

## **The values of different scoring systems in predicting the prognosis of patients with paraquat poisoning.**

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### **Abstract**

**This study aims to explore the values of different scoring systems in predicting the prognosis of patients with paraquat poisoning, and find out the most clinical application value of indicators. The patients with paraquat poisoning were included and treated in the emergency department from January 2016 to October 2016, every patient was underwent different scoring system, and the Receiver Operating Characteristic (ROC) curve was used to calculate the optimal cut-off value of different scoring system, in order to calculate the sensitivity and specificity of different scoring system to compare the value of different scoring system in predicting the prognosis. The COX mode was used to evaluate the scoring system's relationship with the prognosis of patients with paraquat poisoning. A total of 107 cases were included, and there were 37 cases of death. Every scoring system to predict the value of a poor prognosis in patients with paraquat poisoning was not the same. The sensitivity and specificity of lactic combined with Severity Index of Paraquat Poisoning (SIPP) were 0.900 and 0.741 respectively; it was superior to other scoring system. The results of COX model found that the Risk Ratio (RR) value of lactic combined with SIPP was 12.098 (95% CI: 2.473, 59.178), P value was 0.002, and it was superior to other scoring system. Every scoring system can effectively judge the severe degree of the patients with paraquat poisoning and effective predict the prognosis of patients, and the lactic combined with SIPP is superior to other scoring system.**

**Keywords:** The scoring system, Paraquat poisoning, Prognosis, Value.

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### **Introduction**

Paraquat is a high effective non-contact herbicide. It can take effects faster after spraying, rapidly deactivate into the soil, and it has no residues in the soil. Paraquat has very strong toxicity for human and animals, and it has been common reason for pesticide kill events due to drug misuse or taken oneself that cause acute poisoning, especially in developing countries. In China, there are not official statistical data, but many reports have shown that paraquat poisoning is one of the most common pesticide poisoning. In the emergency department, it has been the second after organophosphorus pesticide poisoning, and is the first in the absolute death in pesticide poisoning [1,2].

Paraquat is the most used defoliant and herbicides in the world wide, and oral lethal dose is 5-15 ml. Paraquat can access human body *via* cutaneous absorption, respiratory inhalation and alimentary canal, and it has obvious local stimulation and corrosive effect. Oral absorption rate of paraquat is 5%-15%, and it can rapidly achieve blood drug concentration peak after it enters into the bloodstream and it does not bind to plasma protein. Plasma concentration of paraquat is gradually reduced after 15-20 h, and it is excluded from the kidneys. Paraquat poisoning is common in emergency department in China, and

its poisoning can involve in many visceral organs, and even lead to multiple organ dysfunction syndrome. The paraquat poisoning mechanism remains unclear. Many studies believe that generated a great amount of oxygen radical can cause lipid peroxidation of cell membranes in tissues after absorption of paraquat, and the phenomenon leads to multiple organ dysfunction, especially for injury of lungs that can cause pulmonary edema and pulmonary fibrosis. In early stage, acute lung injury or acute respiratory distress syndrome can be detected, and alveoli and pulmonary interstitial fibrosis would be detected in later stage that is the cause of the patient's death. The fatality rate of paraquat poisoning is near 50-70% [3,4]. Many studies have shown that paraquat poisoning can significantly increase expression of some cell factors and inflammatory factors, such as Tumor Necrosis Factor-alpha (TNF-alpha), Interleukin 6 (IL-6) and Interleukin 10 (IL-10), but inhibit antioxidant factors, such as Superoxide Dismutase (SOD), which further accelerate occurrence and development of pulmonary fibrosis [5-9]. Paraquat lethal dose is low, and paraquat poisoning can cause a very high case fatality rate. However, effective and specific treatment methods lack in clinic, no effective detoxification medicine is found and many treatment methods are explored, and all of these bring great challenges for emergency medical workers. In America,

paraquat has been the first pesticide type with absolute number of pesticide poisoning death [10], and paraquat has been avoided to use in Europe in 2007 due to intense toxicity and high fatality rate [11-13].

Early accurate evaluation of prognosis can contribute to adopt timely and effective therapeutic measure to reduce mortality [14,15]. Currently, there are many indexes to predict prognosis of patients with paraquat poisoning in clinic, but different indexes have various clinical application values. This study aims to discuss the potential application values of different scoring systems, and to search the potential index with the most clinical application value.

## Materials and Methods

### Subjects

Patients with paraquat poisoning were collected in emergency department in our hospital from January 2016 to October 2016. The Early Warning Score (EWS) is a simple physiological scoring system suitable for bedside application. The ability of a modified Early Warning Score (MEWS) to identify medical patients at risk of catastrophic deterioration in a busy clinical area was investigated. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is a scoring system based on 12 parameters of acute physiology and chronic health. This scoring system has been commonly used for the assessment of the severity and prognosis of diseases, especially in intensive care units. Data of indexes used in APACHE II, EWS and MEWS scoring systems were complete when patients were hospitalized, including heart rate, systolic pressure, respiratory rate, body temperature, and conscious state. Data used in SIPP score were complete, including course of disease (unit: hour) and concentration of paraquat (unit: mg/L); concentration of blood lactic acid (unit: mmol/L). The inclusion criteria were: 1) patients had obvious clinical diagnosis of paraquat poisoning based on history of poison and clinical features, and patients accorded with diagnostic criteria of modern diagnosis and treatment of acute poisoning; 2) ages of patients were more than 14 y old; 3) patients were first confirmed cases in our hospital, and they had not history of gastric lavage, hemodialysis, and special treatment; 4) patients were excluded if they had other kinds of drug poisoning, they died within 24 h after hospitalized, or they had a history of severe liver and brain diseases. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of West China Hospital of Sichuan University. Written informed consent was obtained from all participants.

### Selection of parameters

Different indexes used in scoring systems were collected, including heart rate, blood pressure, respiratory rate, body temperature, conscious state, prognostic outcomes (death or survival), course of disease (h), concentration of paraquat (mg/L) and concentration of blood lactic acid (mmol/L). Died patients were recorded, discharged patient were telephone

follow-up, and mortality was used to as prognostic indicator in 60 d after poisoning.

ROC curve was used to the optimal cut-off value in estimate every scoring system (including lactic acid, SIPP, acute physiology and chronic health evaluation II (APACHE II), EWS, MEWS, lactic acid+SIPP, lactic acid+APACHEII, lactic acid+EWS, lactic acid+MEWS, lactic acid+APACHEII+SIPP+EWS, and lactic acid+APACHEII+SIPP+MEWS). Every set of data were changed to two-category data, which was used to estimate sensitivity and specificity of different scoring systems in predicting poor prognosis in patients with paraquat poisoning.

COX proportional hazard model was performed in survival analysis as semi-parameter model, and it could reflect hazard rate function at t time when response variable was i. Basis COX model was constructed, including age, sex, and conscious state. Finally, a set of variable of above mentioned 11 variables was added in COX model in turn, and relevant statistical indexes were collected.

### Statistical analysis

Data analysis was performed with SAS 9.4 and SPSS 20.0 software. Measurement data were described using, enumeration data were described using rate or ratio, and  $P < 0.05$  was considered as statistical difference.

## Results

### The basic characteristics of patients

A total of 107 patients were collected in this study (age:  $34.36 \pm 13.06$ ). There were 37 died patients among the total 107 patients. Concentration of blood paraquat was  $46.892 \pm 75.328$  mg/L, and course of disease was  $17.71 \pm 44.69$  h in the death patients. One hundred patients were survival ( $26.56 \pm 12.01$ ), and concentration of blood paraquat was  $3.363 \pm 9.780$  mg/L, and course of disease was  $18.69 \pm 26.00$  h (Table 1).

**Table 1.** The basic characteristics of patients.

Variable	Patient outcomes	
	Survival	Death
Age (year)	$26.56 \pm 12.01$	$34.36 \pm 13.06$
Lactic acid (mmol/L)	$2.04 \pm 1.05$	$7.87 \pm 5.26$
Concentration of blood paraquat (mg/L)	$3.363 \pm 9.780$	$46.892 \pm 75.328$
Course of disease (h)	$18.69 \pm 26.00$	$17.71 \pm 44.69$
Temperature (°C)	$36.83 \pm 0.69$	$37.08 \pm 0.81$
heart rate (times/min)	$85.86 \pm 18.09$	$90.14 \pm 22.87$
Rebreather (times/min)	$19.97 \pm 2.29$	$20.88 \pm 3.47$
Systolic pressure (mmHg)	$118.42 \pm 15.91$	$122.45 \pm 24.52$

Diastolic pressure (mmHg)	74.03 ± 11.99	74.18 ± 17.71
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**Comparisons of the optimal cut-off value, sensitivity and specificity**

As shown in Table 2, lactic acid had significant advantage in prediction of poor prognosis in single index rating system, and the optimal cut-off value was 2.8 mmol/L, the relevant sensitivity and specificity were 0.875 and 0.690, respectively. In joint index rating system, lactic acid+SIPP had obvious advantage, and the optimal cut-off value was 0.212 mmol/L, the relevant sensitivity and specificity were 0.900 and 0.714, respectively (Table 2).

**Table 2.** The optimal cut-off value, sensitivity and specificity in Receiver Operating Characteristic (ROC) curve of each scoring system.

Variable	Cut-off value	Sensitivity	Specificity
Lactic acid	2.8	0.875	0.69
SIPP	25.25	0.719	0.783
APACHEII	7.5	0.757	0.493
EWS	3.5	0.459	0.62

**Table 3.** Relationship of scoring system and prognosis of patients using COX model.

Variable	B	SE	Wald	RR (95% CI)	P
Lactic acid	2.182	0.654	11.142	8.866 (2.462,31.931)	0.001
SIPP	1.522	0.499	9.294	4.581 (1.722,12.185)	0.002
APACHEII	0.645	0.421	2.344	1.905 (0.835,4.348)	0.126
EWS	0.279	0.359	0.602	1.321 (0.654,2.670)	0.438
MEWS	0.375	0.416	0.814	1.455 (0.644,3.286)	0.367
Lactic acid+SIPP	2.493	0.81	9.475	12.098 (2.473,59.178)	0.002
Lactic acid+APACHEII	1.31	0.521	6.321	3.705 (1.335,10.287)	0.012
Lactic acid+EWS	2.248	0.651	11.908	9.470 (2.641,33.954)	0.001
Lactic acid+MEWS	2.182	0.654	11.142	8.866 (2.462,31.931)	0.001
Lactic acid+APACHEII+SIPP+EWS	2.405	0.707	11.567	11.082 (2.771,44.319)	0.001
Lactic acid+APACHEII+SIPP+MEWS	2.405	0.707	11.567	11.082 (2.771,44.319)	0.001

SIPP: Severity Index of Paraquat Poisoning; APACHE II: Acute Physiology and Chronic Health Evaluation II; EWS: Early Warning Score; MEWS: Modified Early Warning Score.

**Discussion**

This study aims to discuss relationship of different scoring system and prognosis of patients with paraquat poisoning using COX model. We found that different scoring systems can effectively estimate severity levels of patients and predict prognosis of patients, and usage of lactic acid+SIPP has significant advantage than other scoring systems.

MEWS	2.5	0.73	0.366
Lactic acid+SIPP	0.212	0.9	0.714
Lactic acid+APACHEII	0.291	0.75	0.714
Lactic acid+EWS	0.267	0.875	0.714
Lactic acid+MEWS	0.255	0.875	0.69
Lactic acid+APACHEII+SIPP+EWS	0.348	0.75	0.771
Lactic acid+APACHEII+SIPP+MEWS	0.348	0.75	0.771

SIPP: Severity Index of Paraquat Poisoning; APACHE II: Acute Physiology and Chronic Health Evaluation II; EWS: Early Warning Score; MEWS: Modified Early Warning Score.

**Relationship of scoring system and prognosis using COX model**

As shown in Table 3, in single index rating system, there was a strong relationship between lactic acid and poor prognosis after avoiding effects of other factors, and the Risk Ratio (RR) values were 8.866 (95% CI: 2.462, 31.931, P=0.001) (Table 3). In joint index rating system, lactic acid+SIPP and poor prognosis had strong correlation, and the RR values were 12.098 (95% CI: 2.473, 59.178, P=0.002) (Table 3).

EWS as an important evaluation tool in emergency treatment, it has been widely applied to estimate various kinds of emergency and severe cases, and its scores have close association with prognosis of patients [20-22]. Increased score needs increased medical intervention, but mortality risk also increases during hospitalization. Studies have shown that increased concentration of paraquat in blood and urine leads to higher fatality, and some researchers proposed that SIPP and urine paraquat poisoning severity index are used to predict severity of patients [23,24]. Of these, SIPP=plasma concentration of paraquat when admitted  $\times$  poisoning to admission time, larger SIPP value means poorer prognosis of patients. However, it is not widely applied in clinic because detection of plasma concentration of paraquat has higher requirements. Improved early warning score is a scoring system based on blood pressure, heart rate, respiratory rate, temperature and consciousness, and it has been widely applied in emergency department and intensive care unit in developed countries due to data are easy to get and calculation is quick and convenient [25]. Higher MEWS scores indicate heavier illness and higher fatality rate. Changes of these indexes contribute to effective intervene and treatment, which has significant clinical significance for reducing fatality rate and improving rescue success rate. Lactic acid detection and APACHEII score may be simple and practical tools to predict the prognosis of paraquat. Liang et al. [26] showed that the cut-off value of lactic acid was  $\geq 2.75$  mmol/L when patients were admitted to the hospital, sensitivity and specificity were 0.818 and 0.667, respectively, Youden index was 0.485, and sensitivity and specificity of APACHEII were 0.864 and 0.778, respectively, Youden index was 0.642. There are many indexes to predict prognosis of patients with paraquat poisoning, and these indexes have different values based on different clinical application. In order to survey the best and most clinical application value scoring system, we constructed COX model based on age, sex and conscious state to discuss predictive values of single scoring system and combined scoring system using patients in our hospital.

Acidosis is an important factor influencing the prognosis of paraquat poisoning due to paraquat can damage mitochondrial DNA and further influence relevant respiratory chain peptides. After mitochondria damage, pyruvic acid (metabolic product of glycolysis) forms lactic acid *via* Lactate dehydrogenase catalysing in cytoplasmic matrix, and simultaneously inhibits lactic acid oxidation and sugar dysplasia, reduces lactic acid removal rate and leads to higher level of serum lactic acid [16-18,27,28]. Arterial blood lactate has higher value to evaluate prognosis, and positive correlation has been validated between serum lactic acid level and SIPP (higher SIPP leads to higher serum lactic acid level) [29,30]. In this study, we found that lactic acid has significant advantage in single index scoring system (the optimal cut-off value is 2.8 mmol/L, sensitivity and specificity are 0.875 and 0.69, respectively). In combined index scoring system, lactic acid+SIPP also shows obvious advantage: the optimal cut-off value is 0.212 mmol/L, sensitivity and specificity are 0.900 and 0.714, respectively. Stronger correlation can be detected between lactic acid and

poor prognosis of patients with paraquat poisoning in single index scoring system after excluding effects of other factors, and RR value is 8.866 (95% CI: 2.462, 31.931). Similarly, stronger correlation can be detected lactic acid+SIPP and poor prognosis in combined index scoring system, and RR value is 12.098 (95% CI: 2.473, 59.178). The level of blood lactic acid was positively related to other system score. It plays an important role in judging the conditions and prognosis of paraquat poisoning patients admitted to hospital.

Taken together, combined lactic acid and SIPP may be the best selection due to its obvious advantage. Due to higher requirements of detection of paraquat concentration, lactic acid is the best choice because technique is difficult to achieve. Changes of serum lactic acid have higher value to infer severity and prognosis for acute paraquat poisoning patients. The potential mechanism of increased lactic acid may be damaged cell mitochondria and activated systemic inflammatory response by paraquat, and oxygen supply and demand imbalance after severe poisoning can aggravate formation of lactic acid. However, due to small sample size in this study, further studies should be performed to validate it using larger sample sizes.

## Conflicts of Interest

The authors declare no conflict of interest.

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