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Evaluation of treatment outcomes and risk factors of clinical non-improvement in patients with paraquat poisoning: A 10-year retrospective study

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ABSTRACT

A 10-year retrospective study was conducted from 1st January, 2012 to 1st March, 2023 in patients admitted to a tertiary care hospital in South India with acute paraquat (PQ) poisoning. The primary objective of the study was to evaluate clinical outcomes in patients who received extracorporeal removal (ECR) treatment (ECR group) compared to those who did not (non-ECR group). A secondary objective was to assess risk factors associated with clinical non-improvement in these patients. Chi-square and Mann-Whitney tests were used to compare categorical and continuous variables, respectively; and multivariate logistic regression was employed for clinical non-improvement risk factor assessment. We included a total of 304 patients with a median (IQR) age of 25 (13.5) years. The clinical improvement rate was 29.3% (n = 89). There was no significant difference in clinical improvement between ECR and non-ECR treatment groups (p = 0.79). Increased aspartate transaminase (AST) levels (OR: 1.027; 95% CI: 1.011–1.043, p <0.001) and occurrence of sepsis/septic shock (OR: 14.556, 95% CI: 1.798–117.849, p = 0.012) were risk factors associated with clinical non-improvement. In conclusion, no significant difference was observed in clinical improvement rates between ECR and non-ECR groups. Sepsis/septic shock and elevated baseline AST levels were determined as significant risk factors for clinical non-improvement in patients with PQ poisoning.

INTRODUCTION

Paraquat (PQ), a non-selective herbicide is widely employed particularly across developing countries, worldwide. The classification of pesticides in terms of hazard under the World Health Organization classifies PQ under Class II: moderately hazardous [1]. PQ poisoning is regarded as a global threat to public health, because of its high mortality rate, especially in case of suicidal or unintentional ingestion because of lack of specific treatment protocols [2]. Although, marketing of PQ is banned in one-fourth of the countries globally, reports of its intoxication continue to rise significantly [3]. PQ mediates its human toxicity via a redox cycling mechanism, producing reactive oxygen species (ROS), and diminishing the cell's nicotinamide adenine dinucleotide phosphate hydrogen reserves, thus leading to lipid peroxidation in the cell membrane and ultimately resulting in cell death [4]. Upon absorption, PQ is primarily distributed in tissues with high perfusion, such as the lungs, liver and the kidneys, where it exerts organ toxicity. The major complications of PQ poisoning include acute respiratory distress syndrome (ARDS), toxic hepatitis and acute kidney injury (AKI), which can lead to multiple organ dysfunction syndrome (MODS) in severe cases [5]. Thus, several attempts have been made to develop an antidote or optimal strategies for the management of PQ poisoning, however, efforts have largely

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proven futile [6]. Other factors which are known to complicate patient prognosis include varying degrees of PQ exposure, heterogenous clinical presentation among patients, and delays in receiving emergency care [7].

Current management approaches for PQ poisoning, in addition to supportive and symptomatic treatment include antioxidants, N-acetyl cysteine (NAC), tocopherol (vitamin E), and ascorbic acid (vitamin C); immunosuppressive treatment (IST) such as corticosteroids, cyclophosphamide; and extra-corporeal removal (ECR) techniques, consisting of hemoperfusion (HP), conventional hemodialysis (HD), continuous venovenous hemofiltration, and continuous renal replacement therapy [8]. While ECR techniques have been employed to accelerate removal of certain poisonous substances in humans, their application as a therapeutic modality in PQ poisoning is a more recent introduction [9]. A few latest pharmacologic therapies have been introduced for PQ poisoning. Ambroxol, a mucolytic agent commonly used in respiratory conditions, has been applied in the management of lung damage caused by PQ poisoning. According to a meta-analysis by Wang *et al*. [10], adjuvant ambroxol therapy was found to reduce in-hospital mortality in PQ poisoning patients. Xuebijing, a traditional Chinese medicine, has been employed as an adjuvant antioxidant in combination with HP for PQ poisoning. A meta-analysis by Fu *et al*. [11] showed that this combination improved the 7-day survival rate in these patients. Other pharmacological therapies which are being researched for their therapeutic potential in PQ poisoning include rosiglitazone, doxycycline, febuxostat, rapamycin, fluorofenidone, tacrolimus, and octreotide [8].

Despite clinical advances in therapeutic approaches for PQ poisoning, observations regarding their effectiveness in improving patient prognosis remain inconsistent. While the study by Koh *et al*. [12] found that IST might potentially improve patient prognosis, the randomized controlled trial by Gawarammana *et al*. [13] found no significant survival benefit with IST administration. Ambiguities also exist concerning the effectiveness of the various ECR modalities in PQ poisoning. A meta-analysis by Eizadi-Mood *et al*. [14], found no association between HD and improved survival. Hsu *et al*. [15] found that HP administration early in the course of treatment was beneficial in decreasing the fatality rate in patients with PQ poisoning. Similarly, the meta-analysis by Nasr Isfahani *et al*. [16] found HP to be beneficial as an adjunct to traditional approaches in improving patient survival. Moreover, there is a lack of observational studies with a substantial sample size exploring treatment outcomes of PQ poisoning in the Indian clinical scenario. Thus, to address these ambiguities, and strengthen the existing evidence, we aimed to conduct this 10-year retrospective study to compare clinical outcomes between patients receiving ECR treatment and those who did not, in the management of PQ poisoning. In addition, we analyzed the risk factors associated with clinical non-improvement in patients with PQ poisoning.

MATERIALS AND METHODS

Study design and ethical approval

We conducted a medical record-based retrospective cohort study over a 10-year period from 1st January 2012 to 1st March 2023 at our tertiary care hospital in South India. We confirm that patient confidentiality was maintained as per the guidelines of the Institutional Ethics Committee, including anonymization of patient data. Since it was a retrospective study, the requirement of informed consent was waived by the Institutional Ethics Committee, and the study was approved vide approval no. 135/2023. The study has been reported in accordance with the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17]. The additional file 1 contains the STROBE checklist.

Inclusion and exclusion criteria

We included a total of 304 patients who were admitted to our tertiary care hospital with PQ poisoning in this study. Patients were included irrespective of their sex and age, regardless of time from exposure, route of exposure (oral, inhalational, or direct contact), and type of exposure (suicidal/accidental/homicidal). PQ poisoning was confirmed based on the qualitative sodium dithionite test of the serum, urine or stomach residues; or patient history; or circumstantial evidence as presented. Pregnant or lactating patients, patients with critical illness(es) such as cancer, history of organ transplantation, current use of immunosuppressants, mixed poisoning, and those with incomplete data were excluded.

Data collection

A structured data collection form was prepared using Microsoft Excel to record patient data which was gathered from medical records accessed through the hospital's medical record department. The following data was collected: Demographic details, including age and sex; medical and medication history, social history, exposure history (route, time, type, and amount of exposure), time from exposure to first aid, along with presenting symptoms. Baseline laboratory investigations at admission were recorded such as kidney function tests (serum urea, S.urea; serum creatinine, S.Cr), liver function tests (serum aspartate transaminase, AST; alanine transaminase, ALT), serum electrolytes (sodium, potassium), white blood cell count (WBC) and saturation of peripheral oxygen (SpO_2). Additionally, the results of the qualitative toxicological screening of the urine, serum, or stomach residues with the sodium dithionite reagent were recorded. Details on emergency care interventions, if given, such as gastric lavage and activated charcoal were also collected. Details of the in-patient treatments administered were also collected, including NAC, antioxidants such as ascorbic acid (vitamin C), tocopherol (vitamin E); corticosteroids; antimicrobial agents such as antibiotics and antifungals; symptomatic therapy including antacids, antiemetics, antiplatelet agents; and ECR techniques administered, such as HD, HP or their combination (HP + HD). Data regarding patient outcomes, clinical improvement or non-improvement; complications such as AKI, toxic hepatitis, ARDS, sepsis/septic shock, gastrointestinal (GI) bleed and MODS; and hospital-related metrics such as duration of hospitalisation, intensive care unit (ICU), and mechanical ventilation (MV) were also collected.

Definitions

The severity of AKI was determined based on the RIFLE classification (class R, class I, or class F). Patients were diagnosed with AKI if they met any of the RIFLE criteria [18]. When the serum ALT level exceeded 70 IU/l (normal range: 0–35 IU/l), hepatitis was recognised in patients [19]. ARDS was diagnosed with bilateral lung infiltrates on chest radiography or computed tomography scan, and a PaO_2/FiO_2 ratio of less than 300 mm Hg [20]. Sepsis was defined as a life-threatening organ dysfunction because of a dysregulated host response to infection, with the onset recognised by organ dysfunction distant from infection site. Operationally, septic shock is described as necessitating vasopressor therapy to maintain an elevated plasma lactate level over 2 mmol/l and the mean arterial blood pressure above 65 mm Hg [21]. MODS was defined as the onset of a potentially reversible physiologic derangement involving two or more organ systems excluding the condition leading to ICU admission [22]. Hospitalisation days were defined as the duration of hospitalisation of the patient in the hospital from admission to discharge [23]. ICU days were defined as the duration of patient's stay in the ICU during hospitalization [24]. MV days were defined as the duration for which the patient received MV (intubation) during hospitalization [25]. Patients who received any of the ECR methods (HP, HD, or a combination of both) were classified under the ECR group and those who were not administered ECR treatment were classified under the non-ECR group. We have considered clinical non-improvement in patients as worsening of clinical symptoms during discharge, morbidity, discharge against medical advice due to financial reasons, and mortality.

Outcome measures

We classified included patients under two groups on the basis of their clinical outcome: improvement and non-improvement. The primary outcome was to compare the clinical outcomes of patients in the ECR and non-ECR treatment groups. The secondary outcome was to analyze the risk factors associated with clinical non-improvement in the included patients.

Statistical analysis

We presented the categorical data as frequency (percentage). The continuous variables with a normal distribution were presented as mean (standard deviation, SD), and the variables not normally distributed were presented as median (interquartile range, IQR). To compare the outcomes of patients in the ECR and non-ECR treatment groups, we employed the chi-square test for categorical data and the Mann-Whitney *U* test for continuous data was performed. To evaluate risk factors of clinical non-improvement, all recorded variables were examined using univariate binary logistic regression to estimate the unadjusted odds ratio. Variables from the univariate analysis with a p value of < 0.2 were then subjected to a backward conditional stepwise multivariate logistic regression analysis to estimate the adjusted odds ratio [26–29]. The independent risk factors for clinical non-improvement were the variables with a p-value < 0.05 in the multivariate logistic regression analysis. Additionally, to reduce bias, we have conducted the logistic regression analysis by excluding patients who were discharged against medical advice due to financial constraints. We conducted the statistical analysis using the IBM SPSS software (version 22) [30].

RESULTS

Patient demographics and clinical characteristics

Out of 304 patients included in the study, the majority were male (n = 191, 62.8%). The median (IQR) age of the included patients was 25 (13.5) years. Mode of exposure was primarily intentional (n = 300, 98.7%). Most patients were employed (n = 166, 54.6%), and the majority of them were farmers/farm workers (n = 73, 24%). Most of the patients had exposure to an approximate amount of 10–50 ml of 24% PQ dichloride (n = 73, 24%). Almost 254 (83.5%) patients received pre-hospitalisation emergency treatment, with gastric lavage (stomach wash) being the most common modality (n = 166, 54.6%). Most of the patients received emergency treatment within 24 hours of PQ exposure (n = 220, 72.4%). Vomiting was the most frequently observed clinical presentation in 173 (57%) patients. Oropharyngeal lesions were the second most frequently observed clinical presentation in 108 (35.5%) patients. Qualitative toxicology screening with sodium dithionite reagent performed on serum, urine, or stomach residues was positive in 71 (23.3%) patients. There were 89 (29.3%) survivors, 159 (52.3%) non-survivors and 56 (18.4%) patients who were discharged against medical advice from the hospital due to financial constraints. Overall, majority of the patients did not show clinical improvement (n = 215, 70.7%), while 89 (29.3%) patients showed clinical improvement during their hospitalisation. Table 1 contains in detail the patient demographics and clinical characteristics.

Clinical outcomes of the included patients

AKI was the most frequently observed complication (n = 212, 69.7%), followed by MODS (n = 147, 48.3%), and toxic hepatitis (n = 126, 41.4%). The median (IQR) hospitalization

Table 1. Demographic and clinical characteristics of the included patients ($N = 304$).

Patient characteristics	Value, n (%)
Total, *N*	304 (100)
Age, years	25 (13.5)
Male sex	191 (62.8)
Occupations	
Employed	166 (54.6)
Farmers/Farm worker	73 (24)
Others	93 (30.6)
Unemployed	113 (37.2)
Unknown	28 (9.2)
Exposure	
Suicidal	300 (98.7)
Accidental	4 (1.3)

Continued

Patient characteristics	Value, n (%)
Social history	
Alcohol	75 (24.7)
Smoking	32 (10.5)
Tobacco, other forms	11 (3.6)
Comorbidities	24 (7.9)
Amount of exposure	
<10 ml	47 (15.5)
10–50 ml	73 (24)
50–100 ml	52 (17.1)
100–250 ml	33 (10.8)
>250 ml	15 (4.8)
Not specified	84 (27.6)
Pre-hospitalisation treatment	254 (83.5)
Gastric lavage	166 (54.6)
Activated Charcoal	39 (12.8)
Other supportive care	49 (16)
Time from exposure to treatment	
<24 hours	220 (72.4)
24–48 hours	12 (3.94)
>48 hours	72 (23.7)
Clinical presentation	
Gastrointestinal symptoms	
Oropharyngeal lesions	108 (35.5)
Vomiting	173 (57)
Abdominal Pain	18 (5.9)
Vomiting and Abdominal pain	51 (16.8)
Dysphagia	31 (10.2)
Odynophagia	22 (7.2)
Respiratory symptoms	
Cough	12 (3.9)
Breathlessness	28 (9.2)
Neurological symptoms	
Altered sensorium	9 (2.9)
Seizure	3 (0.9)
Other symptoms	46 (15.1)
Qualitative (Sodium Dithionite) test	
Positive	71 (23.3)
Negative	101 (33.2)
Not available	135 (44.4)
In-patient outcomes	
Survivors	89 (29.3)
Non-survivors	159 (52.3)
Discharge against medical advice	56 (18.4)
Outcome in terms of improvement	
Clinical improvement	89 (29.3)
Clinical non-improvement	215 (70.7)

Continuous data expressed as median (interquartile range, IQR) for skewed distribution and categorical data expressed as frequency (percentage)

and ICU days were 4 (8) and 3 (5) days, respectively. Overall, 147 (48.3%) patients required MV, with a median (IQR) of 0 (1) days. The clinical non-improvement group was found to have higher levels of WBC, S.urea, AST, ALT and significantly lower SpO_2 values. The frequency of the complications such as MODS, AKI, ARDS, toxic hepatitis, sepsis/septic shock were also higher in patients with clinical non-improvement. Table 2 depicts in detail the clinical characteristics between clinical non-improvement and improvement patient groups.

Treatment outcomes in the included patients

A total of 205 (67.4%) patients received ECR treatment, with 45 (14.8%) patients receiving HD, 99 (32.6%) receiving HP, and 61 (20%) patients receiving a combination of HP and HD. A total of 218 (71.7%) patients received NAC, either alone or in combination with other antioxidants as shown in Table 3. IST including corticosteroid or cyclophosphamide was administered to 138 (45.4%) of patients. Antimicrobial agents including antibiotics and antifungal agents were prescribed to 196 (64.5%) and 5 (1.6%) of patients, respectively. Table 3 provides detailed treatment modalities administered to the inpatients.

Among the 205 patients who received ECR treatment (ECR group), 29.7% clinically improved. This was similar to the patients who did not receive ECR treatment (non-ECR group), depicting an improvement rate of 28.3%. We found no significant difference in the clinical improvement rate between the ECR and non-ECR treatment groups. AKI was found to be less frequent in the patients receiving ECR treatment (42.2%), compared to those who did not receive ECR treatment (64.6%), however, the difference was insignificant ($p = 0.179$). Similarly, the frequency of the complications ARDS, MODS, sepsis/septic shock, hepatitis, and GI bleed did not differ significantly in between ECR (36.1%, 49.8%, 17.6%, 42%, and 9.3%, respectively) and non-ECR treatment groups (28.3%, 45.5%, 14.1%, 40.4%, and 3%, respectively). MV days were similar in both groups (1%) ($p = 0.114$). Table 4 depicts the clinical outcomes of the patients with respect to treatment groups.

Risk factors associated with clinical non-improvement

The risk factors for clinical non-improvement in the patients included were identified by conducting univariate analysis, which was then succeeded by multivariate logistic regression analysis. The significant variables ($p < 0.2$) in univariate logistic regression were found to be WBC (OR: 1.134, 95% CI: 1.078–1.194. $p < 0.001$); S.Cr (OR: 1.691, 95% CI: 1.367–2.091, $p < 0.001$); S. urea (OR: 1.021, 95% CI: 1.011–1.030, $p < 0.001$); AST (OR:1.038, 95% CI: 1.023–1.053, $p < 0.001$); ALT (OR: 1.036, 95% CI: 1.020–1.052, $p < 0.001$); SpO_2 (OR: 0.991, 95% CI: 0.979–1.002, $p = 0.117$); AKI (OR: 9.960, 95% CI: 5.635–17.604, $p < 0.001$); ARDS (OR: 11.160, 95% CI: 4.670–26.667, $p < 0.001$); toxic hepatitis (OR: 9.25, 95% CI: 4.549–18.836, $p < 0.001$); sepsis/septic shock (OR: 25.976, 95% CI: 3.527–191.297, $p = 0.001$); HP (OR: 0.532, 95% CI: 0.318–0.889, $p = 0.016$); HP + HD (OR: 1.680, 95% CI: 0.860–3.284, $p = 0.129$); immunosuppressive agents (OR:

Table 2. Clinical characteristics between improvement and non-improvement patient groups ($N = 304$).

Patient characteristics	Total ($N = 304$)	Improvement ($n = 89$)	Non-improvement ($n = 215$)
Laboratory investigations, median (IQR)			
White blood cell count, $10^3/\mu l$	14.3 (8.6)	11 (4.8)	16 (8.2)
Serum creatinine, mg/dl	1.6 (2.5)	0.9 (0.7)	2.35 (3.3)
Urea, mg/dl	29 (45.5)	18 (20.5)	32 (63)
Sodium, mEq/l	139 (7)	139 (4)	138 (8)
Potassium, mEq/l	4 (0.8)	4.1 (0.8)	3.9 (0.9)
AST, IU/l	41 (75)	25 (14)	61 (111)
ALT, IU/l	27 (75)	17 (13.5)	42 (135)
Saturation of peripheral oxygen, %	98 (14.5)	98.3 (3.1)	96.4 (18.2)
Complications, n (%)			
Multiorgan dysfunction syndrome	147 (48.3)	04 (4.5)	143 (66.5)
AKI	212 (69.7)	31 (34.8)	181 (84.2)
Acute respiratory distress syndrome	102 (33.5)	06 (6.7)	96 (44.7)
Toxic hepatitis	126 (41.4)	10 (11.2)	116 (54)
GI bleed	22 (7.2)	05 (5.6)	17 (7.9)
Sepsis/septic shock	50 (16.4)	01 (1.1)	49 (22.8)
Hospitalisation days, median (IQR)	4 (8)	10 (9.5)	3 (5)
Intensive care unit days, median (IQR)	3 (5)	5 (5)	2 (4)
Mechanical ventilation, n (%)	147 (48.3)	3 (3.4)	143 (66.5)
Mechanical ventilation days, median (IQR)	0 (1)	0 (0)	1 (1)

Table 3. Treatment modalities administered to inpatients ($N = 304$).

Treatment modality	Total, n (%) ($N = 304$)	Improvement, *n* (%) ($n = 89$)	Non-improvement, *n* (%) ($n = 215$)
Extra-corporeal removal			
Hemodialysis (HD)	45 (14.8)	10 (11.2)	35 (16.3)
Hemoperfusion (HP)	99 (32.6)	38 (42.7)	61 (28.4)
HP + HD	61 (20)	13 (14.6)	48 (22.3)
Antioxidants			
N-Acetyl cysteine (NAC)	218 (71.7)	61 (68.5)	157 (73)
Other antioxidants[a]	89 (29.3)	29 (32.6)	60 (67.4)
Immunosuppressive agents[b]	138 (45.4)	28 (31.5)	110 (51.2)
Antimicrobial agents			
Antibiotics	196 (64.5)	47 (52.8)	149 (69.3)
Antifungals	5 (1.6)	3 (3.4)	2 (0.9)
Symptomatic treatment			
Antacid agents	298 (98)	88 (98.9)	210 (97.7)
Anti-emetic agents	226 (74.3)	66 (74.2)	160 (74.4)
Antiplatelet agents	29 (9.5)	10 (11.2)	19 (8.8)

[a]other antioxidants include Vitamin C and Vitamin E, [b]immunosuppressive agents include corticosteroids or cyclophosphamide therapy

2.282, 95% CI: 1.355–3.844, $p = 0.002$); and antibiotics (OR: 2.017, 95% CI: 1.215–3.350, $p = 0.007$). The above significant variables were then subject to multivariate logistic regression to yield risk factors of clinical non-improvement. Multivariate logistic regression found that increased AST (OR: 1.027, 95% CI: 1.011–1.043, $p < 0.001$) and occurrence of sepsis/septic shock (OR: 14.556, 95% CI: 1.798–117.849, $p = 0.012$) were risk factors associated with clinical non-improvement ($p < 0.05$). Table 5 depicts the results of the univariate and multivariate logistic regression analysis.

Table 4. Clinical outcomes of patients between ECR and Non-ECR treatment groups.

Parameter	ECR treatment group, *n* (%) (*n* = 205)	Non-ECR treatment group, *n* (%) (*n* = 99)	*p* value [a]
Clinical improvement, *n* (%)	61 (29.7)	28 (28.3)	0.791
Clinical non-improvement, *n* (%)	144 (70.2)	71 (71.7)	
Complications, *n* (%)			
AKI	148 (42.2)	64 (64.6)	0.179
ARDS	74 (36.1)	28 (28.3)	0.176
MODS	102 (49.8)	45 (45.5)	0.482
Sepsis/ Septic shock	36 (17.6)	14 (14.1)	0.451
Toxic hepatitis	86 (42)	40 (40.4)	0.797
GI bleed	19 (9.3)	3 (3)	0.049[b]
Days, median (IQR)			
Hospitalisation	5 (11)	2 (4)	<0.001[b]
Intensive care unit	4 (5)	1 (1)	<0.001[b]
Mechanical ventilation	0 (1)	0 (1)	0.114

[a]*p* value estimated using chi-square test for categorical variables and Mann-Whitney U test for continuous variables, [b] denotes significant values at $p < 0.05$; ECR, extra-corporeal removal; IQR, interquartile range, AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; MODS, multiorgan dysfunction syndrome.

Table 5. Univariate and multivariate logistic regression analysis for risk factors of clinical non-improvement.

Variables	Univariate			Multivariate		
Potential variables	**Unadjusted OR**	**95% CI**	***p* value[a]**	**Adjusted OR**	**95% CI**	***p* value[b]**
WBC, $10^3/\mu l$	1.134	1.078-1.194	<0.001	-	-	-
S.Cr, mg/dl	1.691	1.367-2.091	<0.001	-	-	-
S. Urea, mg/dl	1.021	1.011-1.030	<0.001	-	-	-
AST, IU/l	1.038	1.023-1.053	<0.001	1.027	1.011-1.043	<0.001
ALT, IU/l	1.036	1.020-1.052	<0.001	-	-	-
SpO_2, %	0.991	0.979-1.002	0.117	-	-	-
AKI	9.960	5.635-17.604	<0.001	-	-	-
ARDS	11.160	4.670-26.667	<0.001	-	-	-
Toxic hepatitis	9.257	4.549-18.836	<0.001	-	-	-
Sepsis/septic shock	25.976	3.527-191.297	0.001	14.556	1.798-117.849	0.012
HP	0.532	0.318-0.889	0.016	-	-	-
HP + HD	1.680	0.860-3.284	0.129	-	-	-
Immunosuppressive agents[c]	2.282	1.355-3.844	0.002	-	-	-
Antibiotics	2.017	1.215-3.350	0.007	-	-	-

[a]significant variables at $p < 0.2$, [b]significant variables at $p < 0.05$, [c]immunosuppressive agents include corticosteroids or cyclophosphamide therapy; AKI, acute kidney injury; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; CI, confidence interval; HD, hemodialysis; HP, hemoperfusion; MODS, multiorgan dysfunction syndrome; OR, odds ratio; S.Cr, serum creatinine; S.urea, serum urea; WBC, white blood cell count.

The multivariate logistic regression analysis conducted by excluding patients who were discharged against medical advice due to financial constraints found that increased WBC (OR: 1.128, 95% CI: 1.055–1.205, $p < 0.001$), increased AST (OR: 1.027, 95% CI: 1.011–1.042, $p < 0.001$); occurrence of AKI (OR: 2.498, 95% CI: 1.144–5.456, $p = 0.022$), ARDS

(OR: 5.796, 95% CI: 2.101–15.989 and sepsis/septic shock (OR: 15.030, 95% CI: 1.799–125.554, $p = 0.012$) were risk factors associated with clinical non-improvement ($p < 0.05$). The details are provided in the additional file 2 which contains the results of the univariate and multivariate logistic regression analysis conducted by excluding patients who were discharged against medical advice due to financial constraints.

DISCUSSION

PQ poisoning has the highest fatality rates among pesticide toxicities worldwide, making it a major global concern [31]. Despite advances in pharmacological management, there is still no antidote or a specified treatment guideline for managing patients with PQ poisoning [8]. Furthermore, introduction of ECR techniques for PQ elimination has yielded largely conflicting results on its effectiveness [12,13,16,28,32]. Moreover, observational studies with an adequate sample size analysing treatment outcomes in PQ poisoning have been lacking, especially in the Indian context [33–36]. In addition, studies analysing factors contributing to clinical non-improvement in patients are scarce. Thus, we conducted this decade-long retrospective study to analyse treatment outcomes and risk factors of clinical non-improvement in patients admitted with PQ poisoning at a tertiary care teaching hospital in South India.

The median (IQR) age reported in our study, 25 (13.5) years, was similar to the study by Rao *et al*. [33], which observed the mean (SD) age of PQ poisoning patients as 27 (7.7) years. However, the prospective study conducted by Lin *et al*. [37] reported a significantly higher median age of 37 years among the included patients. The proportion of non-survivors in our study (52.3%) was significantly higher than the survivors (29%). We found similar results in the studies performed by Lin *et al*. [37] (78%); Rao *et al*. [33] (61.4%); Rao *et al*. [38] (63%); and Goyal *et al*. [39] 2024 (88%). However, some studies reported higher survival rates. This may be explained by variable treatment protocols in their studies [40,41]. Regarding complications, AKI (69.7%) and MODS (48.3%) were the most frequently observed complications in our study. This observation was in accordance to the research study performed by Goyal *et al*. [39]; however, it was in contrast with the studies of Wu *et al*. [42], reporting highest frequency of respiratory failure; and the studies by Rao *et al*. [33], Tajai *et al*. [41], and Lin *et al*. [37] which reports MODS as the most common cause for mortality. The need for MV in our study (48.3%) was slightly higher than the study by Goyal *et al*. [39] (34.9%) and lower than the study by Rao *et al*. [38] (63%).

HP was administered to a higher population of patients in the study by Rao *et al*. [38], i.e., 53.5%, and to a comparatively lower number of patients in the study by Tajai *et al*. [41] (18.9%). However, IST administration was reported in a similar number of patients in the study of Rao *et al*. [38] compared to our study. The lone study by Goyal *et al*. [39] observed a higher frequency of AKI among patients who did not receive HP, which was consistent with our study findings. Our study found a higher frequency of AKI in the non-ECR treatment group (64.6%), with an absolute difference of 22.4% between the groups, suggesting potential clinical relevance despite statistical insignificance. This lack of statistical significance is likely due to the smaller sample size, data variability, or the influence of associated covariates on specific outcomes.

PQ elimination is primarily through the renal pathway, because of which PQ poisoning accounts for the severe renal damage, often progressing to MODS in later stages [40]. This is consistent with our study finding showing AKI as a significant risk factor for poor clinical outcomes, as evidenced by its association with clinical non-improvement in patients (OR: 2.498, 95% CI: 1.144–5.456, $p = 0.022$). This necessitates the timely clearance of PQ using ECR techniques in enhancing PQ elimination, which further protects multiple organ damage and reduces the need for intensive care. ECR is a critical intervention that should be implemented in emergency settings to improve patient outcomes in PQ intoxication. PQ-induced AKI is primarily mediated by ROS generation in renal proximal tubule cells, leading to lipid peroxidation and cell death [43]. ECR accelerates PQ removal from circulation, reducing ROS-mediated toxicity and alleviating systemic organ damage [14,44]. This was reflected in the lower AKI frequency observed in the ECR treatment group in our study (42.2%). Additionally, ECR has been recognized as an effective strategy for protecting renal function in critically ill patients, further supporting its role in PQ poisoning management [45].

The clinical relevance of our findings lies in the potential effectiveness of ECR in managing PQ-induced toxicity. Even if statistical significance is not achieved, the clinical benefits of reducing AKI are substantial, as a lower incidence of AKI leads to better patient outcomes, fewer complications, and reduced economic burden. Ultimately, clinical improvement and patient recovery should take precedence over statistical significance in evaluating the impact of ECR in PQ poisoning management.

None of the studies investigated the difference in outcomes between the patients receiving ECR and non-ECR modalities. Our study found no significant difference in the clinical improvement rate between patients receiving ECR and non-ECR modalities; however, we could not compare the results with other studies due to limited research focusing on the improvement status of patients. This highlights the need for further research using standard treatment protocols for ECR modalities, for a better understanding of its role in the management of PQ poisoning and to inform clinical decision-making.

The multivariate regression analysis found that the complication of sepsis/septic shock was an independent determinant of clinical non-improvement. This can be due to the role of sepsis in the development of MODS. MODS in sepsis is triggered by a combination of factors including extensive inflammation, oxidative stress, endothelial damage, and microvascular clotting, all of which disrupt blood flow and oxygenation to organs, resulting in cell damage and organ failure. The process is further intensified due to the generation of pro-inflammatory cytokines and ROS, which aggravate tissue injury and contribute to the advancement of MODS [46]. In addition, we found that increased AST levels were an important risk factor for clinical non-improvement, likely due to the hepatic toxicity of PQ [47]. This finding was similar to the research conducted by Gheshlaghi *et al*. [5], wherein, elevated AST levels on day

3 had a 100% specificity in predicting mortality and morbidity in PQ poisoning patients. Altogether, these findings point out the necessity for early identification and timely management of sepsis and hepatotoxicity in PQ poisoning, which may lead to better patient clinical outcomes. The multivariate logistic regression analysis was also conducted by excluding patients who were discharged against medical advice due to financial constraints. Additionally, we observed that increased WBC, occurrence of AKI and ARDS were the additional risk factors for clinical non-improvement.

Our study demonstrated numerous strengths. Our study was the longest (10-year) retrospective study including a large sample of PQ poisoning patients in South India. To the best of our knowledge, it was the most comprehensive Indian study analyzing demographics, clinical presentations, exposure history, and treatment patterns in PQ poisoning patients. In addition, this was the first study highlighting outcomes in terms of clinical improvement and non-improvement, ensuring that the significant number of patients discharged against medical advice in PQ poisoning cases were not excluded.

However, our study had a few limitations. Being a retrospective study, our information was derived from medical records of patients, which restricted us from verifying the accuracy of exposure history and prehospitalisation duration/ treatment. Since the data on ingestion volume was not consistently available in all the included patients, it could not be included as a covariate in the statistical analysis. Additionally, the lack of uniform data on the timing of PQ ingestion limited our ability to analyze outcomes based on early vs late ECR administration. Even though the study includes an appreciable sample size of 304 PQ poisoning patients, the number of patients receiving ECR treatment was limited, indicating potential sample size limitations. Furthermore, being the first study to analyze outcomes in terms of clinical non-improvement, there was a significant lack of research to compare our results, since most studies focused on mortality as the clinical outcome. Future prospective studies with well-defined treatment protocols for ECR regimens are necessary to provide clarity on the effectiveness of ECR approaches in managing PQ poisoning.

CONCLUSION

ECR treatment modalities did not significantly improve clinical outcomes in patients with PQ poisoning. Sepsis/septic shock and high baseline AST levels were identified as risk factors for clinical non-improvement. To strengthen the existing evidence, additional prospective studies are necessary to evaluate the comparative effectiveness of the various ECR modalities considering the timing and duration of their administration.

LIST OF ABBREVIATIONS

AKI, acute kidney injury; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; ECR, extra-corporeal removal; GI, gastrointestinal; HD, hemodialysis; HP, hemoperfusion; ICU, intensive care unit; IQR, interquartile range; IST, immunosuppressive treatment; MODS, multi-organ dysfunction syndrome; MV, mechanical ventilation; NAC, N-acetyl cysteine; PQ, paraquat; S.Cr, serum creatinine; SpO_2, saturation of peripheral oxygen; STROBE, strengthening of the reporting of observational studies in Epidemiology; WBC, white blood cell count.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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Ethical approvals details is given in the ‘Materials and Methods section’.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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