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Prognostic value of copeptin and sequential organ failure assessment score in toxin linked acute respiratory distress syndrome

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Abstract
Background: Acute poisoning with breathing and pulmonary complications is a common cause of admission to emergency departments and often needs treatment in the intensive care unit.
Aim: This study aimed to evaluate the prognostic value of copeptin level and sequential organ failure assessment score (SOFA) as predictors in toxin-linked acute respiratory distress syndrome
Methods: This is a prospective cohort study. Human serum copeptin level was assayed using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of human copeptin in samples and the severity of the cases was evaluated by SOFA score.
Results: Several variables were associated with poor outcome in the poisoned acute respiratory distress patients like delay time between toxicity and hospital admission, conscious level, arterial blood gases with highest significance to copeptin level. Analysis of receiver operating characteristics curves of serum copeptin level as a predictor for toxin-linked ARDS showed that copeptin had an area under curve equals 0.913 with a sensitivity 90% and specificity 75% with cutoff level 1.081 Pmol/L.
Conclusions: Early combination of plasma copeptin and SOFA scores could help in identifying patients at risk of severe fatal toxin – related ARDS.

Keywords: Copeptin, sequential organ failure assessment score, toxin linked acute respiratory distress

Introduction

Acute toxicity is a common cause of admission to emergency departments and often requires treatment in the intensive care unit. Breathing and pulmonary complications are common causes of mortality in acute poisoning [1].

Acute respiratory distress syndrome (ARDS) was initially defined in 1967. It is an acute, diffuse inflammatory lung injury that increases pulmonary vascular permeability, lung weight with loss of aerated tissue [2, 3].

Toxin-linked ARDS is a clinical syndrome that can be caused by direct damage to respiratory cells or indirect through inflammatory mediators due to xenobiotics exposure leading to wide spread lung inflammation with impaired gas exchange [4].

Despite high current overall hospital mortality of ARDS which approximates 40-50% little has been published concerning toxin-linked ARDS. This warrants attention to the risk factors and prognostic criteria of ARDS in acutely intoxicated patients [5].

Common poisons that affect the respiratory system in acute state are anti-cholinesterases, drugs over dose as opioids and other central nervous system depressants, animal bites particularly snake bite, carbon monoxide (CO), hydrocarbons and corrosives [1].

After inhalation of toxic chemicals, there's often a latent period that may last several hours during this time signs and symptoms may not be evident. Early transient symptoms of irritation and cough may not reflect the final clinical outcome. Even at exposure to high concentrations of these inhaled toxic chemicals, there may be a delay in signs and symptoms [6].

Copeptin is a novel biomarker that plays a helpful role in differential diagnosis and risk evaluation of patients with acute dyspnea. This molecule is derived from 39-aminoacid C-terminal fragment of the arginine-vasopressin (AVP) precursor which called pre-pro-vasopressin [7].

Copeptin is easily measured and stable in plasma and serum for at least 7 days in room temperature. The prognostic value of copeptin has been studied in multiple diseases. Previous studies revealed increased copeptin concentration with poor prognosis in sepsis, hemorrhagic shock, myocardial infarction and chronic heart failure. In patients with lower respiratory tract infection, copeptin predict mortality more accurately than C-reactive protein (CRP) and leukocyte count [8].

The severity of respiratory affection was assessed using the sequential organ failure assessment (SOFA) score. This score has become integrated into a range of aspects of critical care, and it is now widely used in the daily monitoring of acute morbidity in critical care units [9].

Patients and Methods

This is a prospective cohort study that was conducted on patients of both sexes with toxin-linked acute respiratory distress admitted to Tanta University Poison Control Centre (TUPCC) during the period that started from October 2020 till the end of December 2021. Informed written consent was obtained from the patient or relatives of the patients. Following approval of medical research ethical committee of Faculty of Medicine, Tanta University. (Approval code 34162/9/20).

Inclusion criteria

All patients of both sexes with moderate to severe toxicity were included in this study. The severity of the cases was evaluated by SOFA score.

Exclusion criteria

Patients who have a history of medical conditions that may be associated with rise in the level of copeptin such diabetes mellitus, myocardial infarction, chronic heart failure, chronic hypertension, chronic obstructive pulmonary diseases, autoimmune diseases, chronic inflammatory diseases, malignancy, and pregnancy.

The patient group: (n=50) was compared to a control group (n=15) apparently healthy subjects with matched age and sex. Then the patient group was subdivided into survivors (n=34) and non-survivors (n=16).

All patients were subjected to full history taking such as socio-demographic data including age and sex, toxicological history include route, mode of poisoning, delay time between toxin intake or exposure and hospital admission and any pre-hospital intervention and history of medical diseases.

Clinical examination

a) Physical examination

Vital signs (pulse, blood pressure, respiratory rate and temperature).

Level of consciousness by GCS, which is composed of three scales, eye, verbal, and motor responses. The sum of the three responses gives the GCS. The highest score is fifteen which represents fully conscious person, while the minimum score is three which represents deep coma, severe (GCS: 8 or less), moderate (GCS:9–12), mild(GCS:13-14) [10].

b) Respiratory examination

Clinical findings as: Feeling of short breath (dyspnea), Cough, Tachypnea and Cyanosis, bilateral chest radiographic infiltration, Hypoxemia (PaO2/FIO2 ≤ 200 mmHg).

c) Cardiovascular examination and Abdominal examination

d) Laboratory investigations

Include arterial blood gases, sodium and potassium level, complete blood count, liver function, kidney function, and serum copeptin level at admission and after 24h.

Electrocardiography (ECG)

e-Radiological investigations: CXR or CT.

Results

Type of poison

Table (1) showed socio-demographic data and toxicological data among the studied cases of toxin-linked ARDS. The most frequent poison causing respiratory distress was aluminium phosphide and anti-psychotics came next. The most frequent route was the oral one with statistically significant association between type of poison and survivors, while mode of poisoning didn't show significant difference.

Table 1: Socio-demographic data and toxicological data among the studied cases of toxin linked ARDS (group I), (n=50)

	Over all Cases (n = 50)		Survivors (n = 34)		Non-survivors (n = 16)		Test of sig. P value
	No.	%	No.	%	No.	%	
Age (Years)							
Min.–Max	1-66		1-66		2-66		t = 2.21
Mean ± SD.	22.0 ± 16.25		21.0 ± 18.15		25.5 ± 15.67		P =0.35
Sex							X^2= 1.75
Male	27	54.0	20	58.8	7	43.8	P =0.73
Female	23	46.0	14	41.2	9	56.3	
Poison	**Over all Cases (n = 50)**		**Survivors (n = 34)**		**Non-survivors (n = 16)**		**Test of sig. P value**
	No.	**%**	**No.**	**%**	**No.**	**%**	
Type of poison							*FE* P= 0.003*
Aluminum phosphate	10	20.0	0	0.0	10	62.5	
Corrosive	7	14.0	6	17.6	1	6.3	
Anti-psychotic	8	16.0	6	17.6	2	12.5	
Hydrocarbon	6	12.0	5	14.7	1	6.3	
Organo - phosphorus	4	8.0	3	8.8	1	6.3	
Benzodiazepines	5	10.0	5	14.7	0	0.0	
Antiepileptic	2	5.1	2	5.9	0	0.0	
Carbamate	2	5.1	1	2.9	1	6.3	

Opioids	2	4.0	2	5.9	0	0.0	
Alcohol	1	2.0	1	2.9	0	0.0	
Theophylline	2	4.0	2	5.9	0	0.0	
Carbon monoxide	1	2.0	1	2.9	0	0.0	
Route of poisoning							
Oral	42	84.0	29	85.3	13	81.3	*FE* P= 0.95
Injection	3	6.0	2	5.9	1	6.3	
Inhalation	2	4.0	1	2.9	1	6.3	
Exposure	3	6.0	2	5.9	1	6.3	
Agent							
Single	44	88.0	28	82.4	16	100.0	*FE* P= 0.02*
Multiple	6	12.0	6	17.6	0	0.0	
Mode of poisoning							
Suicidal	30	60.0	17	50.0	13	81.3	*FE* P= 0.04*
Accidental	15	30.0	14	41.2	1	6.3	
Addiction	5	10.0	3	8.8	2	12.5	

$\chi 2$, p: $\chi 2$ and P values for Chi square test for comparing between the two groups (survivors and non survivors)
t: independent sample Student's t test for comparing the mean between the two groups.
*: Statistically significant at $p \leq 0.05$
n: Number of patients
SD: standard deviation

Table (2) showed pre-hospital intervention, delay time between toxin exposure and hospital admission, ICU admission, period of hospital stay, and co-morbidities among the studied cases of toxin-linked ARDS. There is no statistically significant difference between survivors and non-survivors regarding pre-hospital intervention, time between toxin exposure and hospital admission, period of hospital stay and Co-morbidities.

Table 2: Pre-hospital intervention, Delay time between toxin exposure and hospital admission, ICU admission, Period of hospital stay, and Co-morbidities among the studied cases of toxin-linked ARDS (group I), (n=50).

Pre-hospital intervention	**Over all Cases (n = 50)**		**Survivors (n = 34)**		**Non-survivors (n = 16)**		**Test of sig. P value**
	No.	**%**	**No.**	**%**	**No.**	**%**	
No intervention	45	90.0	30	82.2	15	93.7	*FE* P =0.33
Intervention	5	10.0	4	11.8	1	6.3	
Delay time							
Min.–Max	1-19	1-19	1-14				t= 1.3
Mean ± SD.	3.82 ± 4.25	4.78 ± 4.51	2.82 ± 3.35				P= 0.18
ICU Admission							
Yes	8	16.0	7	20.6	1	6.3	X^2= 1.65
No	42	84.0	27	79.4	15	93.7	P =0.44
Period of hospital stay							
Min.–Max	1 – 14		1 – 14		1 – 10		t= 1.74
Mean ± SD.	2.52±2.73		2.74±2.83		2.12±2.73		P= 0.22
Co-morbidities	**Overall Cases (n = 50)**		**Survivors (n = 34)**		**Non-survivors (n = 16)**		**Test of sig P value**
	No.	**%**	**No.**	**%**	**No.**	**%**	
Positive	10	20.0	6	17.6	4	25.0	P =0.55
Negative	40	80.0	28	82.4	12	75.0	

T: independent sample Student's t-test for comparing the mean between the two groups (survivors and non-survivors), ICU: intensive care unit, *: Statistically significant at $p \leq 0.05$, n: Number of patients
Min: minimum, Max: maximum, SD: standard deviation, $\chi 2$, p: $\chi 2$ and P values for Chi-square test for comparing between the two groups (Survivors and non-survivors) n: Number of patients

Table (3) showed Clinical and Physical examination of studied cases

Clinical examination

There was no statistically significant association between survivors and non survivors regarding blood pressure, heart rate, respiratory rate and conscious level. Regarding Temperature, there is statistically significant association between survivors and non-survivors

Physical examination of studied cases

Chest examination showed statistically significant association between chest condition and survivors. Cardiac examination, There is no statistically significant association between cardiac condition and survivors (P =0.32).

Table (4) showed routine laboratory investigations

Arterial blood gases: there was statistically significant association between ABG and survivors (P =0.01*). Serum sodium and potassium level. There is no statistically significant association between sodium and potassium level and survivors (P =0.44).Random blood sugar, there is no statistically significant association between random blood sugar and survivors (P =0.54). There is no statistically significant association between liver enzymes and survivors (P =0.22).

Complete blood count (CBC) was statistically significant association between CBC and survivors (P =0.02*).

Table 3: Clinical and Physical examination of studied cases of toxin linked ARDS (group I), (n=50)

Vital signs	Over all Cases (n = 50)		Survivors (n = 34)		Non-survivors (n = 16)		Test of sig. P value
	No.	%	No.	%	No.	%	
Blood pressure							
Normal	40	80.0	28	82.4	12	75.0	X^2= 2.64 P =0.35
Hypertension	1	2.0	1	2.9	0	0.0	
Hypotension	8	16.0	4	11.2	4	25.0	
Undetected	1	2.0	1	2.9	0	0.0	
Pulse							
Normal	15	30.0	10	29.4	5	31.3	X^2= 0.91 P =0.22
Tachycardia	32	64.0	22	64.7	10	62.4	
Bradycardia	3	6.0	2	5.9	1	6.3	
Temperature							
Normal	37	74.0	22	64.7	15	93.7	X^2= 4.81 P =0.03*
Fever	12	24.0	11	32.4	1	6.3	
Sub-normal temperature	1	2.0	1	5.9	0	0.0	
Respiratory rate							
Normal	1	2.0	1	2.9	O	0.0	X^2= 1.04 P=0.65
Tachypnea	48	96	32	94.2	16	100	
Bradypnea	1	2.0	1	2.9	0	0.0	
Glasgow coma scale (GCS)							
							t = 2.21 P =0.35
Min.–Max	3-15		3-15		3-15		
Mean ± SD.	11.16 ± 1.25		11.14 ± 4.23		13.06 ± 5.45		
Systemic examination	**Over all Cases (n = 50)**		**Survivors (n = 34)**		**Non-survivors (n = 16)**		
	No.	**%**	**No.**	**%**	**No.**	**%**	
Chest							
Free	14	28.0	5	14.7	9	56.3	X^2= 9.31 P=0.02*
Crepitation	36	72.0	29	85.3	7	43.7	
Heart							
Normal	48	96.0	32	93.1	16	100.0	*MC* P=0.32
Tachycardia	2	4.0	2	5.9	0	0.0	
Abdomen							
Normal	50	100.0	34	100.0	16	100.0	-

χ2, p: χ2 and P values for Chi square test for comparing between the two groups (survivors and non-survivors)
*: Statistically significant at $p \leq 0.05$. n: Number of patients

Table 4: Laboratory finding among the studied cases of toxin linked ARDS (group I), (n=50)

Lab finding	Overall Cases (n = 50)		Survivors (n = 34)		Non-survivors (n = 16)		
	No.	%	No.	%	No.	%	
Arterial blood gases (ABG)							
Normal	7	14.0	6	17.6	1	6.3	
Respiratory alkalosis	28	56.0	23	67.6	5	31.3	X^2= 16.61 P =0.01*
Metabolic acidosis	13	26.0	3	8.8	10	62.4	
Respiratory acidosis	2	4.0	2	5.9	0	0.0	
Sodium and potassium level							
Normal	34	68.0	23	67.6	11	73.3	X^2= 1.65 P =0.44
hypokalemia	15	30.0	11	32.4	4	36.4	
Hyponatremia and hypokalemia	1	2.0	0	0.0	1	6.3	
Blood glucose level							
Normal	42	84.0	29	85.3	13	81.2	X^2= 0.65 P =0.54
Hyperglycemia	8	16.0	5	14.7	3	18.8	
Liver enzymes level							
Normal	46	92.0	30	88.2	16	100.0	X^2= 2.04 P =0.22
elevated enzymes	4	8.0	6	11.8	0	0.0	
CBC							
Normal	20	40.0	10	29.4	10	62.7	X^2= 4.91 P =0.02*
Leukocytosis	30	60.0	24	70.6	6	37.3	

χ2, p: χ2 and P values for Chi square test for comparing between the two groups (survivors and non-survivors)
*: Statistically significant at $p \leq 0.05$, CBC: complete blood count, ABG: arterial blood gases. n: Number of patients.

Table (5) showed Oxygen (O_2) saturation, PaO2/FIO2, Sequential organ failure assessment (SOFA) score at admission and after 24among the studied cases of toxin linked ARDS PaO_2/FIO_2 among the studied patients showed non-significant correlation between it and survivors (P =0.35).There was statistically significant difference between it at admission and after 24 h and survivors. Paired sample t test revealed statistically significant association between SOFA score and survivors and non survivors (P=0.04, P=0.001) respectively.

Table 5: Oxygen (O_2) saturation, PaO2/FIO2, Sequential organ failure assessment (SOFA) score at admission and after 24 among the studied cases of toxin linked ARDS (group I), (n=50).

Oxygen (O_2) Saturation (%)		**Over all Cases (n = 50)**	**Survivors (n = 34)**	**Non-survivors (n = 16)**	**Test of sig. P value**
Min.–Max		28 - 99	75 - 99	28 – 96	t =0.5
Mean ± SD.		84.25±14.25	86.14±7.32	84.75±15.31	P = 0.66
PaO_2/FIO_2		**Over all Cases (n = 50)**	**Survivors (n = 34)**	**Non-survivors (n = 16)**	**Test of sig. P value**
Min.–Max		124 – 700	124 – 660	124 – 660	t = 1.04
Mean± SD.		326.38±184.11	308.32±156.52	366.42±230.41	P =0.35
(SOFA) score		**Over all Cases (n = 50)**	**Survivors (n = 34)**	**Non-survivors (n = 16)**	**Test of sig. P value**
At admission	Min.–Max	0 - 6	0 - 6	4 – 6	t = 3.9
	Mean±SD.	3.35±1.65	2.85 ± 1.72	4.30±0.67	P = (0.002) *
After 24 hours	Min.–Max	0 – 8	0 – 6	2 – 8	t = 4.4
	Mean ± SD.	3.54±1.63	3.22 ± 1.02	4.82±1.32	P = (0.003) *
Paired sample t test (P value)		0.05 (0.95)	3.12 (0.04*)	4.32 (0.001*)	

t: independent sample Student's t test. t: independent sample Student's t test.
*: Statistically significant at $p \leq 0.05$
PaO_2/FIO_2 = Partial arterial oxygen pressure/Fraction of inspired oxygen.
n: Number of patients.
Min: minimum.
Max: maximum.
SD: standard deviation

Table (6) showed results of Serum copeptin level between control and cases at admission and after 24 hours among the studied cases of toxin linked ARDS. Serum copeptin level was higher in cases at admission and after 24 hours than control group. At admission copeptin level was ranging from (1.04-10.68) with a mean (4.68±2.45), while in control group it ranged from (0.84-3.17) with a mean (1.64±2.72) with statistically significant difference between case and control groups at admission, P value (0.001). After 24 hours of admission copeptin level was ranging from (0.98-6.07) with a mean (3.14±1.65), while in control group it ranged from (0.84–3.17) with a mean (1.64±2.72) with statistically significant difference between case and control groups after 24 hrs. P value (0.001).

Table 6: Comparison of Copeptin level between control and cases at admission and after 24 hours among the studied cases of toxin linked ARDS (group I), (n=50)

Copeptin level		**Cases**	**Control**	**Test of sig. (P. value)**
At admission	Min.–Max	1.04-10.68	0.84-3.17	4.32 (0.001) *
	Mean ± SD.	4.68±2.45	1.64 ± 2.72	
After 24 hours	Min.–Max	0.98–6.07	0.84 –3.17	3.35 (0.001) *
	Mean ± SD.	3.14±1.65	1.64 ± 2.72	
Paired sample t test (P. value)		1.70 (0.14)		

Test of sig.: independent sample t test used for comparison between cases and control & paired sample t test was used for comparison between at admission and after 24 hours
*: Statistically significant at $p \leq 0.05$
Min: minimum.
Max: maximum.
SD: standard deviation.

Table (7) showed ECG, Radiological changes the studied cases of toxin linked ARDS. There was statistically significant association between ECG finding and survivors (P=0.001*).

Chest x-ray or CT was done in all cases, with statistically significant association between radiological changes and survivors. (P =0.04*). Table (7)

Table 7: ECG, Radiological changes the studied cases of toxin linked ARDS (group I), (n=50)

ECG	**Over all Cases (n = 50)**		**Survivors (n = 34)**		**Non-survivors (n = 16)**		**Test of sig. P value**
	No.	**%**	**No.**	**%**	**No.**	**%**	
Normal	29	58.0	22	64.7	7	43.8	X^2= 9.52 P =0.001*
Sinus tachycardia	12	24.0	11	32.4	1	6.3	
Arrhythmia	9	18.0	1	5.9	8	50.0	
Radiological changes	**Over all Cases (n = 50)**		**Survivors (n = 34)**		**Non-survivors (n = 16)**		**Test of sig. P value**
	No.	**%**	**No.**	**%**	**No.**	**%**	
Normal	7	14.0	6	17.6	1	6.3	*X2 = 6.32* P =0.04*
Patches	36	72.0	26	76.5	10	62.5	
Patches & effusion	7	14.0	2	5.9	5	31.3	

χ2, p: χ2 and P values for Chi square test for comparing between the two groups (survivors and non survivors)
*: Statistically significant at $p \leq 0.05$
ECG: electrocardiogram. n: Number of patients.
χ2, p: χ2 and P values for Chi square test for comparing between the two groups (survivors and non survivors)
*: Statistically significant at $p \leq 0.05$
n: Number of patients.

Outcome

Table (8) showed number and types of organ failure according to SOFA score on revealed predominance of respiratory failure, either alone or combined with other organ failure. There is statistically significant association between organ failure and survivors.

Table 8: Organ failure among the studied cases of toxin linked ARDS (group I), (n=50)

Organ failure	Over all Cases (n = 50)		Survivors (n = 34)		Non-survivors (n = 16)		Test of sig. P value
	No.	%	No.	%	No.	%	
NO	3	6.0	3	8.8	0	0.0	
CNS	4	8.0	4	11.8	0	0.0	
CVS	5	10.0	0	0.0	5	31.3	
Respiratory	12	24.0	12	35.3	0	0.0	
CNS, CVS	4	8.0	3	8.8	1	6.3	X^2=24.5
CNS, CVS, respiratory	1	2.0	1	2.9	0	0.0	P=0.003*
CNS, respiratory	13	26.0	8	23.5	5	31.3	
CNS, respiratory, liver	1	2.0	1	2.9	0	0.0	
CVS, respiratory	5	10.0	1	2.9	4	25.0	
Liver, renal	2	4.0	1	2.9	1	6.3	

χ2, p: χ2 and P values for Chi square test for comparing between the two groups (survivors and non-survivors)
*: Statistically significant at $p \leq 0.05$
n: Number of patients
CNS: central nervous system,
CVS: cardiovascular system.
Resp. = Respiratory failure defined by $PaO_2/FIO_2 \leq 300$ mm Hg
CVS = Cardiovascular failure in the form of prolonged hypotension (mean arterial pressure ≤60 mm Hg) requiring correction by volume loads or vasoactive drugs
Renal dysfunction: serum creatinine>2 mg/dl and/or presence of artificial renal support
Hepatic impairment: serum bilirubin >2 mg/dl and/or ALT >80 IU/L
Hematological disorders: platelets count＜50 $x10^3$/mm3.

Table (9) showed correlation analysis between serum copeptin level and some studied parameters and correlation analysis between (SOFA) score and PaO_2/FIO_2 and some parameters.

There was weak positive correlation between serum copeptin level at admission and O_2 saturation, while showing negative significant correlation with age and weak negative correlation with delay time between intoxication and hospital admission, period of hospital stay, SOFA score and PaO_2/FIO_2.Copeptin level after 24 hours showed moderate positive correlation with age, period of hospital stay and weak positive correlation with O_2 saturation, delay time between intoxication and hospital admission and PaO_2/FIO_2. While showing negative correlation with SOFA score.

SOFA score had positive correlation with age and period of hospital admission, while had negative significant correlation with O_2 saturation and a negative weak correlation with delay time between intoxication and hospital admission.

Partial arterial oxygen pressure/Fraction of inspired oxygen (PaO_2/FIO_2) showed positive correlation with age, delay time and period of hospital admission, while showed negative correlation with O_2 saturation.

Table 9: Pearson correlation between Copeptin level and between (SOFA) score and PaO_2/FIO_2some studied parameters of cases of toxin linked ARDS

Cases	Copeptin level			
	At admission		After 24 hours	
	r	P-value	r	P-value
Age	- 0.21	0.03*	0.30	0.17
Delay time	-0.23	0.20	0.18	0.53
Period of admission	- 0.08	0.54	0.44	0.87
O2 saturation	0.14	0.37	0.06	0.73
(SOFA) score	- 0.13	0.43	- 0.29	0.36
PaO_2/FIO_2	- 0.04	0.37	0.06	0.73
	(SOFA) score		PaO_2/FIO_2	
	r	P-value	r	P-value
Age	0.21	0.18	0.26	0.06
Delay time	-0.14	0.94	0.01	0.91
Period of admission	0.07	0.62	0.01	0.90
O_2 saturation	- 0.32	0.03	- 0.19	0.16

r: Pearson correlation test
*: Statistically significant at $p \leq 0.05$
PaO_2/FIO_2 = Partial arterial oxygen pressure/Fraction of inspired oxygen.
SOFA: sequential organ failure assessment.

Table (10) showed factors that show significant relation with SOFA score at admission according to our study are age, delay time between toxicity and hospital admission, conscious level (GCS) and arterial blood gases with high significance to copeptin level and survival.

Table 10: Linear regression of the predictor variables affecting (SOFA) score at admission of cases of toxin linked ARDS

Predictor variables	Standardized coefficients	T	P value
	Beta		
Age	-0.391	3.640	0.007*
Delay time	-0.471	3.227	0.009*
Poison	-0.133	0.825	0.418
Prehospital intervention	0.092	0.608	0.558
Pulse	0.115	0.707	0.498
Blood pressure	0.223	1.100	0.300
Temperature	0.276	1.985	0.059
Chest examination	-0.018	-0.106	0.918
Heart examination	-0.191	-1.345	0.211
GCS	-0.534	-3.579	0.005*
RBS	-0.191	-1.345	0.211
O_2 Saturation	-0.113	-0.590	0.570
Liver enzymes	0.065	0.429	0.678
CBC	-0.124	-0.698	0.503
ABG	0.530	3.611	0.005*
ECG	0.021	0.087	0.932
Copeptin level	-0.580	-4.801	0.001*
Radiology	0.048	0.318	0.758
ICU	0.176	0.808	0.440
Survival	-0.580	-4.801	0.001*

GCS: Glasgow coma score, RBS: random blood sugar, CBC: complete blood count, ABG: arterial blood gases, ECG: electrocardiogram, ICU: intensive care unit.

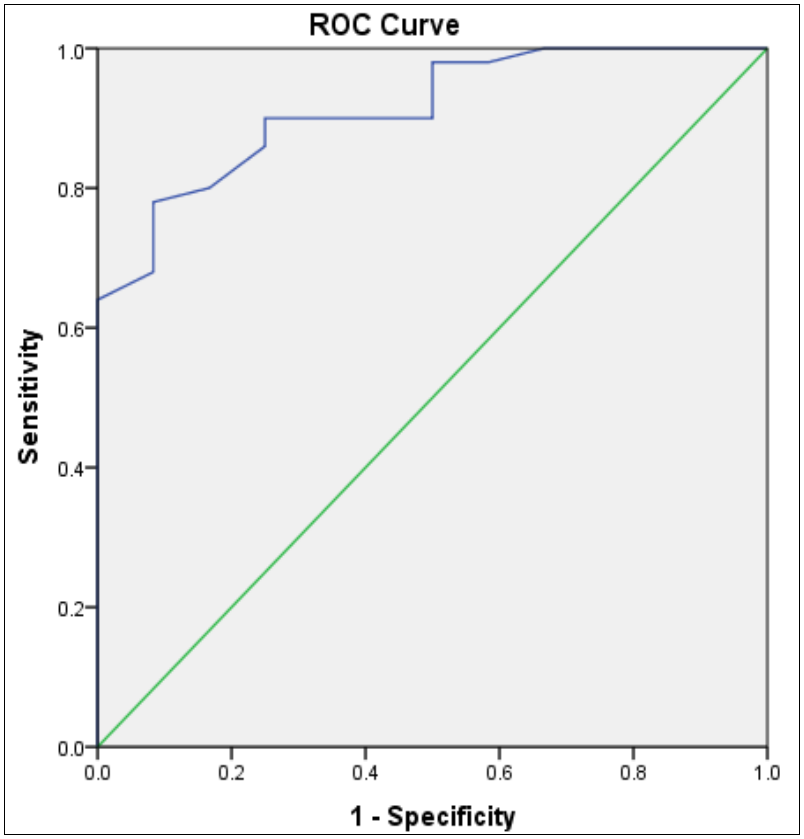
Table (11) showed the sensitivity and specificity of Copeptin level among the studied cases of toxin linked ARDS.

Analysis of receiver operating characteristics (ROC) curves of serum copeptin level as a predictor for toxin linked ARDS showed that copeptin had area under curve (AUC) equals 0.913 with a sensitivity 90% (was able to detect 90% of cases with toxin linked ARDS) and specificity 75% (was able to detect 75% of cases that did not develop toxin linked ARDS) with cutoff level 1.081Pmol/L.

Table 11: Sensitivity and specificity of Copeptin level among the studied cases of toxin linked ARDS

(AUC)	P value	Cut of value	Sensitivity	Specificity
0.913	0.001*	1.081	90.0%	75.0%

AUC: Area under Curve



Discussion

In Egypt, the rate of suicide by self-poisoning in the general population was 26.10/100,000 with obvious increase in cases of suicidal self-poisoning [14].

Respiratory system is commonly affected in acute toxicity due to toxin itself or its complications leading to increasing morbidity and mortality [1]. So determination of case prognosis allow more intensive monitoring for favorable outcome in poisoned patients [15].

Toxin linked ARDS is a clinical syndrome that caused by direct damage to the respiratory cells or indirect through inflammatory mediators due to xenobiotics exposure leading to widespread lung inflammation with impaired gas exchange [15].

Toxicological data of studied cases

In the present study, time elapsed between toxin exposure and hospital admission ranged from (1-19) hours as most of cases in our study were suicidal. Similarly, Hammad *et al*., [1] reported that 71.6% of patients came to within 3 hours after poison exposure. This come in line with Oreby and Elmadah [16], and El-Sarnagawy *et al*., [17].

Regarding the type of the poisonous agent, the present study revealed that aluminium phosphide responsible for 20% of cases of respiratory distress in this study and 62% of death cases as it is commonly used in the agricultural community [18]. Also multi-organ failure and unavailability of any specific antidote causing maximum deaths [14]. Similar results was reported by, Slima [18], and Kasemy *et al*., [14]. Also this result coincide with El-Sarnagawy *et al*., [17] and Elgazzar *et al*., [20] While Beauchamp *et al*., [21] reported that atypical antipsychotics and benzodiazepines were the most common substance associated with intubation and El-Sarnagawy and Hafez [15], results showed that tramadol was the most frequently encountered drug leading to intubation and mechanical ventilation

Corrosives and hydrocarbons came next due to storage of these substances close to the floor, so they are accessible to young children [19]. As well Hammad *et al*., [1] reported that cholinesterase inhibitors and corrosive poisonings were the most common cause of respiratory system affection

The oral route was the most frequent as the oral drugs are easily accessible. Similarly Abdelhamid *et al*., [4] found that the oral route was the most frequent route in drug-related acute respiratory distress.

Toxicity by single agent was found in 88% of all cases There is statistically significant association between it and survival, similar to Abdelhamid *et al*., [4] and El-Sarnagawy and Hafez, [15].

The mode of poisoning was suicidal in (60%) of cases due to many causes as financial problems and economic instability. On the contrary Hammad *et al*., [1] reported that accidental exposure to poisoning was the most common mode of toxicity (79.3%)

No pre-hospital intervention was done to majority of patients before admission, this is because transportation to our poison control centre is easy. This is partially similar to Abdelhamid *et al*., [4]

Regarding ICU admission 45% of cases was in need for ICU admission and mechanical ventilation while 16% only admitted at our hospital ICU as there is only two general intensive care units unspecialized in poisoned cases are present at our hospital. This result is partially similar to Hammad *et al*., [1] who reported that 24% of cases admitted in ICU.

Regarding period of hospital stay among the survivors it ranged from (1-14). Also Abd El Salam *et al*., [22] reported that the hospital stay period for cases who had attempted suicide ranged from 4 h to 18 days, with a mean of (1.56±1.72) days.

Regarding the heart rate most of cases presented with tachycardia, as most of our cases were poisoned by aluminium phosphide which causes tachycardia by the direct toxic effect of phosphine gas on cardiac muscle Singh and Bhalla, [24] followed by psychotropics which cause tachycardia through its anti-cholinergic, antihistaminic and alpha antagonism effect [25].

Tachyapnea was reported in 96% of patients due to respiratory distress without significant association between them and survival. This result shows similarity with Hammad *et al*., [1] and Elgazzar *et al*., [20].

The conscious level in the studied cases, at time of admission ranged between (3-15). This differences is due to poisoning with different types of poisons and the difference in the amount consumed. Similarly, Oreby *et al*., [23] reported that the mean GCS level was 9.7 in poisoned cases that were admitted to intensive care unit.

Chest examination of 72% of cases shows abnormal chest signs as chest crepitations, wheeze and diminished air entry either due to pulmonary edema as in aluminum phosphide toxicity Anand *et al*., [26] aspiration pneumonia due to absent gag reflex especially in psychotropic poisoned cases Mubarak *et al*., [25] and anticholinesterase poisoning which causes increase bronchial secretion [27].

Arterial blood gases was normal in 14% of all cases. Respiratory alkalosis was found in 56% due to tachypnea that lead to increase CO_2 washout. Metabolic acidosis was found in 26% of cases due to blockage of oxidative phosphorylation that leads to lactic acid accumulation and decrease bicarbonate concentration, similar to Hammad *et al*., [1].

Regarding blood glucose level 84% of cases were euglycemic. Similar results was reported by El-Sarnagawy *et al*., [17]. This can be explained in acute toxicity results from the interplay between endocrine, autonomic and endothelial mechanisms with different responses across individuals.

Liver enzymes were normal in the majority of cases this result coincide with Slima, [18].

Regarding O_2 saturation, it was ranging from 28%- 99% in all cases. Similar to El-Sarnagawy *et al*., [17] who reported that O_2 saturation ranged between 35% and 100%.

Concerning PaO_2/FIO_2 it ranged from 124-700 without significant correlation between it and survival. This result is partially similar to Abdelhamid *et al*., [4] who reported that these hypoxemic indices did not show statistically significant difference between survivors and non survivors and the calculated PaO2/FiO2 can be easily manipulated by changing FiO2 and positive end expiratory pressure or change for reasons that are completely independent of the lungs (e.g. a change in CO2 and mixed venous O2).

ECG findings was normal in 58% of cases with statistically significant association between it and survivors similar to Siddique *et al*., [28].

Concerning the copeptin level it was measured at admission and after 24 hours and we found that copeptin peaked on the first day then, its levels dropped after 24 hour. So we can

use copeptin as early predictor of ARDS linked toxicity. Irem *et al*., [30] and Abd Alkareem and Khater, [29] reported that serum copeptin level was positively increases with the increase the severity and poor outcome of cases with acute toxicity.

So copeptin can be used as early predictor in toxin-linked ARDS with high sensitivity 90% and specificity 75%.Similar result by Netto *et al*., [31] who reported that copeptin can be used as predictor for mortality and ICU admission of hospitalized pneumonia patients. In contrary, Henrique *et al*., [32] reported that their results did not show any correlation between copeptin levels in ICU admission and mortality.

Lung patches was found in 72% of cases, while lung patches with pleural effusion was found in 14% of cases with significant association between radiological changes and survival. Similarity with Hammad *et al*., [1].

SOFA score was designed to grade organ dysfunction, which is important in such poisons that cause multi-organ failure. It revealed predominance of respiratory failure, either alone or combined with other organ failure. Similarily, Alkotami *et al*., [33] reported that SOFA score monitor the progression of the case and the outcome of ventilated patients.

This result show partial similarity with Sheta *et al*., [34] who reported that SOFA in the survivors group ranged from 0 to 6, while in the non-survivors group it ranged from 4 to 15 and the mortality rate increase with increasing SOFA score value.

ICU admission according to SOFA score, our study revealed that there was no significant relation between SOFA score and ICU admission. Conversely, Raith *et al*., [35] reported that SOFA score has been demonstrated to be a useful predictor of ICU mortality.

Serum copeptin level revealed weak positive correlation with O_2 saturation, while showing weak negative correlation with age, delay time, period of admission, SOFA score and PaO_2/FIO_2. This result is partially similar to Dobša and Cullen Edozien [36]. In contrary Ostergaard *et al*., [37] reported that copeptin increase in response to hypoxia.

The receiver operating characteristic curve of serum copeptin level showed that copeptin had area under curve equals 0.913 with a sensitivity 90 and specificity 75% with cutoff level 1.081. Similar to, Abd Alkareem and Khater [29].

Conclusions

Respiratory system affection is a major cause of morbidity and mortality in acute poisoned cases. Phosphides, psychotropic drugs, are common respiratory toxicants. Copeptin level can be used as a predictor for toxin linked ARDS As its sensitivity 90% and specificity 75%.

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Conflict of Interest

Nil

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