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Extracorporeal Life Support for Severely Burned Patients with Concurrent Inhalation Injury and Acute Respiratory Distress Syndrome: Experience from a Military Medical Burn Center

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ABSTRACT

Background: Both inhalation injury and acute respiratory distress syndrome (ARDS) are risk factors that predict mortality in severely burned patients. Extracorporeal life support (ECLS) is widely used to rescue these patients; however, its efficacy and safety in this critical population have not been well defined. We report our experience of using ECLS for the treatment of severely burned patients with concurrent inhalation injury and ARDS.

Methods: This was a retrospective analysis of 14 patients collected from a single medical burn center from 2012 to 2019. All patients suffered from major burns with inhalation injury and ARDS, and were treated with ECLS.

Results: The median total body surface area of deep dermal or full thickness burns was 94.5%, ranging 47.7-99.0 %. The median revised Baux score was 122.0, ranging 90.0-155.0. All patients developed ARDS with a median partial pressure of arterial oxygen to a fraction of inspired oxygen ratio of 61.5, ranging 49.0-99.0. Indications for ECLS included sustained hypoxemia and unstable hemodynamics. The median interval for initiating ECLS was 2.5 days, ranging 1.0-156.0 days. The median duration of ECLS was 2.9 days, ranging 0.3-16.7 days. The overall survival to discharge was 42.8%. Causes of death included sepsis and multiple organ failure. ECLS-related complications included cannulation bleeding, catheter-related infection, and hemolysis. The incidence of risk factors reported in literature were higher in non-survivors, including Baux$>$120, albumin $<$ 3.0 g/dL, and lactate $>$ 8 mmol/L.

Conclusions: For severely burned patients with concurrent inhalation injury and ARDS, ECLS could be a salvage treatment to improve sustained hypoxemia. However, the efficacy of hemodynamic support was limited. Identifying definite ECLS indications and rigorous patient selection would contribute to better clinical outcomes.

Introduction

Inhalation injury, large total body surface area (TBSA) burned, and subsequent acute respiratory distress syndrome (ARDS) are significant predictors of mortality in patients with burn injuries [1,2]. Inhalation injury often results in airway inflammation, pulmonary vascular shunting, microvascular pressure gradient, and severe hypoxemia. As a result, inhalation injury itself increases mortality by adding 17 points to the Baux score; this has been termed the revised Baux score [3,4]. As an inflammatory response to burned skin, ARDS causes microvascular damage to the pulmonary endothelium [5,6]. The treatment strategies for inhalation injury and ARDS include mechanical ventilation, adequate fluid resuscitation, and heparin nebulization. However, both remain primary causes of death in major burn patients [7]. Previous cohort

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Table 1
Pre-ECLS characteristics of enrolled patients.

	Overall (n=14)	Survivors (n=6)	Non-survivors (n=8)
	Median (range) or Number (Percentage)		
Patient demographics			
Age (years)	42.0 (19.0-59.0)	33.5 (19.0-49.0)	42.0 (19.0-59.0)
BMI (Kg/m^2)	28.1 (21.0-37.8)	26.7 (21.0-31.0)	28.1 (21.0-37.8)
Male	10 (71%)	3 (50%)	7 (88%)
Explosion injury	10 (71%)	3 (50%)	7 (88%)
Flame injury	4 (29%)	3 (50%)	1 (13%)
TBSA of DD/FT burned (%)	94.5 (47.0-99.0)	71.5 (47.0-99.0)	94.5 (47.0-99.0)
Baux score (Age + TBSA burned)	122.0 (90.0-155.0)	95.5 (90.0-143)	122.0 (90.0-155.0)
Mean blood pressure (mmHg)	82.4 (56.0-133.0)	92.2 (68.7-133.3)	82.4 (56.3-133.3)
Inotropes (ug/kg/min)			
Dopamine (mcg/kg/min)	9.5 (2.0-20.2)	2.0 (2.0-20.2)	9.5 (2.0-20.2)
Epinephrine (mcg/min)	4.5 (0.0-7.4)	0.0 (0.0-7.4)	4.5 (0.0-7.4)
Norepinephrine (mcg/min)	20.7 (5.0-29.3)	5.7 (5.0-21.3)	20.7 (5.0-29.3)
Patient comorbidity			
Diabetes	1 (7%)	0	1 (13%)
Hypertension	1 (7%)	0	1 (13%)
Coronary artery disease	1 (7%)	0	1 (13%)
Concomitant trauma			
Head injury	1 (7 %)	1 (17%)	0
Open fracture	2 (14 %) *	2 (33%)	0
Pneumothorax	2 (14%)	1 (17%)	1 (13%)
Burn-related sequelae			
Hypovolemic shock	13 (93%)	5 (83%)	8 (100%)
Rhabdomyolysis	10 (71%)	3 (50%)	7 (88%)
Acute kidney injury	10 (71%)	3 (50%)	8 (100%)
Hepatic dysfunction	9 (64%)	3 (50%)	6 (75%)
Coagulopathy	7 (50%)	2 (33%)	5 (63%)
Stress GI bleeding	3 (21%)	1 (17%)	2 (25%)
Acute cholangitis or Pancreatitis	2 (14%)	1 (17%)	0

BMI, body mass index; TBSA, Total body surface area; DD/FT, deep dermal or full thickness; MAP, mean arterial pressure
*One suffered from open fracture of right proximal tibia and closed fracture of left humerus. The other suffered from open fracture of bilateral ankles complicated with right anterior tibial, posterior tibial and peroneal artery occlusion.

studies have reported that extracorporeal life support (ECLS) benefits burn victims, which has led to widespread utilization of ECLS for burn- and inhalation-related injuries [8–10]. However, limited studies have reported the efficacy of ECLS in patients with severe burn injury, concomitant inhalation injury, and subsequent ARDS. Furthermore, major burns with concomitant inhalation injury and ARDS are common in wars. It is important for military medical centers to improve their management of such a serious clinical issue. Therefore, this study evaluates the efficacy of ECLS in these extremely critical patients and discussed the potential risk factors of mortality.

This study was approved by the ethical committee of our institution, the Institutional Review Board of Tri-Service General Hospital (TSGHIRB No.: C202005124, Date of Approval: 2020/9/2). Furthermore, all methods were performed in accordance with the relevant guidelines and regulations. The need for informed consent was waived by the ethics committee based on the retrospective nature of the study. Patients' consents were obtained according to the Declaration of Helsinki.

Materials and Methods

Patient characteristics

We retrospectively reviewed our experience with ECLS in patients with major burns at our burn center from January 2012 to December 2019. The data were collected by reviewing medical records during hospitalization and follow-up after discharge. Severely burned adult patients with concurrent inhalation injury and ARDS who had a poor response to maximal conventional ventilator therapy and required ECLS intervention were included in this study. We defined severe burn injury as "TBSA of deep dermal or full thickness (DD/FT) burned more than 40%". Patient characteristics, including overall, survivors, and non-survivors, are shown in Table 1. Fourteen patients, including 10 men and 4 women, were enrolled and reviewed via medical records. The median age was 42.0 years, ranging 19.0-59.0 years. The causes of severe burns included explosions (n = 10, 71%) and flame injuries (n = 4, 29%). The median burned TBSA of DD/FT was 94.5%, ranging 47–99%. The median Baux score was 122, ranging 90–155. Osler *et al.* proposed a revised Baux score for a more accurate prediction of mortality [3], and they stated that inhalation injury adds 17 points to the conventional Baux score. In our cohort, all patients had inhalation injury, thus, the median revised Baux score was 139, ranging 107–172. Five patients had concomitant trauma, including 1 patient with head injury, 2 with open fracture, and 2 with pneumothorax. All patients required inotrope and vasopressor administration with a median arterial pressure of 82.4 mmHg, ranging 56.0-133.0 mmHg. Thirteen patients had hypovolemic shock, 10 had acute kidney injury, 9 had hepatic dysfunction, and 7 had coagulopathies. Generally speaking, the non-survivors had higher median of Baux score (median 122.0, ranging 90.0-155.0) and inotropes and vasopressors, including dopamine, epinephrine, and norepinephrine.

Table 2 shows the biochemical data and ventilation status between survivors and non-survivors. Leukocytosis and high C-reactive protein (CRP) levels indicated severe systemic inflamma-

Table 2
Pre-ECLS biochemistry data and ventilation status.

	Overall (n=14)	Survivors (n=6)	Non-survivors (n=8)
	Median (range)		
Laboratory data			
White blood cell (10^3/mL)	20655.0 (4300.0 – 54480.0)	20655.0 (4300.0 – 33440.0)	21090.0 (6850.0-54480.0)
CRP (mg/dL)	11.6 (0.7-33.2)	11.5 (9.8-15.6)	13.1 (0.7-33.2)
Haemoglobin (g/dL)	9.7 (4.8 – 16.9)	9.9 (4.8-11.7)	9.7 (7.2-16.9)
Albumin (g/dL)	2.9 (1.0 – 4.5)	3.5 (2.7-4.5)	2.5 (1.0-3.4)
Creatinine (mg/dL)	1.6 (0.7 – 4.1)	1.1 (0.7-1.8)	2.1 (1.1-4.1)
AST (U/L)	63.0 (19.0 – 898.0)	45.0 (19.0-156.0)	89.5 (33.0-898.0)
Glucose (mg/dL)	199.5 (105.0 – 497.0)	131.5 (105.0-202.0)	236.0 (193.0-497.0)
Creatine kinase (U/L)	1367.0 (15.0 – 20000.0)	277.0 (15.0-1481.0)	3548.5 (57.0-20000.0)
Troponin I (ng/mL)	0.05 (0.01 – 16.50)	0.04 (0.01-0.06)	0.10 (0.01-16.50)
PH	7.2 (6.9 – 7.4)	7.3 (7.1-7.4)	7.2 (6.9-7.3)
Lactate (mmol/L)	7.9 (2.2 – 15.0)	4.8 (2.2-15.0)	13.1 (5.4-15.0)
Ventilation data			
Peak inspiration pressure (cmH_2O)	39.5 (24.0 – 45.0)	40.0 (24.0 -45.0)	37.5 (24.0-40.0)
Mean airway pressure (cmH_2O)	26.6 (16.7 – 30.7)	27.0 (16.7-30.4)	26.0 (17.5-30.7)
Positive end expiratory pressure (cmH_2O)	12.0 (8.0 – 14.0)	11.0 (8.0-14.0)	12.0 (8.0-12.0)
Tidal volume (mL)	395.0 (250.0 – 603.0)	450.0 (27.0-55.0)	350.0 (250.0-603.0)
Lung compliance (ml/cmH_2O)	17.0 (3.0 – 54.0)	24.0 (3.0 – 54.0)	10.0 (4.0-22.0)
Oxygen index	37.5(13.3 – 49.0)	38.9 (13.3-46.6)	34.8 (14.9-49.0)
PaO_2/FiO_2	61.5 (49.0 – 99.0)	58.4 (49.0-95.0)	66.0 (53.0-99.0)
$AaDO_2$ (mmHg)	573.7 (452.0 – 601.0)	595.4 (526.0-602.0)	550.5 (452.0-578.0)

BMI, body mass index; TBSA, Total body surface area; MAP, mean arterial pressure; CPR, Cardiopulmonary resuscitation; CRP, C-reactive protein; AST, aspartate aminotransferase; PaO_2/FiO_2, the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction).
*One suffered from open fracture of right proximal tibia and closed fracture of left humerus. The other suffered from open fracture of bilateral ankles complicated with right anterior tibial, and posterior tibial and peroneal artery occlusion.

tion response, which increased endothelial permeability and resulted in low albumin levels with a median of 2.9 g/dL, ranging 1.0-4.5 g/dL. Elevated creatinine levels with oliguria, hepatic dysfunction, and acidosis with elevated lactate indicated systemic shock. High creatine kinase implied massive rhabdomyolysis and exacerbated acute kidney injury. Overall speaking, the non-survivors had higher medians of serum creatinine, glucose, lactate, and a lower median of serum albumin. The ventilator settings showed a median peak inspiration pressure of 39.5 cmH_2O (ranging 24.0-45.0 cmH_2O), a median mean airway pressure of 26.6 cmH_2O (ranging 16.7-30.7 cmH_2O), and a median positive end expiratory pressure (PEEP) of 12.0 cmH_2O (ranging 8.0-14.0 cmH_2O). The median tidal volume was 395.0 mL (ranging 250.0-603.0 mL), and the median lung compliance was 17.0 mL/cmH_2O (ranging3.0-54.0 mL/cmH_2O). Poor oxygenation and systemic hypoxia were noted with high oxygen index (median 37.5, ranging 13.3-49.0) and a low partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2; median 61.5, ranging 49.0–99.0). The non-survivors had a lower median of tidal volume (median 350.0, ranging 250.0-603.0) and lung compliance (median 10.0, ranging 4.0-22.0).

Indications for ECLS, general intensive care, and burn-related interventions

ECLS should be considered in burned patients with subsequent severe hypoxemia caused by either inhalation injury or ARDS. Indications include $PaO_2/FiO_2 < 80$, oxygen index > 40, and alveolar-arterial oxygen gradient > 500 mmHg despite optimal conventional ventilator support [11]. Venovenous ECLS (VV-ECLS) was used in 6 patients, whereas venoarterial ECLS (VA-ECLS) was used in 8 patients due to unstable hemodynamic status despite inotrope and vasopressor administration. The ECLS system included a heparin-coated polypropylene oxygenator (AffinityNT1, Medtronic, Minneapolis, MN, USA) and a centrifugal pump (BPX-80 Bio-Pump1, Medtronic). The blood flow was maintained at no more than 3.5 L/min for all patients to avoid blood cell destruction. After ECLS, the ventilator was set with a tidal volume of 6-8 mL/kg, rate of 10–12 /min, and PEEP of 6–10 cmH_2O to prevent alveolar collapse, and the peak airway pressure was strictly maintained at no more than 35 cmH_2O to avoid barotrauma. Partial pressure of carbon dioxide was maintained within 35–45 mmHg, and FiO_2 was maintained at 40–60%. Opioids, propofol, and midazolam were administered for analgesia and sedation. Besides aggressive fluid resuscitation by the modified Parkland formula, 50 mL of 25% human albumin was transfused every 2 hours to maintain oncotic pressure. Norepinephrine was used in all patients for low vascular tone. (Table 1) Furthermore, prophylactic broad-spectrum antibiotics and antibacterial dressings were administered to prevent secondary infection. Bronchoscopy was done to assess the severity of inhalation injury and to remove the sputum plug in the main airway.

Statistical methods

SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all analyses. The continuous variables were displayed with mean and standard deviation, or median with range. The categorical variables were displayed with counts and percentages. The survival condition by time among these subjects was displayed by Kaplan-Meier curve.

Results

ECLS clinical course and outcomes are shown in Table 3. The overall median interval from intubation to ECLS was 2.5 days, ranging 1–156 days, with median intervals of 1.0 days for VV-ECLS and 19.5 days for VA-ECLS, respectively. The median interval from intubation to ECLS was 16.5 and 1.5 days in survivors and non-survivors, respectively. Three of the 6 VV-ECLS patients survived, while only 3 of the 8 VA-ECLS patients survived. During ECLS, 8 patients had trunk escharotomies, and 4 had limb fasciotomies to relieve the compartment syndrome. Two patients required tracheostomy due to airway obstruction caused by severe swelling of the laryngeal tissue. All patients needed wound debridements to prevent burn-related infection. The overall median numbers of wound debridement were 3.5, ranging 0-30, with the median num-

Table 3
ECLS clinical course and outcomes.

	Overall (n=14)	Survivors (n=6)	Non-survivors (n=8)
	Median (range) or Number (Percentage)		
Interval to ECLS (days)	2.5 (1.0-156.0)	16.5 (1.0-156.0)	1.5 (1.0-23.0)
VV-ECLS (n=6)	1.0 (1.0-13.0)	2.0 (1.0-3.0)	1.0 (1.0-13.0)
VA-ECLS (n=8)	19.5 (1.0-156.0)	32.0 (2.0-156.0)	9.0 (1.0-23.0)
Peri-ECLS surgical intervention			
Trunk escharotomy	8 (57%)	2 (33%)	6 (75%)
Limb fasciotomy	4 (29%)	2 (33%)	2 (25%)
Tracheostomy	2 (14%)	2 (33%)	0
Number of operations for wound debridement	3.5 (0.0-30.0)	9.5 (4.0-30.0)	1.5 (0.0-29.0)
Number of operations for wound reconstruction (STSG or FTSG)	2.0 (0.0-13.0)	9.0 (4.0-13.0)	0.0 (0.0-3.0)
ECLS-related complications			
Cannulation bleeding	3 (21%)	2 (33%)	1 (13%)
Catheter-related infection	3 (21%)	1 (17%)	2 (25%)
Haemolysis	11 (79%)	3 (50%)	8 (100%)
Thromboembolism event	0	0	0
Limb ischemia	0	0	0
Outcomes			
Duration of ECLS (days)	2.9 (0.3-16.7)	4.6 (0.5-16.7)	2.2 (0.3-16.5)
VV-ECLS (n=6)	4.6 (1.7-16.5)	4.6 (4.4-4.8)	4.1 (1.7-16.5)
VA-ECLS (n=8)	1.2 (0.3-16.7)	5.8 (0.5-16.7)	1.2 (0.3-2.7)
Overall hospitalization (days)	20.0 (2.0-221.0)	137.0 (34.0-221.0)	15.0 (2.0-22.0)

VV, veno-venous; VA, veno-arterial; STSG, split-thickness skin graft; FTSG, full-thickness skin graft.

Table 4
Cause of death, mean of possible risk parameters, and incidence of risk factor reported in literature.

	Survivor (n=6)	Non-survivors (n=8)
	Cause of death	
Sepsis	0	4 (50%)
Multiple organ failure	0	4 (50%)
	Mean of possible risk parameters	
Baux	105.83±21.40	131.12±17.59
Albumin (g/dL)	3.45±0.68	2.34±0.83
Creatinine (mg/dL)	1.12±0.39	2.29±1.00
Glucose (mg/dL)	141.67±36.11	277.88±109.59
Lactate (mmol/L)	6.02±4.58	11.47±3.81
Lung compliance (ml/cmH_2O)	27.5±17.6	12.1±6.8
	Incidence of risk factor reported in literature	
Baux>120	1 (17%)	7 (88%)
Albumin < 3.0 (g/dL)	2 (33%)	5 (63%)
Lactate > 8 (mmol/L)	1 (17%)	6 (75%)
VA-ECLS	4 (67%)	4 (50%)

VA, veno-arterial

ber of 9.5 for survivors and 1.5 for non-survivors, respectively. Only stable victims had undergone wound reconstruction, which was not carried out in the majority of those with VA-ECLS. Thus, the median number of operations for wound reconstruction, including split-thickness and full-thickness skin grafts, was 9 (ranging 4-13) and 0 (ranging 0-3) in survivors and non-survivors, respectively. ECLS-related complications included cannulation bleeding, catheter-related infection, and hemolysis. No thromboembolic events or distal limb ischemia were noted.

The overall median ECLS duration was 2.9 days, ranging 0.3–16.7 days, with median durations of 4.6 days for all VV-ECLS and 1.2 days for all VA-ECLS, respectively. The overall median hospitalization duration was 20 days, ranging 2–221 days. In survivors (n = 6), the median ECLS duration was 4.6 days, and the median hospitalization duration was 137 days. In non-survivors (n = 8), the median ECLS duration was 2.2 days, and the median hospitalization duration was 15.0 days. The longer hospitalization duration of the survivors included both post-ECLS ICU duration and subacute stage in rehabilitation ordinary ward. These survivors suffered from major burn injury and usually needed longer ventilation period, and longer ICU stay even if ECLS has been removed. Furthermore, they also suffered from burn scar contracture, which was treated with long-term rehabilitation after ICU stage.

Septic shock and multiple organ failure each resulted in the deaths of 4 patients (Table 4). Six of the 14 patients survived to discharge. Figure 1 shows the overall survival curve analyzed using the *Kaplan-Meier* method. Table 4 shows causes of death, means of possible risk parameters, and incidence of risk factor reported in the literature before ECLS use. The non-survivors had higher means of creatinine, glucose, lactate, and Baux score and, in contrast, lower means of albumin and lung compliance. Regarding the risk factors for mortality reported in literature, the non-survivors had higher incidence of Baux score > 120, albumin < 3.0 g/dL, and lactate > 8 mmol/L.

Discussion

ECLS for ARDS

The pathophysiology of respiratory dysfunction after major burns is multifactorial, and ARDS and inhalation injury are the most important factors [3,4,6]. Burn-related ARDS may result from

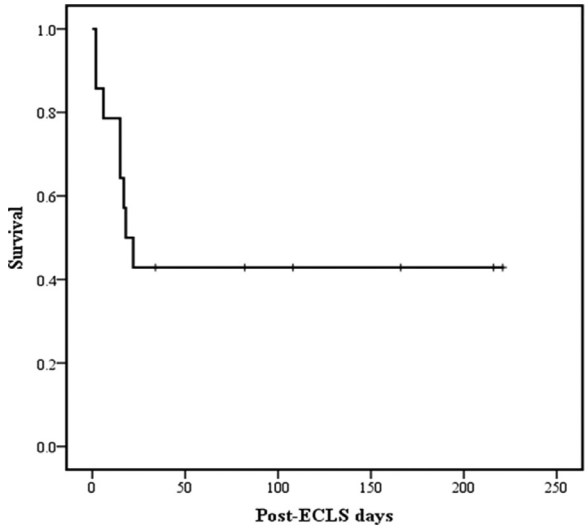

Figure 1.

multiple risk factors, such as pneumonia, smoke inhalation, shock, bacteremia, and blood product transfusion. Pro-inflammatory mediators not only initiate local tissue injury, but also amplify the systemic inflammatory response. Dysregulation of inflammatory cytokines and leukotrienes leads to the breakdown of the pulmonary microvascular endothelial lining and the alveolar epithelial surface, which are together referred to as the alveolar-capillary barrier. The prevalence reported in mechanically ventilated patients after burn injury was 32.6–53.2% by the Berlin definition [12] and 39.5% by the American European Consensus Conference definition [5]. It has been reported that the extent of a full-thickness burn predicts the development of severe ARDS, which is associated with a greater duration of mechanical ventilation and higher mortality [13]. Although ECLS has been documented as a crucial treatment for ARDS in some cohort studies [14], no randomized controlled trial has proven its efficacy in treating burn-related ARDS thus far.

ECLS for inhalation injury

According to current published literature, the extent of burned TBSA, inhalation injury, and age are the best predictors of mortality in burn prognosis [7]. Smoke inhalation injury can be divided into three different types of injury, including direct thermal injury to the upper airway, chemical irritation of the whole respiratory tract, and systemic toxicity owing to toxic gases [15]. Each type of injury may cause systemic inflammatory response syndrome and has the potential to exacerbate into ARDS. To improve hypoxemia, the therapy for inhalation injury mainly includes mechanical ventilation and nebulized inhaled medications. However, once ARDS develops, insufficient pulmonary oxygenation results in sustained systemic hypoxemia and subsequent multiple organ dysfunction. Asmussen *et al.* conducted a systematic review on ECLS in respiratory failure resulting from burn and smoke inhalation injury [9], and they concluded that the level of evidence was limited due to insufficient patient numbers available in the present literature. However, ECLS devices and technology have improved and evolved in recent decades, thereby increasing the survival rate each year. Further research on ECLS for smoke inhalation injury is warranted to prove its efficacy.

In our cohort, all patients had concomitant ARDS and inhalation injury. We suspected that ARDS mainly resulted from large TBSA burned rather than inhalation injury. Although Liffner *et al.* reported that inhalation injury, as assessed by an inhalation lung injury score, did not contribute to the development of ARDS [16], we believe that inhalation injury is also a contributing factor for ARDS, which together exacerbated respiratory dysfunction.

Literature review of ECLS for burn injury

Table 5 [10,17-26] shows literature reviews from 1998 to the present. There were 11 cohorts that supported the application of ECLS in burn patients with respiratory failure, which was mainly caused by ARDS, with a PaO_2/FiO_2 below 100. The average TBSA ranged from 12–89%, and the average Baux score ranged from 55–149. Most used VV-ECLS for systemic hypoxemia, while a few used VA-ECLS for unstable hemodynamics and cardiogenic and septic

Table 5
Literature review of ECLS applied for respiratory failure in severely burned adults.

Study	Year	Number	Baux score(mean)	PaO_2/FiO_2	PEEP(cmH_2O)	Inhalation injury	ECLS Mode	Survival to discharge
Patton et al.[17]	1998	1	55.4	81	17	100%	VV: 1	100%
Chou et al.[18]	2001	3	90.7	46.1	15.7	66.6%	VV: 2 VV → VA: 1 *	66%
Thompson et al.[19]	2005	2	67.5	62.5	21.5	100%	VV: 2	100%
Soussi et al.[21]	2016	11	82.0	66	12	55%	VV: 8 VA: 2† VV + VA: 1	9.0%
Kennedy et al.[20]	2017	2	78.5	43.5	16	0%	VV: 2	100%
Hsu et al.[10]	2017	6	149.1	66.6	12.0	83%	VV: 2 VA: 4 ‡	16.7%
Chiu et al.[22]	2018	5	104.7	87.1	N/A	100%	VV: 4 VA: 1 §	60%
Szentgyorgyi et al.[23]	2018	5	60.2	67.82	13.1	100%	VV: 5	80%
Ainsworth et al.[24]	2018	11	64.2	82	N/A	27%	VV: 11	45.4%
Dadras et al.[25]	2019	8	83.2	61.6	13.5	87.5%	VV: 7 VV → VA: 1 ¶	62.5%
Marcus et al.[26]	2019	20	64.0	N/A	N/A	10%	VV: 20	60%

N/A, not available; VV, veno-venous; VA, veno-arterial; ARDS, acute respiratory distress syndrome.
*One patient was transferred from VV to VA mode due to cardiogenic shock, but he died of inferior vena cava (IVC) rupture.
†VA mode was indicated due to unstable haemodynamic. One patient used combined VV and VA mode simultaneously. All three died of multiple organ failure.
‡VA mode was indicated due to unstable haemodynamic, and three died of multiple organ failure (MOF) and one died of cardiogenic shock.
§VA mode was indicated due to cardiogenic shock, but the patient died of infective endocarditis and subsequent septic shock.
¶One patient was transferred from VV to VA mode due to septic shock, and he survived to discharge.

shock. The average survival rate ranged from 9.0–100%. There have only been three cohorts that enrolled more than 10 patients since 2016 [21,24,26]. For these three cohorts, the mean Baux scores were 82.0, 64.2, and 64.0, with survival rates of 9.0%, 45.4%, and 60%, respectively. Combining these three cohorts for analysis, the overall mean Baux score was 68.7 and the overall mean survival to discharge was only 42.8%. Our cohort was comprised of 14 patients, with a mean TBSA burned of 81.6% and a mean Baux score of 120.3. Osler *et al.* claimed that inhalation injury would increase Baux score by 17 points, which was termed the revised Baux score [3]. According to their scale formula, the predicted mortality of our cohort should be close to 90% with a revised Baux score of 137 points. Table 5 shows that the severity of our study is much more than that of the other cohort studies. Inspiringly, our survival to discharge was 42.8%, which is not inferior to the aforementioned studies. This implies that with adequate rigorous patient selection, ECLS could be a salvage modality therapy for patients with high Baux scores.

Comparing VV- and VA-ECLS survival and outcome

In our study, the survival rates of VV- and VA-ECLS were 50.0% (3/6) and 37.5% (3/8), respectively. The hazard ratio for mortality was 1.66 with VA-ECLS, without significance. We had 3 survivors from VA-ECLS, and all of these patients received VA-ECLS because they were in septic shock [27] or they did not respond to inotropes and vasopressors. However, upon analysis of all cohort study patients in Table 5, the survival rates of VV- and VA-ECLS were 57.8% (37/64) and 10.0% (1/10), respectively. The hazard ratio was as high as 12.33 in VA-ECLS patients. In our preliminary experience, we observed that the most challenging issue in resuscitating burn shock patients was maintaining adequate intravascular volume [10]. Compared to VV-ECLS, the pump flow of VA-ECLS was significantly lower in patients with major burn injuries despite excessive fluid administration and human albumin transfusion. The systemic inflammatory mediators and cytokines would disrupt the inter-endothelial junctional structure, affect vascular actomyosin contraction, and then change vascular permeability by increasing the outflow of macromolecules and fluid from vessels [28]. This capillary leak syndrome would exacerbate in “large burn” patients [29] and would make these patients vulnerable to hypovolemic and septic shock. According to the previous literature mentioned in Table 5, most cases of VA-ECLS involved unstable hemodynamics and septic shock. Notably, hemodynamic instability before ECLS might imply a much more exacerbated capillary leak syndrome. As a result, the efficacy of VA-ECLS is limited in salvaging these patients from either hypovolemic or subsequent septic shock. Likewise, transfer from VV- to VA-ECLS should be applied with caution, despite the report from Dadras *et al.* that claims one survival after transfer to VA-ECLS [25].

Limitations

There are several limitations to this study. First, the nature of this study was retrospective. The data and information were collected via medical records, which might have had intrinsic bias. Second, the number of patients enrolled was small because only a very small proportion of burn patients require ECLS. In this work, we observed that some variables (e.g. Baux, albumin, creatinine, glucose, lactate, and lung compliance) tended to be risk factors for mortality. These preliminary clinical biochemistry data and parameters seemed to be valuable for making decisions of ECLS intervention in these critical patients. Nonetheless, the relationship between these data and outcomes of patients was not "statistically" identified due to the small number of these participants. It is worth further verification of these factors in future studies. Third, these patients are extremely critical; therefore, randomized trials cannot be performed due to ethical concerns. Furthermore, the patient cohort in our study yielded only 14 patients from a single burn center over an 8-year span; hence, it is challenging to perform a prospective study. Nevertheless, to the best of our knowledge, this is the largest number so far in a study reporting the highest Baux score. Due to the rarity of ECLS applied in this scenario, multi-center observational or interventional studies would improve patient selection, ECLS indications, and consequent outcomes.

Conclusions

In this study, we demonstrated the benefits and efficacy of ECLS in major burn patients with concomitant ARDS and inhalation injury. With the improvement and evolution of ECLS devices, including more biocompatible pumps and efficient oxygenators and fewer thrombogenic tubes, these critical patients may benefit from ECLS in the future. Further research with larger sample sizes is necessary for more evidence and robust conclusions.

Ethics approval and consent to participate

This study was approved by the ethical committee of our institution, the Institutional Review Board of Tri-Service General Hospital (TSGHIRB No.: C202005124, Date of Approval: 2020/9/2). The need for informed consent was waived by the ethics committee based on the retrospective nature of the study. Patients’ consents were obtained according to the Declaration of Helsinki.

Consent for publication

Identifying details (names, dates of birth, identity numbers, biometrical characteristics [such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic] and other information) of the participants that were studied are not published in written descriptions.

Availability of data and materials

All data and materials, as well as software applications or custom codes, support the published claims and comply with field standards.

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Authors’ contributions

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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