THE PATTERN AND THE OUTCOME OF ACUTE ANTIPSYCHOTICS' INTOXICATION: POSSIBLE CARDIOTOXICITY

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ABSTRACT

Background: Acute antipsychotic drug poisoning is a frequently encountered intoxication in clinical practice. Antipsychotic poisoning can lead to potentially life-threatening cardiotoxicity; early diagnosis can improve the patient's outcome. **Aim of the Work:** The study aimed to evaluate the pattern of acute antipsychotic poisoning, the incidence of cardiotoxicity among patients poisoned by acute antipsychotics, the factors influencing this risk, and the role of cardiac biomarkers in diagnosing cardiotoxicity. **Patients and Methods**: The study enrolled 80 patients admitted to the Poison Center of Alexandria Main Hospital with a history of acute antipsychotic poisoning from January 1, 2022, to December 31, 2022. Diagnosis of intoxication depended on history, clinical symptoms, and laboratory investigations. Data was collected upon admission, and clinical examinations and laboratory investigations were conducted, including serum levels of NT-proBNP, High sensitivity cardiac troponin I (HscTroponin), Troponin I, and Creatine kinase-MB (CKMB). The Poison Severity Score (PSS) was calculated, and the outcome was recorded. **Results:** The cardiotoxicity was present in 86.25% of the cases. A highly significant association was found between cardiotoxicity and disturbed levels of consciousness. Extrapyramidal effects and abnormal pupil findings were linked to the development of cardiotoxicity (11 times and 7 times risk, respectively). Cardiac biomarkers showed insignificant elevation in the cardiotoxic group. The presence of cardiotoxicity carries a 13-fold increased risk for the development of complications (prolonged retractable disturbed level of consciousness, extrapyramidal manifestations, aspiration, chest infection, liver or renal affection). About two-thirds of the patients developed complications. **Conclusion:** Cardiac toxicity should be suspected in almost all cases of acute antipsychotic poisoning. The presence of central nervous system involvement, abnormal pupil findings, and extrapyramidal effects are alarming risks for the development of cardiotoxicity.

Keywords: *Antipsychotic poisoning, cardiotoxicity, risk factor, PSS, outcome, NT-proBNP.*

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INTRODUCTION

With the increasing magnitude of life stresses, the prevalence of psychiatric disorders rose in recent years, affecting 57.8 million people in 2021 in the United States, according to the National Institute of Health (NIH) ***(Castillo et al 2023)***. Antipsychotic medications have become widely prescribed and are available in different classes and potencies ***(Ceraso et al., 2020)***.

Antipsychotic medications are among the most effective treatments for many psychiatric disorders, such as schizophrenia and bipolar disorder ***(Huhn et al., 2019)***. They are mainly used to treat agitation, hallucinations, and other symptoms of psychosis ***(Lakshmikuttyamma et al., 2021)***. Two main classes of antipsychotics are identified as typical and atypical generations; atypical drugs are so named because they do not cause neurolepsis effects as typical antipsychotics do. Atypical antipsychotics are widely prescribed nowadays and include second-generation (SGA) and third-generation antipsychotics (TGA). All available antipsychotics block the Dopamine (D2 receptor). In addition, atypical antipsychotics block serotonin receptors in the pathways of corticolimbic neurons. Within normal dose ranges, the atypical class has

a lower overall action on D2 receptors, resulting in fewer extrapyramidal side effects ***(Vallianatou, 2020)***. The atypical drugs exhibit some histaminic, muscarinic, and adrenergic receptor modulation properties. Through potassium channel antagonism, they may have a greater effect on cardiac ion currents ***(Kaar et al., 2020)***.

Despite their efficacy, antipsychotics are associated with a wide variety of side effects linked to their chronic use, including neurologic, metabolic, cardiovascular, gastrointestinal, hematologic, genitourinary, musculoskeletal, endocrine, and other side effects ***(Kaar et al., 2020)***. Those medications are widely available, primarily prescribed, and potent, so they are frequently used as a suicidal agent globally and in Egypt ***(Khalaf et al., 2011)***. The clinical manifestations of acute antipsychotic toxicity mainly include varying degrees of central nervous system manifestations, anticholinergic effects, pupil changes, blood pressure changes, and cardiac conduction abnormalities ***(Lakshmikuttyamma et al., 2021).***

Cardiac toxicity is a broad term that encompasses asymptomatic detectable structural changes in the heart, which can manifest in the onset of arrhythmias. It can be detected by electrocardiographic analysis, vital signs (pulse and blood pressure), and cardiac biomarkers testing ***(Cardinale et al., 2021)***.

Antipsychotics-induced cardiotoxicity is considered a life-threatening adverse effect in chronic administration and acute overdose ***(Toft et al., 2017)***. In the last decade, studies have found that antipsychotics tend to produce nonfatal and fatal dysrhythmia. Serious cardiac effects were also reported, including sudden cardiac death and heart failure ***(Li et al., 2021)***.

An electrocardiogram is an integral part of the initial evaluation and monitoring of a patient suspected of having a cardiac problem ***(Manini et al., 2017)***. Heart rate-corrected QT interval (QTc) is an essential parameter in the evaluation of repolarization changes regarding the safety of drugs and disorders of the heart. Congenital disorders or acquired diseases, such as medications, cardiac ischemia, and electrolyte imbalances, might affect this interval ***(Manolis et al., 2018)***.

For a long time, cardiac troponins were used as biomarkers of choice for myocardial ischemia and different cardiac injuries, including drug-induced cardiotoxicity ***(McCarthy et al., 2019)***. In response to cardiac ischemia, the myocardium produces cardiac hormones called natriuretic peptides. While pro-BNP's N-terminal chain is inactive, brain natriuretic peptide (BNP) is physiologically active and has a vasodilating and natriuretic effect ***(Del et al., 2014)***. The inactive N-terminal chain of the pro-BNP (NT-pro-BNP) has good accuracy in the diagnosis of heart failure (HF), and recently, B natriuretic peptide has been used as a prognostic tool in many drug and toxin-induced cardiac insults ***(Cao et al., 2019; Abdel Aziz et al, 2021)***. The creatine kinase isoenzyme CK-MB is an essential enzyme for energy metabolism in the heart. Elevation of CK-MB occurs due to myocardial cell necrosis, myocardial infarction, alcoholic cardiomyopathy, pericarditis, myocarditis, and rhabdomyolysis ***(Gulia et al., 2020)***.

Cardiovascular (CV) toxicity and sudden cardiac arrest have been associated with psychiatric drugs. Newer antipsychotic agents have emerged over the years as safer drugs; however, even these agents are not without CV risk ***(Manolis et al., 2018)***.

THE AIM OF THE WORK

The current study was conducted to evaluate the pattern of acute antipsychotic poisoning, the incidence of cardiotoxicity among acute antipsychotic-poisoned patients, factors influencing this risk, and the role of cardiac biomarkers in the prediction of cardiotoxicity.

PATIENTS AND METHODS

Study Design

This is a cross-sectional study conducted on eighty patients (18 years or more) admitted to the Poison Control Center of Alexandria Main University Hospital (AMUH) suffering from acute poisoning of different classes of antipsychotic medications. The study duration was one year from January 2022 to December 2022. Patients were excluded if they had a history of heart disease, any other chronic diseases (which may affect pharmacokinetics or dynamics of the drugs), or any medications

that can affect the measured cardiac parameters. Patients with multiple drug toxicity, children, and pregnant females were also excluded ***(Sharif et al., 2024)***.

Sample size

By using G Power software ***(Faul et al , 2007)*** for sample size calculation and based on data from similar research showing the mean troponin I level in antipsychotic poisoned patients with cardiotoxicity 0.046±0.073 ng/ml as compared to 0.162±0.260 ng/ml in patients without cardiotoxicity ***(Mohamed et al., 2019)***. The minimum sample size required is 70 patients to achieve 80% study power and a 95% confidence level. To increase the study's power, the sample size was increased to 80 patients.

Ethical considerations: The Research Ethics Committee of the Faculty of Medicine, Alexandria University, approved the study *(IRB number: 00012098, serial number: 0201595).* Before the participants were involved in the study, informed consent was obtained from them or their guardians. The privacy of the data and the results of investigations were considered.

Methods

The patients underwent thorough history taking, which included the type of drug, time since drug intake, and pattern of poisoning. A complete clinical examination was performed, encompassing vital signs, GCS, pupil evaluation, cardiovascular and chest examinations, and a CNS examination, including extrapyramidal manifestations. The diagnosis of acute antipsychotic poisoning was based on a comprehensive evaluation of the patients' history of antipsychotic agent intake, clinical findings, and laboratory investigations. Supporting clinical findings of antipsychotic toxicity included CNS involvement, miosis, extrapyramidal and anticholinergic side effects, hypotension, ECG findings, and neuroleptic malignant syndrome. According to recent guidelines, routine drug screens are unlikely to be beneficial for diagnosing these patients ***(Sharif et al., 2024)***. The initial set of data obtained during the first presentation was used for analysis.

Patient severity was assessed using the Poison Severity Score (PSS), where the severity grades range from 0 to 4: none (0), mild (1), moderate (2), severe (3), and fatal (4) ***(Hammad et al., 2015)***.

Electrocardiogram analysis (ECG)

The standard 12-lead ECG was performed on patients on admission at 25mm/s paper speed and 10 mV/cm standardization, and the rate and rhythm were obtained. Advanced electrocardiogram (ECG) analysis was done, including the following measurements: PR interval, QRS duration, RR duration, and QT duration. QTc was calculated using Bazett's formula (QTC = QT / √ RR)(Dahlberg et al., 2021). The duration and abnormalities of the ST segment, as well as T wave abnormalities, were recorded. Analysis was conducted once and reviewed by a cardiologist.

Laboratory investigations

Blood samples were taken from all patients upon admission, and analyses were performed for arterial blood gases, random blood sugar, sodium, and potassium levels, creatinine, aspartate aminotransferase (AST), and four cardiac biomarkers: creatine kinase (CKMB), troponin I, Hs cTroponin, and pro-brain natriuretic peptide (proBNP).

Cardiac biomarkers

NT-proBNP measurement

All patients had a venous blood sample taken in an EDTA tube upon admission, which was centrifuged for 10 minutes at 10,000 RPM. Before analysis, the supernatant serum was collected in an Eppendorf tube and stored at -20°C. With an analytical range of 5–35,000 pg/mL, the Elecsys NTproBNP electro-chemiluminescence sandwich immunoassay method was used to test the Cobas e 601 and Cobas e 602 immunoassay analyzers (Roche Diagnostics, Mannheim, Germany). A measurement of 125 pg/mL or higher was considered a positive test result ***(Terse et al., 2016)***.

High-sensitivity cardiac troponins (HScTI) were measured on admission, and analysis was done using SIEMENS healthineers, such as ADVIA Centaur TNIH immunoassay, using direct chemiluminometric technology. The analysis ranges from 2.5-25,000 pg/ml for high-sensitivity cardiac troponin, and the

result is considered positive if the level is more than 0.047 ng/ml ***(Roffi et al., 2016)***.

Troponin I (STAT) was also measured on admission, and analysis was done using Elecsys Cobas immunoassay with measuring range (0.16- 25ng/ml) ***(Venge et al., 2002)***.

Creatine kinase-myocardial band (CK-MB) was also done from a heparinized whole blood sample using SIEMENS healthineers ADIVA Centaur. The assay range is from 0.3-150 ng/ml (positive results > 5ng/ml) ***(Cabaniss, 1990)***.

In the present study, patients with acute antipsychotic poisoning were categorized into two groups based on the presence or absence of ECG findings indicating cardiotoxicity as follows ***(Cardinale et al., 2021)***:

a. Group I: Non cardiotoxic group (n=11)
b. Group II: Cardiotoxic group (n=69)

Outcome assessment:

I) Primary outcome: complete recovery, development of complications, or death.
II) Secondary outcome: need for resuscitation room or ICU admission, need for intubation, duration of ICU and hospital stay.

Statistical analysis

Statistical analysis was conducted using the SPSS program (version 25) ***(IBM Corp., Released 2017)***. The Kolmogorov-Smirnov test for normality revealed significant findings in the distribution of the variables, prompting the adoption of non-parametric statistics ***(Field, 2013)***. Data were described using the minimum, maximum, median, 95% CI of the median, and 25th to 75th percentiles (Inter-Quartile Range (IQR). Pearson's Chi-square test was used to test the association between qualitative variables. Monte Carlo correction was carried out when indicated (25% of the expected cells are less than 5) ***(Benjamini et al, 1995)***. Odds ratio (OR) was used to quantify the strength of the association between two events. The 95% CI of the OR was calculated ***(Szumilas, 2010)***.

RESULTS

Personal data and data related to drug intake

The study involved eighty adult patients (27 males and 53 females). The 25^{th} to 75^{th} percentile of age ranged from 19.5 to 31.5 years, with a median age of 22.5 years. Female patients significantly outnumbered males (p=.004). Most of the exposure (92.5%) was suicidal, which was highly significant compared to the accidental exposure (p=.000), as illustrated in **table (1)**.

The study included 6 drugs; atypical antipsychotics comprised the major drug category, with clozapine being the most common (75%), followed by quetiapine (11.25%), risperidone (10%), and olanzapine (3.75%). Only 3 patients were presented with typical medication intake (chlorpromazine hydrochloride).

Patients were categorized into two groups based on the presence or absence of cardiotoxic manifestations in their initial ECG analysis. Group I (non-cardiotoxic group) accounted for 13.75%, while group II (cardiotoxic group) represented 86.25%. A comparison of drugs associated with the risk of cardiotoxicity revealed that risperidone, chlorpromazine, and clopixol depot presented a 100% cardiotoxic risk. Patients with clozapine and quetiapine poisoning faced a nearly 90% risk of cardiotoxicity, while olanzapine showed a 0% cardiotoxic risk, as demonstrated in **figure (1)**.

When comparing the two studied groups, there was no significant difference between them regarding age, sex, or mode of exposure. The time since drug intake varied from 1 to 17 hours in the overall cases. It was slightly longer in the non-cardiotoxic group (5 hours) than in the cardiotoxic one (3.5 hours). However, there was no significant difference between the studied groups regarding time since drug intake (p=0.456).

Clinical examination (Table 2)

Most cases presented with varying degrees of disturbed levels of consciousness. The Glasgow Coma Scale ranged from 7 to 15 across all cases, with the median GCS significantly lower in the cardiotoxic group (p=0.005). Pupil examination showed abnormal constriction in 85% of the cases, with 89.75% of these in the cardiotoxic group. Abnormal pupil findings were significantly associated with the development of cardiotoxic manifestations (odds ratio=7.3).

Extrapyramidal side effects, including movement disorders and dysarthria, were present in 47.5% of all cases and 97% of

patients who presented with cardiotoxic manifestations. A highly significant association existed between extrapyramidal manifestations and cardiotoxic risk (p=0.006). By calculating the odds ratio, the development of extrapyramidal side effects is associated with an 11.56 times higher risk of experiencing cardiotoxicity.

Vital signs assessment showed that pulse rate varied from bradycardia to tachycardia in the overall cases (52-170 beats/min), with the median pulse at 115 beats/min. Tachycardia was evident in the cardiotoxic group (median=120 beats/min), which was significantly higher compared to the non-cardiotoxic group (median=90 beats/min) (p<.001).

On blood pressure examination, patients presented with both hypotension and hypertension. Blood pressure changes were significantly greater in the cardiotoxic group compared to the other group, where the p-values of SBP and DBP were (0.015 and 0.027, respectively).

ECG analysis of the cardiotoxic group revealed that the most common type of dysrhythmia was sinus tachycardia, representing 77.5%, followed by QTc abnormalities at 67.5% (borderline QTc at 22.5% and prolonged QTc at 45%). Other types of arrhythmias, such as sinus bradycardia, respiratory sinus arrhythmia, premature ventricular contractions, supraventricular tachycardia (including atrial fibrillation), bundle branch block, and T-wave abnormalities, were recorded **(Figure 2)**.

Laboratory investigations

Table (3) reveals that in arterial blood gases analysis, pH ranged from severe acidosis (pH=7.2) to alkalosis (pH=7.55) in the overall cases. There was no significant difference between the two studied groups. However, the HCO_3 level was slightly lower in the cardiotoxic group than in the other group (20.7mEq/l and 21.7mEq/l respectively). AST was significantly higher (60 U/L) in the cardiotoxic group ($Z_{(MW)}$=2.042 and p=.041). Regarding serum Random Blood Sugar (RBS) and creatinine level, there was no statistical difference between the two groups, Z(MW)=0.636, p=.525 and Z(MW)=0.163, p=.871, respectively.

However, hyperglycemia was evident in cardiotoxic groups. The median serum levels of sodium and potassium were normal in both groups.

However, hypokalemia was recorded with the lowest serum K level of 2.6 mmol/l. Hypokalemia was found in 28.75% of the overall patients, and 91.3% of them were in the cardiotoxic group **(Table 4)**. Additionally, **figure (3)** shows that the 25th to 75th percentile of potassium level was 3.34-4 mmol/L in the cardiotoxic group and 3.6-4.1 mmol/L in the non-cardiotoxic group, so hypokalemia was more obvious in the cardiotoxic group.

Despite the insignificant difference between the two groups concerning the measured cardiac biomarkers, the median levels of both CKMB and proBNP were higher in the cardiotoxicity group (1.1 ng/ml and 42 pg/ml, respectively) compared to the second group (0.5 ng/ml and 26 pg/ml, respectively) **(Figure 4, 5)**. The HScTroponin levels were higher in the cardiotoxic group compared to the non-cardiotoxic one **(Figure 6)**.

Regarding troponin, no significant difference between the two groups was detected (Z(MW)=1.616, p=.106 NS).

In the current study, the severity scores recorded using the poison severity score were categorized as mild, moderate, and severe **(Table 5)**.

Nearly half of the patients presented with moderate toxicity, followed by severe toxicity (37.5%). It was noted that severity was significantly higher in the cardiotoxic group (p=0.007), where 85% and 96% of moderate and severe PSS, respectively, developed cardiotoxicity. (χ^2=29.922 and $p_{(MC)}$=.015). Increased severity was associated with a high risk of cardiotoxicity. However, 55.56% of the mild cases developed cardiotoxic findings in the advanced ECG analysis. Severe PSS was associated with a 23-fold risk of cardiotoxicity (OR=23.2, 95% CI: 2.130-252.689).

Outcome assessment (Table 6)

Deaths were not reported in the current study. 32.5% of the patients recovered completely, while 67.5% developed complications during their hospital stay, which included prolonged

and retractable disturbances in consciousness, extrapyramidal manifestations, aspiration, chest infections, and liver or renal involvement. 96% of those who developed complications presented with cardiotoxicity, indicating a highly significant association between cardiotoxicity and unfavorable outcomes (p< 0.001). Patients who developed cardiotoxicity were 13 times more likely to experience an unfavorable outcome (odds ratio=13.76).

In overall cases, the duration of hospital stay ranged from 24 to 288 hours. This duration was extended in the cardiotoxic group, where the 25th to 75th percentile was 30 to 72 hours, in comparison to the other group (24 to 48 hours). Nearly 76% of patients required admission to the resuscitation room or intensive care unit, and about 92% of these patients presented with cardiotoxicity, indicating a significant association between cardiotoxicity and ICU admission (p=0.01). The duration of stay in the ICU or resuscitation room ranged from 4 to 168 hours, with the median duration being higher in the cardiotoxic group than in the other group (12 hours and 8 hours, respectively). Fourteen cases (17.5%) required endotracheal intubation, and 92.8% of these cases were in the cardiotoxic group.

Table (1): Personal data and data related to drug intake.

	Total (n=80)	Cardiotoxicity		Test of significance *p*-value
		No (n=11)	Yes (n=69)	
Age				
- Min. – Max.	18.00-70.00	18.00-49.00	18.00-70.00	
- Median	22.50	22.00	23.00	$Z_{(MW)}$=0.512
- 95% CI of the median	21.00-24.00	20.00-24.00	22.00-26.00	*p*=.609 NS
- 25th Percentile – 75th Percentile	19.50-31.50	20.00-24.00	19.00-32.00	
Sex				
- Female	53 (66.25%)	9 (81.82%)	44 (63.77%)	$\chi^2_{(df=1)}$=1.382
- Male	27 (33.75%)	2 (18.18%)	25 (36.23%)	*p*=.240 NS
Circumstances				$\chi^2_{(df=1)}$=1.034
Suicidal	74	11	63	*p*=.309 NS
- n		14.86%	85.14%	
- % within Circumstances	92.50%	100.00%	91.30%	
- % within Cardiotoxicity				
Accidental				
- n	6	0	6	
- % within Circumstances		0.00%	100.00%	
- % within Cardiotoxicity	7.50%	0.00%	8.70%	
Time since intake				$Z_{(MW)}$=0.745
- Min-Max	1-17	1.50-17	1-15	*p*=.456 NS
- Median (95% CI for median)	3.5(3.5- 4)	5 (2-10)	3.5 (3.5-4)	
- 25th -75th percentile	2-5	2.00-8.00	2.00-4.00	

*χ2 Chi-square test, MW Man-Whitney test ; p, p value for comparing between the studied groups, *Statistically significant at p ≤ 0.05*

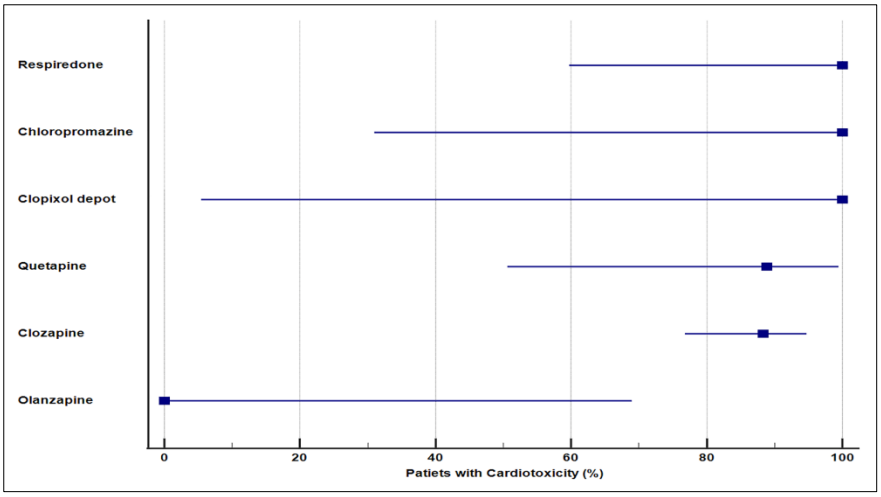

Figure (1): Forest plot graph between different drug classes and the percentage of cardiotoxicity.

Table (2): Clinical examination of antipsychotic poisoned patients.

	Total (n=80)	Cardiotoxicity		Test of significance *p*-value
		No	Yes	
Glasgow coma scale				
- Min-Max	7.00-15.00	7.00-13.00	7.00-15.00	$Z_{(MW)}$=2.841
- Median	10.00	12.00	9.00	*p*=.005*
- 95.0% CI of the median	10.00-12.00	11.00-13.00	9.00-10.00	
- 25th Percentile – 75th Percentile	8.00-12.00	11.00-13.00	8.00-11.00	
Pupil examination				$\chi^2_{(MC)(df=2)}$=8.313
Abnormal:				*p*=.045*
Constricted sluggish reactive	68	7	61	**OR**=7.314
- n		10.29%	89.71%	95%CI=1.58-33.74
- % within Pupil examination	85.00%	63.64%	88.41%	*p*=0.0107
- % within Cardiotoxicity				
Pinpoint pupil				
- n	3	0	3	
- % within Pupil examination		0.00%	100.00%	
- % within Cardiotoxicity	3.75%	0.00%	4.35%	
Normal (Round regular reactive)				
- n	9	4	5	
- % within Pupil examination		44.44%	55.56%	
- % within Cardiotoxicity	11.25%	36.36%	7.25%	
Extrapyramidal manifestations+Dysarthia				$\chi^2_{(\delta}$=7.545
Absent	42	10	32	P=.006*
- n		23.81%	76.19%	OP = 11.563
- % within Extrapyramidal manifestations	52.50%	90.91%	46.38%	95%CI = 1.403–95.311
- % within Cardiotoxicity				
Present				
- n	38	1	37	
- % within Extrapyramidal manifestations	47.50%	2.03% 9.09%	97.37% 53.62%	
- % within Cardiotoxicity				
Pulse (beats/min)				$Z_{(MW)}$=4.336
- Min-Max	52.00-170.00	80.00-100.00	52.00-170.00	*p*<.001*
- Median	115.00	90.00	120.00	
- 95.0% CI of the median	110.00-120.00	85.00-100.00	120.00-130.00	
- 25th - 75th Percentile	100.00-130.00	80.00-100.00	110.00-130.00	
Systolic blood pressure (mmHg)				
- Min-Max	60.00-180.00	70.00-120.00	60.00-180.00	$Z_{(MW)}$=2.425
- Median	110.00	100.00	120.00	*p*=.015*
- 95.0% CI of the median	110.00-120.00	90.00-110.00	110.00-130.00	
- 25th - 75th Percentile	100.00-130.00	90.00-110.00	100.00-130.00	
Diastolic blood pressure (mmHg)				$Z_{(MW)}$=2.212
- Min-Max				*p*=.027*
- Median	40.00-120.00	40.00-80.00	40.00-120.00	
- 95.0% CI of the median	70.00	60.00	70.00	
- 25th - 75th Percentile	70.00-80.00	60.00-70.00	70.00-80.00	
	60.00-80.00	60.00-70.00	60.00-80.00	

*Min-Max: Minimum – Maximum, CI: Confidence interval, MW: Mann-Whitney, NS: Statistically not significant (p≥0.05), *: Statistically significant (p<0.05).*

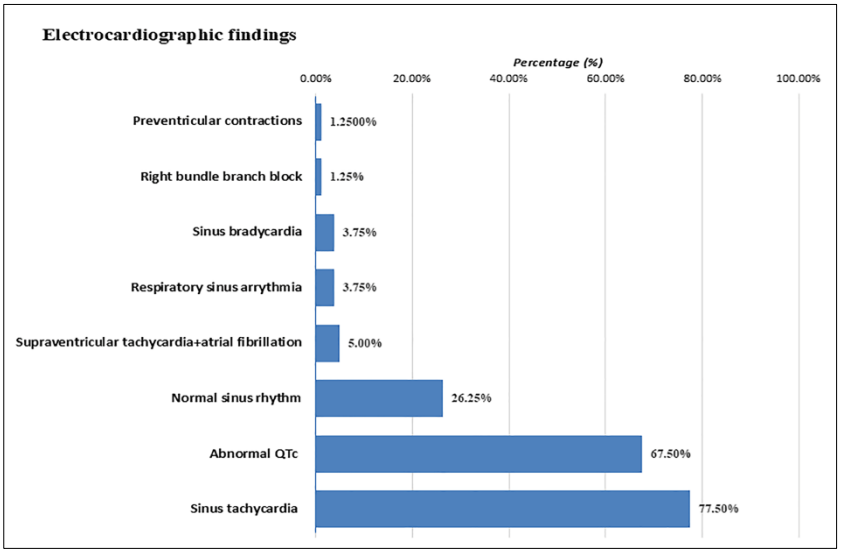

Figure (2): Electrocardiographic findings among acute antipsychotic poisoned patients.

Table (3): Laboratory investigations of antipsychotic poisoned patients.

	Total (n=80)	Cardiotoxicity		Test of significance *p*-value
		No (n=11)	Yes (n=69)	
pH				
- Min. – Max.	7.28-7.55	7.36-7.55	7.28-7.51	
- Median	7.42	7.43	7.42	$Z_{(MW)}$=0.666
- 95% CI of the median	7.42-7.43	7.39-7.48	7.42-7.43	*p*=.505 NS
- 25^{th} – 75^{th} Percentile	7.39-7.45	7.39-7.48	7.39-7.45	
HCO_3 (mEq/L)				
- Min. – Max.	13.10-28.90	13.10-24.00	14.20-28.90	
- Median	20.95	21.70	20.70	$Z_{(M W)}$=0.238
- 95% CI of the median	20.20-22.40	18.90-22.50	20.20-22.60	*p*=.812 NS
- 25^{th} – 75^{th} Percentile	19.20-23.25	18.90-22.50	19.20-23.20	
AST (U/L)				
- Min. – Max.	8.00-60.00	8.00-29.00	8.00-60.00	
- Median	24.00	19.00	26.00	Z(MW)=2.042
- 95% CI of the median	21.00-27.00	16.00-25.00	24.00-29.00	p=.041*
- 25th – 75th Percentile	17.50-31.50	16.00-25.00	19.00-32.00	
RBS (mg/dl)				
- Min. – Max.	76.00-312.00	79.00-123.00	76.00-312.00	
- Median	111.00	110.00	112.00	Z(MW)=0.636
- 95% CI of the median	108.00-114.00	95.00-120.00	110.00120.00	p=.525 NS
25th – 75th Percentile	96.50-130.00	95.00-120.00	98.00-135.00	
Serum creatinine (mg/dl)				
- Min. – Max	0.30-2.40	0.50-1.10	0.30-2.40	
- Median	0.60	0.70	0.60	Z(MW)=0.163
- 95% CI of the median	0.60-0.70	0.70-1.10	0.60-0.70	p=.871 NS
- 25th – 75th Percentile	0.50-0.80	0.50-0.70	0.50-0.80	
Serum Sodium (mmol/L)				
- Min. – Max.	132.00-147.00	133.00-140.00	132.00-147	
- Median	139.00	139.00	140.00	$Z_{(MW)}$=1.5075
- 95% CI of the median	138.00-140.00	138.00-140.00	140.00-141.00	*p*=.132 NS
- 25^{th} – 75^{th} Percentile	137.00-140.00	134.00-140.00	137.00-141.00	
Serum Potassium (mmol/L)				
- Min. – Max.	2.60-4.90	2.60-4.40	2.80-4.90	
- Median	3.70	3.70	3.70	$Z_{(MW)}$=0.350
- 95% CI of the median	3.70-3.90	3.60-4.10	3.60-3.90	*p*=.726 NS
- 25^{th} – 75^{th} Percentile	3.34-4.05	3.60-4.10	3.34-4.00	
CKMB level (ng/ml)				
- Min-Max	0.00-10.00	0.10-10.00	0.00-7.00	
- Median	1.05	0.50	1.10	$Z_{(MW)}$=0.148
- 95% CI for median	0.50-1.50	0.40-1.50	0.70-1.50	*p*=.883 NS
- 25^{th} -75^{th} percentile	0.10-2.10	0.40-1.50	0.00-2.50	
Troponin I (ng/ml)				
- Min-Max	0.00-1.14	0.00-0.50	0.00-1.14	
- Median	0.10	0.10	0.10	$Z_{(MW)}$=1.616
- 95% CI for median	0.10-0.15	0.10-0.50	0.10-0.15	*p*=.106 NS
- 25^{th} -75^{th} percentile	0.10-0.14	0.05-0.10	0.10-0.15	
HSc Troponin (ng/ml)				
- Min-Max	0.00-2.50	0.00-0.07	0.00-2.50	
- Median	0.00	0.00	0.00	$Z_{(MW)}$=0.800
- 95% CI for median	0.00-0.01	0.00-0.00	0.00-0.01	*p*=.424 NS
- 25^{th} -75^{th} percentile	0.00-0.05	0.00-0.00	0.00-0.05	
proBNP (pg/ml)				
- Min-Max	10.00-171.00	12.00-89.00	10.00-171.00	
- Median	39.60	26	42	$Z_{(MW)}$=0.728
- 95% CI for median	27.00-43.00	19.80-40.7	32.00-47.00	*p*=.467 NS
- 25^{th} -75^{th} percentile	16.75-64.00	19.80-40.7	16.70-64.00	

Min-Max: Minimum – Maximum, CI: Confidence interval, MW: Mann-Whitney U, NS: Statistically not significant (p≥0.05).

Table (4): The distribution of acute antipsychotic poisoned patients regarding changes in their serum potassium level (n=80).

Hypokalemia	Total (n=80)	Cardiotoxicity	
		Group I Non cardiotoxic	Group II Cardiotoxic
Normal (3.5-5.5mmol/L)			
- n	57	9	48
- % within Hypokalemia		15.76%	84.21%
- % within Cardiotoxicity	71.25%	81.82%	69.57%
Hypokalemia (<3.5mmol/L)			
- n	23	2	21
- % within Hypokalemia		8.70%	91.30%
- % within Cardiotoxicity	28.75%	18.18%	30.43%
Test of Significance		$\chi^2_{(df=1)}$=0.695	
***p*-value**		*p*=.404 NS	
Odds Ratio		1.969	
95% CI		0.391-9.906 NS	

n: number of patients χ^2*: Pearson Chi-square , OR: Odds ratio, CI: Confidence Interval, NS: Statistically not significant (p≥0.05) df: degree of freedom.*

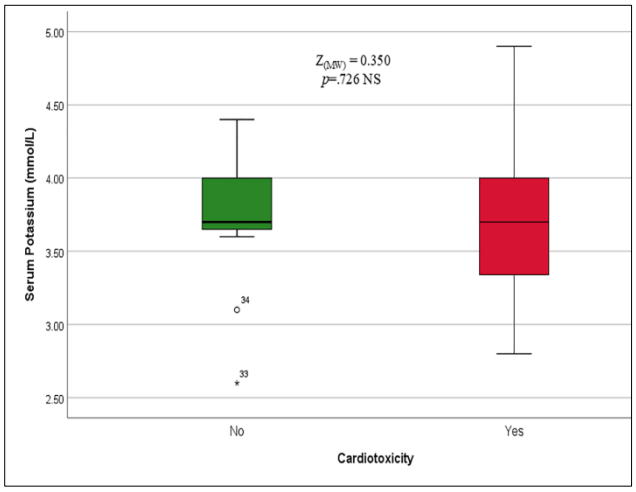

Figure (3): Box and whisker graph of serum potassium level (mmol/L) in the two studied group, the thick line in the middle of the box represents the median, the box represents the inter-quartile range (from 25th to 75th percentiles), the whiskers represents the minimum and maximum after excluding outliers (filled circles).

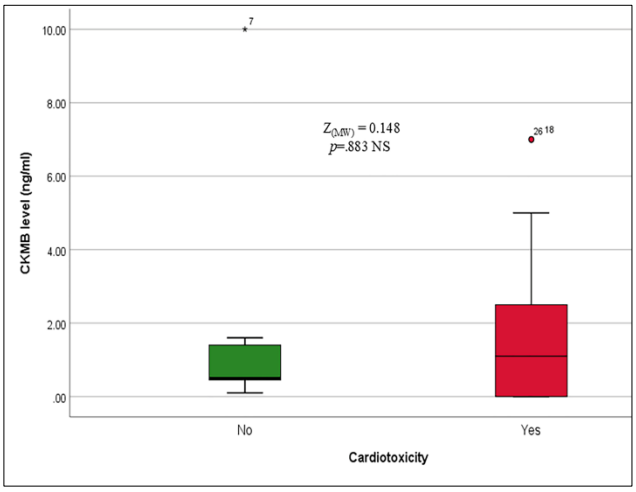

Figure (4): Box and wisker graph showing elevation of the serum level of CKMB among acute antipsychotic patients in cardiotoxic group in comparison to the non-cardiotoxic group.

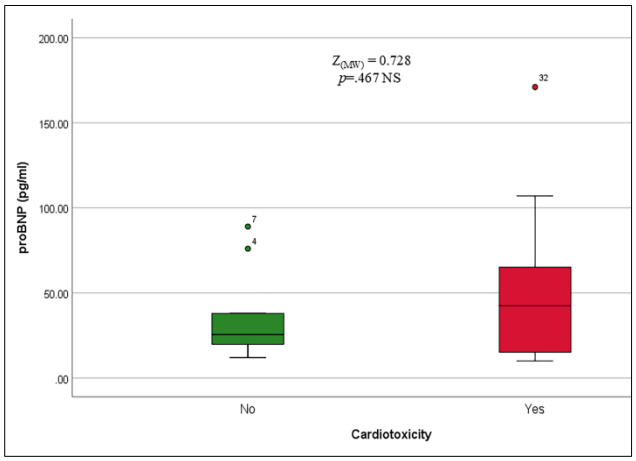

Figure (5): Box and wisker graph showing elevation of the serum level of proBNP among acute antipsychotic poisoned patients in cardiotoxic group in comparison to the non cardiotoxic group.

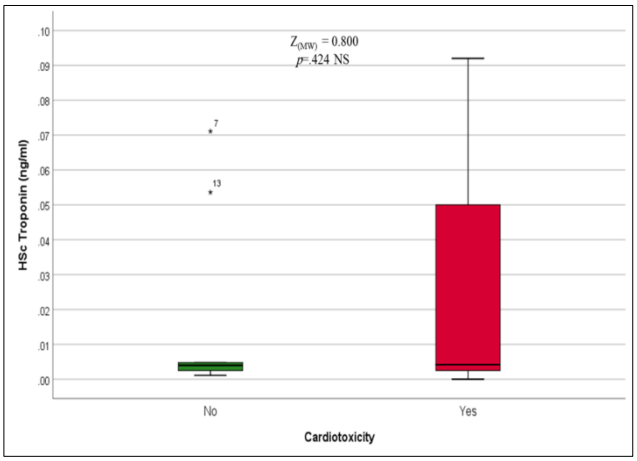

Figure (6): Box and wisker graph showing elevation of the serum level of Hsc Troponin among acute antipsychotic patients in cardiotoxic group in comparison to the non cardiotoxic group.

Table (5): Assessment of patients' severity using Poison severity score (PSS).

Poison severity score	Total	Cardiotoxicity		Test of significance *p*-value
		No	Yes	
Mild				$\chi^2_{(do=2)}$ =29.922
- n	9	4	5	$p_{(MC)}$=.015
- % within Poison severity score		44.44%	55.56%	
- % within Cardiotoxicity	11.25%	36.36%	7.25%	(OR=23.2,
Moderate				95% CI: 2.130-252.689)
- n	41	6	35.00	
- % within Poison severity score		14.63%	85.37%	
- % within Cardiotoxicity	51.25%	54.55%	50.72%	
Severe				
- n	30	1	29	
- % within Poison severity score		3.33%	96.67%	
- % within Cardiotoxicity	37.50%	9.09%	42.03%	
Total				
- n	80	11	69	
- %	100.00%	13.75%	86.25%	

*n: Number of patients, χ^2 : Pearson Chi-Square, df: degree of freedom, MC: Monte Carlo correction for p value of Pearson Chi square test, *: Statistically significant (p<.05).*

Table (6): Primary and secondary outcome assessment of antipsychotic poisoned patients.

Cardiotoxicity	Total (n=80)	Primary Outcome		Test of significance *p*-value
		survived and discharged without complications	survived with complications	
No				
- n	11	9	2	$\chi^2_{(df=1)}$=14.140
- % within Cardiotoxicity		81.82%	18.18%	*p*<.001*
- % within outcome	13.75%	34.62%	3.70%	OR = 13.765
Yes				95% CI [2.705-70.049]
- n	69	17	52	
- % within Cardiotoxicity		24.64%	75.36%	
- % within outcome	86.25	65.38%	96.30%	
Total				
- **n**	80	26	54	
- **%**	100.00%	32.50%	67.50%	
		Secondary Outcome		
	Total (n=80)	**Group I(n=11)**	**Group II(n=69)**	
Duration of Hospital Stay (hours)				
- Min-Max				
- Median	24.00-288.00	24.00-144.00	24.00-288.00	$Z_{(MW)}$=1.557
- 95% CI for median	48.00	48.00	72.00	*p*=.119 NS
- 25th -75th percentile	48.00-72.00	48.00-144.00	72.00-120.00	
	30.00-72.00	24.00-48.00	30.00-72.00	
Duration of ICU stay (hours)				
- n				$Z_{(MW)}$=1.253
- Min-Max	61	5	56	*p*=.210 NS
- Median	4.00-168.00	6.00-24.00	4.00-168.00	
- 95.0% CI of the median	12.00	8.00	12.00	
- 25th - 75th Percentile	12.00-24.00	6.00-24.00	12.00-24.00	
	8.00-16.00	6.00-8.00	8.00-16.00	
Need for ICU Admission	61	5(8.19%)	56(91.8%)	$\chi^2_{(df=1)}$=6.679 *p*=.010*
Need for intubation	14 (17.50%)	1 (9.09%)	13 (18.84%)	$\chi^2_{(df=1)}$=0.625 *p*=.429 NS

*n: Number of patients, χ^2 : Pearson Chi-Square, df: degree of freedom, *: Statistically significant (p<.05), OR odd ratio Min-Max: Minimum – Maximum, CI: Confidence interval, MW: Mann-Whitney, χ^2: Pearson Chi-Square, df: degree of freedom, NS: Statistically not significant (p≥0.05), *: Statistically significant (p<0.05).*

DISCUSSION

The presence of any abnormal changes in the electrocardiographic analysis defines cardiac toxicity ***(Cardinale et al., 2021)***. In the present study, nearly 86% of the patients were found to have cardiotoxicity characterized by various ECG abnormalities. This could be explained by different mechanisms, including immunomodulation and proinflammatory processes, catecholamine activation, stimulation of cardiac muscle apoptosis, ischemia due to decreased coronary blood flow from norepinephrine-induced vasoconstriction, and other substances released by cardiac mast cells, as well as impaired enzymes in cellular metabolism like pyruvate kinase and mitochondrial malate dehydrogenase ***(Daniel et al., 2023)***.

In the present study, more than 85% of cases presented with cardiotoxicity despite the intake of atypical antipsychotic drugs. This finding aligns with ***D'Errico et al. (2021)***,

who noted that there is no evidence that second-generation antipsychotics are safer than first-generation drugs.

However, ***Sharif et al. (2024)*** stated that the newer antipsychotic agents have lower severities compared to the older generations.

Despite the use of antipsychotics to decrease suicidal ideation, the study showed significant evidence that antipsychotic drugs are misused as potent suicidal agents among young individuals, with females predominating ***(Hutton et al, 2019)***.

By comparing the two studied groups, no significant difference was found regarding age. ***He et al. (2022)*** reported an association between older ages and the occurrence of dysrhythmias even in therapeutic doses.

In the current study, most cases developed varying degrees of disturbed consciousness. About 41.1% of the cases in the study conducted with ***Adree, et al. (2023)*** presented with a disturbed level of consciousness. Extrapyramidal manifestations (EPS) are common side effects of antipsychotic medication use ***(Lakshmikuttyamma et al., 2021)***.

In this study, 97% of the cases that developed cardiotoxicity had extrapyramidal movement disorders or dysarthria. EPS were associated with 11 times the risk for the development of cardiotoxicity. The hypothesis could explain this, that oxidative stress through lipid peroxidation is considered to be the mechanism for both neurotoxicity and cardiotoxicity ***(Daniel et al., 2023)***.

Regarding blood pressure changes, both hypotension and hypertension were detected. Orthostatic hypotension could be explained by the blockade of alpha-1 adrenoceptors, as stated by ***Proudman et al. (2020)***. The blockage of α1 receptors decreases the baroreceptor's sensitivity in detecting low blood pressure that has developed cardiotoxicity, which has extrapyramidal orthostatic hypotension ***(Nakamura et al., 2016)***. Hypertension was also reported in acute antipsychotic poisoning as detected by ***Correll et al (2015)***.

In acute overdose, many studies reported transient hypertension that resolves after drug withdrawal, which is thought to be due to dopamine receptor antagonism in the kidneys and catecholamines activation as mentioned by ***Alves et al. (2019)***.

There has been an increased awareness of the application of advanced ECG analysis for predicting sudden cardiac arrest and dysrhythmias in the general population ***(Tan et al., 2009)***. In clinical toxicology, the use of advanced ECG analysis could be vitally important due to its availability, low cost, and non-invasive nature ***(Yates, 2012)***.

By the application of advanced ECG analysis on the studied patients, the following ECG changes were found; sinus tachycardia was the most common dysrhythmia (77.5%) and this can be explained by the antipsychotic-induced antagonism of muscarinic receptors type 2 which could cause cardiovascular adverse effects when vagal tone is decreased ***(Li et al., 2021)***. Any other types of dysrhythmias (sinus bradycardia, supraventricular arrhythmias including atrial fibrillation, bundle branch blocks, ventricular arrhythmia) were detected and supported the study findings ***(Wu et al., 2015; Elsayed et al., 2021)***.

In the current study, QTc abnormalities were found in 67.5 % of the cases, which was in agreement with ***Khalaf et al. (2011)***. Different electrocardiographic disturbances, like flattening or inversion of T-waves (45% of the cases), were detected, which was in agreement with ***Daniel et al. (2023)***.

Those findings are common with antipsychotic use, especially clozapine, and remain relatively unexplained. The variable abnormalities detected could be explained by the different mechanisms of cardiotoxicity, as mentioned before ***(Daniel et al., 2023)***. Therefore, the current work hypothesized that an advanced analysis of the entire ECG, not just the QT interval, could be a more helpful predictive tool. This was also in agreement with ***Johannesen et al. (2014)***.

The study found that the median bicarbonate level was nearly normal except for sporadic cases of metabolic acidosis. That was in contrast to ***Varma et al. (2007)***, who reported severe acidosis with a case of olanzapine. Moreover, respiratory depression and retention of CO2 are other explanations for antipsychotic induced acidemia, as stated by ***Robinson et al. (2004)***.

Regarding the significant increase in the serum AST in the cardiotoxic group, this might be due to the oxidative stress of the antipsychotic metabolites on the liver, as mentioned by ***Platanic et al. (2021)***.

Hyperglycemia was evident among the cardiotoxic group, which could result from impaired glycemic control due to the anticholinergic effects of atypical drugs, in addition to oxidative stress, mitochondrial damage in pancreatic insulin-secreting cells, and increased peripheral resistance to insulin in tissues ***(Kumar et al., 2019)***.

Hypokalemia was present, which could be due to a surge of catecholamines and an increase in insulin levels resulting in potassium shift from the outside to the inside of cells ***(Hoorn et al, 2014)***.

In the current work, elevation of the serum CK-MB was found in both studied groups. Apart from cardiac injury, this elevation could be attributed to the recorded extrapyramidal manifestations, agitation ***(Laoutidis et al., 2014)***.

On the other hand, CKMB is considered a nonspecific cardiac biomarker that cannot be accurately relied on in the detection of myocardial insults. That explains the result of the present study, where CKMB was not significantly elevated in the cardiotoxic group, and is also in agreement with ***Melkersson et al. (2006)***.

Cardiac troponins have always been widely acknowledged as the mainstay for diagnosing a variety of myocardial insults ***(Blaes et al., 2018)***. Mild elevation of cardiac troponins was recognized, but no significant difference was noticed between the two examined groups. The positive results could be explained by antipsychotics-induced myocarditis and decreased coronary blood flow in the acute poisoning, which was reported by ***Klein et al. (2022)*** and ***Wassef et al. (2015)***.

CK-MB, as well as troponin I, are best detected four hours after acute myocardial insult, peak within 24 hours, and gradually normalize within 48-72 hours. The HscTnI assay can be detected within the first three hours of the myocardial insult and identifies much lower levels ***(Patibandla et al., 2024)***. However, in the present study, most cases were presented to emergency settings with acute poisoning at different time intervals, which may have affected the detection of positive cardiac enzymes due to the transient nature of the myocardial insult ***(Li et al., 2021)***. The mechanism of antipsychotics that induces myocarditis remains unclear. Various hypotheses have been proposed, including immunoglobulin IgE-mediated pathways, cytokine responses, and hyper catecholaminergic states related to oxidative stress ***(Vaziriet et al., 2023)***.

Furthermore, antipsychotic-induced tachycardia increases myocardial oxygen demand and exacerbates cardiac ischemia. Those findings were supported by ***Lin et al. (2014)***. In the present study, pro-BNP was measured on admission; a few cases exceeded the normal level. Wide variability in test results was found; higher levels were among cardiotoxic patients, but no significant difference was found in comparison to the non-cardiotoxic group, which disagrees with ***Kropp et al (2005)*** who concluded that, antipsychotic medications influence the plasma concentration of NT-proBNP, which could be used to identify high-risk patients.

The possible mechanism for BNP secretion is thought to involve left ventricular wall strain, along with selective upregulation by proinflammatory cytokines at both transcriptional and translational levels of BNP secretion ***(Hall, 2004)***.

In the present study, cardiac dysrhythmia may induce NT-proBNP secretion. The hemodynamic consequences associated with the loss of atrial contraction, particularly in atrial fibrillation, may contribute to an impairment of cardiac function, thus elevating BNP ***(Nishikimi et al., 2021)***.

Poison severity score was usually used to assess the severity of antipsychotic poisoning ***(Abdel Aziz et al., 2021)***; however, the present work showed that despite being mild in PSS, 55% of patients developed cardiotoxic manifestations, which coincide with ***Hammad et al., (2015)*** at Menoufia University who concluded a significant association between PSS and ECG changes in acute antipsychotics poisoning.

Considering the need for ICU admission, patients in the cardiotoxic group significantly

required admission to the resuscitation room or ICU compared to the non-cardiotoxic group. Moreover, the duration of ICU and hospital stays was noticeably longer among cardiotoxic patients. Those findings were in agreement with ***El-Gharabawy et al. (2018)***.

In the present study, ICU admission is required for cases presenting with a GCS below 9, those with unstable arrhythmia, and those complicated by either hypoventilation or aspiration.

Despite the high morbidity induced by antipsychotic drugs, no mortality was reported among the patients in the current study, which aligns with ***Taipale et al. (2020)*** This stands in contrast to other studies that documented the occurrence of many deaths due to antipsychotic therapy or overdose ***(Torniainen et al., 2015; Wu et al., 2015)***.

Limitations of the study

The primary limitation of this study is that it is conducted at a single center, which limits the generalizability of the results. Additionally, the number of patients was relatively small, and the manual calculation of ECG parameters is somewhat difficult.

CONCLUSION

The current study demonstrated that the presence of central nervous system involvement, abnormal pupil findings, and extrapyramidal manifestations in patients acutely intoxicated with antipsychotics poses an alarming risk for the development of cardiotoxicity. ECG offered a rapid assessment of cardiac affection among those patients. PSS provided a comprehensive assessment of the general condition of the patients. Cardiac biomarkers provided valuable information for the diagnosis of antipsychotic-induced cardiotoxicity however, assessment of NT-proBNP at the time of admission showed wide variability with a non-significant elevation. Also, they may take time to analyze, potentially delaying diagnosis and treatment decisions.

RECOMMENDATIONS

Cardiac toxicity should be suspected in almost all cases of antipsychotic poisoning; advanced ECG and PSS are recommended for all cases, as they are widely available in clinical settings, allowing for quick and comprehensive clinical assessment of toxicity and cardiac affection. NT-proBNP should be measured at different time intervals during management. Future research is needed across multiple centers with a larger sample size to validate the results.

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