Nationwide population-based study of poisoning-induced out-of-hospital cardiac arrest in South Korea

Gihun Park, Chiwon Ahn , Jae Hwan Kim

ABSTRACT
Objective To evaluate the characteristics of poisoning-induced out-of-hospital cardiac arrest (pOHCA) and the factors influencing survival to discharge and good neurological outcomes using a nationwide, population-based database.

Design Nationwide, retrospective, population-based cohort study.

Setting and participants This study included adult patients who had experienced pOHCA and those who had not (non-pOHCA patients) in South Korea from January 2008 to December 2018.

Outcome measures The primary outcome was survival to discharge, and the secondary outcome was a good neurological outcome.

Methods The basic characteristics of pOHCA and non-pOHCA patients were analysed by descriptive analysis. Logistic regression analysis was conducted for related variables, including pOHCA.

Results A total of 173 190 patients were included, and 3582 patients (2.1%) were in the pOHCA group. Some of the pOHCA patients were young (56.2±17.8 vs 69.0±15.5, p<0.001), a few of their cardiac arrests were witnessed (12.8% vs 45.1%, p<0.001), a few were resuscitated by bystanders (8.2% vs 14.8%, p<0.001) and they had low shockable rhythm rates (1.2% vs 8.8%, p<0.001). They showed significantly lower survival to discharge and poorer neurological outcomes than non-pOHCA patients (survival to discharge, 3.7% vs 6.2%, p<0.001; good neurological outcomes, 1.3% vs 3.2%, p<0.001). There were no significant differences between pOHCA and non-pOHCA patients in terms of the adjusted ORs for survival to discharge (adjusted OR 0.608; 95% CI 0.86 to 1.27) and good neurological outcomes (adjusted OR 1.03; 95% CI 0.73 to 1.42).

Conclusion This study shows that apparent aetiology of OHCA caused by poison, did not influence survival to discharge and good neurological outcomes. Furthermore, pOHCA occurs in younger patients and has fewer witnessed and shockable rhythms. pOHCA did not influence survival to discharge and good neurological outcomes. Also, pesticides and gases were the most frequent substances causing pOHCA in South Korea.

INTRODUCTION
Out-of-hospital cardiac arrest (OHCA) is a major public health issue.1 2 OHCA includes both cardiac and noncardiac cause arrests, and non-cardiac cause arrests are characterised by young age and a low incidence of ventricular arrhythmia.3 4 There are various causes of non-psychogenic OHCA, but poisoning-induced OHCA is a global public health issue,3 5 resulting in more than 1000 deaths every year.3 6 Claesson et al reported that 5.9% of all non-medical-aetiological cardiac arrests in Sweden were pOHCA;7 Orkin et al reported the rate was 13.8% in Ontario, Canada8 9 and Kim et al showed that 6.7% of emergency medical services (EMS)-treated OHCA in South Korea were due to poison exposure.10

The generally known characteristics of pOHCA are similar to those of noncardiac cause OHCA, but pOHCA occurs in younger people, have lower shockable rhythm rates and have fewer witnesses.7 8 10 Lower shockable rhythm rates and fewer witnesses are associated with lower OHCA survival rates.6 11 However, the pathophysiological mechanism of a pOHCA is different from that of a cardiac cause arrest.11 12 Despite these differences, similar or better outcomes were observed for some cases of pOHCA.7

Another reason for lower pOHCA survival rates could be differences in the poisoning agents causing the arrests. Opioid and
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cocaine poisoning account for 70% of pOHCA deaths in the USA. However, in some countries, this percentage is significantly lower. A previous study showed that the rate of pOHCA deaths caused by opioid and cocaine poisoning in South Korea was 1/18th that of the USA. In contrast, Kim et al reported a high mortality rate from gases and pesticides among EMS-treated OHCAs in South Korea.

In this study, we analysed the expanded population of pOHCA patients and compared them with the non-pOHCA population based on a nationwide, population-based database of 11 years in South Korea. In addition, we evaluated the factors affecting outcomes, including poison exposure.

METHODS
Study design, setting and data source
This study was a retrospective observational study that evaluated the characteristics of pOHCA patients and prognostic factors associated with survival to discharge and good neurological outcomes from January 2008 to December 2018 using the nationwide, population-based database Out-of-Hospital Cardiac Arrest Surveillance (OHCAS) (managed by the Korea Disease Control and Prevention Agency (https://www.kdca.go.kr/)). The database includes all acute cardiac arrest patients transferred to medical institutions via EMS, which is around 30,000 patients per year.

In South Korea, the government-based public EMS operates 24 hours a day, 365 days a year and is operated through 19 fire headquarters nationwide by the National Fire Agency. When an OHCA occurs, an ambulance is dispatched to where the arrest occurred in response to a phone call, and the patient is transferred to a hospital. Paramedics provide cardiopulmonary resuscitation (CPR) using an automatic external defibrillator before transport to the hospital. CPR can be stopped, or advanced airway techniques can be provided under the supervision of a physician, but poisons for advanced life support (ACLS) cannot be used. At handover to the hospital, any substances related to the poisoning found at the scene and any corresponding information are transmitted. Treatments for resuscitation at the hospital and after the return of spontaneous circulation (ROSC) are performed according to each hospital’s protocol.

OHCAS uses data based on patient information extracted from the EMS data registry and hospital medical records. KCDA medical record reviewers visit medical institutions to investigate arrest patients’ medical records in relation to treatments and outcomes and to check items according to the Utstein Style and the Resuscitation Outcomes Consortium Project. The database consists of individuals and settings, EMSs, care received in the emergency department, hospital procedures and the outcomes at discharge, including survival to discharge and neurological outcomes, using a customised survey form.

Study population and poisoning group pOHCA patients were defined as patients whose causes of cardiac arrest had been marked as poisoning in the database. The major poisoning agents were classified into 10 types in the database, and each item was recategorised into five groups using the method of classification described previously. Group 1 included non-opioid analgesics and antipyretics; antiepileptic, sedative–hypnotic, anti-Parkinsonism and psychotropic drugs; narcotics and hallucinogens; other

Figure 1 Flow chart of study patients and study design. DNR, do-not-resuscitate; OHCA, out-of-hospital cardiac arrest.
drugs acting on the autonomic nervous system; and other unspecified drugs, medicaments and biological substances. Group 2 included other gases and vapours. Group 3 included pesticides. Group 4 included organic solvents and halogenated hydrocarbons and their vapours/alcohol. Group 5 included other unspecified chemicals and noxious substances. We excluded patients aged <18 years old, those with do-not-resuscitate orders, those who experienced traumatic cardiac arrests, those with invalid prehospital data and those with unknown final outcomes.

Variables
Several variables were collected, including age, gender, place of arrest (public, private or in the ambulance), region (metropolitan, urban or rural), whether the arrest was witnessed, whether bystander CPR was performed, whether rhythms were initially monitored in the prehospital interval (non-shockable vs shockable), time from arrest to hospital arrival and prehospital and in-hospital ROSC. A shockable rhythm was defined as an initial rhythm identified as pulseless ventricular tachycardia or ventricular fibrillation.

Outcome measures
The primary outcome of this study was survival to discharge, which was defined as the normal discharge of the patient or transfer to another medical facility for long-term treatment after acute treatment. The secondary outcome was a good neurological outcome. The neurological outcomes were categorised by the Cerebral Performance Category (CPC) score. Good neurological outcomes were defined as CPC scores of 1 and 2.

Statistical analyses
The data were analysed using Excel 2016 (Microsoft, Redmond, Washington, USA) and the R program (V.4.1.1, The R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were applied to describe the baseline characteristics. For continuous variables, values are shown as means±SDs. Normally distributed variables were analysed using the Student’s t-test between groups. For categorical variables, data are expressed as frequencies and percentages. The χ² test or Fisher’s exact test was used to analyse categorical variables using contingency tables. In addition, the ORs for each group for each outcome were obtained and compared within the pOHCA group.

To identify outcome predictors, the covariates, including the binary variable of the cause of arrest (pOHCA or non-pOHCA), were evaluated by multivariate analysis. Logistic regression using the ‘enter’ method was independently performed. Age, gender, prehospital ROSC, witnessed or unwitnessed, bystander CPR, place of arrest, shockable rhythms and the cause of arrest were adjusted. In addition, ORs (95% CIs) were calculated for the outcomes by poison group. A p<0.05 was considered statistically significant.

Patient and public involvement
Neither patients nor the public were involved in the design, planning, conduct or reporting of this study.
RESULTS
Characteristics of the study subjects
We identified 293,852 patients who had experienced OHCA between January 2008 and December 2018. We excluded patients aged <18 years (n=7114), those who had do-not-resuscitate orders (n=7150), those who had experienced traumatic OHCA (n=63,427), those with invalid prehospital data (n=28,126), and those whose survival outcome was unknown (n=14,845). There were 1020 patients with poisoning-induced OHCA among those included among those with invalid and missing outcomes. After exclusions, 173,190 patients were included in this study, of which 35,822 were pOHCA patients (figure 1).

Between the pOHCA and non-pOHCA groups, there were significant differences in age, shockable rhythms, witnessed, bystander CPR and gender. pOHCA patients had significantly lower survival to discharge and poorer neurological outcomes than non-pOHCA patients (survival to discharge, 3.7% (pOHCA) vs 6.2% (non-pOHCA), p<0.001; good neurological outcomes, 1.3% (pOHCA) vs 3.2% (non-pOHCA), p<0.001). Details of the patient population are shown in table 1.

Table 2 shows the distribution of the 35,822 pOHCA patients according to poisoning agent. Pesticides accounted for 44.7% of poisonings (160/35,822), followed by other gases and vapours (33.2%; 1188/35,822). The survival rates were 2.8% and 2.5% for pesticides and gases, respectively, and the lowest survival rate was for poisoning by narcotics (no survivors out of eight patients).

Univariate and multivariate logistic regression analysis of prognostic factors associated with survival to discharge and good neurological outcomes
Univariate analysis showed that all included variables influenced survival to discharge. We then performed multivariate analysis including these variables. Among the variables included in the model, being male (OR 1.06, 95% CI 1.01 to 1.11, p<0.001), prehospital ROSC (OR 34.36, 95% CI 32.11 to 36.77, p<0.001), bystander CPR (OR 1.46, 95% CI 1.38 to 1.55, p<0.001) and shockable rhythms (OR 3.85, 95% CI 3.62 to 4.08, p<0.001) were significantly associated with better survival to discharge. Place of arrest (OR 0.99, 95% CI 0.95 to 1.04, p=0.832) and cause of arrest (OR 0.608, 95% CI 0.86 to 1.27) did not differ significantly between the two groups (table 3).

Good neurological outcomes were also associated with all the included variables in the univariate analysis. In multivariate analysis, being male (OR 1.16, 95% CI 1.06 to 1.27, p<0.001), prehospital ROSC (OR 47.86, 95% CI 44.19 to 51.85, p<0.001), witnessed arrest (OR 3.03, 95% CI 2.76 to 3.33, p<0.001), bystander CPR (OR 1.59, 95% CI 1.47 to 1.73, p<0.001) and shockable rhythms (OR 5.93, 95% CI 5.46 to 6.44, p<0.001) were significantly associated with good neurological outcomes. Place of arrest (OR 1.01, 95% CI 0.94 to 1.08, p=0.820) and cause of arrest (OR 1.03, 95% CI 0.73 to 1.42) did not differ significantly between the two groups (table 3).

Univariate analysis of outcomes of pOHCA patients by poisoning agent group
Other gases and vapours (group 2) and pesticides (group 3) had significantly lower survival to discharge rates than the other groups (group 2: OR 0.57, 95% CI 0.38 to 0.86; group 3, OR 0.61, 95% CI 0.43 to 0.89) (figure 2A).

In addition, other gases and vapours (group 2) and pesticides (group 3) had significantly poorer neurological outcomes than other groups (group 2: OR 0.35, 95% CI 0.16 to 0.78; group 3: OR 0.42, 95% CI 0.22 to 0.81) (figure 2B).

Table 2 Poisonings in pOHCA

<table>
<thead>
<tr>
<th>Poisoning agent</th>
<th>No, n (n=3582)</th>
<th>Survival to discharge, % (n=134)</th>
<th>Good neurological outcome, % (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 Non-opioid analgesics and antipyretics</td>
<td>16 (0.5)</td>
<td>2 (12.5)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Antiepileptic, sedative–hypnotic, anti-Parkinsonism and psychotropic drugs</td>
<td>199 (5.6)</td>
<td>23 (11.6)</td>
<td>13 (6.5)</td>
</tr>
<tr>
<td>Narcotics and hallucinogens</td>
<td>8 (0.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other drugs acting on the autonomic nervous system</td>
<td>16 (0.5)</td>
<td>4 (25.0)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Other and unspecified drugs, medicaments and biological substances</td>
<td>137 (3.8)</td>
<td>9 (6.6)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Group 2 Other gases and vapours</td>
<td>1188 (33.2)</td>
<td>30 (2.5)</td>
<td>7 (0.5)</td>
</tr>
<tr>
<td>Group 3 Pesticides</td>
<td>1601 (44.7)</td>
<td>45 (2.8)</td>
<td>12 (0.7)</td>
</tr>
<tr>
<td>Group 4 Organic solvents and halogenated hydrocarbons and their vapours</td>
<td>29 (0.8)</td>
<td>1 (3.4)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10 (0.3)</td>
<td>2 (20.0)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Group 5 Other and unspecified chemicals and noxious substances</td>
<td>387 (10.8)</td>
<td>28 (5.2)</td>
<td>7 (1.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor</th>
<th>Survival to discharge</th>
<th>Good neurological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate OR</td>
<td>Adjusted OR</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.96 (0.96 to 0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1.80 (1.72 to 1.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prehospital ROSC</td>
<td>82.14 (77.36 to 87.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Witnesses</td>
<td>5.29 (5.04 to 5.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>3.70 (3.55 to 3.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Place of arrest</td>
<td>0.62 (0.60 to 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shockable rhythms</td>
<td>14.62 (14.00 to 15.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cause, pOHCA‡</td>
<td>0.59 (0.49 to 0.70)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Factors included in the final logistic regression model for survival to discharge.
†Factors included in the final logistic regression model for good neurological outcomes.
‡Poisoning-induced OHCA was not selected as a factor in the final logistic regression models.

Model of multivariate logistic regression analysis was backward stepwise and adjusted for the above factors.

CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; pOHCA, poisoning-induced out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.
According to this classification, opioids were not classified as antipyretics, antiepileptics, sedative–hypnotics, anti-Parkinsonism and psychotropic drugs/narcotics and hallucinogens/other drugs acting on the autonomic nervous system/other and unspecified drugs, medicaments and biological substances. Group 2 included other gases and vapours. Group 3 included pesticides. Group 4 included organic solvents and halogenated hydrocarbons and their vapours/alcohol. Group 5 included other and unspecified chemicals and noxious substances.

pOHCA group had fewer witnesses, less bystander CPR and fewer shockable rhythms than those of the non-pOHCA group (age, 42.68 years (41.19±44.18 years) vs 68.50 years (68.26±68.74 years)) fewer witnessed cardiac arrests (27.5% vs 51.6%); less bystander CPR (32.6% vs 40.2%); and fewer shockable rhythms (7.8% vs 23.3%). In this study, in comparison with non-pOHCA, pOHCA had a lower age of occurrence (58.2±17.8 years (pOHCA) vs 69.0±15.5 years (non-pOHCA), p<0.001), a lower witness frequency (12.8% (pOHCA) vs 45.1% (non-pOHCA)), a lower frequency of bystander CPR (8.2% (pOHCA) vs 14.8% (non-pOHCA)), and a lower frequency of shockable rhythms (1.2% (pOHCA) vs 8.8% (non-pOHCA)). In addition, there was a significant difference in prehospital ROSC—for pOHCA, it was 2.1%, and for non-pOHCA, it was 4.0% (p<0.001); this opposes the previous study, which found that poisoning-induced patients had a high prehospital ROSC.

In this study, pOHCA exhibited lower survival to discharge rates and poorer neurological outcomes compared with those of non-pOHCA patients. Additionally, logistic regression analysis of survival to discharge rates and good neurological outcomes, including pOHCA as one factor, showed that the ORs of pOHCA and non-pOHCA were 0.59 and 0.40, respectively, indicating that pOHCA had significantly lower survival to discharge rates and poorer neurological outcomes than those of non-pOHCA. However, after adjusting for other variables, pOHCA was not a factor influencing the survival to discharge rate and good neurological outcomes. Prehospital ROSC, witnesses, bystander CPR, shockable rhythms, and being male were important factors influencing the survival to discharge rates of OHCA patients. These factors were also important influences on good neurological outcomes.

Based on our previous study, the poisoning agents that caused pOHCA were divided into five categories. According to this classification, opioids were not classified separately, and group 1 included non-opioid analgesics, antipyretics, antiepileptics, sedative–hypnotics and anti-Parkinsonian drugs. Analysis of the effects of the five groups of poisoning agents on survival to discharge and good neurological outcomes after pOHCA indicated that other gases, vapours and pesticides resulted in relatively low survival to discharge rates. In the case of opioid poisoning, previous studies indicated poor prognoses, but there were only eight pOHCA caused by narcotics in the domestic pOHCA database; therefore, this could not be analysed. It can be estimated that the poor prognoses of pOHCA caused by other gases, vapours and pesticides, which showed a high incidence rate, are reflected in the prognoses of the overall pOHCA.

There were several limitations to this study. First, it is possible that poisoning exposure, including drug overdose, as a cause of cardiac arrest was underestimated in the database. For accurate analyses of causes, autopsies are required, but pOHCA would have been excluded to a significant extent because these analysed data used clinical information. This has been mentioned in previous studies as well. Second, detailed information about additional treatments other than ACLS could not be obtained. For example, we could not confirm additional information on the use of naloxone as an antidote for opioids and the use of pesticide antidotes. Third, it is difficult to make global generalisations because this study reflects regional characteristics. Fourth, despite including all EMS patients at the national level, the data contain many missing and insufficient values. In this study, the proportion of invalid or missing outcome data was 14.7%, and the proportion for pOHCA specifically was 22.2%. These missing data may have affected the results; for example, it may have limited our interpretation of the outcomes. Finally, in retrospective observational studies, selection bias can occur and potential confounders, such as underlying disease, haemodynamic status and laboratory findings, can be included.

CONCLUSION

This nationwide, population-based study shows that pOHCA is characterised by patients of younger age with fewer witnesses and shockable rhythms. In patients with OHCA,
pOHCA was not a variable influencing survival to discharge and good neurological outcomes, but witnesses, shockable rhythms and bystander CPR were significantly associated with good neurological outcomes. In addition, pesticides and gases were the most frequent causative agents of pOHCA; compared with other substances, they resulted in lower survival to discharge rates and poorer neurological outcomes in South Korean pOHCA patients.

**Contributors** CA conceptualised the study, GP and CA managed data collection, CA and JHK conducted factor analysis and provided statistical technical input. GP and CA wrote the manuscript. All authors reviewed and contributed to the final version of the manuscript. CA is responsible for the overall content as the guarantor.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was exempt from review by the institutional review board of Chung-Ang University Hospital because the study data were anonymous (2104-003-19361).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request.

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A nationwide population-based study of poisoning-induced out-of-hospital cardiac arrest in South Korea

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Supplementary Figure 1. Trend of poisoning induced OHCA occurrence and outcome for 11 years in South Korea. Group 1 include non-opioid analgesics and antipyretics / antiepileptic, sedative-hypnotic, anti-Parkinsonism and psychotropic drugs / narcotics and hallucinogens / other drugs acting on the autonomic nervous system / other and unspecified drugs medicaments and biological substances. Group 2 include other gases and vapors. Group 3 include pesticides. Group 4 include organic solvents and halogenated hydrocarbons and their vapors / alcohol. Group 5 include other and unspecified chemicals and noxious substances.