# THE SIGNIFICANCE OF APACHE II AS A PREDICTOR OF MORTALITY IN PARAQUAT POISONING: A SYSTEMATIC REVIEW AND META-ANALYSIS

**Abstract #122014**

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## INTRODUCTION

Paraquat (PQ) is a highly toxic herbicide to humans. PQ poisoning is a grave concern globally, due to its high mortality rate. There is considerable inter-patient variability on factors which govern patient mortality and morbidity. Various methods to prognose patients with PQ poisoning have been devised, from easier ones such as biochemical markers to complicated ones such as plasma level of paraquat in blood. In this study, we explore the prognostic ability of a widely acceptable tool known as the Acute Physiology and Chronic Health Evaluation tool (APACHE II) used to prognose critically ill patients, in PQ poisoning.

## METHODOLOGY

**Comprehensive search performed in following databases (updated till June 2022)**
PubMed/Medline, Web of Science, Embase, Scopus and Cochrane Library

**Search strategy constructed using PICOS**
"paraquat", "predictors", "prognostic" and "biochemical markers" and appropriate MeSH Terminology

**Inclusion Criteria**
Retrospective or prospective observational studies, reporting APACHE II as a prognostic predictor of mortality in PQ poisoning and reporting APACHE II values of non-survivors and survivors (for patients aged ≥18 years) and/or the prediction accuracy of APACHE II for mortality in PQ poisoning

**Study selection**
Based on inclusion criteria, first pass and second pass screening completed

**Data Extraction**
Title, study region, author and publication year, no. of participants, demographic details of patients (percentage of males, mean age of participants), mortality rate, APACHE II scores of non-survivors and survivors and APACHE II cut-offs. Data was collected to obtain a 2 X 2 contingency table with labels of true negative (TN), true-positive (TP), false-negative (FN) and false-positive (FP) in order to pool study estimates. For pairwise comparison of predictive abilities of APACHE II with other prognostic markers, we recorded the area under the curve (AUC) values of the prognostic markers given in each study for pooling.

**Quality Assessment**
Quality in Prognosis Studies (QUIPS) tool
Five domains: (1) study participation; (2) prognostic factor measurement; (3) outcome measurement; (4) study confounding; and (5) statistical analysis and reporting

**Data synthesis and Statistical analysis**

- *Softwares*: Meta-Disc 1.4 software, Stata Statistical Software, Comprehensive Meta-analysis software, Med-Calc software (short term student license) and Review Manager
- *Effect estimate:* Mean Difference (MD) with 95% CI for APACHE II scores (continuous variable)
- *Formulae*: Sensitivity = TP/(TP + FN), specificity = TN/(TN+ FP), Positive Likelihood ratio (PLR) = sensitivity/specificity, Negative Likelihood Ratio (NLR) = specificity/sensitivity, Diagnostic Odds Ratio = (TP/FN)/(FP/TN)
- Summary ROC curve to obtain AUC and Q* statistic
- *Model*: bivariate generalised linear mixed model
- *Pairwise AUC comparison with other predictors:* plasma PQ concentration, SIPP, amount of PQ ingested, urine PQ concentration, arterial lactate, sequential organ failure assessment (SOFA) score and serum presepsin level
- Pooled AUCs and analysed with two sample z test
- Subgroup analysis, sensitivity analysis and publication bias assessment performed

## RESULTS

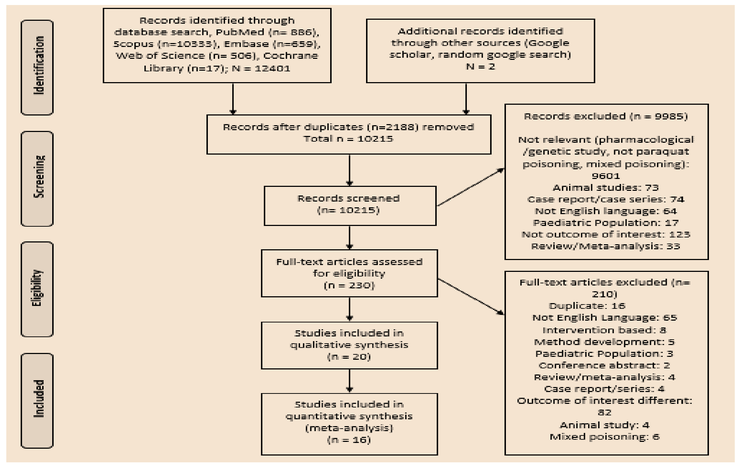



***Fig. 1 The PRISMA Flow diagram***

➢ **Study Characteristics**

- 2524 patients with PQ poisoning, average of 126 participants
- All the studies were observational, 10 were prospective and 10 were retrospective
- Prevalence of mortality = 36.95% to 88.33%

➢ **Quality of included studies**

- Low Risk of bias = 15
- Moderate Risk of bias = 4
- High Risk of bias = 1

➢ **Comparison of APACHE II scores between survivors and non-survivors**

- MD: -5.76[-7.93,-3.60] (Fig.2)
- A total of 16 studies reported significantly lower mean APACHE II scores in survivors than non-survivors.

➢ Sensitivity analysis revealed data stability

➢ Publication Bias

- Funnel plot, Egger's test (p = 0.94) and the Begg's test (p = 0.75) did not reveal any publication bias

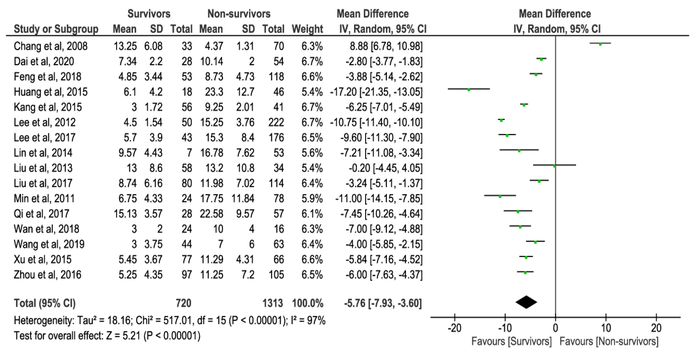
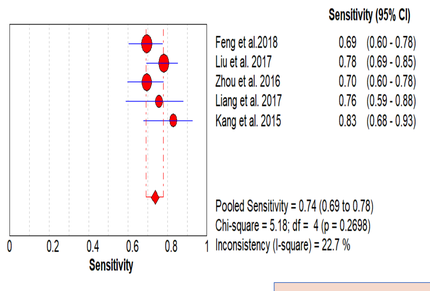



**Fig. 2** ***The forest plot showing the weighed mean difference in APACHE II scores***

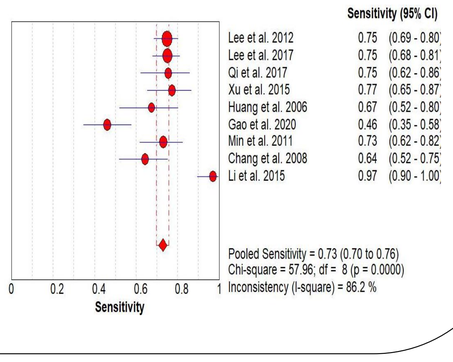
➢ **Prognostic accuracy of APACHE II score for predicting mortality**

A total of 14 studies (out of 20) reported APACHE II cut-offs with 5 studies reporting cut-off of < 9 and 9 studies reporting a cut-off of ≥ 9

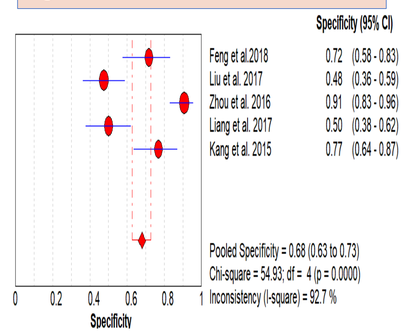
Pooled sensitivity APACHE II Score < 9



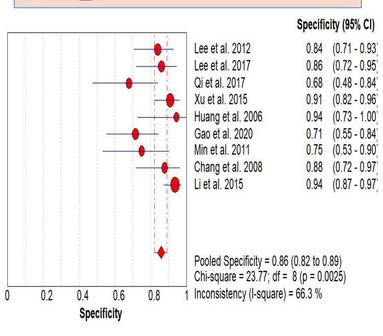

Pooled sensitivity APACHE II Score ≥ 9




Pooled Specificity APACHE II Score < 9

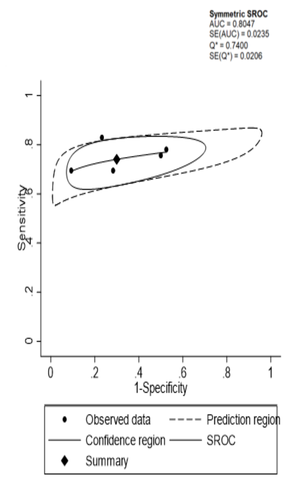



Pooled Specificity APACHE II Score ≥ 9

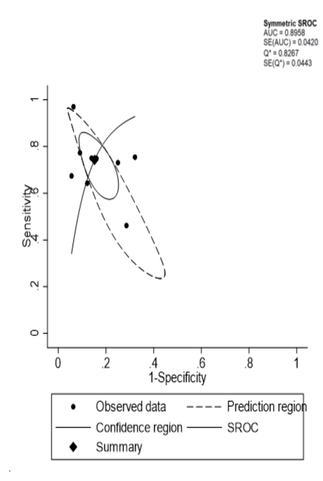



The pooled sensitivity, specificity PLR, NLR and DOR for APACHE II score <9 was 74%, 68%, 2.58, 0.38 and 7.10 respectively. The pooled sensitivity, specificity, PLR, NLR and DOR for APACHE II score ≥9 was 73%, 86%, 4.69, 0.33 and 16.42 respectively. The AUC of SROC curves was 0.80 and 0.89, respectively.

Bivariate summary ROC APACHE II Score < 9




Bivariate summary ROC APACHE II Score ≥ 9




| Category | No. of studies | Pooled AUC[a] (95% CI) | Difference in AUC | z score | p value |
|---|---|---|---|---|---|
| APACHE II vs Plasma PQ concentration | 5 | 0.86 (0.83-0.90) vs 0.82 (0.73-0.91) | 0.04 | 0.86 | p>0.05 |
| APACHE II vs Amount of PQ ingested | 4 | 0.76 (0.65-0.88) vs 0.81 (0.75-0.88) | 0.05 | 0.79 | p>0.05 |
| APACHE II vs SIPP | 4 | 0.85 (0.81-0.89) vs 0.84 (0.77-0.91) | 0.01 | 0.24 | p>0.05 |
| APACHE II vs Arterial lactate level | 3 | 0.77 (0.67-0.87) vs 0.87 (0.83-0.92) | 0.10 | 1.87 | p>0.05 |
| APACHE II vs Urine PQ concentration | 4 | 0.76 (0.67-0.86) vs 0.81 (0.71-0.91) | 0.04 | 0.65 | p>0.05 |
| APACHE II vs SOFA score | 4 | 0.90 (0.82-0.97) vs 0.81 (0.75-0.88) | 0.08 | 1.67 | p>0.05 |
| APACHE II vs Serum Presepsin level | 2 | 0.72 (0.63- 0.80) vs 0.84 (0.78-0.91) | 0.12 | 2.25 | p<0.05 |

[a] AUC, area under the curve

***Table 1 Pairwise AUC comparisons between APACHE II and other prognostic predictors***

## CONCLUSION

This meta-analysis depicted that survivors of PQ poisoning had APACHE II scores lower than non-survivors. Higher APACHE II values showed greater specificity in predicting mortality in these patients. Thus, APACHE II can be used as a functional tool in the hand of physicians to prognose patients with PQ poisoning to aid clinical decision making.

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