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We thank all staff of healthcare facilities who contributed to the Hospital Discharge Database implementation. Restrictions apply to the availability of these data and so they are not publicly available. However, data are available from the authors upon reasonable request and with the permission of the institution.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Sepsis in severe COVID-19 is rarely septic shock: a retrospective single-centre cohort study

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Editor—Severe COVID-19 fulfills both the Sepsis-3 definition of sepsis, namely life-threatening organ dysfunction attributable to a dysregulated host response to infection and the clinical criteria of a rise in Sequential Organ Failure Assessment (SOFA) score ≥ 2 points above the patient's existing baseline.¹ We observed in our cohort of patients requiring intensive care admission that few had hyperlactataemia despite significant hypoxaemia. The Sepsis-3 definition of septic shock identifies a subset in whom profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Clinical criteria for shock include an MAP < 65 mm Hg and serum lactate level > 2 mM in the absence of hypovolaemia.¹ This observation suggests that SARS-CoV-2 does not, in general, trigger significant cellular metabolic dysfunction. Sepsis and acute respiratory distress syndrome represent umbrella syndromes containing multiple sub-phenotypes with relatively distinct clinical or biological

signatures and differing outcomes.^{2,3} Using latent class analysis, similar findings have also been applied to large population cohorts with COVID-19.^{4,5} Currently, only one small study of 18 patients hospitalised with COVID-19 has focused on hyperlactataemia, but did not report associations with the degree of hypoxaemia or vasopressor use.⁶ We thus sought to assess the frequency of hyperlactataemia in patients with COVID-19 admitted to intensive care and receiving vasopressors, and the relationship to hypoxaemia and commencement of vasopressors.

Data were retrospectively extracted from the hospital's EPIC (Verona, WI, USA) electronic healthcare record system for intensive care patients with a primary or secondary Intensive Care National Audit & Research Centre admission code of community-acquired pneumonia from March 2019 to February 2021. These included patient characteristics, organ function, and blood gas measurements (including lactate,

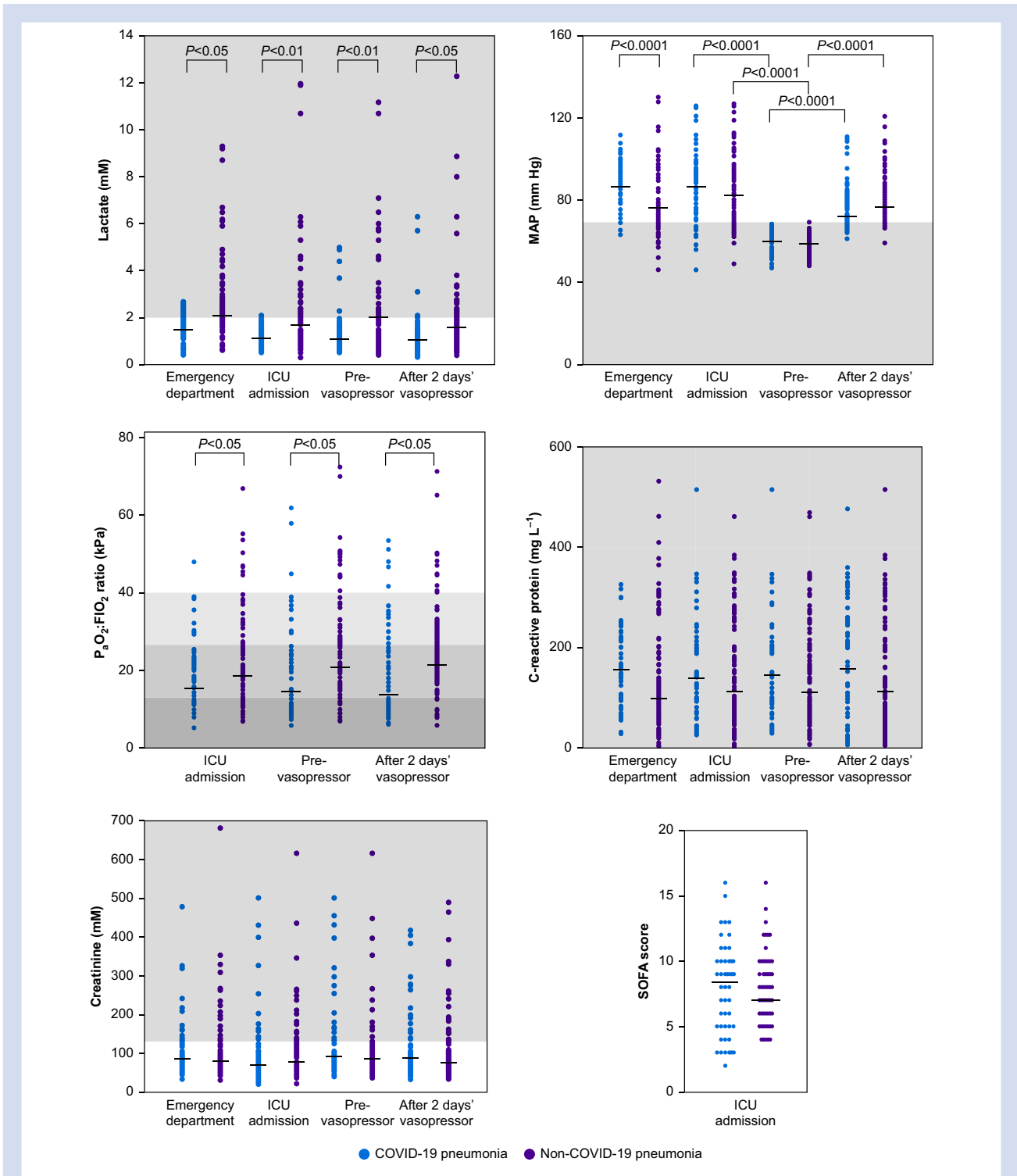


Fig 1. Lactate, MAP, measures of organ dysfunction (Sequential Organ Failure Assessment [SOFA] score, $P_aO_2:FIO_2$ ratio, and creatinine) and C-reactive protein in patients with COVID-19 and non-COVID-19 community-acquired pneumonia requiring vasopressors. Measurements were made on emergency department admission, at ICU admission, before vasopressor commencement, and at 2 days after commencement of vasopressors. Shaded areas for lactate and MAP indicate criteria required for a diagnosis of septic shock. The shaded areas for $P_aO_2:FIO_2$ ratio represent mild (40–27), moderate (26.9–13) and severe (<13 kPa) acute respiratory distress syndrome using the Berlin criteria. Shaded areas for creatinine and C-reactive protein represent abnormal values. Horizontal bars denote median values.

need for mechanical ventilation, and commencement of vasopressor support). Four time points were assessed: in the emergency department, on ICU admission, pre-commencement of vasopressors, and 2 days later (Fig. 1). Comparison was drawn between patients with COVID-19 and a comparable population admitted with non-COVID-19 community-acquired pneumonia of differing aetiologies. Ethical approval was received from the London–Westminster Research Ethics Committee (REC ref 20/HRA/2505; IRAS ID 284088) and the Health Research Authority on July 2, 2020.

From 1043 patients admitted to our ICU, 68 patients with COVID-19 (mainly admitted from March to July 2020 and from December 2020 to February 2021) and 87 patients with non-COVID-19 community-acquired pneumonia (mainly admitted from March 2019 to February 2020 and from July to December 2020) who required vasopressor therapy were identified (Supplementary Fig. 1). Patient characteristics, relevant history, SOFA score, Acute Physiology and Chronic Health Evaluation II score, timing from ICU admission to tracheal intubation, and norepinephrine dose requirements were similar between groups (Supplementary Table 1; Fig. 1). Hypertension and diabetes mellitus were more frequent comorbidities in patients with COVID-19, whereas chronic kidney disease was more common in the non-COVID-19 group. Survival was significantly higher in the non-COVID-19 pneumonia group (80% vs 59%; $P < 0.004$). Patients with COVID-19 were commenced on vasopressors later in their ICU stay (15 [4–59] vs 6 [2–18] h, and were more likely to be mechanically ventilated (99% vs 57%; $P < 0.0001$). More patients with COVID-19 were requiring vasopressors at 48 h. The $P_{aO_2}:FIO_2$ ratio was lower at all three ICU time points in patients with COVID-19 ($P < 0.0001$), whilst SOFA score, creatinine, and C-reactive protein levels were similar (Fig. 1).

Lactate levels were significantly higher in patients without COVID-19 at all four time points assessed (all $P < 0.05$); MAP was significantly higher in patients with COVID-19 only at hospital admission (Fig. 1). At vasopressor commencement, the criteria for ‘Sepsis-3’ septic shock were only met in five (7%) patients with COVID-19 vs 42 (48%) patients with non-COVID-19 pneumonia. Other causes contributing to hyperlactataemia were identified in four of five patients with COVID-19 and seven of 42 patients without COVID-19 (Supplementary Table 1). Thus, septic shock directly related to the underlying community pneumonia only occurred in 1/68 (1%) of patients with COVID-19 vs in 35/87 (40%) of patients without COVID-19 ($P = 0.0001$).

Although many patients with COVID-19 developed sepsis requiring ICU admission and subsequent institution of vasopressors, few fulfilled the Sepsis-3 criteria for septic shock. By contrast, nearly half of patients without COVID-19 with an admission diagnosis of community-acquired pneumonia developed septic shock. The usual absence of hyperlactataemia in COVID-19 suggests cellular/metabolic dysfunction is not a major contributor to COVID-19-related organ dysfunction. Pyruvate is taken up into mitochondria where it is converted via pyruvate dehydrogenase into acetyl coenzyme A, which feeds into the Krebs (tricarboxylic acid) cycle that ultimately supplies electrons to the electron transport chain. Pyruvate can also be converted to lactate by lactate dehydrogenase. Thus, excess pyruvate, either attributable to an upstream increase in glycolysis or decreased utilisation by mitochondrial respiration, will generate increased lactate production. Mitochondrial respiration impairment can arise from decreased oxygen availability to meet cell needs (tissue hypoxia) or direct inhibition/damage to the Krebs cycle or electron transport chain (tissue dysoxia). Lactate is also an important fuel source, especially under

conditions of stress, for many organs, including liver, kidney, and heart. The Cori cycle, predominantly active in the liver, also recycles circulating lactate back into glucose. Multiple factors underlie hyperlactataemia in sepsis.⁷ These include, but are not restricted to, tissue hypoperfusion, accelerated aerobic glycolysis driven by catecholamine-stimulated activation of the muscle sodium pump,⁸ and decreased clearance attributable to liver or renal dysfunction. The general absence of hyperlactataemia in COVID-19 suggests that the cellular mechanisms/dysfunctions are not particularly active. This may be related to the evolution of severe hypoxaemia over days rather than hours or minutes, enabling compensatory metabolic adaptations, and to a lack of physiological/emotional stress. Raised lactate is a good prognosticator in bacterial sepsis,⁹ but this does not apply to COVID-19, where mortality rates are higher than other types of sepsis notwithstanding normal levels of lactate. We previously reported in our population of patients with COVID-19 that need for vasopressor therapy and renal replacement therapy was restricted to those requiring mechanical ventilation.¹⁰ We suggested that this vasopressor requirement was related more to use of heavy sedation and haemodynamic perturbations related to high airway pressures and right ventricular strain rather than underlying cellular dysfunction.

This study has several limitations. It is a retrospective, single-centre cohort study with a relatively small sample size of 155 patients. The non-COVID-19 community-acquired pneumonia group is heterogeneous, but we feel this represents a good comparator with COVID-19, as both are related to respiratory infectious pathogens and present to ICU with respiratory failure often requiring mechanical ventilation. We focused on only those pneumonia patients, COVID-19 or otherwise, requiring vasopressors, as we were particularly interested to see how many of these sicker patients fulfilled the Sepsis-3 criteria for septic shock, where mortality rates were significantly higher.

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2021.08.007>.

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COVID-19: a boost for intensive care authorship?

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Editor—Almost 180 million cases of COVID-19 have been diagnosed, with almost 4 000 000 deaths.¹ As this pandemic had unprecedented worldwide healthcare and socio-economic effects, the scientific world is under exceptional pressure regarding the need for knowledge on this new disease, including its pathophysiology and possible treatments. Such pressure prioritised scientific publications on COVID-19 over other medical conditions, with exponential increases in editorial workload.² Trials on COVID-19 underwent rapid ethical evaluation³; the peer-review process was shortened and was possibly less stringent.⁴ Studies were published as preprints in order to spread immediate knowledge and experience.⁴ Moreover, the emergence of viral variants and the roll-out of vaccines is keeping pressure high to publish on COVID-19.

From a scientific perspective, the pandemic probably boosted research collaboration both as interdisciplinary teamwork (i.e. radiology, pathology, pulmonology) and as multicentre data sharing. In order to evaluate the appropriateness of the authorship patterns during the COVID-19 pandemic, two simplified systematic searches on PUBMED were conducted on January 25, 2021 to retrieve articles on COVID-19 and acute respiratory distress syndrome (ARDS), the latter including non-COVID-19 cases only. The search in both groups consisted of the combination of terms from three sets. The first two were identical: (1) 'retrospective', AND (2) 'intensive care' OR 'critical care' OR 'critically ill'. The third set was 'COVID' OR 'coronavirus' for the COVID-19 group, and 'ARDS' OR 'acute respiratory distress' for the ARDS group. We

applied filters to articles published with an abstract and containing human data. Each article was assessed by three authors. We excluded reviews, meta-analyses, non-human studies, letters, and editorials. For each of the included studies we recorded the number of: patients included, authors (excluding collaborators), and centres involved.

Our primary outcome was the difference between the patient number/author number ratio (P/A ratio) calculated as follows:

$$P / A \text{ ratio} = \frac{n \text{ of patients studied}}{n \text{ of authors listed}}$$

After testing data distribution (Kolmogorov–Smirnov test), variables of interest were reported as mean (standard deviation), or median (inter-quartile range). Statistical analysis was performed with the Student t-test or Mann–Whitney test according to data distribution; P values <0.05 were considered statistically significant. Two sensitivity analyses were conducted. The first included studies of <1000 patients to remove the influence of large registries that may have a very high number of patients and consequently P/A ratio. The second included single-centre studies.

Our simplified search found 701 articles for the COVID-19 group and 778 for the ARDS groups. After screening, we included 535 and 464 articles, respectively (Table 1). When excluding outliers, the number of studies in the COVID-19 and ARDS groups decreased to 485 (–9.3%) and 442 (–4.7%), respectively. The first sensitivity analysis changed only the results on