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ORIGINAL ARTICLE

Extracorporeal blood purification is associated with improvement in biochemical and clinical variables in the critically-ill COVID-19 patients

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Abstract

This study tried to investigate the impact of oXiris filter on both clinical and laboratory parameters in critically-ill COVID-19 intensive care unit (ICU) patients receiving extracorporeal blood purification and the clinical setting for the initiation of therapy. A consecutive sample of 15 ICU patients with COVID-19 was treated with oXiris membrane for blood purification or for support of renal function due to acute kidney injury. We have included 19 non treated ICU COVID-19 patients as a control group. Two chest x-rays were analyzed for determining the chest x-ray severity score. We have found a significant decrease of SOFA score, respiratory status improved and the chest x-ray severity score was significantly decreased after 72 h of treatment. IL-6 significantly decreased after 72 h of treatment while other inflammatory markers did not. Respiratory status in the control group worsened as well as increase in SOFA score and chest x-ray severity score. Survived patients have shorter time from the onset of symptoms before starting with extracorporeal blood purification treatment and shorter time on vasoactive therapy and invasive respiratory support than deceased patients. Critically-ill patients with COVID-19 treated with extracorporeal blood purification survived significantly longer than other ICU COVID-19 patients. Treatment with oXiris membrane provides significant reduction of IL-6, leads to improvement in respiratory status, chest x-ray severity score, and reduction of SOFA score severity. Our results can suggest that ICU COVID-19 patients in an early course of a disease could be potentially a target group for earlier initiation of extracorporeal blood purification.

KEYWORDS

COVID-19, extracorporeal blood purification, IL-6, SOFA score, survival

1 | INTRODUCTION

Although most patients with COVID-19 have mild symptoms the progression of the disease can lead to development of severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure (MOF) and death [1–3]. Many of these hospitalized patients develop ARDS but only 4.5% develop acute kidney injury [4]. Comorbidities like obesity, hypertension or diabetes and older age are prognostic parameters for poor outcome. One of the leading causes for the development of ARDS or MOF is cytokine storm and one of its mediators IL-6 [4] which has been associated with increased mortality in this group of patients [5, 6]. The role of cytokine storm in damaging many organs like lungs and kidneys suggests that organ support therapy is not sufficient and cytokine removal with extracorporeal blood purification therapies (EBP) has emerged as one of effective treatments for COVID-19 intensive care unit (ICU) patients [7, 8]. There are many laboratory and clinical parameters that we should consider when assessing the severeness and prognosis of COVID-19 patients. One of the most cost-effective tools for providing a relevant stratification of respiratory status and disease extent is a chest x-ray severity score [9–12]. In patients with acute kidney injury (AKI), a sequential EBP and the removal of pro-inflammatory cytokines were proposed [7]. The previous studies on COVID-19 patients showed that reducing IL-6 levels with EBP significantly improved their clinical response through cytokine removal and organ support [8, 13–17]. Many studies on EBP effectiveness in COVID-19 patients and preliminary results showed that timely initiation is of profound importance. However, still, there is no firm evidence on a larger scale of patients [2, 16–18]. Adsorbing filters that were previously used to support renal function have an emerging role in treating severe-ill ICU patients. The oXiris membrane (Baxter, IL) is a heparin-coated hemodiafilter by which can extensive production of cytokines and endotoxins be reduced [19, 20]. This study tried to investigate the impact of oXiris on both clinical and laboratory parameters in critically-ill COVID-19 ICU patients receiving EBP and the clinical setting in which the initiation of therapy impacts clinical improvement and survival.

2 | MATERIALS AND METHODS

A consecutive sample of 15 ICU patients with COVID-19 (10 men, 5 women; average age 60.8) treated with EBP with the oXiris membrane between December 2020 and March 2021 was enrolled in this prospective, single-center, observational study. Treatment with oXiris membrane was performed in COVID-19 patients for blood purification or for support of renal function due to AKI. SARS-CoV-2 infection was diagnosed with a positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) at nasal/oral swab. KDIGO criteria were used for the diagnosis of AKI. The main aim of this study was to analyze changes in laboratory and clinical parameters related to disease severity and analyze mortality rates regarding the EBP treatment with oXiris membrane. The protocol, which was not different from the standard practice implemented by clinicians, was approved by the hospital ethics committee (UHC Zagreb, Croatia) following the Helsinki Declaration, and its later amendments and data were handled in agreement with patient informed consent. Indications for EBP treatment with oXiris membrane was based on meeting the inclusion criteria which were the approved local institutional guidelines: laboratory and clinical evidence of systemic inflammation (high levels of inflammatory cytokines such as IL-6 > 25 pg/mL; high values of inflammatory parameters from serum–leukocytes $>15 \times 10^9$/l, CRP > 40 mg/L, procalcitonin >0.9 mg/L and a high SOFA score > 2) with the addition of AKI which was an indication for continuous renal replacement therapy (CRRT); hemodynamic instability with the addition of vasoactive support; MOF with preserved renal function but with fluid overload or deterioration of respiratory status (the increase of respiratory rate [>30/min], a decrease of oxygen saturation [<93%], or PaO_2/FiO_2 ratio ≤ 300 mm Hg) and by the decision of the competent physician that EBP is required. The membranes were used on the PrismaFlex systems (Baxter, IL). All CRRT procedures were continuous veno-venous hemodiafiltration. The mean blood flow rate was between 200 and 250 mL/min, depending on blood-access function and desired ultrafiltration rates. The hemofilter and the extracorporeal circuit were replaced every 24 h. Evaluations of patients treated with EBP were performed every 24 h of treatment. The prescription of ultrafiltration rates depended on cardiac status, fluid overload and hourly urine output. We aimed at the dose of dialysis >35 mL/kg/h and the rates of reinfusion and dialysate were prescribed accordingly. The premature clotting was present in four patients, but the system and the filter were immediately changed, so no treatments were stopped before 72 h. In three patients, we performed an EBP treatment without antioagulation but were on systemic anticoagulation with heparin. We have included 19 ICU COVID-19 patients as a control group who met the inclusion criteria but the competent physicians did not initiate EBP in order to analyze differences in laboratory and clinical parameters regarding EBP. Median time before meeting the inclusion criteria and start of EBP 3.2 days after ICU admission while the median time before meeting the inclusion criteria for the control group was 1.9 days. All the patients were

treated with antimicrobials and corticosteroids while 26 (76%) of patients were treated with remdesivir. Patients with moderate to severe ARDS were placed in the prone position for at least 12 h a day. The data for all clinical parameters, main anthropometric parameters and comorbidities were extracted from ICU charts. The severity of organ dysfunction was assessed by APACHE IV and SOFA score [21]. Complete clinical and laboratory examination for each patient was performed at the time of admission and further on daily basis during hospital stay. Follow-up lasted until the last enrolled patient reached the 60-day time point or death from sepsis, MOF or cardiovascular event. In all patients following laboratory data were collected: complete blood count, international normalized ratio, serum sodium and potassium, plasma creatinine, BUN, C-reactive protein, ferritin, cystatin C, procalcitonin, bilirubin, lactate dehydrogenase (LDH), d-dimers, and IL-6 were analyzed from blood samples at the start and the end of 72 h of EBP treatment. For the control group of patients who were not treated with EBP the same laboratory parameters were collected after meeting the inclusion criteria and after 72 h. The estimated glomerular filtration rate (eGFR) was calculated daily using the simplified Modification of Diet in Renal Disease (MDRD) equation. IL-6 was determined using the automated chemiluminescence immunoassay on the Immulite 2000 XPI analyzer (Siemens Healthcare, Marburg, Germany). The reference interval is up to 4.4 pg/mL, as defined by the manufacturer. Bedside chest x-rays were performed in one center using one of two systems (Mobile DaRt Evolution, Shimadzu, Kyoto, Japan; Mobilett XP, Siemens Healthineers, Erlangen, Germany). Two chest x-rays were analyzed for every patient at the start and at the end of 72 h of EBP treatment and for the control group not treated with EBP after meeting the inclusion criteria and after 72 h. Images were anonymized and reviewed independently by neuroradiologist DG and cardiothoracic imaging expert MHP from one center, with 11 and 17 years of experience in imaging, respectively. The reviewers used the semiquantitative method for determining the chest x-ray severity score described in Monaco et al. [12]. Atelectasis, lousy exposure, or incomplete image were not scored for the affected zone in both sets of chest x-rays for both reviewers.

Statistical analysis was performed using SPSS version 23.0 (IBM Corp.). Normality of data distribution was tested using the Kolmogorov–Smirnov test. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. Categorical data were expressed as numbers and frequencies. Correlations were obtained using Pearson's test for normally distributed variables and Spearman rank correlation for non-normally distributed variables. Normally distributed variables were presented as means ± standard deviations and Student's *t* test for independent samples was used for comparisons between two groups. Non-normally distributed data were presented as median and interquartile range and Mann–Whitney *U*-test was used in the comparison between the two groups. Categorical variables were compared using χ2-test. Boxplots were drawn to describe IL-6, SOFA score, and chest x-ray severity score variations with good inter-observance agreement. Survival analysis was done with Kaplan–Meier curves tested with log-rank test while hazard ratios were estimated with Cox proportional hazards regression. Multiple linear regression was used to explore the influence of different variables on survival, while logistic regression was used for categorical dependent variables. A p value $<.05$ (two-sided tests) was considered significant.

3 | RESULTS

In the study, we have enrolled 15 patients with a confirmed diagnosis of COVID-19 which were treated with extracorporeal blood purification (EBP) and a control group of 19 patients with a confirmed diagnosis of COVID-19 were treated with standard protocols in ICU. All the patients were admitted to ICU for respiratory support. Seven (46.7%) of patients treated with EBP also required renal support with CRRT and one (6.6%) required cardiovascular and renal support with extracorporeal membrane oxygenation and CRRT. Median time before start of EBP from onset of symptoms was 16.8 days and from ICU admission 3.2 days. Patients were treated with EBP for 72 h. Demographic parameters, comorbidities, clinical variables, and laboratory parameters at the time of EBP initiation and after EBP treatment are demonstrated in Table 1. In seven (46.7%) of patients, the cause for EBP initiation with CRRT was AKI. In one (6.6%) the reason was cardiovascular support, while in seven (46.7%) of patients renal indications were absent. Indications for CRRT were fluid overload or anuria in 85.7% of patients and adjustment of electrolytic balance in 14.3% of patients. Seven (46.6%) patients were on vasoactive therapy due to hemodynamic instability while 11 (73.3%) patients were on invasive mechanical ventilation at the time of EBP initiation. The other four (26.7%) patients were on noninvasive respiratory support with high-flow nasal cannula but were on CRRT due to AKI. CRRT modality in all cases was continuous veno-venous hemodiafiltration. We have not found specific complications regarding the treatment like severe bleeding, thromboembolism, or electrolyte disorders. Unfortunately, changing the patient in a prone position during the EBP treatment was not often possible due to invasive respiratory support features and the increase in venous pressures on the dialysis device. Prematurely clotting was present in

TABLE 1 Demographic parameters, comorbidities, and differences between clinical variables and laboratory parameters at the time of EBP initiation and after EBP treatment

Age (years)			60.8 ± 3.8
Sex (males) *N* (%)			10 (66.6)
BMI			29.3 ± 2.3
Days of symptoms before start of EBP			16.8 ± 2.6
Comorbidities *N* (%)			
Chronic kidney disease			3 (20.0)
Diabetes			6 (40.0)
Hypertension			9 (60.0)
Hematological disease			3 (20.0)
Prior cardiovascular event			6 (40.0)
Obesity			7 (46.6)
Pulmonary embolism			4 (26.6)
Chronic obstructive lung disease			2 (13.3)
	Clinical data at EBP initiation	**Clinical data after 72 h of EBP**	***p***
Heart rate (cp/min)	89.4 ± 11.9	86.2 ± 11.2	0.87
Systolic blood pressure (mm Hg)	131 ± 12.2	125 ± 12.0	0.73
Diastolic blood pressure (mm Hg)	77.3 ± 10.1	75.1 ± 9.4	0.82
Mean arterial pressure (mm Hg)	82.0 ± 10.8	83.0 ± 10.9	0.91
SOFA score	12.6 ± 2.2	7.3 ± 1.4	0.03
APACHE IV	113 ± 17.3	69 ± 11.1	0.04
Vasoactive therapy Yes (*N* (%))	8 (53.3)	7 (46.6)	0.89
Adrenaline	2 (25.0)	1 (14.3)	0.66
Noradrenaline	6 (75.0)	6 (85.7)	0.53
Vasoactive inotropic score	11 (4–18)	10 (4–16)	0.83
Urinary output (mL/h)	35 (28–45)	50 (34–65)	0.23
X-ray severity score	13.3 ± 2.2	8.3 ± 1.1	0.04
Tidal volume (mL)	447 (412–484)	358 (292–421)	<0.01
Respiratory rate (breaths/min)	22.8 ± 2.5	17.1 ± 1.6	<0.01
PEEP (cm H_2O)	12 (9–15)	10 (7–14)	0.33
Mean airway pressure (cm H_2O)	31 (23–40)	29 (21–37)	0.45
Plateau pressure (cm H_2O)	25 (20–29)	23 (18–26)	0.39
FiO_2 (%)	80.6 ± 10.4	65.6 ± 10.4	0.04
PaO_2 (kPa)	7.7 ± 1.0	8.6 ± 1.9	0.04
$PaCO_2$ (kPa)	5.7 ± 0.9	4.9 ± 0.5	0.04
FiO_2/PaO_2	105 (98–113)	76 (45–102)	<0.01
SaO_2 (%)	91 (87–95)	93 (85–97)	0.10
	Laboratory data at EBP initiation	**Laboratory data after 72 h of EBP**	***p***
Sodium (mmol/L)	137.5 ± 4.7	136.6 ± 4.2	0.88
Potassium (mmol/L)	4.3 ± 0.6	4.2 ± 0.5	0.81
White blood count ($\times 10^9$/L)	10.3 ± 1.8	9.8 ± 1.1	0.58
Hematocrit (%)	34.6 ± 2.9	34.1 ± 2.2	0.89
Lymphocytes (%)	6.6 ± 1.2	10.8 ± 2.9	0.05
Creatinine (μmol/L)	193.6 ± 6.9	131.4 ± 4.9	<0.01

TABLE 1 (Continued)

	Laboratory data at EBP initiation	Laboratory data after 72 h of EBP	*p*
GFR (mL/min/1.73 m^2)	32 (18–48)	50 (42–58)	<0.01
BUN (μmol/L)	14.1 ± 2.7	9.1 ± 2.1	0.13
Bilirubin (μmol/L)	16 (9–24)	16 (9–24)	0.94
LDH (U/L)	302.7 ± 22.2	184.5 ± 13.4	<0.001
Platelets ($\times 10^9$/L)	187.6 ± 7.8	155 ± 6.2	0.27
INR	1.2 (1.0–1.4)	1.0 (0.8–1.2)	0.58
D-dimers (mg/L)	7.6 ± 1.3	3.0 ± 0.5	0.11
Procalcitonin (mg/L)	4.7 ± 0.7	0.8 ± 0.1	0.15
C-reactive protein (mg/L)	84.4 ± 4.6	50.4 ± 3.9	0.06
Ferritin (μg/L)	3673 (3102–4198)	811 (497–1107)	0.10
Cystatine C (mg/L)	3.2 ± 0.5	1.3 ± 0.2	<0.001
Interleukin-6 (pg/mL)	113.4 ± 4.4	12.7 ± 2.5	<0.01

Note: Results are shown as mean ± SD or median (interquartile range).
Abbreviations: BMI, body mass index; EBP, extracorporeal blood purification; GFR, estimated glomerular filtration rate; INR, international normalized ratio; PEEP, positive end-expiratory pressure.

only 7% of all procedures although we have not used regional citrate anticoagulation and the fact that COVID-19 patients have a tendency of hypercoagulability. One of the possible reasons is the heparin-coated oXiris membrane which might prevent local clotting activation and the reduction of d-dimers after EBP treatment.

3.1 | Clinical variables over time variation in patients treated with EBP

We have not found improvement in termination of vasoactive therapy after EBP treatment while we have found a significant decrease of SOFA score after 72 h of EBP due to improvement of hourly urine output, serum creatinine and FiO_2/PaO_2 ($p = .03$) (Figure 1). Furthermore, respiratory status improved, a significant decrease in number of respiratory rate, FiO_2 and FiO_2/PaO_2 and an increase in PaO_2 after EBP treatment ($p < .01$; $p = .04$; $p = .04$; $p < .01$). The chest x-ray severity score determined by the semiquantitative method was significantly decreased after 72 h of EBP ($p = 0.04$) (Figure 2) and correlated with the severity of SOFA score at baseline ($p = 0.04$).

3.2 | Laboratory parameters over time variation in patients treated with EBP

IL-6 significantly decreased after 72 h of EBP ($p < 0.01$) (Figure 3) as well as cystatine C and LDH ($p < 0.001$; $p < 0.001$) while other inflammatory markers like ferritin, procalcitonin and c-reactive protein did not. Baseline values of IL-6, cystatine C, LDH and ferritin correlated with the baseline SOFA score (all $p < 0.05$), baseline values of IL-6 correlated with PaO_2/FiO_2 ratio ($p = 0.02$) while baseline values of lymphocytes correlated with higher x-ray severity score ($p = 0.03$).

3.3 | Differences in clinical variables and laboratory parameters between survived and deceased patients treated with EBP

We have not found the difference in age, sex and comorbidities between survived and deceased patients treated with EBP while the duration of symptoms before starting of EBP was longer in a deceased group of patients, although not statistically significant (Table 2). All the deceased patients were on vasoactive therapy but had higher baseline GFR levels. Deceased patients had significantly higher baseline SOFA score while there were no differences in levels of IL-6, cystatine C, ferritin, procalcitonin and c-reactive protein between groups. Deceased patients had significantly higher levels of LDH and x-ray severity score (all $p < 0.05$). There was no difference in a number of patients treated with CRRT between these two groups of patients.

3.4 | Differences in clinical variables and laboratory parameters between patients treated and not treated with EBP

There were no differences in age, sex, comorbidities, and the duration of symptoms before ICU admission between

patients treated and not treated with EBP (Table 3). We have not found differences in the number of patients on vasoactive therapy, baseline SOFA score, and the number of patients treated with CRRT between these two groups of patients. Baseline levels of IL-6, LDH, ferritin, procalcitonin and c-reactive protein were not different between groups while cystatine C was significantly higher in group of patients treated with EBP. X-ray severity score was significantly higher in EBP group as well as the number of respiratory rate, FiO_2 and FiO_2/PaO_2, while PaO_2 was significantly lower in EBP group. Respiratory status in non-EBP group worsened after 3 days from inclusion, a significant increase in number of respiratory rate, FiO_2 and FiO_2/PaO_2, and a decrease in PaO_2 and was observed (all $p < 0.05$) as well as increase in SOFA score and in the number of patients on vasoactive therapy. The chest x-ray severity score significantly increased after 3 days in the ICU in non-EBP group ($p < 0.01$) as well as a decrease in hourly diuresis and eGFR levels (all $p < 0.01$). We have not found a decrease in any of the observed inflammatory markers in non-EBP group during the 3 days after inclusion except values of IL-6 which even increased over time. Although we have not found differences in causes of death between EBP and non-EBP patients, EBP patients survived significantly longer.

3.5 | Survival of patients treated with EBP

When we cave calculated the expected mortality rate based on APACHE IV score (113 ± 17.3) it was 61.3% while the ICU mortality in our patients treated with EBP was 53.3% and the ICU mortality rate of patients not treated with EBP was 78.9%. We have not found differences between survived and deceased EBP patients in time from the onset of symptoms before ICU admission but survived EBP patients have shorter time from the onset of symptoms before starting with EBP treatment and shorter time on vasoactive therapy and invasive respiratory support than deceased patients. We have taken a cut-off of 14 days from the onset of symptoms before starting with EBP treatment and divided patients on early and delayed treatment. This cut-off was taken based on results from previous studies [2, 5, 16, 18]. The mortality rate for patients receiving early treatment was 33.3%, while those receiving delayed treatment were 66.6%.

3.6 | Variables associated with survival of ICU patients

In the whole group of EBP and non-EBP patients the linear regression analysis survival was independently negatively associated with vasoactive support ($\beta = -0.566$, $p = 0.002$), cystatine C ($\beta = -0.462$, $p = 0.019$) and IL-6 levels ($\beta = -0.324$, $p = 0.046$) while positively with EBP ($\beta = 0.255$, $p = 0.004$) (Table 4). The presence of vasoactive support and conservative treatment without EBP was associated with higher mortality in the whole group (HR 0.095 [0.015, 0.607] and HR 4.36 [1.28, 14.82], respectively). At the end of the follow-up period of 60 days in the whole group of patients 23 (67.6%) deaths occurred, in the EBP group 8 (53.3%) patients and in the non-EBP group 15 (78.9%) patients died.

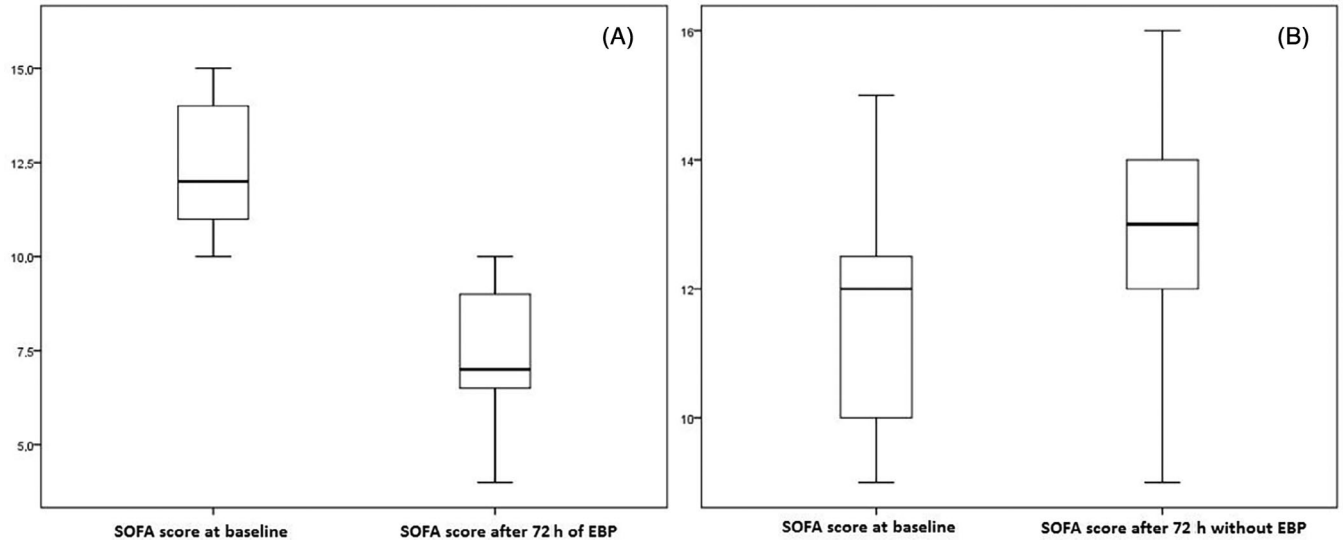

FIGURE 1 SOFA score variations at baseline and after 72 h of EBP (a) and at baseline and after 72 h without EBP (b). EBP, extracorporeal blood purification

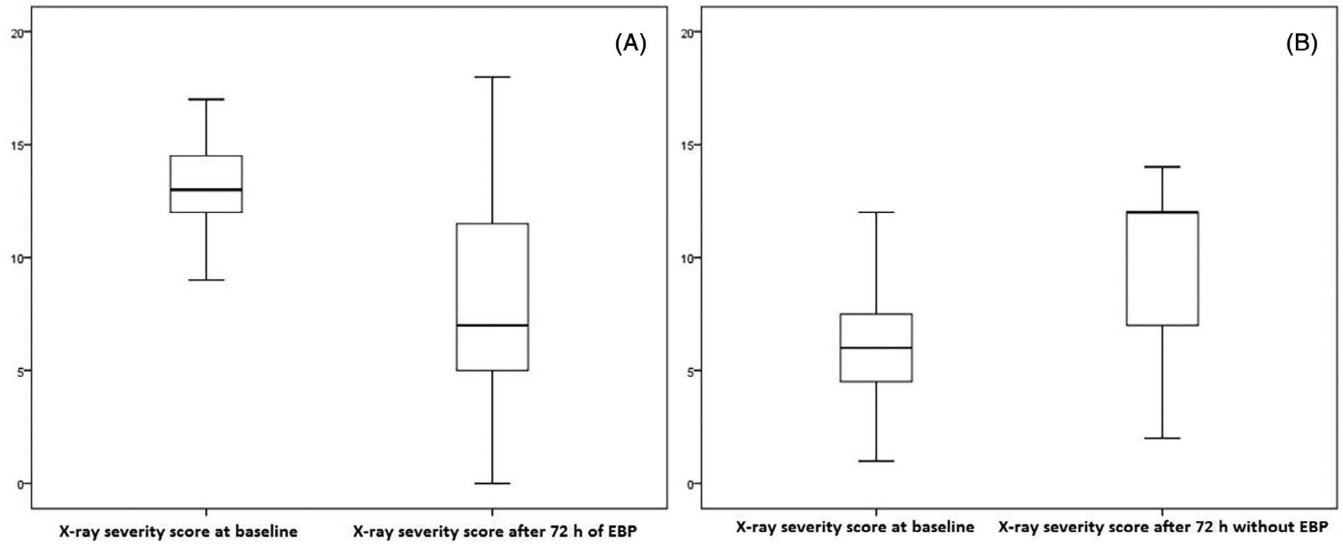

FIGURE 2 X-ray severity score variations at baseline and after 72 h of EBP (a) and at baseline and after 72 h without EBP (b). EBP, extracorporeal blood purification

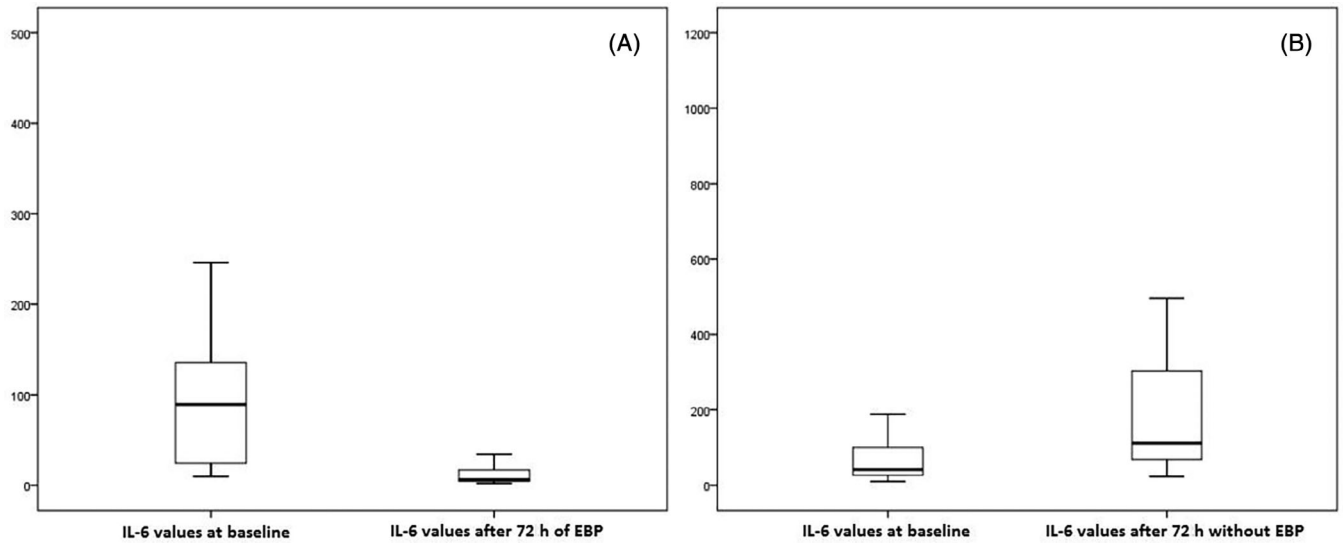

FIGURE 3 IL-6 variations at baseline and after 72 h of EBP (a) and at baseline and after 72 h without EBP (b). EBP, extracorporeal blood purification

Mean survival time was longer in EBP than non-EBP patients (36.5 (95% CI 25.1, 47.9) vs. 20.6 (95% CI 10.5, 30.6) months; $p = 0.03$).

4 | DISCUSSION

The main finding of this study is that ICU patients with COVID-19 treated with EBP had significantly longer survival than other ICU COVID-19 patients. Treatment with EBP leads to improvement in respiratory status as well as reduction of SOFA score severity. Our results on significant reduction of inflammatory markers like IL-6 after a EBP treatment of 72 h and its correlation with prolonged survival are confirming the hypothesis on cytokine storm impact on survival of ICU patients with COVID-19 which is even more emphasized with the IL-6 increase over 72-h period in patients not treated with EBP. Although reduction of cytokines with EBP in ICU COVID-19 patients and its association with prolonged survival was already reported [7, 13, 14, 16, 22] the data on when to start treating patients with EBP are still confusing [2, 16, 18, 22]. Based on our results, earlier initiation of EBP is more beneficial for these patients. A major limitation of this study is the small sample size while its observational nature and lack of randomization of patients have

TABLE 2 Demographic parameters, comorbidities, baseline clinical variables and laboratory parameters between survived and deceased patients treated with EBP

	EBP survived ($N = 7$)	EBP deceased ($N = 8$)	p
Age (years)	54.5 ± 5.6	66.3 ± 4.7	0.13
Sex (males) *N* (%)	4 (57.1)	6 (75.0)	0.46
BMI	28.5 ± 2.1	29.9 ± 2.8	0.53
Days of symptoms before start of EBP	12.1 ± 1.7	21.0 ± 3.2	0.09
Comorbidities *N* (%)			
Chronic kidney disease	1 (14.2)	2 (25.0)	0.60
Diabetes	2 (28.5)	4 (50.0)	0.39
Hypertension	4 (57.1)	5 (62.5)	0.83
Hematological disease	1 (14.2)	2 (24.0)	0.60
Prior cardiovascular event	2 (28.5)	4 (50.0)	0.39
Obesity	3 (42.8)	4 (50.0)	0.78
Pulmonary embolism	2 (28.5)	2 (25.0)	0.87
Chronic obstructive lung disease	1 (14.2)	1 (12.5)	0.92
Clinical data			
Heart rate (cp/min)	88.4 ± 10.3	85.1 ± 10.3	0.71
Systolic blood pressure (mm Hg)	132 ± 12.6	139 ± 12.7	0.69
Diastolic blood pressure (mm Hg)	76.9 ± 10.2	75.1 ± 9.4	0.82
Mean arterial pressure (mm Hg)	81.4 ± 10.3	82.7 ± 10.9	0.93
SOFA score	11.1 ± 1.4	14.3 ± 3.2	0.04
APACHE IV	98 ± 12.8	127 ± 16.2	0.03
Vasoactive therapy Yes (*N* (%))	0 (0)	7 (87.5)	<0.001
Adrenaline	0 (0)	1 (14.2)	<0.001
Noradrenaline	0 (0)	6 (85.8)	<0.001
Vasoactive inotropic score	11 (4–18)	12 (6–19)	0.71
Urinary output (mL/h)	32 (27–38)	39 (35–44)	0.17
CRRT (*N* (%))	3 (42.8)	4 (50.0)	0.83
X-ray severity score	11.7 ± 1.9	14.6 ± 2.3	<0.01
Tidal volume (mL)	412 (345–478)	448 (372–518)	0.38
Respiratory rate (breaths/min)	22.8 ± 2.5	17.1 ± 1.6	<0.01
PEEP (cm H_2O)	11 (9–14)	12 (7–15)	0.47
Mean airway pressure (cm H_2O)	30 (22–40)	32 (23–41)	0.53
Plateau pressure (cm H_2O)	24 (21–30)	26 (22–32)	0.47
FiO_2 (%)	73.4 ± 9.2	81.3 ± 10.8	0.22
PaO_2 (kPa)	7.9 ± 1.2	8.4 ± 1.8	0.13
$PaCO_2$ (kPa)	6.2 ± 1.3	6.9 ± 1.6	0.35
FiO_2/PaO_2	133 (104–161)	161 (119–205)	0.48
SaO_2 (%)	92 (87–96)	90 (83–94)	0.30
Laboratory data			
Sodium (mmol/L)	137.1 ± 4.7	136.9 ± 4.2	0.89
Potassium (mmol/L)	4.3 ± 0.6	4.2 ± 0.4	0.79
White blood count ($\times 10^9$/L)	10.1 ± 1.7	10.8 ± 1.9	0.62
Hematocrit (%)	34.1 ± 2.5	35.0 ± 2.9	0.87

TABLE 2 (Continued)

	EBP survived ($N = 7$)	EBP deceased ($N = 8$)	p
Lymphocytes (%)	8.4 ± 1.9	5.0 ± 1.2	0.22
Creatinine (μmol/L)	235.3 ± 8.2	123.1 ± 4.2	<0.001
GFR (mL/min/1.73m^2)	21 (12–31)	57 (44–70)	<0.01
BUN (μmol/L)	24.4 ± 4.2	11.1 ± 2.8	0.02
Bilirubin (μmol/L)	16 (10–24)	25 (14–35)	0.52
LDH (U/L)	249.4 ± 20.1	349.4 ± 21.8	0.02
Platelets ($\times 10^9$/L)	182.2 ± 7.1	174 ± 6.8	0.68
INR	1.2 (1.0–1.5)	1.2 (0.9–1.4)	0.73
D-dimers (mg/L)	5.8 ± 1.2	9.1 ± 1.8	0.61
Procalcitonin (mg/L)	3.2 ± 0.5	6.0 ± 0.8	0.60
C-reactive protein (mg/L)	86.3 ± 4.6	82.6 ± 4.5	0.93
Ferritin (μg/L)	2504 (2131–2894)	4695 (4022–5307)	0.54
Cystatine C (mg/L)	2.3 ± 0.6	4.0 ± 1.0	0.07
Interleukin-6 (pg/mL)	69.1 ± 3.4	152.1 ± 4.1	0.19

Note: Results are shown as mean ± SD or median (interquartile range).

Abbreviations: BMI, body mass index; CRRT, continuous renal replacement therapy; EBP, extracorporeal blood purification; GFR, estimated glomerular filtration rate; PEEP, positive end-expiratory pressure.

limited us in providing definitive conclusions and associations of EBP therapy with improvement of laboratory and clinical parameters as well as survival. However, this study showed for the first time that EBP treatment leads to significant regression of x-ray severity score (Figure 4) and reduction of cystatine C levels as additional clinical indicators of the effectiveness of therapy. Furthermore, this is the first prospective study which showed differences in both clinical and laboratory parameters in critically-ill COVID-19 ICU patients depending of EBP treatment in favor of patients treated with EBP although they had at inclusion more severe respiratory failure than the control group.

The oXiris membrane (Baxter, IL) is an AN69 membrane, a highly biocompatible heparin-coated hemodiafilter [23], used not only in supporting renal function but also for unselective removal of cytokines and endotoxin. It has been primarily used in septic patients with AKI for cytokine reduction with a mean treatment duration of 72 h and promising results on reducing SOFA score [19, 20]. The application of extracorporeal therapies in patients with COVID-19 and high inflammatory response has started from the early stages of pandemic. However, the preliminary results on its efficiency are still not confirmed on a larger number of patients. Nevertheless, some authors suggested that EBP could be an effective treatment for cytokine removal in this group of patients [14, 17, 24]. Villa et al. [16] reported significant IL-6 reduction, multiorgan dysfunction improvement, and reduction in expected ICU mortality rate after an EBP with oXiris membrane, which is in line with our study results. Levels of IL-6 and other markers of disease severity like LDH and cystatine C significantly decreased after 72 h of EBP and with similar effect on SOFA score improvement. Although the statistical significance was present for only these markers, all other markers of disease severity were decreased after EBP. In contrast, levels of lymphocytes as an independent predictor of disease severity were increased. Clinical features of pulmonary function were significantly improved after the procedure. It has been previously reported that serum concentrations of IL-6 are associated with higher SOFA score, MOF and increased mortality in COVID-19 patients [5, 8, 13–15]. Our study confirmed previous findings and showed that reduction of IL-6 levels with EBP significantly improves clinical response in ICU COVID-19 patients mainly by improving oxygenation and respiratory status. Although other pro-inflammatory markers like LDH and ferritin were correlated with SOFA score severity only cystatine C had a predictive value for risk of mortality, which is similar to results from Li et al. [25], and was significantly reduced after EBP treatment. On the contrary, in our control group of patients which were not treated with EBP IL-6 levels as well as other pro-inflammatory markers increased after a 72-h period. Furthermore, these patients had a more severe SOFA score than baseline values, higher number of patients on vasoactive therapy, a decrease in hourly diuresis and eGFR

TABLE 3 Differences in demographic parameters, comorbidities, baseline clinical variables and laboratory parameters between EBP treated and not treated patients

	EBP ($N = 15$)	Non-EBP ($N = 19$)	p
Age (years)	60.8 ± 3.8	67.0 ± 3.2	0.22
Sex (males) *N* (%)	10 (66.6)	9 (47.4)	0.26
BMI	29.3 ± 2.3	30.2 ± 2.9	0.69
Days of symptoms before ICU admission	13.6 ± 2.2	13.7 ± 2.2	0.89
Comorbidities *N* (%)			
Chronic kidney disease	3 (20.0)	1 (5.3)	0.18
Diabetes	6 (40.0)	6 (31.6)	0.61
Hypertension	9 (60.0)	12 (62.5)	0.85
Hematological disease	3 (20.0)	4 (63.1)	0.93
Prior cardiovascular event	6 (40.0)	8 (42.1)	0.90
Obesity	7 (46.6)	9 (47.4)	0.96
Pulmonary embolism	4 (26.6)	4 (21.0)	0.70
Chronic obstructive lung disease	2 (13.3)	3 (15.8)	0.84
Clinical data			
Heart rate (cp/min)	89.4 ± 11.9	86.6 ± 11.2	0.85
Systolic blood pressure (mm Hg)	131 ± 12.2	132 ± 12.1	0.87
Diastolic blood pressure (mm Hg)	77.3 ± 10.1	74.1 ± 8.2	0.71
Mean arterial pressure (mm Hg)	82.0 ± 10.8	82.8 ± 10.8	0.90
SOFA score	12.6 ± 2.2	13.1 ± 2.6	0.79
APACHE IV	113 ± 17.3	121 ± 18.9	0.58
Vasoactive therapy Yes (*N* (%))	8 (53.3)	14 (73.7)	0.21
Adrenaline	2 (25.0)	2 (14.3)	0.53
Noradrenaline	6 (75.0)	12 (85.7)	0.21
Vasoactive inotropic score	11 (4–18)	13 (5–19)	0.81
Steroid therapy Yes (*N* (%))	15 (100)	19 (100)	0.99
Antiviral therapy Yes (*N* (%))	12 (80.0)	14 (73.7)	0.66
Urinary output (mL/h)	32 (27–38)	26 (22–32)	0.19
CRRT (*N* (%))	7 (46.6)	7 (36.8)	0.33
X-ray severity score	13.3 ± 2.2	6.6 ± 1.9	<0.001
Tidal volume (mL)	447 (412–484)	399 (302–453)	0.04
Respiratory rate (breaths/min)	22.8 ± 2.5	16.2 ± 1.5	<0.01
PEEP (cm H_2O)	12 (9–15)	10 (7–14)	0.33
Mean airway pressure (cm H_2O)	31 (23–40)	28 (21–38)	0.60
Plateau pressure (cm H_2O)	25 (20–29)	22 (17–26)	0.32
FiO_2 (%)	80.6 ± 10.4	62.3 ± 10.5	0.04
PaO_2 (kPa)	7.7 ± 1.0	8.3 ± 1.9	0.04
$PaCO_2$ (kPa)	5.7 ± 0.9	4.8 ± 0.5	0.04
FiO_2/PaO_2	105 (98–113)	70 (40–103)	<0.01
SaO_2 (%)	91 (87–95)	92 (85–96)	0.23
Laboratory data			
Sodium (mmol/L)	137.5 ± 4.7	137.1 ± 4.6	0.95
Potassium (mmol/L)	4.3 ± 0.6	4.3 ± 0.5	0.97
White blood count ($\times 10^9$/L)	10.3 ± 1.8	10.9 ± 2.2	0.76

TABLE 3 (Continued)

	EBP ($N = 15$)	Non-EBP ($N = 19$)	p
Hematocrit (%)	34.6 ± 2.9	35.2 ± 3.2	0.90
Lymphocytes (%)	6.6 ± 1.9	8.5 ± 3.1	0.33
Creatinine (μmol/L)	193.6 ± 6.9	199.4 ± 7.1	0.88
GFR (mL/min/1.73m^2)	32 (18–48)	31 (17–46)	0.92
BUN (μmol/L)	14.1 ± 2.7	13.9 ± 2.8	0.87
Bilirubin (μmol/L)	16 (9–24)	18 (10–27)	0.91
LDH (U/L)	302.7 ± 22.2	342.3 ± 23.9	0.47
Platelets ($\times 10^9$/L)	187.6 ± 7.8	193 ± 7.9	0.84
INR	1.2 (1.0–1.4)	1.1 (0.9–1.3)	0.69
D-dimers (mg/L)	7.6 ± 1.3	6.9 ± 1.2	0.77
Procalcitonin (mg/L)	4.7 ± 0.7	6.1 ± 0.8	0.59
C-reactive protein (mg/L)	84.4 ± 4.6	111.5 ± 5.0	0.32
Ferritin (μg/L)	3673 (3102–4198)	4612 (4122–5231)	0.63
Cystatine C (mg/L)	3.2 ± 0.5	2.0 ± 0.3	0.03
Interleukin-6 (pg/mL)	113.4 ± 4.4	78.3 ± 3.9	0.37
Deceased N (%)	8 (53.3)	15 (78.9)	0.11
Cause of death			
MOF	3 (37.5)	7 (46.6)	0.67
Sepsis	2 (25.0)	3 (20.0)	0.78
Cardiovascular event	3 (37.5)	5 (33.3)	0.84
Survival days	36.5 ± 3.4	20.4 ± 2.8	0.05

Note: Results are shown as mean ± SD or median (interquartile range).
Abbreviations: BMI, body mass index; CRRT, continuous renal replacement therapy; EBP, extracorporeal blood purification; GFR, estimated glomerular filtration rate; MOF, multiorgan failure; PEEP, positive end-expiratory pressure.

TABLE 4 Linear regression analysis

	Unstandardized coefficients		Standardized coefficients		
	B	**SE**	**β**	***t***	**Significance**
(Constant)	26 143	17 727		1475	0.152
Age	−0.057	0.203	−0.034	−0.280	0.782
EBP	12 241	5695	0.255	2149	0.041
Invasive respiratory support	9484	7090	0.194	1338	0.192
Vasoactive support Yes	−28 193	8150	−0.566	−3459	0.002
Days of diagnosis	−0.300	0.340	−0.112	−0.883	0.385
Diabetes Yes	4303	6199	0.085	0.694	0.494
Lymphocytes	0.604	0.340	0.290	1777	0.088
C-reactive protein	0.042	0.046	0.158	0.902	0.376
Ferritin	0.000	0.000	−0.129	−0.735	0.469
Procalcitonin	0.347	0.451	0.147	0.769	0.449
Cystatin C	−6518	2603	−0.462	−2504	0.019
IL6	−0.082	0.039	−0.324	−2100	0.046

Abbreviation: EBP, extracorporeal blood purification.

levels and a higher mortality rate than EBP treated patients. Although pro-inflammatory cytokines and SOFA score are associated with COVID-19 severity a more comprehensive assessment of respiratory status for ICU patients on invasive respiratory support is required. It has been recently reported that chest x-ray is a relevant addition in stratification of patients and determining on different therapy approaches [9–11]. Some authors proposed an x-ray severity score which allowed stratification of disease extension beyond other laboratory and clinical parameters but these results showed weak correlations with clinical parameters [12]. Our results on the contrary showed that chest x-ray severity score at baseline was correlated with the severity of baseline SOFA score. This score was one of the parameters by which we started with EBP in some of the patients and this is the main reason why x-ray severity score was significantly higher in EBP group. The importance of x-ray severity score in evaluating improvement of respiratory status after EBP is confirmed with our results in the non-EBP group where the x-ray score significantly increased after 3 days in the ICU. The mortality in our group of non-EBP patients was 78.9% which is similar to reports from other authors [2, 3]. In comparison, the mortality of EBP patients was 53.3% which was significantly lower than the predicted mortality rate by APACHE IV score and similar to mortality reported in a previous paper on EBP treatment with oXiris filter [16]. In the linear regression analysis, longer survival was independently associated with EBP where patients not treated with this therapy had an HR for death of 4.36. It is still not confirmed on a larger number of patients when to initiate EBP therapy. Some authors suggested that evidence of high circulating cytokines, high SOFA score or requirement of vasopressors are indications for start of EBP [8]. Our results confirmed previous reports [2, 18] that timely initiation of EBP, namely a cut-off of 14 days from onset of symptoms to start of EBP showed a significant improvement not only in clinical and laboratory features but as well in survival. Therefore, our results could suggest the potential role of EBP with oXiris membrane in not only the reduction of cytokines but as well the improvement of SOFA score and multiorgan function, especially respiratory status which could be objectivized not only through the improvement in respiratory parameters but also in reduction of x-ray severity score. Considering our observations, we hypothesize that patients in an early course of a disease, which have not developed MOF and are without a need for vasopressor support, but respiratory deteriorate could be potentially a target group for EBP. Our study has several limitations. First, the study was an observational performed in a single center and a small sample size could limit it. Future trials should be designed to identify high-risk patients, when to timely initiate the treatment and focus on targeted therapy. Second, given the number of included patients the results could not provide the exact point of illness stage when is the best time for EBP initiation. Third, the exact effect of oXiris membrane in cytokine reduction could not be confirmed with our results. This removal could only be supposed with the observational nature of the study. Fourth, our patients were not treated with tocilizumab. Therefore, some may argue that

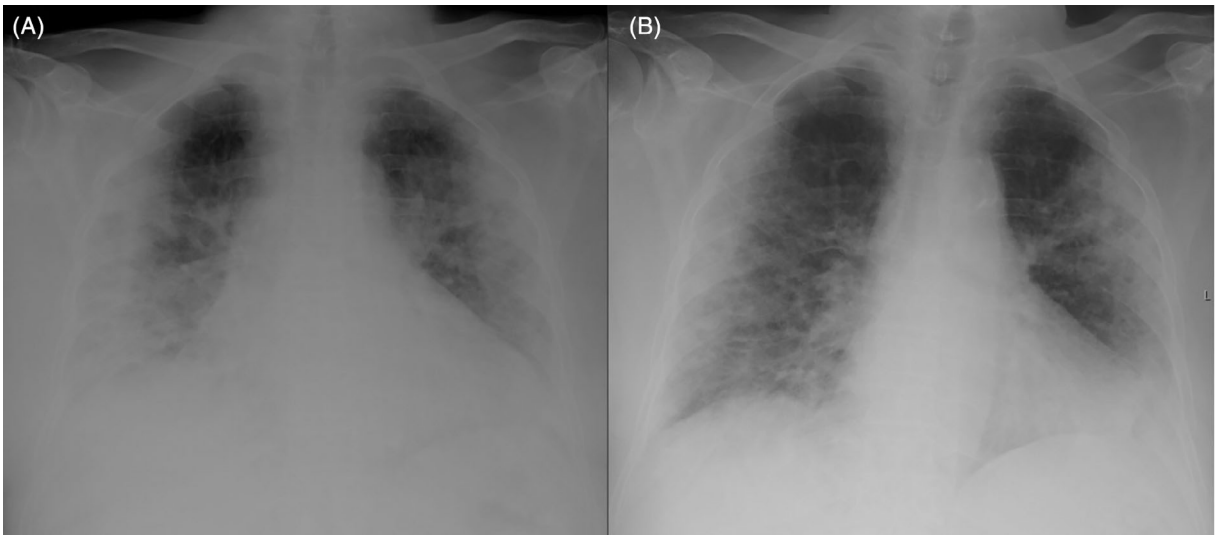

FIGURE 4 Example of chest x-ray scoring in one of the patients as described in Monaco et al. (upper zones R-L; middle zones R-L; lower zones R-L): (a) Chest x-ray at baseline; 0–1, 3–3, 3–2 (total 12); (b) Chest x-ray after 72 h of EBP;0–0, 2–3, 2–2 (total 9). EBP, extracorporeal blood purification

we did not try with all available conservative approaches before starting with EBP therapy. However, the RECOVERY and REMAP-CAP trial results showed that it is challenging to define, although it offers a modest mortality benefit, specific population of patients that would benefit from this therapy [26, 27].

5 | CONCLUSIONS

Critically-ill patients with COVID-19 treated with extracorporeal blood purification survived significantly longer than other ICU COVID-19 patients. Treatment of extracorporeal blood purification with oXiris membrane provides significant reduction of IL-6 and cystatine C, leads to improvement in respiratory status, respiratory parameters and chest x-ray severity score, and reduction of SOFA score severity. Our results can suggest that ICU COVID-19 patients in an early course of a disease, without multiple organ failure and a need for vasopressor support but with respiratory deterioration could be potentially a target group for earlier initiation of extracorporeal blood purification, which should be confirmed in future randomized trials.

CONFLICT OF INTEREST

None.

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