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TRAINING

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**STUDY ON THE EFFECTIVENESS OF CONTINUOUS
BLOOD PURIFICATION THERAPY USING ADSORPTIVE
MEMBRANES IN THE TREATMENT OF SEPTIC SHOCK IN
SEVERE BURNS PATIENTS**

Training: Burn Surgery

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SUMMARY OF THE DOCTOR OF MEDICINE THESIS

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INTRODUCTION

Severe burns in adults are defined as those involving 20% or more of the total body surface area (TBSA). Severe burn patients were characterized by a persistent systemic inflammatory response syndrome (SIRS), an imbalance in inflammatory regulation, increased catabolic activity, and a significant rise in the circulation of pro-inflammatory cytokines and endotoxins. These factors contribute to worsening clinical severity in burn patients, particularly when complicated by septic shock. According to reports, the mortality rate due to septic shock in burn patients can be up to 81.5%. Septic shock is an excessive systemic inflammatory response, marked by a massive release of cytokines into the bloodstream triggered by bacterial endotoxins, creating a “cytokine storm” that leads to multiple organ dysfunction. Elevated blood levels of cytokines and endotoxins correlate directly with disease severity and increased mortality in patients with septic shock. Studies indicate that continuous blood purification with adsorptive hemofilters rapidly attenuates the cytokine storm, thereby improving clinical status, shortening the time to septic-shock resolution, preventing further organ damage, and ultimately reducing mortality. To date, only a limited number of studies have evaluated the role of continuous blood purification with adsorptive hemofilters in severe burn patients complicated by septic shock. In Vietnam, there has been no research on blood filtration using adsorption membranes on burn patients.

1. OBJECTIVES

1.1. Description of clinical and paraclinical characteristics at the time of diagnosis of septic shock with adult severe burn patients.

1.2. Evaluation of the changes in TNF- α , endotoxin, and Interleukin-6 levels and treatment outcomes of septic shock in adult severe burns patients receiving continuous blood purification therapy using an

adsorption membrane.

2. CONTRIBUTIONS

This dissertation represents the first specialized study in Vietnam to evaluate the efficacy of continuous blood purification using adsorptive hemofilters in severe burn patients with septic shock. It offers new insights into the clinical application of extracorporeal blood purification techniques and serves as a valuable resource for burn critical care practice. The study results showed that continuous blood purification using an adsorption membrane significantly reduced endotoxin and interleukin-6 levels in patients with severe burns complicated by septic shock. The study likewise proposes a therapeutic adjunct aimed at reducing mortality by improving prognosis and raising shock-recovery rates, lowering SOFA scores, normalizing blood-lactate levels, and decreasing vasoactive–inotropic requirements in severe burn patients with septic shock. It was an especially important contribution in Vietnam, where dedicated burn research is still limited. The principal findings indicate that this treatment is safe: no procedure-related complications were observed, and there were no significant differences in coagulopathy, body-temperature disturbances, or electrolyte imbalances at any measured time point ($p > 0.05$).

3. LAYOUT

The thesis consists of 12 pages, of which 2 pages are for the problem, 35 pages for the literature review, 25 pages for the research objectives and methods, 31 pages for the research results, 32 pages for the discussion, and 2 pages for the conclusion. The thesis has 35 tables, 17 charts, 5 figures, 5 photos, and 1 diagram. The thesis has 136 references (20 Vietnamese documents and 116 English documents).

Chapter 1. OVERVIEW

1.1. Septic shock in burn patients

1.1.1. Incidence and mortality rate

Septic shock is a frequent complication and the primary cause of death in burn patients, accounting for 58.44–69.14% of all burn-related deaths. According to studies, the incidence of sepsis and septic shock in burn patients ranges from approximately 17% to 26%, depending on age, burn severity, and diagnostic criteria. With advances in treatment, the overall mortality rate of burn patients has steadily decreased; however, the mortality rate among burn patients due to sepsis and septic shock remains high. This underscores the importance of effective treatment and care for sepsis and septic shock in burn patients.

1.1.2. Diagnosis

In 2023, the International Society for Burn Injuries issued guidelines for the diagnosis and management of sepsis and septic shock in patients with severe burns. There was a consensus to adopt the Sepsis-3 criteria for diagnosing sepsis and septic shock in this patient population. According to Sepsis-3, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis characterized by persistent hypotension that does not respond to fluid resuscitation, requiring vasopressor therapy to maintain a mean arterial pressure (MAP) ≥ 65 mmHg and having a blood lactate level > 2 mmol/L.

Sepsis is diagnosed when there is clinical evidence of infection and an increase in the SOFA score by ≥ 2 points from baseline.

1.1.3. Pathophysiology

There is a global consensus that the body's immune response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) initiates the pathophysiological process of sepsis and septic shock. When the body mounts an excessive response to infectious agents, a massive release of pro-inflammatory cytokines occurs in the bloodstream, triggered by bacterial endotoxins. The overwhelming presence of bacterial endotoxins

and cytokines in the circulatory system increases vascular permeability, leading to hypotension, metabolic acidosis, and multi-organ dysfunction. Elevated levels of cytokines and endotoxins in the bloodstream are associated with increased severity and higher mortality rates in patients with septic shock. The removal of endotoxins and pro-inflammatory cytokines has been shown to improve the prognosis of septic shock.

1.2. Continuous blood purification using adsorptive membranes in the treatment of septic shock

1.2.1. Rationale

The purpose of continuous blood purification is to correct fluid, electrolyte, and acid-base imbalances, while simultaneously removing cytokines generated during inflammatory responses. Additionally, this technique is safe and suitable for patients with hemodynamic instability.

Hemoadsorption is an extracorporeal blood purification therapy based on the principle of adsorption. In this technique, the patient's blood and plasma are passed through an extracorporeal circulation system where they come into direct contact with adsorptive materials. Toxins present in the blood are captured and retained within the adsorption column or membrane, and the purified blood or plasma is then returned to the patient's body. Recent studies have demonstrated that hemoadsorption plays a vital role in supporting the removal of cytokines, restoring immune balance, stabilizing blood pressure, improving multi-organ function, and enhancing severity scores as well as reducing mortality in patients experiencing a cytokine storm.

1.2.2. Selection of Adsorptive Hemofilter in the Study

The oXiris hemofilter is essentially a continuous renal replacement therapy (CRRT) membrane that combines multiple functions. It not only has adsorptive properties capable of removing both cytokines and endotoxins, but also functions as a conventional CRRT membrane. Its

effectiveness has been demonstrated in multiple studies involving patients with septic shock unrelated to burns.

In patients with severe burns, local wound management—including eschar excision and autologous or allogeneic skin grafting—is always required. Therefore, we did not use heparin anticoagulation during blood purification in patients who underwent eschar excision and/or skin grafting within 48 hours before or after the diagnosis of septic shock. The oXiris membrane is pre-coated with 4,500 IU/m² of heparin, which helps prolong filter lifespan in patients at high risk of bleeding who are not receiving systemic heparin, and also allows for a reduction in systemic heparin dosage without compromising the effectiveness of the blood purification process.

Convenience: The adsorption capacity for cytokines and endotoxins typically saturates the membrane within 4–8 hours after the start of therapy. If the hemofilter is not replaced after this period, it can still be used as a conventional continuous hemofilter, allowing the removal of cytokines and endotoxins through convective clearance mechanisms.

Feasibility: The oXiris filter is the only hemoadsorption membrane currently reimbursed by the national health insurance for the treatment of sepsis and septic shock. Additionally, for burn patients with septic shock complications, the insurance covers up to three filters per day. Therefore, if we were to use the filter solely as a hemoadsorptive membrane according to the manufacturer's recommendation—replacing up to three filters per day—it would significantly increase treatment costs. In our study, filter replacement was only indicated when signs of membrane clotting were observed. The aim was to assess whether routine replacement every 6–8 hours is truly necessary.

1.2.3. Complications of Continuous Blood Purification Using Adsorptive Membranes

- Technical complications include issues related to vascular access,

microemboli, hemolysis, air embolism, filter clotting, and hypothermia.

- Hemodynamic instability and disturbances in homeostasis.
- Disequilibrium syndrome, thrombocytopenia, and bleeding.
- Unintentional removal of medications and nutrients

Chapter 2. OBJECTS AND METHODS

2.1. Subjects of study

2.1.1. Selection criteria

- Patients with severe burns involving $\geq 20\%$ of total body surface area (TBSA), aged 16 to 60 years, diagnosed with septic shock according to the 2016 Sepsis-3 consensus definitions.

- The patient's legal representative provided informed consent to participate in the study. No comorbid diseases or associated injuries.

2.1.2. Exclusion criteria

- Pregnant patients.
- Death within 24 hours after the diagnosis of septic shock.

2.1.3. Location and time of research: The study was conducted at the Department of Emergency Resuscitation, Le Huu Trac National Burn Hospital, from January 2023 to June 2024.

2.1.4. Research tools

- All equipment and devices used for diagnosis and treatment in the Intensive Care Unit of the National Burn Hospital were certified and approved for clinical use.

- Interleukin-6 and TNF- α assay: IL-6 Human ELISA kit, manufactured by Invitrogen/Thermo Scientific, catalog number: IL-6: EH2IL6/ TNF- α : KHC3011.

- Endotoxin assay: kit manufactured by Charles River, USA.

2.2. Research methods

2.2.1. Research design

Prospective, descriptive, interventional study.

Data collection times: T1: Time of diagnosis of septic shock; T2: Continuous venovenous hemodiafiltration (CVVHDF) start time; T3: CVVHDF implementation time after 6 hours; T4: CVVHDF implementation time after 12 hours; T5: CVVHDF implementation time after 24 hours; T6: CVVHDF implementation time after 48 hours

2.2.2. Sample size

Using the sample size formula for pre–post comparison of a single mean:

$$n = \left(\frac{Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}}{ES} \right)^2$$

$$ES = \frac{\mu_1 - \mu_0}{\sigma} \quad \sigma = \sqrt{\sigma_1^2 + \sigma_2^2 - 2r\sigma_1\sigma_2}$$

n is the sample size, μ_1 is the mean value after treatment, and μ_0 is the mean value before treatment. $Z_{1-\alpha/2} = 1.96$; $Z_{1-\beta} = 0.842$. ES is the effect size (mean difference), σ is the standard deviation, σ_1 is the standard deviation before the intervention, and σ_2 is the standard deviation after the intervention. r is the correlation coefficient between the two measurements.

In 2023, Li B. and colleagues conducted a study on the efficacy of continuous blood purification using the oXiris membrane for the treatment of septic shock in 15 patients with severe burns. At 24 hours after hemofiltration, plasma IL-6 concentrations were significantly reduced compared to pre-treatment levels (89.31 ± 17.26 ng/L vs. 96.06 ± 20.63 ng/L, $p < 0.05$). Since the patients were in the ICU and IL-6 levels were measured within 24 hours of hemofiltration, a correlation coefficient of $r = 0.75$ was used for sample size calculation, resulting in a required sample size of $n = 32.6$. Our study included 38 severe burn patients with septic shock complications (55 episodes of septic shock) who met the selection criteria.

2.2.3. Research content

- General characteristics of the study patients: patient

characteristics, burn injury characteristics, and number of shock episodes/patient.

- Clinical and paraclinical characteristics at the time of diagnosis of septic shock in severe burns patients: changes in signs of systemic inflammatory response, disorders of hemodynamic indices, changes in blood gas indices, disorders of coagulation, hematopoiesis and digestion, disorders of liver and kidney function, changes in some metabolic parameters, characteristics of burn injuries, microbiological results.

- Evaluation of changes in TNF- α , endotoxin, and interleukin-6 levels, as well as treatment outcomes of septic shock in adult patients with severe burns undergoing continuous blood purification therapy using adsorptive membranes

- + Safety of continuous hemodialysis therapy

- + Changes in plasma concentrations of TNF- α , endotoxin, and interleukin-6 in adult patients with severe burns complicated by septic shock undergoing continuous blood purification therapy using adsorptive membranes.

- + Treatment outcomes of septic shock in adult patients with severe burns receiving continuous blood purification therapy using adsorptive membranes.

2.2.4. Implementation method

Each patient enrolled in the study was monitored and documented using a dedicated research medical record. All patients with severe burns admitted to the Intensive Care Unit were treated according to the standardized protocol currently in use at the National Burn Hospital. Upon diagnosis of septic shock, management was carried out in accordance with the Surviving Sepsis Campaign guidelines and the recommendations of the International Society for Burn Injuries (ISBI).

**** Blood Purification Procedure:***

- Technique used: CVVHDF.

- Hemofiltration machine: Prismaflex (Sweden).
- Initiation time of blood purification: Within 6 hours after the diagnosis of septic shock and once the systolic blood pressure has been stabilized above 90 mmHg.
- Selection of adsorptive hemofilter: oXiris hemofilter.
- Vascular access: Femoral vein, subclavian vein, or internal jugular vein. The catheter insertion site for blood purification was selected based on the following priority: no burn injury → superficial burn → granulation tissue → deep burn
- Filtration dose: All patients received an ultrafiltration dose of 25 mL/kg/hour and a dialysis dose of 25 mL/kg/hour.
- Duration of oXiris filter use: Each oXiris filter was used according to its effective lifespan. In case of filter clotting, it was replaced immediately. Monitoring occurred during filtering.
- Discontinuation criteria: Hemoadsorption with oXiris was stopped when vasopressor medications had been withdrawn for at least 12 hours and the patient's blood pressure remained stable. If acute kidney injury persisted, treatment was switched to an M100 hemofilter.

**** Other therapeutic interventions***

- Hemodynamic resuscitation in septic shock: Fluid resuscitation was initiated immediately upon signs of hypotension, using 0.9% sodium chloride solution. The infusion rate was controlled by an infusion pump, with a total volume of 30 mL/kg administered evenly over the first 3 hours. Norepinephrine was initiated or its dose increased when the cardiac index (CI) was $> 2.5 \text{ L/min/m}^2$ and systemic vascular resistance index (SVRI) dropped below $1800 \text{ dyn}\cdot\text{s/cm}^5\cdot\text{m}^2$, with the goal of maintaining a mean arterial pressure (MAP) $\geq 65 \text{ mmHg}$. Epinephrine was added to norepinephrine when the norepinephrine dose exceeded 0.5 mcg/kg/min without achieving a MAP $> 65 \text{ mmHg}$. Dobutamine was used or its dose

increased when CI was < 2.5 L/min/m², stroke volume index (SVI) was < 35 mL/min/m², and SVRI remained within normal limits.

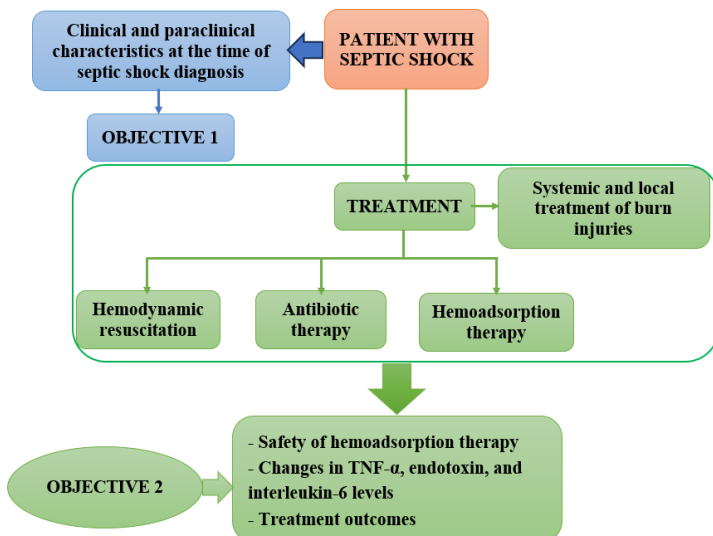
- Intravenous antibiotics were administered as early as possible, ideally within the first hour after the diagnosis of septic shock. A combination antibiotic therapy was used—consisting of at least two antibiotics with different mechanisms of action—targeting all suspected pathogens. Once antibiotic susceptibility results were available, the decision to either continue the current antibiotic regimen or switch to targeted therapy based on the antibiogram was made, depending on the patient's clinical response

2.3. Data analysis: The collected data were analyzed and processed using medical statistical algorithms with Stata version 14.0. A p-value of less than 0.05 was considered statistically significant.

2.4. Research ethics

The study was approved by the Ethics Committee in Biomedical Research of the Military Medical Academy before its implementation (Approval No. 18/2023/CNChT-HĐĐĐ, dated January 10, 2023).

The patient's legal representative (family) was fully informed of the potential benefits and risks associated with participation in the study.



Chapter 3. RESULTS

3.1. General characteristics of study patients

Table 3.1. Characteristics of study patients

Parameter		Value (n = 38)
Age, years, $\bar{X} \pm SD$		35.11 $\pm$ 10.32
Gender, n(%)	Male	33 (86.84)
	Female	5 (13.16)
Burn extent, % DTCT, $\bar{X} \pm SD$		61.08 $\pm$ 17.89
Deep burn area, % DTCT, $\bar{X} \pm SD$		36.89 $\pm$ 16.87
Burn agent, n(%)	Dry heat	31 (81.58)
	Electricity	7 (18.42)
Time of admission after burns, hours, median (Q1 - Q3)		6 (4 – 21)
Inhalation injury, n(%)		22 (57.89)

All patients had severe and very severe burns with burn extent of 61.08% and deep burn area of 36.89%.

Table 3.2. Number of shocks, shock episodes, interval between shock episodes

Parameter		Value
Number of shocks/patient, n (%) (n = 38)	1 time	23 (60.53)
	2 times	13 (34.21)
	3 times	2 (5.26)
Time from burn to first episode of septic shock, days, $\bar{X} \pm SD$, (n = 38)		11.84 $\pm$ 5.42
Interval between shocks, days, median (Q1 - Q3), (n = 17)		5.13 (4.63 – 8.04)

The average time from burn injury to diagnosis of septic shock was 11.84 days. There were 13 patients with septic shock twice (34.21%), 2 patients with septic shock three times (5.26%).

3.2. Clinical and paraclinical characteristics at the time of diagnosis of septic shock in severe burn patients

Table 3.3. Severity characteristics and some signs of

systemic inflammatory response

Parameter	Group	Quantity (n) (n = 55)	Rate (%)
Body temperature, degrees Celsius	< 36.5	12	21.82
	36.5 – 39	32	58.18
	> 39	11	20.00
	Median (Q1 – Q3)	38.1 (36.5 – 39)	
Heart rate, beats/minute	< 110	10	18.18
	≥ 110	45	81.82
	Median (Q1 – Q3)	135 (120 – 145)	
Respiratory rate, times/minute, $\bar{X} \pm SD$		28.58 ± 3.90	
White blood cells, G/L	> 10	41	74.55
	4 – 10	12	21.82
	< 4	2	3.64
	Median (Q1 – Q3)	13.7 (10 – 17.4)	
N/L ratio, median (Q1 – Q3)		11.5 (7.96 – 20.4)	
Procalcitonin, ng/mL, median (Q1 – Q3)		4.95 (1.29 – 10.48)	
TNF- α , pg/mL, median (Q1 – Q3)		20.54 (12.76 – 40.44)	
IL-6, pg/mL, median (Q1 – Q3)		645.45 (244.81 – 1011.28)	
Endotoxin, pg/mL, median (Q1 – Q3)		55.05 (35.65 – 88.8)	
SOFA, score, median (Q1 – Q3)		5 (4 – 6)	
APACHE II, score, $\bar{X} \pm SD$		16.62 ± 4.03	
Number of organ failures, $\bar{X} \pm SD$		1.51 ± 0.90	

Body temperature, heart rate, and respiratory rate all increased. Most patients had leukocytosis (74.55%), and the values of biomarkers were all elevated. The median total SOFA score was 5 points.

Table 3.4. Characteristics of blood oxygenation indices

Parameter	Group	Quantity (n) (n = 55)	Rate (%)
PaO ₂ /FiO ₂ ratio, mmHg	≥ 300	25	45.45
	< 300	30	54.55
	$\bar{X} \pm SD$	314.33 ± 113.53	
Arterial blood lactate,	2.1 - 4	48	87.27
	> 4	7	12.73

mmol/L	Median (Q1 – Q3)	2.6 (2.3 – 3.4)	
ScvO ₂ , %	≥ 70	36	65.45
	< 70	19	34.55
	Median (Q1 – Q3)	76.9 (56 – 84)	

The majority of patients had a PaO₂/FiO₂ ratio below 300 mmHg (52.73%). The median arterial lactate value was elevated (2.6 mmol/L). 34.55% of shock episodes had ScvO₂ < 70%..

Table 3.5. Rate of organ dysfunction according to SOFA score

Organ	SOFA score, n(%), n = 55					Total ≥ 1 point n(%)
	0	1	2	3	4	
Nervous	3 (5.45)	5 (9.09)	47 (85.45)	0	0	52 (94.54)
Circulator	0	51 (92.73)	3 (5.45)	1 (1.82)	0	55 (100)
Respiratory	12 (21.82)	15 (27.27)	19 (34.55)	9 (16.36)	0	43 (78.18)
Kidney	40 (72.73)	7 (12.73)	5 (9.09)	3 (5.45)	0	15 (27.27)
Liver	43 (78.18)	6 (10.91)	5 (9.09)	1 (1.82)	0	12 (21.82)
Hematolog	45 (81.82)	4 (7.27)	5 (9.09)	1 (1.82)	0	10 (18.18)

SOFA score ≥ 2 in the respiratory system occurred in 50.91% of septic shock episodes. Renal, hepatic, and hematological organ disorders according to SOFA score appeared in 27.27%; 21.82%, and 18.18%, respectively.

Table 3.6. Blood culture results

Parameter	Group	Quantity (n) (n = 55)	Rate (%)
Positive culture	No	28	50.91
	Yes	27	49.09
Gram	Negative	23	85.19
	Positive	4	14.81
Bacteria	<i>Acinetobacter baumannii</i>	10	37.04

name	<i>Pseudomonas aeruginosa</i>	11	40.74
	<i>Klebsiella pneumoniae</i>	1	3.7
	<i>Klebsiella aerogenes</i>	1	3.7
	<i>Staphylococcus aureus</i>	1	3.7
	<i>Enterococcus faecium</i>	2	7.41
	<i>Staphylococcus lentus</i>	1	3.7

In 55 episodes of septic shock, 27 episodes of septic shock had bacterial growth in blood cultures, accounting for 49.09%; Gram (-) infection was the main cause (85.19%).

3.3. Changes in TNF- α , endotoxin, and interleukin-6 levels and treatment outcomes of septic shock in adult patients with severe burns undergoing continuous blood purification therapy using adsorptive membranes

3.3.1. Safety assessment of dialysis

Table 3.7. Filter parameters

Parameter	Value (n = 55)	Min - Max
Dialysis time, hours, median (Q1 – Q3)	50 (39.5 – 83.5)	31 – 502
Life/01 oXiris filter, hours, $\bar{X} \pm$ SD	15.87 $\pm$ 4.85	9.38 – 24.63
Time to start dialysis after diagnosis of septic shock, minutes, median (Q1 – Q3)	90 (60 – 120)	30 – 180

The mean filter life was 15.87 hours.

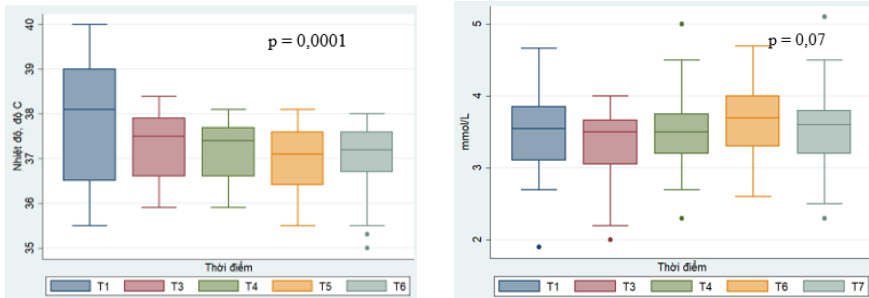


Figure 3.1. Box plot of temperature and blood potassium

concentration changes

After continuous hemodialysis, body temperature and blood potassium concentration remained within the allowable range.

Table 3.7. Changes in blood coagulation status

Parameter	Time, n(%), n = 55				p
	T1	T4	T5	T6	
Blood clotting disorder	55 (100)	55 (100)	55 (100)	49 (89.09)	0.001
Hypocoagulation	44 (80)	51 (92.73)	49 (89.09)	46 (83.64)	0.22
Hypercoagulation	45 (81.82)	44 (80)	41 (74.55)	23 (41.82)	0.0001

Hypercoagulability decreased significantly ($p < 0.001$). There was no difference in hypocoagulability between time points ($p > 0.05$).

3.3.2. Changes in TNF- α , endotoxin, and interleukin-6 levels and treatment outcomes of septic shock in adult patients with severe burns undergoing continuous blood purification therapy using adsorptive membranes

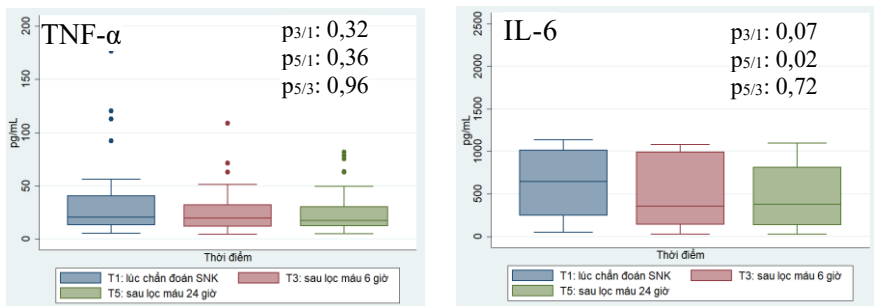


Figure 3.2. Box plot of changes in plasma TNF- α and IL-6 concentrations

After 24 hours of continuous hemodialysis, plasma IL-6 concentration decreased significantly compared to the time of septic shock diagnosis ($p < 0.05$).

Table 3.8. Changes in endotoxin levels over time

Time	Nội độc tố, pg/mL, n = 55	
	Trung vị (Q1 – Q3)	Min – max
T1	55.05 (35.65 – 88.8)	16,2 – 1201.3
T3	68.3 (53.45 – 120.25)	11,5 – 3383,9
T5	47 (27.5 – 89.55)	9,2 – 199,9
p	p _{3/1} : 0.12 - p _{5/1} : 0.45 - p _{5/3} : 0.045	

After 24 hours of continuous hemodialysis, plasma endotoxin concentrations decreased significantly compared with after 6 hours of continuous hemodialysis ($p < 0.05$).

Table 3.9. Treatment results

Thông số	Giá trị
Recover from septic shock rate, n (%) (n = 55)	36 (65.45)
Recovery time after septic shock, (n = 36), hour, median (Q1 – Q3)	29 (23 – 44.5)
Mortality rate, n (%) (n = 38)	23 (60.53)

In 55 episodes of septic shock, 36 episodes of shock recovery (65.45%). The median time of shock recovery was 29 hours. The mortality rate was 60.53%.

Table 3.10. Association between some factors and shock recovery

Parameter	Non-shock recovery (n = 19)	Shock recovery (n = 36)	p	Multivariate analysis	
				Coef.	p
Burn extent	68.68 ± 15.54	58.17 ± 18.22	0.043	0.02	0.74
Deep burn area	51 (30 – 58)	30 (21 – 51)	0.037	-0.06	0.35
SOFA –T ₁ , score, median (Q1 - Q3)	6 (5 – 9)	4, 5 (4 – 5.5)	0.0006	-1.26	0.02
VIS –T ₂ , median (Q1 - Q3)	50 (30 – 70)	27.5 (20 – 37.5)	0.03	-0.02	0.19

HATB $-T_1$, mmHg, $\bar{X} \pm$ SD	55.53 $\pm$ 3.29	58.19 $\pm$ 3.07	0.009	0.34	0.15
Lactate $-T_1$, mmol/L, median (Q1 - Q3)	3 (2.6 – 3.8)	2.45 (2.2 – 2.8)	0.04	-0.59	0.24
IL-6 $-T_1$, pg/mL, median (Q1 - Q3)	1013.20 (640.84 – 1054.09)	456.94 (194.46 – 923.71)	0.003	0.001	0.62
Blood culture bacterial growth, n (%)	13 (68.42)	14 (38.89)	0.041	-0.64	0.68
Secondary necrosis, n(%)	11 (57.89)	6 (16.67)	0.003	-2.35	0.04 7
First filter retention time, hours, median (Q1 - Q3)	14 (11.5 – 20)	10.25 (8.5 – 12.25)	0.002	-0.31	0.04 8
cons.				-3.18	0.80

Multivariate analysis showed that the SOFA score, the presence of secondary necrotic burn injury at the time of septic shock diagnosis, and the duration of the first hemofilter use after septic shock onset were independently associated with shock reversal in patients with severe burns complicated by septic shock ($p < 0.05$)

Table 3.11. Correlation between the first filter retention time and shock recovery

Parameter	First filter maintenance time, hours					
	> 11 hours	$\leq$ 11 hours	> 12 hours	$\leq$ 12 hours	> 13 hours	$\leq$ 13 hours
Non-shock recovery, n(%)	15 (78.95)	4 (21.05)	14 (73.68)	5 (26.32)	12 (63.16)	7 (36.84)

(n = 19)						
Shock recovery, n(%) (n = 36)	14 (38.89)	22 (61.11)	9 (25)	27 (75)	8 (22.22)	28 (77.78)
Coef.	1.77		2.13		1.79	
_cons	-0.17		-0.44		-0.41	
RR (95%CI)	3.36 (1.28 – 9.85)		3.89 (1.63 – 9.29)		3 (1.43 – 6.37)	
AUC	0.70		0.74		0.70	
Sensitivity (%)	61.11		75		77.78	
Specificity (%)	78.95		73.68		63.16	
Accuracy (%)	67.27		74.55		72.73	
p	0.007		0.001		0.004	

Changing the first filter at 12 hours after continuous hemodialysis increased the likelihood of recovery from septic shock 3.89 times ($p < 0.01$).

Chapter 4. DISCUSSION

4.1. Clinical and paraclinical characteristics at the time of septic shock diagnosis in patients with severe burns

The primary mechanism leading to septic shock is the activation of immune response cells that produce and release large amounts of cytokines into the bloodstream in response to bacterial endotoxins. This cytokine storm causes circulatory disturbances and multiple organ dysfunction. Among the cytokines involved, TNF- α plays a central role in the systemic inflammatory response, while IL-6 is a key pro-inflammatory mediator during the early stages of inflammation.

In burn patients, studies have shown that plasma levels of TNF- α and IL-6 are significantly higher in those who develop sepsis or septic shock compared to those without these complications. In our study, plasma concentrations of TNF- α and IL-6 at the time of septic shock diagnosis were markedly elevated—20.54 pg/mL (12.76–40.44 pg/mL) and 645.45 pg/mL (244.81–1011.28 pg/mL), respectively. These findings emphasize the

prognostic importance of plasma TNF- α and IL-6 levels in assessing the severity of septic shock and are consistent with its underlying pathophysiology. Elevated endotoxin levels in the bloodstream are commonly observed in cases of gram-negative bacteremia. In patients with gram-positive or fungal bloodstream infections, endotoxin levels may rise due to the translocation of gram-negative endotoxins from the gastrointestinal tract into the circulation. Our study also found that at the time of septic shock diagnosis, plasma endotoxin levels were elevated, with a median value of 55.05 pg/mL (35.65–88.8 pg/mL).

In patients with sepsis and septic shock, the development of acute respiratory distress syndrome (ARDS) occurs rapidly and is considered a major risk factor for increased in-hospital mortality. Our findings are consistent with this observation: the majority of septic shock episodes in our study were associated with respiratory organ dysfunction, as assessed by the SOFA score (78.18%). Among these, 50.91% had a respiratory SOFA score of ≥ 2 . For patients who were mechanically ventilated during septic shock episodes, we standardized the Glasgow Coma Scale (GCS) score to 10 at all time points (excluding the verbal component), since the precise degree of sedation and drug accumulation could not be reliably assessed. As a result, in our study, most septic shock episodes were associated with a respiratory SOFA score (74.54%), with 52.72% having a score of ≥ 2 . Renal, hepatic, and hematologic dysfunction (as measured by the SOFA score) were present in 27.27%, 21.82%, and 18.18% of septic shock episodes, respectively. These relatively lower rates may be due to the fact that renal and hepatic dysfunction often result from prolonged tissue hypoperfusion. In our study, septic shock was diagnosed in patients already being treated in the intensive care unit, where hypotension was detected early and managed promptly with timely hemodynamic support.

Our culture results were consistent with previous studies conducted in burn patients. Blood culture findings showed that gram-negative bacteremia predominated, accounting for 86.21% of cases. The most commonly isolated pathogens were *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, identified in 37.04% and 40.74% of positive cultures, respectively.

4.2. Changes in TNF- α , endotoxin, and interleukin-6 levels and treatment outcomes of septic shock in adult patients with severe burns undergoing continuous blood purification therapy using adsorptive membranes

4.2.1. Assessment of the safety of blood purification therapy

After blood purification, patients experienced a significant decrease in body temperature ($p < 0.001$); however, temperatures remained within the acceptable range (36.5°C to 38°C).

In our study, the blood withdrawal procedure was carried out strictly according to protocol. Blood flow was initiated at 100 mL/min, and systolic blood pressure was closely monitored. If systolic blood pressure remained stable above 90 mmHg, the flow rate was increased by 20 mL/min every 10–15 minutes, until the target rate of 180 mL/min was achieved. As a result, no cases of immediate hypotension occurred following connection to the hemofilter.

4.2.2. Changes in plasma concentrations of TNF- α , endotoxin, and interleukin-6

In cases complicated by septic shock, plasma concentrations of TNF- α and IL-6 typically reach their first peak within 3 hours, followed by a second TNF- α peak at approximately 24 hours after the onset of septic shock. After 24 hours, both TNF- α and IL-6 levels tend to gradually decline, with concentrations at 48 hours dropping to roughly 50% of their peak levels.

According to the manufacturer, the oXiris hemofilter exhibits its

strongest adsorption capacity within the first 6–8 hours, with effectiveness maintained for up to 24 hours depending on the membrane's saturation level. Based on this information, in our study, we measured plasma TNF- α and IL-6 levels at two specific time points—6 hours and 24 hours after the start of hemofiltration—to evaluate the adsorption performance of the membrane while minimizing the influence of the natural cytokine decline beyond 24 hours of septic shock onset. Due to a median delay of 90 minutes between the diagnosis of septic shock and the initiation of blood purification—and considering resource limitations—we only measured plasma TNF- α and IL-6 concentrations at the time of septic shock diagnosis, and not at the exact initiation of hemofiltration.

Our results showed that plasma TNF- α and IL-6 levels decreased at 6 hours post-filtration compared to baseline (time of diagnosis). However, the differences were not statistically significant ($p > 0.05$). This may be explained by the cytokine release dynamics in septic shock, where peak TNF- α and IL-6 levels occur within 1–3 hours after the onset of septic shock. The aim of hemoadsorption in this context is not necessarily to reduce cytokine levels below baseline, but rather to prevent them from reaching their peak, thereby mitigating the inflammatory cascade.

At 24 hours after hemofiltration, plasma concentrations of TNF- α and IL-6 continued to decrease compared to levels at the time of septic shock diagnosis. However, the reduction in TNF- α was not statistically significant. This may be attributed to the second peak of plasma TNF- α typically occurring around 24 hours after the onset of septic shock. Following the diagnosis, patients were treated according to the standard septic shock management protocol, combined with continuous hemoadsorption therapy, which may have helped prevent TNF- α from reaching its second peak and contributed to its overall decline compared

to baseline levels. The effectiveness of the therapy was further supported by a statistically significant reduction in IL-6 levels at 24 hours post-filtration compared to baseline: 378.51 pg/mL (135.26 – 811.38 pg/mL) vs. 645.45 pg/mL (244.81 – 1011.28 pg/mL) ($p < 0.05$). Recent studies have also demonstrated that the use of the oXiris membrane in patients with septic shock leads to a reduction in plasma cytokine levels following hemofiltration.

“Endotoxin removal” is a key objective in therapeutic interventions for septic shock. With advancements in medical science and in-depth research on sepsis, new membrane materials—such as the oXiris filter—have been developed to adsorb cytokines, endotoxins, and other inflammatory mediators. Studies have demonstrated the efficacy of oXiris in adsorbing endotoxins in patients with septic shock. In our study, after 6 hours of continuous hemofiltration (approximately 7–8 hours after septic shock diagnosis), plasma endotoxin levels were higher compared to baseline levels at the time of diagnosis ($p > 0.05$). This may be explained by the ongoing release of bacterial endotoxins into the circulation, which peaks within 6–12 hours following the onset of septic shock. In addition, antibiotic therapy contributes to bacterial lysis, potentially leading to a massive release of endotoxins into the bloodstream. Consequently, continuous hemoadsorption may initially become saturated, resulting in rising endotoxin levels. We then replaced the saturated hemofilter and continued therapy in combination with immunomodulatory management, which led to a progressive decrease in endotoxin concentrations. This was clearly reflected in our findings: at 24 hours after hemofiltration, endotoxin levels were significantly lower compared to those at 6 hours ($p < 0.05$). These results are consistent with previously reported observations and may further support the effectiveness of continuous blood purification using adsorptive membranes in the management of septic shock.

4.2.3. The recovery rate following septic shock

Improving the treatment of septic shock is essential for increasing the survival rate of patients with severe burns. The primary indicator used to evaluate the effectiveness of septic shock management is shock reversal. Shock reversal represents the outcome of a comprehensive therapeutic strategy, in which blood purification serves as a supportive intervention. In our study, the shock reversal rate was 65.45%, which is higher than that reported in two previous studies involving patients with comparable age, total burn surface area (TBSA), and deep burn extent. Specifically, in a 2017 study, the shock reversal rate was 46.67%, with a mean time to reversal of 86.57 ± 37.14 hours; and in a 2019 study, it was 46.43%, with a mean reversal time of 42.15 ± 11.77 hours. In contrast, the median time to shock reversal in our study was 29 hours (IQR: 23–44.5 hours). This earlier shock reversal resulted in reduced peripheral vasoconstriction, improved tissue oxygenation, and created more favorable conditions for the healing of superficial burns and granulation tissue formation in deep burns, thereby accelerating the overall wound healing process. These findings reflect notable progress in the management of septic shock in severe burn patients and highlight the contributory role of continuous blood purification using adsorptive membranes in achieving better clinical outcomes.

CONCLUSION

1. Clinical and paraclinical characteristics at the time of septic shock diagnosis in patients with severe burns

- A respiratory SOFA score ≥ 2 was observed in 50.91% of septic shock episodes. The rates of renal dysfunction, hepatic dysfunction, and thrombocytopenia (platelet count < 150 G/L) were 27.27%, 21.82%, and 18.18%, respectively. Plasma levels of pro-inflammatory cytokines and endotoxins were markedly elevated at the time of diagnosis.

- Gram-negative bacteremia was predominant, accounting for 85.19% of cases. All gram-negative isolates were classified as multidrug-resistant (MDR) pathogens.

2. Changes in TNF- α , endotoxin, and interleukin-6 levels and treatment outcomes of septic shock in adult patients with severe burns undergoing continuous blood purification therapy using adsorptive membranes

- No cases of complications related to the blood purification technique were observed. There were also no significant differences in coagulation disorders or blood electrolyte imbalances at the evaluated time points ($p > 0.05$).

- After 24 hours of continuous blood purification, plasma IL-6 levels significantly decreased compared to those at the time of septic shock diagnosis (378.51 [135.26–811.38] pg/mL vs. 645.45 [244.81–1011.28] pg/mL, $p < 0.05$). Additionally, plasma endotoxin levels were significantly lower at 24 hours compared to 6 hours after the start of hemofiltration (47 [27.5–89.55] pg/mL vs. 68.3 [53.45–120.25] pg/mL, $p < 0.05$).

- The shock reversal rate was 65.45%. Multivariate analysis showed that the SOFA score, the presence of secondary necrotic burn injury at the time of septic shock diagnosis, and the duration of use of the first hemofilter after septic shock onset were independently associated with shock reversal in patients with severe burns complicated by septic shock ($p < 0.05$). Notably, replacing the first hemofilter at 12 hours after the initiation of blood purification increased the likelihood of shock reversal by 3.89 times ($p < 0.01$).

LIST OF WORKS ANNOUNCING THE RESEARCH RESULTS OF THE THESIS TOPIC

1. Ngo Tuan Hung, Nguyen Nhu Lam, Nguyen Hai An et al. (2024). Evaluation of the effectiveness of continuous hemofiltration using adsorption membranes on the treatment of septic shock in severe burn patients. *Journal of Military Pharmaco-medicine*, 49(9): 163-172.

2. Ngo Tuan Hung, Nguyen Nhu Lam, Nguyen Hai An et al. (2024). To evaluate safety of the adsorption hemofiltration technique for treatment of septic shock in severe burn patients. *Journal of Disaster medicine and burn injuries*, 6: 22-28.

3. Ngo Tuan Hung, Nguyen Nhu Lam, Nguyen Hai An et al. (2025). Prevalence and degree of organ dysfunction at the time of diagnosis of septic shock in severe burn patients. *Journal of Disaster medicine and burn injuries*, 1: 7-14.