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Pulse Dose Methylprednisolone Therapy in a Cohort of Very Severe COVID-19 Patients in a Resource-limited Setting in Myanmar: A Case Series of 13 Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Authors TTA and KM designed the study. Author HPT wrote the first draft of the manuscript. Author TMH performed the statistical analysis. Author TS did data extraction and synthesis. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Coronavirus disease 2019 (COVID-19) has very high mortality in severe forms of disease, where immunopathology plays an important role. Use of immunomodulating therapies including 6 to 12 mg of dexamethasone is well established. Higher doses of corticosteroids were used with reported success in some settings. This study aims to explore the role of pulse dose methylprednisolone therapy in very severe COVID-19 patients in preventing the need for ICU care and death in resource-limited setting.
Study Design: Retrospective case series study.
Place and Duration of Study: Oak-ta-chat-thal-ta-pwint COVID-19 treatment center in Yangon, Myanmar between September 2021 to December 2021.
Methodology: This study included 13 confirmed COVID-19 patients with severe to critical illness, who were treated with pulse dose methylprednisolone therapy. We reviewed the patients' demographics, comorbidities, and disease severity before starting pulse dose methylprednisolone therapy and changes in oxygen requirement, chest X-ray scores, inflammatory markers, development of significant clinical events, and 28 days mortality after therapy.
Results: Before pulse dose methylprednisolone therapy, all 13 patients had very severe disease (mean SPO_2/FiO_2 = 173 mmHg, mean SPO_2 = 88.54%, mean CRP = 115 mg/L, mean ferritin = 1,295.5 ng/mL and mean Brixia Score = 6.54). They received 3-7 days (mean = 5.5 days) of pulse dose methylprednisolone. Ten patients (76%) survived in a setting with limited ICU care. High ferritin was a significant predictor of mortality. Improvement in oxygen requirement was noticeable after 1-11 days (mean = 5.6 days). Hyperglycemia was common and confirmed bacterial infection was found in 3 patients, but all patients received empirical antibiotics therapy.
Conclusion: Pulse-dose methylprednisolone therapy may be an effective salvage therapy in a carefully selected subset of very severe COVID-19 patients. It might be a feasible alternative to other more expensive immunomodulating agents and organ support treatments in a resource-limited setting.

Keywords: COVID-19; pulse dose corticosteroid; methylprednisolone; resource-limited settings.

ABBREVIATIONS

ARDS : Acute Respiratory Distress Syndrome
COVID-19: Coronavirus disease 2019
CRP : C-reactive protein level in serum
ICU : Intensive Care Unit
PDMPT : Pulse Dose Methylprednisolone Therapy
SPO_2 : Peripheral capillary oxygen saturation
SPO_2/FiO_2: Ratio of peripheral capillary oxygen saturation to the inspired fraction of oxygen

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic disease caused by a novel corona virus SARS-Cov-2. Recently, the world health organization declared an end to COVID-19 as a disease of a public health emergency. Yet, many mysteries remain about the disease. Since its emergence in 2019, more than six million lives have been lost to this disease [1]. Hypoxic respiratory failure due to Acute Respiratory Distress Syndrome (ARDS) and multisystem failure due to cytokine release syndromes are significant events in critical cases of COVID-19. Immunopathology plays a major role in these critical stages of COVID-19 [2].

The use of low to moderate-dose dexamethasone therapy in severe COVID-19 has been well accepted [3]. In very severe cases, thrombo-inflammation in the lungs and alveolar damage progress despite low-dose dexamethasone and antiviral agents, requiring ventilatory support and advanced ICU care. The prognoses in these patients are very poor despite every effort with the use of advanced ICU supports [4,5]. In a resource-limited setting, advanced life supports are practically almost unavailable during a pandemic crisis and entering a critical stage in COVID-19 is usually a one-way downward spiral to death. The pathogenesis in these later stages of disease is mainly due to aberrant and dysfunctional inflammatory response and suppressing the inflammatory response theoretically might benefit.

Corticosteroids are potent non-specific immunosuppressive and anti-inflammatory agents [6]. They are also widely available in every setting and their use has been familiar to most clinicians for their historical use in severe autoimmune conditions. Various doses of corticosteroids were reportedly used in severe COVID-19 and the role of high-dose corticosteroids is still uncertain. The studies on high-dose corticosteroids in severe COVID-19 were mainly retrospective observational studies and the success rate has been varied due to the use of various doses of drug and choice of patients [7–19]. There are also concerns for potential harms like delayed viral clearance and superimposed infections. Short-term use of supra-physiological doses of corticosteroids is believed to act through a nongenomic pathway to downregulate immune cell activation and proinflammatory cytokine production [20]. We hypothesized that the high-dose corticosteroid would be beneficial if it is given in a critical time window at the start of severe unchecked inflammation.

This study aimed to explore the role of pulse dose methylprednisolone therapy in very severe COVID-19 patients in preventing the need for ICU care and death. The specific objectives were to describe the characteristics of patients treated with high-dose methylprednisolone therapy, ascertain the timing from disease onset and severity status at the initiation of pulse dose therapy, and describe the outcomes and complications of these patients.

2. METHODOLOGY

This study reports a case series of 13 patients who were treated with pulse dose methylprednisolone therapy. The study was done in a temporary COVID-19 treatment facility in Yangon, Myanmar. The study was conducted from September to December 2021, when the delta B1.617.2 strain of SARS-Cov2 was actively transmitting in the country, coinciding with the later part of the catastrophic "third wave". All patients admitted to the facility during the study period were reviewed for eligibility. There was no sample size calculation and all patients who received the therapy of interest during the study period were included. All adult patients more than 18 years of age with confirmed COVID-19 disease and who received pulse dose methylprednisolone therapy (defined as methylprednisolone >=250mg or equivalent for at least 3 consecutive days by clinician discretion) were included in the review. The variables of interest were extracted from the inpatient medical records of the electronic medical record systems. Outcomes data were extracted from the routine telephone follow-up record of the treatment facility until 28 days from the date of admission. Mortality status (death or survival) was the main outcome and receiving Pulse-Dose Methylprednisolone Therapy (PDMPT) was exposure and changes in SPO_2/FiO_2 status, Brixia Score before and after PDMPT, and biochemical markers (CRP, ferritin, and lymphocytes) were predictors; age and gender are potential confounders and days of COVID 19 and underlying co-morbidity and use of other immunomodulators were effect modifier. The age, sex, and underlying comorbid conditions were extracted from the initial clinical assessment record by the admitting medical officer. The dose and total duration of high-dose corticosteroid therapy was taken from the highest dose of corticosteroid which the patient received during admission and the duration of that dose, irrespective of the tapering doses or if-any previous smaller doses. The timing of therapy initiation was measured by days from the onset of symptoms and the severity of disease at the initiation was measured by oxygen requirement (SaO_2/FiO_2 ratio estimated from the dose of oxygen and pulse oximetry measurement), chest X-ray scores (Brixia score by Borghesi and Maroldi, 2020 [21] and biochemical markers of inflammation. Any other treatments received were also recorded and they were grouped into antiviral agents, anti-thrombotic, other immunomodulators, and antibiotics.

Any event after initiation of therapy until discharge was analyzed as potential complications of therapy. Infection was defined as any event of culture-confirmed or clinically suspected infection, requiring antibiotics therapy. Hyperglycemia was new onset or worsening hyperglycemia requiring any treatment or diet modifications. The clinical severity of the disease was classified as asymptomatic, mild, moderate, and severe, or critical as defined by the COVID-19 treatment guideline by the National Institute of Health [22]. Data were extracted and synthesized in excel spreadsheet. Statistical analysis was done with SPSS version 20. Regarding descriptive statistics, categorical data were analyzed using frequency table and contiunous data were analyzed using mean (SD), median (IQR) and 95%CI in accordance with their distribution. Chi square test was used for

inferential statistics and statistical significance was set at alpha value of 0.05.

3. RESULTS

A total of 13 patients received 3-7 days course of IV methylprednisolone therapy. Twelve patients received 1 G of methylprednisolone each day while only 1 patient was given 250mg of methylprednisolone therapy. Most of them (n=11) were also given oral Baricitinib and 9 patients also received two doses of tocilizumab (according to availability). CRP level was the earliest to fall after high-dose steroid therapy and improvement in hypoxia was noticeable only after 1-11 days with a mean duration of 5.6 days.

4. DISCUSSION

In this study, we reported the outcome of 13 very severe COVID-19 cases, treated with pulse dose methylprednisolone therapy. These patients were treated in a time of pandemic crisis in a very resource-limited setting where advanced ICU care was practically unavailable. Pule dose methylprednisolone therapy was used as a last resort salvage therapy and we could save 76% of them.

Current treatment guidelines for COVID-19 recommend 6-12 mg of dexamethasone in severe cases requiring oxygen therapy [3]. This recommendation was based on the results of clinical trials randomizing all severe patients and the lack of statistically significant results in comparison with a slightly larger dose of dexamethasone. However, we experienced certain subgroups of patients whose COVID-19-related alveolar damage and markers of inflammatory responses were not adequately controlled and who were at imminent risk of progressing into the critical stage. In those patients, we tried pulse dose methylprednisolone therapy with the hope that the dose-dependent non-specific immunosuppressive and anti-inflammatory effect of corticosteroids might rescue those hopeless patients. There were also reports of successful uses of similarly high doses of corticosteroids. These studies were small retrospective observational studies. There were also mixed results with different studies using different doses and different criteria for starting high-dose corticosteroids.

In those studies, the benefits of high-dose corticosteroids were seen in terms of mortality [7,13], oxygen requirement [16], ICU admission [13], and inflammatory markers [17]. These benefits were found especially in age less than 70 years of age (7) and if given not too early or too late [16]. Tromp et al (2021) also reported that high-dose corticosteroid therapy with methylprednisolone 1000mg/day for 3 days did not increase viral replication [17]. However, a recent systematic review and meta-analysis of 12 studies involving 2759 patients reported that high-dose corticosteroid was not better than conventional dose corticosteroid [15]. The trials in this meta-analysis used various doses, duration, and regimens of high-dose corticosteroids, resulting in high heterogeneity. A retrospective cohort study by Yaqoob et al (2022) also found that pulse dose steroid (MP 1G/day) was not better than the conventional dose, with a higher rate of acute kidney injury [18]. However, this study was done in patients admitted already to ICU, which is different from our patient population who are mostly inaccessible to ICU care. Another cohort study of 573 patients also reported higher mortality with corticosteroid doses higher than 250mg/day [12]. In this study, remdesivir use was one of the exclusion criteria and it may be one reason why more intensive immunosuppression resulted in higher mortality due to unchecked viral replication.

In our cohort of patients, we used higher doses of corticosteroids (1 gram of methylprednisolone for 3 to 7 days) and we started this regime as soon as the standard treatment was not working. The criteria for initiation were high oxygen requirement of more than 10 liter/minute, more than 50% of parenchymal involvement in chest X-rays, and high inflammatory markers in the absence of confirmed or suspected co-infection. Rapid progression of disease severity in terms of oxygen requirement and serial chest X-rays was also an important factor in considering the more aggressive treatment. All of our patients were also treated with intravenous remdesivir for 5 days. Intravenous tocilizumab was also given if the patient afforded the cost of the drug. However, this therapy was hard to start immediately since it was not readily available at the time. Nine out of 13 patients received tocilizumab therapy while the other 4 did not. The outcome was not significantly associated with the addition of additional immunomodulator therapy like tocilizumab. All 4 patients who could not afford this therapy survived but some treated with tocilizumab were lost.

Table 1. Description of 13 COVID-19 cases under the study following their outcomes

Variables	Outcomes		Total	Significant Test p-value "*p*"	Remark
	Alive n (%)	Death n (%)			
Age Group					
≤ 40 years	1 (100)	0 (0)	1 (7.7)	Fisher Exact Test X^2 =	
≥ 41-60 years	5 (71.4)	2 (28.6)	7 (53.8)	0.795	
> 61 years	4 (80)	1(20)	5 (38.5)	"*p*" = 1.00	
Minimum age: 27 years					
Maximum age: 85 years					
Mean (± SD): 56.63± 14.86 years					
Gender					
Male	4 (57.1)	3 (42.9)	7 (53.8)	Fisher exact X^2 = 5.424	
Female	6 (100)	0 (0)	6 (46.2)	"*p*" = 0.192	
Comorbidity *					
Yes	8 (80)	2 (20)	10 (79.9*)	X^2 = 0.231	
No	2 (66.7)	1 (33.3)	3 (23.1*)	"*p*" = 1.00	
*Diabetes, Hypertension, Ischemic Heart Disease, Obesity, Peripheral Vasculopathy					
Risk for Severe COVID					
Yes (≥ 61 years± underlying d/s	8 (80)	2 (20)	10 (76.9*)	X^2 = 0.231	
No (≤ 60 without underlying d/s)	2(66.6)	1 (33.3)	3 (23.1*)	"*p*" = 1.00	
Steroid duration (days)					
Minimum days	3	5		95% CI of the difference	
Maximum days	7	5		lower (-1.19)	
Mean ± SD	5.5 (± 1.84)	5 (± 0.0)		upper(2.93)	
Days from the start of steroid to improve in hypoxia					
Minimum days	1	4		95% CI of the difference	
Maximum days	10	11		lower (-6.09)	
Mean ± SD	5.4 (± 3.41)	6.33 (± 4.04)		upper(4.22)	
Additional immunosuppressive					
Baricitinib	3 (100)	0 (0)	3 (23.1)	X^2 = 1.501	
Nil	1 (100)	0 (0)	1 (7.7)	"*p*" = 0.27	
Tocilizumab, Baricitinib	6 (66.6)	3 (33.4)	9 (69.2)		
Symptoms days before admission					
<7 days	5 (83.3)	1 (16.7)	6 (46.2)	X^2 = 0.258	
≥7 days	5 (71.4)	2 (28.6)	7 (53.8)	"p" = 1.000	

Table 2. Comparison of disease severity status before PDMP therapy of 13 COVID-19 cases under study following outcomes

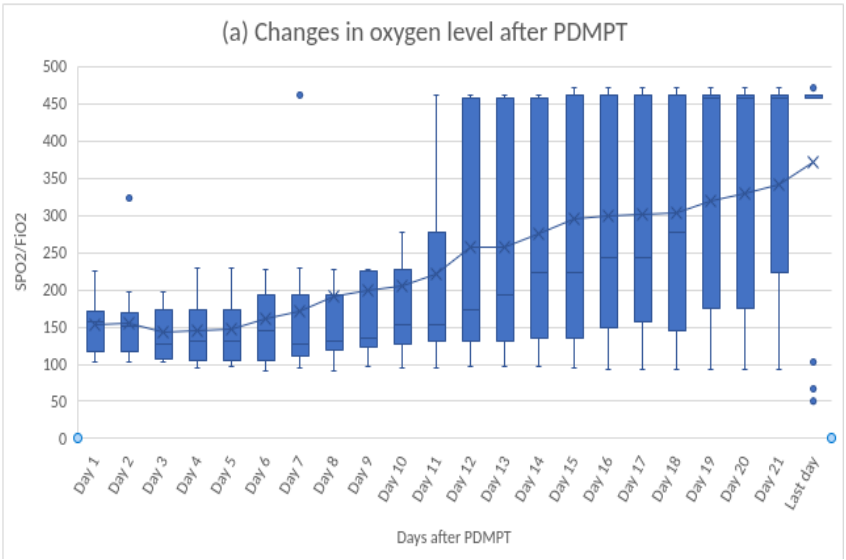
Disease severity parameters	Outcomes		Total	Significant Test p-value ("*p*")	Remark
	Alive	Death			
SPO_2/FiO_2 Before Steroid Therapy					
Minimum	96	100	96	95% CI of the	
Maximum	303	240	303	difference	
Mean (± SD)	168 (± 22.2)	193 (± 46.67)	173 (± 19.46)	lower (-130.06)	
				upper (79.59)	
				"*p*"= 0.61	
CRP Before Steroid Therapy					
Minimum	44.3	68.1	44.3	95% CI of the	
Maximum	264.8	151.5	264.8	difference	
Mean (± SD)	117(±2 4.4)	109.9 (± 46.67)	115 (± 10.16)	lower (-96.74)	
				upper (112.13)	
				"p"= 0.87	
Lymphocytes Before Steroid Therapy					
Minimum	0.37	0.63	0.37	95% CI of the	
Maximum	2.47	1.05	2.47	difference	
Mean (± SD)	0.96 (± 0.21)	0.86 (± 0.12)	0.93 (± 0.57)	lower (-0.76)	
				upper (0.97)	
				"p"=0.79	
Ferritin Before Steroid Therapy					
Minimum	204	1392	204	95% CI of the	
Maximum	1902	3001	3001	difference	
Mean (± SD)	944.76 (± 216.42)	2464.67 (± 536.3)	1295.5 (± 268.8)	lower (-2,854.74)	
				Upper (455.07)	
				"p" = 0.009	
Lowest SPO2 at Home					
Minimum days	75	88	75	95% CI of the	
Maximum days	93	92	93	difference	
Mean ±SD	88.2(± 1.718)	89.67 (±1.2)	88.54(± 1.33)	lower (-8.7)	
				upper (5.77)	
				"p"= 0.66	

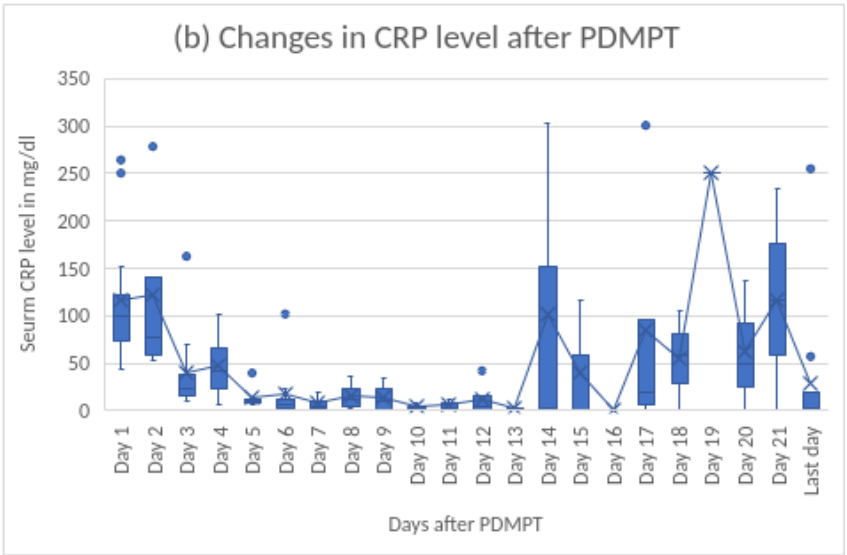
Table 3. Case Summary of 13 severe COVID-19 patients treated with pulse dose methylprednisolone therapy

Case No	Age	Sex	Comorbidities	SPO2 /FiO2	CRP	Lymphocyte	Ferritin	Brixia score	Steroid dose	Steroid duration	Additional immunosuppressives	Events after treatment	Final Outcome
1	60	F	Peripheral vascular disease	95.83	59.86	0.41	326	7	1G	7	tocilizumab, baricitinib	Hyperglycemia	survive
2	43	F	Nil	101.04	73.23	1.01	204	10	1G	7	tocilizumab, baricitinib	Hyperglycemia, Bacterial pneumonia	survive
3	72	F	Hypertension, cardiovascular disease	194.00	264.76	1.09	411.3	2	250mg	5	tocilizumab, baricitinib	Hyperglycemia, GI bleeding	survive
4	42	M	obesity, hypertension	98.96	108.9	0.37	1621	10	1G	6	tocilizumab, baricitinib	Hyperglycemia, Staphylococcus bacteriaemia, Fungal infection	survive
5	55	M	obesity	98.96	75.35	2.47	1902	10	1G	7	tocilizumab, baricitinib	Hyperglycemia, Septicemia	survive
6	61	M	Hypertension, coronary artery disease, obesity	100.00	151.46	0.63	1392	10	1G	5	tocilizumab, baricitinib	GI bleeding, hyperglycemia, Pulmonary edema	die
7	55	M	hypertension	240.00	110.41	0.9	>3000	8	1G	5	tocilizumab, baricitinib	Hyperglycemia, GI bleeding, CNS thrombosis	die
8	59	M	Nil	240.00	68.1	1.05	>3000	4	1G	5	tocilizumab, baricitinib	Hyperglycemia	die
9	85	M	Hypertension, coronary artery disease	240.00	99.15	0.43	1539.3	6	1G	7	tocilizumab, baricitinib	Hyperglycemia	survive
10	27	F	Nil	194.00	79.07	1.33	1707.7	6	1G	7	baricitinib	Hyperglycemia, GI bleeding	survive
11	65	F	diabetes	165.00	250.43	0.45	885.9	2	1G	3	nil	Hyperglycemia, Septicemic shock	survive
12	46	F	hypertension	303.13	44.3	1.36	253	7	1G	3	baricitinib	Hyperglycemia	survive
13	67	M	Coronary artery disease, benign prostate hypertrophy, renal stones disease	190.00	121.87	0.71	487.4	3	1G	3	baricitinib	Hyperglycemia, shock	survive

After initiation of therapy, CRP levels invariably fall after a day or two but rise again in the 3rd week in some cases Fig. 1. Superimposed infection was identified in some of those cases and successfully treated. However, improvement in oxygen level was noticeable only after a week. Ferritin level and Chest X-ray scores showed no noticeable changes after PDMPT until 3 weeks of follow-up. This can be explained by the fact that serum ferritin was not frequently measured in our cohorts and the follow-up period was short to detect the usually slow radiological improvements. In two cases of mortality, there was no improvement in hypoxia, and CRP level rise again after initial falling. This indicates that inflammatory response was not adequately controlled or smoldering co-infection might have been missed. These cases had very high ferritin and CRP before starting PDMPT. In the third case of mortality, oxygenation, and inflammatory markers improved but the patient was lost due to a CNS complication, a thrombotic event, or infection, which we could not confirm. High ferritin was only significantly associated with mortality in our cohort.

Generally, the cases we treated with PDMPT were very severe from the outset and failed to respond to standard treatments. Remdesivir and PDMPT (in combination with tocilizumab in some cases) successfully rescued most of them, even in a setting without advanced ICU care. Hyperglycemia was very common after PDMPT as expected and empirical antibiotics therapies were used in all cases, but the definitive infective infection was proved only in three cases.





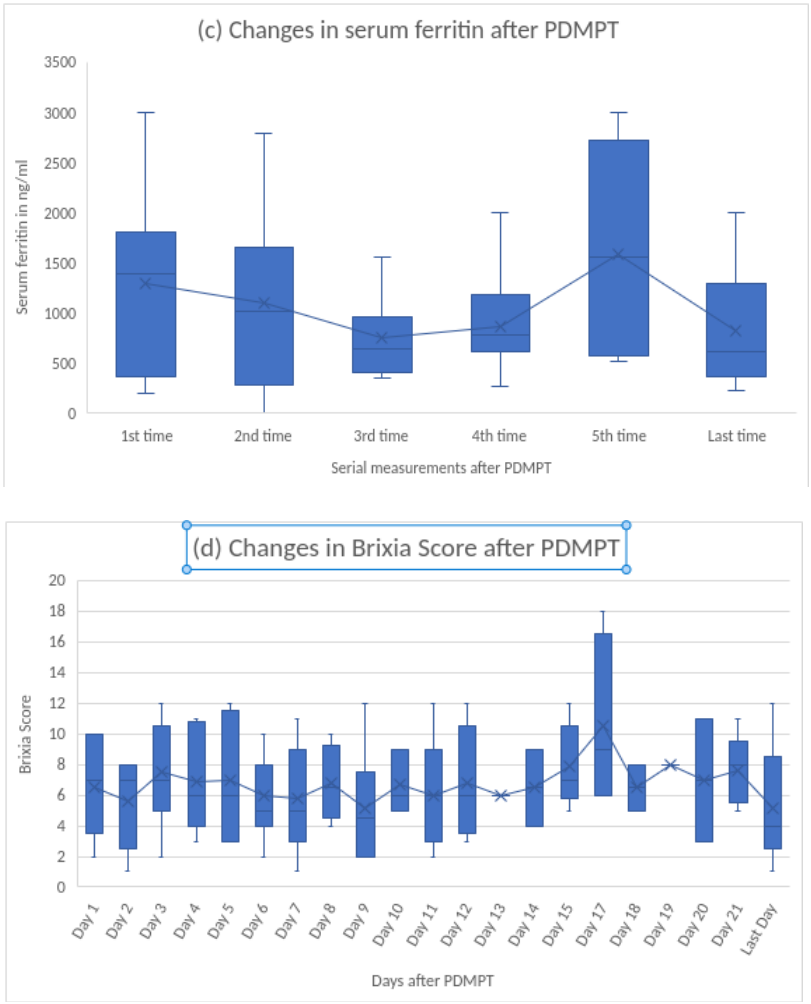


Fig. 1. Box plots showing serial changes in disease severity parameters after PDMPT

Day 1 represents the first day of PDMPT. The horizontal line within each box represents the median and the cross represents the mean, the lower and upper border of each box represent the lower and upper quartiles and the T bar represents 1.5 x IQR and the dots are outliers. For measurement of hypoxia, SpO_2/FiO_2 was used as an estimate of PaO_2/FiO_2, with the value of 200-300 representing mild degree, 100-200 representing moderate degree, and <100 representing severe degree of ARDS

We recommend further randomized controlled trials of pulse dose methylprednisolone therapy in very severe COVID-19 patients with high oxygen requirement, diffuse parenchymal involvement in chest X-rays or rapidly changing X-rays, and high markers of inflammation. Since contextual factors like the availability of high-end supportive care are varied in different healthcare settings, defining healthcare resources settings in future trials might be useful. We observed several limitations of this study. First, we reported the story of a small number of cases, and these cases were not randomly selected, limiting the generalizability of the study results. The cases were followed up for only 28 days and we did not study the long-term complications.

5. CONCLUSION

Intravenous Pulse dose of methylprednisolone 1 gram per day for 3 to 7 days might be an effective salvage therapy for very severe COVID-19 patients. This is especially hopeful for patients in resource-limited settings. Future studies are warranted in carefully selected populations of very severe diseases.

CONSENT

Written informed consent was obtained from the patient or the next of kin for publication of this case series.

ETHICAL APPROVAL

All authors hereby declare that this study was approved by the local ethics committee and has therefore been performed following the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard with vaccination data. [internet]. Available:https://covid19.who.int/ Access on 2023 May 25
2. Lamers MM, Haagmans BL. SARS-CoV-2 pathogenesis. Nature Reviews Microbiology. 2022;20(5):270–84. [internet] Available:https://www.nature.com/articles/s41579-022-00713 Access on 2023 may 25
3. Corticosteroids | COVID-19 Treatment Guidelines. [internet] Available:https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/corticosteroids/ Access on 2023 may 28
4. Anesi GL, Jablonski J, Harhay MO, Atkins JH, Bajaj J, Baston C, et al. Characteristics, outcomes, and trends of patients with covid-19-related critical illness at a learning health system in the United States. Ann Intern Med. 2021;174(5):613–21 [internet]. Available:https://pubmed.ncbi.nlm.nih.gov/33460330/ Access on 2023 may 28
5. Biccard BM, Gopalan PD, Miller M, Michell WL, Thomson D, Ademuyiwa A, et al. Patient care and clinical outcomes for patients with COVID-19 infection admitted to african high-care or intensive care units (ACCCOS): A multicentre, prospective, observational cohort study. Lancet. 2021;397(10288):1885–94. [internet] Available:https://pubmed.ncbi.nlm.nih.gov/34022988/ Access on 2023 may 28
6. Suran K, Pushpa S. Pulse therapy – a newer approach. Indian Journal Of Multidisciplinary Dentistry. 2017;7(1):41.
7. Climente-Martí M, Ruiz-Millo O, López-Cruz I, Atienza-García Á, Martínez-Moragón E, Garijo-Gómez E, et al. Impact of intermediate to high doses of methylprednisolone on mortality rate in patients with COVID-19 pneumonia-induced severe systemic inflammation. Int J Clin Pract. 2021; 75(9):1.
8. Fan Q, Deng K, Huang H, He R, Deng X, Lan Y, et al. Kinetics of severity biomarkers and immunological features of methylprednisolone therapy for severe COVID-19 patients. Front Immunol. 2022;8:13.
9. Go Rc, Nyirenda T, Bojarian M, Hosseini Dk, Kim K, Rahim M, et al. Racial/ethnic disparities on inflammation and response to methylprednisolone in severe COVID-19 pneumonia. Bmc Infect Dis. 2022:1;22(1).
10. Kumar V, Kashyap A, Kaur S, John M, Sibia R, Chopra V, et al. Comparison of tocilizumab and high-dose methylprednisolone pulse on outcomes in severe corona virus disease-2019: Tame-covid, a retrospective multicentric study. Int J Appl Basic Med Res. 2021;11(4):263. [internet] Available:https://pubmed.ncbi.nlm.nih.gov/34912692/ Access on 2022 mar 14
11. Lim Pc, Wong Kl, Rajah R, Chong Mf, Chow Ts, Subramaniam S, et al. Comparing the efficacy of tocilizumab with corticosteroid therapy in treating COVID-19 patients: A systematic review and meta-analysis. DARU. Journal Of Pharmaceutical Sciences. Springer Science And Business Media Deutschland GmbH. 2022;30:211–28.
12. Monreal E, Sainz De La Maza S, Natera-Villalba E, Beltrán-Corbellini Á, Rodríguez-Jorge F, Fernández-Velasco JI, et al. High versus standard doses of corticosteroids in severe COVID-19: A retrospective cohort study. European Journal Of Clinical Microbiology And Infectious Diseases. 2021;1;40(4):761–9.

13. Pinzón MA, Ortiz S, Holguín H, Betancur JF, Arango DC, Laniado H, et al. Dexamethasone vs methylprednisolone high dose for COVID-19 pneumonia. Plos One. 2021;16(5). [internet]
Available:https://pubmed.ncbi.nlm.nih.gov/34033648/
Access on 2022 Dec 27
14. Ro S, Nishimura N, Imai R, Tomishima Y, So C, Murakami M, et al. Identification of patients with COVID-19 who are optimal for methylprednisolone pulse therapy.
15. Tan Rsj, Ng KT, Xin CE, Atan R, Yunos NM, Hasan MS. High-dose versus low-dose corticosteroids in Covid-19 patients: A systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2022;1;36(9): 3576–86.
16. Tokano M, Tarumoto N, Imai K, Sakai J, Ishibashi N, Yokota K, et al. Timing of initiation of methylprednisolone pulse therapy in patients with COVID-19. COVID. 2022; 21;2(5):532–9.
17. Tromp K, Van Der Zee P, Rokx C, Van Kampen J, Gommers D, Endeman H. Effect of methylprednisolone on inflammation and coagulation in patients with severe COVID-19: A retrospective cohort study. Biomarker insights. Sage Publications Ltd; 2021;16..
18. Yaqoob H, Greenberg D, Hwang F, Lee C, Vernik D, Manglani R, et al. Comparison of pulse-dose and high-dose corticosteroids with no corticosteroid treatment for COVID-19 pneumonia in the intensive care unit. J Med Virol. 2022;1;94(1):349–56.
19. Zúñiga Mál, Moreno-Moral A, Ocaña-Granados A, Padilla-Moreno Fa, Castillo-Fernández Am, Guillamón-Fernández D, et al. High-dose corticosteroid pulse therapy increases the survival rate in COVID-19 patients at risk of hyper-inflammatory response. Plos One. 2021;16(1): e0243964. [internet]
Available:https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0243964
Access on 2023 may 17
20. Kumar A, Singh S, Sherawat V. Pulse therapy – A newer approach. Indian Journal Of Multidisciplinary Dentistry. 2017;26;8(11):1739.
21. Borghesi A, Maroldi R. COVID-19 outbreak in italy: Experimental chest x-ray scoring system for quantifying and monitoring disease progression. Radiologia Medica. 2020;125(5):509–13 [internet].
Available:https://link.springer.com/article/10.1007/s11547-020-01200-3
Access on 2023 may 17
22. Clinical Spectrum | COVID-19 Treatment Guidelines [internet].
Available:https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
Access on 2023 may 17

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