Letters to the Editor

Successful use of methylprednisolone for treating severe COVID-19

To the Editor:

As of April 4, 2020, a total of 1,051,635 coronavirus disease 2019 (COVID-19) cases had been reported worldwide, among which 56,985 deaths occurred (5.42%).[1] However, to date, no vaccine and no specific antiviral medicine are available to prevent or treat COVID-19. A previous study suggested that cytokine release syndrome could be involved in the pathophysiology of severe or critical COVID-19 cases and frequently results in death.[2] Hence, early recognition and effective suppression of the cytokine storm may be life-saving in severe or critical patients. The Fifth Affiliated Hospital of Sun Yat-sen University was the first and, at the time of this report, remains the only designated hospital for management of COVID-19 patients in Zhuhai, China. From January 22 to March 2, we treated 101 patients with COVID-19 in total. Although the previously reported fatality rate for severe and critical patients with COVID-19 was considerable,[2] those whom we treated all survived. Despite controversies, we think that timely and appropriate application of glucocorticoid plays a crucial role in the treatment of these patients. Herein, we introduce our clinical experience with corticosteroid administration in these patients for reference and discussion.

During the study period, the Fifth Affiliated Hospital of Sun Yat-sen University was the only designated hospital for the treatment of COVID-19 in Zhuhai, China, and all suspected or confirmed cases in this city were compulsarily admitted to it. All the hospitalized patients were managed by an expert panel consisting of experienced clinicians from pulmonology, critical medicine, infectious diseases, radiology, microbiology, and pathology departments.

Diagnosis of COVID-19 was made on the basis of criteria of the "Diagnosis and Treatment of New Coronavirus-Infected Pneumonia" (Sixth trial version) draft by the National Health Commission of China. Specific IgG antibody had to be tested with the ELISA method before discharge of patients. Furthermore, patients have been followed up and their lung function measured within 1 month of discharge.

This case series was approved by the Institutional Ethics Board of the Fifth Affiliated Hospital of Sun Yat-sen University. Consecutive patients with confirmed COVID-19 admitted from January 22 to March 2, 2020, were enrolled. Oral consent was obtained from patients. We collected and analyzed the clinical data of these patients.

The mean age of the 101 hospitalized patients with confirmed COVID-19 was 45 ± 18.01 years (range, 11 months to 80 years). Forty-seven patients were males, and 69 were from Wuhan (see Table E1 in this article's Online Repository at www.jacionline.org). Of the 101 cases, 26 were classified as severe or critical (25.74%), and all 26 patients had a recorded ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2 ratio) of less than 300 mm Hg at least 1 time during hospitalization. At least 10 patients had a PaO_2/FiO_2 ratio of less than 150 mm Hg. All cases have been treated up to discharge standard successfully. We found that the most important treatment experience is timely and appropriate glucocorticoid application in 15 severe and critical patients (with pulse single dosage of 40-500 mg methylprednisolone according to severity, oxygenation index, speed of progression, production of inflammatory factors, body weight, age, and underlying diseases condition, rather than continuous low-dose glucocorticoid for days) (Fig 1; see Table E2 in this article's Online Repository at www.jacionline.org). With this treatment, oxygenation had been improved significantly, and no deaths occurred in these 15 patients. Only 1 of these 15 patients needed mechanical ventilation for 5 days. When observing pulmonary function during the early convalescence phase in patients with COVID-19, we did not find any difference between the 2 groups with or without glucocorticoids (see Table E3 in this article's Online Repository at www.jacionline.org). We consider that the recovery of lung function in these severe cases received a benefit from using methylprednisolone. Our results also dispelled the worries about the negative impacts of glucocorticoids on virus removal and specific IgG production. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) negative-conversion days were 10.0 ± 5.3 and 10.0 ± 7.9 in patients with and without methylprednisolone therapy, respectively, and there was no statistical difference (see Table E4 in this article's Online Repository at www.jacionline.org). Besides, the more severe patients with glucocorticoid therapy produced more specific IgG to SARS-CoV-2 than others (see Table E5 in this article's Online Repository at www.jacionline.org). All patients who received methylprednisolone were examined by pelvic magnetic resonance imaging scans before hospital release as screening for femoral head osteonecrosis, and no abnormal results were observed for any patient. No apparent side effect has been observed during a 1-month follow-up, probably because of the strictly controlled total dosage of methylprednisolone (the highest dosage of methylprednisolone was 1000 mg due to 100 kg body-weight of the patient).

The application of glucocorticoid for COVID-19 pneumonia has been controversial, considering the inconclusive clinical evidence and their possible adverse effects. Interim guidance for the management of COVID-19 by the World Health Organization recommends against routinely giving systemic glucocorticoids.[3] However, it is well known that glucocorticoids are useful for inhibiting the inflammatory storm via suppression of cytokine levels and proinflammatory gene expression.[4] Glucocorticoids thus can diminish the serous exudate at the site of inflammation, reduce tissue edema and injury, and relieve symptoms of inflammation. However, the first report from the autopsy of a patient with COVID-19 revealed that severe serous exudate occurred in the lungs, which was in accordance with the decrease in the peripheral blood serum albumin level frequently found in critical patients. Therefore, based on pathological changes in patients with COVID-19, glucocorticoids could be useful in critical cases. In addition, there is no specific effective antiviral medicine for the new coronavirus and no effective therapy available for suppressing the inflammatory storm except glucocorticoids in urgent clinical settings. In our study, we found that timely and appropriate application of glucocorticoids could avoid the need for invasive mechanical ventilation and improve the outcomes of critical patients with COVID-19, compared with outcomes in reported studies. In a
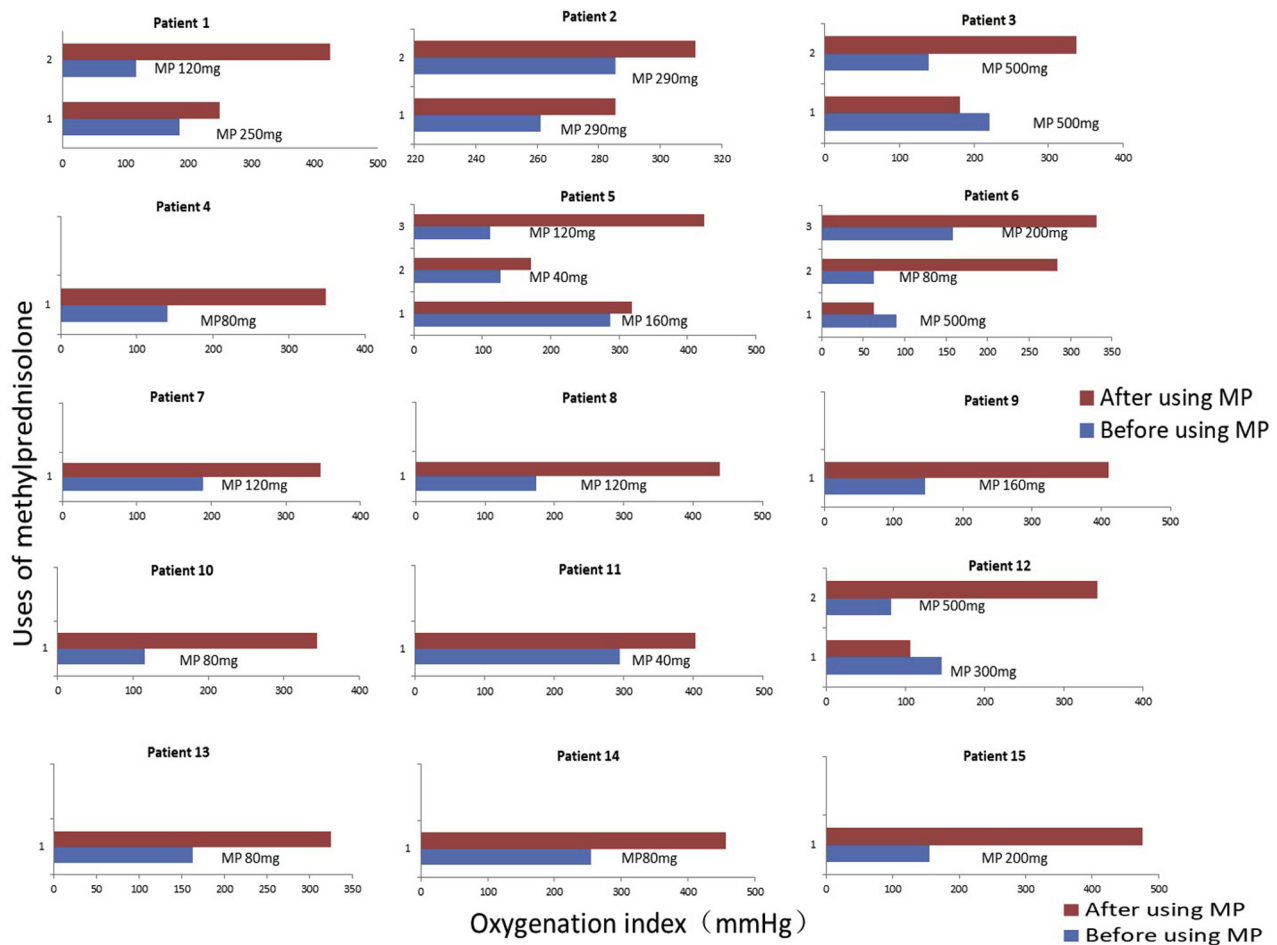
FIG 1. The application and effect of methylprednisolone in patients with COVID-19. The abscissa represents the PaO_2/FiO_2 ratio (mm Hg), and the ordinate represents the times of methylprednisolone injection. The dosage of methylprednisolone was shown in the figure with a unit of milligram. Methylprednisolone was diluted in 50 mL saline and administered intravenously over 30 minutes. The highest single dosage of 500 mg methylprednisolone was administrated according to rapid radiologic progression and high body weight in patient 3 and rapid oxygenation worsening in patient 6 and patient 12. *MP*, Methylprednisolone. Before using MP: 1 to 2 hours before using methylprednisolone. After using MP: 12 to 24 hours after using methylprednisolone.

recently published article,[5] Shang et al also introduced a series of high-quality studies about the successful use of glucocorticoids for treating SARS, influenza A viral pneumonia, and severe community pneumonia, respectively.[6-8] These supported the use of glucocorticoids in COVID-19 because they have similar pathology.

Continuous administration of glucocorticoids may suppress the immune system and slow down viral clearance. However, our study indicated that single-dose pulse methylprednisolone (40-500 mg methylprednisolone) had no apparent negative impact on SARS-CoV-2 removal and production of specific IgG while effectively stopping the inflammatory cascade.

Timely and appropriate application of methylprednisolone in severe and critical patients with COVID-19 may improve outcomes and lung function without negative impacts on the production of specific IgG to SARS-CoV-2.

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Association of asthma and its genetic predisposition with the risk of severe COVID-19

To the Editor:

In individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the severity of illness ranges from asymptomatic to fatal.[1] The Centers for Disease Control and Prevention currently list asthma as a risk factor for severe illness from coronavirus disease 2019 (COVID-19).[2] This is a logical determination because the non–COVID-19 literature indicates that patients with asthma have increased susceptibility to viral respiratory infections.[3] In addition, case series of patients with COVID-19 have reported that the asthma prevalence is higher[4] or nondifferent[5] in more severe cases. However, despite the clinical and research importance, no studies have specifically examined the relationship of asthma—let alone of its phenotypes—with incident COVID-19. To address the major knowledge gap, we examined the relationship of asthma and its major phenotypes with the risk of developing severe COVID-19. We also examined the relations of their genetic predisposition with severe COVID-19. The determination of risk factors and potential mechanisms—such as the contribution of genetic predispositions —of severe illness is instrumental for the development of prevention, risk-stratification, and treatment strategies for COVID-19.

We analyzed data from the UK Biobank—a population-based prospective cohort study. The details of study design, setting, participants, data measurements, and data analysis are described in this article's Online Repository at www.jacionline.org. Briefly, the UK Biobank enrolled approximately 500,000 adults (aged 40-69 years at enrollment) in the period 2006 to 2010.[6] Using standardized protocols, the study has collected comprehensive phenotypic data—for example, demographic characteristics, medical history, physical measures (eg, body mass index), performed genome-wide genotyping, and longitudinally measured health outcomes (eg, hospitalizations) through linkages to national data sets.[6] Starting from March 16, 2020, data of laboratory-confirmed COVID-19 hospitalizations—that is, individuals with severe COVID-19—are available in the UK Biobank.

TABLE I. Baseline characteristics in 492,768 UK Biobank participants

Characteristic	Asthma (n = 65,677; 13%)	No asthma (n = 427,091; 87%)
Demographic		
Age (y), mean ± SD	56 ± 8.3	57 ± 8.1
Sex: female	38,006 (57.9)	231,216 (54.1)
Race/ethnicity		
White	61,555 (94.3)	401,699 (94.6)
Asian or Asian British	1,388 (2.1)	8,400 (2.0)
Black or black British	1,114 (1.7)	6,904 (1.6)
Mixed	506 (0.8)	2,414 (0.6)
Chinese	153 (0.2)	1,408 (0.3)
Other groups	593 (0.9)	3,922 (0.9)
Total annual household income (£)		
≤18,000	14,253 (22.0)	79,252 (18.8)
18,000-30,999	13,482 (20.8)	92,590 (21.9)
31,000-51,999	13,713 (21.2)	95,770 (22.7)
52,000-100,000	10,866 (16.8)	74,809 (17.7)
≥100,000	2,874 (4.4)	19,938 (4.7)
Do not know	3,235 (5.0)	17,396 (4.1)
Prefer not to answer	6,343 (9.8)	42,471 (10.1)
Body mass index (kg/m^2), mean ± SD	28.3 ± 5.4	27.3 ± 4.7
Smoking status		
Never	35,071 (53.4)	236,600 (55.4)
Previous	23,381 (35.6)	145,057 (34.0)
Current	6,809 (10.4)	42,972 (10.1)
Comorbidities		
Allergic diseases		
Allergic rhinitis or eczema	28,852 (44.1)	85,354 (20.1)
Food allergy	626 (1.0)	1,570 (0.4)
Cerebrovascular disease	1,190 (1.8)	5,703 (1.3)
COPD	7,836 (11.9)	0 (0)
Coronary artery disease	3,732 (6.0)	16,928 (4.1)
Hypertension	18,937 (30.2)	107,835 (26.4)
Laboratory test at assessment visit, mean ± SD		
White blood cells (10^9 cells/L)	7.17 ± 2.08	6.82 ± 2.01
Neutrophils (10^9 cells/L)	4.45 ± 1.54	4.18 ± 1.38
Lymphocytes (10^9 cells/L)	1.97 ± 1.04	1.96 ± 1.12
Monocytes (10^9 cells/L)	0.47 ± 0.22	0.49 ± 0.22
Eosinophils (10^9 cells/L)	0.22 ± 0.18	0.17 ± 0.13
Basophils (10^9 cells/L)	0.04 ± 0.05	0.03 ± 0.05
25-HydroxyvitaminD (nmol/L)	47.2 ± 20.9	48.9 ± 21.1
SARS-CoV-2 PCR test during hospitalization, positive	116 ± 0.2	525 ± 0.1

Data are n (%) of participants unless otherwise indicated.

In the current analysis, we identified all participants with asthma and those without asthma or chronic obstructive pulmonary disease (COPD). To investigate the association of asthma with the risk of severe COVID-19, we constructed unadjusted and adjusted logistic regression models. In the multivariable model, we adjusted for potential confounders (ie, causes of both exposure and outcome of interest), including age, sex, race/ethnicity, and body mass index. On the basis of an *a priori* hypothesis, we also examined the heterogeneity of effect according to 4 asthma phenotypes, through stratifying the main analysis by coexistence of allergic disease (eczema, food allergy, and/or allergic rhinitis) or of COPD. Next, we used genotyping data to compute a polygenic risk score (PRS) for each asthma group of interest—the sum of all risk alleles weighted by how