Tocilizumab fails survival benefit in severe Covid-19 – a retrospective cohort study

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Research Article

Keywords: Coronavirus Disease, Experimental therapy, IL-6 inhibitor, Pulse steroid

Posted Date: August 16th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-820144/v1>

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Abstract

Background

Anti IL-6 monoclonal antibody Tocilizumab has produced mixed results in clinical trials for effectiveness against COVID-19. We conducted a retrospective cohort study to compare outcomes at 28 days of a cohort of patients with severe Covid-19 treated with Tocilizumab and standard care, with those receiving standard care only.

Methods

In this record based retrospective cohort study, patients hospitalized with Covid-19 were classified into non-severe and severe disease as per institutional protocol. One cohort received Tocilizumab with standard care and the second cohort received only standard care. Few patients also received high dose steroids as 'pulse' steroids on initial clinical deterioration. Data was collected for the treatment given including oxygen interface, steroids, antimicrobials, duration of hospital stay in survivors, requirement of mechanical ventilation and day of intubation from symptom onset.

Results

There was statistically significant mortality in Tocilizumab cohort as compared to standard care alone (HR 2.43, 95%CI 1.54–3.89). The need for mechanical ventilation was more in Tocilizumab cohort (85% vs 18%, P-value < 0.001). Tocilizumab cohort had delay in day of intubation by a mean of 2.29 days from the day of symptom onset ($p < 0.05$). Pulse steroid administration showed increased all-cause mortality (HR 1.94, 95%CI 1.18–3.20) and risk of mechanical ventilation.

Conclusions

Tocilizumab cohort showed higher mortality and need for mechanical ventilation in our study which contrasts the result of few previous trials. Our study warrants the need for future clinical trials on this subject to ensure better treatment strategies in upcoming Covid-19 waves.

Key Points

In this retrospective cohort, Tocilizumab was compared against standard therapy in non-severe and severe category COVID-19 patients. Results revealed increased mortality with use of Tocilizumab in COVID-19.

Introduction

Coronavirus Disease 2019 (Covid-19) emerged in Wuhan, China on December 2019 and rapidly led to a public health emergency (1). Current treatment guidelines by Infectious Disease Society of America (IDSA) recommend only the use of corticosteroids in severe Covid-19 pneumonia (2). Novel therapies targeting different pathways of viral replication and suppression of immune response are under development to reduce the global health impact of this worldwide pandemic (3).

Covid-19 virus leads to pneumonia, acute respiratory distress syndrome, and finally hypoxemic failure (4). The pathophysiology of the disease highlights development of severe immune response resembling cytokine release syndrome (CRS), leading to increased production of interleukin-6 (IL-6), ferritin, C-reactive protein, and D-dimer among other inflammatory markers (5, 6). Increased levels of IL-6 have been associated with increased viremia, enhanced RNA shedding, and overall increased disease progression and mortality (7).

Tocilizumab is a humanized monoclonal antibody selectively targeting IL-6 receptors, which recently became an option for treatment of CRS (8, 9). Few clinical trials have studied the effect of Tocilizumab on Covid-19 on mortality and clinical progression with mixed results. The RECOVERY trial showed mortality benefit amongst non-ventilated Covid-19 patients but not in those with mechanical ventilation (10). A meta-analysis by Shao et al shows no statistical difference in mortality for patients receiving Tocilizumab vs those with standard care (11). Other clinical trials and some observational studies also provide conflicting data regarding the mortality benefit especially in patients with severe disease (12, 13). The results have also varied amongst different ethnicities and critical care setups (14).

We conducted a retrospective cohort study to compare outcomes at 28days of a cohort of patients with severe Covid-19 treated with Tocilizumab and standard care, with those concomitantly hospitalized and receiving standard care only.

Methods

Study design and setting:

It is a record based retrospective cohort study in a setting of a tertiary care teaching Government hospital (1000 bedded) in Northern India. Patients hospitalized with Covid-19 between June 2020 to March 2021 were eligible for inclusion. Institutional Ethics Committee, AIIMS, Rishikesh approved the study (No. 402/IEC/IM/NF/2020). The data collection was done through the patient's medical e-records on the National Informatics Centre's e-hospital portal being currently used by the hospital.

Study population and patient selection:

All adult (>18 years) hospitalized patients diagnosed with Covid-19 who got admitted within the study period were taken as study population. Covid-19 positivity was defined as having confirmed reverse-transcriptase polymerase chain reaction (RT-PCR) positivity for SARS-Cov-2 on nasopharyngeal swab; or clinical features and chest radiological findings highly suggestive of Covid-19 infection with no other

explainable diagnosis. The patients were classified into non-severe and severe disease as per institutional protocol corresponding to WHO guideline. The patients who were included in other ongoing trials and those who had refused consent for the use of clinical data for research purposes at the time of admission to the hospital were excluded from the study. The two cohorts for the study included one cohort receiving Tocilizumab with standard care and the second comparison cohort receiving only standard care as per institutional protocol. Standard care comprised of paracetamol, oxygen, antiallergy and antibiotics as indicated, anticoagulants, steroids, and other antivirals – remdesivir for selective patients. A few patients also received high dose steroids as 'pulse' steroids (dexamethasone 40mg OD or methylprednisolone 250-500mg OD for 3-5days and then tapered) when high CT severity scores > 24/40 or clinical deterioration after normal dose steroid. A total of 38 patients were included in Tocilizumab cohort and 130 patients were included in non-Tocilizumab cohort.

Study variables:

We collected all the baseline characteristics of relevance including demographics, symptoms, duration of illness, pre-existing co-morbidities, and medications. All the patients were cohorted into non-severe and severe categories. Non-severe cases included patients of mild-moderate severity. Severe cases required oxygen persistently (>24hrs) at the time of hospitalization. Oxygen delivery was through nasal cannula, Hudson face masks, non-rebreather face masks, high flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIV), and invasive mechanical ventilation (IMV).

From the hospital course, data was collected for the treatment given including oxygen interface, steroids, antimicrobials, and experimental therapies. Duration of hospital stay (in days) was calculated in survivors along clinical recovery from symptom onset. Data was also collected for requirement of mechanical ventilation and day of intubation from symptom onset. Lab values studied were D-dimer (mg/l), IL-6 (pg/ml), ferritin (ng/ml), hs-CRP, and CT severity index score (out of 40).

The inclusion criteria for Tocilizumab therapy as per institutional protocol were patients deteriorating after 48 hours of steroid intake with IL-6 levels >40 (or hs-CRP >75). Patients with any other active infection; chronic steroid use; less than 500 neutrophils or less than 50×10^9 platelets; severe hematological, kidney or liver function impairment; or any clinical condition that could predispose to bowel perforation were excluded from administration of the drug. The drug was administered at a dose of 8mg/kg (max dose 800mg per dose) as a single dose or 2 doses in some circumstances when clinical response was not achieved one day after administration. All patients were screened for latent tuberculosis infection via Mantoux test or before the drug administration.

Outcomes:

The primary outcome studied included all-cause mortality within 28 days of hospitalization or till discharge (whichever was longer). Time to clinical recovery (in days) was studied in survivors. The non-severe category patients were analyzed for need of mechanical ventilation (in days) from the day of

symptom onset. Secondary outcomes included association of pulse steroid administration with all-cause mortality and role of biochemical markers like IL-6, ferritin, and D-dimer as predictors of mortality.

Statistical Analysis:

We compared the baseline characteristics of the patients treated with standard care with Tocilizumab and those treated with standard care alone, including age, sex, existing co-morbidities, pulse steroid use, biochemical, and radiological parameters. Categorical variables were expressed as fractions (%) and compared using Chi-squared test across the cohorts. Continuous variables were expressed as mean $\pm$ standard deviation and analyzed using independent t-test between two cohorts and analysis of variance (ANOVA) test for > two cohorts. Relationships were assessed using Pearson or spearman tests depending upon distribution type. Multivariate regressions (logistic for categorical and linear for continuous dependent variables) were used to determine the significance of predictor variables.

We did a survival analysis, following up patients from the date of symptom onset to death. We compared the time to death by treatment cohorts using unweighted Kaplan-Meier curves and uni-variate and multivariate Cox regression analysis. The effect of treatment was studied using an unadjusted and adjusted hazard ratio (HR) with 95% CI. Finally, a forest plot was constructed for multiple variables as role of predictors using HR and 95% confidence intervals.

We considered a two-sided P-value test of less than 0.05 to be statistically significant. The data was entered in the Microsoft EXCEL spreadsheet and analysis was done using IBM Statistical Package for Social Sciences (SPSS) version 26.0 (Chicago, US).

Results

Among patients screened in record sections during the study period (n = 325), 150 patients were excluded from the study (135 were already enrolled in other studies and 15 had missing forms). Out of remaining 175, 42 received at least a single dose of Tocilizumab and 133 did not receive any dose. Four among the Tocilizumab cohort and four among the non-Tocilizumab cohort had majority of variables missing and hence were excluded. Finally, 38 patients in Tocilizumab cohort and 130 patients in non-Tocilizumab cohort were included for per-protocol analysis (Fig. 1).

Out of a total of 168 patients, 126 (75%) were males. The mean age was 54.90 ± 15.09 (SD) years and 41% had either hypertension or diabetes mellitus. A total of 34 patients also received pulse steroids, but the number was more in the Tocilizumab cohort (47.4%) as compared to non-Tocilizumab cohort (12.3%). A total of 20.23% patients belonged to non-severe category which required less than one day oxygen delivery. Majority of the patients required high flow oxygen or mechanical ventilation at the time of admission but the proportion was more in the Tocilizumab cohort (92%) as compared to non-Tocilizumab cohort (76.2%) (Table 1). Overall, more severe patients were included in the Tocilizumab cohort, which can be explained by the hospital indications for use of Tocilizumab in very sick patients with high inflammatory markers.

Table 1
Baseline characteristics of patients of both interventional cohorts (n = 168)

	Tocilizumab with standard care (n = 38)	Standard care (n = 130)	Overall	P- value
Age (Mean $\pm$ SD)	56.62 $\pm$ 14.73	54.20 $\pm$ 15.20	54.90 $\pm$ 15.09	0.349
Sex (%)	28 (73.7%)	98 (75.4%)	126 (75%)	0.833
• Male	10 (26.3%)	32 (24.6%)	42(25%)	
• Female				
Co-morbidities (%)	17 (44.7%)	52 (40%)	69 (41%)	0.520
• Hypertension	13 (34.2%)	56 (43.1%)	69 (41%)	0.331
• Diabetes	5 (13.2%)	25 (19.2%)	30 (17.87%)	0.427
• Heart Disease				
Pulse Steroid Use (%)	18 (47.4%)	16 (12.3%)	34 (20.23%)	< 0.001
Key time Variables – (Mean $\pm$ SD)	26.75 $\pm$ 11.92	20.13 $\pm$ 8.88	20.41 $\pm$ 9.05	0.154
• T to recovery (in survivors)*	17.79 $\pm$ 6.53	15.5 $\pm$ 6.07	17.04 $\pm$ 6.40	0.245
• Day of intubation (from symptom onset)				
Clinical Severity (%)	03 (7.9%)	31 (23.8%)	34 (20.23%)	< 0.05
• Non-severe	35 (92%)	99 (76.2%)	134 (79.76%)	
• Severe				
Lab Values	265 $\pm$ 413	105.94 $\pm$ 262	161 $\pm$ 329	0.041
• IL 6	2.39 $\pm$ 3.23	2.11 $\pm$ 3.07	2.21 $\pm$ 3.11	0.685
• D-dimer	1114 $\pm$ 747	1027.43 $\pm$ 938	1056 $\pm$ 871	0.756
• Ferritin				
Survivors	4 (10%)	90 (69.23%)	94 (47.47%)	< 0.01
Case Fatality rate (%)	89.47%	30.76%	44%	
<i>Note: Data is represented as Mean $\pm$ SD for continuous variables and as total (proportion %) for categorical variables. P-values mentioned are for two tailed independent samples t test. * T = Time to recovery in survivors in days.</i>				

In secondary analysis, Tocilizumab cohort had delay in day of intubation by a mean of 1.21 days from the time of admission and 2.29 days from the day of symptom onset ($p < 0.05$); pulse steroid administration showed increased all-cause mortality and risk of mechanical ventilation compared to cohort without use of pulse steroids ($p < 0.05$); mean values of D-dimer, ferritin, and IL-6 were more in the mortality cohort as compared to discharged alive cohort but statistically significant for ferritin only (Table 2).

Table 2
Various secondary outcomes among different cohorts of all participants

Secondary Outcomes	Tocilizumab plus standard care	Standard care	t- statistic	P-value
Day of intubation from the time of admission	10.21 ± 6.39	9.00 ± 4.47	0.68	0.500
Day of intubation from symptom onset	17.79 ± 6.51	15.50 ± 6.07	1.17	0.245
	Pulse steroid used	Pulse steroid not used	Chi-squared statistic	
All-cause Mortality	24 (70%)	50 (59%)	12.18	< 0.001
Need for mechanical ventilation	10 (55%)	24 (26%)	11.60	0.003
	Death	Discharged alive	t- statistic	
D-dimer (mg/L)	2.58 ± 2.79 (n = 53)	1.71 ± 3.47 (n = 40)	1.326	0.188
Ferritin (ng/mL)	1391.84 ± 1013.53 (n = 25)	637.15 ± 360.04 (n = 20)	3.168	0.03
<i>Note: Data are n (%) or mean ± SD and the P-values refer to differences between overall Tocilizumab and standard of care and were calculated using Chi-square test. Pearson's Chi squared coefficient has been mentioned. Independent samples t-test has been used for t statistic. P-value is 2-tailed with equal variances assumed.</i>				

A Kaplan Meier curve was constructed with a period of duration from day of symptom onset to hospital stay with events as mortality and estimated the cumulative probability of death and compared inbetween Tocilizumab vs non-Tocilizumab cohorts showed the increased cumulative mortality former (Fig. 2A). Similarly, increased cumulative mortality in the pulse steroid cohort was there when compared to non-pulse steroid cohort (Fig. 2B).

The Hazard Ratio (HR) in the forest plot were adjusted for multiple covariates (Fig. 3). Patients treated with Tocilizumab had a higher ratio (HR 2.43, 95% CI 1.54–3.89) while that for pulse steroid therapy too had a statistically significant trend towards increased mortality (HR 1.94 95% CI 1.18–3.12).

Discussion

The retrospective study describes the real-life effectiveness of Tocilizumab in severe Covid-19 patients in an Indian tertiary care hospital compared to patients receiving standard care. At 28 days, the cohort receiving Tocilizumab endured higher mortality as compared to standard care cohort (88% vs 39%, P-value < 0.001) in the severe category. The Tocilizumab cohort also showed higher risk of progression to mechanical ventilation (85% vs 18%, P-value < 0.001).

Since mid 2020s, there have been 7 RCTs comparing Tocilizumab as treatment for Covid-19, the combined result of which does not provide a mortality benefit (HR 0.91, CI 0.72–1.14) (10). The RECOVERY trial showed an overall mortality benefit (HR 0.86, CI 0.71–0.96), but this was not consistent with those requiring mechanical ventilation at randomization (HR 0.94, CI 0.73–1.19) (15). A similar retrospective analysis by Quartuccio et al concluded both increased mortality (HR 14.65, CI 0.81–265.46) and risk of invasive ventilation (HR 3.87, CI 1.76–8.52) in Tocilizumab cohort (16).

Covid-19 disease may be associated with a dysregulated immune response leading to acute respiratory distress syndrome and multi-organ failure (5). A strong correlation between serum IL-6 levels and ongoing hypoxemic respiratory failure have been hypothesized. Increased viral RNA shedding has also been found to be related to increased IL-6 levels. IL-6 promotes TH17 activation leading to neutrophil migration and acts as a pyrogenic for thermostatic response (17). It is also associated with increased IL-1b and TNF activation leading to increased tissue permeability and edema. IL-6 levels may be sub-maximally elevated in Covid-19 and it can't be determined whether they merely represent a marker for severity or can be targeted for therapeutic interventions (18). Thus, IL-6 blockade may act as a double edged sword.

In an RCT by Maryam et al, intravenous methylprednisolone pulse was associated with survival benefit (HR 0.293 95% CI 0.154–0.556, $p < 0.001$) in non-mechanically ventilated hospitalized Covid-19 patients without co-morbidities (19). In the present study, pulse steroids use with dexamethasone was associated with higher mortality (HR 1.94, 95% CI 1.18–3.20, $p < 0.05$). The patients had severe disease and several patients suffered from co-morbidities including diabetes, hypertension, and chronic cardiac disease. As highlighted by previous studies, IL-6 and ferritin levels were higher in those with severe disease and progressing to mortality or invasive ventilation.

The present study has certain limitations. Firstly, the retrospective design fails to rule out unmeasured confounders. Several patients have concomitant steroid administration with varying doses and duration that makes interpretation of results difficult. Secondly, the Tocilizumab cohort includes higher number of patients with clinically severe disease and more patients requiring mechanical ventilation and with pulse steroid administration. Lastly, the adverse events in both cohorts have not been measured that might have brought some clarity in these conflicting results.

To conclude, it is a large study including patients from real-life hospital settings in midst of a pandemic in a developing nation. It highlights the challenges that newer therapies face and the developments needed for us to tackle upcoming waves of Covid-19. Tocilizumab emerged as an attractive weapon against the

virus but the guidelines for its use including the appropriate dosing and timing of administration, may need further revision. The results of this study should guide us to conduct more RCTs especially in developing nations and involving different ethnic cohorts to ascertain the role of novel drugs in the treatment of Covid-19.

Declarations

Contributors

AK and RL contributed to the data collection, their analysis and was involved in manuscript writing. PKP gave the concept, interpreted analysis, critically reviewed the draft, and approved it for publication along with all authors.

Data sharing

It will be made available to others as required upon requesting the corresponding author.

Acknowledgment

Thanks to Covid-19 management team for patient care and helping data collection.

Conflicts of interest

We declare that we have no conflicts of interest.

Funding source

None

References

1. COVID-19 Public Health Emergency of International Concern (PHEIC) Global research and innovation forum [Internet]. [cited 2021 Jul 20]. Available from: [https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-\(pheic\)-global-research-and-innovation-forum](https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(pheic)-global-research-and-innovation-forum)
2. IDSA Guidelines on the Treatment and Management of Patients with COVID-19 [Internet]. [cited 2021 Jul 20]. Available from: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>
3. Majumder J, Minko T. Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19. AAPS J [Internet]. 2021 Jan 1 [cited 2021 Jul 20];23(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/33305456/>
4. M M, H C, A S, S B, N P, A E. COVID-19: Virology, biology and novel laboratory diagnosis. J Gene Med [Internet]. 2021 Feb 1 [cited 2021 Jul 20];23(2). Available from: <https://pubmed.ncbi.nlm.nih.gov/33305456/>

5. J W, M J, X C, LJ M. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. *J Leukoc Biol* [Internet]. 2020 Jul 1 [cited 2021 Jul 20];108(1):17–41. Available from: <https://pubmed.ncbi.nlm.nih.gov/32534467/>
6. Copaescu A, Smibert O, Gibson A, Phillips EJ, Trubiano JA. The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection. *J Allergy Clin Immunol*. 2020 Sep 1;146(3):518–534.e1.
7. BM H, MHS de O, S B, M P, G L. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* [Internet]. 2020 Jun 25 [cited 2021 Jul 20];58(7):1021–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/32286245/>
8. Campochiaro C, Della-Torre E, Cavalli G, Luca G De, Ripa M, Boffini N, et al. Efficacy and safety of Tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med* [Internet]. 2020 Jun 1 [cited 2021 Jul 20];76:43. Available from: </pmc/articles/PMC7242960/>
9. Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, et al. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *Oncologist* [Internet]. 2018 Aug [cited 2021 Jul 20];23(8):943. Available from: </pmc/articles/PMC6156173/>
10. Cohort RC, Horby PW, Pessoa-Amorim G, Peto L, Brightling CE, Sarkar R, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv* [Internet]. 2021 Feb 11 [cited 2021 Jul 20];2021.02.11.21249258. Available from: <https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1>
11. SH L, CC L, HT H, SP C, LC L, PR H. Tocilizumab for severe COVID-19: a systematic review and meta-analysis. *Int J Antimicrob Agents* [Internet]. 2020 Sep 1 [cited 2021 Jul 20];56(3). Available from: <https://pubmed.ncbi.nlm.nih.gov/32712333/>
12. C S, J H, L Y, WG R, B K, JD N, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med* [Internet]. 2021 Jan 7 [cited 2021 Jul 20];384(1):20–30. Available from: <https://pubmed.ncbi.nlm.nih.gov/33332779/>
13. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. <https://doi.org/10.1056/NEJMoa2028836> [Internet]. 2020 Oct 21 [cited 2021 Jul 20];383(24):2333–44. Available from: <https://www.nejm.org/doi/10.1056/NEJMoa2028836>
14. Kopel J, Perisetti A, Roghani A, Aziz M, Gajendran M, Goyal H. Racial and Gender-Based Differences in COVID-19. *Front Public Heal* [Internet]. 2020 Jul 28 [cited 2021 Jul 20];8:418. Available from: </pmc/articles/PMC7399042/>
15. Cohort RC, Horby PW, Pessoa-Amorim G, Peto L, Brightling CE, Sarkar R, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled,

open-label, platform trial. medRxiv [Internet]. 2021 Feb 11 [cited 2021 Jul 21];2021.02.11.21249258. Available from: <https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1>

16. Quartuccio L, Sonaglia A, McGonagle D, Fabris M, Peghin M, Pecori D, et al. Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: Results from a single Italian Centre study on Tocilizumab versus standard of care. J Clin Virol. 2020 Aug 1;129:104444.

17. Jones SA, Hunter CA. Is IL-6 a key cytokine target for therapy in COVID-19? Nat Rev Immunol. 2021 Jun 1;21(6):337–9.

18. Gubernatorova EO, Gorshkova EA, Polinova AI, Drutskaya MS. IL-6: Relevance for immunopathology of SARS-CoV-2. Cytokine Growth Factor Rev. 2020 Jun 1;53:13–24.

19. M E, M A, M S, Z N, A J, S M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J [Internet]. 2020 Dec 1 [cited 2021 Jul 22];56(6). Available from: <https://pubmed.ncbi.nlm.nih.gov/32943404/>

Tables

Figures

Figure 1

The study flow.

*Note: Data is represented as Mean $\pm$ SD for continuous variables and as total (proportion %) for categorical variables. P-values mentioned are for two tailed independent samples t test. * T= Time to recovery in survivors in days.*

Note: Data are n (%) or mean $\pm$ SD and the P-values refer to differences between overall Tocilizumab and standard of care and were calculated using Chi-square test. Pearson's Chi squared coefficient has been mentioned. Independent samples t-test has been used for t statistic. P-value is 2-tailed with equal variances assumed.

Table 1. Baseline characteristics of patients of both interventional cohorts (n=168)

	Tocilizumab standard care (n = 38)	with Standard care (n = 130)	Overall	P- value
Age (Mean $\pm$ SD)	56.62 $\pm$ 14.73	54.20 $\pm$ 15.20	54.90 $\pm$ 15.09	0.349
Sex (%)				
• Male	28 (73.7%)	98 (75.4%)	126 (75%)	0.833
• Female	10 (26.3%)	32 (24.6%)	42(25%)	
Co-morbidities (%)				
• Hypertension	17 (44.7%)	52 (40%)	69 (41%)	0.520
• Diabetes	13 (34.2%)	56 (43.1%)	69 (41%)	0.331
• Heart Disease	5 (13.2%)	25 (19.2%)	30 (17.87%)	0.427
Pulse Steroid Use (%)	18 (47.4%)	16 (12.3%)	34 (20.23%)	<0.001
Key time Variables - (Mean $\pm$ SD)				
• T to recovery (in survivors)*				
• Day of intubation (from symptom onset)	26.75 $\pm$ 11.92	20.13 $\pm$ 8.88	20.41 $\pm$ 9.05	0.154
	17.79 $\pm$ 6.53			0.245
		15.5 $\pm$ 6.07	17.04 $\pm$ 6.40	
Clinical Severity (%)				
• Non-severe	03 (7.9%)	31 (23.8%)	34	<0.05
• Severe	35 (92%)	99 (76.2%)	(20.23%) 134 (79.76%)	
Lab Values				
• IL 6	265 $\pm$ 413		161 $\pm$ 329	0.041

• D-dimer	2.39 ± 3.23	105.94 ± 2.21 ± 3.11	0.685	
• Ferritin	1114 ± 747	262 1056 ± 871	0.756	
		2.11 ± 3.07		
		1027.43 ± 938		
Survivors	4 (10%)	90 (69.23%) 94 (47.47%)	<0.01	
Case Fatality rate (%)	89.47%	30.76% 44%		
Table 2: Various secondary outcomes among different cohorts of all participants				
Secondary Outcomes	Tocilizumab plus standard care	Standard care	t- statistic	P- value
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Day of intubation from symptom onset	17.79 ± 6.51	15.50 ±6.07	1.17	0.245
	Pulse steroid used	Pulse steroid not used	Chi-squared statistic	
All-cause Mortality	24 (70%)	50 (59%)	12.18	<0.001
Need for mechanical ventilation	10 (55%)	24 (26%)	11.60	0.003
	Death	Discharged alive	t- statistic	
D-dimer (mg/L)	2.58 ± 2.79 (n=53)	1.71 ± 3.47 (n=40)	1.326	0.188
Ferritin (ng/mL)	1391.84 ± 1013.53 (n=25)	637.15 ± 360.04 (n=20)	3.168	0.03

Figure 2

Kaplan Meier estimators of survival rate between Tocilizumab and non- Tocilizumab cohorts (A) and pulse steroid therapy and non-pulse steroid cohorts (B).

Figure 3

Forest plot for multivariate analysis. Variables studied listed on the left side and Hazard Ratio (HR) with 95% confidence interval (CI) along with their corresponding P-values on the right side calculated from linear and logistic regression models. HTN – hypertension; DM – diabetes mellitus; TOCI – Tocilizumab; REM – Remdesivir; IL 6 - Interleukin 6; CTSI – Computed Tomography Severity Index for Covid-19.