RISK FACTORS FOR THE NEED OF INTENSIVE CARE UNIT ADMISSION AMONG ACUTE CLOZAPINE POISONED PATIENTS: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Introduction: Clozapine is the most effective antipsychotic drug for the treatment of refractory schizophrenia. It is also seen as the most toxic in its class. Drug poisoning has been detected as one of the major causes of intensive care unit (ICU) admission. **The study** aimed to develop a decision tool using readily available parameters in the emergency room for patients with acute clozapine poisoning to identify patients who need ICU admission. **Patients and Methods:** This retrospective cohort study was carried out on 121 patients with acute clozapine poisoning admitted to the Tanta University Poison Control Center. For each patient, demographic, toxicological, clinical data, laboratory findings, and electrocardiography records were analyzed against ICU admission. **Results:** The results revealed that 29 patients needed ICU admission, and they were significantly older than patients who did not. A significant association was found between the history of addiction and/or psychiatric illness, mode of poisoning, amount and dose of clozapine, and the need for ICU admission. Patients admitted to ICU had a significantly higher percentage of tachycardia, tachypnea, and hyperthermia, while they had a lower Glasgow Coma Scale (GCS) and oxygen saturation. Besides, they had a significantly higher percentage of hyperglycemia, respiratory alkalosis, and prolonged QTc interval. There was a significant association between the need for ICU admission and both electrocardiogram (ECG) severity grading and acute clozapine poisoning severity score. The logistic regression model showed that large doses of clozapine, tachypnea, increased the severity of ECG grading, and decreased level of O_2 saturation on admission significantly increased the probability of requiring ICU admission. Based on receiver operating characteristic curve analysis, take a dose of clozapine at a cut-off value above 250 mg is a good predictor of the need for ICU admission. **Conclusion:** It could be concluded that higher taken doses of clozapine, tachypnea, low O_2 saturation, and increased severity of ECG grading are considered independent predictors of the need for ICU admission in acute clozapine poisoned patients.

Keywords: Clozapine; Acute poisoning; Intensive Care Unit; Predictors, Drug dose

INTRODUCTION

Acute antipsychotic drug poisoning is one of the most important toxicological emergencies that need hospital referral. Clozapine is a highly lipophilic dibenzodiazepine neuroleptic, and it is the firstly synthesized atypical antipsychotic drug **(Goto et al., 2017; Yousefsani et al., 2019)**. It gained the approval of the Food and Drug Administration (FDA) in 1989 for the treatment of resistant schizophrenia, affective disorders, aggression, and some

neurological disorders **(Chiappini et al., 2020)**.

Antipsychotics were detected as one of the top five substance classes most frequently involved in all human exposures according to the 2018 annual report of the American Association of Poison Control Centers (AAPCC) **(Gummin et al., 2019)**. In Egypt, antipsychotic drugs were the second most common central nervous system agents causing poisoning (20%) admitted to the National Poisoning Center, Kasr Alainy Teaching Hospital, and clozapine was the most reported antipsychotic drug (4.2%) among pharmaceutical drugs causing poisonings **(Abdel Rasheed et al., 2020)**. Moreover, clozapine was the highest drug (35%), causing acute antipsychotic poisoning in patients admitted to the Tanta University Poison Control Center (TUPCC) **(Mubarak et al., 2019)**.

Atypical antipsychotics are effective in controlling the positive (delusions, hallucinations) and negative (flat affect, anhedonia) manifestations of schizophrenia with fewer extrapyramidal side effects when compared to typical antipsychotics **(Lebin et al., 2018)**. The exact molecular mechanism of clozapine is unknown; however, it has a high dopamine receptor 4 (D_4) blockade, muscarinic receptor 4 (M_4) agonism, as well as antagonistic activity at serotonin (5HT) 2A, 5HT2C, dopamine receptor 2 (D_2), muscarinic receptor 2 (M_2), and histamine receptor 1 (H_1) **(Leung et al., 2017)**.

The various side effects of clozapine made it limited to the third line in the treatment of schizophrenia despite its clinical superiority compared to other atypical antipsychotics. Clozapine can cause agranulocytosis, neutropenia, sedation, and hypersalivation. It also has other serious side effects, including myocarditis, seizures, gastrointestinal hypomotility, and diabetic ketoacidosis **(Clark et al., 2018)**.

Regarding acute clozapine poisoning, the most common clinical manifestations are tachycardia, respiratory depression, confusion, agitation, drowsiness, hypotension, lethargy, seizures, and prolonged QT interval **(Yuen et al., 2018; Macfarlane et al., 2020)**. In the absence of a specific antidote, acute clozapine poisoning treatment, like other acute antipsychotic poisonings, is based mainly on adequate supportive measures. Furthermore, the intensive care unit (ICU) admission may be needed, especially when cardio-pulmonary instability and other major organ manifestations are present or expected **(Finn et al., 2009; Levine and Ruha, 2012)**.

Drug poisoning has been detected as one of the major causes of ICU admission. Unfortunately, paramedics occasionally admit critically drug poisoned patients to tertiary hospitals. On the other hand, unnecessary ICU admission of stable drug poisoned patients leads to patient harm and high medical costs burden **(Okazaki et al., 2020)**. It is essential to recognize that the patient will benefit from monitoring facilities at ICU at an early stage. The need for ICU admission of poisoned patients can dependably be predicted by clinical observations made while the patient is in the emergency room. This prediction must be exact in identifying all patients that require ICU admission **(van den Oever et al., 2017)**.

Unfortunately, there are limited data about the severity, the clinical course, and outcome of acute clozapine poisoning **(Lebin et al., 2018)**. Hence, this study aimed to develop a decision tool for early identification of acute clozapine poisoned patients who need ICU admission, using readily available parameters in the emergency room.

PATIENTS & METHODS

Study design

This retrospective cohort study was carried out on all acute clozapine poisoned patients who were admitted to Tanta University Poison Control Center (TUPCC) in the period from the start of January 2019 to the end of May 2020 after approval from the head of TUPCC and the

Research Ethics Committee (REC) of Faculty of Medicine, Tanta University (approval number: 34036/8/20). Participants were anonymized with strict consideration of the confidentiality of personal and clinical data.

Eligibility criteria

Inclusion criteria: All patients (from both genders and all ages) with acute clozapine poisoning were included in this study. Diagnosis of acute clozapine poisoning was established based on a history of clozapine intake and/or acute clozapine toxicity manifestations. The combination of CNS depression, tachycardia, prolonged QT, and orthostatic hypotension or antimuscarinic manifestations should indicate the possibility of acute clozapine poisoning as no single feature is pathognomonic for atypical antipsychotic overdose **(Levine and Ruha, 2012)**. A standard sheet was conducted to record the complete clinical assessment of each patient.

Exclusion criteria: Patients with ingestion or exposure to other substances in addition to clozapine, patients with a history of chronic medical conditions (e.g., cardiovascular, respiratory, renal, or hepatic diseases), and patients with insufficient data in the hospital records.

Data collection and definition of variables

Data of included patients with acute clozapine poisoning were retrieved and carefully examined. Demographics (age and sex), past medical history (psychiatric illness or drug addiction), and toxicological history (number of ingested tablets, taken dose of clozapine, mode of poisoning, and delay period between drug intake and hospital arrival) were recorded for each patient in a standard data collection sheet that was designed to record complete data of each patient. Data of complete clinical examination that was performed for all patients at admission were recorded for each patient. It included assessing consciousness level by Glasgow coma scale (GCS) (adult and pediatric score), vital signs, general and systemic examination.

The normal ranges of vital signs vary according to age. In adults, the normal ranges of blood pressure (mmHg), pulse (beats/min.), respiratory rate (cycle/min), and temperature (°C) are 90-140/60-90, 60-100, 16-24 and 35-38 respectively **(Diane and Jillian, 2004; Nelson et al., 2011)**. In pediatrics aged below 18 years, the normal range of temperature is (36.6-37.9°C rectally) **(Nield and Kamat, 2011)**. The normal ranges of blood pressure, pulse, and respiratory rate are determined according to standardized blood pressure, pulse, and respiratory rate tables **(Hartman and Cheifetz, 2011)**.

Results of laboratory investigations done at admission and before treatment of the included patients were collected in the designed sheet. They included random blood sugar (RBS), arterial blood gas analysis (ABG), serum sodium (Na) and potassium (K) levels, liver enzymes (serum aspartate transaminase (AST), alanine transaminase (ALT)) activities, kidney function tests (blood urea, serum creatinine) and complete blood count (CBC).

The severity of symptoms and signs of acute clozapine poisoning was graded according to the WHO International Program on Chemical Safety-Poisoning Severity Score (IPCS-PSS) adopted from **Persson et al. (1998)** into:

-None grade: no symptoms or signs.

-Minor grade: transient, mild, and spontaneously resolving symptoms; vomiting, drowsiness, breathlessness, mild anticholinergic symptoms, mild extrapyramidal symptoms, mild transient hypo/hypertension, mild acid-base disturbances (HCO_3~15-20 mmol/L, pH ~7.25-7.32 or 7.50-7.59) and hyperthermia of short duration.

-Moderate grade: pronounced or prolonged symptoms or signs; vomiting, constipation, unconsciousness with an appropriate response to pain, confusion, agitation, delirium, infrequent local or generalized seizures, pronounced extrapyramidal symptoms, pronounced

anticholinergic symptoms, hypoxemia requiring extra oxygen, pronounced hypo/hypertension, pronounced acid-base disturbances (HCO3-~10-14 mmol/L, pH ~7.15-7.24), pronounced electrolytes disturbances (K+ 2.5-2.9 mmol/L) and hyperthermia of longer duration.

-Severe grade: severe or life-threatening symptoms or signs; pneumonia, deep coma with an inappropriate response to pain or unresponsive to pain, respiratory depression with insufficiency, extreme agitation, shock.

Twelve-lead electrocardiography (ECG) records of the included patients were retrieved for each patient. Any detected ECG abnormalities and corrected QT (QTc) interval were registered. The corrected QT (QTc) interval was measured according to Bazett's formula; $QTc = QT/\sqrt{RR}$ (Normally, QTc is < 440 msec) **(Postema and Wilde, 2014; Miura et al., 2015)**.

ECG changes induced by acute clozapine poisoning were graded according to poisoning severity score (PSS) **(Akdur et al., 2010)** into Minor ECG changes: isolated extrasystoles, sinus tachycardia (HR ≥ 100-140 in adults). Moderate ECG changes: sinus tachycardia (HR =140-180 in adults), frequent extrasystoles, atrial fibrillation/flutter, AV-block I-II, prolonged QRS and QTc-time, repolarization abnormalities, or myocardial ischemia. Severe ECG changes: severe sinus tachycardia (HR≥180 in adults), life-threatening ventricular dysrhythmias, AV block III, asystole, myocardial infarction.

Finally, the need for ICU admission, in-hospital mortality, and the duration of hospital stay for each patient was recorded in the data collection sheet.

Statistical Analysis

Acute clozapine poisoned patients were divided into two groups according to the need for ICU admission. Statistical analysis was performed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015). For quantitative data, the Shapiro-Wilk test for normality was performed besides the visual assessment of graphs. For normally distributed data, variables were summarized as mean ± standard deviation (SD), and comparison between two groups was carried out using independent samples T-test. For abnormally distributed data, the variables were summarized as the median and interquartile range (IQR, expressed as 25^{th} – 75^{th} percentiles), and comparison between two groups was carried out using the Mann-Whitney test. Multivariate backward, stepwise logistic regression was conducted to assess the contribution of relevant variables to the need for ICU admission, which had a p-value less than 0.2 on univariate analysis **(Bursac et al., 2008)**, with odds ratio (OR) and 95% confidence interval for OR (95% CI) calculated for each variable. Analysis of the receiver operating characteristic (ROC) curve was done to assess the relation between true-positive results and false-positive results for each measurement **(DeLong et al., 1988)**. The area under ROC curve was graded as follows: 0.90-1 = excellent; 0.80-0.90 = good; 0.70-0.80 = fair; and 0.60-0.70 = poor. Sensitivity and specificity were calculated. Sensitivity is the proportion of those whom the test indicated requiring ICU admission among those who already had ICU admission. Specificity is the percentage of those who judged not needing ICU out of those who already were not admitted to ICU. A p-value ≤of 0.05 was adopted for interpretation of statistical tests.

RESULTS

The data of 121 patients with acute clozapine poisoning who met the inclusion criteria were analyzed. Patients who needed ICU admission were 29 patients (23.97%), while patients who did not need ICU admission were 92 (76.03%). Demographics and toxicological data of studied patients were shown in table (1). Regarding age, patients who need ICU admission were significantly older than patients who did not, and the majority of

them (86.2%) were adults. Sex was comparable in both groups with no statistical difference. There was a significant association between the need for ICU admission with the history of addiction and/or psychiatric illness, mode of poisoning (suicidal in 89.7% of patients needed ICU admission), number of tablets, and take a dose of clozapine. On the other hand, delay time showed no statistically significant association with the need for ICU admission. Furthermore, based on the Mann-Whitney test, there was a significant association between the taken dose of clozapine and the presence of history addiction and/or psychiatric illness (P-value: 0.049 and 0.001, respectively) (Table 2).

Regarding manifestations and clinical data of acute clozapine poisoned patients, there was a significant association between the presence of urination, agitation, seizures, shock, pallor, and the need for ICU admission, as illustrated in table (3). Moreover, patients who need ICU admission showed a significant association with constricted pupils and chest manifestations.

Comparisons of GCS, vital signs and oxygen saturation between both groups were made (Table 4). Severe loss of consciousness, tachycardia, hyperthermia, and tachypnea was significantly reported in acute clozapine poisoned patients who needed ICU admission. Moreover, these patients had a significantly lower median value of oxygen saturation than patients who were not admitted to ICU. A non-significant statistical difference was detected in systolic and diastolic blood pressure between both groups.

Table (5) shows that patients admitted to ICU had significantly higher mean values of RBS, WBCs, and QTc than patients who were not admitted to ICU. Furthermore, they had a significantly higher median value of pH than the other group. Table (6) shows that patients who need ICU admission had a significantly higher percentage of hyperglycemia, respiratory alkalosis, and prolonged QTc interval (51.7%, 69%, and 58.6%, respectively). There was a significant association between ECG severity grading and the need for ICU admission. Conversely, no significant association was reported between the type of ECG changes and the need for ICU admission. Sinus tachycardia was the most detected ECG change in patients who needed ICU admission and all patients with acute clozapine poisoning (69% and 50.4%, respectively).

Regarding acute clozapine poisoning severity, according to PSS, there was a significant association between it and the need for ICU admission. All patients with severe acute clozapine poisoning and 23.3% of patients with moderate acute clozapine poisoning needed ICU admission. Simultaneously, all patients with no or minor acute clozapine poisoning did not need ICU admission. Moreover, patients admitted to ICU had a significantly more extended period of hospital stay than patients who were not admitted to ICU, as shown in table (7).

Backward stepwise logistic regression analysis was conducted to investigate potential factors which may significantly contribute to the need for ICU admission (Table 8). The variables entered the first step were chosen based on clinical relevance and a p-value <0.2 in univariate analysis. Those variables included age, history of addiction and/or psychiatric disease, a dose of clozapine, vital signs on admission (pulse, respiratory rate, blood pressure, and temperature), O_2 saturation, RBS, acid-base status, ECG severity grading, and QTc interval. The last step of the regression model showed that the factors which increased the probability of requiring ICU admission significantly included a high dose of clozapine (OR=1.003, 95% CI=1.001-1.006, p=0.002), presence of tachypnea compared to the standard rate for age (OR=29.008, 95% CI=2.907-289.441, p=0.004) and increased severity of ECG grading (OR=5.994, 95% CI=1.568-22.922, p=0.009). Increased level of O_2 saturation

on admission was significantly associated with decreased probability of requiring ICU admission (OR=0.903, 95% CI=0.858-0.950, p<0.001). The p-value of age was above the threshold of 0.05 adopted for significance; however, the age variable was retained in the final model as its removal significantly affected the final model.

A ROC analysis was carried out to assess the predictive performance of the taken dose of clozapine and O_2 saturation on admission for the need for ICU admission (Fig. 1, 2). The area under the ROC curve was 0.887 (95% CI = 0.816 to 0.937, p<0.001) for the administered dose, indicating good predictive performance. At a cut-off value above 250 mg, the administered dose had a sensitivity and specificity of 93.1% and 75%. As for O_2 saturation on admission, the area under the ROC curve was 0.689 (95% CI = 0.599 to 0.770, p=0.003), indicating low to acceptable predictive performance. At a cut-off value of 95% or below, O_2 saturation on admission had a sensitivity and specificity of 48.3% and 92.4%.

Table (1): Comparison of demographic and toxicological data between patients needed ICU admission and patients didn't need ICU admission after acute clozapine poisoning

Variables		Need for ICU admission						Tests of significance	
		No (n = 92)		Yes (n = 29)		Total (n = 121)		Test statistic	p
Age (Years)	**Median (IQR] (Range)**	19 [10 - 25] (1.5 - 50)		27 [20 - 35] (15 - 44)		21 [15- 27] (1.5 – 50)		3.115[a]	0.002*
Age groups	**Pediatric**	35	38%	4	13.8%	39	32.2%	5.936[b]	0.015*
	Adult	57	62%	25	86.2%	82	67.8%		
Sex	**Female**	53	57.6%	15	51.7%	68	56.2%	0.310[b]	0.578
	Male	39	42.4%	14	48.3%	53	43.8%		
Past History	**No**	69	75%	16	55.2%	85	70.2%	4.148[b]	0.042*
	Addiction and / or Psychiatric illness	23	25%	13	44.8%	36	29.8%		
	Addiction	7	7.6%	5	17.2%	12	9.9%	FE	0.157
	Psychiatric illness	17	18.5%	8	27.6%	25	10.7%	1.116[b]	0.291
Mode of poisoning	**Suicidal**	58	63%	26	89.7%	84	69.4%	10.960[b]	0.004*
	Accidental	27	29.3%	0	0%	27	22.3%		
	Addict	7	7.6%	3	10.3%	10	8.3%		
Amount (tablets)	**Median (IQR] (Range)**	5 [2 - 8] (0.5 - 30)		10 [7 - 12] (2 - 60)		6 [2 – 10] (0.5 – 60)		4.641[a]	<0.001*
Dose taken (mg)	**Median (IQR] (Range)**	150 [100 - 275] (12.5 - 1000)		1000 [500 - 1000] (100 - 6000)		200 [100 – 750] (12.5 – 6000)		6.288[a]	<0.001*
Delay time (hours)	**Median (IQR] (Range)**	3 [2 - 5.5] (0.5 - 20)		4 [2 - 6] (1 - 12)		3.5 [2- 6] (0.5 – 20)		0.954[a]	0.340

[a]: Mann-Whitney test; [b]: Pearson's Chi square test of independence; FE: Fisher's exact test; IQR: Interquartile range; ICU: Intensive care unit; n: Number; * significant at p≤0.05

Table (2): Comparison between the taken dose of clozapine and past history of addiction and psychiatric illness of acute clozapine poisoned patients (n = 121)

Taken dose of clozapine (mg)	Addiction		Mann-Whitney test		Psychiatric illness		Mann-Whitney test	
	No (n = 109)	Yes (n = 12)	z	p	No (n = 96)	Yes (n = 25)	z	p
Median	200	650	1.972	0.049*	162.5	500	3.355	0.001*
IQR	100 - 600	175 - 1000			100 - 450	325 - 1000		
Minimum	12.5	100			12.5	50		
Maximum	6000	1200			2000	6000		

IQR: Interquartile range; n: Number; * significant at p≤0.05

Table (3): Comparison of clinical data between patients needed ICU admission and patients didn't need ICU admission after acute clozapine poisoning

Variables		Need for ICU admission						Tests of significance	
		No (n = 92)		Yes (n = 29)		Total (n = 121)		Test statistic	p
Vomiting		13	14.1%	8	27.6%	21	17.4%	2.783[a]	0.095
Salivation		1	1.1%	1	3.4%	2	1.7%	FE	0.423
Urination		1	1.1%	3	10.3%	4	3.3%	FE	0.042*
Extrapyramidal syndrome		1	1.1%	1	3.4%	2	1.7%	FE	0.423
Slurred speech		28	30.4%	13	44.8%	41	33.9%	2.039[a]	0.153
Drowsiness		41	44.6%	7	24.1%	48	39.7%	3.844[a]	0.050
Irritability		7	7.6%	0	0%	7	5.8%	FE	0.15
Agitation		10	10.9%	8	27.6%	18	14.9%	FE	0.037*
Hallucination		8	8.7%	4	13.8%	12	9.9%	FE	0.479
Seizures		0	0%	4	13.8%	4	3.3%	FE	0.003*
Shock		0	0%	9	31.0%	9	7.4%	FE	<0.001*
Pallor		0	0%	7	24.1%	7	5.8%	FE	<0.001*
Pupil	Constricted	53	57.6%$	28	96.6%$	81	66.9%	23.052[b]	<0.001*
	Dilated	1	1.1%	1	3.4%	2	1.7%		
	RRR	38	41.3%$	0	0%$	38	31.4%		
Chest examination	Free	85	92.4%$	14	48.3%$	99	81.8%	31.790[b]	<0.001*
	Wheeze	3	3.3%	0	0%	3	2.5%		
	Crepitation	4	4.3%$	12	41.4%$	16	13.2%		
	Wheeze & crepitation	0	0%	3	10.3%	3	2.5%		

[a]: Pearson's Chi square test of independence; [b]: Fisher-Freeman-Halton exact test; FE: Fisher's exact test; ICU: Intensive care unit; n: Number; *significant at p≤0.05; $: significant difference compared to the other group

Table 4: Comparison of Glasgow coma scale and vital data between patients needed ICU admission and patients didn't need ICU admission after acute clozapine poisoning

Variables		Need for ICU admission						Tests of significance	
		No (n = 92)		Yes (n = 29)		Total (n = 121)		Test statistic	p
GCS	**Mean ± SD (Range)**	13 ± 2 (9 – 15)		7.9 ± 2.8 (3 – 15)		11.8 ± 3.1 (3 – 15)		7.003[a]	<0.001*
Degree of loss of consciousness according to GCS	**Minor (13-15)**	61	66.3%$	2	6.9%$	63	52.1%	62.566[b]	<0.001*
	Moderate (9-12)	31	33.7%	8	27.6%	39	32.2%		
	Severe (3-8)	0	0%$	19	65.5% $	19	15.7%		
Pulse rate (beat/min)	**Mean ± SD (Range)**	109.3 ± 22 (66 - 160)		124.2 ± 23 (80 - 177)		112.9 ± 23.1 (66 - 177)		-3.150[a]	0.002*
	Normal	51	55.4%	5	17.2%	56	46.3%	12.937[b]	<0.001*
	Tachycardia	41	44.6%	24	82.8%	65	53.7%		
Blood pressure (mmHg)	**SBP: Mean ± SD (Range)**	110.5 ± 18 (80 - 160)		104 ± 23.2 (60 - 150)		108.9 ± 19.5 (60 - 160)		1.5858[a]	0.116
	DBP: Mean ± SD (Range)	67.3 ± 11.7 (40 - 100)		62.4 ± 15 (40 - 90)		66.1 ± 12.7 (40 - 100)		1.821[a]	0.071
	Normal	79	85.9%	21	72.4%	100	82.6%	3.825[c]	0.134
	Hypertensive	4	4.3%	1	3.4%	5	4.1%		
	Hypotensive	9	9.8%	7	24.1%	16	13.2%		
Temperature (°C)	**Mean ± SD (Range)**	37 ± 0.3 (36.5 - 38.3)		37.3 ± 1 (36 - 40)		37.1 ± 0.6 (36 - 40)		-1.170[a]	0.251
	Normal	69	75%$	20	69%$	89	73.6%	4.244[b]	0.039*
	Hyperthermia	11	12%	9	31%	20	16.5%		
	Not recorded	12	13%	0	0%	12	9.9%	FE	0.068
Respiratory rate (cycle/min)	**Mean ± SD (Range)**	21.5 ± 3.7 (16 - 32)		27.8 ± 9.1 (18 - 50)		23.3 ± 6.2 (16 - 50)		-3.433[a]	0.002*
	Normal	70	76.1% $	12	41.4% $	82	67.8%	22.615[c]	<0.001*
	Tachypnea	10	10.9% $	16	55.2% $	26	21.5%		
	Not recorded	12	13%	1	3.4%	13	10.7%	FE	0.186
Oxygen saturation (%)	**Median [IQR] (Range)**	98 [97 - 99] (91 - 100)		96 [92 - 99] (42 - 100)		98 [97 - 99] (42 - 100)		-3.114[d]	0.002*

GCS: Glasgow coma scale; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; [a]: Independent samples T-test; [b]: Pearson's Chi square test of independence; [c]: Fisher-Freeman-Halton exact test; FE: Fisher's exact test; [d]: Mann-Whitney test; SD: standard deviation; IQR: Interquartile range; ICU: Intensive care unit; n: Number; SD: Standard Deviation; *significant at p≤0.05; $: significant difference compared to the other group

Table (5): Comparison of mean and median values of routine laboratory investigations and corrected QT interval between patients needed ICU admission and patients didn't need ICU admission after acute clozapine poisoning

Variables		Need for ICU admission			Tests of significance	
		No (n = 92)	Yes (n = 29)	Total (n = 121)	Test statistic	p
Random blood sugar (mg/dL)	**Mean ± SD (Range)**	130.4 ± 32 (85 - 250)	159.2 ± 63.1 (77 - 378)	137.8 ± 43.7 (77 - 378)	-3.357[b]	0.024*
pH	**Median (IQR] (Range)**	7.4 [7.4 - 7.5] (7.3 - 7.6)	7.5 [7.4 - 7.5] (7.2 - 7.6)	7.4 [7.4 - 7.5] (7.2 - 7.6)	2.219[a]	0.027*
$PaCO_2$ (mmHg)	**Mean ± SD (Range)**	33.7 ± 5.5 (20.3 - 45.5)	31.2 ± 6.7 (18.3 – 42.9)	33.1 ± 5.9 (18.3 – 45.5)	1.971[b]	0.051
HCO_3 (mmol/L)	**Mean ± SD (Range)**	22.3 ± 3.6 (14.8 - 31.6)	21.6 ± 4.7 (15.2 - 35.9)	22.2 ± 3.9 (14.8 - 35.9)	0.800[b]	0.425
Serum sodium level (mmol/L)	**Mean ± SD (Range)**	140 ± 4.4 (128.5 - 149)	140.2 ± 5.8 (128.1 - 154)	140.1 ± 4.8 (128.1 - 154)	-0.121[b]	0.904
Serum potassium level (mmol/L)	**Mean ± SD (Range)**	3.7 ± 0.6 (2.6 - 4.8)	3.8 ± 0.7 (2.5 - 5.3)	3.7 ± 0.6 (2.5 - 5.3)	-0.303[b]	0.762
AST (U/L)	**Median (IQR] (Range)**	22 [18 - 27] (10 - 46)	22.1 [17 - 28] (16 - 370)	22 [18 - 28] (10 -370)	0.733[a]	0.464
ALT (U/L)	**Median (IQR] (Range)**	18 [15 - 22] (10 - 51)	18.5 [13 - 28] (11 - 207)	18 [14 - 22] (10 - 207)	0.384[a]	0.701
Blood urea (mg/dL)	**Mean ± SD (Range)**	26.1 ± 6 (13 - 40)	27.1 ± 8.6 (15 - 56)	26.3 ± 6.7 (13 - 56)	-0.643[b]	0.522
Serum creatinine (mg/dL)	**Mean ± SD (Range)**	0.79 ± 0.21 (0.3 - 1.4)	0.84 ± 0.24 (0.4 - 1.4)	0.8 ± 0.22 (0.3 - 1.4)	-1.083[b]	0.281
Hemoglobin (gm/dL)	**Mean ± SD (Range)**	11.5 ± 1.5 (8.9 - 15)	12.1 ± 1.5 (9.4 - 15)	11.6 ± 1.5 (8.9 - 15)	-1.681[b]	0.096
White blood cells count ($x10^3/mm^3$)	**Mean ± SD (Range)**	9.2 ± 3.5 (3.9 - 22.7)	11.4 ± 4.4 (5.2 - 22)	9.7 ± 3.8 (3.9 - 22.7)	-2.652[b]	0.009*
Platelets count ($x10^3/mm^3$)	**Mean ± SD (Range)**	223.7 ± 63.9 (111 - 462)	224.5 ± 65.6 (120 - 350)	223.9 ± 64 (111 - 462)	-0.053[b]	0.958
QTc interval (msec)	**Mean ± SD (Range)**	410.1 ± 35.4 (334 - 499)	451.3 ± 40.2 (364 - 520)	420.8 ± 40.7 (334 - 520)	-5.024[b]	<0.001*

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; QTc: Corrected QT; [a]: Mann-Whitney test; [b]: Independent samples T-test; IQR: Interquartile range; ICU: Intensive care unit; n: Number; SD: Standard Deviation; * significant at p≤0.05

Table (6): Comparison of laboratory investigations and ECG interpretation between patients needed ICU admission and patients didn't need ICU admission after acute clozapine poisoning

Variables		Need for ICU admission						Tests of significance	
		No (n = 92)		Yes (n = 29)		Total (n = 121)		Test statistic	p
Random blood sugar	**Normal**	63	68.5%	14	48.3%	77	63.6%	7.092[a]	0.008*
	Hyperglycemia	21	22.8%	15	51.7%	36	29.8%		
	Not recorded	8	8.7%	0	0%	8	6.6%	FE	0.196
Arterial blood gas	**Normal**	34	41%$	4	13.8% $	38	33.9%	10.297[b]	0.012*
	Metabolic acidosis	16	19.3%	4	13.8%	20	17.9%		
	Metabolic alkalosis	3	3.6%	1	3.4%	4	3.6%		
	Respiratory alkalosis	30	36.1% $	20	69%$	50	44.6%		
	Not recorded	9	9.8%	0	0%	9	7.4%	FE	0.112
Serum sodium level	**Normal**	61	66.3%	18	62.1%	79	65.3%	1.398[b]	0.529
	Hyponatremia	8	8.7%	4	13.8%	12	9.9%		
	Hypernatremia	8	8.7%	4	13.8%	12	9.9%		
	Not recorded	15	16.3%	3	10.3%	18	14.9%	FE	0.558
Serum potassium level	**Normal**	51	55.4%	15	51.7%	66	54.5%	0.498[a]	0.481
	Hypokalemia	27	29.3%	11	37.9%	38	31.4%		
	Not recorded	14	15.2%	3	10.3%	17	14%	FE	0.760
QTc interval evaluation	**Normal**	64	69.6%	10	34.5%	74	61.2%	20.680[a]	<0.001*
	Prolonged (≥440 msec)	13	14.1%	17	58.6%	30	24.8%		
	Not recorded	15	16.3%	2	6.9%	17	14%	FE	0.357
ECG severity grading	**None**	34	37%	1	3.4%	35	28.9%	27.217[b]	<0.001*
	Minor	27	29.3%	7	24.1%	34	28.1%		
	Moderate	16	17.4%	17	58.6%	33	27.3%		
	Severe	0	0%	2	6.9%	2	1.7%		
	Not recorded	15	16.3%	2	6.9%	17	14%	FE	0.357
ECG changes	**Normal sinus rhythm**	36	39.1%	4	13.8%	40	33.1%	2.427[a]	0.297
	Sinus tachycardia	41	44.6%	20	69%	61	50.4%	2.742[a]	0.254
	Depressed ST segment	2	2.2%	2	6.9%	4	3.3%	2.050[b]	0.320
	Supraventricular tachycardia	0	0%	2	6.9%	2	1.7%	2.802[b]	0.210
	Pathological Q wave	0	0%	1	3.4%	1	0.8%	4.391[b]	0.076
	Ventricular fibrillation	0	0%	1	3.4%	1	0.8%	1.873[b]	0.511
	Not recorded	15	16.3%	2	6.9%	17	14%	FE	0.357

QTc: Corrected QT; [a]: Pearson's Chi square test of independence; [b]: Fisher-Freeman-Halton exact test; FE: Fisher's exact test; ECG: Electrocardiogram; ICU: Intensive care unit; n: Number; SD: Standard Deviation;*significant at p≤0.05; $: significant difference compared to the other group

Table (7): Comparison of severity according to Poisoning Severity Score, in-hospital mortality and duration of hospital stay between patients needed ICU admission and patients didn't need ICU admission after acute clozapine poisoning

Variables		Need for ICU admission						Tests of significance	
		No (n = 92)		Yes (n = 29)		Total (n = 121)		Test statistic	p
Severity according to PSS	None	10	10.9%	0	0%	10	8.3%	77.073[a]	<0.001*
	Minor	49	53.3%$	0	0%$	49	40.5%		
	Moderate	33	35.9%	10	34.5%	43	35.5%		
	Severe	0	0%$	19	65.5%$	19	15.7%		
In-hospital mortality	Died	0	0%	2	6.9%	2	1.7%	FE	0.056
	Improved	92	100%	27	93.1%	119	98.3%		
Hospital stays (hours)	Median [IQR] (Range)	10 [5 - 16] (2 - 36)		24 [18 - 48] (5 - 144)		12 [6 - 20] (2 - 144)		5.738[b]	<0.001*

PSS: Poisoning Severity Score; [a]: Fisher-Freeman-Halton exact test; [b]: Mann-Whitney test; FE: Fisher's exact test; IQR: Interquartile range; ICU: Intensive care unit; n: Number; *significant at p≤0.05; $: significant difference compared to the other group

Table (8): A logistic regression for prediction of the need for ICU admission in acute clozapine poisoned patients (n = 121)

Variables		Wald test	p	OR	95% CI for OR	
					Lower	Upper
First step	Age (years)	5.090	0.024*	1.188	1.023	1.380
	Past history of addiction/psychiatric illness	1.182	0.277	0.226	0.015	3.300
	Dose taken (mg)	6.924	0.009*	1.005	1.001	1.008
	Pulse (Tachycardia vs normal)	2.247	0.134	0.094	0.004	2.067
	Respiratory rate (Tachypnea vs normal)	5.758	0.016*	95.461	2.305	3952.738
	Blood pressure:					
	Hypotension vs normal blood pressure	1.825	0.177	29.359	0.218	3955.022
	Hypertension vs normal blood pressure	0.113	0.737	2.235	0.020	245.209
	Temperature (Hyperthermia vs normal)	2.736	0.098	0.076	0.004	1.612
	O_2 saturation (%)	8.044	0.005*	0.846	0.753	0.950
	RBS (Hyperglycemia vs normal)	0.786	0.375	0.338	0.031	3.722
	Arterial blood gas:					
	Metabolic acidosis vs normal	0.715	0.398	0.081	0.000	27.627
	Respiratory alkalosis vs normal	1.034	0.309	4.441	0.251	78.606
	Metabolic alkalosis vs normal	0.191	0.662	6.065	0.002	19682.437
	ECG severity grading	2.883	0.090	74.449	0.514	10780.002
	QTc interval (Prolonged vs normal)	0.588	0.443	0.131	0.001	23.607
Final model	Age (years)	3.025	0.082	1.093	0.989	1.207
	Dose taken (mg)	9.199	0.002*	1.003	1.001	1.006
	Respiratory rate (Tachypnea vs normal)	8.232	0.004*	29.008	2.907	289.441
	O_2 saturation (%)	15.608	<0.001*	0.903	0.858	0.950
	ECG severity grading	6.848	0.009*	5.994	1.568	22.922

QTc: Corrected QT; vs: versus; ICU: Intensive care unit; RBS: Random blood sugar; ECG: Electrocardiogram;

***: Statistically significant at p ≤ 0.05; OR: Odd`s ratio; CI: Confidence interval**

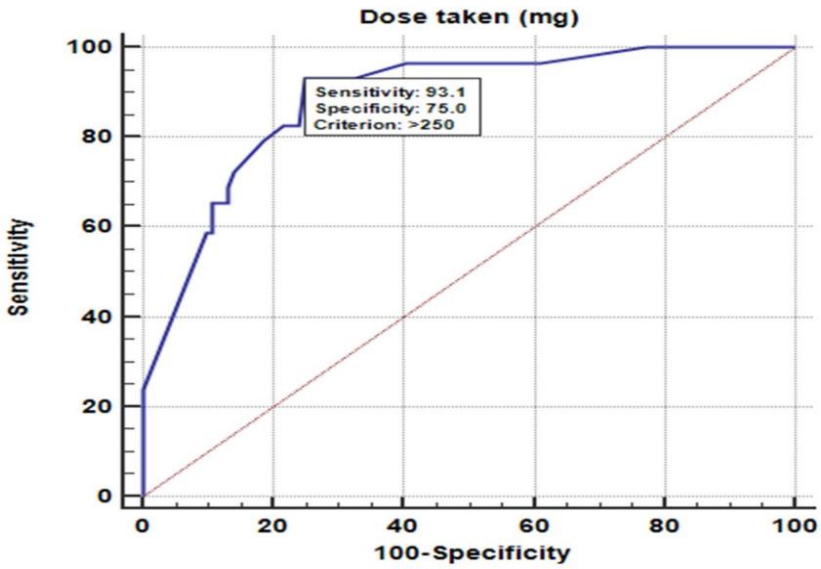

Figure (1): ROC curve of dose taken of clozapine for prediction of ICU admission need in acute clozapine poisoning.

ROC: Receiver operating characteristic; ICU: intensive care unit

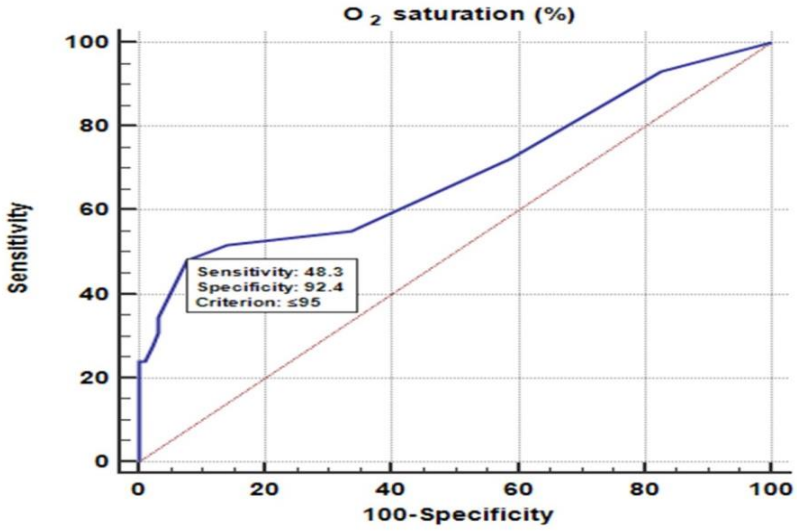

Figure (2): ROC curve of O_2 saturation for prediction of ICU admission need in acute clozapine poisoning.

ROC: Receiver operating characteristic; ICU: intensive care unit

DISCUSSION

Clozapine is considered the most effective antipsychotic drug for refractory schizophrenia, although; it is reported as the most toxic in its class. It has severe adverse effects, such as blood dyscrasia, neutropenia, agranulocytosis, hypotension, sedation, seizures, constipation, sialorrhea, metabolic syndrome, and cardiotoxicity, have transported it to third and fourth in the line of treatment **(Kanniah and Kumar, 2020)**.

Acute poisoning represents a frequent cause of ICU admissions, and even though the overall mortality may be low, they may consume considerable ICU resources. Accurate prognostic information for critically ill poisoned patients could help physicians decide whether and when poisoned patients might benefit from therapy in the ICU. This will decrease hospital morbidity and mortality in patients

with acute poisoning **(Khalifa and Lashin, 2018; Assaf et al., 2019)**. This retrospective cohort study of acute clozapine intoxication was designed to clarify the risk factors for ICU admission in acute clozapine poisoning. To achieve this target, demographic, toxicological, clinical data, ECG records, and laboratory findings were analyzed against ICU admission in acute clozapine poisoned patients.

The main findings of this research confirmed that the median of age, gender, mode of poisoning, the taken dose, delay time, and clinical data of acute clozapine poisoned patients were more or less in agreement with many previous observations in the majority of centers in Egypt and across the world **(Krämer et al., 2010; Meli et al., 2014; Hammad et al., 2016; Bellissima et al., 2018; Mubarak et al., 2019; Abdalwahab and youssof, 2020)**.

Statistical analysis revealed that a significant association was detected between the need for ICU admission and history of addiction and/or psychiatric illness, mode of poisoning, amount, and take a dose of clozapine in the studied patients. Moreover, the mode of poisoning was suicidal in 89.7% of patients who needed ICU admission. Previously published research on clozapine overdose have mainly reported large-dose ingestions in patients who were attempting suicide and who were on psychic therapy **(Krämer et al., 2010; Lebin et al., 2018)**. In the same line, **(Aslan et al., 2011)** have found that (22.5%) of the antipsychotic poisoned patients had prior psychiatric consultation before admission to the emergency room for drug poisoning. Furthermore, **Hammad et al. (2015)** has found a significant relationship between the PSS of antipsychotic overdose and patients who were on psychic therapy.

There was a significant association between the taken dose of clozapine in the studied patients and the presence of a history of addiction and/or psychiatric illness. This could be explained by that schizophrenic patient usually attempt suicide by taking high doses of drugs that they can easily access. Thus, acute poisoning with one of the antipsychotics drugs may be expected among these patients **(Hammad et al., 2016)**.

Regarding clinical manifestations of acute clozapine poisoned patients, there was a significant association between the presence of urination, agitation, seizures, shock, pallor, and the need for ICU admission. In general, the variability in clinical manifestations of acute clozapine poisoning is due to significant inter-personal variability in clozapine levels, response, and adverse events. This may be explained by pharmacogenomic variation in clozapine metabolism through the effect on Cytochrome P450 (CYP450) enzymes by drug interactions, smoking cessation, excessive caffeine, risk of infection, and inflammation **(Williams and Park, 2015; Clark et al., 2018)**.

In the current study, seizures were detected in a few acute clozapine poisoned patients admitted to the ICU. This was in accordance with **Krämer et al. (2010)** and **Lebin et al. (2018)**, who reported few clozapine intoxications complicated by status epilepticus. Seizures have been reported in clozapine overdose previously as clozapine lowers the seizure threshold, possibly through antagonism of the gamma-aminobutyric acid receptor **(Varma et al., 2011)**. Moreover, clozapine overdose can produce an agitated delirium characteristic of anticholinergic toxicity due to significant antagonism of the muscarinic (M1) receptor **(Levine and Ruha, 2012)**.

The patients who need ICU admission in this study showed a significant association with constricted pupils and chest manifestations. The atypical antipsychotic agents' affinity for a-adrenergic receptors in the eye is greater than the affinity for muscarinic receptors; therefore, miosis may occur due to a-adrenergic receptor blockade despite the

presence of anticholinergic toxicity **(Levine and Ruha, 2012)**. Furthermore, pneumonia is an additional common adverse event associated with clozapine that may go unrecognized **(Kuo et al., 2013; Leung et al., 2017)**. The pathophysiology of clozapine-related pneumonia is likely multifactorial. Clozapine is a potent agonist at the muscarinic (m4) receptors leading to the increased production of saliva. Profuse sialorrhea may lead to repeated aspiration and subsequent pneumonia **(Leung et al., 2017)**. Another theory is that clozapine can directly affect the immune system, increasing a patient's susceptibility to pneumonia **(Galappathie et al., 2014)**.

It was noticed that patients admitted to ICU had significantly lower GCS means than patients who were not admitted to ICU in this study. Coma is the most observed symptom in clozapine toxicity **(Lebin et al., 2018)**. Moreover, **Gawlikowski et al. (2011)** had detected a high frequency of CNS depression in acute clozapine poisoned patients in their retrospective analysis. Clozapine induces altered consciousness mainly by inhibition of central histamine H_1 receptors as well as M_1, M_2, M_3, and M_5 muscarinic receptors **(Aringhieri et al., 2018; Lebin et al., 2018)**.

In the current study, tachycardia, hyperthermia, and tachypnea were significantly reported in acute clozapine poisoned patients who needed ICU admission. Moreover, these patients had a significantly lower median value of oxygen saturation than patients who were not admitted to ICU. **Bellissima et al. (2018)** has found that shortness of breath, fever, and tachycardia were the most common clinical presentations of clozapine toxicity. Clozapine induced fever through the immune-modulating effect by increasing soluble tumor necrosis factor (TNF) receptor p55, p75, and soluble interleukin-2 (IL-2) receptor. Interleukin- 6 (IL-6) has also been suggested to induce fever by elevating the set point of body core temperature via temperature-sensitive neurons in the hypothalamus due to pyrogenic cytokines **(Gerasimou et al., 2017)**.

Hyperglycemia was significantly reported in most patients (51.7%) who need ICU admission in this study. Clozapine and olanzapine are the most common antipsychotic drugs that can cause hyperglycemia. This may be due to their interaction with pancreatic β-cell receptors leading to interference with normal insulin secretion **(Cooper et al., 2016)**. Furthermore, clozapine may cause hyperglycemia either by increasing insulin resistance or altering a regulatory molecule as glucagon **(Chathoth et al., 2018)**.

In the current study, patients admitted to ICU had significantly higher mean values of WBCs than patients who were not admitted. The high total leucocytic count was found in all clozapine intoxicated patients in the study done by **Abdalwahab and youssof (2020)**. **Song et al. (2018)** have referred clozapine-induced leukocytosis to the changes in plasma concentrations of granulocyte colony-stimulating factor, IL-2, and IL-6 cytokines TNF-α.

Sinus tachycardia was the most detected ECG change in patients who needed ICU admission and in all patients with acute clozapine poisoning in this study. Furthermore, most of the studied patients who need ICU admission had significantly prolonged QTc interval. This was in accordance with many previous studies **(Gerasimou et al., 2017; Bellissima et al., 2018; El-Gharbawy et al., 2018; Abdalwahab and youssof, 2020)**. Sinus tachycardia was attributed to alpha-adrenergic and muscarinic receptor antagonism while blocking the delayed rectifier potassium channel (KIR) may also occur, leading to delay in cardiac repolarization and prolongation of QTc interval **(Levine and Ruha, 2012; Zhu et al., 2019)**. QT prolongation is considered a risk factor for adverse cardiovascular events such as Torsades de pointes,

ventricular arrhythmias, atrial fibrillation, and sudden cardiac death in patients with acute clozapine poisoning **(Miura et al., 2015; Zhu et al., 2019)**.

Regarding ECG severity grading, there was a significant association between it and the need for ICU admission in the present study. This was in accordance with **El-Gharbawy et al. (2018)**, who reported a significant association between ECG grading and the need for ICU admission in acute antipsychotic poisoned patients. This could be attributed to that ECG findings may reflect myocardial status, ion channel condition, and adrenergic tone alternation in acute drug poisoning **(Yates and Manini, 2012)**. Moreover, there was a significant association between acute clozapine poisoning severity according to PSS and the need for ICU admission in this study. This was in line with **Hammad et al. (2015)**, who reported that 100% of acute antipsychotic poisoned cases admitted to ICU were of both severe and fatal grades, and 32% of cases were of moderate grade. At the same time, all patients with none or minor grades did not need ICU admission.

In the current study, the logistic regression model showed that the factors which significantly increased the probability of requiring ICU admission included a high dose of clozapine, presence of tachypnea, decreased level of O_2 saturation, and increased severity of ECG grading on admission. These results are generally in line with other research analyzing parameters and/or ICU prediction models for acutely intoxicated patients **(Borg et al., 2016; Brandenburg et al., 2017; van den Oever et al., 2017; Okazaki et al., 2020)**. The risk of cardiac dysrhythmias was the primary cause of admission of most patients poisoned by antidepressants or antipsychotics drugs to ICU. Moreover, according to reported guidelines, poisoned patients with respiratory insufficiency and/or hemodynamic instability should be treated in ICU **(Borg et al., 2016)**. Moreover, **van den Oever et al. (2017)** has considered intentional drug overdose patients 'high-acuity' for medium or intensive care admission if one or more of these criteria were present at the emergency room; the need for intubation, abnormal breathing (respiratory rate <8/min or >30/min), abnormal oxygenation (SpO_2 <90%), abnormal cardiac conduction (QTc prolonged), abnormal blood pressure, and abnormal consciousness (GCS <14) and the sensitivity of this proposed decision tool was 95.7%.

Furthermore, ROC curve analysis of the administered dose of clozapine accuracy in predicting the need for ICU admission in this study revealed that administered dose at a cut-off value above 250 mg is a good predictor. This could be attributed to that clozapine is toxic in overdose **(Flanagan et al., 2005)**. Unconsciousness may occur after a dose of 300 mg in a clozapine-naive adult, and a dose of 400 mg may be life-threatening. Additionally, **Okazaki et al. (2020)** has identified the total number of ingested pills as an in-hospital risk factor for prolonged ICU and hospital stay among patients with acute drug overdose within Japan.

CONCLUSIONS

Higher taken doses of clozapine, tachypnea, low O_2 saturation, and increased severity of ECG grading could be considered independent predictors of the need for ICU admission in acute clozapine poisoned patients. The early assessment of these risk factors can be beneficial to detect acute clozapine poisoning severity, decide the pathway of care, and improve the course of treatment.

RECOMMENDATIONS

It is recommended to consider ICU admission for acute clozapine poisoned patients when the taken dose is above 250 mg, and the patient is suffering from tachypnea, low O_2 saturation, and increased severity of ECG grading. These comfortable and ready-in-hand tools can

help young physicians identify critical acute clozapine poisoning cases in the emergency room's initial assessment. Moreover, further research should be done on a larger sample size of acute clozapine intoxicated patients presented to TUPCC or other poison control centers in Egypt.

REFERENCES

Abdalwahab, W.A. and Youssof, H. (2020): Characteristics and outcome of acute clozapine intoxicated patients with special consideration to its cardiac manifestations. The Egyptian Journal of Forensic Sciences and Applied Toxicology, 20(2)**:** 73-84.

Abdel Rasheed, E.A.M.; Elmahdy, N.; Shalaby, E.; Karoube, H.S. and Badawy, S.M. (2020): A study of pharmaceutical drug poisoning cases admitted to the National Poisoning Center, Kasralainy Teaching Hospital in Cairo. Eurasian Journal of Emergency Medicine, 19(1)**:** 10-15.

Akdur, O.; Durukan, P.; Ozkan, S.; Avsarogullari, L.; Vardar, A.; Kavalci, C.; et al. (2010): Poisoning severity score, Glasgow coma scale, corrected QT interval in acute organophosphate poisoning. Human and Experimental Toxicology, 29(5)**:** 419-425.

Aringhieri, S.; Carli, M.; Kolachalam, S.; Verdesca, V.; Cini, E.; Rossi, M.; et al. (2018): Molecular targets of atypical antipsychotics: From the mechanism of action to clinical differences. Pharmacology and Therapeutics, 192**:** 20-41.

Aslan, Ş.; Emet, M.; Cakir, Z.; Akoz, A. and Gür, S.T.A. (2011): Suicide attempts with amitriptyline in adults: a prospective, demographic, clinical study. Turkish Journal of Medical Sciences, 41(2)**:** 243-249.

Assaf, A.; Abd El Kareem, M. and Hasb Elnabi, M. (2019): Outcome prediction in acutely intoxicated patients admitted to intensive care unit. Ain Shams Journal of Forensic Medicine and Clinical Toxicology, 33**:** 16-23.

Bellissima, B.L.; Tingle, M.D.; Cicović, A.; Alawami, M. and Kenedi, C. (2018): A systematic review of clozapine-induced myocarditis. International Journal of Cardiology, 259**:** 122-129.

Borg, L.; Julkunen, A.; Rørbæk Madsen, K.; Strøm, T. and Toft, P. (2016): Antidepressant or antipsychotic overdose in the intensive care unit – identification of patients at risk. Basic & Clinical Pharmacology & Toxicology, 119**:** 110-114.

Brandenburg, R.; Brinkman, S.; De Keizer, N.F.; Kesecioglu, J.; Meulenbelt, J. and De Lange, D.W. (2017): The need for ICU admission in intoxicated patients: a prediction model. Clinical Toxicology, 55(1)**:** 4-11.

Bursac, Z.; Gauss, C.H.; Williams, D.K. and Hosmer, D.W. (2008): Purposeful selection of variables in logistic regression. Source Code for Biology and Medicine, 3**:** 17.

Chathoth, V.; Ramamurthy, P. and Solomon, S. (2018): Clozapine-induced insulin-resistant hyperglycemia in a diabetic patient. Indian Journal of Psychological Medicine, 40(4)**:** 375-377.

Chiappini, S.; Schifano, F.; Corkery, J.M. and Guirguis, A. (2020): Focus on clozapine withdrawal- and misuse-related cases as reported to the European Medicines Agency (EMA) Pharmacovigilance Database. Brain sciences, 10(2)**:** 105.

Clark, S.R.; Warren, N.S.; Kim, G.; Jankowiak, D.; Schubert, K.O.; Kisely, S.; et al. (2018): Elevated clozapine levels associated with infection: A systematic review. Schizophrenia Research, 192**:** 50-56.

Cooper, S.J.; Reynolds, G.P.; Barnes, T.; England, E.; Haddad, P.M.; Heald, A.; et al. (2016): BAP guidelines on the management of

weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. Journal of Psychopharmacology, 30(8)**:** 717-748.

Delong, E.R.; Delong, D.M. and Clarke-Pearson, D.L. (1988): Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics, 44**:** 837-845.

Diane, L. and Jillian, L. (2004): Vital signs measurements. In: Roberts, J.; Hedges, J. and Chanmugam, A. (eds.), Clinical procedures in emergency medicine. 6th edition, Philadelphia, PA: W.B. Saunders;1-22.

El-Gharbawy, D.M. and Ghonem, M.M. (2018): ECG changes as a predictive tool of outcomes in antipsychotics poisoned patients. Ain Shams Journal of Forensic Medicine and Clinical Toxicology, 31**:** 51-61.

Finn, S.D.; Uncles, D.R.; Willers, J. and Sable, N. (2009): Early treatment of a quetiapine and sertraline overdose with Intralipid. Anaesthesia, 64(2)**:** 191-194.

Flanagan, R.J.; Spencer, E.P.; Morgan, P.E.; Barnes, T.R.E. and Dunk, L. (2005): Suspected clozapine poisoning in the UK/Eire, 1992–2003. Forensic Science International, 155(2)**:** 91-99.

Galappathie, N.; Seth, V. and Begum, A. (2014): Clozapine re-trial in a patient with repeated life threatening pneumonias. Acta Bio-Medica: Atenei Parmensis, 85(2)**:** 175-179.

Gawlikowski, T.; Szpak, D.; Balicka-Slusarczyk, B.; Wilimowska, J. and Gomółka, E. (2011): [Acute clozapine poisonings in years 2007 - 2010 in material of Clinic of Toxicology in Kraków]. Przeglad Lekarski, 68(8)**:** 434-435.

Gerasimou, C.; Vitali, G.P.; Vavougios, G.D.; Papageorgiou, C.; Douzenis, A.; Kokoris, S.I.; et al. (2017): Clozapine associated with autoimmune reaction, fever and low level cardiotoxicity-A case report. In vivo (Athens, Greece), 31(1)**:** 141-143.

Goto, A.; Yoshimi, A.; Nagai, T.; Ukigai, M.; Mouri, A.; Ozaki, N.; et al. (2017): Human neutrophils show decreased survival upon long-term exposure to clozapine. Human Psychopharmacology: Clinical and Experimental, 32(6)**:** e2629.

Gummin, D.D.; Mowry, J.B.; Spyker, D.A.; Brooks, D.E.; Beuhler, M.C.; Rivers, L.J.; et al. (2019): 2018 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. Clinical Toxicology, 57(12)**:** 1220-1413.

Hammad, S.; Girgis, N.; Amin, S.; Zanaty, A. and Abou Hatab, H. (2015): A prospective study of Poisoning Severity Score among acute antipsychotic poisoned cases admitted to Menoufia Poison Control Center (MPCC) throughout one year. Ain Shams Journal of Forensic Medicine and Clinical Toxicology, 24**:** 53-63.

Hammad, S.E.H.; Girgis, N.; Amin, S.Z.; Zanaty, A. and Abou Hatab, H.E. (2016): Evaluation of acute antipsychotic poisoned cases. Menoufia Medical Journal, 29(4)**:** 1116-1121.

Hartman, M. and Cheifetz, I. (2011): Pediatric emergencies and resuscitation. In: Kliegman, R.; Stanton, B.; Geme, J.; Schor, N. and Behrman, R. (eds.), Nelson Textbook of Pediatrics. 18th edition, Philadelphia, Elsevier Saunders; 279-295.

Kanniah, G. and Kumar, S. (2020): Clozapine associated cardiotoxicity: Issues, challenges and way forward. Asian Journal of Psychiatry, 50**:** 101950.

Khalifa, H. and Lashin, H. (2018): Predictors for Intensive Care Unit Admission in Acute Theophylline Intoxicated Patients. Ain Shams

Journal of Forensic Medicine and Clinical Toxicology, 31**:** 77-86.

Krämer, I.; Rauber-Lüthy, C.; Kupferschmidt, H.; Krähenbühl, S. and Ceschi, A. (2010): Minimal dose for severe poisoning and influencing factors in acute human clozapine intoxication: a 13-year retrospective study. Clinical Neuropharmacology, 33(5)**:** 230-234.

Kuo, C.J.; Yang, S.Y.; Liao, Y.T.; Chen, W.J.; Lee, W.C.; Shau, W.Y.; et al. (2013): Second-generation antipsychotic medications and risk of pneumonia in schizophrenia. Schizophrenia Bulletin, 39(3)**:** 648-657.

Lebin, J.A.; Villarreal, J.D.; Chen, B.C. and Hall, M.K. (2018): Clozapine intoxication mimicking acute stroke. Clinical practice and cases in emergency medicine, 2(2)**:** 155-157.

Leung, J.G.; Hasassri, M.E.; Barreto, J.N.; Nelson, S. and Morgan, R.J. (2017): Characterization of admission types in medically hospitalized patients prescribed clozapine. Psychosomatics, 58(2)**:** 164-172.

Levine, M. and Ruha, A.M. (2012): Overdose of atypical antipsychotics. CNS Drugs, 26(7)**:** 601-611.

Macfarlane, M.; Shahab, J. and Willis, D. (2020): Clozapine toxicity: a cautionary palliative care tale. BMJ Supportive and Palliative Care, 10**:** 312-313.

Meli, M.; Rauber-Lüthy, C.; Hoffmann-Walbeck, P.; Reinecke, H.J.; Prasa, D.; Stedtler, U.; et al. (2014): Atypical antipsychotic poisoning in young children: a multicentre analysis of poisons centres data. European Journal of Pediatrics, 173(6)**:** 743-750.

Miura, N.; Saito, T.; Taira, T.; Umebachi, R. and Inokuchi, S. (2015): Risk factors for QT prolongation associated with acute psychotropic drug overdose. The American Journal of Emergency Medicine, 33(2)**:** 142-149.

Mubarak, M.; El Madah, E.; El Gharbawy, D. and Ashmawy, M. (2019): Assessment of acute antipsychotic poisoned cases admitted to Tanta University Poison Control Unit. Ain Shams Journal of Forensic Medicine and Clinical Toxicology, 33**:** 113-125.

Nelson, L.; Lewin, N.; Howland, M.; Hoffman, R.; Goldfrank, L. and Flomenbaum, N. (2011): Initial evaluation of the patient: Vital signs and toxic syndromes. In: Nelson, L.; Lewin, N.; Howland, M.; Hoffman, R.; Goldfrank, L. and Flomenbaum, N. (eds.), Goldfrank's Toxicologic Emergencies. 9th edition, New York, Chicago, San Francisco: Mc Graw-Hill; 33-36.

Nield, L. and Kamat, D. (2011): Fever. In: Kliegman, R.;Stanton, B.;Geme, J.;Schor, N. and Behrman, R. (eds.) Nelson Text Book Of Pediatrics. 19th edition, Philadelphia: Elsevier Saunders; 896-899.

Okazaki, Y.; Shimojo, N.; Matsuishi, Y.; Hoshino, H.; Ouchi, A.; Kawano, S.; et al. (2020): Risk factors for prolonged intensive care unit and hospital stay among patients with acute drug overdose in Japan. Acute medicine & surgery, 7**:** e482.

Persson, H.E.; Sjöberg, G.K.; Haines, J.A. and De Garbino, J.P. (1998): Poisoning Severity Score. Grading of Acute Poisoning. Journal of Toxicology: Clinical Toxicology, 36(3)**:** 205-213.

Postema, P.G. and Wilde, A.A.M. (2014): The measurement of the QT interval. Current Cardiology Reviews, 10(3)**:** 287-294.

Song, M.K.; Bahk, W.M.; Kwon, Y.J.; Yoon, B.H.; Lee, S.Y.; Jon, D.I.; et al. (2018): F3. A case of leukocytosis associated with clozapine treatment for the management of chronic schizophrenia. Schizophrenia Bulletin, 44**:** S218-S219.

Van Den Oever, H.L.A.; Van Dam, M.;

Van 'T Riet, E. and Jansman, F.G.A. (2017): Clinical parameters that predict the need for medium or intensive care admission in intentional drug overdose patients: A retrospective cohort study. Journal of Critical Care, 37**:** 156-161.

Varma, S.; Bishara, D.; Besag, F.M.C. and Taylor, D. (2011): Clozapine-related EEG changes and seizures: dose and plasma-level relationships. Therapeutic advances in psychopharmacology, 1(2)**:** 47-66.

Williams, A.M. and Park, S.H. (2015): Seizure associated with clozapine: Incidence, etiology, and management. CNS Drugs, 29(2)**:** 101-111.

Yates, C. and Manini, A.F. (2012): Utility of the electrocardiogram in drug overdose and poisoning: theoretical considerations and clinical implications. Current Cardiology Reviews, 8(2)**:** 137-151.

Yousefsani, B.S.; Mohajeri, S.A.; Moshiri, M.; Jafarian, A.H. and Hosseinzadeh, H. (2019): Effect of intravenous lipid emulsion on clozapine acute toxicity in rats. Journal of pharmacopuncture, 22(3)**:** 147-153.

Yuen, J.W.Y.; Kim, D.D.; Procyshyn, R.M.; White, R.F.; Honer, W.G. and Barr, A.M. (2018): Clozapine-induced cardiovascular side effects and autonomic dysfunction: A Systematic Review. Frontiers in Neuroscience, 12**:** 203.

Zhu, J.; Hou, W.; Xu, Y.; Ji, F.; Wang, G.; Chen, C.; et al. (2019): Antipsychotic drugs and sudden cardiac death: A literature review of the challenges in the prediction, management, and future steps. Psychiatry Research, 281**:** 112598.

الملخص العربي

عوامل الخطر المؤدية للحاجة إلى دخول وحدة العناية المركزة بين مرضى التسمم الحاد بالكلوزابين: دراسة استرجاعية

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المقدمة: الكلوزابين هو أكثر الأدوية المضادة للذهان فعالية في علاج مرض انفصام الشخصية المقاوم للعلاج. كما يُنظر إليه على أنه الأكثر سمية في فئته. تم الكشف عن التسمم الدوائي كأحد الأسباب الرئيسية لدخول وحدة العناية المركزة (ICU). **الهدف من الدراسة:** هدفت هذه الدراسة إلى تطوير أداة لاتخاذ القرار، باستخدام العوامل المتاحة بسهولة في غرفة الطوارئ للمرضى الذين يعانون من التسمم الحاد بالكلوزابين، للتعرف المبكر على المرضى الذين يحتاجون إلى دخول وحدة العناية المركزة. **المرضى و طرق البحث:** تم إجراء هذه الدراسة الاسترجاعية على 121 مريضًا يعانون من التسمم الحاد بالكلوزابين تم إدخالهم إلى مركز طنطا الجامعي لعلاج حالات التسمم. وقد تم تحليل البيانات الديموغرافية والسمية والسريرية والنتائج المختبرية وسجلات رسم القلب لكل مريض. **النتائج:** أظهرت النتائج أن 29 مريضًا احتاجوا إلى دخول وحدة العناية المركزة وكانوا أكبر سنًا بشكل ملحوظ من المرضى الذين لم يحتاجوا الدخول. وقد وجد ارتباط ملحوظ بين التاريخ الماضي للإدمان و/ أو المرض النفسي، طريقة التسمم، كمية وجرعة الكلوزابين والحاجة إلى دخول وحدة العناية المركزة. المرضى الذين تم إدخالهم إلى وحدة العناية المركزة كانت لديهم نسب أعلى بشكل ملحوظ من زيادة ضربات القلب وسرعة التنفس وارتفاع الحرارة، بينما كان لديهم قيم أقل لمقياس جلاسكو للغيبوبة (GCS) وتشبع الدم بالأكسجين. وبالإضافة إلى ذلك، كانت لديهم نسبة أعلى بشكل ملحوظ من ارتفاع السكر في الدم والقلاء التنفسي وطول فترة QTc. كانت هناك علاقة ذات دلالة إحصائية بين الحاجة لدخول وحدة العناية المركزة وكل من درجة شدة تصنيف رسم القلب ودرجة شدة التسمم الحاد بالكلوزابين. وقد أظهر نموذج الانحدار اللوجستي أن الجرعات الكبيرة من الكلوزابين، ووجود سرعة التنفس وزيادة شدة تصنيف رسم القلب وانخفاض مستوى تشبع الدم بالأكسجين زاد بشكل كبير من احتمالية تطلب دخول الحالة الى وحدة العناية المركزة. وبناءً على تحليل منحنى (ROC)، فإن جرعة الكلوزابين المأخوذة بقيمة قاطعة أعلى من 250 مجم تعد مؤشرًا جيدًا للحاجة إلى دخول وحدة العناية المركزة. **الخلاصة:** يمكن استنتاج أن الجرعات العالية التي يتم تناولها من الكلوزابين، وسرعة التنفس، وانخفاض تشبع الدم بالأكسجين وزيادة شدة تصنيف رسم القلب تعتبر بمثابة متنبئات مستقلة للحاجة إلى دخول وحدة العناية المركزة في المرضى المصابين بالتسمم الحاد بالكلوزابين.