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RESEARCH

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Use of Oxiris membrane in real-world clinical practice in critical care patients: a multicenter observational study

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Abstract

Background To characterize current clinical practices and outcomes associated with the use of the extracorporeal blood purification (EBP) device Oxiris® in critically ill patients.

Methods This was a prospective clinical registry database that analyzed patients treated with Oxiris®. Three different clusters of critically ill patients were identified: Group A—patients with chronic kidney disease and systemic inflammation who required postoperative support of renal function; Group B—patients requiring immunomodulation without definitive indications for renal support; Group C—patients with abdominal septic shock necessitating both postoperative renal support and immunomodulation. The primary endpoint was the comparison between mortality rates predicted by the Simplified Acute Physiology Score II (SAPS II) and observed mortality rates 4 days after EBP initiation.

Results Observed 4-day mortality rates were markedly lower than SAPS II-predicted rates: 16.7% vs. 41% in Group A, 30.8% vs. 77% in Group B, and 21.3% vs. 83% [66;89] in Group C. Early mortality was significantly associated with baseline hemodynamic instability (vasopressor requirement, OR = 3.62 [1.59–9.80], $p = 0.005$) and a lower PaO_2/FiO_2 ratio (OR = 0.99 [0.98–0.99], $p = 0.001$).

Conclusions The removal of inflammatory mediators and microbial components is an emerging therapeutic target for Oxiris® use. Oxiris® may offer therapeutic benefit through the removal of inflammatory mediators in critically ill patients with severe systemic inflammation and renal failure. Although observed mortality was lower than historical estimates, these findings must be interpreted cautiously given the lack of a control group and the limitations of SAPS II. Controlled trials are needed to confirm its clinical impact.

Trial registration The study was registered on ClinicalTrials.gov (Identifier: NCT03807414; Registration Date: June 28, 2019).

Keywords Cytokines, Renal replacement therapy, Cluster analysis, Septic shock, SOFA score, Registry, Hemoadsorption

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Background

The postulated capability of extracorporeal blood purification (EBP) to influence severity of multiorgan dysfunction [1, 2] and the high mortality due to septic shock [3], justifies the attraction that critical care medicine has shown to these treatments in the last 50 years. EBP therapies are applied to remove and/or modulate circulating substances that are associated with the etiology and pathophysiology of critical illness [4, 5]. The rationale for EBP has already been demonstrated in several studies [6], where undesired biological components were removed thanks to filter surface adsorption [7, 8]. This phenomenon has been associated with a significant reduction in the circulating concentrations of harmful solutes. A substantial number of studies have demonstrated a significant improvement in patient's clinical condition, particularly hemodynamics [9, 10].

Despite the plausible pathophysiological rationale [11, 12] and the encouraging results on biological effects of EBP, so far, no clinical trial has demonstrated their effectiveness in improving patients' survival [13, 14], and there is still no clear consensus recommending these techniques [3, 15]. Nonetheless, EBP are used worldwide. Physicians prescribe EBP treatments (such as hemoperfusion with cartridges, hemodiafilters with augmented permeability or adsorptive capacity), with the aim of treating several conditions, including systemic inflammation [16, 17]. In the absence of specific guidelines on therapeutic indications or timing to start, and considering the lack of clinical predictors of effectiveness, the physician's judgment on its pathophysiological rationale remains the main driver in the decision-making process around EBP adoption [18]. Moreover, it is crucial to consider the potential unintended removal of essential solutes, including antibiotics and nutrients, during EBP, which may result in suboptimal drug exposure or nutritional deficiencies, particularly in patients with sepsis or those receiving mechanical ventilation. Interestingly, in the last decade, clinical registries [19–21] focused on EBP have emerged to observe and record data on current use of these therapies and on patients' outcomes [22, 23]. This on-going epistemological effort intends to explore the cognitive processes involved in the decision-making to start an EBP and describe the clusters of patients who seem to benefit from these treatments.

The OxirisNet Registry [24] (aRRT: http://www.arrt.eu/) actively records prospective data from patients in Italy undergoing EBP with Oxiris® (Baxter, Deerfield, IL, USA) across multiple centers. Oxiris® is an acrylonitrile, heparin-coated membrane stratified with positively charged polyethylene-imine on the inner surface [1, 25]. Surface modification technology increases the intrinsic adsorptive capability of this high-flux hemodiafilter towards cytokines and endotoxins, thus preserving a high biocompatibility [26]. Use of Oxiris® membrane has been mainly investigated in patients with hyperinflammatory syndromes and has been associated with a reduction in circulating cytokines, blood lactates, vasopressor needs, and clinical scores of multiorgan dysfunction [7, 9, 27, 28]. As with other EBP devices, the lack of definitive evidence on the clinical effectiveness of Oxiris® requires further research, notwithstanding its wide use [15], safety remarks, and empirically demonstrated benefits.

This study aimed to analyze a cohort of critically ill patients treated with Oxiris® to focus on the following objectives, namely (1) to describe and classify patient phenotypes undergoing this type of EBP; (2) to evaluate trends in clinical and biochemical parameters during treatment; and (3) to assess patients' short-term outcomes while exploring associations between specific clinical variables or phenotypic clusters and short-term mortality.

Materials and methods

Study design

This was a prospective, multicenter, observational study utilizing data from the OxirisNet Registry (aRRT: http://www.arrt.eu/). Comprehensive details about the Registry have been previously published [24]. The analysis included clinical data from critically ill patients admitted to intensive care units (ICUs) who underwent EBP treatment with the Oxiris® device (Baxter, Deerfield, IL, USA) between January 2019 and March 2023.

The study protocol was reviewed and approved by the Ethics Committee of Comitato Etico di Area Vasta Centro, Regione Toscana, Florence, Italy [ref. CEAVC 14334]. In accordance with the Italian Data Protection Authority (Prov. No. 497, December 13, 2018), patient consent for data analysis was waived, as most patients were expected to be acutely incapacitated.

Given its observational design, the study did not involve any medical, pharmacological, or behavioral intervention in addition to standard protocols used in physicians practice, regardless of the registry.

This clinical investigation adhered to the approved study protocol, the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH-GCP), and all relevant regulatory requirements. To maintain patient confidentiality, all data that could identify individual participants were either encrypted or appropriately removed.

Study patients

The OxirisNet Registry included all critically ill patients for whom continuous renal replacement therapy (CRRT) with the Oxiris® membrane was prescribed by

the attending physicians. This decision was based on widely accepted guidelines and local clinical practice protocols.

All patients observed in this study received treatments (including antimicrobials, mechanical ventilation, or any other treatment for organ support) based on local policy or practice and according to the physician's judgment. No specific protocol for EBP prescription (including but not limited to vascular cannulation, anticoagulation, or treatment flows) was adopted during this pragmatic study. In the absence of specific guidelines on this topic, the attending physicians decided on EBP initiation and use of Oxiris® membrane based exclusively on their local practice. The decision-making process underpinning EBP prescription has been recorded and described in this paper.

Patients who underwent concomitant or sequential treatments with other hemodiafilters or cartridges for EBP during ICU stay were excluded from the analysis.

Study variables

For each patient, the following data were considered: anthropometric, clinical, and biochemical parameters (including inflammatory markers), comorbidities, disease-associated symptoms, and organ dysfunction severity indexes, such as the Sequential Organ Failure Assessment (SOFA) and the Simplified Acute Physiology II (SAPS II) scores. The main indication for EBP was recorded (e.g., kidney support, cytokines, or endotoxins removal), as well as treatment modality (e.g., continuous veno-venous hemodialysis, hemofiltration or hemodiafiltration), prescription (e.g., flows, prescribed dose, and anticoagulation), and delivery (e.g., delivered dose). Recording of clinical and technical data was performed immediately before EBP initiation (T0), after 12 h from T0 (T1), and thereafter every 24 h from T0 for the next 4 days, and finally at ICU discharge. Data were described for the entire population and for subgroups of patients according to short-term outcome. Mortality rate at 4 days after EBP initiation was the outcome chosen for retrospective dichotomization.

Principal component analysis (PCA) [29] was performed to reduce the baseline variables. This allows to visualize data into a PCA 3D chart, while keeping a large amount of dataset's variance. Then, K-means algorithm [30] was applied in the 3D PCA space to identify clusters of patients nowadays treated with Oxiris®. The relative loadings of the most meaningful clinical features identified through this data-driven approach and the relative distribution of principal components among the different clusters were used to elaborate a detailed description of the clinical scenarios resuming each cluster.

Sample size

We adapted the study from Pölkki et al. [31] that found a cutoff of SOFA score higher than 15 points as associated with higher mortality rates (72%) in a population of 63,756 study patients, to our population. Considering an expected mortality percentage of 75% as calculated with the SAPS II score on our population, we calculated our sample size hypothesizing that a SOFA score lower than 15 would be associated with a 70% mortality percentage, and an 80% mortality rate in the population with a SOFA score higher than 15. With this background, we evaluated a sample size of 150 patients, with a statistical power of 0.80 and a significativity level of 0.05. The sample size calculation was performed with R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Study variables

IL-6 concentrations were measured using a chemiluminescent immunoassay (Immulite 2000 XPI or ADVIA Centaur XP, Siemens Healthcare, Marburg, Germany). Endotoxin activity was determined with the Endotoxin Activity Assay (EAA™, Spectral Diagnostics Inc., Toronto, Canada).

Missing data management

Of 307 Oxiris-only cases, 30 were excluded because of critical missing baseline or outcome data required for analyses, yielding 277 patients in the analytic dataset. For the primary endpoint (4-day mortality), complete-case analysis was used with no imputation. For repeatedly measured continuous variables collected at nominal intervals during the first 72 h (e.g., MAP, PaO_2/FiO_2, lactate, urine output), we harmonized patient-level time series to the scheduled timepoints to facilitate descriptive summaries and model fits that require aligned observations. When a single intermediate timepoint was missing but both adjacent timepoints were available, the missing value was estimated via piecewise linear interpolation (first-order hold) between the two nearest observed values. No extrapolation beyond the outermost observed times was permitted; sequences with > 1 consecutive missing timepoint remained missing. Interpolation was not applied to categorical variables, medication administration variables, or endpoints.

All interpolated values were flagged in the dataset and underwent clinical plausibility review by a senior intensive care physician prior to inclusion in longitudinal summaries or models requiring aligned timepoints. This deterministic approach assumes approximate linear change between adjacent observations over short windows, which is reasonable for the physiologic variables considered and avoids the bias of last/next observation

carried forward. Interpolation was implemented in R (version 4.2.3, R Foundation for Statistical Computing) using standard base "stats" linear-interpolation routines within the analysis scripts; scripts are available from the corresponding author on reasonable request. We acknowledge that interpolation cannot recover unobserved dynamics and therefore restricted its use as described above.

Statistical analysis

Statistical analyses were performed with R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Normality distribution of variables was assessed via the Chen-Shapiro test. Frequencies and percentages were used to summarize qualitative variables, while means and their respective standard deviations were calculated for quantitative variables. Median and interquartile range (IQR) were used to describe non-normally distributed quantitative variables.

Simple logistic regression models were performed to assess which baseline clinical variables were associated with early mortality. In order to assess the early mortality predictive capability of each baseline clinical variable, the Area under the Receiver Operating Characteristics (ROC) curve was used. Considering the number of patients having the outcome of interest (rule of thumb), we performed a multiple logistic regression model including the variables associated with short-term mortality in univariate analysis; in presence of multicollinearity, the most clinically significant variables were selected. Furthermore, multiple logistic regression analyses were performed to study the trend of variables over time in the two populations and to understand if trends over time were different in the two groups (globally and with the effect of time). In these latter analyses, early mortality (dependent variable) was predicted by clinical parameters, time, and the interaction between clinical parameter and time (independent variables). For each logistic regression model, 95% confidence intervals (CIs) and p-values were computed using a Wald z-distribution approximation. A p-value of < 0.05 was considered statistically significant.

Results

Patient selection and study population

Data from 737 critically ill patients who underwent EBP are available in the OxirisNet Registry. Patients treated with Oxiris® as unique type of EBP were 307. Of these, 30 patients were excluded during data quality/data cleaning procedures (mainly for missing values). The final analysis was thus conducted on data from 277 patients recorded in the OxirisNet Registry and admitted to 15 Italian ICUs. All EBP treatments were performed using PrismaFlex/PrismaX machines (Baxter, IL—USA) (Fig. 1).

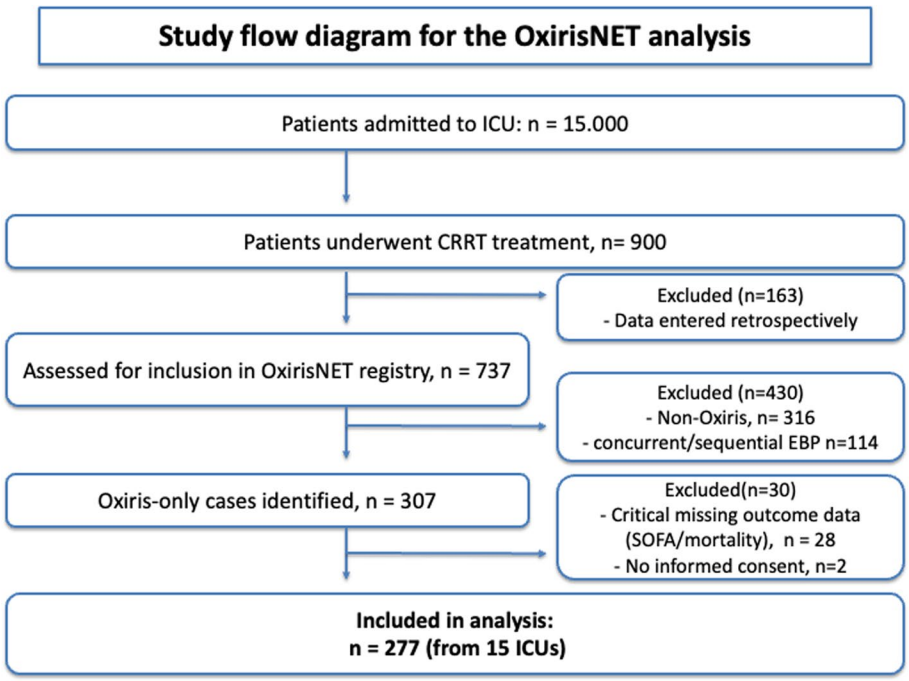

Fig. 1 Enrollment flowchart of patients undergoing CRRT treatment. Among 900 patients treated with CRRT, 163 were excluded because their records were entered retrospectively rather than prospectively. The remaining patients were screened for eligibility, and additional exclusions were applied according to the study protocol, leading to the final study population included in the analysis

Indications for EBP and clinical assessment

ICU physicians started an EBP with an Oxiris® membrane in 70% of cases, whereas in the remaining 30% of cases treatments were discussed with nephrologists. The decision to initiate EBP with Oxiris® was guided by biochemical and clinical evidence of systemic inflammation or endotoxemia under the following conditions, namely (1) in the absence of absolute or relative indication for renal replacement therapy (46 patients, 16.6%); (2) associated with acute kidney injury (AKI) with absolute indications for renal replacement therapy (32 patients, 11.6%); and (3) In patients with hemodynamic instability and/or multiorgan dysfunction, where the renal functional reserve was deemed insufficient to sustain the metabolic burden or anticipated fluid overload (199 patients, 71.8%).

Timing of treatment and early outcomes

Vasoplegia, fever, neutrophil count, serum procalcitonin, and C-reactive protein were the most frequently used markers to identify systemic inflammation. Endotoxin activity assay was used only in 32 patients (11.6%); in most cases, the target of endotoxin removal was set based on patient's medical history (e.g., abdominal sepsis or bacteremia caused by Gram-negative pathogens) [32]. A previous diagnosis of chronic kidney disease and results from furosemide stress tests were the main variables considered to predict the kidney's capability to sustain the expected burden of critical illness (i.e., renal functional reserve).

The main anthropometric parameters, comorbidities, and clinical conditions at ICU admission and at EBP initiation are summarized in Table 1.

Median time from ICU admission to the start of EBP was 2 (7) days. Details on indications for CRRT initiation, treatment parameters, and cannulation sites are reported in Table 2.

Seventy-one patients (25.6%) died within 4 days after start of EBP (non-survivor group): 9 patients died during the first 12 h of treatment, 12 in the following 12 h (21 patients, 7.6%, died within the first 24 h of treatment), 14, 19, and 17 patients died during the second, third, and fourth day of treatment respectively. Table 3 shows baseline clinical variables associated with short-term mortality.

Baseline characteristics and predictors of early mortality

As expected, the non-survivor group showed a higher SOFA score (OR 1.19[1.09–1.30], $p<0.0001$). Lower PaO_2/FiO_2 ratio ($p=0.001$), lower MAP ($p=0.006$), and higher VIS ($p=0.0004$) were also associated with short-term mortality. In Table S1, we show the output of the multiple regression analysis. A greater increase in SOFA score during the treatment is noticeable in the non-survivor group compared to the survivor group (OR 1.01[1.01–1.02], $p=0.03$), where SOFA score declines early on during the treatment. PaO_2/FiO_2 ratio, A-aO_2 gradient and MAP behaved similarly (Figure S1). Although lactate values at baseline were similar in the two groups ($p=0.47$, see Table 3 for details), they decreased relatively more (OR 1.01[1.01–1.02], $p=0.01$) during treatment in patients who survived than those who did not ($p=0.01$, see Table S1 for details). Biomarkers as white blood cells count, C-reactive protein or procalcitonin were similar between survivor and non-survivor patients, but their trend differed between groups, worsening over time in patients who died. Figure 2 shows the overtime trend of selected patients' clinical variables during the first 3 days of extracorporeal treatment.

Cluster analysis and outcome stratification

Considering patients' clinical and biochemical parameters recorded during the period from ICU admission to EBP initiation, Silhouette plot, and Scree plot analysis have been used to determine the best number of K-means clusters into the PCA 3D space. Such analysis identified three main clusters of patients, currently treated with Oxiris® membrane in real-world practice (Fig. 3).

The most relevant features (with relative loading > 0.1 in absolute value) determining the three principal components are presented in Table S2. The principal components distribution among clusters is represented in Figure S2. SOFA score at EBP initiation for patients in each cluster is presented in Figure S3; mortality rates at 4 days after EBP initiation observed in each cluster are 16.70% for the Blue Cluster, 30.8% for the Red Cluster, and 21.3% for the Green Cluster. Table 4 describes the clinical features resuming each cluster.

Figure 4 represents the overtime trends of interleukin (IL)-6 and endotoxin activity assay (EAA).

SAPS II predicted a median ICU mortality of 75% at EBP initiation, while the observed ICU mortality was 43.3%. Although the observed mortality was lower than expected, this might represent an association rather than evidence of treatment effectiveness, given the absence of a control group. Mortality rates varied by cluster: Blue—expected 41% (IQR 20–57), observed 57.1%; Red—expected 77% (IQR 60–88), observed 36.9%; Green—expected 83% (IQR 66–89), observed 49.4%. Notably, the elevated mortality in the Blue Cluster compared to predictions, and the lower-than-expected mortality in the Red Cluster, may reflect underlying heterogeneity in illness severity or possible misalignment between Oxiris® use and actual clinical need.

On average, patients spent 13 days in the ICU. Survivors demonstrated a median length of ICU stay of

Table 1 Patients' anthropometric characteristics and comorbidities at ICU admission, nature of ICU admission, and patients' clinical parameters at EBP initiation

Anthropometric data		**Comorbidities**	
Ethnicity		**CKD**	**65 (23.47%)**
Caucasian	273 (98.55%)	CLD, Child–Pugh ≥ B	9 (3.24%)
Arabic	2 (0.72%)	Heart failure	48 (17.32%)
Asiatic	2 (0.72%)	COPD	45 (16.24%)
Male gender	204 (73.64%)	Diabetes	79 (28.52%)
Age (years)	68 [18]	Previous solid cancer	13 (4.70%)
BMI	26.9 [6.70]	Current solid cancer	15 (5.41%)
Reasons for ICU admission		Previous hematologic cancer	4 (1.44%)
Reason for ICU admission		Current hematologic cancer	16 (5.78%)
Intensive care treatment for medical disease	180 (64.98%)	Metastatic cancer	4 (1.44%)
Postoperative admission after elective surgery	20 (7.22%)	Hypertension	147 (53.07%)
Postoperative admission after emergency surgery	77 (27.80%)	Cerebral vasculopathy	24 (8.66%)
Sepsis	214 (77.25%)	Coronary vasculopathy	35 (12.63%)
Target of ICU admission		Periphery vasculopathy	36 (13.00%)
Respiratory support	227 (81.94%)	Chronic steroid therapy	12 (4.33%)
Cardiovascular support	139 (50.18%)	Immunosuppressive therapy	9 (3.24%)
Kidney support	120 (43.32%)	Congenital immunodeficiency	1 (0.36%)
Support for CNS abnormalities	23 (8.30%)	Acquired immunodeficiency	4 (1.44%)
Hepatic support	20 (7.22%)	Others (not specified)	110 (39.71%)
Clinical data at EBP initiation			
GCS	3.00 [3.00]	Bicarbonate (mEq/L)	21.94 ± 4.47
Heart rate (bpm)	89 [27]	pH	7.32 ± 0.11
Systolic pressure (mmHg)	113.00 ± 22.30	Base excess	-3.52 ± 5.40
Diastolic pressure (mmHg)	60.50 ± 13.10	Baseline creatinine (mg/dL)	1.10 [0.98]
Mean arterial pressure (mmHg)	77.90 ± 14.60	Current creatinine (mg/dL)	2.60 [2.49]
VIS	30.00 [37.50]	Urinary output (mL/h)	24 [57]
Noradrenaline dose (µg/kg/min)	0.38 ± 0.29	Bilirubin (mg/dL)	0.80 [0.96]
Lactates (mmol/L)	2.20 [2.87]	Albumin (g/dL)	2.60 [0.70]
PaO_2 (mmHg)	93 [43]	Platelets (10^3/µL)	163.50 [166.00]
PaO_2/FiO_2	150.00 [126.92]	INR	1.30 [0.51]
$SatO_2$ (%)	95.70 [5.00]	Fibrinogen (mg/dL)	498.68 ± 262.10
$PaCO_2$ (mmHg)	44.50 ± 11.90	CRP mg/L	12.52 [19.37]
Alveolo-arterial oxygen gradient	291.68 [227.65]	PCT (ng/mL)	4.00 [18.79]
Hematocrit (%)	31.00 [7.10]	WBC (10^3/µL)	13.60 [10.81]
Sodium (mmol/L)	138.00 [7.00]	Temperature (°C)	36.80 [1.00]
Potassium (mmol/L)	4.10 [1.00]	Ferritin (ng/mL)	899.50 [1747.00]
Magnesium (mg/dL)	2.24 ± 0.63	Total SOFA score	14.00 [4.00]
Phosphate (mg/dL)	4.00 [2.30]	Total SAPS II score	63.20 ± 14.50
IL-6 (ng/mL)	9.80 [10.18]	EAA (EU/mL)	0.72[0.17]

Qualitative data are expressed as numbers and (percentages); means ± SD are reported for normally distributed variables, while medians and [interquartile range] are reported for variables with non-normal distribution

Abbreviations: ICU intensive care unit, *EBP* extracorporeal blood purification, *BMI* body mass index, *GCS* Glasgow Coma Scale, *VIS* Vasoactive Inotropic Score, PaO_2 oxygen arterial partial pressure, FiO_2 fraction of inspired oxygen, $SatO_2$ oxygen arterial saturation, $PaCO_2$ carbon dioxide arterial partial pressure, *CKD* chronic kidney disease, *CLD* chronic liver disease, *COPD* chronic obstructive pulmonary disease, *pH* potential of hydrogen, *INR* International Normalized Ratio, *CRP* C-reactive protein, *PCT* procalcitonin, *WBC* white blood cells, *SOFA* Sequential Organ Failure Assessment, *SAPS* Simplified Acute Physiology Score, *IL-6* interleukin 6, *EAA* endotoxin activity assay, *EU* endotoxin units

Table 2 Extracorporeal blood purification (EBP) prescription

Treatment targets and strategies			
Primary targets of EBP initiation		Cannulation site	
Kidney function support	231 (83.40%)	*Jugular vein*	65 (23.46%)
Inflammation modulation	235 (84.83%)	*Femoral vein*	210 (75.81%)
Endotoxins removal	114 (41.15%)	*Subclavian vein*	2 (0.73%)
Type of anticoagulation		Treatment modality	
None	23 (8.30%)	*CVVH*	7 (2.52%)
Systemic heparin	85 (30.68%)	*CVVHD*	5 (1.80%)
Citrate	169 (61.02%)	*CVVHDF*	265 (95.67%)
Treatment flows			
Qb (mL/min)	150.00 [30.00]	Qr post-dilution (mL/h)	600.00 [500.00]
Qd (mL/h)	1200.00 [500.00]	Q PBP – citrate	1200.00 [1050.00]
Qr pre-dilution (mL/h)	0.00 [100.00]	UFnet (mL/h)	50.0 [100.00]
Current dose (mL/kg/h)	33.56 [9.64]	Filtration Fraction (%)	27.41 [8.00]

Qualitative data are expressed as numbers and (percentages); medians and [interquartile range] are reported for non-normally distribute variables

Abbreviations: EBP extracorporeal blood purification, *CVVH* continuous veno-venous hemofiltration, *CVVHD* continuous veno-venous hemodialysis, *CVVHDF* continuous veno-venous hemodiafiltration, *Qb* blood inflow line, *Qd* dialysate rate, *Qr* replacement flow rate, *Q PBP* pre-blood pump flow rate, *Ufnet* net ultrafiltration, *ICU* intensive care unit

Table 3 Baseline clinical variables associated with short-term mortality

Variable	**Survivor group (*n* = 206)**	**Non-survivor group (*n* = 71)**	**OR [95% CI]**	***p***	**ROC-AUC**
SOFA score	13 [11,–15]	15 [12,–17]	1.19 [1.09–1.30]	**0.0001**	0.66
SAPS II	62 [53–71]	70 [58–79]	1.03 [1.01–1.04]	**0.0001**	0.65
GCS	3 [3,–7]	3 [3–3]	0.90 [0.82–0.97]	**0.02**	0.59
PaO_2/FiO_2 index	164 [107–246]	114 [83.8–186]	0.99 [0.98–0.99]	**0.001**	0.66
A-a O_2 gradient	276 [175–388]	369 [259–448]	1.01 [1.01–1.01]	**0.002**	0.63
$PaCO_2$ (mmHg)	41 [35–50]	49.3 [42–59.6]	1.06 [1.03–1.08]	**< 0.0001**	0.68
pH	7.34 [7.28–7.41]	7.27 [7.2–7.34]	0.01 [0.01–0.03]	**< 0.0001**	0.67
MAP (mmHg)	79.9 [68.6–89.9]	74.6 [63.3–84.6]	0.97 [0.95–0.99]	**0.006**	0.65
Use of vasoactive drugs	153 (74.3%)	62 (87.3%)	3.62 [1.59–9.80]	**0.005**	0.58
VIS	20 [0–40]	44 [20–69]	1.01 [1.01–1.02]	**0.0004**	0.67
Urine output (mL/kg/h)	0.43 [0.12–0.83]	0.21 [0.10–0.71]	1.01[0.91–1.10]	0.72	
Diuretic therapy (Y/N)	122/206 (59.2%)	37/71 (52.1%)	0.74 [0.43–1.28]	0.28	
Creatinine (mg/dL)	2.58 [1.60–3.82]	2.30 [1.45–3.85]	0.97 [0.86–1.09]	0.63	
Bicarbonates (mEq/L)	22.2 [20,–25]	21.2 [19,–25]	0.96 [0.91–1.02]	0.25	
Bilirubin (mg/dL)	0.77 [0.43–1.40]	0.85 [0.51–1.87]	1.23 [0.96–1.55]	0.09	
Platelets ($\times 10^3$/ µL)	170 [101–267]	145 [81.5–250]	1.00 [1.00–1.00]	0.17	
Lactates (mmol/L)	2.00 [1.40–3.57]	2.60 [1.88–4.92]	1.03 [0.95–1.10]	0.47	
BMI (kg/m^2)	27 [24.5–31.1]	26.6 [24.4–31.2]	0.99 [0.95–1.03]	0.68	
Hematocrit (%)	31 [28,–35]	30 [27,–35]	0.97 [0.92–1.02]	0.28	
WBC ($\times 10^3$/microLiter)	13.9 [9.2–20.0]	14.0 [9.3–23.5]	1.01 [0.98–1.03]	0.49	
PCT (ng/dL)	4.55 [1.09–24.10]	4.67 [2.00–16.94]	1.00 [0.99–1.00]	0.83	
CRP (mg/L)	14 [4.3–24.6]	13.2 [6.9–25.2]	1.00 [0.98–1.02]	0.69	
Ferritin (ng/mL)	918 [502–2200]	906 [677–2443]	1.00 [1.00–1.00]	0.78	

Qualitative data are expressed as numbers and (percentages); medians and [interquartile range] are reported for non-normally distributed variables

Abbreviations: SOFA Sequential Organ Failure Assessment, *SAPS* Simplified Acute Physiology Score, *GCS* Glasgow Coma Scale, *PaO_2* oxygen arterial partial pressure, *FiO_2* fraction of inspired oxygen, *A-aO_2 gradient* oxygen alveolar-arterial gradient, *$PaCO_2$* carbon dioxide arterial partial pressure, *pH* potential of hydrogen, *MAP* mean arterial pressure, *VIS* Vasoactive Inotropic Score, *BMI* body mass index, *WBC* white blood cells, *PCT* procalcitonin, *CRP* C-reactive protein

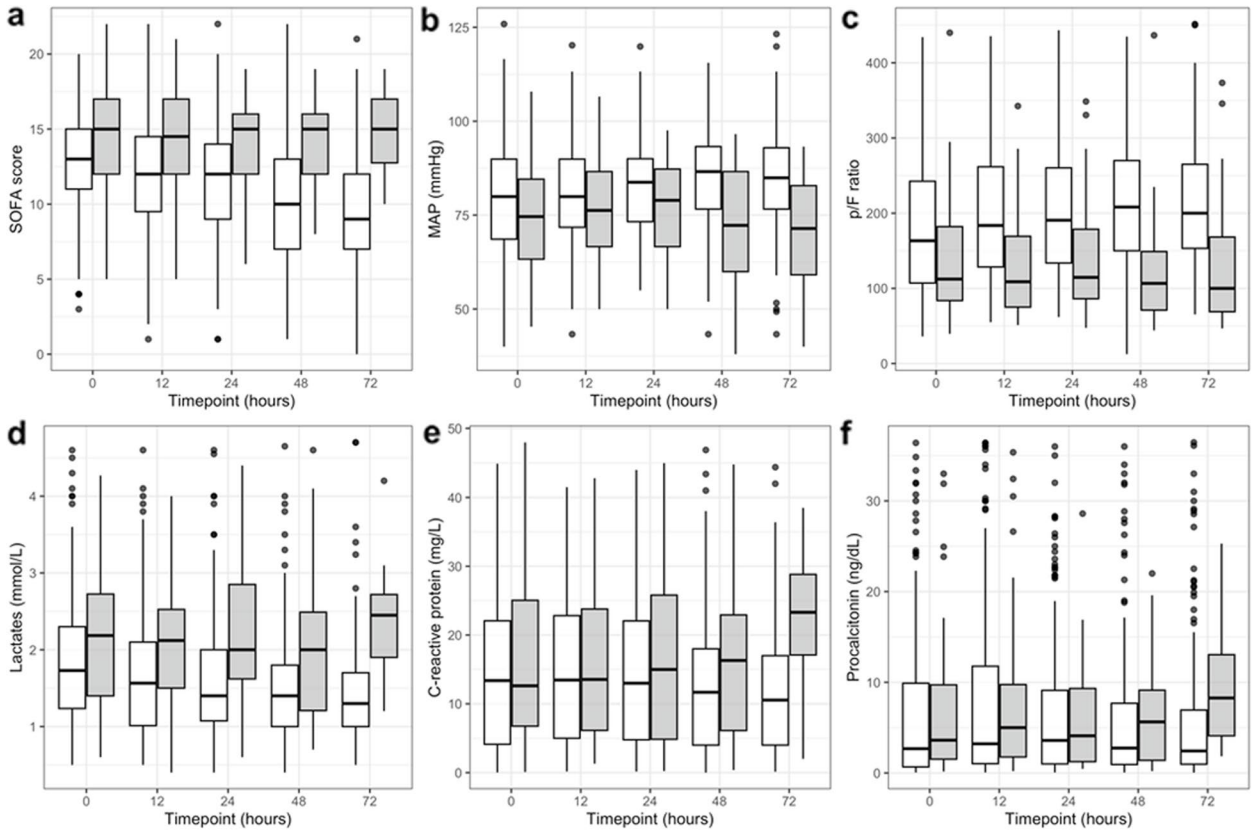

Fig. 2 Overtime trends of selected clinical variables during extracorporeal blood purification (EBP). **A** shows the overtime trend of SOFA score; **B** shows mean arterial pressure (MAP); **C** shows the PaO_2/FiO_2 ratio; **D** shows lactate levels; **E** shows C-reactive protein (CRP); and **F** shows procalcitonin (PCT). White boxplots and grey boxplots represent survivors and non-survivors in the short-term period, respectively. Legends: mmHg = millimeters of mercury; p/F ratio = ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; h = hours; mg = milligrams; dL = deciliters; mmol = millimoles; L = liters; ng = nanograms

17 days. Figure S4 illustrates the evolution of SOFA scores over the first 10 days post-EBP initiation, stratified by the dichotomized 4-day mortality rate.

Discussion

This prospective, multicenter, observational study investigated current practices related to EBP with the Oxiris® membrane across 15 Italian ICUs. The study examined the decision-making processes guiding the initiation of EBP, identifying conditions under which it was deemed appropriate and potentially beneficial. Additionally, it characterized patient clusters treated with Oxiris® and analyzed clinical features that may serve as prognostic markers for short-term mortality at the time of EBP initiation and during the early treatment phase.

The lack of specific recommendations on indications and timing of EBP this membrane (and EBP in general) [33–35] has led to huge variation in clinical practice between medical centers worldwide. This heterogeneity in the adoption and use of EBP is even more complex considering that most EBP therapies are usually applied in clinical syndromes characterized by multiple and extremely different endotypes [2, 36] (e.g., sepsis, acute kidney injury or hyperinflammation). Unsurprisingly, there is a high variability in the results from studies on EBP and definitive evidence is far from being realistically obtainable in the short term. In this uncertain scenario, the decision to initiate the extracorporeal treatment is based on physicians' judgment and perception of appropriateness of EBP in fulfilling the patient's clinical needs. Not surprisingly, the results of this study show that physicians' suspicion of systemic inflammation or endotoxemia was the main driver for the choice of this membrane with high adsorptive properties, as that was also the treatment target in all the observed patients. The geometric and performance characteristics of the Oxiris® membrane support the rationale for its use in terms of cytokines or endotoxin removal (required in 84.83% and 41.15% of patients in this cohort, respectively). Interestingly, we have observed uncertainties also on the ways to

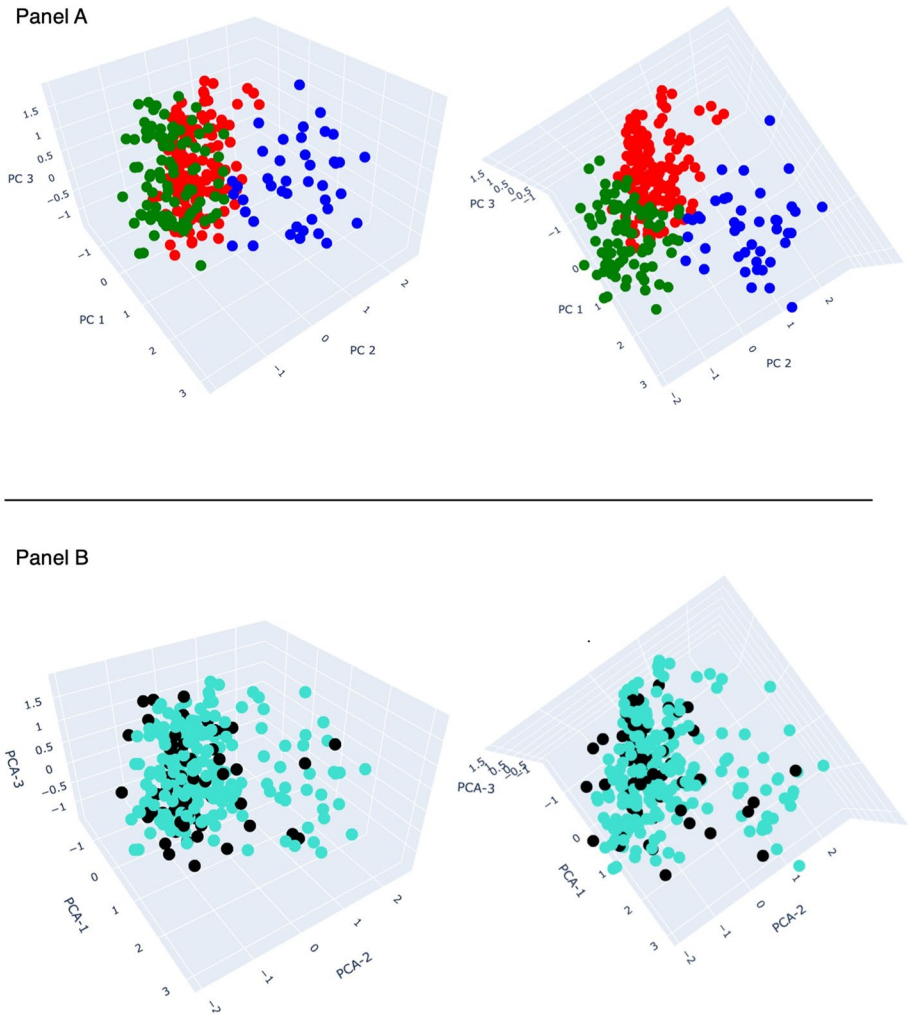

Fig. 3 Cluster of patients currently treated with Oxiris® membrane. Panel **A** shows two projections of PCA analysis identifying the three clusters of patients treated with Oxiris®: Blue, Red and Green Clusters. In Panel **B** (using the same projections of Panel **A**), patients are distinguished according to short-term mortality (survivors in turquoise and non-survivors in black). Legends: PC-1 = Principal Component 1; PC-2 = Principal Component 2; PC-3 = Principal Component 3. PCA: Principal component analysis

detect "systemic inflammation." Most physicians consider vasoplegia as a clinical marker of circulating cytokines [37]; others evaluate biomarkers easily measurable at the bedside, such as neutrophil count, procalcitonin, or C-reactive proteins. In a small minority of hospitals, flow cytometry or cytokine analysis are considered before initiation of EBP to identify overwhelming systemic inflammation. Also, results on endotoxin activity assay are completely missing at baseline, even in those treatments targeted for endotoxin removal. Despite the existence of an international consensus on the importance of measuring all these biomarkers to guide EBP indications [38] in real-world practice, these measurements are not available in real time and surrogate markers are still adopted instead.

Behind its immunomodulatory purpose, Oxiris® membrane was chosen to support renal function in patients with hemodynamic instability and/or multiorgan dysfunction, whose renal capacity was considered inadequate to sustain the metabolic burden or fluid overload. The association between immunomodulation and relative indications for renal replacement therapy [39] is certainly the most common reason for applying Oxiris® membrane in current practice (71.8% of patients in our cohort). Only in 32 patients (11.6%) the immunomodulatory effect was combined with absolute indication for renal replacement therapy. More interestingly, in 46 patients (16.6%), immunomodulation was the only target required for extracorporeal treatment. In these patients, kidney function was considered sufficient to avoid fluid

Table 4 Clinical scenarios resuming each cluster

	Blue Cluster (*n* = 42, 15.2%)	**Red Cluster (*n* = 146, 52.7%)**	**Green Cluster (*n* = 89, 32.1%)**
CKD	+	+	--
ICU admission for cardiovascular support	-	-	++
ICU admission for kidney support	++	-	+
Postoperative admission	+	--	++++
Abdominal sepsis	+	--	+++
Respiratory sepsis	+	+	-
Cognitive impairment	+	-	-
Vasopressor requirements	--	-	+++
Norepinephrine dose	--	-	+++
Mechanical ventilation	--	+	+
Urea (mg/dl)	+	+	-
Renal support for acid–base correction	++	-	-
Renal support for metabolic burden control	+	-	+
Renal support for uremic control	++	-	-
Renal support for fluid overload	-	+	+

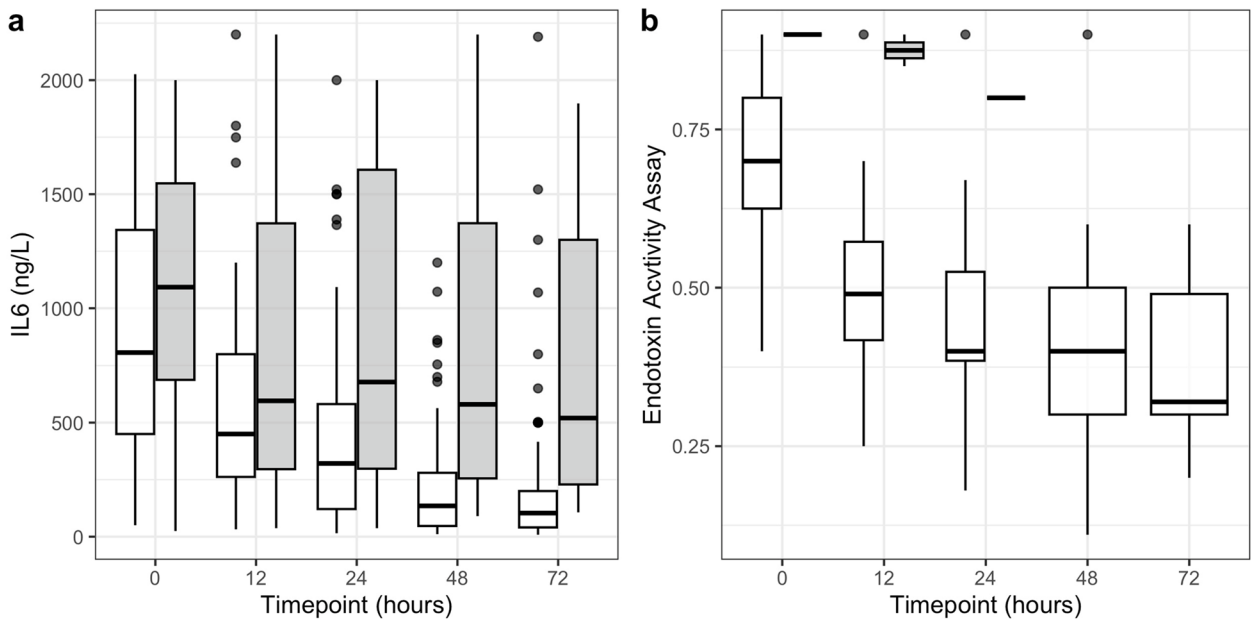

Fig. 4 Overtime trends of interleukin (IL)–6 and endotoxin activity assay (EAA). **A** shows the overtime trend of interleukin-6 (IL-6); **B** shows the endotoxin activity assay (EAA). White boxplots and grey boxplots represent survivors and non-survivors in the short-term period, respectively. Notably, all available EAA data refer to the Green Cluster. Legends: IL-6 = Interleukin-6; EAA = Endotoxin Activity Assay

overload, to remove waste solutes and to maintain electrolytes or acid–base homeostasis. The cluster analysis performed in this study has identified a specific subgroup (the Red Cluster) possibly referring to this latter case. Notably, this cluster was characterized by hemodynamically stable patients, most of whom presented with severe pneumonia requiring mechanical ventilation, who were mainly treated for immunomodulation and in whom extracorporeal support of renal function was not needed. The Red Cluster presented the highest mortality rate at short term (30.8% vs 16.70% and 21.30% for the Blue and Green Clusters, respectively). Although multiple logistic regression analysis indicates that oxygenation impairment at EBP initiation increases the risk for short-term mortality, its occurrence in the Red Cluster only partially explains the higher mortality rate observed,

also considering the lack of hemodynamic instability (i.e., the other important predictor of short-term mortality). Moreover, SOFA score appears similar between the different clusters (Figure S2). In these patients, EBP treatment was intended to prevent multiple organ dysfunction by absorbing circulating cytokines and other inflammatory mediators. Considering the temporal limited binding capacity of the Oxiris membrane, this aim may be more efficiently achieved using EBP disposables characterized by a delayed saturation of its isotherm curve.

Although not demonstrated in this study, it might be hypothesized that the unintended removal of essential solutes, potentially filtered by the Oxiris® membrane, may have played a role in influencing the observed outcome. Certainly, antibiotics or nutrients (e.g., phosphate) removal should be considered carefully [40], particularly during sepsis or in mechanically ventilated patients. A more prudent approach should be preferred during EBP performed via hemodiafilters, particularly in patients without absolute or relative indications for extracorporeal renal support or in the absence of bedside monitoring (e.g., therapeutic drugs monitoring) [41].

Of great interest were the clinical scenarios represented by the Blue and Green Clusters of patients. The Blue cluster identified individuals with a relatively lower predicted mortality but a higher observed rate, suggesting that other unmeasured factors may have contributed to their poor outcome. In contrast, the Green cluster included patients with the highest predicted mortality, yet their observed survival was markedly better, indicating a potential benefit of extracorporeal blood purification in this subgroup. These findings highlight the heterogeneity of critically ill patients and suggest that cluster-based stratification may help refine patient selection and timing for extracorporeal therapies. However, these observations should be interpreted with caution and warrant further validation in prospective studies.

The data-driven approach used for clustering has revealed that physicians chose Oxiris® membrane (1) to support renal function postoperatively in patients with chronic kidney disease and systemic inflammation (Blue Cluster) and (2) to support renal function and to immunomodulate critically ill patients with septic shock due to abdominal sepsis (Green Cluster).

Not surprisingly, the blue cluster was characterized by lower mortality rate in the short term compared with the green cluster. In both cases, renal function support was a quintessential component of the decision-making process resulting in the use of a hemodiafilter with augmented adsorptive properties. Multivariate analysis has found hemodynamic instability as a significant risk factor for short-term mortality. Even though the green cluster included deeply hemodynamically instable patients, the observed mortality rate was lower than expected. We can speculate that a positive effect may be derived by the capacity of Oxiris® membrane to unselectively absorb cytokines and endotoxins while at the same time supporting renal function. Future pragmatic trials aimed at demonstrating the clinical effect of EBP membranes with high adsorptive properties should probably focus on this cluster. Results on endotoxin activity assay available in this study are all related to the green cluster. Although only data from 32 patients are available, a clear reduction can be observed during treatment (Fig. 3).

As previously observed with other EBP techniques, SOFA score early reduction during treatment seems associated with a positive short-term outcome [10, 42–44] (See Table S2). Similarly, improvement in hemodynamic stability, oxygenation indexes, and inflammation biomarkers occur early in patients surviving after the first EBP treatment [45, 46].

This study has several important limitations. First, as an observational, registry-based analysis, it describes outcomes in patients treated exclusively with Oxiris® hemofilters, without comparisons to other EBP modalities or to patients receiving no EBP. The absence of a matched control group significantly limits the ability to draw conclusions about treatment efficacy, and its non-randomized design inherently restricts causal inference. Moreover, detailed treatment parameters—such as the number of filters used, frequency of filter changes, total treatment duration, and associated complications—were not systematically recorded.

Second, treatment with Oxiris® was largely initiated based on clinical judgment rather than guided by objective measures of cytokine or endotoxin activity. This reflects current real-world practice, where only surrogate markers of systemic inflammation are readily available at the bedside. However, this lack of biomarker-driven patient selection introduces variability in indications for treatment and may have contributed to potential mismatches between Oxiris® use and actual clinical need, particularly in subgroups such as those represented by the Red Cluster.

Third, while the clustering analysis stratified patients by clinical characteristics and outcomes, the identified clusters were not externally validated in independent cohorts. This limits the generalizability of these subgroup findings and introduces the risk of overfitting. Additionally, the absence of comparator data from patients treated with CRRT alone, non-Oxiris® membranes, or no extracorporeal support prevents assessment of relative effectiveness across different therapeutic strategies.

Lastly, short-term mortality was defined as death occurring within 4 days of EBP initiation. This time frame was selected to reflect the early biological effects of

extracorporeal therapy, such as improvements in hemodynamics, oxygenation, or immunologic markers, which are expected to emerge within this window. Nevertheless, this definition may be too narrow to capture the full impact of treatment on patient outcomes. For this reason, ICU mortality and longitudinal SOFA score trends over the first 10 days post-EBP are also reported (Figure S4).

To address these limitations, future pragmatic trials should adopt biomarker-guided selection criteria and include appropriate control groups to evaluate whether Oxiris® therapy confers clinical benefit in the specific patient subgroups identified here. A stepwise approach—combining cluster-based stratification with prospective randomized trials—may offer a more targeted and efficient path to validating the role of Oxiris® in critical care.

Conclusions

The extracorporeal removal of inflammatory mediators and microbial components represents a potential therapeutic mechanism of action for Oxiris®. In this cohort of critically ill patients requiring renal replacement therapy and presenting with severe systemic inflammation, including abdominal sepsis, observed mortality rates were lower than historical benchmarks. However, given the absence of a control group and the limitations of comparisons with outdated prognostic models such as SAPS II, these findings should be interpreted with caution. Notably, treatment initiation was predominantly based on clinical judgment rather than guided by real-time measurements of endotoxin activity or cytokine levels, which may have introduced variability in patient selection and treatment response. Future prospective and controlled clinical trials are warranted to evaluate the clinical impact of Oxiris® in well-defined, biomarker-guided patient populations and to substantiate its role in contemporary intensive care practice.

Abbreviations

A-aO2	Alveolar-arterial oxygen gradient
AKI	Acute kidney injury
aRRT	Acute renal replacement therapy (implied from context and URL in document)
CI	Confidence interval
CRRT	Continuous renal replacement therapy
EAA	Endotoxin activity assay
EBP	Extracorporeal blood purification
FiO2	Fraction of inspired oxygen
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
IL-6	Interleukin 6
IQR	Interquartile range
MAP	Mean arterial pressure
OR	Odds ratio
PaO2	Partial pressure of arterial oxygen
PCA	Principal component analysis
ROC	Receiver Operating Characteristics
SAPS II	Simplified Acute Physiology Score II
SOFA	Sequential Organ Failure Assessment
TRN	Trial registration number
VIS	Vasoactive-inotropic score

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s44158-025-00305-3.

Supplementary Material 1.

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Authors' contributions

GV is the corresponding author and has contributed to the preparation of the paper (study concept, study design, data collection, data interpretation, writing, editing of text, approval of the final manuscript, all the above). AF has contributed to study design, data interpretation, statistical analysis, writing and editing of the text. LT has contributed to statistical analysis and data interpretation. SR, CR and ZR have contributed to data interpretation, writing, and approval of the final manuscript. SDR has contributed to study concept, study design, data collection, data interpretation, editing of text, and approval of the final manuscript. MC has contributed to data interpretation, writing, editing of the text and approval of the final manuscript. MG has contributed to data interpretation, writing, and approval of the final manuscript. MVR has contributed to data collection, data interpretation, and editing of text. DPM has contributed to data collection, data interpretation, and editing of the text. FP has contributed to data interpretation and editing of the text. FF has contributed to data interpretation and editing of the text. FP has contributed to data collection, data interpretation, and editing of the text. GR has contributed to data collection, data interpretation, and editing of the text. CR has contributed to data interpretation, writing, and approval of the final manuscript. GS, AM, CS, AC have contributed to data interpretation, writing, and approval of the final manuscript. The authors read and approved the final version of the manuscript, immediately before its submission.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to institutional policy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The present study was approved by the local Ethics Committee, "Comitato Etico di Area Vasta Centro, Regione Toscana," Florence, Italy [rif. CEAVC 14334]. Given its observational design, the study did not involve any medical, pharmacological, or behavioral interventions in addition to standard protocols used in physicians practice, regardless of the registry. Research has been carried out and data concerning patient consent were handled in agreement with the principles laid out in the original Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable.

Competing interests

The authors declare there is no competing interest related to the present manuscript and provide the following disclosures: GV has received support for travel expenses, hotel accommodation and registration to meetings from Baxter.

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