




An analysis of 1344 consecutive acute intoxication cases admitted to an academic emergency medicine department in Turkey

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ABSTRACT

OBJECTIVE: One of the major causes of emergency department (ED) visits is acute poisoning. Acute intoxications occur soon after either single or multiple exposures to toxic substances, and they started to be a more serious problem in developing countries. The objective of this study was to investigate the local patterns of acute intoxications, as well as clinical and sociodemographic characteristics of patients with acute poisoning, admitted to our hospital's ED.

METHODS: This single-center, retrospective study was conducted using medical records of consecutive patients admitted to the ED between January 2016 and December 2017.

RESULTS: A total of 1344 patients were included in the statistical analysis. Of these, 673 (50.1%) were female. Mean (\pm SD) age was 32.2 (\pm 12.0), ranging between 17 and 84 years. The highest number of poisoning cases was observed in summer, especially in July (10.0%) and August (11.8%), whereas lowest number of admissions related to poisoning occurred during winter in November (5.1%) and December (5.2%). Among admitted cases, many were suicide attempts (55.7%) followed by non-intentional (accidental) ingestion of non-pharmaceutical (n=553, 41.2%) and pharmaceutical agents (n=42, 3.1%). Single agents were the most common cause of acute intoxications (63.2%) rather than multidrug intoxications. Most frequently observed causes of poisonings were recreational substances (30.0%) and agents exposed by inhalation (13.2%). INR, lactate, and pH levels at admission were significant predictors of 7-day mortality without a significant paired difference between each other. The AUCs for each were 0.89 (SE 0.04; $p < 0.0001$), 0.84 (SE 0.10; $p = 0.0007$), and 0.79 (SE 0.11; $p = 0.0102$), respectively.

CONCLUSION: We conclude that recreational substances and medicinal drug intoxications were the leading cause of acute poisonings in our region, occurring mostly during the summer.

Keywords: Demographics; poisoning; toxicity.

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Poison is a substance that causes permanent or discontinued damage or injury to exposed person [1]. The amount of exposed substance is also vital while defining the poison, since substances exposed regularly in daily life, such as water, can also be poisonous when ingested in extreme amounts [2]. Toxicity varies according to the dose, route, and duration of exposure to the substance.

Poisoning is defined as exposure to any substance, which results in either damage or functional disturbance to the body [3]. All over the world, acute poisoning is a significant public health problem, and it is associated with high mortality [4]. One of the major causes of emergency department (ED) appointments is acute poisonings [5]. An acute poisoning occurs soon after exposure to either

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single or multiple toxic substances, and they constitute a serious problem in developing countries [6]. Poisoning cases may be intentional or unintentional. In general, unintentional (or accidental) self-poisonings occur due to the overdose of medications, alcoholic beverages or toxic alcohols, recreational drugs, or consumption of contaminated foods. Self-poisoning is the accidental or deliberate self-exposure of an individual to a substance associated with a significant potential to cause harm [7].

Injuries and poisonings accounted for 4.5% (n=18,901) of all the deaths that occurred in Turkey in 2017 [8]. Among all ED appointments, self-poisonings constitute 0.6–2.1%, and 17.3% of the cases are referred to intensive care units (ICUs) [9]. Real-world incidence may be higher than this estimate since most of the poisoning cases remain unreported [1]. The World Health Organization reported in 2012 that approximately 200,000 people died worldwide due to unintentional poisonings. Most of these deaths (about 80%) were from low- and middle-income countries [10]. The trend and causes of acute poisonings vary between geographical regions. In metropolitan regions, poisonings with analgesics, tranquilizers, and antidepressant agents are more commonly reported [11]. On the other hand, in rural regions, poisonings with agricultural pesticides are more frequent [12]. These trends change even in the same country, therefore, knowledge of the local pattern of poisonings helps to diagnose patients earlier and reduce morbidity and mortality [1]. According to the recently published report of Turkish Statistical Institute, 5.1% of all-cause mortality were due to external injuries and poisonings in 2016, and this ratio was reduced to 4.5% in 2017 [8]. Even though regional reports on acute poisonings are available from various cities in Turkey, [13–16], a recent hospital-based, large-scale data from Istanbul (one of the biggest cities of the world with a population of 17 million) are not available.

The primary aim of this retrospective database review was to report the causes and demographics of acute intoxications presented to the ED of a tertiary referral center in 2 calendar years. Our secondary aim was to examine if the baseline laboratory values of routine tests such as pH, INR, or lactate may predict short-term (7-day) mortality.

MATERIALS AND METHODS

This retrospective chart and database review study was conducted at a tertiary referral center located in the southeast of Istanbul, Turkey, as one of the largest among university hospitals with 250,000 adult ED admissions annually. Marmara

Highlight key points

- Intentional poisoning was found to be the leading cause of ED manifestations due to poisonings.
- The three major causes of poisoning were found as misuse of recreational drugs, suicide attempt with either prescribed psychiatric drugs or drugs such as nonsteroidal anti-inflammatory drugs and paracetamol, in respective order.
- INR, lactate, and pH values were found to be accurately predicting 7-day mortality.

University Faculty of Medicine Clinical Research Ethics Committee approval was obtained (05.04.2019/09.2019.419) before the initiation of data collection.

We screened the forensic and medical records from the Hospital Information System (HIS) and Forensic Registry of the Police Force in the past 2 years (between January 2016 and December 2017) to include all consecutive patients attended to the ED due to poisonings. Patient list from the electronic database was retrieved by searching for all official electronic forensic reports. The search criteria were handed to the Information Technology department of the hospital and the complete list was retrieved by from the forensic database. This list was confirmed and expanded by checking the official forensic ledger of the hospital police by hand by the researchers. Three researchers checked the ledger by hand and compared it with the electronic list for missing or incomplete cases. The contents of two lists were combined to compile the final patient list. The data on the demographics (age and gender), time of admission, intoxicating substance, and laboratory values on admission (pH, lactate, pCO₂, COHb, and liver function tests [LFTs]) were collected on standard data retrieval forms, if available. All consecutive patients with the age of 18 or above were included in the study. We still included the patients with any missing data in our final study population and analyzed those cases for the parameters other than the missing ones. We determined the presence of outcomes of the patients (death in 7 days, death in the ED, transfer to ICU, admitting to a hospital ward, and discharge) from the HIS and the National Electronic Registry of the deceased.

Statistical Analysis

Continuous variables were reported as means and standard deviations with their corresponding 95% confidence intervals (CIs, with lower and upper limits) or as medians and interquartile ranges according to the distribution pattern of the variables. Comparison of the con-

TABLE 1. Baseline characteristics of patients presented to the ED with intoxications

	Single agent (n=829)	Multiagent (n=515)	Overall (n=1344)	p
Demographics				
Age, year; median (IQR)	30.0 (24.0–38.0)	29.0 (23.0–38.0)	29.0 (24.0–38.0)	0.670
Male sex, n (%)	471 (56.8)	202 (39.2)	673 (50.1)	<0.001
Concurrent trauma, n (%)	37 (4.5)	9 (1.7)	46 (3.4)	0.008**
Intentional poisoning (n=749), n (%)	275 (36.7)	474 (63.3)	749 (55.7)*	<0.001
Tx and outcome, n (%)				
7-day mortality	5 (0.6)	2 (0.4)	7(0.5)	0.710**
ILE treatment	64 (7.7)	10 (1.9)	74 (5.5)	<0.001**
Lab values, median (IQR)				
pH	7.38 (7.34–7.41)	7.39 (7.36–7.41)	7.4 (7.4–7.4)	0.002
pCO ₂ , mmHg	44.0 (39.0–50.0)	42.0 (38.0–46.0)	44.0 (39.0–49.0)	<0.001
COHb, % (n=1157)	3.0 (1.2–5.1)	3.3 (1.2–5.5)	3.1 (1.2–5.4)	0.256
Lactate, mmol/L	2.0 (1.5–2.8)	2.1 (1.6–2.8)	2.0 (1.5–2.8)	0.468
INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	0.452

*: Percentage refers to the column total. Proportions were compared with Chi-squared test, unless marked with **: Which were assessed with Fisher's exact test. Medians were compared with Mann–Whitney U-test. Statistically significant P values are denoted in bold. ED: Emergency department; IQR: Interquartile ranges; ILE: Intralipid emulsion.

tinuous variables among groups was conducted using a t-test, ANOVA, Mann–Whitney U or Kruskal–Wallis, according to normality and number of groups. Categorical variables were reported with counts and frequencies and compared with a Chi-squared test, or Fisher's exact test using contingency tables. We evaluated the predictive utility of laboratory values for 7-day mortality by the receiver operating characteristics (ROC) curves and compared ROC curves as described by DeLong. The Type 1 error in this study was 5%. We used MedCalc v15.8 (MedCalc Software, Ostend, Belgium) for all statistical analyses.

RESULTS

We retrieved the data files of 1344 patients (50.1% male) presented to our ED with acute poisonings (Table 1). The number of poisoning cases was higher in summer (July: 10.0% and August: 11.8%) and lower in winter (November: 5.1% and December: 5.2%). Poisoning cases presented predominantly in weekdays (67.2%) and at night shifts (5 pm and 8 am, 69.9%). The reason for the poisoning was mostly intended suicide (n=749, 55.7%) followed by non-intentional (accidental) ingestion of non-pharmaceutical (n=553, 41.2%) and pharmaceutical agents (n=42, 3.1%).

Pharmaceutical agents were detected in 57.2% (n=769) and 60.3% (n=464) which were due to over-the-counter agents. Most of the poisonings were caused by a single agent (n=829; 61.7%) rather than multiple agents (n=515; 38.3%) (Table 2), and recreational substances (30.8%) and inhalation agents (13.5%) were the most common offenders. Poisonings with a single agent were significantly more frequent in males (56.8%, p<0.001), whereas multiagent intoxications were more common in females (60.8%, p<0.001). A female predominance was also present among intentional (n=506/749, 67.6%) and drug-related poisonings (n=524/769, 68.1%). On the contrary, we observed a male predominance among alcohol and recreational substance intoxications (67.6% and 92.2%, respectively; both p<0.001).

Summary of the laboratory parameters obtained on admission is presented in Table 1. LFT results and mortality data were available for 1140 patients, and almost all (97.6%) results were within normal limits. Mortality rate was statistically significantly higher in patients with abnormal LFT results (0.3% vs. 10.0%; p<0.001). We found that INR, lactate, and pH levels on admission were significant predictors of 7-day mortality without a significant paired difference between each other (all p values of pairwise ROC comparisons >0.05, Fig. 1, Table 3).

TABLE 2. Distribution of the single- and multiple-agent intoxications

Agent	Single agent (n=829) Frequency (%)	Multiagent* (n=515) Frequency (%)	Overall* (n=1344) Frequency (%)
Recreational substances	30.8	5.2	21.0
Psychiatric drugs	12.2	31.1	19.4
SSRIs/SNRIs	6.3	16.0	10.0
Antipsychotics	2.8	13.2	6.8
Other psychiatric drugs	2.5	8.5	4.8
TCA	0.6	1.7	1.0
NSAIDs	4.5	42.1	18.9
Paracetamol	4.8	28.0	14.4
Other* or N/A	2.2	24.1	10.6
Antibiotics/antivirals	1.7	23.9	10.2
Inhaled gases	13.5	1.2	8.8
Alcohol	3.5	15.9	8.3
Food	13.0	–	8.0
Vitamin and/or mineral supplements	0.6	9.3	3.9
Myorelaxants	0.4	8.7	3.6
PPIs	0.7	8.2	3.5
Spasmolytics	0.5	7.6	3.3
Cardiac agents	1.2	6.0	3.1
Antiepileptics	1.3	5.1	2.8
Antihistamines	0.8	6.4	2.7
Caustics/corrosives	4.0	0.4	2.6
Acetylsalicylic acid	0.2	4.1	1.7
Hormones	1.0	3.1	1.6
Combination of antispasmodics and 7 or paracetamol and/or PPI and/or antibiotics	0.5	2.7	1.3
Antiemetics	0.2	2.7	1.2
Antidiabetics	0.5	2.3	1.2
Warfarin/superwarfarin	1.1	1.0	1.0
Antithrombotic drugs (other than ASA)	0.1	1.9	0.8
Ergotamine	0.4	1.0	0.6
Colchicine	0.4	0.6	0.5
Cholesterol-lowering drugs	–	1.0	0.4

*: Total number was not given at the end of the list due to exceeding the total number of the patients caused by multi agent exposures. SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin–norepinephrine reuptake inhibitors; NSAIDs: Non-steroid anti-inflammatory drugs; TCA: Tricyclic antidepressants; PPIs: Proton pump inhibitors; ASA: Acetyl salicylic acid.

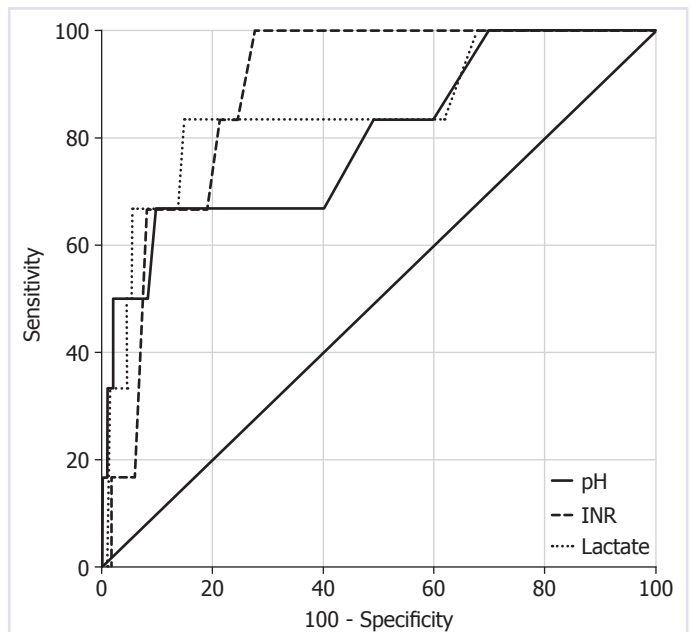


FIGURE 1. Comparison of the receiver operating characteristics curves for pH, INR, and lactate levels at admission for the prediction of 7-day mortality.

The Spearman's rank correlation coefficients of all agents with the level of INR were poor (all $r < 0.06$), and none of them were statistically significant (all $p > 0.05$). However, the agents with the highest Spearman's rank correlation coefficients were methanol ($r = 0.19$, 95% CI 0.14–0.25, $p < 0.001$) and bonsai ($r = 0.25$, 95% CI 0.15–0.26, $p < 0.001$) with the lactate level, and all inhalation agents ($r = 0.15$, 95% CI 0.09–0.20, $p < 0.001$), CO ($r = 0.13$, 95% CI 0.07–0.18, $p < 0.001$), and bonsai ($r = -0.35$, 95% CI -0.30 – -0.40 , $p < 0.001$) with the pH level. However, there was no significant correlation between the pH and COHb levels.

Intralipid emulsion treatment was administered to 74 patients (5.5%) among which, 71 cases were associated with recreational drugs, whereas others were associated with lithium ($n = 1$), tricyclic antidepressant ($n = 1$), or antipsychotic toxicity ($n = 1$) (Table 1).

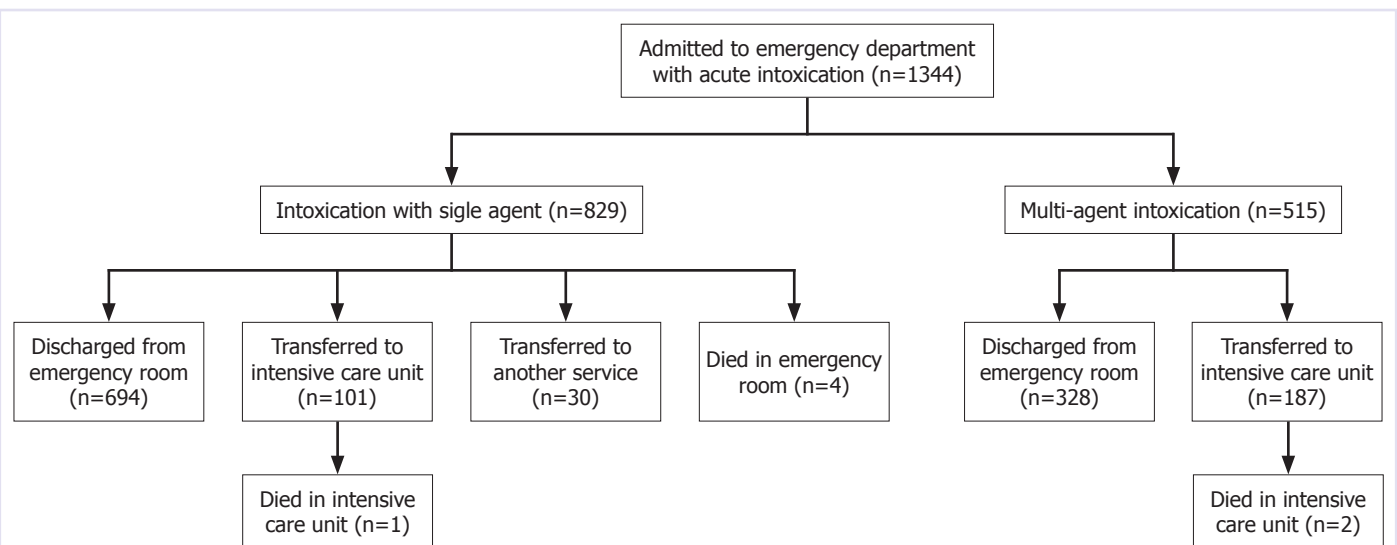
A total of 28 patients (2.1%) were treated by extracorporeal renal replacement therapy. Of these 22 were intoxicated with mushrooms, 3 with methanol, 2 with psychiatric drugs, and 1 with acetylsalicylic acid.

Most of the patients (76.0%) were discharged from the ED. According to the clinical and laboratory findings and the declared amount of the ingested doses, 21.4% were transferred to the ICU, and only 2.2% were transferred to other units. Seven-day mortality information

TABLE 3. Comparison of the ROC curves for pH, INR, and lactate levels at admission for the prediction of 7-day mortality

Value (N, Mortality present/Absent)	AUC (SE)	p	Threshold value by Youden J	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	-LR (95% CI)
INR (n=1114, 6/1108)	0.89 (0.04)	<0.0001	>1.14	100.0 (54.1–100)	72.7 (70.0–75.3)	3.7 (3.3–4.0)	0 (NA)
Lactate (n=1126, 6/1120)	0.84 (0.10)	0.0007	>3.3	83.3 (35.9–99.6)	83.8 (81.6–85.9)	5.2 (3.5–7.6)	0.2 (0.03–1.2)
pH (n=1126, 6/1120)	0.79 (0.11)	0.0102	≤7.31	66.7 (22.3–95.7)	89.0 (87.0–90.8)	6.1 (3.4–10.9)	0.4 (0.1–1.2)
COHb, % (n=1122, 5/1117)	0.58 (0.16)	0.6170	–	–	–	–	–
pCO ₂ (n=1125, 6/1119)	0.63 (0.17)	0.4421	–	–	–	–	–

Bold p values indicate significant AUCs. ROC: Receiver operating characteristics; INR: International normalized ratio; CI: Confidence interval.

**FIGURE 2.** Outcome of patients admitted to emergency department with acute intoxication.

was available for 1291 patients (96.1%), and a total of 7 patients die (0.5%), 3 (0.2%) in the ICU, and 4 (0.3%) in the ED (Fig. 2). The cause of toxicity was recreational drugs in four patients, colchicine in two patients, and caustic agent in one patient.

DISCUSSION

Since patterns of intoxications may vary in different geographies [1, 17], we aimed to investigate the local patterns of acute intoxications, as well as clinical and sociodemographic characteristics of patients with acute poisonings in our region. For this purpose, acute intoxication cases admitted to our ED in 2 years were evaluated.

The event of poisoning may occur through suicidal intention, non-suicidal exposure, or non-suicidal over-

dose. Data obtained from the National Poison Data System for 2011–2015 period for 1.163.249 cases revealed that 54.4% of the poisonings were intentional, which is consistent with our findings [18]. Ozkose and Ayoglu reported that single-agent poisoning cases constituted 74% of all drug poisoning in their study, which is also similar to our findings (61.7%) [19].

The patterns of acute intoxications vary between geographical regions according to the sociodemographic characteristics [11]. The leading toxic agents were opiates/opioids (65%) followed by ethanol (9%) and anti-depressants (4%) in a study conducted in Oslo [20]. Intentional illicit drug overdose was the most frequently reason, and heroin was the leading substance (35%) in a study from Chicago [21]. Results of a study conducted in Iran demonstrated that most frequently involved

drugs were benzodiazepines followed by tricyclic antidepressants and cardiovascular drugs [22]. In a study carried out in Adana, Turkey, which is an agricultural region, Satar and Seydaoglu reported that drugs (59%), followed by pesticides (19%) and rodenticides (7.4%), were the leading causes of poisonings [23]. Moreover, they reported that psychoactive drugs (33.5%) were the most frequently abused agents among drug-related poisoning cases [23]. In the study reported by Ozkose and Ayoglu, analgesics (30.1%) were the most common cause of all drug poisonings followed by psychoactive drugs (20.8%) and antibiotics (6.4%) [19]. Mert and Bilgin reported pharmaceuticals (55.4%) and corrosives (13.3%), as leading agents in acute poisoning [24]. There are two published studies from similar tertiary referral centers in Istanbul [15, 25]. According to these two studies, the most common cause of poisonings was drugs (74% and 70%) followed by inhalation of carbon monoxide (8.7% and 14%), by Saglam et al. and Tufekci et al., respectively [15, 25]. In our study, the leading cause was drugs ($n=769$, 57.2%), similar to the previous local studies mentioned above, and national studies from Malaysia and South Africa [3, 26]. Overall, the leading agent was recreational substances ($n=282$, 21.0%) followed by psychiatric drugs ($n=260$, 19.3%) and nonsteroidal anti-inflammatory drugs ($n=254$, 18.9%).

In the present study, we observed an equal distribution of gender among all poisoning admissions (males: 50.1%, Table 1). Different gender distributions were reported from different regions of the country (males: 25.9% in Diyarbakir, 36.8% in Duzce) [13, 14]. The geographically closest study with the largest sample size was conducted by Saglam et al. [15], and they reported 66% female predominance in 675 patients, which is higher than our findings. International data also vary according to the region. In the USA, 2,710,042 cases were registered to the National Poison Data System in 2016, and results indicate an equal gender distribution in poisoning cases, which is similar to our findings [4]. However, in Ethiopia, female predominance [1], and, in Croatia, male predominance were reported [27]. Because of the high variability in the sample sizes, patient demographics and regions of the studies reported from Turkey, we are unable to form a hypothesis on gender distributions in acute intoxications.

Subgroup analysis revealed a difference in the alcohol and recreational substance toxicity rates of both genders. In general, reports show that women consume less alcohol than men, which is similar to our findings [27–30]. On

the other hand, Peltier et al. reported that this trend has been changing and the number of women who consume alcohol frequently in the USA is increasing rapidly [28].

In general, episodes of acute intoxications are more frequent in the summer in reports from Turkey [13] and other countries [22, 31], which is similar to our findings.

A recent study conducted in Istanbul reported that 88.1% of the acute intoxications were due to suicide attempts [32]. Another study from a rural community in Turkey reported the suicide attempt rate as 68.6% among intoxications [33]. Suicide attempt rate was 91.1% in a study from Morocco [34], and lower in a declining trend in records from Croatia (46, 22, and 17%, respectively, in 2001, 2010 and 2015) [27]. Our study results also suggest a declining trend in the suicide attempt rate, considering the higher rates reported in the previous studies [32, 34].

In this study, we calculated the accuracy (AUC) of INR, lactate, and pH to predict 7-day mortality as 0.89, 0.84, and 0.79, respectively (Table 3). In their study involving acute poisoning cases, Lionte et al. [35] have developed a 7-variable risk-prediction nomogram; among which, lactate was found to have predictive value regarding mortality (AUC: 0.737, 95% CI: 0.577–0.809, $p=0.002$; AUC: 0.657, 95% CI: 0.474–0.840, $p=0.085$ for derivation and validation cohorts, respectively). In a multicenter case–control study conducted by Manini et al. [36], the accuracy of lactate was 0.87 (95% CI: 0.81–0.94), and optimal threshold was 3.0 mmol/L for mortality (84% sensitivity and 75% specificity, $p<0.001$), which was similar to our calculated optimal value of 3.3 mmol/L. In a multicenter study conducted by Cheung et al. [37], initial lactate levels found to correlate with in-hospital all-cause mortality with an accuracy of 0.85 (95% CI: 0.73–0.95) among consecutive adult patients with an acute drug overdose, and a lactate level of 5 mmol/L or more (OR 34.2; 95% CI 13.7–84.2) was 70.8% sensitive (95% CI: 69–73%) and 94.7% specific (95% CI: 93–96%). The findings of all the above studies were similar to our findings for the predictive value of the lactate levels for 7-day mortality (Table 3). There are also several studies in the literature which reported correlation of lactate levels with the severity of acute salicylate, carbon monoxide, glyphosate surfactant, paraquat, and organophosphorus pesticide poisonings [38–45].

Acidemia may occur in poisoned patients due to several mechanisms and often associated with poor prognosis [46]. In a study of 120 patients with acute poisoning, there was a statistically significant difference

between the mean pH levels of survivors and non-survivors (7.38, SD: 0.09 vs. 7.07, SD: 0.28, $p=0.001$) [47]. Similarly, in our study, pH levels predicted 7-day mortality with an AUC of 0.79 (SE 0.11; $p=0.0102$), and the sensitivity and specificity of a pH level of 7.31 or below were 66.7% (95% CI; 22.3–95.7) and 89.0% (95% CI; 87.0–90.8), respectively.

INR was assessed routinely for each poisoned patient at the time of admission, assuming they may have ingested hepatotoxic agents or may have been a candidate for multiorgan failure. We found that INR levels over 1.14 predict mortality with 100% sensitivity and 72.7% specificity; however, the relatively low levels of INR threshold cause lower specificity.

Limitations

First, this study is a retrospective review of relatively high number of cases, and it is the most detailed epidemiological report of intoxications in the region it was conducted, with laboratory findings and predictive values of these findings. Despite those advantages, we admit that the retrospective nature of the study is a limitation to obtain a comprehensive dataset which could have provided further knowledge on the subject. Further studies involving measures such as medical history, comorbidities, and the time between exposure and admission would help us to understand the subject in detail. Second, INR is not a logical predictor for all types of intoxications. However, in most of the cases, it is not possible to gather a complete exposure history and detect all of the intoxicating agents. Therefore, we think that INR may be a cheap and helpful screening test in ambiguous cases. Third, it is obvious that the dose of the ingestion, duration between the ingestion and presentation to the ED, comorbidities, coingestions, medical history, severity of the disease process, quality of the treatment, level of the hospital, and expertise of the providers may be significant confounders, therefore, all conclusions should be corrected for those variables. However, the data of most of those confounders were not available or not frequent enough to conduct a multivariate regression analysis.

Conclusion

We conclude that recreational substances and pharmaceutical drug intoxications were the leading cause of acute poisonings in our region, occurring mostly during the summer. pH, lactate, and INR levels at admission may be of use to predict 7-day mortality.

Ethics Committee Approval: The Marmara University Clinical Research Ethics Committee granted approval for this study (date: 05.04.2019, number: 09.2019.419).

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Authorship Contributions: Concept – MES, HA, OO, ADA; Design – MES, HA, OO, ADA; Supervision – MES, HA, OO, ADA; Materials – MES, HA; Data collection and/or processing – MES; Analysis and/or interpretation – MES, HA; Literature review – MES, OO; Writing – MES; Critical review – MES, HA, ADA.

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