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RESEARCH LETTER

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Hemofiltration with the Seraph® 100 Microbind® Affinity filter decreases SARS-CoV-2 nucleocapsid protein in critically ill COVID-19 patients

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The nucleocapsid protein (N-protein) of SARS-CoV-2 is a structural protein that oligomerizes to form a complex surrounding viral RNA, thus protecting it from the host cell environment. It is abundantly expressed within infected cells, where it facilitates viral RNA transcription, an essential step for viral replication Recently an ultrasensitive Simoa® immunoassay has been described that robustly measures SARS-CoV-2 N-protein in venous blood, dried blood microsamples, and saliva [1]. This study measured N-protein in longitudinal blood samples of COVID-19 patients and demonstrated readily detectable viral antigen two weeks after initial positive PCR testing, with concentrations gradually decreasing, inversely correlated with anti-SARS-CoV2 adaptive immune response. This study supports observations reported elsewhere that viral load in blood correlates with disease severity [2].

The Seraph® 100 Microbind® Affinity adsorber (Exthera Medical, CA, USA) is an extracorporeal treatment currently being explored as an approach to improve the clinical course and outcome of critically ill patients with COVID-19. On April 17, 2020, the FDA granted emergency use authorization for the Seraph® 100 for use in the context of severe and critical disease, for which effective treatment options are limited. Bacteria and viruses bind to the immobilized heparin on the ultra-high molecular weight polyethylene beads of the Seraph® device in a manner similar to the interaction with heparan sulfate on the cell surface and are thereby removed from the bloodstream [3]. The spike protein of SARS-CoV-2 has been shown to bind to cellular heparan sulfate (and heparin) through its receptor-binding domain, and recent studies suggest the heparin binding of the spike protein is much more pronounced in SARS-CoV-2 than in other coronaviruses [4]. In addition to an anecdotal report [5] a recent multicenter study showed that mortality of COVID-19 patients was much lower (37.7%) in the Seraph 100 treated group compared to a control group (67.4%) [6].

Here, we report the effect of the Seraph treatment on the concentration of the N-protein in critically ill COVID-19 patients as part of an ongoing biomarker study, approved by the IRB of the Hannover Medical School (9130_MPG_23b_2020). Six out of seven COVID-19 patients exhibited measurable concentrations of the N-protein prior to treatment with the Seraph® device, that seemed to be related to the severity of the disease and the duration of the disease (Table 1). While hemoperfusion with the Seraph® was executed either alone or in combination with a wide range of supportive treatments, including intermittent hemodialysis and

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Table 1 Patient characteristics (laboratory data obtained on the day of Seraph® treatment)

	# 1	# 2	# 3	# 4	# 5	# 6	# 7
Gender	M	F	M	M	F	M	M
Age (years	77	78	54	41	61	65	72
Weight (kg)	76.5	75	107	119	122	60.5	71
Height (cm)	164	160	188	180	168	166	175
Onset of symptoms-Seraph treatment (d)	5	19	10	13	9	16	12
Died @ hospital day	60	9	7	Survivor	Survivor	Survivor	18
N-protein before Seraph therapy (pg/mL)	1021.3	26.6	121,884.2	1070.2	1036.5	19.5	-
N-protein after Seraph therapy (pg/mL)	769.6	24.1	111,035.2	931.5	376.2	12.1	-
CRP (mg/l)	73	443	87	110	156	129	39
Ferritin (ng/mL)	2957	830	10,005	838	589	756	1,412
PCT (µg/L)	0.7	18.5	4.4	1.1	0.1	0.1	0.1
D-dimer (mg/L)	4.68	35.2	3.26	1.04	0.90	4.00	35.2
Therapy (h)	IHD (4)	CRRT (24)	IHD (4)	IHD (5)	HP (15)	HP (4)	HP (14)
Qb (mL/min)	300	90	250	250	80	200	100

IHD intermittent hemodialysis, *CRRT* continuous renal replacement therapy, *HP* hemoperfusion, Q_b blood flow

continuous renal replacement therapy, N-protein concentration was consistently reduced when comparing pre- and post- Seraph treatment blood samples (Table 1). Calculating the Seraph whole blood clearance (CL) by the nucleocapsid concentration upstream (C_{in}) and downstream (C_{out}) of the Seraph and the blood flow (Q_B) by the formula: $CL = (C_{in} / C_{out}) / C_{in} \times Q_B$, resulted in a measurable device clearance that was not observed with other proteins including total serum protein (Fig. 1).

In conclusion, treating critically ill COVID-19 patients with the Seraph® 100 Microbind® Affinity filter decreased SARS-CoV-2 nucleocapsid protein in blood. The effect of clinically relevant outcome parameters needs to be determined.

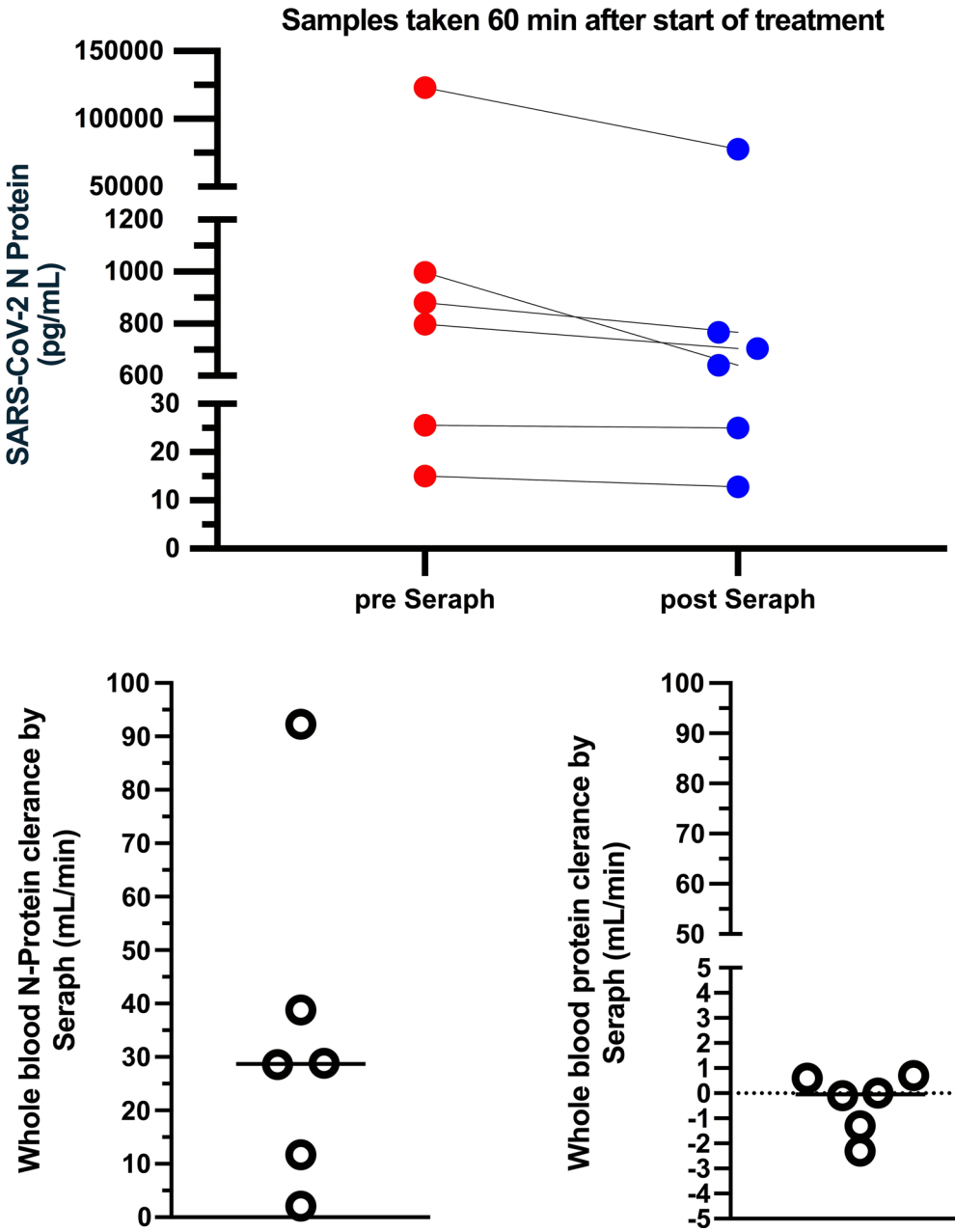

Fig. 1 Concentration of the nucleocapsid protein pre (upstream) and post (downstream) of the Seraph® at 60 min of treatment (upper part of the figure) and the resulting device clearance for the N-protein as well as the total plasma protein (lower part of the figure)

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Authors' contributions
JK, DB and TF treated the patients, analyzed and interpreted the data and were major contributor in writing the manuscript. SH, DM, and AB performed measurements and/or analysis of the N-protein. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approvals
This study was approved by the Ethics Committee of the Medical School Hannover (9130_MPG_23b_2020).

Consent for publication
Not applicable.

Competing interests
SH, DM, and AB are current employees of Quanterix Corporation. JK received research support from ExThera Medical and owns Quanterix stocks.

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References
1. Shan D, Johnson JM, Fernandes SC, Suib H, Hwang S, Wuelfing D, Mendes M, Holdridge M, Burke EM, Beauregard K, et al. N-protein presents early in blood, dried blood and saliva during asymptomatic and symptomatic SARS-CoV-2 infection. Nat Commun. 2021;12(1):1931.
2. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, Worrall D, Giguel F, Piechocka-Trocha A, Atyeo C, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat Commun. 2020;11(1):5493.
3. Seffer MT, Cottam D, Forni LG, Kielstein JT: Heparin 2.0: a new approach to the infection crisis. Blood Purif 2020:1–7.
4. Kim SY, Jin W, Sood A, Montgomery DW, Grant OC, Fuster MM, Fu L, Dordick JS, Woods RJ, Zhang F, et al. Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. Antiviral Res. 2020;181:104873.
5. Pape A, Kielstein JT, Kruger T, Fuhner T, Brunkhorst R. Treatment of a critically Ill COVID-19 patient with the seraph 100 microbind affinity filter. TH Open. 2021;5(2):e134–8.
6. A Multicenter Evaluation of Blood Purification with Seraph 100 Microbind Affinity Blood Filter for the Treatment of Severe COVID-19: A Preliminary Report [https://doi.org/10.1101/2021.04.20.21255810v1]

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