BMJ Open Respiratory Research

Impact of corticosteroids in hospitalised COVID-19 patients

Kam Sing Ho,[1] Bharat Narasimhan,[1] Larry Difabrizio,[2] Linda Rogers,[2] Sonali Bose,[2] Li Li,[3] Roger Chen,[3] Jacqueline Sheehan,[1] Maan Ajwad El-Halabi,[1] Kimberly Sarosky,[4] Zichen Wang,[3] Elliot Eisenberg,[2] Charles Powell,[2] David Steiger[2]

To cite: Ho KS, Narasimhan B, Difabrizio L, *et al*. Impact of corticosteroids in hospitalised COVID-19 patients. *BMJ Open Resp Res* 2021;**8**:e000766. doi:10.1136/bmjresp-2020-000766

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2020-000766).

Received 4 September 2020
Revised 23 February 2021
Accepted 13 March 2021

[1]Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[2]Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[3]Clinical Informatics, Sema4, Stamford, Connecticut, USA
[4]Pharamacy, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Correspondence to
Dr Kam Sing Ho;
kam.ho@mountsinai.org

ABSTRACT

Background Corticosteroids are a potential therapeutic agent for patients with COVID-19 pneumonia. The RECOVERY (Randomised Trials in COVID-19 Therapy) trial provided data on the mortality benefits of corticosteroids. The study aimed to determine the association between corticosteroid use on mortality and infection rates and to define subgroups who may benefit from corticosteroids in a real-world setting.

Methods Clinical data were extracted that included demographic, laboratory data and details of the therapy, including the administration of corticosteroids, azithromycin, hydroxychloroquine, tocilizumab and anticoagulation. The primary outcome was in-hospital mortality. Secondary outcomes included intensive care unit (ICU) admission and invasive mechanical ventilation. Outcomes were compared in patients who did and did not receive corticosteroids using the multivariate Cox regression model.

Results 4313 patients were hospitalised with COVID-19 during the study period, of whom 1270 died (29.4%). When administered within the first 7 days after admission, corticosteroids were associated with reduced mortality (OR 0.73, 95% CI 0.55 to 0.97, p=0.03) and decreased transfers to the ICU (OR 0.72, 95% CI 0.47 to 1.11, p=0.02). This mortality benefit was particularly impressive in younger patients (<65 years of age), females and those with elevated inflammatory markers, defined as C reactive protein ≥150 mg/L (p≤0.05), interleukin-6 ≥20 pg/mL (p≤0.05) or D-dimer ≥2.0 µg/L (p≤0.05). Therapy was safe with similar rates of bacteraemia and fungaemia in corticosteroid-treated and non-corticosteroid-treated patients.

Conclusion In patients hospitalised with COVID-19 pneumonia, corticosteroid use within the first 7 days of admission decreased mortality and ICU admissions with no associated increase in bacteraemia or fungaemia.

Key messages

What is the key question?
- Is corticosteroid therapy associated with potential mortality benefits and safety outcomes for patients hospitalised with COVID-19 pneumonia?

What is the bottom line?
- Corticosteroids, when administered within the first 7 days of admission, are associated with a reduced risk of mortality, particularly among younger patients, females and those with defined elevated inflammatory markers.
- Therapy was not associated with an increase in fungaemia or bacteraemia.

Why read on?
- Corticosteroids may play an important role in reducing mortality in COVID-19 when administered early (≤7 days) after admission.

INTRODUCTION

The appearance of a novel coronavirus disease (SARS-CoV-2) in Wuhan, China, in December 2019 caused a severe acute respiratory syndrome coronavirus 2 (COVID-19) and has led to a global pandemic.[1] Since the first report of COVID-19 in Washington State on 20 January 2020, COVID-19[2] has posed a severe threat to the US health system, particularly in the New York Metropolitan area.[3] Whereas 81% of patients with COVID-19 may have mild disease, 14% develop severe disease, and 5% develop critical illness, including acute lung injury and acute respiratory syndrome (ARDS).[4] Respiratory failure from ARDS is the leading cause of mortality in COVID-19.[5]

Corticosteroids are anti-inflammatory agents and have been studied as a potential therapy for ARDS since the 1980s. Cytokine dysregulation and overproduction of proinflammatory cytokines are believed to be two major causes of ARDS and multiple-organ failure in COVID-19.[6] Recent studies have described the association of an increase in inflammatory markers with rapid deterioration in patients[7] and increased mortality in COVID-19.[5 8 9] Hence, it has been proposed that corticosteroids as an anti-inflammatory agent may be beneficial in reducing the intensity of the inflammatory response to COVID-19.[10] Notably, in vitro studies have shown inhibitory actions of corticosteroids on

coronavirus HCoV-229E replication and cellular inflammatory response.[11]

COVID-19 is associated with physiological and pathological evidence of ARDS.[6] Until the recent RECOVERY trial,[12] there was no evidence from randomised clinical trials identifying a specific therapy, including corticosteroids, that improved outcomes in patients with COVID-19 lung injury.[13] During the early months of the pandemic, the CDC (Centers for Disease Control and Prevention) and IDSA (Infectious Diseases Society of America)[14] did not recommend the use of corticosteroids for COVID-19-related lung disease. Russell *et al* summarised the available clinical evidence for using corticosteroids in MERS-CoV, SARS-Co-V influenza[15] and, consistent with WHO recommendations,[16] argued against the use of corticosteroids for COVID-19 lung injury. There has been concern that corticosteroids may increase viral replication, prolong viral shedding and increase the risk of secondary infections.[10 17] Nevertheless, corticosteroids have been used to treat COVID-19 lung injury.[18] The Chinese Thoracic Society developed a consensus statement on the use of corticosteroids for COVID-19 pneumonia and recommended that corticosteroids be used prudently in critically ill patients using low to moderate doses of methylprednisolone or equivalent for a duration of up to 7 days.[19] The RECOVERY trial demonstrated that dexamethasone 6 mg once a day for 10 days reduced 28-day mortality in patients with COVID-19 who received respiratory support.[12]

In this study, we report our early real-world clinical experience with corticosteroids in a cohort of patients hospitalised for COVID-19 in the New York City metropolitan area and provide evidence of mortality benefit and safety.

METHODS

This analysis included data from six acute care hospitals in the Mount Sinai Health System, which serves approximately 3.5 million patients in the New York metropolitan area. These hospitals included Mount Sinai Beth Israel, Mount Sinai Brooklyn, Mount Sinai Hospital, Mount Sinai Morningside, Mount Sinai Queens and Mount Sinai West Hospitals.

We included all consecutively hospitalised adults (≥18 years of age) between 7 March and 10 May 2020, who had positive RT-PCR for SARS-CoV-2 infection by nasopharyngeal or oropharyngeal swab and who had a completed hospital course (discharged alive or died) at time of analysis, 7 June 2020. Patients who were under the age of 18, who tested negative for COVID-19 by RT-PCR and who were not hospitalised were excluded from the analysis.

Data source

The study used deidentified data from the Mount Sinai COVID Informatics Center (MSCIC). This institutional database contains all health information related to outpatient and inpatient visits to any one of the Mount Sinai facilities. The MSCIC is compliant with HIPAA (Health Insurance Portability & Accountability Act), New York State privacy and security regulations, and institutional policies regarding the protection of human subjects and participation in research.[20]

Variables assessed

We obtained the following categories of clinical variables from the data warehouse: (1) patient-related variables: age, sex, patient-reported race, ethnicity, the first recorded body mass index (BMI), past and current diagnosis reported by physicians; physician-reported smoking status, the first recorded and daily vital signs (max and min), the first recorded and daily inpatient laboratory tests, admission to intensive care unit (ICU); (2) corticosteroids therapy-related variables: formulation, duration, dosing and timing of administration; (3) adjuvant therapy-related variables: use of hydroxychloroquine, azithromycin, tocilizumab; anticoagulation; and (4) outcomes-related variables: status of intubation, discharge or death.

The Mount Sinai Health System treatment guidance for hospitalised patients with COVID-19 classified the severity of COVID-19 based on the lowest obtained oxygen saturation during hospital course (from time of admission to time of discharge) into (1) mild disease—oxygen saturation >93% without oxygen therapy; (2) moderate disease—hypoxia with oxygen saturation <93% without oxygen therapy or >93% with oxygen therapy but without the need for invasive mechanical ventilation; (3) severe disease—respiratory failure requiring invasive mechanical ventilation.[21] Our treatment guidance also recommended the administration of corticosteroids for all patients with COVID-19 with moderate and severe COVID-19 disease. However, the duration of therapy was at the provider's discretion. Charlson Comorbidity Index (CCI), a predictor for mortality in a mixed population, was generated and summed to an index on a 0–33 scale.[22] When comorbid conditions were not available from prior hospital admission, the subcategory of CCI was scored as 0.

Clinical outcomes

Our primary outcome for this study was in-hospital mortality. Additional secondary outcomes included intubation and ICU admission.

Statistical analysis

All analyses were conducted with Stata V.15.1 (StataCorp) statistical software. Descriptive statistics include frequency analysis (percentages) for categorical variables and means±SD or medians for continuous variables. There was no missing data in terms of outcome-related, patient-related and therapy-related variables. There was a small amount of missing data regarding inflammatory markers, including ferritin, interleukin (IL)-6 and procalcitonin (all <5%), which were missing at random.

Although these percentages are relatively small, multiple imputation methods were employed to account for missing data. The multiple imputations procedures were based on an ordinal logistic regression model with 10 iterations that included the rest of the variables with complete data. No significant difference in primary and secondary outcomes was noted before and after accounting for missing data. Comparisons were determined using Student's t-test for continuous variables and by χ^2 test or Fisher's exact test for categorical variables. All p values were two sided, with 0.05 as the threshold for statistical significance. Univariate logistic regression was performed to explore the association of clinical characteristics and laboratory parameters with the risk of death. Confounder variables were selected based on the causal inference model with consideration of any variables with a p value below 0.2 from univariate logistic regression. To attenuate for confounding effects (ie, to separate the effects of hydroxychloroquine and corticosteroids on mortality), these variables were included simultaneously in the final multivariate regression analysis, which included continuous variables (age, BMI) and ordinal variables (gender, race, COVID-19 disease severity, CCI, asthma, C reactive protein (CRP), creatinine, D-dimer, blood culture, adjuvant therapies (hydroxychloroquine+azithromycin+tocilizumab) and anticoagulation).

Patient and public involvement statement

At the time of analysis, the lack of specific therapies for COVID-19 pneumonia drove the development of our research question. We wanted to determine if corticosteroids could have a beneficial role in the treatment of COVID-19 viral pneumonia. The study was a retrospective cohort analysis of outcomes following treatment of patients hospitalised with COVID-19 pneumonia, and therefore because of the retrospective nature of the study, individual patients were not approached to participate in the study. Patients were not involved in the design and conduct of the study. The results will be disseminated via publication of the study findings and social media and press release portals.

RESULTS

Baseline patient characteristics

A total of 4313 consecutive admissions with RT-PCR confirmed COVID-19 were admitted to six Mount Sinai Hospitals between 7 March and 10 May 2020, of whom 1270 (29.4%) died during their hospitalisation. Overall, 13.3% (n=574) of the study population received corticosteroid therapy (table 1). There were no statistically significant differences in age, gender, race, comorbid conditions and CCI between those who did and did not receive corticosteroids. Based on the disease severity of COVID-19, mild cases were more likely to receive corticosteroids than moderate cases. In severe COVID-19, the distribution of corticosteroid use and non-use was similar in both groups. The mean length of hospitalisation was longer among patients who did not receive corticosteroids (9.2 days) compared with those receiving corticosteroids (8.09, p=0.02).

Initial admission inflammatory biomarker values of CRP, D-dimer, procalcitonin, ferritin and lymphocyte count were similar between corticosteroid-treated and non-corticosteroid-treated patients. Levels of IL-6 were higher in the steroid-treated group, but there was no difference in IL-6 levels in survivors versus non-survivors.

Table 2 provides details of the corticosteroid regimens between survivors and non-survivors. There was no statistically significant difference in the rate of corticosteroid therapy between survivors and non-survivors (13.8% vs 12.1%; p=0.13). At baseline, no significant difference in corticosteroids dosing and duration of treatment was noted between survivors and non-survivors (table 2). More specifically, there were similar rates of methylprednisolone, dexamethasone and hydrocortisone usage between COVID-19 survivors and non-survivors except for an increase in the administration of prednisone (unadjusted data, 25.9% vs 19.6%, p=0.04). Methylprednisolone was the most common corticosteroid administered, followed by prednisone and dexamethasone. The durations of methylprednisolone, prednisone, dexamethasone and hydrocortisone therapy were similar between survivors and non-survivors. Durations of corticosteroid therapy among all agents ranged from 6.34 to 9.53 days, and they were similar between COVID-19 survivors and non-survivors. There was no significant difference between groups in the use of adjuvant therapies, including tocilizumab and anticoagulants. Dosing of corticosteroids was categorised according to Williams[23] (online supplemental table 1). There was no significant difference in methylprednisolone, prednisone, dexamethasone and hydrocortisone dosing between COVID-19 survivors and non-survivors.

Primary outcomes

Among the 4313 patients included in the analysis, the primary endpoint of death was observed in 1270 (29.4%) patients. In the univariate unadjusted analysis, corticosteroid therapy appeared to have no significant impact on mortality (OR 0.85, p=0.12). However, following multivariate regression analysis, the administration of corticosteroids was associated with a reduced risk of death (OR 0.73, 95% CI 0.55 to 0.97, p=0.03). Our model simultaneously adjusted for potential confounders including age, female, body mass index, race, COVID-19 disease severity, CCI, asthma, CRP (≥150 mg/L), creatinine (≥2.0 mg/dL), D-dimer (≥2.0 µg/L), positive blood cultures, use of adjuvant therapies including hydroxychloroquine, azithromycin, tocilizumab and anticoagulation (table 3).

Secondary outcomes

Significantly lower mortality (OR 0.67; 95% CI 0.47 to 0.97, p=0.03) and ICU admission rates (OR 0.67; 95% CI 0.31 to 0.71, p=0.02) without a difference in invasive mechanical

Table 1 Clinical characteristics and adjuvant therapies according to corticosteroids administration in patients with COVID-19

Characteristics	Overall (N=4313)	Corticosteroids (n=574)	No corticosteroids (n=3739)	P value
Age—years	65.1±16.8	64.5±16.1	65.2±16.9	0.32
Female sex—n (%)	1872 (43.4)	248 (43.0)	1624 (43.0)	0.93
Obesity	363 (8.4)	36 (6.3)	327 (8.8)	0.05
Race or ethnic group—n (%)*				
White	930 (24.7)	121 (24.0)	809 (25.0)	0.19
Black	921 (24.5)	136 (27.0)	785 (24.0)	0.28
Hispanic	1705 (45.3)	218 (43.0)	1487 (46.0)	0.49
Asian	209 (5.6)	33 (6.5)	176 (5.4)	0.29
Other	548 (12.7)	66 (11.5)	482 (12.9)	0.45
Coexisting conditions—n (%)				
Hypertension	1525 (35.4)	183 (32.0)	1342 (36.0)	0.07
Diabetes	1010 (23.4)	119 (21.0)	891 (24.0)	0.11
Chronic kidney disease	557 (13)	61 (11.0)	496 (13.0)	0.08
Asthma	207 (4.8)	34 (5.9)	173 (4.6)	0.17
COPD	175 (4.1)	16 (2.8)	159 (4.3)	0.11
OSA	97 (2.3)	9 (1.6)	88 (2.4)	0.29
Smokers	1091 (25.3)	133 (23)	958 (26.0)	0.22
Any comorbidity	2364 (54.8)	297 (51.7)	2067 (55.3)	0.12
No comorbidity	1949 (45.2)	277 (48.3)	1672 (44.7)	0.12
COVID-19 disease severity†				
Mild	638 (14.8)	103 (18)	535 (14)	0.02
Moderate	3105 (71.9)	387 (67)	2718 (73)	0.01
Severe (intubated)	570 (13.2)	84 (15)	486 (13)	0.28
Charlson Comorbidity Index (CCI)				
0	609 (14.1)	85 (15)	524 (14)	0.61
1	488 (11.3)	69 (12)	419 (11)	0.57
2	780 (18.1)	111 (19)	669 (18)	0.41
≥3	2436 (56.5)	309 (54)	2127 (57)	0.16
Length of hospital stay (days)				
Mean	9.1±23.4	8.09±6.8	9.2±24.9	0.02
Median	6 (3–12)	6 (3–12)	6 (3–11)	–
Admission laboratory values				
C reactive protein (mg/L)	133.1±22.2	82±44	142±24	0.33
D-dimer (µg/L)	1.21±0.18	1.23±0.35	1.21±0.22	0.63
Ferritin (ng/L)	613.3±124	404.2±225	669±145	0.61
Interleukin-6 (pg/mL)	269±20	316±16	205±42	0.02
Procalcitonin (ng/L)	1.24±0.72	0.23±0.06	1.37±0.81	0.47
Lymphocyte count ($\times 10^9$/L)	1.42±0.22	1.08±0.29	1.47±0.26	0.92
Clinical outcomes				
Death	1270 (29.5)	153 (26.7)	1117 (29.9)	0.13
ICU admission	324 (7.5)	39 (6.8)	285 (7.6)	0.47
Mechanical ventilation	581 (13.5)	86 (15.0)	495 (13.2)	0.27

*Patient-reported variables. COPD = Chronic obstructive pulmonary disease. OSA = Obstructive sleep apnea.
†Mild—oxygen saturation >93%; moderate—oxygen saturation <93%; severe—respiratory failure with oxygen saturation <93% and requiring invasive mechanical ventilation (Mount Sinai Health System Treatment Guidelines).
ICU, intensive care unit.

Table 2 Details of initial corticosteroid therapy among hospitalised patients with COVID-19

Medical therapy	Overall (N=4313)	Survivors (n=3043)	Non-survivors (n=1270)	P value
Corticosteroids—n (%)	574 (13.3)	421 (13.8)	153 (12.1)	0.13
Medication				
Methylprednisolone	282 (49.1)	199 (73.3)	83 (54.2)	0.99
Prednisone	139 (24.2)	109 (25.9)	30 (19.6)	0.04
Dexamethasone	82 (14.3)	62 (14.7)	20 (13.1)	0.33
Hydrocortisone	71 (12.4)	51 (12.1)	20 (13.1)	0.89
Duration of use (days)*				
Methylprednisolone	6.63 (3.45–11.48)	4.99 (2.89–8.33)	5.80 (3.68–8.26)	0.72
Prednisone	8.59 (2.97–21.46)	4.94 (2.29–12.87)	8.15 (1.81–19.59)	0.29
Dexamethasone	6.34 (2.63–12.78)	5.04 (2.48–6.98)	3.72 (2.42–5.45)	0.32
Hydrocortisone	9.53 (4.88–14.28)	9.59 (4.25–12.94)	8.16 (3.45–12.06)	0.92
Timing of corticosteroid initiation				
<7 days	330 (57.6)	244 (58.0)	86 (56.1)	0.52
≥8 to ≤14 days	129 (22.6)	92 (21.9)	37 (24.2)	
>14 days	115 (20.1)	85 (18.0)	30 (19.6)	
Median time from hospital admission to corticosteroid administration (days)	5.96 (3.08–10.62)	5.86 (2.97–10.51)	6.25 (3.58–11.29)	0.58
Adjuvant therapies among corticosteroid users				
Hydroxychloroquine	420 (73.2)	321 (76.2)	99 (64.7)	0.74
Azithromycin	397 (69.2)	289 (68.7)	108 (70.6)	0.55
Tocilizumab	20 (3.5)	13 (3.1)	7 (4.6)	0.62
Anticoagulation	255 (44.4)	191 (45.3)	65 (42.4)	0.55

*Median time of drug administration—(25% percentile–75% percentile).
†Anticoagulation—heparin, enoxaparin, apixaban, rivaroxaban.

ventilation rates were observed when corticosteroids were administered within ≤7 days of admission) (table 3). Among those who received corticosteroids beyond day 8, the rates of mortality, rate of ICU admission and rate of invasive mechanical ventilation did not differ. Patients with CRP ≥150 mg/L, IL-6 ≥20 pg/mL and D-dimer ≥2.0 µg/L on admission had lower mortality associated with corticosteroid treatment(OR 0.67; 95% CI 0.31 to 0.71, p=0.03, table 3). Blood cultures were examined. Corticosteroid users had a lower unadjusted rate of positive blood cultures (8.2% vs 9.6%, p<0.001), with similar rates of Gram-positive, Gram-negative bacteria and fungi on blood cultures as non-corticosteroids users (table 4).

DISCUSSION

This large study of 4313 consecutive patients admitted with COVID-19 pneumonia demonstrates a therapeutic benefit of corticosteroids. In our analysis, corticosteroid use within the first 7 days of admission was associated with a survival benefit after adjusting for confounders with multivariate regression statistical model. Moreover, corticosteroid use was associated with a decrease in ICU admissions when used within 7 days of admission. Corticosteroid therapy was associated with a reduction in mortality in patients with elevated inflammatory markers (CRP ≥150 mg/L, IL-6 ≥20 pg/mL and D-dimer ≥2.0 µg/L) when compared with patients who were not given corticosteroids. When adjusted for the use of other therapeutic agents, including hydroxychloroquine, azithromycin, tocilizumab and anticoagulation, the impact of corticosteroid use on decreasing mortality remained. The frequency, duration, type and dose of corticosteroids were comparable among survivors and non-survivors. Notably, the frequency of corticosteroid use was not higher in patients with the greatest disease severity as determined by the degree of hypoxaemia on admission. There was no significant difference in overall positive bacterial and fungal blood cultures in the corticosteroid-treated group from a safety perspective.

The potential therapeutic role of corticosteroids in viral pneumonia and specifically for COVID-19 was controversial at the time of this study, before the publication of the RECOVERY study.[12] Many authoritative organisations discouraged the use of corticosteroids for COVID-19 at the time of writing this manuscript. The CDC and IDSA did not recommend using corticosteroids outside a clinical trial.[14] On 12 January 2020, the WHO suggested that corticosteroids be avoided to treat SARS-CoV-2-induced

Table 3 Association between corticosteroid use and composite endpoints in univariate and multivariable analyses

	Univariate regression analysis		Multivariate regression analysis	
Composite endpoints	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Corticosteroid therapy*				
Mortality (n=153)	0.85 (0.69 to 1.03)	0.12	0.73 (0.55 to 0.97)	0.03
ICU admission (n=39)	0.88 (0.62 to 1.25)	0.48	0.72 (0.47 to 1.11)	0.14
Invasive mechanical ventilation (n=86)	0.80 (0.46 to 1.39)	0.44	0.73 (0.38 to 1.42)	0.36
Timing of corticosteroids use*				
Mortality				
≤7 days (n=86)	0.42 (0.39 to 0.44)	0.01	0.67 (0.47 to 0.97)	0.03
≥8 days (n=67)	1.23 (0.96 to 1.57)	0.09	0.86 (0.56 to 1.31)	0.49
ICU admission				
≤7 days (n=23)	2.25 (0.86 to 5.87)	0.09	0.67 (0.31 to 0.71)	0.02
≥8 days (n=16)	1.59 (0.61 to 4.16)	0.34	2.59 (0.71 to 9.42)	0.15
Intubation				
≤7 days (n=55)	1.06 (0.59 to 1.91)	0.84	1.35 (0.69 to 2.65)	0.75
≥8 days (n=31)	0.75 (0.42 to 1.30)	0.34	0.89 (0.46 to 1.75)	0.38
Impact of inflammatory biomarkers†				
CRP ≥150 mg/L	0.85 (0.70 to 1.04)	0.12	0.73 (0.55 to 0.97)	0.03
IL-6 ≥20 pg/mL	0.85 (0.70 to 1.04)	0.12	0.73 (0.55 to 0.97)	0.03
D-dimer ≥2.0 µg/L	0.85 (0.6 to 1.02)	0.11	0.73 (0.55 to 0.97)	0.03

*Multivariate logistic regression analysis—adjusted simultaneously for age, female, BMI, race, disease severity, Charlson Comorbidity Index, asthma, C reactive protein, creatinine, D-dimer, blood culture, adjuvant therapies (hydroxychloroquine+azithromycin+tocilizumab) and anticoagulation.
†Multivariable analysis—adjusted simultaneously for age, female, BMI, race, disease severity, Charlson Comorbidity Index, asthma, creatinine, blood culture, adjuvant therapies (hydroxychloroquine+azithromycin+tocilizumab) and anticoagulation.
BMI, body mass index; CRP, C reactive protein; ICU, intensive care unit; IL-6, interleukin-6.

lung injury or shock outside of a clinical trial.[21] There were concerns that corticosteroids may impair the host response to SARS-CoV-2.[10 15 17] Indeed, the results of many clinical trials examining the safety and efficacy of corticosteroids in patients who were critically ill with pneumonia and septic shock were inconclusive. In March 2020, the Surviving Sepsis guidelines for COVID-19 issued a weak recommendation for the use of corticosteroids in patients with COVID-19 ARDS who required mechanical ventilation.[24] In this context, despite institutional guidelines describing the use of corticosteroids for patients admitted with COVID-19, many physicians in the Mount Sinai Health System were reluctant to prescribe corticosteroids, and the final decision regarding the use of corticosteroids was left to the physicians treating the patient.

Prior studies of corticosteroids for patients with respiratory illness from coronavirus SARS and MERS had not demonstrated a survival benefit.[10 25] A meta-analysis that included 6548 patients with influenza pneumonia showed that corticosteroids were associated with a twofold higher risk of secondary infections (p=0.04).[26] However, most of the studies were observational, and it is possible that corticosteroids were administered to the sickest patients. Low to moderate doses of corticosteroids

Table 4 Microbiological results and coinfection rates among hospitalised patients with COVID-19

Microbiological results	Overall (N=4313)	Steroids (n=574)	No steroids (n=3739)	P value
Blood cultures				
Obtained	2951	61	2890	0.001
Positive	284/2951 (9.6)	5/61 (8.2)	279/2890 (9.6)	0.001
Microbiological organism				
Gram-positive	228/2951 (7.7)	4/61 (6.5)	224/2890 (7.2)	0.99
Gram-negative	37/2951 (1.3)	0/61 (0)	37/2890 (1.2)	0.99
Fungal	19/2951 (0.6)	1/61 (1.6)	18/2890 (0.6)	0.33

have been associated with a reduction in mortality in patients with severe lung disease from SARS[27] and in patients with H1N1 viral pneumonia and a PaO_2:FiO_2 ≤300 mm Hg.[28] A retrospective study of 201 patients with COVID-19 in China found that for those who developed ARDS, treatment with methylprednisolone was associated with a decreased mortality.[18] The recent RECOVERY trial has demonstrated a survival benefit with low-dose dexamethasone compared with usual care in hospitalised patients with COVID-19 who required supplemental oxygen therapy or invasive mechanical ventilation. Our main study results are in alignment with the findings of the RECOVERY trial.

Our study builds on recent studies that support the safe and effective use of corticosteroids in severe community-acquired pneumonia (CAP) and in ARDS. Patients with severe CAP and high inflammatory markers, including a CRP ≥150 mg/L who received methylprednisolone versus placebo, had a decrease in the primary endpoint, a composite of early and late treatment failure. Early treatment failure included the development of shock, the need for invasive mechanical ventilation and death within 72 hours of randomisation. Late treatment failure was defined by radiographic progression, the persistence of severe respiratory failure, the development of shock, the need for invasive mechanical ventilation does not present at baseline, or death between 72 and 120 hours after treatment initiation.[29] Non-COVID-19 patients with moderate to severe ARDS randomised to a 10-day course of tapered dexamethasone versus standard of care experienced higher mean ventilator-free days and lowered 60-day mortality. There was no significant difference in adverse events, including no difference in pneumonia or sepsis (24% dexamethasone-treated vs 25% placebo).[30]

A meta-analysis of nine small RCT (randomized clinical trials) studying corticosteroids versus standard of care provided the material for the Society of Critical Care Medicine to give a conditional recommendation for the use of corticosteroids in ARDS[31] (non-COVID-19), and the Surviving Sepsis Campaign recommends a short course of glucocorticoids for moderate to severe ARDS secondary to COVID-19.[24]

The limitations of this study include its retrospective observational design, with non-randomised sampling. With the use of an electronic health record database, there are potential inaccuracies and missing data. There is no data referring to the use of non-invasive ventilation and high flow nasal oxygen in patients with severe hypoxaemia. A small number of patients in this study were treated in a variety of therapeutic clinical trials, but data on the impact of those therapies could not be assessed due to study confidentiality issues as these trials are ongoing. The use of named adjuvant therapies, including anticoagulation, was similar in the corticosteroid-treated and non-corticosteroid-treated cohorts.

CONCLUSION

We present a large study describing the potential benefit and safety of corticosteroids in hospitalised patients with COVID-19 pneumonia when administered within the first 7 days after admission. There was a mortality benefit associated with corticosteroid use in patients aged less than 65 years and in females. Corticosteroids did not confer any benefit when administered after 8 days. Consideration should be given to the early administration of corticosteroids, particularly if inflammatory markers are elevated. Further studies are required to define the optimal time for initiation of corticosteroids in COVID-19, including when to administer corticosteroids based on the severity of illness and inflammatory profiling.

Contributors All authors contributed to the writing of this manuscript. Statistical analyses were performed by KSH, BN, LL, ZW and RC.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Institutional Review Board of Icahn School of Medicine at Mount Sinai approved the research project (IRB-20-03843).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data may be requested from the Mount Sinai COVID Informatics Center (MSCIC) and is not currently publicly available.

REFERENCES

1 Guan W-J, Ni Z-Y, Hu Y, *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
2 Holshue ML, DeBolt C, Lindquist S. Washington state 2019-nCoV case investigation team. first case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020;382:929–36.
3 Centers for Disease Control and Prevention. Cases in the US. Available: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html
4 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA* 2020;323:1239.
5 Ruan Q, Yang K, Wang W, *et al*. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46:846–8.
6 Xu Z, Shi L, Wang Y, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:420–2.
7 Mehta P, McAuley DF, Brown M, *et al*. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4.
8 Wu C, Chen X, Cai Y, *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934.

9 Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.
10 Arabi YM, Mandourah Y, Al-Hameed F, *et al*. Corticosteroid therapy for critically ill patients with middle East respiratory syndrome. *Am J Respir Crit Care Med* 2018;197:757–67.
11 Yamaya M, Nishimura H, Deng X, *et al*. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. *Respir Investig* 2020;58:155–68.
12 RECOVERY Collaborative Group, Horby P, Lim WS, *et al*. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
13 Sanders JM, Monogue ML, Jodlowski TZ, *et al*. Pharmacologic treatments for coronavirus disease 2019 (COVID-19). *JAMA* 2020;382.
14 Morgan R, Shumaker A, Lavergne V. COVID-19 guideline, part 1: treatment and management, 2020. Available: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ [Accessed 2 Jun 2020].
15 Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet* 2020;395:473–5.
16 World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected, 2020. Available: https://www.who.int/publications-detail/clinical-management-of-severe-acute- respiratory-infection-when-novelcoronavirus- (ncov)-infection-is-suspected
17 Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, *et al*. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev* 2016;59.
18 Shang L, Zhao J, Hu Y, *et al*. On the use of corticosteroids for 2019-nCoV pneumonia. *The Lancet* 2020;395:683–4.
19 Jie Z, He H, Xi H. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. *Chin J Tuberc Respir Dis* 2020;43:183–4.
20 Genes N, Chandra D, Ellis S, *et al*. Validating emergency department vital signs using a data quality engine for data Warehouse. *Open Med Inform J* 2013;7:34–9.
21 World Health Organization. Interim guidance: clinical management of severe acute respiratory infection when COVID-19 is suspected, 2020. Available: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
22 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
23 Williams DM. Clinical pharmacology of corticosteroids. *Respir Care* 2018;63:655–70.
24 Alhazzani W, Møller MH, Arabi YM, *et al*. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med* 2020;46:854–87.
25 Stockman LJ, Bellamy R, Garner P. Sars: systematic review of treatment effects. *PLoS Med* 2006;3:e343.
26 Ni Y-N, Chen G, Sun J, *et al*. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care* 2019;23:99.
27 Chen R-chang, Tang X-ping, Tan S-yong, *et al*. Treatment of severe acute respiratory syndrome with Glucosteroids. *Chest* 2006;129:1441–52.
28 Li H, Yang S-G, Gu L, *et al*. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. *Influenza Other Respir Viruses* 2017;11:345–54.
29 Torres A, Sibila O, Ferrer M, *et al*. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015;313:677.
30 Villar J, Ferrando C, Martínez D, *et al*. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med* 2020;8:267–76.
31 Annane D, Pastores SM, Rochwerg B, *et al*. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I). *Crit Care Med* 2017;45:2078–88.

Supplementary Table 1: Details of steroid dosing and impact on mortality

Medical Therapy	Overall (N=4,313)	Survivors (N=3,043)	Non-Survivors (N=1,270)	*P*-value
Methylprednisolone✝ ≤ 40 mg 40 < x < 80 mg 80 ≤ x ≤ 160 mg	167 (59) 76 (27) 39 (14)	117 (59) 55 (28) 27 (14)	50 (60) 21 (25) 12 (14)	0.95
Prednisone✝ ≤ 50mg 50 < x <100 mg 100 ≤ x ≤ 200 mg	96 (69) 43 (31) 0 (0)	74 (68) 35 (32) 0 (0)	22 (73) 8 (27) 0 (0)	0.56
Dexamethasone✝ ≤ 7.5 mg 7.5 < x <15 mg 15 ≤ x ≤ 30 mg	71 (87) 6 (7) 5 (6)	57 (92) 2 (3) 3 (5)	14 (70) 4 (20) 2 (10)	0.11
Hydrocortisone✝ ≤ 50 mg 50 < x < 100 mg 100 ≤ x ≤ 200 mg	71 (100) 0 (0) 0 (0)	51 (100) 0 (0) 0 (0)	20 (100) 0 (0) 0 (0)	1.0
Methylprednisolone✝ ≤ 40 mg 40 < x < 80 mg 80 ≤ x ≤ 160 mg	167 (59) 76 (27) 39 (14)	117 (59) 55 (28) 27 (14)	50 (60) 21 (25) 12 (14)	0.95

✝Dosing of Corticosteroids categorized according to William *et al.* [23]