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# Comparing the Effectiveness of Three Scoring Systems in Outcome Prediction of Acute Tricyclic Antidepressants Poisoning Cases

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**Abstract**

**Background:** Tricyclic antidepressants (TCAs) toxicity continues to be a major problem and an important cause of morbidity and mortality from poisoning all over the world. **Aim of the study:** to compare the effectiveness of poison severity score (PSS), acute physiology and chronic health evaluation (APACHE II) score and rapid emergency medicine score (REMS) for prediction of the need for intensive care unit (ICU) admission and mechanical ventilation (MV) in cases with acute TCAs toxicity. **Methods:** This retrospective observational study was conducted on 109 TCAs poisoned cases who were admitted to Tanta University Poison Control Center during the period from the first of January 2017 to the end of December 2020. Three scoring systems (PSS, APACHE II and REMS) were calculated for all cases at admission. Discrimination was evaluated using receiver operating characteristics curve and calculating the area under the curve (AUC). **Results:** The results of this study revealed that twenty-five cases needed to be admitted to ICU and 8 cases needed MV. The median of the three scores was significantly higher in cases that needed both ICU admission and MV. Although the APACHE II score has the best AUC value for prediction of ICU admission and MV (0.956 and 0.943 respectively), there was no statistically significant difference between the three scores. The AUC value of REMS comes next (0.931 and 0.925 respectively). **Conclusion:** REMS is rapid and simple score that can be easily assessed in emergency situations, it is recommended to be used for outcome prediction in TCAs poisoning.

**Key words** Tricyclic antidepressants, poison severity score, acute physiology and chronic health evaluation score, rapid emergency medicine score, intensive care unit

## Introduction

Tricyclic antidepressants (TCAs) were one of the first groups of antidepressants to be approved by the Food and Drug Administration in the 1950s. They have been used extensively for the management of depression and other psychiatric disorders but because of their severe side effects, their use has now been replaced by newer and safer alternatives. Nowadays, TCAs are still being used for the treatment of depression refractory to other treatments, chronic pain resistant to other modalities in adults and for nocturnal enuresis in children *(Sansone and Sansone, 2008, Liebelt, 2015, Khalid and Waseem, 2020).*

Toxicity by TCAs results from blockade of several receptors. Blockade of alpha-adrenergic receptors leads to vascular dilatation and postural hypotension. Blockade of muscarinic receptors causes signs of anticholinergic toxicity including dry mouth and skin, blurring of vision, decreased bowel sounds, urine retention and altered mental status *(Liebelt, 2008).* Fast sodium channels blockade in myocardial cells slows the action potential and leads to a membrane stabilizing effect or quinidine-like effect *(Kerr et al., 2001).* In addition, potassium channel blockade can cause QT prolongation that may results in torsade de pointes *(Thanacoody and Thomas, 2005, Carrillo-Esper et al., 2012).*

Several scoring systems were developed in the past few decades to provide physicians all over the world with an objective measurement of the severity of illness *(Oprita et al., 2014).* The poison severity score (PSS) is a standardized score for grading the severity of poisoning. It provides qualitative evaluation of morbidity caused by poisoning, better recognition of real risks and comparison of data *(Persson et al., 1998).* The acute physiology and chronic health evaluation (APACHE II) score was described by *Knaus et al. (1985)* and was validated in both general and surgical intensive care unit (ICU) patients *(Berger et al., 1992, Wilairatana et al., 1995, Wong et al., 1995, Bosscha et al., 1997).* The rapid emergency medicine score (REMS) is an attenuated version of APACHE II that allows rapid calculation. Among non-surgical patients who present to the emergency department, REMS has proven to be a valid predictor of mortality *(Olsson et al., 2004).*

Prediction of the progression of clinical toxicity in TCAs overdose is difficult as patients presented initially without any clinical symptoms may develop life-threatening cardiovascular system (CVS) and central nervous system (CNS) toxicity abruptly within the next hours due to the slow absorption caused by their anticholinergic effect *(Blackman et al., 2001).* So,

the aim of the present study was to compare the effectiveness of PSS, APACHE II score and REMS (at admission) for the prediction of the need for ICU admission and mechanical ventilation (MV) in cases with acute TCAs toxicity.

## Patients and Methods

**Study Design and setting:**

This retrospective observational study was conducted in Tanta University Poison Control Center (TUPCC) using the data of four years, from the first of January 2017 to the end of December 2020. Data were recruited from the patients' clinical files after approval from the head of TUPCC.

***Ethical considerations***

Ethical approval was obtained from the Research Ethics Committee of Faculty of Medicine, Tanta University (Approval code: 34458/2/21). The confidentiality of the patients' data was maintained by using coding numbers.

***Inclusion Criteria:***

All admitted cases aged 16 years and more of both genders with acute TCAs poisoning were included in the study. Diagnosis of acute TCAs poisoning was based on history of TCA ingestion from the patient himself or the relatives. In addition to reliable identification of the compound based on the container brought by patient or his/her attendants, and the presence of the highly suggestive symptoms and signs including CNS (seizure and coma) and CVS manifestations (tachycardia and hypotension).

***Exclusion Criteria:***

Cases with co-ingestion or exposure to other substances in addition to TCA compound, cases with history of chronic medical conditions (e.g., cardiovascular, respiratory, renal, or hepatic diseases) or history of any accompanying condition as significant head trauma (as these conditions could affect some of the parameters included in the calculation of the scores and hence could affect the scores' values) and cases with incomplete hospital records were excluded.

**Method of the study:**

Data of cases with acute TCAs poisoning were retrieved and carefully examined as regards the following:

- **History taking:**
  - Sociodemographic data (age, gender, residence, education, and occupation).
  - History of medical diseases other than those mentioned in the exclusion criteria.
  - Toxicological history including name of TCA ingested, mode of poisoning and delay time before hospital admission.
- **Clinical data:**
  - Vital signs (pulse, blood pressure, respiratory rate, and temperature).
  - Level of consciousness by Glasgow coma scale (GCS).
  - Pupil size and reaction.
  - Symptoms and signs of TCAs poisoning.
- **Results of laboratory investigations: (at admission)**
  - Arterial blood gases (ABG).
  - Liver enzymes: alanine aminotransferase (ALT), aspartate transaminase (AST).
  - Kidney function tests (urea, creatinine).
  - Complete blood count (CBC).
  - Electrolytes (sodium and potassium)
  - Random blood sugar (RBS).
- **Electrocardiography (ECG) records**
- **Calculation of scoring systems:** Only the recorded clinical data and results of laboratory investigations on admission and before receiving any treatment were used to calculate the following scoring systems.
  - **PSS** which grades the severity of poisoning in three levels: (1) minor, (2) moderate, and (3) severe poisoning. On both sides of these grades there are the extremes, (0) cases with no symptoms related to poisoning at all and (4) fatal cases *(Persson et al., 1998)*
  - **APACHE II** includes 12-points acute physiological and laboratory values, age point and chronic health evaluation. These parameters are mean arterial pressure (MAP), heart rate, respiratory rate, body temperature, oxygenation of arterial blood ($PaO_2$), arterial pH, serum sodium, serum potassium, white blood count, hematocrit value, serum creatinine and GCS. The score for each parameter was assigned from 0 to 4, with 0 being normal and 4 being the most abnormal. The sum of these values was added to a mark adjusting for patient age and a mark adjusting for chronic health problems to arrive at the APACHE II score which ranged from 0 to 71 *(Knaus et al., 1985)*
  - **REMS** is composed of 6 variables: heart rate, respiratory rate, MAP, GCS, peripheral oxygen saturation and age. All variables were assigned a score from 0 (normal) to 4 (the most abnormal) except age was graded a score from (0 to 6) providing a daily score ranges from 0 to 26 *(Olsson et al., 2004)*
- **The recorded outcome measures (prognosis):**
  - Requirement of ICU admission.
  - Need for mechanical ventilation (MV).
  - Duration of hospital stay.
  - Complications and mortality if present.

**Statistical analysis**

Statistical analysis was performed using MedCalc Statistical Software version 15.8. The Shapiro-Wilk test for normality was carried out to determine the distribution of numerical data. Normally distributed variables were summarized as mean ± standard deviation, whereas abnormally distributed numerical variables were expressed as median and interquartile range (IQR: $25^{th}$-$75^{th}$ percentiles). Mann-Whitney test was used to compare the studied scores between two groups. Correlations between scores and numerical variables were done using Spearman's rank-order correlation. The categorical variables were summarized as frequencies. Receiver operating characteristics (ROC) curve was carried out to determine the optimal cut-off point, sensitivity and specificity. The area under the curve (AUC) was graded as follows: 0.90-1 = excellent; 0.80-0.90 = good; 0.70-0.80 = fair; and 0.60- 0.70 = poor. Pairwise comparisons of the AUCs of the studied scores were done. A p value <0.05 indicated significance in interpreting results of statistical tests.

## Results

During the study period, 109 cases fulfilled the inclusion criteria and were included. Table (1) presents their sociodemographic and toxicological data. The age of the studied cases ranged from 16 to 70 years with a mean of 25.4 ± 9.8. Females outnumbered males (89% versus 11%). Most of the cases came from urban areas and educated up to the secondary school (72.5%, 70.6% respectively). Unemployed persons accounted for 49.5% of the cases while students accounted for 39.4%. Past medical history of psychiatric illness was present in 28.4% of the cases. Nearly all the cases (99.1%) ingested TCAs in suicidal attempts. Amitriptyline was the most used drug (72.5%). The median delay time was 3.5 hours.

Table (2) demonstrates the clinical data of the studied cases. The mean values of vital signs and $O_2$ saturation were within normal ranges. The mean GCS was 12.4± 3.0. Disturbed consciousness level was the most common presenting manifestation (63.3%), while seizures was the least common (9.2%). In addition, the mean value of results of laboratory investigations were within normal ranges (table 3). Hypotension was recorded in 4.6% of cases of the present study while tachycardia was present in 49.5% of the cases.

ECG finding was shown in table (4) and figures (1-3). The most frequently recorded ECG change was sinus tachycardia (49.5%) followed by long QTc (11.9%) then wide QRS (8.3%). The median $QT_C$ interval was 388.0 milliseconds.

Table (5) shows the outcome of the studied cases. Twenty-five cases (22.9%) needed to be admitted to ICU, while only 8 cases (7.3%) needed to be mechanically ventilated. The median duration of hospital stay was 19 hours. Sixteen cases (14.68%) suffered from chest and urinary tract infections as complications of hospital and/ or ICU stay. No mortality was recorded.

Table (6) compares between cases who needed ICU admission and/ or MV and cases who did not need ICU admission and/ or MV as regards the three studied scores. All the median scores were significantly higher ($p<0.001$) in cases who needed ICU admission and MV when compared to those who did not need them.

Table (7) and figure (4) show the ROC curve analysis for the prediction of the need for ICU admission using the studied scoring systems. All the studied scores had an AUC of >0.9 indicating that they are excellent predictors of the need for ICU admission. The APACHE II had the best AUC (AUC=0.956, 95% CI=0.899-0.986) followed by the REMS (AUC=0.931, 95% CI=0.866-0.971), then the PSS score (AUC=0.914, 95% CI=0.845-0.959). There was no statistically significant difference among the AUCs of the three scores (all p values > 0.05). The optimal cut-off values for each score and their associated sensitivities and specificities are demonstrated in table (6).

Table (8) and figure (5) show the ROC curve analysis for the prediction of the need for MV using the studied scoring systems. All the studied scores had an AUC of 0.8- >0.9 indicating that they are very good to excellent predictors. The APACHE II had the best AUC (AUC=0.943, 95% CI=0.882-0.978) followed by the REMS (AUC=0.925, 95% CI=0.858-0.966), then the PSS score (AUC=0.834, 95% CI=0.751-0.899). There was no statistically significant difference among the AUCs of the studied scores (all p values > 0.05). The optimal cut-off values for each score and their associated sensitivities and specificities are shown in table (7).

Table (9) reveals that the three scoring systems correlated significantly and positively with the length of hospital stay. These correlations were strong as the correlation coefficients were >0.5 in all of them.

**Table (1): Sociodemographic data and toxicological history of acute tricyclic antidepressants poisoned cases (n = 109):**

| | All cases (total n = 109) | | |
|---|---|---|---|
| Age (years) | Min-Max | 16.0 - 70.0 | |
| | Mean ± SD | 25.4 ± 9.8 | |
| Gender | Male | 12 | 11.0% |
| | Female | 97 | 89.0% |
| Residence | Rural | 30 | 27.5% |
| | Urban | 79 | 72.5% |
| Education | Illiterate | 4 | 3.7% |
| | Secondary school | 77 | 70.6% |
| | University | 28 | 25.7% |
| Occupation | Unemployed | 54 | 49.5% |
| | Employed | 12 | 11.0% |
| | Student | 43 | 39.4% |
| Past medical history | Not present | 72 | 66.1% |
| | Psychiatric illness | 31 | 28.4% |
| | Urinary incontinence | 2 | 1.8% |
| | Neuropathy | 3 | 2.8% |
| | Epilepsy | 1 | 0.9% |
| Mode of poisoning | Suicidal attempts | 108 | 99.1% |
| | Accidental | 1 | 0.9% |
| Generic name of the TCA drug | Amitriptyline | 79 | 72.5% |
| | Mirtazapine | 8 | 7.3% |
| | Nortriptyline | 5 | 4.6% |
| | Clomipramine | 5 | 4.6% |
| | Dosulepin hydrochloride | 5 | 4.6% |
| | Imipramine | 4 | 3.7% |
| | Modafinil | 3 | 2.8% |
| Delay time (hours) | Min-Max | 0.5 - 24.0 | |
| | Median [IQR] | 3.5 [2.0 - 5.5] | |

*n: number; IQR: interquartile range; Max: maximum; Min: minimum; SD: standard deviation; TCA: tricyclic antidepressant*

**Table (2): Clinical data of acute tricyclic antidepressants poisoned cases (n= 109):**

| | All cases (total n = 109) | | |
|---|---|---|---|
| Systolic Bl/P (mmHg) | Min-Max | 70.0 - 160.0 | |
| | Mean ± SD | 117.5 ± 17.8 | |
| Diastolic Bl/P (mmHg) | Min-Max | 40.0 - 100.0 | |
| | Mean ± SD | 74.4 ± 12.8 | |
| Heart rate (beats/ minute) | Min-Max | 55.0 – 147.0 | |
| | Mean ± SD | 102.6 ± 19.8 | |
| Respiratory rate (cycles/ minute) | Min-Max | 12.0 - 28.0 | |
| | Mean ± SD | 19.9 ± 3.2 | |
| Temperature | Min-Max | 36.0 - 38.0 | |
| | Mean ± SD | 36.9 ± 0.3 | |
| $SO_2$ | Min-Max | 75.0 - 100.0 | |
| | Mean ± SD | 97.6 ± 2.9 | |
| GCS | Min-Max | 4.0 - 15.0 | |
| | Mean ± SD | 12.4 ± 3.0 | |
| Pupil | RRR | 73 | 67.0% |
| | Constricted | 26 | 23.9% |
| | Dilated | 10 | 9.2% |
| Presenting manifestations | Disturbed consciousness level | 69 | 63.3% |
| | Seizures | 10 | 9.2% |
| | Abdominal pain & vomiting | 19 | 17.4% |
| | Slurred speech | 42 | 38.5% |

*n: number; IQR: interquartile range; Max: maximum; Min: minimum; SD: standard deviation; RRR: round, reactive and regular, GCS: Glasgow coma scale*

**Table (3): Results of the laboratory investigations of acute tricyclic antidepressants poisoned cases (n= 109):**

| | All cases (total n = 109) | |
|---|---|---|
| | Min-Max | Mean ± SD |
| pH | 7.30 - 7.56 | 7.43 ± 0.05 |
| $HCO_3$ (mEq/L) | 12.0 - 35.3 | 23.7 ± 4.0 |
| $PCO_2$ (mmHg) | 20.0 - 53.0 | 35.4 ± 7.1 |
| $PO_2$ | 63.0 - 194.4 | 97.9 ± 22.2 |
| Na (mg%) | 133.0 - 152.4 | 141.2 ± 4.0 |
| K (mg%) | 2.4 - 5.9 | 3.8 ± 0.5 |
| RBS (mg%) | 71.0 - 253.0 | 112.8 ± 25.6 |
| WBCs ($\times 10^3$) | 3.9 – 18.1 | 7.9 ± 2.7 |
| HCT value | 27.1 - 47.6 | 36.2 ± 3.5 |
| Creatinine (mg%) | 0.40 - 1.50 | 0.81 ± 0.19 |
| Urea (mg%) | 2.0 - 42.0 | 23.4 ± 7.6 |
| ALT (U/L) | Min-Max | 10.0 - 138.0 |
| | Median [IQR] | 19.0 [16.0 - 23.0] |
| AST (U/L) | Min-Max | 11.0 - 58.0 |
| | Median [IQR] | 20.0 [18.0 - 26.0] |

*n: number; IQR: interquartile range; Max: maximum; Min: minimum; SD: standard deviation; RBS: random blood sugar; WBCs: white blood cells; HCT value: Hematocrit value; ALT: alanine aminotransferase; AST: aspartate transaminase*

**Table (4): Electrocardiographic (ECG) finding of acute tricyclic antidepressants poisoned cases (n= 109):**

| | All cases (total n = 109) | | |
|---|---|---|---|
| ECG | Normal sinus rhythm | 53 | 48.6% |
| | Sinus bradycardia | 2 | 1.8% |
| | Sinus tachycardia | 54 | 49.5% |
| | Wide QRS | 9 | 8.3% |
| | Long QTc | 13 | 11.9% |
| | ST depression | 3 | 2.8% |
| | Inverted T | 2 | 1.8% |
| $QT_C$ interval (ms) | Min-Max | 310.0 - 580.0 | |
| | Median [IQR] | 388.0 [375.0 - 410.0] | |

*n: number; IQR: interquartile range; Max: maximum; Min: minimum; SD: standard deviation; ECG: electrocardiogram; ms: milliseconds*

**Table (5): Outcomes of acute tricyclic antidepressants poisoned cases (n= 109):**

| | | All cases (total n = 109) | |
|---|---|---|---|
| ICU admission | | 25 | 22.9% |
| Intubation and MV | | 8 | 7.3% |
| Complications (chest and urinary tract infections) | | 16 | 14.68% |
| Length of hospital stay (hours) | Min-Max | 10.0 – 96.0 | |
| | Median [IQR] | 19.0 [15.0 – 26.0] | |

*IQR: interquartile range; Max: maximum; Min: minimum; ICU; intensive care unit; MV: mechanical ventilation*

**Table (6): Comparison between cases who needed intensive care unit (ICU) admission and/ or mechanical ventilation (MV) and cases who did not need ICU admission and/ or MV as regards the three studied scores (n= 109):**

| | | ICU admission | | Mann-Whitney test | | MV | | Mann-Whitney test | |
|---|---|---|---|---|---|---|---|---|---|
| | | No | Yes | Z | p | No | Yes | Z | p |
| PSS | Median [IQR] | 1 [1 - 2] | 3 [2 - 3] | 6.924 | <0.001* | 1 [1 - 2] | 3 [3 - 3] | 3.464 | 0.001* |
| APACHE II | Median [IQR] | 3 [1 – 4] | 9 [8 – 11] | 6.956 | <0.001* | 3 [1 – 5] | 11 [9 – 12] | 4.191 | <0.001* |
| REMS | Median [IQR] | 1 [0 – 2] | 4 [3 – 5] | 6.712 | <0.001* | 1 [0- 3] | 5 [5 – 6] | 4.101 | <0.001* |

*IQR: interquartile range; PSS: poison severity score; APACHE II: acute physiology and chronic health evaluation II; REMS: rapid emergency medicine score; ICU; intensive care unit; MV: mechanical ventilation; * significant at p<0.05**

**Table (7): Comparison of the studied scores for prediction of the need for intensive care unit (ICU) admission using ROC curve analysis (n= 109):**

| | **PSS** | **APACHE II** | **REMS** |
|---|---|---|---|
| **AUC (95% CI)** | 0.914 (0.845-0.959) | 0.956 (0.899-0.986) | 0.931 (0.866-0.971) |
| **P** | <0.001* | <0.001* | <0.001* |
| **Cut off value** | > 2 | >6 | > 2 |
| **Sensitivity %** | 64.0 | 92.0 | 92.0 |
| **Specificity %** | 98.8 | 95.2 | 82.1 |
| **P value from pairwise comparisons of AUCs** | | | |
| **PSS** | | 0.198 | 0.658 |
| **APACHE II** | 0.198 | | 0.274 |
| **REMS** | 0.658 | 0.274 | |

*AUC: area under ROC curve; CI: confidence interval; PSS: poison severity score; APACHE II: acute physiology and chronic health evaluation II; REMS: rapid emergency medicine score *significant at p<0.05*

**Table (8): Comparison of the studied scores for prediction of the need for mechanical ventilation (MV) using ROC curve analysis (n 109):**

| | PSS | APACHE II | REMS |
|---|---|---|---|
| **AUC (95% CI)** | 0.834 (0.751-0.899) | 0.943 (0.882-0.978) | 0.925 (0.858-0.966) |
| **P** | <0.001* | <0.001* | <0.001* |
| **Cut off value** | > 2 | >7 | > 3 |
| **Sensitivity %** | 75.0 | 100.0 | 87.5 |
| **Specificity %** | 89.1 | 85.2 | 83.2 |
| **P value from pairwise comparisons of AUCs** | | | |
| **PSS** | | 0.131 | 0.248 |
| **APACHE II** | 0. 131 | | 0.605 |
| **REMS** | 0. 248 | 0. 605 | |

*AUC: area under ROC curve; CI: confidence interval; PSS: poison severity score; APACHE II: acute physiology and chronic health evaluation II; REMS: rapid emergency medicine score *significant at p<0.05*

**Table (9): Correlations between the duration of hospital stay and the three scoring systems (n = 109):**

| | | Hospital stay duration |
|---|---|---|
| PSS | $r_s$ | 0.666 |
| | p | <0.001* |
| APACHE II | $r_s$ | 0.712 |
| | p | <0.001* |
| REMS | $r_s$ | 0.693 |
| | p | <0.001* |

*$r_s$: coefficient of Spearman's rank-order correlation; PSS: poison severity score; APATCH II: acute physiology and chronic health evaluation II; REMS: rapid emergency medicine score; *significant at p <0.05*

**Table (10): Clinical data of acute tricyclic antidepressants poisoned cases (n= 109):**

| | All cases (total n = 109) | | |
|---|---|---|---|
| Systolic Bl/P (mmHg) | Min-Max | 70.0 - 160.0 | |
| | Mean ± SD | 117.5 ± 17.8 | |
| Diastolic Bl/P (mmHg) | Min-Max | 40.0 - 100.0 | |
| | Mean ± SD | 74.4 ± 12.8 | |
| Heart rate (beats/ minute) | Min-Max | 55.0 – 147.0 | |
| | Mean ± SD | 102.6 ± 19.8 | |
| Respiratory rate (cycles/ minute) | Min-Max | 12.0 - 28.0 | |
| | Mean ± SD | 19.9 ± 3.2 | |
| Temperature | Min-Max | 36.0 - 38.0 | |
| | Mean ± SD | 36.9 ± 0.3 | |
| $SO_2$ | Min-Max | 75.0 - 100.0 | |
| | Mean ± SD | 97.6 ± 2.9 | |
| GCS | Min-Max | 4.0 - 15.0 | |
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| Pupil | RRR | 73 | 67.0% |
| | Constricted | 26 | 23.9% |
| | Dilated | 10 | 9.2% |
| Presenting manifestations | Disturbed consciousness level | 69 | 63.3% |
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*n: number; IQR: interquartile range; Max: maximum; Min: minimum; SD: standard deviation; RRR: round, reactive and regular, GCS: Glasgow coma scale*

**Table (11): Results of the laboratory investigations of acute tricyclic antidepressants poisoned cases (n= 109):**

| | All cases (total n = 109) | |
|---|---|---|
| | Min-Max | Mean ± SD |
| pH | 7.30 - 7.56 | 7.43 ± 0.05 |
| $HCO_3$ (mEq/L) | 12.0 - 35.3 | 23.7 ± 4.0 |
| $PCO_2$ (mmHg) | 20.0 - 53.0 | 35.4 ± 7.1 |
| $PO_2$ | 63.0 - 194.4 | 97.9 ± 22.2 |
| Na (mg%) | 133.0 - 152.4 | 141.2 ± 4.0 |
| K (mg%) | 2.4 - 5.9 | 3.8 ± 0.5 |
| RBS (mg%) | 71.0 - 253.0 | 112.8 ± 25.6 |
| WBCs ($\times 10^3$) | 3.9 – 18.1 | 7.9 ± 2.7 |
| HCT value | 27.1 - 47.6 | 36.2 ± 3.5 |
| Creatinine (mg%) | 0.40 - 1.50 | 0.81 ± 0.19 |
| Urea (mg%) | 2.0 - 42.0 | 23.4 ± 7.6 |
| ALT (U/L) | Min-Max | 10.0 - 138.0 |
| | Median [IQR] | 19.0 [16.0 - 23.0] |
| AST (U/L) | Min-Max | 11.0 - 58.0 |
| | Median [IQR] | 20.0 [18.0 - 26.0] |

*n: number; IQR: interquartile range; Max: maximum; Min: minimum; SD: standard deviation; RBS: random blood sugar; WBCs: white blood cells; HCT value: Hematocrit value; ALT: alanine aminotransferase; AST: aspartate transaminase*

**Table (12): Electrocardiographic (ECG) finding of acute tricyclic antidepressants poisoned cases (n= 109):**

| | All cases (total n = 109) | | |
|---|---|---|---|
| ECG | Normal sinus rhythm | 53 | 48.6% |
| | Sinus bradycardia | 2 | 1.8% |
| | Sinus tachycardia | 54 | 49.5% |
| | Wide QRS | 9 | 8.3% |
| | Long QTc | 13 | 11.9% |
| | ST depression | 3 | 2.8% |
| | Inverted T | 2 | 1.8% |
| $QT_C$ interval (ms) | Min-Max | 310.0 - 580.0 | |
| | Median [IQR] | 388.0 [375.0 - 410.0] | |

*n: number; IQR: interquartile range; Max: maximum; Min: minimum; SD: standard deviation; ECG: electrocardiogram; ms: milliseconds*

**Table (13): Outcomes of acute tricyclic antidepressants poisoned cases (n= 109):**

| | | All cases (total n = 109) | |
|---|---|---|---|
| ICU admission | | 25 | 22.9% |
| Intubation and MV | | 8 | 7.3% |
| Complications (chest and urinary tract infections) | | 16 | 14.68% |
| Length of hospital stay (hours) | Min-Max | 10.0 – 96.0 | |
| | Median [IQR] | 19.0 [15.0 – 26.0] | |

*IQR: interquartile range; Max: maximum; Min: minimum; ICU; intensive care unit; MV: mechanical ventilation*

**Table (14): Comparison between cases who needed intensive care unit (ICU) admission and/ or mechanical ventilation (MV) and cases who did not need ICU admission and/ or MV as regards the three studied scores (n= 109):**

| | | ICU admission | | Mann-Whitney test | | MV | | Mann-Whitney test | |
|---|---|---|---|---|---|---|---|---|---|
| | | No | Yes | Z | p | No | Yes | Z | p |
| PSS | Median [IQR] | 1 [1 - 2] | 3 [2 - 3] | 6.924 | <0.001* | 1 [1 - 2] | 3 [3 - 3] | 3.464 | 0.001* |
| APACHE II | Median [IQR] | 3 [1 – 4] | 9 [8 – 11] | 6.956 | <0.001* | 3 [1 – 5] | 11 [9 – 12] | 4.191 | <0.001* |
| REMS | Median [IQR] | 1 [0 – 2] | 4 [3 – 5] | 6.712 | <0.001* | 1 [0- 3] | 5 [5 – 6] | 4.101 | <0.001* |

*IQR: interquartile range; PSS: poison severity score; APACHE II: acute physiology and chronic health evaluation II; REMS: rapid emergency medicine score; ICU; intensive care unit; MV: mechanical ventilation; * significant at p<0.05**

**Table (15): Comparison of the studied scores for prediction of the need for intensive care unit (ICU) admission using ROC curve analysis (n= 109):**

| | PSS | APACHE II | REMS |
|---|---|---|---|
| **AUC (95% CI)** | 0.914 (0.845-0.959) | 0.956 (0.899-0.986) | 0.931 (0.866-0.971) |
| **P** | <0.001* | <0.001* | <0.001* |
| **Cut off value** | > 2 | >6 | > 2 |
| **Sensitivity %** | 64.0 | 92.0 | 92.0 |
| **Specificity %** | 98.8 | 95.2 | 82.1 |
| **P value from pairwise comparisons of AUCs** | | | |
| **PSS** | | 0.198 | 0.658 |
| **APACHE II** | 0.198 | | 0.274 |
| **REMS** | 0.658 | 0.274 | |

*AUC: area under ROC curve; CI: confidence interval; PSS: poison severity score; APACHE II: acute physiology and chronic health evaluation II; REMS: rapid emergency medicine score *significant at p<0.05*

**Table (16): Comparison of the studied scores for prediction of the need for mechanical ventilation (MV) using ROC curve analysis (n 109):**

| | PSS | APACHE II | REMS |
|---|---|---|---|
| **AUC (95% CI)** | 0.834 (0.751-0.899) | 0.943 (0.882-0.978) | 0.925 (0.858-0.966) |
| **P** | <0.001* | <0.001* | <0.001* |
| **Cut off value** | > 2 | >7 | > 3 |
| **Sensitivity %** | 75.0 | 100.0 | 87.5 |
| **Specificity %** | 89.1 | 85.2 | 83.2 |
| **P value from pairwise comparisons of AUCs** | | | |
| **PSS** | | 0.131 | 0.248 |
| **APACHE II** | 0. 131 | | 0.605 |
| **REMS** | 0. 248 | 0. 605 | |

*AUC: area under ROC curve; CI: confidence interval; PSS: poison severity score; APACHE II: acute physiology and chronic health evaluation II; REMS: rapid emergency medicine score *significant at p<0.05*

**Table (17): Correlations between the duration of hospital stay and the three scoring systems (n = 109):**

| | | Hospital stay duration |
|---|---|---|
| PSS | $r_s$ | 0.666 |
| | p | <0.001* |
| APACHE II | $r_s$ | 0.712 |
| | p | <0.001* |
| REMS | $r_s$ | 0.693 |
| | p | <0.001* |

*$r_s$: coefficient of Spearman's rank-order correlation; PSS: poison severity score; APATCH II: acute physiology and chronic health evaluation II; REMS: rapid emergency medicine score; *significant at p <0.05*

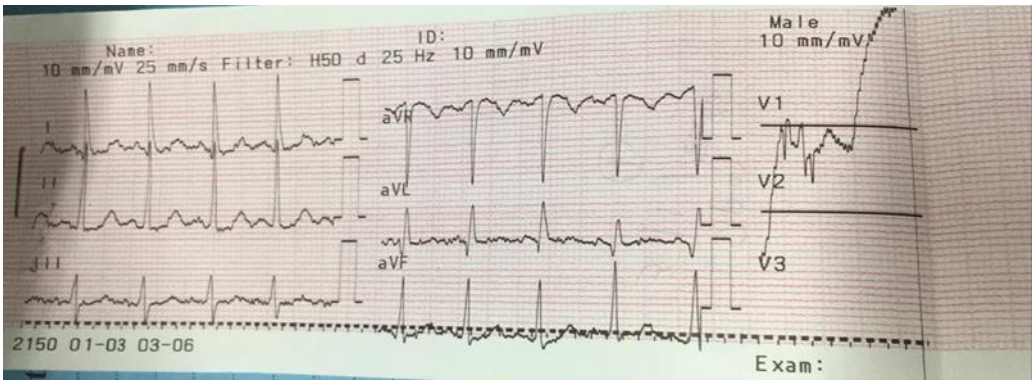


**Fig. (1): An ECG from 25 years old male case with alleged ingestion of 10 tablets of Amitriptyline (50mg/ tablet) in a suicidal attempt showing sinus tachycardia (120 beats/ minute)**

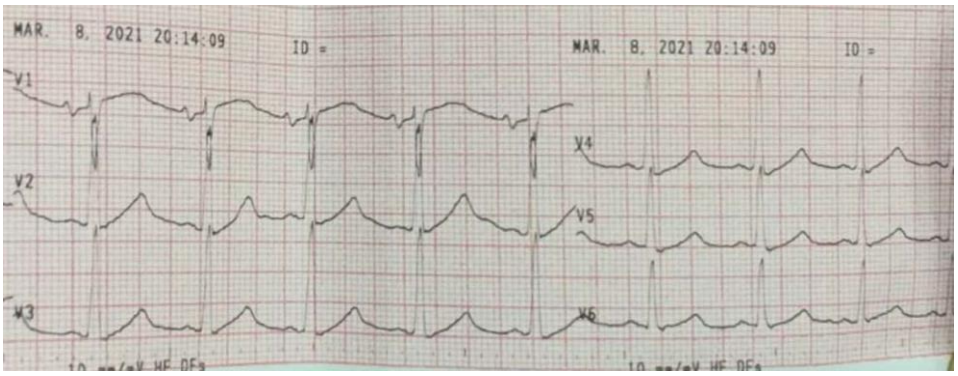


**Fig. (2): An ECG from 33 years old male case with alleged ingestion of 8 tablets of Amitriptyline (75mg/ tablet) in a suicidal attempt showing prolonged QTc (566 milliseconds).**

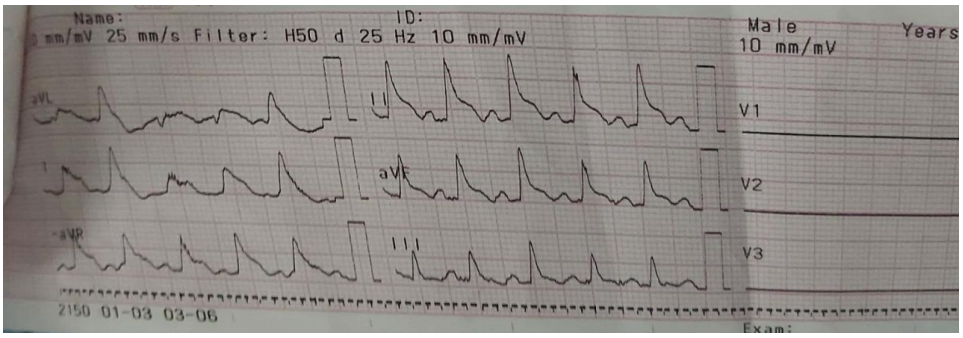


**Fig. (3): An ECG from 19 years old female case with alleged ingestion of 10 tablets of Nortriptyline (25mg/ tablet) in a suicidal attempt showing wide QRS complex.**

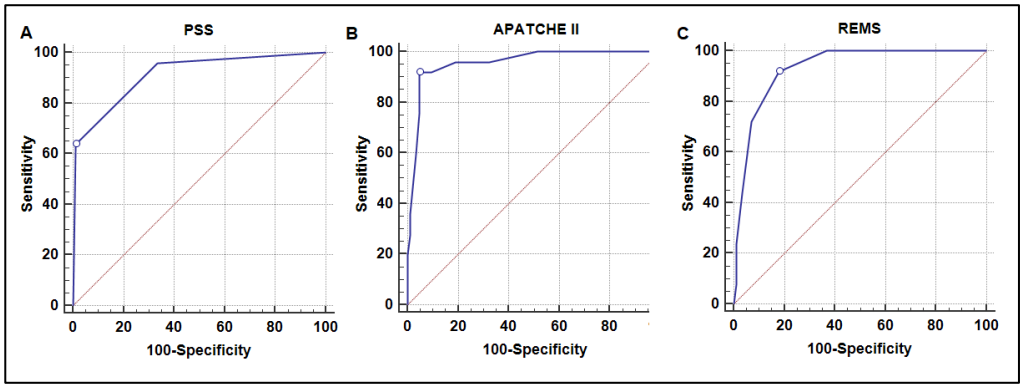


**Fig. (4): ROC curves for prediction of the need of intensive care unit admission using PSS (A), APACHE II (B) and REMS (C) PSS: poison severity score; APACHE II: acute physiology and chronic health evaluation; REMS: rapid emergency medicine score.**

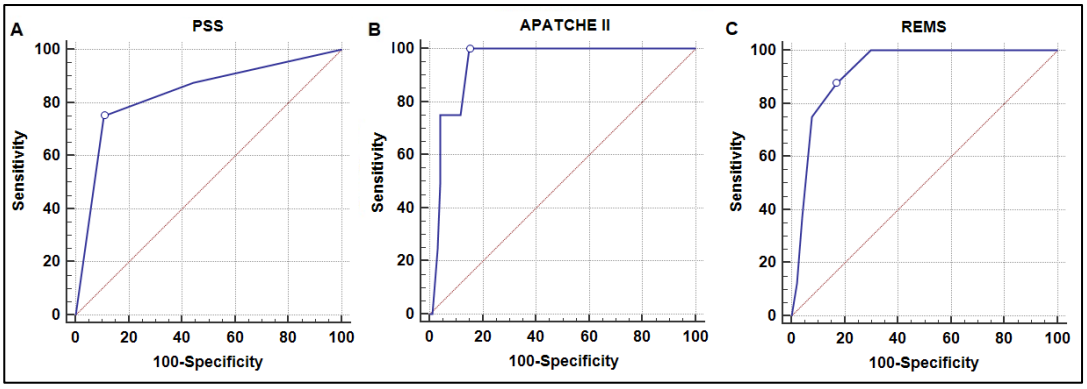


**Fig. (5): ROC curves for prediction of the need for intubation and mechanical ventilation using PSS (A), APACHE II (B) and REMS (C) PSS: poison severity score; APACHE II: acute physiology and chronic health evaluation; REMS: rapid emergency medicine score.**

## Discussion

Tricyclic antidepressants (TCAs) toxicity continues to be a major problem and an important cause of morbidity and mortality from poisoning all over the world *(Koegelenberg et al., 2012)*. Although, new antidepressants with safer profile are introduced to the market, clinicians in different parts of the world including the Middle East still prescribe the older antidepressant drugs including TCAs very often *(Eliasson et al., 2013)*.

Several parameters were studied for prediction of outcome in TCAs poisoned cases including the age, delay time between exposure and hospital admission, type and dose of TCAs, blood TCA level and ECG changes *(Hultén et al., 1992, Bailey et al., 2004, Eyer et al., 2009, Koegelenberg et al., 2012, Saleh et al., 2013)* . However, none of these studies has evaluated the use of scoring systems at hospital admission to predict the need for ICU admission or the need for MV. To the best of the authors' knowledge, this study is the first to compare between different scoring systems to predict these outcome measures in TCAs poisoned cases.

In the current study, the age of the studied cases ranged from 16 to 70 years with a mean of 25.4 ± 9.8.0. This was nearly similar to the mean age reported by *Yaraghi et al. (2015)* and *Eizadi-Mood et al. (2016)*. The majority of cases were females (89%), from urban areas (72.5%) and were unemployed (49.5%). These were in accordance with *Saleh et al. (2013)* who reported female, urban residence and unemployed persons predominance (73%, 92% and 40% respectively) in their study.

History of psychiatric illness (depression) was present in 28.4% of the present study cases and 99% of the cases ingested TCAs in suicidal attempts. These results were in accordance with the results of *Unverir et al. (2006)* and *Saleh et al. (2013)* who reported history of psychiatric illness in 33.1% and 27% of the cases respectively. They also reported exposure to antidepressants in suicidal attempts in 97.5% and 89% respectively. *Pompili et al. (2010)* concluded that the possible rise in suicide rate caused by the rising use of antidepressants continues to be one of the most significant public health concerns. *Rihmer and Akiskal (2006)* advised psychiatrists to be alert about the probable risk of occurrence of adverse effects e.g. suicidal ideations while prescribing potent drugs such as antidepressants.

Amitriptyline was the most frequently encountered antidepressant used by cases in the present study (72.5%). It was also the most common cause of toxicity reported in *Saleh et al. (2013)* and *Yildiz et al. (2020)* studies but with variable incidence (56% and 74.2% respectively). *Malmvik et al. (1994)* found that Amitriptyline is one of the most frequently prescribed and sold TCAs. In addition, they stated that it is a drug that is most frequently involved in suicide or suicide attempts in many countries. Furthermore, *Yildiz et al. (2020)* reported that Amitriptyline is commonly seen in cases of drug overdoses because of its cheap price and wide prescription by physicians.

The median delay time was 3.5 hours. This result partially coincided with *Unverir et al. (2006)* and *Aslan et al. (2011)*. This short delay time could be explained by the presence of TUPCC in the center of Delta region with readily available transportations. Furthermore, a large number of the cases who attempt suicide are just trying to gain sympathy and draw attention of their beloved ones and not aiming to end their lives, therefore, they seek medical advice rapidly *(Abd Elghany et al., 2018)*.

Disturbed consciousness level was the most common presenting manifestation (63.3%) of TCAs poisoning in the present study. The mean GCS was 12.4 ± 3.0. Level of consciousness was altered in 71% of the cases of *Saleh et al. (2013)* study, while it was altered in 84.2% in *Yaraghi et al. (2015)* study. The median GCS was 14 and 15 respectively in *Graudins et al. (2002)* and *Yildiz et al. (2020)* studies. On the other hand, the mean GCS was very low (4.9 ± 2.7) in *Eyer et al. (2009)* study. Altered mental status caused by TCA overdose is associated with their anticholinergic and antihistaminic effects *(Abdollahi and Mostafalou, 2014)*.

The mean systolic and diastolic blood pressure were 117.5± 17.8 and 74.4± 12.8 respectively. This was nearly similar to mean systolic and diastolic blood pressure of *Yaraghi et al. (2015)* study (107.8± 17.4 and 71.4± 12.5 respectively) and of *Avci et al. (2020)* study (116.4± 12.4 and 71.8± 8.5 respectively). Hypotension was recorded in only 4.6% of cases of the present study while it was reported in 15% of cases of *Saleh et al. (2013)* study. The mean heart rate was 102.6 ± 19.8 in this study which is fairly similar to that of *Eyer et al. (2009)* and *Avci et al. (2020)* studies (109± 25 and 99.3± 9. 6 respectively). Tachycardia was present in 49.5% of our cases and in 49% of cases of *Saleh et al. (2013)*.

The most frequently ECG change recorded in this study was sinus tachycardia (49.5%) followed by long QTc (11.9%) then wide QRS (8.3%). This was the same order of ECG changes reported in *Saleh et al. (2013)* study but with lower incidence (44%, 6%, 5% respectively). In *Aslan et al. (2011)* study done on cases of amitriptyline poisoning , the order of reported ECG changes and their incidence were different. Again, the most common change was sinus tachycardia (55%) followed by ST-T changes and widened QRS (15% each) then right bundle branch block (12.5%).

Initially, TCAs act by blocking the reuptake of norepinephrine, serotonin, and dopamine at central and peripheral presynaptic terminals producing a hyperadrenergic state, that causes the initial hypertension and tachycardia. Afterward, peripheral alpha- adrenergic receptors blockade and depletion of norepinephrine in the nerve terminals lead to postural hypotension, causing further tachycardia by reflex mechanism *(Singh et al., 2002)*. Tricyclic antidepressants have quinidine like effect by blocking the fast sodium channels, this delays the propagation of depolarization through the myocardium and the conducting tissue resulting in prolongation of the QRS

complex. The inhibition of sodium flux into the myocardial cells can occur to an extent that results in depressed contractility and this, coupled with the peripheral resistance reduction, contributes to hypotension *(Kerr et al., 2001)*. Furthermore, TCAs causes prolongation of QT interval by causing disruption in the delayed rectifier potassium and the inward slow calcium currents, both lead to delayed repolarization. *(Carrillo-Esper et al., 2012)*.

The mean and median values of the results of laboratory investigations (ABG, serum electrolytes, RBS, kidney and liver function tests) were within normal ranges. Mean values of ABG analysis were also within normal ranges in *Yaraghi et al. (2015)* study. In addition, the mean values of serum electrolytes, RBS, kidney and liver function tests in *Avci et al. (2020)* study were within normal ranges

Intensive care unit admission was needed in 22.9% of cases of the present study. On the other hand, the incidence of ICU admission was higher (76%) in *Foulke (1995)* study. Meanwhile it was lower (12.5%) in *Unverir et al. (2006)*. Mechanical ventilation was needed in 7.3% of our cases. This incidence is to some extent similar to the incidence of MV in *Unverir et al. (2006)* and *Saleh et al. (2013)* studies (11.5% and 8% respectively). On the contrary, the incidence of MV was higher in *Eyer et al. (2009)* and *Yaraghi et al. (2015)* studies (88% and 24.3% respectively). The difference of incidence of ICU admission and MV between studies might be attributed to the difference of severity of toxicity between cases included in each study.

*Liebelt (2015)* stated that criteria for ICU admission in cases with TCAs poisoning are not clear and are institution dependent. *Unverir et al. (2006)* found that cases who had seizures or GCS ≤ 8 had a higher of risk of requiring ICU admission. Furthermore, indications for MV differ between studies. *Unverir et al. (2006)* mentioned that reasons for endotracheal intubation and ventilation were low GCS, respiratory depression and failure to treat seizures. While *Saleh et al. (2013)* reported that the indications for intubation and MV in their study were deep coma, respiratory depression and aspiration of gastric contents

The median duration of hospital stay was 19 hours. This was fairly different from the median length of hospital stay in *Graudins et al. (2002)* study (23.1 hours) and in *Yildiz et al. (2020)* study (2 days). This difference again could be explained by the difference in severity of cases included in each study

Comparing the median scores, on admission, between cases who needed ICU admission and/ or MV and cases who did not need ICU admission and/ or MV revealed a significantly higher median scores in cases who needed ICU admission and MV. This indicates that these scoring systems may have a possible role in the prediction of the need for ICU admission and MV.

In the current study, the median PSS was 1 in non- ICU admitted and non-MV cases and 3 in ICU admitted and MV cases. The median APACHE II score was 3 in non- ICU admitted and non-MV cases while it was 9 and 11 in ICU admitted and MV cases, respectively. Furthermore, the median REMS was 1 in non- ICU admitted and non-MV cases while it was 4 and 5 in ICU admitted and MV cases respectively. No previous studies were found comparing the three studied scores regarding these outcome measures. The mean APACHE II score was found to be 18± 6 and 12.4± 9 in ICU admitted cases of acute TCAs poisoning in both *Eyer et al. (2009)* and *Koegelenberg et al. (2012)* studies respectively but without comparison with non- ICU admitted cases.

The three studied scores were evaluated as predictors of the need for ICU admission and/ or MV in different poisoning cases but not TCAs. *El-Sarnagawy and Hafez (2017)* and *Shahin and Hafez (2020)* found that APACHE II score and REMS were good predictors for the need of MV in overdosed cases with disturbed consciousness and in cases with anticholinesterase inhibitors (AChEIs) poisoning. *Abd Elnoor et al. (2019)* concluded that PSS and APACHE II score are good predictors for the need of ICU admission in aluminum phosphide and digitalis poisoning cases. In addition, *Shama et al. (2020)* revealed that the three scores are good predictors for both ICU admission and MV in organophosphorus poisoning cases

The accuracy of the three scoring systems in prediction of the need for ICU admission and MV was then assessed using ROC curve analysis. It was found that APACHE II showed the best discriminatory power, followed by REMS then PSS with no significant differences between them. Regarding the APACHE II score power for prediction of the need for ICU admission, it has the best AUC (0.956) with a cut-off value >6, 92% sensitivity and 95.2% specificity. While, it has an AUC of 0.943 at a cut off value >7 with 100% sensitivity and 85.2 specificity in prediction of the need for MV. REMS has an AUC of 0.931 at a cut off value >2 with 92% sensitivity and 82.1% specificity in prediction of ICU admission. Meanwhile, it has an AUC of 0.925 at a cut off value >3 with 87.5% sensitivity and 83.2% specificity in prediction of MV. The AUC of ROC curve analysis of PSS for prediction of the need for ICU admission was 0.914 at a cut off value >2 with 64% and 98.8% sensitivity and specificity respectively. While for its prediction of the need of MV, it has an AUC of 0.834 at a cut off value >2. Its sensitivity and specificity were 75% and 89.1% respectively.

Based on the absence of significant difference between the discriminatory power of the three scores, we can suggest using REMS as it is relatively simple and rapid score that can easily be assessed in emergency situations including acute poisoning. On the other hand, APACHE II score contains several laboratory investigations, so it seems not suitable for quick scoring in the emergency conditions. In addition, PSS includes assessment of severity in many body systems, so it is time consuming and does not offer a good help in emergency conditions.

The current study revealed significantly strong positive correlations between each of the three scoring systems and the length of hospital stay. This finding

coincided with the finding of *(Shahin and Hafez ,2020))* who reported that APACHE II score and REMS correlated significantly and positively with the length of hospital stay of their AChEIs- poisoned cases.

## Conclusion and Recommendations

In conclusion, TCAs poisoning is a common cause of morbidity. According to the results of the present study, it necessitates ICU admission and MV in 22.9% and 7.3% of the cases, respectively. The three scores (APACHE II, REMS and PSS) evaluated in this study were similar and effective tools for the prediction of the need for ICU admission and MV. However, REMS proved to be more applicable than the other scores as it is simple, rapid and easily assessed in emergency situations. Therefore, REMS is recommended to be used to predict the outcome of TCAs poisoned cases.

## Limitations:

This study was a retrospective study so, it was not possible to measure the level of TCAs ingested as this is not done routinely in TUPCC. Therefore, the diagnosis of TCAs poisoning was based on the history and the highly suggestive clinical picture.

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# مقارنة فعالية ثلاثة أنظمة قياسيه في توقع نتائج حالات التسمم الحاد بمضادات الاكتئاب ثلاثية الحلقات

أميرة أمين وهدان و ناديه عزت هلال[١]

## الملخص العربي

**المقدمة:** لا تزال سمية مضادات الاكتئاب ثلاثية الحلقات تمثل مشكلة رئيسية وسببًا مهمًا للأمراض والوفيات الناجمة عن التسمم في جميع أنحاء العالم. **الهدف من الدراسة:** هدفت الدراسة الحالية إلى مقارنة فعالية مقياس شدة التسمم (PSS) ومقياس الاباتشي الثاني (APACHE II) ومقياس ريمس (REMS) في التنبؤ بالحاجة إلى دخول وحدة العناية المركزة والحاجة الى جهاز التنفس الصناعي في حالات التسمم الحاد بمضادات الاكتئاب ثلاثية الحلقات. **الطريقة:** أجريت هذه الدراسة الاسترجاعية على ١٠٩ حاله تسمم بمضادات الاكتئاب ثلاثية الحلقات والذين تم إدخالهم إلى مركز طنطا الجامعي لعلاج حالات التسمم خلال الفترة من الأول من يناير ٢٠١٧ إلى نهاية ديسمبر ٢٠٢٠. تم حساب الأنظمة الثلاثة القياسية (PSS وAPACHE II وREMS) في كل الحالات عند الدخول. وقد اعتمدت المقارنة بين كفاءة الأنظمة الثلاثة على استخدام منحنى روك وحساب الانحدار اللوجستي (AUC). **النتائج:** وقد كشفت نتائج هذه الدراسة ان ٢٥ حالة قد احتاجت إلى دخول وحدة العناية المركزة و٨ حالات احتاجت إلى استخدام جهاز التنفس الصناعي. كان متوسط قيمة الأنظمة الثلاثة أعلى بفارق ذو دلالة احصائية في الحالات التي احتاجت إلى دخول وحدة العناية المركزة واستخدام جهاز التنفس الصناعي. وعلى الرغم من أن مقيس الاباتشي الثاني كان له اعلى معدل انحدار لوجيستي في التنبؤ بالحاجة إلى دخول وحدة العناية المركزة والحاجة الى جهاز التنفس الصناعي (٠.٩٥٦ و٠.٩٤٣ على التوالي)، فانه لم يكن هناك فارق ذو دلالة إحصائية بين معدل الانحدار اللوجيستي للأنظمة الثلاثة. وتأتي قيمة معدل الانحدار اللوجيستي لمقياس REMS بعد ذلك (٠.٩٣١ و٠.٩٢٥ على التوالي). **الخلاصة:** من نتائج الدراسة الحالية، نستنتج أنه نظرًا لأن مقياس REMS هو مقياس سريع وبسيط يمكن تقييمه بسهولة في حالات الطوارئ، فيستحسن استخدامه للتنبؤ بمصير حالات التسمم بمضادات الاكتئاب ثلاثية الحلقات.

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