Likelihood Estimation of the Systemic Poison-Induced Morbidity in an Adult North Eastern Romanian Population

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ABSTRACT

Purpose: *Acute exposure to a systemic poison represents an important segment of medical emergencies. We aimed to estimate the likelihood of systemic poison-induced morbidity in a population admitted in a tertiary referral center from North East Romania, based on the determinant factors.*

Methodology: *This was a prospective observational cohort study on adult poisoned patients. Demographic, clinical and laboratory characteristics were recorded in all patients. We analyzed three groups of patients, based on the associated morbidity during hospitalization. We identified significant differences between groups and predictors with significant effects on morbidity using multiple multinomial logistic regressions. ROC analysis proved that a combination of tests could improve diagnostic accuracy of poison-related morbidity.*

Main findings: *Of the 180 patients included, aged 44.7 ± 17.2 years, 51.1% males, 49.4% had no poison-related morbidity, 28.9% developed a mild morbidity, and 21.7% had a severe morbidity, followed by death in 16 patients (8.9%). Multiple complications and deaths were recorded in patients aged 53.4 ± 17.6 years (p .001), with a lower Glasgow Coma Scale (GCS) score upon admission and a significantly higher heart rate (101 ± 32 beats/min, p .011). Routine laboratory tests were significantly higher in patients with a recorded morbidity. Multiple logistic regression analysis demonstrated that a GCS < 8, a high white blood cells count (WBC), alanine aminotransferase (ALAT), myoglobin, glycemia and brain natriuretic peptide (BNP) are strongly predictive for in-hospital severe morbidity.*

Originality: *This is the first Romanian prospective study on adult poisoned patients, which identifies the factors responsible for in-hospital morbidity using logistic regression analyses, with resulting receiver operating characteristic (ROC) curves.*

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Conclusion: *In acute intoxication with systemic poisons, we identified several clinical and laboratory variables, such as GCS, WBC, ALAT, myoglobin, glycemia and BNP, as early predictors for in-hospital morbidity, allowing the physician to provide an accurate diagnosis and management.*

Key words: *systemic poison, likelihood, morbidity, logistic regression, ROC.*
JEL classification: C29; C39; C88; I19.

INTRODUCTION

Acute poisoning with xenobiotics represents a life-threatening situation and a global public health problem. According to the World Health Organization, 370,000 people die of acute self-poisoning each year globally, and the mortality is higher in low- and middle-income countries in Europe, than in any other region in the world (Mathers et al., 2004).

Acute exposure to a systemic poison (which affects the entire body at various degrees, with major effects manifested in at least two organs or systems) represents an important segment of acute poisoning and medical emergencies (Lionte et al, 2016). Our previous experience showed that acute drug poisonings represent the majority of the total number of poisoned patients in our area, with a mortality rate of 0.3% (Sorodoc et al, 2011). After exposure to chemicals such as cholinesterase inhibitors, the mortality rate in our area is 3.8% (Gazzi et al, 2015).

The poison's effect on an organism is measured using vital function parameters and laboratory tests. Based on the severity of a poisoning, the patient may develop one or multiple complications reflecting the poison-related morbidity. The management of a poisoned patient uses laboratory tests and specific biomarkers to assess the morbidity. Thus far, some investigators have documented the use of laboratory tests (i.e. arterial lactate level, MB isoenzyme of creatine kinase – CKMB, and troponin) as prognostic indicators in order to identify high-risk patients in acetaminophen, carbon monoxide (CO) or paraquat poisoning (Shah et al, 2011; Kao et al, 2009; Liu X.W. et al, 2013).

There is little knowledge about the role of routine laboratory tests as early predictors for a systemic poison-induced morbidity.

Our aim was to identify the factors influencing the in-hospital morbidity of a cohort of patients acutely exposed to systemic poisons, and to determine the value of conventional laboratory tests obtained upon admission, combined with different demographic and clinical characteristics, for likelihood assessment of the subsequent morbidity in a tertiary referral center from North East Romania. The physician could immediately use these clinical and laboratory data to identify patients at risk for developing complications

or death and improve their management, early referring these patients to an intensive care unit (ICU).

LITERATURE REVIEW

Acute poisonings represent a worldwide problem. In our area, epidemiological data suggested that 97.27% are acute drug poisoning in suicide attempts, using combinations of drugs in 32.92% cases (Sorodoc et al, 2011). The reports from the National Poison Data Systems in United States show that poisoning with pharmaceutical products is the leading cause of accidental death (Dart et al, 2015), data that are consistent with epidemiological reports from Central Europe (Krakowiak et al, 2011). Poisoning with non-pharmaceutical agents, such as toxic alcohols, gases, and miscellaneous chemicals are associated with the largest number of fatalities, CO being the leading cause of death in the United States (Mowry et al, 2013).

Several retrospective studies attempted to identify prognostic or mortality indicators in acute poisonings, such as CO poisoning (i.e. lactate, cardiac biomarkers – Cervellin et al, 2014; Liu S. et al, 2014), or pesticide poisoning (acid-base status, male sex, or age). (Liu JH. et al, 2008; Hsu et al, 2013).

It was argued before, after a retrospective analysis, that some indicators, such as toxicological history, Glasgow Coma Scale (GCS) score, or serum lactate level, could help the emergency physicians to distinguish between low- and high-acuity poisoned patients with deliberate drug poisoning, in order to avoid excessive morbidity (Maignan et al, 2014).

Our previous experience showed that there are some indices available upon the arrival of a patient acutely exposed to a systemic poison, such as the poisoning severity score, a GCS < 10, initial and 4h-arterial lactate level, brain natriuretic peptide (BNP), and 6h-CKMB, which can early predict a poor short-term outcome, and mortality (Lionte et al, 2016).

The logistic regression models have been extensively used during the last years in medical research, including toxicology (Hunt and Li, 2006), dentistry (Javali and Pandit, 2012), or epidemiology (Bender, 2009), etc. Multivariable statistical models can be useful tools for the prognosis prediction, when are developed accurately (Harrell et al, 1996). The goal of an analysis using a logistic regression model is to find the relationship between response variable and a set of factors. In order to have an accurate model, a reduced number of variables, or a simplified model must be used (Harrell et al, 1996). To investigate the risk factors associated with poison-related morbidity, outcomes or mortality, the regression methods have become an important component of any data analysis regarding to the relationship

between a response variable (i.e. outcome or death) and one or more predictor variables called factors (i.e. age, poisoning severity score, etc).

Receiver operating characteristic (ROC) curve analysis was used extensively for the assessment of diagnostic ability of laboratory tests and for the classification of diseased from the healthy subjects using imaging tests in the last several years (Hajian-Tilaki, 2013).

METHODOLOGY

Study Design and Setting

This work was designed as a prospective observational study in a tertiary referral center for toxicology, admitting patients from North East Romania with acute poisoning. Over a period of 15 months (April 1st 2015 – 31st March 2016), we enrolled consecutive patients with a diagnosis of acute poisoning, which were admitted in the Medical Clinic, or in the intensive care unit (ICU) of the 'Sf. Spiridon' Emergency County Clinic Hospital, Iasi. All subjects or their families (in the situation of an unconscious patient) signed an informed consent prior to the enrollment. The study was funded by an internal research grant of the university, and approved by the Ethics Committee.

Selection of Participants

The study included hospitalized patients acutely exposed to a systemic poison, older than 18 years, irrespective of gender. Patients were poisoned with prescription drugs, illicit drugs, miscellaneous chemicals (pesticides, toxic alcohols, hydrocarbons etc.), toxic gases or were exposed to multiple systemic poisons.

Patients without a signed informed consent, younger than 18 years, with a history of diabetes, with exposure to a poison with a local irritant effect, or with an acute pathology associated to poisoning (i.e. trauma, burns, etc.) were excluded from our study.

Patient assessment

All patients with a confirmed diagnosis of acute intoxication with a systemic poison, based on clinical examination, and toxicological tests, underwent routine assessment (complete blood count, arterial blood gases, glucose, electrolytes, C reactive protein, troponin I, BNP, creatine phosphokinase - CK, CKMB, myoglobin, renal and liver function profile). Patients were clinically monitored, by means of electrocardiogram (ECG), pulse oxymetry and non-invasive blood pressure measurements.

The management of these patients' involved measures of basic life support, special interventions in case of respiratory failure, shock, and cardiac arrest, decontamination measures, supportive and antidote therapy, which were continued after admission in the medical clinic, or ICU, as recommended by the guidelines.

The main objective was to assess the poison-related morbidity during hospitalization. Patients were divided into three groups: without morbidity (no complications during hospitalization), with a mild morbidity (only one complication involving a single organ or system resolved during hospital stay), and with severe morbidity (defined as in-hospital multiple complications and/or death). The presence of an early complication was defined as follows: central nervous system complication (coma, stroke, or seizures); rhabdomyolysis (CK > 1000 IU/L); acute respiratory failure, defined as a condition requiring mechanical ventilation for correction of hypoxia, or hypercapnia, for more than 24 hours; cardiovascular complications (hypotension, defined as systolic blood pressure less than 90 mm Hg, or arrhythmias with circulatory compromise, and acute myocardial injury, based on cardiac biomarkers and ECG); acute liver injury, defined as markedly elevated serum alanine and aspartate aminotransferase levels > 10 times the upper limit of the normal range, accompanied by mild or moderate elevations in alkaline phosphatase levels (Chalasani et al, 2014); acute kidney injury, defined as urine volume < 0.5 ml/kg/h for 6 hours, based on KDIGO criteria (Kidney inter., Suppl, 2012); gastroenteral, defined as lesions indicated by a superior or inferior digestive endoscopy; multiple complications (at least two organs or systems affected).

Statistical analysis

Numerical variables are presented as mean ± SD, median with interquartile range, or frequency for categorical variables. To identify significant differences between the patient morbidity groups defined, taking into account clinical and demographic data, laboratory tests associated with poisoning-related complications and fatalities, Student's t test or Mann-Whitney U test for normal distributed variables, as well as the Chi-square test and Cochrane's statistic for categorical variables were used to perform univariate analysis (Jaba and Grama, 2004). We calculated Sig. for the differences between parameters for patients with or without morbidity. A Sig. < .05 was considered statistically significant. All variables found to be significant in the univariate analyses for morbidity were subjected to a logistic regression analysis. First we applied simple binomial logistic regression for each statistically significant variable. Then we applied multinomial logistic regression on variables characterizing different systems and organs. Risk was

expressed as odds-ratios (OR) with confidence intervals (CI). Goodness-of-fit for multivariate models was confirmed using Hosmer and Lemeshow test. The receiver operating characteristic curve (ROC) was used as a measure of diagnostic performance, to validate the discriminatory power of the model predictive variables (Hajian-Tilaki, 2013). Statistical analyses were performed with SPSS (version 22.0; SPSS, Inc., Chicago, IL).

RESULTS

During the study period, 180 patients were enrolled with a mean age of 44.7 ± 17.2 years (range, 18-90 years), 51.1% males, all Caucasians. The majority of cases were self-poisonings (91.1%), 16 cases being accidental poison exposures. The mean time interval between poison exposure and admission was 5.5 ± 1.9 hours. The population's demographic, clinical, and laboratory characteristics based on the morbidity recorded are presented in the Table 1.

Characteristics of the observed variable distribution in total cohort and groups of patients

Table 1

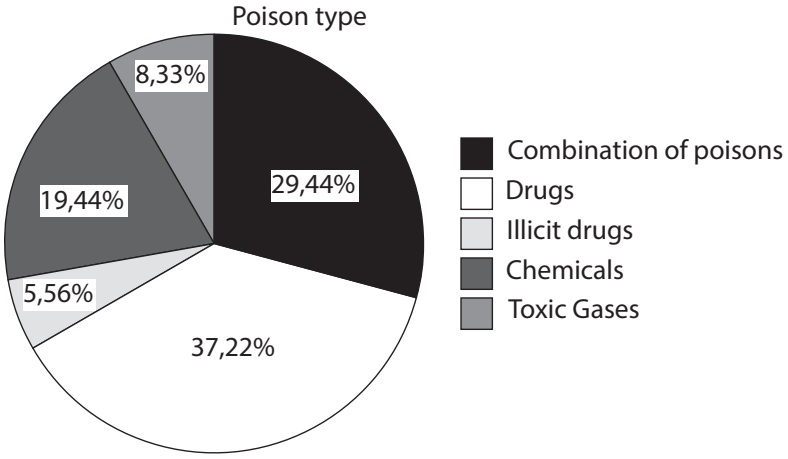
Variable	Total N=180 patients	No complication N=89 patients	Single complication N=52 patients	Multiple complications N=39 patients	Sig.
Demographic data					
Age (years)	44.7 ± 17.2	42.3 ± 15.7	42.1 ± 17.4	53.4 ± 17.6	.001
Gender; F/M (%)	88/92 (48.9/51.1)*	54/35 (61.4/38)	20/32 (22.7/34.8)	14/25 (15.9/27.2)	.007
Origin; R/U (%)	90/90 (50.0/50.0)*	51/38 (56.7/42.2)	23/29 (25.6/32.2)	16/23 (17.8/25.6)	.146
Clinical and toxicological data					
GCS; N (%) > 8 ≤ 8	 146 (81.1)* 34 (18.9)*	 86 (58.9) 3 (8.8)	 42 (28.8) 10 (29.4)	 18 (12.3) 21 (61.8)	.000
HR (beats/min)	91.63 ± 24.47	86.91 ± 18.73	92.81 ± 25.44	100.85 ± 31.61	.011
SBP (mmHg)	123.59 ± 25.40	122.15 ± 21.31	125.54 ± 24.28	124.31 ± 34.44	.734
DBP (mmHg)	75.65 ± 14.71	76.36 ± 12.64	76.71 ± 14.17	72.62 ± 19.19	.346
Poison involved; N (%) Combinations Prescription medicines Drugs of abuse Chemicals Toxic gases	 53 (29.4)* 67 (37.2)* 10 (5.6)* 35 (19.4)* 15 (8.3)*	 31 (58.5) 41 (61.2) 4 (40.0) 10 (28.6) 3 (20.0)	 14 (26.4) 13 (19.4) 6 (60.0) 11 (31.4) 8 (53.3)	 8 (15.1) 13 (19.4) 0 (0.0) 14 (40.0) 4 (26.7)	.001
Laboratory tests					
Lactate (mmol/L)	3.08 ± 3.16	2.49±2.53	2.84±2.31	4.74±4.61	.001
pH	7.36 ± .13	7.41 ± .06	7.37± .09	7.22± .21	.000
Base excess (mmol/L)	22.86±5.17	24.68±2.89	23.39 ± 4.09	17.99 ± 7.19	.000
Sodium (mEq/L)	140.37±5.71	140.29±3.53	141.88±5.35	138.51±8.93	.019
CRP (mg/dl)	1.82±4.59	.63 ± 1.33	1.66 ± 4.84	4.76 ± 7.17	.000
WBC (*1000/mcgL)	10.43 ± 4.88	8.16 ± 2.53	11.09 ± 4.61	14.74 ± 6.10	.000
Hemoglobin (g/dL)	13.78 ± 1.61	13.51 ± 1.56	14.08 ± 1.21	13.98 ± 2.07	.084
Glycemia (mg/dl)	131.05 ± 55.34	115.79±36.92	124.40±32.48	174.74±85.37	.000
Creatinine (mg/dl)	.89 ± .42	.80 ± .22	.81 ± .20	1.18 ± .74	.000
ASAT (U/L)	43.34 ± 78.63	23.22±12.14	41.23±57.242	92.08±144.89	.000
ALAT (U/L)	30.47±34.52	21.35±12.62	33.42 ± 38.64	47.33 ± 52.35	.000
Myoglobin (ng/mL)	109.45 ±151.62	49.29±27.63	96.67±100.33	263.78±244.69	.000
BNP (pg/mL)	77.28 ± 145.16	39.63±109.39	74.55±128.06	166.84±194.89	.000
CK (U/L)	646.76±4240.30	130.84±89.32	303.85±564.16	2281.31±8984.64	.023
CKMB (ng/mL)	8.12±12.87	5.08±7.78	8.05±10.86	15.14±20.24	.000
Management					
ICU therapy; N (%) Not needed Administered	 140 (77.8)* 40 (22.2)*	 85 (60.7) 4 (10.0)	 41 (29.3) 11 (27.5)	 14 (10.0) 25 (62.5)	.000
Antidote therapy; N (%) Nonexistent Unavailable Not indicated Administered	 95 (52.8)* 2 (1.1)* 46 (25.6)* 37 (20.6)*	 47 (49.5) 1 (50.0) 34 (73.9) 7 (18.9)	 26 (27.4) 0 (0.0) 10 (21.7) 16 (43.2)	 22 (23.2) 1 (50.0) 2 (4.3) 14 (37.8)	.000
Hospitalization (days)	4.5 ±3.6	3.2 ±1.7	4.3 ±2.4	7.7 ± 5.8	.000

F, female; M, male; *, % of total; R, rural; U, urban; GCS, Glasgow Coma Scale score; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C reactive protein; WBC, white blood cells; ASAT, Aspartate Aminotransferase; ALAT, Alanine Aminotransferase; BNP, brain natriuretic peptide; CK, creatine kinase; CKMB, MB isoenzyme of creatine kinase; ICU, Intensive Care Unit.

Poisoning with prescription drugs (37.22%), followed by the combination of poisons (29.44%) represented the majority of agents used in self-poisoning by our patients (Fig. 1).

The poisons involved in acute poisoning of the cohort analysed

Fig. 1



Based on the significant differences between means, or frequencies of the considered patients' groups (no complications, a single complication or multiple complications) we identified variables, which were included in the logistic regression analysis. Significant predictors of poison-related morbidity are shown in Table 2.

Variables influencing the morbidity identified using the simple binomial logistic regression

Table 2

	B	S.E.	Wald	Sig.	Exp (B)	95% C.I. for EXP (B)	
						Lower	Upper
CRP	.090	.091	.972	.324	1.094	.915	1.307
Base excess	.017	.070	.060	.807	1.017	.887	1.166
WBC	.240	.073	10.786	.001	1.272	1.102	1.468
Glycemia	.006	.005	1.113	.292	1.006	.995	1.017
Creatinine	-.282	1.032	.075	.785	.754	.100	5.700
ALAT	.035	.013	7.739	.005	1.036	1.010	1.062
Myoglobin	.017	.006	7.522	.006	1.017	1.005	1.029
BNP	.003	.002	2.384	.123	1.003	.999	1.006
CKMB	.039	.024	2.664	.103	1.040	.992	1.089
GCS ≤ 8	-2.625	.814	10.388	.001	.072	.015	.358
Age > 65 years	-.427	.746	.328	.567	.653	.151	2.814
Constant	-3.172	2.568	1.526	.217	.042		

CRP, C reactive protein; WBC, white blood cells; ALAT, Alanine Aminotransferase; BNP, brain natriuretic peptide; CKMB, MB isoenzyme of creatine kinase; GCS, Glasgow Coma Scale score.

Athough patients with multiple complications were significantly older than patients without complications (Table 1), old age (> 65 years) was not correlated with morbidity after logistic regression analysis, in acute intoxication with systemic poisons (Table 2).

Among the cardiovascular parameters, only the heart rate was significantly correlated with complications (Table 1) but was not predictive for morbidity in our patients, after logistic regression analysis.

The significant variables influencing the morbidity identified after multinomial logistic regression.

Table 3

Morbidity[a]		B	Std. Error	Wald	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower Bound	Upper Bound
Single complication	WBC	.232	.076	9.215	.002	1.261	1.086	1.465
	ALAT	.034	.014	6.381	.012	1.035	1.008	1.063
	Myoglobin	.013	.006	5.323	.021	1.013	1.002	1.025
	Prescription drugs	-1.779	.892	3.979	.046	.169	.029	.969
	GCS > 8	-2.325	.867	7.187	.007	.098	.018	.535
Multiple complications	WBC	.289	.101	8.223	.004	1.335	1.096	1.626
	Glycemia	.022	.008	7.504	.006	1.022	1.006	1.039
	ALAT	.055	.016	11.331	.001	1.057	1.023	1.091
	Myoglobin	.022	.007	11.727	.001	1.023	1.010	1.036
	BNP	.006	.003	5.102	.024	1.006	1.001	1.011
	Drugs of abuse	-19.246	.000	.	.	4.381E-9	4.381E-9	4.381E-9
	GCS >8	-4.718	1.171	16.240	.000	.009	.001	.089

[a.] The reference category is: No complications. WBC, white blood cells; ALAT, Alanine Aminotransferase; GCS, Glasgow Coma Scale score; BNP, brain natriuretic peptide.

On multivariable analysis, 4 of the 19 candidate variables were predictive of a single complication, and respectively 6 variables were predictive for multiple complications or death (Table 3).

Upon admission to hospital, the patient characteristics that were most strongly predictive of in-hospital severe morbidity included high WBC count (33.5%), high ALAT level (5.7%), an increased myoglobin and glucose level, whereas a GCS > 8 was associated with a 9.8% reduction in mild morbidity, and 0.9% reduction of severe morbidity.

Interestingly, an exposure to a prescription drug was associated with an 83.1% reduction in occurrence of a single complication (Table 3). Of particular interest was the finding that acute exposure to drugs of abuse was associated with a lower risk of severe morbidity, such as multiple complications or death, particularly because in our region, the illicit drugs are used on a limited extent, while the substances associated with a major morbidity (such as cocaine) are expensive and not readily available.

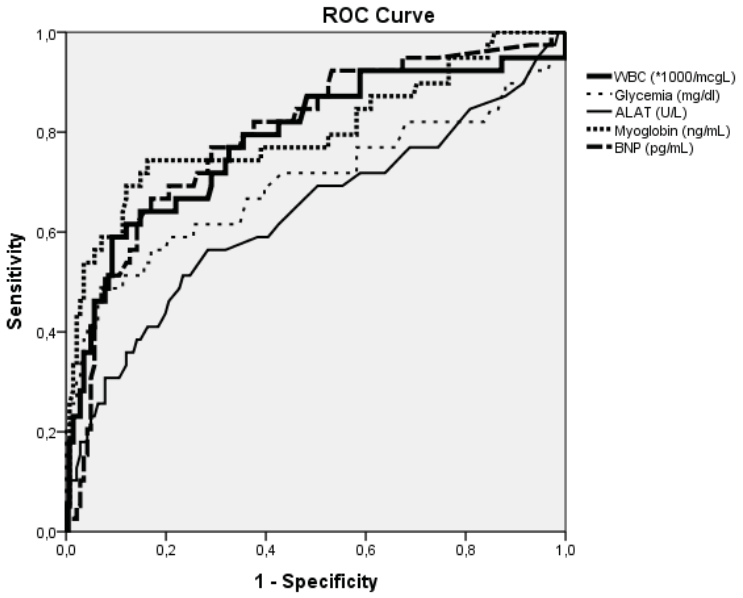
We checked the validity of our model using ROC methodology (Fig. 2). Five of the observed variables showed a good discriminatory capacity, with an area under the ROC curve (AUC) > 0.5, as follows: WBC (AUC, 0.79; CI 95%, 0.69–0.88; p < .001), glycemia (AUC, 0.70; CI 95%, 0.58–0.81; p < .001), ALAT (AUC, 0.64; CI 95%, 0.53–0.75; p .01), myoglobin (AUC, 0.80; CI 95%, 0.71–0.89; p < .001), and BNP (AUC, 0.79; CI 95%, 0.71–0.88; p < .001). The optimal cut-off values, as resulted from this ROC analysis are: WBC 10.56 *1000/mcgL, with a 72% sensitivity and a 71% specificity, glycemia 115 mg/dL, with a 72% sensitivity and a 57% specificity, ALAT 57 U/L, with a 21% sensitivity and a 96% specificity, myoglobin 114 ng/mL, with a 69% sensitivity and a 88% specificity, and BNP 108 pg/mL, with a 49% sensitivity and a 92% specificity.

Complications recorded during hospitalization (Fig. 3) occurred in 91 patients (50.6%). Among those, 39 were patients with multiple complications (21.7%), and 17 were patients with cardiovascular complications (9.4%).

Out of the 180 patients included, 16 patients died during hospitalization (8.9%) as a cause of multi-organ failure, having a length of hospital stay of 6.9 ± 5.9 days, significantly longer compared with the survivors (4.3 ± 3.4 days, Sig. .005).

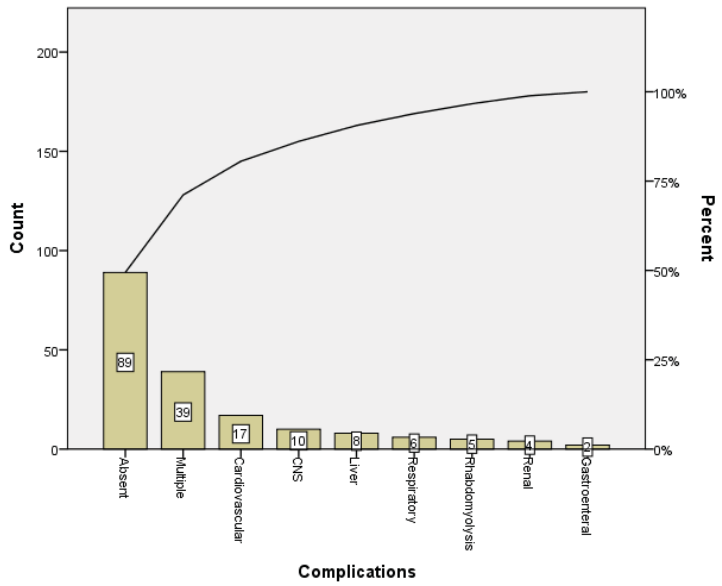
Validation of the predictive variables for systemic poison-related morbidity with receiver operating characteristic curves

Fig. 2



Complications recorded in the cohort analysed

Fig. 3



Some limitations in this study should be mentioned. There could be a possible selection bias in the population studied, which included patients from a single tertiary center in North East Romania, although the epidemiological and toxicological data are consistent with those reported in other areas. (Dart et al, 2015; Krakowiak et al, 2011) We could not calibrate the influence of toxin serum concentration (because the quantitative toxicological tests are not available immediately after admission in the majority of poisoning). We failed to monitor the morbidity of the patients exposed to a systemic poison after discharge from the hospital.

CONCLUSIONS

Early prediction of clinical decompensation and subsequently morbidity in patients acutely exposed to a systemic poison is limited.

The main objective of our study was to identify and analyze the determinants of the morbidity in a cohort of patients with acute systemic poisoning, and to estimate the value of conventional laboratory tests obtained upon admission, combined with different demographic and clinical characteristics, to assess the likelihood of in-hospital morbidity.

To the best of our knowledge, this is the largest cohort of patients exposed to systemic poisons prospectively analyzed in a Romanian tertiary center.

In order to identify the factors that mostly impact the poison-related morbidity, multiple logistic regression analysis was applied taking into account significant variables associated with the occurrence of complications, and the discriminatory power of the model predictive variables was validated using ROC analysis.

Our results suggest that the in-hospital morbidity for poisoned patients can be reliably identified with clinical parameters, such as the Glasgow Coma Scale score and routine laboratory tests obtained upon admission. Admission level of WBC, ALAT, myoglobin, glycemia and BNP are strong independent predictors of in-hospital severe morbidity.

The use of these parameters identifies poisoned patients, after exposure to a systemic toxin, at high risk for in-hospital severe morbidity, and who might benefit from careful monitoring and aggressive intervention.

There is a need for further efforts to define the factors influencing morbidity and mortality risk for all patients hospitalized with acute poisoning.

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