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Short Communication

Determinants of the protective effect of glucocorticoids on mortality in hospitalized patients with COVID-19 Insights from the Cardio-COVID-Italy multicenter study

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ABSTRACT

Background: Glucocorticoid therapy has emerged as an effective therapeutic option in hospitalized patients with coronavirus disease 2019 (COVID-19). This study aimed to focus on the impact of relevant clinical and laboratory factors on the protective effect of glucocorticoids on mortality.
Methods: A sub-analysis was performed of the multicenter Cardio-COVID-Italy registry, enrolling consecutive patients with COVID-19 admitted to 13 Italian cardiology units between 01 March 2020 and 09 April 2020. The primary endpoint was in-hospital mortality.
Results: A total of 706 COVID-19 patients were included (349 treated with glucocorticoids, 357 not treated

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with glucocorticoids). After adjustment for relevant covariates, use of glucocorticoids was associated with a lower risk of in-hospital mortality (adjusted HR 0.44; 95% CI 0.26–0.72; p = 0.001). A significant interaction was observed between the protective effect of glucocorticoids on mortality and PaO_2/FiO_2 ratio on admission (p = 0.042), oxygen saturation on admission (p = 0.017), and peak CRP (0.023). Such protective effects of glucocorticoids were mainly observed in patients with lower PaO_2/FiO_2 ratio (<300), lower oxygen saturation (<90%), and higher CRP (>100 mg/L).
Conclusions: The protective effects of glucocorticoids on mortality in COVID-19 were more evident among patients with worse respiratory parameters and higher systemic inflammation.

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and represents a major cause of morbidity and mortality worldwide (Wiersinga et al., 2020). Systemic glucocorticoids have emerged as an effective therapeutic option in hospitalized patients with COVID-19, especially in cases of moderate-severe acute respiratory distress syndrome or need of respiratory support (RECOVERY Collaborative Group et al., 2021; Tomazini et al., 2020; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al., 2020). However, their use may be associated with drug-related adverse events (e.g., potential pro-thrombotic effect, increased susceptibility to infection, neuro-psychiatric symptoms, etc.) that could be detrimental in patients with COVID-19 (Mishra and Mulani, 2021). Hence, further assessment of the subset of patients most

Table 1
Baseline clinical characteristics, clinical presentation, laboratory data, and in-hospital management.

	No glucocorticoids (n = 357)	Glucocorticoids (n = 349)	p-Value
Baseline characteristics			
Age (years)	68.1 ± 13.8	66.9 ± 12.3	0.22
Male sex	243 (68.1%)	247 (70.8%)	0.44
BMI (kg/m^2)	26.7 ± 5.2	27.8 ± 5.1	**0.011**
Smoking	84 (29.2%)	77 (25.6%)	0.33
Hypertension	200 (56.5%)	202 (58.2%)	0.65
Dyslipidemia	97 (27.4%)	96 (27.7%)	0.92
Diabetes mellitus	89 (25.1%)	75 (21.6%)	0.27
Atrial fibrillation	67 (18.9%)	41 (11.8%)	**0.009**
Coronary artery disease	83 (23.4%)	66 (19.0%)	0.15
History of HF	58 (16.4%)	36 (10.4%)	**0.020**
COPD	37 (10.5%)	31 (8.9 %)	0.50
CKD	71 (20.1%)	59 (17.0%)	0.30
History of neoplasia	32 (9.0%)	26 (7.5%)	0.46
Clinical presentation (hospital admission)			
Fever	213 (60.0%)	241 (69.3%)	**0.010**
Respiratory rate ≥ 22 bpm	110 (45.8%)	174 (56.7%)	**0.012**
Systolic blood pressure (mmHg)	129.5 ± 21.6	130.0 ± 21.6	0.74
Diastolic blood pressure (mmHg)	74.4 ± 13.2	75.1 ± 12.9	0.53
Heart rate (bpm)	86.5 ± 18.0	86.8 ± 18.0	0.83
Oxygen saturation (%)	92.1 ± 6.3	88.8 ± 8.6	<**0.001**
PaO_2/FiO_2 ratio	269.7 ± 133.4	201.9 ± 120.5	<**0.001**
SOFA score ≥ 3	85 (38.5%)	111 (47.2%)	0.06
Laboratory data			
Increased troponin	158 (45.9%)	121 (44.0%)	0.63
Hemoglobin (g/dL)	12.9 [11.6, 14.1]	13.7 [12.1, 14.6]	<**0.001**
WBC count (per μL)	6820 [5100, 9150]	6610 [4890, 9550]	0.88
Lymphocyte count (per μL)	1015 [700, 1490]	840 [570, 1100]	<**0.001**
Platelet count (10^9/L)	210 [159, 280]	198 [150, 257]	0.06
Creatinine (mg/dL)	1.0 [0.8, 1.4]	1.0 [0.8, 1.2]	0.14
eGFR ($mL/min/1.73\ m^2$)	71.6 [45.6, 89.0]	77.1 [55.7, 90.6]	0.07
CRP on admission (mg/L)	40 [6, 100]	66 [21, 154]	<**0.001**
Peak CRP (mg/L)	84 [21, 153]	110 [44, 210]	<**0.001**
D-dimer (ng/mL)	743 [358, 1703]	930 [473, 1686]	**0.024**
Serum ferritin (ng/mL)	623 [332, 1321]	802 [429, 1550]	0.13
NT-proBNP (pg/mL)	392 [111, 2584]	230 [83, 940]	0.06
Lactate dehydrogenase (U/L)	340 [241, 505]	379 [273, 531]	0.14
In-hospital management			
No oxygen support	89 (25.6%)	28 (8.2%)	<**0.001**
Oxygen support with FiO_2 ≥ 50%	138 (39.7%)	245 (71.4%)	<**0.001**
Non-invasive ventilation	88 (24.8%)	215 (62.1%)	<**0.001**
Intubation (invasive ventilation)	34 (9.6 %)	74 (21.3%)	<**0.001**
Antiviral therapy			
Lopinavir/ritonavir	114 (31.9%)	75 (21.5%)	**0.002**
Darunavir/ritonavir	83 (23.3%)	93 (26.7%)	0.30
Remdesivir	4 (1.1%)	1 (0.3%)	0.19

Data are presented as n/N (%), mean standard deviation or median [Q25, Q75]. Significant p-values are reported in bold.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.

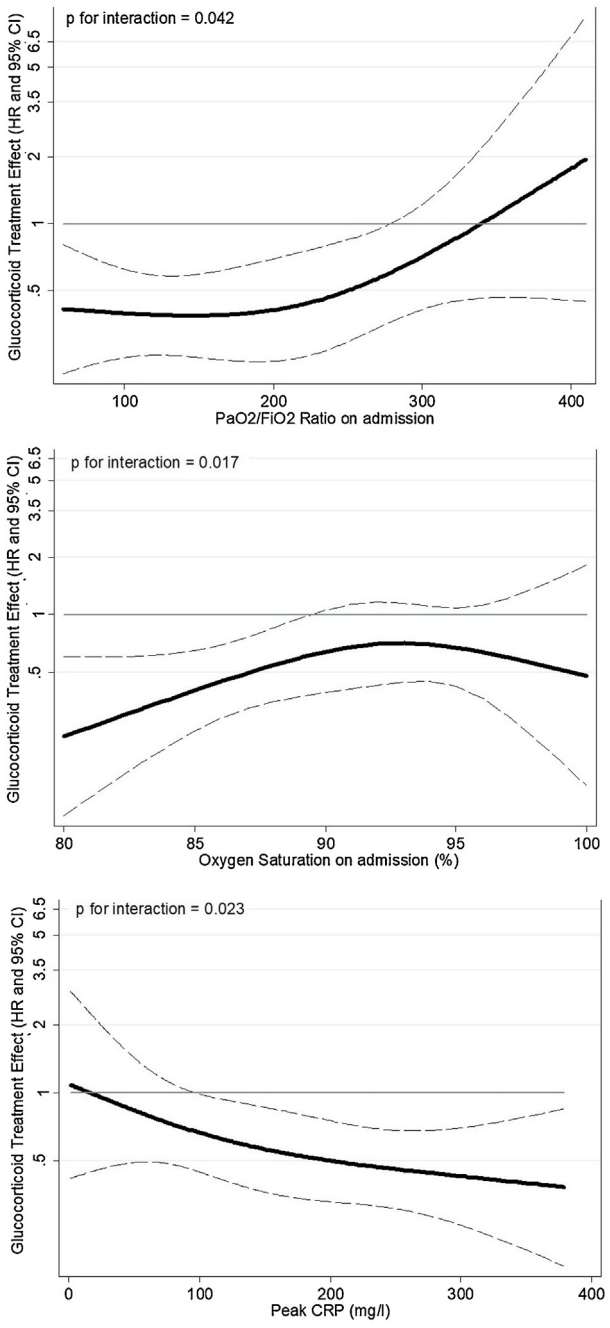

Figure 1. The association between glucocorticoid treatment effect on in-hospital mortality and PaO2/FiO2 ratio on admission, oxygen saturation on admission, and peak C-reactive protein (CRP). The hazard ratio (HR) and 95% confidence interval (CI) are shown across the spectrum of the continuous variables of interest (PaO_2/FiO_2 ratio on admission, oxygen saturation on admission, and peak CRP); p-values for interaction between glucocorticoid use and the continuous variables of interest are also reported.

responsive to glucocorticoids could be useful to refine the use of these drugs in hospitalized patients with COVID-19. This study aimed to confirm the protective effect of glucocorticoid use on mortality in a real-world, inpatient COVID-19 population, and to focus on the impact of relevant clinical and laboratory factors on such protective effect.

Methods

A multicenter registry of consecutive patients with laboratory-confirmed COVID-19 and admitted to 13 Italian cardiology units between 01 March and 09 April 2020 was analyzed. Details on study design and study population have already been described (Lombardi et al., 2020; Tomasoni et al., 2020). Baseline characteristics, laboratory data, and details on clinical presentation, in-hospital management, and in-hospital outcomes were compared between patients who received vs. those who did not receive systemic glucocorticoids during hospital stay. The association between glucocorticoid use and in-hospital mortality was assessed by means of univariate and multivariate Cox regression analysis; the results are presented as hazard ratio (HR) and 95% confidence interval (CI). Kaplan–Meier analysis was also performed to report the estimated rate of in-hospital mortality and to compare mortality between groups (log-rank test). The interaction between glucocorticoid use and several variables of interest with respect to in-hospital mortality was tested by means of formal interaction testing analysis; the relationship between the levels of continuous variables of interest and the treatment effect of glucocorticoids (HR for in-hospital mortality) was displayed using restricted cubic spline models. A p-value < 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed using Stata version 14 (Stata Corp., College Station, Texas).

Results and discussion

A total of 706 patients were included in the present analysis (349 treated with glucocorticoids and 357 not treated with glucocorticoids). Mean age was 68 $\pm$ 13 years, and 69.4% of patients were male. As shown in Table 1, patients treated with glucocorticoids had higher body mass index (BMI) and less frequently reported a history of heart failure (HF) or atrial fibrillation (AF), as compared with patients not treated with glucocorticoids. At clinical presentation, oxygen saturation and PaO_2/FiO_2 ratio were significantly lower and the presence of fever and respiratory rate $\geq$22 bpm was more frequent in the glucocorticoids group. Regarding laboratory findings at hospital admission, patients treated with glucocorticoids had significantly lower levels of lymphocytes and higher levels of hemoglobin, C-reactive protein (CRP), and D-dimer; furthermore, peak CRP during hospital stay was significantly higher in the glucocorticoids group. During hospital stay, oxygen support with $FiO_2 \geq 50\%$, non-invasive ventilation, and intubation were more frequent in the glucocorticoids group, whereas patients not treated with glucocorticoids more frequently did not receive oxygen support (Table 1). Median hospital stay in the overall population was 14 [interquartile range 9–24] days, and a total of 166 patients (23.5%) died during hospital stay (78 in the glucocorticoid group, 88 in the no glucocorticoid group). Glucocorticoid use was associated with lower in-hospital all-cause mortality (HR 0.61; 95% CI 0.45–0.83; p = 0.002). Kaplan–Meier estimated rates of cumulative 28-day mortality were 38.0% and 45.2% in the glucocorticoids and no glucocorticoids groups, respectively (log-rank p = 0.001; Supplementary Figure 1). After adjustment for age, participating center, hypertension, AF, coronary artery disease, history of HF, chronic kidney disease, PaO_2/FiO_2 ratio, increased troponin, peak CRP, lymphocyte count, and hemoglobin values, glucocorticoid use remained independently associated with lower in-hospital mortality (adjusted HR 0.44; 95% CI 0.26–0.72; p = 0.001). The Harrel's C-index for the multivariable model was 0.80 (95% CI 0.75–0.85). With respect to in-hospital mortality, a significant interaction was observed between glucocorticoid use and PaO_2/FiO_2 ratio on admission (p = 0.042), oxygen saturation on admission (p = 0.017), and peak CRP (p = 0.023), but not BMI (p = 0.282), history of HF (p = 0.733), AF (p = 0.836), coronary artery disease (p = 0.577), hemoglobin (p = 0.794), lymphocyte count (p = 0.274), increased troponin (p = 0.527), D-dimer on admission (p = 0.450), and CRP on admission (p = 0.478). As shown in Figure 1, the protective effect of glucocorticoids on

mortality was mainly observed in patients with lower values of PaO_2/FiO_2 ratio on admission (<300), lower values of oxygen saturation on admission (<90%), and higher values of peak CRP (>100 mg/L).

In line with recent studies reporting lower mortality in COVID-19 patients treated with glucocorticoids only in case of need of oxygen therapy or mechanical ventilation (RECOVERY Collaborative Group et al., 2021), this analysis showed a significant interaction between the protective effect of glucocorticoids on mortality and levels of PaO_2/FiO_2 ratio and oxygen saturation on admission. Furthermore, such protective effect was more pronounced in patients with higher values of peak CRP during hospital stay, which is similar to a recent study reporting benefit of early glucocorticoid use only in patients with CRP $\geq$ 200 mg/L and harm in patients with CRP < 100 mg/L (Keller et al., 2020). Of note, the protective effects of glucocorticoids could not merely be a class-effect, but may depend also on duration of therapy and the type of drug used, as suggested by the conflicting results of the RECOVERY trial with dexamethasone and the Metcovid trial with methylprednisolone (Jeronimo et al., 2021; RECOVERY Collaborative Group et al., 2021). Unfortunately, details on type and doses of glucocorticoids and duration of therapy were not available in the current registry, and data on glucocorticoid therapy prior to hospital admission, pre-existing autoimmune or rheumatological diseases, and time from symptom onset to hospital admission were not collected. Considering the potential glucocorticoid-related adverse events, a detailed assessment of risk-benefit ratio and the identification of patients most responsive to such therapy are fundamental. Future, larger studies are needed to further refine the use of glucocorticoids in patients with COVID-19.

Disclosures

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Ethical approval

This study complied with the edicts of the Declaration of Helsinki and was approved by the ethical committee of Civil Hospitals of Brescia Italy (no. NP 4105) and of each recruiting center.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.05.056.

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