The Journal of Infectious Diseases

CORRESPONDENCE

Role of Cell Adhesion Molecules for Prognosis of Disease Development of Patients With and Without COVID-19 in the Emergency Department

To the Editor—While the coronavirus disease 2019 (COVID-19) is mostly characterized by mild symptoms, some infections provoke a cytokine storm, leading to septic shock and multiorgan failure (MOF) [1–3]. A severe course of the disease may be accompanied by coagulopathy and endotheliopathy, leading to thrombotic and microvascular complications [4]. Therefore, endothelial markers [4–6] might predict the outcome of COVID-19 patients an early stage after diagnosis, with direct impact on decisions regarding therapy requirements.

With great interest we have read the recent articles by Tong et al and Li et al examining blood levels of endothelial cell adhesion molecules (CAMs) in COVID-19 patients [5, 7]. They showed that vascular CAM-1 (VCAM-1), intercellular CAM-1 (ICAM-1), and platelet endothelial CAM-1 (PECAM-1) were elevated in patients with mild disease and strongly elevated in severe cases compared to an uninfected cohort. In further studies, COVID-19 patients who were later admitted to the intensive care unit (ICU) had increased soluble E-selectin (sE-selectin) plasma levels at hospital admission compared to hospitalized COVID-19 patients in conventional wards [6]. Moreover, elevated levels of soluble P-selectin (sP-selectin) were shown in ICU patients compared with non-ICU patients [4]. Indeed, CAMs critically involved in inflammatory responses may predict organ dysfunction in septic patients [8]. However, this has not been evaluated in detail in comparison to patients with clinically comparable symptoms in the emergency department (ED) but ruled-out severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, that is non–COVID-19 infectious diseases. Importantly, it has not yet been fully elucidated whether changes in CAMs are superior when compared to traditional biomarkers.

Therefore, we set out to measure CAM levels with regard to prognosis of disease progression (subsequent ICU admission, MOF, mortality) in ED patients. We prospectively enrolled 69 patients presenting to the ED between 20 March and 6 June 2020 with clinically suspected SARS-CoV-2 infections and isolated serum samples for further investigation. Chest computed tomography along with polymerase chain reaction (PCR) assays of pharyngeal swab samples were performed, resulting in 19 patients diagnosed with COVID-19 and 46 patients in whom COVID-19 was ruled out. Additionally, 4 patients had inconclusive findings and were removed from the analysis. The routine biomarkers lactate, C-reactive protein (CRP), and procalcitonin (PCT) were determined immediately as standard of care; ICAM-1, VCAM-1, sP-selectin, sL-selectin, and sE-selectin were measured using enzyme-linked immunosorbent assays (ELISAs; all R&D Systems, except sL-selectin, Invitrogen) (Table1).

The disease course was assessed regarding the clinical endpoints (1) admission to the ICU, and (2) MOF (defined by the clinical need for organ replacement of at least 2 organ systems within the SOFA [Sequential Organ Failure Assessment] score [9]), within 72 hours after presentation. We calculated *P* values and compared the area under the receiver operating characteristic curve (AUROC) with 95% confidence intervals (CI) for predicting the end points (Table 1).

Serum concentration of VCAM-1 was significantly higher in COVID-19 patients than in non–COVID-19 patients (2095 vs 1367 pg/mL, $P < .01$). In contrast, sP-selectin concentration was significantly lower in COVID-19 patients (57.1 vs 84.2 ng/mL, $P = .03$).

Among COVID-19 patients, serum sL-selectin displayed a significant decrease in patients developing MOF within 72 hours compared to non-MOF patients (1947 ng/mL vs 1358 ng/mL, $P = .04$), and also showed the highest AUROC (0.85) as compared to lactate (0.79), CRP (0.70), and PCT (0.75).

In patients requiring ICU treatment, interestingly, no significant differences in serum CAM concentrations were observed between COVID-19 and non–COVID-19.

To summarize, our study assessed the association of serum CAM levels at an early stage of suspected COVID-19, that is when patients presented to the ED. We show that VCAM-1 was not only elevated in COVID-19 patients compared to uninfected/healthy controls [5], but also compared to non–COVID-19 patients presenting with suspicion of and symptoms comparable to COVID-19 but ruled-out SARS-CoV-2 infection. Furthermore, sP-selectin concentration was significantly lower in COVID-19 patients with a positive correlation to platelet counts ($R = 0.47$, $P < .0001$, data not shown) with lower platelets found in COVID-19 compared to non–COVID-19 patients (191/nL vs 240/nL, $P = .02$; data not shown). This is in accordance with the concept that thrombocytopoiesis may be affected by COVID-19 [10]. While the sP-selectin reduction seems to be associated with COVID-19, it does not predict further disease outcome, rather representing a disease bystander, at least at early stages of the disease. Our data further suggest sL-selectin as a valuable prognostic biomarker in COVID-19 patients ($P = .04$, AUROC = 0.85) with regard to subsequent MOF, which performs better than traditional biomarkers, including lactate. Our results might add to the diagnostic biomarker repertoire, characterizing the early inflammatory immune response, that is

Table 1. Characteristics of Study Patients and Levels of CAMs

	Lactate, mg/dL	CRP, mg/L	PCT, μg/L	ICAM, pg/mL	VCAM, pg/mL	sP-Selectin, ng/mL[a]	sL-Selectin, ng/mL[a]	sE-Selectin, ng/mL[a]
Controls, median (IQR)								
All, n = 46	16.0 (11.0–18.7)	33.1 (9.90–100.5)	0.11 (0.06–0.35)	334 (264–490)	**1367 (1029–1979)**	43; 84.2 (57.2–118.5)	43; 1593 (1346–1954)	43; 40.6 (31.5–57.5)
Non-MOF, n = 45	16.0 (11.0–18.9)	35.1 (9.30–101.7)	0.10 (0.06–0.36)	339 (268–496)	1383 (1022–1982)	42; 80.5 (56.0–115.1)	42; 1599 (1330–1955)	42; 41.5 (31.2–58.6)
MOF, n = 1[b]	12	26.4	0.11	255	1088	120.2	1393	40.5
Non-ICU, n = 37	15.5 (11.0–18.0)	30.1 (8.40–102.5)	0.08 (0.05–0.32)	366 (265–507)	1330 (923–1760)	35; 84.2 (54.8–130.3)	35; 1613 (1383–1978)	35; 42.4 (31.7–57.5)
ICU, n = 9	16.0 (12.0–21.0)	64.5 (19.8–77.1)	0.14 (0.10–0.37)	268 (263–339)	1439 (1255–2148)	8; 77.9 (63.7–95.2)	8; 1447 (1277–1649)	8; 40.2 (31.0–51.6)
COVID-19 patients, median (IQR)								
All, n = 19	15.0 (11.7–21.5)	37.7 (22.3–93.4)	0.11 (0.06–0.21)	320 (295–402)	**2095 (1478–3149)**	57.1 (37.6–93.9)	1770 (1483–2130)	36.0 (23.9–42.8)
Non-MOF, n = 15	13.5 (11.7–18.0)	36.6 (22.3–72.2)	0.09 (0.06–0.16)	322 (291–402)	1963 (1454–3341)	57.1 (41.0–74.9)	**1946 (1736–2206)**	36.0 (23.3–42.8)
MOF, n = 4	32.5 (25.3–44.0)	93.4 (61.6–165.3)	0.45 (0.18–0.93)	309 (297–452)	2515 (2032–2864)	124.5 (32.8–215.9)	**1358 (1329–1458)**	33.3 (27.1–43.9)
Non-ICU, n = 11	13.0 (11.2–15.0)	36.6 (23.6–65.9)	0.11 (0.07–0.16)	322 (291–402)	1963 (1454–3031)	57.1 (45.2–74.9)	1844 (1736–2236)	28.7 (20.4–39.8)
ICU, n = 8	21.5 (16.8–31.3)	93.4 (22.5–175.7)	0.15 (0.06–0.70)	319 (297–393)	2516 (1480–3257)	49.0 (33.2–130.3)	1537 (1329–2024)	37.1 (27.3–58.1)
***P* values**								
All controls vs all COVID-19	.62	.53	.75	.91	**<.01**	**.03**	.12	.08
COVID-19: MOF vs no MOF	.09	.26	.15	.89	.76	.8	**.04**	.96
COVID-19: ICU vs no ICU	**.03**	.27	.51	.97	.46	.87	.24	.40
Control ICU vs COVID-19 ICU	.23	.54	.74	.42	.20	.51	.44	.57
AUROCs (95% CI)								
All controls vs all COVID-19	0.46 (.30–.62)	0.55 (.40–.70)	0.47 (.32–.63)	0.51 (.36–.66)	**0.72 (.58–.86)**	0.68 (.51–.84)	0.62 (.47–.78)	0.64 (.49–.79)
COVID-19: MOF vs no MOF	0.79 (.38–1.00)	0.70 (.34–1.00)	0.75 (.37–1.00)	0.53 (.17–.89)	0.56 (.28–.84)	0.55 (.03–1.00)	**0.85 (.67–1.00)**	0.48 (.17–.80)
COVID-19: ICU vs no ICU	0.80 (.58–1.00)	0.66 (.36–.96)	0.60 (.29–.90)	0.51 (.23–.79)	0.61 (.33–.89)	0.53 (.21–.85)	0.67 (.40–.94)	0.62 (.36–.89)
Control ICU vs COVID-19 ICU	0.68 (.41–.95)	0.60 (.29–.90)	0.44 (.12–.76)	0.62 (.34–.91)	0.69 (.41–.98)	0.61 (.27–.95)	0.62 (.32–.93)	0.59 (.29–.90)

Controls are suspects for COVID-19 with ruled-out SARS-CoV-2 infections. *P* values were calculated with Mann-Whitney *U* test for continuous variables and Fisher exact test for nominal variables. Values in bold (significant values and data) are elaborated in the text

Abbreviations: AUROC, area under the receiver operating characteristics curve; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ICAM, intercellular cell adhesion molecule; ICU, intensive care unit; IQR, interquartile range; MOF, multiorgan failure; PCT, procalcitonin; VCAM, vascular cell adhesion molecule.

[a]Selectin concentrations were measured in 62 patients due to missing samples in 3 control patients. The number of patients is shown before the semicolon for median concentrations with missing samples.

[b]Due to the low number of non–COVID-19 patients with MOF, IQRs cannot be calculated.

when COVID-19–suspected patients are presenting to the ED.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Wolfgang Bauer,[1] Jannis Ulke,[2] Noa Galtung,[1] Leonore Claudia Strasser-Marsik,[3] Nick Neuwinger,[2,3] Rudolf Tauber,[2,3] Rajan Somasundaram,[1] and Kai Kappert[2,3]

[1]Department of Emergency Medicine, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, [2]Institute of Laboratory Medicine, Clinical Chemistry and Pathobiochemistry, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, and [3]Labor Berlin – Charité Vivantes GmbH, Berlin, Germany

References

1. Rieder M, Wirth L, Pollmeier L, et al. Serum protein profiling reveals a specific upregulation of the immunomodulatory protein progranulin in COVID-19 [published online ahead of print 29 November 2020]. J Infect Dis doi: 10.1093/infdis/jiaa741.
2. Mangalmurti N, Hunter CA. Cytokine storms: understanding COVID-19. Immunity **2020**; 53:19–25.
3. Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A, Hassanzadeh G. COVID-19 and multiorgan failure: a narrative review on potential mechanisms. J Mol Histol **2020**; 51:613–28.
4. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol **2020**; 7:e575–82.
5. Tong M, Jiang Y, Xia D, et al. Elevated expression of serum endothelial cell adhesion molecules in COVID-19 patients. J Infect Dis **2020**; 222:894–8.
6. Smadja DM, Guerin CL, Chocron R, et al. Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. Angiogenesis **2020**; 23:611–20.
7. Li L, Huang M, Shen J, et al. Serum levels of soluble platelet endothelial cell adhesion molecule 1 in COVID-19 patients are associated with disease severity. J Infect Dis **2021**; 223:178–9.
8. Reinhart K, Bayer O, Brunkhorst F, Meisner M. Markers of endothelial damage in organ dysfunction and sepsis. Crit Care Med **2002**; 30:S302–12.
9. Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med **1996**; 22:707–10.
10. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol **2020**; 99:1205–8.

Received 17 December 2020; editorial decision 20 January 2021; accepted 24 January 2021; published online January 27, 2021.

Correspondence: W. Bauer, MD, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Department of Emergency Medicine, Hindenburgdamm 30, 12203 Berlin, Germany (wolfgang.bauer@charite.de).

The Journal of Infectious Diseases® 2021;XX:1–3

DOI: 10.1093/infdis/jiab042