International Journal Dental and Medical Sciences Research
Volume 4, Issue 2, Mar-Apr 2022 pp 115-126 www.ijdmsrjournal.com ISSN: 2582-6018

Tocilizumab In Severe Covid-19 pneumonia - A Single Center Retrospective Observational Cohort Study of 50 patients.

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Submitted: 05-03-2022 Accepted: 16-03-2022

ABSTRACT

BACKGROUND

The number of cases in COVID-19 pandemic is rising rapidly. There has not been a single effective proven medication for COVID-19 disease. Highest mortality has been reported among subjects who develop hyperinflammation. Tocilizumab (TCZ), a monoclonal antibody against interleukin-6 (IL-6), emerged as an alternative treatment for COVID-19 patients with a risk of cytokine storms recently but the safety and efficacy of this drug in patients with severe Covid-19 pneumonia are unclear.

METHODS

Patients hospitalized with severe Covid-19 pneumonia who met with inclusion and exclusion criteria were received standard treatment with one or two doses of Tocilizumab (8 mg per kilogram of body weight intravenously) The primary outcome was peripheral oxygen saturation after 24 hr,3rd day,7th day ,more than 7th day and clinical improvement and various hematological parameters like CBC,LFT,RFT,IL-6 etc.

RESULTS

A total of 50 patients took Tocilizumab treatment. In our study onset of symptoms before admission in hospital was 6.5± 2.79 days whereas Tocilizumab was administered 8.18±3.27 days after onset of symptoms in severe Covid-19 pneumonia .In our study Mean age of presentation of severe Covid pneumonia was 64.28±12.54 years .Most of the patients of severe Covid-19 pneumonia presented in JNUIMSRC were above 60 yrs of age which account for about 70% of total cases . A male preponderance was seen in severe Covid-19 pneumonia with male to female ratio was 4.5:1[82%vs18%] in our cross sectional study . In our study a large number of patients had comorbidities in which DM,HTN,CAD were most common.They account for 56%,52%and 12% respectively. In our study there were highest number of patients belonging to B^+ blood group[36%] while lowest number of patients were of B^-blood group[4%] in severe COVID-19 pneumonia. The Rh negative group comprises 8% while Rh positive constitute 92% of severe Covid-19 pneumonia cases. In our study highest number of patient mortality was seen in B blood group which account for around 40 % which was followed by A blood group mortality which was around 28% .In other words non O blood group mortality was 78 % while O blood group patients shares only 22%. In our study Majority of Patient admitted in JNUIMSRC hospital had fever ,cough,dyspnea as presenting complaints which account for 82%,76% and 72% while headache ,sneezing and diarrhea account for only small number of patients. in our study Oxygen saturation before and after the first Tocilizumab dose was noted in patients with severe COVID-19. This chart shows gradually increasing O_2 saturation after Tocilizumab administration .In our study less oxygen saturation on presentation had increased number of death [51.72%]where as 90% or more O_2 saturation group before Tocilizumab administration had lesser number of death [14.28%]. Clinical improvement after 24 hrs of Tocilizumab administration was more in both group [48.27% and 61.9%] in comparison to earlier. In our study IL-6 level increases after 1-5 days of Tocililizumab injection [**CI=95%,**p value ‹.05, cl -95%] which was significant.Creatinine level slightly increase after Tocilizumab injection but p value was more than .05[**CI=95%,**] which was not significant means this value was by chance.TLC increase after administration of Tocilizumab [p value<.05 , **CI=95%**] which was significant. ALT level decreases after Tocilizumab use [p value ‹.05, **CI=95%**] . AST level decrease after Tocilizumab use [p value ‹.05, **CI=95%**] .

CONCLUSIONS

In hospitalized patients with severe Covid-19 pneumonia Tocilizumab increases peripheral oxygen saturation ,decreases mortality and ventilator requirement. Tocilizumab appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms. Critically ill patients who were not managed by steroid and conventional treatment regime with elevated IL-6, the repeated dose of the TCZ is recommended.

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KEY WORD: Covid-19,Tocilizumab,IL-6,CRS,SPO_2,RTPCR Etc

I. INTRODUCTION

A novel corona virus disease (Severe Acute Respiratory Syndrome- Corona virus 2 [SARS- CoV- 2]), which is now designated coronavirus disease 2019 (COVID- 19) by the World Health Organization (WHO) has become a pandemic.[1]

As of 3rd January 2021 there were 83 million confirmed cases and 1.8 million deaths globally.[1]SARS-CoV-2 first identified in Wuhan, China in late 2019.As at 7th January2021 there had been 10.4 million confirmed cases of COVID- 19 infection in India of which 1.5 lakh(1.45%)have died.[2]

The presentation of COVID- 19 can range from asymptomatic infection to hypoxic respiratory failure.

COVID-19 is a novel emerging infectious disease associated with a complicated pathogenesis;

Although many proinflammatory cytokines are involved in COVID-19 infection interleukin-6 (IL-6) is the most important, although it was also found to be a poor prognostic factor [3,4]

Tocilizumab is a humanised monoclonal antibody that can target both membrane-bound and soluble forms of the IL-6 receptor, and several studies have evaluated its efficacy in the treatment of severe COVID-19. [5,6]

The objective of this analysis was to evaluate the clinical outcome with COVID-19 treated with Tocilizumab in a single medical center.

There are currently no approved treatments for COVID- 19 but there are numerous clinical trials evaluating pharmacologic agents, including antivirals and immunomodulators.

However, no consistent results were reported among these studies comparing Tocilizumab and other treatment regimens for COVID-19. Therefore, this study was conducted to investigate the impact of Tocilizumab on the clinical improvement and to assess the role of Tocilizumab in reducing the risk of invasive mechanical ventilation and death in patients with severe COVID-19 pneumonia who received standard of care treatment.

AIMS

To find out Tocilizumab effect on oxygen saturation($SP0_2$) ,clinical improvement, ,IL-6 level, mortality and other hematological parameter in severe Covid-19 pneumonia.

Objectives

- Age distribution of severe Covid -19 pneumonia
- Sex distribution of severe Covid- 19 pneumonia
- Comorbidities distribution in severe Covid- 19 pneumonia
- Blood group distribution in severe Covid- 19 pneumonia
- Symptoms in severe Covid -19 pneumonia
- Oxygen saturation before and after 1stTocilizumab dose.
- Clinical improvement and mechanical ventilation following Tocilizumab
- Serum IL-6 concentration before and after 1st Tocilizumab dose.
- Various hematological parameters before and after Tocilizumab
- Proportion of patients showing improvement or death following Tocilizumab depending upon number of comorbidities.

II. REVIEW OF LITERATURE

A study in 15 patients by Luo et al[7] showed decreased CRP and IL- 6 levels in patients who received Tocilizumab.

Current guidelines from China state that Tocilizumab may be used for up to two doses in patients with severe COVID– 19.[8]

Following the publication of two small, uncontrolled, retrospective case series from China, there has been considerable interest in Tocilizumab use in patients with COVID–19.[9]

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III. METHODOLOGY

Source of data

Fifty patients (aged ≥18 years) admitted in JNUIMSRC Hospital Jaipur with confirmed severe SARS-CoV-2 infection who were administered Tocilizumab between 25 June and 31 dec 2020. Tocilizumab was administered intravenously to patients who met criteria per hospital and AIIMS protocol. Patients that did not receive Tocilizumab therapy were not evaluated.

Inclusion criteria [10,]

We included symptomatic adult patients (aged ≥18 years) with COVID-19 who met the following criteria:

1-positive result of a Polymerase Chain Reaction (RTPCR) test for SARS-CoV-2 from a pharyngeal and nasopharyngeal swab
2-Respiratory rate >30/min or
3-SPO2 <90% at room air or <94% with oxygen
4-deteriorating clinical condition with worsening of PaO2/FiO2 ratio (more than
25% deterioration from the immediate previous values or
5-IL-6 >5 times
6-worsening trend of inflammatory markers (Ferritin, LDH, CRP)

Exclusion criteria

1-COVID-ve[negative]patients
2-Sepsis
3-Acute diverticulitis
4-Gastrointestinal tract perforation
5-Thrombocytopenia(<100*10^3cells/ul)

Sample size :50 cases
Study subjects :patients who fulfill the inclusion and exclusion criteria.
Study design :retrospective observational cohort study.
Study period :1 year
Statistical analysis :

Continuous Data were summarized as median [interquartile range], mean ± standard deviation and categorical data as number[percentage] and chi-square test to look for statistical significance[p-value]. A $p < 0.05$ was consideredsignificant.TheRsoftware(version-3.6)andwebsite https://www.calculatorsoup.com/legal.php,https://www.socscistatistics.com/tests/ were used for all calculations.

Tocilizumab to severe patient :

Tocilizumab was dosed at 8 mg/kg with a maximum of 800 mg per dose. The treatment protocol allowed for a maximum of two doses of Tocilizumab if patients had no clinical improvement at least 8 hours after the first dose. Tocilizumab was reconstituted in 100 mL of 0.9% sodium chloride solution and administered intravenously over 60 minutes, according to package insert recommendations.[10,11].

Data were collected via chart review at pre- Tocilizumab baseline, and at one to 7 days post- Tocilizumab.

Study outcomes included clinical improvement ,invasive ventilation ,mortality after Tocilizumab in the overall group. Other endpoints included SPO_2 and symptomatic improvement at 24 hours72 hours 7 days, and more than 7 days post- Tocilizumab. IL-6, TLC, N/L ratio,Platelet count,SGPT,SGOT,serum creatinine were evaluated in patients that had documented values at baseline and one to 7 days post- Tocilizumab. Parameters for evaluation included the patient's age, sex, symptoms onset before admission Tocilizumab administration after symptoms onset, use of mechanical ventilation.Comorbidities like DM, systemic HTN,CVA,CAD ,COPD, CKD,CLD ,thyroid disorder etc. noted

Specimen collection :

All patients who were symptomatic nasopharyngeal and oropharyngeal swab were taken .The sample was transported in viral Transport Medium (VTM) tube then series of procedures make corona virus testing using RTPCR test.

IV. RESULT

Mean age of presentation of severe COVID pneumonia was 64.28±12.54 years.

Most of the patients of severe COVID pneumonia presented in JNUIMSRC were above 60 yrs of age which account for about 70% of total cases . Lowest number of cases were below 30 year age group.

Total no of cases were 50 .Males out number the females.

A male preponderance was seen in severe covid pneumonia with male to female ratio was 4.5:1[82%vs18%]in our cross sectional study .

In our study a large number of patients had comorbidities in which DM,HTN,CADwere most common.They account for 56%,52%and 12% respectively.

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CHART 3: COMORBIDITIES IN SEVERE COVID-19 PNEUMONIA

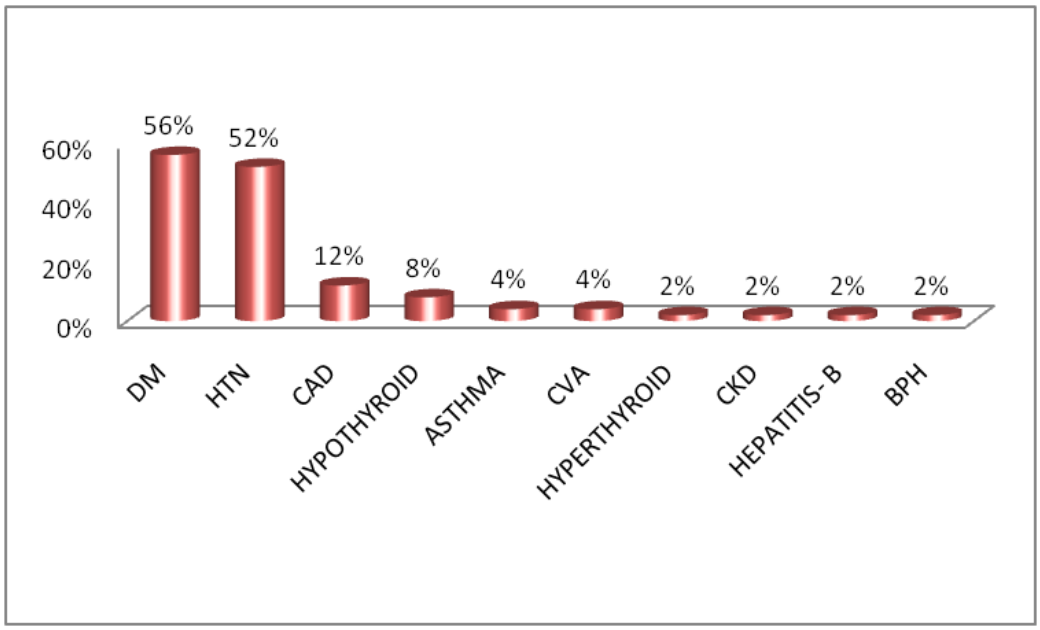

TABLE4: BLOOD GROUP DISTRIBUTION IN SEVERE COVID-19 PNEUMONIA

There were highest number of patient belonging to **B^+ve**blood group[36%] while lowest number of patients were of **B^-ve** blood group in severe COVID-19 pneumonia.
The **Rh^-ve** group comprises 4%while **Rh^+ve** constitute 96% of cases in severe Covid-19 pneumonia .

CHART 4: BLOOD GROUP DISTRIBUTION IN SEVERE COVID-19 PNEUMONIA

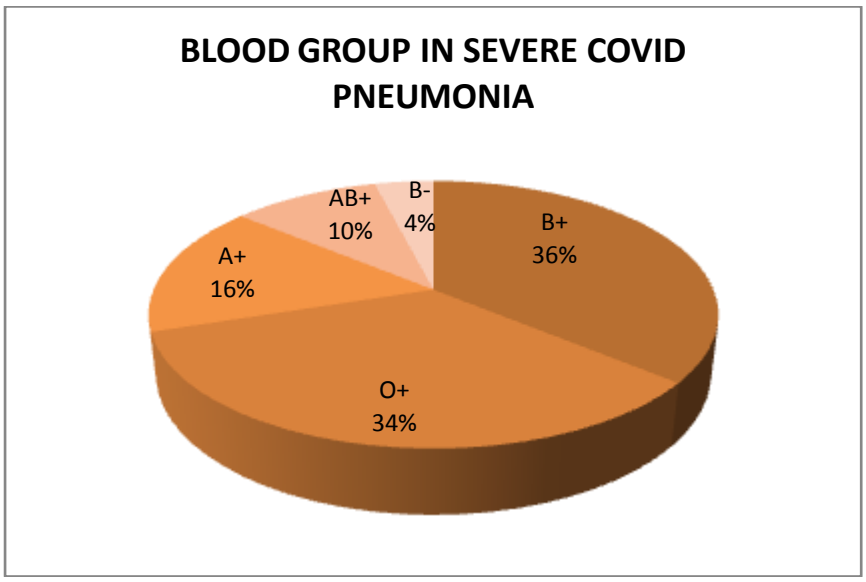

TABLE 5: BLOOD GROUP AND MORTALITY IN SEVERE COVID-19 PNEUMONIA

In our study highest number of patient mortality was seen in **B** blood group which account for around 40 % which was followed by **A** blood group mortality which was around 28% .

In other words non **O** blood group mortality was 78 % while **O** blood group patients shares only 22%.

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We conclude **Rh**-negative blood group type have a protective effect[2%] .Our results add to the growing body of evidence suggesting blood type may play a role in COVID-19.

CHART 5: BLOOD GROUP AND MORTALITY IN SEVERE COVID-19 PNEUMONIA

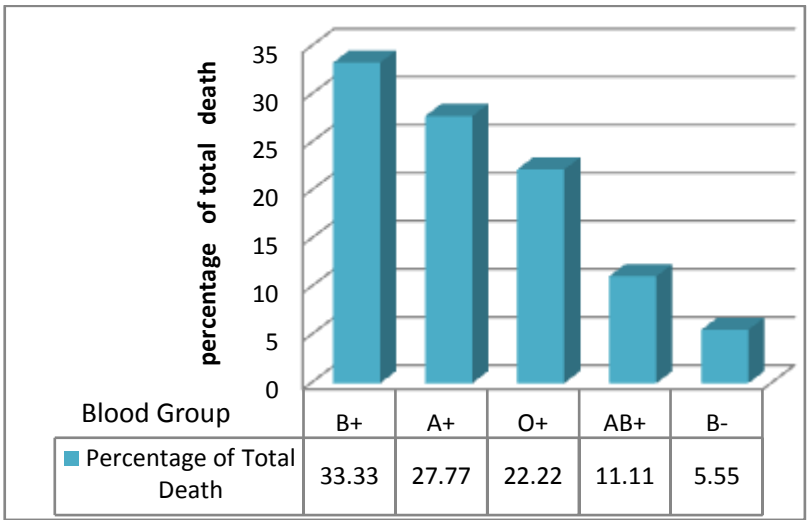

CHART6: BLOOD GROUP AND MORTALITY IN SEVERE COVID-19 PNEUMONIA

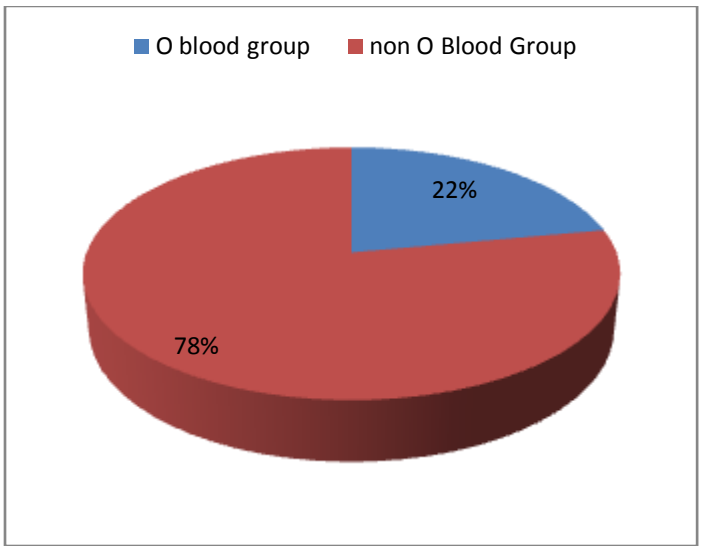

TABLE 6: SYMPTOMS IN SEVERE COVID-19 PNEUMONIA

Majority of Patient admitted in JNUIMSRC hospital had fever ,cough,dyspnea aspresenting complaints which account for 82%,76% and 72% respectively while headache,sneezing and diarrhea account for only small number of patients.

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CHART 7: SYMPTOMS IN SEVERE COVID-19 PNEUMONIA

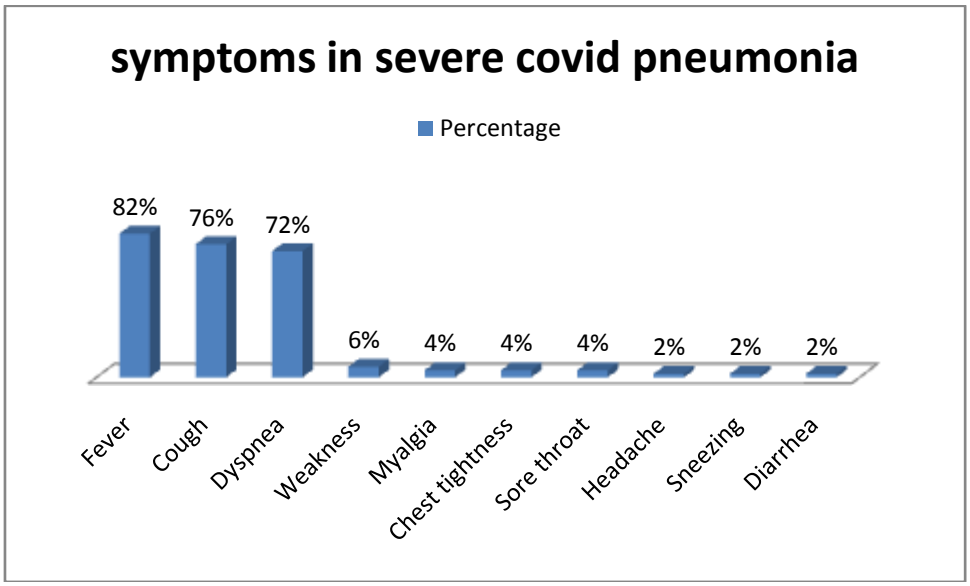
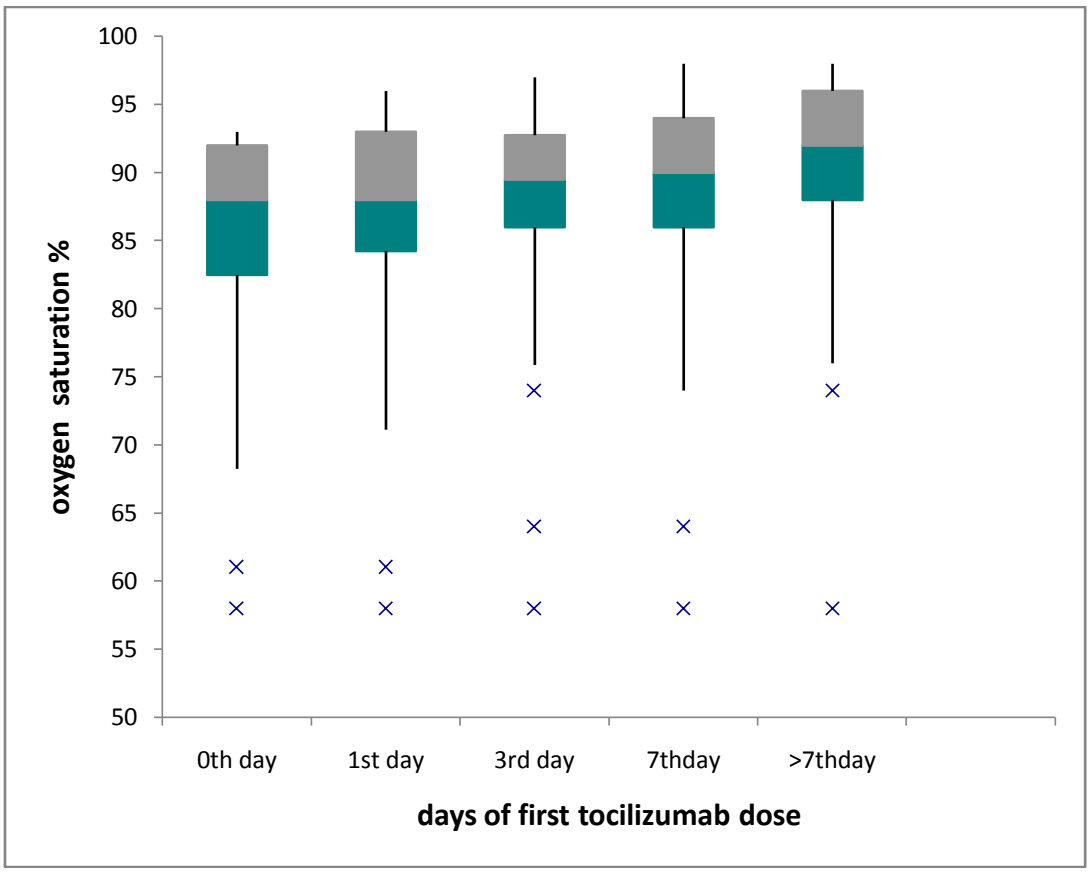


CHART 8: OXYGEN SATURATION BEFORE AND AFTER THE FIRST TOCILIZUMAB DOSE IN PATIENTS WITH SEVERE COVID-19 INFECTION.MIDDLE BAR SHOWS MEDIANS ;UPPER AND LOWER BARS SHOW INTERQUARTILE RANGE .



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This chart shows gradually increasing O_2 saturation after Tocilizumab administration .

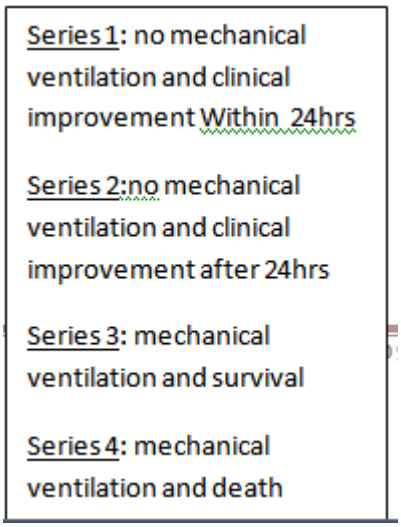
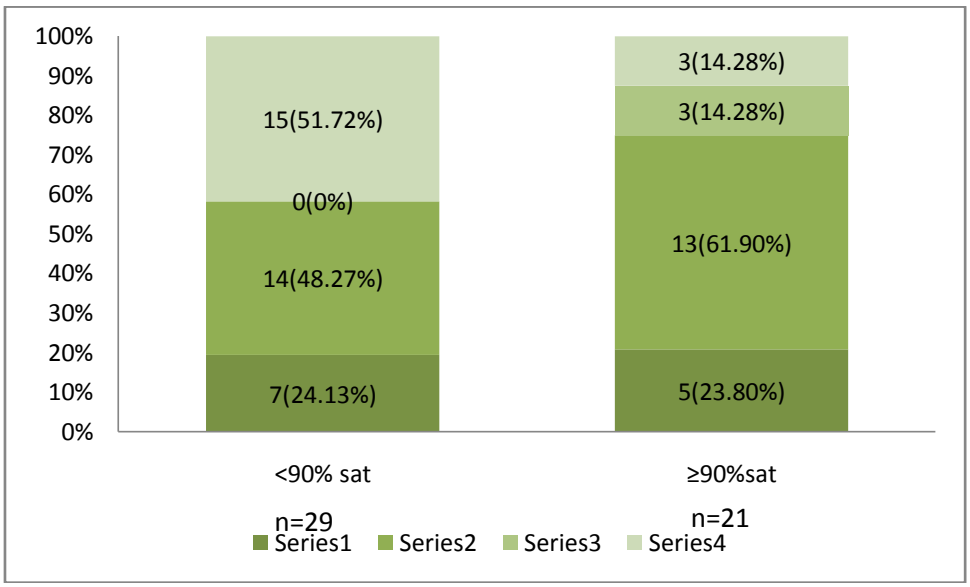


CHART9: A SEMI-OBJECTIVE SCALE FOR ASSESSING OUTCOMES AFTER TREATMENT BASED ON THE BASELINE LEVEL OF OXYGEN SATURATION[<90% VS ≥90%].FOLLOWING TOCILIZUMAB TREATMENT ,THE OUTCOMES INCLUDED :MECHANICAL VENTILATION AND DEATH ,MECHANICAL VENTILATION AND SURVIVAL ,NO MECHANICAL VENTILATION AND CLINICAL IMPROVEMENT AFTER 24hrs AND NO MECHANICAL VENTILATION AND CLINICAL IMPROVEMENT WITHIN 24 HRS.



Our study showed less oxygen saturation on presentation had increased number of death [51.72%]where as 90% or more o2 saturation group before Tocilizumab administration had lesser number of death [14.28%].clinical improvement after 24 hrs of Tocilizumab administration was more in both group [48.27% and 61.9%]

Note :one person in 2nd group [≥90% sat]admitted on mechanical ventilation and after tocilizumab treatment patient survived.

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TABLE 7: MEDIAN [INTERQUARTILE RANGE] ,MEAN VALUE AND STANDARD DEVIATION OF LABORATORY VARIABLE BEFORE AND 1-7 DAYS AFTERTHE FIRST DOSE OF TOCILIZUMAB AND P-VALUE

Variable	**median**		**mean**		**p-value (CI-95%)**
	Before Tocilizumab	**After Tocilizumab**	**Before Tocilizumab**	**After Tocilizumab**	
TLC	10.55[6.8-15]	12.7[9.4-17.1]	11.09±5.19	13.7±6.42	**<0.05**
N/L RATIO	11.66[8.7-17]	18[11-27]	14.93±10.48	22.94±16.67	**<0.05**
PLATELETS	259.5[197-322]	234[182-316]	266.44±104.81	263.28±120.57	**<0.05**
ALT	39.5[24-57]	36.5[23-57]	43.36±22.72	44.22±31.81	**<0.05**
AST	42.5[28-61]	32.5[25-48]	47.64±26.05	42.08±29.17	**<0.05**
CREATININE	1.025[0.9-1.32]	1.03[0.82-1.34]	1.23±0.68	1.14±0.47	**>0.05**
IL-6	73.55[26.9-193.3]	351[77.1-789]	147.9±167.86	1751.9±7519.18	**<0.05**

In our study TLC,N/L RATIO,PLATELETS,ALT,AST and IL-6 showed significant p-value[CI=95%,<0.05] after Tocilizumab administration .

CHART10: PROPORTION OF PATIENTS SHOWING RAPID [<24 HOURS]OR SLOW [>24 HOURS] IMPROVEMENT OR DEATH FOLLOWING TOCILIZUMAB TREATMENT DEPENDING ON THE NUMBER OF COMORBIDITIES.

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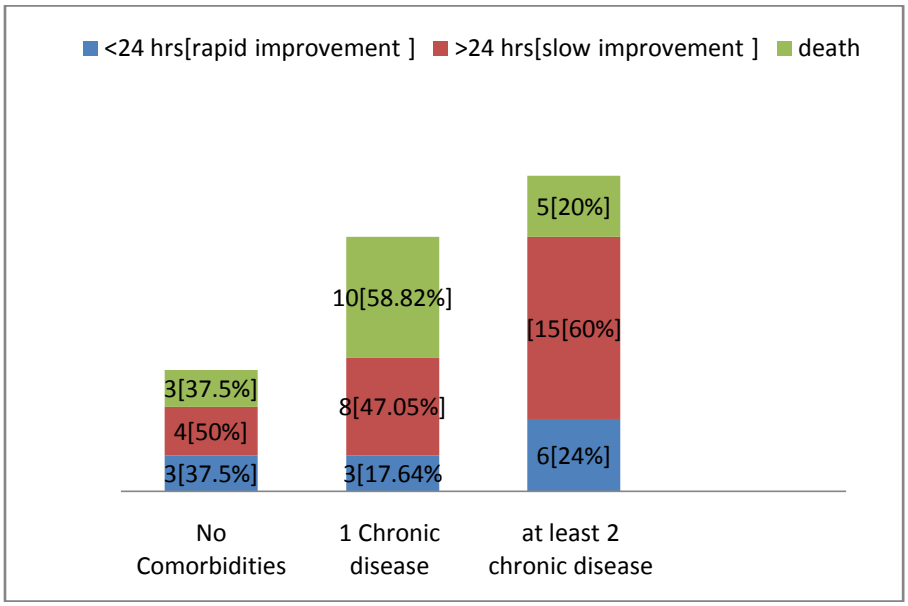

In our study no comorbidities group had highest number[37.5%] of rapid improvers while group who had at least 2 chronic disease had large number of late[slow] improvers .

V. DISCUSSION

Data were analysed statistically by mean,standard deviation ,median[inter quartile ranges] and Categorical variables were expressed as number (percentage). Differences between groups were assessed using Pearson χ^2 test or the continuity correction χ^2 teststo look for statistical significance[p-value].

-------In our study onset of symptoms before admission in hospital was 6.5± 2.79 days whereas Tocilizumab was administered 8.3±3.15 days after onset of symptoms in severe Covid-19 pneumonia .

-------In our study Mean age of presentation of severe covid pneumonia was 64.28±12.54 years Most of the patients of severe Covid-19 pneumonia presented in JNUIMSRC were above 60 yrs of age which account for about 70% of total cases .

Study done by Kunhua Li, MS, Jiong Wu,MS[12] also showed similar results where average age for severe pneumonia was 53.7±12.31 yrs.

In another study done by Jun Mi, Weimin Zhong,[13] Showed also similar results where average age of severe Covid-19 pneumonia was 64.5yrs[52.5-71.75 yrs].

----- A male preponderance was seen in severe Covid pneumonia with male to female ratio was 4.5:1[82%vs18%] in our cross sectional study .

Study done by Kunhua Li, MS, Jiong Wu,MS[12] also showed similar results where male preponderance[60%vs40%] was seen in severe pneumonia.

Study done by Ivan O. Rosas, M.D., Norbert Bräu, M.D[14] also showed similar results with male dominance [69.7% vs 30.3%]

Study done by prof Giovanni Guaraldi, Marianna Meschiari[15] showed similar results.Overall 66% were male and median age was 67 years.

------- In our study a large number of patients had comorbidities in which DM,HTN,CAD were most common.They account for 56%,52%and 12% respectively.Study done by Tao Yao, Yan Gao[16] showed similar results with three major comorbidities [DM[26%],HTN[57%],CAD[31%]]in severe COVID-19 pneumonia .

Another study done by Adekunle Sanyaolu, Chuku Okorie[17]

showed some how similar results where DM,HTN,CAD accounts for 9%,15% and 11% respectively as major comorbidities.

----------In our study there were highest number of patients belonging to $\mathbf{B^+}$ blood group[36%] while lowest number of patients were of $\mathbf{B^-}$blood group[4%] in severe COVID-19 pneumonia. The **Rh** negative group comprises 8% while **Rh** positive constitute 92% severe Covid-19 pneumonia cases.

Study done byYanardag Acik D, Bankir M[18].showed similar results with 90% cases were **Rh+** and10% cases were **Rh-**but blood group A was predominant figure .Study done by Iti Garg ,Swati Srivastav[19] Showed similar majority of **B+**ve patient in severe Covid-19 pneumonia which was 41% while blood group **A** and **O** share 34% and 17 % respectively. The **Rh+** and **Rh –** were 90% and 10%.

In our study highest number of patient mortality was seen in **B** blood group which account for around 40 % which was followed by **A** blood group mortality which was around 28% .In other words non O blood group mortality was 78 % while **O** blood group patients shares only 22%.
Meta analysis done by F.Pourali,M.Afshari[20] showedlower odds of COVID-19 infection among subjects with blood group **O** and also decreased mortality in **O** blood group patient in comparision to non **O** blood group.

-------- in our study Majority of Patient admitted in JNUIMSRC hospital had fever ,cough,dyspnea as presenting complaints which account for 82%,76% and 72% while headache ,sneezing and diarrhea account for only small number of patients.
Study done by Michael C. Grant,Luke Geoghegan[21] showed fever [78%],cough[57%],myalgia[31%] as dominant symptoms which matches our study Another study carried out by Annemarie B.Docherty,EwenM.Harrison[22] showed similar observation with fever [71.6%],cough [68.9%],shortness of breath [71.2%]
---------in our study Oxygen saturation before and after the first Tocilizumab dose was noted in patients with severe COVID-19. This chart shows gradually increasing O_2 saturation after Tocilizumab administration .
Study done by Krzysztof Tomasiewicz,Anna Piekarska[23] showed similar pattern in O2saturation after Tocilizumab administration.
Similar results were also shown by Faryal Farooqi , Naveen Dhawan[24] which showed gradually increasing oxygen saturation after tocilizumab administration
----------In our study less oxygen saturation on presentation had increased number of death [51.72%]where as 90% or more O_2 saturation group before Tocilizumab administration had lesser number of death [14.28%]. Clinical improvement after 24 hrs of Tocilizumab administration was more in both group [48.27% and 61.9%] in comparison to earlier.Similar results were obtained by Imad M. Tlevieh,Zakaria Kashour[25]
Study done by Krzysztof Tomasiewicz,Anna Piekarska[23] showed similar pattern in O2saturation after Tocilizumab administration .
In our study IL-6 level increases after 1-5 days of Tocililizumab injection [**CI=95%,**p value ‹.05] which was significant.Study done by Krzysztof Tomasiewicz,Anna Piekarska[23] showed similar pattern in IL-6 after Tocilizumab administration.
Creatinine level slightly increase after Tocilizumab injection but p value was more than .05 which was not significant means this value was by chance.TLC increase after administration of Tocilizumab [**CI=95%,**p value<.05] which was significant.Study done by prof. Giovanni Guaraldi,Marianna Meschiari[26] showed similar results .
ALT level decreases after Tocilizumab use [CI=95%,p value ‹.05] which was significant. AST level decrease after Toci use **[**p value ‹.05] which was significant which match the study done by Jianbo Tian, Ming Zhang.[27]
Creatinine,IL-6,AST,Platelets reports before and after Tocilizumab were similar in study done byTimothéeKlopfenstein,SouheilZayet[28]

Limitation-Our study has limitations.
First, the study cohort was a small and heterogeneous sample (i.e., patients with different comorbidities,age,sex,race,BMI etc.).
Second, the study was retrospective in nature, which could be associated, for example, with selection bias.
Third, there was no comparative group due to no registered standard of care with confirmed effectiveness in COVID-19 at the moment of data collection.
Fourth there had been using concomitant medication with Hydroxychloroquine Lopinavir/Ritonavir,Ivermectin ,Remdesivir,steroid for variable duration and doses in majority of patients.

VI. CONCLUSION-

Tocilizumab shows promise in the treatment of severe COVID-19 infection. Tocilizumab improve the clinical status in patients with COVID-19 infection and reducing need for oxygen therapy or mechanical ventilation.
Advice-There should be randomized, controlled trials to provide more evidence on the efficacy and safety of Tocilizumab in patients with COVID-19 infection.

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ANNEXURE – II

Normal values of laboratory parameters in our hospital

SARS-COV-2 PCR : Ct value(E target) <35
Ct value(RdRp Target) <35
Ct value(RP Target) <35 for positive
TLC : 4-11 Thousand /cumm
N [NEUTROPHIL] : 40-80 %
L [LYMPHOCYTE] : 20-40 %
PLATELETS : 150-500 Thousand /cumm
ALT [SGPT] : 0-40 U/L
AST [SGOT] : 0-37 U/L
Serum CREATININE : 0.7-1.3 mg/dl
IL-6 : 0-4.4 pg/ml
SPO2 : >90% at room air

ANNEXURE – III

PRE TOCILIZUMAB

International Journal Dental and Medical Sciences Research
Volume 4, Issue 2, Mar-Apr 2022 pp 115-126 www.ijdmsrjournal.com ISSN: 2582-6018

S.N	gistration	sex	age (yrs)	onset of symptom	symptoms			
					cough	dyspnea	fever	other
1	202011250	m	70	6	✓		✔	headache
2	202011280	m	71	2		✔	✔	
3	202011180	m	68	7		✔	✔	
4	202009220	m	58	7	✓		✔	myalgia
5	202010120	m	28	5	✓	✔	✔	
6	202010150	m	64	7			✔	sneezing
7	202010150	m	57	7	✓	✔	✔	
8	202010220	m	55	5	✓	✔		
9	202010240	m	69	7		✔		
10	202010280	f	53	10	✓	✔	✔	chest tightness

ANNEXURE – IV

POST TOCILIZUMAB

S.N.	gistration	preTOCI SPO2(%)	on ventilato	symptoms improvement within (days)				requireme nt
				24 hrs	3 rd day	7 th day	other	
1	202011250	82		✓		W		✔
2	202011280	93				v		✔
3	202011180	70		✔		v		✔
4	202009220	93	✔	✔			without v	
5	202010120	92		✔				
6	202010150	92		✔				
7	202010150	92		✔				
8	202010220	78		✔				
9	202010240	86		✔				
10	202010280	93		✔		v		✔
11	202010280	86		✔				