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A Retrospective Data Audit of Outcome of Moderate and Severe Covid-19 Patients Who Had Received MP and Dex: A Single Center Study

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Purpose: To evaluate the necessity of the application of glucocorticoid (GC) in moderate COVID-19 patients, and which is the optimal choice between methylprednisolone (MP) and dexamethasone (DEX) in the clinical use of GC in different types of COVID-19 patients.

Patients and Methods: The study included patients with COVID-19 in Shanxi, China, from December 18, 2022, to March 1, 2023. The main clinical outcomes were 30-day mortality, disease exacerbations, and hospitalization days. Secondary outcomes included the demand for non-invasive ventilator-assisted ventilation (NIPPV)/invasive mechanical ventilation (IMV), the need for GC regimen escalation in follow-up treatment, duration of GC treatment, and complications including hyperglycemia and fungal infection.

Results: In moderate patients (N = 351), the rate of exacerbation and the need for GC regimen escalation in follow-up treatment was highest in the no-use GC group (P = 0.025, P = 0.01), the rate of fungal infections was highest in the DEX group (P = 0.038), and MP 40 mg/day or DEX 5 mg/day reduced exacerbations with consistent effects. In severe patients (N = 371), the two GC regimens do not affect their 30-day mortality and exacerbation rate, but the number of hospital days was significantly lower in the MP group compared with the DEX group (P < 0.001).

Conclusion: GC use is beneficial in mitigating exacerbations in moderate patients and in patients with moderate COVID-19. In severe patients, MP reduces the number of hospitalization days compared with DEX and may be a superior choice.

Keywords: COVID-19, Glucocorticoid, Methylprednisolone, Dexamethasone

Introduction

The coronavirus disease 2019 (COVID-19) has emerged as a major global health risk and has been declared the sixth global public health emergency.[1] By combining with angiotensin-converting enzyme 2 (ACE2) to enter cells, the novel coronavirus can induce excessive activation of immune cells, resulting in excessive oxidative stress and cytokine storm. It can eventually lead to adult respiratory distress syndrome (ARDS), septic shock, multiple organ failure, and even death. This cytokine storm plays a critical role in the pathogenesis of severe and long-term COVID-19.[2] It has been found that rational use of glucocorticoid (GC) can reduce the mortality and complications of COVID-19 patients and improve the prognosis of patients.[3]

The mechanism of GC therapy for COVID-19 includes the following aspects. On the one hand, for severe patients, cytokine release syndrome (CRS) is an important feature and the main cause of disease exacerbation in the development

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of COVID-19. CRS is closely related to the occurrence of ARDS and multiple organ failure, and GC can effectively inhibit CRS.[4–6] On the other hand, GC inhibited the entrance of the SARS-CoV-2 spike pseudotyped virus into cells by binding to ACE2.[7] In addition, systemic GC can regulate lung injury caused by inflammatory mediators, reduce pulmonary edema, increase the absorption of inflammation, improve oxygenation, and also play a role in alleviating pulmonary fibrosis.[3]

WHO guidelines recommend the use of systemic GC therapy in severe and critical cases, but not in non-severe cases.[8] The US National Institutes of Health treatment guidelines suggest that the use of GC in patients hospitalized for COVID-19, and dexamethasone (DEX) 6 mg/day alone is preferred.[9] The above recommendations are mainly based on a controlled, open-label trial in the United Kingdom which showed that in patients hospitalized with COVID-19, the use of DEX 6 mg/day resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation (IMV) or oxygen alone at randomization. Methylprednisolone (MP) was not included in the study.[10]

During the COVID-19 pandemic, diverse GC formulations and dosages have been applied, resulting in varying outcomes. Studies indicate that MP is more effective than DEX at shortening hospital stays, reducing morbidity, and decreasing severity markers in COVID-19 treatment.[11–13] Conversely, other studies either contradict these findings or show no significant difference in primary outcomes between the two treatments.[14–16] MP is almost always the first choice for the application of GC in lung diseases.[17–19] This preference is partly due to MP's rapid onset of action. MP, an exogenous hormone processed by the liver, predominantly accumulates in the lungs, making it ideal for ARDS treatment to lessen interstitial lung edema and prevent pulmonary fibrosis.[20] Furthermore, GC operates through two mechanisms: as physiological hormones, they primarily affect gene expression—a process with a dose limit. In pharmacological doses, they act via second-messenger signaling, necessitating higher than physiological levels.[21] MP, at these doses, preferentially targets pulmonary tissues, concentrating effectively in affected lung areas. In contrast, DEX exhibits more systemic effects and lacks such targeted specificity.[21–23] This targeted delivery likely contributes to MP's superiority in treating lung diseases.

In conclusion, glucocorticoids are recognized as effective in mitigating cytokine storms; however, their types and dosages for COVID-19 remain controversial. Based on existing studies using different doses of MP and DEX, and the lack of clinical studies on the use of GC in moderate patients. And considering that different ethnic populations may exhibit varying responses to COVID-19 infection and GC therapy. We collected clinical data of different types of COVID-19 patients admitted to the Second Affiliated Hospital of Shanxi Medical University in China during the COVID-19 pandemic to evaluate the necessity of using GC in moderate patients with COVID-19 and the merits of different types of GC in the treatment of moderate and severe COVID-19 patients, aiming to provide theoretical evidence for the standardized use of GC in COVID-19 patients.

Material and Methods

Study Design and Settings

In this study, we retrospectively collected clinical data on 722 patients with moderate and severe COVID-19 who met the "Diagnostic and Treatment Protocol for COVID-19 Infection (Trial Version 10)" at the Second Hospital of Shanxi Medical University between December 18, 2022, and March 1, 2023.[24] The Ethics Committee of the Second Hospital of Shanxi Medical University approved this study, approval number 2023 YX 131.

Moderate patients were divided into the no-use GC group, the MP 40 mg/day group, and the DEX 5 mg/day group. Severe patients were divided into the MP 40 mg/day group and the DEX 5 mg/day group. We also included the MP group 20 mg/day for comparison of exacerbation rates with the MP group 40 mg/day to explore the optimal dose of GC.

Participants Characteristics

Study Participants Included the Following Patients

1. According to the diagnostic criteria in the "Diagnostic and Treatment Protocol for COVID-19 Infection (Trial Version 10)",[24] Patients exhibited clinical manifestations of COVID-19 infection and had one or more positive results from the following etiological or serological tests: (1) Novel coronavirus nucleic acid test positive. (2)

Novel coronavirus antigen test results positive. (3) Novel coronavirus culture and isolation are positive. (4) Compared to the acute phase, the convalescent phase showed four times or more increase in novel coronavirus IgG antibodies.

2. Patients with moderate and severe COVID-19 who meet the "Diagnostic and Treatment Protocol for COVID-19 Infection (Trial Version 10)".[24]

Classification Criteria for Severity of COVID-19 Patients

According to the "Diagnostic and Treatment Protocol for COVID-19 Infection (Trial Version 10) ",[24] COVID-19 patients are classified into four types, with the specific criteria as follows:

1. Mild: The main symptoms are upper respiratory tract infections, such as dry throat, sore throat, cough, and fever.
2. Moderate: persistent high fever >3 days and/or cough, shortness of breath, etc., but respiratory rate (RR) <30 breaths/min, oxygen saturation >93% at rest. Imaging shows the characteristic features of COVID-19 pneumonia.
3. Severe: In adults, one of the following criteria is met and cannot be explained by anything other than COVID-19 infection: (1) Shortness of breath with RR >30 times/min; (2) Finger oxygen saturation at rest is less than 93% on inspiration; (3) Arterial oxygen partial pressure (PaO2)/Fraction of inspired oxygen (FiO2)<300mmHg (1mmHg = 0.133kPa); (4) Progressive worsening of clinical symptoms and significant progression of >50% of the lesion on lung imaging within 24 to 48 hours.
4. Critical: Patients who fulfill one of the following conditions: (1) Respiratory failure requiring mechanical ventilation; (2) Shock; (3) Combined with other organ failure requiring ICU monitoring.

The Following Patients Were Excluded

1. Mild and critical patients in "Diagnostic and Treatment Protocol for COVID-19 Infection (Trial Version 10)".[24]
2. Patients who had used GC and related products within 2 months before inclusion.
3. Patients who died within 48 hours of admission.
4. Use of GC other than MP and DEX in the patient's admission regimen, or the presence of a combination of MP and DEX.

Research Methodology

All clinical data was obtained from electronic medical records and extracted by two independent researchers using a standardized data collection form. Clinical data including general information, laboratory indicators, days of hospitalization, complications, post-admission treatment measures, etc.

The primary outcomes were 30-day mortality, disease exacerbation, and length of hospital stay. Secondary outcomes included the demand for NIPPV /IMV, the need for GC regimen escalation in follow-up treatment, the duration of GC treatment, and complications including hyperglycemia and fungal infection.

Deterioration Assessment for COVID-19 Patients is Subject to the Following Conditions

The criteria for 'Deterioration assessment' in our study were based on specific indicators for early warning of severe or critical illness, derived from the Diagnosis and Treatment Protocol for COVID-19 Patients (Tentative 10th Version).[24] These criteria included:

1. Progressive worsening of hypoxemia or respiratory distress.
2. Significant changes in tissue oxygenation indicators (such as oxygen saturation and oxygenation index) or a marked increase in lactate levels.
3. Decrease in peripheral blood lymphocyte count or a significant increase in inflammatory markers (such as IL-6, CRP, and ferritin).
4. Noticeable rise in D-dimer and other coagulation-related indicators.
5. Evident progression of pulmonary lesions on chest imaging.

Additionally, two senior physicians with extensive clinical experience evaluated each patient's condition based on these indicators and the COVID-19 classification criteria to determine whether deterioration had occurred. Specifically,

this was defined as moderate COVID-19 cases progressing to severe, critical, or resulting in death, and severe COVID-19 cases progressing to critical or resulting in death.

Statistical Analysis

Statistical analysis was performed using SPSS25.0 and GraphPad Prism v8.3.0. A normality test was performed first for numerical variables. If all groups met normality, the mean (standard deviation) was used for statistical description, the *T*-test was used for comparison between two groups, and the analysis of variance was used for comparison between three or more groups. Otherwise, the median (interquartile distance) was used for statistical description, and the non-parametric test was used for inter-group comparison. Categorical variables were expressed as frequency (percentage), and unordered categorical variables were tested with chi-square or Fisher's exact tests. Binary logistic regression analysis was performed to estimate the univariate and multivariate odds ratios (OR) and 95% confidence intervals (CI) for the risk of 30-day mortality and deterioration. Finally, Kaplan–Meier survival curves revalidate the effect of two regimens on 30-day mortality in severe patients. Statistical significance was considered two-tailed $p < 0.05$.

Results

Demographic Characteristics and General Information of COVID-19 Patients

A total of 722 patients were divided into 351 patients in the moderate group, and 371 patients in the severe group. The number of patients in the no-use GC, MP, and DEX groups in the moderate patient group were 135, 81, and 94, respectively. Forty-one moderate patients used the MP 20mg/day regimen, and given their small sample size, their baseline information was not performed. The number of patients in the MP group versus the DEX group in the severe patient group was 243 and 128, respectively.

The median age was 69(18) years in the moderate group and 75(15) years in the severe group. 50.3% of the moderate patients were male and 63.9% of the severe patients. The BMI for moderate and severe patients was 23.437 (5.507), 23.5 (5.26) kg/m2. Among 722 patients, hypertension, diabetes mellitus, cardiac ischemia, and dyslipidemia were the most common comorbidities. Moreover, 32.1% of the severe patients had a history of smoking, compared to 17.8% of the moderate group. 21.9% of moderate patients had a history of prior medication and 67.9% of severe patients. The median time from onset to admission was 10 (10) days and 10.18 (4) days for moderate and severe patients, respectively. Fever, cough, expectoration, fatigue, and anorexia were the most common clinical symptoms, followed by dizziness/headache, myalgia, nausea and vomiting, and pharynx-ache (Table 1 and Table 2).

Table 1 General Demographics and Characteristics of the 310 Moderate COVID-19 Patients

General Information	All patients (n=310)	Routine Treatment (n=135)	MP 40 mg/d (n = 81)	DEX 5 mg/d (n = 94)	P-value
Age,(years)	69(18)	66(15)	70(19)	70 (15)	**0.002**
Sex (male)	156(50.3%)	65(48.1%)	47(58%)	44(46.8%)	0.267
BMI (kg/m2)	23.437(5.507)	23.335(5.795)	23.588(5.438)	24.141(5.57)	0.315
Comorbidities, n(%)	237(76.5%)	94(69.6%)	67(82.7%%)	76(80.9%)	**0.044**
Smoke	55(17.8%)	19(14.1%)	20(24.7%)	16(16%)	0.14
Hypertension	126(40.6%)	52(39.5%)	34(42%)	40(42.6%)	0.797
Diabetes	82(26.5%)	31(23%)	24(29.6%)	27(28.7%)	0.469
Cardiac ischaemia	48(15.5%)	17(12.6%)	13(16%)	18(19.1%)	0.397
COPD, asthma	25(8.1%)	13(9.6%)	9(11.1%)	3(3.2%)	0.107
Liver and kidney diseases	19(6.1%)	4(3.0%)	8(9.9%)	7(7.4%)	0.1
Hematological Disease	17(5.5%)	5(3.7%)	5(6.2%)	7(7.6%)	0.43
CNS diseases	34(11%)	10(7.4%)	12(14.8%)	12(12.8%)	0.193

(*Continued*)

Table 1 (Continued).

General Information	All patients (n=310)	Routine Treatment (n=135)	MP 40 mg/d (n = 81)	DEX 5 mg/d (n = 94)	P-value
Autoimmune disease	12(3.9%)	8(6%)	2(2.5%)	2(2.1%)	0.291
Neoplasma	16(5.2%)	5(3.7%)	7(8.6%)	4(4.3%)	0.31
Other diseases	68(21.9%)	229(21.5%)	19(23.5%)	20(21.3%)	0.928
Medication history	37(21.9%)	26(22.6%)	7(23.3%)	4(16.7%)	0.797
Antihypertensives drugs	123(39.7%)	46(34.1%)	35(43.2%)	42(44.7%)	0.204
Hypoglycemic drugs	62(20%)	27(20%)	13(16%)	22(23.4%)	0.479
Antihyperlipidemic drugs	61(19.7%)	25(18.5%)	16(19.8%)	20(21.3%)	0.875
Antiplatelet drugs	61(19.7%)	20(14.8%)	18(22.2%)	23(24.5%)	0.156
Other drugs	55(17.7%)	15(11.1%)	19(23.5%)	21(22.3%)	**0.027**
COVID–19 characteristics					
Time to Admission (days)	10(10)	10 (13)	9(6)	10(7)	0.43
Fever	242(78.1)	97(71.9%)	67(82.7%)	78(83%)	0.067
Maximum temperature	38.58(1)	38.5(0.92)	38.5(1)	38.5 (0.55)	0.146
Cough	230(74.2%)	88(65.2%)	66(81.5%)	76(80.9%)	**0.006**
Expectoration	220(71%)	84(62.2%)	64(79%)	72(76.6%)	**0.011**
Dyspnea	134(43.2%)	59(43.7%)	36(44.4%)	39(41.5%)	0.915
Pharynx-ache	28(9%)	10(7.4%)	6(7.4%)	12(12.8%)	0.318
Myalgia	37(11.9%)	15(11.1%)	9(11.1%)	13(13.8%)	0.794
dizziness /headache	42(13.5%)	14(10.4%)	12(14.8%)	16(17%)	0.326
Fatigue	140(45.2%)	58(43%)	35(43.2%)	47(50%)	0.528
Anorexia	127(41%)	50(37%)	35(43.2%))	42(44.7%)	0.457
Nausea and vomiting	33(10.6%)	13(9.6%)	7(8.6%)	13(13.8%)	0.475

Note: Bold font indicates statistically significant values ($p < 0.05$).

Table 2 General Demographics and Characteristics of the 371 Severe COVID-19 Patients

General Information	All patients (n=371)	MP 40 mg/d (n = 243)	DEX 5 mg/d (n = 128)	P-value
Age,(years)	75(15)	74.5(11)	74.5(15)	0.60
Sex (male)	237(63.9%)	159(65.4%)	78(60.9%)	0.39
BMI (kg/m2)	23.5(5.26)	24(5.57)(	23.46(5.2)	**0.01**
Comorbidities, n(%)	309(83.3%)	202(83.1%)	107(83.6)	0.91
Smoke	119(32.1%)	84(34.6%)	35(27.3%)	0.16
Hypertension	176(47.4%)	114(46.9%)	72(48.4%)	0.78
Diabetes	94(25.3%)	55(22.6%)	39(30.5%)	0.09
Cardiac ischaemia	74(19.9%)	43(17.7%)	31(24.2%)	0.14
COPD, asthma	21(5.7%)	18(7.4%)	3(2.3%)	0.05
Liver and kidney diseases	8(2.2%)	4(1.6%)	4(3.1%)	0.46
Hematological Disease	16(4.3%)	11(4.5%)	5(3.9%)	0.78
CNS diseases	41(11.1%)	31(12.8%)	10(7.8%)	0.15
Autoimmune disease	16(4.3%)	13(5.3%)	3(2.3%)	0.16
Neoplasma	30(8.1%)	15(6.2%)	15(11.7%)	0.06
Other diseases	63(17.0%)	41(16.9%)	22(17.2%)	0.94
Medication history	252(67.9%)	163(64.7%)	89(69.5%)	0.63
Antihypertensives drugs	175(47.2%)	113(64.6%)	62(48.4%)	0.723
Hypoglycemic drugs	94(25.5%)	54(22.4%)	40(31.3%)	0.063
Antihyperlipidemic drugs	79(21.3%)	44(18.1%)	35(27.3%)	0.039

(*Continued*)

Table 2 (Continued).

General Information	All patients (n=371)	MP 40 mg/d (n = 243)	DEX 5 mg/d (n = 128)	P-value
Antiplatelet drugs	67(18.1%)	37(15.4%)	30(23.4%)	0.051
Other drugs	46(12.4%)	32(13.2%)	14(10.9%)	0.535
COVID–19 characteristics				
Time to Admission (days)	10.18(4)	9(4)	8(6)	0.49
Fever	306(82.5%)	207(85.2%)	99(77.3%)	0.06
Maximum body temperature	38.58(1)	38.5(1)	38.65(0.9)	0.06
Cough	314(84.6%)	214(88.1%)	100(78.1)	**0.02**
Expectoration	301(81.4%)	204(84.3%)	97(75.8%)	**0.05**
Dyspnea	244(65.8%)	166(68%)	78(60.9%)	0.16
Pharynx-ache	30(8.1%)	20(8.2%)	10(7.8%)	0.89
Myalgia	45(12.2%)	33(13.6%)	12(9.4%)	0.23
dizziness /headache	42(11.3%)	27(11.1%)	15(11.7%)	0.86
Fatigue	171(46.1%)	114(46.9)	57(44.5%)	0.66
Anorexia	137(36.9%)	89(36.6%)	48(37.5%)	0.87
Nausea and vomiting	8(2.2%)	5(2.1%)	3(2.3%)	1

Note: Bold font indicates statistically significant values ($p < 0.05$).
Abbreviations: BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; CNS, Central nervous system.

Laboratory Parameters Within 24 hours of COVID-19 Patients

In moderate patients, glycosuria, proteinuria, and electrolyte disturbances were 46 (14.8%), 42 (13.5%), and 142 (45.8%), respectively, the remaining indicators are expressed as medians (interquartile spacing) and are within the normal range except for hemoglobin, CRP, and LDH. The MP group and DEX group had lower absolute lymphocyte values ($P < 0.001$), higher CRP ($P = 0.003$), LDH ($P = 0.004$), α-hydroxybutyrate dehydrogenase (HBDH) ($P < 0.001$), fibrinogen ($P = 0.001$), and electrolyte disturbance ($P = 0.012$) compared to the no-use GC group, the MP group had higher absolute hemoglobin values compared to the other two groups ($P = 0.004$), and the rest of the laboratory parameters were not statistically different between the groups (Table 3).

Table 3 Laboratory Parameters Within 24 hours of Admission in Moderate COVID-19 Patients

	Normal range	All patients (n=310)	Routine Treatment (n=135)	MP 40 mg/d (n = 81)	DEX 5 mg/d (n = 94)	P-value
WBC(×109/L)	3.50–9.50	5.715(3.17)	5.63(3.09)	6.12(2.80)	5.24(4.36))	0.881
Neutrophils(×109/L)	1.80–6.30	3.875(2.71)	3.56(2.35)	4.66(2.89)	4.03(3.65)	0.147
Lymphocytes (×109/L)	1.10–3.20	1.145(0.92)	1.26(0.94)	0.95(0.65)	0.78(0.4)	**0.001**
Platelet (×109/L)	125.00–350.00	207.5(122)	208(125)	212(109)	180(159)	0.489
Hemoglobin (g/L)	130.00–175.00	126.5(22)	126(17)	131(27.25)	124(37)	**0.004**
PCT (ng/mL)	0.00–0.51	0.4(0.21)	0.4(0.24)	0.385(0.19)	0.43(0.09)	0.297
CRP (mg/L)	<5	22.5(42.17)	18.2(31.03)	30.415(53.05)	48.66(73.26)	**0.003**
ALT(U/L)	9.00–50.00	22.2(21.95)	21.5(20.8)	22.95(28.47)	26.6(24.3)	0.371
Total protein(g/L)	65.00–85.00	68.2(9.6)	68.3(10.1)	69.2(8.3)	66.6(7.75)	0.283
Albumin(g/L)	40.00–55.00	36.4(5.85)	36.5(5.7)	37(6.68)	34(3.85)	0.083
Globulin(g/L)	20.00–40.00	32(6.22)	31.8(6.5)	32.2(6.1)	33.4(4.55)	0.948
Ratio of albumin to globulin		1.105(0.338)	1.101(0.355)	1.130(0.373)	1.053(0.273)	0.546
BUN (mmol/L)	3.60–9.50	5.1(2.38)	5.1(2.8)	5.1(1.92)	5(2.81)	0782
Cr(μmol/L) b	57.00–111.00	64(25.25)	66(26.41)	56.445(20.24)	62(25.61)	0.326
LDH(U/L)	120.00–250.00	231.65(85.25)	228(73)	240(123.1)	272(77.35)	**0.004**

(*Continued*)

Table 3 (Continued).

	Normal range	All patients (n=310)	Routine Treatment (n=135)	MP 40 mg/d (n = 81)	DEX 5 mg/d (n = 94)	P-value
HBDH(U/L)	72.00–182.00	158(52.25)	155(46.2)	160(61.98)	179(28.3)	**0.001**
Fibrinogen(g/L)	2.38–4.98	3.62(1.47)	3.53(1.33)	4.01(1.99)	4.28(2.37)	**0.001**
D-dimer(ng/mL)	0.00–243.00	183(251.75)	177(182)	221(306)	186(386.5)	0.390
Urine sugar (n, %)		46(14.8%)	18(13.3%)	10(12.3%)	18(19.1%)	0.364
Urinary protein (n, %)		42(13.5%)	16(11.9%)	10(12.3%)	16(17%)	0.497
Electrolyte disturbance(n, %)		142(45.8%)	52(38.5%)	48(59.3%)	42(44.7%)	**0.012**

Note: Bold font indicates statistically significant values ($p < 0.05$).

Of all severe COVID-19 Patients, urinary glucose, urinary protein, and electrolyte disturbances were 74 (19.9%), 67 (18.1%), and 234 (63.1%), respectively, and the remaining indicators are expressed as medians (interquartile spacing) except for total protein expressed as Mean ± standard deviation. We can note that both groups had lower absolute lymphocyte values, hemoglobin, higher CRP, LDH, HBDH, and D-dimer compared to the normal range, and there were no significant differences between the MP and DEX group for the laboratory parameters, except for statistically significant differences in lymphocytes ($P < 0.001$), total protein ($P = 0.025$), hemoglobin ($P = 0.004$)(Table 4).

Post-Admission Treatment Measures in COVID-19 Patients

78.1% of moderate patients and 96.8% of severe patients require oxygen therapy, and the most common form of oxygen is nasal cannula oxygen. Nasal catheter oxygen was 74.5% and 83.8% for moderate and severe patients, respectively, and mask oxygen therapy was 7.1% and 16.2%. Antibacterial drug use was 80%, and 95.7% in moderate and severe patients, respectively.

Table 4 Laboratory Parameters Within 24 hours of Admission in Severe COVID-19 Patients

	Normal range	All patients (n=371)	MP 40 mg/d (n = 243)	DEX 5 mg/d (n = 128)	P-value
WBC(×109/L)	3.50–9.50	6.15(4.56)	6.15(4.13)	6.19(4.91)	0.366
Neutrophils(×109/L)	1.80–6.30	4.76(4.43)	4.89(3.88)	4.58(4.90)	0.388
Lymphocytes (×109/L)	1.10–3.20	0.74(0.67)	0.75(0.7)	0.74(0.6)	0.470
Platelet (×109/L)	125.00–350.00	185(115)	182(110)	195(123)	0.165
Hemoglobin (g/L)	130.00–175.00	127(25)	128(24)	123(28)	**0.004**
PCT (ng/mL)	0.00–0.51	0.44(0.47)	0.44(0.46)	0.435(0.563)	0.966
CRP (mg/L)	<5	37(65.48)	43.62(66.39)	30.175(61.66)	0.225
ALT(U/L)	9.00–50.00	25.5(27.6)	26.4(26)	24.2(29.7)	0.254
Total protein(g/L)	65.00–85.00	64.507±7.874	65.338±7.979	63.248±7.541	0.025
Albumin(g/L)	40.00–55.00	32.9(6.4)	33.7(6.6)	31.8(6.02)	**0.004**
Globulin(g/L)	20.00–40.00	31.6(6.0)	31.7(5.9)	31.1(6.3)	0.398
Ratio of albumin to globulin		1.045(2.095)	1.064(0.284)	0.992(0.283)	0.098
BUN (mmol/L)	3.60–9.50	6.16(4.8)	6(4.1)	6.675(5.675)	0.133
Cr(μmol/L) b	57.00–111.00	68.89(33)	69(30)	68.83(38.57)	0.837
LDH(U/L)	120.00–250.00	277(118)	282(125)	286.5(111.1)(	0.065
HBDH(U/L)	72.00–182.00	183(75.8)	184(89.8)	178.3(73.7)	0.309
Fibrinogen(g/L)	2.38–4.98	3.84(1.29)	3.9(1.31)	3.795(1.38)	0.331
D-dimer(ng/mL)	0.00–243.00	352(598)	314(618)	400(599.25)	0.212
Urine sugar (n, %)		74(19.9%)	50(20.6%)	24(18.8%)	0.676
Urinary protein (n, %)		67(18.1%)	41(16.9%)	26(20.3%)	0.423
Electrolyte disturbance(n, %)		234(63.1%)	154(63.4%)	80(62.5%)	0.868

Note: Bold font indicates statistically significant values ($p < 0.05$).

Abbreviations: WBC, leukocyte; CRP, C-reactive protein; ALT, Alanine transaminase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; Cr, Creatinine; PCT, Procalcitonin; LDH, lactic dehydrogenase; HBDH, α-hydroxybutyrate dehydrogenase.

Antiviral therapy was given to 23.2% and 41% of moderate and severe patients, respectively, of these, paxlovid was used in 7.7% and 18.6% of moderate and severe patients, respectively. Anticoagulant drug was given to 25.2% of moderate patients and 45.3% of severe patients. The remaining therapeutic measures include antifibrotic, sedative prophylactic, antifungal, etc. There were no statistically significant differences in the type of treatment received between the groups except for mask oxygen therapy in severe patients (P = 0.014)(Table 5 and Table 6).

Primary and Secondary Efficacy Variables in Patients

Of the moderate patients, the number of days of hospitalization in the three groups was 9(5) days, 10(6) days, and 9.5(6) days, respectively (P = 0.132). The 30-day mortality rate for moderate patients was 1.6% (P = 0.861). The no-use GC group had the highest rates of deterioration and need for escalation of GC regimens, 24.4% and 16.3%, respectively (P = 0.025, P = 0.01). The demand for NIPPV /IMV in moderate patients was 7.4% (P = 0.065). The Duration of GC treatment in the MP and DEX groups was 7(5) and 6.5(4) days, respectively (P = 0.441), and the incidence of hyperglycemia in the three groups was 7%, 10%, and 4.2%, respectively (P = 0.733), and the incidence of fungal infections was 7.4%, 7.4%, and 17% (P = 0.029), suggests that fungal infections were more likely to occur in the DEX group. In severe patients, the number of hospital days was significantly lower in the MP group compared with the DEX group (P < 0.001), and there were no significant differences in other primary and secondary outcomes (Table 7 and Table 8).

Table 5 Post-Admission Treatment Measures in Moderate COVID-19 Patients

	All patients (n=310)	Routine Treatment (n=135)	MP 40 mg/d (n = 81)	DEX 5 mg/d (n = 94)	P-value
Antiviral drugs	72(23.2%)	35(25.9%)	19(23.5%)	18(19.1%)	0.489
Azvudine tablet	31(23%)	17(21%)	18(19.1%)	66(21.3%)	0.784
Paxlovid	24(7.7%)	9(6.7%)	9(11.1%)	6(6.4%)	0.417
Anticoagulant drug	78(25.2%)	28(20.7%)	24(29.6%)	26(27.7%)	0.276
Antibacterial drug	248(80%)	106(78.5%)	70(86.4%)	72(76.6%)	0.228
IVIG	36(11.6%)	10(7.4%)	14(17.3%)	12(12.8%)	0.538
Anti-fibrotic drug	2(0.6%)	1(0.7%)	1(1.2%)	0(0%)	0.735
Oxygen inhalation	242(78.1%)	99(73.3%)	63(77.8%)	80(85.1%)	0.106
Nasal cannula for oxygen	231(74.5%)	96(71.1%)	61(75.3%)	74(78.7%)	0.422
Mask oxygen therapy	22(7.1%)	6(4.4%)	6(7.4%)	10(10.6%)	0.198

Abbreviation: IVIG, Intravenous Immunoglobulin.

Table 6 Post-Admission Treatment Measures in Severe COVID-19 Patients

	All patients (n=371)	MP 40 mg/d (n = 243)	DEX 5 mg/d (n = 128)	P-value
Antiviral drugs	152(41%)	107(44%)	45(35.2%)	0.098
Azvudine tablet	106(28.6%)	72(29.6%)	34(26.6%)	0.534
Paxlovid	69(18.6%)	43(17.7%)	26(20.3%)	0.538
Anticoagulant drug	168(45.3%)	104(42.8%)	64(50%)	0.185
Antibacterial drug	355(95.7%)	235(96.7%)	120(93.8%)	0.182
Antifungal agents	52(14%)	34(14%)	18(14.1%)	0.985
IVIG	32(9.2%)	24(9.9%)	10(7.8%)	0.083
Anti-fibrotic drug	5(1.3%)	4(1.6%)	1(0.8%)	0.492
Oxygen inhalation	359(96.8%)	237(97.5%)	122(95.3%)	0.354
Nasal cannula for oxygen	311(83.8%)	208(85.6%)	103(80.5%)	0.202
Mask oxygen therapy	60(16.2%)	31(12.8%)	29(22.7%)	0.014

Abbreviation: IVIG, Intravenous Immunoglobulin.

Table 7 Primary and Secondary Efficacy Variables in Moderate COVID-19 Patients

Efficacy Variable	All patients (n=310)	Routine Treatment (n=135)	MP 40 mg/d (n = 81)	DEX 5 mg/d (n = 94)	P-value
Primary outcomes					
30-day mortality, n (%) Exacerbation, n (%) Length of hospital Days, Mean(SD)/ Median(IQR) days	5(1.6%) 55(17.7%) 10.58(5.42)/ 9(6)	3(2.2%) 33(24.4%) 10.17(5.42) /9(5)	1(1.2%) 10(12.3%) 11.07(5.32)/10(6)	1(1.1%) 12(12.8%) 11.04(4.69)/9.5(6)	0.861 **0.025** 0.132
Secondary outcomes					
Demand for NIPPV /IMV, n (%) *the need for GC regimen escalation, n (%) Duration of GC treatment, Mean(SD)/ Median(IQR) days	23(7.4%) 32(10.3%) ——	6(4.4%) 22(16.3%) ——	7(8.6%) 5(6.2%) 7.67(2.47)/7(5)	10(10.6%) 5(5.3%) 6.71(2.73)/6.5(4)	0.065 **0.01** 0.441
Complications					
Hyperglycemia *Fungal infection	36(11.7%) 32(10.3%)	16(11.9%) 10(7.4%)	9(11.1%) 6(7.4%)	11(11.7%) 16(17%)	0.983 **0.038**

Note: Bold font indicates statistically significant values ($p < 0.05$).

Table 8 Primary and Secondary Efficacy Variables in Severe COVID-19 Patients

Efficacy Variable	All patients (n=371)	MP 40 mg/d (n = 243)	DEX 5 mg/d (n = 128)	P-value
Primary outcomes				
30-day mortality, n (%) Exacerbation, n (%) Length of hospital Days, Mean(SD)/Median(IQR) days	41(11.1%) 127(34.2%) 14.14(7.928)/12(8)	28(10.4%) 85(34.7%) 13.43(8.21)/12(7)	13(10.3%) 42(33.3%) 15.53(7.17)/14(10)	0.746 0.794 **0.001**
Secondary outcomes				
Demand for NIPPV /IMV, n (%) The need for GC regimen escalation, n (%) Duration of GC treatment, Mean(SD)/Median(IQR) days	52(14%) 43(11.6%) 8.8(4.75)/8(6)	37(15.1%) 23(9.4%) 8.42(4.41)/8(5)	15(11.9%) 20(15.9%) 9.54(5.304)/8(6)	0.401 0.065 0.104
Complications				
Hyperglycemia, n (%) Fungal infection, n (%)	135(36.4%) 52(14%)	94(38.4%) 37(15.1%)	41(32.5%) 15(11.9%)	0.269 0.401

Note: Bold font indicates statistically significant values ($p < 0.05$).
Abbreviations: NIPPV, Non-invasive positive pressure ventilation; IMV, Invasive mechanical ventilation; SD, Standard Deviation; IQR, Interquartile distance.

Binary logistic regression showed that in moderate patients, 30-day mortality was not significantly different among the three groups (MP vs Con: OR 0.55, CI 95% 0056~5.378, p = 0.607, DEX vs Con: OR 0.471, CI 95% 0.048~4.619, P = 0.52), but the possibility of exacerbation in the MP group, and DEX group was 0.435 and 0.452 times of that in the no-use GC group, respectively (MP vs Con: OR 0.435, CI 95% 0.202~0.940, p = 0.034, DEX vs Con: OR 0.452, CI 95% 0.220~0.931, P = 0.031), there was no significant difference in exacerbation rate between MP and DEX group (MP vs DEX: OR 0.962, CI 95% 0.392~2.361, P = 0.933). The likelihood of exacerbation rate in the MP 40 mg/day group was 0.315 times of that in the MP 20 mg/day group (MP 40 mg/day vs MP 20 mg/day: OR 0.315, CI 95% 0.129~0.771, P = 0.011). In severe patients, the two treatment regimens do not cause a difference in 30-day mortality (MP vs DEX: OR 0.647, CI 95% 0.304~1.375, P = 0.258) and exacerbation rates (MP vs DEX: OR 1.162, CI 95% 0.7288~1.856, P =

Table 9 30-Day Mortality in Moderate and Severe Patients

30-Day Mortality				
Unadjusted			**Adjusted ***	
Treatment	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
MP^1 vs DEX^1	0.843(0.422~1.772)	0.691	0.647(0.304~1.375)	0.258
MP^2 vs Con	0.550(0.056~5.378)	0.607	0.201(0.015~2.626)	0.221
DEX^2 vs Con	0.473(0.048~4.619)	0.520	0.209(0.019~2.807)	0.249

Note: * Adjusted by age, and clinical lab index including CRP, LDH, and absolute lymphocyte.

Abbreviations: MP^1, methylprednisolone 40 mg/day group in severe patients; MP^2, methylprednisolone 40 mg/day group in moderate patients; DEX^1, dexamethasone 5 mg/day group in severe patients; DEX^2, dexamethasone 5 mg/day group in severe patients; Con, no-use glucocorticoid group; OR, Odds ratio; CI, Confidence interval.

Table 10 Exacerbation in Moderate and Severe Patients

Exacerbation				
	Unadjusted		**Adjusted ***	
Treatment	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
MP^1 vs DEX^1	1.062(0.675~1.674)	0.794	1.101(0.694~1.746)	0.683
MP^2 vs Con	0.435(0.202~0.940)	0.034	0.179(0.071~0.452)	**0.001**
DEX^2 vs Con	0.452(0.220~0.931)	0.031	0.237(0.014~0.539)	**0.001**
MP^2 vs DEX^2	0.962(0.392~2.361)	0.933	0.614(0.209~1.801)	0.374
MP^2 vs MP^3	0.315(0.129~0.771)	0.011	0.301(0.114~0.795)	0.015

Note: * Adjusted by age, and clinical lab index including CRP, LDH, and absolute lymphocyte. Bold font indicates statistically significant values ($p < 0.05$).

Abbreviations: MP^1, methylprednisolone 40 mg/day group in severe patients; MP^2, methylprednisolone 40 mg/day group in moderate patients; MP^3, methylprednisolone 20 mg/day group in moderate patients; DEX^1, dexamethasone 5 mg/day group in severe patients; DEX^2, dexamethasone 5 mg/day group in severe patients; Con, no-use glucocorticoid group; OR, Odds ratio; CI, Confidence interval.

0.544). Multivariable logistic regressions adjusted by age, and clinical lab index including CRP, LDH, and absolute lymphocyte still confirm the above results. Kaplan–Meier curve verified that the two treatment regimens do not cause significant 30-day mortality (P = 0.642). Given the lower 30-day mortality rate in the moderate patient, we did not plot Kaplan–Meier curve for the moderate patient group (Table 9 and Table 10, Figure 1).

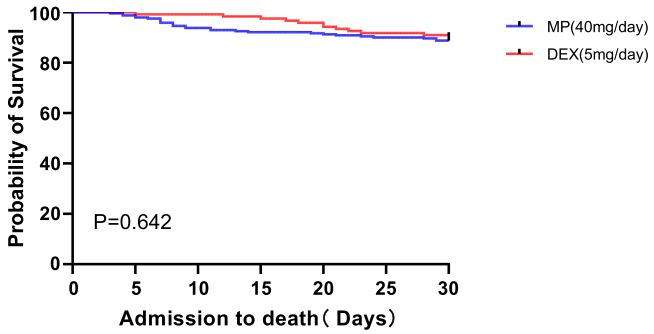

Figure 1 Kaplan–Meier curve which represents the general survival probability from admission to death when using different GC regimens in severe patients (P=0.642).

Discussion

Systemic GC is considered effective in treating severe COVID-19 patients in both international consensus and guidelines. DEX 6 mg/day is usually recommended.[10,25]

COVID-19 is not only a respiratory disease, instead, it is a multisystem disease. Pulmonary and extrapulmonary manifestations should be considered for early diagnosis and to control the spread of the infection. Thus, clinical symptoms in COVID-19 patients are an important factor in assessing the severity of the disease and its efficacy.[26] Lymphocyte values and CRP are effective indicators for assessing the severity of COVID-19 patients.[27] During the disease, it may be helpful to longitudinally evaluate the dynamics of lymphocyte count dynamics and inflammatory indices, such as LDH, CRP, and IL-6, to identify cases with a poor prognosis and promptly intervene to improve outcomes.[28] Chest CT changes are also important prognostic factors in patients with COVID-19.[29] We evaluate patients for exacerbations through a combination of clinical symptoms, chest CT changes, and laboratory markers. COVID-19 is characterized by an over-activated cytokine storm syndrome. One of the mechanisms by which GC improves the patient's condition is by suppressing the immune response. The required dose of GC correlates with the degree of inflammatory response.[30,31] Patients who required NIPPV or IMV had a significantly worse prognosis than those who did not require such oxygen support. Additionally, it has been found that GC benefits the ventilatory function of severe/critical COVID-19 patients.[32] GC therapy can lead to numerous adverse effects, especially in the elderly. These effects include elevated blood sugar, secondary infections, peptic ulcers, gastrointestinal bleeding, elevated blood pressure, and water and sodium retention.[33] A wide range of opportunistic infections have been described in patients with COVID-19. Aspergillus and Candida have been reported as the main fungal pathogens for co-infection in these patients.[34] Therefore, we also considered the need for NIPPV/IMV after treatment, the need for GC regimen escalation in follow-up treatment, the number of days of GC use, complications including hyperglycemia, and fungal infections as secondary clinical outcomes.

On the primary outcome, the results showed that there was no significant difference in 30-day mortality between the groups in moderate, but the rate of exacerbations was highest in the no-use GC group, suggesting that DEX 5 mg/day or MP 40 mg/day reduced the rate of exacerbations in moderate patients, as evidenced by binary logistic regression. In severe patients, two GC regimens did not affect the 30-day mortality rate and exacerbation rate. In terms of hospitalization days, the average hospitalization days in severe patients was 9 days in the MP group and 11 days in the DEX group ($P<0.001$). As mentioned above, COVID-19 is typically characterized by inflammatory storms. It has been well established that among various GC, MP, but not DEX, is the clinically preferred agent for its anti-inflammatory effect with a high dose required to achieve the therapeutic effect of the GC.[11] By comparing the dynamic changes of laboratory tests, Pinzon et al also found that the treatment of severe COVID-19 pneumonia with high-dose MP, compared with 6 mg DEX, statistically significantly decreased the severity markers C-reactive protein (CRP) and LDH.[35,36] Similarly, one recent study revealed that low-dose MP might be an optimal treatment compared to using other types of steroids or no steroids in terms of ventilator-free days, and low-dose MP was associated with decreased mortality in patients with ARDS.[17,18] Therefore, we hypothesized that the reason why the number of hospital days in the MP group was significantly lower than that in the DEX group was that the 40 mg of MP had a more potent inhibitory effect on inflammatory storms compared to the 5mg of DEX.

Of the secondary outcomes, our findings suggest the prevalence of hyperglycemia among severe COVID-19 patients was 36.4%, while the prevalence of fungal infection was 14%. Among moderate patients, the prevalence of hyperglycemia was 11.3% and the prevalence of fungal infection was 10.3%. Additionally, the study found that the group receiving DEX among moderate patients had the highest prevalence of fungal infections in moderate ($P=0.038$). It is recommended to actively monitor any adverse reactions associated with the use of GC and address them promptly to optimize the effectiveness of GC.

It should be noted that our study was limited to a regimen of DEX 5 mg/day versus MP 20 mg or 40 mg/day for moderate and severe patients. We further compared the MP 20mg/day versus MP 40 mg/day regimens in moderate patients and found that MP 40 mg/day better prevented exacerbations in moderate patients. We assumed that 20mg/day may not be sufficient for better control of the disease when using MP in those patients, 40 mg/day is a better choice. Additional studies have explored the most appropriate dose of GC in COVID-19 patients by comparing high-dose GC with guideline-recommended GC use. A systematic retrospective analysis found that GC improved overall mortality in

COVID-19 patients hospitalized. It was also observed that high-dose GC reduced overall mortality over 30 days compared to low-dose GC.[37] Some studies have found that high-dose GC can benefit patients with COVID-19 presenting with ARDS in the ICU and that the combination of high-dose DEX based on the standard treatment can benefit patients with moderate to severe ARDS in the ICU in terms of improved survival and freedom from the application of invasive ventilators, as compared with the standard treatment group.[38,39] Pinzon et al found that high doses and long courses of GC were more beneficial for patients with COVID-19 requiring oxygen therapy than those receiving the recommended dose of DEX, with a markedly shorter time to improvement, a reduced chance of ICU transfer, and markedly improved levels of inflammation such as CRP.[35] Granholm et al found that the DEX 12 mg/day group resulted in benefits and lower GC-related adverse effects in patients with severe COVID-19 compared to the DEX 6 mg/day group.[40] Ko et al found that the rate of death was significantly lower in the full-dose MP group compared to the other two groups.[11] However, there is no consensus on the efficacy of high-dose GC. In another study, the high-dose GC group showed no benefit in reducing the rate of death without life support at 28 d.[41] Tan et al did not find an advantage of high-dose GC in improving the rate of death in a meta-analysis.[42] López et al found that patients with COVID-19 in an over-activated inflammatory state benefited from high doses of GC, while high-dose GC may be harmful when inflammation levels are not high.[43] Most patients at risk of acute exacerbations of COVID-19 are characterized by advanced age and underlying disease, such patients may have a disturbed immune status. Indeed, some studies have shown that even in the absence of underlying disease, the differences in the health problems and immune status of the elderly, especially the elderly, should not be ignored,[44–46] which may partly explain the discrepancy in the results of the different studies mentioned above.[47] GOGALI A. et al also suggested that GC doses should not be the same in different COVID-19 patients, severe COVID-19 patients may benefit even more from higher GC doses.[48] Therefore, the dosage of GC needs to be urgently individualized for patients with COVID-19.

Regarding the duration of GC use, most of the clinical studies used GC for a duration of 7 to 10 days, with some studies extending it to 2 weeks.[8,25] Our study showed that in severe patients, the duration of GC use in the MP group versus the DEX group was 8.42 days and 9.54 days, respectively. In moderate patients, the duration of GC use in the MP group versus the DEX group was 7.67 days and 6.71 days, respectively. However, some patients improve or are cured with the recommended dose and duration of GC treatment, while others do not show improvement or develop pulmonary fibrosis. In some cases, discontinuing GC therapy after a 10-day course of treatment leads to recurrent or progressive pneumonia. Therefore, patients who have not recovered from COVID-19 after receiving the recommended dose of GC regimen may experience further improvement in their condition after the re-administration of GC.[49,50]

Conclusion

In Conclusion, our study provides new insights into the use of GC in patients with COVID-19. In the treatment of severe COVID-19 patients with GC therapy, MP 40 mg/day has a significantly greater advantage in reducing the number of hospital days compared to DEX 5mg/day. In the treatment of moderate COVID-19 patients, GC therapy may be more effective in preventing disease progression compared to no-use GC. Furthermore, when comparing a dosage of 20mg/day of MP to a dosage of 40 mg/day of MP, the latter may be a preferable option. However, it is important to note that this conclusion should be validated through larger-scale studies.

Abbreviations

COVID-19, The coronavirus disease 2019; GC, glucocorticoid; MP, methylprednisolone; DEX, dexamethasone; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; CNS, Central nervous system; WBC, leukocyte; CRP: C-reactive protein; ALT: Alanine transaminase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; Cr, Creatinine; PCT, Procalcitonin; LDH, lactic dehydrogenase; HBDH, α-hydroxybutyrate dehydrogenase; IVIG, Intravenous Immunoglobulin; NIPPV, Non-invasive positive pressure ventilation; IMV, Invasive mechanical ventilation; SD, Standard Deviation; IQR, Interquartile distance; MP^1, methylprednisolone 40 mg/day group in severe patients; MP^2, methylprednisolone 40 mg/day group in moderate patients; MP^3: methylprednisolone 20 mg/day group in moderate patients; DEX^1, dexamethasone 5 mg/day group in severe patients; DEX^2, dexamethasone 5 mg/day group in severe patients; Con, no-use glucocorticoid group; OR, Odds ratio; CI, Confidence interval.

Data Sharing Statement

All the data of this article are available from the corresponding author upon reasonable request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the second Hospital of Shanxi Medical University (approval number 2023 YX 131) and with the 1964 helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all volunteers, and the anonymity of each participant was strictly preserved.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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