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Toxicology Reports

Development of a risk-prediction nomogram for in-hospital adverse cardiovascular events in acute cardiotoxic agents poisoning

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ARTICLE INFO

ABSTRACT

Adverse cardiovascular events (ACVE) are serious sequelae of acute poisoning with cardiotoxic agents. They include shock, acute myocardial injury, ventricular dysrhythmias, and cardiac arrest. Early identification of high-risk patients could improve their prognosis. Therefore, this study developed a risk-prediction nomogram to assess the risk of ACVE in patients with acute cardiotoxicities. This prospective cohort study was conducted at Tanta University Poison Control Center, Tanta, Egypt, from April 2023 to March 2024. It included 186 patients with acute cardiotoxic agent poisoning. ACVE occurred in 36 % of patients and were significantly associated with ICU admission and mortality ($P<0.001$). A multivariable logistic regression model was generated that included six significant predictors; modified shock index (AOR of 6.431, 95 % CI: 1.361–30.398, $P = 0.02$), serum bicarbonate level (AOR of 0.747, 95 % CI: 0.661–0.843, $P = 0.001$), oxygen saturation (AOR of 0.867, 95 % CI: 0.810–0.929, $P = 0.001$), ST segment changes (AOR of 9.196, 95 % CI: 1.989–42.508, $P = 0.011$), prolonged QTc (AOR of 3.015, 95 % CI: 0.975–9.325, $P = 0.044$), and QRS width (AOR of 1.032, 95 % CI: 1.001–1.064, $P = 0.009$). The nomogram was statistically significant ($P <0.001$) and could predict ACVE with 89.2 % accuracy. A Receiver Operating Characteristics analysis was conducted to ensure the nomogram's discrimination ability (Area under the curve =0.956). Also, the calibration curve was drawn using the bootstrapping method to ensure the nomogram's internal validity. The current study provided an easily applicable nomogram that could accurately predict ACVE following acute cardiotoxicities, regardless of the causative agent.

1. Introduction

Acute poisoning is responsible for high morbidities and mortalities worldwide. To date, acute poisoning is one of the leading causes of cardiac arrest at a young age. Thus, cardiotoxic agents that exhibit serious cardiovascular effects have gained attention in the last few years [1,2]. In this context, numerous pharmaceutical and non-pharmaceutical compounds exert their cardiotoxic effects through different mechanisms [3].

Cardiotoxic agents could promote cardiac arrhythmia due to the affection of the autonomic nervous system, disruption of ion channels, or interference with the cardiac conduction system. Also, some cardiotoxic agents could impair myocardial perfusion and induce coronary vasoconstriction. Diminished myocardial perfusion ultimately results in myocardial ischemia [3,4]. Additionally, certain cardiotoxic agents interfere with the normal functions of cardiomyocytes through the

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induction of oxidative stress, mitochondrial dysfunction, or disruption of intracellular calcium homeostasis. Altogether, these mechanisms denote the multifaceted ways through which the cardiotoxic agents exert their toxic effects on the cardiovascular system [5,6].

Adverse cardiovascular events (ACVE) include shock, acute myocardial injury, ventricular dysrhythmias, and cardiac arrest. ACVE could be associated with high mortality. Thus, the relationship between ACVE and cardiovascular diseases has been investigated [7]. From a clinical toxicology perspective, ACVE might take place following acute poisoning with cardiotoxic agents. Hence, early identification of high-risk patients likely to develop ACVE could improve their prognosis [8]. Yet, Manini et al. predicted ACVE following acute drug overdose in adult patients [9]. Whereas Carreiro et al. identified the ACVE predictors in children following acute drug poisoning [10]. Both Manini et al. [9] and Carreiro et al. [10] were concerned only with the cardiotoxicity of pharmaceutical agents only. While El-Sarnagawy et al. pointed to QT as a valuable parameter that could predict ACVE among adult patients who suffered from cardiotoxicity following exposure to pharmaceutical and non-pharmaceutical agents [8].

Risk-prediction nomograms are predictive multivariable regression models that govern healthcare providers' decisions in clinical situations. They represent graphical calculators that display the adopted statistical models, allowing direct calculation of outcome probabilities. The length of each scale in the nomogram denotes the importance of each parameter in outcome prediction [11]

In the last few years, nomograms have emerged as valuable predictive tools in clinical toxicology for anticipating intensive care unit (ICU) admission [12], need for mechanical ventilation [13] and mortality [14] among intoxicated patients. Nomograms have also been developed to predict the outcome of particular poisonings, such as clozapine [15] and carbon monoxide [16]. To date, no model could accurately predict ACVE among patients suffering from cardiotoxicity due to exposure to pharmaceutical and non-pharmaceutical agents. Thus, the current study aimed to generate a risk-prediction nomogram to assess the risk of ACVE in patients with acute cardiotoxicities.

2. Patients and methods

2.1. Study design, setting, and duration

This prospective cohort study was carried out at Tanta University Poison Control Center (TUPCC), Emergency Hospital, Tanta University. The study was conducted from April 2023 to March 2024. The TUPCC is a tertiary poison control centre located in the Delta region that offers emergency and supportive management, followed by in-patient care to all acutely poisoned patients in EL-Gharbia and neighbouring governorates [17].

2.2. Ethical considerations

This study was conducted in compliance with the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Research Ethics Committee, Faculty of Medicine, Tanta University (Approval Code: FWA00022834, IRB0010038, 36264PR175/4/23). After describing the study's aim, written informed consent was obtained from all eligible patients. To ensure confidentiality, all patients' data was coded and anonymously analyzed. The study reporting followed the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) for prediction model development [18].

2.3. Sample size

We calculated the sample size based on the construction of a risk stratification model for ACVE following acute cardiotoxic agents poisoning. The calculation was performed using the equation that was recommended by Peduzzi et al. [19] for a minimum number of cases to conduct logistic regression analysis: N = 10 k / p, where k is the number of independent variables, and p is the smallest proportion of positive or negative cases in the study population.

The regression model for ACVE prediction was assumed to include, at maximum, six independent variables. The proportion of ACVE following acute cardiotoxic agents poisoning in the Egyptian population is nearly 0.37 [8]. Therefore, the minimum sample size was N = 10 ×6 / 0.37. Additionally, 15 % of the calculated sample size was added to compensate for incomplete data. So, the final required sample size was 186.

2.4. Inclusion criteria

The study included patients aged 18 years or older of both genders presented to the TUPCC with acute cardiotoxicities. The cardiotoxic agents are any drug or substance that could induce cardiac rhythm disturbance, myocardial impairment, thromboembolism, or affecting blood pressure [20]. According to the International Classification of Disease, 10th revision (ICD-10), we included and coded acute poisoning with drugs and substances that were associated with cardiotoxic effects [21].

2.5. Exclusion criteria

We excluded patients who gave a history of exposure to drugs or poisons other than the cardiotoxic agents, chronic pathological conditions (e.g., cardiac, respiratory, hepatic, or renal diseases), rhythm disorders, and/or those treated with medications that could affect the cardiac conduction system Further, patients with incomplete data, transferrable patients, and those who received any medical intervention before admission to the TUPCC were not included in the study, as illustrated in Fig. (1).

The diagnosis of the included patients was based on the history of cardiotoxic drug or poison exposure, the presence of characteristic clinical manifestations, recognition of the substances/container, and available investigations [3]. Acute poisonings with aluminum phosphide (AlP), cholinesterase inhibitor insecticides, theophylline, and digoxin were confirmed by silver nitrate test, serum pseudocholinesterase levels, serum theophylline concentration, and serum digoxin concentrations, respectively. Also, qualitative urine screening was conducted for illicit drugs such as opioids, benzodiazepines, or barbiturates using the ACON® DOA™ kits [22].

2.6. Data collection

The extracted variables included demographic data (gender and age), poisoning data (type of the drug or poison and circumstances of poisoning), delay time, the first attained values of the vital signs (pulse rate, blood pressure, respiratory rate, and temperature) that were assessed according to reference ranges. We calculated the mean arterial pressure (MAP), shock index (SI) (heart rate/systolic blood pressure (SBP)), and the modified shock index (MSI) (heart rate/MAP). Also, the Glasgow Coma Scale (GCS) and oxygen saturation (%) were documented on admission as assessed by the attending toxicologist. Arterial blood gases (ABG), in addition to serum sodium and potassium levels, were recorded.

Furthermore, a twelve-lead electrocardiogram (ECG) was recorded on admission for all patients as clinically indicated according to the standard of care [6]. Each ECG was interpreted by two cardiologists blinded to the study hypothesis, the clinical condition of patients, and whether ACVE occurred. For this purpose, unidentified copies of the initial ECG and a standard ECG interpretation form were used. The initial ECG patterns were examined according to the Lausanne criteria for ECG evaluation that the European Society of Cardiology recommended. ECGs were analyzed for rhythm, axis, intervals, QRS duration,
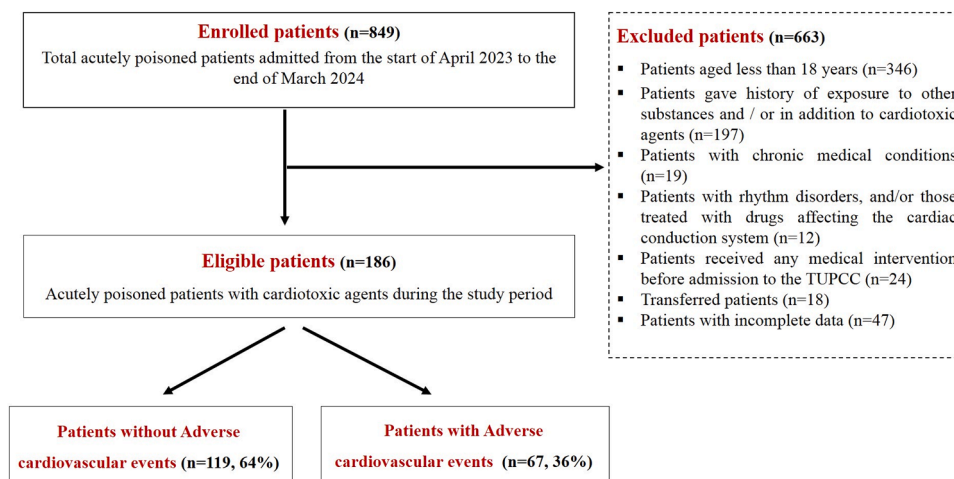
Fig. 1. Flow chart for the included patients and their outcomes.

and the presence of any conduction abnormalities, atrial/ventricular dysrhythmias, or ischemic changes, including ST changes (elevation or depression), T wave changes, pathological Q wave, and poor R wave progression. Also, Bazett's corrected QT (QTc) interval ($QT/RR^{1/2}$) was calculated, and QTc >440 msec in males or >460 msec in females was considered prolonged QTc [6,23,24].

Additionally, P-wave dispersion (PWD) was recorded, which represents the difference between the minimum and the maximum P-wave duration measured from multiple different-surface ECG leads [25]. Corrected QT dispersion (QTdc) was also calculated as the difference between the shortest and the longest QTc intervals in the 12-lead ECG [8].

2.7. Treatment

The patients received medical care according to the TUPCC protocol, including emergency and supportive therapies, appropriate decontamination measures, and specific antidotes as indicated. Atropine and oximes were used for acute organophosphorus poisoning, digibind for digitalis poisoning, and naloxone for opioid overdose. Patients were admitted to the ICU for hemodynamic stabilization, breathing support, mechanical ventilation, or adequate care of comatose patients.

2.8. Outcomes

Adverse cardiovascular events (ACVE) were the primary outcome of this study. ACVE were the occurrence of one of the following events: shock (hypotension with the need for vasopressors), myocardial injury based on the increased serum cardiac troponin in one measurement> 0.10 ng/mL, ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation), and cardiac arrest (pulse collapse that necessitate cardiopulmonary resuscitation) [26,27]. Moreover, the need for ICU admission and in-hospital mortality were documented.

2.9. Statistical analysis

The data were analyzed using the statistical package for the social sciences software program IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, N.Y., USA). The inter-rater reliability for ECG interpretation was assessed by calculating Cohen's kappa statistics. The categorical data were presented as frequencies and percentages. The possible associations between categorical variables were analyzed using Pearson's Chi-square test. Alternatively, the Fishers' Exact test was applied when more than 20 % of cells had expected counts of less than 5. For continuous data, the normality was tested using the Shapiro–Wilk test. Normally distributed data were analyzed by the independent t-test

and denoted as mean± standard deviation (SD). Meanwhile, the Mann–Whitney *U* test was used to compare the skewed data, which were expressed as the median and interquartile range (IQR) (25th–75th percentiles). Variables that had a significant association ($P < 0.05$) in the univariate analysis were entered in a multivariable binary logistic regression analysis (Forward conditional method) for developing a prediction model for the ACVE. Some of these variables were not considered predictors in regression analysis because of multicollinearity. The default probability for stepwise at 0.05 for entry and 0.10 for removal of predictors were kept while performing the regression analysis. Finally, STATA/SE 16.0 and the nomogram program were used to create a graphical calculator known as a nomogram. A Kattan-style nomogram suitable for binary logistic regression predictive models was implemented [28]. We also evaluated the discrimination power of the predictors that significantly contributed to the prediction model by the receiver operating characteristics (ROC) curve analysis.

2.9.1. Internal validation

The developed model was subjected to internal validation via the bootstrapping method for 1000 samples replicated from the derivation data set to obtain bias-corrected and accelerated confidence intervals to avoid overfitting. The optimism estimate was calculated as an average of the coefficients (B) differences from bootstrapping results. Additionally, the optimism-adjusted discrimination (area under the curve [AUC]) and calibration (Hosmer and Lemeshow fit test) were calculated by subtracting the optimism estimate from their values.

3. Results

The current work enrolled 186 acutely poisoned adult patients with acute cardiotoxic agents. It was found that 36 % of all studied patients developed ACVE. They included shock, cardiac arrest, VT/VF, and myocardial injury, which represented 29.6 %, 28.5 %, 11.3 %, and 7 % of all included patients, respectively. Cohen's kappa statistics revealed excellent inter-rater agreement (k= 0.95).

Table (1) reveals that the studied patients were nearly equally distributed between both genders. The median age of the patients with acute cardiotoxic agent poisoning was 23 years, with no significant difference in age medians between patients with ACVE and others. More than half (55.4 %) of patients aged less than 25 years. Regarding the type of exposure, poisoning with non-drug agents was significantly higher among patients who developed ACVE (P <0.001). Aluminum phosphide (32.3 %), cholinesterase inhibitors pesticides (18.8 %), and CNS drugs (14.5 %) were the most common poison classes among enrolled cases.

Regarding patients with ACVE, AlP (71.6 %) was the most common

Table 1
Demographic and toxicological characteristics of the studied patients with acute cardiotoxic agents poisoning.

Variables		Adverse Cardiovascular Events		Total (n=186)	P- Value
		No (n=119, 64 %)	Yes (n=67, 36 %)		
Age (years)	Median (IQR)	24 (19–32)	20 (19–30)	23 (19–31)	0.431
Age groups	18-<25 years	63 (52.9 %)	40 (59.7 %)	103 (55.4 %)	0.825
	25-<35 years	29 (24.4 %)	14 (20.9 %)	43 (23.1 %)	
	35-<45 years	14 (11.8 %)	6 (9 %)	20 (10.8 %)	
	≥45 years	13 (10.9 %)	7 (10.4 %)	20 (10.8 %)	
Gender	Male	51 (42.9 %)	28 (41.8 %)	79 (42.5 %)	0.888
	Female	68 (57.1 %)	39 (58.2 %)	107 (57.5 %)	
Type of toxic exposure	Non-drug	68 (57.1 %)	62 (92.5 %)	130 (69.9 %)	<0.001*
	Drug	51 (42.9 %)	5 (7.5 %)	56 (30.1 %)	
Classes of cardiotoxic agents	Aluminum phosphide	12 (10.1 %)	48 (71.6 %)	60 (32.3 %)	<0.001*
	Cholinesterase inhibitors	27 (22.7 %)	8 (11.9 %)	35 (18.8 %)	
	CNS drugs[a]	27 (22.7 %)	0 (0 %)	27 (14.5 %)	
	Cardiovascular drugs	17 (14.3 %)	3 (4.5 %)	20 (10.8 %)	
	Zinc phosphide	15 (12.6 %)	3 (4.5 %)	18 (9.7 %)	
	Carbon monoxide	13 (10.9 %)	2 (3 %)	15 (8.1 %)	
	Methyl xanthines	4 (3.4 %)	2 (3 %)	6 (3.2 %)	
	Miscellaneous	4 (3.4 %)	1 (1.5 %)	5 (2.7 %)	
Alleged manner of poisoning	Suicidal	81 (68.1 %)	63 (94 %)	144 (77.4 %)	<0.001*
	Accidental	33 (27.7 %)	4 (6 %)	37 (19.9 %)	
	Abuse	5 (4.2 %)	0 (0 %)	5 (2.7 %)	
Delay (hours)	Median (IQR)	3 (1.5–5)	2 (1.5–5)	3 (1.5–5)	0.551

n: number, IQR: interquartile range, CNS: central nervous system

[a] CNS drugs included drugs coded T40, T42 and T43 according to International Classification of Disease, 10th revision (ICD-10).

* Significant at $P<0.05$.

poison. Nevertheless, cholinesterase inhibitors pesticides, and CNS drugs were the most common poison classes among those who did not develop ACVE (22.7 % for each). It was found that the classes of cardiotoxic agents were significantly different between the two patient groups ($P <0.001$). Regarding the manner of exposure, 77.4 % of the studied cases were intentionally exposed to cardiotoxic agents. It is observed that a significantly higher percentage of those who developed ACVE had suicidal intent compared with those who did not develop ACVE (94 % versus 68.1 %) ($P <0.001$).

Table (2) shows that nearly all mean or median values of clinical and laboratory parameters on admission were significantly worse among patients with ACVE than other patients who did not develop ACVE (P values <0.05). These parameters were GCS, vital signs along with related indices (pulse, SBP. DBP, MAP, respiratory rate, temperature, SI, and MSI), ABG parameters (pH, PaCO₂, HCO₃), oxygen saturation, and serum potassium level. In addition, it was observed that significant portions of patients with ACVE had severe GCS, bradycardia, tachypnea, hypothermia, metabolic acidosis, and abnormal sodium levels (P values <0.05).

Table (3) illustrates that ECG abnormalities were observed in 36 % of the studied patients. It was observed that a significantly higher percentage of patients with ACVE had ECG abnormalities compared with patients who did not develop ACVE (58.2 % versus 23.5 %), with P <0.001.

As regards ST segment and QTc interval, a significantly higher percentage of patients with ST-segment changes had a higher rate of ACVE (versus 22.4 % versus 5.9 %), with $P <0.001$. Also, a significantly higher percentage of patients with prolonged QTc interval had ACVE than others (74.6 % versus 47.1 %), with $P <0.001$. The median QTc interval was significantly longer among patients with ACVE than other patients (464.8 msec versus 447.2 msec), with $P = 0.003$. Considering the QRS complex, the median of QRS width was significantly longer among patients who developed ACVE than patients who did not develop ACVE (80 msec versus 60 msec), with $P <0.001$.

Regarding rhythm and conduction abnormalities, non-sinus rhythm was significantly prevalent among those who developed ACVE (34.3 % versus 0.8 %). Among patients with ACVE AF, ventricular ectopy and SVT were detected in 25.4 %, 20.9 %, and 4.5 % of patients,

respectively. None of these ECG abnormalities were recorded among those who did not develop ACVE (P values <0.05). On the other hand, there was no significant association between ACVE and other ECG abnormalities, including PWD, pathological Q wave, poor R wave progression, T wave changes, QTdc, axis, PR interval, and atrial ectopy (P values > 0.05).

The secondary analysis of ECG parameters in relation to each ACVE was provided in the supplemental Table (1).

Considering ICU admission, 80 out of 186 patients were admitted to ICU, representing 43 % of included cases. The development of ACVE was significantly associated with the need for ICU admission ($P <0.001$), as 98.5 % of patients who developed ACVE were admitted to ICU. In comparison, only 11.8 % of patients who did not develop ACVE were admitted to ICU.

Regarding mortality, 54 patients, who constituted 29 % of enrolled cases, died, and all of them suffered from ACVE. Thus, ACVE was significantly associated with the fatal outcome among patients with acute cardiotoxic agent poisoning ($P<0.001$).

Table (4) describes a multivariable logistic regression analysis that generated the predictive model for the probability of ACVE following acute poisoning with cardiotoxic agents. After adjusting for MSI, serum HCO₃ level, O₂ saturation, ST segment changes, prolonged QTc interval, and QRS width, the adjusted odds ratio (AOR) of the probability of ACVE increased significantly by about 6.431-fold for each one-unit increase in MSI of patients acutely poisoned with cardiotoxic agents (AOR of 6.431, 95 % CI: 1.361–30.398, $P = 0.02$). Moreover, the AOR increased significantly by about 9.196, 3.015 and 1.032 folds for each one-unit increase in the incidence of occurrence of ST segment changes, prolonged QTc interval, and QRS width, respectively (AOR = 9.196, 3.015 and 1.032, 95 % CI: 1.989–42.508, 0.975–9.325 and 1.001–1.064, $P = 0.011, 0.044$ and 0.009, respectively). While the AOR of the probability of ACVE following acute poisoning with cardiotoxic agents decreased significantly by about 0.747 and 0.867 for each unit increase in serum HCO₃ level and O₂ saturation, respectively (AOR = 0.747 and 0.867, 95 % CI: 0.661–0.843 and 0.810–0.929 respectively, $P = 0.001$ for each).

The performance of the quantitative predictors of ACVE in acutely poisoned patients with cardiotoxic agents was assessed using ROC

Table 2

Initial clinical and laboratory assessments of the studied patients with acute cardiotoxic agents poisoning.

Variables		Adverse Cardiovascular Events		Total (n=186)	P- Value
		No (n=119, 64 %)	Yes (n=67, 36 %)		
GCS	Median (IQR)	15 (15−15)	15 (14−15)	15 (15−15)	0.011*
Level of consciousness according to GCS	13–15	114 (95.8 %)	54 (80.6 %)	168 (90.3 %)	<0.001*
	9–12	3 (2.5 %)	2 (3 %)	5 (2.7 %)	
	3–8	2 (1.7 %)	11 (16.4 %)	13 (7 %)	
Pulse (beats /minute)	Mean± SD	96±24.4	81±34.1	90±29	0.004*
Pulse changes	Normal	50 (42 %)	16 (23.9 %)	66 (35.5 %)	0.002*
	Bradycardia	17 (14.3 %)	23 (34.3 %)	40 (21.5 %)	
	Tachycardia	52 (43.7 %)	28 (41.8 %)	80 (43 %)	
SBP (mmHg)	Mean± SD	118.2 ±15.6	81.3±35.1	104.9±30.1	<0.001*
DBP (mmHg)	Mean± SD	71.1±11.7	46.5±23.6	62.3±20.7	<0.001*
MAP (mmHg)	Mean± SD	86.8±11.9	58.1±27.1	76.5±23.3	<0.001*
Shock index	Mean± SD	0.81±0.23	1.04±0.3	0.9±0.28	<0.001*
Modified shock index	Mean± SD	1.11±0.32	1.51±0.49	1.26±0.43	<0.001*
Blood pressure changes	Normal	99 (83.2 %)	19 (28.4 %)	118 (63.4 %)	<0.001*
	Hypotensive	8 (6.7 %)	44 (65.7 %)	52 (28 %)	
	Hypertensive	12 (10.1 %)	4 (6 %)	16 (8.6 %)	
Respiratory rate (breaths /minute)	Mean± SD	19.6±3.24	25.75±7.33	22.38±6.27	<0.001*
Respiratory rate changes	Normal	99 (83.2 %)	21 (31.3 %)	120 (64.5 %)	<0.001*
	Bradypnea	7 (5.9 %)	3 (4.5 %)	10 (5.4 %)	
	Tachypnea	13 (10.9 %)	43 (64.2 %)	56 (30.1 %)	
Temperature (°C)	Mean± SD	37±0.3	36.9±0.4	37±0.4	<0.001*
Temperature changes	Normal	104 (87.4 %)	49 (73.1 %)	153 (82.3 %)	0.001*
	Hypothermia	6 (5 %)	15 (22.4 %)	21 (11.3 %)	
	Hyperthermia	9 (7.6 %)	3 (4.5 %)	12 (6.5 %)	
pH	Mean± SD	7.41±0.06	7.32±0.12	7.38±0.1	<0.001*
P$_a$CO$_2$ (mmHg)	Mean± SD	36.6±6.8	27.5±10.2	33.3±9.3	<0.001*
Serum HCO$_3$ levels (mmol/L)	Mean± SD	23.6±3.8	15.2±6.3	20.6±6.3	<0.001*
Acid base disturbances	Metabolic acidosis	6 (5 %)	42 (62.7 %)	48 (25.8 %)	<0.001*
	Metabolic alkalosis	12 (10.1 %)	1 (1.5 %)	13 (7 %)	
	Normal	76 (63.9 %)	12 (17.9 %)	88 (47.3 %)	
	Respiratory acidosis	7 (5.9 %)	4 (6 %)	11 (5.9 %)	
	Respiratory alkalosis	18 (15.1 %)	8 (11.9 %)	26 (14 %)	
Oxygen saturation (%)	Median (IQR)	98 (97−99)	92 (79−97)	97 (94−98)	<0.001*
Serum sodium levels (mmol/L)	Mean± SD	141.9±4.3	142.1±5.8	142±4.9	0.807
Sodium levels changes	Normal	87 (73.1 %)	37 (55.2 %)	124 (66.7 %)	0.017*
	Hyponatremia	5 (4.2 %)	9 (13.4 %)	14 (7.5 %)	
	Hypernatremia	27 (22.7 %)	21 (31.3 %)	48 (25.8 %)	
Serum potassium levels (mmol/L)	Mean± SD	3.9±0.6	3.7±0.5	3.8±0.6	0.009*
Potassium levels changes	Normal	89 (74.8 %)	44 (65.7 %)	133 (71.5 %)	0.132
	Hypokalemia	27 (22.7 %)	23 (34.3 %)	50 (26.9 %)	
	Hyperkalemia	3 (2.5 %)	0 (0 %)	3 (1.6 %)	

n: number, SD: standard deviation, IQR: interquartile range, GCS: Glasgow Coma Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, PaCO2: partial arterial carbon dioxide pressure, HCO3: bicarbonate

* Significant at $P <0.05$.

analysis. Serum HCO$_3$ has the highest discriminatory power (AUC = 0.865), followed by oxygen saturation and MSI (AUCs = 0.801 and 0.758, respectively). Meanwhile, QRS width exhibited the least discriminatory power in predicting ACVE (AUC = 0.664), as shown in Table (5).

Fig. (2) illustrates the six parameters-nomogram for predicting the probability of ACVE in patients with cardiotoxic agent poisoning. Fig. (3) demonstrates how to apply actual data of acutely poisoned patient with cardiotoxic agent to the adopted nomogram to estimate the patient's probability of developing ACVE. The nomogram was composed of three types of scales (score, total, and probability scales). The following steps should be done to determine the probability of ACVE for each patient. First, mark the patient's actual value for each predictor on its specific scale. Second, draw imaginary perpendicular lines from these marks downwards to determine the corresponding score of each predictor. Third, the total score is calculated, and then an imaginary vertical line is drawn upwards to the corresponding point on the probability scale, indicating the likelihood of ACVE development in this patient.

The nomogram was subjected to internal validation; the adjusted AUC was 0.876, and the Hosmer and Lemeshow fit test was 0.283 (Table 4). Also, ROC analysis was carried out to ensure the nomogram's discrimination ability. The nomogram's AUC was 0.956 (Fig. 4A), which

is higher than the AUC of the predictors constituting the adopted model individually. To ensure internal nomogram validity, we conducted the calibration curve for the predicted probability corresponding to the actual occurrence of ACVE. The bootstrapping method compared the observed and predicted probabilities and was presented as a calibration curve. The diagonal line represents the ideal performance of the model, while the dotted line represents the actual nomogram performance (Fig. 4B).

4. Discussion

Acute cardiotoxicities are among the most serious and potentially lethal conditions in clinical toxicology. ACVE are alarms denoting that cardiotoxicity might end with patient death [10,20]. Early identification of high-risk patients following exposure to cardiotoxic agents contributes to improving their outcomes. Thus, this study aimed to develop an accurate predictive nomogram for ACVE that could be easily applied in a clinical setting.

The study enrolled 186 patients acutely poisoned with cardiotoxic agents. It was observed that 36 % of patients developed ACVE, which was a much higher percentage than reported by Manini et al. [9] and Manini et al. [29], who reported ACVE among 5.3 % and 16.12 % of

Table 3

Initial electrocardiogram findings of the studied patients with acute cardiotoxic agents poisoning.

Variables		Adverse Cardiovascular Events		Total (n=186)	P- Value
		No (n=119, 64 %)	Yes (n=67, 36 %)		
ECG abnormalities	No	91 (76.5 %)	28 (41.8 %)	119 (64 %)	<0.001*
	Yes	28 (23.5 %)	39 (58.2 %)	67 (36 %)	
PWD (msec)	Median (IQR)	40 (20−40)	40 (20−40)	40 (20−40)	0.969
QRS width (msec)	Median (IQR)	60 (40−80)	80 (60−80)	60 (50−80)	<0.001*
Pathological Q wave	No	113 (95 %)	66 (98.5 %)	179 (96.2 %)	0.425
	Yes	6 (5 %)	1 (1.5 %)	7 (3.8 %)	
Poor R wave progression	No	119 (100 %)	65 (97 %)	184 (98.9 %)	0.203
	Yes	0 (0 %)	2 (3 %)	2 (1.1 %)	
ST segment changes	No	112 (94.1 %)	52 (77.6 %)	164 (88.2 %)	<0.001*
	Yes	7 (5.9 %)	15 (22.4 %)	22 (11.8 %)	
T wave changes	No	115 (96.6 %)	61 (91 %)	176 (94.6 %)	0.172
	Yes	4 (3.4 %)	6 (9 %)	10 (5.4 %)	
QTc (msec)	Median (IQR)	447.2 (402.5−465)	464.8 (413−535)	452.5 (402.5−491.9)	0.003*
Prolonged QTc	No	63 (52.9 %)	17 (25.4 %)	80 (43 %)	<0.001*
	Yes	56 (47.1 %)	50 (74.6 %)	106 (57 %)	
QTdc (msec)	Median (IQR)	45 (40−51.8)	49.9 (40−54)	45 (40−51.8)	0.263
Axis	Normal	94 (79 %)	56 (83.6 %)	150 (80.6 %)	0.554
	Left axis	15 (12.6 %)	5 (7.5 %)	20 (10.8 %)	
	Right axis	10 (8.4 %)	6 (9 %)	16 (8.6 %)	
Rhythm	Sinus rhythm	118 (99.2 %)	44 (65.7 %)	162 (87.1 %)	<0.001*
	Non-sinus rhythm	1 (0.8 %)	23 (34.3 %)	24 (12.9 %)	
PR interval (msec)	Median (IQR)	160 (130−160)	160 (120−160)	160 (120−160)	0.832
AF	No	119 (100 %)	50 (74.6 %)	169 (90.9 %)	<0.001*
	Yes	0 (0 %)	17 (25.4 %)	17 (9.1 %)	
SVT	No	119 (100 %)	64 (95.5 %)	183 (98.4 %)	0.045*
	Yes	0 (0 %)	3 (4.5 %)	3 (1.6 %)	
Atrial ectopy	No	116 (97.5 %)	62 (92.5 %)	178 (95.7 %)	0.139
	Yes	3 (2.5 %)	5 (7.5 %)	8 (4.3 %)	
Ventricular ectopy	No	119 (100 %)	53 (79.1 %)	172 (92.5 %)	<0.001*
	Yes	0 (0 %)	14 (20.9 %)	14 (7.5 %)	

n: number, IQR: interquartile range, ECG: electrocardiogram, msec: millisecond, QTc: corrected QT interval, QTdc: corrected QT dispersion, AF: atrial fibrillation, SVT: supraventricular tachycardia, PWD: P-wave dispersion

* Significant at $P<0.05$.

Table 4

Development and internal validation of a prediction model for adverse cardiovascular events following acute poisoning with cardiotoxic agents by multivariable logistic regression analysis.

Variables	Beta coefficient	P-Value	AOR	95 % CI AOR	BCa 95 % CI
Modified shock index	1.861	0.020*	6.431	1.361–30.398	0.332–4.228
Serum HCO₃ level (mmol/L)	−0.292	0.001*	0.747	0.661–0.843	(−0.512)-(−0.172)
Oxygen saturation (%)	−0.142	0.001*	0.867	0.810–0.929	(−0.337)-(−0.091)
ST segment changes	2.219	0.011*	9.196	1.989–42.508	272–5.073
Prolonged QTc	1.104	0.044*	3.015	0.975–9.325	(−0.098)−2.613
QRS width (msec)	0.032	0.009*	1.032	1.001–1.064	0.007–0.066
Constant	13.134	0.003*			
P-value of the model: <0.001*					
Nagelkerke R²: 74.3 %					
Accuracy: 89.2 %					
AUC (95 % CI): 0.956 (0.931–0.981)					
Adjusted AUC: 0.876					
Hosmer and Lemeshow fit test: 0.283					
Adjusted Hosmer and Lemeshow fit test: 0.203					

AOR: adjusted odds ratio, CI: confident interval, AUC: area under the curve, BCa: bias-corrected accelerated, HCO₃: bicarbonate, QTc: corrected QT interval, msec: millisecond

* Significant at $P<0.05$.

their patients following an acute drug overdose, respectively. The high percentage of ACVE among our cases could be explained by focusing the present work on patients acutely poisoned with cardiotoxic agents rather than including any poisoned patients; in addition, the spectrum of the current study extended to include drugs and non-drugs that have cardiotoxic effects, rather than being restricted to pharmaceutical agents.

In the present work, more than half of the included patients were under 25, and more than three-quarters of patients were exposed to cardiotoxic agents with suicidal intent. Previous studies declared high percentages of suicidal poisoning among teenagers, which coincides with the current study [17,30].

The pesticides were the most common cardiotoxic agents among enrolled cases, followed by CNS drugs. It is noteworthy that pesticides, including AlP and cholinesterase inhibitor insecticides, are popular suicidal agents, particularly in agricultural countries, including Egypt, which explains the high percentage of pesticide poisoning in the current study [31]. The high percentage of patients poisoned with CNS drugs could be attributed to the escalating incidence of psychiatric disorders and the tendency of these patients to commit suicide with their readily available psychotropic medications [32].

Previous studies tried to unveil the risk factors for the occurrence of ACVE following acute drug overdoses in general [29,33]. In addition, other studies were concerned with the investigation of ACVE following acute poisoning with particular agents such as dapsone [34], carbon monoxide [35], and bupropion [27]. Nevertheless, the current study aimed to generate a universal model for predicting ACVE following intoxication with cardiotoxic agents. Hence, a comparative analysis was conducted to explore clinical, laboratory, and ECG parameters significantly associated with the development of ACVE.

Regarding the circumstances of poisoning, suicidal poisoning and

Table 5
Diagnostic performance of some significant predictors of adverse cardiovascular events following acute poisoning with cardiotoxic agents by ROC curve analysis.

Predictors	Cut off	Sensitivity %	Specificity %	AUC	95 % CI of AUC	P-Value
Modified shock index	>1.28	71.64	74.79	0.758	0.690–0.818	<0.001*
Serum HCO$_3$ (mmol/L)	≤18.6	73.13	91.6	0.865	0.807–0.910	<0.001*
Oxygen saturation (%)	≤94	65.67	91.6	0.801	0.736–0.856	<0.001*
QRS width (msec)	>70	52.24	71.43	0.664	0.591–0.731	<0.001*

ROC: Receiver Operating Characteristics, AUC: area under the curve, CI: confidence interval, HCO$_3$: bicarbonate, msec: millisecond
* significant at $P<0.05$.
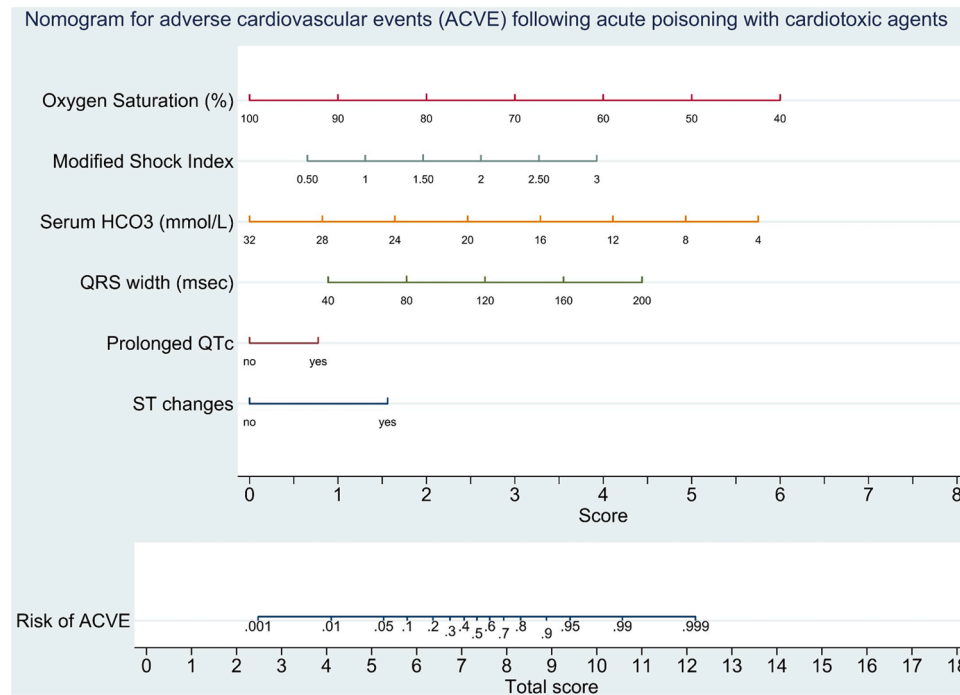
Fig. 2. Nomogram for adverse cardiovascular events following acute cardiotoxic agents poisoning.

using non-drug agents were significantly associated with ACVE, and AlP was the most common poisoning among these patients. It is noteworthy that suicidal poisoning usually occurs via ingesting large doses of highly toxic agents. AlP gained popularity as an effective suicidal tool because of its high mortality in the absence of definitive treatment. The resistant cardiogenic shock stands behind high AlP poisoning-related deaths [36–40]. This explains why such circumstances of suicidal poisoning in the current study were associated with severe cardiotoxicity, including ACVE.

Considering routine clinical and laboratory assessment, almost all on-admission parameters were significantly worse among those who developed ACVE later. Electrocardiographic analysis revealed that abnormal ECG findings were significantly associated with ACVE, including ST segment changes, prolonged QTc interval, and prolonged QRS width. The current results agree with those of Manini et al. [33] and Manini et al. [29] who referred to these ECG abnormalities as significant predictors of ACVE. In addition to these ECG abnormalities, the current study found that AF, ventricular ectopy, and SVT were only reported among patients with ACVE, which denotes the gravity of these ECG findings.

Notably, ACVE was significantly associated with ICU admission, as these critical cases required advanced medical care. As regards mortality, there was a significant association between ACVE and the fatal outcome among patients with acute cardiotoxic agent poisoning. In addition, all patients who died in the present study suffered from ACVE, which reflected the seriousness of these events and highlighted the

importance of their early prediction.

Therefore, this study provided a nomogram to predict the probability of ACVE following poisoning with cardiotoxic agents. Six significant predictors were used to formulate the predictive model, including one clinical parameter (MSI), two laboratory parameters (serum bicarbonate level and oxygen saturation), and three ECG parameters (ST segment changes, QTc prolongation, and QRS width).

When selecting these predictors, statistical and clinical perspectives were considered. From a statistical standpoint, these parameters resulted in a significant regression model with 89.2 % accuracy in predicting the ACVE probability. The nomogram's developed AUC was 0.956, surpassing the AUCs of the individual predictors constituting the adopted model. The internal nomogram's validity was confirmed by using the calibration curve.

From a clinical point of view, incorporating clinical, laboratory and ECG parameters into a unified model allows for a thorough assessment of the patient's condition. Furthermore, previous literature has highlighted the significance of each parameter in relation to cardiotoxicity.

MSI is a clinical predictor that reflects patients' hemodynamic stability. MSI is calculated by dividing the heart rate by MAP. Numerous studies have pointed to the predictive value of MSI in predicting the outcomes of pathological conditions impeding the cardiovascular system [41–43]. In clinical toxicology, Lau and Wong 2023 found that a high shock index was associated with poor outcomes in calcium channel blocker poisoning [44]. Also, Ghonem et al. recommended the use of MSI as a reliable predictor for the prognosis of AlP-related
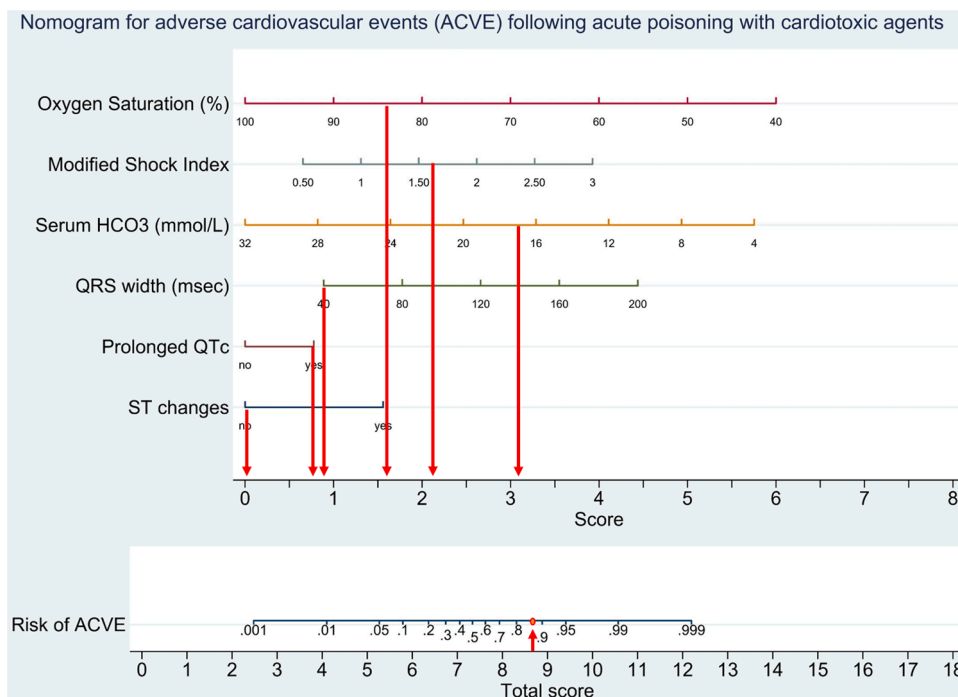
Fig. 3. Example of a nomogram for adverse cardiovascular events prediction following acute aluminum phosphide poisoning. The poisoned patient on-admission parameters included O_2 saturation = 84 %, modified shock index = 1.62, HCO_3 = 16.6 mmol/L, QRS width = 40 msec with presence of prolonged QTc interval and absent ST changes. The risk probability was estimated as follows: O_2 saturation of 84 % corresponds to 1.6 points, modified shock index of 1.62 corresponds to 2.2 points, HCO_3 of 16.6 mmol/L corresponds to 3.2 points, QRS width of 40 msec corresponds to 0.9 point, presence of prolonged QTc interval corresponds to 0.8 point and absence of ST changes corresponds to zero point. The sum of these patient points is 8.7 points, which means 86 % associated risk of adverse cardio-vascular events.
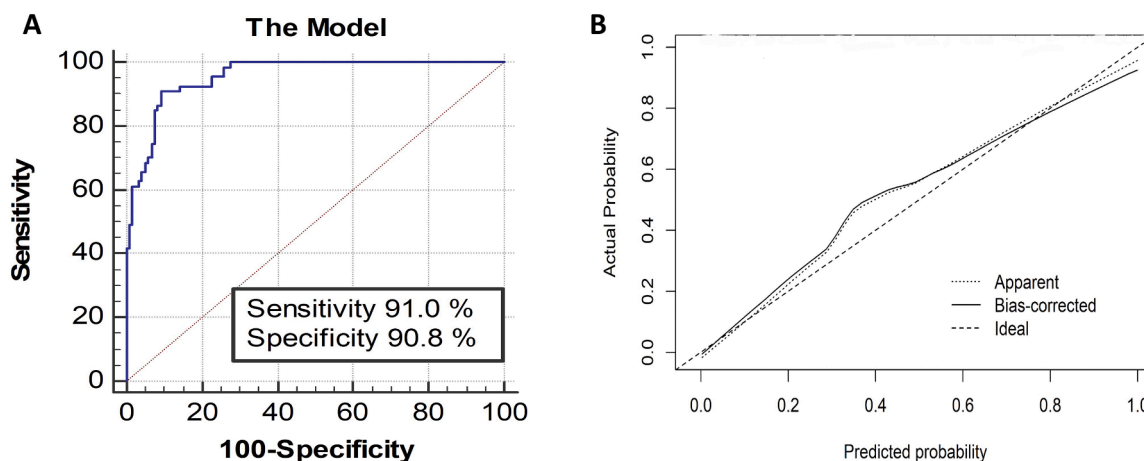
Fig. 4. (**A**) Receiver operating characteristics curve shows the predictive ability of the developed model for predicting adverse cardiovascular events (AUC=0.956). (**B**) Calibration curve of the actual and predicted probability.

cardiovascular toxicity, which coincides with the current results [45].

Among ABG variables, serum bicarbonate was included as a predictor in the current nomogram because metabolic acidosis has well-established deleterious effects on myocardial functions [46]. Moreover, Manini et al. [9], and Carreiro et al. [10] found that low serum bicarbonate concentration was significantly associated with ACVE in acutely intoxicated patients. Also, El-Sarnagawy et al. declared that diminished serum bicarbonate was significantly associated with adverse outcomes in acute cardiotoxicities [8].

Oxygen saturation was included in the nomogram because diminished oxygen saturation directly and seriously affects heart functions. Decreased oxygen supply to the myocardium suppresses cardiac aerobic

metabolism and increases acidity in the cardiomyocytes, which impedes cardiac contractility. In addition, hypoxia increases myocardium vulnerability to developing serious arrhythmias [47,48].

Regarding ECG parameters, the generated nomogram included ST segment changes, whether depressions or elevations, which were considered ECG signs of myocardial ischemia. Manini et al. found that the presence of ischemic features on the initial ECG was associated with ACVE in acutely intoxicated patients [33]. In this context, the cardiotoxic agents might induce myocardial injury through different mechanisms. Acute poisoning with AlP or calcium channel blockers is associated with severe hypotension along with impairment of myocardium perfusion [36,49]. Whereas toxic exposure to carbon monoxide or

cyanide could precipitate myocardial injury by producing generalized tissue hypoxia [50,51]. Nevertheless, sympathomimetic agents, such as cocaine, could induce coronary vasoconstriction with subsequent myocardial ischemia [52].

Prolonged QTc interval is another ECG parameter included in the current nomogram because of its high clinical significance in cardiotoxicity. QT prolongation occurs due to the blockage of potassium channels, which disrupts the rectifying potassium current and slows ventricular repolarization. The prolonged QT increases the myocardial vulnerability for the development of polymorphic ventricular arrhythmias, including torsades des pointes, which is a fatal condition [53,54]

In clinical toxicology, the prolongation of the QTc interval is a well-established cardiotoxic feature of acute antipsychotic poisoning [55,56] Prolonged QTc proved to be a significant risk factor for ACVE among acutely intoxicated patients, as mentioned by Manini et al. [9], Carreiro et al. [10], Shastry et al. [26], and El-Sarnagawy et al. [8].

We also included QRS width as a nomogram predictor in the current study. The QRS complex represents ventricular depolarization; thus, sodium channel blockage results in QRS widening. Wide QRS is one of the established features of tricyclic antidepressant poisoning [57]. However, recently, Simon et al. declared that prolonged QRS following toxic exposure to various xenobiotics was associated with an increased probability of poor outcomes [58].

In the context of drug-induced arrhythmia, Chan et al. developed a QT nomogram that accurately predicts the risk of torsades des pointes for drug-induced QT prolongation [59]. Also, El Gameel et al. provided a risk prediction nomogram for serious arrhythmias following acute digoxin poisoning among pediatrics [60].

The current study outperforms previous studies that predicted ACVE in acute poisoning. The adopted six-predictor nomogram could predict ACVE with 89.2 % accuracy among adult patients poisoned with acute cardiotoxic agents, either pharmaceutical or non-pharmaceutical. El-Sarnagawy et al. investigated QTc as a predictor for ACVE following exposure to cardiotoxic agents. They found that QTc >497.9 ms could predict ACVE with good accuracy (AUC=0.619)[8]. Manini et al. were concerned with the cardiotoxic effects of drugs only, as they developed a multivariable logistic regression model (QTc > 500 msec, bicarbonate < 20 mEq/L, and presence of cardiac disease). It was found that the probability of ACVE increased in the presence of multiple predictors, peaking at 90.9 % [9]. In pediatric patients, Carreiro et al. investigated clinical predictors of ACVE following acute drug poisoning and identified QTc ≥500 ms and serum bicarbonate concentration as reliable predictors [10].

5. Strengths and limitations

The current study adopted a nomogram that predicted ACVE with high accuracy. The proposed model could be applied to patients with cardiotoxicity, regardless of the causative agent. Being an uni-centred study and lacking external validation are considered the main limitations of the current study. Yet, future studies are needed for external validation of the current nomogram, preferably using validation cohorts from other populations to ensure its universal applicability. Also, the current study excluded patients with chronic diseases and those who received pre-hospital management to ensure statistical inference and eliminate potential confounding factors. However, these exclusion criteria might add limitations on study applicability.

6. Conclusion

Acute cardiotoxicities are among the toxicological emergencies that endanger patients' lives. Thus, early identification of poisoned patients with a high probability of ACVE could improve their prognosis. Therefore, the current study proposed a nomogram that could be easily applied upon patient admission. Clinical, laboratory, and ECG predictors were incorporated into a unified model to ensure a thorough evaluation

of the patient and enhance statistical accuracy. These predictors were MSI, serum bicarbonate level, oxygen saturation, ST segment changes, QTc, interval, and QRS width. The adopted nomogram could predict the probability of ACVE among patients with acute cardiotoxicities, regardless of the causative agent, with 89.2 % accuracy.

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

Heba I. Lashin: Writing – review & editing, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Fatma M. Elgazzar:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Sara I. El sharkawy:** Methodology, Formal analysis, Data curation, Conceptualization. **Sally M. Elsawaf:** Methodology, Formal analysis, Data curation, Conceptualization. **Zahraa Khalifa Sobh:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis.

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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxrep.2024.101826.

Data Availability

Data will be made available on request.

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