ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

*International Journal of Medical Science and Advanced Clinical Research (IJMACR)*

*Available Online at:www.ijmacr.com*

*Volume – 7, Issue – 5, September - 2024, Page No. : 29 – 35*

# Effect of Tocilizumab in Covid 19 Patients

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**How to citation this article:** Dr. Krishnakant Bhatt, Dr. Cecil Parmar, Dr. Shwetha Swaminath, Dr. Yashaswi Patel, Dr. Jay Mehta, "Effect of Tocilizumab in Covid 19 Patients", IJMACR- September - 2024, Volume – 7, Issue - 5, P. No. 29 – 35.



**Type of Publication:** Original Research Article

**Conflicts of Interest:** Nil

## Introduction

Covid- 19 pandemic was the greatest turmoil of the 21st century the world has witnessed. The World Health Organization (WHO) officially declared the SARSCoV-2 outbreak a Public Health Emergency of International Concern on January 30, 2020 and a global pandemic on March 11, 2020. Countries were urged by WHO to adopt strict social distancing and quarantine measures to avoid virus spread and to protect public health [1].

The novel corona virus disease has also infiltrated into India; hitherto over 250 000 cases have been reported in the country. With a population of more than 1.3 billion people, India could become the new epicenter of COVID-19. Due to the remarkable population density, poor socioeconomic conditions and health care resources, the World Health Organization (WHO) recently stated that the "future of the pandemic will depend on how India handles it." [2].

Severe and critical cases of COVID-19, which occur respectively in 14% and 5% of patients, lead to acute respiratory distress syndrome (ARDS) due to COVID-19-associated pneumonia. The COVID-19 mortality rates appeared to be associated with the presence of severe ARDS and range widely, from 12 to 78 percent, with an average range of 25 to 50 percent.

The use of Tocilizumab, the IL-6 receptor blocker, is important as it may disrupt the inflammatory cascade at this key disease stage. However, some studies have not

reported a benefit of TCZ use, mostly because of selection bias, failure to reach 80% power or due to very wide confidence intervals that lead to missing of potential benefit. To address this gap, we wished to evaluate the effect of Tocilizumab treatment on mortality in the group of patients with severe (50–75%) and critical (>75%) lung involvement. [3].

**Keywords:** Ventilation, Tocilizumab, Respiratory, global pandemic.

**Aim & Objectives:**

This study was aimed to investigate the effect of Tocilizumab in nCOVID 19 positive patient.

1. Time to Clinical Improvement (TTCI)
2. Average days of Mechanical Ventilation
3. Incidence of Intensive Care Unit (ICU) Stay
4. Duration of ICU Stay
5. Time to Hospital Discharge

**Methodolgy**

Patients diagnosed and admitted in the Covid ward of New Civil Hospital, Surat, with nCovid -19 positive during the period of June 2020 to December 2020 were been analyzed for Tocilizumab therapy initiated, which made a total of 121 study subjects. The Criteria for initiation of Tocilizumab in patients, who were at high-risk for developing cytokine storm, were of the following category:

1. COVID-19 positive
2. High clinical suspicion for cytokine release syndrome supported by:

a. Serum IL-6 ≥3x upper normal limit
b. Ferritin >300 ug/L (or surrogate) with doubling within 24 hours
c. CRP > 100 mg/L with doubling within 24 hours
d. Elevated D-dimer (>1 mg/L).

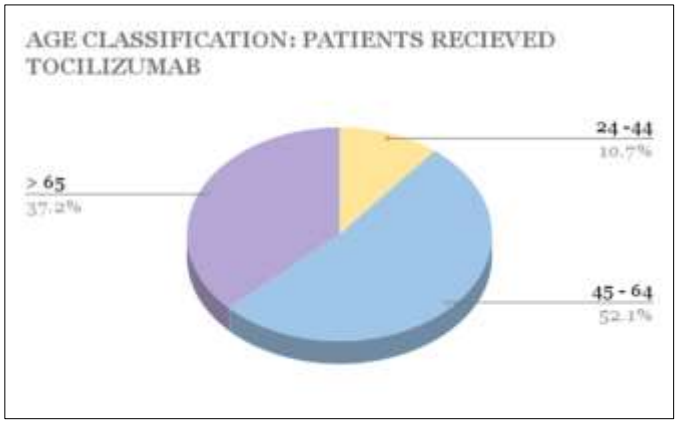
**Exclusion Criteria**

1. Active Tuberculosis
2. Presence of Active Hepatitis B and Hepatitis C
3. Sepsis by other pathogens (definitive)
4. Transaminases 10 times above reference values (relative)
5. Neutropenia (<1000 cell/mm3) (relative)
6. Thrombocytopenia (<50,000 /mm3) (relative)
7. Patients on concomitant immunosuppressants, such as methotrexate or corticosteroids.

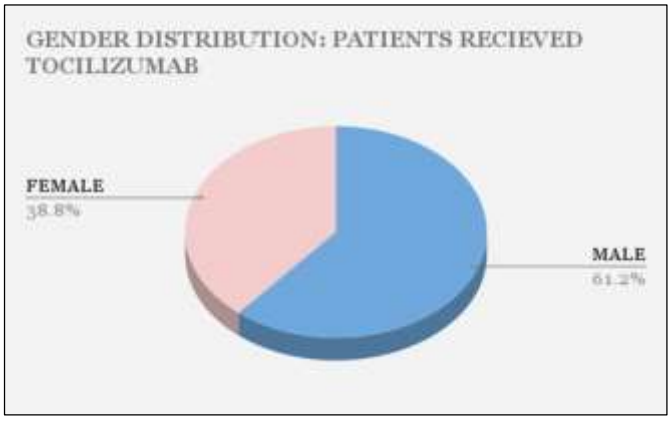
The data analysis was done using MS Excel and the results were obtained.

**Results:**

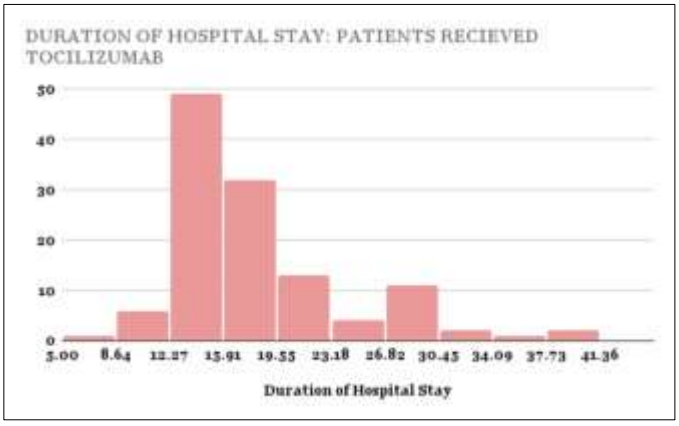
Demographics of Patients Obtained Tocilizumab:




Graph 1: Age Classification of Patients received Tocilizumab




Graph 2: Gender Distribution of Patients who received Tocilizumab

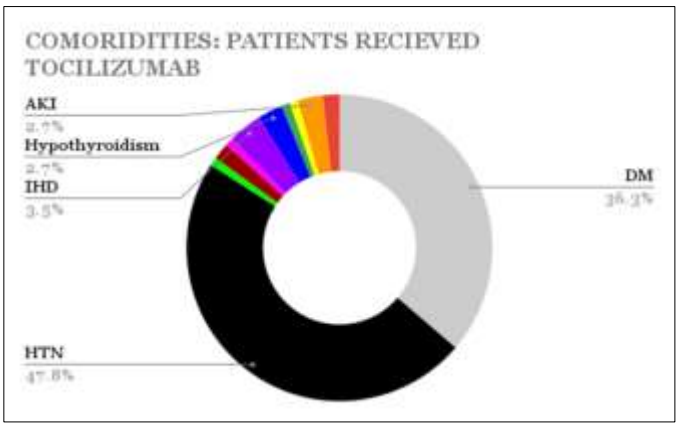



Graph 3: Duration of Hospital Stay of Patients who received Tocilizumab

Minimum No. of Days: 7 Days

Maximum No. of Days: 40 Days

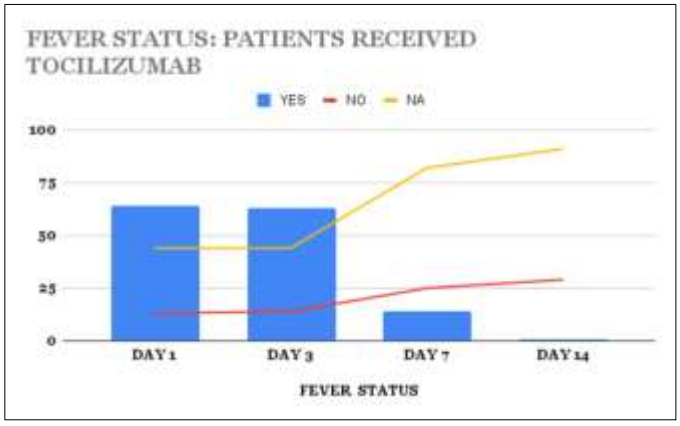
Average Bed Stay: 18.23 ± 5.93 Days



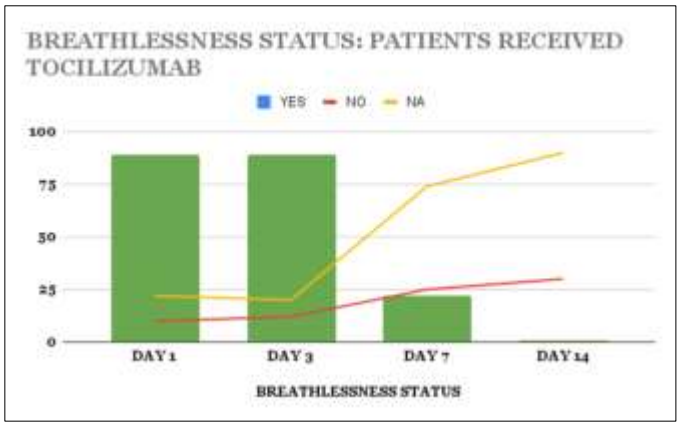

Graph 4: Co morbidities among the patients who received Tocilizumab

| | Systolic Blood Pressure | Diastolic Blood Pressure |
|---|---|---|
| Average | 123.38 | 79.16 |
| Median | 120 | 80 |
| Minimum Value | 100 | 60 |
| Maximum Value | 160 | 100 |

Table 1: Average Value Median Minimum Value & Maximum Value of Systolic and Diastolic Blood Pressure.




Graph 5: Fever Status of Patients Received Tocilizumab




Graph 6: Breathlessness Status of Patients Received Tocilizumab

| C Reactive Protein | Average | Median | Minimum Value | Maximum Value |
|---|---|---|---|---|
| DAY 1 | 96.09 | 80.4 | 1.9 | 295 |
| DAY 3 | 124.07 | 45.6 | 1.7 | 4930 |
| DAY 7 | 146.67 | 42.6 | 0.6 | 7010 |
| DAY 14 | 59 | 27.6 | 0.2 | 2741 |

Table 2: Average Value Median Minimum Value & Maximum Value of CRP.

| Interleukin - 6 | |
|---|---|
| Average | 257.23 ± 523.42 |
| Median | 68.24 |
| Minimum Value | 3.2 |
| Maximum Value | 3430 |

Table 3: Average Value Median Minimum Value & Maximum Value of IL-6.

| Ferretin | Average | Median | Minimum Value | Maximum Value |
|---|---|---|---|---|
| Day 1 | 938.18 | 573 | 47.4 | 4254 |
| Day 3 | 936.25 | 582.4 | 34.2 | 4725 |
| Day 7 | 1095.86 | 585 | 20.9 | 5943 |
| Day 14 | 988.82 | 482.5 | 71.5 | 4694 |

Table 4: Average Value Median Minimum Value & Maximum Value of Ferretin

| D - Dimer | Average | Median | Minimum Value | Maximum Value |
|---|---|---|---|---|
| Day 1 | 2363.54 | 1309 | 22 | 15240 |
| Day 3 | 2640.48 | 1307.5 | 112 | 14050 |
| Day 7 | 2900.04 | 1478.5 | 123 | 13941 |
| Day 14 | 2769.85 | 1566 | 226 | 14875 |

Table 5: Average Value Median Minimum Value & Maximum Value of D- dimer

| Respiratory Rate | Average | Median | Minimum Value | Maximum Value |
|---|---|---|---|---|
| Day 1 | 23.39 | 22 | 12 | 50 |
| Day 3 | 21.48 | 20 | 15 | 32 |
| Day 7 | 22.20 | 22 | 16 | 36 |
| Day 14 | 23.23 | 22 | 14 | 50 |

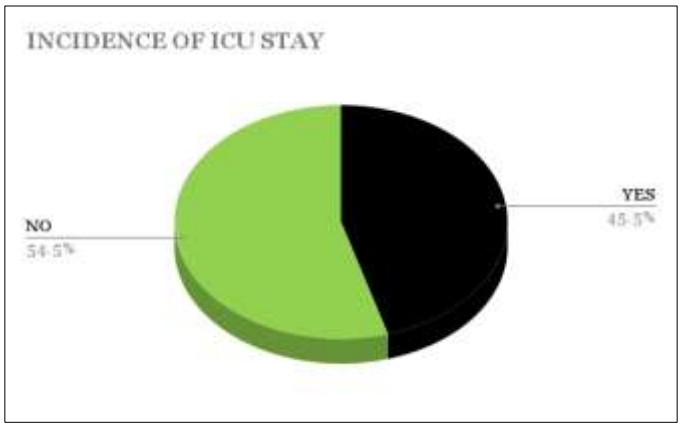
Table 6: Average Value Median Minimum Value & Maximum Value of Respiratory Rate

| Number of days on ventilation | |
|---|---|
| Average | 17.067 ± 6.07 |
| Median | 15 |
| Minimum Value | 1 |
| Maximum Value | 40 |

Table 7: Average Value Median Minimum Value & Maximum Value of No. of Days on Ventilation

| Clinical Improvements Based On $Spo_2$ Levels | | |
|---|---|---|
| DAY I | DAY 14 | |
| 81% on room | 98% on room | Improved |
| 90% on 15L NRBM | 97% on room | Improved |
| 98% with 8L NRBM | 98% on room | Improved |
| 97% on 4L O2 | 96% on room | Improved |
| 100% on 10L O2 | 96% on room | Improved |
| 94% on 5L NRBM | 97% on room | Improved |
| 87% on room | 94% on room | Improved |
| 91% on room | 96% on room | Improved |
| 96% on 10L O2 | 96% on room | Improved |
| 87% on room | 97% on room | Improved |
| 98% on 80% FiO2 | 96% on room | Improved |
| 97% on 15L NRBM | 94% on room | Improved |
| 98% on 15L NRBM | 96% on room | Improved |
| 90% on room | 95% on room | Improved |
| 94% on 15L NRBM | 96% on room | Improved |
| 78% on room | 99% on room | Improved |
| 87% on room | 95% on room | Improved |
| 98% on 15L NRBM | 97% on room | Improved |
| 97% on 5L mask | 98% on room | Improved |
| 89% on room | 98% on room | Improved |
| 87% on room | 99% on room | Improved |

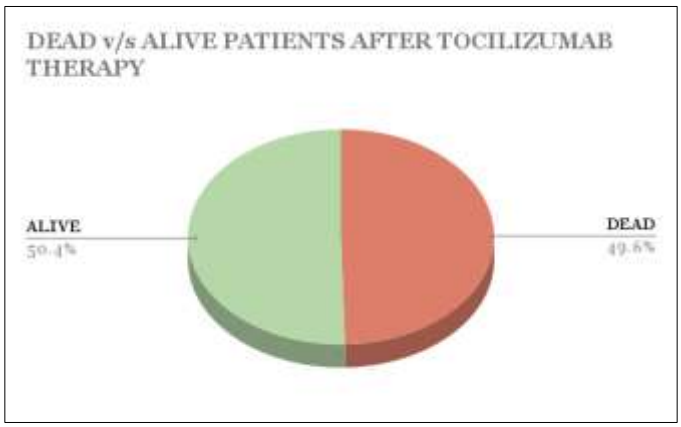
Table 8: Clinical improvements based on $SPO_2$ levels




Graph 7: Incidence of ICU stay

| Number Of Days In ICU | |
|---|---|
| Average | 10.69 ± 6.58 |
| Median | 10 |
| Minimum Value | 1 |
| Maximum Value | 34 |

Table 8: Average Value Median Minimum Value & Maximum Value of No. of Days in ICU




Graph 8: Dead v/s alive patients after Tocilizumab therapy

**Discussion**

Among the 121 nCovid -19 positive patients who have been admitted in the ward, 61.2% were males and 38.8% were females comprised of a majority of 52.1% belonging to the age group of 45 – 54, 37.2% who were > 65 years of age and 10.7% belonged to the age group

of 24-44. There weren't any admission from the age group of 18- 23. Major existing co morbidities among the patients were Hypertension which made a total of 47.8%, Diabetes Mellitus 36.3% and other minorities were composed of Ischemic Heart Disease, Hypothyroidism, Acute Kidney Injury, Chronic Kidney Disease, Tuberculosis, Sickle Cell Anemia, Asthma, Rheumatoid Arthritis, G6 PD Deficiency respectively.

According to a study conducted by S Carlos et.al, among the patients hospitalized with Covid-19 pneumonia, who were treated with Tocilizumab, it has mentioned that Covid-19 may be associated with a deregulated immune response and hyperinflammation, which can lead to or exacerbate acute respiratory distress syndrome and multiorgan failure. Higher levels of interleukin-6 have been positively correlated with cases of critical and severe Covid-19, whereas lower levels of interleukin-6 have been correlated with mild disease, in addition, elevated levels of interleukin-6 have been found to be predictive of the likelihood of mechanical ventilation. Tocilizumab, an anti– interleukin-6 receptor monoclonal antibody, has been approved for the treatment of multiple inflammatory diseases and appeared to improve outcomes in patients with Covid-19 pneumonia in observational studies in the United States and globally. However, randomized trials of Tocilizumab have shown mixed results in patients with varying degrees of Covid-19 disease severity as well as in populations with various background standards of care. [4]

In the current study it has been observed that there was a drastic elevation in the Serum IL-6 which was three times greater than the upper normal limit, Ferritin greater than 300 ug/L (or surrogate) with doubling within 24 hours, CRP greater than 100 mg/L with doubling within 24 hours and Elevated D-dimer (>1 mg/L) which lead to high clinical suspicion for cytokine release syndrome. Tocilizumab therapy was given to the patients who were according to the hospital guidelines which were majorly adopted from Guidance for Treatment of COVID-19 in Hospitalized Adults and Children by University of Michigan, since the initial Tocilizumab treatment recommendation by Covid guidelines India was officially published on May 24, 2021.

According to the Guidance for Treatment of COVID-19 in Hospitalized Adults and Children by University of Michigan, Doses should be rounded to nearest available full vial (80 mg, 200 mg, 400 mg vials). [5]

There was a drastic decline in the fever status, breathlessness status of the patients as well as the minimum value of C - reactive protein, Interleukin -6, Ferretin and D-dimer on the Day 7 of therapy, which can be considered as the Time to Clinical Improvement of the Covid -19 patients. The Average days on mechanical ventilation was 17.067 ± 6.07, median 15, Minimum days on ventilation – 01 and the maximum days on ventilation was 40. On Day 14 there was a prominent improvement in the $SPO_2$ levels on room air, of the patients who were initially under mechanical ventilation or < 90% $SPO_2$. Among the total study subjects 45.5% were shifted to Intensive Care Unit, out of which the average ICU stay was 10.69 ± 6.58 with a minimum stay of one day and maximum stay of 34 days. The average duration of hospital bed stay was 18.23 ± 5.93 days with a minimum of 7 days and maximum of 40 days. The death cases constituted 49.6% of the total study subjects when there was 50.4% recovered patients.

We should know that Tocilizumab is not an anti-viral drug and may only be effective in a group of patients with inflammation and lung damage caused by the coronavirus. Another important point is that excessive

production and activity of Tocilizumab can cause auto-immune diseases and damage body tissues. This drug is very sensitive and can be used in a specific age and certain patients. As a result of review of the published data and based on the mechanism of action of Tocilizumab, we may be able to claim that this drug can be a better or more suitable choice to be used for in patients with higher IL-6 level than normal. Tocilizumab may have a positive effect on improving immune damaging, lung functional injuries and arterial oxygen saturation. Researchers, who had the successful experience of using this drug for treating inflammation lungs diseases, hope it will make effective and promising treatment to improve lung tissue inflammation in patients with fatal COVID-19 virus. However, further accurate clinical trial studies are needed to determine its efficacy in patients with specific characteristics such as age, level of IL-6, and different clinical symptoms. [6]

**Conclusion**

Though the alive to dead ratio of the patients were almost equal in the study, we need to consider the fact that the study subjects were majorly suspected to have cytokine release syndrome, with drastic elevated levels of serum IL-6, Ferritin, CRP and D-dimer prior to Tocilizumab therapy, which had significantly reduced within seven days after therapy initiation. Also the incidence of fever and breathlessness which is an indication of infection has been reduced on the seventh day after therapy. The outcome received can be considered as a valid reason to show that inclusion of Tocilizumab in the therapy had showed improvement in the overall COVID-19 severity.

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