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## Letters to the Editor

### **High-dose corticosteroids adjusted to oxygen requirement and monitoring of serum C-reactive protein to improve outcome of non-critically ill Covid-19 patients – The CocAA-CoLa Plus Study**

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### **Availability of data and materials**

J.P.K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

### **Consent for publication**

All the authors agree to publish.

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## Letters to the Editor

### High-dose corticosteroids adjusted to oxygen requirement and monitoring of serum C-reactive protein to improve outcome of non-critically ill Covid-19 patients – The CocAA-CoLa Plus Study

*Dear Editor,*

Corticosteroids are effective in reducing all-cause 28-day mortality in COVID-19 patients on oxygen or mechanical ventilation.<sup>1</sup> Since inflammatory response parallels the disease progression,<sup>2</sup> personalized immunomodulation should be more effective than the “one-size-fits-all” corticosteroids currently used.<sup>1</sup> Biomarkers may define risk categories to adapt immunomodulation.<sup>2</sup> However, whether the time-course of readily available biomarkers predicts response to corticosteroids in non-critically ill Covid-19 patients remains uncertain. Therefore, we designed this study to investigate possible benefits from individual corticosteroid regimen adaptation combined to biomarker monitoring at the bedside.

We conducted a single-center cohort study including consecutive non-critically ill COVID-19 patients requiring oxygen managed in the medical ward from 03/2020 to 06/2021. Sars-CoV-2 infection was diagnosed using RT-PCR based on nasopharyngeal swabs. Patients with limitation of therapeutic effort were not included.

During the first wave (03/2020-06/2020), i.e., before the release of RECOVERY trial results,<sup>1</sup> no patient received corticosteroids. During the second (09/2020-12/2020) and third waves (03/2021-06/2021), patients received either the RECOVERY 6mg/day dexamethasone regimen (~0,5mg/kg/day prednisone-equivalent)<sup>1</sup> or a strengthened five-drug regimen combining corticosteroids (1mg/kg/day prednisone-equivalent), aspirin, anticoagulant, colchicine, and furosemide<sup>3</sup> for 5-10days. Physicians in charge determined care and drugs to administer including increase in corticosteroid dose by 1mg/kg/day prednisone-equivalent steps if oxygen requirement increased.

The usual clinical parameters were collected. For each patient, differences in percentage ( $\Delta$ ) between baseline and day5 values of serum C-reactive protein (CRP), procalcitonin and D-dimer were calculated. For analysis, patients were split in three groups according to the daily prednisone-equivalent dose used for 5-10days, i.e., none, ~0.5mg/kg/day (low-dose), and  $\geq 1$ mg/kg/day (high-dose). The primary

composite endpoint was requirement of high-flow oxygen or mechanical ventilation (corresponding to care escalation from ward to critical care) or 28-day mortality.

Data are expressed as median [25<sup>th</sup>-75<sup>th</sup>percentiles] or percentages. Univariate comparisons were performed using Kruskal-Wallis, Wilcoxon or Fisher exact tests as appropriate. Odds ratios (OR) and their 95%-confidence intervals (95%CI) were determined. Stratified categorical data were compared using Cochran-Mantel-Haenszel tests. To evaluate each biomarker performance, we determined the areas under its receiver operating characteristic (ROC) curve (AUC) and 95%CI and compared them using the DeLong method. The sensitivity, specificity, and cutoff-point maximizing the Youden index were determined. Analyses were performed using the R4.1.3-environment and pROC/cutpointr packages. *P*-values $\leq$ 0.05 were considered significant.

Overall, 309 non-critically ill COVID-19 patients (age, 68years [54-77]; M/F sex-ratio, 2.5; body-mass index, 27kg/m<sup>2</sup> [25-31]; hypertension, 51%; diabetes, 43%; cardiovascular disease, 32%; chronic lung disease, 13%) were included (Table1). Patients were recruited during the first (N=80), second (N=74), and third waves (N=155). Infection was related exclusively to the original Sars-CoV-2 strain during the first wave, while prevalence of alpha and beta/gamma strains increased in the next waves. Patients received no (N=80), low-dose (N=126; 0.5mg/kg/day [0.4-0.6]), and high-dose (N=103; 1.5mg/kg/day [1.0-2.3] prednisone-equivalent) corticosteroids. Requirement for ventilation support or 28-day mortality significantly differed between the groups, being lower with high-dose than low-dose (OR=0.32 [0.15-0.67]; *p*=1.4x10<sup>-7</sup>) or no corticosteroids (OR=0.15 [0.06-0.31]; *p*=3.5x10<sup>-8</sup>). The main corticosteroid-attributed adverse-effect was moderate hypokalemia (3%, never <2.8mmol/L), without significant differences between groups.

Serum CRP, procalcitonin and D-dimer did not significantly differ between the groups at baseline but differed on day5. Only  $\Delta$ CRP was associated to the primary endpoint ( $\Delta$ CRP-OR=1.008 [1.005-1.011], *p*=6.1x10<sup>-7</sup>;  $\Delta$ PCT-OR=1.001 [1.000-1.003], *p*=0.06;  $\Delta$ D-dimer-OR=1.000 [0.998-1.001], *p*=0.69). Decrease in  $\Delta$ CRP was more marked in corticosteroid-treated patients who did not validate the primary endpoint than those who did, contrasting with decrease in  $\Delta$ PCT in only high-dose corticosteroid-treated patients and no significant decrease in  $\Delta$ D-dimer (Fig1A).  $\Delta$ CRP most accurately identified patients

who validated the primary endpoint, with -19% (AUC, 0.83;  $p=0.002$ ) and -59% cut-off values (AUC, 0.85;  $p=0.003$ ) in the low-dose and high-dose, respectively, *versus* no corticosteroid patients (Fig.1B). Impact of  $\Delta$ CRP on the primary endpoint in patients treated with *versus* without corticosteroids and comparisons in each treatment group between patients with  $\Delta$ CRP below or above the Youden's cutoff are shown in Fig.1C and 1D.

Our findings support that high-dose corticosteroids adapted to oxygen requirement improves outcome of non-critically ill COVID-19 patients. Early decrease in serum CRP accurately identifies responders to corticosteroids.

Theoretically, high-dose corticosteroids could more effectively modulate inflammation and treat acute fibrinous and organizing pneumonia, which predominates in some non-critically ill COVID-19 patients. However, its effectiveness remains controversial. Registries and case-series failed to demonstrate improvement due to patient heterogeneity altering group comparability. A cohort study suggested that 250-500mg/day-methylprednisolone for 3days followed by 50mg/day-prednisone for 14days compared with 6mg/day dexamethasone for 7-10days significantly improved biomarkers and reduced recovery time and ICU transfer.<sup>4</sup> By contrast, a propensity score-matched study suggested that 6mg/day-dexamethasone for 10days was superior to 3-day methylprednisolone pulses  $\geq 100$ mg/day in preventing ICU transfer and in-hospital mortality.<sup>5</sup> Randomized trials also resulted in discrepancies. A three-arm trial comparing once, twice or thrice daily 8mg-dexamethasone for up to 10days showed that higher dose worsened survival and increased adverse-events.<sup>6</sup> By contrast, another trial showed that 2mg/kg/day-methylprednisolone reduced hospital stay and need for ventilation support compared to 6mg/day-dexamethasone.<sup>7</sup> Interestingly, in critically ill COVID-19 patients, despite non-significantly more days alive without life support at day28, high probabilities of benefit and low probabilities of harm was associated with 12mg/day *versus* 6mg/day dexamethasone on outcomes up to 90days.<sup>8</sup>

Pre-treatment lymphopenia and inflammatory biomarkers including CRP can predict mortality;<sup>2</sup> however, their usefulness to predict response to corticosteroids is debated. Admission ferritin was associated with methylprednisolone-attributed improvement in the upper tertile of values.<sup>9</sup> Elevation in CRP during management was associated with death<sup>10</sup> and consistent with our findings, reduction in CRP by  $\geq 50\%$  within 72h of corticosteroid initiation predicted reduced mortality.<sup>11</sup>

Our study presents limitations due to its observational design. We did not investigate serum lactate dehydrogenase, ferritin, and interleukin-6 in comparison to CRP since not routinely measured. We did not monitor the biomarkers daily, missing the slope that could have improved prediction. Contribution of co-administered immunomodulatory therapies could not be evaluated.

To conclude, our data suggest that high-dose corticosteroids adjusted to oxygen requirement improves outcome of non-critically ill COVID-19 patients compared to the usual low-dose regimens. Responders can be identified using decrease in serum CRP. Benefits of a strategy based on tailored high-dose corticosteroids incorporating laboratory parameters of oxygenation and inflammation is worthy investigating.

### **Declaration of Competing Interest**

The authors declare that they have no competing interests.

### **Ethics approval and consent to participate**

This study was part of the French COVID-19 cohort registry conducted by the REACTing consortium (REsearch and ACTION targeting emerging infectious diseases) and directed by INSERM (Institut national de la santé et de la recherche médicale) and ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium). Our institutional ethics committee approved the study (N°, IDRCB, 2020-A00256-33; CPP, 11-20 20.02.04.68737).

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**Figure 1. A-** Comparison of the difference in percentage ( $\Delta$ ) between values at day5 and baseline of three readily available biomarkers (serum C-reactive protein (CRP), procalcitonin (PCT) and D-dimer) in non-critically ill COVID-19 patients according to the primary endpoint (i.e., requirement of high-flow oxygen therapy or mechanical ventilation or 28-day death) in the three corticosteroid dose regimen groups [none,  $\sim 0.5$ mg/kg/day (low-dose) or  $\geq 1$ mg/kg/day prednisone-equivalent (high-dose)]. Patients who validated the primary endpoint are represented in blue and patients who did not validate the primary endpoint in green. Comparisons were performed using Wilcoxon tests. *P*-values are presented at the highest part of the graph. **B-** The receiver operating characteristic (ROC) curves of  $\Delta$ CRP according to the corticosteroid regimen group, allowing determining the Youden's cutoff-value that maximizes the sensitivity and specificity to predict the validation of the primary endpoint. **C-** Forest plot showing the impact on the primary endpoint of  $\Delta$ CRP in the patients treated with (low-dose or high-dose) *versus* without corticosteroids. Odds ratios (OR) and their 95%-confidence intervals were determined. **D-** Forest plot representing the primary endpoint in each corticosteroid regimen group with the comparison of patients above and below the Youden's cut-off value of  $\Delta$ CRP. Odds ratios (OR) and their 95%-confidence intervals were determined.

N: number of patients validating the primary endpoint. The percentage was calculated relative to the number of patients in the groups defined by the corticosteroid dose regimen.  $\Delta$ CRP was missing for one patient in the low-dose group.

**Table 1**

Characteristics and outcome of 309 non-critically ill COVID-19 patients according to the corticosteroid dose regimen.

<b>Parameters</b>	<b>Total (n = 309)</b>	<b>No corticosteroids (N = 80)</b>	<b>Low-dose corticosteroids [~0.5 mg/kg/day prednisone-equivalent] (N = 126)</b>	<b>High-dose corticosteroids [≥1 mg/kg/day prednisone-equivalent] (N = 103)</b>	<b><i>p</i>-values</b>
<b>Demographics and medical history</b>					
<b>Age (years)</b>	68 [54-77]	72 [60-81]	68 [54-75]	63 [52-75]	<b>0.002</b>
<b>Male gender, n (%)</b>	220 (71)	59 (74)	86 (68)	75 (73)	0.64
<b>Body-mass index (kg/m<sup>2</sup>)</b>	27 [25-31]	27 [25-29]	28 [25-32]	27 [25-31]	0.34
<b>Past hypertension, n (%)</b>	154 (51)	47 (59)	57 (45)	50 (51)	0.17
<b>Diabetes mellitus, n (%)</b>	132 (43)	28 (35)	46 (37)	58 (56)	<b>0.003</b>
<b>Past cardiovascular disease, n (%)</b>	99 (32)	29 (36)	41 (33)	29 (28)	0.51
<b>Chronic lung disease, n (%)</b>	41 (13)	18 (23)	14 (11)	9 (9)	<b>0.02</b>
<b>Epidemiological characteristics</b>					
<b>Epidemic waves, n (%)</b>					<b>&lt;0.0001</b>
<b>First wave</b>	80 (26)	80 (100)	0 (0)	0 (0)	

<b>Second wave</b>	74 (24)	0	40 (32)	43 (33)	
<b>Third wave</b>	155 (50)	0	86 (68)	69 (67)	
<b>Sars-CoV-2 strains, n (%)</b>					<b>&lt;0.0001</b>
<b>Original</b>	179 (58)	80 (100)	63 (50)	36 (35)	
<b>Alpha</b>	111 (38)	0 (0)	61 (48)	57 (55)	
<b>Beta + gamma</b>	12 (4)	0 (0)	2 (2)	10 (10)	
<b>Clinical and biological parameters on admission</b>					
<b>Symptom duration (days)</b>	8 [5-10]	9 [5-11]	7 [4-10]	7 [5-10]	<b>0.007</b>
<b>SpO<sub>2</sub> on room air (%)</b>	92 [90-94]	92 [90-94]	92 [90-94]	92 [90-94]	0.88
<b>PaO<sub>2</sub> on room air (mmHg)</b>	62 [57-71]	62 [57-75]	63 [58-68]	62 [56-72]	0.74
<b>Peak oxygen flow (L/min)</b>	4 [2-6]	3 [2-5]	4 [2-10]	4 [3-9]	<b>0.01</b>
<b>White blood cells (G/L)</b>	6.5 [4.9-8.4]	6.7 [5.1-8.8]	6.5 [4.9-8.4]	6.4 [4.9-8.3]	0.11
<b>Lymphocytes (G/L)</b>	0.94 [0.67-1.2]	0.90 [0.65-1.10]	0.91 [0.67-1.18]	0.98 [0.71-1.30]	0.82
<b>Blood neutrophil-lymphocyte ratio on admission</b>	5 [3-9]	6 [4-11]	6 [3-9]	5 [3-8]	0.13
<b>Blood neutrophil-lymphocyte ratio on day5</b>	6 [3-10]	5 [3-10]	5 [3-8]	8 [4-12]	<b>0.0009</b>
<b>Serum creatinine (µmol/L)</b>	88 [69-112]	96 [68-125]	85 [65-104]	82 [70-108]	<b>0.05</b>
<b>Serum troponin Ic high-sensitivity (ng/mL)</b>	9 [4-20]	10 [4-23]	9 [4-19]	8 [4-19]	0.48
<b>Serum brain natriuretic peptide (ng/L) (N=283)</b>	28 [10-94]	48 [16-138]	27 [11-90]	23 [10-79]	<b>0.05</b>
<b>Serum brain natriuretic peptide ≥ 100 ng/L (n, %)</b>	65/283 (23)	21/73 (30)	25/111 (23)	19/99 (19)	0.34

<b>Serum biomarkers of inflammation</b>					
<b>C-reactive protein (mg/L) on admission</b>	87 [53-139]	107 [60-151]	82 [50-137]	83 [52-134]	0.29
<b>C-reactive protein (mg/L) on day5</b>	37 [10-106]	109 [44-181]	50 [13-114]	12 [6-34]	<b>&lt;0.0001</b>
<b>Procalcitonin (µg/L) on admission</b>	0.13 [0.06-0.7]	0.17 [0.07-0.57]	0.11 [0.06-0.23]	0.13 [0.07-0.24]	0.13
<b>Procalcitonin (µg/L) on day5</b>	0.06 [0.03-0.15]	0.23 [0.07-1.86]	0.06 [0.04-0.14]	0.04 [0.02-0.07]	<b>&lt;0.0001</b>
<b>D-dimer (ng/mL) on admission</b>	980 [620-1,568]	1,285 [722-1,955]	930 [620-1,560]	960 [580-1,460]	0.14
<b>D-dimer (ng/mL) on day5</b>	730 [467-1,415]	1,620 [762-2,443]	690 [455-1,235]	650 [445-985]	<b>0.0003</b>
<b>Administered drugs</b>					
<b>Corticosteroid dose (prednisone-equivalence, mg/kg/day)</b>	0.5 [0.0-1.0]	0.0 [0.0-0.0]	0.5 [0.4-0.6]	1.5 [1.0-2.3]	<b>&lt;0.0001</b>
<b>Standard-dose prophylactic anticoagulation, n (%)</b>	243 (79)	60 (75)	103 (82)	80 (78)	0.48
<b>Intensified-dose anticoagulation, n (%)</b>	62 (20)	16 (20)	23 (18)	23 (22)	0.74
<b>Salicylate, n (%)</b>	153 (50)	23 (29)	27 (21)	103 (100)	<b>&lt;0.0001</b>
<b>Colchicine, n (%)</b>	103 (33)	0 (0)	0 (0)	103 (100)	<b>&lt;0.0001</b>
<b>Furosemide, n (%)</b>	146 (47)	21 (26)	22 (18)	103 (100)	<b>&lt;0.0001</b>
<b>Antibiotics, n (%)</b>	188 (61)	70 (88)	82 (65)	36 (35)	<b>&lt;0.0001</b>
<b>Outcomes</b>					
<b>Ventilation support requirement in the ICU, n (%)</b>	53 (17)	16 (20)	28 (22)	9 (9)	<b>0.01</b>

<b>28-day death, n (%)</b>	39 (13)	24 (30)	11 (9)	4 (4)	<b>&lt;0.0001</b>
<b>Ventilation support requirement in the ICU or 28-day death, n (%)</b>	92 (30)	40 (50)	39 (31)	13 (13)	<b>&lt;0.0001</b>
<b>Length of hospital stay (days)</b>	7 [5-10]	6 [4-11]	6 [4-9]	7 [6-10]	0.06

ICU, intensive care unit; Sars-CoV-2, Severe acute respiratory syndrome coronavirus-2. Data are presented as percentages or medians [25<sup>th</sup>-75<sup>th</sup> percentiles]. Comparisons were performed using Kruskal-Wallis or Fisher exact tests as appropriate.

