MALONDIALDEHYDE, TOTAL ANTIOXIDANT CAPACITY, AND TROPONIN I ROLE IN PREDICTING MORBIDITY AND MORTALITY OF CASES WITH CARDIOTOXICITY ADMITTED TO MENOUFIA POISON CONTROL CENTER.

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ABSTRACT

Background: Poisoning with substances that have cardiotoxic effects has become the major cause of early deaths globally. These substances include several compounds that are used for medical or non-medical purposes. The objective of the study was to assess the role of biomarkers like total antioxidant capacity (TAC), malondialdehyde (MDA), and Troponin I (cTnI) in predicting morbidity and mortality of cases with acute cardiotoxicity arriving at the Menoufia poison control center. Methods: A cross-sectional hospital-based comparative study included acutely poisoned cases with cardiotoxic substances (80 participants) who arrived at Menoufia Poison Control Centre (MPCC) over six months and a control group of 80 healthy individuals. Sociodemographic and intoxication characters were registered, and a full clinical systemic examination was done. Blood samples were collected on admission to measure (MDA), (TAC), and (cTnI). Results: The mean age of the cases was 25.67±10.57 years, and they were mostly females (72.5%), students (48.7%), and from rural areas (61.25%). Phosphides intoxicated 45.0%. Theophylline was the most common cardiotoxic drug (20.0%). Suicide was the most common form of poisoning (78.75%). 68.8% of the cases survived, while the mortality rate was 31.2%. MDA and TAC were both sensitive and accurate in predicting the severity and mortality of cardiotoxic poisoned cases when assessed in the early hours of poisoning. On the other hand, cTn1 showed no significant changes in cases in comparison to the control healthy individuals. Conclusion: MDA and TAC are sensitive and specific biomarkers for predicting morbidity and mortality outcomes in acute cardiotoxic poisoning and were more efficient than cTn1 in the early hours of acute cardiotoxicity assessment.

Keywords: Malondialdehyde, Total antioxidant capacity, Troponin I, cardiotoxicity, prediction

INTRODUCTION

Cardiotoxicity is a grave health problem that could affect the myocardium, endocardium, pericardium, and coronary vessels, leading to a decrease in cardiac output by 10% to 55% and subsequently causing cardiac failure (**Nicol et al.,2019**).

This cardiac injury is commonly caused by pesticides like aluminum phosphide (ALP) intoxication and organophosphorus compounds (OPC), particularly in developing countries as they are cheap and accessible (**Aardema et al.,2008; Farahani et al.,2016**). Moreover, cardiovascular medication overdose, which represents about 3.5% of all drug intoxication, could also cause poisoning morbidities and mortalities due to the extension of their pharmacological activity (Zeinvand et al.,2017).

Some drugs have narrow therapeutic indexes, such as adenosine receptor antagonists such as theophylline; this narrow therapeutic window may give way to adverse effects within therapeutic levels and serious complications due to overdoses, which may be represented as arrhythmias and other life-threatening cardiac clinical assaults (Shannon et al., 1990; Reilly et al.,2011). Additionally, antidepressant overdoses are common and dangerous, and bv toxicity is characterized sudden cardiovascular deteriorations, which are mediated by several mechanisms, including quinidine-like effects on the myocardium (Mills,2004; Yakistiran,2004). Drugs could also stimulate tissue apoptosis and autophagy by overproduction of free oxygen radicals, such as the anions of hydroxyl and superoxide radicals (Zorov et al.,2014).

Free radicals and overproduction of ROS (reactive oxygen species) have been recognized as mechanisms of cardiac injury that are particularly damaging to the tissue macromolecules causing lipid peroxidation and malondialdehyde formation of (MDA). furthermore, causing severe exhaustion of tiny particles like ascorbic acid, alpha-tocopherol, beta-carotene, reduced glutathione, and other antioxidants that alleviate the oxidative stress resulting from ROS (Khan et al., 2018). The amount of endogenous antioxidants in the system equals its total antioxidant capacity (TAC). Similarly, they initiate cell membrane denaturation protein and ultimately uncontrolled cell death and destruction of the continuity of sarcolemma (Mehrpour et al.,2012). Additionally, elevated serum levels of creatine kinase-myocardial (CK-MB) and Troponin I (cTnI) are expressive of severe myocardial injury due to tachyarrhythmias and massive myocarditis (Xue et al.,2014).

Electrocardiography (ECG) changes and high cardiac biomarker levels are the main tools for diagnosing cardiac injury. However, ECG alone is not conclusive in most patients because the heart suffers silently at first (**Cha et al.,2014**).

Hence, the objective of this study was to assess the role of biomarkers such as total antioxidant capacity (TAC), MDA, and Troponin I (cTnI) in predicting morbidity and mortality outcomes of cases with cardiotoxicity arriving at the Menoufia poison control center.

SUBJECT AND METHODS

Design of the study: A cross-sectional hospital-based comparative study was carried out on cases of acute poisoning with cardiotoxic substances (80 participants) who arrived at Menoufia Poison Control Center (MPCC) within six months starting from the 1st of December 2022 to the 31st of May 2023 and a control group of 80 healthy individuals.

Inclusion and exclusion criteria: The study included patients with a history of acute cardiotoxic substance exposure, whose age was 12-50 years, who arrived at MPCC within 1st six hours post-exposure, with symptoms of

acute toxicity, and who didn't receive any previous medical treatment before arrival.

Patients with known concomitant toxin intake or those who presented after 6 hours of exposure were excluded from this study. Additionally, pregnant or breastfeeding women, as well as cases with a medical history of cardiovascular, pulmonary, liver, brain, kidney, endocrine, or immunological disorders, were also excluded, as individuals suffering from conditions frequently encounter these oxidative stress and modified antioxidants defense systems, so their inclusion could result in variability that distorts the study's conclusions (Marrocco et al., 2017). The research also excluded cases of imminent death upon arrival.

Ethical Considerations: Before beginning work, the protocol of the current study was approved by the Ethics Committee of Medicine Faculty, Menoufia University, with IRB approval number and date (11/2022 FORE24-2). Subjects included in the study or their legal guardians provided valid informed consent before the beginning of the study. The confidentiality of records was maintained, and all personal information was kept anonymous.

Data collection: The sociodemographic data, including gender, age, residence, occupation, and marital status, in addition to poisoning data, including poison type and mode of exposure, were collected. A clinical full systemic examination was carried out for all cases; pulse, blood pressure, body temperature, and respiratory rate were assessed, and normal ranges were standardized according to values described by Rees et al. (2017). Hypotension was diagnosed when blood pressure was less than 90/60 mmHg (Dunn et al., 2018). An electrocardiogram (ECG) was also done and including the analyzed. rate. rhythm, measurement of PR and QT intervals, ST/T abnormalities, and conduction defects.

The included cases were categorized at the time of initial assessment into minor (transient, mild, and spontaneously resolving clinical manifestations), moderate (prolonged or pronounced clinical manifestations), and severe (life-threatening or severe clinical manifestations) according to the poisoning severity score (PSS) described by Zaazoq et al., (2012) which is a modified score from Persson et al., (1998). The history of intake confirmed diagnosis of the poisoning type, clinical symptoms /signs, and investigations, including silver nitrate in phosphides, cholinesterase level and thin layer chromatography in organophosphate, and drug testing in drug overdose.

Investigations (arterial blood gases "ABG" and electrolytes), outcome, place of treatment, and duration of hospital stay were also recorded for all cases. The ABG changes and serum electrolytes were assessed according to agespecific norms (**Burtis et al. 2006**).

Blood sampling: A sample of 5cm blood was taken from all cases on admission, and the normal control group was then left for a few hours for clotting and then centrifugation for 15 minutes at 4000 rpm at a temperature of 4°C. Pipette. The layer of yellow top serum was taken and separated without distorting the buffy white layer and then stored at minus 80°C to be further utilized for measurement of TAC, malondialdehyde, and Troponin I.

Plasma TAC level measurement: The commercial kits Biodiagnostic; Egypt was used to measure the level of serum TAC, which is an oxidative stress biomarker. The antioxidant capacity was determined through the reaction between antioxidants present in the sample and a certain amount of hydrogen peroxide (H2O2), which was exogenously added to the sample. Part of the added H2O2 is eliminated by the antioxidant compounds present in the blood sample, and the residual H2O2 is measured calorimetrically through the reaction of a certain enzyme (3,5, dichloro -2- hydroxy benzenesulfonate) and its conversion to a product with a certain color (Koracevic et al., 2001).

Measurement of plasma malondialdehyde level: Measurement of serum MDA levels as an oxidative stress biomarker was done using commercial kits supplied by Biodiagnostic, Egypt. Determination of MDA level is done through the reaction between MDA present in the sample and thiobarbituric acid in an acid media at 95°C temperature for 30 minutes. A reactive product of thiobarbituric acid is formed, and then serum MDA level is determined by measuring the resultant-colored product absorbance at 534 nm (**Ohkawa et al. 1979**).

Measurement of plasma troponin I level: The commercial kits obtained from SunRedBio, Egypt, were used to measure serum troponin I (cTn-I) level in human samples through double-antibody sandwich immunoassay, ELISA.

Statistical analysis: Version 24 of the SPSS program was used to study the results. Qualitative data were expressed in numerical figures and percentages, while mean and standard deviation were used to represent quantitative data. The Chi-squared test was applied to investigate the connection between categorical variables. For analysis of nonparametric data, the Mann-Whitney U test was applied to compare differences between two independent groups. In contrast, the Kruskal-Wallis significance test was used to compare more than two groups. The ROC (receiver operating curve) was applied to assess the sensitivity and specificity at various cut-off points. The significance level was set at a Pvalue less than 0.05.

RESULTS

In the current work, 160 individuals of both sexes were separated into 80 poisoned patients and 80 healthy control persons. Nearly three-quarters of the patients were females (72.5%). The mean age of the cases was 25.67 ± 10.57 years, who were mostly students (48.7%) and from rural areas (61.25%). No significant statistical differences were observed between the case and control groups regarding gender, age, residency, occupation, and marital status, as demonstrated in (**Table 1**).

Table (1). Sociodemographic	data of the poisoned	patients and the control group.
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Patient group (N=80)	Control group (N=80)	Test of significance	P value
25.67±10.57	25.26±10.58	<i>U</i> =0.37	0.71
22 (27.5%)	23 (28.8%)	$\chi^2 = 0.03$	0.86
58 (72.5%)	57 (71.3%)	<i>,</i> ,,	
	. ,		
49 (61.25%)	48 (60.0%)	$\chi^{2} = 0.02$	0.87
31 (38.75%)	32 (40.0%)	<i>,</i> ,	
	(N=80) 25.67±10.57 22 (27.5%) 58 (72.5%) 49 (61.25%)	$(N=80) (N=80) (N=80)$ $25.67\pm10.57 25.26\pm10.58$ $22 (27.5\%) 23 (28.8\%)$ $58 (72.5\%) 57 (71.3\%)$ $49 (61.25\%) 48 (60.0\%)$	$(N=80) \qquad (N=80) \qquad ($

Occupation				
Student	39 (48.7%)	38 (47.5%)	$\chi^2 = 0.42$	0.93
Housewife	21 (26.3%)	20 (25.0%)		
Worker	13 (16.3%)	16 (20.0%)		
Farmer	7 (8.7%)	6 (7.5%)		
Marital status				
Single	48 (60.0%)	51 (63.8%)	$\chi^2 = 0.23$	0.62
Married	32 (40.0%)	29 (36.3%)		
<i>U</i> = Mann-Whitney test.	$\chi^2 = chi s$	quare test. N=num	ber $\mathbf{p} \ \mathbf{value} > 0.$	05 = non-significant

Regarding poisoning characteristics, the majority of cases (45.0%) were intoxicated by phosphides through ingestion (100%). Theophylline was the most common cardiotoxic drug (20.0%). Regarding the manner of poisoning, suicide was the prevalent method among the cases (78.75%). Cases were categorized into three different groups based on their poisoning severity score (PSS): mild

(18.8%), moderate (48.7%), and severe (32.5%). Most cases (73.8%) were treated in the care unit, with an average hospital stay of 2-5 days. In terms of patient outcomes, 68.8% of the cases survived, while the mortality rate was 31.2% (**Table 2**). The deaths were mostly due to phosphide poisoning (22 cases), two cases due to organophosphate toxicity, and one case due to theophylline drug overdose.

Table (2): Intoxication data of the poisoned patients (N=80).

Intoxication data	Patient group
	(N=80)
Type of poison	
Phosphides	36 (45.0%)
Organophosphate	19 (23.8%)
Theophylline	16 (20.0%)
TCA	6 (7.5%)
others	3 (3.8%)
Route of intake	
Oral	80 (100%)
Mode of exposure	
Accidental	17 (21.25%)
Suicidal	63 (78.75%)
Poisoning severity score	
Mild	15 (18.8%)
Moderate	39 (48.7%)
severe	26 (32.5%)
Place of treatment	
MPCC	21 (26.3%)
Care unit	59 (73.8%)
Duration of hospital stay.	
< 2 days	26 (32.5%)
2-5 days	40 (50.0%)
> 5 days	14 (17.5%)
Outcome	
Survived	55 (68.8%)
Died	25 (31.2%)
N-number	

N=number

As regards the clinical manifestations of the poisoned patients, 81.2% of the cases were hypotensive, 52.5% of them presented with tachypnea, and 28.8% of them were hypothermic. The most common gastrointestinal manifestations were abdominal pain (78.8%) followed by vomiting (73.8%), while (61.2%) of the cases were presented with drowsiness. ECG findings among studied Tal

patients revealed that most of the patients in the study (51.3%) had sinus tachycardia, followed by T wave inversion (26.3%), prolonged QT interval (21.2%), sinus bradycardia, and atrial fibrillation (20%), and wide QRS complex (17.5%). Additionally, 65% of cases had metabolic acidosis, and 33.8% of them had hypokalemia (Table 3).

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Clinical manifestations	Patient group (N=80)	
Pupil	Normal	38 (47.5%)
	Constricted	22 (27.5%)
	Dilated	20 (25.0%)
	Vomiting	59 (73.8%)
GIT manifestations	Abdominal pain	63 (78.8%)
	Diarrhea	14 (17.5%)
	Tachypnea	42 (52.5%)
	Bradypnea	14 (17.5%)
espiratory manifestations Pulmonary eden		13 (16.3%)
F	Pulmonary edema	14 (17.5%)
	Aspiration pneumonia	15 (18.8%)
	Normal Conscious level	18 (22.5%)
CNS manifestations	Drowsiness	49 (61.2%)
Cros municipations	Coma	13 (16.3%)
	Convulsions	15 (18.8%)
	Sinus tachycardia	41 (51.3%)
	Sinus bradycardia	16 (20.0%)
	Atrial fibrillation	16 (20.0%)
ECG	Ventricular tachycardia	9 (11.3%)
Findings	Ventricular fibrillation	3 (3.8%)
	Prolonged QTc	17 (21.2%)
	Wide QRS	14 (17.5%)
	T wave inversion	21 (26.3%)
Blood Pressure	Hypotension	65 (81.2%)
Temperature	Hypothermia	23 (28.8%)
ABG	Normal	28 (35.0%)
	Metabolic acidosis	52 (65.0%)
	Normal	38 (47.5%)
K level	Hypokalemia	27 (33.8%)
	Hyperkalemia	15 (18.7%)

N=number

Regarding cardiac markers, a highly significant difference was demonstrated in the levels of TAC and malonaldehyde between the two studied groups (patients and control) (P ≤ 0.001); however, troponin I levels exhibited non-significant statistical changes in patients when compared with the healthy controls (Table 4).

groups				
Variables	Patient group (n=80)	Control group (n=80)	Test of significance	P value
Blood MDA level (nmol/ml) Mean ±SD	0.72±0.30	0.19±0.11	<i>U</i> = 10.51	<0.0001**
Blood TAC level (mM/L) Mean ±SD	0.67±0.63	1.31±0.47	<i>U</i> = 7.04	<0.0001**
Blood Troponin I level (ng/ml) Mean ±SD	0.15±0.08	0.12±0.03	<i>U</i> = 1.61	0.11
n=number U= Mann-Whitney	test. **P v	alue < 0.001 = hig	hly significant	

 Table (4): Comparison of blood level of MDA, TAC, and Troponin I between poisoned and control groups

The changes in TAC and malonaldehyde levels showed significant statistical differences in dead cases in comparison to the survived

group; meanwhile, troponin I levels exhibited non-significant changes between the dead and survived instances (**Table 5**).

 Table (5): Comparison of the blood level of MDA, TAC, and Troponin between survived and died cases

Variables	survived cases (n=55)	Died cases (n=25)	Test of significance	P value			
Blood MDA level (nmol/ Mean ±SD	ml) 0.61±0.24	0.95±0.29	<i>U</i> = 4.76	<0.0001**			
Blood TAC level (mM/) Mean ±SD	L) 0.92±0.61	0.13±0.19	<i>U</i> =6.60	<0.0001**			
Blood Troponin I level (ng Mean ±SD	g/ml) 0.14±0.06	0.17±0.11	<i>U</i> = 1.58	0.20			
n =number U = Mann-							

As regards the relation between the three biomarkers and poisoning severity score, the TAC and malonaldehyde levels exhibited highly significant changes between mild, moderate, and severe cases (P <0.001). In contrast, non-significant changes in Troponin I levels were detected between the instances (P>0.05) (Table 6).

Table (6): Comparison of the blood level of MDA, TAC, and Troponin I between mild, moderate, and severe cases

Variables	Mild cases (n=15)	Moderate cases (n=39)	Severe cases (n=26)	Test of significance	P value			
Blood MDA level (nmol/ml) Mean ±SD	0.37±0.05	0.61±0.10	1.08±0.22	<i>K</i> = 64.93	<0.0001** (k1)			
Blood TAC level (mM/L) Mean ±SD	1.39±0.92	0.64±0.40	0.32±0.31	<i>K</i> = 28.67	<0.0001** (k1)			
Blood Troponin I level (ng/ml) Mean ±SD	0.13±0.11	0.15±0.06	0.16±0.09	<i>K</i> =0.97	0.83			
n =number \mathbf{K} = Kruskal Wallis Test **P value < 0.001 = highly								

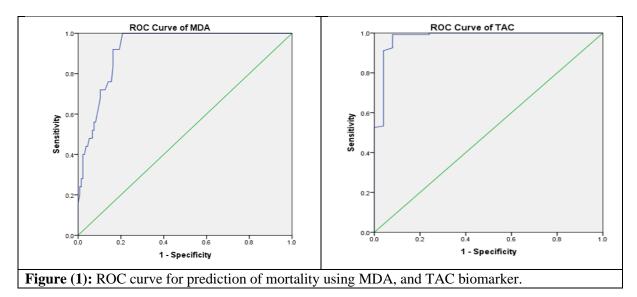
significant **K1**: Post-hoc of the Kruskal Wallis test is significant between the three groups.

ROC curve was applied to assess mortality early prediction among the poisoned cases using MDA and TAC biomarkers, where the area under the ROC curve for **MDA** was 0.83 with the best cut-off value of 0.66 nmol /ml, 91.2% sensitivity, 65% specificity, and 78.6% accuracy of mortality prediction. Furthermore, the area under the ROC curve for **TAC** was 0.96, with the best cut-off value of 0.17 mM/L with 94% sensitivity, 87.5% specificity, and 90.6% accuracy of mortality early prediction **Table (7) and Fig (1)**.

Table (7): The best cut-off value, sensitivity, and specificity of MDA and TAC for prediction of mortality in the poisoned cases.

Parameter	The area under the ROC curve (95% CI)	Cut- off value	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy (%)
MDA level	0.83	0.66	91.25%	65%	72.2%	89.6%	78.6%
(nmol/ml) TAC level	0.96	0.17	94%	87.5%	88.2%	93.3%	90.6%
(mM/L)	0.90	0.17	9470	07.370	00.270	93.370	90.070

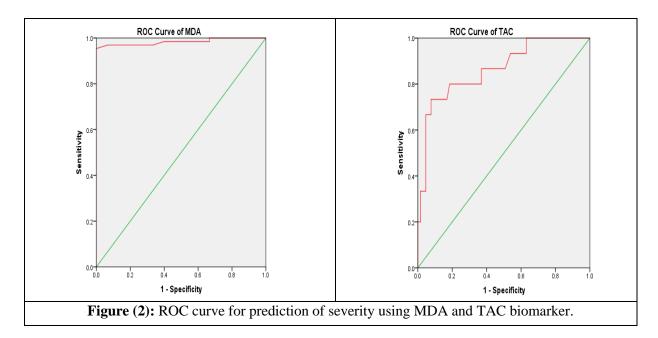
CI: Confidence interval **PPV**: Positive predictive value **NPV**: Negative predictive value



Similarly, the ROC curve was applied to evaluate severity prediction in the patients using both MDA and TAC biomarkers where the area under the ROC curve for **MDA** was 0.98 with the best cut-off value of 0.42 nmol /ml, 95% sensitivity, 80% specificity, and 87.5% accuracy of severity prediction. Additionally, the area under the ROC curve for **TAC** was 0.86 with the best cut-off value,0.69 mM/L with 87.5% sensitivity, 65% specificity, and 76.3% accuracy **Table (8) and Fig (2)**.

Table (8): The best cut-off value, sensitivity, and specificity of MDA and TAC for prediction of
severity in the poisoned cases (mild Vs. moderate and severe cases)

Parameter	The area under the ROC curve (95% CI)	Cut- off value	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy (%)
MDA level	0.98	0.42	95%	80%	82.6%	94.1%	87.5%
(nmol/ml)							
TAC level (mM/L)	0.86	0.69	87.5%	65%	71.4%	83.8%	76.3%
CI: Confidence	interval	PPV : Posi	tive predictive	value	NPV: Nega	ative prec	lictive value



Regarding the place of treatment, TAC and malonaldehyde levels exhibited significant changes in those who were treated in the care unit when compared to those who were treated in MPCC. As regards length of hospital stay, significant differences were demonstrated in MDA level in those with hospital stay between 2-5 days and more than 5 days, while the TAC level of those with 2-5 days hospital stay was significantly different when compared with those less than 2 days and those with more than 5 days hospital stay. On the contrary, Troponin I levels exhibited a non-significant difference in terms of both the place of treatment and length of hospital stay (**Table 9**).

Table (9): Comparison of the blood level of MDA, TAC, and Troponin I regarding the place of treatment and length of hospital stay.

Variables	Blood MDA level	Blood TAC level	Blood Troponin I level	
	Mean ±SD	Mean ±SD	Mean ±SD	
Place of treatment				
MPCC	0.43±0.11	1.13±0.65	0.13±0.04	
Care unit	0.82 ± 0.28	0.51 ± 0.54	0.16 ± 0.09	
Mann-Whitney test	5.68	4.45	1.87	
P value	<0.0001**	<0.0001**	0.11	
Length of hospital stay				
< 2 days	0.76±0.36	0.45 ± 0.50	0.16±0.11	
2-5 days	0.61±0.19	0.88 ± 0.74	$0.14{\pm}0.08$	
>5 days	0.95 ± 0.29	0.52 ± 0.26	0.15 ± 0.03	
Kruskal Wallis test	13.42	7.67	5.08	
P value	0.001* ^{K1}	0.02* K1 &K2	0.07	

K1: Post-hoc of Kruskal Wallis test is significant between 2-5 days and > 5 days **K2**: Post-hoc of Kruskal Wallis test is significant between < 2 days and 2-5 days

P value** <0.05 = significant ***P value <0.001 = highly significant

No significant statistical changes were detected between the survived and dead cases regarding ECG abnormalities except for prolonged QTc, which was significantly higher in dead cases (Table 10).

Variables	Survived cases (n=55)	Died cases (n=25)	Chi-squared test	P value
v al lables				
Sinus tachycardia				
Yes	28 (50.9%)	13 (52.0%)	0.008	0.92
No	27 (49.1%)	12 (48.0%)		
Sinus bradycardia				
Yes	9 (16.4%)	7 (28.0%)	1.45	0.23
No	46 (83.6%)	18 (72.0%)		
Atrial fibrillation				
Yes	8 (14.5%)	8 (32.0%)	3.27	0.07
No	47 (85.5%)	17(68.0%)		
Ventricular tachycardia				
Yes	8 (14.5%)	1 (4.0%)	1.91#	0.16
No	47 (85.5%)	24 (96.0%)		
Ventricular fibrillation	· · · ·			
Yes	2 (3.6%)	1 (4.0%)	0.006#	0.93
No	53 (96.4%)	24 (96.0%)		
Prolonged QTc	· · · ·			
Yes	7 (12.7%)	10 (40.0%)	7.63	0.006*
No	48 (87.3%)	15 (60.0%)		
Wide QRS	· · · ·			
Yes	7 (12.7%)	7 (28.0%)	2.77#	0.09
No	48 (87.3%)	18 (72.0%)		
T wave inversion	× ,			
Yes	13 (23.6%)	8 (32.0%)	0.62	0.43
No	42 (76.4%)	17 (68.0%)		

Table (10): ECG changes and outcome of poisoned cases (n=80).

n=number # Fisher's Exact Test (it is a statistical test) * P value <0.05 = significant

DISCUSSION

The emergence of phosphides as one of the most fatal poisonings in recent years in Egypt, as the widespread use of theophylline in the COVID era plus the presence of the already common substances like organophosphate made the cardiotoxic substances one of the reasons for poisoning-related primary morbidity and death in Menoufia. Therefore, this work aimed to explore the role of biomarkers in the prediction of morbidity and mortality of cases with cardiotoxicity due to poisoning for proper management and better prognosis.

Poisoning with substances that have cardiotoxic effects has become the major cause of early deaths globally; they include several compound classes that are used for medical or non-medical purposes (**Kruchinin et al., 2022**).

The cardiotoxic terminology 'refers not only to cardiovascular medications but also to a variety of other toxins, like organophosphates, antidepressants, theophylline, H1antihistaminics, cocaine, and cyanide. Despite advances in critical care facilities, substanceinduced cardiovascular toxicity continues to be a primary cause of death (Mégarbane et al.,2008).

The participants in this research had an average age of 25.67 ± 10.57 years. This result is consistent with multiple research (Wasserman et al., 2005; Elghany et al., 2018); they attributed it to several factors, such as a decline in the availability of social support, erratic financial circumstances, joblessness, and a rise in the frequency of depressive illnesses. Unlike the current study, where the majority of cases are young adults, Ayan et al. (2016) found that most of their cardiotoxic drug poisoned cases were among older people.

It was noticed that young individuals frequently suffer from phosphide toxicity, as this was attributed to the age group's exposure to financial instability and unemployment (**Abdel Wahab et al., 2020**).

Most cases in the current research were suicidal and females, and this was confirmed by other studies, which attributed this finding to women's higher susceptibility to stress, their sensitive nature, parental suppression of personal freedom, lower levels of education, and lower employment rate (**Yasan et al., 2008**; **El-Hady Hammad et al., 2014**). Contrary to this study, **Garg and Verma (2010)** concluded male predominance in suicidal attempts, and this disparity could be attributed to variations in social and cultural features, traditions, and backgrounds.

According to **Abdelrahman et al. (2016)**, the suicide prevalence shown in their study is attributed to the fact that Egypt has experienced financial and social turbulence, especially in recent years, along with problems related to religion and culture, accessibility of drugs, and other factors.

Students and singles made up the majority of cases in this study. This is in line with the findings of **Sagah et al. (2015)** and **Abdel Wahab et al. (2020)**, who showed that most of their patients were secondary school children as a result of teacher reprimands and failing or receiving low test percentages. In disagreement with this work, in India, **Anand et al. (2011)** discovered that the majority of the patients they revealed were laborers or farmers in the agricultural industry, and this contrast could be due to different study designs.

The predominance of rural residence in this research may be due to the criteria of Menoufia as an agricultural area; these results are going with a study done in Iran by **Mehrpour et al. (2012),** who attributed this to that the most risky groups were those who engaged in rural society and were working in agricultural.

Regarding the kind of poison, the majority of the cases with cardiotoxic manifestations were due to poisoning with phosphides (zinc or aluminum phosphides), and this may be due to the essence of having phosphides, especially in rural areas. There is a considerable increase in morbidity and mortality from acute phosphide poisoning, and cardiac dysrhythmia was the frequent reason for early death. In contrast, hepatic failure or persistent shock was responsible for late deaths (Neki et al., 2017). Theophylline was the most common cardiotoxic drug poisoning in the current study, and this may be attributed to its widespread use in the treatment of COVID-19 patients with the increase of its popularity among people. In a study done by El-Hady Hammad et al. (2014), theophylline was the predominant cardiotoxic drug, while it was a beta blocker in studies done by Hussien et al. (2018) and Omar et al. (2022). As explained by Kruchinin et al. (2022) who concluded that differences highly

PSS includes standard laboratory data such as the electrolytes and ABG in addition to clinical and Electrocardiogram findings (Akdur et al., 2010; Zaazoq et al., 2012). Most of the cases of this study were in moderate and severe degrees of PSS who mainly needed care unit admissions (intermediate care or ICU) and stayed more than 2 days in hospital. That result is attributed to the need for continuous heart monitoring in such patients. Also, most of the cases were due to phosphide poisoning, which is known for its high morbidity. That was in line with Zaazoq et al. (2012), who found most of their patients with cardiotoxicity manifestations were in moderate and severe degrees, while Omar et al. (2022) found mild cases predominance that needed mainly observation.

As stated by the American Association of Poison Control Centers, those with moderate (prolonged and pronounced) to severe (lifethreatening) clinical manifestations are more likely to need admission and treatment in ICU (Schwarz et al., 2017).

In terms of patient outcomes, the majority of the cases survived. Still, there was a considerable mortality rate as most of the fatalities were due to poisoning by aluminum phosphide, which is characterized by its high toxicity.

Regarding the cardiovascular findings (manifestations and ECG changes), hypotension and sinus tachycardia were the most common, and this was consistent with **Ayhana et al. (2015)** and **Hussien et al. (2018)**, who concluded the same.

The common association between phosphide poisoning and shock and sinus tachycardia is one of the reasons for these findings, as proved by Gurjar et al. (2011) and Navabi et al. (2018). Moreover, sinus tachycardia, atrial /ventricular arrhythmia, and wide QRS complex could be observed in theophylline toxicity because it increases epinephrine and norepinephrine plasma levels (Altaie et al.,2011). Additionally, peripheral vasodilatation brought on by excessively stimulated muscarinic receptors or cholinergic circulatory activation of vascular receptors in case of organophosphate poisoning may result in hypotension (**Davies et al., 2008**).

Vomiting, abdominal pain, tachypnea, and drowsiness were the commonest extracardiac manifestations among the studied patients. El-Hady Hammad et al. (2014) found a significant relationship between cardiovascular drug poisoning and clinical manifestations such as vomiting and loss of consciousness. Pleuvry (2006) reported that vomiting may be exacerbated by some mechanisms underlying cardiovascular disturbances, particularly in patients exposed to anticholinesterases (acetylcholine accumulation). The gastrointestinal and CNS manifestations could also be precipitated by theophylline overdose, as supported by Mladenka et al. (2018), additionally vomiting, abdominal pain and drowsiness are common presentations in acute phosphide poisoning, especially in moderate to severe toxicities, as reported by Goel, and Aggarwal (2007).

Metabolic acidosis, hypokalemia, or hyperkalemia were the observed metabolic disorders in this study. These findings were supported by **Kruchinin et al. (2022)**, who concluded that the different classes of cardiotoxic substances have direct toxic effects on the heart, blood vessels, or CNS and indirect toxicological impacts, which are usually associated with some metabolic changes such as acidosis, hypoxia, and electrolyte disturbances.

Moreover, metabolic disorders are common findings in poisonings with aluminum phosphide (ALP), and this was supported by a study done in India by **Jaiswal et al. (2009)**, who observed that all their cases of ALP poisoning were complicated with severe metabolic acidosis.

As significant cardiac damage after substances or drug poisoning can be lethal, early diagnosis is essential for using therapeutic measures that are supportive and preventative. Since all cardiac biomarkers are macromolecules that are present in cardiac circulating myocytes, the presence of cardiovascular biomarkers in the blood may be sign of myocyte damage and loss a of sarcolemma integrity. They were regarded as crucial instruments for cardiovascular disease diagnosis, risk assessment, and treatment decision-making (Hasan et al., 2016). Markers of oxidative stress in living tissues have included lipid peroxidation and total antioxidant enzyme activity (Mada et al., 2020).

Consequently, the current study presented a significant increase in the level of MDA with a significant decrease in TAC levels in the blood sample of the poisoned patients compared to the control group. Furthermore, a significant increase was observed in MDA with a significant decrease in TAC levels in the severe group in comparison with mild and moderate groups and also between lived and dead cases. This result demonstrates the significant and quick oxidative stress brought on by cardiotoxic substance poisoning, which releases ROS, compromises antioxidant defense systems, and inhibits antioxidant enzymes compared to healthy controls that were not exposed to poisoning. This Extreme production of ROS that exceeds life-threatening levels can surpass most of the heart's defense mechanisms. resulting in oxidative stress that harms the biological tissues of the heart and may lead to which disrupts myocardial degeneration, myocardial function and reduces the interstitium space of the heart (Robertson et al., 2004).

A previous experimental study by **Qurat-**Ul-Ain et al. (2022) supported this hypothesis; they suggested that there was a significant increase in the lipid peroxidation markers MDA and a significant decrease in the antioxidant enzymes in doxorubicin-induced cardiac toxicity in rats., also Kariman et al., (2012), Baghaei et al., (2016) and Halvaei et al. (2017) stated that after exposure to ALP, TAC decreases, the production of free radicals oxidative produces stress. and the mitochondrial electron transport chain is disrupted. And fluctuating the antioxidant enzyme protection machinery, which improved when vitamin E was given as an antioxidant (Abdel Wahab et al., 2020).

In contrast, there were no appreciable differences in the cTn1 between the poisoned patient and the control group. That can be explained by the timing of the blood sample that was taken for markers evaluation at the time of admission of the cases who presented within 6 hours of exposure, as it is known that Troponin shows up in the serum after 4–8 hours of the beginning of symptoms and can stay increased for 7–10 days following heart muscle injury (Abass et al.,2017). Similar results were reported by Wan et al. (2012), Aghabiklooei et al. (2013), and Hasan et al. (2016), who stated

that no significant differences regarding serum Troponin I levels in the first 6 hours of organophosphorus poisoning compared to other markers. Alternatively, **Kalawat et al. (2016)** found that a rise in Troponin I was associated with cardiac damage and occurred in 26 percent of patients after severe ALP poisoning. According to **Hakimoğlu et al. (2015)**, an increase in the levels of certain cardiac enzymes, including CK-MB or troponin T (Tn T), may suggest cardiotoxicity and cause death. However, their absence does not rule out cardiotoxicity following acute phosphide exposure.

Regarding sensitivity and specificity of MDA and TAC for prediction of severity in the cardiotoxic poisoned patient, the area under the curve "AUC" for **MDA** was 0.98, and the best cut-off value was 0.42 nmol/ml with 95% sensitivity, 80% specificity, and 87.5% accuracy. On the other hand, the area under the curve "AUC" for **TAC** was 0.86, and the best cut-off value was 0.69 mM/L with 87.5% sensitivity, 65% specificity, and 76.3% accuracy.

In addition, when assessing the ROC curve of these markers for predicting death among the poisoned cases, the area under the curve "AUC" for **TAC** was 0.96. The best cut-off value was 0.17 mM/L with 94% sensitivity, 87.5% specificity, and 90.6% accuracy, while the area under the curve "AUC" for MDA was 0.83. The best cut-off value was 0.66 nmol/ml, with 91.2% sensitivity, 65% specificity, and 78.6% accuracy for the prediction of mortality.

These results showed that MDA and TAC were both sensitive and accurate in predicting the severity and mortality of cardiotoxic poisoned cases within the early hours of poisoning. The MDA level showed more specificity and accuracy in predicting severity, while TAC was more specific and accurate in predicting poor outcomes and mortality. This result was in agreement with **Emam et al.** (2021), who found similar results about the sensitivity of MDA and TAC in their research about the estimation of the severity and lethality of ALP intoxication in the early stages of manifestation.

In comparison to ECG changes, the markers were more advantageous in predicting mortality as there hadn't been any significant differences between the survived and dead cases regarding almost all ECG abnormalities detected within the present study. As stated by **Cha et al. (2014),** the primary methods for identifying cardiac damage are electrocardiography (ECG) and elevated cardiac biochemical markers. However, in most cases, an ECG by itself is inconclusive since the heart first suffers quietly.

MDA had the highest values, while TAC showed the lowest values among those who were treated in the care unit and stayed in the hospital for more than 5 days. This difference was statistically significant, which indicates that these markers can be used as predictors of the level of needed care. Not all patients with acute poisoning are treated in intensive care units since facilities and resources are scarce in developing nations. Therefore, it's essential to understand the signs that point to the need for an intensive care unit (ICU). Lee HW and Cho YJ (2020) made conclusions that the length of hospital stay was longer in cases that required ICU and assessed breathing.

CONCLUSION

Based on the findings of the present research, MDA and TAC can be utilized as substantial prognostic screening indicators for the early presence of cardiac affection and stress that may arise earlier than cTnI throughout acute cardiotoxic poisoning, allowing for early targeted cardioprotective therapy. Biomarkers are simpler and quicker to use than other tests, as they only require a blood draw; besides that, there are no technological difficulties or operator variability while interpreting results, unlike ECG and echocardiography.

RECOMMENDATIONS:

The current study suggested using MDA and TAC as helpful markers for early predicting cardiotoxicity manifestation and mortality in individuals suffering from acute poisoning. Those who use phosphide substances or other heart-related drugs should be made more aware of their use and their toxicity. Additional investigation is required to assess the potential function of biomarker agents in forecasting morbidity and mortality in situations of acute cardiotoxic poisoning, utilizing larger sample sizes and collaboration across multiple toxicological centers to enhance the precision of marker evaluation.

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الملخص العربى

في التنبؤ بالمرض والوفاة [دور المالونديالدهيد، والقدرة الكلية لمضادات الأكسدة ، والتروبونين لحالات السمية القلبية الواردة الي مركز علاج التسممم والادمان بالمنوفية

ستهم السيد العجمي¹ و هدى ابر اهيم عبدالحفيظ ² و مروى محمد محفوظ ³ و فيروز ابر اهيم نور الدين ¹ و أميرة محمد الصعيدى¹ و غدير ماهر الشيخ⁴ و ريهام حسن الفر عونى¹ ¹قسم الطب الشرعي والسموم الاكلينيكية - كليه الطب - جامعه المنوفيه- جمهورية مصر العربية ² قسم الفار ماكولوجيا الاكلينيكيه كليه الطب – جامعه المنوفيه ³ قسم الأدوية والسموم كليه الصيدلة – جامعه المنوفيه ⁴ قسم الصحة العامة وطب المجتمع كليه الطب – جامعه المنوفيه

المقدمة: ان التسمم بالمواد التي لها تأثيرات سامة على القلب سبب الرئيسي في الوفيات المبكرة على مستوى العالم، وتشمل هذه المواد عدة فذات مركبة تستخدم لأغراض طبية أو غير طبية. الهدف: هدفت هذه الدراسة إلى دراسة دور المؤشرات الحيوية مثل المالونديالدهيد في التنبؤ بنتائج المرض والوفاة لحالات السميه القلبيه (Tnc) I)، والتروبونين TAC)، والقدرة الكلية لمضادات الأكسدة (MDA) في التنبؤ بنتائج المرض والوفاة لحالات السميه القلبيه (Tnc) I)، والتروبونين TAC)، والقدرة الكلية لمضادات الأكسدة (MDA) في التنبؤ بنتائج المرض والوفاة لحالات السميه القلبيه (Tnc) I)، والتروبونين TAC)، والقدرة الكلية لمضادات الأكسدة (ADD) والذين أدخلوا إلى مركز علاج السموم بالمنوفية. طرق البحث: أجريت هذه الدراسة على مرضى التسمم القلبي الحاد (80 مشاركا) والذين أدخلوا إلى مركز مكافحة السموم بالمنوفية على مدى ستة أشهر بالإضافة إلى 80 فردا سليما كمجموعة مراقبة طبيعية. تم جمع والذين أدخلوا إلى مركز مكامح رالية وبيانات التسمم كما تم إجراء الفحص السريري الكامل لجميع الحالات وتم جمع عينات الدم لقياس . النتائج: غالبية حالات (Tnc))، والذين القلبي 250)، والذين أدخلوا إلى مركز ملاهية وبيانات التسمم كما تم إجراء الفحص السريري الكامل لجميع الحالات وتم جمع عينات الدم لقياس مثل الطلاب حوالي (3.5%)، ومن المناطق (7.5%)، بمتوسط عمر 25.5±25.100 سنة، التسمم القابي كامل المونديالدهيد (الريفية (2.5%). (6.6%)، ومن المناطق (7.5%)، بمتوسط عمر 2015±25.200 سنة، التسمم القلبي كانت من الإناث بنسبة مثل الطلاب حوالي (3.5%)، ومن المناطق (7.5%)، بمتوسط عمر 2015±25.200 سنة، التسمم القلبي كانت من الإناث بنسبة مثل الطلاب حوالي (3.5%)، ومن المناطق (7.5%)، بمتوسط عمر 2015±25.200 سنة، التسمم القلبي كان مان الريفية (1.25%). ومال الموني يا المرضى. ونجا 8.8% من الحالات بينما بلغت نسبة الوفيات 2.1%). وكان ال رابي في وي الاناث بنسبة عن مريق الزيفي ينيما بلغت نسبة الوفيات 2.15%. كما كان كلا من الريفية (2.5%). (3.65%)، ومال طرق التسمم بلغون الماي ورال%). ومال ورال ولوبي في التنبع زليقا معامي وروبي في 2.1% مار وروبي في الاتلاع وبينما بلغت نسبة الوفيات 2.1%. كام مان وربي في ورال%). ومال (3.5%) معن طريق الابلامة. الاستني بلغت نسبة الوفيات 2.1% مان مان مان ولوبي في ورال الموبي ولالي عابي (3.5%). ومالم ما