Critical Care

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The INTOXICATE study: methodology and preliminary results of a prospective observational study

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Abstract

Background There is currently no practice-based, multicenter database of poisoned patients admitted to intensive care units (ICUs). The INTOXICATE study, endorsed by the ESICM and EAPCCT, aimed to determine the rate of eventful admissions among acutely intoxicated adult ICU patients.

Methods Ethical approval was obtained for this multicenter, prospective observational study, and data-sharing agreements were signed with each participating center. An electronic case report form was used to collect data on patient demographics, exposure, clinical characteristics, investigations, treatment, and in-hospital mortality data. The primary outcome, 'eventful admission', was a composite outcome defined as the rate of patients who received any of the following treatments in the first 24 h after the ICU admission: oxygen supplementation with a FiO2 > 40%, mechanical ventilation, vasopressors, renal replacement therapy (RRT), cardiopulmonary resuscitation, antidotes, active cooling, fluid resuscitation (> 1.5 L of intravenous fluid of any kind), sedation, or who died in the hospital.

Results Seventy-eight ICUs, mainly from Europe, but also from Australia and the Eastern Mediterranean, participated. A total of 2,273 patients were enrolled between November 2020 and June 2023. The median age of the patients was 41 years, 72% were exposed to intoxicating drugs. The observed rate of patients with an eventful ICU admission was 68% (n = 1546/2273 patients). The hospital mortality was 4.5% (n = 103/2273).

Conclusions The vast majority of patients survive, and approximately one third of patients do not receive any ICU-specific interventions after admission in an intensive care unit for acute intoxication. High-quality detailed clinical data have been collected from a large cohort of acutely intoxicated ICU patients, providing information on the pattern of severe acute poisoning requiring intensive care admission and the outcomes of these patients.

Trial registration: OSF registration ID: osf.io/7e5uy.

Keywords Toxicology, Poisoning, Intensive care units, Critical care outcomes, Database management systems

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Background

The severity of poisoning depends on many factors, such as the type and dose of xenobiotics, patient characteristics (age, sex, comorbidities), clinical features at hospital presentation (level of consciousness, blood pressure, pulse rate, respiratory rate, temperature), time to treatment, poisoning circumstances (intentional or accidental; coingestions) and/or laboratory findings (electrolyte imbalances, coagulation abnormalities, renal function etc.) [1–5]. In addition to these predictors, the ICU mortality rate after poisoning also depends upon the class of medications/chemicals to which a patient is being exposed (e.g. opioids, sedatives, street drugs, etc.…), which differs between low- and middle-income countries and countries such as the USA, Australia or European countries. ICU mortality in the USA and European ICUs is ranging from 0 to 6% depending on the study [4, 6–9].

Previously published studies have reported conflicting data on ICU admission and mortality rates. Comparisons between these studies is difficult because they often lacked common methodology and definitions, were relatively small single-center retrospective studies, or missed information on exposure and on treatment. Additional file 1: Table S1 in the Supplement contains information on the source, number of centers, population, age range, number of patients, most prevalent intoxications, important findings and limitation per study.

The limitations of these previous studies and the lack of multinational database of ICU patients with severe poisonings in Europe were the basis for our prospective study. The INTOXICATE study aims to collect data on admissions to ICUs after acute poisoning in Europe and other continents to determine the rate of eventful admissions among acutely intoxicated adult ICU patients and to provide information on the prognosis of these patients.

Methods

Study design, registration and approval

This prospective multicenter observational cohort study was prospectively registered in an Open Science Framework (OSF) (OSF registration ID: osf.io/7e5uy). The accredited Medical Research Ethics Committee of the University Medical Centre Utrecht (UMCU) did not consider the Dutch Medical Research Involving Human Subjects Act to be applicable to this study (ethics reference number: 20-495/C). The original name was the "TOXIC-Europe study", but the name was changed to the INTOXICATE-study in October 2021 at the request of researchers involved in the Toxicology Investigators Consortium (ToxIC) run by the American College of Medical Toxicology, to avoid confusion.

Setting

ICU physicians in Europe and other continents were invited to participate in the INTOXICATE study through the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) [10] and the European Society of Intensive Care Medicine (ESICM) [11]. The eligibility criteria for ICUs were that they were university affiliated-, community teaching-, and community non-teaching hospitals in Europe or other continents. The ICU could be medical, surgical, specialized in toxicology or any other specialty, or mixed. An ICU was defined as a unit where a patient can be endotracheally intubated and mechanically ventilated. Therefore, high-dependency units (HDUs) or high-care units (HCUs) that can mechanically ventilate patients, were considered an ICU in this study. Ethics approval and signing a data sharing contract were mandatory.

Data were collected between 1st November 2020 and 30th June 2023. A list of collaborators is provided in the Acknowledgments section. The study was managed by a central coordinating team supervising the national coordinators. All participating units provided either local research ethics committee approval or a waiver of consent. A data-sharing contract had to be signed between the participating unit and the coordinating center.

Patients

The patient inclusion criteria were adult patients (aged 18 years or older); patients admitted to the ICU from an emergency department, ambulance, or ward; intoxication (due to poisoning) as the main reason for ICU admission; and patients who stayed in the ICU for four hours or more. Patients were excluded if they were younger than 18 years; admitted to the ICU because of another serious comorbidity (e.g., trauma from a car accident while intoxicated as the management, outcome and duration of admission were likely to be dictated by the comorbidity rather than the intoxication); and an ICU stay of less than four hours. Toxicity was defined as the occurrence of any toxic effect to humans following a single or repeated exposure to a mixture of natural or synthetic substances available on the market or present in the environment. Pure ethanol intoxication was covered by the exposure definition. Informed consent of the participating patients was either required or not, depending on the country and/or the unit.

Variables

The primary outcome, 'eventful ICU admission', was a composite outcome defined as the rate of patients who received any of the following treatments in the first 24 h after the ICU admission: oxygen supplementation with a

FiO2 > 40%, mechanical ventilation, vasopressors, renal replacement therapy (RRT), cardiopulmonary resuscitation, antidotes, active cooling, fluid resuscitation (> 1.5 L of intravenous fluid of any kind), sedation, or who died in the hospital.

Exposure variables were the exposure exact name, category, dose, and route. Human medications were categorized according to the underlying pharmacological group based on [4]: alcohol (ethanol, other alcohols); analgesics; antidepressants (cyclic antidepressants, lithium); street drugs (opiates, cocaine, amphetamine); sedatives (hypnotics, antipsychotic, benzodiazepines); 'other poisons' (carbon monoxide, arsenic, cyanides); other toxins; and mixed intoxications (combination of two or more subtypes of intoxication).

Data were collected on potential predictors (type of units, unit size, country, patient's age, sex, comorbidities, possible second reason for ICU admission, vital signs, investigations (including ECG).

Data sources

The data entered by local investigators included only information that would have been collected as part of routine clinical care. Local investigators reported only pseudoanonymized data. The data were entered into two study-specific databases (one for units and one for patients) developed in Castor EDC (Electronic Data Capture) [12]. Local investigators could access Castor through an account that required two-factor authentication (2FA). Local investigators entered their data into the database for patients identified as eligible, usually after hospital discharge. Data from Denmark were imported into Castor EDC in a single block (all patients from all Danish units at the same time) because Danish investigators collected patient data using the Redcap system; this made it easier for the Danish investigators to obtain the necessary institutional approval.

Bias

Standard definitions of the variables were provided on the study website. To ensure complete case ascertainment, any missing or inconsistent data were identified at the end of the overall study data collection period and the local investigator was contacted to update/provide the data. We predicted that there would be enough eligible patients in one year. However, the COVID-19 pandemic hit almost immediately after the start of the study, forcing us to extend the study by a further year and eight months.

Study size

Before the study began, we calculated the sample size, based on the hypothesized proportion of outcome in the population of interest, using the following formula:

$$n = \left(z \frac{\sqrt{p(1-p)}}{d} \right)^2 DE$$

Taking the values $p = 6.5\%$ (based on [4]); $z = 1.96$ for a 95% level of confidence; $d = 0.065/2$ (the allowable error); a correction factor $DE = 7.65$ for 20 clusters (the 20 countries where the study would be conducted, we get $n = 1691$. We applied a non-response rate of 10%, which resulted in n = 1691/0.9 = 1879 patients.

Quantitative variables

Quantitative variables concerning the ICUs were the number of ICU beds, the total number of ICU admissions in the last year, and the number of ICU admissions related to poisoning in the last year. All were grouped in categories.

Patient's age, Body Mass Index (BMI), time elapsed between exposure and hospital admission, number of exposures, systolic blood pressure, heart rate, body temperature, SaO2, arterial pH, potassium, lactate, leucocytes, serum creatinine were considered as quantitative variables. None of them were categorized. The Glasgow Coma Score was categorized in four categories (GCS ≥ 14; GCS > 9 and < 14; GCS > 6 and ≤ 9; GCS < 6).

Statistical methods

Quantitative variables related to ICUs are expressed as numbers and percentages by category. Continuous patient data are expressed as median ± interquartile range. Patient categorical data are expressed as numbers (percentages). Rates were calculated as the number of outcomes divided by the total number of included patients, with the corresponding 95% confidence interval (CI). Rates were calculated before and after exclusion of patients who received mechanical ventilation, vasopressors or cardiopulmonary resuscitation before ICU admission.

Patients with missing data were identified. Percentages were calculated for those with available data, and the denominator with missing data removed is reported throughout. When patients were transferred to another ICU, this second ICU was contacted by the local investigator to obtain the patient data.

In a post-hoc analysis, we used two alternative definitions of 'eventful ICU admission' in order to compare our findings with previous studies [4, 13]. The alternative definitions of "eventful ICU admission" included fewer ICU treatments. In alternative definition 1, according to [13], an eventful ICU admission was defined as having received mechanical ventilation and/or vasopressors and/or renal replacement therapy (RRT) and/or cardiopulmonary resuscitation in the first 24 h in ICU or who died in-hospital. In alternative definition 2, according to [4],

eventful ICU admission was defined as having received mechanical ventilation and/or vasopressors and/or cardiopulmonary resuscitation in the first 24 h in the ICU, or having died in hospital (similar to alternative definition 1 except that RRT was not considered).

We hypothesized that the rate of eventful admission (with alternative definition 1 and definition 2) was greater than previously reported in the two studies [4, 13]. A one-sample z test was used to test the difference in outcome in this study compared with the rate reported in each study (15.4% in [13] and 6.5% in [4]).

We also performed two sensitivity analyses. First, to mitigate the potential influence of the heterogeneity in enrollment rates between ICUS, we repeated the main analysis after including only units that included at least 80% of the patients admitted to their unit in the study. Second, to minimize the potential influence of a mandatory informed consent, we repeated the main analysis to units where an informed consent was not mandatory.

Statistical analyses were carried out in SPSS Statistics 29.0 and/or R studio version 2023.06.2 for Windows (R version 4.2.2.). The STROBE checklist was used in the preparation of this manuscript following the EQUATOR guidelines.

Results

During the study period, 237 units contacted us (Fig. 1), yet only 78 ICUs that met the inclusion criteria contributed data to the INTOXICATE study (Table 1). Data collection was complicated by various technical challenges, including the COVID-19 pandemic, the data sharing agreement, and the different application of the General Data Protection Regulation (GDPR) in European countries, which may or may not require patient informed consent (Additional file 1: Table S2).

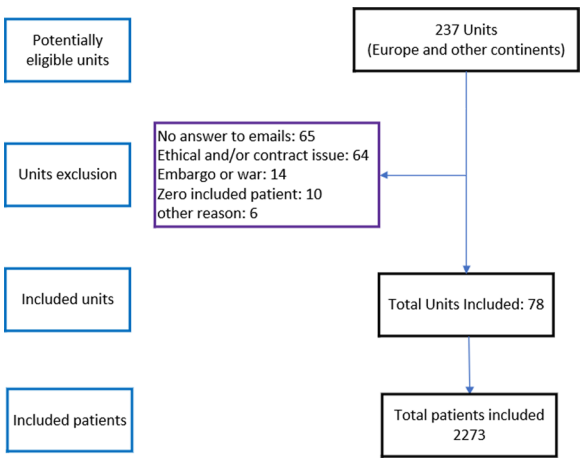

Fig. 1 Study Flow Diagram for units. Data entered by local investigators (black outlines), reasons for exclusion (purple), and study phase (blue) are represented

Characteristics of intensive care units

Table 2 shows the characteristics of the units. The majority (N = 49, 62%) were university-affiliated ICUs. The size of ICUs was also usually less than 30 beds, and the number of admissions was usually less than 2000 per year per unit. Most units had fewer than 60 poisoning-related admissions in the year before the study. In the majority of ICUs, the doctors who wrote the orders (laboratory tests and medication prescriptions) were specialists in intensive care medicine (62%), and 42% of the units had physicians certified in medical toxicology.

Patient characteristics

A total of 2,273 patients were enrolled during this extended data collection period. The Netherlands was the largest contributor, followed by Denmark and Spain. Table 3 shows the characteristics of the patients. The median patient age was 41 years (IQR 28–56) and slightly more women were affected (53.2% women). Most patients presented a comorbidity, either psychiatric and/or somatic; fifty-nine percent of patients had a coexisting psychiatric illness (other than addiction)diabetes was the most common somatic comorbidity. Most patients were admitted from the emergency department (92.5%), a second reason for ICU admission was recorded in 16.2% of the patients (Table 3).

Exposure

The vast majority of the patients (72%) were exposed to intoxicating drugs, and almost a quarter were exposed to alcohol, most often mixed with another drug. The group of mixed intoxications accounted for 1131 cases (49.8%) in all patients (Table 3). When considering isolated intoxications, sedatives (10.6%) and street drugs (8.9%) were most frequently used.

Clinical features

Neurological signs and symptoms were the most common on admission, with the top three most common neurological symptoms being altered consciousness (N = 979 patients, 43% of admissions), coma (N = 747 patients, 32.9% of admissions), and agitation (N = 294 patients, 12.9% of admissions). Respiratory and gastrointestinal signs were also frequently observed (at least one sign observed in 41.1% and 23.5% of admission, respectively). The most frequently observed cardiologic signs or symptoms were palpitations (4.8%) and hypotension (4.7%).

Table 1 Location of the INTOXICATE intensive care units (ICUs) (N = 78)

City	Institution	Unit
Australia		
Brisbane	Redcliffe Hospital	Intensive care unit
Austria		
Salzburg	Paracelsus Medical University Salzburg	Medical intensive care unit
Belgium		
Ghent	Ghent University Hospital	Intensive care unit
Brussels	Cliniques Universitaires St Luc	SIM/SIT
Ottignies	Clinique Saint Pierre Ottignies	Intensive care unit
Brugge	AZ Sint-Jan Brugge-Oostende AV	Intensieve zorgen
Charleroi	CHU Charleroi	Medico surgical ICU
Brunei Darussalam		
Bandar Seri Begawan	Hospital RIPAS	Critical care medicine
Croatia		
Split	University Hospital of Split	Internal medicine department, division of emergency and intensive medicine
Denmark		
Copenhagen	Bispebjerg Hospital	Department of anaesthesia and intensive care
Herlev	Herlev Hospital	Afdeling for bedøvelse, operation og intensiv behandling
Roskilde	Zealand University Hospital	Intensive care unit I 12, Roskilde. dept. of anesthesiology
Køge	University Hospital Zealand—Køge	Intensive care unit, SUH Køge
Odense	OUH—Odense University Hospital	Department of intensive care
Viborg	Viborg Regional Hospital	Intensive care unit
Aalborg	Aalborg University Hospital	Anesthesia and intensive care department
Slagelse	Slagelse Hospital	Department of anaesthesia and intensive care
Egypt		
Tanta	TANTA University Emergency Hospital	Emergency medicine and traumatology intensive care unit
Ismailia	Suez Canal University Hospitals (SCUH)	Department of anaesthesia and intensive care
Germany		
Munich	Rechts der Isar Hospital	Toxikologische intensivstation
Essen	University Hospital Essen	Anästhesiologische intensivstation IT 2
Greece		
Thessaloniki	Saint Paul ("Agios Pavlos") General Hospital	Intensive care unit
Iraq		
Najaf	Al-Sader Medical city Teaching Hospital	Intensive care unit
Italy		
Milan	Humanitas Research Hospital	Department of anesthesiology and intensive care
Jordan		
Amman	Jordan University Hospital, Amman	Medical intensive care unit
Amman	Islamic hospital	Surgical ICU
Amman	Amman Field Hospital	Intensive care unit
Lithuania		
Vilnius	Republic Vilnius University hospital	Toxicology Centre
Netherlands		
Utrecht	University Medical Center Utrecht	Department of intensive care medicine
Utrecht	Diakonessenhuis Utrecht	Intensive care unit
Enschede	Medisch Spectrum Twente	Intensive care center
Den Haag	Haaglanden Medisch centrum	Intensive care unit
Leeuwarden	Medisch Centrum Leeuwarden	Afdeling intensive care
Amsterdam	Onze Lieve Vrouwe Gasthuis (OLVG) hospital	Intensive care
Arnhem	Rijnstate Hospital	Intensive care unit

Table 1 (continued)

City	Institution	Unit
Maastricht	Maastricht University Medical Center +	Intensive care
Rotterdam	Franciscus Gasthuis & Vlietland	Afdeling intensive care
Amsterdam	Antoni van Leeuwenhoek ziekenhuis	Intensive care
Groningen	University Medical Center Groningen	Department of critical care
Rotterdam	Maasstad Hospital	Intensive care unit
Rotterdam	Ikazia Ziekenhuis	Intensive care unit
Deventer	Deventer Ziekenhuis	Intensive care unit
Portugal		
Lisbon	Hospital de São Francisco Xavier, Unidade Local de Saúde de Lisboa Ocidental, EPE. Lisboa, Portugal	Unidade de cuidados intensivos polivalente
Vila Nova de Gaia	Centro Hospitalar de Vila Nova de Gaia, ULS Gaia e Espinho, Vila Nova de Gaia, Portugal	Serviço de medicina intensiva polivalente
Santiago do Cacém	Hospital do Litoral Alentejano, Unidade Local De Saúde de Lisboa Ocidental, EPE, Santiago do Cacém, Portugal	Serviço de medicina intensiva
Romania		
Bucharest	Clinical Emergency Hospital Bucharest	Anesthesiology and intensive care—toxicology
Cluj	Clinical Emergency County Hospital Cluj-Napoca	Anaesthesia and intensive care I department
Spain		
Valencia	Consorcio Hospital General Universitario	UCI anestesia
Santiago de Compostela	University Clinic Hospital of Santiago de Compostela	Intensive care unit, intensive care medicine department
Tortosa	Hospital Verge de la Cinta	Servicio de medicina intensiva
Zaragoza	Hospital Universitario Lozano-Blesa	Unidad de cuidado intensivos
Girona	Hospital Santa Caterina de Salt	Unidad de cuidados intensivos
Girona	Hospital Universitario Dr Josep Trueta	Unidad de cuidados intensivos
Octubre Madrid	Hospital Universitario 12 de Octubre	Trauma and emergency ICU. Intensive care medicine service
Valencia	IMED Hospital Valencia	UCI
Huesca	University San Jorge Hospital	Intensive care medicine
Granollers	Hospital General Granollers	Intensive care unit
Valladolid	Hospital Universitario RíoHortega	Servicio de medicina intensiva, unidad 1
Valladolid	Hospital Universitario Río Hortega	Servicio de medicina intensiva, unidad 2
Sudan		
Khartoum-EastNile	East Nile (Sharg Alneel) Hospital	Intensive care unit
Sweden		
Stockholm	South hospital	Intensive care unit
Stockholm	Capio St Görans hospital	Intensivvårdsavdelningen (IVA)
Lund	Skånes University Hospital Lund	Intensivvårdsavdelning lund
Hudiksvalls	Hudiksvalls sjukhus	ICU Hudiksvall
Norrtälje	Norrtälje Hospital	Intensive care unit
Malmö	Skånes University Hospital, Malmö	Intensive care unit
Turkey		
Istanbul	Dr. Lutfi Kirdar Training and Research Hospital General	General ICU
Ankara	Hacettepe University Faculty of Medicine, Ankara	Medical intensive care unit
Istanbul	Kanuni Sultan Suleyman Education and Training Hospital	Anesthesiology intensive care unit (Reanimation)
Giresun	Giresun Training and Research Hospital	Reanimation
Sakarya	Sakarya University Faculty of Medicine	Department of internal medicine-intensive care unit
Trabzon	Karadeniz Technical University, Farabi Hospital	Anesthesia ICU-2
Kahramanmaraş	Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Training and Research Hospital	Anesthesiology intensive care unit (Reanimation)
Adana	Seyhan Public Hospital	Mixed-intensive care unit
Ankara	Ataturk Sanatorium Training and Research Hospital	General intensive care unit

Table 1 (continued)

City	Institution	Unit
United Kingdom		
Nottingham	Nottingham University Hospitals NHS Trust	Intensive care unit
London	Guy's and St Thomas' NHS Foundation Trust	Intensive care unit
Cramlington	Northumbria Healthcare NHS foundation trust	Northumbria specialist emergency care hospital

Primary outcome and in-hospital mortality

The observed rate of patients with an eventful ICU admission was 68% (95% CI: 64.6%; 71.4%) (n = 1546/2273 patients) in all patients. Six hundred and eighty-eight patients (n = 688/2273, 30.3%) received an ICU intervention (CPR or mechanical ventilation or vasopressors for at least one hour) prior to their ICU admission, and for 2 patients, it was unknown whether they had had a treatment before their ICU admission (n = 2/2273, 0.1%). The observed rate of patients with an eventful admission) was 56.5% (95% CI: 53%; 60%) (n = 895/1583 patients) after exclusion of patients who received an IC intervention before their ICU admission (Fig. 2). For 9 patients, the treatment received in ICU was missing (n = 9/1583, 0.6%).

The majority of patients survived to hospital discharge, with 3.7% (n = 85/2273 patients) dying in the ICU and 0.8% (n = 18/2273 patients) dying in the ward following discharge from the ICU, resulting in an in-hospital mortality of 4.5% (n = 103/2273) (95% CI: 3.7%; 5.4%).

With the post-hoc analysis, the rate of ICU eventful admission after exclusion of the patients who received an ICU intervention before their ICU admission was 21.1% (n = 335/1583) when alternative definition 1 was used (Fig. 3, left panel). This rate was significantly greater than 15.4%, the rate reported previously in [13] (z-statistic = 6.47, $p < 0.001$). When alternative definition 2 was used, the rate of ICU eventful admission after exclusion of the patients who received an ICU intervention before their ICU admission was 18.9% (n = 299/1583) (Fig. 3, right panel). This rate was significantly greater than 6.5%, the rate of ICU eventful admission reported in [4] (z-statistic = 20.1; $p < 0.001$).

When including only the units that included at least 80% of the patients admitted due to intoxication to their unit in the study, the rate of eventful ICU admission was 68.7% (n = 574/835) before exclusion of the patients who received an ICU treatment before their ICU admission (versus 68% [95% CI: 64.6%; 71.4%] in the 2273 patients. The in-hospital mortality rate was 4.2% (n = 35/835) versus 4.5% [95% CI: 3.7%; 5.4%] in the 2273 patients.

When including only the units where an informed consent was not mandatory, the rate of eventful ICU admission was 71.6% (n = 756/1056 patients) before exclusion of the patients who received an ICU treatment before their ICU admission (versus 68% [95% CI: 64.6%; 71.4%] in the 2273 patients). The in-hospital mortality rate was 4.5% (n = 48/1056) versus 4.5% [95% CI: 3.7%; 5.4%] in the 2273 patients.

Discussion

The primary findings of our study show that almost all patients presenting with acute intoxication had comorbidities, with psychiatric comorbidities being the most common. The majority of intoxications in our study involved human medications. The overall mortality rate was low (4.5%). About two thirds of the patients admitted to the ICU received ICU-specific treatments, but this percentage drops to about 56.5% when excluding patients who had already received an ICU intervention before admission.

Our study confirms several findings from previous research. Consistent with previous studies, we observed a slightly higher number of females than males among the intoxicated patients [8]. The predominance of mixed intoxication [7, 13–17] and intoxicating drugs as the cause of intoxication [7, 9, 16, 18–20] is also in line with the existing literature. The low mortality rates both in the ICU (3.7%) and in the hospital (4.5%) are in accordance with the mortality rates reported in the literature. The ICU mortality rate ranged from 0.4 to 5.9% when considering studies with more than 100 intoxicated patients (Table S1) [4, 7–9, 19–22], while the in-hospital mortality rate reported in the literature ranged from 0.7 to 6.7% [1, 4, 9, 13, 14, 18, 20, 22].

However, our study differs significantly in the proportion of intoxicated patients admitted to the ICU who required mechanical ventilation, vasopressors or died in hospital. We found this proportion to be significantly

Table 2 Characteristics of intensive care units (ICUs) (N = 78 units)

Parameter	N (%)
Institution/hospital type	
University affiliated	49 (62)
Community teaching	22 (28)
Community nonteaching	6 (8)
Private sector–teaching hospital	1 (1)
Number of ICU beds	
< 10	17 (22)
10–15	20 (25)
15–30	24 (30)
30–45	10 (13)
> 45	7 (9)
Total number of ICU admissions in the last year	
< 500	18 (23)
500–1000	25 (32)
1000–2000	25 (32)
2000–3000	6 (8)
> 3000	4 (5)
ICU admissions related to poisoning last year	
< 30	38 (48)
30–60	21 (27)
60–120	12 (15)
120–180	1 (1)
> 180	6 (8)
What kind of doctors write orders in the ICU?	
Non-IC doctors can write orders	22 (28)
Only IC doctors write orders	49 (62)
Other doctors	5 (6)
Unknown	2 (3)
Specialties[a]	
Medical	71 (90)
Toxicological	33 (42)
Respiratory or pulmonary	61 (77)
Surgical	56 (71)
Trauma	44 (56)
Cardiothoracic surgery	15 (19)
Cardiac or coronary	25 (32)
Transplantation	13 (16)
Burns	6 (8)
Neurological and/or neurosurgical	40 (51)
Other[b]	11 (14)
Informed consent needed	
No	33 (42)
Yes	45 (57)

No missing values in the parameters related to the ICUs

[a] Total greater than 78 because most ICUs have multiple specialties

[b] 'Addiction care' (n = 1); 'ECMO' (Extra Corporeal Membrane Oxygenation) or 'renal disease' (n = 2); 'General' or 'mixed' or 'multidisciplinary' or 'no specialty' (n = 5); 'Obstetrics and gynecology' (n = 1); 'Oncology' or 'Palliative' (n = 2)

higher than that reported in a French study that also included renal replacement therapy (RRT) as part of ICU-specific treatment (15.4%)[13] and a Dutch study that did not include RRT (6.5%) [4]. This suggests that our cohort had a higher severity of intoxication, as our criteria for ICU treatment were similar to prior studies [4, 13].

The strengths of our study are many. We achieved a high level of data completeness and quality, with very few missing values. Our prospective study design, in contrast to the retrospective nature of most previous studies, increases the reliability of our findings. The international scope of our study, covering approximately 20 countries, increases the generalizability of our findings. With 2,273 admissions, the sample size of our study is robust and exceeds many previous single-center or single-country studies. In addition, our inclusive criteria, covering all types of poisoning rather than focusing solely on suicides or intoxicating drugs, provide a comprehensive overview of the problem.

However, our study has limitations. There was an imbalance in enrolment between countries, with six countries (the Netherlands, Denmark, Spain, Sweden, Turkey and Belgium) contributing more than 75% of the patients. This bias does not reflect the population size of these countries in Europe. However, we believe that the management of ICU patients after acute poisoning does not differ significantly between European countries or between Europe and Australia. Therefore, the 3.7% ICU mortality observed in the study seems to be a plausible estimate for European countries, although variations may be more pronounced in regions with different resources, inpatient care or patients' exposure. The sensitivity analysis showed that the effect of the heterogeneity of enrollment between units represented a limited bias since the rates of eventful ICU admission and in-hospital mortality rate were comparable (68% eventful ICU admissions and 4.5% in-hospital mortality rate in the total study sample versus 68.7% eventful ICU admissions and 4.2% in-hospital mortality rate in the units that included at least 80% of the patients admitted to their unit).

In addition, the over-representation of university hospitals in our study may indicate a bias towards more complex cases due to the research focus and capabilities of the centers. Future analyses will need to investigate whether patients at university centers had more severe exposures or comorbidities. Finally, written informed consent was mandatory in many intensive care units, which meant that we could not know how many patients were excluded from the study. We have therefore missed a certain number of patients. This may cause a selection

Table 3 Collected patient data with missing values per variable (n = 2,273 patients)

Parameter	N = 2,273 (100%)	Missing value N (%)
Age, median (IQR)	41 (28;56)	0 (0)
Sex		4 (0.2)
Female, n (%)	1209 (53.2)	
Male, n (%)	1054 (46.4)	
Non-binary, n (%)	6 (0.3)	
BMI, median (IQR)	24.98 (21.95;29.30)	212 (9.3)
Comorbidities, n (%)		
Psychiatric comorbidity, n (%)		
Other than addiction[a], n (%)	1338 (58.9)	
Addiction[b], n (%)	511 (22.5)	
Somatic comorbidity, n (%)		
Diabetes, n (%)	227 (10)	
Chronic obstructive pulmonary disease, n (%)	126 (5.5)	
Heart Failure[c], n (%)	67 (2.9)	
Metabolic or endocrine disease, n (%)	56 (2.5)	
Chronic kidney disease, n (%)	46 (2)	
Source of ICU admission		0 (0)
Emergency department, n (%)	2103 (92.5)	
Ward, n (%)	117 (5.1)	
Other ICU, n (%)	53 (2.3)	
No second reason for admission, n (%)	1899 (83.5)	5 (0.2)
Second reason for admission, n (%)	369 (16.2)	
Time from exposure to presentation (h), n (%)		8 (0.4)
Known, n (%)	667 (29.3)	
Estimated, n (%)	481 (21.2)	
Unknown, n (%)	1117 (49.1)	
Time from exposure to presentation (among known or estimated times, in h), median (IQR)	4 (2.8; 8)	30 (2.6)
Poisoning-related factors		
Intent of poisoning		8 (0.4)
Unintentional, n (%)	272 (12.0)	
Intentional, n (%)	1993 (87.7)	
Number of exposures, median (IQR)	2 (1; 3)	24 (1.1)
Category of substances		56 (2.5)
Combination of two or more intoxications types	1131 (49.8)	
Sedatives, n (%)	241 (10.6)	
Street drugs, n (%)	203 (8.9)	
Alcohols, n (%)	123 (5.4)	
Analgesics, n (%)	105 (4.6)	
Antidepresseurs, n (%)	89 (3.9)	
Other poisons (e.g., CO, arsenic, cyanide), n (%)	18 (0.8)	
Toxins not otherwise specified, n (%)	307 (13.5)	
Initial vital signs		
Systolic Blood pressure (mmHg), median (range)	115 (95; 139)	18 (0.8)
Heart rate (beat/mn), median (range)	95 (74; 115)	6 (0.3)
Respiratory rate, median (IQR)	17 (12; 22)	62 (2.7%)
Temperature (Celsius degree), median (IQR)	36.3 (35.7; 37)	35 (1.5)
Glasgow Coma Score (GCS)		101 (4.4)
GCS available, n (%)	2089 (91.9)	
GCS not available because the patient was intubated or sedated, n (%)	83 (3.7)	

Table 3 (continued)

Parameter	N = 2,273 (100%)	Missing value N (%)
GCS ≥ 14	696 (30.6)	
GCS > 9 and < 14	411 (18.1)	
GCS > 6 and ≤ 9	360 (15.8)	
GCS < 6	622 (27.4)	
Most common signs or symptoms		0 (0)
Neurological signs		
Altered consciousness	979 (43.1)	
Coma	747 (32.9)	
Agitation	294 (12.9)	
Confusion	250 (11.0)	
Miosis	155 (6.8)	
Seizures	133 (5.9)	
Cardiologic signs or symptoms		0 (0)
Palpitations	108 (4.8)	
Hypotension	107 (4.7)	
Tachycardia	86 (3.8)	
Bradycardia	63 (2.8)	
Cardiac arrest or asystole	35 (1.5)	
Chest pain	32 (1.4)	
Gastro-intestinal signs or symptoms		0 (0)
Vomiting, n (%)	359 (15.8)	
Nausea, n (%)	227 (10.0)	
Abdominal pain, n (%)	141 (6.2)	
Diarrhea, n (%)	64 (2.8)	
Respiratory signs		1 (0.04)
Respiratory depression, n (%)	339 (14.9)	
Bradypnea, n (%)	274 (12.1)	
Tachypnea, n (%)	157 (6.9)	
Apnea, n (%)	134 (5.9)	
Initial blood performed, n (%)		
Arterial gas	1598 (70.3)	
SaO2 in %, median (IQR)	95 (91; 98)	7 (0.4)
Arterial pH, median (IQR)	7.34 (7.27; 7.40)	10 (0.6)
Electrolytes measured, n (%)	2169 (95.4)	
Potassium (mmol/L), median (IQR)	3.87 (3.50; 4.21)	36 (1.7)
Lactate measured, n (%)	1645 (72.4)	
Lactate (mmol/L), median (IQR)	1.89 (1.0; 3.1)	2 (0.1)
Leucocytes measured, n (%)	1940 (85.3)	
Leucocytes (10^9/L), median (IQR)	9.5 (7.0; 12.9)	11 (0.6)
Creatinine measured, n(%)	2101 (92.4)	
Creatinine (micromole/L), median (IQR)	72.5 (59.8; 93.2)	11 (0.5)
Blood toxicology screening performed, n (%)	949 (41.8)	
Blood toxicology screening performed and positive, n (% among performed)	549 (57.9)	2 (0.2)
Urine toxicology screening performed, n (%)	688 (30.3)	
Urine toxicology screening performed and positive, n (% among performed)	520 (75.6)	2 (0.3)
ECG performed, n (%)	1982 (87%)	5 (0.2)
ECG with abnormalities, n (%)	498 (25.1)	43 (2.2)
Care measures before admission		2 (< 0.1)
Mechanical ventilation before, n (%)	647 (28.5)	

Table 3 (continued)

Parameter	N = 2,273 (100%)	Missing value N (%)
Antidote before, n (%)	670 (29.5)	
Gastro-intestinal decontamination before, n (%)	550 (24.2)	
Oxygen with FiO2 > 0.4 before, n (%)	364 (16)	
Vasopressors before, n (%)	66 (2.9)	
Cardiopulmonary resuscitation before, n (%)	61 (2.7)	
Intensive care measures first 24H, n (%)		7 (0.3)
Mechanical ventilation first 24H, n (%)	809 (35.6)	
Vasopressors first 24H, n (%)	447 (19.6)	
Calming medication first 24H, n (%)	379 (16.7)	
Renal Replacement Therapy first 24H, n (%)	132 (5.8)	
Serum alkalinization first 24H, n (%)	121 (5.3)	
Active cooling first 24H, n (%)	22 (1.0)	
Cardiopulmonary resuscitation first 24H, n (%)	13 (0.6)	
ICU mortality, n (%)	85 (3.7)	11 (0.5)
In-hospital mortality, n (%)	103 (4.5)	11 (0.5)
Mortality 30 days after ICU admission, n (%)	117 (5.1)	243 (10.7)

[a] Including depression, borderline personality disorder, schizophrenia, bipolar disorders, eating disorders, posttraumatic stress disorder, anxiety and neurodevelopmental disorders including deficits in intellectual functioning

ICU intensive care unit, *IQR* interquartile range, *SaO2* oxygen saturation, *FiO2* fraction of inspired oxygen

[b] Addiction as defined in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5: American Psychiatric Association, 2013), including gambling or sex addiction

[c] Heart failure including cardiomyopathy, severe heart valve or coronary diseases with angina or symptoms at rest or minimal physical effort such as changing clothing and day-to-day care (New York Heart Association or NYHA Class VI)

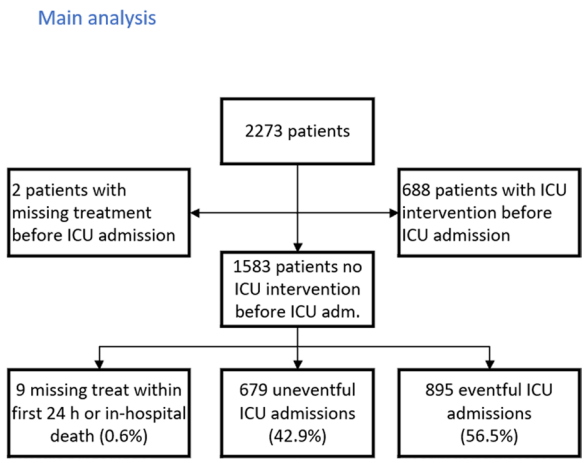

Fig. 2 Study Flow Diagram for patients in the main analysis. An "eventful ICU admission" was defined as receiving an ICU intervention within the first 24 h after ICU admission or in-hospital death. An ICU intervention was defined as receiving any of the following treatments: oxygen supplementation with a FiO2. 40%, mechanical ventilation, vasopressors, renal replacement therapy (RRT), cardiopulmonary resuscitation, antidote, active cooling, fluid resuscitation (> 1.5 L of intravenous fluid of any kind), and sedation. ICU intervention before ICU admission was defined as receiving mechanical ventilation or cardiopulmonary resuscitation or vasopressors (over at least 1 h) before ICU admission

bias, because the prognosis of the patients may vary according to whether an informed consent was considered necessary or not. However, the sensitivity analysis showed that this effect was limited.

Conclusions

Our results show a higher rate of intoxicated patients being treated in the ICU than has been reported in previous studies. Comprehensive data has been successfully collected on a large cohort of patients admitted to the ICU after acute intoxication, predominantly from European ICUs, with some representation from other continents. Future research needs to look more closely at outcomes by type of intoxication, externally validate existing prediction models predicting the need for ICU admission, identify risk factors for complicated intoxications, perform competing risk analysis for likelihood of discharge, and assess the prognosis of patients after specific exposures, such as street drugs. However, this requires large and detailed databases. INTOXICATE is a first step towards such a granular database. The findings from this study will inform future research efforts, particularly in understanding prognosis and refining data collection methods for similar studies.

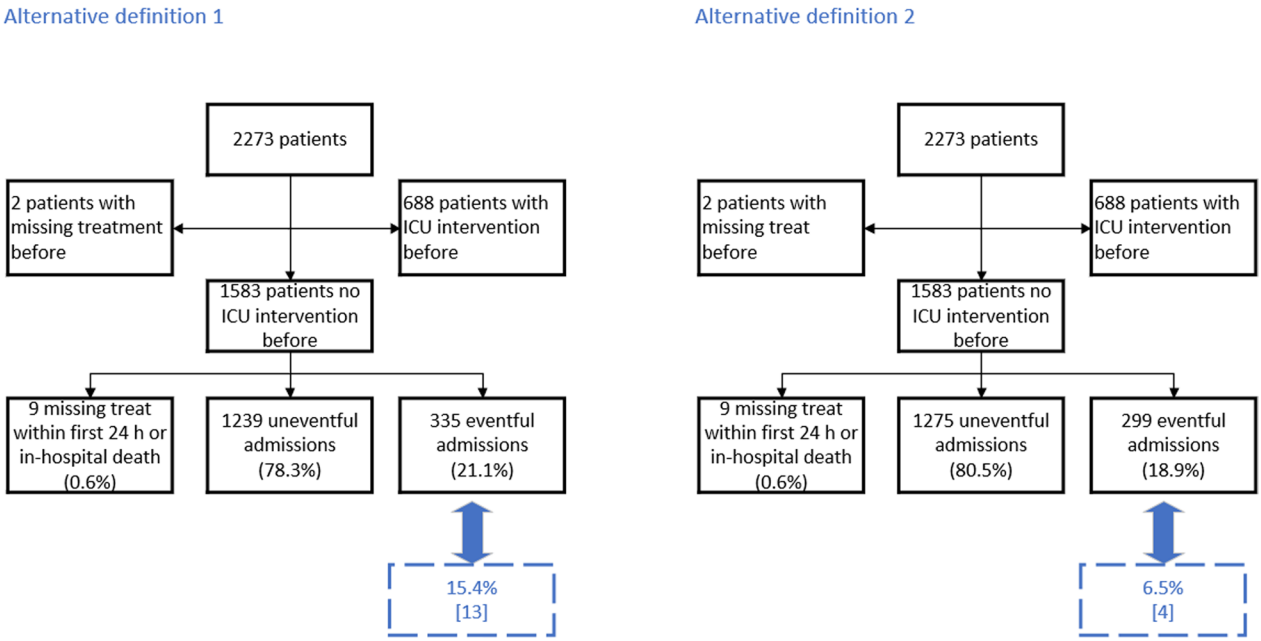

Fig. 3 Study Flow Diagram for patients in the post-hoc analysis (using alternative definitions 1 and 2 for "eventful ICU admission"). In alternative definition 1, an "eventful admission" was defined as receiving mechanical ventilation and/or vasopressors and/or renal replacement therapy and/or cardiopulmonary resuscitation in the first 24 h after ICU admission, or in-hospital death (as in [13]. In alternative definition 2, only receiving mechanical ventilation and/or vasopressors, or in-hospital death were included in the definition of an "eventful ICU admission" (as in [4]. ICU intervention before ICU admission was defined as receiving mechanical ventilation or cardiopulmonary resuscitation or vasopressors (over at least 1 h) before ICU admission

Abbreviations

APC	America's Poison Centers
DPIC	Dutch Poisons Information Centre
EAPCCT	European Association of Poison Centres and Clinical Toxicologists
ECMO	Extra Corporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
ESICM	European Society of Intensive Care Medicine
FiO2	Fraction of inspired oxygen
GDPR	General Data Protection Regulation
HDU	High Dependency Unit
ICU	Intensive Care Unit
IQR	Interquartile range
OSF	Open Science Framework
SaO2	Oxygen saturation

Supplementary Information

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Additional file 1: **Table S1**. Summary of the prior observational studies conducted with patients admitted to an intensive care unit (ICU) after acute intoxication. Search criteria: (1) setting: intensive care unit (ICU) in Europe or North-America or Australia or Hong Kong; (2) adult patients admitted to an ICU after an acute intoxication; (3) Design: observational study; (4) Studies reporting at least one of the outcomes of interest *i.e.* ICU mortality, in-hospital mortality and/or mortality 30 days after ICU admission. The studies are ordered from the most recent to the oldest year of publication and within each year by study size. A study population with fewer than 100 included patients was considered as being a "small size population study", and with fewer than 300 included patients as a "relatively small size population study". **Table S2**. Technical challenges related to multicenter data collection in the INTOXICATE study.

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Author contributions
SMZ and CCH performed the analysis, prepared the figures and wrote the manuscript. All the authors contributed to the data collection. All authors have thoroughly reviewed and approved the manuscript. DWdeL and CCH supervised the study.

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Availability of data and materials
The participants of the study did not give written consent for their personal data to be shared publicly, so supporting data are not available.

Declarations

Ethics approval and consent to participate
Data collection was approved by the accredited Medical Research Ethics Committee of the University Medical Centre Utrecht, The Netherlands (ethics reference number: 20-495/C). All participating units provided either local research ethics committee approval or a waiver of consent. The study was registered prospectively with an Open Science Framework (OSF) (OSF registration ID: osf.io/7e5uy).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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