Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Glucocorticoid benefits the ventilatory function of severe/critical COVID-19 patients

Dear Editor,

The coronavirus disease 2019 (COVID-19) has become a global pandemic.[1] With our accumulating experience of combatting COVID-19, many medications were repurposed to counteract it.[2] Cytokine storm and immune disorders are reportedly major mediators in acute respiratory distress syndrome and multiple organ failure, leading to poor prognosis of COVID-19.[3] Therefore, glucocorticoid (GC), an affordable, nonspecific anti-inflammatory and immunoregulatory drug, has been suggested to treat patients with COVID-19, especially those with critical diseases. Though GC has been used in more and more COVID-19 patients, the benefit of GC is still controversial. Because of the immunosuppressive function of GC, it is inclined to delay viral clearance,[4] cause secondary infections, lead to physiological deterioration,[5] and relate to higher mortality, longer length of hospitalization.[6] However, the effects of GC on the ventilatory function of COVID-19 patients were incompatible.[7,8] This study aims to investigate how GC affects the duration of oxygen supply for COVID-19 patients.

In this retrospective study, we included 1447 survivors of COVID-19 with oxygen therapy (30 patients with invasive ventilation and 1417 patients with noninvasive ventilation) in Tongji Hospital, Tongji Sino-French New City Hospital, and Tongji Optical Valley Hospital from January 27, 2020 to March 21, 2020. The demographics and laboratory data of included patients at admission are shown in Table 1. 428 (29.6%) of these 1447 patients received GC therapy and patients in GC group were severer ($p<0.0001$). Meanwhile, the hospitalization time (median [interquartile range, IQR], 26 [20–33] days) and oxygen supply duration (median [IQR], 19 [12–26] days) of GC group were significantly longer than the hospitalization time (median [IQR], 20 [14–27] days) and oxygen supply duration (median [IQR], 15 [9–22] days) of non-GC group (both $p<0.0001$). The laboratory tests shown in Table 1 also indicated that the disease severity of GC group was worse than that of non-GC group. However, the concomitant diseases were not significantly different between two groups.

We further divided the 1447 patients into different severities according to the Chinese Recommendations for Diagnosis and Treatment of Novel Coronavirus (SARS-CoV2) Infection (Trial 8th version) (Table 2).[9] There were 795 (54.9%) general patients and 652 (45.1%) severe/critical patients. In the general group, 174 (21.9%) cases received GC treatment and 621 (78.1%) cases did not. In the severe/critical group, 254 (39%) cases received GC treatment and 398 (61%) cases did not. The proportion of patients receiving GC therapy was prominently higher in the severe/critical group (Table 2). Some laboratory tests, known as severity indicators, showed the situation of GC group was more serious than that of non-GC group in both general and severe/critical patients. Consequently, the hospitalization time and oxygen supply duration of GC group were longer than those of non-GC group in general patients. However, among severe/critical COVID-19 patients, we did not observe longer oxygen supply duration in GC group (Table 2). Since the disease in GC group was severer, we concluded that GC therapy could improve the ventilatory function of severe and critical patients though there was no significant difference in oxygen supply duration between GC group (median [IQR], 18 [11–26.3] days) and non-GC group (median [IQR], 17 [11–24] days) among severe/critical patients. Marla et al. uncovered GC treatment benefitted COVID-19 patients with initial CRP $\geq$ 20 mg/L.[7] Thus, we further divided 1379 patients into two groups with a CRP cut-off = 20 mg/L according to CRP level at admission. We did not observe any difference in oxygen supply duration between GC group (median [IQR], 20 [13–27] days) and non-GC group (median [IQR], 18 [12–26] days) among patients with CRP $\geq$ 20 mg/L (p=0.1443), though the disease of GC group with CRP $\geq$ 20 mg/L was still worse (Supplementary Table 1).

We next conducted univariable and multivariable time-dependent Cox proportional hazards models to recognize risk factors related to oxygen supply duration. In multivariable analysis, we noted GC use (hazard ratio [HR], 0.742 [95% confidence interval {CI} 0.654–0.842]) was related to longer oxygen supply duration, which might attribute to the worse situation of GC group (Supplementary Table 2). But when we focused on the patients with initial CRP $\geq$ 20 mg/L, GC use was not associated with longer oxygen supply duration (HR, 0.845, [95% CI, 0.710–1.006]) (Supplementary Table 3), notwithstanding the worse disease GC group suffered (Supplementary Table 1).

This multicenter study showed COVID-19 patients with GC therapy were more serious at admission. However, there was no significant difference in oxygen supply duration between GC group and non-GC group among severe/critical patients, as well as patients with an initial CRP $\geq$ 20 mg/L, indicating these patients might benefit more from GC therapy.

There are some limitations in our study. First, we did not consider the types of ventilation and only calculated the total duration of oxygen supply. Second, the patients involved in our study were mainly from hospitals in Wuhan, which might cause some bias to this study. Finally, the dosage of GC use for patients was ignored, and we just considered whether patients used GC or not.

In summary, we did not observe shorter oxygen supply duration of severe/critical COVID-19 patients with GC treatment, but we have faith in the benefit of GC on the ventilatory function of these patients.

Authors' contributions

QLG, XMX and XFJ conceived this project. XMX, XFJ, HYL, SQZ, and YW collected the data. XMX and XFJ analyzed the data. XMX wrote the primitive manuscript. XFJ, HYL and QLG reviewed and

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Table 1
Demographics and laboratory data at admission of COVID-19 patients with GC therapy and non-GC therapy.

Demographics, clinical characteristics	Overall ($N = 1447$)	Non-GC group ($N = 1019$)	GC group ($N = 428$)	P value
Age (years), median (IQR)	62 [50, 70]	63 [50, 70]	62 [51, 69]	0.3888
Sex, *n* (%)				0.0153
Male	656 (45.3)	441 (43.3)	215 (50.2)	
Female	791 (54.7)	578 (56.7)	213 (49.8)	
Severity, *n* (%)				<0.0001
General group	795 (54.9)	621 (60.9)	174 (40.7)	
Severe and critical group	652 (45.1)	398 (39.1)	254 (59.3)	
Hospitalization time, days (IQR)	22 [16, 29]	20 [14, 27]	26 [20, 33]	<0.0001
Oxygen supply duration, days (IQR)	16 [10, 24]	15 [9, 22]	19 [12, 26]	<0.0001
Hypertension§, *n* (%)	574 (39.8)	395 (38.9)	179 (41.8)	0.2964
CHD§, *n* (%)	132 (9.1)	93 (9.2)	39 (9.1)	0.9801
Diabetes§, *n* (%)	255 (17.7)	169 (16.6)	86 (20.1)	0.1154
Malignancy§, *n* (%)	38 (2.6)	26 (2.6)	12 (2.8)	0.7908
COPD§, *n* (%)	10 (0.7)	7 (0.7)	3 (0.7)	0.98
CKD§, *n* (%)	21 (1.5)	12 (1.2)	9 (2.1)	0.1815
Inflammatory response, median (IQR)				
CRP#, (mg/L)	15.4 [2.6, 58.8]	7.8 [1.8, 38.1]	46.4 [13.6, 94.1]	<0.0001
D-dimer$^{\varphi}$, (mg/L)	0.7 [0.36, 1.53]	0.58 [0.31, 1.343]	1.05 [0.53, 1.923]	<0.0001
IL-6Ж, (pg/mL)	4.96 [2.02, 18.75]	4.11 [1.83, 12.49]	9.35 [2.73, 30.38]	<0.0001
IL-8К, (pg/mL)	10 [5.9, 18.05]	9 [5.6, 16.25]	12.7 [7.33, 21.78]	<0.0001
IL-1βК, (pg/mL)	5 [2, 5]	5 [5, 5]	5 [5, 5]	0.3016
TNFαЮ, (pg/mL)	7.6 [5.7, 9.9]	7.4 [5.5, 9.6]	8.3 [6, 10.9]	0.0002
Fibrinogen^{Я}, (g/L)	4.76 [3.7, 5.93]	4.49 [3.51, 5.76]	5.34 [4.36, 6.22]	<0.0001
WBC, (10^9/L)	5.46 [4.33, 7.02]	5.35 [4.29, 6.37]	6.06 [4.45, 7.75]	<0.0001
Lymphocyte^{г}, (10^9/L)	1.14 [0.81, 1.53]	1.26 [0.91, 1.64]	0.89 [0.64, 1.21]	<0.0001
Platelet^{Ъ}, (10^9/L)	228 [172, 297]	233 [178.5, 304.5]	211 [160, 282]	<0.0001

§: 1444 patients (1016 patients with non-GC use and 428 patients with GC use) with information about concomitant diseases were included in this analysis.
#: 1379 patients (960 patients with non-GC use and 419 patients with GC use) with CRP test results at admission were included in this analysis.
φ: 1396 patients (986 patients with non-GC use and 410 patients with GC use) with D-dimer test results at admission were included in this analysis.
Ж:1199 patients (834 patients with non-GC use and 365 patients with GC use) with IL-6 test results at admission were included in this analysis.
К: 1189 patients (825 patients with non-GC use and 364 patients with GC use) with IL-1β and IL-8 test results at admission were included in this analysis.
Ю: 1187 patients (824 patients with non-GC use and 363 patients with GC use) with TNFα test results at admission were included in this analysis.
Я: 1226 patients (911 patients with non-GC use and 315 patients with GC use) with fibrinogen test results at admission were included in this analysis.
г: 1446 patients (1018 patients with non-GC use and 428 patients with GC use) with lymphocyte test results at admission were included in this analysis.
Ъ: 1443 patients (1017 patients with non-GC use and 426 patients with GC use) with platelet test results at admission were included in this analysis.

Abbreviations:
GC: glucocorticoid
IQR: interquartile range
CHD: coronary heart disease
COPD: chronic obstructive pulmonary disease
CKD: chronic kidney disease
CRP: C-reactive protein
IL-6: interleukin-6
IL-8: interleukin-8
IL-1β: interleukin-1 beta
TNFα: tumor necrosis factor α
WBC: white blood cell

polished the manuscript. All authors read and approved the final manuscript for publication.

Declaration of Competing Interest

The authors declared that there are no conflicts of interest.

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Consent for publication

All authors reviewed the manuscript and approved the publication.

Availability of data and materials

The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study design was approved by ethics committees of Tongji hospital (TJ-IRB20200406), and the requirement for informed con-

Table 2
Analysis of glucocorticoid on oxygen supply duration of COVID-19 patients with different severities.

Variables	General group ($N=795$)			Severe and critical group ($N=652$)		
	Non-GC group ($N=621$)	GC group ($N=174$)	*P* value	Non-GC group ($N=398$)	GC group ($N=254$)	*P* value
Age (years), median (IQR)	61 [47.5, 68]	59 [48, 67]	0.3502	65 [55,72]	62 [52,70]	0.0796
Sex, *n* (%)			0.44			0.0819
Male	251 (40.4)	76 (43.7)		190 (47.7)	139 (54.7)	
Female	370 (59.6)	98 (56.3)		208 (52.3)	115 (45.3)	
Hospitalization time, days (IQR)	19 [13, 25]	23.5 [19, 29]	<0.0001	22 [17, 28.3]	28.5 [21, 36]	<0.0001
Oxygen supply duration, days (IQR)	14 [8, 21]	21 [14, 26]	<0.0001	17 [11, 24]	18 [11, 26.3]	0.0877
Inflammatory response, median (IQR)						
CRP#, (mg/L)	4.1 [1.1, 19.9]	26.4 [9.2, 56.9]	<0.0001	22.5 [4.7, 66.95]	66.95 [27.45, 105.7]	<0.0001
D-dimer$^{\varphi}$, (mg/L)	0.48 [0.28, 1.19]	0.65 [0.42, 1.23]	0.0004	0.79 [0.41, 1.68]	1.32 [0.7, 2.35]	<0.0001
IL-6^{Ж}, (pg/mL)	3.27 [1.5, 8.075]	8.12 [2.49, 21.48]	<0.0001	7.2 [2.69, 23.83]	11.71 [2.95, 39.78]	0.0199
IL-8^{К}, (pg/mL)	8.7 [5.5, 15]	11.8 [7.1, 20.3]	0.0004	9.5 [5.7, 17.9]	13.4 [7.4, 22.7]	0.0001
TNF$\alpha^{Ю}$, (pg/mL)	7.15 [5.48, 9]	7.8 [5.95, 10.4]	0.0111	7.85 [5.6, 10.63]	8.6 [6.1, 11.38]	0.1229
Fibrinogen^{Я}, (g/L)	4.09 [3.34, 5.35]	4.95 [4, 5.93]	<0.0001	5.09 [4.08, 6.17]	5.58 [4.53, 6.49]	0.0021
WBC, (10^9/L)	5.32 [4.25, 6.64]	5.29 [3.92, 7.04]	0.8205	5.42 [4.38, 6.83]	6.6 [4.74, 8.41]	<0.0001
Lymphocyte^{г}, (10^9/L)	1.38 [1.02, 1.76]	0.99 [0.68, 1.39]	<0.0001	1.08 [0.78, 1.41]	0.84 [0.61, 1.09]	<0.0001
Platelet^{Ѫ}, (10^9/L)	233 [182.3, 304.8]	210 [161.8, 277.8]	0.0027	233 [173.5, 304.5]	211.5 [159.3, 283.8]	0.0129

#:1379 patients (583 patients with non-GC use and 171 patients with GC use in general group and 377 patients with non-GC use and 248 patients with GC use in severe and critical group) with CRP test results at admission were included in this analysis.
φ: 1396 patients (600 patients with non-GC use and 165 patients with GC use in general group and 386 patients with non-GC use and 245 patients with GC use in severe and critical group) with D-dimer test results at admission were included in this analysis.
Ж:1199 patients (501 patients with non-GC use and 146 patients with GC use in general group and 333 patients with non-GC use and 219 patients with GC use in severe and critical group) with IL-6 test results at admission were included in this analysis.
К: 1189 patients (494 patients with non-GC use and 145 patients with GC use in general group and 331 patients with non-GC use and 219 patients with GC use in severe and critical group) with IL-8 test results at admission were included in this analysis.
Ю: 1187 patients (494 patients with non-GC use and 145 patients with GC use in general group and 330 patients with non-GC use and 218 patients with GC use in severe and critical group) with TNFα test results at admission were included in this analysis.
Я: 1226 patients (556 patients with non-GC use and 138 patients with GC use in general group and 355 patients with non-GC use and 177 patients with GC use in severe and critical group) with fibrinogen test results at admission were included in this analysis.
г: 1446 patients (620 patients with non-GC use and 174 patients with GC use in general group and 398 patients with non-GC use and 254 patients with GC use in severe and critical group) with lymphocyte test results at admission were included in this analysis.
Ѫ: 1443 patients (620 patients with non-GC use and 174 patients with GC use in general group and 397 patients with non-GC use and 252 patients with GC use in severe and critical group) with lymphocyte test results at admission were included in this analysis.

Abbreviations:
GC: glucocorticoid
IQR: interquartile range
CRP: C-reactive protein
IL-6: interleukin-6
IL-8: interleukin-8
TNFα: tumor necrosis factor α
WBC: white blood cell

sent was waived by the ethics committees. The trial has been registered in Chinese Clinical Trial Registry (ChiCTR2000032161).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.11.017.

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