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RESEARCH ARTICLE

The Immunoadsorption Effect of Veno-arterial Extracorporeal Membrane Oxygenation in Refractory Septic Shock, Ventilator-associated Pneumonia, and Acute Respiratory Distress Syndrome Following Severe Pulmonary Contusions

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Abstract:

Background:

The utilization of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for immunoadsorption has proven efficacious in reducing mortality rates among neonatal and pediatric patients afflicted with severe sepsis and septic shock. However, the effectiveness of this treatment in adult patients with septic shock remains controversial.

Objective:

This study was designed to assess the potential of VA-ECMO as an immunoadsorption therapy in patients with severe sepsis and septic shock. The primary objective of this study is to evaluate the efficacy of VA-ECMO in improving clinical outcomes, including acute respiratory distress syndrome (ARDS) and ventilator-associated pneumonia (VAP), weaning from mechanical ventilation, the length of intensive care unit (ICU) stay, and mortality rates in patients with concurrent severe pulmonary contusions, septic shock, and respiratory failure resulting from ARDS and VAP.

Methods:

This study enrolled a cohort of 100 adult patients with severe pulmonary contusions resulting in persistent respiratory failure despite ten days of mechanical ventilation. These patients subsequently developed severe sepsis, VAP with ARDS presentation, and high Murray score (>3 points), Sequential Organ Failure Assessment (SOFA) score (> 12 points), and Clinical Pulmonary Infection Score (CPIS) (> 6 points). The patients were then divided into two groups: group A (n = 50) received conventional management, while group B (n = 50) underwent VA-ECMO. Moreover, the outcomes, including improvement in ARDS and VAP, successful weaning from mechanical ventilation, length of ICU stay, improvement of one or all parameters of Murray, SOFA, and CPIS scores, morbidity rate, and mortality rate were compared between the two groups and recorded after 14 days of treatment.

Results:

This study revealed that patients in group B showed significant improvement in Murray, SOFA, and CPIS scores. Furthermore, a large percentage of patients in group B were successfully weaned from both inotropic support and mechanical ventilation and were discharged from ICU. However, no significant difference in the mortality rate was observed between the two groups.

Conclusion:

VA-ECMO notably impedes the progression of sepsis, shortens ICU stay, and expedites the weaning from inotropic support and mechanical ventilation. However, it has no impact on the mortality rate of adult patients with septic shock.

Keywords: Severe sepsis, Septic shock, ARDS, VAP, Prolonged ventilation, AVECMO.

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1. INTRODUCTION

The application of extracorporeal membrane oxygenation (ECMO) in adult patients with septic shock remains a matter of contention. ECMO serves as a supplementary treatment for severe acute respiratory distress syndrome (ARDS) cases with respiratory failure, particularly for those suffering from circulatory failure due to septic shock. Veno-arterial ECMO (VA-ECMO) may benefit patients who exhibit no improvement with conventional mechanical ventilation and standard management methods, including poor responses to

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inotropes and vasopressors [1]. Recent evidence has emerged regarding the effectiveness of VA-ECMO in adult patients experiencing septic shock, as it is a reliable circulatory and ventilatory support method [1, 2] with immunoadsorption effects on bacteremia and toxemia. This treatment option has been shown to improve short- and long-term outcomes in patients with bacterial septicemia, severe sepsis, and septic shock. Although its effectiveness in reducing mortality rates in neonatal and pediatric patients with septic shock has already been established [3 - 5], its effect on adult patients with septic shock remains controversial, despite the publication of successful cases. Further research is required to establish a final protocol for the use of VA-ECMO in adult patients with severe sepsis, septic shock, ARDS, and ventilator-associated pneumonia (VAP) [6, 7]. VA-ECMO was successfully employed during the influenza A (H1N1) outbreaks, significantly reducing morbidity and mortality rates. Nonetheless, further research is necessary to determine its efficacy in non-influenza patients with ARDS [8, 9].

1.1. Objective

The objective of this study is to assess the potential VA-ECMO as an immunoadsorption therapy in improving the clinical outcomes in adult patients with severe sepsis complicated by septic shock, including ARDS and VAP, weaning from mechanical ventilation, the length of intensive care unit (ICU) stay, and mortality rates in patients with concurrent severe pulmonary contusions, septic shock, and respiratory failure attributed to ARDS and VAP.

2. MATERIALS AND METHODS

This prospective cohort study enrolled 100 patients aged 18 – 65 years who had severe pulmonary contusions due to severe chest trauma and who showed respiratory failure with severe ARDS as determined by the Murray score (> 3 points) from King Abdul-Aziz Specialist Hospital between September 2020 and February 2022. The Research Ethics Committee of the hospital approved this study. All patients received controlled mechanical ventilation (CMV) for ten days with a respiratory rate of 12/min, a positive end-expiratory pressure (PEEP) of 5 cm/H_2O, and the fraction of inspired oxygen (FIO_2) adjusted to maintain arterial oxygen saturation above 90%. They were also administered sedatives, including fentanyl and midazolam intravenous infusion, to achieve a Richmond Agitation-Sedation Scale (RASS) score of -2–-3 points (Table **1**) [10]. In addition, all patients were administered broad-spectrum antibiotics in the form of 1 gm meropenem *via* slow intravenous infusion at eight-hour intervals. Subsequent to three days of ventilation, a qualitative sputum culture was obtained from all patients, and the antibiotic regimen was adjusted in accordance with the culture results. On the second day of ventilation, enteral feeding was initiated using a feeding pump. The feeding rate was established at 70 mL of Ensure plus (Abbot) with a caloric density of 1.47 kcal/mL, designed to provide patients with an estimated 2500 kcal within 24 hours, based on an approximation of 35 kcal/kg [20]. Furthermore, all patients underwent percutaneous tracheostomy on the 7^{th} day of ventilation. To prevent VAP, a five-point bundle was implemented on all patients. This included raising the head of the bed by 30º to 45º, conducting a daily assessment for potential extubation, unitizing an endotracheal tube with subglottic secretion drainage, administering oral care with oral antiseptics, and initiating safe enteral nutrition within 24–48 hours of admission to the ICU and ventilation.

The sample size of this study was restricted to 100 patients. Inclusion criteria were set as follows: 1) Patients who exhibited no improvement in respiratory function despite ten days of ventilation, and 2) those who continued to experience severe ARDS with a Murray score of > 3 points (Table **2**) [11 - 20]. Exclusion criteria involved: 1) Patients who developed severe sepsis with a SOFA score of > 12 points (Table **3**) [12, 13], 2) those who developed VAP with a CPIS score of > 6 points (Table **4**) [14], or 3) those who required nor-adrenaline infusion > 2 mg/kg/min as circulatory support due to circulatory failure (septic shock).

The parameters of the 100 patients mentioned earlier indicated the need for VA-ECMO. However, given the controversial nature of VA-ECMO as a treatment modality, the study subjects were randomly assigned to a control group (group A, n = 50) and an intervention group (group B, n = 50). Group A received standard conventional management, while group B received VA-ECMO. The study spanned two weeks, during which all patients in both groups were assessed at regular intervals, specifically at the end of the first five days, the end of the second five days, and the end of the final four days.

Table 1. Richmond's agitation sedation scale [10].

Score	Term	Description
+4	Overtly combative and violent to staff	
+3	Very agitated and removes tube(s) or catheter(s)	
+2	Agitated and fights ventilator	
+1	Anxious but no aggressive movements	
0	Alert and calm	
−1	Drowsy but has sustained awakening (eye contact to voice >10 s)	
−2	Light sedation and awakens with eye contact to voice (<10 s)	
−3	Moderate sedation with eye-opening to voice (but no eye contact)	
−4	Deep sedation with no response to voice, but movement or eye opening to physical stimulation	
−5	Unarousable with no response to voice or physical stimulation	

Table 2. Murray score [11].

Clinical parameter of Murray score	0	1	2	3	4
Hypoxic index PaO_2/FIO_2 On FIO_2 100%	≥ 300	299-225	224-175	174-100	<100
Chest X-ray	Non	1 quadrant infiltrated	2 quadrant infiltrated	3 quadrant infiltrated	4 quadrant infiltrated
PEEP	≤ 5	6-8	9-11	12-14	≥ 15
Compliance ml /1 cm H_2O	≥ 80	79-60	59- 40	39-20	≤ 19

Table 3. SOFA score [12-13]

SOFA score	1	2	3	4
Respiration: PaO_2/FIO_2 (mm Hg)	<400	<300	<220	<100
Coagulation profile: Platelets count in $10^3/mm^3$	<150	<100	<50	≤20
Liver: Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6.0-11.9	≥12.0
Cardiovascular: Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS: Glasgow Coma Score as indicator for septic encephalopathy	13-14	10-12	6-9	<6
Renal: Creatinine (mg/dL) or urine output (UOP) (mL/d)	1.2-1.9	2.0-3.4	3.5-4.9 or UOP<500	≥5.0 or UOP <200

Note: MAP: mean arterial blood pressure, PaO_2: partial pressure of oxygen in arterial blood

Table 4. shows CPIS score [14].

CPIS	0	1	2
Tracheal secretion	Rare	Abundant	Abundant & purulent
Chest X-ray infiltrate	No infiltrate	Diffuse	Localized
Temperature ºC	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
Leucocytic count per mm3	≥ 4000and ≤ 11000	< 4000 or > 11000	< 4000 or > 11000 +band form ≥ 500
Hypoxic index PaO2/FIO2 mmHg	>240 or ARDS	-	≤ 240 and no evidence of ARDS
Microbiology	Negative	-	Positive

Throughout the study period, both groups of patients were closely monitored using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system [15 - 20], as well as the scores for severe sepsis (SOFA) and ARDS (CPIS). The findings of these measurements were compared between the two groups [17 - 20].

To evaluate lung tissue recovery from ARDS and VAP, laboratory indicators such as lactate dehydrogenase (LDH) and C-reactive protein (CRP) were utilized. These indicators were collected concurrently and compared between groups A and B. Additionally, improvements in lung mechanics, including compliance measurements and the response of patients to lung recruitment maneuvers, were used to assess the restoration of lung ventilatory functions [17 - 20]. A lung recruitment maneuver is a clinical procedure used to assess lung compliance in patients with ARDS or other conditions that cause difficulty in breathing. It involves increasing the peak inspiratory pressure to 40 cm/H_2O for 40 seconds, followed by observing oxygen saturation (SpO_2) levels. A positive response to the maneuver is typically defined as an improvement in SpO_2 levels to more than 95% [16 - 20].

This study involved recording and comparing the number of patients in both groups who were successfully weaned from mechanical ventilation according to our established protocol. Specifically, extubated patients were closely observed in the ICU for 24 hours before being discharged, and the number of discharged patients was recorded and compared between the two groups. With the aim of validating bacteriological cure, three sputum cultures were collected from all patients during the study period: one at the end of the first five days, another at the end of the second five days, and a final one at the end of the study period. Patients who had not shown any improvement in their SOFA and CPIS measurements by the end of the study period were classified as cases of morbidity. The number of such cases was documented and compared between the two groups. Similarly, failure to be weaned from mechanical ventilation during the study period was also an indicator of morbidity [17 - 20]. The number of patients with this condition was also documented and compared between the two groups. Finally, the number of patients discharged from the ICU during the study period was recorded and compared between the two groups.

The process of connecting patients to VA-ECMO involved accessing their venous blood from a large central vein, particularly the right femoral vein, through an "access line." The blood was then directed through an oxygenator and back into the arterial system near the right atrium *via* a "return line." In severe respiratory and circulatory failure cases where the flow through a single access cannula was not enough to sustain the high ECMO flow rate needed, a second venous access cannula was used, usually the right internal jugular. However, in these specific cases, the left femoral artery was used instead of the right femoral vein to direct the blood back into the arterial system. Once VA-ECMO was fully connected and the flow established, the mechanical ventilation was discontinued, and a PEEP was set to 3 cm H_2O, while FIO_2 was kept at 100%. For up to 72 h after ECMO initiation, cytokine adsorption filters (CytoSorbents Europe, Berlin, Germany) were used, with regular replacement every 24 hours. A team of experts was responsible for applying and maintaining ECMO equipment. At the end of the study, all patients with a Glasgow Coma Scale (GCS) [19, 20] score < 9 points underwent a computerized axial tomography (CAT) scan to rule out any potential organic brain damage in either group.

2.1. Statistical Analysis of the Data

Data were fed to the computer using IBM *SPSS software package version 21.0.*

Qualitative data were described using numbers and percentages. Comparison between different groups regarding categorical variables was tested using Chi-square test [17 - 20].

2.2. Chi-square Test

It tests the association between qualitative nominal variables, it is performed mainly on frequencies. It determines whether the observed frequencies differ significantly from the expected frequencies [17 - 20].

2.3. Sample Size Calculation

The sample size should depend on the research context, including the researcher's objectives and proposed analyses.

The following formula was used to calculate the required sample size in this study;

Where n is the sample size, Z is the statistic corresponding to the level of confidence, P is expected prevalence, and d is precision (corresponding to effect size). The level of confidence was 95%. By using this equation the sample size was 100 cases (i.e. 50 cases in each group). A number of expired patients from the two groups were collected and compared, then the new number of patients was recalculated after the expired patients were subtracted from the total sample size giving us a new sample size. This was done 3 times in the study at the end of the first 5 days, at the end of the second 5 days, and at the end of the last four days.

X^2 is the value of the chi-square test is used to calculate the p-value. The P value is considered highly significant if less than 0.05 and marked by (*) beside the significant number in our study [17 - 20].

3. RESULTS

Table **5** represent the demographic data of patients in both groups and shows no significant difference between the two groups as regard age and sex.

Table **6** compares the mortality rate in both groups all over the studied duration and shows a non-significant difference between the two groups in all studied duration as (2, 2 and 3 patients) died at the end of 5,10,14 days consecutively from group A while (2, 2 and 2 patients) died from group B at the same duration of the study.

Table **7** compares the APACH II score of patients in both groups all over the studied duration and shows significant improvement in that score in patients of group B in all studied duration as 19, 31 and 39 patients had scoreless <15 at the end of 5,10,14 days consecutively, while 9, 14 and 20 patients in group A achieved a same score at the same duration of the study.

Table **8** compares the GCS score of patients in both groups all over the studied duration and shows significant improvement in that score in patients of group B in all studied duration as 21, 32 and 40 patients had scores>12 at the end of 5, 10, 14 days consecutively, while 11,16 and 21 patients in group A achieved the same score at the same duration of the study.

Table **9** compares the MAP of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 18, 30 and 36 patients had MAP >95 mmHg without inotropic support at the end of 5, 10, 14 days consecutively, while 7,18 and 20 patients in group A achieved same MAP at the same duration of the study.

Table **10** compares the bilirubin level of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 20, 33 and 41 patients had bilirubin ≤1.9 mg/dL at the end of 5,10,14 days consecutively, while 9, 19 and 22 patients in group A achieved same bilirubin level at the same duration of the study.

Table **11** compares the creatinine level of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 19, 28 and 38 patients had creatinine ≤1.9 mg/dL at the end of 5,10,14 days consecutively, while 9,16 and 18 patients in group A achieved same creatinine level at the same duration of the study.

Table **12** compares the platelets count of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 18,25 and 34 patients had platelets > 100.000 at the end of 5,10,14 days consecutively, while 10,17 and 20 patients in group A achieved same platelets count at the same duration of the study.

Table **13** compares the nature of the tracheal secretion of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 20, 30 and 42 patients had normal tracheal

secretion at the end of 5,10,14 days consecutively, while (12, 16 and 20 patients) in group A achieved same tracheal secretion at the same duration of the study.

Table **13** compares parenchymatous lung infiltrate on the chest X-ray of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 23, 32 and 43 patients had almost normal chest X-rays at the end of 5,10,14 days consecutively, while 12, 18 and 21 patients in group A achieved same chest Xray at the same duration of the study.

Table **13** compares the core temperature of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 21, 31 and 41 patients had core temperatures≥ 36.5 and ≤ 38.4 at the end of 5,10,14 days consecutively, while 10, 20 and 22 patients in group A achieved same core temperature at the same duration of the study.

Table **13** compares the total leucocytic count of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 23, 33 and 40 patients had leucocytic count ≥ 4000and ≤ 11000 thousand/mL at the end of 5,10,14 days consecutively, while 10, 21 and 24 patients in group A achieved same leucocytic count at the same duration of the study.

Table **13** compares the hypoxic index(PaO_2/FIO_2) of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 28, 38 and 44 patients had hypoxic index >240 at the end of 5,10,14 days consecutively, while 19, 24 and 33 patients in group A achieved same hypoxic index at the same duration of the study.

Table **13** compares the microbiological results of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 29, 35 and 43 patients had negative qualitative BAL culture and at the end of 5,10,14 days consecutively, while 20, 25 and 30 patients in group A had negative qualitative sputum culture at the same duration of the study.

Table **14** compares lung compliance in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 19, 28 and 35 patients had measured lung compliance of ≥ 80 ml/ 1 cm H_2O at the end of 5,10,14 days consecutively, while 10,13 and 20 patients in group A achieved same measured lung compliance at the same duration of the study.

Table **15** compares the number of patients who respond to the recruitment maneuver in both groups all over the studied duration and shows a significantly higher number of patients who respond to this maneuver in group B in all studied duration as 21, 31 and 40 patients were responder at the end of 5,10,14 days consecutively, while 12, 18 and 22 patients in group A were responder at the same duration of the study.

Table **15** compares the number of patients who failed to be weaned in both groups at the end of the studied duration and shows a significant lower number of patients in group B (only 3 patients out of 44 patients) compared to group A (16 patients out of 43 patients).

Table **15** compares the total number of patients discharged from the ICU at end of the studied period and shows a significantly higher number of patients discharged from group B (41 patients) compared to group A (27 patients).

Table **16** compares the LDH levels of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 23, 32 and 42 patients had LDH < 200 U/L at the end of 5, 10, 14 days consecutively, while 8,19 and 25 patients in group A achieved same LDH level at the same duration of the study.

Table **17** compares the C-reactive protein levels in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as 20, 33 and 43 patients had C-reactive protein level <100 mg/L at the end of 5,10,14 days consecutively, while 8, 20 and 27 patients in group A achieved same C-reactive protein level at the same duration of the study.

Table **18** compares the morbidity recorded in all patients between the two groups in the studied periods.

Table 5. Demographic data of the studied patients' groups.

-	Group A		Group B		X^2 P value
Age Group	**(n=50)**	**%**	**(n=50)**	**%**	
18-22years	18	36.0	19	38.0	0.212 0.9755 N.S.
23-35	13	26.0	12	24.0	
36-45	14	28.0	15	30.0	
46-50	5	10.0	4	8.0	
Sex	**(n=50)**	**%**	**(n=50)**	**%**	-
Male	43	86.0	42	84.0	0.078 0.779 N.S.
Female	7	14.0	8	16.0	

Table 6. Mortality recorded in both groups during the studied period.

Mortality reported	Group A (n=50)		Group B (n=50)		P value
	NO	%	NO	%	
End of 1ST 5 Days	**2**	**4.0**	**2**	**4.0**	**1.0 N.S.**
End of 2nd 5 Days	2	4.0	2	4.0	1.0 N.S.
End of 3rd 4 Days	3	6.0	2	4.0	0.21051.0 N.S.
Total mortality	7	14.0	6	12.0	0.23 1.0 N.S.

Table 7. APACHII score [15] for all patients in the studied period.

APACHII	Group A		Group B		X^2 P value
End of the 1st 5 days	**(n = 48 patients)**	**%**	**(n = 48 patients)**	**%**	7.512 0.032*
>25	18	37.5	8	16.7	
25-21	11	22.9	10	20.8	
20-15	10	20.8	11	22.9	
<15	9	18.8	19	39.6	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	14.502 0.0022*
>25	9	19.6	0	0.0	
25-21	11	23.9	7	15.2	
20-15	12	26.1	8	17.4	
<15	14	30.4	31	67.4	
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	**%**	15.77 0.0012*
>25	6	14.0	0	0.0	
25-21	7	16.3	0	0.0	
20-15	10	23.3	5	11.4	
<15	20	46.5	39	88.6	

Table 8. GCS of all patients in the studied period.

Conscious level by GCS	Group A		Group B		X^2 P value
End of the 1st 5 days	**(n = 48 patients)**	**%**	**(n = 48 patients)**	**%**	6.797 0.032*
<6	14	29.2	6	12.5	
6-9	12	25.0	9	18.75	
10-12	11	22.9	12	25.0	
>12	11	22.9	21	43.75	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	18.26 0.0003*
<6	8	17.4	0	0.0	
6-9	10	21.7	0	0.0	
10-12	12	26.1	14	30.4	
>12	16	34.8	32	69.6	
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	**%**	15.86 0.0012*
<6	5	11.6	0	0.0	
6-9	8	18.6	0	0.0	
10-12	9	20.9	4	9.1	
>12	21	48.8	40	90.9	

Table 9. Mean arterial blood pressure of all patients in the studied period.

MAP by mmHg	Group A		Group B		X^2 P value
End of the 1st 5 days	**(n = 48 patients)**	**%**	**(n = 48 patients)**	**%**	9.804 0.0203*
Inot. ≥5µg/kg/min.	18	37.5	8	16.6	
Inot. <5µg/kg/min.	13	27.1	9	18.8	
70-95 without Inot.	10	20.8	13	27.1	
>95 without Inot.	7	14.6	18	37.5	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	13.153 0.0043*
Inot. ≥5µg/kg/min.	6	13.0	0	0.0	
Inot. <5µg/kg/min.	11	23.9	2	4.3	
70-95 without Inot.	11	23.9	14	30.4	
>95 without Inot.	18	39.1	30	65.2	
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	%	13.56 0.0035*
Inot. ≥5µg/kg/min.	6	14.0	0	0.0	
Inot. <5µg/kg/min.	8	18.6	0	0.0	
70-95 without Inot.	9	20.9	8	18.2	
>95 without Inot.	20	46.5	36	81.8	

Note: Inot. Inotropic support (nor-adrenaline infusion), µg/kg/min. microgram per kilogram body weight per minute.

Table 10. Bilirubin level in all patients in the studied period.

Bilirubin level in mg/dL	Group A		Group B		X^2 P value
End of the 1st 5 days	**(n = 48 patients)**	**%**	**(n = 48 patients)**	**%**	14.404 0.0024*
≥12	17	35.4	4	8.3	
6-11.9	12	25.0	8	16.7	
2-5.9	10	20.8	16	33.3	
≤1.9	9	18.8	20	41.7	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	12.277 0.006*
≥12	3	6.5	0	0.0	
6-11.9	10	21.7	1	2.2	
2-5.9	14	30.4	12	26.1	
≤1.9	19	41.3	33	71.7	
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	**%**	17.26 0.0006*
≥12	0	0.0	0	0.0	
6-11.9	6	14.0	0	0.0	
2-5.9	15	34.9	3	6.8	
≤1.9	22	51.2	41	93.2	

Table 11. Creatinine level in all patients in the studied period.

Creatinine Level in mg/dL	Group A		Group B		X^2 P value
End of the 1st 5 days	**(n = 48 patients)**	**%**	**(n = 48 patients)**	**%**	10.632 0.0138*
≥5	17	35.4	6	12.5	
4.9-3.5	12	25.0	8	16.7	
3.4 -2	10	20.8	15	31.3	
≤1.9	9	18.8	19	39.6	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	11.433 0.0096*
≥5	8	17.4	0	0.0	
4.9-3.5	10	21.7	4	8.7	
3.4 -2	12	26.1	14	30.4	
≤1.9	16	34.8	28	60.9	

(Table 11) contd.....

Creatinine Level in mg/dL	Group A		Group B		X^2 P value
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	**%**	17.696 0.0005*
≥5	4	9.3	0	0.0	
4.9-3.5	10	23.3	0	0.0	
3.4 -2	11	25.6	6	13.6	
≤1.9	18	41.9	38	86.4	

Table 12. Platelets count in all patients in the studied period.

Platelets Count in 10^3 mL	Group A		Group B		X^2 P value
End of the 1st 5 days	**(n = 48 patients)**	**%/**	**(n = 48 patients)**	**%**	6.677 0.041*
≤20	15	31.3	7	14.6	
21-<50	13	27.1	10	20.8	
50-≤100	10	20.8	10	20.8	
>100	10	20.8	21	42.8	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	6.276 0.048*
≤20	7	15.2	0	0.0	
21-<50	10	21.7	8	17.4	
50-≤100	12	26.1	13	28.3	
>100	17	37.0	25	54.3	
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	**%**	10.16 0.017*
≤20	3	7.0	0	0.0	
21-<50	8	18.6	0	0.0	
50-≤100	12	27.9	10	22.7	
>100	20	46.5	34	77.3	

Table 13. Number and percentage of patients who had either a score of 0,1 or 2 for all CPIS parameters in the studied period.

	Group A (n = 48patients)						Group B (n = 48patients)						P value
CPIS Score	**0**		**1**		**2**		**0**		**1**		**2**		-
End of 1ST 5 Days	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	
Tracheal secretion	12	25.0	15	31.3	21	43.8	20	41.7	18	37.5	10	20.8	0.012*
Chest x-ray infiltrate	12	25.0	16	33.3	20	41.7	23	47.9	15	31.3	10	20.8	0.033*
Temperature	10	20.8	17	35.4	21	43.8	21	43.8	16	33.3	11	22.9	0.017*
Leucocytic count/mm^3	10	20.8	18	37.5	20	41.7	23	47.9	13	27.1	12	25.0	0.022*
PAO_2/FIO_2 mmHg	19	39.6	-	-	29	60.4	28	58.3	-	-	20	41.7	0.014*
Microbiology	20	41.7	-	-	28	58.3	29	60.4	-	-	19	39.6	0.027*
End of 2nd 5 Days	**Group A (n = 46 patients)**						**Group B (n = 46patients)**						-
	NO	%	**NO**	%	**NO**	%	NO	%	NO	%	NO	%	-
Tracheal secretion	16	34.8	16	34.8	14	30.4	30	65.2	10	21.7	6	13.0	0.01*
Chest x-ray infiltrate	18	39.1	16	34.8	12	26.1	32	69.6	9	19.6	5	10.9	0.021*
Temperature	20	43.5	16	34.8	10	21.7	31	67.4	11	23.9	4	8.7	0.016*
Leucocytic count/mm^3	21	45.7	12	26.1	13	28.3	33	71.7	8	17.4	5	10.9	0.022*
PAO_2/FIO_2 mmHg	24	52.2	-	-	19	41.3	38	82.6	-	-	8	17.4	0.01*
Microbiology	25	54.3	-	-	18	39.1	35	76.1	-	-	11	23.9	0.01*
End of 3rd 4 Days	**Group A (n = 43 patients)**						**Group B (n = 44 patients)**						-
	0		**1**		**2**		**0**		**1**		**2**		-
	NO	%	NO	%	NO	%	NO	%	NO	%	NO	%	-
Tracheal secretion	20	46.5	14	32.6	9	20.9	42	97.7	2	4.7	0	0.0	0.001*
Chest x-ray infiltrate	21	48.8	15	34.9	7	16.3	43	100.0	1	2.3	0	0.0	0.001*
Temperature	22	51.2	13	30.2	8	18.6	41	95.3	3	7.0	0	0.0	0.001*
Leucocytic counts/mm^3	24	55.8	12	27.9	7	16.3	40	93.0	4	9.3	0	0.0	0.001*

(Table 13) contd.....

	Group A (n = 48patients)						Group B (n = 48patients)						P value
CPIS Score	**0**		**1**		**2**		**0**		**1**		**2**		-
End of 1ST 5 Days	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	
PAO_2/FIO_2 mmHg	33	76.7	-	-	10	23.3	44	102.3	-	-	0	0.0	0.001*
Microbiology	30	69.8	-	-	13	30.2	43	100.0	-	-	1	2.3	0.001*

Table 14. Course of lung compliance in all patients in the studied period.

Lung compliance in ml/1cmH_2O	Group A		Group B		X^2 test P value
End of the 1st 5 days	**(n = 48 patients)**	**%**	**(n = 48 patients)**	**%**	4.681 0.0433*
≤19	14	29.2	6	12.5	
20-40	13	27.1	11	22.9	
41-79	11	22.9	12	25.0	
≥80	10	20.8	19	39.6	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	12.47 0.005*
≤19	10	21.7	2	4.3	
20-40	11	23.9	6	13.0	
41-79	12	26.1	10	21.7	
≥80	13	28.3	28	60.9	
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	**%**	10.222 0.016*
≤19	6	14.0	0	0.0	
20-40	7	16.3	3	6.8	
41-79	10	23.3	6	13.6	
≥80	20	46.5	35	79.5	

Table 15. Response to recruitment maneuver in all patients in the studied period and patients had a failure of weaning from the ventilator at the end of the studied period.

-	Group A		Group B		P value
Days	**NO**	**%**	**NO**	**%**	
End of 1st. 5 days	12/48	25.0	21/48	43.8	0.036*
End of 2nd. 5 days	18/46	39.1	31/46	67.4	0.022*
End of 3rd. 4 days	22/43	51.2	40/44	90.9	0.001*
Failure of weaning	16/43	37.2	3/44	6.8	0.001*
N. discharged from ICU	27/50	54.0	41/50	82.0	0.0031*

Table 16. LDH level recorded for all patients in the studied period.

LDH Level in U/L	Group A		Group B		X^2 test P value
End of the 1st 5 days	**(n = 48 patients)**	**%**	**(n = 48 patients)**	**%**	6.85 0.041*
>600	18	37.5	6	12.5	
400-600	12	25.0	9	18.8	
200-400	10	20.8	10	20.8	
<200	8	16.7	23	47.9	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	7.25 0.013*
>600	3	6.5	0	0.0	
400-600	10	21.7	6	13.0	
200-400	14	30.4	8	17.4	
<200	19	41.3	32	69.6	

(Table 16) contd.....

LDH Level in U/L	Group A		Group B		X^2 test P value
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	**%**	12.9 0.001*
>600	0	0.0	0	0.0	
400-600	8	18.6	0	0.0	
200-400	10	23.3	2	4.5	
<200	25	58.1	42	95.5	

Table 17. C reactive protein level recorded for all patients in the studied period.

CRP in mg/L	Group A		Group B		P value
End of the 1st 5 days	**(n = 48 patients)**	**%**	**(n = 48 patients)**	**%**	0.002*
>300	19	39.6	8	16.7	
201-300	11	22.9	9	18.8	
100-200	10	20.8	11	22.9	
<100	8	16.7	20	41.7	
End of the 2nd days	**(n = 46 patients)**	**%**	**(n = 46 patients)**	**%**	0.0322*
>300	4	8.7	1	2.2	
201-300	9	19.6	5	10.9	
100-200	13	28.3	7	15.2	
<100	20	43.5	33	71.7	
End of the 3rd 4 days	**(n = 43 patients)**	**%**	**(n = 44 patients)**	**%**	0.021*
>300	0	0.0	0	0.0	
201-300	8	18.6	0	0.0	
100-200	18	41.9	1	2.3	
<100	27	62.8	43	97.7	

Table 18. Morbidity recorded for all patients in the studied period.

The Morbidity	Number of Patients in Group A (n=43)		Number of Patients in Group B (n=44)		P Value
	No.	**%**	**No.**	**%**	**0.013***
APACH II score >25	**6**	**14.0**	**0**	**0.0**	
GCS <6	5	11.6	0	0.0	0.018*
MAP <70 mmHg +or- inotropes	6	14.0	0	0.0	0.013*
Bilirubin level 6- 11.9 mg/dL	6	14.0	0	0.0	0.013*
Creatinine level ≥ 5 mg/dL	4	9.3	0	0.0	0.021*
Platelets count <50 10^3/ml	11	25.5	0	0.0	0.001*
Hypoxic index <100	10	23.3	0	0.0	0.001*
X-ray chest (all quadrant lung infiltrate)	7	16.3	0	0.0	0.001*
Lung compliance ≤19 ml/ cmH2O	6	14.0	0	0.0	0.013*
NO response to recruitment	21	48.8	4	9.1	0.001*
Core temperature ≥39 or ≤36	9	20.9	1	2.3	0.001*
Tracheal secret. Abundant &purulent	9	20.9	0	0.0	0.001*
Leucocytic count 2 on CPIS	7	16.3	0	0.0	0.041*
High LDH 400-600 U/L	8	18.6	0	0.0	0.023*
C-reactive protein 201-300 mg/L	8	18.6	0	0.0	0.023*
Positive microbiology results after 10 days	18	41.8	11	25.0	0.001*
Positive microbiology results after 14 days	13	30.2	1	2.3	0.001*
Failure of weaning from the ventilator at the end of the study period	16	37.2	3	6.8	0.001*
Cerebrovascular complications either hemorrhage or infarction	2	4.7	5	11.4	0.044*
Local complications from cannulation (pseudo-aneurysms or disruption)	0	0.0	6	13.6	0.036*
Mortality	7	16.3	6	13.6	0.421 N.S.

4. DISCUSSION

In relation to enhancing the overall health condition of patients [17 - 21], noteworthy improvements were observed in the APACHE II score, total leucocyte count, and core body temperature in patients of group B compared with those of group A. These improvements can be attributed to the use of ECMO, which provided better tissue oxygenation compared with non-functional, infected, and contused lungs. The better tissue oxygenation resulted in improved systemic oxygenation and improved the patient's cellular and humoral immunity in group B, which helped manage both bacteremia and toxemia caused by VAP. Consequently, this facilitated the management of all general signs of systemic inflammatory response syndrome (SIRS) and helped quickly control various parameters, such as CPIS score, SOFA score, and weaning from inotropic support and mechanical ventilation.

The improvement of pulmonary function can be classified into two different categories. The first category is clinical improvement, which refers to the significant improvement in clinical parameters such as oxygen saturation, hypoxic index, compliance, and response to recruitment maneuvers in patients of group B compared with those in patients of group A throughout the study period [17 - 21]. The second category is a radiological improvement, which refers to the significant improvement in imaging findings of the lungs, such as reduced infiltrates or opacities on chest X-ray or CT scan in patients of group B compared with those in patients of group A over the same duration [17 - 21]. This phenomenon may be attributed to the enhancement of local immunity of the lung induced by improved oxygenation. Physiologically, increased oxygenation of lung tissue causes pulmonary vasodilatation and increases local blood supply, resulting in a concomitant enhancement of local immunity of the lung. In addition, ECMO provides lung protection against the deleterious effect of mechanical ventilation (especially PEEP), thus facilitating the acceleration of the healing process of lung tissue from both septic inflammation (VAP) and traumatic inflammation (pulmonary contusions). Furthermore, the utilization of VA-ECMO in the delivery of tissue oxygenation appears to be superior to the use of inotropes in supporting the patient's circulation. This superiority can be attributed to the vasoconstrictive of all inotropes due to their alpha-agonist actions, which improve brain and vital organ tissue perfusion, while also potentially resulting in severe systemic tissue ischemia as a consequence of severe peripheral vasoconstriction.

In this study, bacteriological improvement [17 - 21] was evaluated by analyzing the qualitative sputum cultures of all patients on days 10 and 14. The results revealed a statistically significant increase in positive results between groups A and B. This difference may be attributed to the superior immunity of patients in group B, including both local immunity of the lung and systemic immunity. Additionally, the enhanced oxygenation observed in group B could play a role in this outcome. Improved local tissue oxygenation in the lung and systemic oxygenation might result from the aforementioned factors contributing to the higher positive culture rates in group B.

This study also demonstrated notable decreases in LDH and CRP levels in group B, indicating a significant improvement in controlling laboratory indicators related to tissue destruction compared with that in group A [17 - 21]. The observed difference is likely attributed to the faster lung tissue healing and more efficient management of tissue destruction caused by trauma and sepsis in group B. The positive outcome is plausibly ascribed to the superior both lung and systemic oxygenation and immunity achieved with VA-ECMO relative to group A.

In patients receiving VA-ECMO (group B), immunoadsorption, a process of removing bacteria, toxins, antigens, and cytokines from the bloodstream, positively affected patient outcomes. These substances are known to potentiate the sepsis cascade, aggravate tissue destruction, and trigger a vicious circle of immune response and further tissue destruction, accompanied by circulatory failure. The immunoadsorption effect of VA-ECMO intervenes in this circle by removing or reducing the concentration of these harmful substances. This results in a rapid recovery from a low tissue perfusion state and restoration of the MAP with sufficient tissue perfusion pressure in all organs. As a result of this intervention, patients in group B experienced significant improvements in their GCS score, creatinine level, bilirubin level, and platelet count. These improvements were attributed to the restoration of proper perfusion pressure, which allowed organs such as the brain (recovery from septic encephalopathy), kidney, liver, and bone marrow to function more effectively. Additionally, a faster improvement in global tissue perfusion and reduction in the release of systemic toxins and pyrogens led to better control of other measures of patient health, such as the APACHE II score, leucocyte count, core temperature, CPIS score, SOFA score, and Murray score. This resulted in improved ventilatory function and quicker weaning from mechanical ventilation, further supporting the idea that immunoadsorption can have positive effects on patient outcomes. Several case reports [22 - 27] have been published describing the use of cytokine adsorption techniques. One such technique is the Cytosorb hemoadsorption column (Linc Medical, Leicestershire, United Kingdom), which is installed in the ECMO circuit to stabilize septic shock patients more rapidly and improve their outcomes. These reports suggest that Cytosorb is effective in removing proinflammatory cytokines from the bloodstream, which can halt the injurious cascade of sepsis and manage tissue destruction. Furthermore, it has been shown to reduce vasopressor doses and serum inflammatory cytokines in septic patients.

In terms of morbidity and mortality rates [17 - 21], several factors were observed to exert substantial impacts on patient outcomes in this study. These factors include an APACHE II score > 25 points, a GCS score < 6 points, MAP < 70 mmHg with/without inotropic support, a bilirubin level > 6 mg/dL, a creatinine level > 5 mg/dL, a platelet count < 5×10^4/mL, hypoxic index < 100, chest X-ray showing infiltrates in all lung quadrants, lung compliance > 19 mL/cmH_2O, no response to recruitment, core temperature > 39°C or < 36°C, abundant and purulent tracheal secretion, a leucocytic count of 2 on the CPIS score, an LDH level > 400 U/L, CRP > 200 mg/L, and positive sputum cultures after 10 d and 14 d of treatment, and failure to wean from mechanical ventilation at the end of the study period. Notably, these factors were significantly higher in group A than those in group B. However, patients in group B exhibited significantly higher incidence rates of cerebrovascular and local complications from cannulation than those in group A. This can be attributed to the use of anticoagulants in group B. Moreover, the two groups had no

significant difference in the mortality rate.

The findings of this study corroborate the results of previous research conducted by Peek *et al.* (2009) [28] in the United Kingdom. Peek's study examined 90 patients with ARDS who received VA-ECMO for 6–16 days. The study reported a mortality rate of 37%, while the remaining patients showed improved lung function and were discharged from the hospital earlier than those treated with conventional ventilation. In 2011, Noah *et al.* [8] conducted a study involving 69 patients with H1N1 influenza-induced ARDS who received ECMO for 6–16 d. The study showed a marked improvement in lung condition and a lower mortality rate of 24%. Similarly, Pham *et al.* (2013) [29] studied 123 patients with severe ARDS due to an H1N1 influenza epidemic and found a mortality rate of 36% with ECMO use for 8–22 days. Brechot *et al.* (2013) [30] examined 14 patients with refractory septic shock who received VA-ECMO within 24 hours of onset. The study reported an 86% weaning success rate and a 71% discharge rate with good quality of life after a median follow-up of 13 months (3–43). Schmidt *et al.* (2014) [31] developed a reliable survival prediction score for ECMO patients based on a study involving 2,355 patients with ARDS respiratory failure who received ECMO for 14 days. The study reported that 1,338 patients were discharged alive from the hospital in good condition, while the remaining patients had a mortality rate of 57%. Finally, Nesseler *et al.* (2015) [32] investigated the use of ECMO in patients with intra-abdominal sepsis-induced ARDS. The study found a significantly larger number of patients being weaned from both inotropic support and mechanical ventilation compared with that in the control group, although the ECMO group consisted of only 40 patients who received ECMO for two weeks due to ARDS-induced respiratory failure.

Several studies have investigated the efficacy of VA-ECMO in adult patients with septic shock and respiratory failure associated with ARDS. These studies reveal that the VA-ECMO group does not significantly differ from the control group concerning the length of ICU stay and mortality rate. A prospective study by Huang *et al.* (2013) [33] included 52 adult patients who had refractory septic shock and required VA-ECMO for circulatory support. The study found no significant difference between the VA-ECMO group and the control group in terms of outcomes, and only 15% of included patients were discharged home, suggesting poor outcomes. Similarly, a recent multicenter study by Takauji *et al.* (2017) [34] enrolled 3195 patients from 42 Japanese ICUs. Out of 570 patients who suffered from severe respiratory failure, 285 experienced respiratory failure induced by lung infections. Overall, the study included 40 patients in the ECMO group (supported by ECMO) and 150 patients in the control group. The two groups had comparable SOFA scores (12 points *vs.* 13 points). In addition, there were no significant differences in the mortality rate and length of ICU stay between the ECMO group and the control group. Although the studies above suggest that further multicenter research is needed to prove the efficacy of VA-ECMO in patients with sepsis-induced circulatory and respiratory failure, the therapy has demonstrated favorable outcomes in our center.

This study exhibited limitations, namely, a small sample size and the inclusion of only ARDS cases induced by infected contused lungs. Therefore, large-scale investigations are imperative, encompassing all etiologies of ARDS, such as trauma, lung infection, and other systemic causes, to assess the efficacy of VA-ECMO in all types of ARDS with septic shock.

CONCLUSION

VA-ECMO notably impedes the progression of sepsis, shortens ICU stay, and expedites the weaning from inotropic support and mechanical ventilation. However, it has no impact on the mortality rate of adult patients with septic shock.

LIST OF ABBREVIATIONS

(VA-ECMO)	=	Veno-arterial Extracorporeal Membrane Oxygenation
(SOFA)	=	Sequential Organ Failure Assessment
(CPIS)	=	Clinical Pulmonary Infection Score

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

King Abdul-Aziz Specialized Hospital Research and Ethical committee approved the project.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans were used in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931

CONSENT FOR PUBLICATION

Written consent from all patients was taken from the first-degree relatives of the patients.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data suporting thr findings of the article in the available in reference section [22-34].

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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