# Role of Methylprednisolone for COVID-19 Patients Admitted to a Tertiary Care Hospital

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## ABSTRACT

*Objective:* To determine the role of Methylprednisolone in managing COVID-19 patients.

*Study Design:* Cross-sectional study.

*Place and Duration of Study:* Pakistan Emirates Military Hospital (PEMH), Rawalpindi Pakistan, from Jan to Feb 2021.

*Methodology:* This study was carried out at the Department of Medicine. Medical records of all moderate, severe and critical COVID-19 patients admitted and receiving Methylprednisolone were reviewed. Methylprednisolone was used in all patients at doses 0.-2 mg per kg.

*Results:* A total of 200 cases were included. The most common presenting symptoms were cough (77.5%), fever (67.5%) and shortness of breath (63.5%). Most patients (85%) presented within the first week of their illness. One or more comorbidities were present in 75% of patients. Most common being hypertension in 70(35%) and diabetes mellitus in 63(31.5%). Complications seen in the study were Cytokine release storm 92(46%) and acute respiratory distress syndrome 44(22%). The median time for initiation of corticosteroid therapy was 4 hours (range 1-96 hours). Overall survival (OS) in the study was 83.5%. OS for patients with moderate, severe and critical diseases was 97.8%, 86.2% and 62%, respectively (*p*<0.001).

*Conclusion:* Corticosteroids are useful in COVID-19-admitted patients and provide excellent survival outcomes.

**Keywords:** Acute respiratory distress syndrome, COVID-19, Cytokine release storm, Methylprednisolone.

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has affected over 2.2 million lives globally till now.[1] Despite continuous research efforts and clinical trials over the last six months, there has yet to be much success in establishing effective treatment options against COVID-19.[2] Trials of Remdesivir, interleukin-6 inhibitors and novel drugs are in progress but limited to the developed world.[3] For developing countries, treatment options beyond supportive care are limited.[4] After the initial viremic phase, the majority of complications associated with coronavirus disease 2019 (COVID-19) are attributable to immune dysregulation, cytokine release syndrome (CRS) and secondary hemophagocytic lymphohistiocytosis (sHLH).[5,6] Steroids are an attractive treatment option for patients requiring hospitalization with severe and critical disease or clinical evidence of CRS. Recently reported interim results of the Recovery trial documented survival benefits in critically ill patients requiring respiratory intervention.[4,7] However, little evidence is available regarding using Methylprednisolone (MP) in hospitalized patients. Moreover, limited data is available from South Asia regarding hospitalised patients' outcomes. This study showed the outcome of hospitalized patients treated with MP in a tertiary care centre in Pakistan.

## METHODOLOGY

This study was carried out at the Department of Medicine, Pak Emirates Military Hospital (PEMH), Rawalpindi Pakistan. Approval was sought from the Hospital Ethical Review Committee and the Institutional Review Board (Certificate number: A/28/EC/ 246/2021). Medical records of all moderate, severe and critical COVID-19 patients admitted to PEMH from January to February 2021 and receiving Methylprednisolone were reviewed.

**Inclusion Criteria:** Patients aged 20 to 80 years, of either gender with SARS-CoV2 positivity documented by PCR and use of Methylprednisolone, with hospital admission, and at least 48 hours of steroids use were included in the study.

**Exclusion Criteria:** Patients with the use of steroids other than Methylprednisolone or death within 48 hours of admission or patients of haematological or solid organ malignancies or patients receiving other investigational drugs, including convalescent plasma, mesenchymal stem cells, plasmapheresis or Patients with mild COVID-19 were excluded from the study.

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A confirmed case was patients with a positive reverse transcriptase (RT)-PCR for SARS-CoV2 in a nasopharyngeal specimen. Severity classification was done as per WHO criteria.[7] The moderate disease was defined as COVID-19 positivity with <50% lung infiltrates and peripheral ground glass opacities (GGOs) on the HRCT chest but no evidence of hypoxemia.[8] Severe disease defined as COVID-19 pneumonia with hypoxemia (respiratory rate >30/minute or $PaO_2$ on ABGs <80mmHg or lung infiltrates > 50% of the lung field).[9] The critical disease was defined as evidence of either respiratory failure ($PaO_2$<60mmHg) or multiorgan dysfunction syndrome (MODS) with SOFA score >10 or septic shock (Systolic BP less than 90 or less than 40mmHg of baseline in hypertensive or Urine output <0.5ml/kg/hour).[10] Treatment was given according to disease severity per institutional guidelines for COVID-19 management. Patients with moderate disease received protocol-B (a combination of tablet Aspirin 75mg daily, Injection Enoxaparin 1mg/kg once daily, and Methylprednisolone (MP) 0.5mg/kg).

In addition to Aspirin 150mg and Enoxaparin 1.5-2mg/kg, patients with severe disease were treated with 1mg/kg Methylprednisolone (Protocol C). For patients with pulmonary infiltrates and hypoxia, awake proning 12-14 hours (when GGOs>50%) and those unable to maintain oxygen saturation above 92% on room air, protocol D was used, which was similar to protocol C except for the use of CPAP 8-10cm $H_2O$. Methylprednisolone 2mg/kg was given to patients with cytokine release syndrome (CRS). Recovery was defined as improving the patient's condition from critical/severe to moderate or moderate to mild, normalization of inflammatory markers (CRP, LDH, ferritin), ALC >1000 and PT/APTT normalization.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. The primary endpoint was overall survival. The outcome measures were death or discharge. Secondary outcome measures were, median days of hospitalization and number of days to PCR negativity. Continuous variables were reported as median and range using the Mann-Whitney test. Continuous variables were reported as median (interquartile range), and compared using the Mann-Whitney test. The categorical data were reported as the number (n) and percentage (%). Kaplan-Meier survival analysis was done to analyze survival outcomes. The *p*-value ≤0.05 was considered statistically significant.

## RESULTS

A total of 200 patients were enrolled in the study per inclusion and exclusion criteria. Median duration of symptoms at presentation was five days (rang 1-15). Cough (77.5%), fever (67.5%) and shortness of breath (63.5%) were the commonest presenting symptoms.

**Table: Demographic and Clinical Characteristics of the Study Participants (n=200)**

| Characteristics | n(%) |
|---|---|
| Age years, median (range) | 59 (20-80) |
| **Gender, n (%)** | |
| Male | 176 (88) |
| Female | 24 (12) |
| Clinical features n(%) | |
| Fever | 135(67.5) |
| Cough | 155(77.5) |
| Shortness of breath | 127(63.5) |
| Duration of symptoms at admission in days, median (range) | 5(1-15) |
| **Laboratory Values** | |
| Absolute Lymphocyte count x 109/l, median (range) | 1200(130-2400) |
| Platelet count x 109/l, median (range) | 181(60-450) |
| CRP (ug/ml), median (range) | 61(2-480) |
| IL-6 , median (range) | |
| D-dimers, median (range) | 64(1500) |
| Ferritin (ng/ml), median (range) | 477(36-8000) |
| ALT (IU/l), median (range) | 41(11-312) |
| LDH (U/l), median (range) | 670(160-2570) |
| **Cardiac Biomarkers, n(%)** | |
| Normal | 96(48) |
| Raised | 104(52) |
| HRCT Chest findings,n(%) | |
| Typical | 137(69) |
| Indeterminate | 19(9.5) |
| Atypical | 22(11) |
| Normal | 21(10.5) |
| **Lung Involvement, n(%)** | |
| <50 | 84(42) |
| >50 | 94(47) |
| Normal | 21(11) |
| Oxygen support Liter/min, median (range) | 4 (0-15) |
| Non-invasive ventilation | 37(18.5) |
| Invasive ventilation | 5(2.5) |
| **Disease Severity at Presentation, n(%)** | |
| Moderate | 100(50) |
| Severe | 58 (29) |
| Critical | 42 (21) |
| **Treatment Protocol, n (%)** | |
| Protocol B | 72(36) |
| Protocol C | 49(24.5%) |
| Protocol D | 79(39.5%) |
| Day 7 PCR positivity, n (%) (n=170) | 63(37%) |
| Day 14 PCR Positivity, n (%), n=(145) | 20(14%) |
| Discharge days, median (range) | 11(4-32) |

Four patients (2%) expired within 48 hours of admission. The most common presenting symptoms were cough (77.5%), fever (67.5%) and shortness of breath (63.5%). Other symptoms included myalgias (23%), gastrointestinal symptoms (14.5%), vertigo (9%), headache (6.5), anosmia (9.5%), and sore throat (6.5%). Most patients (85%) presented within the first week of their illness. One or more comorbidities were present in 75% of patients. Most common was hypertension in 70(35%), diabetes mellitus in 63(31.5%), ischemic heart disease in 45(22.5%), and obstructive airway disease in 18(9%). Laboratory abnormalities were summarized in the previous Table.

Cardiac biomarkers were found elevated in 52% patients but did not associate with disease severity (*p*=0.08). Ten patients (5%) developed clinical symptoms of angina and ECG changes, while 6(3%) had a myocardial infarction. Complications seen in the study participnats were CRS 92(46%), ARDS 44(22%), multiorgan dysfunction 17(8.5%), and the Median time for initiation of corticosteroid therapy was 4 hours (range 1-96 hours). Treatment Protocol-B (MP 0.5mg/kg) was used for moderate COVID-19 patients in 36% of the patients, Protocol-C (MP 1mg/kg) in 24.5% of cases, while protocol D (MP 1mg/kg) plus CPAP or invasive ventilation for 37% cases. Patients with CRS received an MP dose of 2mg/kg. Treatment escalation is needed for 12 patients. 5(2.5%) required invasive ventilation, while seven patients (3.5%) required non-invasive ventilatory support.

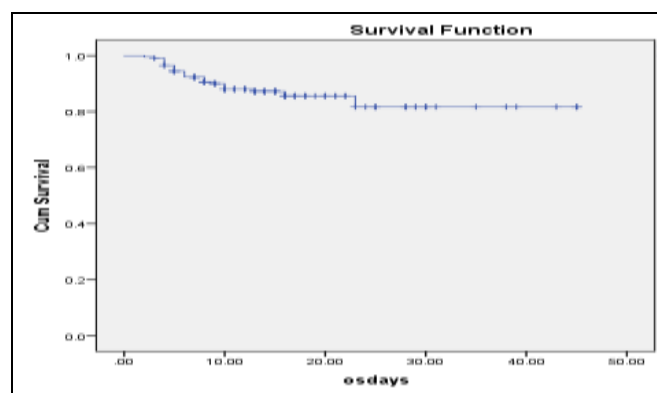Overall survival (OS) in the study was 83.5% (Figure-1).



**Figure-1: Overall Survival of the Study Participants (n=200)**

Overall survival for patients with moderate, severe and critical disease was 97.8%, 86.2% and 62% respectively, median 95% CI: 11.07-34.92, (*p*<0.001) (Figure-2).
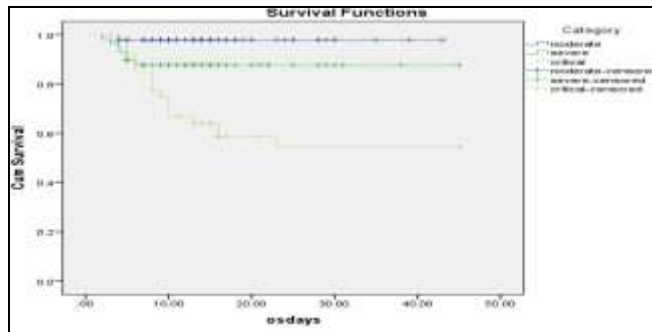


**Figure-2: Overall Survival for Patients with Moderate, Severe and Critical Disease (n=200)**

## DISCUSSION

Conflicting data is available regarding the efficacy of Tocilizumab and convalescent plasma while the role of therapeutic plasma exchange is being investigated.[9,10] Initial guidelines from the Infectious disease society of America advised against the routine use of corticosteroids for COVID pneumonia.[11]

Similarly, the American thoracic society (ATS) did not recommend corticosteroid use during COVID-19. Later studies by Yang *et al.* and Fadel *et al.* suggested the benefit of corticosteroids in COVID patients, particularly when used early in the disease course.[11,12] Another study suggested Methylprednisolone pulse could be an efficient therapeutic agent for hospitalized severe COVID-19 patients at the pulmonary phase.[13] The interim report of the a study documented survival benefits in patients receiving dexamethasone, thus paving the way for further trials with corticosteroids in COVID-19.[14]

The most common presenting symptoms in our study were cough, fever and SOB in 77.5%, 67.5% and 63.5%, respectively. A study by Fadel *et al.* reported a similar presentation with cough (74.2%), fever (70.4%) and SOB (69.5%).[12] In our study, 100 patients (50%) had severe or critical disease at the time of initiation of steroids compared to 23% in the study by Fadel *et al.* Mortality in the study was 16.5%. In studies employing routine supportive care with our corticosteroids, mortality rates in the range of 20-37% have been documented.[15,16] One study documented Dexamethasone as the first drug providing survival benefits in COVID-19 patients.[17] Mortality in another studies was higher than in our study, 21.6% versus 16.5%. Moreover, Dexamethasone was the only steroid used in that study and comparison with other steroids is not available.[18]

## LIMITATIONS OF STUDY

Our study has a few limitations. As per institutional policy, Methylprednisolone was used, and Dexamethasone

data was unavailable. Different doses were used per disease severity, and no randomization was done to select the optimal dose.

## CONCLUSION

Corticosteroids added to standard care in hospitalized patients results in excellent outcomes. Therefore, it is necessary to carry out randomized trials with different steroid formulations to document the efficacy and safety of corticosteroids in COVID-19.

**Conflcit of Interest:** None.

**Author's Contribution**

Following authors have made substantial contributions to the manuscript as under:

KA & ZH: Conception, study design, drafting the manuscript, approval of the final version to be published.

SMK & RI: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AY & MUS: Critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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