Comparison of Tocilizumab and High-dose Methylprednisolone Pulse on Outcomes in Severe Corona Virus Disease-2019: TAME-COVID, a Retrospective Multicentric Study

Abstract

Background: India recently encountered fierce second wave of coronavirus disease (COVID-19), and scarcity of novel medications added to the management challenges. Various studies have highlighted the effectiveness of tocilizumab and high-dose steroids in severe COVIDs, but none has compared their efficacy. Materials and Methods: This retrospective multi-centric analysis compares intravenous tocilizumab (8 mg/kg/day, maximum dose-800 mg), and intravenous Methylprednisolone Pulse (MPS-1 g/day for 3 days) in severe COVID-19. Both the groups had additionally received the standard of care COVID treatment as per protocol. Outcomes were assessed at 30 days. Results: A total of 336 patients, with 249 receiving MPS and 87 receiving tocilizumab were compared. Majority of these were males (72.9%) with a mean age of 57.4 ± 13.6 years. Diabetes was the most common comorbidity. Patients in both groups had comparable age distribution, comorbidities, presenting mean-arterial pressures, d-Dimer levels, serum ferritin, serum leukocyte-dehydrogenase, and procalcitonin. However, the tocilizumab group had more number of males, higher incidence of coronary artery disease, more tachypnea and leukocytosis, more number of patients with severe acute respiratory disease syndrome (PaO2/FiO2 ratio <100), and higher C-reactive protein levels at presentation. Both groups had comparable adverse events’ profile. Tocilizumab group had lesser requirement of invasive ventilation than MPS group (17% vs. 29%, P = 0.038), however mortality at the end of 30 days follow-up was similar (36% vs. 34% respectively; P = 0.678). Conclusions: Tocilizumab decreased the need for invasive ventilation in severe COVID-19; however, it did not translate to improved survival. A planned prospective randomized study is recommended in this respect to compare their efficacy.

Keywords: High dose intravenous methylprednisolone, invasive ventilation, outcome, severe COVID-19, tocilizumab

Introduction

The year 2020 witnessed global challenge due to coronavirus disease 2019 (COVID-19) pandemic, which continued unabated in the first half of 2021. After the first case of COVID-19 in India in the end of January 2020, the first wave figures grew gradually to peak in September 2020, after which downward trends started with occasional regional spurts in some states. By the end of March 2021, India, with its total COVID mortality of 162 K, at a case fatality ratio of 1.3% and 11.99 deaths per 100,000 population, had fared better than many developed countries worldwide.[1] The fierce second wave that followed in the months of April and May leads to records of the highest single day positive cases being made and broken with each passing day, overwhelming the Indian health care system and lead to total cases in India crossing the 30 Million mark by the end of June, with mortality crossing 400K, bringing us to second worst-hit nation after the United States.[1]

The medical fraternity worldwide has strived with different treatment modalities in the past year and a half to tackle this life-threatening disease. As the pathogenesis of SARS-CoV-2-induced cytotoxic inflammatory response became clearer, the emphasis shifted from antivirals to anti-inflammatory drugs such as corticosteroids and tocilizumab. The low dose steroids are recommended in almost all cases requiring supplemental oxygen,[2] but in severe cases, high-dose intravenous
methylprednisolone pulse and tocilizumab have been widely used. However, none of the studies till date have compared these two anti-inflammatory therapies in severe COVID-19.

**Materials and Methods**

This retrospective observational multi-centric cohort study was conducted in patients of severe COVID-19 admitted in three Level-III facilities of the North India from May 2020 to October 2020. The study was approved by the institutional ethical committee.

Diagnosis of severe disease was based on history suggestive of COVID-pneumonia, with COVID-19 antigen or reverse transcription-polymerase chain reaction positivity and any one or more of following including respiratory rate ≥30 per min, SpO₂ ≤ 93%, while on room air, PaO₂/FiO₂ (P/Fr) ≤ 300 mmHg, hypotension, or any organ failure at presentation. All patients had baseline chest radiographs showing ground-glass opacities and pulmonary infiltrates. The choice of administration of MPS pulse or tocilizumab in severe COVID was based on the decision of the treating team, with informed consent of the patient or guardians.

Records of all COVID patients were reviewed, and adult patients (age ≥18 years), who received intravenous tocilizumab (8 mg/kg/day with maximum cumulative dose of 800 mg) or high-dose intravenous methylprednisolone (MPS pulse-1 g/day for 3 days), were included in the study. The exclusion criteria were patients on invasive ventilation at the time of admission or requiring invasive ventilation within 72 h of admission or before completion of dose of either drugs, patients receiving incomplete dose of either drugs due to any adverse reaction, refusal to continue therapy or death of patient before dose completion, patients receiving both the drugs simultaneously or sequentially during their hospital admission, and patients receiving plasma therapy.

All patients in tocilizumab group also received low dose IV MPS (1 mg/kg/day twice a day), as per protocol for severe-COVID pneumonia with hypoxia.[3] All the patients in MPS group were also on low dose IV MPS on other days before and following IV MPS pulse. All patients received standard of care treatment as per the COVID-19 management protocol.[3] Antivirals, anticoagulation, and other supportive treatment were given as per indication. Antibiotics and antifungals were used on the basis of direct microscopic examination, histopathology, culture, and serology as indicated.

The outcomes were compared in the group of patients receiving Tocilizumab (Tocilizumab group) and those receiving high-dose MPS pulse (MPS group). The need of invasive ventilation and the time of requirement for the same was assessed in both the groups. Patients were put on invasive ventilation in case of respiratory failure, with hypoxemia not improving with noninvasive ventilator or high-flow nasal cannula. Other adverse events in the two groups were also studied. Incidence of acute kidney injury (AKI), acute on underlying chronic kidney disease (CKD), and need for renal replacement therapy were noted. AKI was diagnosed and staged based on the AKI network classification/staging system.[4] CKD was diagnosed based on history and recorded suggestive of estimated glomerular filtration rate <60 ml/min/1.73 m² body surface area for more than 3 months.[3] Hepatic dysfunction was labeled if there was new-onset hyper-bilirubinemia and/or transaminitis. The incidence of sepsis and fungal infections were compared. Patients were diagnosed having sepsis based on blood, urine, body fluid culture positivity, and rise in procalcitonin levels. Fungal infection was diagnosed based serological markers for invasive fungal infection (serum galactomannan and 1→3-beta-d-Glucan fentigull assay), tissue diagnosis on fine-needle aspiration cytology/biopsy of the involved organ, blood or body fluid culture positivity. The incidence of thromboembolic events in both the groups was studied. Pulmonary embolism was diagnosed based on computed tomography of the chest with pulmonary angiography. Deep vein thrombosis was diagnosed on Color Doppler ultrasonography of the involved area.

The effect of these two treatment modalities was also compared in patients presenting with mild (P/Fr = 200–300), moderate (P/Fr = 100–200), and severe (P/Fr ≤ 100) acute respiratory distress syndrome (ARDS).

**Statistical analysis**

Data were described in terms of range, mean ± standard deviation, frequencies (number of cases), and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using Student’s *t*-test and Mann–Whitney U test for independent samples, for parametric and nonparametric data, respectively. For comparing categorical data, Chi-square ($\chi^2$) test was performed, and exact test was used when the expected frequency was <5. A probability value ($P$ value) <0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

**Results**

A total of 396 patients had received either of these drugs during the study period, out of which 60 were excluded due to various exclusion criteria and 336 included in the final analysis ($N = 336$). Out of these, 249 patients received high dose intravenous methylprednisolone pulse (MPS group, $N_{MPS} = 249$), and 87 received intravenous Tocilizumab (Toci group, $N_{TOCI} = 87$) [Figure 1].
Most of the patients were males (72.9%) aged 41–60 years (45.8%) with a mean age of 57.4 ± 13.6 years (range: 20–88 years). Diabetes was the most common comorbidity, followed by hypertension. Majority of the patients had PaO2/FiO2 ratio (PFR) <100 at presentation, and 22.8% required invasive ventilatory support during their hospital course, and the total mortality was 35.4%.

Patients in both the groups had comparable mean age, age distribution, incidence of comorbidities such as diabetes, hypertension, obesity, malignancy, chronic kidney, and chronic airway disease [Table 1]. However, Tocilizumab group had more number of males (P = 0.016), with higher incidence of coronary artery disease (CAD, P = 0.007). The lag-period from onset of symptoms to admission and admission to the administration of test drug was comparable. The presenting mean arterial pressure, temperature, serum ferritin, serum leucocyte dehydrogenase, d-Dimer, and procalcitonin were comparable in both groups. However, the patients in tocilizumab group had more tachypnea (P = 0.000), more leukocytosis (P = 0.041), higher baseline mean C-reactive protein (CRP) levels (P = 0.005), higher number of patients with CRP >100 (P = 0.003), and more number of patients with P: Fr <100 (55%, P = 0.007) at presentation, than patients in the MPS group [Tables 2 and 3].

The incidences of AKI, acute on CKD, need for renal replacement therapy, jaundice, transaminitis, pulmonary embolism, and other thrombotic-embolic complications were comparable. The rate of bacterial and fungal infections was statistically similar. Antibiotics were given to all the patients, and antifungal use was also comparable in the two groups [Table 3]. There was no significant difference in the use of antivirals and anticoagulants.

Tocilizumab group however had significantly lesser number of patients requiring invasive ventilation than MPS group (P = 0.038). The need for invasive ventilation in the first 4–7 days, 7–14 days and 15–30 days were not different. The patients in tocilizumab group also had higher mean days of hospital stay. The survival in the both the groups at 30 days of follow-up was similar [Tables 2 and 3].

On comparing the two treatment modalities in different severities of ARDS, the need for invasive ventilation was found to decrease in severe ARDS with the use of tocilizumab, but overall mortality was similar with both the drugs [Table 4].

**Discussion**

Lesser number of patients had received tocilizumab in our cohort, possibly due to its higher cost and limited availability in India. The baseline characteristics showed patients receiving tocilizumab to be poorer risk group due to male predominance, higher co-morbid CAD, worse baseline inflammatory parameters, and more number of patients with severe ARDS. In spite of this, there was a lesser propensity of tocilizumab treated patients to go on to invasive ventilation than MPS pulse group. However, at 30 days of follow-up, it did not translate to improved survival in them, questioning the ultimate benefit of former over the later. The incidence of serious adverse events including pulmonary embolism was comparable in both the groups. MPS pulse, used in majority cases, served as an economical alternative, with similar survival benefits, in our study.

The failure to document survival benefit with tocilizumab could be due to higher number of males in the group, as they have been found to have higher severity and more mortality as compared to females in global data.[6-9] However, Indian analysis showed the reverse with female-to-male case fatality ratio of 3.07:2.62.[8]

Tocilizumab group also had higher co-morbid CAD. Studies reveal that the presence of CAD adds to poor prognosis in COVID with higher mortality, thromboembolic events, and septic shock rates,[10,11] but another study contradicts this by showing that CAD itself was not associated with increased mortality and poorer outcome, when other covariates were adjusted.[12]

Direct comparison between tocilizumab and high-dose MPS not been reported by studies, but numerous studies have discussed their role in severe COVID-19 individually.

The preliminary data on the use of Tocilizumab in China in a small number of patients concluded lowered oxygen support within few days of administration[13] and also improvement in outcome in cytokine storm in severe COVID.[14] A retrospective analysis of 25 patients from Qatar, who received tocilizumab observed reduced ventilatory requirement at days 7 and 14, and 36% survival at 14 days.[15] Another Italian prospective study in 100 patients from Brescia, on the use of tocilizumab showed encouraging results, with significant clinical improvement.[16]
Table 1: Baseline characteristics of patients in the high-dose intravenous methylprednisolone and tocilizumab group

| Parameters                        | MPS group (n=249) | Tocilizumab group (n=87) | Total patients | χ² | P   |
|----------------------------------|-------------------|--------------------------|----------------|----|-----|
| Age distribution of patients     |                   |                          |                |    |     |
| <40                               | 30 (12)           | 8 (9)                    | 38             | 0.620 | 0.734 |
| 40-60                             | 112 (45)          | 42 (48)                  | 154            |     |     |
| >60                               | 107 (43)          | 37 (43)                  | 144            |     |     |
| Gender                            |                   |                          |                |    |     |
| Female                            | 76 (31)           | 15 (17)                  | 91             | 5.758 | 0.016 |
| Male                              | 173 (69)          | 72 (83)                  | 245            |     |     |
| Diabetes                          |                   |                          |                |    |     |
| Present                           | 124 (50)          | 50 (57)                  | 174            | 1.520 | 0.218 |
| Hypertension                      |                   |                          |                |    |     |
| Present                           | 113 (45)          | 46 (53)                  | 159            | 1.452 | 0.228 |
| CAD-Present                       | 18 (7)            | 15 (17)                  | 33             | 7.298 | 0.007 |
| Obesity-Present                   | 5 (2)             | 2 (2)                    | 7              | 0.431 | 0.512 |
| COAD-Present                      | 5 (2)             | 2 (2)                    | 7              | 0.027 | 0.870 |
| CKD-Present                       | 9 (4)             | 5 (6)                    | 14             | 0.734 | 0.391 |
| Malignancy-Present                | 5 (2)             | 1 (1)                    | 6              | 0.271 | 0.603 |
| Remdesvir-Given                   | 146 (59)          | 49 (56)                  | 195            | 0.142 | 0.707 |
| Anticoagulatio-Given              | 231 (93)          | 79 (91)                  | 310            | 0.349 | 0.555 |
| Antifungals-Given                 | 72 (29)           | 25 (29)                  | 97             | 0.001 | 0.975 |
| PaO₂/FiO₂ ratio                   |                   |                          |                |    |     |
| <100                              | 91 (37)           | 47 (54)                  | 138            | 9.854 | 0.020 |
| 101-200                           | 87 (35)           | 17 (20)                  | 104            |     |     |
| 200-300                           | 29 (12)           | 9 (10)                   | 38             |     |     |
| >300                              | 42 (17)           | 14 (16)                  | 56             |     |     |
| CRP                               |                   |                          |                |    |     |
| 0-50                              | 85 (34)           | 22 (25)                  | 107            | 7.731 | 0.021 |
| 51-100                            | 52 (21)           | 11 (13)                  | 63             |     |     |
| >101                              | 112 (45)          | 54 (62)                  | 166            |     |     |

CRP: C-reactive protein; CVD: Cardio-vascular disease; COAD: Chronic obstructive airway disease; CKD: Chronic kidney disease; MPS: Methylprednisolone

Table 2: Comparison of intravenous high-dose methylprednisolone group with tocilizumab group

| Parameters                        | Mean±SD         | Z   | P   |
|----------------------------------|-----------------|-----|-----|
| Age (years)                      | 57.48±14.28     | 0.310 | 0.756 |
| Lag-period between first symptoms and admission (days) | 5.53±4.69 | 0.898 | 0.3370 |
| Baseline parameters              |                 |     |     |
| Respiratory rate (per minute)    | 22.86±3.46      | -3.969 | 0.000 |
| Heart rate (per minute)          | 92.69±20.25     | -2.886 | 0.004 |
| Mean arterial pressure (mm of Hg)| 93.89±11.14     | 1.872 | 0.062 |
| Temperature (Fahrenheit)         | 98.34±1.06      | 1.707 | 0.089 |
| PaO₂/FiO₂ ratio                  | 175.11±131.44   | 1.311 | 0.191 |
| CRP (in mg/L)                    | 121.24±98.37    | -2.804 | 0.005 |
| D-Dimer (ng/ml)                  | 741.75±689.91   | 0.154 | 0.878 |
| Total leucocyte count (in cells/cm) | 11.34±5.36     | -2.055 | 0.041 |
| Neutrophil/lymphocyte ratio      | 12.40±12.36     | -1.197 | 0.232 |
| Leucocyte dehydrogenase (U/L)    | 445.76±288.03   | 0.923 | 0.357 |
| Ferritin (ng/ml)                 | 885.47±1248.61  | 0.888 | 0.375 |
| Procalcitonin (ng/ml)            | 0.47±0.89       | 0.459 | 0.647 |
| Hospital course                  |                 |     |     |
| Lag-time from admission to administration of drug (days) | 2.41±1.12 | -0.344 | 0.731 |
| Hospital stay (days)             | 13.23±6.00      | -2.342 | 0.020 |

CRP: C-reactive protein; SD: Standard deviation
Multicentric retrospective studies have shown a reduction in mortality in COVID patients treated with tocilizumab. The United States (US) experience showed mortality to reduce from 61% to 49% with tocilizumab therapy in intensive care unit (ICU) patients although their total mortality was high (57%). Another multicentric study from the US also found lowering of in-hospital mortality in tocilizumab-treated patients. Their tocilizumab cohort had patients with similar median age (58 years), with higher prevalence of hypoxemia on ICU admission, and they had a total ICU mortality of 39.3%, with better outcome in patients treated with tocilizumab (28.9% mortality), than those who did not receive this drug (40.6%). Italian TESEO cohort study also found lowering of in-hospital mortality and need for mechanical ventilation with tocilizumab.

The recent multiethnic randomized study evaluating minority patients with Actemra comparing tocilizumab with placebo has reported a decreased risk of mechanical ventilation or death by 28 days with tocilizumab (12.0%) versus placebo (19.3%). However, an earlier single center New Jersey study did not support tocilizumab for the management of cytokine storm in COVID-19. Italian prospective short-term outcome study, the SMAtteo COvid19 REgistry (SMACORE), did not report any reduced ICU need or mortality at 7 days in 21 patients when tocilizumab was compared with standard of care treatment (not including steroids). Later, a randomized controlled trial in nonventilated patients also concluded that tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19. Recently published Indian randomized trial (COVINTOC) does

### Table 3: Comparison of outcomes in intravenous high-dose methylprednisolone group with tocilizumab group

| Parameters                          | Total patients (n=336), number of patients (%) | Total patients | χ²  | P     |
|-------------------------------------|-----------------------------------------------|----------------|-----|-------|
|                                      | MPS group (n=249)                              | Tocilizumab group (n=87) |     |       |
| Extra-pulmonary organ dysfunction    |                                               |                |     |       |
| AKI                                 | 25                                            | 7              | 32  | 0.298 | 0.676 |
| AKI requiring RRT                   | 4                                             | 3              | 7   | 1.072 | 0.381 |
| Acute on CKD                        | 7                                             | 4              | 11  | 0.650 | 0.484 |
| Hyperbilirubinemia                  | 9                                             | 4              | 13  | 0.168 | 0.748 |
| Transaminitis                       | 24                                            | 6              | 30  | 0.596 | 0.440 |
| Thrombo-embolic complications       |                                               |                |     |       |
| Total                               | 5                                             | 4              | 9   | 1.659 | 0.245 |
| Pulmonary embolism                  | 3                                             | 3              | 6   | 1.850 | 0.182 |
| Sepsis                              |                                               |                |     |       |
| Bacterial                           | 20                                            | 7              | 27  | 0.000 | 0.997 |
| Fungal                              | 9                                             | 3              | 12  | 0.005 | 0.943 |
| Disseminated mucormycosis           | 1                                             | 2              | 3   | 2.623 | 0.166 |
| Invasive ventilation                |                                               |                |     |       |
| Required                            | 71 (29 of total patients given MPS)            | 15 (17)        | 86  | 4.302 | 0.038 |
| In 4-7 days                         | 36 (51 of ventilated)                         | 11 (73.3 of ventilated) | 47  | 2.559 | 0.109 |
| In 8-14 days                        | 32 (45.1 of ventilated)                       | 4 (26.7 of ventilated) | 36  | 1.723 | 0.169 |
| In 15-30 days                       | 3 (3.9 ventilated)                            | 0 (0)          | 3   | 0.166 | 0.683 |
| Death on invasive ventilation       |                                               |                |     |       |
| Total deaths                        | 64 (90 of ventilated patients)                 | 14 (93.3 of ventilated patients) | 78  |       |       |
| In 4-7 days                         | 12 (18.8 of deaths on ventilator)              | 1 (7.1)        | 13  | 1.114 | 0.291 |
| In 8-14 days                        | 27 (42.2 of deaths on ventilator)              | 8 (57.2 of deaths on ventilator) | 35  | 1.038 | 0.308 |
| In 15-30 days                       | 25 (39 of deaths on ventilator)                | 5 (35.7 deaths on ventilator) | 30  | 0.054 | 0.816 |
| Final outcome at 30 days            |                                               |                |     |       |
| Survived                            | 163 (65 of total patients on MPS)              | 56 (64 of total patients on Tocilizumab) | 219 | 0.778 | 0.678 |
| Loss to follow-up                   | 2 (1 of total patients on MPS)                 | 0 (0)          | 2   |       |       |
| Mortality                           | 84 (34 of total patients on MPS)               | 31 (360f total patients on Tocilizumab) | 115 |       |       |
| Total deaths (days)                 |                                               |                |     |       |
| 4-7                                 | 19 (22.6 of total Deaths on MPS)               | 3 (9.6 of total deaths on Tocilizumab) | 21  | 2.451 | 0.117 |
| 8-14                                | 35 (41.7 of total deaths on MPS)               | 14 (45.2 of total deaths on Tocilizumab) | 49  | 0.113 | 0.736 |
| 15-30                               | 30 (35.7 of total deaths on MPS)               | 14 (45.2 of total deaths on Tocilizumab) | 44  | 0.855 | 0.355 |

MPS: Methylprednisolone; AKI: Acute kidney injury; CKD: Chronic kidney disease; RRT: Renal replacement therapy
not support the routine use of tocilizumab in moderate-to-severe COVID-19; however, their post hoc analysis showed some effectiveness in severe disease.\textsuperscript{[24]}

The experience with high-dose intravenous methylprednisolone pulse has also been similarly varied. A small Japanese case series of seven patients demonstrated the beneficial role of IV MPS pulse in ventilated patients, with 100% extubation rate and recovery from ARDS in patients with initial PaO\textsubscript{2}/FiO\textsubscript{2} ratio $\leq$150, with no increased infections or serious adverse events.\textsuperscript{[25]}

The WAYFARER Study from Russia retrospectively compared two groups of 17 patients each with one group receiving IV MPS and other were controls. They concluded that pulse MPS exerted a rapid anti-inflammatory effect but increased the N/L ratio and the D-dimer level, which in turn increased the risk of thromboembolism.\textsuperscript{[26]}

On the contrary, a randomized study compared high dose MPS ($\geq$250 mg/day) with standard dose (1–1.5 mg/kg/day) and concluded that the MPS pulse was associated with a higher mortality ($P < 0.001$) and an increased risk of mechanical ventilation ($P = 0.001$). The risk of developing a severe ARDS was similar between groups. The interaction analysis had showed that higher dose increased mortality exclusively in elderly patients.\textsuperscript{[27]}

CHIC study from the Netherlands has tried combining both these anti-inflammatory therapies. Their patients received 250 mg of intravenous methylprednisolone on day 1 followed by 80 mg on days 2–5, and 43% of them also received tocilizumab on or after day 2 if respiratory 8 condition had not improved sufficiently after MPS alone. On comparing with historical cohort, they found accelerated respiratory recovery, lowered hospital mortality, and reduced likelihood of invasive mechanical ventilation in these patients.\textsuperscript{[28]}

Being retrospective study, there is every likelihood that baseline characteristics were not completely matched. The mortality benefit in tocilizumab group could have been masked due to patients with relatively more severe disease receiving this drug. The use of both Tocilizumab and IV MPS pulse were at the discretion of the treating team and as per the informed consent. However, this analysis might help in the treatment of severe COVID in the present deadly second COVID wave when scarcity of tocilizumab is being encountered in India, especially in our Northern region.

**Conclusions**

Tocilizumab decreased the propensity of severe COVID-19 patients to require invasive mechanical ventilation when compared to high-dose methylprednisolone pulse, especially in those with severe ARDS, but this did not translate to improved 30-day survival in them. A planned randomized prospective study is advocated to compare these two different treatment modalities with respect to morbidity and mortality, along with cost-analysis in the management of cytokine storm in COVID-19.

**Acknowledgments**

We would like to thank Ms. Baljit Kaur (Incharge, Department of Research and Development) and Ms. Namita (Statistical expert), Dayanand Medical College and Hospital, Ludhiana, Punjab, India, for their valuable assistance from inception to culmination of this study.

**Ethical clearance**

The study was approved by the Institutional ethical committee vide letter number DMCH/R and D/2020/127.

**Financial support and sponsorship**

Nil.
Conflicts of interest

There are no conflicts of interest.

References

1. Johns Hopkins University of Medicine. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU); July 07, 2021. Available from: https://coronavirus.jhu.edu/map.html. [Last accessed on 2021 Jul 07].

2. Horby P, Lim WS, Emberson J, Mathem M, Bell J, Landary MJ. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384:693-704. doi: 10.1056/NEJMoa201436.

3. Ministry of Health & Family Welfare. Guidelines on Clinical Management of COVID-19. New Delhi: MoHFW, Government of India; 2020.

4. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150.

6. The Sex, Gender, and COVID-19 Project. The COVID-10 Sex-Disaggregated Data Tracker. Available from: https://globalhealth5050.org/covid19/. [Last accessed 2021 Apr 04].

7. Pradhan A, Olsson PE. Sex differences in severity and mortality from COVID-19: Are males more vulnerable? Biol Sex Differ 2020;11:53.

8. Dehingia N, Raj A. Sex differences in COVID-19 case fatality: Do we know enough? Lancet Glob Health 2021;9:E14-5.

9. Dörre A, Doblhammer G. The effect of gender on COVID-19 infections and mortality in Germany: Insights from age- and sex-specific modelling of contact rates, infections, and deaths. medRxiv 2020. doi: https://doi.org/10.1101/2020.10.06.20207951.

10. Inciardi RM, Adamo M, Lupi L, Cani DS, Pasquale MD, Tomasoni D, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in northern Italy. Eur Heart J 2020;41:1821-9.

11. Toniatì P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev 2020;19:102568.

12. Biran N, Ip A, Ahn J, Go RC, Wang S, Mathura S, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: A multicentre observational study. Lancet Rheumatol 2020;2:e603-12.

13. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Tocilizumab treatment of severe COVID-19 patients with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med 2021;181:41-51.

14. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: A retrospective cohort study. Lancet Rheumatol 2020;2:e603-12.

15. So C, Ro S, Murakami M, Imai R, Jinta T. High-dose, short-term corticosteroids for ARDS caused by COVID-19: A case series. Respiroli Case Rep 2020;8:e00596.

16. Mareev VY, Orlovka EP, Matskeplishvili ST, Krasnova TN, Malahov PS, et al. Steroid pulse therapy in patients with coronavirus Pneumonia (COVID-19), sYstemic inFlammation And Risk of vEnous thRomboembolism (WAYFAHER Study). Kardiology 2020;60:15-29.

17. Monreal E, de la Maza SS, Villalba EN, Corbellini AB, Rodriguez-Jorge F, Fernandez-Velasco JJ. High versus standard doses of corticosteroids in severe COVID-19: A retrospective cohort study. Eur J Clin Microbiol Infect Dis 2021;40:761-9.

18. Ramiro S, Mostard RL, MagroCechia C, Van Dongen CM, Dormans T, Jacqueline Buijs J, et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: Results of the CHIC study. Ann Rheum Dis 2020;79:1143-51. doi: 10.1136/annrheumdis-2020-218479.