

Emergency department poisoning and toxicology patients admitted to the high dependency and intensive care units: an eight-year analysis

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Abstract

Data on patients with poisoning requiring ICU (Intensive Care Unit) & HD (High Dependency) care in Singapore is inadequate. In this study, we describe the epidemiological, clinical characteristics, implicated agents, interventions, and outcomes of patients with toxic exposures admitted to HD & ICU. We conducted a retrospective and observational study. Hospital records of all cases referred to CGH Toxicology Service from 1 January 2015 to 31 December 2022 were reviewed. A total of 245 (9.6%) out of 2547 patients reviewed required HD or ICU care. 131 patients were admitted to ICU, while 114 patients were admitted to HD beds. Amongst those admitted to ICU, male to female ratio was approximately 60:40, and the commonest age group was 31-40 years old (19.9%), while deliberate self-harm poisoning accounted for 52.7 % of these cases. Benzodiazepines, anti-psychotics, anti-depressants, and opioids class of drugs and medications were the most associated with ICU admissions. The fatality rate was 3.2 %. Car-diotoxic drugs, anti-psychotics, and anti-depressants class of medications were associated with most fatalities.

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Introduction

Poisoning poses a significant health problem worldwide. Locally a significant proportion (36%)¹ of patients presenting to the Emergency Department (ED) for acute poisoning require inpatient care. Previous local studies found between 1.7 – 9 %¹⁻³ of hospitalizations for poisoning required admission to a High Dependency (HD) ward or Intensive Care Unit (ICU). There is still very limited information about the poisoning characteristics of patients with toxic exposures requiring HD or ICU care, and there is a paucity of local studies^{1,2,4} illustrating patients presenting with poisoning admitted to these units in Singapore.

The aim of this study is to describe the types and patterns of toxic exposures associated with HD and ICU stay, their epidemiological, demographic, and clinical characteristics, severity and certainty, interventions and outcomes including length of stay and mortality.

Materials and Methods

The study was conducted at the Changi General Hospital (CGH) Accident and Emergency Department (A&E). This is a tertiary care center and an academic hospital of over 1000 beds capacity. The A&E has an annual attendance of over 143,000 patients.⁵ The Toxicology Service at CGH (now integrated with the SingHealth Cluster Toxicology Service) provides round-the-clock consultation for patients with poisoning, and is run by clinical toxicologists, who have a primary training background in emergency medicine.

This is a retrospective review of all poisoning cases referred to the toxicology service from 1/1/2015 to 31/12/2022, which required either HD or ICU admission. The toxicology service consultation records and database during the study period were reviewed to identify the cases. The A&E and in-patient case note records were reviewed as well. The data analysis was done by the various authors and in case of doubts and uncertainties, there was intra-group consultation to arrive at a consensus between the study authors. Analysis was done by descriptive statistics and Microsoft[®] Excel was mostly used for the statistical calculations.

The poisoning severity score (PSS)⁶ was used to grade poisoning severity for all patients. The score ranges from 0 to 4 in clinical severity and the highest score for the patient in the A&E was counted. The organ system effect that resulted in the score was also determined.

The likelihood of poisoning exposure was adapted from the WHO Uppsala Monitoring Centre system on causality assessment⁷ and we classified the certainty of poisoning as a score of either 4) definite, 3) probable, 2) possible, and 1) unlikely.

For mortality cases, a Relative Contribution to Fatality (RCF)⁸ scale was assigned. A RCF score of 1 to 3 is considered to be associated with the poisoning exposure, whereas a RCF score of 4 to 6 was deemed not to be associated with the poisoning exposure.

For the purpose of this study, we included multiple drug classes under the group cardiotoxic drugs like Beta-Blockers (BBs), Calcium Channel Blockers (CCBs), aconite like Traditional Chinese Medications (TCM), and anti-arrhythmic medications like amiodarone, due to their predominantly potentially lethal cardiotoxic effects in poisoning. Multi-substance ingestions were classified based on the presentation history as well as the biochemical drug analysis results.

Results

During the 8-year period 2015 to 2022, 2547 patients were referred to the toxicology service; of the 250 patients who were admitted to HD or ICU, 5 were excluded as poisoning was deemed unlikely in them, leaving 245 (9.6%) for analysis (Figure 1). Amongst the 245 patients, 131 were admitted to ICU, while 114 patients were admitted to HD. Patients who were admitted to both HD and ICU were categorized under the ICU group. The trend showed an unexplainable dip in the ICU and overall admissions in

2018 which improved slightly in 2019 and showed a downwards trend again during the pandemic years of 2020-2021 (Figure 2).

Characteristics of patients admitted to ICU

There were 79 males and 52 females. The age groups 31-40, 41-50 and 21-30 had the highest numbers at 26, 24 and 24 respectively (Figure 3). Deliberate self-harm exposures accounted for 69 (52.7 %) while drug abuse was noted in 31 (23.7 %) patients. Certainty of poisoning⁷ score of 4 was determined in 81 (61.8 %), 36 patients had score of 3 while 14 patients were thought to have score of 2. Highest PSS⁶ in the A&E were 3 for 99 (75.6 %), 2 for 25 and 1 for 7 patients.

Highest PSS involving Central Nervous system was found in 87 (66.4 %), Cardiovascular System in 36, Renal System in 14, Gastrointestinal and Hepatic System in 11, Respiratory System in 9 while musculoskeletal system involvement was found in 1 patient. Twenty-six (19.8 %) patients had multiple systems' involvement wherein the PSS was equal for each organ system. The routes of exposures were determined to be via oral route in 119 (90.8 %), via inhalational route in 6, via intravenous route in

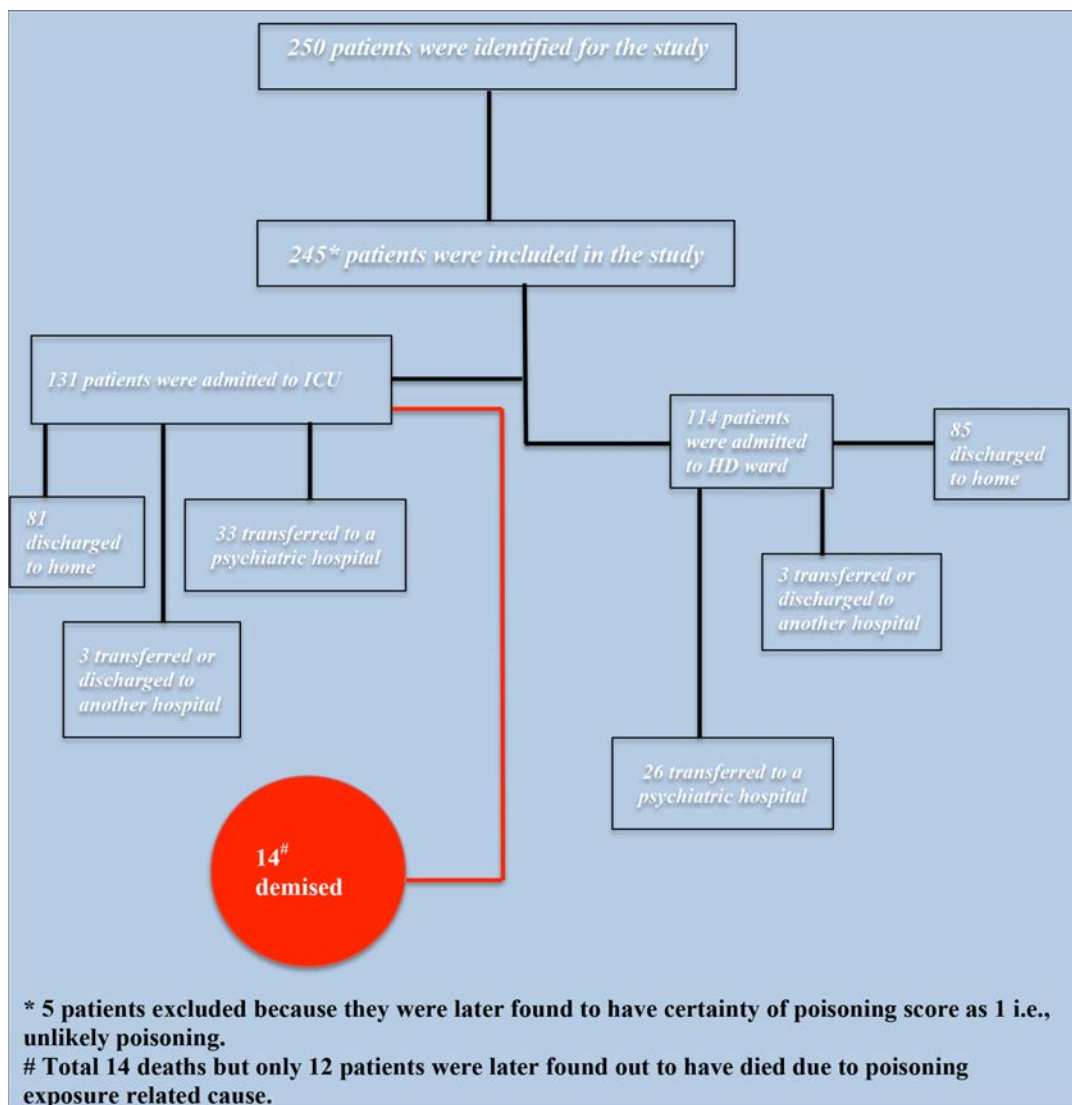


Figure 1. Study recruitment and eventual outcomes.

2, and both oral and inhalational in 1 patient while route of exposure could not be determined for the remaining 3 patients.

Benzodiazepines were implicated in 51, anti-psychotic medications in 36, anti-depressants in 32, opioids in 32, while cardiotoxic agents were implicated in 18 patients. Ethanol was ingested by 5 patients while Paracetamol was detected in 13 patients. Drug withdrawal syndrome accounted for 11, stimulants and sympathomimetics in 18, 5 were exposed to anti-diabetic and hypoglycemic agents while 4 others were exposed to household bleach. Benzodiazepines had nitrazepam (n=14), diazepam (n=13), alprazolam (n=8), anti-psychotic medications had quetiapine (n=19), olanzapine (n=9), while the anti-depressants had fluoxetine (n=6), and amitriptyline (n=4) as the commonest individual agents.

Opioids had codeine (n=14) and tramadol (n=10) while cardiotoxic drugs had amlodipine (n=6), digoxin (n=2) and nifedipine (n=2) as the commonest agents.

Serum lactate levels done in the ED were available only for 37 patients, wherein the median lactate level was 4.96 (2.93-11.56). Similarly, lactate levels in the ICU were available only for 39 patients and the median lactate level was 2.72 (1.78-4.91). The pH levels done in ED were available for 44 patients, and the median pH level was 7.278 (7.18 - 7.38) while the pH levels done in the ICU were available for 43 patients wherein the median pH level was 7.319 (7.25 - 7.36). The APACHE II scores were available only for 23 patients in the ICU and the median score was 17 (12-26.5).

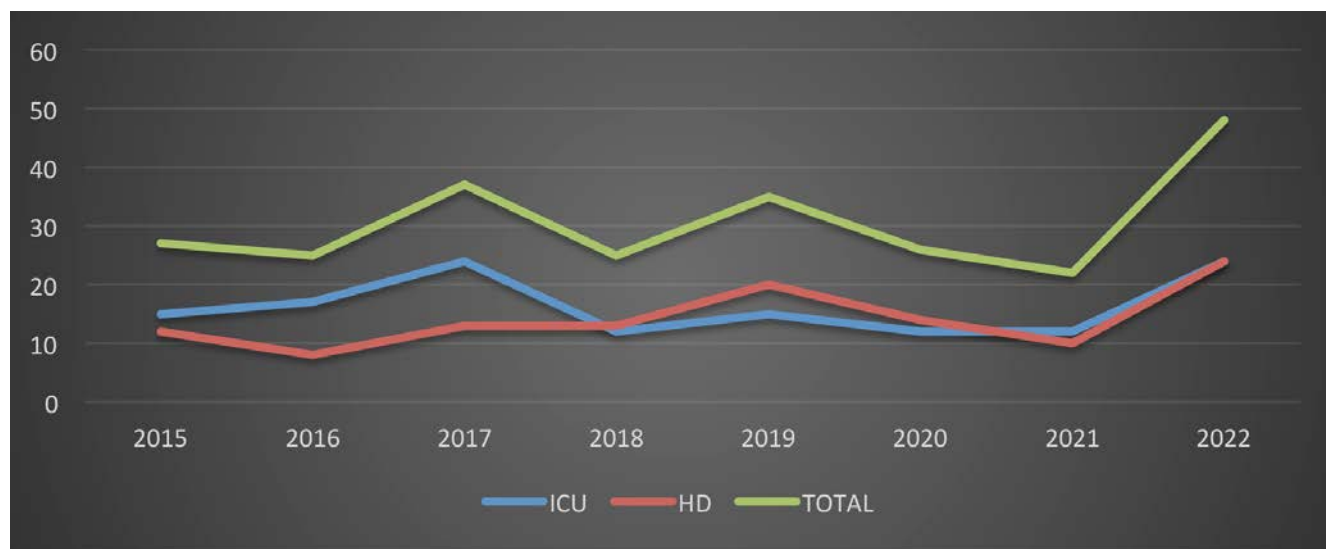


Figure 2. ICU, HD and overall admissions by year.

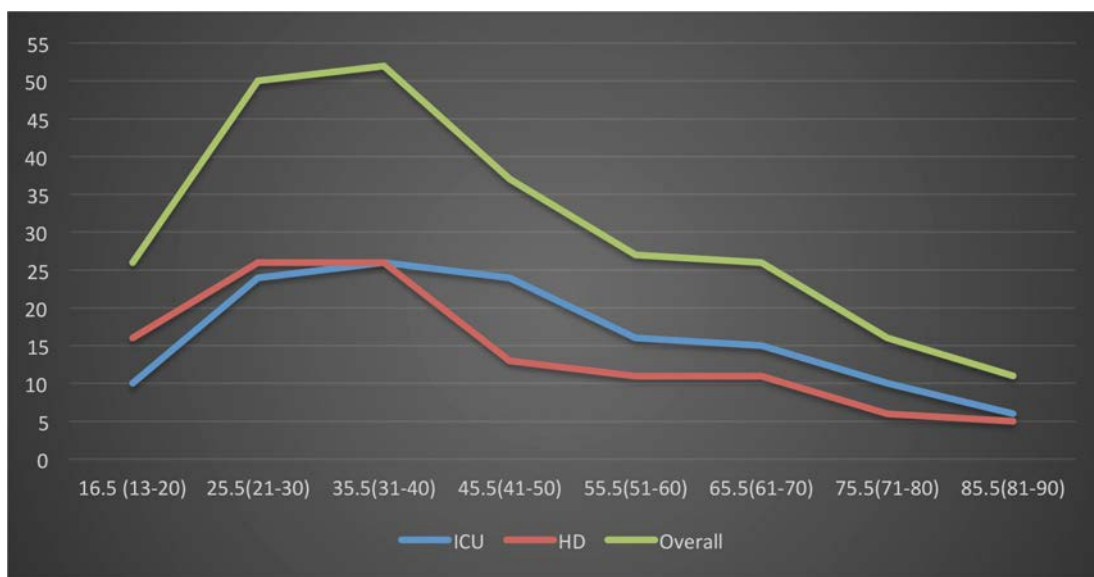


Figure 3. Age distribution of ICU, HD patients and overall numbers.

A trial of an anti-dote either in the A&E or in ICU was given for 54 (41.2%) patients. Intravenous Naloxone (n=17), IV N-Acetylcysteine (n=13), IV Sodium Bicarbonate (n=11) and IV Flumazenil (n=7) were used most. Decontamination measures were administered in 29 patients. Activated Charcoal was used in 27, gastric lavage in 4 and whole bowel irrigation (WBI) in 1 patient. Three patients underwent a gastric lavage and were given activated charcoal as well.

Intubation was performed for 98 (74.8 %) patients, of which majority (n=74) were intubated in the A&E. Most common exposures requiring intubations were benzodiazepines (n=43), anti-psychotic medications (n=29), anti-depressants (n=26), antihistamines (n=16), opioids (n=15), stimulants & sympathomimetics (n=14) and cardiotoxic drugs (n=12). Some common agents associated with the intubations were quetiapine (n=16), diazepam (n=12), promethazine (n=9), nitrazepam (n=9), olanzapine (n=7), and lorazepam (n=4).

Vasopressor or inotropic support was required in 46 patients. Cardiotoxic agents (n=16) were most associated with their usage followed by benzodiazepines (n=12), anti-depressants medications (n=7) and anti-psychotic medications (n=7) while calcium channel blockers (n=7; amlodipine=5, nifedipine=2), diazepam (n=4), amphetamine (n=4) and aconite (n=3) were the most associated individual agents. Single agent was used in 16 patient, dual agents in 14, while more than two agents were required in 16 patients. Five patients were administered HIET (High Insulin Euglycemic therapy)⁹ and were exclusive to the cardiotoxic drugs. Amlodipine (n=4) and nifedipine (n=1) exposure was found in these and the nifedipine patient had also ingested atenolol concurrently. ECMO (Extra Corporeal Membrane Oxygenation) therapy was instituted for two patients. First ECMO patient had ingested massive amounts of amlodipine (550 mg) together with paracetamol (13 grams). The patient successfully underwent a VA (Veno-Arterial)^{10,11} ECMO therapy for 3 days concurrently with Therapeutic Plasma Exchange (TPE) using 2/3 albumin and 1/3 Fresh Frozen Plasma (FFP). The second ECMO patient had ingested massive amounts of Quetiapine and unfortunately died from the poisoning effects. The Quetiapine blood levels were 5.3 mcg/ml.

Our study noted the usage of Extracorporeal Treatments (ECTRs)^{12,13} for 21 patients (17 in the ICU patients' group and 4 in the HD patients' group). Out of these 22 patients, 20 patients did not have any regular dialysis requirement prior to their toxicologic exposure. Cardiotoxic drugs (n=8) followed by stimulants & sympathomimetics (n=3), alcohols including ethanol (n=3), drug withdrawals (n=2) and metformin (n=2) required Renal Replacement Therapy (RRT). Most common indications were acidosis, and oliguric acute kidney injury. Two of these 22 patients in the ICU group had pre-existing end stage renal failure requiring regular dialysis prior to their toxicologic exposure.

Drug removal was the primary requirement in 6 patients and the most common drugs were ethylene glycol, methanol, salicylate, metformin induced lactic acidosis (n=2) and Theophylline.

We also noted that there was progression of the initial ED Poisoning severity Scores in the inpatient ward for 30 patients, including the 14 patients who demised eventually. This progression was associated with anti-depressants medications, benzodiazepines, drug withdrawal syndromes, anti-psychotic medications, caustic agents, cardiotoxic drugs, unknown medications and poisons, non-opioid analgesics and salicylates, anti-epileptics, alcohols including ethanol, opioids, cellular asphyxiants, antihistamines, stimulants and sympathomimetics and non-benzodiazepine sedatives in decreasing order of frequency. Benzodiazepine withdrawal, lorazepam, household bleach inges-

tion, ethanol, fluoxetine, olanzapine, pregabalin and quetiapine were the most common individual agents associated with worsening of PSS after transfer to inpatient ward, in the order of their frequency.

Outcomes

Eighty-one patients (61.8 %) were eventually discharged home, 33 patients required transfer to a long-term psychiatric hospital, 1 patient requested transfer to a private hospital, 1 was transferred to a rehabilitation hospital, 1 to a specialized neurology intensive care unit under a different hospital, while 14 patients died.

Amongst the 14 deaths, only 12 were deemed to be poisoning related wherein 6 with RCF score of 1, the respective implicated agents were nifedipine and atenolol; amlodipine; amphetamine; salicylate; hydrogen peroxide; and quetiapine. One patient with RCF score of 2 had amitriptyline while another one had exposure to fluoxetine, olanzapine and fentanyl. Two patients with RCF score of 3 had ethanol, sotalol and unknown exposures respectively. 1 patient who died from spontaneous intracranial hemorrhage had RCF score of 4 and the nature of the poisoning involved was not clear in this case. Another patient with RCF score of 4, blood toxicology analysis revealed nitrazepam. He had presented with cardiogenic shock, acute pulmonary oedema, and severe metabolic acidosis. Emergency coronary angiography showed clean and unobstructed coronary vessels with TIMI 3 flow.¹⁴ Even though blood toxicology revealed nitrazepam, it was unlikely to account for the presentation and mortality. The median ICU length of stay (LOS) was 1.72 days or 41.30 hours (IQR=25.73 Hours – 75.21 Hours). During the same admission, 42 patients were admitted to both the HD as well as the ICU. Agents associated with longest ICU LOS were sotalol (17.8 days), malathion (15.3 days), amiodarone (14.8 days), ethanol (14.4 days) and household bleach (12.6 days).

Characteristics of patients admitted to HD only

There were 74 (64.9 %) males and 40 (35.1 %) females. Deliberate self-harm exposures accounted for 51 (44.7 %) while drug abuse was noted in 38 (33.3 %) and unintentional overdose in 16 (14 %) patients. Highest PSS in the A&E were 3 for 54, 2 for 43 and 1 for 17 patients. Highest PSS involving central nervous system was found in 80, and cardiovascular system in 29. The routes of exposures were determined to be via oral route in 108 patients.

Benzodiazepines were implicated in 90 patients, opioids in 57, anti-depressants in 48, antihistamines in 43, anti-psychotic medications in 28, stimulants and sympathomimetics in 24, anti-epileptics in 17 and cardiotoxic agents in 16 patients. A trial of anti-dotes was given in 53 (46.5%) patients. IV naloxone (n=25), IV n-acetylcysteine (n=8), and IV flumazenil (n=8) were the commonest used anti-dotes. Decontamination measures were administered in 12 patients. Activated charcoal was used in 10, Whole Bowel Irrigation (WBI) in 1 patient while one patient with organophosphate poisoning was scrub washed and showered. Ten patients required vasopressors and inotropes while five patients required RRT and dialysis. Eighty-five patients were eventually discharged home, 26 patients required transfer to a long-term psychiatric hospital, and 1 patient to a specialized women's hospital while two were transferred to a long-term rehabilitation hospital. The median HD length of stay (LOS) was 1.39 days or 33.3 hours (IQR=21 Hours -48.1 Hours). Paracetamol Poisoning with concomitant hepato-biliary sepsis (12.4 days), Methamphetamine (7.5 days) and Lithium (5.9 days) were associated with the longest HD LOS.

The results of the patients admitted to both HD and ICU wards are illustrated in the Figure 2 and 3 and Supplementary Materials Table 1a, 1b and 1c.

Discussion

Benzodiazepines,¹⁵ anti-psychotic medications, anti-depressant medications, opioids, antihistamines, cardiotoxic drugs and stimulants and sympathomimetics for the ICU group while benzodiazepines,¹⁵ opioids, anti-depressants, antihistamines, anti-psychotic medications, and stimulants and sympathomimetics were the commonest class of agents associated with the HD admissions. This contrasts with the local study by Tay *et al.*⁴ in 1998, where the predominant agents were organophosphates and carbamates, benzodiazepines, tri-cyclic antidepressants and phenothiazines. Forty-one patients in the ICU group and 48 patients in the HD only group had three or more implicated agents, which makes it somewhat difficult in these patients to link the associations with any individual class of agent. Ethanol and Toxic alcohols did not rank amongst the top 10 class of agents in our study unlike an Italian based demographic study by Botti *et al.*¹⁶ where in alcohol accounted for more than one-third of the exposures. Some of the indications for ICU admissions¹⁷ were initial depressed GCS with anticipated further deterioration, severe cardiovascular instability, arrhythmias, recurrent seizures at presentations, severe end organ dysfunctions and requiring intubation with mechanical ventilation in ED. For HD admissions, the indications were usually low GCS but not comatose and not requiring intubation or mechanical ventilation, moderate cardiovascular instability requiring low doses of inotropes and vasopressors.

Deliberate Self Harm (DSH) or attempted suicide as a reason for exposure accounted for about 52.3 % of ICU and about 44.7 % of the HD patients. This is similar to another study by Banderas-Bravo *et al.*¹⁸ More patients were above 40 years age in the ICU group (<40:>40=60:71) while the ratio was inverse in the HD group (<40:>40=68:46). There was a male preponderance in this study contrary to a local study by Chiu *et al.*¹ in 2011. From 2015 to 2017, the blood and urine toxicology screening tests were not available readily, whereas from 2018 onwards their availability became more common. Hence 2018 onwards, more patients had certainty of poisoning score at 4. Our study also shows a male preponderance with over 60% of patients as males in both the ICU and HD groups. This contrasts with other studies which show a predominance of the female sex using pharmacological method for deliberate self-harm.^{19,20}

Lactate levels and pH have shown to be good prognostic factors for poisoned patient in studies by Manini *et al.*,²¹ Golaghaei *et al.*,²² and Uzucek *et al.*²³ The results for serum pH, lactate levels, and APACHE II scores were not available for all the patients in this study. In our study the lactate levels were available for less than 30% while pH levels were available for about 33% of the total number of ICU patients. The median lactate levels done in the ED were higher than that in the ICU while the median pH levels in done in ED were lower than that in the ICU, indicating a relatively favorable prognosis over time for these patients.

The main indication for intubations²⁴ was low GCS^{15,25} with decreased level of consciousness and inability to protect airways requiring a definitive airway. Other reasons were airways' oedema and an impending loss of airway, respiratory failure, severe cardiovascular instability leading to cerebral hypoperfusion and decreased GCS, and to reduce the cardiac workload from likely

increased ventilatory requirements. The requirement for a vasopressor and inotropic support was indicated due severe hemodynamic instability.

A total of five (5) patients in our study from the ICU patients' group required HIET (Hyperinsulinemic-Euglycemic Therapy) which were exposed to significant amounts of Calcium Channel Blocking Agents (CCB) and Beta Blocking Agents (BB).

Two patients underwent an ECMO therapy wherein one had presented after massive Amlodipine overdose²⁶ concurrently with Paracetamol while the other had taken massive amounts of Quetiapine. ECMO therapy for poisoning patients has gained popularity rapidly over the last few years due to improved outcomes. Wang *et al.*²⁷ showed that only 10 patients (0.0004 %) out of 26,271 toxicologic exposures received ECMO therapy over a period of 4 years from 2010 to 2013 which included 4 paediatric patients. Another retrospective study by Ramanathan *et al.*²⁸ analysing data from the Extracorporeal Life Support Organization registry from 1999 to 2014 showed increasing use of ECMO for poisoning cases, with survival in majority (59%) of adults receiving ECMO. ECMO can be a very effective treatment modality for patients with toxicological exposures as it provides haemodynamic and oxygenation support while the toxic agent is either metabolized by the body over time or is eliminated using a simultaneous ECTR therapy.

Some patients in this cohort required ECTR and Dialysis therapy for metabolic acidosis, acute kidney injury and anuria, which is associated with many classes of poisonings, as illustrated by Rogliano *et al.*²⁹

The Median ICU and HD Length of Stay (LOS) were 1.72 days and 1.39 days respectively and is comparable to other studies.¹⁵ More than one substance was identified in 149 patients (60.8 %) based on available history, laboratory biochemical testing, and blood & urine drug analysis. Overall, acute poisoning accounted for about 367.53 ICU bed days and about 308.38 HD bed days during the 8-year study period. The hospitalisation costs for these patients are substantial as they may require many additional invasive interventions.

The fatality rate for this selected cohort of patients was determined as 3.2%, which is higher than other local studies^{1,3,4} and other international studies^{15,30,31,32} done in Iran, the UK, and USA. Rezar *et al.*³² described lower mortality rates in patients with poisoning compared to other critically ill patients in the ICU. The authors feel the mortality rate in our study is higher as only ICU & HD patients were considered while the other studies compared it with a larger cohort. A local ICU study by Tay *et al.*⁴ showed a higher mortality rate at 8%.

Limitations of the study

This study did neither ascertain the poisoning patients as a percentage of all the HD & ICU admissions nor did it perform any health care costs comparison with those patients. Laboratory analytical confirmation for the implicated agents, serum lactate levels, pH and ICU disease severity score of APACHE II was not available for all the patients. The study did not factor in the quantification of the drugs and toxins involved leading to the HD & ICU admissions. Even though this study attempts to establish the associations with various drug classes, it is difficult to interpret in many cases if the association is due to the individual class of drug alone or due to the combined effects of more than one class of drug. Statistical and regression analysis have not been performed in this study. There might have been patients with poisoning who were admitted to the HD & ICU wards and not consulted by the

Toxicology service during their hospital stay, implying that the actual numbers may be marginally higher. The patients' occupational, medical, and social history was not ascertained and factored in for this study, which may have shed some light on the reasons for the poisoning.

Conclusions

Benzodiazepines, anti-depressants, anti-psychotic medications, opioids, antihistamines medications and cardiotoxic drugs were the most common class of agents associated with ICU & HD admissions. The most common reasons were high PSS scores involving either the CNS or the CVS systems. More than 60% of the cases had exposure to more than 1 agent. Cardiotoxic effect drugs, anti-psychotic medications, and anti-depressant medications were found to be the most lethal. This study is one of the biggest studies in toxicology regionally involving the critical care patients and the conclusions can potentially form basis of better prediction models^{2,17} as well health care planning in future.

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Online Supplementary Materials

Table 1a. Patient demographics and poisoning characteristics.

Table 1b. Therapeutic interventions.

Table 1c. Length of stay and outcomes.