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Prognostic Value of White Blood Cell Count, C-reactive protein, and Pentraxin-3 Levels in Patients with Acute Paraquat Poisoning

Yu Zhang, Hui Sun and Li Jiang*

First affiliated hospital of Dalian Medical University, China

***Corresponding author:** Li Jiang, Department of Emergency Medicine, First Affiliated Hospital of Dalian Medical University, Tel: +86041183622841; **E-mail:** fangrong928@163.com

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Abstract

Objective: To assess the prognostic value of white blood cell (WBC) count, C-reactive protein (CRP), and pentraxin-3 in patients with acute paraquat poisoning.

Methods: The study was performed on patients presenting in the emergency room with history of oral ingestion of paraquat. Blood samples of were tested for WBC count, CRP and pentraxin-3 levels at day 0, 1, 2, and 3 of hospital stay. Survival or non-survival during the hospital stay was recorded. Statistical analyses were performed to compare the levels of these biomarkers between survival and non-survival groups. Prognostic value of these biomarkers was assessed with Receiver operating characteristic (ROC) curve analysis.

Results: 58 patients were enrolled in the study. Serum levels of all three biomarkers were higher in the non-survival group as compared to that in the survival group. WBC count tended to increase rapidly in the early phase after poisoning, whereas the increase in CRP and pentraxin-3 levels was relatively delayed. The earliest time when these biomarker levels could be used to predict survival was on day 1 of hospital stay, with serum pentraxin-3 levels observed to be the strongest predictor of in-hospital mortality.

Conclusions: White blood cell count increased rapidly after acute paraquat poisoning. Pentraxin-3 appeared to have the best predictive value for in-hospital mortality.

Keywords: Paraquat poisoning; White blood cell count; C-reactive protein; Pentraxin-3

Introduction

Paraquat (N,N′-dimethyl-4,4′-bipyridinium dichloride) is an organic compound that is widely used as a herbicide. Though paraquat poisoning occurs less frequently when compared to organophosphate poisoning, studies have demonstrated paraquat poisoning to be the leading cause of death due to herbicide poisoning, in both the developing and developed countries [1,2].

Although paraquat poisoning can occur after skin exposure or inhalation, accidental or deliberate oral ingestion is known to be the commonest route. Paraquat poisoning may result in renal insufficiency, respiratory distress, hemodynamic instability, hepatic failure, and central nervous systemic disorders [3]. The diagnosis of paraquat poisoning is usually based on the history of paraquat exposure. Laboratory assay for the detection of paraquat in the blood is not commonly available in most hospitals [4]. Most diagnostic studies are focused on the evaluation of organ function [5].

There is no specific antidote available for paraquat poisoning. Treatment in acute phase usually involves decontamination (washing skin in patients with skin exposure, and administration of activated charcoal or Fuller's earth in patients with oral ingestion), hemodialysis or hemoperfusion to enhance elimination, and, supportive care to maintain organ function (intravenous fluids, cardiovascular medications, mechanical ventilation) [6]. The most common cause of death during acute poisoning is respiratory failure (acute respiratory distress syndrome, ARDS). If patients survive the acute phase, most common long-term outcome is lung fibrosis [7].

Since there is no effective antidote for acute paraquat poisoning, various treatment modalities, including early hemoperfusion, may not effectively prevent death [8]. Early identification of patients at high-risk of severe outcomes and who require aggressive end organ supportive care is important to improve the outcomes. In cases of oral poisoning, the volume of ingested paraquat directly correlates with disease severity and mortality rate [9,10]. However, the reported volume of paraquat ingested tends to be unreliable [11]. As blood or urine tests to detect paraquat quantitatively are not commonly available in most hospitals, identification of prognostic markers, which correlate with the disease severity and patient outcomes, are required.

Studies have examined different markers to predict organ failure and mortality rate in patients with acute paraquat poisoning. Several clinical data (such as patient demographics and vital signs) and laboratory tests for organ function have been studied [5,12]. However, these clinical markers or laboratory tests tend to be influenced by other factors and, thereby, may show considerable variability. Several models for predicting patient mortality have been studied; [10,13,14] however, these models are usually too complex to be used at the bedside. Recent studies have suggested a potential utility of inflammatory biomarkers for predicting disease severity and outcomes in patients with acute paraquat poisoning [11,15,16].

Systemic inflammation and production of reactive oxygen species through redox cycling is the main pathway leading to multi-organ failure in patients with paraquat poisoning [17]. Suppression of inflammatory response has been considered as an approach for amelioration of disease

severity and to prevent death [18,19]. Serum levels of several acute-phase reactive proteins such as, pentraxin-3 and C-reactive protein (CRP) have been shown to be of prognostic value in some studies [11,15,16]. However, due to the relative paucity of such studies, further studies are required to confirm their results. In addition, these studies assessed only a single biomarker, with no head-to-head comparison of the different laboratory parameters.

In the current study, we assessed the white blood cell (WBC) count, pentraxin-3, and CRP levels in patients with acute oral paraquat poisoning, and compared the levels of these biomarkers between survivors and non-survivors, at different time points of hospitalization, to determine their prognostic value.

Materials and Methods

Study design and patient selection

The present study was a prospective observational study performed at the emergency room and intensive care unit at the First Affiliated Hospital, Dalian Medical University, China, between March, 2012 and January, 2014. The study protocol was approved by the institutional ethics committee at our hospital. Informed consent was obtained from the patients or their family members. The inclusion criteria were: 1) oral ingestion of paraquat; 2) positive urine paraquat qualitative test; 3) less than 12 hours elapsed since oral ingestion of paraquat at admission. The exclusion criteria were: 1) co-poisoning with other substances; 2) presence of other inflammatory conditions such as sepsis, viral or bacterial infections and chronic connective tissue disorders; 3) history of cardiac, pulmonary, liver, or renal disease; 4) length of stay <24 hours after hospital admission (Table 1).

Study protocol

All patients enrolled in the study immediately received standard treatment, according to pre-written acute paraquat poisoning treatment protocol, at the time of admission at our emergency department. This included gastric lavage (if presenting <6 hours after oral ingestion); catharsis; antioxidants (vitamin C, vitamin E, and glutathione); high-dose glucocorticoids, antiadrenergic agents (propranolol); and hemoperfusion therapy immediately following hospital admission, and continued twice a day for 3 days). Patients were followed up until hospital discharge or death.

Data collection

Patients' age, gender, time period between oral ingestion and gastric lavage, and outcomes (survival or non-survival) during hospital stay were recorded. Laboratory testing for white blood cell (WBC) count and serum levels of CRP and pentraxin-3 were performed at day 0 (at admission), 1, 2, and 3. WBC count and serum CRP levels were tested as per the standard hospital laboratory protocol. The blood samples for determining pentraxin-3 levels were collected in ethylenediaminetetraacetic acid (EDTA), the plasma separated and stored at -80°C until further processing. Serum pentraxin-3 levels were determined by enzyme linked immunosorbent assay (ELISA) (Shanghai Xinyu Biotechnology Co., Ltd, Shanghai, China) as per the manufacturer's protocol.

Table 1: Exclusion criteria by study group

Cause	Definite cause	Number of patients	total
co-poisoning with other substances	Co-sedative poisoning	6	69
	Co-organophosphorus poisoning	3	
	Co-raticide poisoning	4	
length of stay <24hours after hospital admission	Death during 24 hours	12	
	Withdraw from hospital during 24 hours	15	
history of cardiac, pulmonary, liver, or renal disease	Cardiac history	1	
	Pulmonary history	2	
	Liver history	4	
	Renal history	8	
others	Viral infection	2	
	Bacterial infection	3	
	chronic connective tissue disorders	9	

Data analysis

Patients were categorized into survival and non-survival groups. Baseline characteristics and the time period between ingestion and gastric lavage were compared using Chi-square test, Bonferronit-test, or Mann-Whitney test, as applicable. WBC count, CRP, and pentraxin-3 levels were compared between the two groups at day 0, 1, 2, and 3, by Bonferroni t-test or Mann-Whitney test, after assessing the distribution and variance. Receiver operating characteristics (ROC) curve analysis was used to determine the area under the curve (AUC) for the three markers at day 0,1,2, and 3 of hospital stay. The best cut-off values were determined by calculating the Youden index. All statistical analyses were performed using SPSS statistical software (version 19.0, Microsoft, U.S.A); Inter-group differences with associated P value of <0.05 were considered to be statistically significant.

Results

58 case from total of 127case paraquat poisoning patients (age: 35 (18 ~ 50) years old) of whom 29 (50%) were men, were enrolled in the study. Mean survival in the non-survival group was 5 ± 2 days. No statistically significant differences were observed between the two groups with respect to age or gender distribution, and the time period between oral paraquat ingestion and gastric lavage (Table 2).

White blood cell count, C-reactive protein, and pentraxin-3 levels at different time points As compared to the survival group, the non-survival group was associated with significantly higher WBC count, C-reactive protein, and pentraxin-3 levels at day 0, 1, 2, and 3. The only exception pertained to the WBC count at day 3, which did not significantly differ between the two groups (Figure 1). WBC count was highest at day 0 followed by a decrease. Levels of C-reactive protein and pentraxin-3 increased gradually and peaked at day 2 and 3of hospital stay, respectively.

Receiver operating characteristics curve analysis

ROC curve analysis showed that the earliest time when these biomarkers could be used to statistically distinguish between survival and non-survival groups was from day 1 of hospital stay (Table 3, Figure 2A). At day 1of hospital stay, AUC of pentraxin-3 (0.73, 95% Confidence Interval [CI] 0.61-0.81) was higher than that of WBC count (0.68, 95% CI 0.56-0.83) and CRP (0.70, 95% CI 0.61-0.82) (Table 3). The optimal cut-off values for WBC count, CRP, and pentraxin-3 were 14.4 (sensitivity 63.4%, specificity 72.8%, Youden index 0.36); 17.1 (sensitivity 68.5%, specificity 70.7%, Youden index 0.39); and 8.9 (sensitivity 67.7%, specificity 76.1%, Youden index 0.44), respectively (Figure 2B).

Table 2: Baseline characteristics by study group

Characteristics	Survival group (N=27)	Non-survival group (N=31)	P
Gender (M/F)	15/12	14/17	> 0.05
Age (year)	32.1 ± 13.9	37.2 ± 13.4	> 0.05
Hospital stay(day)	6.2 ± 3.6	5.7 ± 3.2	>0.05
Time period between ingestion and gastric lavage (hour)	3.0 ± 1.2	3.6 ± 1.4	> 0.05

Table 3: ROC curve analysis: Area under the curve at different time-points

	Area under the curve (95% confidence interval)			
	Day 0	Day 1	Day 2	Day 3
C-reactive protein	0.63 (0.37, 0.89)	0.70 (0.61, 0.82)*	0.64 (0.53, 0.73)*	0.58 (0.50, 0.68)*
Pentraxin-3	0.48 (0.15, 0.82)	0.73 (0.61, 0.81)*	0.71 (0.60, 0.79)*	1.68 (0.56, 0.75)*
White blood cell count	0.76 (0.57, 0.95)	0.68 (0.56, 0.83)*	0.49 (0.17, 0.81)	0.41 (0.05, 0.77)

*$P < 0.05$

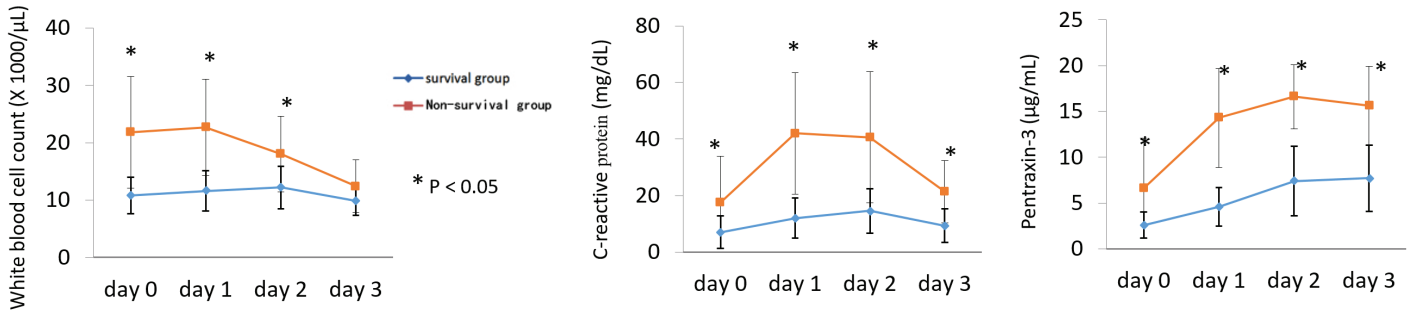

Figure 1. Comparison of white blood cell count, C-reactive protein, and pentraxin-3 levels in the survival and non-survival groups at different time-points

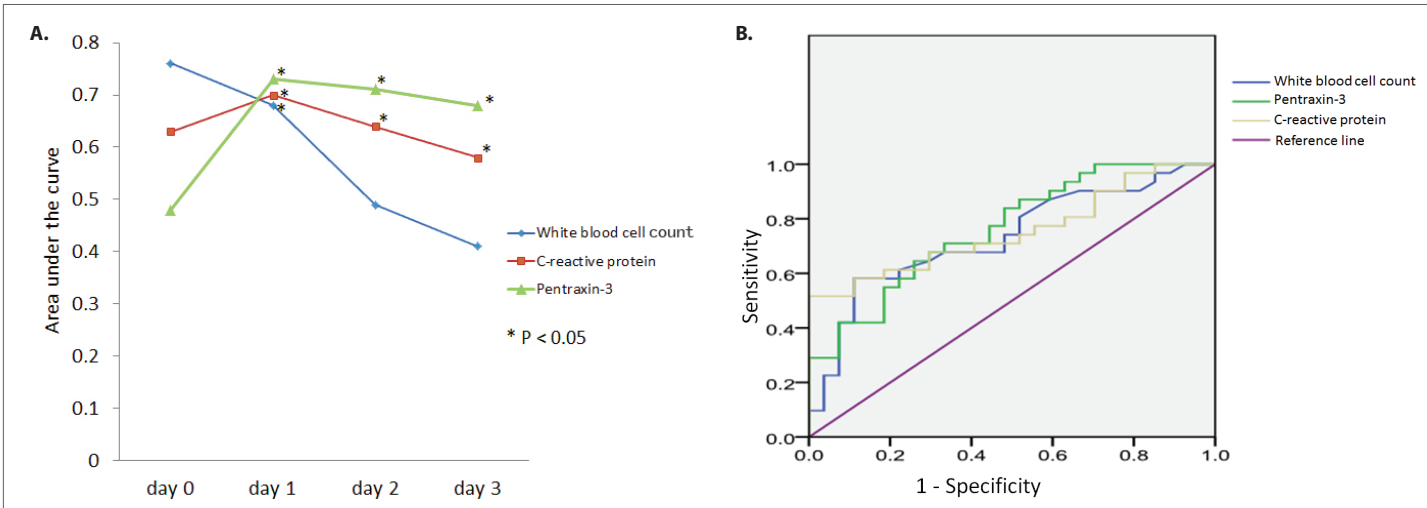

Figure 2: ROC curve analysis for prognostic value of WBC count, CRP, and pentraxin-3 levels. **A.** Area under the curves at different time-points. **B.** ROC curves at hospital day 1

Discussion and Conclusion

In this study, the WBC count, CRP, and pentraxin-3 levels were higher in the non-survival group as compared to that in the survival group in patients with acute oral paraquat poisoning. WBC count increased rapidly after poisoning, which was subsequently followed by a rapid fall. C-reactive protein and pentraxin-3 levels increased relatively slowly but their high levels persisted for days. The earliest time point at which statistical prediction of survival was possible was at day 1of hospital stay, with serum pentraxin-3 level carrying the highest predictive value for in-hospital mortality.

Paraquat is highly toxic to humans with oral ingestion being the most common route of acute poisoning. Pharmacokinetic studies have shown a 5-15% absorption rate after oral ingestion and that the peak serum concentration is reached in 1-4 hours of ingestion.6 Majority of paraquat is eliminated through the kidneys without undergoing metabolism within 12-24 hours of ingestion.20 The median lethal dose (LD50) for paraquat is considered to be 30-50 mg/kg; however, clinical estimation of the ingested volume is typically unreliable. Hence, other clinical or laboratory markers are needed to identify patients who are at a high-risk for mortality so that immediate aggressive treatment can be instituted. Paraquat poisoning is associated with inflammatory damage and treatment to suppress the inflammatory process have been tried to improve the survival rate. Inflammatory markers may prove to be useful in identifying patients with poor prognosis.

These stimuli may include infectious pathogens, injured cells or tissue, and physical or chemical irritants. Once the body is exposed to these stimuli, an acute immune response involving a cascade of reactions, that include cell and fluid migration, cytokine release, and vascular dilation, may develop. The intensity of this reaction usually correlates with the severity of the inflammation. For example, WBCs play an important role in the immune response. During the acute phase of inflammation, the initial response includes the release of WBCs from their reservoirs, including spleen and lung, and migration of these cells towards the stimuli or injured tissues. This manifests as an early increase in white blood cell count. The increase in WBC is known to correlate with the extent of the inflammatory reaction [21].

C-reactive protein is a member of the family proteins which function as acute phase reactants. It is produced in the liver, mainly in response to interleukin-6. It is a highly sensitive inflammatory marker, but carries low specificity, since its level usually increases in response to several inflammatory conditions, such as infection, trauma, ischemia, cardiovascular disease, and autoimmune disease [22]. Due to the lack of specificity, high CRP levels should be interpreted in the clinical context.

Pentraxin-3 is a relatively newly identified inflammatory marker produced by endothelial cells, neutrophils, mononuclear phagocytes, and dendritic cells, in response to stimulation by interleukin-1β, tumor necrosis factor-α, and other inflammatory signals [23]. Since the production of both C-reactive protein and pentraxin-3 is stimulated by other cytokines, there may be a short delay before their levels rise.

Acute paraquat poisoning is systemic infectious response syndrome (SIRS). So the several inflammatory mediators are the peak at 12-24 hours. So, WBC count, CRP, pentraxin-3 were significant raised at day 1.

Several pre-clinical studies and clinical investigations have shown a correlation of the peripheral WBC count with disease severity as well as prognosis after acute paraquat poisoning [15,24]. Increased WBC counts were shown to be associated with a higher risk of multi-organ failure and mortality [25]. In the present study, WBC counts at admission (Day 0) were higher in the non-survival group as compared to that in the survival group, but the levels rapidly decreased thereafter. At day 3 of hospitalization, the levels were not found to be statistically different between non-survival and survival groups. This suggests that WBC count at the time of hospital admission might be useful as an early marker of severe disease. However, the prognostic values of WBC count decreases once the treatment is instituted.

Our results showed that the patients in the non-survival group had significantly higher CRP levels as compared to that in the survival group, at all times points. Unlike WBC count which appeared to peak at day 0, peak CRP levels were observed at day 1. C-reactive protein is secreted by the hepatic cells on stimulation by other early inflammatory cytokines, such as interleukin-6, which may explain the relative delay in the increase of CRP levels. Future studies focusing on the early inflammatory cytokines, such as interleukin-6, may help in identifying patients with severe poisoning at the time of admission.

Mauri et al. [26] demonstrated a correlation between serum levels of pentraxin-3 and pulmonary function as well as the extent of multi-organ damage in patients with ARDS, which is the most common cause of death in patients with acute paraquat poisoning. In the present study, the level of pentraxin-3 was significantly higher in the non-survival group as compared to that in the survival group. However, unlike CRP levels, which attained peak level at day 1of hospital stay, pentraxin-3 level showed a more gradual increase and reached peak level on day 2 of hospital admission. Pharmacokinetic studies have shown that a major proportion of paraquat is eliminated through the kidneys without undergoing metabolism within the first 12-24 hours of ingestion. Generally, by day 2 of hospital admission, patients have already received treatment, such as catharsis, antioxidants (vitamin C, vitamin E, and glutathione), high-dose glucocorticoids, and hemoperfusion. The fact that pentraxin-3 level was still found to be increased at day 2 suggests that inflammatory reaction persists, or even escalates, even after removal of paraquat and suppression of inflammatory response. These persistently high levels of inflammation appear to have contributed to the patient's death. This is also consistent with findings from an earlier study which showed that patients with early hemoperfusion therapy still had high mortality rate [8,27]. Future treatment should be targeted not only to remove paraquat but also to suppress inflammatory response in order to improve the survival rate.

Our results demonstrated that the levels of all three inflammatory biomarkers increased after acute paraquat poisoning. This is consistent with the previous findings that inflammatory process is involved in the pathophysiology of paraquat poisoning. Our results also showed that the levels of inflammatory biomarkers, such as CRP and pentraxin-3, increased even after treatment. These findings suggest that instituting treatment to remove paraquat by gastric lavage, catharsis, and hemoperfusion, and administering immunosuppressant's, such as glucocorticoids, might not be enough to significantly improve the survival rate. Our hospital's paraquat poisoning treatment protocol did not include the recently proposed aggressive immunosuppressive regimen consisting of glucocorticoids and cyclophosphamide treatment, which has been shown to improve survival in several small randomized clinical trials [28]. Further studies to investigate the prognostic role of various inflammatory biomarkers should be performed in patients receiving aggressive immunosuppressive regimen.

In the current study, we also calculated the AUC on ROC curves to compare the prognostic value of WBC, CRP, and pentraxin-3 levels. At the time of initial presentation at the emergency room, even if all of these three markers had statistically higher levels in the non-survival group as compared to that in the survival group, they did not show statistically significant AUC values. This suggested that initial testing for these markers at the time of admission could not identify patients at high risk of in-hospital mortality. However, at day 1 of admission, all three markers were associated with statistically significant AUC values, suggesting that they could all be used to predict survival. Among these three markers, pentraxin-3 appeared to be the best marker to predict mortality since it was associated with the highest AUC value.

Our study had several limitations. We performed the study in a single hospital and therefore, the results might not be applicable to other hospitals with different clinical settings. All patients were treated as per our hospital's acute paraquat poisoning treatment protocol, which may not be identical to those used in other hospitals. In addition, the treatment protocol itself might have influenced the levels of biomarkers. We only observed a small group of 58 patients and followed their disease course during their stay in the hospital. Our results may not be applicable for predicting long-term outcomes in patients with paraquat poisoning. Furthermore, only those patients presenting in the emergency room within 12 hours of oral paraquat ingestion were included in the study. Therefore, the results of our study may not be representative of patients with delayed hospital admission, or those with other routes of poisoning.

In conclusion, we studied three biomarkers WBC count, CRP, and pentraxin-3 levels, in patients with acute paraquat poisoning. WBC count increased earlier than the other two biomarkers. Pentraxin-3 demonstrated the best predictive value for in-hospital mortality. In patients with persistently high pentraxin-3 levels, more aggressive treatment may help improve survival rate.

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