

Serum anion gap at admission as a predictor of the survival of patients with paraquat poisoning

A retrospective analysis

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Abstract

Paraquat (PQ) poisoning is associated with high mortality rate. Therefore, an accurate method for predicting the survival of patients with PQ poisoning is required. This study evaluated the value of serum anion gap (AG) at admission in predicting the survival of such patients.

Cases of patients with PQ poisoning admitted to Cangzhou Central Hospital between May 2012 and March 2019 were retrospectively analyzed. The patients were classified into survival and nonsurvival groups on the basis of their 90-day prognosis. Correlation analysis, Cox regression analysis, and receiver operating characteristic and Kaplan–Meier curve analyses were performed to assess the value of AG in predicting the 90-day survival of patients with PQ poisoning.

Only 44 of the 108 patients with PQ poisoning survived; thus, the 90-day survival was 40.74%. AG levels at admission were significantly higher in nonsurvivors (26.53 ± 4.93 mmol/L) than in survivors (20.88 ± 2.74 mmol/L) ($P < .001$) and negatively correlated with 90-day survival ($r = -0.557$; $P < .001$). Cox regression analysis revealed that AG at admission is an independent prognostic marker of the 90-day survival of patients with PQ poisoning. AG level at admission had an area under the receiver operating characteristic curve of 0.836 (95% confidence interval: 0.763–0.909) and an optimal cut-off value of 25.5 mmol/L (59.4% sensitivity and 95.5% specificity).

AG level at admission may serve as a candidate marker for predicting the survival of patients with PQ poisoning.

Abbreviations: AG = anion gap, AUC = area under the curve, CI = confidence interval, OR = odds ratio, PQ = paraquat.

Keywords: anion gap, paraquat, prediction

1. Introduction

Paraquat (PQ) has an excellent weeding effect, but it is highly toxic to humans and animals. Its misuse or intentional self-use can induce acute poisoning and has become a common cause of death. The lethal ingestion dose of PQ for humans is approximately 35 mg/kg, which is equivalent to 10 to 15 mL of a 20% solution.^[1,2] Suicidal or accidental ingestion of PQ results in rapid multiple organ failure with a mortality rate that exceeds 60%.^[3–6] These poor outcomes are attributed to the

severe toxicity of PQ and the lack of effective detoxification therapies. Management of PQ poisoning is mainly directed at the following aspects: reduced absorption, increased excretion, anti-inflammation, anti-oxidation, and supportive treatment.^[6–9] The serious clinical problem of PQ poisoning has prompted comprehensive research on its pathogenesis, prevention, and treatment. However, no relevant breakthrough has been achieved to date.

The current assessment of patients with PQ poisoning primarily depends on blood PQ concentration with relatively good sensitivity and specificity.^[10,11] Unfortunately, PQ assays are not widely available, particularly in developing countries. PQ level detection often requires expensive devices, professional operators, and high cost and is thus limited for clinical use. Therefore, the most effective and appropriate therapy for PQ poisoning must be determined.

Anion gap (AG) can be easily and rapidly determined and is therefore suitable in clinical situations, such as sepsis,^[12] acute pancreatitis,^[13] and kidney diseases.^[14,15] However, to the best of our knowledge, the correlation of AG level at admission with the prognosis of PQ poisoning remains unclear. The relevance of AG level at admission in terms of PQ toxicity has not been fully investigated. Therefore, this study aimed to evaluate the clinical predictive value of AG level at admission in patients with PQ poisoning.

2. Materials and methods

2.1. Ethics, consent, and setting

This retrospective clinical study was approved by the ethics committee of Cangzhou Central Hospital (no: 2017-090-01).

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Informed consent was waived because demographic, clinical, and biologic data were collected from medical records. All information on patients with PQ poisoning was analyzed anonymously and securely protected. All data were available to the investigators only.

2.2. Patients

Data were obtained from all patients admitted to the emergency department from May 2012 and March 2019 for intentional or accidental ingestion of PQ as verified by plasma PQ concentration test. Patients with acute oral PQ poisoning were selected according to the following criteria: the time from poison ingestion to hospital admission was within 12 hours and the age of the patients was >14 years. The exclusion criteria were as follows: PQ was ingested in combination with any other poison; the patients had a history of a chronic disease or an end-stage disease; known pregnancy; lost to follow-up; and time of exposure was unknown.

2.3. Protocol for PQ detoxification

The PQ detoxification protocol involved gastric lavage with a large amount of 0.9% saline, followed by 1g/kg activated charcoal, 1g/kg Fuller earth, and 250 mL of 20% mannitol through a nasogastric tube.^[16] All patients received 1 to 3 courses of 3 hours active charcoal hemoperfusion therapy based on the results of urine PQ detection and clinical condition.^[17,18] The protocol also included pulse therapies of methylprednisolone (0.375–1 g/d for 3 days), vitamin C (3.0 g/d for 10–14 days), and glutathione (2.4 g/d for 10–14 days).^[1,18] Hemofiltration was performed when acute renal failure occurred.

2.4. Data collection

All data obtained from the patients were recorded and standardized in a Microsoft Excel spreadsheet by 2 physicians who were unaware of the purpose of this investigation. Information on patient demographics, clinical presentations, laboratory findings, and outcomes upon patient admission were collected by reviewing their medical records. The primary endpoint of this study was 90-day mortality. Patients were categorized into survivor or nonsurvivor groups on the basis of whether they survived after the 90-day follow-up period.

2.5. Statistical analysis

Statistical analysis was performed using the SPSS 13.0 software (SPSS Inc, Chicago, IL). Student *t* test or a Wilcoxon rank-sum test was performed on the numerical data between the groups. Chi-squared test was used for categorical data. Spearman correlation was performed to analyze the relationship between 2 metabolites. Correlation analysis, Cox regression analysis, and receiver operating characteristic (ROC) and Kaplan–Meier curve analyses were used to assess the predictive value of AG in mortality. $P < .05$ indicated a statistically significant difference.

3. Results

3.1. Patient characteristics

A total of 123 patients were admitted to our hospital from May 2012 to March 2019 because of PQ poisoning. Fifteen of the

patients were excluded because of incomplete data ($n=7$), unsuccessful follow-up ($n=3$), transfer to another hospital ($n=2$), and incomplete blood gas analysis ($n=3$). A total of 108 patients met the inclusion criteria and were finally included in this study. The total survival rate was 40.74% (44/108) after the 90-day follow-up period. The clinical characteristics and biologic data upon admission of the nonsurvival and survival groups are presented in Table 1. Nonsurvivors had high AG, alanine aminotransferase (ALT), creatinine, and plasma PQ concentration but low alveolar oxygen partial pressure. Clinical characteristics and biologic data upon admission were stratified on the basis of AG level at admission, as shown in Table 2. Patients with AG >25.5 mmol/L had high ALT, creatinine, and plasma PQ concentration.

3.2. Correlation analysis

Bivariate analysis revealed that AG was positively associated with plasma PQ concentration ($r=0.337$; $P<.001$) and negatively correlated with survival time ($r=-0.512$; $P<.001$) and 90-day survival ($r=-0.557$; $P<.001$).

3.3. Cox proportional hazard regression analysis

Univariate and multivariate Cox proportional hazard analyses (Table 3) showed that the high AG level at admission was an independent risk factor for 90-day survival (hazard ratio: 1.152, 95% confidence interval [CI]: 1.102–1.206, $P<.001$; hazard ratio: 1.067, 95% CI: 1.008–1.128, $P=.025$, respectively).

3.4. ROC curve analysis for 90-day mortality

Table 4 shows that the area under the ROC curve (AUC) was 0.836 for AG (59.4% sensitivity and 95.5% specificity), 0.845 for creatinine (75.0% sensitivity and 88.6% specificity), and 0.965 for plasma PQ concentration (89.1% sensitivity and 93.2% specificity). Pairwise comparison using Hanley and McNeil method (Fig. 1) showed that the predictive power of AG was lower than that of plasma PQ concentration ($Z=0.189$; $P=.001$) and similar to that of creatinine ($Z=3.304$; $P=.851$).

Table 1
Clinical characteristics and biologic data at admission of the nonsurvival and survival groups.

	Nonsurvival group (n=64)	Survival group (n=44)	P value
Age, yrs	42.50 (31.75)	32.50 (19.50)	.040
Gender, male/female	27/37	20/24	.737
Time from ingestion to gastric lavage, h	1.00 (1.00)	1.00 (0.88)	.691
Time from ingestion to hemoperfusion, h	2.50 (1.50)	2.50 (0.50)	.504
Alanine aminotransferase, IU/L	32.65 (16.93)	26.55 (9.88)	.004
Creatinine, $\mu\text{mol/L}$	104.00 (69.50)	62.50 (22.00)	<.001
Alveolar oxygen partial pressure, mm Hg	89.82 \pm 10.50	93.87 \pm 8.91	.039
Plasma paraquat concentration, ng/mL	3.65 (8.53)	0.30 (0.75)	<.001
Anion gap, mmol/L	26.53 \pm 4.93	20.88 \pm 2.74	<.001
Na ⁺ , mmol/L	143.35 (5.40)	140.05 (3.23)	<.001
K ⁺ , mmol/L	3.135 (0.94)	3.665 (0.82)	<.001
Cl ⁻ , mmol/L	102.95 (4.08)	101.40 (1.75)	.003
HCO ⁻³ , mmol/L	16.56 \pm 4.51	21.77 \pm 2.64	<.001

Data are reported as mean \pm standard deviation, median (interquartile range) or numbers.

Table 2
Clinical characteristics and biologic data stratified on the basis of AG level at admission.

	AG ≤ 25.5 (n=68)	AG > 25.5 (n=40)	P value
Age, yrs	34.50 (26.50)	41.00 (26.75)	.588
Gender, male/female	27/41	20/20	.297
Time from ingestion to gastric lavage, h	1.00 (0.50)	1.00 (1.38)	.828
Alanine aminotransferase, IU/L	26.35 (9.55)	34.55 (15.03)	<.001
Creatinine, μmol/L	70.00 (27.25)	123.50 (76.50)	<.001
Alveolar oxygen partial pressure, mm Hg	91.31 ± 9.02	91.75 ± 11.70	.826
Plasma paraquat concentration, ng/mL	1.00 (2.58)	3.65 (10.75)	<.001

Data are reported as mean ± standard deviation, median (interquartile range) or numbers.
AG = anion gap, ALT = alanine aminotransferase.

3.5. Kaplan–Meier survival analysis

The Kaplan–Meier curve during the 90-day follow-up period showed that survival was significantly higher in the low AG group than in the high AG group (log rank test, *P* < .001; Fig. 2).

4. Discussion

Patients with PQ poisoning have a low survival rate of 40.74%; thus, accurate prognostic indicators must be identified. Appropriate prognostic indicators can aid physicians in evaluating the severity of poisoning and predicting overall outcomes. Furthermore, the early determination of prognosis can prevent patients with inevitable deaths to undergo inappropriate treatments.

Several parameters have been suggested to predict clinical outcomes after PQ ingestion. Plasma PQ levels are an excellent prognostic indicator for patient outcome.^[10,11] However, most hospitals cannot readily measure plasma PQ levels. Another important predictor of mortality is the oral dose of the poison.^[5] Unfortunately, estimates on the amount ingested are often unobtainable or unreliable in a number of intoxicated patients. The use of Acute Physiology and Chronic Health Evaluation II,^[15,19] Sequential Organ Failure Assessment,^[3] and machine-learning

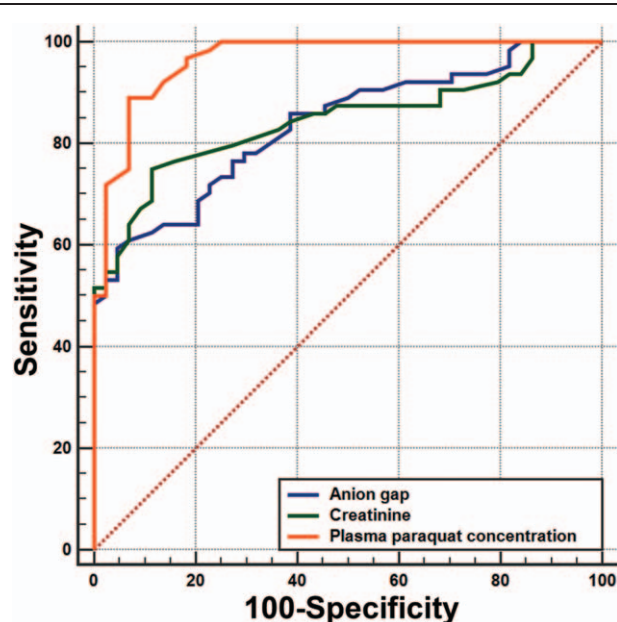


Figure 1. Area under the receiver operating characteristic curve analysis.

methods^[20] to prognosticate patients with PQ poisoning by combining coagulation, liver, and kidney indices can provide a perfect predictive value for the outcome of PQ poisoning. However, many variables are required in using these scores. The extent of lung injury as shown by computed tomography scans and the presence of pulmonary emphysema are also correlated with the prognosis of PQ poisoning.^[21–23] Lung injury in computed tomography scans and pulmonary emphysema may take 24 hours or more to determine; thus, these diagnostic methods would prevent the early application of treatment.

This study examined for the 1st time the predictive value of AG on the 90-day survival of patients with PQ poisoning. Results suggested that elevated AG was present in nonsurviving patients,

Table 3
Cox regression model.

	Univariate Cox model		Multivariate Cox model	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, yrs	1.015 (1.001–1.030)	.032	1.017 (1.001–1.032)	.031
Gender, male/female	0.893 (0.544–1.467)	.655	N/A	
Time from ingestion to gastric lavage	1.035 (0.875–1.224)	.686	N/A	
Alanine aminotransferase	1.021 (1.005–1.038)	.008	N/A	
Creatinine	1.019 (1.013–1.024)	<.001	1.011 (1.004–1.018)	.002
Alveolar oxygen partial pressure	0.977 (0.951–1.003)	.082	N/A	
Plasma paraquat concentration	1.067 (1.048–1.086)	<.001	1.031 (1.009–1.053)	.005
Anion gap	1.152 (1.102–1.206)	<.001	1.067 (1.008–1.128)	.025

CI = confidence interval, N/A = not applicable, OR = odds ratio.

Table 4
ROC curve analysis.

Variable	Area under ROC curve	95% CI	Cut-off	Sensitivity, %	Specificity, %	Youden index
Plasma paraquat concentration	0.965	0.934–0.996	1.55	89.1	93.2	0.823
Creatinine	0.845	0.771–0.919	74.5	75.0	88.6	0.636
Anion gap	0.836	0.763–0.909	25.5	59.4	95.5	0.549

CI = confidence interval, ROC = receiver operating characteristic.

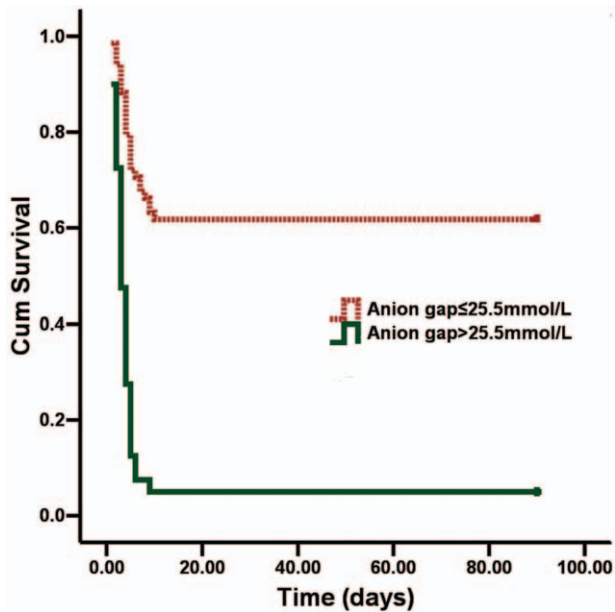


Figure 2. Kaplan–Meier curve analysis of survival curves for the groups stratified according to anion gap level at admission.

and the AUC of AG was 0.836 (95% CI: 0.763–0.909); thus, the diagnostic accuracy of AG was relatively high.

High AG in patients with PQ poisoning possibly has a complicated mechanism. First, an increased amount of lactate acid accounts for a considerable proportion in the increments in AG.^[24,25] Deteriorated circulation^[26,27] is also common in moderate and severe PQ poisoning and causes lactic acid accumulation. Second, kidneys, as the main detoxification organ, encounter extremely high concentrations of PQ during the body's process of eliminating the poison; hence, proximal tubular cells undergo vacuolization, which ultimately results in acute tubular necrosis.^[28] The loss of tubular function decreases the clearance of various organic anions,^[29] and the accumulation of organic anion contributes to the high AG in patients with PQ poisoning.

The limitations of our study must be acknowledged. First, a severely high triglyceride level may underestimate Na^+ and Cl^- concentrations; thus, AG level at admission might also be underestimated. Second, potential residual confounders owing to unavailable information in the dataset used may be present because of the retrospective design of this study. Third, the study was conducted in a single center, and almost the entire population was native. Therefore, the findings may not be generalizable to all countries.

In conclusion, acute PQ poisoning is a highly fatal condition that requires rapid and precise assessment. AG and creatinine can be used as prognosis predictors of PQ poisoning if plasma PQ concentration cannot be determined in real time because of the unavailability of testing materials.

Author contributions

Conceptualization: Yong Zhao, Shun Yi Feng, Yong Li.

Data curation: Yong Zhao.

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Writing – original draft: Yong Zhao.

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