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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Research

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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 treatment of severely burned patients with concurrent inhalation injury and ARDS.

Methods: This is a retrospective analysis of 14 patients, including 10 males and four females, collected from a single medical burn center from 2012 to 2019. The mean age was 38.6±12.3 (range, 19-59) years. All suffered from major burns with inhalation injury. The average total body surface area of deep dermal or full thickness (DD/FT) burns was 81.6±20.0% (range, 47–99%). The average revised Baux score was 137.3 ± 22.6 (range, 107 – 172). All had developed ARDS with mean PaO_2/FiO_2 of 67.8±17.3. Indications for ECLS included sustained hypoxemia and unstable hemodynamics. The mean interval for initiating ECLS was 20.3 ± 40.8 days (range, 1-156 days).

Results: The mean duration of ECLS was 5.0±5.6 days (range, 0.3-16.7 days). The overall survival to discharge was 42.8%. Causes of death included sepsis (n=4) and multiple organ failure (n=4). The ECLS-related complications included cannulation bleeding, catheter-related infection, and hemolysis. The predicted risk factors of mortality before ECLS included lactate>8 mmol/L and Baux score>120.

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 seemed limited. Definite ECLS indications and rigorous patient selection would contribute to better clinical outcomes.

Background

Inhalation injury, large total body surface area (TBSA) burned, and subsequent acute respiratory distress syndrome (ARDS) are significant predictors of mortality in burn injury.[1,2] Inhalation injury mostly results in airway inflammation, pulmonary vascular shunting, micro-vascular 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 as the revised Baux score.[3,4] ARDS causes microvascular effects of inflammatory response to the burned skin on the pulmonary endothelium.[5,6] The treatment strategies for inhalation injury and ARDS include mechanical ventilation, adequate fluid resuscitation, and heparin nebulization. However, both are still the primary cause of death in major-burn patients.[7] Some cohort studies have reported that extracorporeal life support (ECLS) benefits burn victims, which led to wide utilization of ECLS for burn- and inhalation-related injuries. [8–10] However, limited studies have reported the efficacy of ECLS applied in patients with severe burn injury, concomitant inhalation injury, and subsequent ARDS. Besides, major burns with concomitant inhalation injury and ARDS are common in wars. It’s important for military medical center to improve management of such critically clinical issue. Therefore, in this study, we aim to assess the efficacy of ECLS in these extremely critical patients.

Methods

Patient characteristics

We retrospectively reviewed our experience with ECLS for major burns at our burn center from January 2012 to December 2019. The data was collected by review of medical records during hospitalization and follow-up after discharge. This study was approved by our ethical committee of the institution, Institutional Review Board of Tri-Service General Hospital (TSGHIRB No.: C202005124, Date of Approval2020/9/2). 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. Adult severely burned patients with concurrent inhalation injury and ARDS, who had 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%". The patient characteristics are shown in Table 1. A total of 14 patients, including 10 males and four females, were enrolled and reviewed via medical records. The mean age was 38.6 ± 12.3 years, ranging 19–59 years. The causes of severe burns included explosions (n = 10, 71.4%) and flame injuries (n = 4, 28.5%). The mean burned TBSA of DD/FT was 81.6 ± 20.0%, ranging 47–99%. The mean Baux score was 120.3 ± 22.6, ranging 90–155. Osler *et al.* proposed revised Baux score for more accurate prediction of mortality,[3] and stated that inhalation injury adds 17 points more than conventional Baux score. In our cohort, all subjects had inhalation injury. As a result, the average revised Baux score was 137.3 ± 22.6, ranging 107–172. A total of five patients had concomitant trauma, including one patient with head injury, two with open fracture, and two with pneumothorax. All patients required inotropic vasopressor with mean arterial pressure of 89.8 ± 22.1 mmHg. A total of 13 patients had hypovolemic shock, 10 had acute kidney injury, 9 had hepatic dysfunction, and 7 had coagulopathies. Table 2 shows the biochemistry data and ventilation status. Leucocytosis and high C-reactive protein (CRP) indicated severe systemic inflammation response, which increased the endothelial permeability and resulted in low albumin level with a mean 2.8 ± 0.9 g/dL. Elevated creatinine level with oliguria, hepatic dysfunction, and acidosis with elevated lactate level indicated systemic shock. High creatine kinase implied massive rhabdomyolysis, and exacerbated acute kidney injury. The ventilator setting had a mean peak inspiration pressure (PIP) of 35.9 ± 6.4 cmH_2O, a mean airway pressure (MAP) of 25.3 ± 4.7 cmH_2O, and the mean positive end expiratory pressure (PEEP) of 11.0 ± 1.9 cmH_2O. The mean tidal volume was 425.3 ± 117.8 mL, and the mean lung compliance was 19.5 ± 14.3 ml/cmH_2O. Poor oxygenation and systemic hypoxia were noted with high oxygen index (mean 34.7 ± 12.2, ranging 13.0–49.0) and a low ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2, mean 67.8 ± 17.3, ranging 49–99).

Table 1
Pre-ECLS characteristics of enrolled patients

	Mean ± SD or Number	Range or Percentage
Patient demographics		
Age (years)	38.6 ± 12.3	19–59
BMI (Kg/m^2)	28.2 ± 5.1	21-37.8
Male	10	71.4%
Explosion injury	10	71.4%
Flame injury	4	28.5%
TBSA of DD/FT burned (%)	81.6 ± 20.0	47–99
Baux score (Age + TBSA burned)	120.3 ± 22.6	90–155
Mean blood pressure (mmHg)	89.8 ± 22.1	56–133
Inotropes (ug/kg/min) Dopamine (mcg/kg/min) Epinephrine (mcg/min) Norepinephrine (mcg/min)	9.9 ± 9.3 3.9 ± 5.1 17.2 ± 10.5	2-20.2 0-7.4 5-29.3
Patient comorbidity		
Diabetes	1	7.1%
Hypertension	1	7.1%
Coronary artery disease	1	7.1%
Concomitant trauma		
Head injury	1	7.1 %
Open fracture	2*	14.3 %
Pneumothorax	2	14.3 %
Burn-related sequelae		
Inhalation injury	14	100%
Hypovolemic shock	13	92.9%

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.

	Mean ± SD or Number	Range or Percentage
Rhabdomyolysis	10	71.4%
Acute kidney injury	10	71.4 %
Hepatic dysfunction	9	64.3 %
Coagulopathy	7	50%
Stress GI bleeding	3	21.4 %
Acute cholangitis or Pancreatitis	2	14.2%

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.

Table 2
Pre-ECLS biochemistry data and ventilation status.

	Mean ± SD or Number	Range or Percentage
Laboratory data		
White blood cell (10^3/mL)	21533.6 ± 14054.9	4300–54480
CRP (mg/dL)	14.6 ± 8.1	1–33.19
Haemoglobin (g/dL)	9.9 ± 3.0	5–16.9
Albumin (g/dL)	2.8 ± 0.9	1–4.5
Creatinine (mg/dL)	1.6 ± 1.0	1–4.1
AST (U/L)	142.8 ± 225.2	19–898
Glucose (mg/dL)	221.0 ± 108.9	105–497
Creatine kinase (U/L)	5175.3 ± 7558.8	15–20000
Troponin I (ng/mL)	1.6 ± 4.4	0–16.5
PH	7.2 ± 0.1	7–7.42
Lactate (mmol/L)	8.8 ± 4.9	2–15
Ventilation data		
Peak inspiration pressure (cmH_2O)	35.9 ± 6.4	24–45
Mean airway pressure (cmH_2O)	25.3 ± 4.7	17–30.7
Positive end expiratory pressure (cmH_2O)	11.0 ± 1.9	8–14
Tidal volume (mL)	425.3 ± 117.8	250–603

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.

	Mean ± SD or Number	Range or Percentage
Lung compliance (ml/cmH_2O)	19.5 ± 14.3	3–54
Oxygen index	34.7 ± 12.2	13.0–49.0
PaO_2/FiO_2	67.8 ± 17.3	49–99
$AaDO_2$ (mmHg)	561.9 ± 41.4	452–601.6

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.

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. The indications include $PaO_2/FiO_2 < 80$, oxygen index > 40, and alveolar-arterial oxygen gradient (AADO2) > 500 mmHg despite optimal conventional ventilator support.[11] Venovenous ECLS (VV-ECLS) was used in six patients, whereas venoarterial ECLS (VA-ECLS) was used in eight patients due to unstable hemodynamic status despite of inotropes and vasopressors (Table 3). The ECLS system included a heparin-coated polypropylene oxygenator (AffinityNT1, Medtronic, Minneapolis, MN) and a centrifugal pump (BPX-80 Bio-Pump1, Medtronic). The blood flow was maintained no more than 3.5L/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 no more than 35 cmH_2O to avoid barotrauma. $PaCO_2$ 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 modified Parkland formula, 50 mL of 25% human albumin was transfused every two hours to maintain oncotic pressure. Norepinephrine was used in all patients for low vascular tone. Furthermore, prophylactic broad-spectrum antibiotics and antibacterial dressing were both applied to prevent secondary infection. Bronchoscopy was done to assess the severity of inhalation injury and to remove the sputum plug in the main airway.

Table 3
ECLS clinical course and outcomes

	Mean ± SD or Number	Range or Percentage
Interval to ECLS (days)		
All (n = 14)	20.3 ± 40.8	1-156
VV-ECLS (n = 6)	3.3 ± 4.8	1–13
VA-ECLS (n = 8)	33.0 ± 51.4	1-156
Peri-ECLS surgical intervention		
Trunk escharotomy	8	57.1%
Limb fasciotomy	4	28.5%
Tracheostomy	2	14.2%
Number of operations for wound debridement	7.8 ± 10.0	0–30
Number of operations for wound reconstruction (STSG or FTSG)	4.0 ± 4.8	0–13
ECLS-related complications		
Cannulation bleeding	3	21.4%
Catheter-related infection	3	21.4%
Haemolysis	11	78.5%
Thromboembolism event	0	0%
Limb ischemia	0	0 %
Duration of ECLS (days)		
ALL (n = 14)	5.0 ± 5.6	0.3–16.7
VV-ECLS (n = 6)	8.0 ± 6.7	2.7–16.7
VA-ECLS (n = 8)	2.7 ± 3.6	0.3–10.8
Outcomes		
Overall hospitalization (days) (n = 14)	66 ± 80	2-221
Survivor (n = 6)		
Duration of ECLS	6.3 ± 2.3	1-16.7
Hospitalization (days)	137.8 ± 75.6	34–221
Mortality (n = 8)		

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

	Mean ± SD or Number	Range or Percentage
Duration of ECLS	4.0 ± 6.1	0.3–16.5
Hospitalization (days)	12.1 ± 8.9	2–22
Cause of death		
Sepsis	4	28.6%
Multiple organ failure	4	28.6%
VV, veno-venous; VA, veno-arterial; STSG, split-thickness skin graft; FTSG, full-thickness skin graft.		

Statistical methods

SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all analyses. Categorical variables were analyzed using the Fisher's exact test. Due to the small number of cases, normality test was performed. Among continuous variables, normal distribution data were presented as means ± standard deviations and compared using Student's *t*-test. Kaplan–Meier curve was presented using the Gehan–Breslow–Wilcoxon test, and Cox-regression test. P-value less than 0.05 was defined as statistically significant. Predictive factors and odds ratio were chosen and calculated by Chi-square test and multivariate logistic regression analysis with 95% confidence interval of the difference.

Results

ECLS clinical course and outcomes are shown in Table 3. The overall mean interval from intubation to ECLS was 20.3 ± 40.8 days, ranging 1-156 days, with mean interval of 3.3 ± 4.8 days in VV-ECLS and 33.0 ± 51.4 days in VA-ECLS, respectively. VV-ECLS with 50% survival and VA-ECLS with 37.5% survival was weaned by three patients each. During ECLS, eight patients had trunk escharotomies and four had limb fasciotomies to release the compartment syndrome. The mean number of procedures for repeated wound debridement was 7.8 ± 10.0 and 4.0 ± 4.8 for wound reconstruction, including split-thickness skin graft (STSG) and full-thickness skin graft (FTSG). A total of two patients needed tracheostomy due to airway obstruction caused by severe swelling of laryngeal tissue. The ECLS-related complications included cannulation bleeding, catheter-related infection, and hemolysis. No thromboembolism event or distal limb ischemia was noted. The overall mean ECLS duration was 5.0 ± 5.6 days, ranging 0.3–16.7 days, with mean duration of 8.0 ± 6.7 days in VV-ECLS and 2.7 ± 3.6 days in VA-ECLS, respectively. The overall mean hospitalization was 66 ± 80 days, ranging 2-221 days. In survivors (n = 6, 42.8%), the average duration was 6.3 ± 2.3 days, and hospitalization was 137.8 ± 75.6 days. In mortality (n = 8, 57.1%), the average duration was 4.0 ± 6.1 days, and hospitalization was 12.1 ± 8.9 days. Septic shock and multiple organ failure resulted in death of four patients each. The survival to discharge was 42.8%. Figure 1 shows the overall survival curve analyzed by Kaplan-Meier method. Table 4 shows the predicted risk factors of mortality before ECLS use. Serum creatinine, albumin, glucose, lactate, and Baux score had statistical significance between survivors and non-survivors by univariate analysis. After multinomial logistic regression, the predicted risk factors of mortality before ECLS included lactate > 8 mmol/L and Baux score > 120 with odds ratios 15.5 and 35.1, respectively.

Table 4
Predicted risk factors of mortality before ECLS

Parameter	Survivor (n = 6)	Non-survivors (n = 8)	*P*-value
Univariate analysis			
Creatinine (mg/dL)	1.12 ± 0.39	2.29 ± 1.00	0.013
Albumin (g/dL)	3.45 ± 0.68	2.34 ± 0.83	0.029
Glucose (mg/dL)	141.67 ± 36.11	277.88 ± 109.59	0.005
Lactate (mmol/L)	6.02 ± 4.58	11.47 ± 3.81	0.026
CRP	12.14 ± 2.37	14.72 ± 10.75	0.852
Baux	122.83 ± 21.40	148.13 ± 17.59	0.029
Predicted risk factors of mortality			
	Odds ratio	**95% confidence interval**	P-**value**
Albumin < 3.0 (g/dL)	14.2	0.944-207.597	0.055
Lactate > 8 (mmol/L)	15.5	1.031–218.300	0.047
Baux > 120	35.1	1.74–702.9	0.020
VA-ECLS	1.66	0.195–14.266	0.641
CRP, C-reactive protein; VA, veno-arterial			

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 multiple risk factors, such as pneumonia, smoke inhalation, shock, bacteraemia, and blood product transfusion. The pro-inflammatory mediators not only initiate local tissue injury but also amplify the systemic inflammatory response. Eventually, 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 ranged from 32.6–53.2%, by Berlin definition,[12] and 39.5% by American European Consensus Conference definition.[5] It has been reported that the extent of full thickness burn predicts the development of severe ARDS, which is associated with 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] none of the randomized controlled trials could prove its efficacy on burn-related ARDS so far.

ECLS for inhalation injury

According to current published literature, extended 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 might 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 inhalation medication. However, once ARDS develops, the insufficient pulmonary oxygenation always results in sustained systemic hypoxemia and subsequent multiple organ dysfunction. Asmussen *et al.*, reported a systematic review about ECLS in respiratory failure resulting from burn and smoke inhalation injury.[9] They concluded that the level of evidence is limited due to insufficient patient numbers available in present literature. However, ECLS device and technology have improved and evolved over the last decades, thereby increasing the survival rate year by year. Similarly, 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 thought that ARDS mainly resulted from large TBSA burned rather than inhalation injury. Although Liffner *et al.* reported that inhalation injury assessed by an inhalation lung injury score did not contribute to the development of ARDS,[16] we believe that the inhalation injury is also a contributing factor for ARDS, which together exacerbated the respiratory dysfunction.

Literature review of ECLS for burn injury

Table 5[10,17–26] shows literature reviews from 1998 to present. There were eleven cohorts that supported the application of ECLS in burns with respiratory failure, which is mainly caused by ARDS, with PaO_2/FiO_2 below 100. The average TBSA ranged from 12–89%, and the average Baux score ranged from 55 to 149. The majority used VV-ECLS for systemic hypoxemia, while the minority used VA-ECLS for unstable hemodynamics, and cardiogenic and septic shock. The average survival rate ranged from 9.0–100%. There are only three cohorts enrolling more than 10 patients since 2016.[21,24,26] For these three cohorts, each mean Baux score was 82.0, 64.2, and 64.0, with survival 9.0%, 45.4%, and 60%, respectively. Taking these three cohorts together for analysis, the overall mean Baux score was 68.7, and overall mean survival to discharge was only 42.8%. Our cohort had 14 patients enrolled, with a mean TBSA burned 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 137-point revised Baux score. Table 5 shows that the severity of our study is much more than that of all 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 high-Baux patients.

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%

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 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 survived to discharge.

Study	Year	Number	Baux score (mean)	PaO_2/FiO_2	PEEP (cmH_2O)	Inhalation injury	ECLS Mode	Survival to discharge
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 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 survived to discharge.								

Compare VV and VA survival and outcome

In our study, the survival rate of VV- and VA-ECLS were 50.0% (3/6) and 37.5% (6/8), respectively. The hazard ratio for mortality was 1.66 in VA-ECLS without significance. We had three survivors from VA-ECLS, and all these victims applied VA-ECLA on the basis of septic shock[27], who did not respond to inotropes and vasopressors. However, on analyzing all patients of cohort studies in Table 5, the survival 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 to maintain adequate intravascular volume.[10] Compared to VV-ECLS, the pump flow of VA-ECLS was significantly lower in major burn injury 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 burn shock patients vulnerable to hypovolemic and septic shock. According to past literature mentioned in Table 5, the majority of VA-ECLS were set for unstable hemodynamics and septic shock. It is noteworthy that 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 reports available by Dadras that claim one survival after transfer to VA-ECLS.[25]

Limitations

There are several limitations in this study. First, the nature of this study is retrospective. The data and information were collected via medical records, which might have intrinsic bias. Second, the number of patients enrolled was too small. A very small proportion of burn patients require ECLS; hence, it is challenging to perform a prospective study. Third, these patients are extremely critical; hence, randomized trials cannot be performed due to ethical concerns. The patient cohort in our study yielded only 14 patients over an eight-year span, collected from a single burn center. Due to the rarity of ECLS applied in this scenario, multi-center observational or interventional studies would improve patient selection, ECLS indication, and consequent outcomes.

In conclusion, our study enrolled 14 patients. To the best of our knowledge, this

is the largest patient number so far. Our Baux score has been the highest. We demonstrate the benefits and efficacy of ECLS in major-burn patients with concomitant ARDS and inhalation injury through this study. With improvement and evolution of ECLS devices, including more biocompatible pumps and efficient oxygenators, and less thrombogenic tubes, these critical patients may benefit from ECLS in future. Further research with more cases is necessary to draw more solid evidence and robust conclusions.

Abbreviations

ARDS - acute respiratory distress syndrome

ECLS - extracorporeal life support

TBSA **-** total body surface area

CRP - C-reactive protein

PIP **-** peak inspiration pressure

MAP **-** mean airway pressure

PEEP - positive end expiratory pressure

STSG - split-thickness skin graft

FTSG - full-thickness skin graft

Declarations

- **Ethics approval and consent to participate -** This study was approved by our ethical committee of the institution, 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**
- **Availability of data and materials**
- **Competing interests -** The authors declare that they have no competing interests.

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- **Authors' contributions**
  Conception and design: Po-Shun Hsu, Chih-Han Huang, Hung-Hui, Liu
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- **Authors' information (optional)**

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Figures

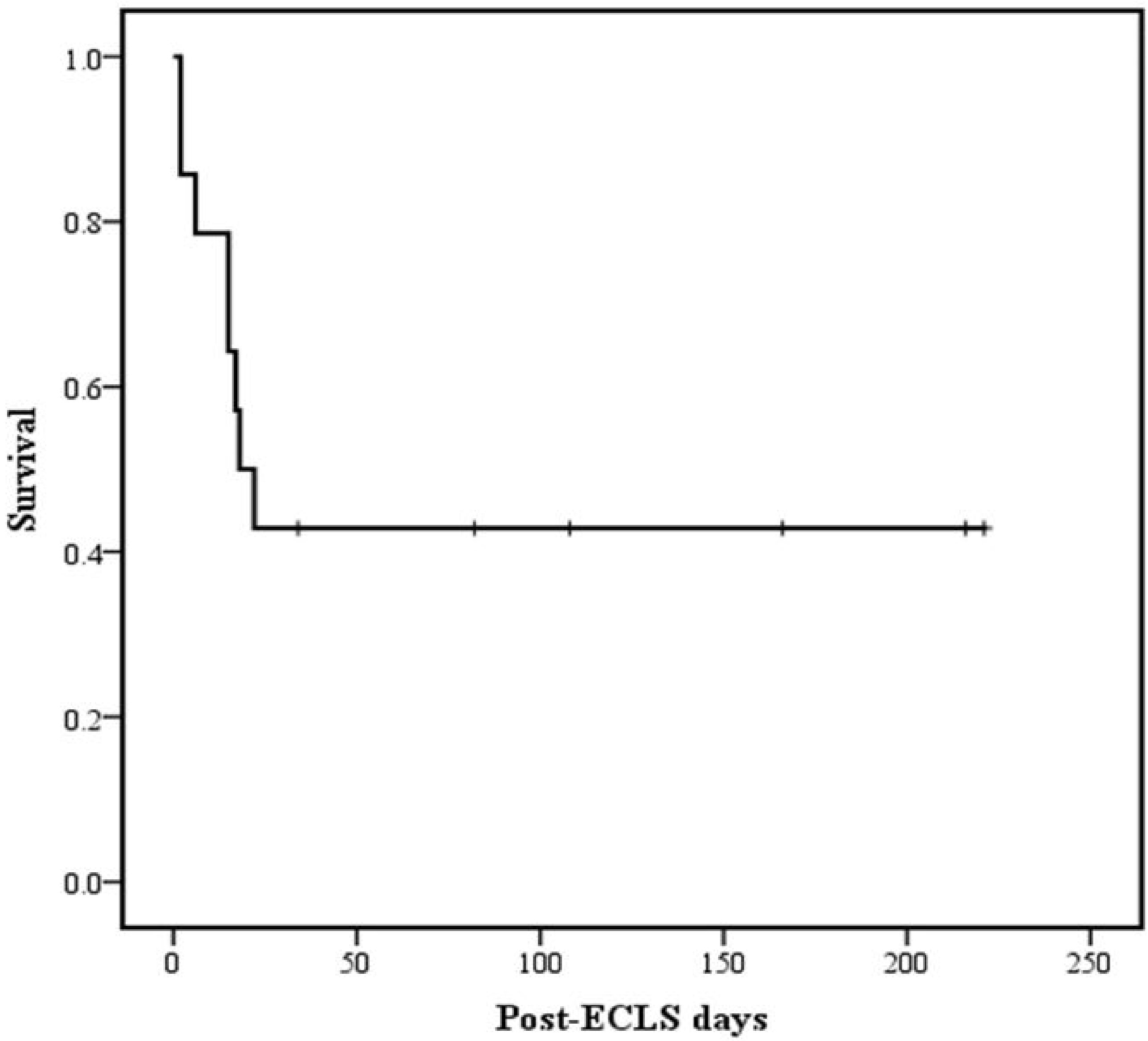

Figure 1

Kaplan–Meier analysis shows the survival rate after ECLS - The figure demonstrates the association between the survival rate and post-ECLS days. The survival to discharge was 42.8%.