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## COVID-19 and non-COVID ARDS patients demonstrate a distinct response to low dose steroids- A retrospective observational study

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### ARTICLE INFO

#### Keywords:

Steroids  
ARDS  
Inflammation  
COVID-19

### ABSTRACT

Patients with COVID-19 ARDS have distinct physiological and immunological phenotypes compared to patients with non-COVID ARDS. Patients with COVID-19 ARDS ( $n = 32$ ) had a significant improvement in  $\text{PaO}_2$ :  $\text{FiO}_2$  ratio ( $p = 0.046$ ) following low-dose steroid treatment, unlike patients with non-COVID ARDS ( $n = 16$ ) ( $p = 0.529$ ). Patients with COVID-19 ARDS had a greater fall in CRP compared to patients with non-COVID ARDS, albeit not statistically significant ( $p = 0.07$ ). Our novel findings highlight differences in the underlying physiological and immunological phenotypes between COVID-19 and non-COVID ARDS, with implications for future ARDS studies.

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Dear Editor,

Patients with COVID-19 ARDS have distinct physiological [1,2] and immunological [3,4] phenotypes compared to patients with non-COVID ARDS. We hypothesised that differences in immunological and physiological phenotypes between patients with COVID-19 and non-COVID ARDS are associated with differences in changes to inflammation and  $\text{PaO}_2$ :  $\text{FiO}_2$  ratio in response to steroid treatment.

We conducted a single-centre retrospective case-control study of COVID-19 patients with ARDS treated with low-dose systemic steroids at University College London Hospital between 1st March and 30th June 2020. During the COVID-19 pandemic, methylprednisolone was prescribed for ARDS with persistent or worsening hypoxaemia, hydrocortisone was prescribed for septic shock. As the period of data collection preceded the results of the RECOVERY study, dexamethasone was not routinely prescribed for patients with COVID-19. Data on consecutive patients with non-COVID ARDS receiving steroids between January 2018 to March 2020 were used as comparison.

Data were extracted from electronic healthcare records on patient demographics, corticosteroid type and dose, and sequential C-reactive protein (CRP), neutrophil, and temperature. Where patients received more than one course of steroid, only the first course of steroid was

considered. We included patients receiving either methylprednisolone 1–2 mg/kg daily or hydrocortisone 50–100 mg four times daily. As the half-life of CRP is 19 h [5], we collected data on CRP change 3 days following steroid administration. Ten patients in the non-COVID group and 12 patients in the COVID-19 group did not survive for at least 3 days following steroid administration and were therefore excluded. Haemato-oncology patients ( $n = 18$ ) who had received recent chemotherapy were excluded as the inflammatory response could be confounded by chemotherapy.

Continuous and categorical variables are reported as median (interquartile range) and  $n$  (%), respectively. For comparison of continuous variables, Mann Whitney  $U$  test for comparison between 2 groups and Wilcoxon sign rank test was used to assess change of CRP,  $\text{PaO}_2$ :  $\text{FiO}_2$  ratio, neutrophil count, and daily peak temperature. Categorical data were compared using the chi-squared test. Statistical analysis was performed, and graphs constructed using Prism (GraphPad Software, Version 5.0d, San Diego, California, US).

A total of 32 patients with non-COVID ARDS and 16 patients with COVID-19 ARDS were included in the final analysis. Patients with COVID-19 ARDS received steroids later following ICU admission ( $p = 0.002$ ) and had a lower  $\text{PaO}_2$ :  $\text{FiO}_2$  ratio on initiation of steroids ( $p = 0.001$ ) compared to patients with non-COVID ARDS (Table 1). Age, gender, CRP on day of steroid initiation, requirement for renal replacement therapy, vasopressors, mechanical ventilation, and hospital mortality were similar between patients with COVID-19 ARDS and non-COVID ARDS (Table 1).

Patients with COVID-19 ARDS and non-COVID ARDS had significant reductions in CRP following initiation of steroids. Only patients with COVID-19 ARDS had a significant improvement in  $\text{PaO}_2$ :  $\text{FiO}_2$  ratio (93

Abbreviation list: ARDS, Acute respiratory distress syndrome; CRP, C-reactive protein; IL-6, interleukin-6;  $\text{PaO}_2$ ,  $\text{FiO}_2$  ratio: Ratio of partial pressure of oxygen to fraction of inspired oxygen; TNFR1, soluble tumour necrosis factor receptor superfamily member 1A.

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**Table 1**  
Demographics and baseline characteristics of patient with COVID-19 and non-COVID ARDS.

	COVID-19 ARDS N = 16	Non-COVID ARDS N = 32	P-value
Age (years)	61 (51–65)	56 (38–68)	0.622
Gender: Male	12/16 (75%)	14/32 (44%)	0.065
Days from ICU admission to steroid	11 (2–14)	1 (0–5)	0.002
Mechanical ventilation	14/16 (88%)	28/32 (88%)	>0.999
Renal replacement therapy	10/16 (63%)	20/32 (63%)	>0.999
Vasopressors	14/16 (88%)	23/32 (72%)	0.225
Day 0 PaO <sub>2</sub> : FiO <sub>2</sub> ratio (mmHg)	91 (75–133)	155 (127–192)	0.001
Day 0 CRP (mg/L)	253 (145–365)	178 (119–302)	0.365
Hospital mortality	11/16 (69%)	23/32 (72%)	>0.999

(76–147) to 142 (85–214) mmHg;  $p = 0.046$ ) following steroid treatment, unlike patients with non-COVID ARDS (155 (127–193) vs. 148 (114–207)mmHg;  $p = 0.529$ ). Only patients with non-COVID ARDS had a significant reduction in temperature with steroid treatment (Fig. 1). Patients with COVID-19 ARDS had a greater fall in CRP compared to patients with non-COVID ARDS following steroid treatment, albeit not statistically significant ( $-56$  ( $-74$  to  $-28$ )% vs.  $-34$  ( $-63$  to  $12$ )%;  $p = 0.07$ ). Neither patients with COVID-19 ARDS or non-COVID ARDS demonstrated any change in neutrophil count following steroid treatment (Fig. 1).

We report a distinct response in CRP and PaO<sub>2</sub>: FiO<sub>2</sub> ratio to steroids between COVID-19 ARDS and non-COVID ARDS patients. The underlying pathophysiology of COVID-19 ARDS is distinct to non-COVID ARDS, with significant differences in serum levels of interleukin-6 (IL-6) and soluble tumour necrosis factor receptor superfamily member 1A (TNFR1) between patients with COVID-19 and non-COVID ARDS [3]. COVID-19 ARDS is associated with a marked vasculopathy, distinct to

other forms of ARDS [6]. It is unclear if has any implications on responsiveness to steroids, given the success of steroid treatment in pulmonary vasculopathies [7]. A higher CRP is associated with survival in patients with non-COVID ARDS, although the opposite has been observed with COVID-19 ARDS [8,9]. As such, the ability of steroid treatment to ameliorate the underlying inflammatory process may be more advantageous in COVID-19 compared to non-COVID ARDS. This may underpin the association between steroid use and reduced mortality among critically ill patients with COVID-19 [10]; (although heavily weighted by the RECOVERY study), whereas the benefit of steroids in non-COVID ARDS has been less clear cut.

As with all retrospective analyses, we acknowledge the possibility of residual confounding, and that results are associative. The small number of patients included also warrants caution in interpreting the findings. There were differences in baseline demographics between groups and the use of steroids was confounded by indication bias and timing of initiation. We were unable to adjust for these differences due to the limited sample size.

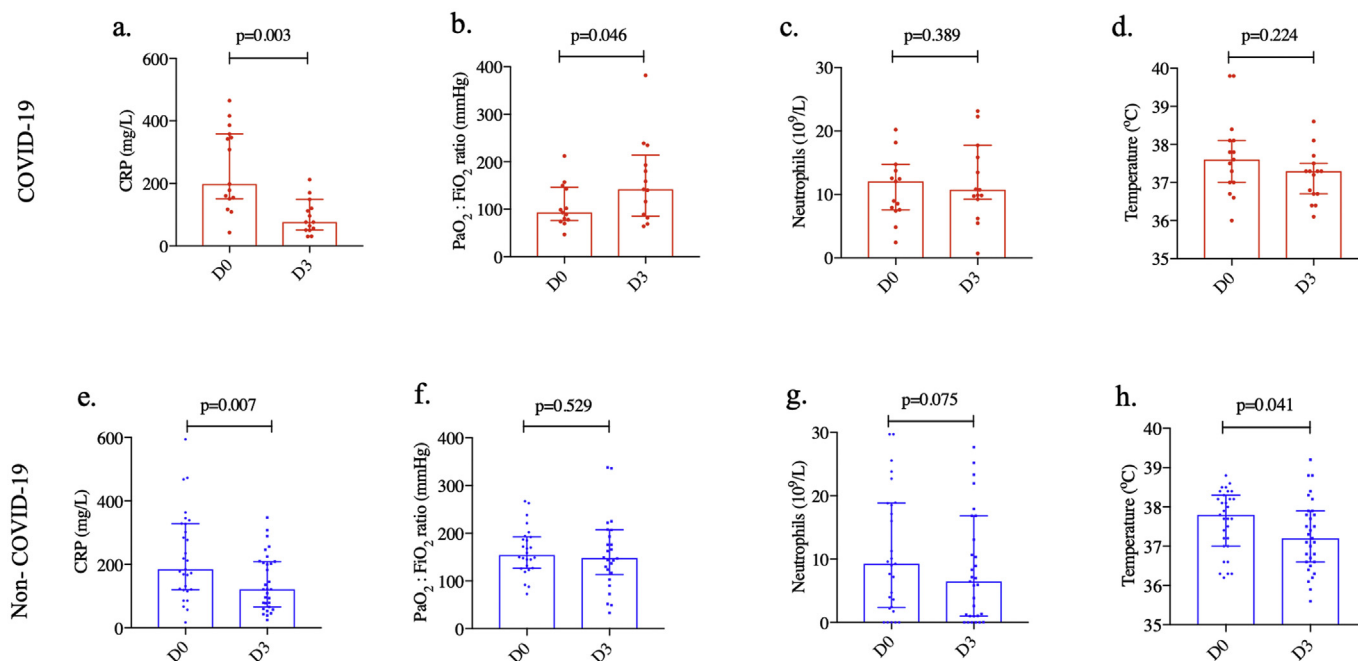
We describe novel findings on the distinct responses in CRP and PaO<sub>2</sub>: FiO<sub>2</sub> ratio between ARDS patients with and without COVID-19. Our data highlight the importance of defining the underlying aetiology and immune phenotype to enable trial enrichment, therefore targeting patients most likely to benefit for future ARDS studies.

**Ethics approval**

Ethics to report observational data on critical care patients at UCLH is covered by the National Research Ethics Service (14/LO/103).

**Consent for publication**

N/A.



**Fig. 1.** Change in CRP, PaO<sub>2</sub>: FiO<sub>2</sub> ratio, neutrophil count, and temperature between patient (a-d) with and (e-h) without COVID-19 between initiation of low dose steroid and 3 days after steroid treatment (either hydrocortisone (50-100 mg 6- hourly) or methylprednisolone (1-2 mg/kg daily)). Patients with (a) COVID-19 and (e) Non-COVID-19 ARDS demonstrate significant reduction in CRP over 3 days from steroid initiation. Only patients with (b) COVID-19 ARDS demonstrate an increase in PaO<sub>2</sub>: FiO<sub>2</sub> ratio following steroid treatment, but not patients with (f) Non-COVID-19 ARDS. Core temperature however, only falls in patients with (h) Non-COVID-19 ARDS but not in those with (d) COVID-19 ARDS following steroid treatment. Data represent median and interquartile range. Data are assessed using Wilcoxon sign rank test.

**Availability of data and materials**

Upon reasonable request.

**Funding**

None.

**Authors' contributions**

Study design (NA), data collection (AL, RS, CM), Statistics (NA), Drafting manuscript (NA, TS). All authors read and approved the final manuscript.

**Declaration of Competing Interest**

None.

**Acknowledgements**

UCLH Intensive Care.

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