Comparison of elevated cardiac troponin I with SAPS-II and APACHE-II score in predicting outcome of severe intoxications

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ABSTRACT

Background and Aims: To date, different methods have been invented to risk-stratify critically ill patients, however, there is a paucity of information regarding assessing the severity of poisonings. This study was designed to determine the comparative efficacy of Simplified Acute Physiology Score-II (SAPS-II) and Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score with cardiac troponin I (cTnI) in predicting severe intoxication outcomes.

Methods: This was a prospective study conducted on patients who fulfilled defined severe intoxication criteria necessitating intensive care unit (ICU) admission over a period of 6 months. SAPS-II and APACHE-II scores were calculated and cTnI concentrations were measured. These indicators were compared to determine which has the better ability to prognosticate mortality and complications.

Results: A total of 55 cases (median age, 35 [24‑49] years) were enrolled. Eight patients (14.5%) died. Mean SAPS-II, median APACHE-II score and median cTnI concentrations were 32.05 ± 11.24, 13 [10‑17] and 0.008 [0.002‑0.300] ng/ml, respectively, which were significantly different between the survivors and non-survivors. Receiver operating characteristics curve results of SAPS-II, APACHE-II score and cTnI concentrations in predicting mortality were 0.945, 0.932 and 0.763 and in predicting complications were 0.779, 0.739 and 0.727, respectively. High cTnI concentration (>0.37 ng/ml) correlated with soft clinical outcomes, including length of ventilatory support, length of ICU stay and length of hospital stay (LOS) (r: 0.928, 0.881 and 0.735 respectively; all P < 0.001).

Conclusion: SAPS-II scores were superior in predicting death and complications, while cTnI correlated more closely with soft clinical outcomes, such as the length of ventilator support, length of ICU stay or LOS.

Key words: APACHE, mortality, poisoning, simplified acute physiology score, troponin

INTRODUCTION

Acute poisonings are increasingly exerting a significant burden of costs and efforts on healthcare services worldwide. Patients are brought to emergency departments, requiring various levels of care.¹ The effectiveness of prognostic scales in predicting the outcome of intoxicated patients has become a matter of investigation globally, both to determine which patients will have more serious complications necessitating intensive monitoring and care or can afford to be observed in general wards for periods of time.² The outcomes in critically ill patients can be improved by applying risk assessment and scoring systems.² Simplified Acute Physiology
Score (SAPS)-II and Acute Physiology and Chronic Health Evaluation (APACHE)-II prognostic scoring systems have frequently been assessed in acute poisoning settings.\[^{[3]}\] Meanwhile, there exists a considerable body of literature that suggests that elevation of cardiac troponins particularly cTnI, indicative of the presence of cardiac injury, can also occur in critically ill patients.\[^{[4]}\] However, the research regarding the evaluation of the prognostic value of troponin elevation in severely intoxicated patients still remains limited.\[^{[5]}\] Myocardial injuries due to non-thrombotic mechanisms leading to elevated cardiac troponins have been reported in diverse categories of patients in the intensive care unit (ICU) and may act as an adverse prognostic marker.\[^{[6]}\] Accordingly, the elevation of troponin is not confined only to poisoning with myocardial involvement and is associated with in-hospital mortality of patients with a drug overdose. The cTnI is released into the circulation following myocardial necrosis due to damage from both ischaemia and drug-induced cardiotoxicity.\[^{[6]}\] It is speculated that the effect seen may be due to (but not limited to) microinjury and minimal myocardial cell damage occurring during myocardial ischaemia (e.g., hypotension, hyperthermia, coronary vasospasm), ion-channel poisoning, as well as direct cardiotoxicity (i.e., through inhibition of metabolic pathways such as oxidative phosphorylation).\[^{[6]}\] Although several other studies are reported taking into account SAPS-II and APACHE-II as scoring systems, to our knowledge, no previous study has been performed to compare the prognostic efficacy of three different measurements, two using physiologic scoring systems (SAPS-II and APACHE-II), and one using the laboratory measurement of cTnI concentration in patients with severe intoxications. We aimed to detect serum cTnI concentration and calculate SAPS-II and APACHE-II scores in severely intoxicated patients requiring intensive care and compare them to see which one is more sensitive and specific for predicting mortality and complications in these patients. Moreover, the correlation of these models with soft clinical outcomes, such as the length of ventilator support, length of hospital stay (LOS) were assessed.

**Methods**

The ethical committee of Qazvin University of Medical Sciences approved the study with an assigned ethical code: IR.QUMS.REC.1396.201. The procedure follows the guidelines laid down in the 7th revision of the Declaration of Helsinki 2008. Informed written consents were obtained from the patients or their relatives.

This was a prospective observational cohort study. During a 6-month period (between April 2018 and September 2018), all patients referred to our emergency department (ED) with severe deliberate or accidental intoxication and who required ICU admission based on a defined diagnostic guideline were sequentially included. We looked for criteria to do early recognition of the critically intoxicated patients mandating ICU admission. Most critically ill patients are immediately admitted to the ICU following initial ED procedures, but many of them may remain for a significant period of time in the ED as a result of ICU bed shortages.\[^{[7]}\] Therefore, the placement of patients in the early phase of their critical situation varies among institutions. We aimed to investigate critical intoxications, regardless of the location of the patient’s stay. We enroled a patient as a severe intoxication if any of the following criteria were met: Glasgow coma scale (GCS) score equal or <8, unstable haemodynamic status on admission confirmed by senior review, need for doing invasive interventions or procedures (e.g., glucose/insulin protocol or haemodialysis), unresolved rapid response team (RRT) criteria and repeated RRT calls. To elicit a RRT call, three clinical indicators of ten proposed clinical indicators including potentially threatened airway, sustained tachypnoea, cyanosis despite inspired oxygen concentration (FiO2) >0.4, tachycardia (heart rate >100/min), systolic blood pressure <100 mmHg, altered skin colour, altered state of consciousness, frequent seizures, increasing creatinine and rising lactate level need to be present.\[^{[8]}\] All patients requiring ICU admission were directly transferred from the ED. Included cases underwent testing within the first 6 h (for troponin) and evaluation and testing within the first 24 h (for calculating APACHE-II and SAPS-II scores) of admission. Testing and evaluation of all included cases were started in the ED and continued in the ICU. The blood samples for cTnI measurement were measured using ARCH STAT Troponin-I, Abbott Diagnostics (cut-off value: 0.009 µg/L, 99th percentile: 0.012, 10% coefficient of variation: 0.032, ROC curve: 0.3). The patients with incomplete data (i.e., early death, discharged against medical advice, transferred to an outside institution), patients with pre-hospital cardiac arrest were excluded. Both SAPS-II and APACHE-II scores were calculated using online calculators within the first 24 h after ED admission. Mortality was defined as in-hospital death.
in study cases. A pre-defined questionnaire containing the demographic characteristics (age and gender), the alleged medications/toxins, variables of APACHE-II and SAPS-II scores, complications including adult respiratory distress syndrome, acute renal failure and mortality as well as soft clinical outcomes including duration of stay at ICU, length of intubation period, LOS and haemodialysis (i.e., major therapeutic interventions) during hospital stay were recorded for every single patient. We instituted a consistent and organised guideline for the emergency management of poisoned patients.\textsuperscript{[9]} Data were analysed by Statistical Package for Social Sciences (SPSS, version 25; SPSS Inc., Chicago, IL) for Windows and MedCalc version 19.4 (MedCalc Inc., Mariakerke, Belgium). Descriptive statistics including frequency, percentage, mean, and standard deviation were calculated. Using the Kolmogorov-Smirnov test, the normality of quantitative variables distribution was assessed. Mann-Whitney and Kruskal-Wallis tests were used to analyse quantitative variables with non-normal distribution. Data were expressed as mean ± standard deviation (SD) and frequencies for normally distributed variables and median and interquartile range [IQR] for non-normally distributed variables, as appropriate. Chi-square and Student t-test of statistical significance were applied for categorical and continuous variables, respectively. Pearson’s correlation coefficient was used to describe both the strength and the direction of the relationship. The area under a receiver operating characteristic (ROC) curve and the 95% confidence interval (CI) were used to test the ability of the model to discriminate between patients who died and developed complications from patients who survived and did not contract complications. A model with a higher area under the ROC curve was assessed. Mann-Whitney and Kruskal-Wallis tests were used to analyse quantitative variables with non-normal distribution. Data were expressed as mean ± standard deviation (SD) and frequencies for normally distributed variables and median and interquartile range [IQR] for non-normally distributed variables, as appropriate. Chi-square and Student t-test of statistical significance were applied for categorical and continuous variables, respectively. Pearson’s correlation coefficient was used to describe both the strength and the direction of the relationship. The area under a receiver operating characteristic (ROC) curve and the 95% confidence interval (CI) were used to test the ability of the model to discriminate between patients who died and developed complications from patients who survived and did not contract complications. A model with a higher area under the curve (AUC) will have a better prognostic value. Cut-off values were determined by analysing the best Youden index (sensitivity + specificity - 1) and the maximal area under the ROC curve. Pearson’s correlation analysis was performed to assess the association between three prognostic scoring systems with soft clinical outcomes. \textit{P} value of <0.05 was considered to be statistically significant.

**RESULTS**

A total of 55 patients met the inclusion criteria and were evaluated during the study period. The median [IQR] age of the study population was 35 [24-49] years (range; 15-80 years) and 38 (69.1%) were male. 8 (14.5%) died and 47 survived. The most common toxic agent was opioids (16; 29.1%), followed by multidrug toxicity (12; 21.8%), tramadol (5; 9.1%), aluminum phosphide (ALP) (4; 7.3%), carbon monoxide (CO), organophosphates and benzodiazepines (each 3; 5.5%), and tricyclic antidepressants (TCAs in 2; 3.6%). In seven cases (12.7%), the cause of toxicity was unknown [Table 1].

The causative agents in fatal cases were as follows; three with ALP, two with CO, two with opioid, one with organophosphate. Major complications included acute respiratory distress syndrome (ARDS) in 13 (23.6%); aspiration pneumonia in 7 (12.7%); acute renal failure (ARF) in 6 (10.9%); haemodialysis in 5 (9.1%); and mixed complications in sixteen (29.1%) patients. A significant difference was detected between ARDS, ARF and haemodialysis, and the length of ventilatory support of the survivors and the non-survivors (\textit{P} 0.013, 0.003 and 0.018, respectively); however, such a significant difference was not detected between the two groups with respect to age, gender, length of ICU stay, LOS and the type of intoxicating agents. The median LOS was 5 [3-9] days (range: 1-62 days). There was no significant correlation between age and LOS (\textit{r} = -0.15, \textit{P} = 0.915). LOS increased significantly with increased APACHE-II scores (\textit{r} = 0.460, \textit{P} < 0.0001), SAPS-II scores (\textit{r} = 0.317, \textit{P} = 0.018) and cTnI levels (\textit{r} = 0.763, \textit{P} < 0.0001) [Table 1].

Median APACHE-II scores and cTnI measures and mean SAPS-II scores of the study population were 13 [10-17], 0.008 [0.002-0.300] \textmu g/L and 32.05 ± 11.24, respectively. The APACHE-II and SAPS-II scores have a range of 0-71 and 0-163, respectively. The means of SAPS-II score were significantly higher in non-survivors and complicated cases than in the survivors and non-complicated cases (\textit{P} 0.001 and <0.0001, respectively) [Table 2]. The APACHE-II scores and cTnI level data did not follow the normal distribution based on Kolmogorov–Smirnov test in the study population, and hence non-parametric Mann-Whitney U test was used for the analyses. Medians of APACHE-II scores and cTnI levels were significantly higher in those who died (\textit{P} 0.017 and <0.001 respectively) and patients with complications (\textit{P} 0.005 and 0.007, respectively) [Table 2].

SAPS-II showed better discriminative capability in predicting mortality and development of complications (AUC: 0.945, 95% CI: 0.849-0.989
The troponin level was found to possess a significant positive linear relationship with soft clinical outcomes, including length of ventilator support, length of ICU stay and LOS (Pearson correlation: r = 0.928; r = 0.881; r = 0.735, all P < 0.001), respectively) [Table 4].

**DISCUSSION**

The results of this study showed that SAPS-II is a better prognostic indicator as compared to APACHE-II score and elevated cTnI level both for mortality (AUC: 0.945, versus 0.932 and 0.763 respectively) and the occurrence of complications (AUC: 0.779 versus 0.739 and 0.727 respectively). Also, SAPS-II score of higher than 37, APACHE-II score of higher than 16 and cTnI level higher than 0.37 ng/ml in severe intoxications can predict the poisoned patients’ mortality rate with a sensitivity of 100%, 87.5% and 62.5%, respectively and with less specificity of 80.8%, 80.8% and 63.8%, respectively. Also, elevated cTnI levels (>0.37 ng/ml) correlate significantly with higher soft clinical outcomes.

Various prognostic scoring systems and scales are being used to grade the severity of critical illnesses.\[10-17\] Determining the severity of critically ill patients can
Poisoned patients are resource-intensive visits and place a significant burden on EDs. Thus, differentiating low-grade acuity patients from those requiring high-acuity areas is of importance and needs investigation. We investigated cTnI and two generally applicable severity scoring tools (SAPS-II and APACHE-II) to determine the value of each scheme in prognosticating mortality and major adverse events in critically intoxicated patients. The SAPS-II and APACHE-II scoring system predominately evaluate haemodynamic changes, whereas, cTnI features the heart function and identifies myocardial damage. To our knowledge, this is the first study that evaluated simultaneously the ability of SAPS-II and APACHE-II, as well as cTnI level to predict the mortality and complications in critical intoxications.

**Table 3: Comparison of the Simplified Acute Physiology II (SAPS-II) score, Acute Physiology and Chronic Health Evaluation II (APACHE-II) score and troponin level in prediction of mortality and complications**

| Test                        | Mortality | Complications |
|-----------------------------|-----------|---------------|
|                            | SAPS >37  | APACHE >16    |
| True positive               | 8         | 7             |
| False positive              | 9         | 9             |
| False negative              | 0         | 1             |
| True negative               | 38        | 38            |
| Sensitivity (95% CI)        | 100       | 87.5          |
| Specificity (95% CI)        | 80.8      | 80.8          |
| Positive predictive value   | 47.1      | 43.8          |
| Negative predictive value   | 100       | 97.4          |
| Diagnostic accuracy (95% CI)| 83.6      | 81.8          |
| Likelihood ratio of a positive test (95% CI) | 5.2 | 4.6 |
| Likelihood ratio of a negative test (95% CI) | 0 | 0.15 |
| Diagnostic odd (95% CI)    | 68.9      | 29.5          |
| Cohen's kappa (unweighted) (95% CI) | 0.55 | 0.48 |

CI: Confidence interval

**Table 4: Correlation coefficients (r) between three soft clinical outcomes and different models studied**

| Soft clinical outcomes (days) | SAPS II Score | APACHE II Score | Troponin level |
|------------------------------|---------------|-----------------|----------------|
| length of ventilatory support| 0.409**       | 0.590**         | 0.928**        |
| length of ICU stay           | 0.390**       | 0.587**         | 0.881**        |
| length of hospital stay (LOS)| 0.317*        | 0.460**         | 0.735**        |

**Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed). SAPS: Simplified Acute Physiology Score, APACHE: Acute Physiology and Chronic Health Evaluation, ICU: Intensive care unit.**

Influence management strategies and will assist care providers, particularly critical care physicians with risk stratifications and resource allocations.[9,18] Poisoned patients are resource-intensive visits and place a significant burden on EDs.[1,19,20] Thus, differentiating low-grade acuity patients from those requiring high-acuity areas is of importance and needs investigation. We investigated cTnI and two generally applicable severity scoring tools (SAPS-II and APACHE-II) to determine the value of each scheme in prognosticating mortality and major adverse events in critically intoxicated patients. The SAPS-II and APACHE-II scoring system predominately evaluate haemodynamic changes, whereas, cTnI features the heart function and identifies myocardial damage.[6,10,11] To our knowledge, this is the first study that evaluated simultaneously the ability of SAPS-II and APACHE-II, as well as cTnI level to predict the mortality and complications in critical intoxications. The two

![Figure 1](a and b). ROC curves of SAPS-II, APACHE-II and troponin level in prediction of mortality and complications. (ROC: Receiver Operating Curve, AUC: Area Under the Curve, SAPS: Simplified Acute Physiology Score, APACHE: Acute Physiology and Chronic Health Evaluation, SE: Standard Error)
commonly applicable scoring systems (SAPS-II and APACHE-II) have been investigated to predict the mortality and later development of complications in ICU admitted poisoned patients, critically generally ill patients, ICU paraquat poisoned patients and ICU organophosphate poisoned patients, but cTnI levels have not been assessed in any of these studies.

Pearson’s correlation analysis was carried out to see the association between three prognostic scoring systems with soft clinical outcomes, including length of ventilatory support, length of ICU stay and LOS (days). A high positive correlation was observed between troponin I level (>0.37 ng/ml) and length of ventilatory support, length of ICU stay and LOS (r: 0.928, 0.881 and 0.735 respectively). Wu et al. found that elevated cTnI levels and a high APACHE-II score were independent prediction factors for shorter survival in non-cardiac critically ill patients, but did not provide their discriminative power as assessed by area under the ROC. Docherty et al. demonstrated that cTnI is an independent predictor of hospital mortality in ICU patients, but APACHE-II showed better calibration and discrimination power than cTnI. Their study does not advocate the adoption of routine troponin analysis on admission to ICU and recommends the measurement only if clinically indicated.

The performance of cTnI levels in poisoned patients is a lesser elucidated matter of investigation published in the literature. Our study demonstrated that even though elevated cTnI was associated with higher mortality and complications, its area under the ROC curve was lesser than SAPS-II and APACHE-II scores. We believe that the cTnI failed to achieve the higher level of AUC because the laboratory parameters only evaluate the cardiac system precisely. However, poisoning affects multiple organ systems. Therefore, APACHE and SAPS are likely to be better.

We searched the literature for studies that have focused on the prognostic utility of cTnI in drug overdose mortality. We found a single study wherein 437 overdoses were analysed, and out of which, there were 20 (4.6%) deaths. The study concluded that the initial cTnI result was strongly associated with in-hospital mortality. However, in that study, APACHE-II or SAPS-II were not investigated, and the patients were not stratified by causative agents of intoxications. In accordance with our results, a review article by Lim et al. reviewing a total of 23 studies and involving 4492 critically ill patients revealed that elevated cTnI was associated with an increased risk of mortality and with an increased length of ICU stay of 3.0 days and an increased LOS of 2.2 days.

Calculation of positive and negative likelihood ratios (LR + and LR −) in the present study yielded the corresponding values for SAPS-II, APACHE-II, and cTnI as 5.2, 4.6 and 1.7 for mortality and 2.6, 2.9 and 2.2 for development of complications, respectively. In other words, the increase in SAPS-II, APACHE-II scores and cTnI levels significantly increase the probability of mortality in decreasing order; nevertheless, APACHE-II increases the probability in cases with complications.

**CONCLUSION**

In summary, SAPS-II shows better calibration and discrimination power than APACHE-II score and cTnI concentration as a prognostic tool for mortality and development of complications. A high positive correlation was observed between troponin I level (>0.37 ng/ml) with soft clinical outcomes including length of ventilatory support, length of ICU stay and LOS, and thus cTnI can be proposed as a standard prognostic tool in this regard.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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