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CORRESPONDENCE

Immunologic response in bacterial sepsis is different from that in COVID-19 sepsis

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Dear Editor,

A cytokine storm has repeatedly been discussed as a predominant mechanism driving severe manifestations of SARS-CoV-2 infection [1]. Critically ill COVID-19 patients fulfill the current SEPSIS-3 criteria [2]. However, there might be substantial differences in phenotype and the pattern of inflammatory parameters compared to bacterial sepsis [3]. This retrospective pilot study was conducted to investigate differences between severe COVID-19 and bacterial sepsis defined by SEPSIS-3 criteria.

For this purpose, we evaluated patients diagnosed with bacterial sepsis according to SEPSIS-3, treated at the medical ICU of the University Hospital Innsbruck from September 2018 to October 2020, and compared them to patients with severe COVID-19 from the second wave (August 2020–April 2021). Both cohorts were matched in a 1:2 ratio (bacterial: COVID-19—2nd wave) by age, sex, Simplified Acute Physiology Score III (SAPS III) and invasive mechanical ventilation (SI Fig. 1). Since there was a significant difference in the use of corticosteroids between the first and second wave, we included patients from the first wave (March 2020–July 2020) as an additional control cohort. COVID-19 patients were treated at the same ICU and were included in the Tyrolean COVID-19 intensive care registry [4]. For diagnosis of COVID-19 at least one positive polymerase chain reaction (PCR) test for SARS-CoV-2 was required. Patients with confirmed SARS-CoV-2 infection and concomitant positive aerobic or anaerobic blood culture were excluded from the study. For the diagnosis of bacterial sepsis, the pathogen causing bacterial sepsis had to be diagnosed by at least one positive blood culture, by isolation of bacterial pathogens from the highly suspected focus or specific findings in the autopsy (sepsis signs, definite focus of infection). Exclusion criteria comprised chemotherapy during the past year, immunosuppression or missing interleukin-6 (IL-6) measurements within 48 h after ICU admission (Table 1).

In all patients, we determined maximum levels of C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT), ferritin, arterial lactate and minimal lymphocyte count within 48 h after ICU admission.

Seventeen patients with bacterial sepsis were included and compared to 34 patients with severe COVID-19 from the second and 14 patients with severe COVID-19 from the first wave.

Baseline characteristics were similar in all three cohorts as presented in Table 1. All detected pathogens as part of routine care are shown in SI Table 1. Maximum CRP, PCT and IL-6 levels were significantly lower in patients with severe COVID-19 (2nd wave) compared to patients with bacterial sepsis. The same pattern was observed in the analysis of patients from the first wave, of whom only 14% received corticosteroids. Ferritin levels showed no significant differences between bacterial sepsis and the second wave of COVID-19. The divergence of ferritin values was wider when bacterial sepsis was compared with the first COVID-19 wave, but there was no statistically significant difference. Arterial lactate levels were higher in bacterial sepsis compared to COVID-19 (1st and 2nd wave, respectively) (Table 1, Fig. 1).

Serum IL-6, as well as PCT and CRP levels were dramatically higher in bacterial sepsis compared to severe COVID-19. This pattern did not change when grouping the patients according to different sources of infection (SI Table 2). When comparing COVID-19 to bacterial sepsis from respiratory origin only, the aforementioned differences in pattern of laboratory levels remained (SI Table 3). Steroid effects

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Table 1 Patient characteristics and inflammatory parameters (COVID-19 [2nd wave] vs. Bacterial sepsis vs. COVID-19 [1st wave])

	COVID-19 sepsis 2nd wave ($n=34$)	*p* value	Bacterial sepsis ($n=17$)	*p* value	COVID-19 sepsis 1st wave ($n=14$)
Baseline characteristics					
Age[a]	64.0 (53.3–76)	0.719[c]	62.0 (52.5–74.5)	0.499[c]	68.0 (54.3–79.3)
Female[b]	13.0 (38)	0.838[d]	6.0 (35)	0.690[d]	4.0 (29)
SAPS III[a]	56.5 (46–63.8)	0.889[c]	54.0 (49.5–62.5)	0.310[c]	61.5 (46.8–76.5)
ICU treatment					
IMV within 48h[b]	13.0 (38)	0.839[d]	7.0 (41)	0.376[d]	8.0 (57)
IMV within 7d[b]	16.0 (47)	1[d]	8.0 (47)	0.337[d]	9.0 (64)
Vasopressor within 48h[b]	16.0 (47)	< 0.001[d]	17.0 (100)	0.003[d]	8.0 (57)
ECMO during ICU stay[b]	3.0 (9)	0.207[d]	0.0 (0)	–	0.0 (0)
RRT during ICU stay[b]	7.0 (21)	0.002[d]	11.0 (65)	0.005[d]	2.0 (14)
Glucocorticoids within 48h[b]	33.0 (97)	< 0.001[d]	10.0 (59)	0.011[d]	2.0 (14)
Laboratory parameters					
IL-6 (ng/l)[a]	74.4 (17.3–246.3)	< 0.001[c]	5624.0 (1203.3–24,157.5)	< 0.001[c]	228.7 (124.3–533.3)
PCT (µg/l)[a]	0.2 (0.1–0.4)	< 0.001[c]	33.1 (9.3–167.8)	< 0 .001[c]	0.5 (0.2–1.4)
CRP (mg/dl)[a]	9.4 (4.7–20.2)	< 0.001[c]	32.3 (24.3–49.7)	0.006[c]	16.9 (14.2–23.2)
Ferritin (µg/l)[a]	1143.5 (442.3–1851.3)	0.669[c]	571.0 (430–1837.5)	0.096[c]	1719.0 (868.5–2916)
Lactate (mg/dl)[a]	18.0 (13.8–22.3)	< 0.001[c]	38.0 (22–71)	< 0.001[c]	12.5 (10–17)
Lactate > 18 mg/dl[b]	15.0 (44)	0.009[d]	14.0 (82)	< 0.001[d]	1.0 (7)
Absolute Lymphocytes (10^9/l)[a]	0.7 (0.5–0.9)	0.779[c]	0.7 (0.2–1.3)	0.236[c]	1.1 (0.7–1.3)
Lymphopenia (< 0.8[c] 10^9/l)[b]	19.0 (56)	0.754[d]	9.0 (53)	0.073[d]	3.0 (21)
Infection focus					
Respiratory[b]	34.0 (100)		3.0 (18)		14.0 (100)
Intestinal[b]	0.0 (0)		3.0 (18)		0.0 (0)
Urogenital[b]	0.0 (0)		5.0 (29)		0.0 (0)
Dermal[b]	0.0 (0)		4.0 (24)		0.0 (0)
Others[b]	0.0 (0)		2.0 (12)		0.0 (0)
Outcome					
ICU mortality[b]	9.0 (26)	0.286[d]	7.0 (41)	0.756[d]	5.0 (36)

SAPS III simplified acute physiology score III, *IMV* invasive mechanical ventilation, *ECMO* extracorporeal membrane oxygenation, *RRT* renal replacement therapy, *IL-6* interleukin-6, *PCT* procalcitonin, *CRP* c-reactive protein, *ICU* intensive care unit

[a][median (IQR)],

[b][n (%)];

[c]Mann-Whitney-*U* Test;

[d]Chi Quadrat Test

may not explain our findings between bacterial sepsis and second wave of COVID-19, because COVID-19 patients, treated during first wave, showed similar results, despite considerably less frequent use of glucocorticoids (Table 1).

Despite COVID-19 patients meeting SEPSIS-3 criteria, phenotypes of dysregulated host response following infection by bacteria or SARS-CoV-2 appear to be substantially different. Lower lactate levels observed in COVID-19 patients suggest further substantial differences to bacterial sepsis. This is also supported by similar findings reported for COVID-19 associated ARDS from the early phase of the pandemic [5]. Our pilot study questions the classification of severe COVID-19 as sepsis. Furthermore, it raises doubts about cytokine storm being a predominant pathophysiological factor in severe COVID-19 sepsis and might have implications for therapeutic interventions aiming at cytokine removal. However, only IL-6 was measured in our study, it is conceivable that differences in other relevant cytokines like IL-8, IL-10 and interferon gamma are less pronounced. Further, limitations of our study include the small sample size and slight differences in the SAPS-III score between COVID-19 patients from the first and the second wave. Finally, severe COVID-19 patients with primarily respiratory failure were compared to bacterial sepsis from various sources of infection not only the lung. However, when comparing only the subgroup of bacterial

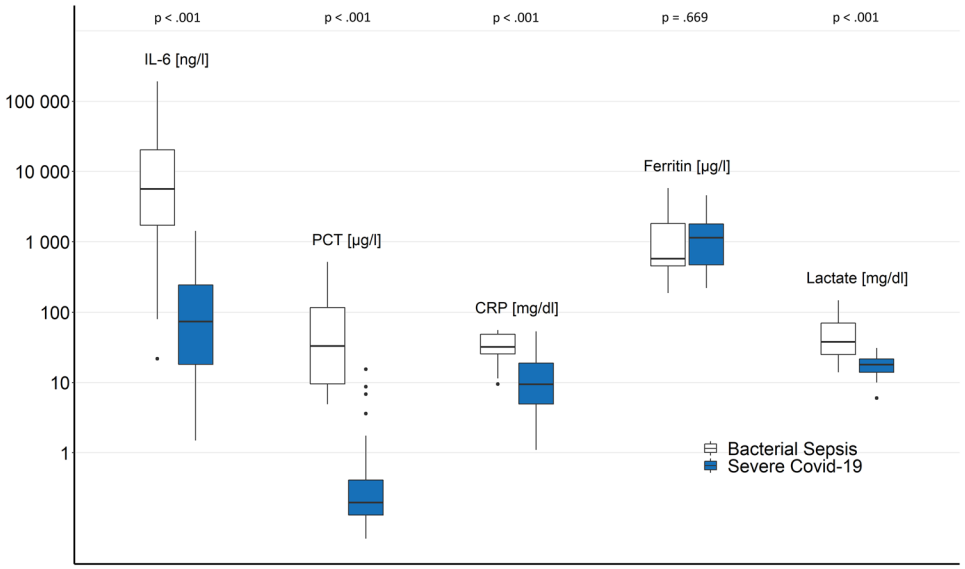

Fig. 1 Maximum inflammatory parameters within 48 h after ICU admission (Bacterial sepsis vs. COVID-19 [2nd wave]), *IL-6* interleukin-6, *PCT* procalcitonin, *CRP* c-reactive protein

sepsis from a pulmonary focus with COVID-19 patients the observed differences persisted. The findings of this pilot study might provide a basis for discrimination of severe COVID-19 from bacterial sepsis using standard inflammatory parameters. This, however, needs to be substantiated in larger trials also performing supplementary analysis of inflammatory parameters.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest None of the authors have any conflicts of interest to declare.

Ethical approval This study was approved by the ethics committee of the Medical University Innsbruck (Nr. 1099/2020).

Consent for publication Not applicable–manuscript contains no individual patient data.

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