

REUE | Original Article

# Mortality from acute poisoning in Spanish hospitals (EXITOX Registry 2012–2019)

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**INTRODUCTION.** Although in the emergency department setting, in-hospital mortality due to acute poisoning is a rare finding, its analysis gives valuable insights for future care.

**MATERIAL AND METHODS.** We conducted an observational study of patients who died from acute poisoning in the emergency departments of 13 Spanish public hospitals from 2012 through 2019 based on the EXITOX registry promoted by the Spanish Foundation of Clinical Toxicology (FETOC). The registry includes epidemiological, clinical, therapeutic variables and death-related data.

**RESULTS.** A total of 172 cases were recorded (58.7%, men). The mean age was 58.4 years (SD, 20.9). A total of 40.7% of the cases were due to suicide and 30.2% to drug overdoses. The main route of exposure was oral (75%), and in 127 cases (76.1%) poisoning involved a single substance. Chemical/household products (32.6%) and drugs (31.4%) were the most common toxic agents. The most common substances were hydrochloric acid (14%), cocaine (11%), and metformin (9.9%). Ethanol and benzodiazepines were involved in 63.2% of cases, almost always as part of polysubstance use. The most common initial clinical presentation was decreased level of consciousness, followed by cardiac arrest. The leading mechanisms of death were multiple organ failure, anoxic encephalopathy, or internal injuries due to caustic ingestion. Antidotes were administered in 30.4% of cases, extracorporeal elimination in 9.8%, and GI decontamination in 6.4%.

**CONCLUSION.** This is the first Spanish study on in-hospital mortality from acute poisoning, which identified 2 primary profiles of deceased patients: caustic ingestions in the context of suicide and drug-related iatrogenic complications (metformin, digoxin) in elderly patients. Deaths were also observed in young individuals after polysubstance use involving alcohol, cocaine, and benzodiazepines. The study should support the implementation of preventive measures in avoidable cases.

**Keywords:** Mortality. Acute poisoning. Emergency Department.

## Mortalidad por intoxicación aguda en hospitales españoles (Registro EXITOX 2012-2019)

**INTRODUCCIÓN.** En urgencias, la mortalidad hospitalaria tras una intoxicación aguda (IA) es poco habitual, pero su análisis aporta información relevante para establecer medidas preventivas.

**MATERIAL Y MÉTODOS.** Estudio observacional de pacientes fallecidos por IA en los servicios de urgencias de 13 hospitales públicos españoles entre los años 2012 y 2019, a partir del registro EXITOX promovido por la Fundación Española de Toxicología Clínica (FETOC), el cual recoge variables epidemiológicas, clínicas, terapéuticas y epicrisis del fallecimiento.

**RESULTADOS.** Se registraron 172 casos, siendo el 58,7% varones. La edad media fue de 58,4 (DE 20,9) años. El 40,7% fueron de causa suicida y el 30,2% sobredosificaciones medicamentosas. La principal vía de contacto con el tóxico fue oral (75%) y en 127 casos (76,1%) el producto implicado en la intoxicación fue único. Los productos químicos/domésticos (32,6%) y los fármacos (31,4%) fueron los grupos de tóxicos más habituales. El ácido clorhídrico (14%), la cocaína (11%) y la metformina (9,9%) fueron los agentes más frecuentes. El etanol y las benzodiazepinas estuvieron implicadas en 63,2% de los episodios, casi siempre en un consumo múltiple. La clínica inicial más habitual fue la disminución del nivel de conciencia, seguido de la parada cardiaca. Los mecanismos que con mayor frecuencia provocaron la muerte fueron el fracaso multiorgánico, la encefalopatía anóxica o las lesiones orgánicas tras causticación digestiva. Se administraron antidotos en el 30,4%, depuración extrarrenal en el 9,8% y descontaminación digestiva en el 6,4% de los casos.

**CONCLUSIONES.** Se identificaron dos perfiles de fallecidos por IA: las causticaciones en contexto suicida y los problemas iatrogénicos con fármacos (metformina, digoxina) en ancianos. También se ha observado el fallecimiento de jóvenes tras policonsumo con alcohol, cocaína y benzodiazepinas.

**Palabras clave:** Mortalidad. Intoxicación aguda. Servicio de Urgencias.

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## Introduction

Knowledge of the effects of toxic agents on the human body is, for evident ethical reasons, at odds with most of the scientific evidence tools available to other fields of medicine (controlled clinical trials, tests in healthy volunteers, etc). This limitation requires that knowledge in clinical toxicology be advanced through other sources, such as epidemiology and, within it, mortality registries.

Epidemiological and mortality studies of poisonings indicate that both depend on many factors, including social and geographic variables (eg, pesticides and herbicides in countries such as Sri Lanka or China),<sup>1,2</sup> ecological or climatic variables (eg, a higher number of venomous snakebites in India),<sup>3</sup> cultural or accessibility factors (eg, paracetamol in the United Kingdom),<sup>4</sup> as well as fashions or trends in consumption patterns (eg, opioids in the United States).<sup>5</sup>

The incidence rate of poisonings in Spanish emergency departments (EDs) represents approximately 1% of all ED visits,<sup>6</sup> or 0.3% if referring exclusively to non-alcohol drug abuse poisonings.<sup>7</sup> However, when attempting to determine poisoning-related mortality, data are scarce. Although official mortality statistics from forensic studies are available<sup>8</sup>, indispensable for estimating the prevalence of this phenomenon, they provide little clinically relevant information to plan interventions aimed at treating future poisoned patients at the hospital level, as well as preventive measures.

To this end, in 2012, the Spanish Foundation of Clinical Toxicology (FETOC), which since 1999 has coordinated the Spanish Toxicovigilance Program for the detection of major health problems related to exposure to chemical substances and preparations,<sup>9</sup> promoted the EXITOX registry (Registry of mortality from acute poisoning). This registry collects epidemiological and clinical care data from poisoned patients who died in Spanish public hospitals. In an initial report, the mortality rate from poisoning in the areas of the 8 hospitals that participated at that time was defined as 0.5 cases per 100,000 inhabitants.<sup>10</sup>

The present study analyzes mortality following acute poisoning (AP) in Spain.

## Materials and methods

We conducted a cross-sectional, multicenter, descriptive study from January 1<sup>st</sup>, 2012 through December 31<sup>st</sup>, 2019, of poisonings treated in 13 Spanish public hospitals. These centers, regular collaborators of the Spanish Toxicovigilance Program and members of the EXITOX working group, reported cases of patients who died due to AP.

To this end, a specific password-protected online database was designed. Epidemiological variables (age, sex), the toxic agent(s) responsible, clinical status, diagnostic and therapeutic measures, death-related data (hospital service and final cause), were included. Subsequently, an epicrisis of each case was prepared, detailing relevant aspects of the episode not previously recorded in the electronic file.

Finally, the degree of relationship between the poison-

ing and death was established at the discretion of the attending physician and stratified as "definite" (death was a direct and exclusive consequence of the poisoning; for example, paracetamol ingestion leading to death from hepatic failure), "contributory" (the poisoning led to hospital admission but was not the direct cause of death; for example, a benzodiazepine poisoning with final death due to bronchial aspiration), and "probable" (the poisoning neither caused the admission nor was the direct cause of death, but was related to both; for example, a patient in whom cocaine use was detected on a urine test during hospital care for a cardiac arrest).

Quantitative variables were expressed as mean with standard deviation (SD) or median with range, and qualitative variables were presented as total number of events and percentage of occurrence.

The study was approved by University Hospital Universitario de Canarias Research Ethics Committee (Canary Islands, Tenerife, Spain) (Ref. CHUC\_2020\_65).

## Results

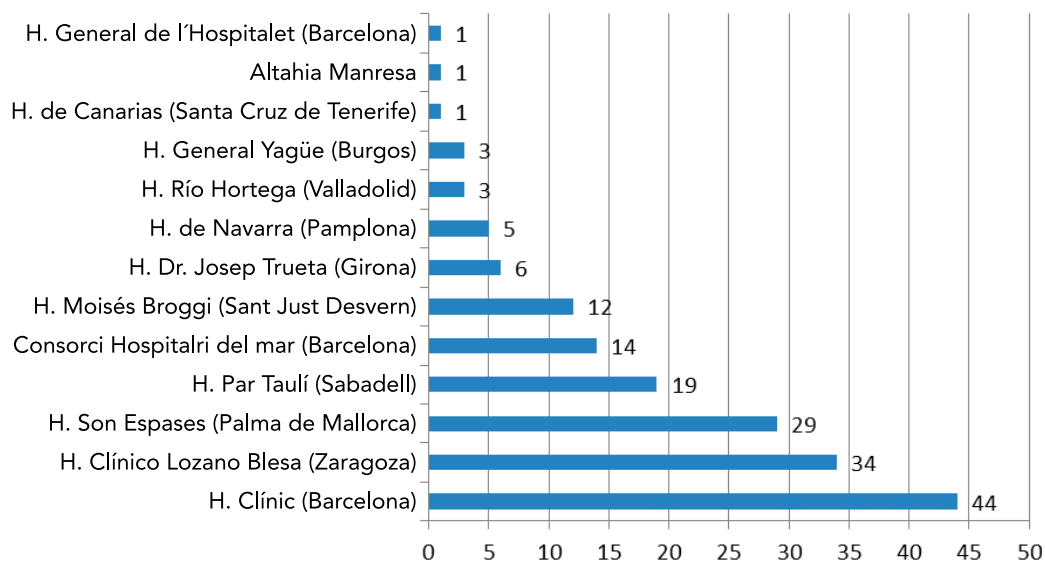
A total of 172 cases were recorded during the 8-year study period, with a non-uniform distribution among participating hospitals; 88.3% of cases were concentrated in 6 centers (Figure 1). Of these, 58.7% were men (101 cases), with a mean age of 58.4 (SD, 20.9) years and an age range of 18 to 97 years. The annual distribution of cases varied from 13 (2017) to 31 (2019), with a mean of 21.5 cases per year. In the 7 hospitals that contributed the highest number of episodes (154 of 172), mortality represented 0.25% of all poisonings treated during the study period.

The principal cause was suicide (40.7%), followed by overdoses in 30.2% of patients. An iatrogenic cause was suspected in 12.8% of cases, and the occupational setting was implicated in 1.1%. The oral route was the most frequent route of toxic exposure (75%), followed by inhalational (18.6%); parenteral or cutaneous routes accounted for 6.4% combined.

The most frequent toxic agents were household/chemical products and drugs, with 32.6% and 31.4%, respectively. The most prevalent were hydrochloric acid (14%), benzodiazepines and cocaine (11%), ethanol (10.5%), and metformin (9.9%) (Table 1). Ethanol, benzodiazepines, and cocaine were almost always involved in multiple-substance poisonings, present in 80.3% of the 38 cases (16 benzodiazepines, 13 ethanol, 10 cocaine). A single toxic agent was involved in 141 cases (76.1%).

Regarding the relationship between toxic agent, intent, and age groups, among decedents older than 60 years, 78% of deaths from suicidal ingestion of hydrochloric acid (commonly available household cleaner) were concentrated, as well as 92% of deaths from metformin (iatrogenic or suicidal ingestion) and all deaths from digoxin. In contrast, in the group younger than 40 years, cocaine (almost all men, 94.4%) was involved in 62.5% of episodes, and methanol (all women) in 60% (Table 2).

Distribution of poisonings by day of the week or month of the year, according to toxic agent, was gener-



**Figure 1.** Distribution of cases reported by each of the hospitals participating in EXITOX (2012–2019).

ally similar, except for ethanol- and cocaine-related cases, which occurred mainly on weekends and in summer.

The main presenting syndromes in the ED were coma or depressed level of consciousness (51.1%), followed by cardiac arrest (2.7%), acidosis (21.5%), shock (19.1%), and abdominal pain (18%) (Table 3). The mechanisms most frequently leading to death were multi-organ failure (21.5%), anoxic encephalopathy (20.3%), and organ damage due to digestive caustication (18%) (Figure 2). Trauma was always associated with proven drug abuse.

Treatment consisted of respiratory or hemodynamic support in critically ill patients (Table 4). Antidotes were administered in 30.4% of cases, extracorporeal detoxification in 9.8%, and gastrointestinal decontamination in 6.4%. In 31.9% of patients, therapeutic effort was limited, with priority given to symptomatic and palliative measures.

Death most often occurred in an intensive care unit (56.9%), followed by the ED (27.3%), medical wards (8%), and surgical area (5.2%). Death was considered definitely related to poisoning in 56.4% of cases, contributory in 22.1%, and probable in 18.5%.

**Table 1.** List of toxic agents recorded in EXITOX (2012–2019)

	N	N	
Hydrochloric acid (muriatic acid)	24	Heroin	2
Benzodiazepines*	19	Ammonia	2
Cocaine	19	Propranolol	2
Ethanol**	18	Quetiapine	2
Metformin	17	Mushrooms	2
Methanol	13	Diltiazem	1
Digoxin	10	Aluminium phosphide	1
Amphetamines	10	Glibenclamide	1
Smoke	8	Butane gas	1
Cannabis	7	Insulin	1
Opiates	7	Levomepromazine	1
Paracetamol	7	Lithium	1
Sodium hypochlorite (bleach)	6	Olanzapine	1
Tricyclic antidepressants	5	Datura stramonium	1
Caustic soda	5	Organophosphate	1
Carbon monoxide	4	Oxcarbazepine	1
Potassium cyanide	3	"Piedras China" (aphrodisiac pill)	1
Selective serotonin reuptake inhibitor	3	Sildenafil (Viagra)	1
Fentanyl	3	Hydrogen sulfide	1
γ-Hydroxybutyric acid (GHB)	2	Vipera aspis (viper venom)	1

\*Involved in multiple-substance poisoning in 78.9% of cases.

\*\*Involved in multiple-substance poisoning in 75% of cases.

**Table 2.** Age distribution (grouped in years) and cause of death for the five most prevalent toxic agents in the registry (present in ≥10 cases as a single agent)

Cause	Toxic agent						
	Age range	Hydrochloric acid	Cocaine	Digoxin	Methanol	Metformin	Total
IAT		0	0	10	0	13	23
61–70		0	0	0	0	4	4
71–80		0	0	2	0	3	5
> 81		0	0	8	0	6	14
OD		0	17	0	6	0	23
21–30		0	1	0	0	0	1
31–40		0	11	0	4	0	15
41–50		0	3	0	1	0	4
51–60		0	2	0	1	0	3
SUI (suicide)		24	0	0	6	3	33
21–30		1	0	0	0	0	1
21–40		1	0	0	4	0	5
41–50		2	0	0	2	1	5
51–60		2	0	0	0	1	3
61–70		7	0	0	0	0	7
71–80		8	0	0	0	1	9
> 81		3	0	0	0	0	3
Total		24	17	10	12	16	79

OD: overdose; IAT: iatrogenic; SUI: suicide.

**Table 3.** Most common symptoms or clinical presentations in poisoned patients who died

	N (%)	N (%)
Decreased consciousness	88 (51.1)	Caustic lesions 8 (4.6)
Cardiac arrest	47 (27.3)	Hepatic failure 6 (5.5)
Acidosis	37 (21.5)	Hyperkalaemia 5 (2.9)
Shock	33 (19.2)	Head trauma 5 (2.9)
Abdominal pain	31 (18.0)	Hypoglycaemia 4 (2.3)
Respiratory distress	29 (16.8)	Fever/hyperthermia 3 (1.7)
Respiratory arrest	28 (16.3)	Chest pain 3 (1.7)
Vomiting	24 (14.0)	Rhabdomyolysis 3 (1.7)
Arrhythmias	20 (11.6)	Encephalopathy 2 (1.2)
Renal failure	13 (7.6)	Wounds 2 (1.2)
Agitation	12 (7.3)	Syncope 2 (1.2)
Seizure	10 (6.9)	Bite 1 (0.6)
Focal neurological deficit	8 (4.6)	

## Discussion

Countries with standardized, routine registries of AP, such as the United States, have been able to accurately define the annual number of poisoning-related deaths (3255 cases in 2022), the percentage of mortality relative to the total number of poisonings treated (0.015%)—including calls to poison control centers—and the agents involved in these fatal cases (predominantly analgesics, sedatives, and new psychoactive substances [NPS]).<sup>2,14</sup>

The mean age of decedents in this series was higher than that reported in epidemiological studies of AP in Spain overall (33 [18.1] years).<sup>6</sup> The reasons are diverse: first, the greater presence of suicidal intent, which is more typical in older age groups;<sup>16</sup> and second, because this advanced age often coincides with a higher prevalence of comorbidities and, consequently, polypharmacy, sometimes involving high-risk drugs, which increases the likelihood of poor outcomes.<sup>17</sup>

Suicidal ingestion of caustics (generally hydrochloric acid available in households) was the leading cause of death in this series, almost always among older patients. This finding aligns with a study of poisonings in older adults,<sup>17</sup> suggesting cultural factors in this population group that predispose to its use as a suicide method. This is further facilitated by the wide availability of the product, as it can be purchased in any supermarket. Commercial restrictions on its availability would undoubtedly limit this severe poisoning, as proposed in rural Sri Lanka for pesticides.<sup>1</sup>

Also related to older age, a notable number of deaths were due to iatrogenic causes associated with chronic treatments with drugs such as metformin and digoxin, whose potential toxicity in older patients is well established.<sup>17-19</sup> The need for dose adjustment of these drugs during decompensation of concomitant diseases may not always be undertaken with the required timeliness, leading to fatal consequences. Computerized prescription management programs should help design preventive strategies to avoid such outcomes, particularly in countries with universal health care.<sup>20</sup>

Benzodiazepines were the drug class most frequently implicated in episodes in this study, although almost always in combination with other substances and usually in a

**Table 4.** Therapeutic measures applied in poisoned patients who died

	N (%)	N (%)
<b>Nonspecific therapies</b>		
Intubation with MV	119 (69.2)	Corticosteroids 9 (5.2)
Fluid therapy	76 (44.2)	Antibiotics 8 (4.6)
Vasopressor drugs	52 (30.2)	Physical restraint 6 (3.5)
Oxygen therapy	39 (22.7)	Anticonvulsant 5 (2.9)
Analgesia	33 (19.2)	Pacemaker 3 (1.7)
Inotropic drugs	21 (12.2)	Parenteral nutrition 2 (1.1)
Surgical technique	19 (11.0)	Fibrinolysis 1 (0.6)
Bronchodilators	13 (7.6)	ECMO 1 (0.6)
Bicarbonate	11 (6.4)	Vasodilators 1 (0.6)
Plasma expanders	9 (5.2)	
LTE	55 (31.9)	
<b>Specific toxicological therapies</b>		
GI decontamination	12 (7.0)	
Gastric lavage	4 (2.3)	Activated charcoal 8 (4.6)
Extrarenal detoxification	17 (9.9)	
Haemofiltration	12 (7.0)	Haemodialysis 4 (2.3)
Forced diuresis	1 (0.6)	
Antidotes	59 (34.3)	
Naloxone*	17 (9.9)	Dantrolene 1 (0.6)
Flumazenil*	16 (9.3)	Physostigmine 1 (0.6)
N-acetylcysteine	8 (4.6)	Fab AD 1 (0.6)
Hydroxocobalamin	7 (4.0)	Methylene blue 1 (0.6)
Ethanol	6 (3.5)	Glucagon 1 (0.6)
Bicarbonate	6 (3.5)	Lipid emulsion 1 (0.6)
Hypertonic glucose	5 (2.9)	Antivenom (Vipera) 1 (0.6)
Atropine/Pralidoxime	2 (1.1)	Phytomenadione 1 (0.6)
Silibinin/Penicillin	2 (1.1)	

MV: mechanical ventilation; Fab AD: anti-digoxin antibodies; LTE: limitation of therapeutic effort; ECMO: extracorporeal membrane oxygenation; GI: gastrointestinal.

\*In 12 cases (7%), naloxone and flumazenil were administered simultaneously.

nontherapeutic context.<sup>21</sup> Their presence should always be considered, especially in cases of decreased level of consciousness, given the high prevalence of consumption in the general population. The EURO-Den group reported in 2019 that 17.7% of patients poisoned by drugs of abuse had benzodiazepine involvement, with a mortality rate of 0.5% of total presentations.<sup>22</sup>

Cocaine, the 2<sup>nd</sup> most frequent toxic agent, followed a different pattern from pharmaceuticals. It primarily affected younger individuals in a recreational overdose context, often involving polysubstance use (57.9% in this study). This pattern is consistent with data published by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA): mean age 32 years, male predominance (77%), combined use with alcohol (56.8%) and with other drugs (58.6%).<sup>23</sup> Cocaine and alcohol, sometimes together, were implicated in cases of trauma- and accident-related deaths. These findings remain relevant today, as reflected by the 2023 report of the Spanish National Institute of Toxicology and Forensic Sciences, which identified these 2 substances in 53.6% of traffic accident fatalities that year.<sup>24</sup>

Methanol poisonings showed an age distribution similar to that of cocaine overdoses, although suicidal intent predominated, with a female tendency. This finding contradicts previous series of methanol poisonings, which consistently reported male predominance: 76% in Nor-

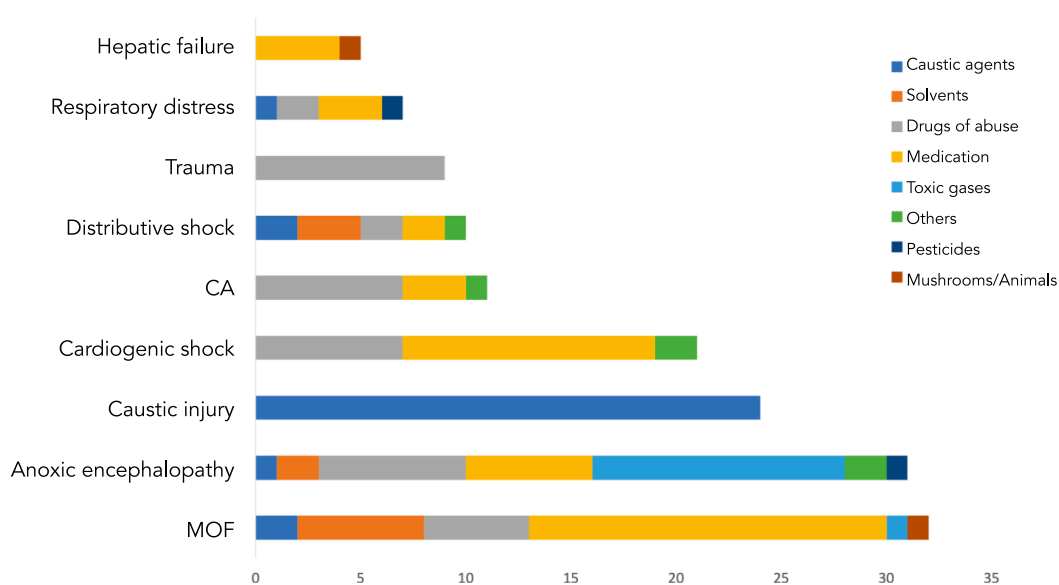


Figure 2. Final cause of death after poisoning. CA: cardiac arrest; MOF: multiple organ failure.

way,<sup>25</sup> 79% in the Czech Republic,<sup>26</sup> and 96% in Malaysia.<sup>27</sup>

Finally, our results for opioid-related deaths (therapeutic or otherwise) diverge markedly from those reported in recent years in some Anglo-Saxon countries, where overdose deaths due to these agents—mainly heroin and prescription opioids—play a leading role in poisoning-related mortality, with an annual increase of 23% since 2013.<sup>5</sup> Similar data have recently been reported in New Zealand.<sup>28</sup>

A similar situation exists with another toxic agent, paracetamol, historically prominent in poisoning-related mortality in these same countries. Despite well-defined severity, mechanisms of toxicity, and therapeutic measures, it continues to cause more than 100 annual deaths in the United States (254 in the most recent year),<sup>14</sup> vs only 7 cases over 8 years in our series.

This study has several limitations. The registry is based on voluntarily contributed cases from sentinel hospitals and therefore does not ensure homogeneous representation of all Spanish autonomous communities. Moreover, as a hospital-based registry, it excludes deaths from AP not transported to hospital. This may explain the low proportion of carbon monoxide poisonings in our study. Similarly, there may be underdiagnosis of fatal alcohol-related poisonings associated with trauma (eg, traumatic brain injury, traffic

accidents). Finally, the retrospective nature of the study may have resulted in missing information in some cases.

The 8-year study period ending in 2019 reflects the scarcity of cases reported during the pandemic, particularly in 2020, which might have biased results from preceding years. Without question, a mandatory national registry would provide more comprehensive and detailed information. In its absence, we believe the opportunity offered by systematic, continuous data collection by participating hospitals should be maximized. Addressing this deficit, while providing a standardized data collection tool, was one of the goals for the creation of the EPITOX registry, an initiative promoted by FETOC in January 2024.<sup>29</sup> From the FETOC, a multicenter registry has been promoted in Spain that provides relevant information on mortality following acute poisoning in the country. This study identifies certain profiles of deceased patients, such as suicidal caustic ingestions in older adults, or iatrogenic problems with metformin and digoxin in the elderly. Deaths of young individuals have also been observed after polysubstance use involving alcohol, cocaine, and benzodiazepines (the latter in non-therapeutic use). From this point forward, it is essential to establish preventive measures in the field of public health, primary care, and psychiatric evaluation of patients at risk of suicide.

## ARTICLE INFORMATION

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**Author Contributions (CRediT):** Blanca Rodríguez: final drafting and statistical analyses. Santiago Nogué: data collection at Hospital Clinic (largest contributor), initial drafting, and final review of the manuscript. Ana Ferrer: centralized collection of all cases and data collection from the second-largest contributing center. Guillermo Burillo: statistical analysis of the registry and final manuscript review. Jordi Puiguriquer: original idea and coordinator of the EXITOX registry, as well as responsibility for final manuscript drafting. Other EXITOX group collaborators: contributed cases from their respective centers.

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## ADDENDUM

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