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Darren George Norman Craig, Thomas Wdj Reid, Kirsty G Martin, Janice S Davidson, Peter C Hayes, K J Simpson

► **To cite this version:**

Darren George Norman Craig, Thomas Wdj Reid, Kirsty G Martin, Janice S Davidson, Peter C Hayes, et al.. The systemic inflammatory response syndrome (SIRS) and sequential organ failure assessment (SOFA) scores are effective triage markers following paracetamol overdose. *Alimentary Pharmacology & Therapeutics*, 2011, 34 (2), pp.219. <10.1111/j.1365-2036.2011.04687.x>. <hal-00639782>

HAL Id: hal-00639782

<https://hal.science/hal-00639782v1>

Submitted on 10 Nov 2011

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HAL Authorization

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Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0221-2011.R1
Wiley - Manuscript type:	Original Scientific Paper
Date Submitted by the Author:	31-Mar-2011
Complete List of Authors:	Craig, Darren; Royal Infirmary of Edinburgh, Scottish Liver Transplantation Unit Reid, Thomas; University of Edinburgh Martin, Kirsty; Royal Infirmary of Edinburgh, Scottish Liver Transplantation Unit Davidson, Janice; Royal Infirmary of Edinburgh, Scottish Liver Transplantation Unit Hayes, Peter; University of Edinburgh, Division of Clinical and Surgical Sciences Simpson, K; Royal Infirmary of Edinburgh, Centre for Liver and Digestive Disorders; University of Edinburgh, Division of Clinical and Surgical Sciences
Keywords:	Liver < Organ-based, Liver transplantation < Hepatology, Encephalopathy < Hepatology, X keyword = no topic

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4 **The systemic inflammatory response syndrome (SIRS) and sequential organ failure**
5 **assessment (SOFA) scores are effective triage markers following paracetamol**
6 **(acetaminophen) overdose**
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10 **Darren G N Craig¹, Thomas WDJ Reid², Kirsty G Martin², Janice S Davidson², Peter C**
11 **Hayes², Kenneth J Simpson²**
12

13
14 ¹ Scottish Liver Transplantation Unit, Royal Infirmary of Edinburgh, Little France, Edinburgh,
15 EH16 4SA, UK
16

17
18 ² Division of Clinical and Surgical Sciences, University of Edinburgh, Edinburgh, EH16 4SA,
19 UK
20

21
22 **Corresponding author:** Dr Kenneth J Simpson, Scottish Liver Transplantation Unit, Royal
23 Infirmary of Edinburgh, Little France, Edinburgh, EH16 4SA, UK
24

25
26 Telephone 0044 1312421717 Fax: 0044 1312421633 Email: k.simpson@ed.ac.uk
27

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29 Electronic word count: 3999
30

31
32 Figures: 2; Tables: 5
33

34 Running head: SIRS and SOFA scores following paracetamol overdose
35

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38 **Key words :** Acetaminophen; liver failure, acute; liver transplantation; Systemic
39 Inflammatory Response Syndrome ; multiple organ failure
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44 **Abbreviations**

45 ALF, acute liver failure;

RRT, renal replacement therapy;

47 OLT, orthotopic liver transplantation;

NAC, *N*-acetyl cysteine;

49 SIRS, systemic inflammatory response
50 syndrome;

ALT, alanine aminotransferase;

52 HE, hepatic encephalopathy;

PT, prothrombin time;

53 KCC, King's College Hospital poor
54 prognostic criteria;

INR, international normalised ratio;

56 SOFA, Sequential Organ Failure
57 Assessment;

IQR, interquartile range;

58 APACHE, Acute Physiology and Chronic
59 Health Evaluation;

ROC, receiver operator characteristic;

DOR, diagnostic odds ratio;

60 CI, confidence intervals

ABSTRACT

BACKGROUND:

The Systemic Inflammatory Response Syndrome (SIRS) and Sequential Organ Failure Assessment (SOFA) scores are widely used as prognostic markers in critical care settings and could improve triage of high-risk paracetamol (acetaminophen) overdose patients.

AIM: To evaluate the prognostic accuracy of the SIRS and SOFA scores following single time point paracetamol overdose.

METHODS

Analysis of 100 single time-point paracetamol overdoses admitted to a tertiary liver centre, with subsequent prospective validation of identified thresholds. Individual laboratory samples were correlated with the corresponding clinical parameters in relation to time post-overdose, and the daily SOFA and SIRS scores calculated.

RESULTS

A total of 74 (74%) patients developed the SIRS, which occurred significantly earlier in patients who died ($n=21$) compared with spontaneous survivors ($n=53$, $p=0.05$). The SIRS occurred in 70 (70%) patients by 96 hours post-overdose, with a 30% mortality rate; compared with 0% mortality in the 30 non-SIRS patients ($p=0.001$). Median SOFA scores were significantly higher in non-survivors at 48 ($p=0.009$), 72 ($p<0.001$), and 96 hours ($p<0.001$). A SOFA score >7 during the first 96 hours post-overdose predicted death/transplantation with a sensitivity of 95.0 (95% CI 78.5-99.1) and specificity of 70.5 (95% CI 66.3-71.6). A validation cohort of 38 single time-point paracetamol overdoses confirmed the extremely high negative predictive value of both the SIRS and SOFA thresholds.

CONCLUSIONS

The absence of either a SOFA score >7 or a SIRS response during the first 96 hours following paracetamol overdose could improve triage and reduce transfers of lower risk patients to tertiary liver centres.

INTRODUCTION

Paracetamol (acetaminophen) overdose remains the main aetiological factor responsible for acute liver failure (ALF) in the developed world.(1) The only effective treatment for the condition remains emergency orthotopic liver transplantation (OLT).(2) Paracetamol-induced ALF is strongly associated with the development of the systemic inflammatory response syndrome (SIRS) and a subsequent cascade of complications including hepatic encephalopathy (HE), coagulopathy, and multiple organ dysfunction syndrome.(3) In human studies, development of the SIRS following paracetamol-induced hepatotoxicity has been associated with both an increased risk of worsening HE grade,(4) and with poorer overall outcome, irrespective of the presence of infection.(3) Existing prognostic systems, such as the King's College Criteria (KCC), utilise features of HE and extrahepatic organ injury to predict a hopeless prognosis without OLT, but their use has been criticised for their relatively low negative predictive value (5) and by the inherent requirement for multiorgan failure to have developed before considering definitive treatment. Several studies have therefore examined the prognostic accuracy of multiorgan failure assessment scores such as the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores to predict outcome following paracetamol hepatotoxicity,(6-8) but these studies have tended to apply the prognostic test in question at the point of hospital admission, rather than in relation to the time from overdose.(9) This inevitably introduces temporal confounding, since many patients present to hospital following paracetamol overdose due to psychological, rather than physical, morbidity. Therefore, a better understanding of the temporal evolution of the SIRS and multiorgan failure following paracetamol overdose could improve prognostication in this condition, and could aid early identification of high-risk patients.

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4 To our knowledge, no studies exist which examine the temporal relationship between
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6 the initial hepatotoxic insult (i.e. paracetamol overdose) and development of the SIRS and
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8 multiorgan failure. The aims of this study were to examine these temporal changes in a
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10 cohort of patients who required tertiary level care after taking a single intentional
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12 paracetamol overdose. It was hypothesised that the absence of a SIRS response or
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14 extrahepatic organ injury following overdose would be associated with a low risk of in
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16 hospital mortality, and that the SIRS and SOFA scores could therefore act as quantitative
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18 triage instruments to identify those patients at lower risk of requiring emergency OLT.
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PATIENTS, METHODS, AND DEFINITIONS

Since its inception in 1992, the Scottish Liver Transplantation Unit (SLTU) has prospectively collected and maintained a dedicated database of all acute liver injury patients admitted to the unit. Data recorded in this database includes details of patient history, clinical examination, and laboratory results along with therapeutic interventions, including intensive care admission, need for renal replacement therapy (RRT), or inotropic support. Where possible the paracetamol preparation, number of tablets, type (whether intentional, accidental, single time point or staggered) and timing of overdose, delay to presentation, and use of *N*-acetyl cysteine (NAC) are all recorded. The cohort analysed were 100 consecutive single time point intentional (defined as a paracetamol overdose (>4g) taken at a single defined time point with the objective of self-harm) paracetamol overdoses admitted to the SLTU with acute liver injury between April 2003 and February 2009, and a prospectively collected cohort of 38 patients admitted between March 2009 and July 2010. Ethical approval for the study was obtained from the Scotland 'A' Research and Ethics Committee. We specifically excluded patients with staggered overdoses, or overdoses taken accidentally in an attempt to relieve pain, due to the confounding temporal and diagnostic problems associated with these overdoses.(10)

Paracetamol overdose was defined as at least 2/3 of: a history of ingestion of potentially toxic amounts of paracetamol (>4g/day); detection of paracetamol in the serum >10mg/L; or a serum alanine aminotransferase (ALT) level > 1000 IU/L within 7 days of a history of paracetamol ingestion irrespective of the serum paracetamol concentration.(1) All 138 patients fulfilled all of these three criteria. Severe acute liver injury was defined as sudden deterioration in liver function with associated coagulopathy in the absence of a history of chronic liver disease, whilst the term ALF (i.e. fulminant liver failure) was restricted to those patients developing HE.(11) Guidelines for accepting patients from referring

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4 hospitals were based on previously published criteria from the British Society of
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6 Gastroenterology and remained unchanged over the time course of the study.(12) Patients
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8 admitted to the SLTU are managed using a standard protocol as previously described,(13)
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10 the main goals of which have remained similar over the duration of this cohort study. The
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12 KCC are used in this unit and throughout the UK to determine patients who will most likely
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14 die without OLT.(14) Since the purpose of this study was not to develop transplantation
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16 listing criteria, death and OLT were considered equivalent when undertaking survival
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18 analysis.
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23 **LABORATORY PARAMETERS**

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30 Retrospective analysis of all hospital electronic laboratory records was performed to
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32 obtain all standard haematological, biochemical, and coagulation samples obtained for each
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34 patient during the first 10 days of admission. Each sampling time point was noted from either
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36 the clinical notes and/or the laboratory receipt, and the corresponding haemodynamic and
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38 clinical parameters for each sampling time point retrieved from the clinical notes. These data
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40 were then individually compared against the reported time from overdose for each patient,
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42 and the corresponding laboratory and clinical values recorded in a dedicated database.
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48 **SIRS**

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53 The presence of the SIRS was defined as two or more of: temperature $<36^{\circ}\text{C}$ or
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55 $>38^{\circ}\text{C}$, heart rate >90 beats/minute, leucocyte count $<4 \times 10^9/\text{L}$ or $>12 \times 10^9/\text{L}$, and
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57 tachypnoea > 20 breaths/minute or $\text{PaCO}_2 < 4.3 \text{ kPa}$.(15) The daily presence or absence of
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59 the SIRS, and the number of the SIRS components fulfilled, were retrospectively calculated
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for each patient by correlating the daily leucocyte count with the most abnormal temperature

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4 and heart rate recorded during each corresponding day of admission. Respiratory rate was
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6 only included for non-ventilated patients, as the majority of patients in our unit are electively
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8 mechanically ventilated following the development of grade III or IV HE.
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10 11 12 **SOFA SCORE AND ORGAN FAILURE** 13

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17 Organ failure was assessed using the SOFA score, which assesses six organ
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19 systems: hepatic; renal; coagulation; cardiovascular; respiratory; and central nervous; and
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21 provides a graded score from 0-4 points for each organ system, **table 1**.(16) The SOFA
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23 score was calculated for each 24-hour period following overdose, using the most deranged
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25 values for each parameter in each 24 hour period. Organ failure was defined as a SOFA
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27 score ≥ 3 points for the organ concerned (**table 1**). Due to potential confounding, SOFA
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29 scores were not calculated following the administration of platelet transfusions.
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SOFA score					
Organ system	Score				
	0	1	2	3	4
Respiratory: PaO ₂ /FiO ₂	>400	≤400	≤300	≤200	≤100
Renal: Creatinine, μmol/l (mg/dL)	≤110 (≤1.2)	110–170 (1.2-1.9)	171–299 (2.0-3.4)	300–440 (3.5-5.0); urine output ≤500 ml/day	>440 (>5.0); urine output <200 ml/day
Hepatic: bilirubin, μmol/l (mg/dL)	≤20 (≤1.2)	20–32 (1.2-1.9)	33–101 (2.0-5.9)	102–204 (6.0-12.0)	>204 (>12.0)
Cardiovascular: hypotension	No hypotension	MAP <70 mmHg	Dopamine ≤5 ^a , dobutamine (any dose)	Dopamine >5 ^a or epinephrine ≤0.1 ^a or norepinephrine ≤0.1 ^a	Dopamine >15 ^a or epinephrine >0.1 ^a or norepinephrine >0.1 ^a
Haematologic: platelet count	>150	≤150	≤100	≤50	≤20
Neurologic: Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
^a Adrenergic agents administered for at least one hour (doses given are in μg/kg per minute).					

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Table 1 The Sequential Organ Failure Assessment (SOFA) score

FiO₂, fractional inspired oxygen; MAP, mean arterial pressure; PaO₂, arterial oxygen tension;

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Statistical Analysis

Statistical analysis was performed using SPSS (SPSS 16.0, Chicago IL, USA) and Graphpad Prism (GraphPad Software Inc., La Jolla, CA). Data values are presented as median +/- interquartile range (IQR) or percentages unless otherwise stated. When undertaking survival analysis, death and OLT were considered equivalent. Receiver operating characteristic (ROC) analysis was used to identify optimum threshold values to discriminate non-survivors. Continuous data were compared using either analysis of variance or the Kruskal-Wallis test if inter-group variances were unequal, with post-hoc Dunn's testing used to compare selected groups. Categorical data were analysed using Chi-squared tests or Fishers exact test. Bonferroni corrections were undertaken for repeated measures. **Missing data were treated in a last observation carried forward manner.** Results were considered statistically significant when $p < 0.05$.

RESULTS

Patients and details of overdose

A total of 100 patients (46 male, 54 female) admitted to the SLTU between April 2003 and February 2009 were included in the study. During this period, a total of 347 patients had been admitted, of whom 111 were classified as 'non-paracetamol' cases, 62 patients had taken a staggered paracetamol overdose, 45 patients had overdosed on paracetamol accidentally, and in the remaining 29 cases the details of the paracetamol overdose were unclear. The median patient age of the 100 included patients was 34 (IQR 24-43) years. A total of 83 patients were transferred to the SLTU from outlying health boards, at a median time of 50 (36-66.5) hours following overdose. The remaining patients were admitted to the SLTU from wards within the Royal Infirmary of Edinburgh or from local hospitals. The median ingested paracetamol dose was 25 (17.5-41) g. All 100 patients received NAC treatment at their local hospital, at a median time from overdose of 22.75 (9.5- 42.25) hours. A total of 47 (47%) of patients had taken a mixed overdose. As shown in **table 2**, none of these demographic parameters or potential confounders differed significantly between survivors and patients who died/required OLT. Other baseline demographic and clinical characteristics of the paracetamol study group are outlined in **table 2**.

Variable	Dead/OLT	n	Spontaneous survival	n	<i>p</i>
Sex (male/female)	6/15 (28.6%/71.4%)	21	40/39 (50.6%/49.4%)	79	0.071
Age (years)	37 (28-44)		33 (22-43)		0.115
Ingested paracetamol dose (g)	27.5 (15.5-40.0)		25.0 (17.0-40.5)		0.226
Admission paracetamol level (µmol/L)	56 (37-146)		70 (24-145)		0.545
Mixed OD	8 (38.1%)		39 (49.4%)		0.115
Previous OD	8 (57.1%)	14	29 (46.0%)	63	0.388
Active drug abuse	3 (14.3%)	21	11 (14.5%)	76	0.654
Weekly alcohol consumption (units)	50 (4-140)	13	20 (2-68)	57	0.182
Time from OD to NAC (hours)	15.5 (10.0-34.5)	21	23.5 (11.0-43.5)	79	0.791
Time from OD to SLTU admission (hours)	41.0 (29.5-49.0)		53.0 (45.5-67.0)		0.045

Table 2. Demographics of study population and details of paracetamol overdose.

Date are presented as median (+/- interquartile range) or percentages as appropriate

Hepatic encephalopathy & other outcomes

A total of 29 (29.0%) of paracetamol-induced acute liver injury patients were encephalopathic on admission to the SLTU, and a further 18/71 (25.4%) went on to develop HE during admission. A total of 47 (47%) patients therefore developed HE, and thus ALF, at some point during their illness. Of these patients, 22 (46.8%) subsequently met the modified KCC, at a median time from overdose of 51.5 (39.0-73.0) hours from overdose. Of these 22 patients, 3 were transplanted, 14 died without OLT, and 5 recovered spontaneously. A total of 4 patients died without meeting the modified KCC. The sensitivity, specificity, and diagnostic odds ratios (DOR) of the KCC were 81.0 (95% confidence intervals (CI) 65.0-90.7), 93.7 (95% CI 89.4- 96.3), and 62.9 (95% CI 15.7- 251.3) respectively. Of the non-transplanted patients who met the KCC, a total of 13 patients were excluded from listing for OLT due to active and resistant alcohol dependence (11 patients) and active intravenous drug abuse (2 patients). A total of 4 patients were listed but subsequently deemed medically unfit to survive OLT, whilst a further two patients showed clear signs of spontaneous recovery and were delisted prior to an organ becoming available. **On admission patients who later died or were transplanted were significantly more coagulopathic (PT 80 (53-103) s vs. 48 (33-70) s, $p=0.002$), had lower serum albumins (30 (23-35) g/L vs. 34 (31-37) g/L, $p=0.013$), and had significantly higher serum creatinine levels (174 (118-239) $\mu\text{mol/L}$ vs. 94 (75-145) $\mu\text{mol/L}$, $p=0.006$) compared with spontaneous survivors. A significantly greater proportion of patients who died or were transplanted required multiple organ support, such as RRT, inotropic support, and mechanical ventilation (**Supplementary Table 1**).**

SIRS and temporal relationship to overdose

Examination of the cumulative incidence of the SIRS revealed that by 48 hours post overdose, a total of 27/40 (67.5%) patients had mounted a SIRS response, with a mortality rate in the SIRS group of 44.4%, compared with 7.7% for those patients not mounting a

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4 SIRS response (Fisher's $p=0.020$). By 72 hours post-overdose, a total of 59/86 (68.6%)
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6 patients had developed a SIRS during admission, with a mortality rate of 28.8%, compared
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8 with a mortality rate of only 3.7% (1/27 patients, Fisher's $p=0.007$) in patients without a SIRS
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10 at this point. By 96 hours, the cumulative incidence of the SIRS had risen to 70 (70%)
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12 patients, with a mortality rate of 30% in this group; compared with a mortality rate of 0% in
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14 the 30 patients without the SIRS (Fisher's $p=0.001$). The sensitivity, specificity, negative
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16 predictive values, and DORs of the SIRS occurring by each time point post-overdose are
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18 shown in **table 3**. In total, 74 (74%) of patients developed the SIRS post-overdose, but this
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20 occurred significantly earlier following overdose in patients who died (median 43.0 (28.5-
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22 61.0) hours, $n=21$) compared with patients who survived (60.0 (36.5-81.0) hours, $n=53$,
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24 $p=0.05$). In contrast, the presence of the SIRS at the time of hospital admission, or at the
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26 development of HE, resulted in reduced sensitivity and DORs compared with the values
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28 obtained at 48, 72, and 96 hours post-overdose (**table 3**). The number of SIRS components
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30 fulfilled following overdose was significantly related to increasing mortality at 48 ($p=0.047$),
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32 72 ($p=0.0057$), and 96 ($p<0.0001$) hours post-overdose.
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Time from overdose (hours)	N/deaths	Cumulative incidence of SIRS/ deaths	Sensitivity (95% CI)	Specificity (95% CI)	Negative predictive value (95% CI)	Diagnostic Odds Ratio (95% CI)
48	40/13	27/12	92.3 (64.0- 99.8)	44.4 (25.5- 64.7)	92.3 (71.9-98.6)	9.6 (1.1- 84.6)
72	86/18	59/17	94.4 (76.7- 99.0)	38.2 (33.5- 39.4)	96.3 (84.5-99.3)	10.5 (1.7-64.8)
96	100/21	70/21	100.0 (83.9- 100.0)	38.0 (27.3- 49.6)	100.0 (90.3-100.0)	∞ (3.3-∞)
At SLTU admission	100/21	52/17	81.0 (62.4-92.1)	55.7 (50.8-58.7)	91.7 (83.6-96.5)	5.3 (1.7-16.5)
At onset of HE	47/21	30/18	85.7 (70.7- 94.6)	53.8 (41.7- 61.0)	82.4 (63.8-93.4)	7.0 (1.7- 27.6)
Modified KCC	100/21	KCC +ve/ deaths 22/17	81.0 (65.0- 90.7)	93.7 (89.4- 96.3)	94.9 (90.6-97.5)	62.9 (15.7- 251.3)

Table 3. Predictive accuracy of the presence of the Systemic Inflammatory Response Syndrome (SIRS) following single time point paracetamol overdose.

The SIRS was defined as the presence of ≥ 2 SIRS components in any 24-hour period. The accuracy of the SIRS is compared with the modified King's College Hospital poor prognostic criteria (KCC).

CI, confidence intervals; HE, hepatic encephalopathy; SLTU, Scottish Liver Transplantation Unit

Temporal relationship between overdose and SOFA score

SOFA scores could be calculated for 99/100 patients. SOFA scores ranged from 1-15 by 48 hours post-overdose, 0-17 by 72 hours, and 1-18 by 96 hours post-overdose. Median SOFA score (+/- IQR) was significantly higher in patients who died or were transplanted at each of these three time points (48 hours: 9 (6.25-12.25) vs. 5 (3-7), $p=0.009$; 72 hours: 12.5 (8.75-17) vs. 5 (3-7), $p<0.001$; 96 hours: 15 (9-19) vs. 5 (3-8), $p<0.001$). The number of organ systems failing by both 72 ($p=0.0003$) and 96 ($p<0.0001$) hours post-overdose was significantly related to mortality, which ranged from 5.9% for patients without any organ system failure at 72 hours post-overdose to 71.4% for those patients with 3 or more organ system failures at this time point, **figure 1**. ROC analysis of SOFA scores showed an area under the curve of 0.80 (95% CI 0.65-0.95), 0.90 (95% CI 0.82-0.97), and 0.91 (95% CI 0.85-0.98) at 48, 72, and 96 hours post-overdose respectively. The optimal SOFA score thresholds for discriminating non survivors at these three time points were >4 at 48 hours, >6 at 72 hours, and >7 at 96 hours respectively, **table 4**.

A SOFA score >7 at any time during the first 96 hours post overdose predicted outcome with excellent accuracy, with a significantly higher median maximum SOFA score amongst patients who died (17 (12-18.75) compared with spontaneous survivors (6 (3-8), $p<0.0001$), and an area under the ROC of 0.92 (95% CI 0.86-0.98). Further analysis using this SOFA threshold of >7 during the first 96 hours post overdose revealed that only 2/56 (3.6%) patients not fulfilling this criteria required RRT, and only 1/56 (1.8%) patients required intracranial pressure monitoring.

A previous report also evaluated SOFA scores following paracetamol overdose, and reported that a SOFA score >8 early after admission, or >12 at the onset of HE, were the

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4 most discriminatory thresholds for determining prognosis.(8) At admission, the area under
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6 the ROC for SOFA was 0.80 (95% CI 0.68-0.93), but using the previously reported threshold
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8 of >8 to predict a poor prognosis resulted in a low sensitivity of 38.1 (95% CI 23.7- 48.7).
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10 The area under the ROC for a SOFA >12 at the onset of HE (n=47) was 0.71 (95% CI 0.56-
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12 0.86), with a low sensitivity of 23.8 (95% CI 12.2- 34.2).
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Time from overdose (hours)	Threshold SOFA score	N/ deaths	SOFA >threshold / deaths	Sensitivity (95% CI)	Specificity (95% CI)	Negative predictive value (95% CI)	Diagnostic Odds Ratio (95% CI)
48	>4	37/12	25/11	91.7 (61.5- 99.8)	44.0 (24.4- 65.1)	91.7 (70.2-98.5)	8.6 (1.0- 77.5)
72	>6	84/18	40/17	94.4 (72.7- 99.9)	65.2 (52.4- 76.5)	97.7 (90.4-99.6)	31.8 (4.0-254.2)
96	>7	92/15	35/14	93.3 (68.1- 99.8)	72.7 (61.4- 82.3)	98.2 (92.8-99.7)	37.3 (4.6-301.8)
Up to 96	>7	98/20	42/19	95.0 (78.5- 99.1)	70.5 (66.3- 71.6)	98.2 (92.3-99.7)	45.4 (7.2- 278.7)
48 (Modified SOFA)	>3	37/12	19/11	91.7 (61.5- 99.8)	56.0 (34.9-75.6)	94.4 (79.9-99.0)	23.4 (3.1-160.4)
72 (Modified SOFA)	>4	84/18	33/17	94.4 (72.7-99.9)	75.8 (63.6-85.5)	98.0 (91.9-99.6)	53.1 (8.2-332.1)
96 (Modified SOFA)	>4	92/15	38/14	93.3 (68.1-99.8)	70.1 (58.6-80.0)	98.1 (92.3-99.7)	31.7 (4.9- 196.7)
Up to 96 (Modified SOFA)	>5	98/20	37/19	95.0 (78.7-99.1)	76.9 (72.8-78.0)	98.4 (93.0-99.7)	63.3 (9.9-391.4)
Modified KCC	N/A	100/21	KCC +ve/ deaths 22/17	81.0 (65.0- 90.7)	93.7 (89.4- 96.3)	94.9 (90.6-97.5)	62.9 (15.7- 251.3)

Table 4. Predictive accuracy of the Sequential Organ Failure Assessment (SOFA) score following single time point paracetamol overdose.

Optimal thresholds for predicting death or liver transplantation were derived from receiver operator characteristic analysis.

The accuracy of the SOFA score is compared with the modified King's College Hospital poor prognostic criteria (KCC). The modified SOFA score excludes the hepatic failure component.

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CI, confidence intervals; HE, hepatic encephalopathy; SLTU, Scottish Liver Transplantation Unit; N/A, not-applicable

For Peer Review

SOFA score and outcome

Univariate analysis of the individual components of the SOFA score at 72 and 96 hours post-overdose was performed to identify those components which best predicted an adverse outcome (**Supplementary table 2**). All the organ failure components except the hepatic failure element were strongly associated with mortality, so a modified SOFA score, which excluded points for hepatic failure, was computed. ROC analysis of this modified SOFA score showed an area under the curve of 0.81 (95% CI 0.67-0.95), 0.90 (95% CI 0.84-0.97), and 0.91 (95% CI 0.84-0.98) at 48, 72, and 96 hours post-overdose respectively. A modified SOFA threshold score of >3 at 48 hours, and >4 at 72 hours, improved upon the specificity of the original SOFA score at both these time points without affecting sensitivity. A modified SOFA threshold score of >5 at any point during the first 96 hours following overdose was highly predictive of death or OLT, with a sensitivity of 95.0 (95% CI 78.7-99.1), specificity of 76.9 (95% CI 72.8-78.0), and negative predictive value of 98.4 (95% CI 93.0-99.7) (**table 4**).

Association between SIRS and SOFA scores

We then explored whether those patients with high SOFA scores also manifested a SIRS response. By 96 hours post-overdose, the median (+/- IQR) SOFA score in those patients who manifested a SIRS response was significantly higher (8 (5-15)) compared with those patients with no SIRS at that point (5 (3-6.25), $p=0.0011$). There was a strong correlation between these two variables (Spearman's $r=0.474$, $p<0.0001$), as shown in **figure 2**, with those patients who died tending to have both a SIRS response and a higher SOFA score than spontaneous survivors.

Prospective validation of multiorgan failure scores

The prognostic accuracy of the SIRS and SOFA thresholds outlined above was then examined in a prospectively collected cohort of paracetamol-induced acute liver injury patients admitted to the Royal Infirmary of Edinburgh between March 2009 and July 2010. A total of 38 patients were included, and their demographic details, admission laboratory parameters, and clinical outcomes are outlined in **table 5**. All 7 patients who died or underwent emergency OLT manifested a SIRS response, had a SOFA score >7 , and had a modified SOFA >5 within 96 hours of overdose. The specificity of the two SOFA predictors was 77.4 (95% CI 70.5-77.4) and the specificity of the SIRS was 74.2 (95% CI 67.2-74.2).

Variable (n= 38)		Value
Sex (male/female)		16/22 (42.1%/57.9%)
Age (years)		35 (26.5-44.5)
Received NAC in referring hospital		38 (100%)
Admission laboratory parameters	WCC (x10 ⁹ /L)	8.4 (6.5-11.4)
	Platelets (x10 ⁹ /L)	122 (71-192)
	Creatinine, $\mu\text{mol/L}$ (mg/dL)	117 (61-241) (1.3 (0.7-2.7))
	ALT (IU/L)	5198 (2974-7978)
	Bilirubin, $\mu\text{mol/L}$ (mg/dL)	81 (32-113) (4.7 (1.9-6.6))
	PT (seconds)	41 (29-73)
Ever encephalopathic (ALF)		18 (47.4%)
Grade 3-4 HE encephalopathy		12 (31.6%)
Mechanical ventilation		13 (34.2%)
KCC met		9 (23.7%)
SIRS response by 96 hours post-overdose		15 (39.5%)
SOFA score >7 by 96 hours post-overdose		14 (36.8%)
Modified SOFA score >5 by 96 hours post-overdose		14 (36.8%)
Overall outcome		
Transplanted		4 (10.5%)
Spontaneous survival		31 (81.6%)
Died without transplantation		3 (7.9%)

Table 5. Validation cohort of 38 single time point paracetamol overdoses

DISCUSSION

This study has explored the temporal relationship between paracetamol overdose and the development of systemic inflammation and organ failure. Development of the SIRS and extrahepatic organ failure are both strongly associated with adverse clinical outcomes, and both SOFA and SIRS scores are highly sensitive markers of poor outcome following paracetamol overdose. A SOFA score ≤ 7 during the first 96 hours post-overdose is highly predictive of spontaneous survival, with a risk of death of $< 2\%$, and these patients also have a low risk of requiring specialist intracranial pressure monitoring or renal support. Due to the high negative predictive values of both SOFA and SIRS, these scores may have a future role as 'gatekeepers' when considering patient transfer to tertiary liver centres.

Predicting individual prognosis accurately following paracetamol overdose is fraught with difficulty.⁽¹⁷⁾ For a predictive model to be clinically useful, it should be easy to use, accurate, reproducible, and accepted by clinical staff. Both SOFA and SIRS scores are dynamic tests, which can be rapidly recalculated throughout admission, and are attractive as prognostic indicators due to their widespread use in intensive care units and their ease of use. Recently, the SOFA score was demonstrated to outperform liver-specific prognostic scores in predicting outcome amongst a cohort of critically ill chronic liver disease patients.⁽¹⁸⁾ Whilst both the SOFA and SIRS scores have similarly high negative predictive values following paracetamol overdose, the SOFA score is more attractive as a quantitative triage tool as, unlike the SIRS, it is an ordinal rather than dichotomous variable, and therefore a rising SOFA score may help to identify deteriorating patients. Although neither SIRS nor SOFA were originally developed to predict outcome, the high sensitivity of these scores makes them attractive as a means of identifying all those high-risk paracetamol overdose patients who might die without transplant, although their relatively lower specificity suggests that they should not replace the KCC as definitive listing criteria. Additionally,

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3 there are some specific limitations of both SOFA and SIRS scores that should be addressed.
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5 The SIRS does not incorporate a hepatic failure component at all, whilst the hepatic failure
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7 component (serum bilirubin) of the SOFA score lacks specificity or the ability to differentiate
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9 acute from chronic hepatic dysfunction. Indeed, of all the 6 organ failure components
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11 combined in the SOFA score, only the hepatic failure element was not associated with an
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13 increased risk of death, a finding in keeping with several previous studies of this scoring
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15 system.(19,20) Future studies should validate whether the modified SOFA score outlined
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17 above, which excludes hepatic organ failure, is a more accurate triage marker in this setting
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19 than the original SOFA score.
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27 The principal strength of this study lies in its novel evaluation of SIRS and SOFA
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29 scores in relation to the timing of overdose, rather than in relation to the time of admission or
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31 the onset of HE. The initial symptoms of ALF are often vague, and as a result there may be
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33 a significant delay between the overdose and subsequent hospitalisation. Additionally, some
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35 patients present as a result of the psychological consequences of their overdose, rather than
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37 as a result of physical morbidity. Thirdly, since the majority of previous studies of prognostic
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39 variables of paracetamol-induced ALF have been performed at academic referral centres
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41 following patient transfer from smaller hospitals,(9) attempting to apply a prognostic score at
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43 the time of 'hospital admission' is considerably hindered by patient heterogeneity. Equally,
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45 accurately applying a prognostic score at the onset of HE may be problematic since the
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47 presence or absence of HE is subjective, and subtle encephalopathy may be wrongly
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49 interpreted as resulting from alcohol or narcotic withdrawal. We have therefore attempted to
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51 minimise clinical heterogeneity by selecting single time point overdoses, and have examined
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53 the evolution of systemic inflammation and organ failure in relation to this fixed time point.
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55 Using this approach, we demonstrate that the prognostic accuracy of both SIRS and SOFA
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57 scores are enhanced compared with previous reports which applied these markers at either
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59 the time of hospital admission or the onset of HE.(9) We recognise that this approach is
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3 dependent upon the temporal accuracy of the patients' overdose history, but previous
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5 studies have suggested that the patient history is usually reliable following paracetamol
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7 overdose.(21) Heterogeneity is further reduced by the single centre nature of this study,
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9 where both criteria for patient admission and clinical management protocols have remained
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11 unchanged during the time course of the study.
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18 However, we recognise that this study has several important limitations. Clearly, the
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20 results of this study are not directly applicable to patients who have taken a staggered
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22 overdose, an increasingly recognised subtype of paracetamol overdose,(22) or in cases
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24 where accurate timings of the overdose are unavailable. Although we have examined the
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26 applicability of multiorgan failure scores in relation to time from overdose, patients access
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28 treatment at different time points in their clinical evolution, which may influence the
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30 development of the SIRS or organ failure. A further caveat is that some patients were
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32 transferred to the SLTU from a number of surrounding hospitals, each of which may have
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34 had different management protocols, clinical expertise, and referral thresholds following
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36 paracetamol overdose. Whilst the SLTU is the single referral point for all severe
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38 paracetamol overdoses in Scotland, we recognise the possibility of selection bias and that
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40 some patients with severe organ failure secondary to paracetamol overdose may not have
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42 been transferred to the SLTU.(23) We also recognise that not all of the patients in this study
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44 developed HE, and therefore ALF. However, predicting the development of HE can be
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46 equally problematic, and the mere absence of HE following severe acute liver injury does not
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48 preclude the development of other complications such as acute kidney injury.(24)
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56 A potential application for SIRS and SOFA scores may be as gatekeepers to tertiary
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58 level care. In the SLTU, transfer criteria are based broadly upon guidelines previously
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60 published by the British Society of Gastroenterology.(12) These guidelines recognise that "A

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3 significant proportion of cases will make an unremarkable recovery without intensive
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5 measures but this level of unnecessary transfer is justified if the potential for transplantation,
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7 in what is often a narrow window of time, is to be realised". Due to the rapid progression of
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9 paracetamol-induced ALF and the risks involved in transferring patients with HE or with
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11 incipient cerebral oedema, up to 50% of UK liver centre patients never develop HE.
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13 Developing sensitive markers to identify high-risk patients at an earlier time point, prior to HE
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15 developing, could accelerate safe patient transfer, but equally the high negative predictive
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17 value of the multiorgan scores outlined above could effectively rule out the need for
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19 emergency OLT by identifying those patients highly likely to survive with supportive care
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21 alone, thereby potentially avoiding patient transfer.
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29 In conclusion, this retrospective cohort study of 100 severe acute paracetamol-
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31 induced acute liver injury patients has evaluated the incidence and temporal kinetics of both
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33 the SIRS and SOFA scores following single time point paracetamol overdose, and
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35 demonstrates that these markers are highly sensitive at identifying patients with a poor
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37 prognosis. The high negative predictive value of these markers was validated in a
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39 prospective cohort. Both the SIRS and SOFA scores deserve further evaluation and external
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41 validation as potential gatekeepers to improve clinical decision making models following
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3 **FIGURE LEGENDS**
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6 **Figure 1. Association between mortality rate and the number of organ failures**
7 **identified by the Sequential Organ Failure Assessment (SOFA) score at (A) 48, (B) 72,**
8 **and (C) 96 hours following single time point paracetamol overdose.**
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14 Numbers above the bars indicate number of deaths.

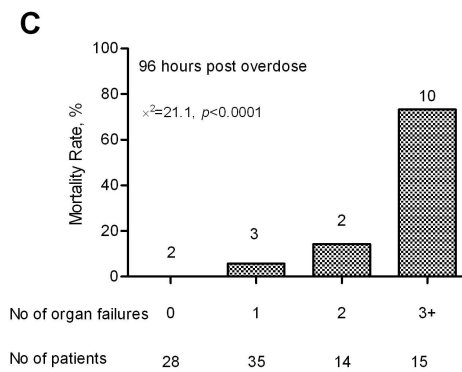
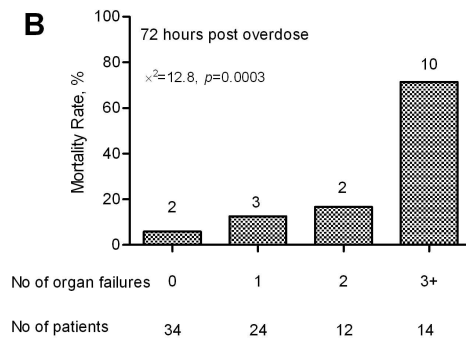
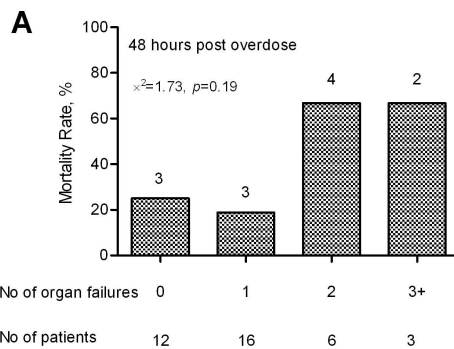
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17 Death and liver transplantation were considered equivalent.
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22 **Figure 2. Association between Sequential Organ Failure Assessment (SOFA) scores**
23 **and the number of Systemic Inflammatory Response Syndrome (SIRS) components**
24 **fulfilled by 96 hours following single time point paracetamol overdose.**
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30 OLT; orthotopic liver transplantation
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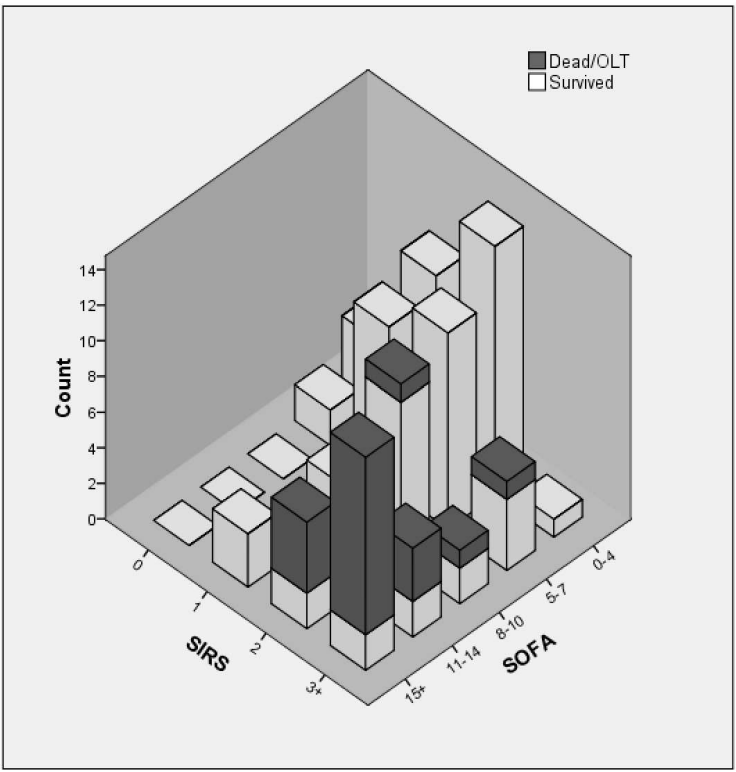
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Association between mortality rate and the number of organ failures identified by the Sequential Organ Failure Assessment (SOFA) score at (A) 48, (B) 72, and (C) 96 hours following single time point paracetamol overdose.
129x277mm (300 x 300 DPI)

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Association between Sequential Organ Failure Assessment (SOFA) scores and the number of Systemic Inflammatory Response Syndrome (SIRS) components fulfilled by 96 hours following single time point paracetamol overdose.
 OLT; orthotopic liver transplantation
 508x407mm (72 x 72 DPI)

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Variable		Dead/OLT (n=21)	Spontaneous survival (n=79)	<i>p</i>
Admission laboratory parameters	Platelets (x10 ⁹ /L)	100 (34-167)	120 (74-160)	0.186
	Sodium (mmol/L)	135 (132-138)	136 (133-138)	0.545
	Creatinine, μmol/L (mg/dL)	174 (118-239) 2.0 (1.3-2.7)	94 (75-165) 1.1 (0.8-1.9)	0.006
	ALT (IU/L)	6697 (4278-11920)	9132 (6117-12360)	0.154
	Bilirubin, μmol/L (mg/dL)	76 (56-90) 4.4 (3.3-5.3)	86 (56-110) 5.0 (3.3-6.4)	0.369
	Albumin (g/L)	30 (23-35)	34 (31-37)	0.013
	PT (seconds)	80 (53-103)	48 (33-70)	0.002
Developed encephalopathy		21 (100%)	26 (32.9%)	<0.001
Met King's College Criteria		17 (81.0%)	5 (6.3%)	<0.001
Renal replacement therapy		17 (81.0%)	14 (17.7%)	<0.001
Intracranial pressure monitor		17 (81.0%)	7 (8.9%)	<0.001
Inotropic support		17 (81.0%)	6 (7.6%)	<0.001
Mechanical ventilation		20 (95.2%)	15 (19.0%)	<0.001
Transplanted		3	0	-

Supplementary Table 1. Admission laboratory parameters and clinical outcomes for study population.

ALT, alanine aminotransferase; PT, prothrombin time;

Variable	72 hour univariate OR (95% CI) n=84	<i>p</i>	96 hour univariate OR (95% CI) n=92	<i>p</i>	
Sex (male)	0.90 (0.33-2.50)	1.00	1.58 (0.59-4.24)	0.360	
Age (>40 years)	0.77 (0.25-2.36)	0.78	1.03 (0.99-1.07)	0.102	
SIRS (yes/no)	10.52 (1.66-64.80)	0.009	∞ (3.26- ∞)	<0.001	
SOFA (per 1 additional unit)	1.42 (1.22-1.65)	<0.001	1.39 (1.21-1.60)	<0.001	
SOFA organ failures (≥3 points per component)	Cardiovascular failure	22.75 (4.13-125.37)	<0.001	49.33 (10.20-238.64)	<0.001
	Respiratory failure	24.00 (5.36-107.47)	<0.001	152.00 (16.09-1436)	<0.001
	Neurologic failure	9.21 (2.79-30.39)	0.001	40.00 (9.06-176.54)	<0.001
	Renal failure	5.16 (1.65-16.10)	0.005	4.03 (1.28-12.72)	0.018
	Haematologic failure	22.50 (5.56-91.10)	<0.001	25.00 (4.37-142.90)	<0.001
	Hepatic failure	0.55 (0.16-1.88)	0.255	1.06 (0.35-3.20)	0.574

Supplementary Table 2. Risk factors for in-hospital mortality at 72 and 96 hours post-paracetamol overdose: Results of univariate analysis