Acute Kidney Injury Predicts Mortality after Charcoal Burning Suicide

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A paucity of literature exists on risk factors for mortality in charcoal burning suicide. In this observational study, we analyzed the data of 126 patients with charcoal burning suicide that seen between 2002 and 2013. Patients were grouped according to status of renal damage as acute kidney injury (N = 49) or non-acute kidney injury (N = 77). It was found that patients with acute kidney injury suffered severer complications such as respiratory failure (P = 0.002), myocardial injury (P = 0.049), hepatic injury (P < 0.001), rhabdomyolysis (P = 0.045) and out-of-hospital cardiac arrest (P = 0.028) than patients without acute kidney injury. Moreover, patients with acute kidney injury suffered longer hospitalization duration (16.9 ± 18.3 versus 10.7 ± 10.9, P = 0.002) and had higher mortality rate (8.2% versus 0%, P = 0.011) than patients without injury. In a multivariate Cox regression model, it was demonstrated that serum creatinine level (P = 0.019) and heart rate (P = 0.022) were significant risk factors for mortality. Finally, Kaplan-Meier analysis revealed that patients with acute kidney injury suffered lower cumulative survival than without injury (P = 0.016). In summary, the overall mortality rate of charcoal burning suicide population was 3.2%, and acute kidney injury was a powerful predictor of mortality. Further studies are warranted.

Charcoal burning suicide was firstly introduced by media to the crowd as a painless and peaceful suicide method in 1998, and soon overwhelmed several Asia countries¹. In the East/Southeast areas, charcoal-burning suicide significantly increased in Taiwan, Hong Kong, Japan, Korea, and Singapore, but not in Malaysia, Philippines and Thailand. Media reports of charcoal-burning suicide played a role in spreading the idea, and there was an increase of charcoal-burning suicide incidence⁵. It was proposed that widespread media coverage of this apparent painless suicide method and easy access to barbecue charcoal may have contributed to the epidemic in Asia countries⁵. The rise of charcoal-burning suicide in Taiwan started at 2000⁶, and the method soon occupied 10 out of 22 cities/counties in 2006 as the leading suicide method². The increase of charcoal-burning suicide influenced mainly in urban areas than rural areas, and metropolitan regions had the highest rate¹. In addition, Taiwan showed the largest magnitude of increase during 1995/1996–2011, about 65-fold increase in rate in affected Asian countries¹. That made an increase of 39% suicide rates during 1998–2002 in urban Taiwan⁴. Moreover, suicide by gases (mainly charcoal-burning) also showed a marked increase in suicide mortality data recently, which caused 6,822 deaths during the period form 1999–2007 in Taiwan¹, and had become a severe public health problem⁴.

Acute kidney injury is a common and serious complication that is associated with high mortality rates in critically ill patients. The primary causes of acute kidney injury include ischemia, hypoxia, or nephrotoxicity⁸. Carbon monoxide toxicity is the result of a combination of tissue hypoxia-ischemia secondary to carboxyhemoglobin

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renal failure (P<0.001), acute respiratory failure (49.0% versus 22.1%, P<0.001), acute hepatic injury (55.1% versus 22.1%, P<0.001), acute rhabdomyolysis (49.0% versus 31.2%, P=0.045) and out-of-hospital cardiac arrest (6.1% versus 0%, P=0.028) than patients without acute kidney injury.

Patients with acute kidney injury demonstrated a higher heart rate than patients without acute kidney injury (102.2±27.3 versus 92.0±23.3, P=0.030, Table 4). Additionally, patients with acute kidney injury had poorer

| Variable                        | Acute kidney injury (N = 49) | Non-acute kidney injury (N = 77) | P value |
|---------------------------------|-----------------------------|---------------------------------|---------|
| Age (year-old)                  | 35.5±12.2                   | 37.6±11.4                       | 0.309   |
| Male, n (%)                     | 40 (81.6)                   | 44 (57.1)                       | 0.004** |
| Carboxyhemoglobin (g/dL)        | 20.7±18.7                   | 23.5±17.9                       | 0.408   |
| Time elapsed between poisoning and hospital arrival (hour) | 7.0±11.0 | 7.9±14.0 | 0.822 |
| Hypertension, n (%)             | 2 (4.1)                     | 9 (11.7)                        | 0.140   |
| Diabetes mellitus, n (%)        | 4 (8.2)                     | 7 (9.1)                         | 0.857   |
| Chronic viral hepatitis, n (%)  | 3 (6.1)                     | 5 (6.5)                         | 0.934   |
| Liver cirrhosis, n (%)          | 2 (4.1)                     | 0 (0)                           | 0.074   |
| Chronic pulmonary disease, n (%)| 3 (6.1)                     | 4 (5.2)                         | 0.825   |
| Smoking habit, n (%)            | 29 (59.2)                   | 32 (41.6)                       | 0.019*  |
| Alcohol consumption, n (%)      | 24 (49.0)                   | 31 (40.3)                       | 0.040*  |

Table 1. Baseline characteristics of patients with charcoal burning suicide, stratified according to status of renal damage as acute kidney injury (creatinine ≥1.2 mg/dL) or non-acute kidney injury (creatinine < 1.2 mg/dL) group (N = 126). Note: *P < 0.05, **P < 0.01, ***P < 0.001.
laboratory data, i.e., white blood count (19847.1 ± 9180.8/mm³ versus 15112.0 ± 12834.5/mm³, \( P = 0.027 \)), blood urea nitrogen (31.2 ± 33.7 mg/dL versus 11.3 ± 2.8 mg/dL, \( P < 0.001 \)), creatinine (2.7 ± 2.4 mg/dL versus 0.9 ± 0.2 mg/dL, \( P < 0.001 \)), creatinine kinase (63010.5 ± 11317.0 ng/mL versus 8664.7 ± 1291.7, \( P = 0.011 \)), myoglobin (24012.9 ± 59481.9 ng/mL versus 1305.3 ± 5343.1, \( P = 0.022 \)), troponin I (5.4 ± 7.5 versus 1.8 ± 4.9, \( P = 0.003 \)), aspartate aminotransferase (404.5 ± 966.5 U/L versus 72.2 ± 93.1 U/L, \( P = 0.005 \)), alanine aminotransferase (200.4 ± 400.5 U/L versus 49.0 ± 44.4 U/L, \( P = 0.016 \)) and total bilirubin (1.2 ± 1.0 mg/dL versus 0.5 ± 0.2 mg/dL, \( P = 0.030 \)) than patients without acute kidney injury. Moreover, arterial blood gas analysis also showed a higher degree of metabolic acidosis in the patients with acute kidney injury than without acute kidney injury (pH 7.3 ± 0.1 versus 7.4 ± 0.6, \( P < 0.001 \)); HCO₃⁻ 18.6 ± 5.1 versus 21.8 ± 3.5, \( P < 0.001 \)).
The overall mortality rate in our charcoal burning suicide population was 3.2% (Table 5). It was demonstrated that patients with acute kidney injury received less hyperbaric oxygen therapy (26.5% versus 50.6%, P = 0.007), but suffered longer duration of hospitalization (16.9 ± 18.3 versus 10.7 ± 10.9, P = 0.002) and higher mortality rate (8.2% versus 0%, P = 0.011) than patients without acute kidney injury.

In a Cox regression model (Table 6), it was disclosed that serum creatinine level (odds ratio 1.761, confidence interval 1.097–2.828, P = 0.019) and heart rate (odds ratio 1.117, confidence interval 1.016–1.228, P = 0.022) were significant risk factors for mortality. In other word, each increment of 1.0 mg/dl in serum creatinine level was associated with a 1.761-fold risk of mortality. Finally, the Kaplan-Meier analysis also revealed patients with acute kidney injury suffered lower cumulative survival than patients without acute kidney injury (Fig. 1, log-rank test, Chi-square = 0.011***). The overall mortality rate in our charcoal burning suicide population was 3.2% (Table 5). It was demonstrated that patients with acute kidney injury received less hyperbaric oxygen therapy (26.5% versus 50.6%, P = 0.007), but suffered longer duration of hospitalization (16.9 ± 18.3 versus 10.7 ± 10.9, P = 0.002) and higher mortality rate (8.2% versus 0%, P = 0.011) than patients without acute kidney injury.

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### Discussion

The overall mortality rate in our charcoal burning suicide population was 3.2%. This favorable mortality figure was comparable with data from other poison centers. One previous study of charcoal burning suicide reported that their mortality rate was 4.1%13, and another study of CO poisoning reported 2.6%10. Furthermore, there was comparable with data from other poison centers. One previous study of charcoal burning suicide reported that their mortality rate was 4.1%13, and another study of CO poisoning reported 2.6%10. Furthermore, there was only 5% of in-hospital mortality even in patients with moderate to severe CO poisoning11. Additionally, our recent study of Taiwanese with CO poisoning reported a mortality rate of 7.3%12.

The analysis indicates that acute kidney injury was most strongly associated with a higher risk of mortality. In a Cox regression model, it was disclosed that serum creatinine level (P = 0.019) was a significant risk factor for mortality. Kaplan-Meier analysis also revealed patients with acute kidney injury suffered lower cumulative survival than patients without injury (P = 0.016). There were occasional case reports14–16 of acute kidney injury and rhabdomyolysis after CO poisoning. The affinity of carbon monoxide to hemoglobin was about 200 times greater than oxygen17, therefore CO poisoning would lead to hypoxia damage to human body. The CO mainly affects the central nervous system and the myocardium; acute kidney injury might occur due to acute rhabdomyolysis and hypoxia.

Interestingly, CO is also an endogenously produced gas resulting from the degradation of heme by heme oxygenase or from fatty acid oxidation18. Recent researches using CO inhalation therapy and carbon monoxide releasing molecules have demonstrated that very small increase in CO could be beneficial to the kidney in several forms of acute renal injury by limiting oxidative injury, decreasing cell apoptosis, and promoting cell survival18.

In a Cox regression model, it was also disclosed that heart rate (P = 0.022) was a significant risk factor for mortality. Each increment of 1 beat per minute in heart rate was associated with a 1.117-fold risk of mortality. Since our body suffered hypoxic stress in CO poisoning due to high affinity of CO to hemoglobin17, and the systemic hypoxia could induce rapid heart rate so as to compensate for the stress.

The majorities of the charcoal burning suicide patients were young to middle age (36.8 ± 11.7 years), male (66.7%), whereas 46.0% was single, 11.9% were divorced, 11.9% living alone, 42.1% senior high school educated, but only 31.7% were jobless. In previous studies, people committed charcoal burning suicide were also mostly young to middle age19, male2,13,20–23, had job13,24, educated21,22, single or divorced13,21,22,24, but not living alone25. It was reported that the men-to-women ratio seemed to be greater in Taiwan than in Hong Kong26, and people committed charcoal burning suicide tended to have non-manual jobs21,22. Notably, a total of 21.4% of the patients had previous suicide history, 49.2% had depressive disorder, 39.7% had adjustment disorder, and 11.1% had substance abuse disorder. Other groups also had observed a high incidence of mood disorder in their studies13,20,25. Furthermore, the percentage of previous suicide history was reported as 33% in a study25, and 38.4% in another13. Overall, the baseline demographic characteristics of charcoal burning suicide in our study were similar to previous reports.

| Variable | Acute kidney injury (N = 49) | Non-acute kidney injury (N = 77) | P value |
|----------|----------------------------|---------------------------------|---------|
| Glasgow Coma Scale |                            |                                 |         |
| Severe injury (3–8), n (%) | 28 (57.1) | 29 (37.7) | 0.135   |
| Moderate injury (9–12), n (%) | 4 (8.2) | 11 (14.3) |         |
| Mild injury (13–15), n (%) | 17 (34.7) | 35 (45.5) |         |
| Fever, n (%) | 20 (40.8) | 15 (19.5) | 0.009** |
| Acute respiratory failure, n (%) | 24 (49.0) | 17 (22.1) | 0.002** |
| Acute myocardial injury, n (%) | 21 (42.9) | 20 (26.0) | 0.049*  |
| Acute hepatic injury, n (%) | 27 (55.1) | 17 (22.1) | <0.001*** |
| Acute rhabdomyolysis, n (%) | 24 (49.0) | 24 (31.2) | 0.045*  |
| Acute gastrointestinal upset, n (%) | 6 (12.2) | 4 (5.2) | 0.154 |
| Stroke, n (%) | 5 (10.2) | 3 (3.9) | 0.157 |
| Shock, n (%) | 5 (10.2) | 3 (3.9) | 0.157 |
| Out-of-hospital cardiac arrest, n (%) | 3 (6.1) | 0 (0) | 0.028* |
| Burn injury (%) | 0.9 ± 2.5 | 0.3 ± 1.5 | 0.112 |
| Neuropsychological impairment, n (%) | 21 (42.9) | 26 (33.8) | 0.538 |

Table 3. Clinical manifestations of patients with charcoal burning suicide, stratified according to status of renal damage as acute kidney injury (creatinine ≥ 1.2 mg/dL) or non-acute kidney injury (creatinine < 1.2 mg/dL) group (N = 126). Note: *P < 0.05, **P < 0.01, ***P < 0.001.
Table 4. Laboratory analysis of patients with charcoal burning suicide, stratified according to status of renal damage as acute kidney injury (creatinine ≥1.2 mg/dL) or non-acute kidney injury (creatinine < 1.2 mg/dL) group (N = 126). Note: *P < 0.05, **P < 0.01, ***P < 0.001.

| Variable                  | Acute kidney injury (N = 49) | Non-acute kidney injury (N = 77) | P value |
|---------------------------|------------------------------|----------------------------------|---------|
| Systolic blood pressure (mmHg) | 116.4 ± 32.8                 | 121.9 ± 26.8                     | 0.308   |
| Diastolic blood pressure (mmHg) | 69.2 ± 22.3                  | 73.5 ± 18.6                      | 0.257   |
| Heart rate (/minute)      | 102.2 ± 27.3                 | 92.0 ± 23.3                      | 0.03*   |
| White blood count (/mm³)  | 19847.1 ± 9180.8             | 15112.0 ± 12834.5               | 0.027*  |
| Polymorphs (%)            | 82.6 ± 12.9                  | 81.6 ± 10.9                      | 0.620   |
| C reactive protein (mg/L) | 65.7 ± 82.0                  | 57.8 ± 90.6                      | 0.778   |
| Hemoglobin (g/dL)         | 15.3 ± 2.3                   | 14.2 ± 2.2                       | 0.008** |
| Hematocrit (%)            | 44.1 ± 6.0                   | 41.2 ± 5.7                       | 0.009** |
| Platelet count (10³/mm³)  | 232.7 ± 80.8                 | 230.9 ± 61.2                     | 0.888   |
| Blood urea nitrogen (mg/dL)| 31.2 ± 33.7                  | 11.3 ± 2.8                       | <0.001*** |
| Creatinine (mg/dL)        | 2.7 ± 2.4                    | 0.9 ± 0.24                       | <0.001*** |
| Creatine kinase (MB) (ng/mL)| 651.2 ± 2187.5              | 29.5 ± 87.61                     | 0.052   |
| Creatine kinase (total) (U/L)| 63010.5 ± 11317.0          | 8664.7 ± 1291.7                 | 0.011*  |
| Myoglobin (mg/mL)         | 24012.9 ± 59481.9           | 1305.3 ± 5343.1                 | 0.022*  |
| Urine myoglobin (ng/mL)   | 1125308.1 ± 1402720.7       | 206308.1 ± 459525.7             | 0.208   |
| Troponin I (ng/mL)        | 5.4 ± 7.5                    | 1.8 ± 4.9                        | 0.003** |
| Aspartate aminotransferase (U/L) | 404.5 ± 966.5             | 72.2 ± 93.1                      | 0.005** |
| Alanine aminotransferase (U/L) | 200.4 ± 400.5              | 49.0 ± 44.4                      | 0.016*  |
| Alkaline phosphatase (U/L) | 67.3 ± 23.1                  | 55.8 ± 37.7                      | 0.365   |
| Total bilirubin (mg/dL)   | 1.2 ± 1.0                    | 0.5 ± 0.2                        | 0.030*  |
| Albumin (g/dL)            | 3.3 ± 1.1                    | 3.5 ± 0.6                        | 0.536   |
| Calcium (mg/dL)           | 7.9 ± 1.1                    | 8.2 ± 0.6                        | 0.278   |
| Phosphate (mg/dL)         | 3.9 ± 1.9                    | 2.8 ± 0.9                        | 0.032*  |
| Sodium (mmol/L)           | 140.7 ± 4.8                  | 140.7 ± 2.7                      | 0.983   |
| Potassium (mmol/L)        | 6.8 ± 17.1                   | 4.5 ± 5.1                        | 0.311   |
| Arterial blood gas        |                             |                                  |         |
| pH                        | 7.3 ± 0.1                    | 7.4 ± 0.6                        | <0.001*** |
| PCO₂ (mmHg)               | 35.1 ± 8.8                   | 34.9 ± 5.3                       | 0.878   |
| PO₂ (mmHg)                | 241.0 ± 153.6                | 227.2 ± 137.5                    | 0.610   |
| HCO₃⁻ (mmol/L)            | 18.6 ± 5.1                   | 21.8 ± 3.5                       | <0.001** |
| SaO₂ (%)                  | 95.6 ± 9.9                   | 95.7 ± 11.7                      | 0.967   |
| Urine benzo diazepine, n (%)| 8 (16.3%)                   | 16 (20.8%)                       | 0.371   |
| Urine ethanol, n (%)      | 1 (2.0%)                     | 7 (9.1%)                         | 0.125   |
| Urine amphetamine, n (%)  | 3 (6.1%)                     | 2 (2.6%)                         | 0.143   |
| Urine morphine, n (%)     | 2 (4.1%)                     | 0 (0.0%)                         | 0.047*  |
| Globus pallidus necrosis on imaging, n (%) | 20 (40.8%)                | 20 (26.0%)                       | 0.218   |

Table 5. Detoxification protocol and outcome for patient with charcoal burning suicide, stratified according to status of renal damage as acute kidney injury (creatinine ≥1.2 mg/dL) or non-acute kidney injury (creatinine < 1.2 mg/dL) group (N = 126). Note: *P < 0.05, **P < 0.01, ***P < 0.001.

| Variable                  | Acute kidney injury (N = 49) | Non-acute kidney injury (N = 77) | P value |
|---------------------------|------------------------------|----------------------------------|---------|
| Hyperbaric oxygen therapy, n (%) | 13 (26.5)                   | 39 (50.6)                        | 0.007** |
| Duration of hospitalization (days) | 16.9 ± 18.3                | 10.7 ± 10.9                      | 0.002** |
| Mortality, n (%)          | 4 (8.2)                      | 0 (0)                            | 0.011*  |

The carboxyhemoglobin level detected in hospital was greatly affected by the timing of hospital arrival because different patients had different time elapsed between termination of CO exposure to hospital arrival. The rescue intervention of oxygen supply before arriving to hospital might be another interference\(^2\). In the present study, the level of carboxyhemoglobin was not related to the mortality of charcoal burning suicide patients, and our finding
was similar to a retrospective analysis of 1505 patients. Also, there was no statistical difference between patients with and without acute kidney injury in term of carboxyhemoglobin level ($P > 0.05$). One study analyzed 1407 CO poisoning patients from 1978 to 2005 reported that compared to those survived, the carboxyhemoglobin level was significantly higher in 37 patients who died in 30 days. However, due to limitation of that study, it was suggested that the clinical correlation between carboxyhemoglobin level and medical conditions was not sure. Furthermore, a 10-year-period study that divided 476 patients into 3 groups based on carboxyhemoglobin levels reported that no correlation was found between carboxyhemoglobin levels and vital signs. One study also noted that the initial carboxyhemoglobin level was unrelated to subsequent cognitive sequel. Nevertheless, the level of carboxyhemoglobin still has its clinical role. In order to rapidly estimate carboxyhemoglobin level, venous carboxyhemoglobin level could also be used due to it has high accuracy to predict arterial carboxyhemoglobin level, and the pulse CO oximeter could be another choice for fast rescue management.

In the present study, 52 cases (41.3%) received hyperbaric oxygen therapy. A Cox regression analysis revealed that hyperbaric oxygen therapy was not a significant factor that associated with good outcome. Previous papers mentioned the correlation between hyperbaric oxygen therapy and mortality rate were variable. Applying hyperbaric oxygen therapy was considered to use oxygen to compete the binding sites of hemoglobin, and to shorten the half-life of carboxyhemoglobin into 15–30 minutes. Hyperbaric oxygen therapy seemed to have the potential to reduce hypoxic effects, and therefore oxygen-consuming organs were protected. One study reported hyperbaric oxygen therapy was better than normobaric oxygen therapy in reducing risk of cognitive sequel. Another cell-based study reported hyperbaric oxygen had better protective effect over rat astrocytes. Our data revealed that patients with acute kidney injury received less hyperbaric oxygen therapy than patients without acute kidney injury (26.5% versus 50.6%, $P = 0.007$). The reason was unclear. One possible explanation was since there were more incidences of acute respiratory failure in patients with acute kidney injury than without injury (49.0% versus 22.1%, $P = 0.002$); it was possible that these patients could not receive hyperbaric oxygen therapy simply because of intubation. Notably, a Cochrane systemic review of 6 studies reported that the existing data did not establish whether the administration of hyperbaric oxygen therapy to patients with carbon monoxide poisoning could reduce the incidence of adverse neurologic outcomes.

Conclusions and Limitations

In summary, the overall mortality rate in our charcoal burning suicide population was 3.2%. Furthermore, the analysis indicates that acute kidney injury was most strongly associated with a higher risk of mortality. Nevertheless, our data was limited by retrospective nature of the study, small sample size, single-center study, difficulty in obtaining the initial ambient carbon monoxide concentrations or carboxyhemoglobin levels at the scene, lack of measurement of serum inflammation markers, lack of psychoanalytical data, and finally lack of standard indications for hyperbaric oxygen therapy. Notably, the primary and most obvious shortcoming of most single-center studies is their potentially limited external validity. Results from a single clinical hospital are not necessarily generalizable to a broader population, and this may be particularly true in critically ill patients such as charcoal burning suicide. Further studies are warranted.

Methods

Ethics. The present retrospective observational study complied with the guidelines of the Declaration of Helsinki, and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital, a tertiary referral center (with 24-hour hyperbaric oxygen service) located in the northern part of Taiwan. Since this study involved a retrospective review of existing data, Institutional Review Board approval was obtained without specific informed consent from the patients. However, informed consent was obtained from all patients at their initial admission for risk of acute CO poisoning and all treatments. Additionally, all individual information was securely protected by delinking identifying information from main data set and was only available to investigators. Furthermore, all of the data were analyzed anonymously. The Institutional Review Board of the Chang Gung Memorial Hospital approved the study protocol. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
and mortality data were recorded. Electrolytes and arterial blood gas were collected. Moreover, the detoxification treatment, hospitalization duration, detecting globus pallidus necrosis, and laboratory examinations such as blood test, carboxyhemoglobin test, electrolytes and arterial blood gas were collected. Moreover, the detoxification treatment, hospitalization duration, and mortality data were recorded.

**Patients.** We enrolled all patients with the diagnosis of acute CO poisoning with the intention of charcoal burning suicide at Chang Gung Memorial hospital from 2002 to 2013. Clinical history, clinical manifestations, physical examinations, and blood carboxyhemoglobin test were examined for the diagnosis of CO poisoning. Social demographic information such as gender, underlying diseases, personal habits, marriage status, educational status, working condition, living condition, and previous psychiatric diseases was examined. Medical data of enrolled patients including Glasgow coma scale, vital signs, clinical manifestations, radiographic image for detecting globus pallidus necrosis, and laboratory examinations such as blood test, carboxyhemoglobin test, electrolytes and arterial blood gas were collected. Moreover, the detoxification treatment, hospitalization duration, and mortality data were recorded.

**Inclusion and exclusion criteria.** All patients committed charcoal burning suicide with the diagnosis of acute CO poisoning and sent to the emergency room of Chang Gung Memorial Hospital from 2002 to 2013 were included into the present study. We excluded CO poisoning patients with suicide intention by using other methods (i.e. wasting gas of cars, burning other materials) instead of charcoal burning.

**Detoxification protocol.** Treatments included administering a high concentration of oxygen therapy via a non-rebreather mask or providing hyperbaric oxygen therapy. Similar to other international Poison Centers, there was no standard indication for such hyperbaric oxygen treatment.

**Hyperbaric oxygen therapy.** All patients breathed 100% oxygen via a facial mask at elevated pressure of 2.5 atmospheric absolute for 90–95 minutes daily. The absolute contraindication for hyperbaric oxygen therapy was an untreated pneumothorax. On the other hand, the relative contraindications included asthma, chronic obstructive pulmonary disease, history of seizure, high fever, upper respiratory infections, viral infections, pregnancy, active cancerous condition, congenital spherocytosis, claustrophobia, diseases related to ears, nose, and eyes, and those patients who need intensive care.

**Definitions of clinical events.** Fever was defined as a body temperature of above 38.3°C. Acute respiratory failure implied that a patient needed intubation and mechanical ventilation. Acute myocardial injury was defined as troponin-I of more than 5 ng/mL or abnormal electrocardiogram. Acute hepatic injury was defined as elevation of alanine aminotransferase level greater than 2 times of upper normal limit (i.e., >68 U/L, normal: 0–34 U/L) or total bilirubin levels of >1.5 mg/dL. Acute rhabdomyolysis was defined as increase of myoglobin in the urine, and marked elevation of total creatinine kinase for more than 5 times of upper limit (i.e., >10000 U/L, normal: 200 U/L). Shock was defined as a condition with an abnormality of the circulatory system that results in inadequate organ perfusion and tissue oxygenation. Globus pallidus necrosis was defined as bilateral and symmetric lesions in globus pallidus using brain radiographic studies such as magnetic resonance imaging or computed tomography.

**Statistical analysis.** All data were tested for normality of distribution and equality of standard deviation prior to analysis. Continuous variables were expressed as the means ± standard deviations for the number of observations. In the meantime, categorical variable were expressed as number (percentages). For comparison between two groups, the Student's t test for quantitative variables and Chi-square or Fisher's exact tests for categorical variables were used. The Kaplan-Meier method was applied for mortality comparison and significance was tested using a log-rank test. A univariate Cox regression analysis was performed to compare the frequency of possible risk factors associated with mortality. To control for confounding factors, a multivariate Cox regression analysis (stepwise backward approach) was performed with the factors that were significant in univariate models (P < 0.05) and met the assumptions of a proportional hazard model. We considered P < 0.05 as statistical significance. All statistical analyses were performed using IBM SPSS Statistics Version 20 (IBM Corporation, Armonk, NY, USA).

|                  | Uni-variable analysis | Multi-variable analysis |
|------------------|-----------------------|-------------------------|
|                  | Odds ratio (95% confidence interval) | P value | Odds ratio (95% confidence interval) | P value |
| Creatinine (each increase of 1 mg/dL) | 1.474 (1.185–1.834) | <0.001*** | 1.761 (1.097–2.828) | 0.019* |
| Heart rate (each increase of 1 beat per minute) | 1.063 (1.022–1.106) | 0.002** | 1.117 (1.016–1.228) | 0.022** |
| Bicarbonate (each decrease of 1 mmol/L) | 1.235 (1.027–1.484) | 0.025* | 1.224 (0.810–1.852) | 0.337 |

Table 6. A Cox regression model for analysis of mortality (N = 126). *P < 0.05, **P < 0.01, ***P < 0.001.
Author Contributions
Y.-C.C., Y.-C.T. performed study and wrote manuscript, W.-H.H., C.-W.H., C.-H.W., S.-H.L., H.-Y.Y. and K.-H.C. managed patient, H.-L.C., J.-F.F., W.-R.L. and I.-K.W. analyzed data, T.-H.Y. designed and supervised study.

Additional Information
Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Chen, Y.-C. et al. Acute Kidney Injury Predicts Mortality after Charcoal Burning Suicide. Sci. Rep. 6, 29656; doi: 10.1038/srep29656 (2016).

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