Retrospective Study

Risk factors and optimal predictive scoring system of mortality for children with acute paraquat poisoning

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Abstract

BACKGROUND
There is no suitable scoring system that can be used to predict mortality in children with acute paraquat intoxication (APP).

AIM
To optimize a predictive scoring system for mortality in children with APP.

METHODS
A total of 113 children with APP from January 1, 2010 to January 1, 2020 were enrolled in this study. These patients were divided into survivors and non-survivors. We compared the clinical characteristics between the two groups and analyzed the independent prognostic risk factors. The survival rates of patients with different values of the pediatric critical illness score (PCIS) were assessed using kaplan-meier survival analysis. The best scoring system was established by using the area under the receiver operating characteristic curve analysis.

RESULTS
The overall mortality rate was 23.4%. All non-survivors died within 20 days; 48.1% (13/27) died within 3 days, and 70.3% (19/27) died within 7 days. Compared to survivors, the non-survivors were older, had higher white blood cell count, alanine aminotransferase (ALT), aspartate aminotransferase, serum creatinine, blood urea nitrogen, glucose, and pediatric early warning score, and had lower platelet count, albumin, Serum sodium (Na⁺) and PCIS. ALT and PCIS were the independent prognostic risk factors for children with APP. The survival rate of children classified as extremely critical patients (100%) was lower than that of children classified as critical (60%) or noncritical (6.7%) patients. The specificity...
of ALT was high (96.51%), but the sensitivity was low (59.26%). The sensitivity and specificity of ALT combined with PCIS were high, 92.59% and 87.21%, respectively. The difference in mortality was significantly higher for ALT combined with PCIS (area under the receiver operating characteristic: 0.937; 95%CI: 0.875-0.974; \( P < 0.05 \)).

**CONCLUSION**

In our study, ALT and PCIS were independent prognostic risk factors for children with APP. ALT combined with PCIS is an optimal predictive mortality scoring system for children with APP.

**Key Words:** Acute paraquat poisoning; Children; Pediatric critical illness score; Alanine aminotransferase; Prognosis

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**INTRODUCTION**

Paraquat (PQ) is a widely used herbicide worldwide. Since paraquat began to be used in agriculture in 1962, the number of patients with acute paraquat intoxication has gradually increased [1]. With the participation of reduced coenzyme II-cytochrome P450 reductase, xanthine oxidase and other enzymes, PQ produces a single cationic free radical \( \text{PQ}^+ \) **in vivo**, and \( \text{PQ}^+ \) rapidly reoxidizes into \( \text{PQ}^{2+} \). \( \text{PQ}^{2+} \) receives electrons from coenzyme II and generates superoxide anions, which then produce peroxynitrite by combining with nitric oxide free radicals. These highly reactive oxygen species and peroxynitrite lead to mitochondrial dysfunction and apoptosis through lipid peroxidation and the activation of nuclear factor-\( \kappa \)B, which results in multiple organ damage [2-4]. In the absence of specific antidotes, the mortality rate in children with acute paraquat intoxication (APP) was 14.38%-63.6% [5-7]. Therefore, the early and accurate prediction of mortality is very important in clinical decision-making for children with APP.

At present, several scoring systems have been used to predict the mortality of adult patients with APP, such as the sequential organ failure assessment [8], severity index of paraquat poisoning (SIPP) [9], acute physiology and chronic health evaluation II [10], early warning score (EWS) [11], and modified EWS [12]. However, the predictive powers of the above scoring systems are different, and most importantly, they are unsuitable for children.

There is no scoring system that can be used to predict mortality in children with APP. Because of the simple calculation and available indices, the pediatric critical illness score (PCIS) and pediatric EWS (PEWS) are scoring tools widely used for critically ill children [13-16]. However, there is no report in which the PCIS and PEWS were used to predict the prognosis of children with APP. Our study aimed to investigate the performance of the PCIS, the PEWS, as well as a single clinical index for predicting mortality in children with APP and to provide a theoretical basis for clinical application.

**MATERIALS AND METHODS**

**Patients**

We performed a single-center, retrospective, observational study, which was approved by the ethics committee of the West China Second University Hospital, Sichuan University.
Pediatric patients with APP enrolled in this study were < 18 years old and were admitted to our hospital between January 1, 2010 and January 1, 2020. The inclusion criteria were as follows: (1) A diagnosis of APP[17]; and (2) first visit to the hospital with no history of special treatment, such as gastric lavage and hemodialysis. The diagnostic criteria of APP were as follows: (1) The children or family members could provide the history of paraquat exposure; (2) for those who denied paraquat exposure, evidence was found to the contrary, including black-green residue on the skin, an empty paraquat bottle, vomiting, oral mucosal erosion with unknown causes; and (3) blood or urine was positive for paraquat. The exclusion criteria were as follows: (1) Complicated with chronic diseases; (2) other drug exposure; (3) death within 24 h of admission; and (4) discharge against medical advice.

Data collection
Age, sex, time to blood purification and consultation and related symptoms (vomiting, abdominal pain, oral ulcer and gastrointestinal bleeding) were collected at admission. Routine laboratory tests, including routine blood tests, blood gas, liver function, renal function and electrolytes, were performed. The PCIS [18] (Table 1) and PEWS[19] (Table 2) were calculated within 24 h after admission. Patients with the score of > 80 were considered noncritical, 71-80 critical, and ≤ 70 extremely critical. All children were followed up for at least 90 days.

Treatment
Routine blood tests, liver function, renal function, electrolytes, random blood glucose and chest computed tomography tests were performed upon admission. Routine treatments (vomiting induction, oral activated carbon and diuresis) were adapted. Some critically ill children were administered methylprednisolone 15 mg/(kg/d) for 3 d. The patients with infective symptoms were given anti-infective drugs, and those with respiratory failure were given oxygen inhalation or mechanical ventilation. Some critically ill children were treated with hemoperfusion 3-5 times or plasma exchange 3-4 times. Hemodialysis or continuous renal replacement therapy was used for patients with multiple organ dysfunction.

Statistical analysis
All statistical analyses were conducted using IBM SPSS statistics version 21 (IBM Corp & licensors 1989, 2011). Continuous variables are presented as the mean ± SD or median (interquartile range) [mean (P<0.05), P<0.01]. Categorical variables were expressed as percentages. The two groups were compared using student’s t-tests, chi-square tests, wilcoxon tests, and mann–whitney U tests. Multivariable logistic regression model was computed to identify whether variables were associated with unfavorable outcomes. The receiver operator characteristic [area under the receiver operating characteristic (AUROC)] curve was used to predict probability of mortality. We analyzed the survival rate of children with different PCIS by kaplan-meier survival analysis. P < 0.05 was considered statistically significant.

RESULTS
Comparison of clinical characteristics between survivors and non-survivors
In total, 113 patients were included. During the 90-day follow-up, the overall mortality rate was 23.4% (27/113). All non-survivors died within 20 d; 48.1% (13/27) died within 3 d, and 70.3% (19/27) died within 7 d. The causes of poisoning were suicide (22.1%) and accidental ingestion (77.9%).

Among the 113 children, 96 (85%), 15 (13.3%) and 2 (1.8%) were categorized as noncritical (PCIS > 80 points), critical (PCIS 71-80 points) and extremely critical (PCIS ≤ 70 points), respectively, and the mortality rates were 16.7% (16/96), 60% (9/15), and 100% (2/2), respectively. As shown in Figure 1, the survival rate of children classified as extremely critical patients (100%) was significantly lower than that of children classified as critical (60%) or noncritical (6.7%) patients (P < 0.05).

Compared to survivors, the non-survivors were older (8.11 ± 4.72 vs. 11.48 ± 2.99 years); had higher white blood cell count, serum creatinine (Scr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase, glucose, and PEWS; and had lower platelet count, albumin, Serum sodium (Na⁺) and PCIS (Table 3) (all P < 0.05).

The median time to consultation in survivors and non-survivors was 22.5 (8.75, 48) and 20 (8, 48) hours, respectively. In addition, there was no significant difference between the survivors and non-survivors in the time to consultation < 6 h, 6-24 h, and > 24 h subgroups.

Prognostic risk factors for children with APP
In order to explore the prognostic risk factors for children with APP, we selected variables with P < 0.1 in the univariate analysis to perform a multivariable logistic regression analysis. The indices of Scr, BUN, Na⁺, Serum potassium (K⁺), hemoglobin, abdominal pain, vomiting, and gastrointestinal bleeding were included in the PCIS system and were not introduced into the multivariable logistic regression analysis. ALT and PCIS were independent prognostic risk factors for those children with APP (P < 0.05).
### Table 1 Pediatric critical illness score

| Parameter                          | Age < 1 yr                                                                 | Age ≥ 1 yr                                                                 | Scores |
|-----------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------|
| Heart rate (beats/min)            | < 80 or > 180                                                              | < 60 or > 160                                                               | 4      |
|                                  | 80-100 or 160-180                                                          | 60-80 or 140-160                                                            | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |
| Blood pressure (systolic) [kPa (mmHg)] | < 7.5 (55) or > 17.3 (130)                                                  | < 8.7 (65) or > 20 (150)                                                   | 4      |
|                                  | 7.5-8.7 (55-65) or 13.3-17.3 (100-130)                                     | 8.7-10 (65-75) or 17.3-20 (130-150)                                        | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |
| Breathing rate (breaths/min)      | < 20 or > 70 or irregular breathing                                       | < 15 or > 60 or irregular breathing                                       | 4      |
|                                  | 20-25 or 40-70                                                             | 15-20 or 35-60                                                             | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |
| PaO₂ [kPa (mmHg)] (no oxygen inhalation) | < 6.7 (50)                                                             | 6.7-9.3 (50-70)                                                            | 4      |
|                                  | Others                                                                      | 6.7-9.3 (50-70)                                                            | 6      |
|                                  | 10                                                                          | 10                                                                          |        |
| pH                               | < 7.25 or > 7.55                                                            | 7.25-7.30 or 7.50-7.55                                                     | 4      |
|                                  | Others                                                                      | Others                                                                      | 6      |
| Na⁺ (mmol/L)                     | < 120 or > 160                                                             | 120-130 or 150-160                                                         | 4      |
|                                  | 120-130 or 150-160                                                         | 120-130 or 150-160                                                         | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |
| K⁺ (mmol/L)                      | < 3.0 or > 6.5                                                             | 3.0-3.5 or 5.5-6.5                                                         | 4      |
|                                  | 3.0-3.5 or 5.5-6.5                                                         | 3.0-3.5 or 5.5-6.5                                                         | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |
| Scr (μmol/L)                     | > 159                                                                       | 106-159                                                                     | 4      |
|                                  | 106-159                                                                     | 106-159                                                                     | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |
| BUN (mmol/L)                     | > 14.3                                                                      | 7.1-14.3                                                                    | 4      |
|                                  | 7.1-14.3                                                                    | 7.1-14.3                                                                    | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |
| Hb (g/L)                         | < 60                                                                        | 60-90                                                                       | 4      |
|                                  | 60-90                                                                       | 60-90                                                                       | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |
| Digestive system symptoms        | Stress ulcer bleeding and intestinal paralysis                               | Stress ulcer bleeding                                                      | 4      |
|                                  | Stress ulcer bleeding                                                      | Stress ulcer bleeding                                                      | 6      |
|                                  | Others                                                                      | Others                                                                      | 10     |

pH: Pondus hydrogenii; Na⁺: Serum sodium; K⁺: Serum potassium; Scr: Serum creatinine; BUN: Blood urea nitrogen; Hb: Hemoglobin.

*(Table 4)*

**Predictive scoring system development of mortality for children with APP**

Because the multiple logistic regression analysis revealed that ALT and PCIS were independent prognostic risk factors for children with APP, we further analyzed the predictive performance of ALT, PCIS and ALT combined with PCIS for mortality in children with APP. Table 5 and Figure 2 show the predictive power of ALT, PCIS and ALT combined with PCIS. The specificity of ALT was high (96.51%), but its sensitivity was low (59.26%). The sensitivity and specificity of PCIS and ALT combined with PCIS were high, 92.30% vs. 92.59% and 82.21% vs. 87.21%, respectively. The difference in-outcomes was
### Table 2 The pediatric early warning score

| Behavior                        | 0   | 1   | 2   | 3   |
|---------------------------------|-----|-----|-----|-----|
| Playing; alert; appropriate; at baseline |     |     |     |     |
| Sleeping; fussy but consolable   |     |     |     |     |
| Irritable/inconsolable          |     |     |     |     |
| Lethargic; confused; reduced response to pain |     |     |     |     |
| **Cardiovascular status**       |     |     |     |     |
| Pink cap refill 1.2 s           |     |     |     |     |
| Gray; cap refill 3 s            |     |     |     |     |
| Gray; cap refill 4 s; tachycardia of 20 beats/min above the normal rate |     |     |     |     |
| Gray; mottled; cap refill 5 s; tachycardia of 30 beats/min above the normal rate; bradycardia |     |     |     |     |
| **Respiratory status**          |     |     |     |     |
| Within normal parameters       |     |     |     |     |
| Greater than 10 breaths/min above normal parameters; accessory muscle use; 30% FiO<sub>2</sub> 3 liters/minute |     |     |     |     |
| Greater than 20 breaths/min above normal parameters; retractions; 40% FiO<sub>2</sub> 6 liters/minute; tracheostomy- and ventilator-dependent |     |     |     |     |
| Below normal parameters with retractions; grunting; 50% FiO<sub>2</sub> 8 liters/minute |     |     |     |     |

FiO<sub>2</sub>: Fraction of inspiration O<sub>2</sub>.

**Figure 1 The survival curves for different pediatric critical illness score.** A score of > 80 is classified as noncritical, 71-80 critical, and ≤ 70 extremely critical. All the non-survivors died within 20 d.

significantly higher for ALT combined with PCIS (AUROC: 0.937; 95% CI: 0.875-0.974) than for PCIS (AUROC: 0.905; 95% CI: 0.836-0.952) and ALT (AUROC: 0.814; 95% CI: 0.730-0.881) (all \( P < 0.05 \)). Thus, ALT combined with the PCIS was the optimal scoring system.

### DISCUSSION

The early prediction of mortality is important in clinical decision-making for patients with APP. Previous studies have indicated that plasma paraquat concentration can effectively predict the mortality of patients with APP [20,21]. However, Gil *et al.* [21] found that some patients with low paraquat concentration in plasma still had poor outcomes. The reasons are as follows. The plasma paraquat concentration reached a peak value within 0.5-2 h after ingestion[22], and the half-life is 5 h[23]. The concentration of paraquat in plasma decreased obviously in the early stage, and the survival expectations would decrease from 70% to 30% for a delay of 1 h[23]. The time of detecting paraquat concentration in plasma had an impact on the accuracy of paraquat measurements. In addition, most children with APP accidentally ingested paraquat; therefore, clinicians cannot estimate the dose of paraquat they ingested. Paraquat measurement was unavailable in almost all primary hospitals. Therefore, the paraquat concentration in plasma was not included in the prognostic risk factor analysis of children with APP. In addition, clinical indices such as serum lactic acid[24], K[25], blood amylase[26] and peripheral blood monocyte count[27] were considered to be effective in predicting the prognosis of patients with APP. Paraquat binds to plasma protein after entering the bloodstream and is quickly distributed to many organs, resulting in multiple organ damage[28]. Therefore, using a single index to predict the mortality of APP patients is inaccurate, while the combination of multiple indicators is more comprehensive and reasonable[29].
### Table 3 Comparison of clinical characteristics between survivors and non-survivors (n = 113)

| Variable                              | Survivors     | Non-survivors  | P value |
|---------------------------------------|---------------|----------------|---------|
| Age (yr), n (%)                       |               |                | 0.003   |
| ≤ 3 yr                                | 22 (25.6)     | 0 (0.0)        |         |
| 3-6 yr (not including 3 yr)           | 12 (13.4)     | 3 (11.1)       |         |
| 6-12 yr (not including 6 yr)          | 27 (31.2)     | 10 (37.0)      |         |
| > 12 yr                               | 25 (29.1)     | 14 (51.9)      |         |
| Sex, n (%)                            |               |                | 0.039   |
| Female                                | 41 (47.7)     | 19 (70.4)      |         |
| Male                                  | 45 (52.3)     | 8 (29.6)       |         |
| Cause of intoxication, n (%)          |               |                | 0.585   |
| Accidental                            | 68 (79.1)     | 20 (74.1)      |         |
| Suicide                               | 18 (20.9)     | 7 (25.9)       |         |
| Time to blood purification, n (%)     |               |                | 0.185   |
| < 6 h                                 | 3 (5.0)       | 2 (8.7)        |         |
| 6-12 h                                | 12 (20.0)     | 7 (30.4)       |         |
| 12-24 h (not including 12 h)          | 13 (21.7)     | 5 (21.7)       |         |
| > 24 h                                | 32 (53.3)     | 9 (39.1)       |         |
| Time to consultation, n (%)           |               |                | 0.191   |
| < 6 h                                 | 28 (32.6)     | 11 (40.7)      |         |
| 6-24 h                                | 22 (25.6)     | 6 (22.2)       |         |
| > 24 h                                | 36 (41.9)     | 10 (37.1)      |         |
| Vomiting, n (%)                       | 30 (34.9)     | 19 (70.4)      | 0.001   |
| Abdominal pain, n (%)                 | 14 (16.3)     | 9 (33.3)       | 0.055   |
| Oral ulcer, n (%)                     | 32 (37.2)     | 16 (66.7)      | 0.043   |
| Gastrointestinal bleeding, n (%)      | 3 (3.5)       | 5 (18.5)       | 0.001   |
| WBC count (× 10^9/L)                  | 11.27 ± 4.57  | 15.45 ± 7.15   | 0.007   |
| PLT count (× 10^9/L)                  | 267.79 ± 102.52 | 222.48 ± 79.15 | 0.038   |
| ALT [M (P_{25}, P_{75})]              | 32.5 (25, 42) | 99 (41, 494)   | < 0.001 |
| AST [M (P_{25}, P_{75})]              | 28 (20, 40)   | 108 (38, 295)  | < 0.001 |
| Albumin (g/L)                         | 44.34 ± 5.33  | 40.54 ± 6.23   | 0.002   |
| Glucose (mmol/L)                      | 6.60 ± 3.43   | 6.75 ± 1.31    | 0.805   |
| Na⁺ (mmol/L)                          | 137.04 ± 4.84 | 133.84 ± 6.49  | 0.024   |
| K⁺ (mmol/L)                           | 3.72 ± 0.58   | 3.70 ± 0.668   | 0.882   |
| Scr (mmol/L)                          | 74.17 ± 74.70 | 441.04 ± 267.86 | < 0.001 |
| BUN (mmol/L)                          | 7.62 ± 6.65   | 23.06 ± 14.99  | < 0.001 |
| PEWS, n (%)                           |               |                | < 0.001 |
| 0                                     | 66 (78.6)     | 9 (33.3)       |         |
| 1                                     | 12 (14.0)     | 9 (33.3)       |         |
| 2                                     | 5 (5.8)       | 3 (11.1)       |         |
| 3                                     | 1 (1.1)       | 3 (11.1)       |         |
| 4                                     | 1 (1.1)       | 0 (0.0)        |         |
| ≥ 5                                   | 1 (1.1)       | 3 (11.1)       |         |
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; WBC: White blood cell; PLT: Platelet; Scr: Serum creatinine; BUN: Blood urea nitrogen; PCIS: Pediatric critical illness score; PEWS: Pediatric early warning score; Na⁺: Serum sodium; K⁺: Serum potassium.

Table 4 Analysis of mortality due to paraquat poisoning using multivariate logistic regression (n = 113)

| Variables | β Coefficient | SE  | Odds ratio (95%CI) | P value |
|-----------|---------------|-----|--------------------|---------|
| ALT       | 0.024         | 0.010 | 1.024 (1.003-1.045) | 0.022   |
| PCIS      | -0.151        | 0.046 | 0.860 (0.785-0.942) | 0.001   |

ALT: Alanine aminotransferase; PCIS: Pediatric critical illness score; SE: Standard error; CI: Confidence interval.

Table 5 Predictive value of risk factors for mortality in children with acute paraquat poisoning (n = 113)

| Predictive factors | Sensitivity (%) | Specificity (%) | AUROC (95%CI) | Youden index | P value |
|--------------------|-----------------|-----------------|---------------|--------------|---------|
| ALT                | 59.26           | 96.51           | 0.814 (0.730-0.881) | 0.557 | < 0.001 |
| PCIS               | 92.30           | 82.21           | 0.905 (0.836-0.952) | 0.774 | < 0.001 |
| ALT and PCIS       | 92.59           | 87.21           | 0.937 (0.875-0.974) | 0.798 | < 0.001 |

ALT: Alanine aminotransferase; PCIS: Pediatric critical illness score; AUROC: Area under the receiver operating characteristic; CI: Confidence interval.

The poisoning severity score[30,31] and pediatric logistic organ dysfunction (PELOD) score[32] can be used to predict the prognosis of children with APP. Nevertheless, complex calculations and the availability of indices (such as PO₂/FiO₂) in the general ward limit their application in clinical work. In addition, the SIPP[9] and clinical classification of APP[33] have good predictive ability for the prognosis of children with APP. Due to the unavailability of ingestion doses and paraquat concentrations, the clinical classification of APP and SIPP was not adopted in this study.

The EWS is widely used in adult patients. However, the vital signs and physiological indices of children of different ages vary widely, and there is a long compensation period before rapid deterioration due to disease. Therefore, the PEWS was established according to the physiological and
The mortality rate in children with APP was high. ALT and PCIS were independent prognostic risk factors for children with APP. ALT combined with PCIS is an optimal predictive scoring system for mortality in children with APP.

**ARTICLE HIGHLIGHTS**

**Research background**
The mortality rate in children with acute paraquat intoxication (APP) was 14.38%-63.6%, the early and accurate prediction of mortality is very important in clinical decision-making for children with APP.

**Research motivation**
The mortality rate in children with APP was high. The early prediction of mortality is important in clinical decision-making for patients with APP. Therefore, our aim is to optimize a predictive scoring system for mortality in children with APP.
**Research objectives**
Our aim is to optimize a predictive scoring system for mortality in children with APP, and help doctors to make clinical decisions.

**Research methods**
We compared the clinical characteristics between the two groups and analyzed the independent prognostic risk factors. The survival rates were assessed using kaplan-meier survival analysis. The best scoring system was established by using the area under the receiver operating characteristic curve analysis.

**Research results**
Alanine aminotransferase (ALT) and pediatric critical illness score (PCIS) were independent prognostic risk factors for children with APP. The survival rate of children classified as extremely critical patients was significantly lower than that of children classified as critical or noncritical patients. The sensitivity and specificity of ALT combined with PCIS were high.

**Research conclusions**
ALT and PCIS were independent prognostic risk factors for children with APP. ALT combined with PCIS is an optimal predictive mortality scoring system for children with APP.

**Research perspectives**
The results of this study need to be further verified by large-sample and multicenter research.

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**FOOTNOTES**

**Author contributions:** Song Y and Wang H designed the study, made the review, and wrote the manuscript; Song Y, Wang H, and Tao YH made the literature search, made table, and reviewed the manuscript; all authors read and approved the final manuscript.

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