

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

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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 blood 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 negative likelihood ratio from 0.25 to 0.10.

Interpretation Arterial blood lactate measurement rapidly and accurately identifies patients who will die from paracetamol-induced acute liver failure. Its use could improve the speed and accuracy of selection of appropriate candidates for transplantation.

Lancet 2002; **359**: 558–63

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Introduction

Acute liver failure resulting from severe hepatotoxic effects of paracetamol is a short intense illness, with rapid progression from initial hepatic failure to involvement of multiple organ systems, with acute renal failure, haemodynamic instability, and encephalopathy.^{1,2} In patients with advanced acute liver failure, the only therapy of proven benefit is emergency transplantation.^{2,3} Current clinical management of paracetamol-induced acute liver failure therefore relies on early identification and transplantation for those patients who will die without it, and the provision of supportive medical care to those in whom a spontaneous recovery of liver function is possible.^{2,4}

Although there are no standard clinical selection criteria for transplantation in use worldwide, the King's College Hospital (KCH) criteria⁵ are the most widely applied.^{3,6} Validation studies have consistently shown that without transplantation, survival in patients who meet the KCH criteria is less than 15%.^{6–9}

However, most of the patients who meet these criteria do not undergo transplantation.⁹ At the time of fulfilling the criteria, many patients are already too unwell for transplantation to be contemplated, and a substantial proportion of those listed for transplantation deteriorate before grafts become available.^{9,10} Furthermore, although the KCH criteria seem to have a clinically acceptable specificity in identifying patients with a poor prognosis, their sensitivity may be limited, in that they fail to identify a significant proportion of those who will die.^{6,9,11} Earlier, more accurate identification of patients who require transplantation is therefore important if survival is to be improved.

In critical illness other than acute liver failure, prolonged high blood lactate concentrations are associated with a poor prognosis.^{12–15} Hyperlactataemia in this setting has been accepted as a marker of systemic tissue dysoxia or microcirculatory perfusion abnormalities and increased anaerobic metabolism.^{15,16} Since circulating lactate is metabolised mainly by the liver, high blood lactate concentrations may also reflect decreases in clearance secondary to impaired hepatic function.^{16–18} The injured liver may itself also act as a source of lactate.¹⁹

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,⁴ 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,⁵ 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 after adequate fluid replacement. Evidence of irreversible brainstem dysfunction, major escalating inotrope 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 L-lactate concentration is 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

Feature	Sample	
	Initial (n=103)	Validation (n=107)
Demography		
Male/female	52/51	42/65
Age (years)*	35 (16–60)	36 (16–78)
Admission values*		
INR	3.40 (1.20–150)	2.93 (1.17–15.0)†
Creatinine (µmol/L)	145 (45–581)	136 (54–684)
pH	7.39 (6.93–7.52)	7.40 (6.96–7.50)
Lactate (mmol/L)	2.50 (0.53–21.0)	1.98 (0.5–26.5)‡
Outcome		
Died	36 (35%)	21 (20%)§
Survived	57 (55%)	78 (73%)
Transplanted	10 (10%)	8 (7%)

INR=international normalised ratio. *Median (range). Other data are number of patients. †p=0.02; ‡p=0.04; §p=0.025.

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

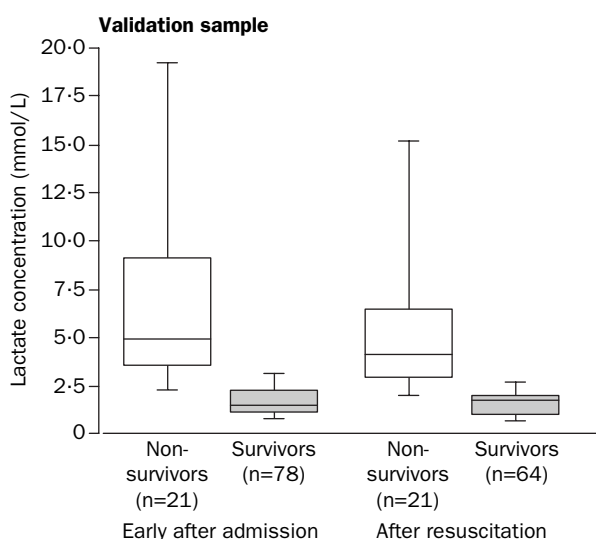
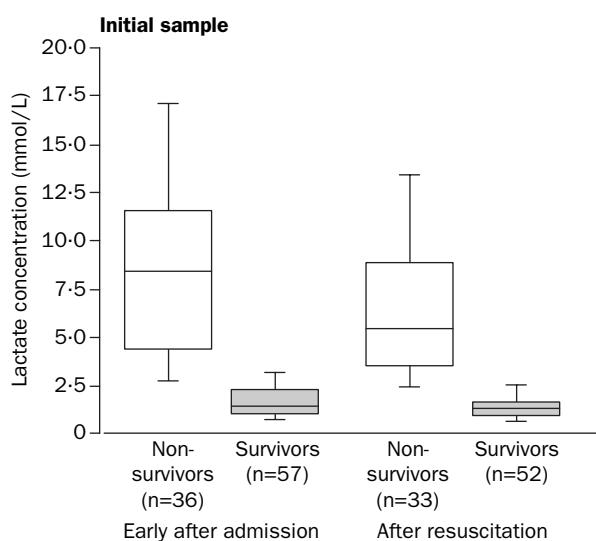
Predictor	Coefficient (95% CI)	p
pH	-7.5 (-11.8 to -3.3)	0.001
Temperature	-0.6 (-1.0 to -0.2)	0.004
Mean arterial pressure	-0.05 (-0.1 to -0.01)	0.01
INR	0.28 (0.1 to 0.5)	0.01
Serum creatinine	0.007 (0.002 to 0.01)	0.01

INR=international normalised ratio.

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

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.



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.

Predictor	Odds ratio (95% CI)	p
pH*	13.4 (2.7–66)	0.001
Encephalopathy grade†	10.8 (3.9–30)	<0.0001
Temperature	0.4 (0.2–0.6)	<0.0001
INR	2.4 (1.5–3.9)	0.0002
White-blood-cell count	1.2 (1.1–1.3)	0.002
Mean arterial pressure	0.9 (0.90–0.97)	<0.0001
Early lactate concentration	2.3 (1.6–3.3)	<0.0001
Postresuscitation lactate concentration	6.8 (2.7–18)	0.0001

INR=international normalised ratio. * >7.3 vs ≤ 7.3 . †Grades 0–2 vs grades 3–4.

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

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. On multivariate 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

Predictor	Odds ratio (95% CI)	p
Early lactate concentration		
pH*	13.4 (2.7–66)	0.001
Early lactate†	43 (9.1–201)	<0.0001
Postresuscitation lactate concentration		
pH*	11.6 (2.2–61)	0.004
Postresuscitation lactate‡	63 (10.4–385)	<0.0001

* >7.3 vs ≤ 7.3 . † >3.5 mmol/L vs ≤ 3.5 mmol/L. ‡ >3.0 mmol/L vs ≤ 3.0 mmol/L.

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

Indicator	n	Number of deaths	Sensitivity	Specificity	Accuracy	PLR	NLR	Time (h)*
Lactate criteria								
Early value >3.5 mmol/L	18	14	67	95	89	13	0.35	4 (3–6)†
Postresuscitation value >3.0 mmol/L	18	16	76	97	93	30	0.24	12 (7–13)
Either of these criteria	21	17	81	95	92	16	0.21	4 (3–13)‡
KCH criteria								
	20	16	76	95	91	15	0.25	10 (3–19.5)
KCH and either lactate criteria	27	20	95	91	92	11	0.05	4 (3–13)§
KCH and postresuscitation value >3 mmol/L	24	19	91	94	93	14	0.1	12 (3–19.5)

PLR=positive likelihood ratio; NLR=negative likelihood ratio. *Median (range) time from admission to criteria being fulfilled. For comparison with KCH criteria: †p=0.007; ‡p=0.01; §p=0.002.

Table 5: Assessment of arterial blood lactate measurement and King's College Hospital (KCH) criteria as prognostic indicators in 99 patients from validation sample

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 blood 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 3.3 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 ($p=0.13$).

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.^{15,16} 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,¹⁶ there is increasing evidence of the importance of hepatic clearance and of the effects of changes in hepatic metabolic capacity.^{20,21}

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.²² 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.¹⁷ 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.^{23,24}

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 had significant 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,^{25,26} 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 failure²⁷ 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.^{8,9,11} 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.^{7,9,11} Second, less than 50% of patients who meet the criteria undergo transplantation, primarily because of the development of clinical contraindications while awaiting transplantation.⁹

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

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 μ mol/L, INR is above 6.5, and there is encephalopathy of grade 3 or greater.

INR=international normalised ratio.

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 should 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 post-resuscitation lactate of 3.0 mmol/L seems to be the best compromise. Although it has a similar positive likelihood ratio 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%.²⁸

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 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.

Acknowledgments

We thank John O'Grady for his critical reading of the report, Eileen Withrington for editorial assistance, and the nursing and technical staff of the Liver Intensive Care Unit, King's College Hospital, for their help.

References

- 1 Williams R. Classification and clinical syndromes of acute liver failure. In: Lee W, Williams R, eds. *Acute liver failure*, 1st edn. Cambridge: Cambridge University Press, 1997: 1–9.
- 2 O'Grady J. Acute liver failure. In: O'Grady J, Lake J, Howdle P, eds. *Comprehensive clinical hepatology*, 1st edn. London: Mosby, 2000: 30.1–30.20.
- 3 Riordan S, Williams R. Use and validation of selection criteria for liver transplantation in acute liver failure. *Liver Transplant* 2000; **6**: 170–73.
- 4 Wendon J, Williams R. Acute liver failure. In: Williams R, Portmann B, Tan K, eds. *The practice of liver transplantation*. Edinburgh: Churchill Livingstone, 1995: 93–103.
- 5 O'Grady J, Alexander G, Hayllar K, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439–45.
- 6 Shakil A, Kramer D, Mazariegos G, Fung J, Rakela J. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. *Liver Transplant* 2000; **6**: 163–69.
- 7 Makin A, Wendon J, Williams R. A 7 year experience of severe acetaminophen-induced hepatotoxicity (1987–1993). *Gastroenterology* 1995; **109**: 1907–16.
- 8 Mitchell I, Bihari D, Chang R, Wendon J, Williams R. Earlier identification of patients at risk from acetaminophen induced acute liver failure. *Crit Care Med* 1997; **26**: 279–84.
- 9 Bernal W, Wendon J, Rela M, Heaton N, Williams R. Use and outcome of liver transplantation in acetaminophen induced acute liver failure. *Hepatology* 1998; **27**: 1050–55.
- 10 O'Grady J, Wendon J, Tan K, et al. Liver transplantation after paracetamol overdose. *BMJ* 1991; **303**: 221–23.
- 11 Anand AC, Nightingale P, Neuberger JM. Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria. *J Hepatol* 1997; **26**: 62–68.
- 12 Bakker J, Coffernils M, Leon M, Grils P, Vincent J-L. Blood lactate levels are superior to oxygen derived variables in predicting outcome in human septic shock. *Chest* 1991; **99**: 956–62.
- 13 Manikis P, Jankowski S, Zhang H, Khan R, Vincent J-L. Correlation of serial blood lactate levels to organ failure and mortality after trauma. *Am J Emerg Med* 1995; **13**: 619–22.
- 14 Bakker J, Gris P, Coffernils M, Khan R, Vincent J-L. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996; **171**: 221–26.
- 15 Mizock B, Falk J. Lactic acidosis in critical illness. *Crit Care Med* 1992; **20**: 80–93.
- 16 Subramanian S, Kellum J. The meaning of lactate. In: Vincent J-L, ed. *Yearbook of intensive care and emergency medicine*. Berlin: Springer-Verlag, 2000: 743–51.
- 17 Record C, Chase R, Williams R, Appleton D. Disturbances in lactate metabolism in patients with liver damage due to paracetamol overdose. *Metabolism* 1981; **30**: 638–43.
- 18 Almenoff P, Leavy J, Weil M, Goldberg N, Vega D, Racklow E. Prolongation of the half-life of lactate after maximal exercise in patients with hepatic dysfunction. *Crit Care Med* 1989; **17**: 870–73.
- 19 Clemmesen J, Hoy C, Kondrup J, Ott P. Splanchnic metabolism of fuel substrates in acute liver failure. *J Hepatol* 2000; **33**: 941–48.
- 20 Levraut J, Ciebiera J, Chave S, et al. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *Am J Respir Crit Care Med* 1998; **157**: 1021–26.
- 21 DeJonghe B, Cheval C, Misset B, et al. Relationship between blood lactate and early hepatic dysfunction in acute circulatory failure. *J Crit Care* 1999; **14**: 7–11.
- 22 Chiolero R, Tappy L, Gillet M, et al. Effect of major hepatectomy on glucose and lactate metabolism. *Ann Surg* 1998; **229**: 505–13.
- 23 Bihari D, Gimson A, Lindridge J, Williams R. Lactic acidosis in fulminant hepatic failure: some aspects of pathogenesis and prognosis. *J Hepatol* 1985; **1**: 405–16.
- 24 Bihari D, Gimson A, Waterson M, Williams R. Tissue hypoxia during fulminant hepatic failure. *Crit Care Med* 1985; **13**: 1034–39.
- 25 Gray T, Buckley B, Vale J. Hyperlactataemia and metabolic acidosis following paracetamol overdose. *QJM* 1987; **246**: 811–21.
- 26 Esterline R, Ray S, Ji S. Reversible and irreversible inhibition of hepatic mitochondrial respiration by acetaminophen and its toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). *Biochem Pharmacol* 1989; **38**: 2387–90.
- 27 Bihari D, Gimson A, Williams R. Cardiovascular, pulmonary and renal complications of fulminant hepatic failure. *Semin Liver Dis* 1986; **6**: 119–28.
- 28 Sackett D, Straus S, Richardson WS, Rosenberg W, Hayes R. *Evidence based medicine: how to practice and teach EBM*, 2nd edn. Edinburgh: Churchill Livingstone, 2000.