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CytoSorb® in burn patients with septic shock and Acute Kidney Injury on Continuous Kidney Replacement Therapy is associated with improved clinical outcome and survival

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ABSTRACT

Background: In burn patients, septic shock and acute kidney injury (AKI) with use of continuous renal replacement therapy (CRRT) severely increase morbidity and mortality. Sorbent therapies could be an adjunctive therapy to address the underlying metabolic changes in inflammatory and anti-inflammatory cytokines dysregulated production.

Methods: A retrospectively observational study of 35 severe burn patients admitted to the Burn Center (Turin, Italy, from January 2017 to December 2022), who underwent CRRT for AKI-associated septic shock. Out of 35 patients, 11 were treated with CytoSorb® as adjunctive therapy to CRRT (Sorbent group) and 24 patients only with CRRT (Control group).

Results: The application of CytoSorb® took place in a very dispersed way. Out of 11 patients, 7 started the CRRT together with the sorbent application. The patients of the sorbent group exhibited a significant reduction in norepinephrine use compared to that of the control group. A clinical improvement over the first 4 days of Cytosorb® was observed in both survivors and no survivors of the sorbent group, with significant norepinephrine decreased use on day 4 compared to day 1. In-hospital mortality was 45.4% and 70.8% in the sorbent

Abbreviations: CRRT, Continuous Kidney Replacement Therapy; AK, Acute Kidney Injury; MAP, Mean Arterial Pressure; %TBSA, Total burned surface area; KRT, Kidney Replacement Therapy

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and control group, respectively, and significantly better at Kaplan-Meier survival analysis at 270 days (p = 0.0445). In both groups, all survivor patients recovered renal function at discharge, whereas no survivors did not.

Conclusions: Adjunctive treatment with CytoSorb® for burn patients with AKI-CRRT and septic shock poorly responsive to standard therapy led to a significant clinical improvement, and was associated with a lower mortality rate compared to CRRT alone.

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1. Introduction

Patients with severe burns represent a subset that, despite constant improvement in the therapeutic strategies for their management, is still affected by a high rate of various complications that severely impair overall survival, of whom the main is sepsis [1,2].

The episodes of sepsis can be severe and recurrent, often leading to AKI and continuous renal replacement therapy CRRT, and in these patients the reported mortality rates could be as high as 50–80% [1,3–8]. Several extracorporeal techniques have been applied to septic shock burn patients to address the underlying metabolic changes in inflammatory and anti-inflammatory cytokines production, the so-called "cytokine storm" [9], with mixed results. In this perspective, burn patients could represent a category of interest, since it has been established how they undergo an uncontrolled, dysregulated host response with marked changes in mediators like IL-8, MCP-1, IL-6, and activation of apoptosis pathway [10,11].

So far, the main approach applied for this purpose has been the use of high volume hemofiltration: in particular, data from the RESCUE trial showed a reduction in vasopressor dependency after 48 h of treatment at a dose of 70 ml/kg/h, and a reduction in the MODS score at 14 days; no significant difference in survival or changes in inflammatory markers were detected [12]. With such premises, blood purification through hemoadsorption could represent an alternative option to reduce morbidity and mortality in burn patients with sepsis and AKI, but it has remained largely unexplored. Recently, a retrospective observational single-center study of burn patients with septic shock from multidrug-resistant bacterial strains and severe AKI undergoing CRRT compared patients treated with or without the addition of the coupled plasma filtration and adsorption technique, and it seemed to bring out a marked improvement in mortality rate (51.3% vs 77.1% in the control group), as well as a favorable trend of the hemodynamic and laboratory parameters [13].

About the sorbent technologies, the CytoSorb® cartridge has been gaining popularity during the last few years as an adjunctive blood purification option for patients with severe sepsis and septic shock. Several observational and retrospective studies highlighted its effects on the reduction of vasopressor requirements, the ability to remove cytokines from the blood, and a reduction in mortality in some analyses [14–18]. Not all studies agree with significant results, as so far data from randomized clinical trials have failed to show any significant benefit on mortality in patients with severe sepsis or COVID-19 [19,20].

Data regarding the clinical use of CytoSorb® in burn patients is scarce, and limited to 2 case reports [21,22]. In the first case, CytoSorb® was used to reduce bilirubin levels to promote skin wound healing [21], and in the second it was added to a CRRT and ECMO circuit as an adjunct therapy for septic shock in a situation where conventional strategies had failed, with promising results and evidence of safety [22]. Moreover, hemoadsorption with CytoSorb® was evaluated in a pig model with combined severe smoke inhalation and burn trauma (40% body surface area), although it did not result in significant systemic or pulmonary reductions in the measured cytokines (IL-1b, IL-6, IL-8, IL-10, TNF-alpha) or myoglobin despite efficient transmembrane reductions [23].

The present study aimed to analyze the impact of the adjunctive CytoSorb® cartridge in a cohort of burn patients with septic shock-associated AKI undergoing CRRT, assessing the trend of clinical parameters of shock recovery in the initial 4 days of treatment as the primary end-point, and evaluating survival as secondary end-point.

2. Material and methods

2.1. *Patients and study design*

Out of 461 admitted burn patients to the Burn Center ICU of CTO University Hospital in Turin, between January 2017 and December 2022, 35 developed AKI-associated septic shock receiving CRRT for more than 72 h. Among them, 11 patients were treated with CytoSorb® as adjunctive therapy for refractory septic shock (Sorbent group) and 24 patients were not (Control group).

We collected data about demographic and clinical characteristics (age, gender, total body surface burned area (%TBSA), type of burn, revised Baux Score and Baux index expected mortality, ICU-mortality (in 180 days interval), in-hospital mortality (the period of ICU stay, ward stay, and rehabilitation in 270 days interval), the need of mechanical ventilation, interval days from admission to start CRRT, days of CRRT/Cytosorb® cartridges, % of patients with regional citrate anticoagulation, interval days survival from CRRT/Cytosorb start to death, % of patients recovered from CRRT, Sequential Organ Failure Assessment (SOFA) score, diuresis and biochemical and dialytic parameters (mean arterial pressure (MAP), blood pH and lactate level, norepinephrine requirement, WBC and platelet count).

The primary outcome included monitoring MAP, norepinephrine requirement, SOFA score, urine output, blood pH, lactate levels, WBC count, and platelet count over the

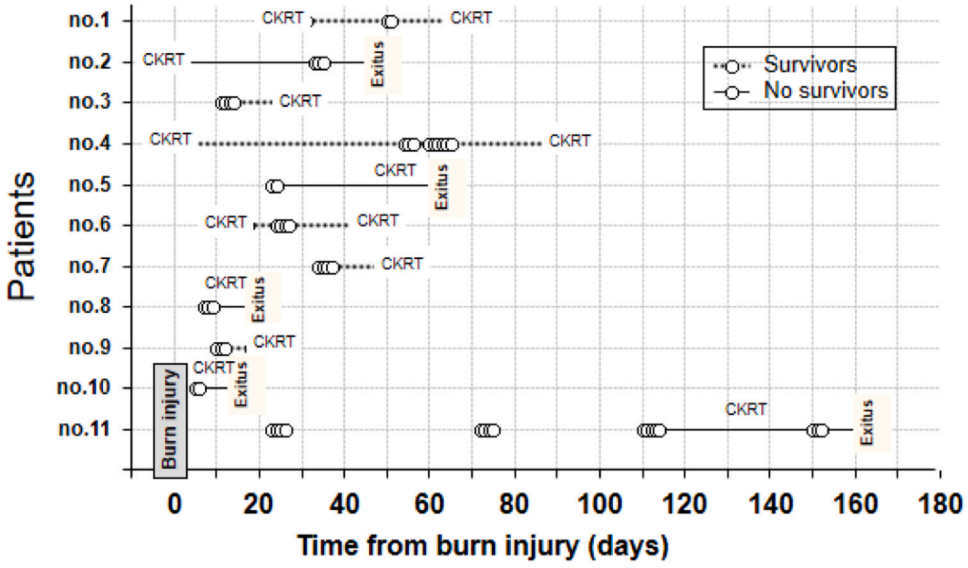

Fig. 1 – Timing of application of CRRT and CytoSorb® in the Sorbent group. The figure shows the ICU mortality and the detailed outcome of the 11 treated patients.

initial 4 days of treatment, and the secondary outcome measured was in-hospital mortality.

All patients included in the study were without brain injury at Burn Center admission. As for the sedated patients, suspension of sedation for score evaluation was not possible for safety reasons, and the SOFA score of the central nervous system was conventionally considered + 1. The probability of survival was calculated in each patient using the revised Baux score at the initiation of treatment [24].

Septic shock was defined following the 2016 Third International Consensus (Sepsis-3), specified as a subset of sepsis with a vasopressor requirement to maintain a mean arterial pressure of ≥ 65 mmHg and serum lactate level greater than 2 mmol/L [25]. According to the defined protocol by the multidisciplinary team of nephrologists, intensivists and plastic surgeons, CytoSorb® treatment was chosen as an additional therapy for patients with septic shock refractory to conventional therapy: 1) the patients with septic shock with AKI-CRRT and multiorgan failure, and: 2) microbiological confirmation of the septic event by positive blood cultures for multidrug-resistant strains, and: 3) no clinical response after 72 h of appropriate antibiotic treatment [13,26].

The study was conducted according to the Helsinki Declaration and approved by the Ethics Committee of our Hospital (dossier n. CS2/908 on August 6, 2018). Informed consent to the proposed treatments and the consent to review the medical notes and analyze the collected data were obtained from the patients or substitute decision-makers.

2.2. *Management of septic shock and AKI*

Systemic treatment of burn patients, diagnosis and treatment of septic shock was managed by a multidisciplinary team based on current guidelines [27,28].

CRRT was started when patients were in a trend of fluid overload not responsive to conservative management including maximal diuretic therapy and: 1) oliguria or 2) severe hyperkalemia, or 3) severe acidosis or 4) uremic complications [27,28].

CytoSorb® treatment was done for a minimum cycle of 2 sessions, and a maximum of 6 sessions. The indications for CytoSorb® were evaluated daily after 2 sessions and stopped when the conditions of septic shock and severe hemodynamic instability reversed (vasopressor requirement decreased below 20% of the initial dose) or when the patient's clinical condition was not improving or worsening. If deterioration of clinical status after cessation of the treatment cycle was observed and the indications for CytoSorb® were present again, a new treatment cycle was recommenced (see Fig. 1).

2.3. *CytoSorb® treatment and CRRT procedures*

CytoSorb® and CRRT were coupled in all patients of the sorbent group, with the sorbent cartridges placed in a pre-filter position following the manufacturer's instructions. The CytoSorb® cartridge was changed after 24 h, as well as the extracorporeal circuit.

CRRT was performed in hemodialysis modality (CVVHD) with regional citrate anticoagulation or heparin (3 patients of CRRT group) using the dedicated machine Multifiltrate (Fresenius Medical Care, Bad Homburg, Germany), with high permeability biocompatible synthetic polysulfone dialysis membranes (AV1000/EMiC2, Fresenius Medical Care) according to the manufacturer's instructions [29,30].

Blood flow and effluent rates were set by the target of dialysis adequacy, accomplishing the dialysis target of 20–25 ml/Kg/die [31]. Moreover, as these rates were occasionally limited by the efficiency and patency of the vascular access, a dedicated nurse recorded the effective flow rates.

As citrate was at risk of accumulation when patients presented lactate levels > 6 mmol/L, and with an increasing

trend of lactate levels [32,33], in the presence of these clinical conditions CRRT with CytoSorb® was performed with citrate at the low blood flow rate (from 60–80 ml/min) with circuit citrataemia of 2–3 mmol/L. CRRT was discontinued for renal recovery defined as independence from CRRT or for the patient's death.

Vascular access was provided by a temporary double-lumen venous catheter inserted in the jugular or femoral vein.

2.4. Statistical analysis

Continuous data are expressed as median with quartiles (25th and 75th percentiles), and categorical data as frequencies and percentages. The normality of the distribution was analyzed using the Kolmogorov–Smirnov test. The chi-square or Fisher's exact test was used to compare categorical variables. Student's t-test or the Mann–Whitney U test was used for continuous variables with or without normal distribution. ANOVA with multicomparison Newman-Keuls test or Kruskal-Wallis ANOVA and multicomparison test were used when appropriate.

Kaplan-Meier estimate of survival was constructed to compare 270-day survival between the patients on CRRT treated with CytoSorb® (Sorbent group) and CRRT alone (Control group). Cox's F-test was used to test the difference in survival rates.

A value of $p < 0.05$ was considered statistically significant. Statistical computing and graphics were performed by Statistica v.10.1 (Statsoft, Tulsa, OK, USA).

3. Results

3.1. Characteristics of Sorbent group and Control group patients on CRRT

Characteristics and details of the 11 patients on CRRT treated with CytoSorb® (Sorbent group) are depicted in Table 1. On admission, all patients suffered from a flame burn injury, and the expected mortality following the Baux score varied from 1% to 88% (Table 1). The CRRT and CytoSorb® length days varied from 5 to 88 and from 2 to 16 days, respectively (Table 1),

As shown in Fig. 1, during the long hospitalization in the Burn Center the application of CytoSorb® took place in a very dispersed way. Out of 11 patients 7 started the CRRT together with the sorbent application. All patients received at least a cycle of 2 cartridge treatments, and for 2 patients (no. 4 and 11) repetitive cycles with additional treatments were done (see Fig. 1).

As shown in Table 2, no significant difference was found for age, burn size, and days of CRRT between all patients of Sorbent and Control groups, as well as for baseline diuresis, SOFA score, lactate, norepinephrine, expected mortality by the Baux index (54.0% and 55.1%, respectively). However, in the separate analysis limited to surviving patients, the SOFA score for patients in the Sorbent group was significantly higher, while the remaining variables showed similarity in both groups (refer to Table 3).

Observed mortality for sorbent and control groups was 45.4% and 70.8%, respectively, and significantly better by Kaplan-Meyer survival analysis at 270 days (p 0.0445, Cox's F-test)(Fig. 2). In the sorbent group the causes of death were multi-organ failure (3 patients) and septic shock (2 patients), and in the control group were multi-organ failure (12 patients), septic shock by fungi (2 patients), and massive hemorrhage in the respiratory tract (1 patient).

As for AKI outcome for the study participants, no survivors of both groups recovered renal function (see Table 2), whereas all surviving patients were no longer on CRRT upon hospital discharge (see Table 3).

3.2. Dialytic and metabolic parameters during CytoSorb® application

Figs. 3 and 4 show the outcome of pH, blood lactate, WBC and platelets count, MAP, norepinephrine requirement, SOFA score and Urine Output in the first 4 days for Sorbent (n 11 patients) and Control groups (n 24 patients). A significant difference was observed between the groups for pH, WBC count (days 1–4, Fig. 3), and norepinephrine use (days 1–4, Fig. 4). Moreover, the norepinephrine use significantly decreased on day 4 compared to day 1 for patients of the sorbent group (Fig. 4).

However, comparing the trend of these parameters between survivors and non-survivors in the sorbent group only, a marked improvement for diuresis and norepinephrine requirement, as well as a fall in platelet count, was observed for

Table 1 – Baseline characteristics of the 11 burn patients on CKRT treated with Cytosorb.

Caseno/Sex	Survival	Age years	%TBSA	Type	Cytosorb days	CRRT days	Baux mortality index
1/M	YES	43	45	Flame	2	15	0.30
2/M	NO	54	65	Flame	3	46	0.88
3/M	YES	69	30	Flame	4	16	0.54
4/M	YES	77	35	Flame	9	88	0.79
5/M	NO	78	25	Flame	2	38	0.63
6/M	YES	54	10	Flame	4	26	0.05
7/F	YES	89	15	Flame	4	15	0.32
8/M	NO	63	35	Flame	3	18	0.52
9/F	YES	40	8	Flame	3	8	0.01
10/M	NO	85	50	Flame	2	5	0.97
11/M	NO	29	90	Flame	16	63	0.88

Table 2 – Baseline characteristics of 11 septic shock burn patients on CRRT treated with CytoSorb® (Sorbent group) and 24 burn septic shock patients treated with only CRRT [a] (Control group).

	Sorbent group	Control group	p
Patients (n)	11	24	——
In-hospital mortality (%, n)	45.4%, 5	70.8%, 17	0.143
Age (years)	63.0 (43.0-78.0)	72.0 (49.0-79.0)	0.647
Total body surface area (%)	35.0 (15.0-50.0)	35.0 (20.0-60.0)	0.634
Revised Baux score	115.8 (103.0-139.3)	116.4 (101.2-141.2)	0.452
Baux index expected mortality	54.0 (30.2-87.8)	55.1 (27.4-89.3)	0.749
Gender ratio (male/female)	8/3	20/4	0.381
Septic shock (%, n)	100%, 11	91.7%, 22	0.334
Mechanical ventilation (%, n)	100%, 11	87.5%, 21	0.309
CRRT start interval (days from admission)	10 (5-23)	8.5 (2-19.5)	0.716
Patients survival (days from CRRT /Cytosorb start)	46 (18-47)	11 (7-32)	0.132
Recovery from CRRT (%, n)	54.5%, 6	29.2%, 7	0.154
CRRT duration (days)	26 (15-46)	11 (7-26)	0.250
Citrate anticoagulation (%, n)	100%, 11	87.5%, 21	0.309
Diuresis (at 1st day of CRRT)	560 (120-2150)	385 (115-1350)	0.566
SOFA score[b] (at 1st day of CRRT)	12 (11-12)	12 (11-13)	0.839
Lactate (mmol/L, at 1st day of CRRT)	1.7 (1.5-3.0)	2.0 (1.5-3.6)	0.369
Norepinephrine (ug/Kg/min, at 1st day of CRRT)	0.50 (0.20-0.80)	0.35 (0.20-0.55)	0.115

Data are given as median (the 25th and 75th percentiles) or as percentage when appropriate. Student T-test or Fisher's exact test was done when appropriate

[a] CKRT = Continuous Kidney Replacement Therapy

[b] SOFA score = Sequential Organ Failure Assessment score

both survivors and non-survivors, without any significant difference (data not shown).

4. Discussion

CytoSorb® treatment for burn patients on CRRT with refractory septic shock, poorly responsive to therapy was associated with an improvement in clinical outcome and reduced in-hospital mortality rate in comparison with subjects treated with CRRT alone.

Although much data supports the hypothesis of the benefit of CytoSorb® therapy for patients with septic shock [14–22], a clear demonstration of its effect on improved survival is lacking. In the analysis of the international CytoSorb® registry data including 1434 patients, a statistically significant benefit in mortality in the overall cohort was not confirmed [14]. Many potential confounding factors can

Table 3 – Baseline characteristics of the 6 survivors treated with CRRT and CytoSorb® (Sorbent group) and 7 survivors treated with only CRRT [a] (Control group).

	Sorbent group	Control group	p
Patients (n)	6	7	——
Age (years)	61.5 (43.0-77.0)	60.0 (39.0-80.0)	0.886
Total body surface area (%)	22.5 (10.0-35.0)	25.0 (18.0-50.0)	0.431
Revised Baux score	103.5 (75.0-116.0)	91.2 (86.6-111.0)	0.731
Baux index expected mortality	31.1 (5.7-54.0)	14.9 (10.9-44.7)	0.731
Gender ratio (male/female)	4/2	4/3	0.587
Septic shock (%, n)	100%, 6	71.4%, 5	0.154
Mechanical ventilation (%, n)	100%, 6	57.1%, 4	0.122
CRRT start interval (days from admission)	13.5 (9-31)	9.0 (2-54)	0.836
Recovery from CRRT (%, n)	100%, 6	100%, 7	1.000
CRRT duration (days)	21 (15-35)	23 (7-26)	0.369
Citrate anticoagulation (%, n)	100%, 6	85.7%, 6	0.538
Diuresis (at 1st day of CRRT)	880 (300-2150)	1500 (0.0-2400)	0.445
SOFA score[b] (at 1st day of CRRT)	11.5 (11-12)	10.0 (7-12)	0.035
Lactate (mmol/L, at 1st day of CRRT)	1.6 (0.8-2.2)	1.6 (0.9-2.8)	0.835
Norepinephrine (ug/Kg/min, at 1st day of CRRT)	0.50 (0.20-0.70)	0.20 (0.00-0.60)	0.073

Data are given as median (the 25th and 75th percentiles) or as percentage when appropriate. Mann-Whitney U Test or Fisher's exact test was done when appropriate

[a] CKRT = Continuous Kidney Replacement Therapy

[b] SOFA score = Sequential Organ Failure Assessment score

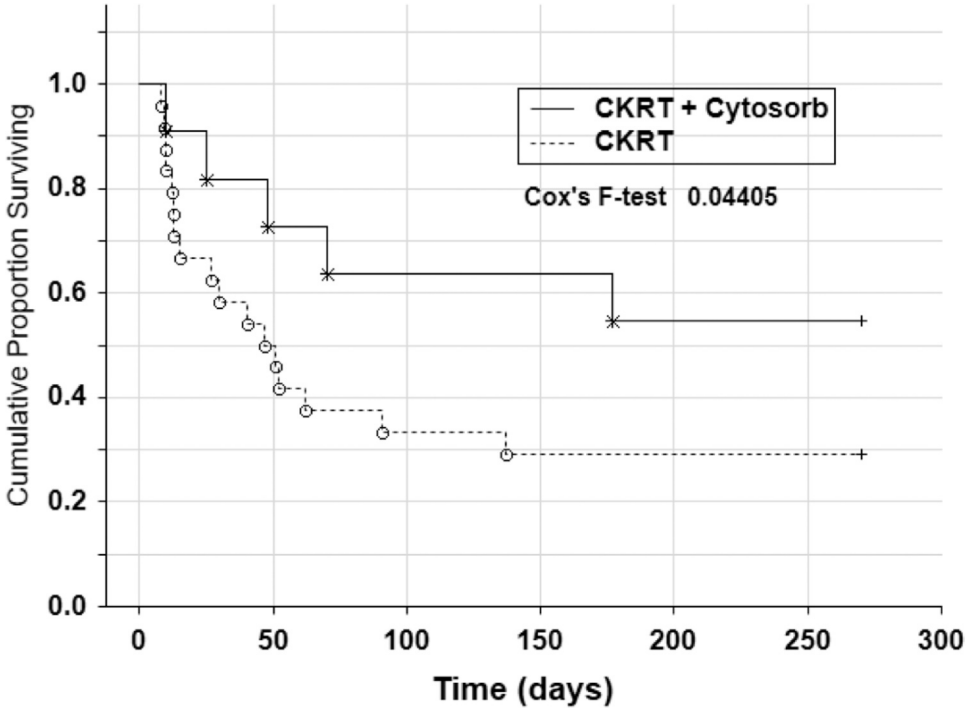

Fig. 2 – Survival analysis by Kaplan-Meyer curves for Sorbent and Control groups. The figure shows the in-hospital mortality encompassing the period of ICU stay, ward stay, and rehabilitation for the Sorbent (n 11 patients) and Control groups (n 24 patients).

influence the result, such as the use in unselected patient populations, variability in demographic characteristics, comorbidities, use of medication, time since disease onset, source of the infection, or duration of CytoSorb® therapy. Therefore, as recently underlined, the selection of patients and the time of intervention [34], may be crucial for demonstrating the efficacy and clinical impact of a new treatment option in ICU patients. In this scenario, burn patients are a particular population, in which the initial injury is defined in its pathophysiological characteristics, and quantifiable in its severity, and probability of sepsis and death [35,36].

Our studied cohort included all burn patients with septic shock-associated AKI treated with CRRT between 2017 and 2022. Of these, 11 patients were treated with CytoSorb® as adjunctive therapy, and 24 patients were not. All patients were by the same multidisciplinary team managed in the same period. Both groups exhibited similar baseline demographic and clinical characteristics. Upon comparison solely among surviving patients, the baseline SOFA score was significantly worse for the Sorbent group of patients treated with Cytosorb®. Hence, the heightened severity of prognosis in the Sorbent group indicates the actual treatment's effectiveness with Cytosorb on survival, excluding the potential interference from deceased patient data. The Sorbent and Control groups had a superimposable expected mortality rate of 54% and 55% by the revised Baux score. However, revised Baux index was developed in the general population of burn patients, not taking into account that septic shock-associated AKI requiring renal replacement therapy was a risk factor for death. In effect, the observed in-hospital mortality rate of 45% at 270 days in the Sorbent group was significantly better at K-M survival analysis than that of 71% in the Control group, which was consistent with data reported in the literature, at about 75–80% for severe burn patients with septic shock-associated AKI on CRRT [3,6–8,37].

A recent multicenter observational study highlighted a notable in-hospital mortality rate of 50% among a cohort of 170 CRRT-treated burn patients. The average duration of CRRT was 13 days, at the onset of CRRT 46% of these patients were under vasopressor therapy, and notably, treatment initiation occurred quite early, with half of the patients at a stage lower than 3 KDIGO AKI. Upon discharge and after a 6-month follow-up, 21% and 6% of patients, respectively, remained on dialysis [38]. Our observed mortality rate in the Sorbent group aligns with these findings. However, it's crucial to note that the baseline characteristics and outcomes of our patient cohort differed significantly. All our patients experienced septic shock with multi-organ failure, severe hemodynamic instability necessitating high-dose vasopressors, and exhibited a lack of clinical response after 72 h of appropriate treatment. According to previous data indicating a sustained preservation of renal function in septic shock burn patients necessitating CRRT [39], it's noteworthy that among our survivors, complete recovery from kidney injury was the typical outcome. In contrast, non-survivors from both the Sorbent and Control groups did not exhibit sufficient recovery to be entirely free from kidney replacement therapy.

In burn patients the main causes of death are sepsis and septic shock, which through repeated episodes over time sustain relapsing periods of inflammatory and/or immunosuppression

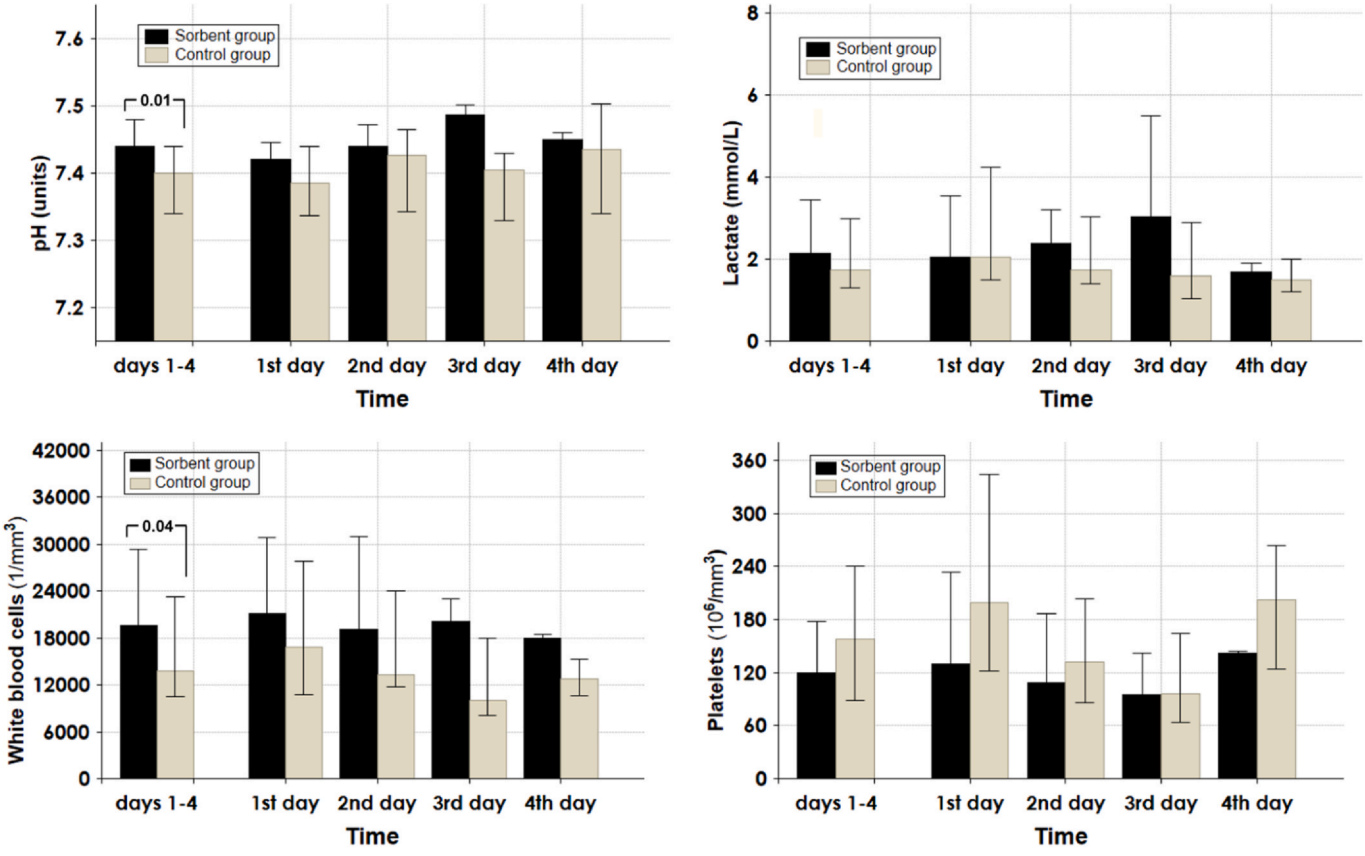

Fig. 3 – Outcome of pH, blood lactate, WBC and platelets count in the first 4 days for Sorbent (n 11 patients) and Control groups (n 24 patients). A significant difference was found between pH and WBC count on days 1–4. Data were given as median with quartiles (25th and 75th percentiles). p > 0.05 with Kruskal-Wallis ANOVA and multi-comparison test.

state, and organ injury in the heart, lung, liver and kidney [40,41]. These immune derangements are mediated by a plethora of circulating mediators, suggesting that a process able to "clear" the burn patient plasma could be favorable for the outcome [35,36].

In the nineties, a non-selective removal of a broad spectrum of inflammatory cytokines by extracorporeal diffusive/convective techniques in patients with septic shock and AKI was documented, but without any significant changes in their serum concentrations or clinical outcomes [42,43]. Similar results were recently reported for the RESCUE trial in burn patients, where the use of high-volume hemofiltration at a dose of 70 ml/kg/h did not lead to a significant difference in survival or changes in inflammatory markers [12].

Sorbent technologies have great theoretical potential in the treatment of septic shock burn patients. It has been recently demonstrated that CytoSorb® hemoperfusion effectively attenuated circulating cytokine concentrations during systemic inflammation in humans in vivo, and it did not affect long-term immune function [44]. As shown in Fig. 1, all burn patients received at least 2 CytoSorb® cartridges, and according to the protocol of treatment indication 2 patients (no. 4 and no. 11) had additional treatments (up to 16 cartridges) for relapsed septic shock episodes.

All our patients suffered from AKI requiring extracorporeal substitutive treatment. Following the initiation of CRRT , both groups showed general improvements in hemodynamics, fluid overload control, and correction of acid-base and electrolyte imbalances. Notably, within the initial 4 days, patients treated with CytoSorb® exhibited a significant reduction in norepinephrine requirement compared to those in the Control group. This reduction was observed from the 1st to the 4th day, along with a decrease in mean cumulative dosage. Therefore, it is conceivable that the CytoSorb® cartridge, applied with clear indications in a precise moment of burn patient history, was always able to overcome the microvascular derangement related to septic shock, acting as a rescue therapy, and the beneficial effect was not lost in further application for repetitive septic shock episodes.

A recent meta-analysis including a high heterogeneity of the patient groups and their underlying pathologies showed that there is no evidence for a positive effect of CytoSorb®® on mortality across a variety of diagnoses in ICU patients [45]. However, in our burn patients CytoSorb® treatment, taken as an adjunctive therapy for patients with a more severe SOFA score, and for whom the standard care was not reaching the expected improvement, was associated with improved survival. A favorable hemodynamic response was observed for all CytoSorb® treated patients, both survivors and no survivors. In detail, the median survival time from the start of CRRT and the death was 46 days (5 patients) and 11 days (17 patients) for the sorbent and control groups, respectively (Table 1). Like others reports

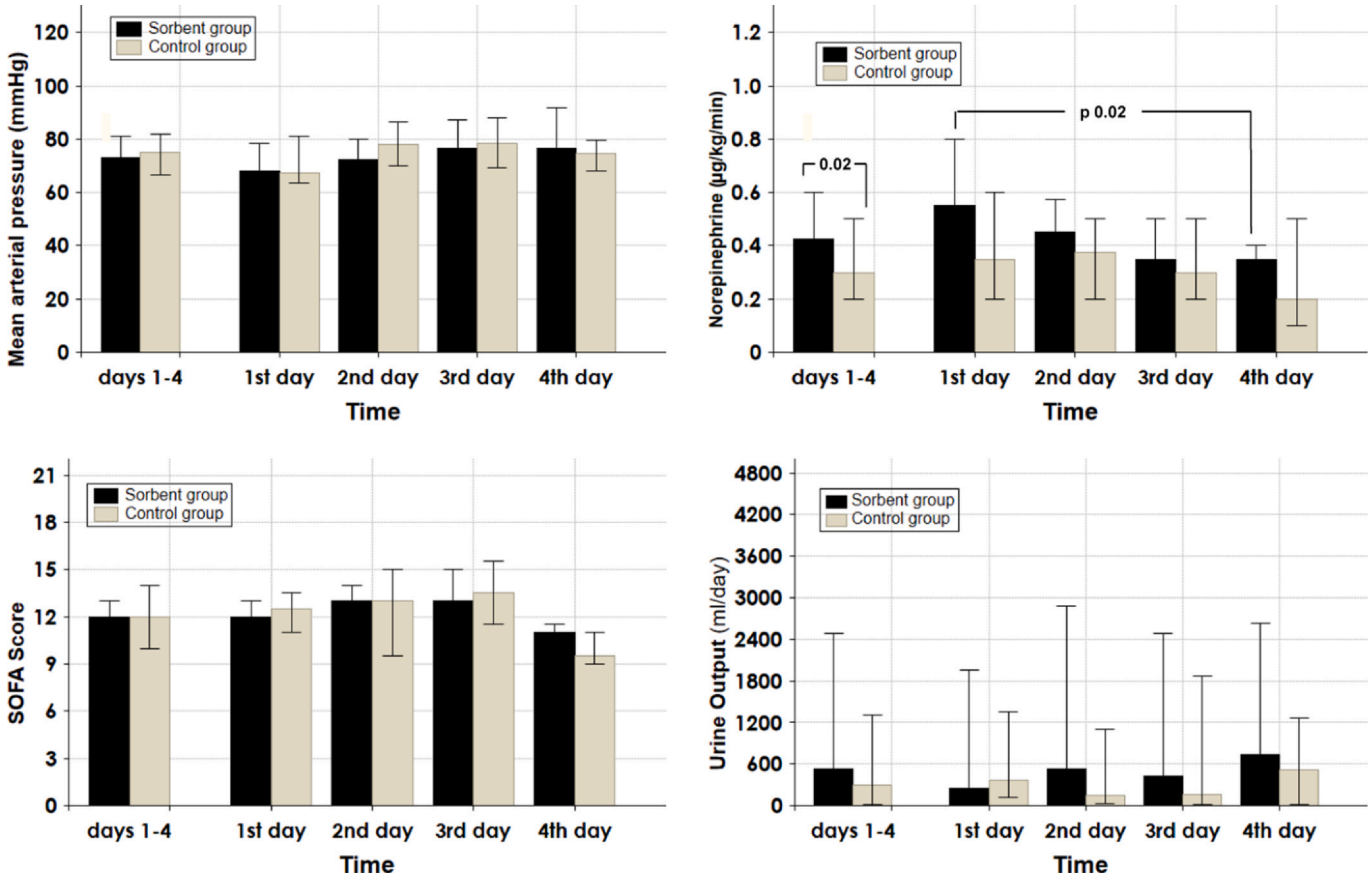

Fig. 4 – Outcome of MAP, norepinephrine requirement, SOFA score and Urine Output in the first 4 days for Sorbent (n 11 patients) and Control groups (n 24 patients). A significant difference was found between the norepinephrine requirement of days 1–4 and between day 1 and day 4 for patients of the Sorbent group. Data were given as median with quartiles (25th and 75th percentiles). p > 0.05 with Kruskal-Wallis ANOVA and multi-comparison test.

[14–19,45], these observations supported the notion that the sorbent technology could be not primarily aimed at reducing mortality "per se", but indirectly it could improve survival by acting as an adjunctive therapy where the standard of care alone was going to fail [46]. CytoSorb®® application was able to reach stabilization of patient hemodynamics, and so time was gained for the other crucial interventions for burn patient's survival such as surgery and antibiotics.

The present paper reported our clinical experience with CytoSorb® treatment options for the specific ICU population of burn patients with septic shock. We compared subjects treated over a limited time when comprehensive burn care measures and team expertise were similar. These could be the strength of our study and one possible reason for the observed improved survival rate. According to other experiences, these data also suggest that the actual benefit demonstration of extracorporeal therapies in ICU patients is deeply related to the rational choice of appropriate patients, and timing of intervention with appropriate indications [47]. These results, far from being conclusive, should be considered as a starting point for further studies.

On the other hand, our study has some limitations. First, the number of subjects is limited in such a specific population, and our results should be considered preliminary. Secondly, the percentage of septic shock patients in the Control group was similar to the Sorbent group, and the study was not randomized. Therefore, it suffers from inherent limitations associated with this study design, and a potential for bias in patient selection, which warrants consideration, could not be ruled out. Thirdly, severe burn patients suffer from a complex condition, and they undergo multiple interventions. Isolating the effect of a single treatment on the outcome could be not possible. And finally, the primary outcome of mortality was also related to factors beyond the burn injury, such as comorbidities, or the onset of multi-organ failure [41,48]. Moreover, a similar reversal of septic state by CytoSorb® treatment was also observed in non-survivor patients.

5. Conclusion

Repetitive CytoSorb® applications as adjunctive therapy for burn patients with AKI-CRRT and septic shock were followed by a clinical improvement, irrespective of the in-hospital survival, and associated with a lower mortality rate compared to patients treated with CRRT alone. However, these results, far from being conclusive, should be considered as a

starting point for further research, such as randomized control trials, aimed to clarify the role of CytoSorb® and CRRT timing in the treatment of septic shock burn patients.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the City of Health and Science of Turin (dossier n. 278/2022 on June 14, 2022).

Competing interests and conflict of interest

The authors declare that they have no competing interests and/or conflict of interest.

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CRediT authorship contribution statement

FM and DG conceived the study, collected, analyzed, and interpreted the data, and elaborated the manuscript. ND, AM, AS, DR, and MS performed the enrollment of patients in the study. LB, RG, MB, and MS corrected the final version of the manuscript. All authors read and approved the final version of the manuscript. We state that the results presented in this paper have not been published previously in whole or part, except in abstract format.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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