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Review Article

Extracorporeal Membrane Oxygenation for Severe Paraquat Intoxication: A Systematic Review of Clinical Cases

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ABSTRACT

Background: Paraquat is a widely used, inexpensive contact herbicide that can cause fulminant multi-organ failure and death after ingestion, and no specific antidote is available. Extracorporeal membrane oxygenation (ECMO) has been used sporadically as rescue therapy in patients with severe paraquat intoxication, but its impact on clinical outcomes remains uncertain. This study systematically reviews the existing evidence on ECMO use in paraquat poisoning.

Methods: We searched Web of Science, PubMed, Scopus, Embase, the Cochrane Library, and Google Scholar from database inception to 1 November 2023 for human studies reporting paraquat-poisoned patients treated with ECMO. Eligible designs included case reports and case series. Two reviewers independently screened records, extracted data, and assessed methodological quality using the Joanna Briggs Institute critical appraisal tools. Quantitative synthesis was descriptive, comparing survivors and non-survivors.

Results: After removal of duplicates, 21 records were screened, and 14 full-text articles were assessed for eligibility. Nine studies published between 1985 and 2023, comprising 15 ECMO-treated patients, were included. The mean age was 27.3 ± 12.4 years. Survivors started ECMO later after paraquat ingestion than non-survivors (32.6 ± 8.8 vs 7.7 ± 8.4 days, $P < 0.001$). Survivors also had a longer hospital stay (78.5 ± 2.1 vs 21.8 ± 33.1 days, $P = 0.049$). In contrast, ECMO duration, indication for ECMO, concomitant extracorporeal therapies, and ECMO configuration (veno-venous vs. veno-arterial) were not significantly associated with survival. Most survivors underwent bilateral lung transplantation during or after ECMO support.

Conclusion: The limited evidence suggests that ECMO may have a role, often alongside lung transplantation, in selected patients with paraquat poisoning. Larger registries and observational studies are needed to clarify patient selection, timing, and outcomes of ECMO in this setting.

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Introduction

Paraquat is a highly toxic contact herbicide widely used in agriculture because of its low cost, easy accessibility, high efficacy, and minimal soil persistence [1]. It does not have any known antidote, making paraquat ingestion potentially fatal, with mortality rates ranging from 40% to 80% globally and between 36% and 56% in Iran [2, 3]. Within tissues, paraquat undergoes redox cycling that generates superoxide radicals, a highly reactive type of reactive oxygen species (ROS) that can directly damage cells and promote the formation of additional ROS and reactive nitrogen species [4]. The lungs, heart, kidneys, and liver are particularly vulnerable because of their high blood flow and metabolic demands [3, 5-7]. Current clinical management includes hemoperfusion, early gastric lavage, emesis induction, laxatives, immunosuppressive regimens, and mesenchymal stem cell infusions. These measures may slow disease progression, but paraquat poisoning is often incurable, and long-term survival is limited by progressive lung injury [8].

The lungs represent the principal target organ in paraquat poisoning, with early-stage manifestations including pulmonary edema, intra-alveolar hemorrhage, and inflammatory cell accumulation. Studies have shown that acute respiratory distress syndrome and pulmonary fibrosis are the most common causes of death in paraquat poisoning cases [9]. Lung transplantation may be beneficial in treating respiratory failure induced by end-stage paraquat-induced pulmonary fibrosis [10]. Extracorporeal membrane oxygenation (ECMO) is an advanced form of life support used in patients with severe respiratory or cardiac failure when standard therapy is ineffective [11, 12]. While ECMO does not neutralize or remove toxins, it can support hemodynamics and oxygenation while the body eliminates toxins and organs recover [13].

Although the published experience with ECMO in paraquat poisoning is limited and largely restricted to case reports and small series, these reports offer important insights. Some describe successful outcomes in paraquat-poisoned patients treated with ECMO, whereas others suggest limited benefits. ECMO can support severe respiratory failure and may serve as a bridge to lung transplantation. However, a systematic evaluation of ECMO's impact on outcomes in paraquat intoxication is lacking. This review therefore aims to summarize the indications, benefits, complications, and outcomes of ECMO use in patients with severe paraquat intoxication.

Materials and Methods

Search Strategy and Study Selection

Two investigators from the research team conducted a comprehensive search of international databases, including Web of Science, PubMed, Google Scholar, Scopus, Cochrane Library, and Embase, from database inception to 1 November 2023. We used combinations of controlled vocabulary (e.g., "Extracorporeal Membrane Oxygenation"[Mesh], "Paraquat"[Mesh]) and free-text terms related to extracorporeal membrane oxygenation and paraquat intoxication (e.g., "extracorporeal membrane oxygenation", "ECMO", "extracorporeal life support", "paraquat", "methyl viologen", "Gramoxone", "Weedol", "poisoning", "intoxication", "overdose", "toxicity"), combined with Boolean operators. No restrictions were placed on language or article type. The full electronic search strategies for each database, including all keywords, field tags, and Boolean operators, are provided in Supplementary Table S1.

We planned to include all human studies that reported patients with paraquat poisoning treated with ECMO, regardless of study design. Eligible designs were interventional (randomized or non-randomized trials), observational (prospective or retrospective cohorts, case–control, and cross-sectional studies), and descriptive reports (case reports and case series).

For this review, the research question was structured using a PICO/PIO framework. Population (P) comprises patients of any age with confirmed or strongly suspected paraquat poisoning, whether accidental or intentional ingestion. Intervention/Exposure (I) was any form of ECMO (veno-venous or veno-arterial), irrespective of cannulation strategy, timing, or concomitant treatments. Because almost all available evidence consisted of single-arm case reports and small series without a standardized non-ECMO control group, no formal comparator (C) could be defined at the study level. Instead, we descriptively compared clinical characteristics and management between survivors and non-survivors within the ECMO-treated patients. The primary outcome (O) was survival to hospital discharge. Secondary outcomes included indications for ECMO initiation, ECMO configuration and duration, major complications, need for lung transplantation, and length of hospital stay.

We included full-text articles written in English or Persian that examined patients with paraquat toxicity in whom ECMO was used as part of the treatment and that reported at least the patient's vital status (survival or death). Two researchers independently screened titles

and abstracts, reviewed full texts, and selected studies that met the inclusion criteria. For reports without immediate full-text access, we attempted to obtain the necessary information from the abstract and, when needed, by contacting the corresponding author; articles for which sufficient data could not be retrieved were excluded. We also excluded animal studies, narrative reviews, editorials, and articles that reported ECMO for toxic exposures other than paraquat.

Quality Assessment

The methodological quality of the included studies was evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal tools. Case reports were assessed with the JBI Critical Appraisal Checklist for Case Reports, and case series were assessed with the JBI Critical Appraisal Checklist for Case Series [14]. Each item was rated as Yes, No, Unclear, or Not applicable. For quantitative grading, we assigned 1 point to Yes and 0 points to No or Unclear and calculated the proportion of Yes responses for each study. Overall risk of bias was then classified as low (≥70% Yes), moderate (50–69% Yes), or high (<50% Yes) [15]. These correspond to the following raw-count ranges: case reports (8 items): low 6–8, moderate 4–5, high 0–3; case series (10 items): low 7–10, moderate 5–6, high 0–4. Two reviewers performed the quality assessment independently, and disagreements were resolved through discussion. Detailed quality-assessment results are provided in Supplementary Table S2.

Data Extraction

Two researchers extracted the following information from the articles and recorded it in an Excel table. This data encompassed various aspects, including bibliographic details (such as the first author's name, publication year, and country), participant characteristics (including gender and age), volume and concentration of paraquat used, primary treatment, indication for using ECMO, type of ECMO, time to start ECMO after paraquat poisoning, duration of ECMO, other specific treatments, total hospitalization time, and the outcome of patients, indicating whether the patient survived or experienced mortality.

Statistical Analysis

The available data were entered into Stata (version 17) for descriptive analysis. Continuous variables are presented as mean ± standard deviation, and categorical variables as frequencies and percentages. Comparisons between survivors and non-survivors were performed using the independent t-test for continuous variables and Fisher's exact test for categorical variables. A two-sided p-value < 0.05 was considered statistically significant.

A priori, we extracted several clinical variables as potential prognostic factors and confounders, including age, sex, estimated amount of paraquat ingested, time from ingestion to hospital arrival, time from ingestion to ECMO initiation, ECMO configuration (veno-venous or veno-arterial), concomitant extracorporeal therapies (e.g., hemoperfusion, continuous renal replacement therapy), and need for lung transplantation. However, because the available evidence consisted of individual case reports and a single small case series, with substantial heterogeneity and incomplete reporting across studies, no formal pooled meta-analysis or multivariable regression modelling could be performed. Instead, these covariates were summarized descriptively and explored only in univariable comparisons between survivors and non-survivors, and the findings should be interpreted as hypothesis-generating.

Results

The literature search identified 38 records (PubMed: 12; Scopus: 9; Web of Science: 6; Embase: 5; Cochrane Library: 2; Google Scholar: 4). After removing 17 duplicates, 21 articles remained for screening. Of these, 12 were excluded based on title and abstract or full-text review, leaving 9 studies for inclusion in the qualitative synthesis (Figure 1). The main characteristics of these studies are summarized in Table 1.

Quantitative synthesis

All 9 included studies contributed data for quantitative synthesis, yielding a total of 15 patients treated with ECMO for paraquat intoxication. Because the available evidence consisted exclusively of individual case reports and one small case series, and all patients received ECMO without a standardized non-ECMO comparison group, a formal pooled meta-analysis of treatment effects was not feasible. Instead, we performed descriptive analyses and univariable comparisons between survivors and non-survivors.

Among the 15 patients, the mean age was 27.3 ± 12.4 years overall, 28.7 ± 11.2 years among survivors, and 26.4 ± 13.7 years among non-survivors. Survivors started ECMO later than non-survivors (32.6 ± 8.8 vs 7.7 ± 8.4 days after ingestion; P < 0.01). The mean duration of hospitalization was 78.5 ± 2.1 days in survivors and 21.8 ± 33.1 days in non-survivors (P < 0.05). Four patients received gastric lavage as the initial treatment, one received activated charcoal alone, and two received both gastric lavage and activated charcoal. ECMO duration and the type

The most common indication for ECMO was respiratory failure, observed in 5 (41.6%) of the patients, followed by a combination of respiratory

failure and lung transplant. Patients were most commonly treated with hemoperfusion concurrently with ECMO. There was no statistically significant correlation between survival and the indication for ECMO or concurrent treatment ($p > 0.05$) (Table 3).

Study Characteristics

A total of 9 studies met the inclusion criteria, comprising 8 single-patient case reports and 1 small observational case series, yielding 15 patients who received ECMO for paraquat intoxication (Table 1). Most reports originated from tertiary or academic centers and were published between the mid-1980s and 2023, reflecting the gradual adoption of ECMO and lung transplantation in this context [8, 10, 16-22]. The majority of patients were adolescents or young adults, although one pediatric patient was included in a series of six children with paraquat poisoning from a single center [18]. When specified, ingestion was intentional in several cases, often in the setting of deliberate self-harm [8, 10], whereas accidental exposure was reported in at least two patients [17, 20].

Exposure characteristics were variably reported. In those studies that estimated the ingested dose, patients typically consumed 30–60 mL of a 20–25% paraquat formulation [8, 10, 19]. Time from ingestion to hospital presentation was documented in a subset of reports and was usually within a few hours, including the pediatric case who arrived approximately 2 hours after ingestion [18]. Early gastrointestinal decontamination with gastric lavage and activated charcoal was common in adult cases, whereas the pediatric ECMO case notably did not receive either [8, 10, 17, 18]. Adjunctive medical therapy frequently included antioxidants and immunosuppressive regimens such as high-dose methylprednisolone and cyclophosphamide, sometimes combined with other agents (e.g., tamoxifen) aimed at limiting pulmonary fibrosis [10, 17]. Hemoperfusion was used in most modern reports, and several patients also received continuous renal replacement therapy or hemodialysis in the setting of acute kidney injury [18, 19, 21].

Despite aggressive initial management, the majority of patients progressed to severe respiratory failure with radiologic features of diffuse lung injury or evolving pulmonary fibrosis. ECMO was typically initiated when conventional respiratory support and mechanical ventilation were no longer sufficient, or as elective intraoperative support for lung transplantation [8, 10,

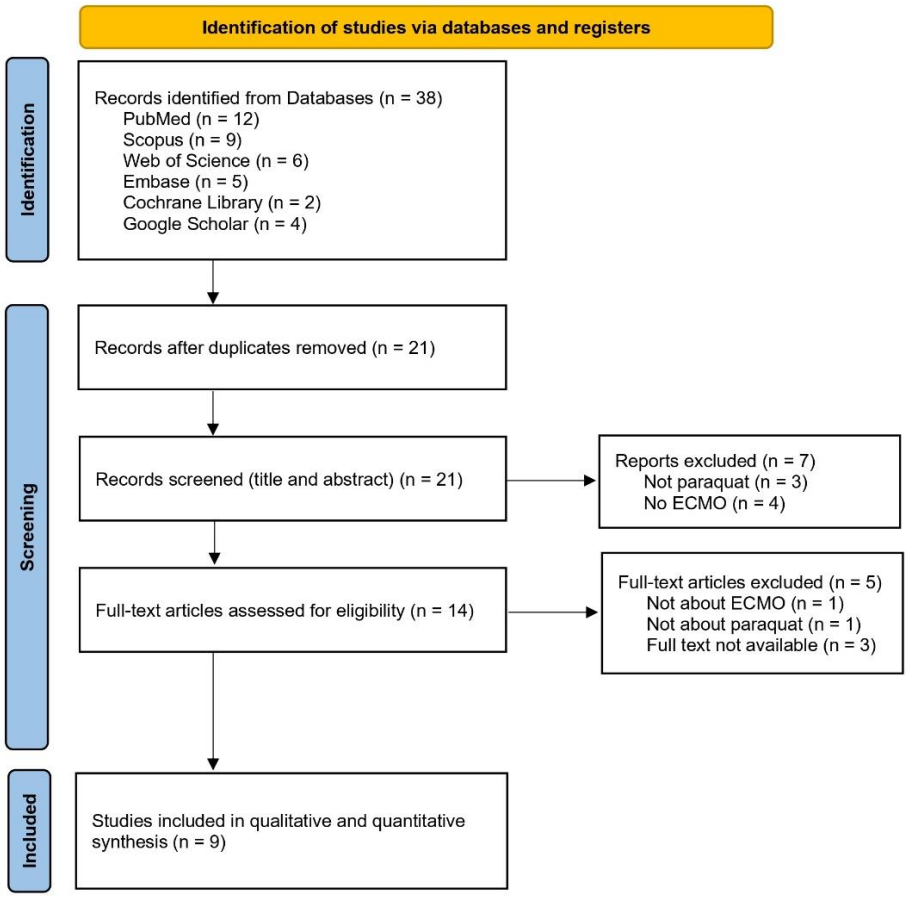

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Figure 1. PRISMA flow diagram of study identification and selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Table 1. Characteristics of patients treated with ECMO for paraquat intoxication

No.	Author	Year	Country	Patient profile	Substance ingested	Early treatment	ECMO indication	ECMO type	Time from ingestion to ECMO start	Duration of ECMO	Concomitant treatment	Duration of stay	Outcome	Study type
1	Li	2023	China	17-year-old boy	30–50 mL 25% paraquat	Lavage	Pulmonary fibrosis + LT	V/V	26 days	1 day	Hemoperfusion ×2	77 days	Discharged	Case report
2	Jiao	2021	China	45-year-old man	60 cc paraquat 20%	Lavage	Respiratory failure + LT	V/V	40 days	NR	Hemoperfusion	NR	Discharged	Case report
3	Jiao	2021	China	38-year-old man	50 cc paraquat 20%	Lavage	Respiratory failure + LT	V/A	25 days	NR	Hemoperfusion	NR	Discharged	Case report
4	Jiao	2021	China	30-year-old man	60 cc paraquat 20%	Lavage	Respiratory failure + LT	V/V	28 days	NR	Hemoperfusion	NR	Discharged	Case report
5	Wu	2022	China	18-year-old woman	Unknown amount	NR	Pulmonary fibrosis	NR	NR	NR	NR	NR	Discharged	Case report
6	Feng	2021	China	14-year-old woman	100 cc paraquat 20%	NR	Cardiopulmonary failure	V/A	4 days	7 h	Hemoperfusion	79 h	Dead	Observational study
7	Feng	2021	China	15-year-old woman	150 cc paraquat 20%	NR	Circulatory failure	V/A	21 h	41 h	Hemoperfusion	58 h	Dead	Observational study
8	Feng	2021	China	45-year-old man	110 cc paraquat 20%	NR	Respiratory failure	V/V	72 h	24/5 h	Hemoperfusion + CRRT	72/5 h	Dead	Observational study
9	Feng	2021	China	25-year-old woman	90 cc paraquat 20%	NR	Respiratory failure	V/V	144 h	245/5 h	CRRT	365/5 h	Dead	Observational study
10	Feng	2021	China	33-year-old woman	100 cc paraquat 20%	NR	Respiratory failure	V/V	72 h	236 h	Hemoperfusion + CRRT	298 h	Dead	Observational study
11	Bertram	2013	Germany	23-year-old man	8–10 cc paraquat 20%	Charcoal + lavage	Respiratory failure + LT	V/V + V/A	12 days	20 days	Hemodialysis	32 days	Dead	Case report
12	Tang	2015	China	24-year-old woman	50 cc paraquat 20%	Charcoal + lavage	Respiratory failure + LT	V/V	44 days	12 days	NR	80 days	Discharged	Case report
13	Toronto Lung Transplant Group*	1985	Canada	31-year-old man	NR	Charcoal	Respiratory failure	V/V	NR	19 days	Hemoperfusion	+100 days	Dead	Case report
14	Hsieh	2013	Taiwan	6-year-old girl	NR	NR	Respiratory failure	V/V	NR	NR	Hemoperfusion	NR	Dead	Case report
15	Girgin	2017	Turkey	46-year-old man	NR	NR	Respiratory failure + LT	V/V	25 days	36 h	Corticosteroid pulse + cyclophosphamide	6 days	Dead	Case report

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* Manuscript prepared by Saunders NR, Alpert HM, and Cooper JD for the Toronto Lung Transplant Group. Abbreviations: NR, not reported; LT, liver transplantation; V/V, veno-venous; V/A, veno-arterial; CRRT, continuous renal replacement therapy.

19, 20]. Both veno-venous and veno-arterial ECMO configurations were described, with veno-venous ECMO more commonly used in cases of isolated respiratory failure and veno-arterial ECMO reserved for patients with concomitant hemodynamic compromise [17, 19]. In several contemporary cases, ECMO was instituted days to weeks after ingestion as a bridge to bilateral lung transplantation, sometimes maintained throughout the perioperative period [8, 10, 19, 20]. In contrast, older reports and some pediatric cases provided limited detail on ECMO indications, configuration, or duration [16, 18, 22].

Outcomes varied markedly according to whether lung transplantation was ultimately performed. In four recent reports, patients who received ECMO as a bridge to bilateral lung transplantation survived to hospital discharge and showed favorable short-term follow-up, with reported hospital stays ranging from approximately 77 to 80 days in individual cases [8, 10, 19, 20]. By contrast, cases in which ECMO was used without subsequent lung transplantation were generally associated with poor prognosis, with deaths attributed to progressive respiratory failure, septic multiorgan failure, or refractory cardiorespiratory collapse despite maximal support [16-18, 22]. Taken together, these reports indicate that, in the published literature, ECMO in paraquat poisoning has predominantly been deployed in highly selected patients as part of an aggressive strategy to bridge to lung transplantation, rather than as a stand-alone life-saving intervention

Discussion

Pesticide self-poisoning is an important public health problem in developing nations, accounting for an estimated 300,000 deaths each year in the Asia-Pacific area alone [23, 24].

Table 2. Comparison of age, time to ECMO, ECMO duration, hospital stay, paraquat dose, and first treatment between survivors and non-survivors.

Variable	Statistic / Category	Survivors	Non-survivors	Total	P value
Age, years	Mean ± SD	28.67 ± 11.20	26.44 ± 13.73	27.33 ± 12.40	0.747
	Minimum–maximum	17–45	6–46	6–46	
Time to ECMO, days	Mean ± SD	32.60 ± 8.76	7.70 ± 8.41	18.07 ± 15.19	<0.001*
	Minimum–maximum	25–44	0.9–25	0.9–44	
ECMO duration, hours	Mean ± SD	156.00 ± 186.68	190.75 ± 195.24	183.80 ± 183.67	0.827
	Minimum–maximum	24–288	7–480	7–480	
Hospitalization duration, days	Mean ± SD	78.50 ± 2.12	21.79 ± 33.10	33.13 ± 37.74	0.049*
	Minimum–maximum	77–80	2.4–100	2.4–100	
Paraquat dose, mg	Mean ± SD	52.00 ± 8.37	93.17 ± 46.26	74.45 ± 39.50	0.083
	Minimum–maximum	40–60	9–150	9–150	
First treatment, n	Lavage	4	0	4	0.061†
	Charcoal	0	1	1	
	Lavage + charcoal	1	1	2	

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Values are mean ± standard deviation (SD) unless otherwise indicated. *P < 0.05 was considered statistically significant. P values were calculated using independent t-tests for continuous variables and †Fisher's exact test for categorical variables. Abbreviations: ECMO, extracorporeal membrane oxygenation; SD, standard deviation.

Over the past few decades, many cases of paraquat intoxication have been reported, with the most common causes being extensive skin contamination or accidental or voluntary ingestion. Clinicians must remain attentive to the high mortality rate associated

Table 3. Indication for ECMO, concomitant treatments, ECMO type, and survival status of the patients.

Variable	Category	Survivors, n	Non-survivors, n	Total, n	P value
Indication for ECMO	Cardiopulmonary failure	0	1	1	0.725
	Circulatory failure	0	1	1	
	Pulmonary fibrosis	1	0	1	
	Pulmonary fibrosis + LT	1	0	1	
	Respiratory failure	0	5	5	
	Respiratory failure + LT	1	2	3	
Concomitant treatment	Medical only	0	1	1	0.461
	CRRT	0	1	1	
	Hemodialysis	0	1	1	
	Hemoperfusion	4	4	8	
	Hemoperfusion + CRRT	0	2	2	
ECMO type	V/A	1	2	3	0.725
	V/V	4	7	11	

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P values were calculated using Fisher's exact test; P < 0.05 was considered statistically significant. Abbreviations: ECMO, extracorporeal membrane oxygenation; LT, lung transplantation; CRRT, continuous renal replacement therapy; V/V, veno-venous; V/A, veno-arterial.

with paraquat poisoning. Lethal concentrations of paraquat in the lungs are less likely if plasma levels are substantially reduced within the first 30 hours by enhancing elimination with extracorporeal techniques and limiting gastrointestinal absorption [25]. Therefore, gastric lavage and activated charcoal to decrease absorption and hemoperfusion for increased elimination are effective in reducing mortality, as reported in many studies [7, 16, 26, 27]. Pulmonary fibrosis was noted in over half of the patients who died in Kavousi-Gharbi's research. Lung fibrosis was found in 14.8% of hospitalized patients who survived [28].

For patients experiencing end-stage pulmonary fibrosis following paraquat poisoning, lung transplantation appears to be the only treatment modality that offers effectiveness [29]. The timing of transplantation seems crucial for success following Paraquat intoxication, as Paraquat-induced transplanted lung injury can occur when Paraquat is not completely eliminated from the body [30, 31]. Consequently, respiratory support is needed until paraquat is sufficiently eliminated and lung transplantation can be performed. Conventional invasive mechanical ventilation alone is often insufficient, whereas ECMO can provide prolonged cardiorespiratory support and serve as a bridge to lung transplantation [19]. ECMO does not eliminate substances, it provides hemodynamic support and oxygenation until toxins are eliminated and the organs have recovered or been transplanted [32].

In our series of 15 reported cases, pulmonary fibrosis and respiratory failure were the most common indications for ECMO. Notably, none of the patients treated with ECMO alone survived without lung transplantation, suggesting that, in advanced paraquat-induced lung injury, ECMO by itself is unlikely to be lifesaving. Therefore, ECMO should be used for respiratory support as a bridge to lung transplantation in cases of pulmonary failure. Circulatory failure is a less common indication and requires a different type of VA-ECMO. Both patients with VA-ECMO in our study died, but due to the low number of patients, no conclusions can be drawn about mortality and survival. Our data analysis showed a connection between the time to start ECMO and survival, with longer times to start ECMO correlating with higher survival probabilities. This may be due to patients with better lung conditions experiencing delayed respiratory failure and thus benefiting more from ECMO.

We also observed a longer hospital stay among survivors; however, this finding is difficult to interpret, because the shorter length of stay in non-survivors likely reflects early death rather than more favorable disease. Based on the limited and heterogeneous case-level data, we were unable to demonstrate a clear survival benefit of ECMO in paraquat-poisoned patients. However, several other factors play a critical role in patient outcomes, including the quantity of paraquat consumed, whether the patient experienced post-ingestion vomiting, the duration between ingestion and hospital arrival, prompt implementation of gastric lavage or activated charcoal treatment, and the degree of paraquat toxicity as measured by serum levels [33].

Future work should focus on systematically collecting paraquat intoxication cases treated with ECMO through multicenter registries, using standardized definitions for indications, timing, co-interventions, and outcomes. Prospective observational studies are needed to evaluate structured treatment pathways that combine gastrointestinal decontamination, extracorporeal toxin removal, immunosuppressive regimens, and ECMO. In addition, clearer criteria for lung transplantation candidacy and referral, along with longer-term follow-up of transplanted patients, would help define when ECMO-supported management is justified and how it affects survival and quality of life.

Conclusion

In conclusion, this study is, to our knowledge, the first comprehensive systematic review of ECMO use in patients with paraquat intoxication. The available evidence suggests that ECMO may be most useful as a bridge to lung transplantation in patients with severe respiratory failure. Larger, systematically collected data are needed to clarify its indications, timing, and impact on survival.

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Conflicts of Interest

The authors report there are no competing interests to declare.

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