Toxicology Reports 13 (2024) 101705

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Assessment of co-ingestion effects on poisoning patterns, drug-drug interactions, and adverse outcomes in acute toxic exposure

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ARTICLE INFO

Keywords:
Drug-drug interactions
Multiple ingestion
Intensive care unit
Drug poisoning
Mechanical ventilation

ABSTRACT

Multiple toxic exposures are increasing nowadays. In cases of acute poisoning involving multiple agents, there is a potential for additional toxicity that goes beyond the effects and toxicity of each drug. Very scarce studies have investigated the problem of multiple toxic exposures where the information on drug-drug interactions (DDIs) originates from clinical experience, which is inconclusive and cannot be generalized to patients. Therefore, the current study aimed to explore the influence of co-ingestion on the clinical presentation of exposed patients and to identify the common associated DDIs and their effect on poisoning outcomes, including the need for mechanical ventilation (MV), intensive care unit (ICU) utilization, and prolonged hospital stay. The current study is a retrospective cross-sectional study that was conducted using medical records of 169 adult patients admitted to a poison control center and diagnosed with acute drug poisoning. Of them, 40.8 % were exposed to multiple drugs. The total number of drugs reported in the current study was 320 preparations, with an average of 1.9 drugs per patient. There were about 726 potential DDIs; more than half of these interactions were significant ($n = 486$). Antidepressants and psychotropics showed the highest total number of DDIs. Patients with multiple ingestion were significantly older and this pattern of exposure was more frequent among suicidal attempters, substance abusers, cardiac patients, and patients diagnosed with neurological and psychological problems. Moreover, patients with multiple ingestions showed severe presentations indicated by higher grades of Poison Severity Score and lower Glasgow Coma Scale. Multiple ingestion was associated with higher liability for MV, ICU admission, and prolonged length of hospital stay ($p < 0.001$). There was a significant moderate direct correlation between the number of drugs consumed and the number of resulting DDIs ($r = 0.542$, $p < 0.001$). There was a significant direct correlation between the occurrence of significant chronic/chronic drug interactions from one side and the history of substance abuse ($r = 0.596$, $p = 0.041$) and psychological illness ($r = 0.662$, $p = 0.019$) from the other side. Moreover, significant acute/acute drug interactions were correlated with being male ($r = 0.969$, $p < 0.001$) of older age ($r = 0.672$, $p = 0.024$). Similarly, significant acute/chronic drug interactions were moderately correlated with being a male ($r = 0.692$, $p = 0.013$). The presence of epilepsy and psychological problems were the main significant predictors of multiple acute toxic exposures. Among the patients exposed acutely to more than one agent who were on long-term treatment, exposure to three drugs or more could significantly predict the need for MV with excellent area under the curve (AUC) of 0.896 and 77.0 % accuracy. Moreover, and it was a fair predictor of ICU admission (AUC = 0.625), with an 88.9 % ability to exclude patients unlikely to need ICU admission. Particular attention should be paid to the patients at risk of potential DDIs. When prescribing drugs, the minimum number of drugs with the lowest effective doses, and minimal potential DDIs should be prioritized.

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https://doi.org/10.1016/j.toxrep.2024.101705
Received 22 June 2024; Received in revised form 23 July 2024; Accepted 2 August 2024
Available online 8 August 2024

1. Introduction

Acute poisoning is a significant health issue contributing to mortality and morbidity. Although acute drug poisoning is preventable, it remains a significant problem [1]. Acute poisoning is defined as developing adverse effects following exposure to pharmacological, non-pharmacological agents, and a broad set of environmental and occupational toxins [2]. In alignment with the technological and social advancement that increased the accessibility of different toxic agents, there is a pronounced increase in acute poisoning, which negatively affects the community's economic status and depletes resources [3,4].

There are vast reported primary adverse outcomes following acute toxic exposure, including mortality [5], respiratory failure [6], cardiotoxicity, renal failure [7], and seizures [8]. Most of the previous studies aimed to predict acute poisoning-associated adverse outcomes established their findings based on a single unique type of exposure. Many of these studies included the exposure to a single substance among the inclusion criteria to limit the confounding factors and eliminate the risk of bias in data analysis. Nevertheless, this is not the case in realistic contexts, where co-ingestion or multiple exposure is common [9–11].

Multiple toxic exposure is increasing nowadays, since single disease is treated with several drugs. The non-medical use and self-prescription of drugs, besides the aging of populations with the advancement of health care systems, are other factors contributing to multiple medication use [12]. The complications and treatment in individuals who have been drug poisoned may vary according to the type of drug, the dosage, and the usage of other drugs. Identifying the poisoning agents allows appropriate medical care and prevents recurrence [13].

In cases of acute poisoning involving multiple drugs, there is a potential for additional toxicity that goes beyond the effects and toxicity of each drug [14]. Jayakrishnan et al., defined the drug-drug interaction (DDI) as *"two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered."*[15]. DDI occurs when a medication modifies how another drug is absorbed, distributed, metabolized, or eliminated. It can also occur when a drug competes with the receptor of another drug or due to a pharmaceutical reaction [16].

In the context of acute toxic exposure, very scarce studies investigated the problem of multiple toxic exposures [14,17]. The information on DDIs originates from clinical experience, which is inconclusive, and their findings cannot be generalized to patients [18]. Therefore, the current study aimed to explore the influence of co-ingestion on the clinical presentation of exposed patients and to identify the common associated DDIs and their effect on the pattern and outcomes of acute toxic exposure. Moreover, we aimed to assess the liability of those patients to develop several adverse clinical outcomes, including the need for mechanical ventilation (MV), intensive care unit (ICU) utilization, and prolonged hospital admission.

2. Subjects and methods

2.1. Study design and setting

The present study was a retrospective cross-sectional study. The study was conducted using data from medical records of patients who presented to King Fahad Medical City (KFMC) Emergency Department between January 2020 and December 2022 and diagnosed with acute toxic exposure.

2.2. Sampling and sample size calculations

Convenience sampling was deployed to approach all available medical records meeting the inclusion criteria. However, to ensure that the studied sample is sufficient to answer the research question, the sample size was calculated using Open Epi software Version 3, open-source calculator-SSPropor. Among acutely intoxicated patients reported to the American Association of Poison Control Centers 1984–2013, the frequency of exposure to more than one substance was estimated to be 8.3 [12]. Thus, the estimated sample size should be not less than 117 patients. However, we could increase the number to 169, maintaining a confidence level of 95 %, design effect of 1 and margin of error of 5 %.

2.3. Inclusion and exclusion criteria

The present study was conducted among adult patients aged 18 and above who were diagnosed with acute toxic exposure and presented to KFMC during the stated period. All patients with complete medical records were included regardless of the manner and circumstances of exposure. Patients with missing or incomplete medical records were excluded. Besides, we excluded patients diagnosed with a history of expsoure to unconfirmed and non-pharmacological agents, those with significant respiratory problems necessitating MV, and those admitted to ICU for other causes not related to toxic exposure.

2.4. Compliance with ethical standards

The current study was commenced after obtaining Institutional Review Board (IRB) approval from KFMC (1RB Log Number:23-588). According to the Declaration of Helsinki and its later amendment, which states that the interest of privacy and safety to the patient is over the interests of science and society, medical records were handled anonymously, and the patients 'confidentiality was preserved using coding system for case report forms. The IRB waived informed consent due to the observational nature of the study.

2.5. Grouping and outcomes

The patients enrolled in the current study were categorizied into two groups; Group [1] representing the patients of single exposure and Group [2] inlcuding patients with multiple expsoure (co-ingestion). The Group of multiple exposures included patients exposed to more than one drug, involving at least one drug/poison in a supratherapeutic dose at a single time. The other co-ingested agent might be another superimposed toxic exposure in an acute manner or a drug consumed on a chronic basis as a long-term treatment. Hence, the group of multiple ingestions was divided into three subgroups: Group 2 A included patients with acute co-ingestion but no chronic exposure, Group 2B included single acute ingestion and chronic long-term exposure (exposed to only a single drug acutely, besides the long-term drug), and Group 2 C included acute co-ingestion and chronic long-term exposure also. The investigated adverse outcomes included the respiratory failure indicated by the need for MV), the need for ICU admission, and the prolonged length of hospital stay.

2.6. Data collection tool

2.6.1. Pattern of poisoning

For every included patient, a predesigned case report form was completed, inlcuding the personal and demographic data, comorbid conditions, and an exposure history involving the manner of exposure, the type of the drug, and the delay time between the exposure and receiving the emergency treatment.

Initial vital data were reported. Furthermore, we reported the presenting complaints, including gastrointestinal, respiratory, cardiovascular, sensory, and motor manifestations. The analysed data included the clinical findings like abnormal breath sounds, shock, electrocardiographic abnormalities, abdominal tenderness, and pupil size. Every patient was scored using the Glasgow Coma Scale (GCS) and Poison Severity Score (PSS), in addition to thorough laboratory investigations. Furthermore, we reported the used therapeutic regimen (antidotes, sodium bicarbonate (HCO_3), IV fluids, and vasopressors), and the need of the patient for MV, ICU admissions, and the length of hospital stay

(hours) from admission until discharge.

2.6.2. Drug categories

The encountered drug groups were reported, and twenty groups were identified as acutely consumed agents, including the nonsteriodal anti inflammatory drugs (NSAIDs), acetaminophen, antidepressants, psychotropics, antiepileptics, alcohol, sedative hypnotics, opioids, central nervous system (CNS) stimulants, anticholinergics, antihistamines, cardiovascular drugs, diuretics, vitamins and supplements, antibiotics, muscle relaxants, oral antidiabetics, antitussive, and antacid drugs. Moreover, we identified nine chronic ingestants, including aardiovascular drugs, insulin and oral antidiabetic drugs, diuretics, psychotropics, antidepressants, antiepileptics, CNS stimulants, aitamins and supplements, and antihistamines. Medical records were screened, and the type and number of agents every patient was exposed to were identified.

2.6.3. Types of drug/drug interactions (DDIs)

The used drugs were screened for acute/acute DDI, acute/chronic DDI, and chronic/chronic DDI. To assess the potential DDI, the types of used drugs were fed to the Medscape™ interaction checker software [19]. Three types of DDIs were identified, including serious (use alternative), significant (monitor closely), and minor (monitor).

2.7. Data analysis

The collected data were organized and statistically analyzed using SPSS software statistical computer package for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). The Shapiro-Wilk for normality test was performed to assess the distribution of the numerical data. Quantitative data were represented by mean, standard deviation (SD), range, median and interquartile ranges (IQR) (25th −75th percentiles). Qualitative data were presented by number and percent.

The results were tabulated, grouped and statistically analyzed using the Independent t Test (t) to compare between 2 independent groups regarding parametric quantitative variables. Mann Whitney U Test (U) was used for comparison between 2 independent groups regarding nonparametric quantitative variables. ANOVA Test (F) comapred more than two independent groups (Group 2 A, 2B, 2 C) regarding parametric quantitative variables, while Kruskal Wallis Test compared these subgroups regarding nonparametric quantitative variables. Pearson Chi-Square Test (χ^2) was performed to detect whether there is a significant association between different categorical variables and when it was inappropriate, it was replaced by Fischer Exact or Monte Carlo Exact test. Spearman Correlation Test was used to study the relationship (direction and power) of different types of drug interactions (serious, significant, minor) and some epidemiological and exposure factors. Univariate and multivariate regression analyses were performed to identify predictors of multiple acute ingestions and to assess the predictors of adverse outcomes in each subgroup.

Ultimately, Receiver Operating Characteristic (ROC) curve analyses were performed to evaluate the diagnostic performance of the predictors identified in the regression analysis (the number of drugs a patient was exposed to) in identifying the patient's need for MV and ICU admission. The outcome measures included sensitivity, specificity, accuracy, poistive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios at various threshold levels. The analysis followed these steps:

1. Data Segregation: Data was split twice into positive and negative cases based on the patient's need for MV/ICU admission. Cases were coded as one if the patient experienced any of these outcomes and 0 if not.
2. Threshold Determination: Multiple thresholds were applied to the predictor variable to determine sensitivity and specificity. Due to the ordinal nature of the predictor (number of drugs a patient was exposed to), multiple pairs of (x, y) are possible, leading to multiple points on the ROC curve, giving a stair-step appearance. Each point represents a sensitivity/specificity pair value corresponding to a particular test threshold value that produces it [20]. The smallest threshold value is the minimum observed test value minus 1, and the largest threshold value is the maximum observed test value plus 1. All the other points are the averages of two consecutive ordered observed test values. The cut-off point is the threshold point chosen to yield the optimal sensitivity and specificity with the most clinical relevance.
3. Plotting the ROC Curve: The ROC curves were generated by connecting these multiple points by plotting the true positive rates on the y-axis against the false-positive rates (1-specificity) on the x-axis for each threshold [20].
4. The area under the ROC curve (AUC) was calculated to quantify the overall performance of the predictor. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system for the area under the curve was applied for AUC value ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination), where 0.90–1 means excellent, 0.80–0.90 means good, 0.70–0.80 means fair, 0.60–0.70 means poor and 0.50–0.60 means fail. P value < 0.05 and 95 % confidence interval were adopted as significant [21].

3. Results

The current study was conducted, enrolling 169 patients admitted to KFMC and diagnosed with acute drug poisoning, where 40.8 % of them suffered from multiple toxic exposures. The total number of drugs reported in the current study was 320 different preparations, with an average of 1.9 drugs per patient. Of them, 77 preparations were used for long-term therapy with no significant variations between Groups 2B and 2 C ($p < 0.679$). The mean age of studied patients was 17.5 ± 16.07 years, where the patients with single ingestion were significantly younger than patients diagnosed with co-ingestions ($p < 0.001$). However, the age did not influence the type of co-ingestion. Males and females were equally distributed among the studied groups. While preschool children were significantly more among the group of single exposure (55 %), they constituted only 17.4 % of the multiple ingestion group, where 33.3 % were of older age, students, or not working ($p < 0.001$). Though about half of the studied patients (49.7 %) and 67 % of single group ingestion were admitted after accidental exposure, significantly more suicidal attempts were responsible for multiple ingestions (36.3 %) ($p < 0.001$). Moreover, more substance abusers presented with multiple drug ingestion. Chronic hypertensive and cardiac patients and those diagnosed with neurological and psychological problems were significantly more vulnerable to multiple ingestions; significant neurological and psychological problems were among those exposed to acute and long-term drugs, as Table (1) shows.

Table (2) depicts those patients with single ingestion showed significantly higher pulse and respiratory rates than patients with multiple ingestion ($p < 0.05$). No significant variations in the gastrointestinal, respiratory, cardiac, sensory, or motor manifestations were noticed between the patients with single or multiple ingestions. However, 15.4 % of patients acutely exposed to a single agent besides the long-term drugs suffered from seizures, 7.7 % suffered from gait abnormalities, and 3.8 % suffered from hypotonia ($p < 0.05$). Patients with multiple ingestions suffered from significantly more wheezes and gastrointestinal (GI) tenderness compared to the single ingestion group ($p < 0.05$). Moreover, 70 % of patients in the multiple ingestion group suffered from significantly higher grades of PSS (minor, moderate, and severe grades) and lower GCS. Among the multiple ingestion group, the patients exposed to more than one agent acutely and more than one agent chronically showed significantly more crepitations (14.3 %), and combined crepitations and wheeze (7.1 %), higher PSS (21.4 % of severe grade) and lower GCS compared to the other two subgroups ($p < 0.05$) as shown in Table (3).

Regarding the laboratory investigations, the patients with multiple

Table 1
Demographic data and history of exposure of studied patients.

	Total (n=169)		Group (1) Single exposure group (n=100)		Group (2) Co-ingestion group								Test of sig.	p
					Total (n=69)		Group (2 A) (n=29)		Group (2B) (n=26)		Group (2 C) (n=14)			
Sex	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	χ^2	**p1=0.224**
Female	86	50.9	47	47.0	39	56.5	18	62.1	12	46.2	9	64.3	**1.481**	**p2=0.389**
Male	83	49.1	53	53.0	30	43.5	11	37.9	14	53.8	5	35.7	χ^2 **1.844**	
Age													**U**	**p1<0.001***
Mean ± SD.	17.5 ± 16.07		13.3 ± 14.55		23.7 ± 16.25		19.3 ± 13.31		25.1 ± 18.38		30.4 ± 15.96		**2027.5**	**p2=0.089**
Min. – Max.	0.6 – 84.0		0.6 – 54.0		1.0 – 84.0		1.0 – 50.0		2.0 – 84.0		13.0 – 64.0		**Kruskal Wallis** **4.844**	
Median (IQR)	16.0 (3.0 – 27.0)		4.0 (2.0 – 23.75)		20.0 (13.5 – 32.0)		18.0 (8.5 – 28.5)		22.0 (14.75 – 33.0)		27.5 (17.75 – 38.25)			
Occupation	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**MC**	**p1<0.001***
Employee	6	3.6	4	4.0	2	2.9	0	0.0	1	3.8	1	7.1		**p2=0.468**
Hand craft worker	9	5.3	2	2.0	7	10.1	2	6.9	2	7.7	3	21.4		
Student	37	21.9	14	14.0	23	33.3	11	37.9	7	26.9	5	35.7		
Housewife	8	4.7	6	6.0	2	2.9	0	0.0	1	3.8	1	7.1		
Vacant	42	24.9	19	19.0	23	33.3	9	31.0	10	38.5	4	28.6		
Preschool children	67	39.6	55	55.0	12	17.4	7	24.1	5	19.2	0	0.0		
Manner													χ^2	**p1<0.001***
Accidental	84	49.7	67	67.0	17	24.6	7	24.1	8	30.8	2	14.3	**30.628**	**p2=0.320**
Suicidal	43	25.4	18	18.0	25	36.2	10	34.5	9	34.6	6	42.9	**MC**	
Homicidal	1	0.6	0	0.0	1	1.4	0	0.0	1	3.8	0	0.0		
Inebriation	19	11.2	8	8.0	11	15.9	8	27.6	1	3.8	2	14.3		
Undetermined	22	13.0	7	7.0	15	21.7	4	13.8	7	26.9	4	28.6		
History of substance abuse	27	16.0	11	11.0	16	23.2	9	31.0	4	15.4	3	21.4	χ^2 **4.518**	**p1=0.034*** **p2=0.384**
													χ^2 **1.916**	
Diabetes	6	3.6	2	2.0	4	5.8	1	3.4	1	3.8	2	14.3	**FE**	**p1=0.227**
													MC	**p2=0.412**
Hypertension and/or cardiac disorders	8	4.7	1	1.0	7	10.1	0	0.0	4	15.4	3	21.4	**FE**	**p1=0.008***
													MC	**p2=0.061**
Bronchial asthma	6	3.6	4	4.0	2	2.9	2	6.9	0	0.0	0	0.0	**FE**	**p1=1.000**
													MC	**p2=0.357**
Neurological problems (epilepsy)	7	4.1	1	1.0	6	8.7	0	0.0	5	19.2	1	7.1	**FE**	**p1=0.019***
													MC	**p2=0.026***
Renal disorders	1	0.6	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0	**FE**	**p1=1.000**
Psychological illness	43	25.4	7	7.0	36	52.2	5	17.2	18	69.2	13	92.9	χ^2 **43.921**	**p1<0.001*** **p2<0.001***
													χ^2 **26.500**	
Delay time (hrs.)													**U**	**p1=0.559**
Mean ± SD.	6.7 ± 11.16		7.5 ± 13.91		5.5 ± 4.83		4.6 ± 3.48		7.0 ± 6.50		4.6 ± 2.74		**3268.5**	**p2=0.429**
Min. – Max.	0.0 – 96.0		0.25 – 96.0		0.0 – 24.0		1.0 – 15.0		0.0 – 24.0		1.0 – 9.0		**Kruskal Wallis**	
Median (IQR)	4.0 (2.0 – 6.0)		4.0 (2.0 – 6.0)		4.0 (2.0 – 7.5)		3.0 (2.0 – 6.0)		6.0 (1.75 – 8.25)		4.0 (2.0 – 6.0)		**1.693**	

Group (1) Single exposure group: neither acute co-ingestion nor chronic long-term exposure
Group (2) Co-ingestion group: patients exposed to any 2 drugs or more regardless to if its acute or chronic including:
2 A. Acute co- ingestion but no chronic exposure
2B. Single acute ingestion with chronic long-term exposure (only exposed to single drug acutely, besides the long-term drug)
2 C. Acute co-ingestion and chronic long-term exposure
χ^2: Chi square test FE: Fischer Exact test MC: Monte Carlo Exact test U: Mann Whitney U test *p≤ 0.05 (Statistically significant)
p1: between Group 1, 2 p2: between subgroups of Group 2

ingestions exhibited significantly higher PCO_2, random blood glucose level, serum glutamic pyruvic transaminase (SGPT), and serum creatinine levels but lower platelet count compared to the single ingestion group ($p < 0.05$), as Table (4) reveals. Furthermore, significantly more patients exposed to multiple drugs were given benzodiazepines, bicarbonate therapy, IV fluids, and vasopressor therapy than patients exposed to single agents ($p < 0.05$). Additively, patients with multiple ingestion showed higher liability for MV, ICU admission, and prolonged length of hospital stay. About 43 % of the patients exposed to multiple drugs acutely and chronically underwent MV ($p = 0.025$). The mean length of hospital stay among the multiple ingestion group was 43.3 hours, which significantly exceeded the mean of hospital stay in the case of single ingestion (mean = 23.2 hours), as Table (5) shows.

The current study reveals that antidepressants were the most frequently encountered long-term drug, where 22 patients reported chronic exposure, followed by psychotropics in 11 patients and antiepileptics in 10 patients. However, long-term exposure to insulin and oral antidiabetics in addition to CNS stimulants was reported only in one patient. There were no significant variations in the distribution of long-term therapy among the patients acutely exposed to single or multiple agents except the antidepressants, which were significantly higher among patients exposed to more than one agent in the acute manner ($p = 0.028$). Regarding acute drug exposure, acetaminophen was the most frequent agent in about 20.1 % of the studied patients, followed by antidepressants, vitamins, and supplements, which were equally distributed (12.4 %). About 11.8 % were exposed to antiepileptics, psychotropics (11.2 %), CNS stimulants (10.7 %), and NSAIDs (10.1 %). Nevertheless, the other drug classes were reported in a less frequent way

Table 2
Vital data and presenting complains upon admission among the studied patients.

	Total (n=169)		Group (1) Single exposure group (n=100)		Group (2) Co-ingestion group								t F	p
					Total (n=69)		Group (2 A) (n=29)		Group (2B) (n=26)		Group (2 C) (n=14)			
Mean Blood pressure													**t = 1.123 Mean difference **95 % CI**	**p1=0.263**
Mean ± SD.	84.1 ± 13.63		83.1 ± 14.39		85.5 ± 12.39		83.4 ± 11.90		86.9 ± 12.37		87.5 ± 13.78		**−2.4 (−6.6 – 1.8) F = 0.737**	**p2=0.483**
Min. – Max.	36.67 – 123.67		36.67 – 123.67		68.67– 123.0		69.0 – 117.0		70.3 – 110.3		68.67 – 123.0			
Median (IQR)	83.3 (73.67 – 91.58)		83.0 (72.4 – 90.0)		85.3 (74.08 – 92.58)		80.0 (72.83 – 91.0)		87.8 (73.92 – 96.25)		84.67 (78.0 – 92.67)			
Temperature													**t = 0.343 Mean difference **95 % CI**	**p1=0.732**
Mean ± SD.	36.8 ± 0.38		36.8 ± 0.41		36.8 ± 0.34		36.8 ± 0.35		36.8 ± 0.38		36.8 ± 0.25		**−0.02 (−0.13 – 0.09) F = 0.049**	**p2=0.952**
Min. – Max.	36.1 – 39.0		36.1 – 39.0		36.1 – 38.2		36.1 – 37.8		36.2 – 38.2		36.5 – 37.3			
Median (IQR)	36.8 (36.6 – 37.0)		36.8 (36.5 – 36.9)		36.8 (36.6 – 37.0)		36.8 (36.6 – 37.0)		36.8 (36.6 – 37.0)		36.8 (36.6 – 37.0)			
O2 saturation													**t = 0.715 Mean difference **95 % CI**	**p1=0.475**
Mean ± SD.	97.8 ± 2.20		97.9 ± 2.14		97.6 ± 2.30		97.2 ± 2.91		97.8 ± 1.79		98.1 ± 1.59		**0.247 (−0.43 – 0.92) F = 0.747**	**p2=0.478**
Min. – Max.	86.0 – 100.0		86.0 – 100.0		88.0 – 100.0		88.0 – 100.0		93.0 – 100.0		95.0 – 100.0			
Median (IQR)	98.0 (97.0 – 99.0)		98.0 (97.0 – 99.0)		98.0 (97.0 – 99.0)		98.0 (97.0 – 99.0)		98.0 (97.0 – 99.0)		98.0 (97.75 – 99.25)			
Respiratory rate (cycle/min)													**t = 5.582**	**p1<0.001***
Mean ± SD.	22.2 ± 4.44		23.6 ± 4.80		20.3 ± 2.92		20.9 ± 3.31		20.4 ± 2.47		18.7 ± 2.43		**Mean difference**	**p2=0.067**
Min. – Max.	12.0 – 40.0		14.0 – 40.0		12.0 – 30.0		12.0 – 30.0		16.0 – 26.0		14.0 – 24.0		**95 % CI**	
Median (IQR)	21.0 (20.0 – 25.0)		23.0 (20.0 – 26.0)		20.0 (18.0 – 21.0)		20.0 (19.5 – 22.5)		20.0 (18.75 – 21.25)		19.0 (17.5 – 20.0)		**3.33 (2.15 – 4.51)** **F = 2.809**	
Pulse (beat/minute)													**t = 2.190**	**p1=0.030***
Mean ± SD.	103.7 ± 21.14		106.7 ± 22.72		99.5 ± 17.94		102.8 ±20.05		95.5 ± 15.82		100.1 ± 16.74		**Mean difference**	**p2=0.319**
Min. – Max.	58.0 – 180.0		58.0 – 180.0		63.0 – 160.0		73.0 – 160.0		63.0 – 130.0		75.0 – 130.0		**95 % CI** **7.16 (0.707 – 13.6)** **F = 1.162**	
Median (IQR)	102.0 (89.0 – 115.0)		106.5 (89.25 – 117.5)		96.0 (86.0 – 111.0)		98.0 (86.0 – 117.0)		92.0 (85.75 – 104.0)		98.5 (88.5 – 113.25)			
GI symptoms	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**χ^2**	**p1=0.229**
Vomiting, colic, diarrhea	73	43.2	47	47.0	26	37.7	14	48.3	7	26.9	5	35.7	**1.445** **χ^2** **2.691**	**p2=0.260**
Respiratory affection													**MC**	**p1=0.627**
Chest tightness and breathlessness	12	7.1	7	7.0	5	7.2	2	6.9	2	7.7	1	7.1		**p2=1.000**
Cough	6	3.6	5	5.0	1	1.4	1	3.4	0	0.0	0	0.0		
Cardiovascular symptoms													**MC**	**p1=0.739** **p2=0.311**
Postural hypotension	4	2.4	3	3.0	1	1.4	0	0.0	0	0.0	1	7.1		
Palpitation	11	6.5	5	5.0	6	8.7	2	6.9	3	11.5	1	7.1		
Chest pain	5	3.0	3	3.0	2	2.9	2	6.9	0	0.0	0	0.0		
Sensory manifestations													**MC**	**p1=0.124** **p2=0.592**
Drowsiness and DCL	36	21.3	16	16.0	20	29.0	8	27.6	7	26.9	5	35.7		
Coma	13	7.7	6	6.0	7	10.1	2	6.9	4	15.4	1	7.1		
Hallucinations	3	1.8	1	1.0	2	2.9	0	0.0	1	3.8	1	7.1		
Agitations	11	6.5	7	7.0	4	5.8	1	3.4	3	11.5	0	0.0		
Motor manifestations													**MC**	**p1=0.944**
Hypotonia	2	1.2	1	1.0	1	1.4	0	0.0	1	3.8	0	0.0		**p2=0.047***
Tremors	5	3.0	3	3.0	2	2.9	1	3.4	0	0.0	1	7.1		
Gait abnormalities	6	3.6	4	4.0	2	2.9	0	0.0	2	7.7	0	0.0		
Seizures	7	4.1	3	3.0	4	5.8	0	0.0	4	15.4	0	0.0		

t: independent t test F: ANOVA *p≤ 0.05 (Statistically significant)
χ^2: Chi square test MC: Monte Carlo Exact test *p≤ 0.05 (Statistically significant)
p1: between Group 1, 2 p2: between subgroups of Group 2
** 95 % CI of mean difference

in < 10 % of the studied patients. Significant higher exposure to antidepressants (24.6 %), sedative-hypnotics (14.5 %), and antihistamines (14.5 %) was reported among patients exposed to multiple agents (p < 0.05). Moreover, antidepressants and psychotropics were more frequent among the patients exposed to more than one agent, acutely and chronically. Fig. (1) illustrates the proportion breakdown of the used drugs among the studied groups. Still, acetaminophen was the most frequent acute ingestion in the single ingestion group (19 %) and Group 2 A (41.4 %), while antiepileptics were the most frequent among Group 2B and 64.3 % of Group 2 C exposed to antidepressants.

The current study shows that among the 69 poisoned patients due to multiple ingestion, 28 patients developed at least one DDI (40.6 %). There were about 726 potential drug interactions, including 201 chronic/chronic drug interactions, 171 acute/acute drug interactions, and 354 acute/chronic drug interactions. More than half of these interactions were significant (n = 486). In contrast, serious interactions

Table 3
Clinical examination and scoring on admission among the studied patients.

	Total (n=169)		Group (1) Single exposure group (n=100)		Group (2) Co-ingestion group								Test of sig.	p
					Total (n=69)		Group (2 A) (n=29)		Group (2B) (n=26)		Group (2 C) (n=14)			
Abnormal chest finings	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**MC**	**p1=0.005***
Only wheeze	9	5.3	1	1.0	8	11.6	7	24.1	0	0.0	1	7.1		**p2<0.001***
Only crepitation	5	3.0	3	3.0	2	2.9	0	0.0	0	0.0	2	14.3		
wheeze and crepitations	1	0.6	0	0.0	1	1.4	0	0.0	0	0.0	1	7.1		
Shock													χ^2	**p1=0.582**
	17	10.1	9	9.0	8	11.6	8	27.6	0	0.0	0	0.0	**0.304**	**p2=0.002***
													MC	
ECG findings													**MC**	**p1=0.413**
Normal sinus rhythm	141	83.4	86	86.0	55	79.7	27	93.1	18	69.2	10	71.4		**P2=0.125**
Sinus arrhythmia	18	10.7	9	9.0	9	13.0	2	6.9	5	19.2	2	14.3		
Heart block	5	3.0	4	4.0	1	1.4	0	0.0	0	0.0	1	7.1		
ST segment elevation	1	0.6	0	0.0	1	1.4	0	0.0	1	3.8	0	0.0		
Prolonged Qt interval	2	1.2	1	1.0	1	1.4	0	0.0	0	0.0	1	7.1		
Wide QRS complex	1	0.6	0	0.0	1	1.4	0	0.0	1	3.8	0	0.0		
T wave abnormalities	1	0.6	0	0.0	1	1.4	0	0.0	1	3.8	0	0.0		
GIT													χ^2	**p1<0.001***
Tenderness or other findings	20	11.8	5	5.0	15	21.7	8	27.6	5	19.2	2	14.3	**10.964**	**p2=0.567**
													χ^2 **1.136**	
Pupil													**MC**	**p1=0.085**
Normal	161	95.3	98	98.0	63	91.3	27	93.1	24	92.3	12	85.7		**p2=0.696**
Miosis	2	1.2	1	1.0	1	1.4	1	3.4	0	0.0	0	0.0		
Dilated	6	3.5	1	1.0	5	7.2	1	3.4	2	7.7	2	14.3		
PSS													χ^2	**p1<0.001***
None	33	19.5	30	30.0	3	4.3	1	3.4	2	7.7	0	0.0	**43.406**	**p2<0.001***
Minor	92	54.4	61	61.0	31	44.9	10	34.5	19	73.1	2	14.3	**MC**	
Moderate	35	20.7	8	8.0	27	39.1	16	55.2	2	7.7	9	64.3		
Severe	9	5.3	1	1.0	8	11.6	2	6.9	3	11.5	3	21.4		
GCS													**U**	**p1<0.001***
Min. – Max.	3.0 – 15.0		3.0 – 15.0		3.0 – 15.0		3.0 – 15.0		3.0 – 15.0		9.0 – 15.0		**2235.5**	**p2=0.037***
Median (IQR)	15.0 (13.5 – 15.0)		15.0 (15.0 – 15.0)		15.0 (12.0 – 15.0)		13.0 (12.0 – 15.0)		15.0 (13.75 – 15.0)		13.0 (11.75 – 14.25)		**Kruskal Wallis 6.578**	

χ^2: Chi square test MC: Monte Carlo Exact test U: Mann Whitney U test *p≤ 0.05 (Statistically significant)
p1: between Group 1, 2 p2: between subgroups of Group 2

were 146, and minor interactions were the least frequent, amounting to approximately 13 % (n = 94) of total noticed interactions. As shown in Fig. (2), antidepressants and psychotropics resulted in the highest number of acute/acute drug interactions, inducing 28 and 22 interactions, respectively. These two classes were followed by sedative-hypnotics (n = 21), antiepileptics (n = 20), and CNS stimulants (n = 19). Fig. (3) illustrates that antidepressants showed the highest total number of chronic/chronic interactions (n = 39), followed by psychotropics (n = 35). However, the serious and significant interactions were higher following chronic exposure to these agents than the other long-term therapies. Additively, antidepressants and psychotropics also constituted the highest proportion of acute/chronic drug interactions as Fig. (4) depicts.

The findings of the current study unveil a significant moderate direct correlation between the number of drugs consumed, regardless of their chronicity, and the number of resulting drug interactions ($r = 0.542$, $p < 0.001$). There was a moderate correlation between the number of long-term drugs used and the chronic/chronic drug interactions ($r = 0.679$) and a weak correlation between the number of drugs consumed acutely and the acute/acute drug interactions ($r = 0.398$) ($p < 0.05$). Additionally, there was a significant direct relationship between the occurrence of significant chronic drug interactions from one side and the history of substance abuse ($r = 0.596$, $p = 0.041$) and psychological illness ($r = 0.662$, $p = 0.019$) from the other side. Moreover, significant acute drug interactions were correlated with being male ($r = 0.969$, $p < 0.001$) of older age ($r = 0.672$, $p = 0.024$). Similarly, significant acute/chronic drug interactions were moderately correlated with being a male ($r = 0.692$, $p = 0.013$). Minor drug interactions were correlated with being diabetic or suffering from bronchial asthma ($p < 0.001$), as shown in Table (6). Table (7) shows that the presence of epilepsy and psychological problems are the main significant predictors of multiple acute toxic exposures.

Wrapping up on the studied adverse outcomes, Table (8) shows that among the patients exposed acutely to more than one agent who were also on long-term treatment, the number of all drugs the patient exposed was a significant predictor of the need for MV ($p < 0.001$) and ICU admission ($p = 0.045$). Exposure to three drugs or more significantly predicted the need for MV with excellent AUC of 0.896, 100 % sensitivity, 75 % specificity, 25 % PPV, 100 % NPV and 77.0 % accuracy. Moreover, exposure to 3 drugs or more was a fair predictor of ICU admission (AUC = 0.625, sensitivity = 50 %, specificity = 72.7 %, PPV = 25 %, NPV = 88.9 % and accuracy = 69.2 %) as Fig. (5) and Table (9) demonstrate.

4. Discussion

The current study aimed to address the impact of multiple ingestions on the clinical presentation of exposed patients and to identify the common associated DDIs and their effect on the pattern and outcomes of acute toxic exposure. Multiple drug exposure was reported in 40.8 % of studied patients, which is lower than that reported earlier (84.5 %) [15]. Furthermore, the current study yielded that 40.6 % of the patients exposed to multiple agents experienced at least one DDI, which agrees with an earlier study reporting a similar prevalence (38 %-51 %) [14]. This is midway between the reported proportions internationally (65 %) [22], (51.6 %) [15], (46 %) [23], and (33 %) [24]. Variations are attributed to the discrepancy in the number of drugs involved and the sampling procedure in each study.

Table 4
Laboratory investigations on admission among the studied patients.

	Total (n=169)	Group (1) Single exposure group (n=100)	Group (2) Co-ingestion group				Test of sig.	p
			Total (n=69)	Group (2 A) (n=29)	Group (2B) (n=26)	Group (2 C) (n=14)		
pH							**t=1.195 Mean difference**	**p1=0.234**
Mean ± SD.	7.36 ± 0.08	7.36 ± 0.08	7.35 ± 0.08	7.34 ± 0.09	7.35 ± 0.05	7.35 ± 0.12	****95 % CI 0.014 (−0.009 – 0.039) F=0.092**	**p2=0.912**
Min. – Max.	6.84 – 7.503	6.84 – 7.48	7.0 – 7.503	7.0 – 7.48	7.275 – 7.496	7.1 – 7.503		
Median (IQR)	7.37 (7.35 – 7.4)	7.37 (7.35 – 7.4)	7.37 (7.33 – 7.39)	7.37 (7.33 – 7.38)	7.35 (7.33 – 7.39)	7.39 (7.34 – 7.40)		
HCO_3 (mEq/L)							**t=0.437 Mean difference**	**p1=0.662**
Mean ± SD.	21.8 ± 2.76	21.7 ± 2.54	21.9 ± 3.05	21.2 ± 3.46	22.6 ± 2.24	21.8 ± 3.33	****95 % CI −0.18 (−1.04 – 0.66) F=1.539**	**p2=0.222**
Min. – Max.	13.0 – 28.0	14.0 – 27.0	13.0 – 28.0	13.0 – 28.0	19.6 – 26.0	16.0 – 26.8		
Median (IQR)	21.8 (20.0 – 24.0)	21.35 (20.0 – 23.4)	22.0 (20.0 – 24.05)	22.0 (19.0 – 23.55)	23.0 (20.0 – 24.4)	22.7 (18.75 – 24.25)		
Lactate (millimole/L)							**U**	**p1=0.385**
Mean ± SD.	1.8 ± 1.38	1.8 ± 1.32	1.9 ± 1.47	2.1 ± 1.98	1.6 ± 0.72	2.1 ± 1.23	**3147.0**	**p2=0.494**
Min. – Max.	0.5 – 10.4	0.6 – 8.8	0.5 – 10.4	0.5 – 10.4	0.7 – 3.6	0.6 – 4.8	**Kruskal Wallis**	
Median (IQR)	1.4 (1.0 – 2.075)	1.4 (1.0 – 2.0)	1.4 (1.0 – 2.3)	1.4 (0.9 – 2.45)	1.4 (1.0 – 2.05)	1.5 (1.35 – 2.75)	**1.411**	
PCO_2							**t=3.497 Mean difference**	**p1<0.001***
Mean ± SD.	39.2 ± 6.59	37.7 ± 4.86	41.5 ± 8.03	40.8 ± 8.13	44.1 ± 8.50	38.1 ± 5.29	****95 % CI −3.7 (−5.7 - −1.8) F=2.956**	**p2=0.059**
Min. – Max.	19.0 – 63.0	19.0 – 47.0	21.7 – 63.0	23.0 – 63.0	21.7 – 62.0	28.0 – 45.0		
Median (IQR)	39.0 (36.0 – 41.0)	38.45 (35.0 – 41.0)	41.0 (37.0 – 44.0)	39.0 (35.5 – 45.35)	41.5 (40.0 – 51.0)	40.0 (33.25 – 42.0)		
Random blood glucose level (mmol/dl)							**U**	**p1=0.030***
							2773.0	**p2=0.047***
							Kruskal Wallis	
Mean ± SD.	5.7 ± 3.11	5.4 ± 3.37	6.1 ± 2.65	5.9 ± 2.86	5.7 ± 2.36	7.1 ± 2.65	**6.102**	
Min. – Max.	3.0 – 33.0	3.0 – 33.0	3.4 – 14.3	3.4 – 14.3	3.9 – 13.5	4.0 – 13.2		
Median (IQR)	5.0 (4.0 – 5.95)	4.85 (4.0 – 5.47)	5.0 (4.2 – 7.0)	4.6 (3.9 – 7.0)	5.0 (4.625 – 5.675)	6.8 (5.52 – 7.62)		
Na (mmol\L)							**t=1.008 Mean difference**	**p1=0.315**
Mean ± SD.	137.6 ± 3.16	137.4 ± 3.26	137.9 ± 3.02	137.9 ± 2.43	139.1 ± 3.02	135.6 ± 3.00	****95 % CI −0.49 (−1.47 – 0.478) F=6.935**	**p2=0.002***
Min. – Max.	121.0 – 147.0	121.0 – 143.0	128.0 – 147.0	134.0 – 145.0	134.0 – 147.0	128.0 – 140.0		
Median (IQR)	138.0 (136.0 – 139.0)	137.0 (135.25 – 139.75)	138.0 (136.0 – 139.0)	138.0 (136.5 – 139.0)	139.0 (136.75 – 141.25)	136.0 (134.5 – 138.0)		
K (mmol\L)							**t=0.817 Mean difference**	**p1=0.415**
Mean ± SD.	3.9 ± 0.53	3.9 ± 0.59	3.9 ± 0.42	3.9 ± 0.41	4.0 ± 0.48	3.9 ± 0.35	****95 % CI −0.06 (−0.23 – 0.09) F=0.566**	**p2=0.570**
Min. – Max.	2.42 – 6.9	2.42 – 6.9	3.0 – 5.42	3.2 – 5.4	3.0 – 5.42	3.1 – 4.4		
Median (IQR)	3.9 (3.66 – 4.2)	3.9 (3.6 – 4.2)	3.95 (3.7 – 4.2)	3.9 (3.76 – 4.15)	4.01 (3.69 – 4.25)	3.92 (3.66 – 4.1)		
Total bilirubin level (umol/L)							**U**	**p1=0.470**
							3191.5	**p2=0.460**
Mean ± SD.	9.8 ± 8.55	10.2 ± 8.01	9.3 ± 9.30	10.3 ± 12.82	9.6 ± 6.52	6.9 ± 2.93	**Kruskal Wallis**	
							1.552	
Min. – Max.	2.2 – 70.0	2.2 – 47.0	2.2 – 70.0	2.2 – 70.0	3.4 – 32.2	3.1 – 12.7		
Median (IQR)	7.3 (4.55 – 11.27)	7.4 (4.5 – 13.0)	7.1 (4.7 – 10.4)	7.3 (4.15 – 10.25)	7.35 (5.62 – 11.6)	6.4 (4.62 – 8.52)		
SGOT (AST) (U/L)							**U**	**p1=0.257**
Mean ± SD.	79.8 ± 397.83	62.8 ± 301.93	104.3 ± 507.21	173.2 ± 775.05	63.3 ± 129.80	37.7 ± 27.08	**3096.0**	**p2=0.941**
							Kruskal Wallis	
Min. – Max.	7.0 – 4202.0	8.0 – 3047.0	7.0 – 4202.0	7.0 – 4202.0	13.0 – 629.0	13.0 – 87.0	**0.121**	
Median (IQR)	26.0 (18.25 – 43.6)	28.0 (19.0 – 43.0)	22.0 (18.0 – 46.1)	23.0 (17.0 – 41.0)	23.0 (18.0 – 44.25)	19.0 (15.5 – 64.75)		
SGPT (ALT) (u/L)							**U**	**p1=0.005***
Mean ± SD.	75.9 ± 397.63	53.9 ± 294.79	107.9 ± 512.21	151.9 ± 720.73	109.0 ± 353.10	14.4 ± 4.96	**2565.0**	**p2=0.629**
							Kruskal Wallis	
Min. – Max.	5.0 – 3899.0	5.0 – 2968.0	6.0 – 3899.0	7.0 – 3899.0	6.0 – 1733.0	6.0 – 21.0	**0.927**	
Median (IQR)	17.0 (12.0 – 29.0)	19.0 (13.25 – 32.75)	15.0 (10.5 – 23.5)	16.0 (10.5 – 26.5)	15.0 (10.75 – 33.0)	13.5 (10.0 – 19.25)		
Serum Albumin level (gm\l)							**t=1.847 Mean difference**	**p1=0.063**
							****95 % CI 3.05 (−0.16 – 6.27) F=1.303**	**p2=0.278**
Mean ± SD.	44.2 ± 10.49	45.5 ± 12.50	42.4 ± 6.25	43.7 ± 4.36	40.9 ± 8.49	42.4 ± 4.15		
Min. – Max.	8.0 – 159.0	32.8 – 159.0	8.0 – 53.3	32.4 – 53.3	8.0 – 51.9	35.6 – 49.0		
Median (IQR)	43.4 (41.25 – 46.35)	43.5 (41.42 – 46.27)	43.4 (40.25 – 46.5)	43.9 (41.75 – 46.9)	42.95 (39.37 – 46.45)	42.7 (38.6 – 45.37)		
Serum urea (mmol/L)							**U**	**p1=0.054**
							2789.0	**p2=0.153**
							Kruskal Wallis	
Mean ± SD.	4.3 ± 2.29	4.5 ± 2.25	4.0 ± 2.32	4.2 ± 2.40	4.3 ± 2.68	3.1 ± 0.99	**3.751**	
Min. – Max.	1.4 – 16.2	1.5 – 14.2	1.4 – 16.2	1.9 – 14.0	1.4 – 16.2	1.6 – 5.0		
Median (IQR)	3.9 (3.0 – 4.9)	4.0 (3.1 – 5.12)	3.6 (2.9 – 4.35)	3.9 (2.65 – 4.7)	3.85 (2.97 – 4.52)	3.25 (2.25 – 4.0)		

(*continued on next page*)

Table 4 (*continued*)

	Total (n=169)	Group (1) Single exposure group (n=100)	Group (2) Co-ingestion group				Test of sig.	p
			Total (n=69)	Group (2 A) (n=29)	Group (2B) (n=26)	Group (2 C) (n=14)		
Serum creatinine (umol/L)							**U 2681.5 Kruskal Wallis 0.365**	**p1=0.014* p2=0.833**
Mean ± SD.	54.4 ± 28.76	51.4 ± 31.88	58.7 ± 23.04	59.2 ± 25.95	59.9 ± 24.57	55.7 ± 12.40		
Min. – Max.	2.0 – 222.0	2.0 – 222.0	18.0 – 112.0	20.0 – 112.0	18.0 – 112.0	35.0 – 87.0		
Median (IQR)	52.0 (29.0 – 70.0)	44.0 (26.0 – 70.0)	57.0 (42.5 – 74.5)	57.0 (36.0 – 80.5)	59.0 (41.75 – 76.5)	52.0 (47.75 – 63.75)		
Hemoglobin (gram/dL)							**t= 0.703 Mean difference **95 % CI −0.2 (−0.77 – 0.36) F=0.814**	**p1=0.483 p2=0.447**
Mean ± SD.	13.0 ± 1.85	12.9 ± 1.73	13.2 ± 2.03	12.8 ± 2.20	13.4 ± 2.14	13.4 ± 1.33		
Min. – Max.	4.29 – 18.6	9.3 – 18.6	4.29 – 17.7	4.29 – 16.0	8.2 – 17.7	10.6 – 15.6		
Median (IQR)	13.1 (12.1 – 14.0)	13.0 (12.0 – 13.7)	13.2 (12.35 – 14.4)	12.6 (12.3 – 14.0)	13.35 (12.4 – 14.73)	13.25 (12.65 – 14.55)		
RBCs (million/microliter)							**t= 0.714 Mean difference **95 % CI 0.05 (−0.09 – 0.20) F=0.082**	**p1=0.476 p2=0.921**
Mean ± SD.	4.7 ± 0.49	4.7 ± 0.49	4.7 ± 0.48	4.7 ± 0.35	4.7 ± 0063	4.7 ± 0.46		
Min. – Max.	2.9 – 6.48	3.8 – 6.48	2.9 – 6.23	4.08 – 5.31	2.9 – 6.23	4.09 – 5.64		
Median (IQR)	4.7 (4.4 – 5.0)	4.715 (4.46 – 5.0)	4.64 (435 – 5.01)	4.65 (4.35 – 4.97)	4.64 (4.35 – 4.97)	4.725 (4.35 – 5.05)		
WBCs /microliter)							**U 2969.5 Kruskal Wallis 1.781**	**p1=0.124 p2=0.411**
Mean ± SD.	10.0 ± 3.89	10.5 ± 4.19	9.4 ± 3.32	9.2 ± 2.94	8.9 ± 3.57	10.4 ± 3.60		
Min. – Max.	3.7 – 25.46	3.7 – 25.46	3.82 – 17.47	3.82 – 14.5	4.13 – 17.47	4.48 – 16.8		
Median (IQR)	9.55 (7.23 – 11.99)	9.535 (7.48 – 13.14)	9.7 (6.65 – 11.75)	9.7 (6.65 – 11.65)	7.78 (5.76 – 11.74)	10.435 (7.46 – 12.56)		
Platelet count *10^3/microliter							**U 2821.5 Kruskal Wallis 7.991**	**p1=0.044* p2=0.018***
Mean ± SD.	335.3 ± 103.38	348.2 ± 98.64	316.6± 107.90	351.8 ±125.17	286.7 ± 87.47	299.4 ± 87.03		
Min. – Max.	4.21 – 767.0	28.0 – 629.0	4.21 – 767.0	4.21 – 767.0	149.0 – 551.0	158.0 – 466.0		
Median (IQR)	324.0 (269.5 – 390.0)	332.5 (290.25 – 409.0)	313.0 (245.0 – 383.5)	368.0 (290.5 – 403.0)	274.0 (221.25 – 338.25)	282.0 (232.5 – 374.5)		

t: independent t test F: ANOVA U: Mann Whitney U test *p≤ 0.05 (Statistically significant)
p1: between Group 1, 2 p2: between subgroups of Group 2

The presented results emphasized that patients with multiple drug exposure showed more severe clinical presentation and worsened laboratory investigations, indicated by the higher PSS, the lower GCS, and the significant airway embarrassment, particularly among patients of combined acute and chronic multiple exposure, which was agreed elsewhere [14]. Galicia et al. mentioned that disturbed consciousness, indicated by the low GCS, was the most common feature following exposure to a combination of ethanol and gamma-hydroxybutyrate/gamma-butyrolactone [25]. Adversely, although about 35 % of the studied cases were exposed to multiple agents, the co-ingestion was not significantly associated with worsened clinical outcomes or higher PSS in an earlier study. This discrepancy is attributed to the variations in the sampling and the nature of the co-ingested substances [26].

Consistent with the current study, GI affection, metabolic disorders and bradycardia were the most frequent presentations following hospital admission due to DDIs [18]. Likewise, Roversi et al. mentioned that most patients admitted following self-poisoning using single or multiple agents exhibited GI symptoms [26]. Moreover, the current study showed significant respiratory affection among patients with multiple acute and chronic ingestions, in which antidepressants and psychotropics predominated among that group. Furthermore, Sharif et al. reported that respiratory distress was a genuine presenting symptom among patients poisoned with CNS affecting drugs [27]. Equally, it was reported that a combination of some antidepressants with beta blockers induces significant bradycardia [28].

Several mechanisms explain the co-ingestion associated with cardiorespiratory suppression. Aside from DDIs, most of the studied drugs have CNS depressing action. When these substances are ingested together, they synergistically augment CNS depression, leading to reduced respiratory drive and cardiac output, leading to hypoventilation, hypoxia, and ultimately respiratory arrest [29]. Peripheral non-central involvement, including pulmonary edema, interstitial pneumonitis, pleural effusion, drug-induced bronchospasm, and bronchitis, are other proposed mechanisms of drug-induced respiratory suppression [30]. Another mechanism explaining the co-ingestion-associated cardia suppression, including shock and bradycardia, is the interference with autonomic regulation of the heart, mainly if the drug combination contains alcohol [31]. A systematic review reported that bradycardia and hypotension in two case reports following exposure to drug combinations, including cardiotoxic drugs [32].

In the current study, acetaminophen was the most frequently acutely consumed drug, followed by supplementary vitamins and antidepressants, which were equally reported. The latter constituted the most frequently reported long-term drug, followed by psychotropics and antiepileptics. The widespread use of antidepressants is attributed to their additional indications for the management of other psychiatric and medical illnesses besides the depression [33]. In partial agreement with the current study, acetaminophen was the most frequently involved agent among patients committing suicidal self-poisoning [34], while vitamins and supplements were among the most frequently reported drugs in an earlier study [35]. Furthermore, psychotropic drugs were reported as one of the most common intoxicants in about 55 % of studied patients in another study [14]. It seems to be highly plausible assuming that though acetaminophen was the most frequent drug consumed in an acute manner, its liability for causing potential DDIs was not the highest.

Animal models designed to assess the pattern of toxicity in multiple

Table 5
Therapeutic regimen & some adverse outcomes among the studied patients.

	Total (n=169)		Group (1) Single exposure group (n=100)		Group (2) Co-ingestion group								Test of sig.	p
					Total (n=69)		Group (2 A) (n=29)		Group (2B) (n=26)		Group (2 C) (n=14)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
N-acetyl cysteine	23	13.6	15	15.0	8	11.6	5	17.2	2	7.7	1	7.1	χ^2 0.403 MC	p1=0.526 p2=0.551
Benzodiazepine	36	21.3	15	15.0	21	30.4	6	20.7	8	30.8	7	50.0	χ^2 5.802	p1=0.016* p2=0.147
Naloxone	8	4.7	5	5.0	3	4.3	0	0.0	3	11.5	0	0.0	χ^2 3.833 FE MC	p1=1.000 p2=0.053
Flumazenil	1	0.6	0	0.0	1	1.4	0	0.0	1	3.8	0	0.0	FE MC	p1=0.408 p2=0.572
Sodium bicarbonate	15	8.9	5	5.0	10	14.5	4	13.8	4	15.4	2	14.3	χ^2 4.549 MC	p1=0.033* p2=1.000
Fomepizole	5	3.0	1	1.0	4	5.8	3	10.3	0	0.0	1	7.1	FE MC	p1=0.160 p2=0.252
IV Fluids	104	61.5	54	54.0	50	72.5	23	79.3	15	57.7	12	85.7	χ^2 5.881	p1=0.015* p2=0.093
Vasopressors	12	7.1	1	1.0	11	15.9	8	27.6	1	3.8	2	14.3	χ^2 4.756 FE MC	p1<0.001* p2=0.054
Mechanical ventilation	14	8.3	1	1.0	13	18.8	5	17.2	2	7.7	6	42.9	χ^2 17.104 MC	p1<0.001* p2=0.025*
ICU admission	23	13.6	4	4.0	19	27.5	10	34.5	4	15.4	5	35.7	χ^2 19.237	p1<0.001* p2=0.213
													χ^2 3.095	
Length of hospital stay (hrs.)													U	p1<0.001*
Mean ± SD.	31.4 ± 30.91		23.2 ± 19.12		43.3 ± 39.83		36.5 ± 20.12		38.7 ± 31.01		66.1 ± 69.76		1640.0	p2=0.132
Min. – Max.	3.0 – 288.0		3.0 – 96.0		10.0 – 288.0		12.0 – 96.0		10.0 – 168.0		20.0 – 288.0		Kruskal Wallis	
Median (IQR)	24.0 (12.0 – 42.5)		17.5 (10.0 – 27.0)		35.0 (24.0 – 48.0)		35.0 (22.5 – 48.0)		28.0 (24.0 – 48.0)		48.0 (27.75 – 76.5)		4.048	

χ^2: Chi square test MC: Monte Carlo Exact test FE: Fischer Exact test U: Mann Whitney U test *p≤ 0.05 (Statistically significant)
p1: between Group 1, 2 p2: between subgroups of Group 2

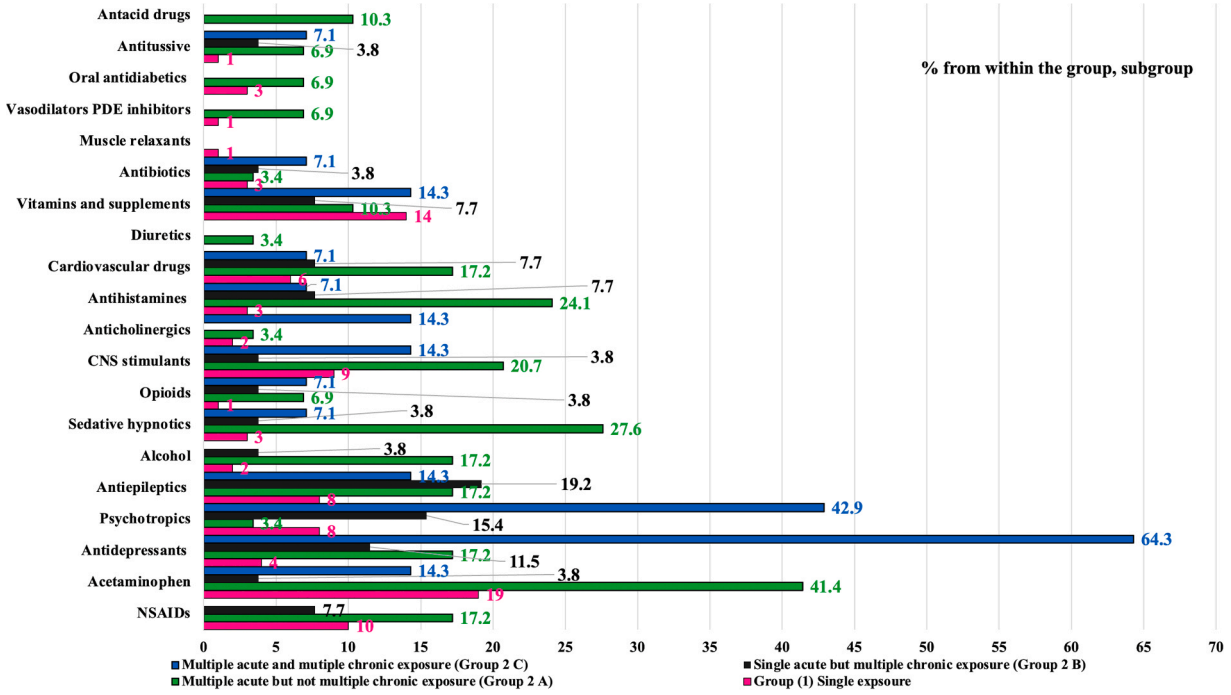

Fig. 1. Proportion of patients (% from within the group, or subgroup) exposed to drugs consumed in acute manner in the current study.

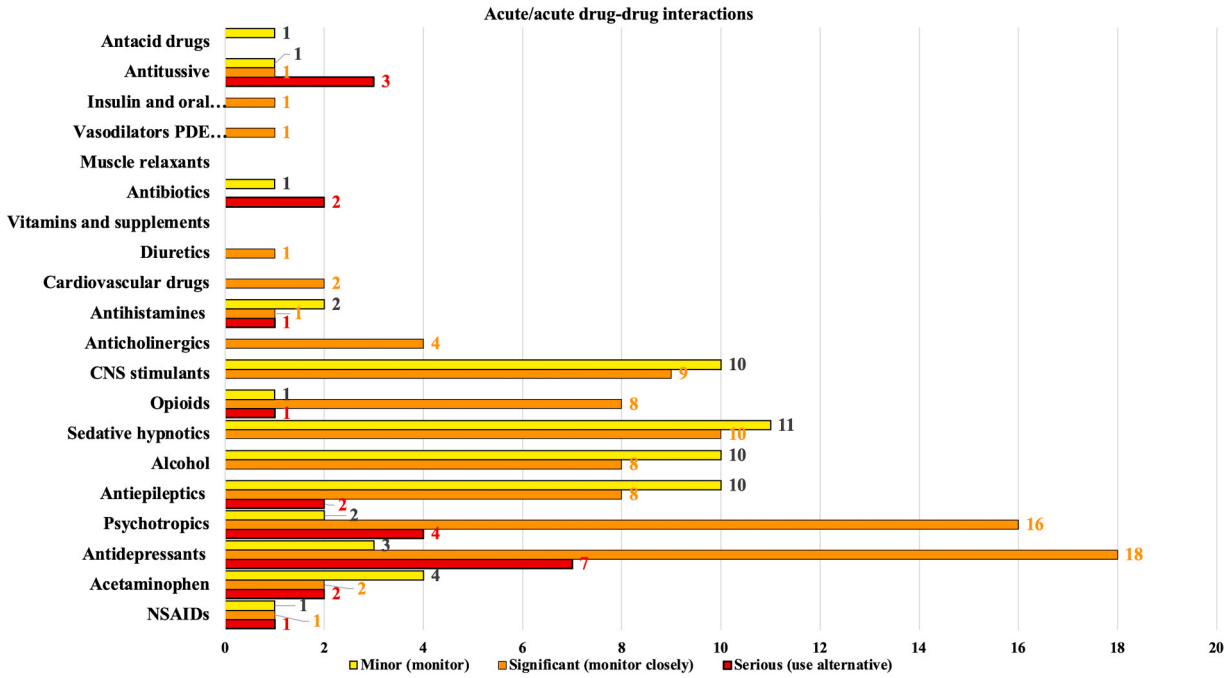

Fig. 2. Number of potential acute/acute drug-drug interactions.

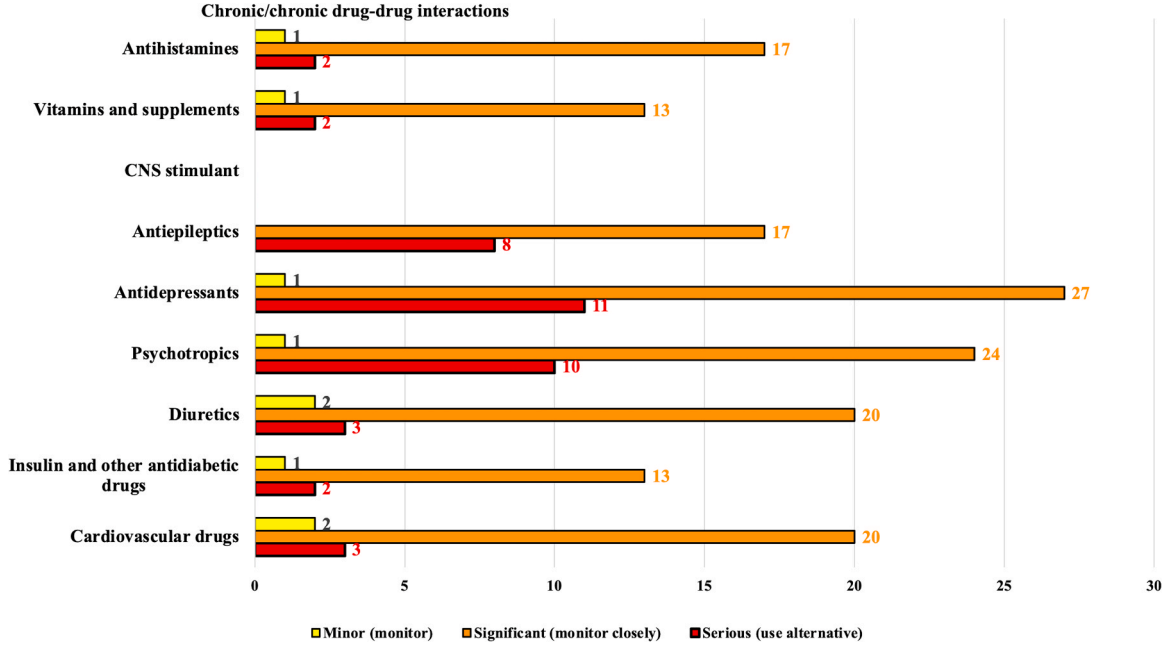

Fig. 3. Number of potential chronic/chronic drug-drug interactions.

drug ingestions revealed an alteration in the toxicity profile of drug combinations [36]. This alteration results from pharmacokinetic or pharmacodynamic interactions [14]. Pharmacodynamics describes an alteration in the drug effect at the site of the action, while pharmacokinetic interactions describe the alteration of drug effect during the movement of the drug inside the body[18]. It may thus be inferred that although exposure to vitamins and supplements is considered non-toxic, this is applicable only to a single exposure. Preparations like ascorbic acid change the stomach pH and prevent other drugs' absorption, which aggravates their toxicity, particularly drugs with narrow therapeutic indices [18].

The current study conveyed that some laboratory changes were significant in patients exposed to multiple agents, including hyperglycemia, elevated PCO_2, serum alanine transaminase, and serum creatinine, and lowered platelet count. However, the reported mean and median values of the PCO_2, serum creatinine, and platelet count were within the normal reference ranges. Regarding hyperglycemia, although we could not find studies explaining the association between co-ingestion and hyperglycemia, the latter was considered a bad prognostic factor indicating morbidity and mortality in patients with acute drug poisoning [37]. The linkage between hyperglycemia and bad prognosis in acute poisoning was reported with organophosphorus [38], theophylline [39], methanol [40], carbon monoxide [41], and aluminum phosphide [42]. Hyperglycemia was considered part of the

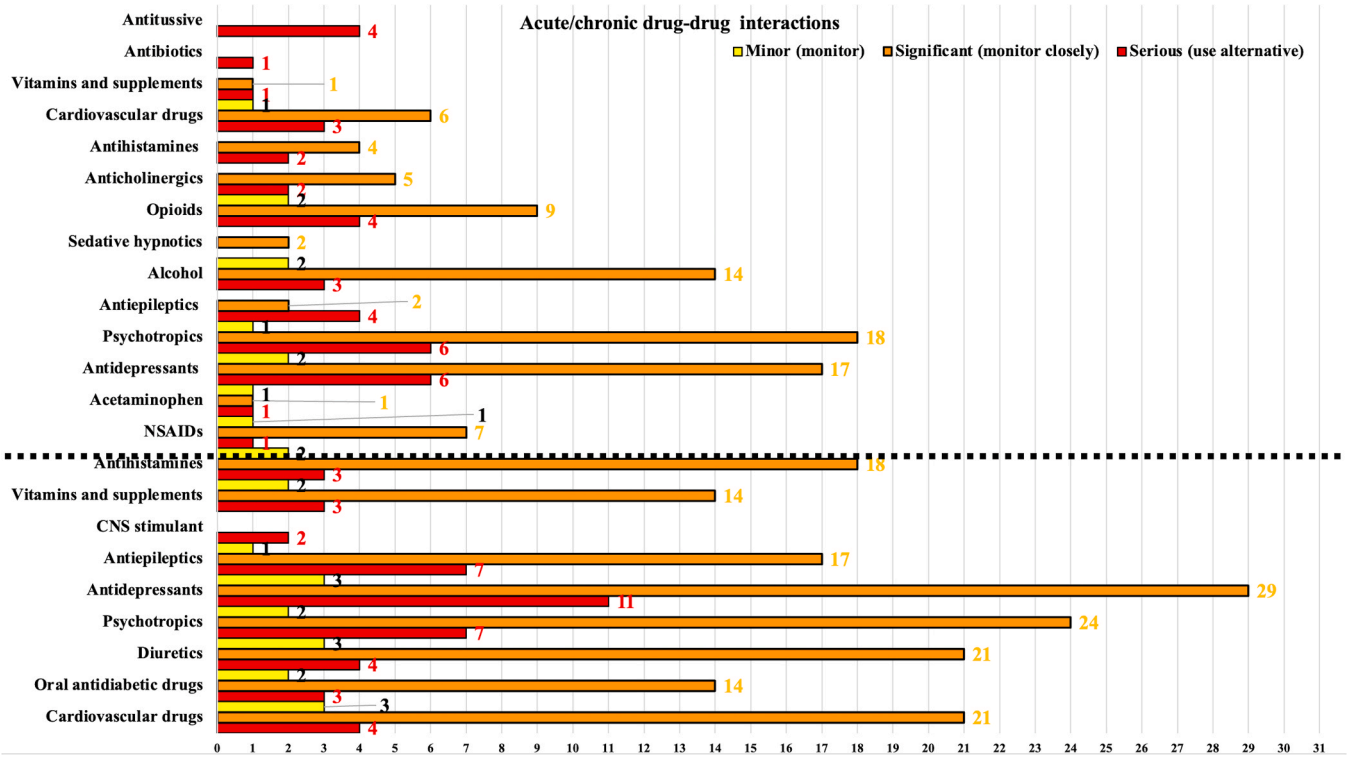

Fig. 4. Number of potential acute/chronic drug-drug interactions.

stress response, referring to counterregulatory hormones, the production of inflammatory mediators, excessive glucose administration by physicians, and underlying diabetic conditions [37]. Given the significant severity of patients with co-ingestion and the more frequently reported hyperglycemia among the patients with acute and chronic long-term exposure, this hyperglycemia could be considered a reflection of poisoning severity. Likewise, utilizing hyperglycemia as a severity indicator was agreed elsewhere [43].

Another meaningful laboratory change consistent with the multiple exposures was the elevation in liver transaminases, especially the alanine transaminase, which yielded statistical significance. Liver impairment was described after exposure to multiple agents. A combination of acetaminophen and salicylates was associated with a significant elevation of liver transaminases, and the resultant hepatic failure attributed to synergistic and bi-directional depletion of hepatic glutathione [44]. Aside from acetaminophen, which is known for its hepatotoxicity, liver affection was reported after exposure to fluspirilen and citalopram, diclofenac and ethinyl estradiol [45], Atorvastatin and ketoconazole or erythromycin and other several drug combinations significant drug combinations [46].

Although nonspecific, alanine transaminase is used historically to monitor drug-induced liver injury (DILI), where 3-fold elevation is considered trophosome. Inappropriate dosing, including overdose, is among the common causes of DILI through several mechanisms [47]. The underlying pathophysiological hepatic changes in exposure to multiple drugs ingested reflect the synergistic toxicity [45]. The liver metabolic capacity is overwhelmed, accumulating toxic metabolites, which can damage the hepatocytes, which are shown by elevated liver enzyme levels. Besides, an overdose of some drugs can trigger an inflammatory response and release cytokines, contributing to hepatocellular damage [47,48]. Production of reactive oxygen species during drug metabolism induces lipid peroxidation, mitochondrial damage, and apoptotic hepatocellular cell death, resulting in elevated liver enzymes [46]. Benesic et al. mentioned that a combination of amoxicillin/clavulanate, and diclofenac and steroid hormones increased hepatotoxicity and associated idiosyncratic DILI. As both amoxicillin and clavulanate substances undergo extensive hepatic metabolism, DDIs via synergetic toxicity were a proposed cause of DILD. A possible mechanism of diclofenac interaction with a wide set of drugs is the inhibition of CYP450 enzymes and UGT2B7, which play a significant role in diclofenac metabolism, leading to delayed hepatic clearance and prolonged hepatic exposure [45].

Noteworthy, antidepressants and psychotropics were the most frequent substances involved in the potential DDIs of all types. Vancayseele et al. noticed that repeated suicidal attempters tend to use antidepressants and psychotropics more than first suicidal attempters. Long-term use of these drugs in psychiatric disorders explains their frequent use [49]. In suicidal drug poisoning, patients usually ingest multiple drugs. Using several types of drugs in suicidal attempts was reported in different populations, including fatal and non-fatal self--poisoning [50–52]. The significant prevalence of death following acute exposure to multiple drugs supports the possibility that DDI contributed to the toxicity [53].

DDIs associated with antidepressants are surrounded by uncertainty and controversy [33]. Old-generation antidepressants, including Tricyclic antidepressants (TCA), were described as the most toxic and lethal antidepressants. Nonetheless, literature described the combination of different antidepressants, TCAs with monoaminoxidase inhibitors (MAOIs), as an appropriate treatment in some depressive disorders [33]. Others criticized the wide use of (MAOIs) and advised their restriction due to their potential food and DDIs [54]. Though the newer antidepressant generations were privileged for being more effective, of less adverse drug reactions, and of less toxicity, their significant involvement in potential DDIs was warranted. Combinations containing antidepressants were described as serious and of higher toxicity [55].

The current study found a significant association between multiple toxic exposures from one side and substance abuse, suicidal exposure, and psychological illnesses from the other side. Additively, we noticed a positive correlation between drug abuse, psychological illness, and significant chronic DDI. Besides, epilepsy was a significant predictor of acute multiple ingestion. In agreement with the current study, Mainoli et al. concluded that chronic alcoholism and tobacco smoking were

Table 6
Correlations between different types of drug interactions (serious, significant, minor) and some epidemiological and exposure factors.

	Parameters	Serious		Significant		Minor	
		r_s	p	r_s	p	r_s	p
Chronic/chronic drug interactions	**Sex (being male)**	0.606	0.084	0.576	0.052	**Minor interactions constant (1)**	
	Age	0.287	0.454	0.050	0.877		
	Occupation	−0.623	0.073	0.350	0.265		
	Manner	0.606	0.084	−0.347	0.270		
	History of substance abuse			0.596	0.041*		
	Diabetes	0.227	0.556	0.331	0.293		
	Hypertension and/or cardiac disorders	−0.253	0.512	0.262	0.411		
	Bronchial asthma						
	Neurological problems (epilepsy)			−0.223	0.486		
	Renal disorders						
	Psychological illness	0.057	0.884	0.662	0.019*		
	Delay time (hrs.)	−0.622	0.074	−0.450	0.142		
Acute/acute drug interactions	**Sex (being male)**	0.761	0.135	0.969	<0.001*	−0.200	0.704
	Age	0.527	0.361	0.672	0.024*	−0.266	0.611
	Occupation	0.162	0.794	−0.131	0.701	0.139	0.793
	Manner	0.460	0.436	0.350	0.291	0.417	0.410
	History of substance abuse	0.186	0.764	0.173	0.612	0.632	0.178
	Diabetes			0.347	0.295		
	Hypertension and/or cardiac disorders			0.347	0.295		
	Bronchial asthma			−0.232	0.493	1.000	<0.001*
	Neurological problems (epilepsy)	0.186	0.764				
	Renal disorders						
	Psychological illness	−0.186	0.764	0.000	1.000	−0.632	0.178
	Delay time (hrs.)	−0.189	0.760	0.139	0.684	0.674	0.142
Acute to chronic drug interactions	**Sex (being male)**	0.471	0.122	0.692	0.013*	0.316	0.541
	Age	0.239	0.454	−0.007	0.983	0.655	0.158
	Occupation	0.052	0.871	0.248	0.436	0.000	1.000
	Manner	0.325	0.302	0.006	0.986	0.447	0.374
	History of substance abuse	0.000	1.000	−0.176	0.584		
	Diabetes	0.426	0.167	0.392	0.207	1.000	<0.001*
	Hypertension and/or cardiac disorders	−0.272	0.392	0.207	0.519	0.632	0.178
	Bronchial asthma						
	Neurological problems (epilepsy)	0.000	1.000	−0.176	0.584		
	Renal disorders						
	Psychological illness	0.000	1.000	−0.523	0.081	−0.632	0.178
	Delay time (hrs.)	0.053	0.871	−0.316	0.318	−0.531	0.278

r_s: Spearman correlation *p≤ 0.05 (Statistically significant)

Table 7
Univariate and multivariate Regression analysis to identify predictors of acute multiple ingestions.

	Parameters	Univariate		Multivariate	
		B (95 % CI)	p	B (95 % CI)	p
Acute co-ingestion	**Sex**	−0.159 (−0.394 – 0.076)	0.182		
	Age	−0.002 (−0.009 – 0.005)	0.595		
	Occupation	−0.032 (−0.115 – 0.051)	0.440		
	Manner	0.020 (−0.057 – 0.098)	0.605		
	History of substance abuse	0.165 (−0.112 – 0.442)	0.239		
	Diabetes	0.135 (−0.370 – 0.639)	0.596		
	Hypertension and/or cardiac disorders	−0.217 (−0.604 – 0.171)	0.269		
	Bronchial asthma	0.388 (−0.310 – 1.086)	0.271		
	Neurological problems (epilepsy)	0.500 (0.901–0.099)	0.015*	0.561 (0.947–0.174)	0.005*
	Renal disorders				
	Psychological illness	0.258 (0.486–0.030)	0.027*	0.294 (0.512–0.076)	0.009*

* p≤ 0.05 (Statistically significant)

associated with DDIs. Moreover, they reported an association between suicidal exposure and ploy-medication use [14]. An earlier study reported that about 11 % of DDIs occur among patients suffering from neurological disorders [56]. Clinicians should actively inquire about the history of recreational drug abuse and consider the alteration of toxicity, and possible serious DDIs [57].

The findings obtained in the present work depicted that DDIs correlated with male gender and advancement of age. Advancement of age increases the risk of drug toxicity due to DDIs, notably in cases of chronic co-morbid conditions and organ dysfunctions [35]. Additively, hospital admission among the elderly is higher than in other age groups, yielding better reporting of DDIs [58]. Approximately 10 % of adverse drug interactions related to hospital admissions occurred among older patients [59], and about 5 % of the hospital admittances of the elderly were thought to be caused by DDIs [60]. In agreement with the current study, where 55 % of single-drug exposure was reported in children, DDIs were described as less frequent in pediatrics, who are prescribed fewer medications and closely monitored [59]. A longitudinal study monitored pediatric exposure to overdose of psychoactive substances during 1999–2018 showed that all drugs were consumed in single form. The only exceptions in which the reported drug was part of combinations were the benzodiazepines and heroin, indicating that single exposure in pediatrics was the rule [61]. Inconsistent with these findings, Johnell and Klarin reported more DDI among younger patients

Table 8
Regression analysis to identify predictors of mechanical ventilation, length of hospital stay and intensive care unit admission.

	Parameters	Univariate	
		B (95 % CI)	p
G2A	1. **Mechanical ventilation**		
	• Total number of drug interactions	0.017 (−0.051 – 0.084)	0.617
	• Number of all drugs the patient exposed to (acute and chronic)	0.012 (−0.092 – 0.116)	0.821
	2. **Length of hospital stay**		
	• Total number of drug interactions	−0.007 (−0.096 – 0.082)	0.877
	• Number of all drugs the patient exposed to (acute and chronic)	0.035 (−0.102 – 0.172)	0.607
	3. **Intensive care unit admission**		
	• Total number of drug interactions	−0.030 (−0.114 – 0.054)	0.464
	• Number of all drugs the patient exposed to (acute and chronic)	0.023 (−0.108 – 0.154)	0.719
G2B	1. **Mechanical ventilation**		
	• Total number of drug interactions	−0.011 (−0.045 – 0.023)	0.501
	• Number of all drugs the patient exposed to (acute and chronic)	0.072 (0.037 – 0.107)	<0.001*
	2. **Length of hospital stay**		
	• Total number of drug interactions	−0.037 (−0.098 – 0.025)	0.229
	• Number of all drugs the patient exposed to (acute and chronic)	0.039 (−0.045 – 0.124)	0.344
	3. **Intensive care unit admission**		
	• Total number of drug interactions	−0.022 (−0.067 – 0.023)	0.317
	• Number of all drugs the patient exposed to (acute and chronic)	0.059 (0.002 – 0.117)	0.045*
G2C	1. **Mechanical ventilation**		
	• Total number of drug interactions	0.028 (−0.056 – 0.112)	0.484
	• Number of all drugs the patient exposed to (acute and chronic)	0.099 (−0.070 – 0.268)	0.225
	2. **Length of hospital stay**		
	• Total number of drug interactions	0.034 (−0.047 – 0.114)	0.380
	Number of all drugs the patient exposed to (acute and chronic)	0.113 (−0.046 – 0.272)	0.149
	3. **Intensive care unit admission**		
	• Total number of drug interactions	−0.012 (−0.094 – 0.071)	0.758
	• Number of all drugs the patient exposed to (acute and chronic)	0.079 (−0.089 – 0.246)	0.326

* $p \leq 0.05$ (Statistically significant)

[62].

Nonetheless, the relationship between multiple exposures to DDIs and age and sex seems to be inconclusive in the literature. Agreeing with the current study, the males showed a higher probability of type D potential DDIs than females [62]. Contradicting that, it was reported that female gender was more associated with potential acute/long-term DDIs [14]. Nonetheless, Schneider et al. denied any association between age, sex, and potential DDIs [35]. Part of this discrepancy is attributed to the variation in grouping between the current study and others. Schneider et al. 's study was exclusively conducted among elderly, poly-medicated patients on antithrombotic drugs, and Mainoli et al. considered the recreational drug users as separate entities [14,35].

In agreement with the current study, Salwe et al. described a positive correlation between the number of drugs used and potential DDIs [58]. Mainoli et al. stated that the number of the used drugs was an independent predictor of potential DDIs [14]. Schneider et al. went further and mentioned that it is the number of active constituents, not the number of the drugs, per se, which have positive correlations with the number of potential DDIs [35]. The positive correlation between the number of drugs and the number of DDIs was in concordance with other publications [59,62]. Nevertheless, up to the present time, very few studies have investigated the nature of the association between the number of drugs consumed and potential DDIs[63,64]. Exponential and linear relationships between the number of drugs and their resultant potential DDIs were reported [62].

The current study conveyed that utilization of resources was significantly higher in patients with multiple ingestions (benzodiazepines, HCO_3, fluids and vasopressors). Moreover, we noticed a significant increase in the length of hospital stay among patients with multiple ingestions. In agreement, Mainoli et al. described an association between DDIs and infused catecholamine dosage [14]. Furthermore, the present study revealed that the number of drugs the patients were exposed to and the number of DDIs were significant predictors of the patient's need for MV. Patients who consumed three or more drugs were at higher risk of MV and ICU admission. Association between DDIs and the need for MV was reported elsewhere, where aspiration pneumonia played a mediating role in this association [14]. ICU admission and hospital admissions constitute a burden on the healthcare system, particularly during the pandemic and in resources restricted countries [65]. A great proportion of hospital admissions were attributed to adverse drug reactions, which occur primarily in patients taking multiple medications [15]. Salwe et al. reported a positive correlation between the duration of hospital stay and the number of drugs used. Increasing one day hospital stay led to increasing the number of drugs by 0.296 in admitted elderly [58]. An earlier systematic review reported a median prevalence rate of 1.1 % of hospital admissions due to DDIs [59]

Even though there were no reported deaths in the studied cohort, the literature conveyed that fatality rates following exposure to multiple drugs were significantly higher than single exposure. The American Association of Poison Control Centers reported that more than half of the deaths were associated with multiple drug combinations. Deaths due to single exposure declined significantly from more than 60 % of poisoned patients in 1980 to less than 40 % after 2010 [12]. Jones et al. reported that exposure to a mean of four drugs was responsible for 35 % of deaths among impaired drivers. The death happened at significantly lower concentrations in case of multiple drug exposure [66]. Interestingly, Preskorn attributed the cause of death among four patients to pharmacokinetic DDIs following multiple drug exposure to Fluvoxamine and other combinations involving TCAs, benzodiazepines, alcohol, opioids, and neuroleptics. The antidepressant fluvoxamine at a low dose was found to increase the serum level of the antipsychotic thioridazine and its metabolites threefold, even in therapeutic doses, which increases the chance of ventricular polymorphic arrhythmias [53]. Thus, we may hypothesize that the severity of DDI increases with drug toxicity due to the increasing serum level of a particular drug. There is a proportion between the hepatic drug level and the free fraction of the drug in the serum. Increasing the serum level of the drug increases its elimination half-life and the chance for DDIs [28]. Drugs affecting renal clearance are associated with more DDIs [15].

The reported predominance of DDIs with antidepressants and psychotropics does not support the assumption of some previous studies reporting more DDIs with other xenobiotics. Ethanol was the primary

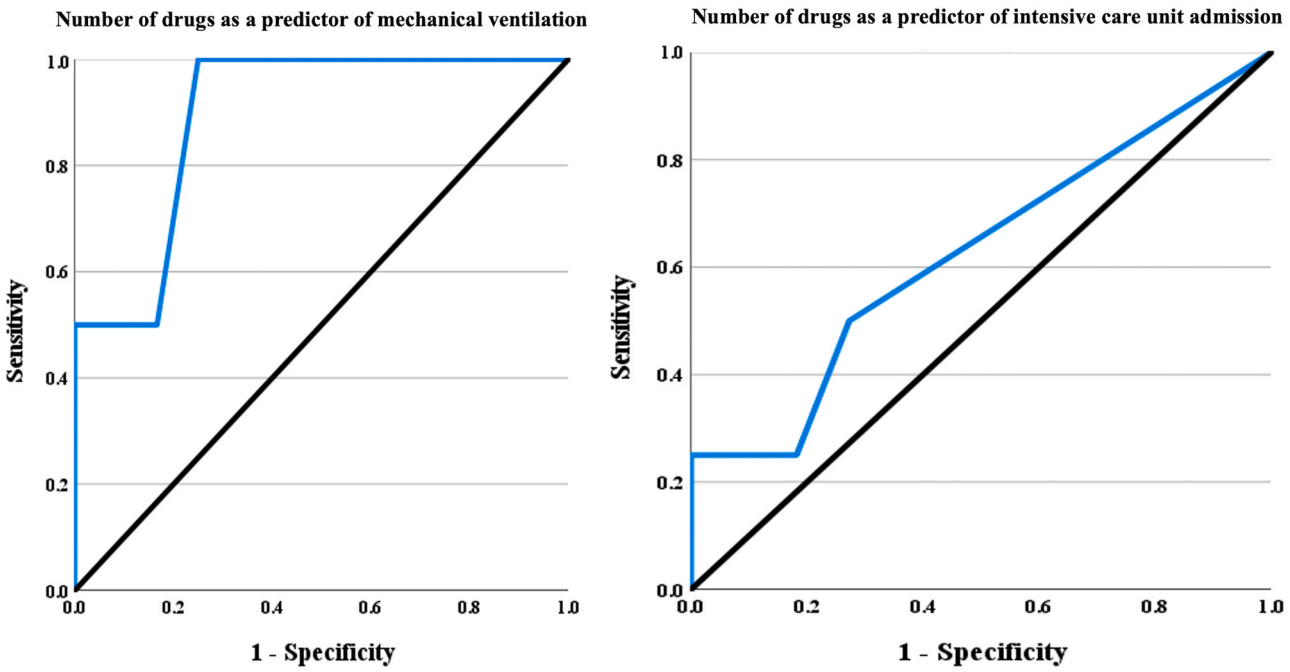

Fig. 5. Receiver Operating characterstic curve of the number of drugs the patient exposed as a predictor for the need of mechnaicl ventilation and intensive care unit admission.

Table 9
ROC curve analyses for number of all drugs the patient exposed as predictors of mechanical ventilation and ICU admission.

	AUC	95 % CI	p	Cut off	Sensitivity 95 % CI	Specificity 95 % CI	PPV 95 % CI	NPV 95 % CI	Accuracy 95 % CI	+ve likelihood ratio 95 % CI	-ve likelihood ratio 95 % CI
Mechanical ventilation											
Number of all drugs	0.896	0.720 – 1.000	0.068	>2.5	100.0 % 15.8 % - 100.0 %	75.0 % 53.29 % - 90.23 %	25.0 % 14.3 % - 40.02 %	100.0 % 81.47 % - 100.0 %	77.0 % 56.35 % - 91.03 %	4 2–8	0 0–0
ICU admission											
Number of all drugs	0.625	0.298 – 0.952	0.434	>2.5	50.0 % 6.76 % - 93.24 %	72.7 % 49.78 % - 89.27 %	25.0 % 9.18 % - 52.42 %	88.9 % 74.37 % - 95.65 %	69.2 % 48.21 % - 85.67 %	1.8 0.56 – 6.05	0.69 0.25 – 1.89

CI: Confidence interval AUC: Area Under a Curve NPV: Negative predictive value PPV: Positive predictive value

substance associated with potential DDIs in an earlier study [14]. Inconsistent with the current study, cardiovascular drugs, including digoxin, warfarin, and analgesic drugs (NSAIDs) were considered the most frequently involved in DDI-related emergency visits and hospital admissions [60,67]. Likewise, NSAIDs, particularly aspirin, were the leading cause of potentially serious DDIs among elderly Swedish populations [62]. An earlier study reported that vitamin K. antagonists were the leading cause of potential DDIs [35] The variation in the sampling and patients' criteria like the age of studied patients justifies this discrepancy.

Eventually, DDIs are considered predictable and preventable [62]. Clinicians should be vigilant about the risk of co-ingestion and the associated potential DDIs when prescribing these medications to vulnerable patients. Unfortunately, in primary care, little attention is paid to reviewing medical prescriptions to assess for potential DDIs, though patients on long-term medications are followed by general practitioners [35]. Replacing the drug of potential DDIs with another or closely intensifying monitoring if drug replacement is impossible are two proposed decisions that might attenuate potential adverse effects [35]. The WHO general prescribing rules stated that "practitioners are advised to remember that discontinuing a drug is as important as starting it" [68].

Preskorn said, *"not seeing a DDI is not the equivalent of a DDI not occurring"* [53]. It is also to be borne in mind that several potential DDIs don't precisely reflected clinically in the realistic contexts. Different software checkers may overestimate the risk of some potential DDIs. Not all resultant DDIs are clinically significant [28]. Kulkarni et al. thought about 89 % of DDIs were clinically irrelevant [56]. The therapeutic benefits of using drug combinations should be weighed against the risk of potential DDIs. Not all interactions reported by the software or in the literature are clinically significant. Whenever the DDIs are neglectable or well tolerated by the patient, treatment could be continued with close monitoring [69].

5. Conclusions and recommendations

Considering the typical encounter of co-ingestion in the setting of acute toxic exposure, particular attention should be paid to the patients at risk of multiple exposure and potential DDIs, including the elderly, males, and patients with comorbid conditions, particularly those suffering from neurological or psychological disorders on antidepressants and psychotropics. Also, caution should be given to patients admitted because of suicidal exposure. Patients with multiple ingestions showed severe presentations indicated by higher grades of PSS and

lower GCS. Multiple ingestion was associated with higher liability for MV, ICU admission, and prolonged length of hospital stay. Among the patients exposed acutely to more than one agent who were on long-term treatment, exposure to three drugs or more could significantly predict the need for MV and ICU admission. When prescribing drugs, the minimum number of drugs with broad therapeutic value at the lowest effective doses should be prioritized.

We advise regular monitoring of DDIs and discontinuing or substituting the drugs that interact strongly. Introducing DDI checker software to hospitals and primary health care centers is encouraged. Moreover, the clinical toxicologist should be warranted with the potentially hazardous effect of multiple exposures in the setting of acute drug poisoning.

Strength and limitations

Compared to previous research, one strength in the present work is the inclusion of drugs the patients already used instead of the prescribed or dispensed drugs, as not all of them are used. Besides, most of the previous literature was focused on DDIs in long-term therapy rather than acute intoxication status, where studies are sparse. In the present study, DDIs were identified using Medscape™ interaction checker software, which was acknowledged for their accuracy, publicity, and free charge. However, the lack of standardized criteria among the different software is a limiting factor [17].

Our study has several other potential confounders, such as age, sex, and comorbid conditions, which are usually present in an older population and associated with multiple ingestions. Furthermore, we did not have comprehensive data on other confounders, such as substance abuse history, physical activity, diet, and other exposures. Though these factors are essential, their omission is a recognized limitation of retrospective studies. As these factors could influence the outcomes, prospective studies with comprehensive data collection are needed to address these gaps. Future studies should aim to collect and analyze such data to provide a more holistic understanding of the predictors of MV and ICU admission in the context of multiple ingestions. Moreover, we recommend conducting studies correlating the potential DDIs detected by the software checkers with the actual DDIs reported in real practices. In the current study, we did not include medication dosages as a contributing factor, although they were thought to have an influence in some cases [35].

Funding

This research was funded by the General Directorate of Scientific Research & Innovation, Dar Al Uloom University, through the Scientific Publishing Funding Program, Riyadh, Saudi Arabia.

Author statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

CRediT authorship contribution statement

Asmaa Fady Sharif: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Rayan Yousef Alshammari:** Writing – review & editing, Data curation, Conceptualization. **Fawaz Talaat Alghamdi:** Writing – review & editing, Data curation, Conceptualization. **Sultan Ahmed Almutairi:** Writing – review & editing, Data curation, Conceptualization. **Abdullah Saeed AlGhamdi:** Writing – review & editing, Data curation, Conceptualization. **Abdulaziz Saad Al-Nazhan:** Writing – review & editing, Data curation, Conceptualization. **Shahd AlNasser:** Writing – review & editing, Data curation. **Khalid A. Al-Mulhim:** Writing – review & editing, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

This research was funded by the General Directorate of Scientific Research & Innovation, Dar Al Uloom University, through the Scientific Publishing Funding Program. The authors extend their appreciation for funding this research

Disclaimer

The views expressed in this paper are those of the authors and not do not necessarily reflect those of the SFDA or its stakeholders. Guaranteeing the accuracy and the validity of the data is a sole responsibility of the research team.

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