Abstract. The present study investigated the predictive values of urine paraquat (PQ) concentration, dose of poison, arterial blood lactate and Acute Physiology and Chronic Health Evaluation (APACHE) II score in the prognosis of patients with acute PQ poisoning. A total of 194 patients with acute PQ poisoning, hospitalized between April 2012 and January 2014 at the First Affiliated Hospital of P.R. China Medical University (Shenyang, China), were selected and divided into survival and mortality groups. Logistic regression analysis, receiver operator characteristic (ROC) curve analysis and Kaplan-Meier curve were applied to evaluate the values of urine paraquat (PQ) concentration, dose of poison, arterial blood lactate and APACHE II score for predicting the prognosis of patients with acute PQ poisoning. Initial urine PQ concentration ($C_0$), dose of poison, arterial blood lactate and APACHE II score of patients in the mortality group were significantly higher compared with the survival group (all P<0.05). Logistic regression analysis revealed that $C_0$, dose of poison, arterial blood lactate and APACHE II score correlated with mortality risk of acute PQ poisoning (all P<0.05). ROC curve analysis suggested that the areas under the curve (AUC) values of $C_0$, dose of poison, arterial blood lactate and APACHE II score in predicting the mortality of patients within 28 days were 0.921, 0.887, 0.808 and 0.648, respectively. The AUC values of urine paraquat concentration the day after poisoning ($C_{sec}$) and the rebound rate of urine paraquat concentration in predicting the mortality of patients within 28 days were 0.919 and 0.805, respectively.

The 28-day survival rate of patients with $C_0 \leq 32.2$ µg/ml (42/71; 59.2%) was significantly higher when compared with patients with $C_0 > 32.2$ µg/ml (38/123; 30.9%). These results suggest that the initial urine PQ concentration may be the optimal index for predicting the prognosis of patients with acute PQ poisoning. Additionally, dose of poison, arterial blood lactate, $C_{sec}$ and rebound rate also have referential significance.

Introduction

Paraquat (PQ; 1,1'-dimethyl-4,4'-bipyridinium), also known as Gramoxone or methyl viologen, is an organic nitrogen heterocyclic herbicide utilized in agriculture worldwide (1,2). PQ can gradually damage human health via bioaccumulation in the food chain, and ingestion of >15-30 ml of 20% (w/v) PQ can be fatal in humans (3). Severe PQ poisoning affects multiple organs, predominantly the lung, liver, kidneys, adrenal cortex and myocardium (4). Severe cases of acute PQ poisoning may also exhibit neurological symptoms, such as dysphoria, somnolence, and impaired consciousness (5). It is estimated that 250,000-370,000 individuals succumb to pesticide poisoning each year globally, and >90% of patients with acute poisoning have attempted suicide by ingesting concentrated PQ in a liquid form (6). The principal biochemical mechanism of PQ poisoning is based on redox cycling and intracellular oxidative stress generation, and pulmonary fibrosis and edema are the major clinical symptoms (7). A previous study has investigated various treatment modalities for acute PQ poisoning, but the fatality rate remains high (8). In this context, biomarkers for the prognosis and clinical monitoring of acute PQ poisoning are urgently required to guide appropriate treatment plans and develop future PQ antidotes (2).

To date, several diagnostic methods have been developed to evaluate the severity of acute PQ poisoning in patients, including urine PQ concentration, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, arterial blood lactate and ingestion dose of PQ (9,10). Plasma and urine PQ concentrations obtained within the first 24 h after ingestion are excellent predictors of the outcomes of PQ poisoning (2). However, the measurement of plasma PQ concentrations requires personnel support and apparatus, including strict
quality standards and controls to predict severity, which may not be readily available in most hospitals because of the expense of equipment and the associated technical problems (11). Therefore, urine analysis may have a higher predictive value and may more rapidly assess prognosis compared with estimating PQ concentrations in plasma (7). APACHE II is a severity-of-disease classification system applied within 24 h of admission of a patient to an intensive care unit (ICU), which has been extensively used in the prediction of the outcomes of PQ poisoning (12). Lactate estimation is a prognostic tool that can predict the mortality rate among patients with severe sepsis and ST elevation myocardial infarction (13,14). It is used in numerous critical-care patients, including patients who have recently undergone surgery and those with burns, trauma, and septic shock. Arterial blood lactate is a manifestation of organ dysfunction and has good predictive power in evaluating patient prognosis during acute PQ poisoning (9,13).

Materials and methods

Subjects. A total of 194 patients with acute PQ poisoning who were hospitalized between April 2012 and January 2014 at the First Affiliated Hospital of China Medical University (Shenyang, China) in the Intensive Care Unit of the Emergency Department were selected as the research subjects. Selection criteria were as follows: i) Patients were selected according to the diagnostic criteria of acute PQ poisoning in The Diagnosis and Treatment of Acute Poisoning (15), and clinical diagnostic results were available; ii) patients were treated within 24 h after poisoning, and there was evidence of PQ poisoning or circumstantial evidence of PQ poisoning provided by patients or caregivers; iii) patients had not received therapy before admission to the hospital, including blood purification treatment or gastric lavage; and iv) patients had no history of serious heart, liver, kidney and lung diseases. Exclusion criteria were: i) Patients had a history of chronic kidney disease; ii) PQ combined with other drug poisoning; iii) emergency observation was no more than 24 h; iv) patients were admitted 24 h after they took poison; and v) pregnant women, patients that gave up therapy or died due to reasons unrelated to PQ poisoning. A total of 194 patients (72 men; 122 women) aged 12-75 years (mean, 32.51±12.72 years) were enrolled in this study. The characteristics of PQ pesticide treatment were as follows: 20% PQ pesticide dose, 10-150 ml; mean dose, 55.00±33.27 ml; time interval between PQ exposure and the first urine sample, 0.5-11.5 h; and mean time interval, 4.8±6.9 h.

This study was performed in accordance with the standard in medical ethics and was approved by the Medical Ethics committee the First Affiliated Hospital of China Medical University (Shenyang, China). Written informed consent was obtained prior to treatment from patients or their family members. This study conformed to the guidelines outlined in the Declaration of Helsinki (16).

Data collection. Patients received auxiliary examinations immediately, and 4 h (immediately following the peak of drug plasma concentration) and within 24 h after poisoning, peripheral venous blood and arterial blood samples were collected and immediately sent to the Pathology Department to test the relevant indices. Patient data were collected by two clinicians based on the unified form, including sex and age of patients, poison dose, the time interval between PQ exposure and the first urine sample, results of routine blood and urine tests, fasting blood glucose, liver function, kidney function, myocordial enzymes, serum potassium, artery blood gas analysis, and amylase detection at admission to hospital and at deterioration or improvement. Within the first 24 h after admission to hospital, the APACHE II score was evaluated according to the general condition and vital signs of patients and the worst inspection results. Urine PQ concentration of patients was dynamically monitored. Initial urine PQ concentration (C\textsubscript{i}) and urine PQ concentration after hemoperfusion (HP) were calculated. C\textsubscript{i} indicates the urine PQ concentration after undergoing HP x times, and C\textsubscript{hp} indicates the urine PQ concentration the following day after HP was measured. The rebound rate of urine PQ concentration the following day after HP was also calculated, as follows: Rebound rate=(C\textsubscript{i}-C\textsubscript{hp})/C\textsubscript{i}, where C\textsubscript{i} is urine PQ concentration after the final round of HP. Urine PQ concentration was detected each day during the observation period until the PQ concentration in urine was below the detectable level for 2 consecutive days, which was defined as the point at which the urinary concentration became negative.

Patients were divided into either the mortality group, which included an early mortality subgroup (fatality within 7 days after poisoning) and a delayed mortality subgroup (fatality between 7-28 days after poisoning), or the survival group (alive at the 28-day follow-up). There were 80 patients in the survival group (29 men and 51 women; mean age, 30.58±12.34 years) and 114 patients in the mortality group (43 men and 71 women; mean age, 33.68±12.19 years). The levels of all the indices between the mortality and survival groups were compared, the comparable indices were analyzed, and superior predictors of mortality in patients were explored using receiver operator characteristic (ROC) curve.

Treatment methods. The 194 patients were treated with unified treatment options, including: i) removing unabsorbed poison via gastric lavage and catharsis (oral administration of 100-250 ml of 20% mannitol); ii) excluding absorbed poison via HP, hydration and diuresis; iii) antioxidant therapy in the form of applying vitamins C and E; and iv) symptomatic and supportive treatments, including organ function support and correction of acid-base and electrolyte imbalance.

Detection of urine paraquat concentration. The PQ concentration in urine was detected using colorimetric methods based on sodium hyposulfite (17). Under alkaline conditions, the sodium hyposulfite deoxidizes PQ into blue-colored products. Based on the change in color at different concentrations of PQ dichloride and excess sodium hyposulfite under alkaline conditions, a standard curve for determining
PQ concentration was obtained and the PQ concentration in the urine of patients was quantitatively detected. A total of 100 g sodium dithionite was added to sodium hydroxide solution (2 ml; 2 M) and remained stable for approximately 2 h. Urine samples were collected from patients in colorless tubes and maintained at -20˚C for 10 min, followed by centrifugation at 9660 x g for 5 min at room temperature. A total of 200 µl alkaline dithionite solution was added to 2 ml of the pretreated urine. Following gentle mixing, 50 µl supernatant was collected to measure the absorbance. Absorbance was measured at 395 nm and a working curve of concentration-absorbance was prepared. Linear regression curve: y=0.0895x+0.0151, with a correlation coefficient of r=0.9999 when the urine PQ concentration was 0.01 to 100 µg/ml. Recovery rate ranged from 92.5 to 104.0%, with relative standard deviation (RSD) ranging from 2.7 to 4.5%, and the limit of detection (LOD) was 0.01 µg/ml. According to the test sample and above formula, the urine PQ concentration was calculated.

### Table I. Comparisons of all indexes between survival and mortality groups.

| Characteristic                           | Survival group (n=80) | Mortality group (n=114) | t/χ² | P-value |
|------------------------------------------|-----------------------|-------------------------|------|---------|
| Age, years                               | 30.58±12.34           | 33.68±12.19             | 1.530| 0.128   |
| Sex, N (%)                               | 29 (32.58)            | 43 (40.09)              | 1.511| 0.223   |
| Male                                     | 51 (67.42)            | 71 (59.91)              |      |         |
| Dose of poison, ml                       | 30.72±15.14           | 72.52±31.42             | 12.31| <0.001* |
| Mean arterial pressure, mmHg             | 92.29±17.08           | 88.67±15.94             | 1.512| 0.132   |
| Heart rate, beats/min                    | 88.49±19.25           | 92.87±26.25             | 1.262| 0.209   |
| Respiratory frequency, breaths/min       | 24.26±7.13            | 26.31±8.84              | 1.358| 0.176   |
| Body temperature, °C                     | 36.29±0.914           | 36.34±0.71              | 0.429| 0.668   |
| White blood cells, per 10^9/l            | 12.30±4.39            | 13.65±5.22              | 1.891| 0.060   |
| Hemoglobin, g/dl                         | 14.07±4.15            | 14.45±5.86              | 0.499| 0.619   |
| Platelet, per 10^9/l                     | 243.77±89.32          | 251.04±101.74           | 0.515| 0.607   |
| Alanine aminotransferase, U/l            | 44.74±25.89           | 52.04±30.03             | 1.760| 0.080   |
| Total bilirubin, µmol/l                  | 21.14±12.56           | 24.09±12.52             | 1.613| 0.108   |
| Albumin, g/l                             | 37.97±9.82            | 36.26±10.70             | 0.158| 0.248   |
| Serum amylase, U/l                       | 90.65±42.66           | 97.52±46.22             | 1.052| 0.294   |
| Serum lipase, U/l                        | 101.14±38.27          | 112.63±58.14            | 1.659| 0.099   |
| Urea nitrogen, mmol/l                    | 7.69±3.79             | 8.40±4.64               | 1.129| 0.260   |
| Creatinine, µmol/l                       | 92.83±44.39           | 106.38±56.22            | 1.873| 0.063   |
| Serum CK-MB isoenzyme, U/l              | 20.26±13.15           | 23.19±12.98             | 1.361| 0.175   |
| Serum troponin I, ng/ml                  | 0.23±0.14             | 0.27±0.19               | 1.688| 0.093   |
| Blood glucose, mmol/l                    | 9.70±5.41             | 10.79±5.84              | 1.319| 0.189   |
| Serum potassium, mmol/l                  | 4.24±1.39             | 3.94±2.05               | 1.138| 0.257   |
| Serum sodium, mmol/l                     | 140.35±41.95          | 137.96±40.86            | 0.397| 0.692   |
| pH                                       | 7.36±0.25             | 7.40±0.30               | 0.978| 0.329   |
| PaO₂, mmHg                               | 94.87±33.03           | 97.70±40.66             | 0.515| 0.607   |
| PaCO₂, mmHg                              | 32.86±10.24           | 30.41±7.8              | 1.804| 0.073   |
| HCO₃⁻, mmol/l                            | 21.31±4.27            | 20.31±3.51             | 1.785| 0.076   |
| Base excess, mmol/l                      | -2.82±1.35            | -3.21±1.89             | 1.677| 0.095   |
| Arterial blood lactate, mmol/l           | 1.50±0.97             | 2.90±1.21              | 8.925| <0.001* |
| C₀, µg/ml                                | 20.28±19.95           | 48.67±17.27            | 11.350| <0.001* |
| APACHE II                                | 8.74±6.16             | 11.98±7.02            | 3.326| <0.001* |

*P<0.05 between the survival group and mortality group. CK, creatine kinase; C₀, initial concentration of paraquat in urine; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Statistical analysis. SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data were expressed as the mean ± standard deviation, Student's t-test was applied to detect inter-group comparisons, and χ² test was performed to detect enumeration data. Valuable detection indices were screened out by logistic regression analysis and ROC curve analysis and Kaplan-Meier curve was applied to evaluate their diagnostic efficiency. P<0.05 was considered to indicate a statistically significant difference.
Results

Comparisons of baseline characteristics. The 194 patients were all poisoned with oral doses of PQ. Within the 28-day follow-up period after poisoning, 114 patients succumbed to poisoning and 80 patients survived, with a mortality rate of 58.8%. Dose of poison, arterial blood lactate, initial urine PQ concentration and APACHE II score were all significantly higher in the mortality group compared with the survival group (all P<0.05). Additionally, no significant difference in the comparisons of other indices, including but not limited to mean arterial pressure, heart rate, respiratory frequency and body temperature, were observed between the two groups (all P>0.05; Table I).

Logistic regression analysis. Logistic regression analysis was performed on the independent variables that had statistical differences in single factor analysis, suggesting that only dose of poison (OR, 1.081; 95% CI, 1.046-1.118; P<0.001), initial urine PQ concentration (C₀) (OR, 1.076; 95% CI, 1.038-1.115; P<0.001) and arterial blood lactate (OR, 2.580; 95% CI, 1.462-4.556; P=0.001) were associated with the risk of mortality from PQ poisoning (Table II).

Receiver operating characteristic curve analysis. Results of ROC curve analysis of dose of poison, initial urine PQ concentration and arterial blood lactate in predicting the mortality rate of patients within 28 days of poisoning are presented in Table III and Fig. 1. The area under the curve (AUC) of initial urine PQ concentration (C₀) was the largest at 0.921, which has a relatively more accurate discrimination for patient prognosis. The AUC of dose of poison and arterial blood lactate were 0.887 and 0.808, respectively, and their discrimination for the prognosis of acute PQ poisoning was only second to initial urine PQ concentration (C₀). The AUC of APACHE II score was 0.648, suggesting it is relatively poor at predicting the prognosis of acute PQ poisoning.

Among the 80 patients in the survival group and 114 in the mortality group, 20 patients died within 7 days of poisoning, including 11 from sudden cardiac arrest and 9 from multiple organ failure. The remaining 94 patients died within 7-28 days of poisoning, including 81 from refractory hypoxemic respiratory failure (minimum value of arterial partial pressure of oxygen, 27-46 mmHg; mean value, 38±16 mmHg) and 13 from multiple organ failure. Initial urine PQ concentration of patients in the early and delayed mortality groups was significantly higher than in the survival group (all P<0.01), and initial urine PQ concentration in early mortality group was significantly higher compared with the delayed mortality group (86.7±16.2 vs. 40.57±12.36; t=3.808; P=0.001) (Fig. 2). The AUC of the initial urine PQ concentration of patients in predicting early mortality after poisoning was 0.890 (95% CI, 0.837-0.944) with a cutoff value of 49.3 µg/ml, sensitivity and specificity values of 100.0 and 69.0%, respectively, and a Youden index score of 0.690 (Fig. 3). The AUC of the initial urine PQ concentration of patients in predicting delayed mortality was 0.764 (95% CI, 0.693-0.834) with a cutoff value of 37.5 µg/ml, sensitivity...
and specificity values of 89.4 and 64.0%, respectively, and a Youden index score of 0.534 (Fig. 4). These findings indicate that the efficacy of the initial urine PQ concentration in predicting early mortality was higher when compared with delayed mortality.

Prognostic value of urine paraquat concentration. Patients were divided into two groups according to the initial urine PQ concentration ($C_0$, 32.2 µg/ml). During the observation period (28-day follow-up after poisoning), the survival rate of patients with $C_0 \leq 32.2$ µg/ml (42/71; 59.2%) was significantly higher when compared with those with $C_0 > 32.2$ µg/ml (38/123; 30.9%; Fig. 5), suggesting that $C_0$ was an important index for predicting mortality rate in patients within 28 days (OR: 14.33, 95% CI, 1.728-5.838; $\chi^2$=14.33; P<0.001).

Rebound rate of urine paraquat concentration after hemoperfusion. Selected patients received HP 2-5 times (3.7±2.2) within 24 h after poisoning, among which 11 received HP 5 times, 123 received HP 4 times, 46 received HP 3 times and 14 received HP 2 times. Urine PQ concentration levels in patients who received HP 4 times within 24 h after poisoning was dynamically monitored. We found that the average urine PQ concentration of patients in the mortality and survival groups dropped to 1 µg/ml, but both rebounded the next day to different degrees. On the day after poisoning, urine PQ...
concentration in the mortality group was significantly higher compared with the survival group (t=2.232; P=0.036). The rebound rate in the mortality group was also markedly higher compared with the survival group (t=2.254; P=0.022; Table IV).

In the 123 patients that received HP 4 times within 24 h of poisoning, the area under the ROC curve of urine PQ concentration on the day after HP (C_0) in predicting the mortality rate within 28 days was 0.919 (95% CI, 0.878-0.960; P<0.001). The area under the ROC curve of the rebound rate of urine PQ concentration on the next day in predicting mortality rate within 28 days was 0.805 (95% CI, 0.742-0.867; P<0.001; Fig. 6).

**Discussion**

This study investigated the efficacy of urine PQ concentration, dose of poison, arterial blood lactate and APACHE II scoring in predicting the prognosis of patients with acute PQ poisoning. By comparing indices between the survival and mortality groups, we found that initial urine PQ concentration, dose of poison, arterial blood lactate and the APACHE II score of patients in the mortality group were all significantly higher compared with the survival group, suggesting that all four indices were able to predict the prognosis of patients with acute PQ poisoning to some extent, compared with other indices, such as arterial pressure, heart rate and serum potassium. Consistent with our results, Ruan et al (7) reported that the PQ concentration in urine served as an invaluable predictive index for the prognosis of patients in acute PQ poisoning and, in another study, urine PQ concentrations reflected the severity of acute PQ poisoning (18). PQ can cause acute tubular necrosis and therefore lead to renal failure at high doses (19). However, if patients ingest <40 mg/kg PQ, renal damage is reversible and the mortality rate is lower compared with patients who have ingested higher doses of PQ (20). Consequently, dose of PQ is a stable index for predicting the prognosis of patients with acute PQ poisoning. APACHE II is a severity-of-disease classification system applied within 24 h of admission of a patient to the Intensive Care Unit (12). It has also been used as a proxy indicator to reflect the intermediate effect of PQ poisoning dose and the severity of PQ intoxication.
and the rebound rate also have
within the 28-day period. In addition, the rebound rate of PQ
compared with patients exhibiting C
its efficiency in predicting delayed mortality. The survival rate
PQ concentration in predicting early mortality was higher than
ROC curve analysis suggested that the efficacy of initial urine
concentration in the early mortality group was also signifi-
compared with the survival group. Notably, initial urine PQ
early and delayed mortality groups was significantly higher
that the initial urine PQ concentration of patients in the
survival, in the early and delayed mortality groups suggested
as follows: Initial urine PQ concentration with the best accu-
curves revealed that only dose of poison, initial urine PQ
concentration (C0) and arterial blood lactate were associated
with the risk of mortality from PQ poisoning, suggesting
that, compared with APACHE II scoring, dose of poison,
initial urine PQ concentration and arterial blood lactate were
more sensitive in predicting the mortality risk of PQ
poisoning. However, in direct contrast with our results, a
study by Huang et al (21), showed that an APACHE II score of>
13, calculated 24 h after admission, predicted in-hospital
mortality with relatively high sensitivity (67%) and speci-
ficity (94%) and concluded that the APACHE II system
yielded superior discriminatory power than plasma PQ
concentration or estimated PQ ingestion dosage. Limitations
of the APACHE II system, including reduced applicability
in patients with more severe disease, may contribute to this
difference (21). and APACHE II scoring does not include
parameters reflecting liver damage, which is a major
complication in PQ poisoning (15). Therefore, evaluation
of APACHE II score is complex and not advisable for typical
hospital inpatients (20).

ROC curve analysis ranked the accuracy of the three indices
as follows: Initial urine PQ concentration with the best accu-
curacy, dose of poison, and arterial blood lactate. Though arterial
blood lactate is a useful index in predicting the prognosis of
acute PQ poisoning patients, determination of the circulating
levels of lactate is more practical and technically simpler, is
frequently used, and is a clinically available technique with a
rapid turnaround (23). Initial urine PQ concentrations, and a
comparison of urine PQ concentrations associated with patient
survival, in the early and delayed mortality groups suggested
that the initial urine PQ concentration of patients in the
early and delayed mortality groups was significantly higher
compared with the survival group. Notably, initial urine PQ
concentration in the early mortality group was also signifi-
cantly higher compared with the delayed mortality group.
ROC curve analysis suggested that the efficacy of initial urine
PQ concentration in predicting early mortality was higher than its
efficiency in predicting delayed mortality. The survival rate
of patients with C0≤32.2 µg/ml was significantly higher when
compared with patients exhibiting C0>32.2 µg/ml, suggesting
that C0 is an important index for predicting mortality rate
within the 28-day period. In addition, the rebound rate of PQ
concentration in the mortality group was also markedly higher
when compared with the survival group, suggesting that the
rebound rate may be an important risk factor for fatality from
acute PQ poisoning and may have a predictive role in the prog-
nosis of patients with acute PQ poisoning.

In conclusion, the initial urine PQ concentration may be
the optimal index for predicting the prognosis of patients
with acute PQ poisoning. Additionally, dose of poison,
arterial blood lactate, C0 and the rebound rate also have
some referential significance. In view of the relatively
small sample size, the results of this study will need to be
confirmed in future studies that involve larger sample sizes.

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