Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study

William Bernal, Nora Donaldson, Duncan Wyncoll, Julia Wendon

Summary

Background Although the King’s College Hospital (KCH) selection criteria for emergency liver transplantation in paracetamol-induced acute liver failure are widely used, strategies to improve sensitivity and facilitate earlier transplantation are required. We investigated the use of arterial blood lactate measurement for the identification of transplantation candidates.

Methods In a single-centre study, we measured arterial lactate early (median 4 h) and after fluid resuscitation (median 12 h) in patients admitted to a tertiary-referral intensive-care unit. Threshold values that best identified individuals likely to die without transplantation were derived in a retrospective initial sample of 103 patients with paracetamol-induced acute liver failure and applied to a prospective validation sample of 107 patients. Predictive value and speed of identification were compared with those of KCH criteria.

Findings In the initial sample, median lactate was significantly higher in non-surviving patients than in survivors both in the early samples (8.5 [range 1.7–21.0] vs 1.4 [0.53–7.9] mmol/L, p = 0.0001) and after fluid resuscitation (5.5 [1.3–18.6] vs 1.3 [0.26–3.2], p = 0.0001). Applied to the validation sample, a threshold value of 3.5 mmol/L early after admission had sensitivity 67%, specificity 95%, positive likelihood ratio 13, and negative likelihood ratio 0.35; the corresponding values for a threshold of 3.0 mmol/L after fluid resuscitation were 76%, 97%, 30, and 0.24. Combined early and postresuscitation lactate concentrations had similar predictive ability to KCH criteria but identified non-surviving patients earlier (4 [3–13] vs 10 [3.5–19.5] h, p = 0.01). Addition of postresuscitation lactate concentration to KCH criteria increased sensitivity from 76% to 91% and lowered corresponding values for a threshold of 3 mmol/L, p < 0.0001). Early and postresuscitation lactate concentrations may also reflect decreases in clearance secondary to impaired hepatic function. The injured liver may itself also act as a source of lactate.

In critical illness other than acute liver failure, prolonged high blood lactate concentrations are associated with a poor prognosis. Hyperlactataemia in this setting has been accepted as a marker of systemic tissue dysxia or microcirculatory perfusion abnormalities and increased anaerobic metabolism. Since circulating lactate is metabolised mainly by the liver, high blood lactate concentrations may also reflect decreases in clearance secondary to impaired hepatic function. The injured liver may itself also act as a source of lactate.

In acute liver failure, hyperlactataemia may therefore indicate the severity of both the hepatic injury sustained and the accompanying multiple organ failure. Blood lactate can be rapidly and accurately measured by point-of-care testing and thus could provide a practical early indicator of outcome.

We assessed the clinical use of blood lactate measurements to identify patients likely to die without transplantation. We examined the clinical and biochemical correlates of blood lactate in a large cohort of patients with paracetamol-induced acute liver failure, and investigated threshold values that best identified non-survivors. These threshold values were applied to a second prospective sample of patients and compared with the KCH criteria for prognostic accuracy and speed of identification of patients who will not survive without transplantation.
**Patients and methods**

**Patients**

The criteria for transfer of patients with paracetamol-induced hepatotoxicity to the liver intensive-care unit include a progressive coagulopathy, in which the prothrombin time (measured in seconds) exceeds the time in hours after overdose, or an international normalised ratio (INR) of more than 5.0 at any time, or evidence of metabolic acidosis, hypoglycaemia, or renal failure. All patients are managed to a standard protocol, with volume resuscitation and use of invasive haemodynamic and intracranial monitoring as appropriate. Norepinephrine is used as the primary vasopressor, and continuous venovenous haemofiltration with lactate-free fluid is used for renal replacement therapy. Intravenous N-acetylcysteine is infused at a rate of 150 mg/kg for 24 h until the INR is below 2.

Patients are considered for transplantation if they meet the KCH criteria, with either the concurrent finding of a serum creatinine concentration above 300 μmol/L, prothrombin time of more than 100 s (INR >6.5), and grade III or IV encephalopathy within a 24 h period in patients with a normal pH, or the single finding of a pH below 7.3 following adequate fluid replacement. Evidence of irreversible brainstem dysfunction, major escalating intrathecal dependence, and culture-positive systemic sepsis unresponsive to 48 h of antimicrobial therapy are considered medical contraindications to transplantation.

As part of routine monitoring, 2.5 mL heparinised whole blood is withdrawn from an arterial catheter every 4–6 h and immediately analysed in a point-of-care testing facility. Blood lactate concentration was measured with an automated analyser that uses membrane-bound enzyme electrode technology (YSI 2300; Yellow Springs Instrument Co; Yellow Springs, OH, USA). The instrument is checked twice daily according to the manufacturer’s recommendations, and in addition the machine self-calibrates after every 50 samples or every 120 min. During the study period, the coefficient of variation for the measurement of standards was less than 5%.

The initial retrospective sample consisted of 103 patients with severe paracetamol-induced hepatotoxicity admitted between January, 1998, and February, 1999. The prospective validation sample consisted of 107 patients consecutively admitted between July, 1999, and June, 2000. As part of their care, nursing staff were asked to take their routine samples at 4 h and 12 h after admission, and the volumes of intravenous fluid administered up to these times were recorded.

**Statistics**

**Initial sample**—Lactate values measured early after admission (at a median of 4 h [IQR 3–6]) and after fluid resuscitation (at 12 h [7–15]) were examined in the initial sample. Where the timing of overdose was known, these values were obtained a median of 56 h and 64 h after overdose, respectively. A multiple linear regression model was used to model early lactate concentration, accounting for the effects of demographic, biochemical, and clinical variables after other transformations and quadratic terms were explored. Variables included in this analysis were taken from the Riyadh ICU program (Medical Associated Software House, London, UK) dataset for the first 24 h of the hospital stay of each patient, and included those used for the calculation of APACHE II and III scores. The relations of these variables and their interactions with mortality were analysed by multiple logistic regression. Patients who underwent transplantation were excluded from this analysis. The potential prognostic variables were dichotomised according to optimum threshold values obtained by minimising the proportion of misclassification. This procedure used receiver operating characteristic (ROC) techniques and the logistic discriminant given by the logistic regression model. Multiple regression models were developed in a stepwise manner, for demographic, biochemical, and clinical variables, including at the last stage the best sets of variables and interactions and adding unselected variables to the later models.

**Validation sample**—Threshold values for early and postresuscitation lactate calculated in the initial sample were applied to the validation sample to assess diagnostic accuracy in comparison with the KCH criteria. Two assessors (JW and DW) independently reviewed clinical records of selected patients on two separate occasions to assess whether and at what time after admission lactate or KCH criteria were satisfied. This group included all patients who died or underwent transplantation and all survivors who had pH values of 7.325 or less, INR of 5.0 or more, early lactate concentration above 3.0 mmol/L, or postresuscitation lactate above 2.5 mmol/L. The assessors were unaware of patients’ identity, outcome, and the variables required for the criteria that were not being assessed. Patients were judged to have met each set of criteria only if there was agreement between assessors. Diagnostic accuracy was assessed by standard measures and likelihood ratios.

**Statistical methods**—Data are presented as median and range or IQR. Univariate analysis was done with Statview (version 5.0) and used non-parametric testing, and all multivariate analysis used SPSS (version 8.0). Because the study relied on measurements used as part of routine clinical management, the research ethics committee of King’s Healthcare NHS Trust waived the need for consent/assent.

**Results**

**Initial sample**

In the retrospective cohort there were 52 men and 51 women, with a median age of 35 years (table 1). 57 patients from this cohort survived with medical management, 36 died, and ten underwent transplantation. The median dose of paracetamol ingested was 25 g (range 9–100), and the median time of presentation to the referring hospital was 24 h (5–78; unknown in 43 cases). The median time between admission to the referring hospital and transfer to this unit was 19 h (2–67). Among patients for whom the timing of overdose was known, the

**Outcome**

- Died: 36 (35%)
- Survived: 57 (55%)
- Transplanted: 5 (5%)

**Admission values**

- INR: 3.40 (1.20–150)
- Creatinine (μmol/L): 145 (45–581)
- pH: 7.39 (7.53–7.52)
- Lactate (mmol/L): 2.50 (0.53–21.0)

**Demography**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sample</th>
<th>Initial (n=103)</th>
<th>Validation (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
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<td>52/51</td>
<td>42/65</td>
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<tr>
<td></td>
<td></td>
<td>35 (16–60)</td>
<td>36 (16–78)</td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td>3.40 (1.20–150)</td>
<td>2.93 (1.17–15.0)</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td></td>
<td>145 (45–581)</td>
<td>136 (54–664)</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td>7.39 (7.53–7.52)</td>
<td>7.40 (7.96–7.50)</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td></td>
<td>2.50 (0.53–21.0)</td>
<td>1.98 (0.5–26.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sample</th>
<th>Initial (n=103)</th>
<th>Validation (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td></td>
<td>36 (35%)</td>
<td>21 (20%)</td>
</tr>
<tr>
<td>Survived</td>
<td></td>
<td>57 (55%)</td>
<td>78 (73%)</td>
</tr>
<tr>
<td>Transplanted</td>
<td></td>
<td>5 (5%)</td>
<td>8 (7%)</td>
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</table>

<table>
<thead>
<tr>
<th>p-value</th>
<th></th>
<th>Initial</th>
<th>Validation</th>
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</thead>
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<tr>
<td>Died</td>
<td>p=0.02</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Survived</td>
<td>p=0.02</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Admission clinical features and outcome of initial and validation samples

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median time from overdose to transfer to this unit was 51 h (18–98).

On multiple linear regression, pH, tympanic temperature, mean arterial pressure, INR, and serum creatinine concentration were each independently associated with early lactate concentrations (table 2). Together, these five variables accounted for about 70% of the variance of lactate concentration. Temperature and pH had a stronger association than other variables and were also independently associated with encephalopathy grade.

**Table 2: Multiple regression analysis of clinical variables independently associated with early lactate concentration in 103 patients of initial sample**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>-7.5 (-11.8 to -3.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Temperature</td>
<td>-0.6 (-1.0 to -0.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-0.05 (-0.1 to 0.01)</td>
<td>0.01</td>
</tr>
<tr>
<td>INR</td>
<td>0.28 (0.1 to 0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.007 (0.002 to 0.01)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

INR=international normalised ratio.

**Blood lactate concentrations early after admission and after fluid resuscitation in 93 patients of initial sample and 99 patients of validation sample**

**Initial sample**

Non-survivors (n=36)

Survivors (n=57)

Early after admission

Non-survivors (n=33)

Survivors (n=52)

After resuscitation

**Validation sample**

Non-survivors (n=21)

Survivors (n=78)

Early after admission

Non-survivors (n=21)

Survivors (n=64)

After resuscitation

Blood lactate concentrations early after admission and after fluid resuscitation in 93 patients of initial sample and 99 patients of validation sample

Boxplot shows 50th (central horizontal line), 25th and 75th (limits of box), and 5th and 95th centiles (error bars). p=0.0001 Mann-Whitney U test, for comparison of survivors and non-survivors in each cohort.

Eight patients (five survivors, three who died) did not have lactate measured after fluid resuscitation. Early lactate concentrations were significantly higher in patients who died than in those who survived (8-5 [1-7–21.0] vs 1-4 [0-53–7-9] mmol/L; p<0.0001 Mann-Whitney U test) and after resuscitation (5-5 [1-3–18-6] vs 1-3 [0-26–3-2], mmol/L; p<0.0001; figure). 40 (95%) of 42 patients with early lactate concentrations below 2 mmol/L survived, compared with 17 (72%) of 23 with concentrations of 2-4 mmol/L, and only four (13%) of 33 with concentrations above 4 mmol/L. In relation to lactate values after fluid resuscitation, the numbers surviving were 43 (96%) of 45 patients with lactate concentrations below 2 mmol/L and nine (50%) of 18 with concentrations of 2-4 mmol/L; no patient with lactate concentrations above 4 mmol/L survived.

The results of the univariate logistic regression for the significant predictors of mortality are shown in table 3. In univariate logistic analysis, pH and blood lactate concentrations (both early and after fluid resuscitation) were the only independent clinical predictors of a fatal outcome (table 4). The ROC analysis with the greatest sensitivity and specificity for the threshold of early lactate concentration to identify patients who will not survive was 3-5 mmol/L; that after fluid resuscitation was 3-0 mmol/L. Early blood lactate concentration of more than 3-5 mmol/L had sensitivity of 86%, specificity of 92%, and accuracy of 90%. A lactate concentration of more than 3-0 mmol/L after fluid resuscitation gave similar predictive values (sensitivity 82%, specificity 96%, accuracy 90%).

Paired measurements were made in 32 of the 35 patients in whom early lactate was above 3-5 mmol/L; blood lactate remained above 3-0 mmol/L after fluid resuscitation in 25 of these patients, of whom 24 (95%) died. Three of the seven patients in whom lactate fell below 3-0 mmol/L survived.

Ten patients from the initial cohort underwent transplantation; all met KCH criteria. Median early lactate concentration was 3-72 mmol/L (2-17–18-5) and that after fluid resuscitation 3-51 mmol/L (1-46–18-5). Five of these ten patients had early lactate concentrations above 3-5 mmol/L at 4 h and eight had concentrations above 3-0 mmol/L after fluid resuscitation. Four of the five patients with early lactate concentrations above

**Table 3: Univariate logistic analysis of admission clinical predictors of a fatal outcome in 93 patients from initial sample**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early lactate concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH†</td>
<td>13-4 (2-7–66)</td>
<td>0.001</td>
</tr>
<tr>
<td>Encephalopathy grade‡</td>
<td>10-8 (3-9–30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temperature</td>
<td>0-4 (0-2–0-6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>INR</td>
<td>2-4 (1-5–3-9)</td>
<td>0-002</td>
</tr>
<tr>
<td>White blood-cell count</td>
<td>1-2 (1-3–1-3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0-9 (0-90–0-97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Early lactate concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postresuscitation lactate concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH†</td>
<td>11-6 (2-2–61)</td>
<td>0-004</td>
</tr>
<tr>
<td>Postresuscitation lactate concentration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Grades 0–2 vs grades 3–4.

**Table 4: Multivariate logistic analysis of independent clinical predictors of a fatal outcome in 93 patients from initial sample**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early lactate concentration</td>
<td></td>
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<tr>
<td>pH†</td>
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<td>0.001</td>
</tr>
<tr>
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<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temperature</td>
<td>0-4 (0-2–0-6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>INR</td>
<td>2-4 (1-5–3-9)</td>
<td>0-002</td>
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<tr>
<td>White blood-cell count</td>
<td>1-2 (1-3–1-3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0-9 (0-90–0-97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Early lactate concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postresuscitation lactate concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH†</td>
<td>11-6 (2-2–61)</td>
<td>0-004</td>
</tr>
<tr>
<td>Postresuscitation lactate concentration</td>
<td></td>
<td></td>
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</tbody>
</table>
3·5 mmol/L had postresuscitation concentrations above 3·0 mmol/L.

Validation sample
This cohort consisted of 42 men and 65 women of median age 36 years (range 16–78). 78 (73%) survived with medical management, 21 (20%) died, and eight (7%) underwent transplantation (table 1).

Early lactate concentrations were measured in the validation sample at a median of 4 h (IQR 3–4) after admission, and postresuscitation concentrations at 12 h (IQR 12–14). 14 surviving patients did not have postresuscitation lactate concentrations measured. The median volume of intravenous colloid and crystalloid administered up to the time of measurement was 1·5 L (0·2–4·7) and 3·9 L (1·1–10·0), respectively. Median early lactate concentration was 1·49 mmol/L (0·50–7·37) in survivors and 4·90 mmol/L (1·04–26·5) in patients who died (p<0·0001); the median values after fluid resuscitation were 1·7 mmol/L (0·46–6·10) and 4·17 mmol/L (0·78–28·0), respectively (p<0·0001, figure). 15 (83%) of the 18 patients who had early lactate concentrations above 3·5 mmol/L had postresuscitation values above 3·0 mmol/L, and of these 13 (87%) died.

The application of the threshold values of early and postresuscitation lactate concentrations was explored in the validation sample, and comparison made with the KCH criteria applied to the same cohort (table 5). Early lactate concentration above 3·5 mmol/L alone had lower sensitivity and accuracy than the KCH criteria, although it identified patients significantly earlier (p=0·007). Postresuscitation lactate concentration above 3·0 mmol/L had equivalent sensitivity and higher specificity and accuracy than the KCH criteria, with a higher positive likelihood ratio. There was no significant difference in the time of identification of patients between postresuscitation lactate and KCH criteria.

In comparison with the KCH criteria, the finding of early lactate concentrations of more than 3·5 mmol/L or postresuscitation concentrations above 3·0 mmol/L (lactate criteria) showed higher sensitivity and similar specificity, accuracy, and positive and negative likelihood ratios, but they identified patients significantly earlier (p=0·01).

When patients who met either of the lactate criteria or the KCH criteria were compared with those who met the standard KCH criteria alone, the sensitivity was higher, the time of patients’ identification shorter, and both negative and positive likelihood ratios were lower. The combination of the KCH criteria and postresuscitation lactate above 3·0 mmol/L had higher sensitivity and a lower negative likelihood ratio than the KCH criteria alone, with no reduction in positive likelihood ratio, though there was no significant change in the time of patients’ identification.

Eight patients in the validation sample underwent transplantation. Median early lactate concentration was 4·45 mmol/L (2·06–16·2) and that after fluid resuscitation was 5·56 mmol/L (3·14–10·5). Six of these patients had early lactate concentrations above 3·5 mmol/L and all had values above 3·0 mmol/L after fluid resuscitation. Lactate criteria were met at a median of 4 h (3–13) and KCH criteria at 12 h (4–32) after admission (p=0·013).

When patients transplanted were classified as non-survivors, the sensitivity, specificity, accuracy, and positive and negative likelihood ratios for the lactate criteria were 86%, 95%, 93%, 17, and 0·15, respectively. KCH criteria gave values of 79%, 95%, 91%, 15, and 0·22. Lactate criteria identified non-surviving patients at a median of 4 h (3–13) after admission and KCH criteria did so at 12 h (3–32; p=0·003).

Discussion
High blood lactate concentrations may result from both increased production and decreased clearance, and the predominant mechanism is likely to vary with the clinical circumstance. Better understanding of the metabolic abnormalities in critical illness is showing that the explanation of hyperlactataemia occurring in critical illness simply as a consequence of overproduction resulting from systemic hypoperfusion and consequent cellular hypoxia is an oversimplification. Although the mechanisms underlying disturbed tissue oxygen utilisation are not fully understood, and the sites of lactate production debated, there is increasing evidence of the importance of hepatic clearance and of the effects of changes in hepatic metabolic capacity.

The liver has a large functional reserve for lactate metabolism, and even with significantly compromised liver function, in normal physiological conditions, normolactataemia is generally maintained. However, the response to a lactate load may be abnormal; although a reduction in liver cell mass by 50% after major hepatectomy does not lead to hyperlactataemia, the clearance of an exogenous lactate load is delayed. In patients with paracetamol-induced hepatotoxicity but without multiple organ dysfunction, blood lactate concentration can be normal, but hepatic lactate clearance is lower than normal. In patients with established acute liver failure and multiple organ dysfunction, rises in lactate are common and closely parallel indices of systemic haemodynamic dysfunction and oxygen utilisation.

Both increased systemic lactate production and decreased hepatic clearance may thus be important in determining blood lactate concentration in critically ill patients with acute liver failure. Severe hyperlactataemia is likely to develop only when a significantly compromised liver is presented with an increased lactate load after peripheral production increases.
Without specific measurement of indices of extrahepatic tissue oxygen utilisation and hepatic lactate handling, we cannot directly assess from our data the relative contributions of excess lactate production and decreased hepatic clearance. A plausible conclusion is that observed blood lactate concentration represents the combination of both, and thus the overall severity of acute liver failure. This speculation is supported by the multivariate analysis of determinants of blood lactate concentration in our study, in which association was found with measures of both hepatic and extrahepatic organ dysfunction.

In this study we found that, in patients with advanced acute liver failure presenting to a transplantation centre, blood lactate concentrations show a close relation to survival. Use of blood lactate concentrations alone, with cut-off values of 3-5 mmol/L early after admission and 3-0 mmol/L after volume resuscitation, identifies patients likely to die earlier and with equivalent accuracy to the currently applied KCH criteria.

Caution should be exercised in the extrapolation of these results to other groups of patients with paracetamol intoxication. Blood lactate concentrations were measured some time after drug ingestion, and most patients admitted to this unit 2 or 3 days after overdose suffered established hepatic necrosis. The limited published data on lactate metabolism soon after paracetamol overdose suggest a direct toxic effect of the drug on cellular respiration, and the prognostic importance of blood lactate concentrations measured soon after drug ingestion is unknown. Similarly, extrapolation to under-resuscitated patients is inadvisable. Hypovolaemia is common in patients with acute liver failure, and results in peripheral hypoperfusion; initially raised blood lactate concentrations may be corrected by volume resuscitation. Although fluid resuscitation was started at the referring hospitals in our study, most of the patients required substantial fluid replacement after arrival. Persistently high blood lactate concentrations despite fluid resuscitation are associated with a particularly poor prognosis and identify non-survivors very early in their clinical course.

Assessment of the performance of the KCH criteria in our study shows results similar to those of the original study and of subsequent validation studies. Despite the changes in clinical management that have occurred in the decade since their formulation, the KCH criteria remain an easily applicable, robust, and reliable means of identification of the patient unlikely to survive without transplantation.

However, published data on the use of these criteria identify two problems in their clinical application. First, they have limited sensitivity; although the patient who meets the criteria is very likely to die without transplantation, a proportion of patients die without meeting the criteria. Second, less than 50% of patients who meet the criteria undergo transplantation, primarily because of the development of clinical contraindications while awaiting transplantation.

In the context of outcome prediction in acute liver failure, likelihood ratios indicate the extent to which fulfilment of particular criteria will increase or decrease the pretest probability of a fatal outcome. The positive likelihood ratio indicates the extent to which a positive test result will increase the pretest probability of death without transplantation, and the negative likelihood ratio the extent to which a negative test will reduce this probability.

Application of the KCH criteria to the validation sample with a positive likelihood ratio of 15 and negative likelihood ratio of 0.25 is associated with a probability of death in patients who meet the criteria from 20% to nearly 80%, whereas in those who do not meet the criteria the probability falls to between 5% and 10%. By comparison, a post-resuscitation lactate concentration of more than 3-0 mmol/L alone with a positive likelihood ratio of 30 is associated with a probability of death of more than 90%.

To decrease the proportion of patients who die without identification as transplantation candidates, any criteria used must have a lower negative likelihood ratio than the currently used criteria, but an equivalent or better positive likelihood ratio. The simple addition of early and postresuscitation lactate concentrations to the KCH criteria improved speed of identification and negative likelihood ratio but decreased positive likelihood ratio.

Thus the combination of the KCH criteria and postresuscitation lactate concentrations to the KCH criteria improved speed of identification and negative likelihood ratio but decreased positive likelihood ratio. The combination of the KCH criteria and postresuscitation lactate concentrations to the KCH criteria, this combination has a lower negative likelihood ratio, resulting in a post-test probability of death in the validation sample of less than 2%.

These combined criteria do not address the second problem with the use of the KCH criteria—identification of patients too late for successful transplantation. For a time advantage to be obtained, any criteria used must include early lactate values, with consequent loss of time advantage to be obtained, any criteria used must include early lactate values, with consequent loss of positive likelihood ratio. An alternative strategy would be to use early lactate values as part of risk stratification. Patients with an early lactate concentration above 3-5 mmol/L can be viewed as being at high risk of subsequently meeting transplantation criteria, and early listing for transplantation should be considered. The practical delays in obtaining a graft are likely to mean that patients will meet formal criteria well before transplantation is undertaken. On the basis of this analysis, we propose modification of the KCH criteria (panel) to include blood lactate concentrations measured early in the course of and after completion of volume resuscitation.

We expect that this approach will further improve the speed and accuracy of selection of appropriate candidates for transplantation.

Contributors
W Bernal and J Wendon had the original idea for the study, W Bernal planned and coordinated the study and was responsible for data collection and initial analysis. N Donaldson did the statistical analysis, and J Wendon and D Wyncoll acted as data assessors. All the investigators were involved in the writing of the paper.

Conflict of interest statement
None declared.

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Proposed modification of the KCH criteria for transplantation in paracetamol-induced acute liver failure

Strongly consider listing for transplantation if:
- Arterial lactate concentration is above 3-5 mmol/L after early fluid resuscitation.

List for transplantation if:
- Arterial pH is below 7-3 or arterial lactate concentration is above 3-0 mmol/L after adequate fluid resuscitation;

or concurrently
- serum creatinine is above 300 μmol/L, INR is above 6-5, and there is encephalopathy of grade 3 or greater.

INR=international normalised ratio.
References


