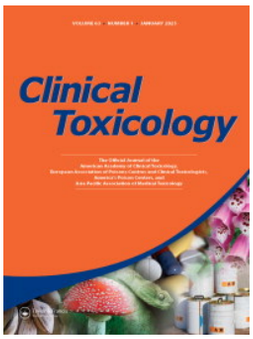

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CLINICAL RESEARCH

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) for acute poisonings in United States: a retrospective analysis of the Extracorporeal Life Support Organization Registry

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ABSTRACT

Introduction: Veno-arterial extracorporeal membrane oxygenation is frequently considered and implemented to help manage patients with cardiogenic shock from acute poisoning. However, utilization of veno-venous extracorporeal membrane oxygenation in acutely poisoned patients is largely unknown.
Method: We conducted a retrospective study analyzing the epidemiologic, clinical characteristics and survival of acutely poisoned patients placed on veno-venous extracorporeal membrane oxygenation using the Extracorporeal Life Support Organization registry. Adult cases in the United States were included after a systematic search of the registry between January 1, 2003, and November 30, 2019. Study outcomes included survival to discharge, time to cannulation, and changes in metabolic, hemodynamic, and ventilatory parameters stratified by survival.
Results: One hundred and seventeen cases were included in the analysis after excluding 216 non-poisoning-related cases. Their median age was 34 years and 69.2% were male. Opioids (45.3%) were most commonly implicated, followed by neurologic drugs (e.g., antidepressants, antiepileptics) (14.5%) and smoke inhalation (13.7%); 23 patients (19.7%) had a pre-extracorporeal membrane oxygenation cardiac arrest. The median time from admission to extracorporeal membrane oxygenation was 47 h with a median duration of extracorporeal membrane oxygenation support of 146.5 h. Survivors were cannulated significantly earlier than non-survivors (25 h versus 123 h; $P=0.02$). Eighty-four patients (71.2%) survived to hospital discharge. Clinical parameters (hemodynamic, metabolic, and ventilatory) improved with veno-venous extracorporeal membrane oxygenation support, but no statistically significant difference was noted between survivors and non-survivors.
Discussion: Our study showed that veno-venous extracorporeal membrane oxygenation was infrequently utilized for poisoning-associated acute respiratory distress syndrome. Opioids were the most frequently reported exposure among the cases in which indirect lung injury may have occurred from aspiration. Although no specific clinical parameters were associated with survival, early initiation of extracorporeal membrane oxygenation may improve clinical outcomes.
Conclusions: The use of veno-venous extracorporeal membrane oxygenation for refractory respiratory failure due to poisoning was associated with a clinically significant survival benefit compared to other respiratory diagnoses requiring veno-venous extracorporeal membrane oxygenation.

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Introduction

In the United States (US), the incidence of acute poisoning and poisoning-associated morbidity and mortality are increasing [1]. Over the past 15 years, self-harm attempts and mortality due to suicide have steadily increased along with drug overdose deaths, especially from opioid misuse [2]. The medical management of the clinical sequelae of acute poisoning such as acute respiratory failure and cardiovascular shock has not changed significantly. Nevertheless, there has been a renewed interest in previously available medical tools and pharmacologic therapies such as high-dose insulin euglycemic therapy and extracorporeal membrane oxygenation (ECMO) in patients with acute poisoning [3–6].

There is accruing evidence supporting the use of veno-arterial ECMO (VA-ECMO) to manage patients with refractory cardiogenic shock from cardiotoxins (e.g., beta-adrenoceptor antagonists, calcium-channel blockers, and poisons with type 1 A and 1 C antidysrhythmic effects) [6–8]. In contrast, the role of veno-venous ECMO (VV-ECMO) in the management of acute respiratory distress syndrome (ARDS) from acute poisoning is largely unknown. The majority of the

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clinical outcome data of VV-ECMO, and the guideline for its use comes from studies involving severe ARDS from various medical conditions such as viral infections (influenza A H1N1 and COVID-19), and cancer, among others [9–15]. Although there are several different classes of pulmonary toxins (e.g., paraquat) and pulmonary irritants (various gases, chemicals, and fumes) that can induce ARDS, pulmonary toxicity involving these poisons occurs infrequently [1,16]. Consequently, the literature on VV-ECMO use in patients with acute poisoning consists of published case reports and case series [17,18]. Therefore, we conducted an analysis of the Extracorporeal Life Support Organization (ELSO) Registry to determine the use of VV-ECMO in patients with acute poisoning and their clinical outcomes, and to better understand the epidemiology of their exposures.

Methods

We performed a retrospective analysis of VV-ECMO use in acutely poisoned adults in the US using the Extracorporeal Life Support Organization Registry. The Extracorporeal Life Support Organization maintains one of the largest ECMO registries (over 200,000 reported ECMO cases at the time of this writing) in which over 400 US and international member centers report cases involving ECMO support via a standardized data reporting website (www.ELSO.org); the definition of each variable collected by the Extracorporeal Life Support Organization registry is available on the website (https://www.elso.org/registry/datadefinitions,forms,instructions.aspx) [19]. The International Classification of Diseases (ICD) codes [9th and 10th revisions] for poisoning (ICD-9: 960–989, ICD-10: T36–T65) were used to identify poisoning-related adult patients (age >18 years old) among the ECMO cases. The Extracorporeal Life Support Organization registry was systematically searched between January 1, 2003 and November 30, 2019 for US cases only. De-identified data were provided by the ELSO in Excel format (Microsoft Corporation, Redmond, WA). This study was exempted from the Institutional Review Board at the University of Maryland, Baltimore.

All ICD codes and their definitions associated with each case were independently reviewed by two study investigators (HKK and KMJ) to identify cases in which ECMO support was likely to be initiated due to poisoning. For example, cases with ICD codes for intentional self-poisoning by drugs (X60-64) and substance specific codes for intentional overdose or poisoning (e.g., T44.7X2A: poisoning by beta-adrenoceptor antagonists, intentional self-harm) were considered likely acute poisoning by self-harm intent. On the other hand, cases with ICD codes for unspecified adverse effect of drug or medicament (T88.7) or similar were considered as sequelae of adverse drug effects. Cases were determined as poisoning-related when two reviewers agreed regarding the indication of ECMO support based upon the review of the ICD code definitions. Disagreements were resolved through consensus after each case in question was discussed between the two study investigators. Inter-rater reliability was assessed by calculating inter-observer percent agreement and Cohen's kappa coefficient. Only VV-ECMO cases were included in the study. Cases with hybrid cannulation (veno-venous-arterial, veno-arterial-venous and veno-pulmonary ECMO) were excluded. Cases with unknown substance exposures and cases likely experiencing an adverse drug reaction or event to unspecified medications, substances, or anti-neoplastics were excluded. For the remaining cases, the substance was classified into the following categories: cardiovascular drugs (antihypertensives, vasodilators, antidysrhythmics), neurologic drugs (antidepressants, sedative and hypnotics, neuroleptics and antiepileptics), opioids (illicit and prescribed opioids), amfetamines (amphetamines), ethanol, anesthetics, non-opioid analgesics (paracetamol [acetaminophen] and nonsteroidal anti-inflammatory drugs), smoke inhalation (i.e., fire exposure, carbon monoxide). Other substances that did not belong to the above classification were categorized as "others."

The goal of the study was to evaluate the hemodynamic and ventilatory parameters as well as the overall survival in poisoned patients undergoing VV-ECMO. Subgroup survivor analysis was also performed as well as an analysis of the factors associated with mortality. Survival to hospital discharge (discharged home or transferred to a non-ECMO facility) was the primary outcome of interest. We also evaluated changes in hemodynamic parameters, acid-base status (metabolic acidosis and pH), and ventilatory status – including positive inspiratory pressure and positive end-expiratory pressure – pre- and 24 h post-ECMO initiation by survival. Additional secondary outcomes of interest were time from admission to ECMO cannulation, ECMO duration, and ECMO complications. Hypotension was defined as a systolic blood pressure of less than 90 mmHg or a mean arterial pressure of less than 65 mmHg [20].

Descriptive analysis, chi-square and Wilcoxon rank-sum tests were performed, comparing demographic and clinical parameters of the entire cohort as well as for subgroup analysis of survivors and non-survivors. Median and interquartile ranges (IQR) were determined for continuous variables. To determine factors associated with hospital mortality, logistic regression analyses were performed. Multivariate analysis was performed using the Akaike information criterion method. Results were presented as odds ratio (OR) with 95% confidence intervals (95% CI). R Statistical Software (Version 3.6.2; The R Foundation of Statistical Computing, Vienna, Austria) was used for all statistical analysis.

Results

A total of 506 VV-ECMO cases were identified from the search of the Extracorporeal Life Support Organization Registry during the study period. Of these cases, 94 were excluded for hybrid ECMO configuration. Two hundred and sixteen cases were excluded, as they were deemed unlikely to be poisoning-related, while 79 cases had unknown exposures. Of the remaining cases, 117 cases received VV-ECMO and were included in the final analysis. For much of the study period, the annual number of VV-ECMO cases remained five or less per year. Starting in 2016, the number of VV-ECMO cases gradually increased, reaching 32 cases in 2019. The two study

investigators who reviewed the ECMO cases had an inter-rater agreement of 92.3% on poisoning-related cases (kappa coefficient: 0.87; 95% CI: 0.81-0.83). The median age of included cases was 34.1 years and 69.2% ($n=81$) were male. Approximately 30% of the exposures were due to misuse, followed by unintentional exposure (23.1%) and suicide attempts (13.7%); the intention of exposure was unknown in approximately 25% of the cases. Opioids were the most reported substance (45.3%) and the most commonly coded as misuse, followed by neurologic drugs (14.5%), smoke inhalation (13.7%), and cardiovascular drugs (9.4%). Ninety-five (81.2%) cases involved single substance exposure, while 22 (18.8%) cases involved multiple exposures. Multi-substance exposure frequently involved opioids (22.7%), benzodiazepines (27.0%), and diacetylmorphine (heroin) (18.2%). Data on the route of exposure was not available from the Extracorporeal Life Support Organization registry.

Twenty-three cases (19.7%) experienced cardiac arrest prior to ECMO cannulation. The most common substance exposures among pre-ECMO cardiac arrest cases were diacetylmorphine ($n=7$; 30.4%) and other opioids ($n=5$; 21.7%). Pre-ECMO pharmacologic interventions included: vasopressor infusions (norepinephrine (48.7%), epinephrine (22.2%), and vasopressin (15.4%)) and sodium bicarbonate (22.2%) (Supplementary Table 1). Pulmonary support was the primary indication for VV-ECMO in most cases (97.4%), while cardiac support ($n=2$) and extracorporeal cardiopulmonary resuscitation ($n=1$) were infrequent indications (Table 1). The median time from hospital admission to VV-ECMO cannulation was 47 h (IQR: 10–43 h), while the median duration of VV-ECMO was 146.5 h (IQR: 78.8–234.5 h) for the study cohort. Prior to VV-ECMO, 27.3% of the cases experienced hypotension, respiratory acidosis with a median $PaCO_2$ of 59.0 mmHg [7.87 kPa] (IQR: 50.0–76.0 mmHg) and hypoxemia with a median PaO_2 of 59.0 mmHg [7.87 kPa] (IQR: 45.8–77.3 mmHg) and a median oxygen saturation of 85.5% (IQR: 76.5–92.8%). With respect to the ventilatory setting, the median positive inspiratory pressure was 35 cm H_2O (IQR: 30–40 cm H_2O) with positive end-expiratory pressure of 14 cm H_2O (IQR: 10–16 cm H_2O). The median pH was 7.21 (IQR: 7.12–7.3) and the median serum lactate concentration was 2.8 mmol/L (IQR:1.7–6.1 mmol/L). While on VV ECMO all clinical parameters significantly improved except for the serum bicarbonate concentration, for which pre- and post-ECMO values were similar: 24.2 mmol/L versus 25.3 mmol/L, respectively (Supplementary Table 2).

The survival rate in this cohort was 71.2% ($n=84$). Most of the demographic characteristics and substance exposures were similar between survivors and non-survivors, but there was a significant difference with respect to the intention of exposure ($P=0.001$). A larger proportion of survivors involved misuse (32.1% versus 24.2%) and suicide or self-harm (16.7% versus 6.1%), while adverse drug effect was more frequently reported among non-surviving VV-ECMO cases (27.3% versus 2.4%). Additionally, survivors were cannulated significantly earlier after hospital admission compared to non-survivor group (25 h [IQR: 9–19 h] versus 123 h [IQR: 19–311 h]; $P=0.02$) and had significantly longer lengths of hospitalization (504 h

Table 1. Demographic and clinical characteristics of veno-venous extracorporeal membrane oxygenation cases for acute poisoning.

Variables	Study cohort ($n=117$)	Non-survivors ($n=33$)	Survivors ($n=84$)	*P*-value
Female, *n* (%)	36 (30.8)	9 (27.3)	27 (32.1)	0.77
Age (years), median (IQR)	34.1 (24.5–43.5)	37.6 (26.8–48.6)	30.5 (24.3–42.1)	0.19
Weight (kg), median (IQR)	91.2 (76.2–103.6)	90.0 (73.6–101.4)	94 (77.9–103.8)	0.30
Time from admission to VV- ECMO cannulation (h), median (IQR)	47 (10–143)	123 (19–311)	25 (9–109)	0.02
Duration of VV-ECMO (h), median (IRQ)	146.5 (78.8–234.5)	171.0 (78.0–247.0)	139.0 (80–211.5)	0.33
Length of stay (h), median (IQR)	436.0 (305.0–725.0)	313.0 (189.0–507.6)	504 (325.2–782.2)	0.01
Pre-ECMO cardiac arrest, *n* (%)	23 (19.7)	5 (15.2)	18 (21.4)	0.61
Intention				0.001
Misuse, *n* (%)	35 (29.9)	8 (24.2)	27 (32.1)	
Suicide, *n* (%)	16 (13.7)	2 (6.1)	14 (16.7)	
Adverse drug effect, *n* (%)	11 (9.4)	9 (27.3)	2 (2.4)	
Unintentional, *n* (%)	27 (23.1)	6 (18.2)	21 (25.0)	
Unknown, *n*	28	8	20	
Type of exposure				
Opioids, *n* (%)	53 (45.3)	11 (33.3)	42 (50.0)	0.16
Neurologic drugs, *n* (%)	17 (14.5)	5 (15.2)	12 (14.3)	>0.99
Smoke inhalation, *n* (%)	16 (13.7)	6 (18.2)	10 (11.9)	0.56
Cardiovascular drugs, *n* (%)	11 (9.4)	3 (9.1)	8 (9.5)	1.00
Non-opioid analgesics, *n* (%)	8 (6.8)	0	8 (9.5)	0.15
Ethanol, *n* (%)	2 (1.7)	0	2 (2.4)	0.92
Amfetamines, *n* (%)	1 (0.9)	0	1 (1.2)	>0.99
Local anesthetics, *n* (%)	1 (0.9)	0	1 (1.2)	>0.99
Others, *n* (%)	16 (13.7)	9 (27.3)	7 (8.3)	0.02
Ventilation type				
Conventional oxygen, *n* (%)	93 (79.5)	28 (84.8)	65 (77.4)	0.63
High flow oxygen, *n* (%)	8 (6.8)	2 (6.1)	6 (7.1)	–
Unknown, *n*	16	3	13	–
Support type				
Pulmonary, *n* (%)	114 (97.4)	32 (97.0)	82 (97.6)	0.65
Cardiac, *n* (%)	2 (1.7)	1 (3.0)	1 (1.2)	–
Extracorporeal cardiopulmonary resuscitation, *n* (%)	1 (0.9)	0	1 (1.2)	–

VV-ECMO: veno-venous extracorporeal membrane oxygenation.

Table 2. Comparison of pre and post veno-venous extracorporeal membrane oxygenation data by survival[#].

Variables	Non-survivors ($n=33$)	Survivors ($n=84$)	*P*-value
Pre-extracorporeal membrane oxygenation			
Systolic hypotension, *n* (%)	6 (27.3)	18 (27.3)	>0.99
pH (mmHg), median (IQR)	7.24 (7.14–7.3)	7.19 (7.12–7.30)	0.40
$PaCO_2$ (mmHg), median (IQR)	55.2 (47.8–78.8)	58.0 (49.0–75.8)	0.72
$PaCO_2$ [kPa], median (IQR)	7.4 (6.4–10.5)	7.7 (6.5–10.1)	0.72
PaO_2 (mmHg), median (IQR)	57.0 (42.2–74.0)	59.0 (47.5–78.5)	0.26
PaO_2 [kPa], median (IQR)	7.6 (5.6–9.9)	7.9 (6.3–10.5)	0.26
Serum bicarbonate concentration (mmol/L), median (IQR)	25.9 (19.3–31.0)	23.8 (20.0–27.2)	0.28
Oxygen saturation by pulse oximetry (%), median (IQR)	84.0 (75.0–90.0)	85.5 (78.0–94.0)	0.39
Positive inspiratory pressure (cm H_2O), median (IQR)	38 (34–40)	35 (30–38)	0.12
Positive end expiratory pressure (cm H_2O), median (IQR)	15 (11–18)	14 (10–16)	0.66
Serum lactate concentration (mmol/L), median (IQR)	2.7 (1.4–4.3)	2.9 (1.8–6.4)	0.32
24 h post-extracorporeal membrane oxygenation			
Systolic hypotension, *n* (%)	1 (4.5)	3 (4.5)	>0.99
pH (mmHg), median (IQR)	7.40 (7.30–7.40)	7.40 (7.40–7.50)	0.90
$PaCO_2$ (mmHg), median (IQR)	40.0 (38.5–46.0)	41.0 (37.0–45.0)	0.85
$PaCO_2$ (kPa), median (IQR)	5.3 (5.1–6.1)	5.5 (4.9–6.0)	0.85
PaO_2 (mmHg), median (IQR)	71.0 (60.0–89.5)	80.0 (65.0–124.0)	0.11
PaO_2 (kPa), median (IQR)	9.5 (8.0–11.9)	10.7 (8.7–16.5)	0.11
Serum bicarbonate concentration (mmol/L), median (IQR)	25.3 (22.6–28.4)	25.5 (23.2–27.6)	0.99
Oxygen saturation by pulse oximetry (%), median (IQR)	94.0 (89.5–97.5)	96.0 (92.0–99.0)	0.054
Positive inspiratory pressure (cm H_2O), median (IQR)	28 (24–33)	25 (22–30)	0.07
Positive end expiratory pressure (cm H_2O), median (IQR)	10 (8–12)	10 (10–12)	0.72
Serum lactate concentration (mmol/L), median (IQR)	1.9 (1.6–7.8)	1.8 (1.2–2.5)	0.18

[#]Data were only available in 21 non-survivors and 64 survivors.

Table 3. Complications and adverse events during veno-venous extracorporeal membrane oxygenations*.

Variables	Study cohort ($n=117$)	Non-survivors ($n=33$)	Survivors ($n=84$)	*P*-value
Kidney replacement therapy, *n* (%)	27 (23.1)	10 (30.3)	17 (20.2)	0.36
Inotropic support during extracorporeal life support, *n* (%)	23 (19.7)	9 (27.3)	14 (16.7)	0.30
Creatinine concentration (mg/dL) [µmol/L]				
1.5–3.0 [132.6–265.3]	22 (18.8)	7 (21.2)	15 (17.9)	0.88
>3.0 [>265.3], *n* (%)	5 (4.3)	1 (3.0)	4 (4.8)	1.00
Infection, *n* (%)	12 (10.3)	7 (21.2)	5 (6.0)	0.04*
Pneumothorax, *n* (%)	11 (9.4)	8 (24.2)	3 (3.6)	0.02*
Dysrhythmia, *n* (%)	10 (8.5)	5 (15.2)	5 (6.0)	0.22
Gastrointestinal bleeding, *n* (%)	9 (7.7)	5 (15.2)	4 (4.8)	0.13
Hemolysis, *n* (%)	6 (5.1)	2 (6.1)	4 (4.8)	1.00
Hyperbilirubinemia, *n* (%)	5 (4.3)	4 (12.1)	1 (1.2)	0.03
Central nervous system injury, *n* (%)	4 (3.4)	3 (9.1)	1 (1.2)	0.12
Brain death, *n* (%)	3 (2.6)	3 (9.1)	0	0.03
Pulmonary hemorrhage, *n* (%)	3 (2.6)	1 (3.0)	2 (2.4)	1.00
Clinical seizure, *n* (%)	2 (1.7)	1 (3.0)	1 (1.2)	1.00
Electroencephalographic seizure, *n* (%)	2 (1.7)	2 (6.1)	0	0.14
Disseminated intravascular coagulation, *n* (%)	1 (0.9)	0	1 (1.2)	1.00
Limb ischemia, *n* (%)	1 (0.9)	1 (3.0)	0	0.68

*Data from univariate analysis.

Table 4. Univariate analysis on clinical factors associated with mortality.

	Odd ratio	95% CI	*P*-value
Age	1.01	(1.00–1.02)	0.18
Sex	0.79	(0.31–1.89)	0.61
Pre-ECMO cardiac arrest	0.66	(0.20–1.83)	0.44
Intraaortic balloon pump	1.48	(0.56–3.71)	0.41
Epinephrine administration	1.48	(0.56–3.71)	0.41
Norepinephrine administration	0.83	(0.37–1.87)	0.66
Vasopressin administration	1.33	(0.43–3.81)	0.60
Serum bicarbonate concentration	0.92	(0.33–2.36)	0.87
Pre-extracorporeal membrane oxygenation serum lactate concentration	0.89	(0.67–1.07)	0.29
Kidney replacement therapy	1.71	(0.67–4.24)	0.25
Hyperbilirubinemia	11.45	(1.61–228.92)	0.03
Central nervous system injury	8.30	(1.02–171.36)	0.07
Pneumothorax	8.64	(2.32–41.77)	0.003
Infection during extracorporeal life support	4.25	(1.25–15.48)	0.02
Dysrhythmia	2.82	(0.74–10.86)	0.12

[IQR: 325.2–782.2 h] versus 313 h [IQR: 189.0–507.6 h]; $P=0.01$). The duration of VV-ECMO was not significantly shorter in those who survived [139 h (IQR: 80.5–211.5 h) versus 171 h (IQR: 78.0–247.0 h)] ($P=0.33$). The indications for ECMO support and type of ventilation were similar between the two groups (Table 1). There was no significant difference in hemodynamic, ventilatory and acid-base parameters between survivors and non-survivors before or after VV-ECMO cannulation (Table 2).

Complications of ECMO reported in the cohort during VV-ECMO are summarized in Table 3. Acute kidney injury (serum creatinine concentration >1.5 mg/dL [>132.6 µmol/L]) was reported in approximately 25% of the study cohort. Kidney replacement therapy was used in 23.1% of cases, while approximately 20% of cases received inotropic support during VV-ECMO cannulation. Other leading complications included infections (10.3%), pneumothorax (9.4%), and dysrhythmias (8.5%) (Table 3). The remaining ECMO complications were similar between the two groups.

Univariate analysis showed that in-hospital mortality was associated with hyperbilirubinemia (OR: 11.4; 95% CI: 1.6–228.9), pneumothorax (OR: 8.6; 95% CI: 2.3–41.8), and infections (OR: 4.3; 95% CI: 1.3–15.5). (Table 4). No other tested clinical characteristics or variables showed a significant difference between the two groups. However, these associations did not persist following multivariate analysis (Supplementary Table 3).

Discussion

Our analysis of the Extracorporeal Life Support Organization registry (years 2003–2019) showed that the use of VV-ECMO for poisoning was quite rare (117 cases reported) compared to other respiratory diagnoses reported in the registry [9,15,21]. Nevertheless, its use was associated with higher survival to hospital discharge when compared to the overall survival rate of VV-ECMO cases in North America reported by the Extracorporeal Life Support Organization (71% versus 62%) [19]. Single-substance poisoning was more common than poisoning from multiple substances, while opioids, neurologic drugs, and smoke inhalation were the most common exposures associated with the use of VV-ECMO. Survivors received ECMO cannulation earlier than non-survivors and reported fewer complications during ECMO.

The term ARDS is applied to a wide spectrum of conditions with different etiologies that generally share a common clinical phenotype including increased permeability of the alveolo-capillary membrane, reduced lung compliance, and increased alveolar shunt and dead space. All these characteristics result in hypoxemia and hypercapnia [22]. The early medical management of patients with ARDS generally includes the use of non-invasive respiratory support techniques and then invasive mechanical ventilation when these techniques fail [23]. The use of ECMO is indicated when adequate gas exchange cannot be maintained using lung and diaphragm protective ventilation strategies.

Several case reports and case series [3,6,17,18] have suggested that that ECMO can be used to provide adequate gas exchange for these patients during the process of lung healing, while waiting for the poison to be metabolized and excreted and eventual organ recovery. However, there are no specific guidelines to initiate and manage VV-ECMO in these patients. Therefore, most centers follow the classic respiratory ECMO criteria [10] and evaluate the likelihood of survival with VV-ECMO on a case-by-case basis. In general, the presence of irreversible organ damage is considered an absolute contraindication for ECMO (e.g., dinitrophenol, fluoroacetate, sodium azide, and cyanide) [6].

Consistent with the current opioid epidemic [1], opioid exposure was most frequently reported. Opioids are not commonly thought of as a pulmonary toxin, although acute pulmonary edema from intoxication is well reported [24,25]. Currently, it is unclear how opioids induce ARDS. Proposed mechanisms of direct lung injury after opioid overdose include histamine release, bronchospasm, hypoxia and increased permeability of pulmonary vasculature [26–28]. Several cases of diffuse alveolar hemorrhage have been also described following opioid overdose [26,28]. Notably, in our cohort, we were not able to discriminate if the ARDS was due to opioid overdose or naloxone-associated lung injury. There are several reports showing the development of pulmonary edema following naloxone administration in patients with opioid overdose [29,30]. In these patients, naloxone can induce pulmonary edema via increased sympathetic tone immediately after the opioid reversal. This phenomenon can abruptly increase pulmonary blood flow and increase pulmonary permeability. Additionally, patients with opioid intoxication, as well as central nervous system depression such as from sedative-hypnotics, may have developed pneumonitis and ARDS due to pulmonary aspiration. However, given that we did not have access to medical records, we were unable to determine or differentiate the exact cause of ARDS in this subgroup.

Notably, our study also suggests that early VV-ECMO cannulation was a potential factor contributing to survival of acutely poisoned patients with ARDS. The time to ECMO cannulation after hospital admission was significantly shorter in survivors compared with non-survivors. Although statistically significant improvement in shock and ventilatory parameters was noted 24 h after ECMO initiation, none of these improvements were independently associated with survival. Currently, it is unclear if early versus late cannulation strategy is beneficial in patients with ARDS due to poisoning as evidence is very limited [6]. Previous studies including ARDS patients supported with VV-ECMO for viral pneumonia including COVID-19 reported conflicting results [31–33]. During the influenza A H1N1 pandemic early use of ECMO was associated with a survival benefit while during COVID-19 pandemic this survival benefit was not consistently observed [33]. We believe that our findings are not directly comparable with previous studies [33], including patients with ARDS due to viral infections as different pathophysiologic mechanisms are involved in the development of ARDS. Additionally, in our cohort, patients were cannulated much earlier compared to those involving COVID-19 infection [32]. However, several anecdotal case reports showed that in patients with ARDS due to poisoning, severe and prolonged hypoxemia may contribute to multiorgan failure and that rapid VV-ECMO deployment may increase the likelihood of survival [16,18].

A recent systematic review [32] on the use of VV-ECMO for refractory respiratory failure reported that sepsis (26%), acute kidney injury (25%) and multiorgan failure (25%) were the most common ECMO complications, followed by cannulation-related complications and central nervous system complications (stroke and hemorrhage). In COVID-19 patients, increased antibiotic days, leukocytosis, and need for multiple transfusions were also associated with increased mortality [35]. In our cohort, the univariate analysis suggested that hyperbilirubinemia, pneumothorax, and infections were the most common ECMO complications associated with increased odds of mortality. However, none of these associations remained following multivariate analysis. Hyperbilirubinemia during VV-ECMO can be the first sign of liver dysfunction following right ventricular failure [36]. When both develop, VV-ECMO may not be sufficient to maintain adequate gas exchange and perfusion, therefore a change in configuration (veno-arterial or veno-pulmonary ECMO) is needed to avoid multiorgan failure [37–39]. Additionally, there is also a possibility of co-ingestion of paracetamol leading to acute liver toxicity and hyperbilirubinemia. Pneumothorax can develop during VV-ECMO for two clinical reasons: a) the use of non-protective ventilation settings because VV-ECMO is unable to grant adequate gas exchange and b) the development of self-inflected lung injury in patients awake and supported with ECMO [40,41]. In both cases, the presence of pneumothorax may increase the likelihood of death if timely

pneumothorax treatment is not performed [42]. Development of infections during VV-ECMO is often associated with an increased risk of death especially when they become refractory to maximal medical therapy and induce septic shock. In these situations, VV-ECMO is not sufficient to provide adequate gas exchange because of hypotension and conversion to VA-ECMO is needed to grant systemic perfusion [42,43]. Conversion from VV- to VA-ECMO is often challenging and may also increase the risk of death [43].

Our study has several limitations. First, the retrospective nature of the study may introduce biases and confounding factors as the study population may not be representative of all patient population requiring ECMO for poisoning or may include cases from ECMO centers with high-volume ECMO capacity and experience affecting the clinical outcomes. The literature shows that high-volume ECMO centers have better clinical outcomes compared to low-volume centers [44,45]. Selection and reporting biases may have been introduced to our data where high-volume centers likely reported more cases to the Extracorporeal Life Support Organization registry compared to low-volume centers. Moreover, providers at low-volume centers may have selected candidates for ECMO with higher likelihood of positive outcome over candidates who were deemed to have poor prognosis. Additionally, using the Extracorporeal Life Support Organization registry data is inherently prone to issues such as missing data, reporting bias, coding errors, and availability bias. For example, three cases in our cohort received VV-ECMO for cardiac ($n=2$) and extracorporeal cardiopulmonary resuscitation ($n=1$) support indications. We were unable to determine the reason for these classification as we did not have access to medical records. However, the Extracorporeal Life Support Organization registry data as a whole showed that approximately 7% and 1% of the VV-ECMO were performed for "cardiac" and "extracorporeal cardiopulmonary resuscitation" support, respectively (https://www.elso.org/registry/elsoliveregistrydashboard.aspx). All cases of VV-ECMO and poisonings may not have been reported to the Extracorporeal Life Support Organization database as the reporting is voluntary using a predetermined data form which is not specific to acute poisoning. In addition, cases may have been miscoded especially involving substance characteristics (e.g., identity of substance(s), exposure route or intentions) as such information may not have been known or suspected by the treating providers due to the critically ill state of the patients. This may have resulted in missed cases as case identification was performed using ICD-9 and ICD-10 codes and their definitions. Third, there was no confirmatory test data available regarding toxicological exposure. Therefore, some of the cases in our cohort may have been miscoded or misclassified and inappropriately included in the analysis. The Exracorporeal Life Support Organization data did not include antidotal (e.g., naloxone) or pharmacologic therapy specific to the suspected poisoning. Therefore, the clinical management of acute poisoning in these cases is largely unknown. Additionally, our study focused only on short-term outcomes and did not evaluate long-term effect of ECMO for poisoning. In contrast, the major strength of our study is the use of a large dataset from the Extracorporeal Life Support Organization registry, which does have quality control standards [46].

Conclusions

Our study showed that the use VV-ECMO for refractory respiratory failure due to poisoning was associated with a clinically significant survival benefit compared to other respiratory diagnoses requiring VV-ECMO. In poisoned patients, early ECMO deployment may increase the likelihood of survival compared to late deployment. Further research is needed to establish the optimal timing for cannulation or referral for VV-ECMO as well as specific modalities aimed at complication avoidance to confer a lower mortality.

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Data availability statement

Data available on request from the authors with permission from the Extracorporeal Life Support Organization.

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