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# A Multicenter Evaluation of the Seraph 100 Microbind Affinity Blood Filter for the Treatment of Severe COVID-19

**OBJECTIVES:** The Seraph100 Microbind Affinity Blood Filter (Seraph 100) (ExThera Medical, Martinez, CA) is an extracorporeal therapy that can remove pathogens from blood, including severe acute respiratory syndrome coronavirus 2. The aim of this study was to evaluate safety and efficacy of Seraph 100 treatment for COVID-19.

**DESIGN:** Retrospective cohort study.

**SETTING:** Nine participating ICUs.

**PATIENTS:** COVID-19 patients treated with Seraph 100 ( $n = 53$ ) and control patients matched by study site ( $n = 53$ ).

**INTERVENTION:** Treatment with Seraph 100.

**MEASUREMENTS AND MAIN RESULTS:** At baseline, there were no differences between the groups in terms of sex, race/ethnicity, body mass index, and need for mechanical ventilation. However, patients in the Seraph 100 group were younger (median age, 54 yr; interquartile range [IQR], 41–65) compared with controls (median age, 64 yr; IQR, 56–69;  $p = 0.009$ ). Charlson comorbidity index scores were lower in the Seraph 100 group (2; IQR, 0–3) compared with the control group (3; IQR, 2–4;  $p = 0.006$ ). Acute Physiology and Chronic Health Evaluation II scores were also lower in Seraph 100 subjects (12; IQR, 9–17) compared with controls (16; IQR, 12–21;  $p = 0.011$ ). The Seraph 100 group had higher vasopressor-free days with an incidence rate ratio of 1.30 on univariate analysis. This difference was not significant after adjustment. Seraph 100-treated subjects were less likely to die compared with controls (32.1% vs 64.2%;  $p = 0.001$ ), a difference that remained significant after adjustment. However, no difference in mortality was observed in a post hoc analysis utilizing an external control group. In the full cohort of 86 treated patients, there were 177 total treatments, in which only three serious adverse events were recorded.

**CONCLUSIONS:** Although this study did not demonstrate consistently significant clinical benefit across all endpoints and comparisons, the findings suggest that broad spectrum, pathogen agnostic, blood purification can be safely deployed to meet new pathogen threats while awaiting targeted therapies and vaccines.

**KEY WORDS:** COVID-19; critical care outcomes; extracorporeal circulation; hemoperfusion; medical countermeasure; severe acute respiratory syndrome coronavirus-2; viremia

COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is characterized by a profoundly dysregulated inflammatory response and concomitant endothelial dysfunction that results in end-organ damage (1). To date, SARS-CoV-2 has infected over 262 million people and killed 5 million worldwide (2). Although advancements have been made in treating COVID-19, novel therapeutics are still needed, particularly in those with critical illness.

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For patients with sepsis, the development of “pathogenemia” (i.e., bacteremia, viremia, and fungemia) is consistently associated with worse outcomes (3–6). Similarly, emerging evidence suggests that SARS-CoV-2 viremia in symptomatic patients is common and directly linked to COVID-19 disease severity and poor outcomes. One meta-analysis examined the association of viremia with outcomes, including data from 2,181 patients in 21 studies (7). The authors reported that viremia was detected in 9.4–74.1% of patients in these studies, yielding a pooled estimate of 34%, and found that it was associated with COVID-19 severity. The high variability of RNAemia rates in the 21 studies was likely due in part to differing sensitivity and/or specificity of analytical techniques used to detect viral RNA, clinical characteristics of the patient cohorts, and sampling protocols. Furthermore, viremia was associated with the risk of ICU admission, need for mechanical ventilation, multiple organ failure, and death. The strengths of these associations were compelling, with odds ratios (ORs) ranging from 4.3 for ICU admission to 11.1 for mortality. Although causality cannot be determined from retrospective data, these results suggest that viremia itself may contribute to worse outcomes by allowing broad metastasis of viral invasion into nonpulmonary organs. Based on these data, we hypothesized that decreasing viremia in critically ill patients with COVID-19 might improve outcomes.

The Seraph100 Microbind Affinity Blood Filter (Seraph 100) (ExThera Medical, Martinez, CA) is an extracorporeal medical countermeasure designed to remove a multitude of pathogens from the blood. The Seraph 100 is a sorbent hemoperfusion filter containing polyethylene beads coated with immobilized heparin (8). This heparin surface mimics the endothelial glycocalyx, allowing for broad spectrum extracorporeal pathogen removal that is inclusive of viruses, bacteria, and fungi (see **Supplemental Table 1**, <http://links.lww.com/CCX/A955>). A recent report demonstrated that the Seraph 100 device is capable of clearing the nucleocapsid protein (N-protein) of the SARS-CoV-2 virus (9). Given prior work demonstrating the association between viremia and poor outcomes, clearance of SARS-CoV-2 from the bloodstream could be beneficial to critically ill patients with COVID-19 by providing adjunctive source control. Importantly, the ability of the Seraph 100 to bind SARS-CoV-2 is highly unlikely to be affected by S protein mutations,

which means that this type of therapy is not susceptible to immune escape.

As a result of early experience with this device in patients with COVID-19 (10) accompanied by sufficient safety data, the Food and Drug Administration granted Emergency Use Authorization (EUA) for patients with COVID-19 with respiratory failure on April 17, 2020. We sought to retrospectively collect data on patients treated under the EUA for a retrospective observational study to evaluate early evidence for safety and efficacy. We hypothesized that the treatment would be safe and associated with improved outcomes compared with contemporaneous controls.

## MATERIALS AND METHODS

The Blood purification with Seraph100 Microbind Affinity Blood Filter for the treatment of severe COVID-19: an Observational Study (PURIFY-OBS-1) was reviewed and approved by the Advarra institutional review board (IRB; approval number: Pro00047577) in accordance with all applicable Federal regulations governing human research protections (Clinicaltrials.gov Identifier NCT04606498). The PURIFY-OBS-1 study included Seraph 100-treated patients and a contemporaneous control group. To be included, patients must have met the EUA criteria for treatment. These criteria required that patients be at least 18 years old and have either: 1) early acute lung injury or acute respiratory distress syndrome, 2) severe disease (defined by dyspnea, respiratory rate > 30 breaths/min, oxygen saturation ≤ 93%, or lung infiltrates > 50%), or 3) life-threatening disease (respiratory failure, septic shock, or multiple organ dysfunction).

The Seraph 100-treated cohort was composed of patients that were admitted to the ICU at a participating institution, had severe COVID-19 meeting EUA inclusion criteria, and whose Seraph 100 therapy was initiated between the date of EUA approval (April 17, 2020) until IRB approval at the study site. The contemporaneous control group was composed of patients who were admitted to the ICU at a participating institution with COVID-19 meeting inclusion criteria per the EUA but were not treated with the Seraph 100 device during the same period. Since each site had slightly different clinical criteria for when they considered therapy with the Seraph 100 device, the investigators at each site were asked to identify all patients during

the time period that they would have treated with the Seraph 100 device had it been available. Exclusion criteria were age greater than 75 years and ICU admission greater than 7 days after hospital admission.

Data collected at admission to the ICU included demographic variables (age, sex, and race/ethnicity), body mass index (BMI), comorbid conditions (defined by the Charlson comorbidity index (11) derived from chart review), and the Acute Physiology and Chronic Health Evaluation (APACHE II) score (12). Data on other COVID-19 treatments, including remdesivir and corticosteroids, were collected throughout the hospital stay. Data on mortality, ICU length of stay, need for kidney replacement therapy (KRT), and hospital length of stay were also recorded. Study personnel entered data into an online electronic data capture form in REDCap (Vanderbilt University, Nashville, TN). Missing data were addressed through multivariate imputation only for missing continuous physiologic data that are underlying components of the APACHE II score using R version 3.6.2 (The R Foundation, Vienna, Austria). For each of these variables, we specified a predictive mean matching model (13). Multiple imputation was conducted under the assumption that the missing observations were missing at random. We confirmed the acceptability of the imputations by graphical comparison of plots of the distribution of original and imputed values among applicable APACHE II component variables.

Demographic distributions were compared using the chi-square test for categorical variables, unless cell sizes were small, in which case a Fisher exact test was used. For continuous variables, data were analyzed to determine the distribution, and none were normally distributed. Therefore, Wilcoxon rank-sum tests were used to compare continuous variables between the groups. Vasopressor-free days, ICU-free days, and ventilator-free days were calculated as the number of days that a subject was alive and not requiring vasopressors, ICU-level care, and mechanical ventilation, respectively, in the first 28 days after ICU admission. The primary efficacy outcome of the analysis was vasopressor-free days, which was examined by use of negative binomial regression models, incidence rate ratios (IRRs), 95% CIs, and *p* values. Negative binomial models were used to account for overdispersion of the vasopressor-free day variable. The secondary efficacy outcome examined was inhospital mortality, which was evaluated using logistic regression. Since

different sites had different considerations for when to initiate therapy with the Seraph 100, we matched control and treated subjects by study site in a 1:1 fashion (see **Supplemental Table 2**, <http://links.lww.com/CCX/A955>, for the breakdown of enrolled subjects by study site) using random selection. Both univariate and multivariable analyses were performed to account for the potential confounding effects of variables that have been associated with mortality in patients with COVID-19, including age (14), sex (14), race/ethnicity (15), BMI (16), APACHE II score (17), and Charlson comorbidity index (18). Data were analyzed using Stata Version 16.1 (StataCorp, College Station, TX). Statistical significance was set at an alpha level of 0.05, and all tests were two-tailed.

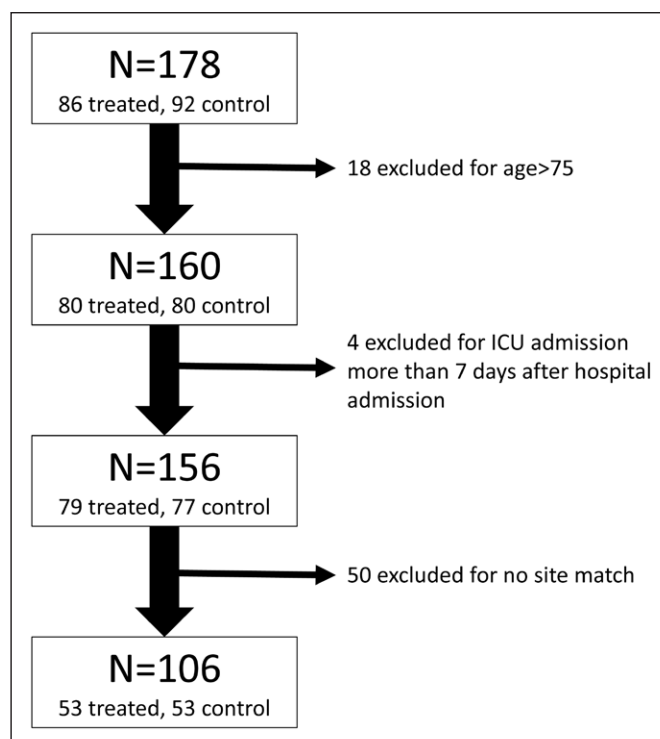
Given concerns about the potential for selection bias in the original control group, we conducted post hoc analyses that compared the Seraph 100-treated patients with an alternative external control group from a study of COVID-19-related critical illness conducted during a similar time period at the University of Pennsylvania Health System (Penn Medicine) (19). The Seraph 100 device was not in use at Penn Medicine during the period these data were collected; therefore, it was not an option that treating physicians could prescribe to their patients. The outcome for this analysis was 28-day mortality. We used propensity score matching with replacement using multivariable logistic regression to approximate a 1:1 match between the Seraph 100 arm of the PURIFY-OBS-1 data to the Penn Medicine data in two analyses. In the first, we considered only the Seraph 100 patients that were included in our primary analysis. In the second, we considered all Seraph 100-treated patients in the PURIFY-OBS-1 database. Matching similar patients in the treatment group with those in the control group was achieved based on propensity scores that were generated using age, sex, race/ethnicity, BMI, APACHE II score, and need for mechanical ventilation to generate the scores. Although Seraph 100 patients had a high rate of KRT, this variable was not included in the propensity matching with the Penn Medicine cohort. Many of the PURIFY-OBS-1 sites started patients on KRT as soon as they started treatment with Seraph 100 for logistical reasons (i.e., to run the treatment), not because they met a clinical indication for KRT. Therefore, including this variable would bias the results in favor of Seraph 100 treatment. A standard caliper size of  $0.2 \times \log(\text{SD of the$

propensity score) was used as the maximum tolerated difference between propensity scores for any match, and density plots were produced to assess the balance of the propensity score matching. Average treatment effects (ATEs) were estimated from the propensity matched groups. Since not all elements of the APACHE II were available in the external control group data, to allow for direct comparison between Penn Medicine and PURIFY-OBS-1 data, we formulated a derivation of the APACHE II score with all available input data to generate a modified APACHE II score that did not require acute kidney injury (AKI) data, history of immunocompromise or other chronic medical condition, and recent surgical history. Although the maximum APACHE II score is 71, the maximum modified APACHE II score is 62. The modified APACHE II score was, therefore, calculated identically for both Penn Medicine and PURIFY-OBS-1 data.

## RESULTS

In the 11-month period from April 2020 to March 2021, data were collected for 178 subjects across nine participating clinical sites. This included 86 subjects treated with the Seraph 100 and 92 control subjects. The characteristics of the full cohort from the PURIFY-OBS-1 study subjects are shown in **Supplemental Table 3** (<http://links.lww.com/CCX/A955>). After applying exclusions and matching by study site (**Fig. 1**), 106 subjects were included in the primary analysis.

The characteristics of the study cohort, stratified by Seraph 100 versus control, are presented in **Table 1**. Patients treated with Seraph 100 had a median age (interquartile range [IQR]) of 56 (41–65), which was significantly younger than controls (64 [56–69];  $p = 0.009$ ). The median Charlson comorbidity index (IQR) was higher in the control group (3 [2–4]) compared with the Seraph 100-treated group (2 [0–3];  $p = 0.006$ ). APACHE II scores were also higher in the control group (16 [12–21]), compared with the Seraph 100 treated group (12 [9–17];  $p = 0.011$ ). There were no significant differences noted between the groups in terms of sex, race/ethnicity, BMI, or preexisting diabetes. Similar numbers of subjects in both groups required mechanical ventilation (67.3% and 75.5% in Seraph 100-treated and control patients, respectively). Most of the patients in both groups were treated with remdesivir and corticosteroids; however,



**Figure 1.** Cohort derivation.

these treatments were significantly more common in the Seraph 100 group. More subjects in the Seraph 100 group required KRT compared with the control group (66.0% vs 24.5%;  $p < 0.001$ ). With respect to outcomes, Seraph 100-treated subjects also had higher vasopressor-free days in the first 28 days (24.5 [13–28] vs 14.5 [6–28];  $p = 0.022$ ) compared with control subjects. Patients in the Seraph 100 group were less likely to die compared with the control group (32.1% vs 64.2%, respectively;  $p = 0.001$ ). No significant differences were observed for ICU-free survival at 28 days, ventilator-free survival at 28 days, or hospital lengths of stay.

Univariate results for our primary analysis of vasopressor-free 28 day survival found an IRR of 1.30 with a 95% CI of 1.00–1.69 ( $p = 0.048$ ), favoring treatment with Seraph 100. However, these results were no longer significant in multivariable models that considered potentially confounding variables (**Supplemental Table 4**, <http://links.lww.com/CCX/A955>). The univariate and multivariable logistic regression models for our secondary outcome of mortality are shown in **Table 2**. On univariate analysis, treatment with Seraph 100 was associated with a decrease in mortality with an OR of 0.26 and 95% CI of 0.12–0.59 ( $p = 0.001$ ). Other significant variables in the univariate analysis were age (OR, 1.08 per 1-yr increase; 95% CI, 1.04–1.12;



**TABLE 1.**  
**Characteristics of the Study Cohort**

Characteristics	Treatment ( <i>n</i> = 53)	Control ( <i>n</i> = 53)	<i>p</i>
Age, median (IQR)	56 (41–65)	64 (56–69)	0.009
Sex (%)			
Male	81.1	69.8	0.176
Female	18.9	30.2	
Race/ethnicity (%)			
NH White	45.3	50.9	0.773
NH Black	24.5	17.0	
Hispanic	13.2	11.3	
Other	17.0	20.8	
Body mass index, median (IQR) <sup>a</sup>	33.1 (28.6–40.7)	33.2 (28.8–40.1)	0.803
Acute Physiology and Chronic Health Evaluation II, median (IQR)	12 (9–17)	16 (12–21)	0.011
Charlson Comorbidity Index, median (IQR)	2 (0–3)	3 (2–4)	0.006
Diabetes (%)	28.3	43.4	0.105
Invasive mechanical ventilation (%)	67.3	75.5	0.388
Kidney replacement therapy (%)	66.0	24.5	< 0.001
COVID treatments			
Remdesivir (%)	86.8	69.8	0.034
Corticosteroids (%)	100.0	88.7	0.012
Outcomes			
Mortality (%)	32.1	64.2	0.001
Vasopressor-free days, median (IQR) <sup>b</sup>	24.5 (13–28)	14.5 (6–28)	0.022
ICU-free days, median (IQR)	0 (0–19)	0 (0–10)	0.112
Ventilator-free days, median (IQR) <sup>c</sup>	15 (2–28)	5.5 (1–25)	0.077
Hospital length of stay, median (IQR) <sup>d</sup>	21 (9.5–39.5)	17 (11–32)	0.462

IQR = interquartile range, NH = non-Hispanic.

<sup>a</sup>Missing information for one observation.

<sup>b</sup>Ninety-eight subjects with data available.

<sup>c</sup>Ninety-nine subjects with data available.

<sup>d</sup>Among survivors (*n* = 55).

*p* < 0.001), APACHE II (OR, 1.07 per one point increase; 95% CI, 1.01–1.14; *p* = 0.020), Charlson comorbidity index (OR, 1.46 per one point increase; 95% CI, 1.17–1.83; *p* = 0.001), and mechanical ventilation (OR, 5.81; 95% CI, 2.13–15.86; *p* = 0.001). Sex, race/ethnicity, BMI, treatment with remdesivir, and treatment with corticosteroids were not associated with mortality in the univariate analysis. Multivariable model 1 considered all univariates. In this model, response to treatment with the Seraph 100 device (OR, 0.27; 95% CI, 0.10–0.73; *p* = 0.010) remained significant after adjustment. Similar findings were observed in model 2, which considered only the variables that were

significant in the univariate analysis (OR for Seraph 100 treatment 0.31; 95% CI, 0.12–0.80; *p* = 0.016).

The characteristics of the groups before and after matching the Seraph 100 treated patients in our primary analysis with the external Penn Medicine cohort are shown in **Table 3**. After propensity score matching, the groups (*n* = 35 for Seraph 100-treated cohort and *n* = 39 for the Penn Medicine cohort) did not differ in characteristics. In this analysis, the average difference in mortality risks between treated and control subjects was not significant (ATE = –1.6% in favor of Seraph 100 treatment; 95% CI, –16.1% to 48.9%; *p* = 0.818). The characteristics of all Seraph 100-treated patients

**TABLE 2.**  
Univariate and Multivariable Models for the Outcome of Mortality

Characteristics	Univariate		Model 1		Model 2	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Treatment						
Control	Ref	-	Ref	-	Ref	
Seraph 100	0.26 (0.12–0.59)	0.001	0.27 (0.10–0.73)	0.010	0.31 (0.12–0.80)	0.016
Age (per yr)	1.08 (1.04–1.12)	< 0.001	1.08 (1.01–1.14)	0.018	1.07 (1.01–1.13)	0.016
Sex						
Female	Ref	-	Ref	-		
Male	0.49 (0.20–1.20)	0.118	0.77 (0.23–2.54)	0.669		
Race/ethnicity						
NH White	Ref	-	Ref	-		
NH Black	0.74 (0.27–2.02)	0.558	1.05 (0.28–3.87)	0.943		
Hispanic	0.40 (0.11–1.45)	0.161	0.63 (0.12–3.33)	0.583		
Other	0.89 (0.32–2.50)	0.823	0.64 (0.17–2.50)	0.524		
Body mass index (per 1 point increase) <sup>a</sup>	0.99 (0.95–1.03)	0.621	1.01 (0.94–1.07)	0.864		
Acute Physiology and Chronic Health Evaluation II (per 1 point increase)	1.07 (1.01–1.14)	0.020	1.03 (0.95–1.12)	0.438	1.00 (0.94–1.07)	0.898
Charlson Comorbidity Index	1.46 (1.17–1.83)	0.001	0.97 (0.69–1.37)	0.870	0.98 (0.71–1.35)	0.891
Mechanical ventilation	5.81 (2.13–15.86)	0.001	4.85 (1.38–17.06)	0.014	5.62 (1.71–18.42)	0.004
Remdesivir	0.81 (0.32–2.05)	0.660	2.07 (0.54–7.93)	0.290		
Corticosteroids	1.92 (0.34–10.97)	0.462	4.23 (0.43–41.25)	0.215		

NH = non-Hispanic, OR = odds ratio, Ref = Reference.

<sup>a</sup>Missing information for one observation.

in the PURIFY-OBS-1 and the Penn Medicine cohorts are shown in **Table 4**. After propensity score matching, there were  $n = 57$  in the Seraph 100 group and  $n = 56$  in the Penn Medicine cohort. The characteristics of the groups were not significantly different after matching. The average difference in mortality risks between the groups was not significant (ATE = 1.7 % in favor of the Penn Medicine control group; 95% CI, -26.9% to 30.3%;  $p = 0.906$ ).

In the full Seraph 100-treated cohort, 86 subjects underwent 177 total treatments. The median treatment time was 830 minutes (IQR, 372–3,129 min). Three serious adverse events (SAEs) were reported during Seraph 100 treatment. One subject developed respiratory distress, then subsequently had a cardiac arrest, and eventually expired. This SAE was felt to be expected by the local study team and not related to the device. Another patient had an episode of supraventricular

tachycardia that was deemed to be due to hypovolemia that resolved with discontinuation of therapy. This was felt to be an unexpected event that was possibly related to the therapy. The final reported SAE was in a subject that developed hypotension requiring initiation of norepinephrine. The local study team determined that this event was expected and possibly related to therapy. Both of these subjects were subsequently discharged alive from the hospital.

## DISCUSSION

In this study, we have shown that a medical countermeasure pathogen reduction hemadsorption column was safely deployed in response to the COVID-19 pandemic. We observed that treatment with the Seraph 100 device was associated with an improvement vasopressor-free survival and decreased mortality compared

**TABLE 3.**  
**Characteristics of the Seraph 100 Subjects in the Primary Analysis Compared With External Controls**

Characteristics	Prematching			Postmatching		
	Treatment (n = 53)	External Control (n = 337)	p	Treatment (n = 35)	External Control (n = 39)	p
Age, median (IQR)	56 (41–65)	62 (50–68)	0.051	56 (41–67)	54 (47–63)	0.626
Sex (%)						
Male	81.1	61.4	0.005	80.0	79.5	0.956
Female	18.9	38.6		20.0	20.5	
Race/ethnicity (%)						
NH White	24.3	23.4	< 0.001	42.9	25.6	0.289
NH Black	24.5	54.3		22.9	41.0	
Hispanic	13.2	10.1		14.3	10.3	
Other	17.0	12.2		20.0	23.1	
Body mass index, median (IQR) <sup>a</sup>	33.1 (28.6–40.7)	30.0 (25.9–36.2)	0.003	32.9 (28.1–38.5)	36.4 (27.6–41.6)	0.420
Modified Acute Physiology and Chronic Health Evaluation II, median (IQR)	12 (9–17)	23 (15–30)	< 0.001	14 (10–19)	13 (10–21)	0.970
Mechanical ventilation (%)	67.9	68.3	0.962	62.9	69.2	0.563

IQR = interquartile range, NH = non-Hispanic.

with contemporaneous controls. Although the difference in vasopressor-free survival was not significant after adjustment, we found that mortality improvement remained significant in various multivariable models. In an expanded post hoc analysis, we did not observe a mortality benefit with the Seraph 100-treated cohort compared with an external control cohort. Therapy was well tolerated and associated with only three SAEs over the course of 177 Seraph 100 treatments. Notably, this is in the context of a critically ill patient population and treatments that lasted for a prolonged period of time (median of 13 hr). This low rate of SAEs is consistent with the only other large series of Seraph 100 in patients with COVID 19, which reported nine adverse events over the course of 102 treatments (20). Most of these events were circuit failure, and none were considered serious. Taken together, these data suggest that this therapy was safe and well tolerated.

As the COVID-19 pandemic has evolved, several therapeutic agents have been shown to have important impacts on outcomes. Remdesivir was found to be beneficial when given early in the disease course, prior to patients requiring advanced respiratory support

(21). Tocilizumab, a monoclonal antibody that binds to the interleukin-6 receptor, is another promising therapy that has been shown to decrease mortality in hospitalized patients among those requiring advanced respiratory support (22). Glucocorticoid therapy has demonstrated mortality benefit across illness severity among critically ill patients (23, 24). The RECOVERY trial demonstrated a 17% decrease in the age-adjusted mortality rate ratio in patients treated with dexamethasone (24). The neutralizing antibodies, casirivimab, and imdevimab have been demonstrated to benefit nonhospitalized patients with mild-to-moderate COVID-19 (25) and also have a role in prophylaxis for high risk patients (26). Recently, the experimental antivirals molnupiravir and PF-07321332/ritonavir have shown promise in reducing mortality; however, these results have not yet been published. Although we did not capture Tocilizumab data, most of our patients received remdesivir (86.8% and 69.8% in the Seraph 100 group and the control group, respectively), whereas nearly all patients received glucocorticoids (100% and 88.7% in the Seraph 100 and the control group, respectively). Although we did not find clear

**TABLE 4.**  
**Characteristics of All Seraph 100 Subjects Compared With External Controls**

Characteristics	Prematching			Postmatching		
	Treatment (n = 86)	External Control (n = 450)	p	Treatment (n = 57)	External Control (n = 56)	p
Age, median (IQR)	61 (49–70)	65 (54–74)	0.001	61 (52–70)	63 (50–71.5)	0.5893
Sex (%)						
Male	75.3	57.8	0.002	67.9	80.4	0.131
Female	24.7	42.2		32.1	19.6	
Race/ethnicity (%)						
NH White	50.0	24.9	< 0.001	45.6	32.1	0.360
NH Black	26.7	52.9		31.6	44.6	
Hispanic	11.6	9.8		10.5	7.1	
Other	11.6	12.4		12.3	16.1	
Body mass index, median (IQR) <sup>a</sup>	32.9 (28.3–38.5)	28.9 (24.9–34.1)	< 0.001	32.9 (29.5–37.6)	29.8 (26.6–37.1)	0.090
Modified Acute Physiology and Chronic Health Evaluation II, median (IQR)	13.5 (9–19)	24 (16–30)	< 0.001	16 (11–19)	14 (10.5–18)	0.435
Mechanical ventilation (%)	75.6	67.3	0.131	71.9	64.3	0.383

IQR = interquartile range, NH = non-Hispanic.

evidence for efficacy, our results provide evidence that extracorporeal blood purification with the Seraph 100 can be safely used during critical illness and should be evaluated further for efficacy against novel pathogens.

Improving outcomes in critically ill patients with COVID-19 by removing virions and viral particles directly from the blood are biologically plausible. Jacobs et al (27) examined the prevalence of viral RNA in the plasma of 51 patients with COVID-19. They found that viral RNA was present in 100% of ICU patients compared with 52.6% of non-ICU inpatients and 11% of nonhospitalized outpatients. These investigators also presented convincing evidence that the viral RNA was from intact virus. They found that a level greater than 6000 copies/mL was associated with both an increase in mortality (hazard ratio, 10.7) in the full cohort and an increase in hospital stays among survivors. Although viral RNA levels significantly decreased over time among survivors, there was no significant decrease in levels among nonsurvivors. Furthermore, both SARS-CoV-2 N-protein (28) and viral RNA (29) have been postulated to be pathogen-associated molecular patterns. There is evidence to suggest that the Seraph 100 can remove both N-protein (9) and viral

RNA (10). Taken together, these results imply that artificially lowering viral levels, N-protein, and RNA using Seraph 100 might improve outcomes. These potential benefits need to be weighed against potential harms of therapy. One concern is that the device could remove beneficial medications such as remdesivir and dexamethasone. Although data are limited, the device does not appear to remove remdesivir (30). Although binding of dexamethasone has not been examined, it is a nonionic molecule and is not known to interfere with heparin therapy.

The notion that infection can be treated with an extracorporeal approach is novel as the foundation of the treatment of infection for 7 decades has been antimicrobial therapy. However, the first tenet of sepsis treatment is source control (31). In patients infected with either new pathogens or pathogens with high levels of resistance, existing antimicrobials may be ineffective. The concept of a dialysis-like therapeutic to enhance source control is rational. For example, when a drain is placed into an abscess, which removes large amounts of infected material, some purulent material remains for the immune system to clear. Similarly, the Seraph 100 is an adjunctive treatment to clear the bloodstream of



pathogens. This concept of debulking or blood stream clearance has been used to treat malaria and babesiosis when the pathogen burden is high, even against a background of effective antimicrobial treatment (32). The Seraph 100 was developed as an extracorporeal medical countermeasure that can be used as adjunctive therapy for patients infected with a multitude of pathogens (see Supplemental Table 1, <http://links.lww.com/CCX/A955>). SARS-CoV-2 requires heparin/heparan sulfate to bind to cells (33), and thus, the Seraph 100 is likely to remain highly effective for SARS-CoV-2 blood clearance regardless of the COVID-19 variant. This point is important, as COVID-19 variants have demonstrated immune escape from both vaccines and monoclonal antibodies (34). In particular, the recently identified Omicron variant of SARS-CoV-2, which has 32 mutations on the spike protein, and additional emerging variants may also achieve immune escape in a significant fraction of infected patients (35). Additionally, resistance to remdesivir and other antiviral therapies is also possible (36). In the rapidly evolving COVID-19 pandemic, a pathogen agnostic device that removes viral particles directly from the bloodstream is an attractive potential therapy.

Our study has several important limitations. This is a retrospective analysis of a limited number of subjects and not a randomized controlled trial. Since each study site had slightly different local criteria for initiating therapy with Seraph 100, we were unable to establish standardized criteria for control subjects. Each site was asked to apply their clinical practice criteria to patients treated at their institution prior to the availability of the Seraph 100 at their site to select control patients. This introduces the possibility of selection bias in the control group, which we attempted to mitigate by including an external control group post hoc. However, this comparison used a single center. Therefore, unmeasured patient or treatment characteristics could have influenced the outcome. The sample size for this comparison was also small, limiting our power to observe differences in mortality. In our analysis for mortality, the effect was large and the CIs were wide, implying insufficient power. Third, treatments with the Seraph 100 device were not standardized, and treatment times were highly variable, which could have affected outcomes. Furthermore, at some centers, treatment with the Seraph 100 necessitated initiation of KRT for logistical reasons, not necessarily for severe AKI. This did not allow us to adjust

for severe AKI in our models. Another limitation is the fact that not all centers were able to supply control patients for comparison (Supplemental Table 2, <http://links.lww.com/CCX/A955>). Unfortunately, enrollment of additional patients was not possible due to budgetary limits. Finally, although the majority of patients in both groups were treated with remdesivir and glucocorticoids, these treatments were not standardized, and data on other treatments (such as tocilizumab) were not available.

## CONCLUSIONS

In conclusion, a nonpharmacologic medical countermeasure, the Seraph 100, was safely deployed during the COVID-19 pandemic. Although this therapy was associated with increased vasopressor-free survival on univariate analysis, the difference was not significant after adjustment. Mortality was lower in the Seraph 100-treated group compared with controls, but not compared with an external cohort. Although efficacy has yet to be consistently demonstrated, these data suggest that a broad spectrum, pathogen agnostic, extracorporeal, blood purification device can be safely deployed to meet new pathogen threats as an adjunct to standard treatments while awaiting the development of directed pharmacologic countermeasures or vaccines. These findings are particularly relevant as new strains of the SARS-CoV-2 virus have decreased the effectiveness of currently approved vaccines and monoclonal antibody therapies. A prospective arm of this study has completed enrollment and will examine viral loads, the efficacy of viral clearance, and inflammatory markers. Furthermore, a multicenter, randomized controlled trial of this novel therapeutic for septic shock due to any pathogen has been initiated (ClinicalTrials.gov Identifier: NCT05011656).

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A full list of PURIFY Investigators are listed in the Supplemental File (<http://links.lww.com/CCX/A955>).

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