25 (16.3)      |         |
| F                         |                    |                |         |
| Oxygen saturation         | 91 (86–93)         | 88 (83–92)     | 0.002   |
| CRP                       | 97.5 (63.5–159)    | 90 (56–136)    | 0.264   |
| Respiratory rate          | 30 (30–36)         | 36 (30–40)     | 0.001   |
| Serum Creatinine          | 1 (1–1.2)          | 1.3 (1–2)      | 0.001   |
| SGOT                      | 49 (37–75)         | 57 (42–72)     | 0.169   |
| SGPT                      | 40 (30–58)         | 44 (28–68)     | 0.977   |
| LDH                       | 666 (275–990)      | 978 (369–2000) | 1.000   |
| Ferritin                  | 437 (293–947)      | 690 (369–1257) | 0.364   |
| D-dimer                   | 1000 (1000–1927)   | 1411 (1000–5000) | 0.079  |
| IL-6                      | 455 (75–984)       | Not available  |         |
| WBC counts (x10^9/L)      | 8.9 (5.85–13.6)    | 8.55 (6.1–12.15) | 0.799 |
| Platelet count (x10^9/L)  | 200 (200–300)      | 200 (200–300)  | 0.314   |
| CT CORAD                  | 6 (6–6)            | 6 (6–6)        | 1.000   |
| CT severity score         | 21 (17–24)         | 24 (21–25)     | 0.343   |
| Thrombosis on CT          | 2 of 8             | 1 of 2         | 0.490   |
| Tocilizumab               | 72 (62.1)          | 79 (51.6)      | 0.088   |
| Variable                   | Survived (n = 116) | Died (n = 153) | P value |
|----------------------------|--------------------|----------------|---------|
| Day of tocilizumab         | 3 (2–6)            | 3 (2–5)        | 0.865   |
| Non-invasive ventilation   | 22 (19)            | 34 (22.2)      | 0.515   |
| Invasive ventilation       | 1 (0.9)            | 29 (19)        | 0.001   |
Table 3
Univariate and multivariate cox regression analysis

| Variable                        | Univariate |          |          | Multivariate |          |          |
|---------------------------------|------------|----------|----------|--------------|----------|----------|
|                                 |            | HR       | 95% CI   | P value      | HR       | 95% CI   | P value |
| Age                             | 1.017      | 1.002–1.032 | 0.029 | 1.012 | 0.994–1.029 | 0.200 |
| Male Sex                        | 0.813      | 0.577–1.145 | 0.237 |          |          |          |
| Hypertension                    | 0.887      | 0.638–1.233 | 0.476 |          |          |          |
| Diabetes                        | 0.983      | 0.714–1.353 | 0.916 |          |          |          |
| Obesity                         | 0.805      | 0.435–1.489 | 0.489 |          |          |          |
| Other comorbidities             | 0.926      | 0.487–1.761 | 0.815 |          |          |          |
| Number of comorbidities         | 1.090      | 0.903–1.315 | 0.371 |          |          |          |
| Oxygen saturation               | 0.979      | 0.962–0.996 | 0.017 | 0.969 | 0.950–0.989 | 0.002 |
| CRP                             | 0.999      | 0.996–1.002 | 0.379 |          |          |          |
| Creatinine                      | 1.157      | 1.031–1.298 | 0.013 | 1.123 | 0.995–1.267 | 0.061 |
| Respiratory rate                | 1.045      | 1.006–1.084 | 0.023 |          |          |          |
| LDH                             | 1.000      | 0.997–1.003 | 0.880 |          |          |          |
| Ferritin                        | 1.000      | 1.000–1.001 | 0.626 |          |          |          |
| D-dimer                         | 1.000      | 1.000–1.000 | 0.043 |          |          |          |
| WBC counts                      | 1.000      | 1.000–1.000 | 0.875 |          |          |          |
| Tocilizumab                     | 0.655      | 0.476–0.901 | 0.009 | 0.621 | 0.427–0.903 | 0.013 |
| CT severity score               | 1.084      | 0.810–1.449 | 0.588 |          |          |          |
| Thrombosis                      | 2.160      | 0.135–34.608 | 0.586 |          |          |          |
| Non-invasive ventilation        | 0.770      | 0.525–1.131 | 0.183 |          |          |          |
| Invasive ventilation            | 2.028      | 1.349–3.049 | 0.001 | 2.31   | 1.442–3.701 | 0.001 |

Data on respiratory rate was available only for 142 patients while d-dimer was available for 78 patients. Hence these parameters were not included in the multivariate analysis.
Table 4
Comparison of the characteristics of the patients receiving tocilizumab who survived versus those who did not

| Variable                        | Survived (n = 72) | Died (n = 79) | P value |
|---------------------------------|-------------------|---------------|---------|
| Age                             | 52 (42–59)        | 55 (46–60)    | 0.105   |
| Male sex                        | 48 (66.7)         | 59 (74.7)     | 0.279   |
| Hypertension                    | 19 (26.4)         | 21 (26.6)     | 0.979   |
| Diabetes                        | 33 (45.8)         | 45 (57)       | 0.172   |
| Obesity                         | 3 (4.2)           | 11 (13.9)     | 0.039   |
| Other comorbidities             | 2 (2.8)           | 3 (3.8)       | 0.727   |
| Number of comorbidities         | 1 (0–1)           | 1 (0–2)       | 0.082   |
| Category                        | 63 (87.5)         | 62 (78.5)     | 0.143   |
| E                               | 9 (12.5)          | 17 (21.5)     |         |
| F                               |                   |               |         |
| Oxygen saturation               | 88 (85–93)        | 85 (79–90)    | 0.014   |
| CRP                             | 97.5 (63.5–159)   | 90 (56–136)   | 0.264   |
| Respiratory rate                | 30 (30–36)        | 36 (30–40)    | 0.002   |
| Serum Creatinine                | 1 (1–1)           | 1 (1–2)       | 0.001   |
| SGOT                            | 49 (37–75)        | 57 (42–72)    | 0.169   |
| SGPT                            | 40 (30–58)        | 44 (28–68)    | 0.977   |
| LDH                             | 701 (515–988)     | 608 (462–753) | 1.000   |
| Ferritin                        | 437 (293–947)     | 978 (369–2000)| 0.364   |
| D-dimer                         | 1000 (1000–1927)  | 1411 (1000–5000) | 0.079 |
| IL-6                            | 455 (75–984)      | Not available |         |
| WBC counts (x10^9/L)            | 8.9 (5.85–13.6)   | 8.4 (6.1–12.0) | 0.799   |
| Neutrophil percentage           | 72 (65–78)        | 72 (70–75)    | 1.000   |
| Lymphocyte percentage           | 25 (17–29)        | 23 (10–27)    | 0.469   |
| Platelet count (x10^9/L)        | 200 (200–300)     | 200 (200–300) | 0.314   |
| Day of tocilizumab              | 3 (2–6)           | 3 (2–5)       | 0.865   |
| Non-invasive ventilation        | 22 (30.6)         | 34 (43)       | 0.113   |
| Variable       | Survived (n = 72) | Died (n = 79) | P value |
|---------------|------------------|---------------|---------|
| Invasive ventilation | 1 (1.4)          | 21 (26.6)     | 0.001   |

**Figures**

**Figure 1**

Survival analysis show the effect of tocilizumab on survival. (The median survival in the tocilizumab group was significantly longer than in the control group; 18 days (95% CI: 11.3 to 24.7) versus 9 days (95% CI: 5.7 to 12.3); log rank p 0.007)