Original Article

Kidney Res Clin Pract 2023;42(3):349-357
pISSN: 2211-9132 • eISSN: 2211-9140
https://doi.org/10.23876/j.krcp.22.051

KIDNEY RESEARCH AND CLINICAL PRACTICE

Clinical characteristics of acute kidney injury in patients with glyphosate surfactant herbicide poisoning

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Background: In this study, we investigated the clinical characteristics of acute kidney injury (AKI) in patients with glyphosate surfactant herbicide (GSH) poisoning.
Methods: This study was performed between 2008 and 2021 and included 184 patients categorized into the AKI (n = 82) and non-AKI (n = 102) groups. The incidence, clinical characteristics, and severity of AKI were compared between the groups based on the Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease (RIFLE) classification.
Results: The incidence of AKI was 44.5%, of which 25.0%, 6.5%, and 13.0% of patients were classified into the Risk, Injury, and Failure categories, respectively. Patients in the AKI group were older (63.3 ± 16.2 years vs. 57.4 ± 17.5 years, p = 0.02) than those in the non-AKI group. The length of hospitalization was longer (10.7 ± 12.1 days vs. 6.5 ± 8.1 days, p = 0.004) and hypotensive episodes occurred more frequently in the AKI group (45.1% vs. 8.8%, p < 0.001). Electrocardiographic (ECG) abnormalities on admission were more frequently observed in the AKI group than in the non-AKI group (80.5% vs. 47.1%, p < 0.001). Patients in the AKI group had poorer renal function (estimated glomerular filtration rate at the time of admission, 62.2 ± 22.9 mL/min/1.73 m^2 vs. 88.9 ± 26.1 mL/min/1.73 m^2, p < 0.001) on admission. The mortality rate was higher in the AKI group than in the non-AKI group (18.3% vs. 1.0%, p < 0.001). Multiple logistic regression analysis showed that hypotension and ECG abnormalities upon admission were significant predictors of AKI in patients with GSH poisoning.
Conclusion: The presence of hypotension on admission may be a useful predictor of AKI in patients with GSH intoxication.

Keywords: Acute kidney injury, Glyphosate, Hypotension, Poisoning

Introduction

Glyphosate is currently the most common post-emergent, nonselective herbicide used in worldwide agriculture [1]. The 2012 paraquat ban in South Korea was followed by an increase in the annual number of suicide attempts using glyphosate surfactant herbicides (GSH) [2] with approximately 1,000 cases of GSH toxicity occurring annually in South Korea [2,3]. GSH poisoning is known to cause gastrointestinal dysfunction, acute respiratory failure, cardiovascular instability, central nervous system complications, and acute kidney injury (AKI) [4,5], all of which are associated with GSH-mediated toxicity including mitochondrial dysfunction, lipid peroxidation, oxidative stress, and DNA

Received: March 16, 2022; **Revised:** August 16, 2022; **Accepted:** September 14, 2022
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injury [6–9].

Previous studies have reported GSH-induced AKI; direct GSH toxicity or renal ischemia secondary to circulatory failure has been implicated as a possible pathophysiological mechanism underlying AKI [6,10,11]. Moderate-to-severe GSH intoxication typically presents with renal dysfunction, which is also an important predictor of poor outcomes [6,12]. However, few studies have investigated the incidence and clinical characteristics of AKI in patients with GSH intoxication [13]. A variety of definitions are used in clinical practice; therefore, the incidence of GSH poisoning-induced AKI remains unclear [14,15]. The Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease (RIFLE) criteria, which were originally validated for ischemic AKI [16], are used to define and classify AKI [17].

In this study, we investigated the incidence and clinical characteristics of GSH poisoning-induced AKI using the RIFLE criteria.

Methods

Patient selection

We enrolled 202 patients with a history of GSH ingestion who visited our hospital between 2008 and 2021. Exclusion criteria were as follows: unclear history of exposure, co-exposure with non-pharmaceutical agents including other pesticides, non-oral exposure, discharge against medical advice, and transfer to another hospital. Eventually, 184 patients were included in this study and were categorized into the AKI or non-AKI group. This study was approved by the Institutional Review Board of the Presbyterian Medical Center, Jeonju, Republic of Korea (No. 2020-06-029). Written informed consent was waived due to its retrospective nature.

Clinical and laboratory data

All data were obtained through retrospective chart review. Acute GSH intoxication was defined based on a history of exposure, container labels, or product information provided by the patient or family. Following detailed clinical history taking, all patients underwent thorough physical and biochemical evaluation including complete blood counts, liver and renal function tests, arterial blood gas analysis, urinalysis, and chest radiography. Electrocardiographic (ECG) recordings obtained upon arrival at the emergency department were interpreted by a cardiologist. The corrected QT interval (QTc) was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$) [18]. QTc interval of >470 ms was defined as QTc interval prolongation [19]. Hypotension was defined as a systolic blood pressure (BP) of <90 mmHg. The estimated amount of GSH ingestion was defined as follows: a spoonful (5 mL), a mouthful (25 mL), a cupful (100 mL), and a bottleful (300 mL) [20].

AKI was defined based on the RIFLE criteria, and patients were categorized into the Risk (R), Injury (I), and Failure (F) categories [17]. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [21]. In patients for whom the baseline serum creatinine value was unavailable, it was calculated using the standard four-variable MDRD formula considering an eGFR of 75 mL/min/1.73 m^2. The RIFLE class was determined based on the worst serum creatinine value, eGFR, and urine output criteria. RIFLE classes I and F were defined as severe AKI in this study. Renal replacement therapy was initiated based on standard indications. All data are presented as the mean ± standard deviation unless otherwise specified. Baseline characteristics of patients in the non-AKI and AKI groups were compared using t test, chi-square test, or Fisher exact test. Using paired t test, the lowest eGFR during AKI was compared following recovery eGFR. Fisher exact test was used to compare frequencies between AKI and ECG findings.

Clinically, the variables that were significantly associated with AKI on univariate analysis were subjected to multivariate analysis using binary logistic regression analysis. Survival curves for mortality were calculated using the Kaplan-Meier method and compared using the log-rank test. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS version 22.0 (IBM Corp.).

Results

Comparison of clinical characteristics between the acute kidney injury and non-acute kidney injury groups

Compared with those in the non-AKI group, patients in the

AKI group were older (63.3 ± 16.2 years vs. 57.4 ± 17.5 years, p = 0.02) and had ≥1 comorbidities such as hypertension or diabetes (52.4% vs. 32.7%, p = 0.005) (Table 1). The length of hospitalization was longer (10.7 ± 12.1 days vs. 6.5 ± 8.1 days, p = 0.004), and hypotensive episodes upon admission were more frequent in the AKI group (45.1% vs. 8.8%, p < 0.001). Moreover, ECG abnormalities were observed more frequently in the AKI group than in the non-AKI group (80.5% vs. 47.1%, p < 0.001). Patients in the AKI group had poorer renal function (62.2 ± 22.9 mL/min/1.73 m^2 vs. 88.9 ± 26.1 mL/min/1.73 m^2, p < 0.001) and lower serum bicarbonate levels (18.0 ± 5.1 mmol/L vs. 21.0 ± 3.9 mmol/L, p < 0.001) upon admission. Notably, intensive care unit admissions (57.3% vs. 20.6%, p < 0.001) and mechanical ventilatory support (36.6% vs. 4.9%, p < 0.001) were more frequently required in the AKI group. The mean amount of GSH ingested was higher in the AKI group than in the non-AKI group (236 ± 150 mL vs. 174 ± 122 mL, p = 0.004). The mortality rate was higher in the AKI group than in the non-AKI group (18.3% vs. 1.0%, p < 0.001).

Clinical course of acute kidney injury in patients with glyphosate surfactant herbicide poisoning

Based on the RIFLE criteria, 46 (56.1%), 12 (14.6%), and 24 patients (29.3%) were categorized into the R, I, and F categories, respectively (Table 2). Among patients with AKI, 14 (17.1%) underwent renal replacement therapy. Of the total 82 patients with AKI, renal function returned to baseline values within 72 hours in 59 patients (72.0%). Posttreatment renal function (indicated by eGFR measurements) improved significantly from the lowest renal function (89.3 ± 42.9 mL/min/1.73 m^2 vs. 44.3±22.1 mL/min/1.73 m^2, p < 0.001). Of 82 AKI patients, only 23 patients (28.0%) could be followed-up beyond 3 months.

We found no significant change in the renal function of these 23 patients at the time of discharge and 3 months later (94.2 ± 25.5 mL/min/1.73 m^2 vs. 88.4 ± 29.1 mL/min/1.73 m^2, p = 0.08). Univariate analysis revealed that age, comorbidities, hypotension, ECG abnormalities on admission, serum bicarbonate concentration, and amount of GSH ingested were significant predictors of AKI. Multivariate

Table 1. Comparison of baseline characteristics between the non-AKI and AKI groups

Characteristic	AKI (n = 82)	Non-AKI (n = 102)	p-value
No. of patients	82	102	
Age (yr)	63.3 ± 16.2	57.4 ± 17.5	0.02
Male sex	61 (74.4)	64 (62.7)	0.06
Comorbidities	43 (52.4)	33 (32.7)	0.005
Length of hospitalization (day)	10.7 ± 12.1	6.5 ± 8.1	0.004
Amount of GSH ingested (mL)	236 ± 150	174 ± 122	0.004
Hypotension	37 (45.1)	9 (8.8)	<0.001
ECG abnormalities	66 (80.5)	48 (47.1)	<0.001
ICU admission	47 (57.3)	21 (20.6)	<0.001
Ventilator support	30 (36.6)	5 (4.9)	<0.001
Serum creatinine (mg/dL)	1.42 ± 1.21	0.90 ± 0.24	<0.001
$eGFR_{adm}$, mL/min/1.73 m^2	62.2 ± 22.9	88.9 ± 26.1	<0.001
Serum ALT (IU/L)	63.0 ± 310.6	27.6 ± 19.3	0.25
Serum bilirubin (mg/dL)	0.75 ± 0.65	0.63 ± 0.39	0.09
Serum albumin (g/dL)	4.41 ± 0.56	4.32 ± 0.45	0.23
Serum hemoglobin (g/dL)	14.4 ± 2.1	14.1 ± 1.6	0.15
Total leukocyte count (×10^3/mL)	12.4 ± 5.2	10.9 ± 4.4	0.04
Sodium (mEq/L)	141.9 ± 4.1	141.8 ± 3.3	0.55
HCO_3 (mmol/L)	18.0 ± 5.1	21.0 ± 3.9	<0.001
Death	15 (18.3)	1 (1.0)	<0.001

Data are expressed as number only, mean ± standard deviation, or number (%).
AKI, acute kidney injury; ALT, alanine transaminase; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; GSH, glyphosate surfactant herbicide; HCO_3, bicarbonate; ICU, intensive care unit.

Table 2. Clinical characteristics of 82 patients with acute kidney injury

Characteristic	Data
RIFLE category	
Risk	46 (56.1)
Injury	12 (14.6)
Failure	24 (29.3)
FENa < 1%[a]	20 (49.0)
Recovery of renal function within 72 hr	59 (72.0)
Renal replacement therapy	14 (17.1)
Renal function, eGFR (mL/min/1.73 m^2)	
$eGFR_{adm}$	62.2 ± 22.9
$eGFR_{low}$	44.3 ± 22.1
$eGFR_{rec}$	89.3 ± 42.9
$eGFR_{3m}$[b]	88.4 ± 29.1

Data are expressed as number (%) or mean ± standard deviation.
eGFR, estimated glomerular filtration rate; $eGFR_{adm}$, eGFR at the time of admission; $eGFR_{low}$, the lowest eGFR during hospitalization; $eGFR_{rec}$, eGFR at the time of recovery; $eGFR_{3m}$, eGFR at the time of 3 months later; FENa, fractional excretion of sodium; RIFLE, Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease criteria.
[a]FENa was available in 41 patients. [b]$eGFR_{3m}$ (mL/min/1.73 m^2) was available in 23 patients.

logistic regression analysis performed after adjustment for these factors showed that hypotensive episodes and ECG abnormalities, such as ST-T abnormality on admission, remained significant predictors of AKI (Table 3). The most common ECG abnormality in patients with AKI was QTc interval prolongation followed by sinus tachycardia (Table 4). However, compared to the non-AKI group, only the ST-T abnormality was observed to be more prevalent in the AKI group. Furthermore, multiple logistic regression analysis for prediction of mortality showed that severe AKI was an important prognostic factor in patients with GSH intoxication (Table 5). Fig. 1 shows the Kaplan-Meier curves comparing the in-hospital mortality rates between the groups. The cumulative survival rate was lower in patients with AKI than in those without it.

Discussion

Hypotension and ECG abnormalities on admission were more frequently observed in patients with AKI than in

Table 3. Univariate and multivariate analysis of predictors of acute kidney injury

Variable	Univariate		Multivariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.02 (1.00–1.04)	0.02	1.01 (0.98–1.03)	0.63	1.01 (0.98–1.03)	0.59
ECG change	4.64 (2.37–9.07)	<0.001	3.40 (1.49–7.74)	0.004		
ST-T change	26.40 (3.43–203.20)	<0.001			22.10 (2.61–187.20)	0.005
Comorbidity	2.27 (1.25–4.14)	0.007	1.19 (0.50–2.84)	0.7	1.01 (0.42–2.44)	0.99
HCO_3^-	1.16 (1.08–1.24)	<0.001	1.03 (0.95–1.12)	0.49	1.08 (0.99–1.17)	0.09
Hypotension	8.22 (3.66–18.48)	<0.001	5.38 (2.14–13.6)	<0.001	5.18 (2.09–18.8)	<0.001
Amount of GSH ingested	1.00 (1.00–1.01)	0.01	1.00 (0.995–1.00)	0.24	1.00 (0.999–1.00)	0.14

CI, confidence interval; ECG, electrocardiographic; HCO_3, bicarbonate; GSH, glyphosate surfactant herbicide; HR, hazard ratio.

Table 4. Initial electrocardiographic findings in patients with glyphosate surfactant herbicide intoxication

Variable	Total (n = 184)	AKI (n = 82)	Non-AKI (n = 102)	p-value
Patients	114 (62.0)	66 (80.5)	48 (47.1)	
Prolonged QTc	49 (43.0/26.6)	23 (34.8/28.0)	26 (52.2/25.5)	0.74
Sinus tachycardia	32 (28.1/17.4)	17 (25.8/20.7)	15 (32.6/14.7)	0.33
1 AV block	5 (4.4/2.7)	3 (4.5/3.7)	2 (4.3/2.0)	0.66
ST-T abnormality	16 (14.0/8.7)	15 (22.7/18.3)	1 (2.2/1.0)	<0.001
Sinus bradycardia	4 (3.5/2.2)	2 (3.0/2.4)	2 (4.3/2.0)	>0.99
PSVT	1 (0.9/0.5)	1 (1.5/1.2)	0 (0/0)	0.45
Atrial fibrillation	4 (3.5/2.2)	2 (3.0/2.4)	2 (6.5/2.0)	>0.99
Wide QRS tachycardia	3 (2.6/1.6)	3 (4.5/3.7)	0 (0/0)	0.09
NSR	70 (61.4/38.0)	16 (24.2/19.5)	54 (112.5/52.9)	<0.001

Data are expressed as number (%) or number (% for GSH patients/% for total patients).
AKI, acute kidney injury; AV, atrioventricular; PSVT, paroxysmal supraventricular tachycardia; QTc, corrected QT interval; NSR, normal sinus rhythm.

Table 5. Univariate and multivariate analysis of predictors of mortality

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Severe AKI	46.45 (9.88–218.40)	<0.001	9.99 (1.64–58.81)	0.01
Amount of GSH ingested	1.01 (1.00–1.01)	0.002	1.00 (0.997–1.01)	0.43
Age	1.05 (1.01–1.09)	0.01	1.07 (1.00–1.15)	0.04
Hypotension	29.75 (6.44–137.50)	<0.001	10.05 (1.37–73.95)	0.02
HCO_3	1.29 (1.15–1.46)	<0.001	1.09 (0.92–1.28)	0.33

AKI, acute kidney injury; CI, confidence interval; GSH, glyphosate surfactant herbicide; HCO_3, bicarbonate; HR, hazard ratio.

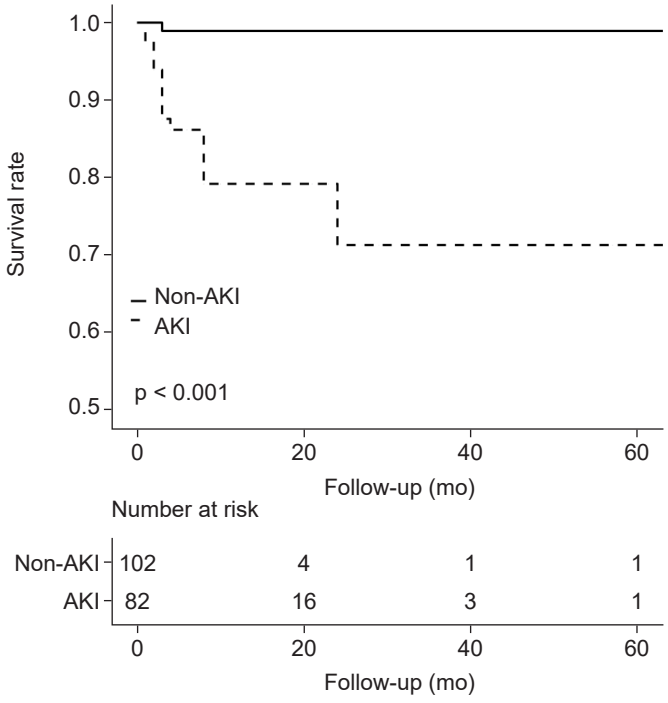

Figure 1. Survival outcomes in patients with glyphosate surfactant herbicide intoxication according to AKI. Patients without AKI had longer overall survival than patients with AKI (p < 0.001). AKI, acute kidney injury.

those without AKI, and these variables recorded on admission were significant predictors of AKI in patients with GSH poisoning. Therefore, our findings provide a strong rationale for close monitoring of BP and ECG findings such as ST-T change on admission as useful predictors of AKI in patients with GSH intoxication.

The percentage of suicide attempts using GSH increased from 10.0% in 2010 to 29.5% in 2014 following the paraquat ban in Korea in 2012 [2]. GSH poisoning may precipitate multi-organ dysfunction and death [6]. GSH intoxication-induced mortality rates were shown to range from 2.0% to 30.0% [5,6,12,22,23]. The fatality rate of 8.6% observed in our study was similar to that reported in previous studies [5,12]. The incidence of AKI in patients with GSH intoxication varied from 10.0% to 51.0% [12,13,22,24]. In our view, the wide variation in incidence rates may be attributable to differences in AKI definitions and cohort characteristics such as age or disease severity. Based on the RIFLE criteria, we identified a 44.5% incidence of AKI. AKI is known to be associated with poor clinical outcomes in cases of GSH poisoning [22,24], which is consistent with our observations in this study. Mild AKI was not associated with poor clinical outcomes in our study (data not shown); however, severe AKI was a significant predictor of mortality in patients with GSH poisoning, which is similar to the findings reported by Mohamed et al. [13]. Therefore, aggressive supportive therapy is important for reducing mortality in patients with GSH intoxication and severe AKI.

The definition of AKI evolved rapidly following the 2004 introduction of the RIFLE, Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Global Outcome (KDIGO) classifications. AKIN published their AKI classification for adults by incorporating the absolute increase in the serum creatinine level among the defining criteria [25–27]. The KDIGO's guidelines merged the RIFLE and AKIN classifications. However, AKIN criteria are intended to exclude transient changes in creatinine or urine output due to volume depletion [28]. In addition, changes in eGFR are not included in the AKIN or KDIGO AKI classification systems in cases in which steady-state serum creatinine concentrations are unavailable for eGFR measurement [25–27]. In contrast, the RIFLE criteria consider changes in any measure of renal function from baseline values, which

serves as a major strength of this classification system [25]. In this study, baseline renal function data were available in only 36 patients (19.6%), and 72.0% of AKI patients had pre-renal AKI. Therefore, we defined AKI based on the RIFLE classification system instead of the AKIN classification or the KDIGO AKI guidelines. Furthermore, the diagnostic criteria for AKI based on the AKIN and KDIGO systems necessitate measurement of at least two serum creatinine values within 48 hours. However, 41 patients (50.0%) with GSH poisoning-induced AKI presented with poor renal function on admission. Considering the clinical characteristics of AKI in GSH intoxication, our data may be more reliable and useful for estimating AKI incidence in patients with GSH.

To the best of our knowledge, only one study to date has described AKI severity in patients with GSH poisoning. The authors reported that acute renal dysfunction was common following GSH intoxication, which led to mild AKI [13]. However, in our study, 54 of 82 patients (65.9%) with AKI were classified into the I and F categories of AKI based on the RIFLE criteria. Furthermore, 14.0% of patients with AKI received renal replacement therapy in the present study. This discrepancy may be attributable to differences in the characteristics of patients enrolled in these studies. The patients in our study were older and had ingested larger amounts of GSH than those included in the study by Mohamed et al. [13]. Notably, appropriate therapy led to significant improvement in renal function (from its lowest level) in the AKI group. Therefore, we emphasize the role of aggressive supportive therapy for effective management of GSH intoxication in patients with AKI. Recent studies have reported that AKI can lead to chronic kidney disease (CKD) and eventually end-stage kidney disease in the long term [29,30]. In this study, of the 82 patients with AKI, only 23 (28.0%) could be followed-up beyond 3 months. No significant changes were observed in the renal parameters during the follow-up period in these patients. Future prospective studies are needed to investigate the incidence of AKI-to-CKD transition.

In addition to GSH-induced mitochondrial toxicity, GSH causes renal injury secondary to circulatory failure following dehydration or myocardial suppression [6,10,11]. Here, we found that hypotension and ECG abnormalities recorded on admission were significant predictors of AKI. Notably, 75.0% of patients with AKI either had fractional sodium excretion of <1.0% or showed a return of renal function to baseline levels within 72 hours after proper replacement of volume depletion, both of which are suggestive of prerenal failure [31–33]. Additionally, 66 patients (80.5%) with AKI showed ECG abnormalities upon admission. Volume depletion and cardiovascular abnormalities may contribute to hypotension observed in patients with GSH intoxication with consequent development of AKI. Therefore, close and cautious monitoring of initial BP and ECG findings is important for optimal management of patients with GSH poisoning.

ECG abnormalities associated with GSH intoxication have been reported frequently in previous literature [20,24,34]. Various ECG findings have been reported in patients with GSH intoxication including QTc prolongation, sinus tachycardia, and ST-T abnormalities; these were also found in our study. Although the exact mechanism underlying the ECG changes induced by glyphosate herbicides in humans is unknown, the associated hypoxemia, acidosis, and electrolyte abnormalities may cause cardiac complications in glyphosate-poisoning patients [35]. In addition, sympathetic activation, which is related to hemodynamic alterations, has been shown to cause myocardial damage [36,37]. In this study, patients with AKI had lower serum bicarbonate levels and received ventilator care more frequently than those without AKI. We believe that such clinical presentations, including acidosis and hypoxemia, induce hypotension during GSH intoxication resulting in subsequent myocardial damage. Furthermore, surfactants in glyphosate herbicides have been suggested to contribute to hypotension through myocardial depression [38]. Therefore, such mixed pathomechanisms may cause cardiac toxicity during GSH intoxication.

Previous studies have reported that prolonged QTc is not only the most common ECG finding but also predicts mortality in patients with GSH intoxication [20,24,34]. However, there are few studies on the clinical implications of ECG findings in patients with AKI after GSH ingestion. In this study, ECG abnormalities on admission were observed more frequently in the AKI group than in the non-AKI group. However, with the exception of the ST-T change, comparing individual ECG changes between the two groups showed no significant differences in individual ECG findings. In our study, out of the ECG abnormalities, the ST-T change was the only finding that was useful in predict-

ing AKI in patients with GSH intoxication. The ST-T change was also detected during episodes of hypotension [39], which is an important predictor of AKI. Therefore, larger prospective studies are needed to clarify the relationship between ECG changes and GSH intoxication.

The epidemiologic characteristics of toxic agent-related AKI, including herbicides, differ by country, socioeconomic status, and healthcare facility [40]. The incidence of GSH-poisoning–associated AKI was 44.5% in this study, which is higher than that (10%–15%) of general patients admitted to the hospital [41]. The rate of renal replacement therapy initiation in our cohort was 17.1%, which was similar to that of patients admitted to intensive care units reported by Hwang et al. [42]. However, Vilay et al. [43] reported that poisoned patients with renal impairment had a higher rate of renal replacement therapy (27.7%). In addition, the mortality rate identified in the present study was 8.7%, which is significantly lower than that (56%–81%) of herbicide poisoning, including paraquat [44–46]. Therefore, out of toxic agent-related AKI, renal dysfunction after GSH poisoning is considered as a mild type of AKI despite its high incidence. Furthermore, initial hypotension, a risk factor for AKI in previous studies [47,48], was also a predictor of AKI in patients with GSH poisoning. However, further studies are needed to clarify the characteristics of GSH-poisoning–associated AKI.

Our study did have some limitations. First, it was a retrospective single-center design. Second, we did not obtain patient medication history; therefore, data regarding the use of medications that may be associated with ECG abnormalities were unavailable in this study. Large-scale prospective randomized controlled studies are warranted to investigate the clinical characteristics of patients with GSH toxicity.

In this study, the incidence of AKI in patients with GSH intoxication was 44.5%. Hypotension and ECG abnormalities on admission were predictors of AKI in patients with GSH poisoning. Additionally, hypotension and severe AKI were significant predictors of mortality. Therefore, close monitoring of BP is important for optimal management of patients with GSH intoxication.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization: IOS
Investigation: AYC, JHO, KYL, IOS
Data curation: AYC, JHO, SSO, IOS
Formal analysis: AYC, IOS
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