

## ORIGINAL ARTICLE

# Parameters influencing in-hospital mortality in acutely poisoned patients hospitalized in a medical or ICU ward: is there an influence of toxin-induced myocardial injury?

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**Abstract:** Acute poisonings represent a challenge for the hospital practitioners, the burden of morbidity and mortality being significant worldwide. The prognostic utility of combined analysis using troponin I (TnI), electrocardiogram (ECG), and transthoracic echocardiography (TTE) parameters in acute poisoning, upon admission in a medical or intensive care unit (ICU) ward, was not evaluated. This prospective observational cohort studied 222 acutely poisoned adults with an in-hospital mortality rate of 4.5%. Multivariate logistic regression showed, as predictors for in-hospital mortality, TnI measured 6 hours from admission [odds ratio (OR) 1.752; CI 95%: 1.201-2.558; p 0.004], the QTc interval (OR 1.882; CI 95%: 1.022-3.466; p 0.043), and deceleration time (DT) of the E wave (OR 3.653; CI 95%: 1.460-9.137; p 0.006). The receiver operating characteristic (ROC) analysis confirmed that 6h-troponin (AUC, 0.889; CI, 0.789-0.990; p < 0.001), and DT (AUC, 0.801; CI, 0.644-0.958; p 0.001), have the capacity to indicate a risk for in-hospital mortality. Among the parameters influencing in-hospital mortality of acutely poisoned patients, myocardial injury assessed upon admission based on the dynamic of cardiac troponins, ECG and TTE can be used to predict the outcome and mortality in this setting.

**Keywords:** poisoning, myocardial injury, in-hospital mortality.

**Rezumat:** Intoxicațiile acute reprezintă o provocare pentru practicienii din spital, povara morbidității și mortalității lor fiind semnificativă în toată lumea. Valoarea prognostică a analizei combinate folosind troponina I (TnI), parametrii electrocardiograamei (ECG) și ecocardiografiei transtoracice (ETT) în intoxicațiile acute la internarea într-un salon medical sau de terapie intensivă nu a fost încă evaluată. Acest studiu prospectiv observațional a analizat 222 de adulți intoxicați acut, cu o rată a mortalității intra-spitalicești de 4,5%. Regresia logistică multinomială a arătat ca TnI determinată la 6 ore după internare [odds ratio (OR) 1.752; CI 95%: 1.201-2.558; p 0.004], intervalul QT corectat (OR 1.882; CI 95%: 1.022-3.466; p 0,043) și timpul de decelerare al undei E (TDE) determinat prin ETT (OR 3.653; CI 95%: 1.460-9.137; p 0.006) sunt predictorii ai mortalității pe durata spitalizării. Analiza ROC a confirmat că valoarea troponinei la 6 ore (AUC, 0,889; CI, 0,789-0,990; p < 0,001) și TDE (AUC, 0,801; CI, 0,644-0,958; p 0,001) pot indica riscul de deces intra-spitalicesc. Între parametrii care influențează mortalitatea în spital la pacienții cu intoxicații acute, injuria miocardică evaluată la internare pe baza dinamicii troponinei, ECG și ETT poate fi utilizată ca predictor al prognosticului și mortalității în această situație clinică.

**Cuvinte cheie:** intoxicație, injuria miocardică, mortalitate intraspitalicească.

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## INTRODUCTION

Acute poisonings have a high morbidity and mortality and represent an important challenge for hospital practitioners<sup>1,2</sup>. Myocardial injury frequently occurs after exposure to different poisons, such as pharmaceutical agents with a recognized cardiotoxicity<sup>3,4</sup>, carbon monoxide (CO)<sup>5</sup> and other toxic gases, pesticides<sup>6</sup>, drugs of abuse<sup>7,8</sup>, or vegetal toxins<sup>9,10</sup>, and it was proved to be a predictor of mortality in several toxin exposures.<sup>3,5,11</sup> There are studies which investigated the potential role of biomarkers<sup>12,13</sup>, transthoracic echocardiography (TTE)<sup>14</sup>, or both<sup>15</sup>, in some toxin exposures, especially those related with a high cardiovascular morbidity. Electrocardiogram (ECG) parameters have a predictive role for the outcome and mortality in patients suspected of acute poisoning.<sup>16</sup> Our previous experience showed the benefit of using some clinical scores, lactate, B-type natriuretic peptide, and MB isoenzyme of creatine kinase to early predict the complications, poor short-term outcomes, and mortality in systemic poison exposures<sup>17</sup>, and the usefulness of E-wave deceleration time (DT) and B-type natriuretic peptide to predict mortality in patients acutely intoxicated with undifferentiated poisons<sup>18</sup>. However, the combined analysis of troponin I with ECG and TTE parameters upon admission of an acutely poisoned patient in a medical or Intensive Care Unit (ICU) ward, with respect to the outcomes and in-hospital mortality, was not performed.

The aim of this study was to analyze if myocardial injury, assessed using troponin I (TnI) measured upon admission and 6 hours after presentation, ECG, as well as the parameters of cardiac function using TTE in a cohort with acute poisoning hospitalized in a medical or ICU ward can be useful as an early predictor for a poor outcome and in-hospital mortality in acutely poisoned patients with different xenobiotics. Thus, the practitioners could optimize the strategies to identify the poisoned patients with acute myocardial injury and adjust their management to improve the outcome of these patients.

## MATERIALS AND METHODS

We performed a prospective observational study in a cohort of patients acutely poisoned with different xenobiotics, over a period of 18 months (October 2016 – March 2018). We enrolled consecutive patients older than 18 years, which were addressed to the Emergency Department (ED) within 12 hours from poison exposure and admitted in a medical or ICU ward with

a diagnosis of acute poisoning, after obtaining an informed consent. The study was partially funded by an internal research grant of the university, approved by the review board of the hospital and university.

Patients had either an accidental acute exposure, or a self-poisoning with pharmaceutical agents (prescription drugs and over-the-counter [OTC] medicines), illicit drugs, nonpharmaceutical agents (i.e. pesticides, rodenticides, chemicals, toxic alcohols), vegetal toxins, toxic gases, or a combination of multiple poisons. Patients without a signed informed consent, younger than 18 years of age, with an associated disease that can influence biomarkers, ECG or TTE pattern (i.e. diabetes, acute myocardial infarction or heart failure, chronic renal disease, severe liver disease), patients with an acute pathology associated to poisoning (i.e. trauma, burns, anaphylaxis etc.), or patients with incomplete data were excluded from our study.

Poisoning severity score (PSS) was determined in all patients using the grading system described by Persson et al.<sup>19</sup> The venous blood was collected immediately after admission for conventional laboratory tests and troponin I (TnI) analysis, 6 hours after the admission for TnI (6h-troponin), also during the hospital stay at the discretion of the attending physician, to assess acute myocardial injury, according to the European Society of Cardiology guidelines<sup>20</sup>. Cardiovascular biomarkers were determined from the blood sample with PATHFAST® Cardiac Biomarker Analyser (LSI Medience Corporation, Japan), and with ARCHITECT cI6000 clinical chemistry analyser (Abbott Laboratories, USA). A standard 12-lead ECG was recorded upon ED presentation using a CardioM Medica ECO-Net 12 channels electrocardiograph and repeated during hospitalization when needed. The QTc was calculated using the Bazett formula<sup>21</sup> and was considered prolonged if greater than 440 milliseconds (ms).

We performed immediately after admission a standard TTE in all poisoned patients, using a Fukuda Denshi Full Digital Ultrasound System UF-850XTD (Fukuda Denshi Co., Ltd., Japan). The parameters' normal values were considered upon guidelines' recommendations<sup>22,23</sup>.

We observed as an outcome measure the status at hospital discharge. A poor outcome was defined as multiple complications or in-hospital death. Patients with a myocardial injury detected during hospitalization were programmed for a follow-up thirty days post-discharge, but unfortunately not all patients were compliant with this recommendation.

### Statistical analysis

The categorical variables were expressed as numbers and percentages and compared using the Chi-square test. The continuous variables were expressed as medians with interquartile ranges (IQR) and compared with the Mann-Whitney test. The variables were compared in univariate analysis (survivors vs deceased patients). All significant variables in the univariate analyses for in-hospital mortality were subjected to a multivariate logistic regression analysis. Risk was expressed as odds-ratios (OR) with confidence intervals (CI). Goodness-of-fit for multivariate models was confirmed using the Hosmer and Lemeshow test. The receiver operating characteristic (ROC) methodology was used to analyze the discriminatory capacity of predictive variables. ROC analyses were expressed as curve plots and calculated area under the curve (AUC) with 95% CI and the associated p value representing the likelihood of the null hypothesis (AUC = 0.5). P values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software for Windows (V.22.0; SPSS, Chicago, IL, USA).

### RESULTS

We analyzed 222 patients, with a median age of 43 years (range 18-91 years), 50.9% men. Time to ED ar-

rival was  $4.2 \pm 1.8$  hours (range 30 minutes-12 hours). The selected clinical characteristics (demographics, PSS, GCS, poison types, vital signs, etc.) with respect to mortality are included in Table 1, and Figure 1.

43 patients in our cohort were exposed to combinations of poisons (15.5%), 40 were exposed to non-pharmaceutical agents (14.4%), 33 patients were poisoned with sedative-hypnotics (11.9%), 31 cases were exposed to pesticides (11.2%), 16 patients to antidepressant/ antipsychotic medication (5.8%).

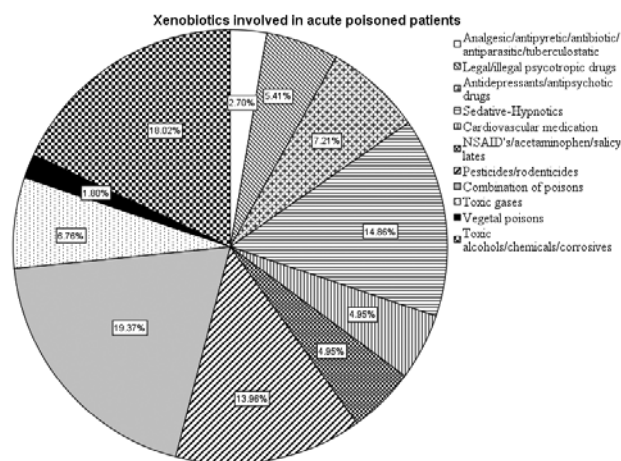


Figure 1. Xenobiotics involved in acute poisoning in cohort studied.

Characteristics	Total (n=222)	Survivors (n=212)	Non-survivors (n=10)	P
Age <sup>1</sup> (years)	41 (31-56)	41 (30.25-54.75)	59 (54.50-69.50)	.003
Male gender <sup>2</sup> (%)	50.9	48.6	2.3	.953
Ethanol <sup>1</sup> (mg/dL)	1 (1-79)	1 (1-82)	1.5 (1-16)	.599
PSS <sup>2</sup> (%)				<.001
Minor	35.2	35.2	0	
Moderate	39.4	38.5	0.9	
Severe	25.4	21.8	3.6	
Clinical signs (ED)				
GCS <sup>2</sup> ≤8 (%)	11.3	9	2.3	.002
HR <sup>1</sup> (bpm)	87 (73.75-100)	87 (75-100)	89.5 (57.75-107)	.754
SBP <sup>1</sup> (mmHg)	120 (109.25-139)	120 (109.25-139)	120 (109.25-139)	.031
DBP <sup>1</sup> (mmHg)	76 (67-83)	78 (70-83.5)	65 (40.5-81)	.053
Laboratory tests				
Hemoglobin <sup>1</sup> (g/dL)	13.70 (12.60-14.63)	13.70 (12.63-14.60)	13.95 (11.80-15.23)	.791
pH <sup>1</sup>	7.40 (7.35-7.43)	7.40 (7.36-7.43)	7.04 (6.80-7.24)	<.001
Creatinine <sup>1</sup> (mg/dL)	.76 (.68-0.91)	.76 (.68-.88)	1.11 (.86-1.24)	.002
ASAT <sup>1</sup> (U/L)	22 (17-37)	22 (17-35)	56.5 (30.5-93.5)	.001
Myoglobin <sup>1</sup> (ng/mL)	53.60 (36.70-107)	53 (35.95-90.45)	193 (46.71-542)	.008
Biomarkers				
ED-TnI <sup>1</sup> (ng/mL)	.007 (.001-.050)	.006 (.001-.050)	.040 (.010-.050)	.055
6h-TnI <sup>1</sup> (ng/mL)	.002 (.001-.008)	.002 (.001-.006)	.101 (.014-1.004)	<.001
ED-CKMB <sup>1</sup> (ng/mL)	10 (1.55-22)	11 (1.50-22)	6.45 (3.84-23.96)	.849
Outcomes				
Complications <sup>2</sup> (%)	47.2	37.98	9.52	<.001
Hospitalization <sup>1</sup> (days)	3 (2-5)	3 (2-5)	2.5 (1.75-6.75)	.767

<sup>1</sup> Data are presented as median (25–75 percentiles) and p value by Mann-Whitney test; <sup>2</sup> % within entire cohort and p value by Chi square proportion test.

There were 15 patients exposed to toxic gases, mainly carbon monoxide (5.4%), and 11 patients with cardiovascular drugs poisoning (4%). The rest of the cases were poisoning with OTC medication, or other prescription drugs (Figure 1), and only 4 patients had vegetal toxins exposure (1.4%). There were no significant differences in the outcomes based on the poison involved. Ethanol co-ingestion had no influence on the outcome or death.

Although there was a significant statistical difference in the age, PSS, GCS score of survivors versus non-survivors, these variables did not predict in-hospital mortality after multivariate logistic regression.

169 patients of the entire cohort (76.2%) developed complications, while 35 patients had multiple complications, involving at least two major organs or systems, and cardiovascular complications were recorded in 15.76 % patients. Patients with a poor outcome didn't have a significantly prolonged hospitalization (Table 1). Deaths were recorded in 10 patients (4.5%) in our cohort, as follows: 4 patients (1.8%) intoxicated with combinations of poisons, 3 patients exposed to toxic alcohols and chemicals (1.4%), one pesticide exposure, one toxic gas exposure, and one patient poisoned

with antidepressants. The direct cause of death was represented by multiple complications (dysrhythmias, toxic-induced myocardial injury, refractory shock, acute respiratory distress syndrome, and multiple organ failure).

There was no significant statistical difference in Tnl level within age and gender groups, while the mean initial levels of Tnl were higher in non-survivor group (Table 1) but didn't reach the statistical significance (p 0.55). Assessment of 6h-Tnl showed a significantly higher value in the fatalities group (Table 1).

When analyzing ECG, 40% subjects had an abnormal rhythm, while ST – T changes were seen in 36.8% patients and were predictive for a poor outcome (Table 2). There were no significant differences in PR interval, QRS complex width within the outcome groups, however the QTc interval was significantly prolonged in patients with the poor outcome (Table 2). There were no significant differences in the ECG parameters among poison groups.

At the time of the TTE, 8 subjects (3.6%) were in atrial fibrillation (Table 2). Alteration in both diastolic and systolic LV function, along with presence of LV regional or global wall abnormalities had a significant impact on the outcome (Table 2).

**Table 2. Selected ECG and TTE parameters in acute poisoning based on the outcomes**

Parameter	Total (n=222)	Favorable outcome (n=187)	Poor outcome (n=35)	p value
<b>ECG parameters</b>				
Rhythm (%)				0.03
Bradycardia	3.2	2.4	0.8	
Normal rhythm	60	56	4	
Tachycardia	31.2	23.2	8	
Paroxysmal AF	5.6	4	1.6	
ST-T pattern (%)				0.07
Normal	63.2	56	7.2	
Inverted T waves	10.4	8.8	1.6	
ST/T changes	16	10.4	5.6	
ST elevation	10.4	9	1.4	
PR interval (s) a,*	0.16 (0.14-0.20)	0.16 (0.14-0.20)	0.16 (0.16-0.20)	0.302
QRS width (s)*	0.08 (0.08-0.10)	0.08 (0.08-0.10)	0.09 (0.08-0.11)	0.214
QTc interval (ms)*	423.99 (366.48-461.88)	421.64 (363.65-461.88)	472.95 (420.53-602.32)	.044
<b>TTE parameters</b>				
LVEF (%) <sup>1</sup>	56 (49.5-60)	56 (50-61)	40 (32.5-49)	<.001
LVSF (%) <sup>1</sup>	28 (24-32)	28 (25-32)	20 (14.5-24)	<.001
EDT (ms) <sup>1</sup>	210 (179-234)	207.5 (178.25-229)	256 (236-270.5)	.001
E/A ratio a, <sup>1</sup>	1.14 (0.86-1.53)	1.18 (0.89-1.55)	0.80 (0.72-1.00)	.006
Kinetics (%) <sup>2</sup>				<.001
Global hypokinesia	23.2	14.4	8.8	
Segmental hypokinesia	4.8	4	0.8	
Normal kinetics	70.4	66.4	4	
Hyperkinesia	1.6	0.8	0.8	

<sup>1</sup> Data are presented as median (25–75 percentiles) and p value by Mann-Whitney test; <sup>2</sup> % within entire cohort and p value by Chi square proportion test; a, 8 patients were excluded from this analysis because of paroxysmal AF; AF, atrial fibrillation; ECG, electrocardiogram; ST-T, ST segment and T wave; TTE, transthoracic echocardiography; DT, deceleration time of the E wave; LVEF, left ventricle ejection fraction; LVSF, left ventricle shortening fraction.

**Table 3. Univariate and multivariate logistic regression analysis for selected significant variables associated with mortality in acute poisoning.**

Variable	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	p	OR	95% CI	p
Age	1.055	1.015-1.097	0.006	1.654	0.680-4.023	0.267
QTc interval	1.011	1.003-1.019	0.005	1.882	1.022-3.466	0.043
DT	1.026	1.009-1.043	0.002	3.653	1.460-9.137	0.006
6h-Tnl	7.775	1.799-33.602	0.006	1.752	1.201-2.558	0.004

OR, odds ratio; CI, confidence interval; BNP, brain natriuretic peptide; DT, E wave deceleration time; 6h-Tnl, troponin I detected 6 hours after the admission.

### Logistic regression analysis

After univariate logistic regression analysis, age, the QTc interval, DT and 6h-Tnl correlated with in-hospital mortality (Table 3). The multivariate logistic regression analysis including the same predictor variables showed that only the QTc interval (OR 1.882; CI 95%: 1.022-3.466; p 0.043), DT (OR 3.653; CI 95%: 1.460-9.137; p 0.006) and 6h-Tnl (OR 1.752; CI 95%: 1.201-2.558; p 0.004) are predictive for mortality in acute poisoning with different xenobiotics. The ROC analysis demonstrated two predictive variables to have a good discriminatory power for mortality (Figure 2).

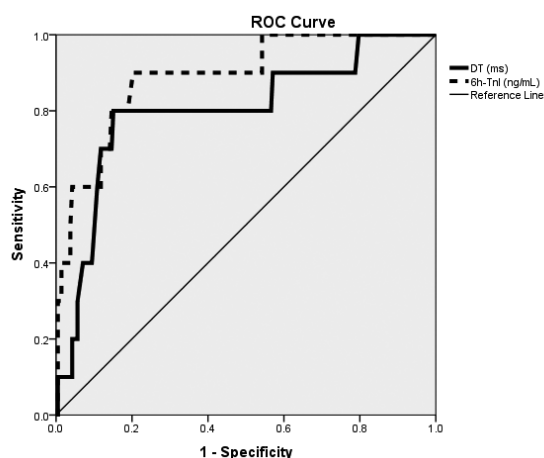
### DISCUSSION

This is the first study, to our knowledge, which prospectively and concomitantly correlates the Tnl levels upon arrival and 6 hours after admission in a medical or ICU ward with ECG parameters and TTE indices in a heterogeneous cohort of acutely poisoned patients admitted to a medical or ICU ward within 12 hours

of poison exposure. Despite a relatively small number of fatalities (10 patients, 4.5%), we observed a strong relationship between Tnl dynamic, and alteration in LV function evaluated using TTE with the risk of a poor outcome and death.

ECG changes were analyzed in different poison exposures<sup>3,5,13,24,25</sup>. Some studies demonstrated a correlation between the prolonged QT interval with cardiovascular events in patients with drug self-poisoning<sup>26</sup>, and with mortality, in herbicide poisoning<sup>11</sup>. A QTc interval greater than 500 ms was predictive for cardiotoxicity in antipsychotic overdose<sup>27</sup> and, along with QT interval dispersion, was proved to be an independent predictor of adverse cardiovascular events in a heterogeneous cohort of 34 patients with suspected poisoning involving different types of drugs, alcohols, and herbal/OTC medication<sup>16</sup>, also for cardiovascular complications in acute poisoning with cardiotoxic medication or poisons<sup>3</sup>. However, in methanol poisoning, abnormalities on the ECG suggestive for cardiotoxicity failed to predict mortality<sup>25</sup>. Our results based on a larger cohort of poisoned patients, with acute exposure to heterogeneous xenobiotics, showed that the prolonged QTc interval >472 ms is correlated with a poor outcome and increases by 88% the odds of in-hospital mortality. This observation is important, because in our cohort, the proportion of agents proved to determine QTc prolongation and subsequent death (i.e. cardiovascular drugs, antidepressants, antipsychotics, pesticides) was 26.2%, the rest being poisons that were not associated until now with QTc interval prolongation-induced mortality. Also, it is consistent with our previous results on patients acutely poisoned with a systemic toxin<sup>17</sup>.

Tnl is a biomarker with increased levels in pesticide poisoning<sup>13,28</sup>, and a negative Tnl on admission excludes fatality with an extremely high predictive value in undifferentiated patients with acute drug overdose<sup>12</sup>. Our results showed that in acute poisoning with he-



**Figure 2.** Receiver Operating Characteristic Curves validates the discriminatory power of the parameters predicting mortality. Areas under the curves: DT (E wave deceleration time): 0.801 (95% confidence interval 0.644-0.958, p 0.001); 6h-Tnl (troponin detected 6 hours after admission): 0.889 (95 % confidence interval 0.789-0.990, p<0.001).

terogeneous toxins, initial elevated Tnl, but mainly elevation of 6-h Tnl as a consequence of acute myocardial injury, is a biomarker predictive for a poor outcome and shows a 74% increased risk for in-hospital mortality in this setting. This is an interesting observation, mainly because we tried to include in our study patients without the comorbidities which could be associated with an increased troponin level<sup>29</sup>.

The possible mechanisms involved in acute poisoning complicated with myocardial injury might be the imbalance between the oxygen supply (decreased in CO exposure, after coronary vasospasm or toxin induced dysrhythmias or hypotension) and increased myocardial oxygen demands (in febrile patients such as neuroleptic poisoning, hypertension occurring in stimulants acute poisoning etc.), or as a consequence of direct myocardial cell death after inhibition of oxidative phosphorylation<sup>12,30,31</sup>.

Echocardiography showed a better accuracy, as opposed to ECG changes, in detecting CO-induced cardiac damage, where changes in diastolic function, preceding systolic function abnormalities<sup>32</sup>, or various patterns of LV systolic dysfunction were observed<sup>32-34</sup>. Our previous experience with TTE in acute poisoned non-diabetic patients proved that assessment of diastolic function correlated with BNP level are useful to predict mortality<sup>18</sup>.

The results obtained in this cohort of acutely poisoned patients showed that the assessment, using TTE upon admission in a medical or ICU ward, of cardiac function parameters, especially the diastolic function of the LV, accurately predicted the risk for a poor outcome and death in this setting, showing 2.65 times increased odds of mortality. We hypothesize that a prolonged DT may reflect the poison-induced subclinical heart damage, or the setting of acute myocardial injury, being recognized that diastolic dysfunction is a feature that precedes systolic dysfunction<sup>32,33</sup>. Although several changes in systolic function were observed in the analyzed cohort, they failed to significantly correlate with in-hospital mortality, possibly because of a relatively low prevalence of recognized cardiotoxins in our cohort.

To the best of our knowledge, this is the largest study to prospectively demonstrate the utility of troponin, combined with ECG and TTE parameters as markers of acute myocardial injury to predict, upon admission in a medical or ICU ward, the risk of a poor outcome and in-hospital death for acutely poisoned patients with different xenobiotics.

## Limitations

The main limitation of the study may be that too few patients died during hospitalization to deliver reliable statistical data about in-hospital mortality. A larger sample was not available for this analysis given the constraints applied from the exclusion criteria, to avoid bias from co-morbidities in the cardiovascular biomarkers, ECG and echocardiography analysis. We could not calibrate the influence of toxin serum concentration, and we could not monitor all patients at least 30 days after the acute poisoning. Future prospective studies are warranted to confirm and further explore the implications of toxin-induced acute myocardial injury in every patient admitted with an acute poisoning in a medical or ICU ward.

## CONCLUSIONS

In acutely poisoned adult patients, assessment of myocardial injury using initial and 6h-Tnl, the QTc interval on initial ECG and the parameters of LV diastolic function obtained using TTE upon admission in a medical or ICU ward accurately predicted the outcomes and mortality. As Tnl, ECG, and TTE are routinely used and not expensive, are less invasive, and are widely available, they can be successfully applied in everyday practice as part of the initial evaluation of acutely poisoned patients with different xenobiotics, to assess their outcomes. They may help hospital practitioners to improve the management of these poisonings and to early address the worst outcome and mortality.

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**Conflict of interest:** none declared.

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