Analysis of Prognostic Factors in Patients with Paraquat Poisoning for Better Therapy Regimen

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Abstract

Background

Paraquat poisoning is associated with very high mortality rate and extremely difficult to manage due to lack of antidotes. The purpose of this study was to identify prognostic factors after paraquat poisoning and discuss the efficacy of current therapy regimen.

Methods

In this retrospective study, 211 paraquat poisoning cases admitted to the First Affiliated Hospital, School of Medicine, Zhejiang University between 1 June 2010 and 30 April 2016 were enrolled. The demographic characteristic, medical records of clinical features, laboratory parameters, therapy regimen and the prognosis were analyzed.

Results

The overall survival rate was 55.45%. the mean age was 35.85 years old. Twelve patients who ingested paraquat combined with alcohol had a higher survival rate. The patients in survival group ingested less amount of paraquat, presented with lower serum creatinine level at admission, developed lower incidence of acute kidney injury and pulmonary CT deterioration. The survivors were treated with higher dosage of methylprednisolone, daily dose of aspirin, daily dose of rapamycin and lower dose of vitamin C. The frequency of hemoperfusion was much more in the survival group. The Cox regression survival analysis demonstrated larger amount of paraquat ingestion, abnormal renal function at admission or developing acute kidney injury (AKI) after admission were independent risk factors for mortality. Higher dose of methylprednisolone and aspirin were independent protective prognostic factors.

Conclusions

Non-survivor characteristics are larger amount of paraquat ingestion, manifestation of abnormal renal function at admission or developing AKI after admission, whereas the survivor characteristics are higher dose of methylprednisolone and aspirin.

Introduction

Paraquat (N, N-dimethyl-4, 4'-bipyridinium dichloride; PQ) is a widely used herbicide in developing countries for weed elimination. It exerts herbicidal activity through redox-cycling and leads to formation of reactive oxygen species (ROS). ROS interacts with the unsaturated lipids on cellular membranes, resulting in destruction of plant organelles and inevitably leading to cell death[1].

However, PQ has been demonstrated to be highly toxic to human and animal, and PQ poisoning accounts for a high mortality rate each year either by accidental or intentional exposure for suicide[2, 3]. PQ enters into the body mainly by ingestion, dermal exposure or inhalation. Even a teaspoon of concentrated PQ can result in death, which is usually due to respiratory failure within days up to a month after exposure. Besides the lung, PQ also damages the kidneys, liver, heart and central nervous system and leads to multiple organ dysfunction[4, 5].

Unfortunately, there are neither effective antidotes nor widely accepted guidelines for treatment of PQ poisoning up till now. The therapy regimen varies from supportive care alone to various combinations of glucocorticoid, cyclophosphamide, anti-oxidants and immunosuppression therapy [6, 7]. The activated charcoal hemoperfusions are used to increase the elimination of PQ from plasma [8–11]. Even though, the overall mortality rate are still higher than 50%, ranging from 60–80%[12, 13].

Therefore, more effective therapies are urgently required. Although researchers have been dedicated to exploring new insights from numerous animal studies, conclusions from large sample clinical studies are more practical. Due to the difficulty of designing perspective clinical trials in suicide population, this retrospective study enrolled 211 PQ poisoning patients in the aim of identifying prognostic factors and determining the efficacy of therapy regimen from one single center in China.

Materials And Methods

Ethics statement

This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (Reference Number 2016 – 273). Because all information obtained from the medical records was kept confidential, the review board of the Ethics Committee stated that written consent from patients was not required. The study was conducted according to the principles expressed in the Declaration of Helsinki. Authors had access to information that could identify individual participants during or after data collection.

Study population

Between 1 June 2010 and 30 April 2016, there were 224 PQ poisoning patients admitted to the medical wards of the First Affiliated Hospital, School of Medicine, Zhejiang University. We excluded eight cases who ate the vegetable or fruits sprayed by PQ and five cases who exposed to PQ by skin accidentally. This retrospective study enrolled 211 patients, they were divided into the survivor group (n = 117) and non-survivor group (n = 94) according to the prognosis (**Fig. 1 Enrollment and grouping of PQ poisoning patients**). The patients were followed up till 30 April 2016.

Clinical variables

Demographic characteristics, the medical records of clinical features (the amount of PQ ingested, whether combined with alcohol drink and time interval from exposure to admission), laboratory

parameters (the blood oxygen saturation, arterial oxygen pressure, serum creatinine level, glomerular filtration rate and serum uric acid level at admission, the variation trend of renal function and pulmonary CT scan), therapy regimen (gastric lavage, frequency of hemoperfusion, dose of cyclophosphamide, methylprednisolone, rapamycin, vitamin C and aspirin) and prognosis (survival and mortality) in 211 patients were retrospectively analyzed. The patients who survived at discharge were followed up by telephone.

Statistical analysis

Results were presented as the mean ± standard deviation and percentage. Chi-square test, Fisher exact test, independent t-tests and Mann-Whitney U tests were used for comparisons between groups where appropriate. The Cox regression survival model was applied to determine the independent prognostic factors. The hazard ratios (HRs) for mortality and 95% confidence intervals (CIs) were calculated. All the data were analyzed by SPSS statistical software (version 16.0; SPSS, Inc., Chicago, IL). All p-values were two-tailed and a p-value < 0.05 was considered significant.

Results

The mean age of 211 cases was 35.85 ± 15.29 (13–83) years-old with 55.45% being female. The average amount of PQ (20% concentration) ingested was 30.79 ± 39.22 (1-300) ml. The average time interval between PQ ingestion and admission was 23.00 ± 35.82 (0.2–240) hours. The overall survival rate was 55.45%. According to the prognosis, we divided the patients into the survivor (n = 117) and the non-survivor (n = 94) group. Till the end of the follow-up, the median survival time was 147 (1-1942) days. The longest survival time in the non-survivor group was 29 days.

Differences between the survivor and non-survivor group

There were no significant differences in the distribution of most baseline variables (the gender, time interval between ingestion and admission, gastric lavage percentage, blood oxygen saturation, arterial oxygen pressure and serum uric acid level at admission) between the two groups. The majority were treated with hemoperfusion, intravenous methylprednisolone (MP), cyclophosphamide (CP) and vitamin C (VC). The pulse use of MP, pulse use of CP and intravenous use of VC in PQ poisoning patients were 97.16%, 82.46% and 93.84%, respectively. In order to block the redox cycling and pulmonary fibrosis, less than 50% patients were treated with oral aspirin (34.12%) and rapamycin (23.70%).

Twelve Patients who ingested PQ combined with alcohol had a higher survival rate (83.33% vs 53.77%, p = 0.045). The patients in the survivor group ingested less amount of PQ, presented with lower serum creatinine level and higher glomerular infiltration rate at admission, developed lower incidence of acute kidney injury and pulmonary CT deterioration. As to the therapy regimen, the survivors were treated with higher dosage of methylprednisolone, aspirin and rapamycin. The frequency of hemoperfusion was more in the survivor group (Table 1).

Table 1
The characteristics of patients with PQ poisoning according to different prognosis

Variable	Survivor (n = 117)	Non-survivor (n = 94)	P-value
Age (years)	36.36 ± 14.29	35.21 ± 16.50	0.288
Gender (male/female)	50/67	38/56	0.735
Amount of PQ ingestion (ml)	18.16 ± 23.81	46.52 ± 48.12	< 0.001*
Combined with alcohol drink (%)	10/117(8.55%)	2/94(2.13%)	0.045*
Interval between ingestion and admission (hr)	27.11 ± 38.14	17.89 ± 32.18	0.118
Gastric lavage percentage (%)	93/117(79.49%)	82/94(87.23%)	0.137
Blood oxygen saturation (%)	97.06 ± 3.80	95.38 ± 9.20	0.221
Arterial oxygen pressure (mmHg)	93.22 ± 19.49	93.62 ± 22.61	0.833
Abnormal pulmonary CT imaging (%)	49/117(41.88%)	54/94(57.45%)	0.025*
Serum creatinine at admission (μmol/l)	96.77 ± 88.90	156.00 ± 169.99	0.001*
Glomerular filtration rate at admission (ml/min)	105.85 ± 53.04	72.04 ± 49.01	< 0.001*
Serum uric acid at admission (μmol/l)	313.70 ± 112.89	338.16 ± 136.25	0.320
Abnormal renal function at admission (%)	36/117(30.77%)	60/94(63.83%)	< 0.001*
Acute kidney injury incidence after admission (%)	20/117(17.09%)	32/94(34.04%)	0.005*
Use of methylprednisolone (%)	116/117(99.15%)	89/94(94.68%)	0.091
Total dose of methylprednisolone (g)	1.87 ± 1.23	1.30 ± 1.09	< 0.001*
Use of cyclophosphamide (%)	94/117(80.34%)	80/94(85.11%)	0.366
Total dose of cyclophosphamide (g)	1.43 ± 1.22	1.37 ± 1.27	0.734
Use of vitamin C (%)	112/117(95.73%)	86/94(91.49%)	0.203

Definition of abnormal pulmonary CT imaging: pulmonary segment involvement, effusion, consolidation and fibrosis, or rapid lesion progression;

Definition of abnormal renal function at admission: Glomerular filtration rate was lower than 90 ml/min;

Definition of acute kidney injury after admission: The increase of serum creatinine level ≥ 26.4umol/l or 50% of the baseline

* symbolizes p-value < 0.05

Variable	Survivor (n = 117)	Non-survivor (n = 94)	P-value
Total dose of vitamin C (g)	47.10 ± 50.67	18.61 ± 23.25	< 0.001*
Daily dose of vitamin C (g/d)	3.99 ± 2.35	5.24 ± 4.09	0.026*
Use of aspirin (%)	53/117(45.30%)	19/94(20.21%)	< 0.001*
Total dose of aspirin (g)	1.99 ± 9.23	0.26 ± 0.76	< 0.001*
Daily dose of aspirin (mg/d)	144.43 ± 194.54	68.44 ± 163.76	< 0.001*
Use of rapamycin (%)	34/117(29.06%)	16/94(17.02%)	0.041*
Total dose of rapamycin (mg)	4.63 ± 8.51	0.90 ± 2.42	0.007*
Daily dose of rapamycin (mg/d)	0.56 ± 0.89	0.32 ± 0.73	0.031*
Use of hemoperfusion (%)	101/117(86.32%)	83/94(88.30%)	0.670
Frequency of hemoperfusion	3.31 ± 2.19	2.75 ± 2.24	0.005*
Definition of abnormal pulmonary CT imaging: pulmonary segment involvement, effusion, consolidation and fibrosis, or rapid lesion progression;			
Definition of abnormal renal function at admission: Glomerular filtration rate was lower than 90 ml/min;			
Definition of acute kidney injury after admission: The increase of serum creatinine level ≥ 26.4umol/l or 50% of the baseline			
* symbolizes p-value < 0.05			

Renal function and prognosis

At admission, 115 (54.50%) patients presented with normal renal function (the GFR ≥ 90 ml/min),the average GFR was 131.38 ± 34.98 (90-375.78) ml/min. Among the 115 patients, 52 (45.22%) patients developed acute kidney injury (AKI, defined as the increase of serum creatinine level ≥ 26.4umol/l or 50% of the baseline) after admission, 31 patients died with impaired renal function whereas only 1 patient's renal function recovered to normal range before her death. Another 20 patients survived, with 14 patients' renal function recovered while 6 patients' renal function impaired when discharged with no further renal function follow-up (**Fig. 2 Survival according to different renal function grouping**). The cumulative survival rate was significantly higher in patients who presented normal renal function at admission (**Fig. 3 Kaplan-Meier survival analysis between two groups according to the GFR at admission. Log-rank test, p < 0.001**) and keep normal after admission (**Fig. 4 Kaplan-Meier survival analysis between two groups according to the AKI incidence after admission. Log-rank test, p < 0.001**).

Independent prognostic factors for PQ poisoning

In order to determine the independent prognostic factors for PQ poisoning, we applied the Cox regression survival model to calculate the HRs for mortality and 95% CIs. Patients who ingested larger amount of PQ [HR 1.006, 95% CI (1.002–1.009), p = 0.003], presented with abnormal renal function at admission [HR 12.540, 95% CI (2.910-54.038), p = 0.001] or developed AKI after admission [HR 21.327, 95% CI (6.328–71.875), p < 0.001] were high-risk population for mortality. However, higher dose of methylprednisolone [HR 0.577, 95% CI (0.453–0.735), p < 0.001] and aspirin [HR 0.998, 95% CI (0.996-1.000), p = 0.027] were protective factors for survival (Table 2).

Table 2
Cox regression survival analysis of the prognostic factors after PQ poisoning

Prognostic factors	HR	95% CI	P-value
Gender (male/female)	0.855	0.541–1.352	0.502
Age (years)	0.991	0.977–1.005	0.217
Combined with alcohol drink (%)	0.293	0.068–1.251	0.097
Amount of PQ ingestion (ml)	1.006	1.002–1.009	0.003*
Abnormal pulmonary CT scan (%)	0.998	0.644–1.546	0.992
Serum creatinine at admission (μmol/l)	1.000	0.998–1.002	0.863
Glomerular filtration rate at admission (ml/min)	0.994	0.983–1.006	0.336
Abnormal renal function at admission (%)	12.540	2.910-54.038	0.001*
Acute kidney injury incidence after admission (%)	21.327	6.328–71.875	< 0.001*
Total dose of methylprednisolone (g)	0.577	0.453–0.735	< 0.001*
Daily dose of aspirin (mg/d)	0.998	0.996-1.000	0.027*
Daily dose of rapamycin (mg/d)	1.128	0.784–1.622	0.518
Daily dose of vitamin C (g/d)	1.037	0.984–1.093	0.178
Frequency of hemoperfusion	0.940	0.842–1.049	0.268
HR: Hazard Ratio;			
CI: confidence interval.			
* symbolizes p-value < 0.05			

Discussion

Management of PQ poisoning is a medical challenge due to its high toxicity without effective antidote. PQ is rapidly distributed to lung, liver, kidney and muscle upon ingestion and selectively accumulates in

the lungs, leading to irreversible pulmonary fibrosis and resulting in death within days up to a month. The clinical manifestations depend upon the quantity ingested. Large amounts of liquid concentrate (> 50–100 ml of 20% ion w/v) could result in fulminant organ failure and death within several hours to a few days, while smaller quantities could be harmful to the key target organs (kidneys and lungs) and develop over the next 2–6 days with the mortality rate still over 50%[14].

In the present study, our retrospective analysis revealed that the mortality rate was 44.55%, a little better than the previous reports. Most baseline variables had no significant differences between the survivor and non-survivor group. However, patients in the survivor group ingested less amount of PQ, which is consistent with previous reports[14]. We also found patients presented with lower serum creatinine level and higher glomerular infiltration rate at admission, developed lower incidence of acute kidney injury in the survivor group (Table 1). Cox regression survival analysis revealed that patients with abnormal renal function at admission or developed AKI after admission were high-risk population for mortality (Table 2). In the present study, 54.50% patients presented with normal renal function at admission and 45.22% patients among them developed AKI. The AKI incidence rate was similar with a previous study (51.4% reported by Hong et al. in 2009)[15]. In their study, AKI developed fully at the fifth day after PQ ingestion and normalized within 3 weeks without exception; Serum uric acid level could be a marker for mortality and acute kidney injury in patients with acute PQ intoxication[15, 16]. We could not characterize the evolution of AKI in present study because six patients who had impaired renal function at discharge did not have further renal function examinations. We could not find the association between serum uric acid level and AKI development or prognosis, but Cox regression analysis demonstrated that the amount of PQ ingested was the only independent risk factor for the development of AKI [HR 1.042, 95% CI (1.016–1.069), p = 0.002].

The percentage of abnormal pulmonary CT imaging in the survivor group was lower than the non-survivor group (41.88% vs 57.45%, p = 0.025) in our study, the lesions were consisted of pulmonary segment involvement, effusion, consolidation and fibrosis, or rapid lesion progression. Previous study reported that CT imaging could be a prognostic indicator for patients with pulmonary injury from acute PQ poisoning[17]. However, Cox regression analysis in the present study could not identify it as an independent risk factor for the prognosis. Further study should put emphasis on unified grouping of pulmonary lesion and identify characteristic early features.

Another interesting finding was that 12 Patients who ingested PQ combined with alcohol had a higher survival rate than those ingested PQ alone. PQ induced redox cycling rapidly oxidizes NADPH and leads to secondary changes on cellular metabolism and impairs defenses against oxidative stress[18]. Previous animal studies and medical case reports drew different conclusions about the impact of ethanol on PQ poisoning. Ethanol may decrease PQ toxicity partly through competitive consumption of NADPH and oxygen during the metabolism process [19–23]. The acute and chronic ethanol ingestion may have different impact on PQ metabolism. Further detailed studies are needed.

As to the therapy regimen, the survivors in the present study were treated with higher dosage of methylprednisolone, aspirin and rapamycin. The frequency of hemoperfusion was more in the survivor group. In the past decades, attempts to reduce absorption by gastric lavage, administration of Fueller's earth and skin decontamination have been used routinely[24]. Early hemoperfusion is suggested in the aim of eliminating plasma PQ [9, 25]. A combination of glucocorticoid and cyclophosphamide was reported to be beneficial[26]. The survival benefit of additional immunosuppressive treatment has been demonstrated in the combination of methylprednisolone, cyclophosphamide and daily dexamethasone [6]. Intravenous anti-oxidants such as N-Acetylcysteine, L-Glutathione, vitamin C, vitamin E and thioctic acid have been used with various success[7, 27]. Our previous animal study revealed that rapamycin has significant inhibitory effects on progressive pulmonary fibrosis in the PQ intoxication mice model which may be partly ascribed to the inhibition of TGF-β1[28], however, the results in clinical settings differed[29, 30]. Some other potential agents, such as docosahexaenoic acid[31], naringin[32] and lysine acetylsalicylate[33] have been shown to ameliorate PQ-induced pulmonary fibrosis in animal models. Our results demonstrated positive effects of the therapy regimen consisted of cyclophosphamide, methylprednisolone, vitamin C, aspirin and rapamycin combined with hemoperfusion, higher dose of methylprednisolone and aspirin were protective factors for survival.

Ananieva et al. reported that salicylic acid (SA) mediates tolerance in barley plants to PQ, exogenous treatment with SA could antagonize PQ toxicity via elicitation of an antioxidative response in barley plants over ten years ago[34]. Recent studies have shown that salicylates, including sodium salicylate (NaSAL)[35, 36] and lysine acetylsalicylate (LAS)[33] may form complexes with PQ, prevent its toxicity through anti-inflammatory, anti-oxidant and anti-thrombogenic properties. LAS (also named Aspirin-DL-Lysine) has been shown to be a promising intravenous antidote for the treatment of PQ poisoning in animal studies[33]. To our knowledge, there have been no published human studies about the SA therapy in PQ poisoning. The present study firstly reported beneficial effect of oral aspirin therapy in PQ poisoning patients. Because LAS are not available in our hospital, we used oral aspirin in 72 patients (34.12%) with a mean daily dosage of 110.58 mg. Patients treated with aspirin had superior survival (73.61% vs 46.04%, log rank test, $p < 0.001$). Larger trials will be needed to verify the effect of aspirin on survival in patients with PQ poisoning.

Previous study showed that the addition of high-dose vitamin C to the treatment can reduce the development of acute kidney injury and mortality in PQ poisoning patients [7]. The optimal dosage of vitamin C is unknown. Hong et al. suggested that the loading and maintenance dosages should be 2278 mg and 146 mg/h based on pharmacokinetic data in patients with PQ intoxication[27]. A much larger dose (1.5 g/kg or daily 10 g) of vitamin C recommended as the upper limit has been beneficial for the treatment of pancreatitis and advanced malignancies[37, 38]. In the present study, the median daily dosage of vitamin C was 3000 mg. Further investigation is needed to determine the optimal dosage of vitamin C.

There are some limitations in present study. First, we used the amount of PQ ingestion as a variable. It's not accurate because sometimes the patient provided mistake information. We used semi-quantitative

urine PQ test instead of quantitative dithionite concentration determination. As we know, 90% of the absorbed PQ is rapidly excreted unchanged in urine within 12–24 h after ingestion[39], the urine test has a good correlation between PQ concentration and intensity of the blue color formed[40]. However, due to the different time interval between ingestion and admission, we could not decide the therapy intensity according to the urine semi-quantitative results alone. Second, the dosage of aspirin was determined according to our own experience; further studies are needed to verify the conclusion and illuminate the optimal dosage.

Conclusions

In conclusion, patients who ingested larger amount of PQ and presented with abnormal renal function at admission or developed AKI after admission are high-risk population for mortality after PQ poisoning. Present study proved that either higher dose of methylprednisolone or aspirin help to improve survival. As to our knowledge, it's the first report about the efficacy of aspirin on PQ poisoning. However, further investigations are needed to determine the optimal dosage.

Abbreviations

AKI
acute kidney injury
PQ
paraquat
ROS
reactive oxygen species
HR
hazard ratio
CI
confidence interval
MP
methylprednisolone
CP
cyclophosphamide
VC
vitamin C
GFR
glomerular filtration rate
SA
salicylic acid
LAS
Aspirin-DL-Lysine

Declarations

Ethic approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (Reference Number 2016-273). Because all information obtained from the medical records was kept confidential, the review board of the Ethics Committee stated that written consent from patients was not required.

Consent to publication

Not appliable.

Availability of data and material

The datasets generated and analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ying Xu, Yang Chen, Jingyun Le and Zhimin Chen. The first draft of the manuscript was written by Ying Xu and Yang Chen. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

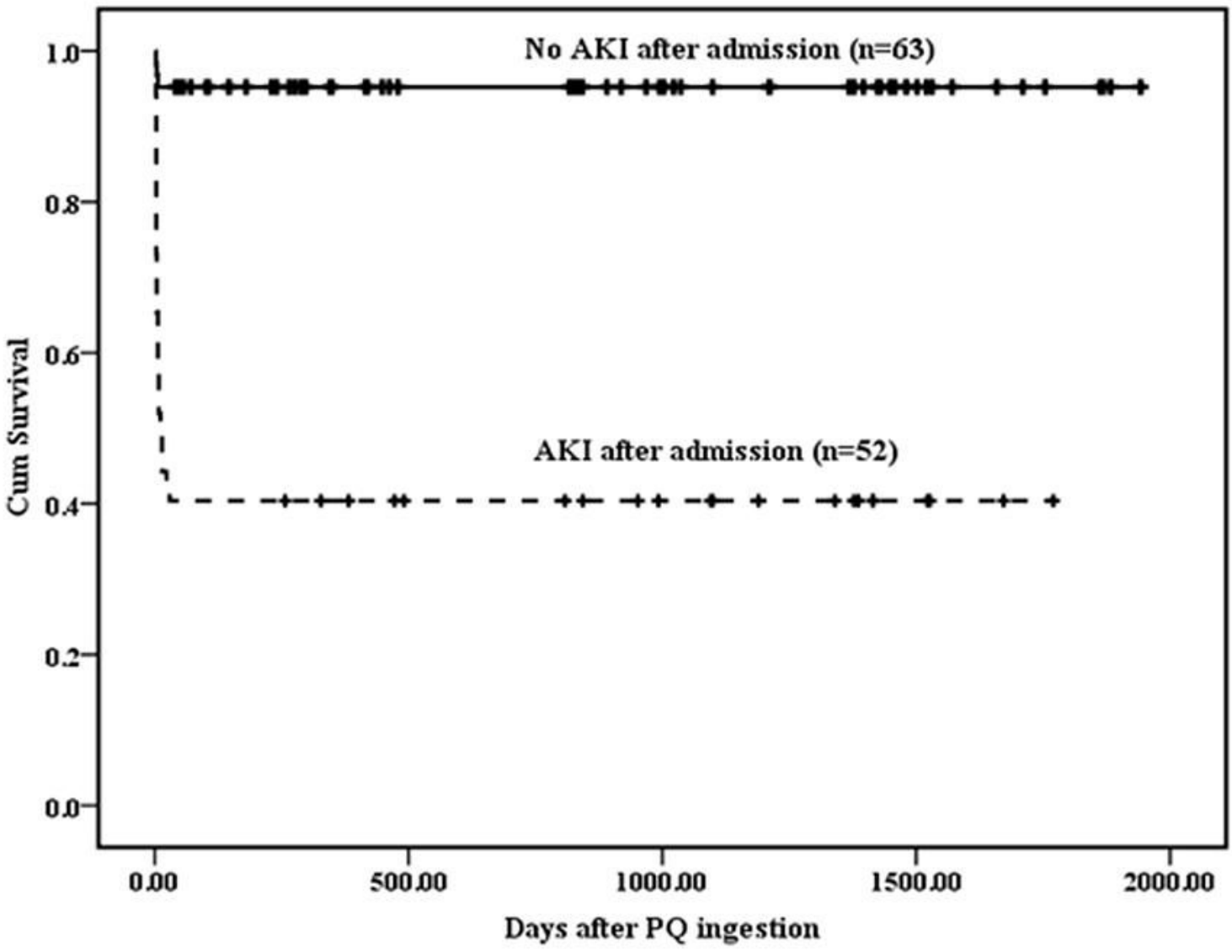

Figure 1

Kaplan-Meier survival analysis between two groups according to the AKI incidence after admission. Log-rank test, p<0.001

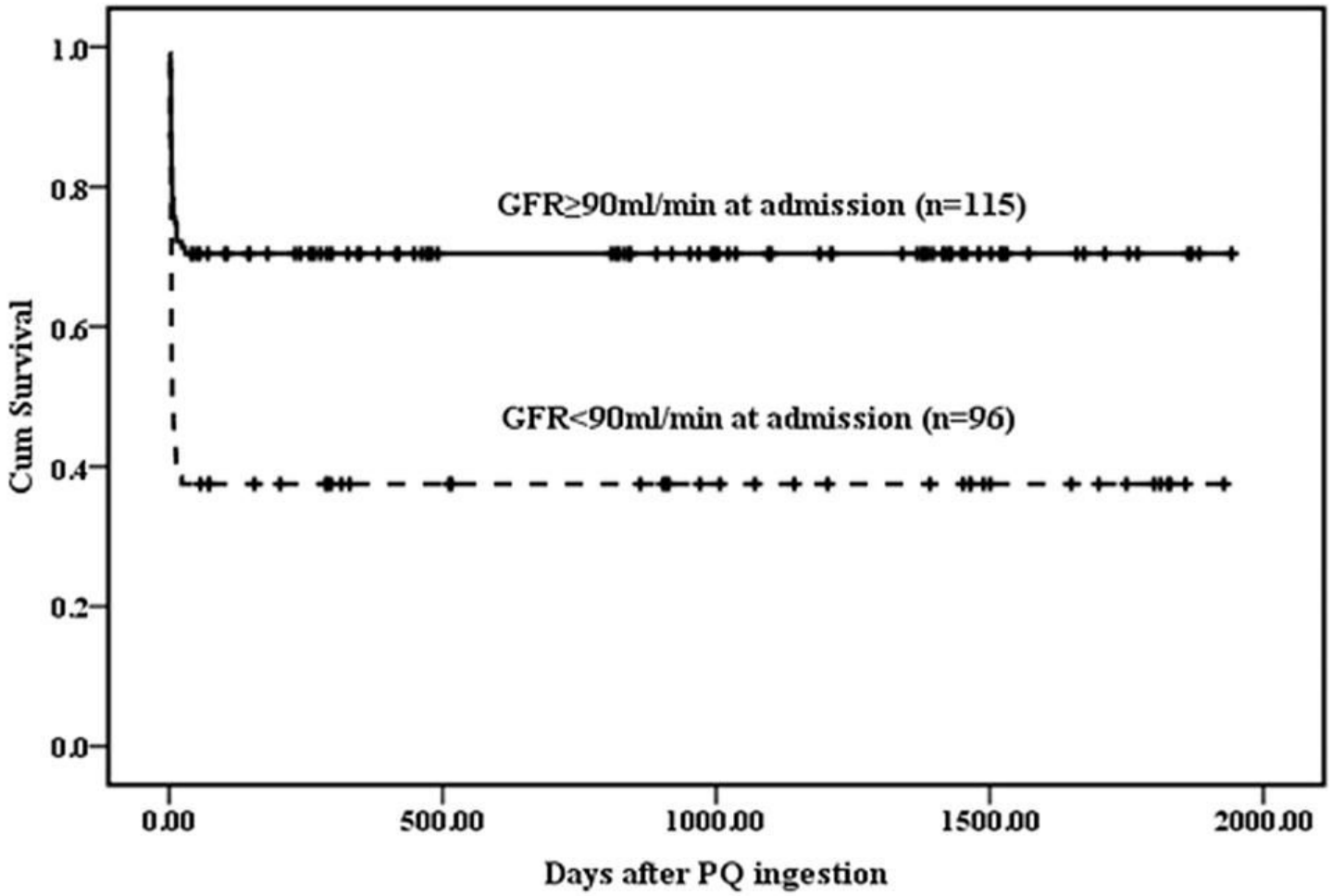

Figure 2

Kaplan-Meier survival analysis between two groups according to the GFR at admission. Log-rank test, p<0.001

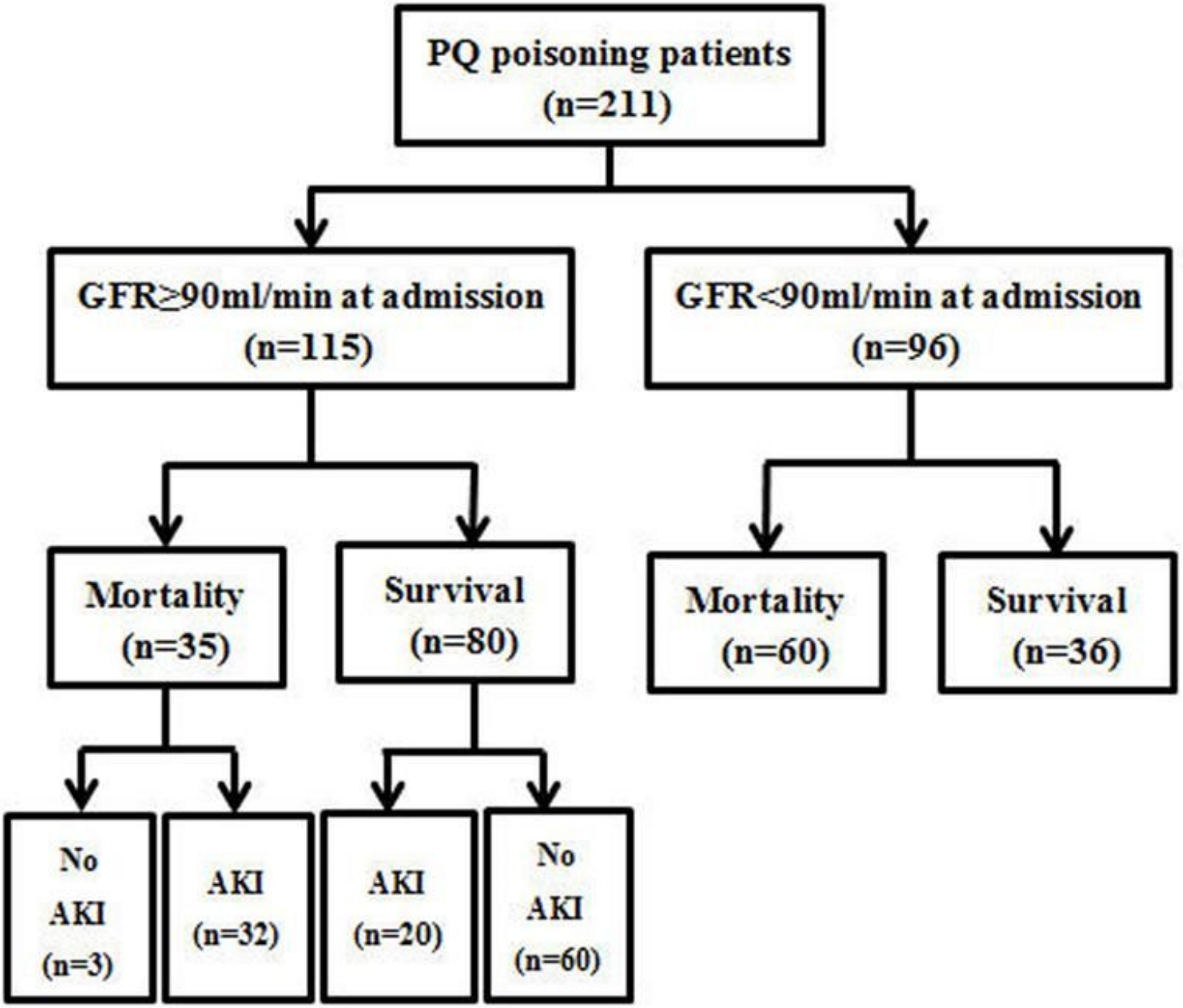

Figure 3

Survival according to different renal function grouping

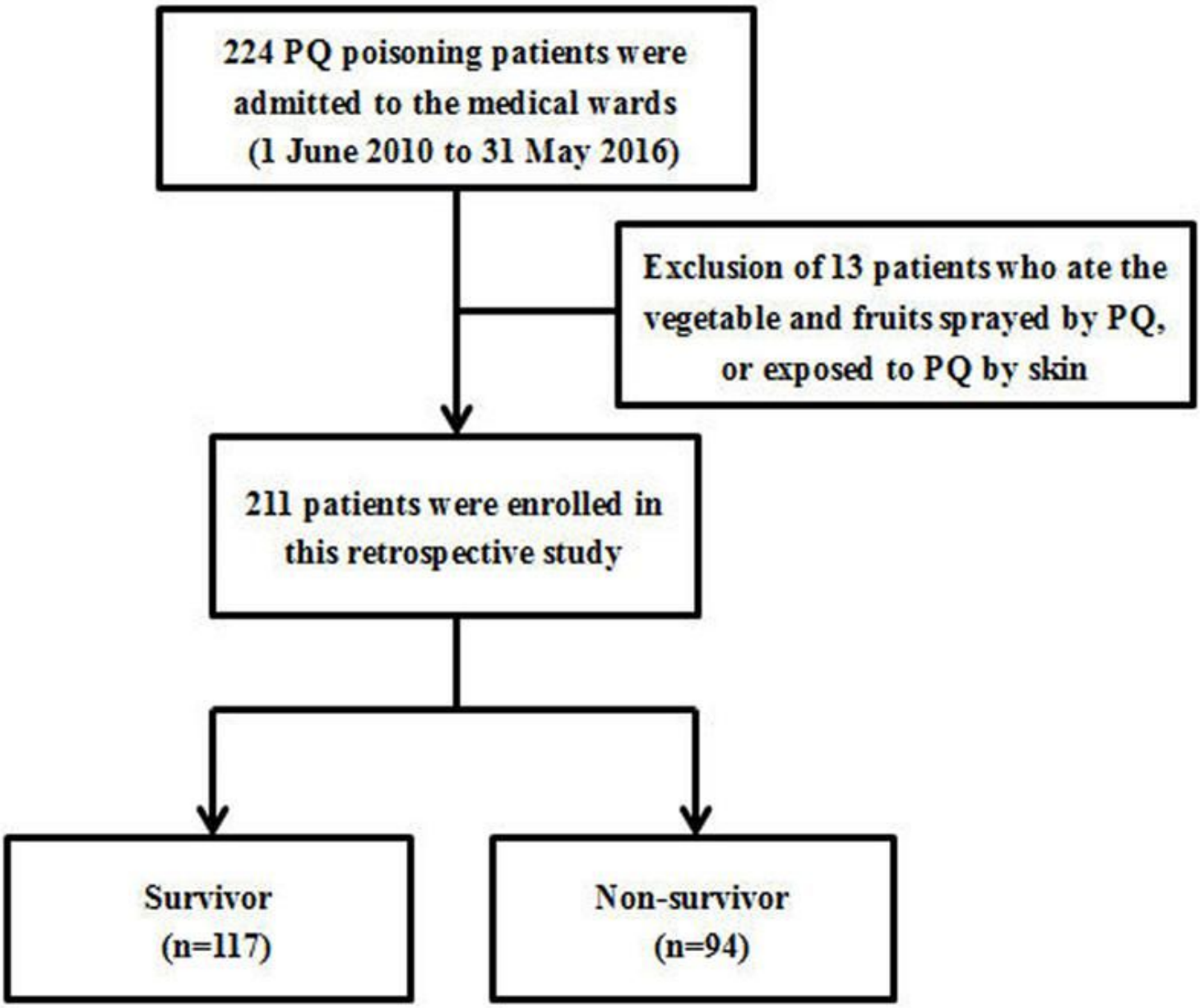

Figure 4

Enrollment and grouping of PQ poisoning patients