DR. LUCA CIOCCARI (Orcid ID : 0000-0003-4993-427X)

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The Outcome of Acetaminophen-Induced Acute Liver Failure managed without Intracranial Pressure Monitoring or Transplantation

Jennifer Porteous[1], Luca Cioccari[1-3], Paolo Ancona[1], Eduardo Osawa[1], Kelly Jones[1], Paul Gow[4], Peter Angus[4], Stephen Warrillow[1] and Rinaldo Bellomo[1,3]

[1]Department of Intensive Care, Austin Hospital, Melbourne, Victoria, Australia
[2]Department of Intensive Care Medicine, University Hospital, University of Bern, Switzerland
[3]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Prahran, Victoria, Australia
[4]Liver Transplant Unit, Austin Hospital, Melbourne, Victoria, Australia

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List of abbreviations:

4-H	'Quadruple-H': Hyperventilation, Hemodiafiltration, Hypothermia and Hypernatremia.
ALF	Acute Liver Failure
ANZROD	Australian And New Zealand Risk Of Death
APACHE	Acute Physiology And Chronic Health Evaluation
CVC	Central Venous Catheter
ICP	Intracranial Pressure
ICU	Intensive Care Unit
INR	International Normalized Ratio
IQR	Inter-Quartile Range
KCH	King's College Hospital
LT	Liver Transplantation
NAC	N-Acetylcysteine
SOFA	Sequential Organ Failure Assessment
UKRC	UK registration criteria for super-urgent liver transplantation

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Address correspondence to:
Prof. Rinaldo Bellomo
The University of Melbourne
Department of Intensive Care, Austin Hospital
145 Studley Rd, Heidelberg 3084
Australia
Email: rinaldo.bellomo@austin.org.au
Tel: +61-3-9496 5992
Fax: +61-3-94963932

Abstract

Background & Aims: Acetaminophen-induced acute liver failure (ALF) may require emergency liver transplantation (LT) in the presence of specific criteria, and its management may also include intracranial pressure (ICP) monitoring in selected patients at high risk of cerebral edema. We aimed to test the hypothesis that management of such patients without ICP monitoring or LT would yield outcomes similar to those reported with conventional management.

Methods: We interrogated a database of all patients treated in ICU for acetaminophen-induced ALF between November 2010 and October 2016 and obtained relevant information from electronic medical records.

Results: We studied 64 patients (58 females) with a median age of 38 years. Such patients had a high prevalence of depression, substance abuse or other psychiatric disorders and had ingested a median acetaminophen dose of 25g. No patient received ICP monitoring or LT. Overall, 51 (79.7%) patients survived. Of the 42 patients who met King's College Hospital (KCH) criteria, 29 (69.1%) survived without transplantation. Forty-five patients developed severe hepatic encephalopathy, and 32 (71.1%) of these survived. Finally, compared to KCH criteria, the current UK registration criteria (UKRC) for super-urgent LT had better sensitivity (92.3%) and specificity (80.4%) for hospital mortality.

Conclusions: In a center applying a no ICP monitoring and no LT approach to the management of acetaminophen-induced ALF, over six years, overall survival was 79.7% and for patients fulfilling KCH criteria 69.1%, both higher than for equivalent patients treated with conventional management as reported in the literature. Finally, the current UKRC may be a better predictor of hospital mortality in this patient population.

Introduction

Acetaminophen overdose is among the leading causes of acute liver injury in the USA, Australia and the UK, accounting for up to 74% of cases in some studies.(1-4) The majority of these patients are young.(5) Although most patients recover with the early administration of n-acetyl cysteine (NAC) and do not require intensive care unit (ICU) admission, some develop massive hepatic necrosis causing acute liver failure (ALF) characterized by jaundice, deranged clotting parameters and hepatic encephalopathy with the potential to develop cerebral edema. These patients are typically admitted to ICU and, in some centers, may receive intracranial pressure (ICP) monitoring and emergency liver transplantation (LT) in the presence of specific criteria.(6, 7) However, improvements in survival with medical therapy(8) suggest that the use of ICP monitoring may not be necessary and that some patients undergoing LT based on published criteria might now survive with medical management alone.(9)

Identification of patients at highest risk of death underpins the current guidelines for LT, with King's College Hospital (KCH) criteria being the most popular criteria for this purpose.(10) However, the performance of such prognostic criteria is limited due to an imbalance between sensitivity and specificity.(11) Subsequent modifications like the current UK registration criteria for super-urgent LT (UKRC)(12) have tried to address these imbalances, but the ideal prognostic model has not been established.

Moreover, the use of ICP monitoring in ALF is controversial and should only be considered in a highly selected subgroup of patients(13), as this practice is challenging in patients with clotting abnormalities and may not improve survival.(14)

At our institution, we have a restrictive policy with regards to ICP monitoring and LT for patients with acetaminophen-induced ALF. This is because of the potential for spontaneous recovery,(15) the high prevalence of psychiatric conditions(16) and the unclear benefit of invasive ICP monitoring in this unique patient population.(17) However, to date, few studies have reported

detailed analyses of patient-centered outcomes with standardized medical management of acetaminophen-induced ALF, in the absence of any surgical component to its management.

We hypothesized that the above highly restrictive approach to ICP monitoring and LT would yield outcomes similar to those reported with conventional management. To test this hypothesis, we studied all patients treated for acetaminophen-induced ALF and admitted to the ICU of our liver disease and transplantation referral center.

Methods

Study design and patient selection

We conducted a retrospective observational cohort study of adult patients admitted to our ICU with acetaminophen-induced acute liver injury between November 2010 and October 2016. The study was approved by Austin Hospital Human Research Ethics Committee (Ethics approval number LNR/17/Austin/460). The need for informed consent was waived.

Data collection

We reviewed the patients' medical records and obtained data from the Australian and New Zealand Intensive Care Society Adult Patient Database,(18) extracting demographic data such as age, gender, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II and III score, Australian and New Zealand Risk of Death (ANZROD),(19) referral site, time of ingestion, acetaminophen dose, staggered ingestion, serum acetaminophen concentration and contraindications to LT. Data regarding treatment and monitoring, hemodynamic and laboratory data were collected daily for the first 7 days after admission to the ICU of our liver transplant referral center. Outcome data included ICU and hospital mortality, cause of death, liver transplantation, blood transfusions, and complications such as major bleeding (defined as bleeding requiring angiographic, endoscopic or surgical intervention or transfusion of blood products), sepsis (defined as proven or suspected infection with signs of organ dysfunction), cerebral edema, bowel ischemia, and cerebrovascular events.

Medical management of ALF

According to our institutional protocol, intravenous NAC was administered to all patients until discharge from ICU. Medical management of ALF comprised a protocolled combination of four different treatment modalities referred to as the 'quadruple-H' (4-H) approach:(20) mild hyperventilation, high-dose hemodiafiltration, hypothermia and hypernatremia. Patients with Glasgow Coma Scale ≤ 8 and/or respiratory acidosis in the setting of severe encephalopathy (defined as encephalopathy grade ≥ 3) were intubated and mechanically ventilated to achieve a $PaCO_2$ between 32 and 35 mmHg. Noradrenaline infusion via a central venous catheter (CVC) was titrated to maintain a mean arterial pressure > 60 mmHg as continuously measured via an arterial catheter. The adjunctive use of intravenous hydrocortisone, vasopressin and the use of additional hemodynamic monitoring was at the discretion of the treating physician. In patients with severe hepatic encephalopathy (including all those who were intubated), oliguria, acidosis or hyperammonaemia (> 80 µmol/L), we use high-dose hemo(dia)filtration (40-60 ml/kg/h) with anticoagulant free circuits or prostacyclin anticoagulation. Mild hypothermia (target temperature of 35°C) was achieved by circulating the extra-corporeal circuit at room temperature or with external cooling. We targeted for a serum sodium concentration of 148-152 mmol/L, using a continuous infusion of hypertonic saline (20% NaCl via CVC) as required. The presence or absence of cerebral edema was assessed by daily neurological examination for signs of intracranial hypertension, with additional cranial computed tomography (CCT) when clinically indicated. Of note, our institutional protocol suggests transfusion of fresh frozen plasma, cryoprecipitate or platelets for patients with severe coagulopathy (defined as INR > 5, fibrinogen < 0.8 g/L, and platelets < 20 x 10^9/L).

Statistics

Statistical analysis was performed using STATA software, version 14.2 (StataCorp, College Station, Texas). Continuous variables are expressed as medians with inter-quartile ranges (IQR), categorical variables as frequencies with percentages. Patients were stratified retrospectively using the modified

King's College Hospital (KCH) criteria for LT:(10, 21) Arterial pH <7.3 after volume resuscitation, blood lactate level >3.0 mmol/L at 12 hours after admission or the combined findings of encephalopathy grade 3 or higher, creatinine > 300 µmol/L (or hemodiafiltration within 24 hours of admission) and international normalized ratio (INR) of > 6.5. Patients were also stratified using the current UKRC for super-urgent LT(12): pH <7.25 more than 24 hours after overdose and after fluid resuscitation, blood lactate >5 mmol/l on admission and >4 mmol/l 24 hours later in the presence of hepatic encephalopathy, or the combined findings of encephalopathy grade 3 or higher, creatinine > 300 µmol/L and INR of > 6.5. Continuous data were compared using Mann-Whitney test. Categorical data were compared using Fisher's exact test. A p-value of < 0.05 was considered significant.

Results

Patient characteristics

We identified 64 patients treated in the ICU between November 2010 and October 2016. The majority of patients were females (90.6%), their median (IQR) age was 38 (32 – 47) years, and the majority had a history of depression, alcohol or illicit drug abuse or other psychiatric disorders (Table 1). Forty-two patients (65.6%) satisfied KCH criteria (the KCH group).

In the KCH group, 22 patients had severe acidosis, 34 had a lactate level > 3mmol/l at 12 hours after admission to our ICU, and 12 patients fulfilled the combined criteria of coagulopathy, encephalopathy and acute renal failure. The cumulative ingested dose of acetaminophen was 25 (14 – 43) grams, and the ingestion was staggered in 26 (44.1%) cases. More than 50% of all cases were accidental overdoses. Peak acetaminophen levels were significantly higher in the KCH group, as were illness severity scores (APACHE, SOFA, ANZROD) and blood levels of lactate, ammonia, INR and white cell counts.

Contraindications to LT were present in 23 patients (35.9%). Such contraindications included major psychiatric disorder or multiple suicide attempts in 10 patients (15.6%), ongoing alcohol or drug abuse in 6 patients

(9.4%), medical reasons in 3 patients (4.7%) and multiple or unspecified reasons in 4 patients (6.3%).

Interventions

In this study population, no patient received invasive ICP monitoring or LT. All patients received intravenous N-acetylcysteine, and the majority were treated with prophylactic antibiotics (90.6%), hemo(dia)filtration (75.0%) and hypertonic saline (71.9%). The proportion of patients requiring mechanical ventilation, vasopressor support and transfusion of blood products was higher in the KCH group compared to the non-KCH group (Table 2). In patients requiring mechanical ventilation, the mean PaCO2 over the first 10 days in ICU was 35 ± 4.9 mmHg in the KCH group and 36 ± 4.3 in the Non-KCH group. Invasive cardiac output monitoring was used in 12 (18.8%) patients, and jugular venous oxygen saturation was measured in 4 (6.2%) cases.

Outcomes

Of 64 patients treated for acetaminophen-induced ALF, 51 (79.7%) patients survived and 13 (20.3%) patients died. The majority of deaths occurred within the first two weeks of ICU admission (Figure 1). In the KCH group, 29/42 (69.1%) survived with medical management. In predicting hospital mortality, the KCH criteria had sensitivity [95% CI] of 100.0 [75.3 – 100.0] % and specificity of 43.1 [29.3 – 57.8)] %. In total, 45 (70.3%) patients developed severe hepatic encephalopathy (≥ grade 3), 32 (71.1%) of whom survived.

Overall, the most common complications were sepsis (37.5%) and major bleeding (26.6%). The most common sources of sepsis were bloodstream infections (33.3%), abdominal (29.2%) and pulmonary infections (20.8%). Blood cultures were positive for bacteria in 11 patients (45.8%), and for Candida species in 3 patients (12.5%). Major bleeding occurred from the upper and lower gastrointestinal tract (29.4% each), from vascular access sites (11.8%), from pulmonary (5.9%) or multiple sources (23.5%). The most common therapeutic interventions were transfusion of blood products (all bleeding patients), endoscopy (29.4%), surgery (11.8%) and angiographic embolization (5.9%). Bowel ischemia occurred in 3 patients (4.7%) and was

associated with sepsis in each case (Table 3). Compared with survivors, non-survivors had significantly higher illness severity scores, degree of encephalopathy, lactate levels and white cell counts, and were more likely to require noradrenaline at ICU admission (Table 4).

Of the 13 patients who died, 11 (91.7%) had documented relative contraindications to LT, the majority being refractory psychiatric disorders or severe multi-organ failure. Causes of death included overwhelming sepsis (8 patients, 61.5%), multi-organ failure without proven sepsis (3 patients, 23.1%), ischemic bowel and major ischemic stroke (1 case each). Clinical findings and available CCT images suggest that no patient died of cerebral edema–induced tonsillar herniation. The two patients who died despite not having contraindications to LT (both in the KCH group) deteriorated rapidly within 48 hours of ICU admission and died of refractory shock.

UK registration criteria for super-urgent liver transplantation (UKRC)

Twenty-two patients (34.4%) fulfilled the UKRC and 12 of them (54.6%) died (Table 5). Sensitivity for hospital mortality using UKRC criteria was 92.3% (64.0 – 99.8%) and specificity was 80.4% (66.9 – 90.2%). Of note, in the UKRC-negative group, 20 patients fulfilled KCH criteria, but only one of them died.

Discussion

Key findings

In this study of patients treated for acetaminophen-induced ALF, no patient received ICP monitoring or liver transplantation. In this setting, no patient died of cerebral-edema-induced tonsillar herniation. Moreover, 79.7% of patients survived with medical management alone, and, of those fulfilling KCH criteria, 69.1% survived. Finally, the application of the recently modified UKRC criteria resulted in higher sensitivity and specificity for hospital mortality.

Relationship to previous studies

Survival rates for ALF secondary to acetaminophen overdose are well documented in the literature. At King's College Hospital, hospital survival

between 1999 and 2008 in this population was 66%.(11) This is in accordance with a large, prospective, multi-center study from the United States,(22) and slightly higher than in earlier studies.(23) Other authors have reported higher survival rates up to 78%.(1, 2, 15, 24, 25) In summary, these studies suggest an overall survival of 51 to 78%. Our survival was 79.7%.

In patients fulfilling KCH criteria, survival rates vary from 19% to 68% with LT,(2, 22, 23, 25, 26) and from 6% to 52% without LT.(2, 8, 25) In our study, survival in the KCH group was 69.1% without LT.

No patient received invasive ICP monitoring during the study period. This practice is divergent from previous literature (27, 28) and in accordance with modern recommendations.(13) Mortality of patients with severe hepatic encephalopathy has been reported between 23 and 50%.(14, 28) In our cohort, 71.1% of patients with severe hepatic encephalopathy survived without invasive ICP monitoring. This is comparable to the survival of patients treated with ICP monitoring and LT, which have a reported 10% complication rate.(27)

Several prognostication criteria have been developed to identify patients who are at high risk of death from acetaminophen induced ALF. The original KCH criteria for acetaminophen-induced ALF have a low pooled sensitivity (58%) and high pooled specificity (95%), in predicting mortality.(29) Using the arterial lactate modifications to the KCH criteria, our data confirm improved sensitivity, but lower specificity,(21) whereas, when applying the current UKRC, sensitivity and specificity were substantially higher.

Finally, in contrast to current recommendations and practice,(7, 13) a substantial proportion of our patients received blood products, including coagulation factors (Table 2). However, in our cohort, bleeding complications were common and severe in 26.6% of patients, which may, in part, explain this finding. Moreover, at our institution, prophylactic transfusions of blood products are used in patients with severe coagulopathy.

Implications of study findings

Our results provide further evidence that medical management as described in this unique group of patients, applied in the absence of ICP-monitoring, does not appear to expose patients to increased risk of cerebral edema or death. Moreover, they imply that a highly conservative treatment approach in this setting may lead to outcomes equivalent to those of centers that apply LT. In patients fulfilling KCH criteria and in those with severe encephalopathy, our mortality was comparable to any reported series. Like the KCH criteria, many prognostic tools may, therefore, not reflect recent improvements in outcome with medical management of acetaminophen overdose. In the United Kingdom, this has resulted in further modification of the criteria for super-urgent liver transplantation,(12) and the current UKRC may be a better predictor of mortality in this patient population.

Recent improvements in survival with medical therapy(8) suggest that some patients undergoing liver transplantation based on existing criteria might have survived with medical management alone. Importantly, the risk of death after LT remains significant (30) when compared with spontaneous recovery. In this context, our findings support the assertion that standardized medical management may be appropriate for most patients with acetaminophen-induced ALF, and that the role for LT in in this setting requires re-evaluation.(9, 11)

Strengths and limitations

Our study has several strengths. It provides novel and granular information on the modern outcome of acetaminophen-induced ALF in the absence of any surgical component to its management. It reports data from an Australian state referral center for patients with ALF irrespective of their suitability for liver transplantation. All patients were treated according to our institutional protocol, ensuring consistency and homogeneity in medical management, thereby increasing internal validity. Moreover, referral and admission criteria remained unchanged during the study period, further reducing patient heterogeneity, which may have been a problem in previous studies.(31, 32) Finally, definitions of ALF, KCH and UKRC, are objectively verifiable, and

cerebral edema and mortality are patient-centered outcomes, unlikely to be affected by selection, ascertainment and performance bias.

Our study has the inherent limitations of retrospective observational studies. However, acetaminophen-induced ALF is a relatively rare disease and its diagnosis is rarely in question. Furthermore, all outcome data were extracted from the Australian and New Zealand Intensive Care Society Adult Patient Database, a high-quality, published and monitored database.(18) Our study population is limited in size, and, therefore, we were not able to perform extensive exploratory analyses to identify predictors of outcome. However, our key observations are clear and the outcomes reported are objective and patient-centered. Finally, we describe the outcomes in the setting of a particular approach to treatment (so-called 4-H therapy). As such, our results may not apply to centers that do not use such an approach.

Conclusion

In a center applying a restrictive transplantation policy to the treatment of acetaminophen-induced ALF over six years, no patient received intracranial pressure monitoring or LT. However, overall survival was 79.7% and survival for patients fulfilling KCH criteria was higher than in equivalent patients treated in a more liberal transplantation setting. These findings suggest that a restrictive approach to ICP monitoring and LT may be at least equivalent to conventional management in terms of patient outcomes. Finally, the current UKRC may be a better predictor of mortality in patients with acetaminophen-induced ALF.

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Figure legends

Figure 1 – Cumulative survival of patients admitted to the ICU with acetaminophen-induced acute liver failure, censored at day 30 after ICU admission.

KCH: Patients fulfilling King's College Hospital criteria for liver transplantation.
Non-KCH: Patients not fulfilling KCH criteria

Table 1 – Characteristics of 64 patients treated for acetaminophen-induced acute liver failure.

Patient characteristics	Non-KCH	KCH group	Total	P
Number of patients	22 (34.4)	42 (65.6)	64 (100.0)	-
Age, years	39 (33 - 47)	38 (31 - 45)	38 (32 - 47)	0.62
Female gender	19 (86.4)	39 (92.9)	58 (90.6)	0.41
APACHE II score	13 (8 - 18)	20 (13 - 25)	18 (10 - 23)	0.001
APACHE III score	53 (37 - 76)	78 (61 - 105)	73 (53 - 92)	<0.001
ANZROD	0.21 (0.09 - 0.37)	0.44 (0.19 - 0.70)	0.31 (0.13 - 0.52)	0.003
SOFA score	8 (4 - 9)	11 (8 - 14)	10 (6 - 13)	<0.001
Comorbidities				
Depression	12 (54.6)	29 (69.1)	41 (64.1)	0.25
Substance abuse	5 (22.7)	11 (26.2)	16 (25.0)	>0.99
Alcohol abuse	8 (36.4)	12 (28.6)	20 (31.3)	0.52
Psychiatric disorder	7 (31.8)	13 (31.0)	20 (31.3)	0.94
Overdose characteristics				
Accidental overdose	13 (59.1)	21 (50.0)	34 (53.1)	0.49
Staggered ingestion	10 (45.4)	16 (43.2)	26 (44.1)	0.87
Delay to ICU admission, days	3.9 (2.1 – 8.0)	2.4 (1.8 - 3.7)	2.6 (1.8 - 4.7)	0.06
Ingested acetaminophen dose, g	24 (12 - 50)	25 (15 - 40)	25 (15 - 43)	0.81
Highest acetaminophen level, µmol/L	30 (30 - 264)	226 (83 - 749)	180 (30 - 532)	0.02
Physiology at ICU admission				
pH	7.4 (7.4 - 7.5)	7.3 (7.2 - 7.4)	7.4 (7.3 - 7.4)	<0.001
Lactate, mmol/L	2.4 (1.8 - 3.3)	7.1 (4.3 – 10.0)	4.5 (2.5 - 7.8)	<0.001
ALT, U/L	5388 (2848 - 8420)	5890 (2552 - 8413)	5877 (2552 - 8420)	0.93
GGT, U/L	182 (85 - 288)	134 (60 - 289)	155 (73 - 288)	0.36
ALP, U/L	111 (79 - 161)	123 (101 - 156)	116 (90 - 157)	0.50
Bilirubin, µmol/L	70 (39 - 107)	70 (53 - 96)	70 (53 - 99)	0.99
Creatinine, µmol/L	134 (55 - 248)	144 (90 - 229)	143 (83 - 246)	0.65
Urea, mmol/L	7.3 (3.8 – 13.0)	6.2 (3.5 - 9.7)	6.3 (3.5 - 9.9)	0.34
INR	3.3 (2.1 - 4.4)	4.4 (3.3 - 5.8)	4.1 (2.6 - 5.6)	0.005

Fibrinogen, g/L	1.8 (1.4 - 2.5)	1.4 (1.1 - 1.7)	1.4 (1.2 - 2.4)	0.07
Hemoglobin, g/L	115 (107 - 131)	111 (96 - 131)	114 (101 - 131)	0.38
White cell count, x 10^9/L	9.9 (5.1 – 14.0)	13.0 (6.8 – 19.0)	11.0 (6.1 – 17.0)	0.04
Platelet count, x 10^9/L	152 (113 - 183)	149 (106 - 224)	149 (106 - 208)	0.85
Ammonia level, µmol/L	80 (60 - 104)	142 (92 - 176)	112 (74 - 159)	<0.001
Hepatic encephalopathy at ICU admission, grade				0.006
Grade 0	12 (54.6)	5 (11.9)	17 (26.6)	
Grade 1	2 (9.1)	4 (9.5)	6 (9.4)	
Grade 2	2 (9.1)	6 (14.3)	8 (12.5)	
Grade 3	1 (4.6)	4 (9.5)	5 (7.8)	
Grade 4	5 (22.7)	23 (54.8)	28 (43.8)	

Values are presented as median (IQR) or n (%). KCH: King's College Hospital; APACHE: Acute Physiology And Chronic Health Evaluation; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ANZROD: Australian and New Zealand Risk of Death mortality prediction model; GGT: Gamma-glutamyl transferase; ICU: Intensive Care Unit; INR: International Normalized Ratio; SOFA: Sequential Organ Failure Assessment.

Table 2 – Therapeutic interventions

Intervention	Non-KCH	KCH group	Total	P
N-Acetylcysteine	22 (100.0)	42 (100.0)	64 (100.0)	-
Noradrenaline	6 (27.3)	31 (73.8)	37 (57.8)	<0.001
NaCl 20%	9 (40.9)	37 (88.1)	46 (71.9)	<0.001
Haemodiafiltration	10 (45.5)	38 (90.5)	48 (75.0)	<0.001
Mechanical ventilation	8 (36.4)	35 (83.3)	43 (67.2)	<0.001
Antibiotics	17 (77.3)	41 (97.6)	58 (90.6)	0.02
Cardiac output monitoring	3 (13.6)	9 (21.4)	12 (18.8)	0.52
Jugular venous oximetry	0 (0.0)	4 (9.5)	4 (6.2)	0.29
Transfusions				
Red blood cells	8 (36.4)	35 (83.3)	43 (67.2)	<0.001
Fresh frozen plasma	4 (18.2)	32 (76.2)	36 (56.2)	<0.001
Cryoprecipitate	2 (9.1)	26 (61.9)	28 (43.8)	<0.001
PCC	0 (0.0)	7 (16.7)	7 (10.9)	0.09
Platelets	2 (9.1)	25 (59.5)	27 (42.2)	<0.001

Values are presented as n (%). KCH: Patients with King's College Hospital Criteria for transplantation. PCC: Prothrombin complex concentrate.

Table 3 – Clinical outcomes of 64 patients with acetaminophen-induced acute liver injury

Outcomes	Non-KCH	KCH group	Total	P
Mortality				0.003
Died	0 (0.0)	13 (31.0)	13 (20.3)	
Survived	22 (100.0)	29 (69.0)	51 (79.7)	
Length of stay				
ICU	3 (1.8 – 6.0)	9.8 (4.5 – 17.0)	6.3 (2.3 – 13.0)	<0.001
Hospital	9.0 (5.0 – 13.0)	16.0 (6.0 – 27.0)	12.0 (5.5 – 19.0)	0.03
Complications				
Sepsis	1 (4.6)	23 (54.8)	24 (37.5)	<0.001
Bowel ischemia	0 (0.0)	3 (7.1)	3 (4.7)	0.54
Stroke	1 (4.6)	2 (4.7)	3 (4.7)	>0.99
Major bleeding	1 (4.6)	16 (38.1)	17 (26.6)	0.003

Values are presented as median (IQR) or n (%). Major bleeding defined as bleeding requiring angiographic, endoscopic or surgical intervention. ICH: Intracranial hemorrhage; ICU: Intensive Care Unit; KCH: Patients with King's College Hospital Criteria for transplantation.

Table 4 – Comparison of survivors and non-survivors

	Non-survivors	Survivors	Total	P
Number of patients	13 (20.3)	51 (79.7)	64 (100.0)	
Age	35 (33 - 43)	38 (31 - 47)	38 (32 - 47)	0.90
Female gender	11 (84.6)	47 (92.2)	58 (90.6)	0.59
APACHE III SCORE	125 (92 - 138)	64 (45 - 81)	73 (53 - 92)	<0.001
ANZROD	0.77 (0.54 - 0.87)	0.25 (0.11 - 0.45)	0.31 (0.13 - 0.52)	<0.001
SOFA score	15 (12 - 17)	9 (5 - 10)	10 (6 - 13)	<0.001
Mechanical ventilation	13 (100.0)	30 (58.8)	43 (67.2)	0.006
Vasopressor need	10 (76.9)	11 (21.6)	21 (32.8)	<0.001
KCH criteria fulfilled	13 (100.0)	29 (56.9)	42 (65.6)	0.003
Contraindications to LT, n=52	11 (91.7)	12 (26.7)	23 (40.4)	<0.001
Overdose characteristics				
Accidental overdose	4 (30.8)	30 (58.8)	34 (53.1)	0.12
Staggered ingestion	1 (10.0)	25 (51.0)	26 (44.1)	0.03
Ingested acetaminophen dose, g	37 (15 - 43)	24 (15 - 42)	25 (15 - 43)	0.66
Peak acetaminophen level, µmol/L	544 (162 - 809)	134 (30 - 322)	180 (30 - 532)	0.02
Physiology				
pH at admission	7.16 (7.05 - 7.27)	7.39 (7.30 - 7.46)	7.37 (7.26 - 7.44)	<0.001
Lowest pH	7.08 (6.97 - 7.27)	7.36 (7.30 - 7.41)	7.34 (7.26 - 7.40)	<0.001
Lactate at admission, mmol/L	12.4 (8.6 - 20.0)	3.5 (2.2 - 6.3)	4.5 (2.5 - 7.6)	<0.001
Peak Lactate, mmol/L	20.0 (10.6 - 22.0)	4.2 (2.7 - 7.6)	5.0 (3.0 - 8.6)	<0.001
INR at admission	4.8 (3.6 - 6.9)	4.1 (2.5 - 4.6)	4.1 (2.6 - 5.6)	0.11
Peak INR	5.8 (4.6 - 7.7)	4.4 (2.5 - 6.4)	4.5 (3.2 - 6.5)	0.05
WCC at admission, x 109/L	19.4 (10.7 - 27.7)	10.0 (5.8 - 15.7)	10.7 (6.1 - 17.4)	0.005

Peak WCC, x 109/L	20.7 (13.4 - 27.7)	13.5 (10.0 - 19.6)	14.9 (10.3 - 21.7)	0.03
Ammonia level at admission, µmol/L	155 (96 - 176)	111 (73 - 148)	112 (74 - 159)	0.11
Peak Ammonia, µmol/L	165 (118 - 176)	123 (89 - 182)	130 (94 - 180)	0.16
Peak ALT, U/L	7652 (6268 - 10548)	5877 (2848 - 9162)	6646 (3017 - 9299)	0.15
Peak Bilirubin, µmol/L	163 (123 - 346)	144 (73 - 245)	151 (77 - 248)	0.28
Peak Creatinine, µmol/L	210 (169 - 317)	148 (97 - 264)	167 (102 - 280)	0.06
Peak Urea, mmol/L	9.6 (4.2 - 11.0)	9.4 (4.5 - 14.6)	9.5 (4.4 - 12.5)	0.49
Encephalopathy grade				0.004
Grade 0	0 (0.0)	15 (31.2)	15 (25.0)	
Grade 1	0 (0.0)	6 (12.5)	6 (10.0)	
Grade 2	0 (0.0)	8 (16.7)	8 (13.3)	
Grade 3	2 (16.7)	3 (6.2)	5 (8.3)	
Grade 4	10 (83.3)	16 (33.3)	26 (43.3)	
KDIGO				0.02
Stage 0	3 (23.1)	33 (64.7)	36 (56.2)	
Stage 1	2 (15.4)	5 (9.8)	7 (10.9)	
Stage 2	4 (30.8)	6 (11.8)	10 (15.6)	
Stage 3	4 (30.8)	7 (13.7)	11 (17.2)	
Complications				
Sepsis	9 (69.2)	15 (29.4)	24 (37.5)	0.01
Bowel ischemia	1 (7.7)	2 (3.9)	3 (4.7)	0.50
Stroke / ICH	2 (15.4)	1 (2.0)	3 (4.7)	0.10
Major bleeding	5 (38.5)	12 (23.5)	17 (26.6)	0.31

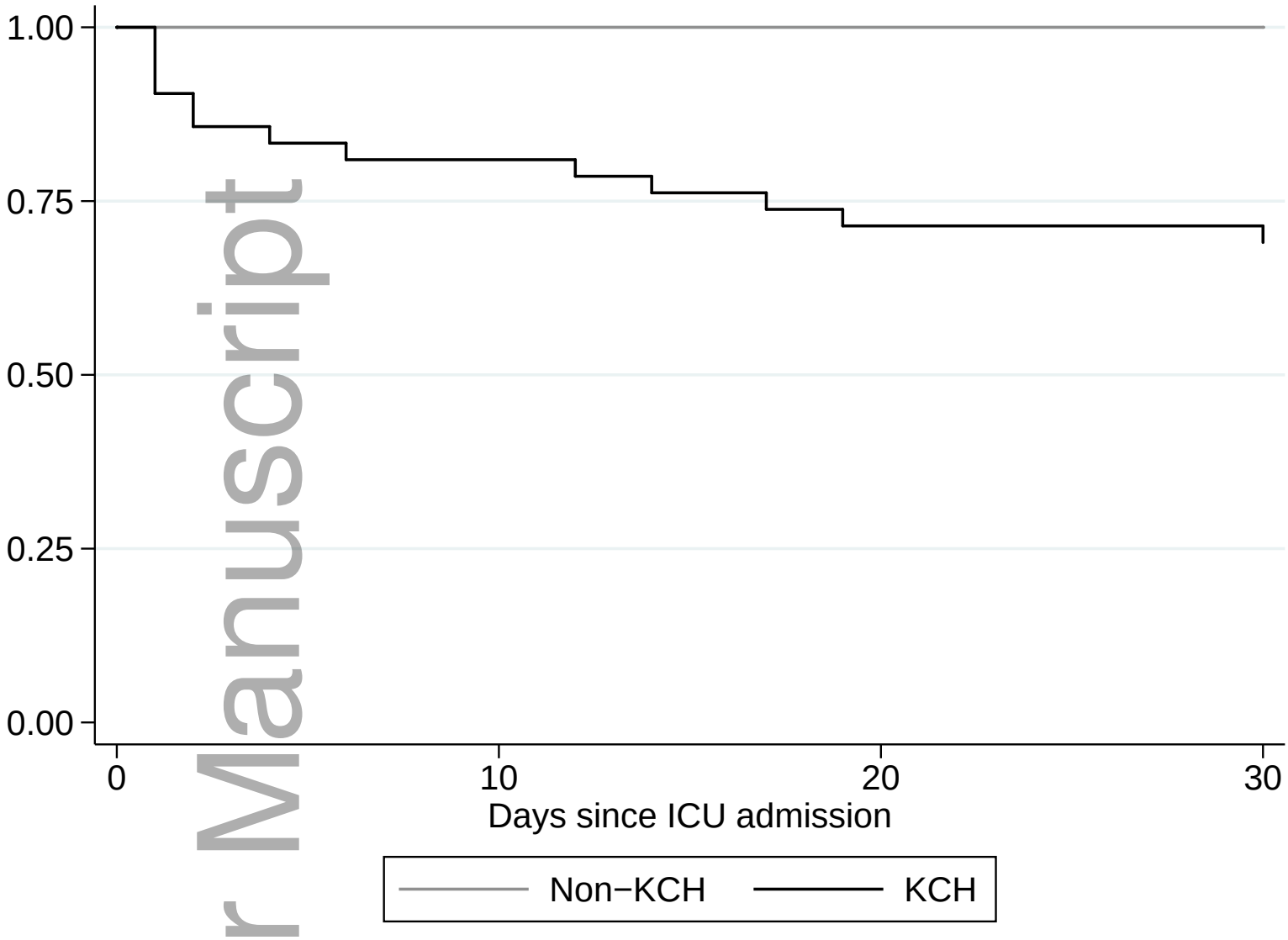
Values are presented as median (IQR) or n (%). APACHE: Acute Physiology And Chronic Health Evaluation; ANZROD: Australian and New Zealand Risk of Death mortality prediction model; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; ICH: Intracranial hemorrhage; ICU: Intensive Care Unit; LOS: Length of stay; INR: International Normalized Ratio; KCH: King's College Hospital; KDIGO: Kidney Disease Improving Global Outcomes classification of acute kidney injury; LT: Emergency liver transplantation; SOFA: Sequential Organ Failure Assessment; WCC: White cell count.

Table 5 - Clinical and laboratory characteristics according to the UK registration criteria for super-urgent liver transplantation (UKRC)

	UKRC negative	UKRC positive	Total	P
Number of patients	42 (65.6)	22 (34.4)	64 (100.0)	
Age	41 (33 - 48)	34 (21 - 41)	38 (32 - 47)	0.03
Gender				0.41
Male	3 (7.1)	3 (13.6)	6 (9.4)	
Female	39 (92.9)	19 (86.4)	58 (90.6)	
Accidental overdose	27 (64.3)	7 (31.8)	34 (53.1)	0.01
Staggered ingestion	22 (56.4)	4 (20.0)	26 (44.1)	0.01
Cumulative acetaminophen dose, g	25 (15 - 42)	25 (15 - 43)	25 (15 - 43)	0.98
APACHE III SCORE	63 (43 - 81)	91 (64 - 125)	73 (53 - 92)	<0.001
ANZROD	0.25 (0.11 - 0.44)	0.55 (0.26 - 0.81)	0.31 (0.13 - 0.52)	0.003
SOFA score	9 (5 - 10)	12 (9 - 15)	9.5 (6 - 13)	0.002
Mechanical ventilation	23 (54.8)	20 (90.9)	43 (67.2)	0.004
Vasopressor need	17 (40.5)	20 (90.9)	37 (57.8)	<0.001
KCH criteria fulfilled	20 (47.6)	22 (100.0)	42 (65.6)	<0.001
Contraindications to LT, n=52	9 (27.3)	14 (73.7)	23 (44.2)	0.002
Physiology				
pH at admission	7.4 (7.3 - 7.5)	7.3 (7.1 - 7.4)	7.4 (7.3 - 7.4)	0.004
Lactate at admission, mmol/L	3.3 (2.1 - 4.8)	8.6 (7.1 - 13.0)	4.5 (2.5 - 7.8)	<0.001
INR at admission	3.3 (2.3 - 4.4)	5.3 (4.1 - 7.0)	4.1 (2.6 - 5.6)	<0.001
WCC at admission, x 109/L	9.7 (5.2 - 14.0)	16.0 (10.0 - 26.0)	11.0 (6.1 - 17.0)	0.001
Ammonia level at admission, µmol/L	92 (73 - 141)	143 (96 - 165)	112 (74 - 159)	0.07
Peak acetaminophen level, mg/L	120 (30 - 322)	270 (108 - 809)	180 (30 - 532)	0.04
Peak Lactate, mmol/L	3.5 (2.7 - 5.2)	9.6 (7.7 - 21.0)	5.0 (3.0 - 8.8)	<0.001

Peak ALT, U/L	5175 (2552 - 8671)	7448 (5890 - 10340)	6646 (3017 - 9299)	0.04
Peak Bilirubin, µmol/L	117 (70 - 221)	232 (124 - 290)	151 (77 - 248)	0.02
Peak Creatinine, µmol/L	149 (94 - 266)	188 (123 - 294)	167 (102 - 280)	0.28
Peak Urea, mmol/L	9.7 (6.0 - 16.0)	6.6 (3.3 - 10.0)	9.4 (4.4 - 13.0)	0.02
Peak INR	3.8 (2.3 - 4.6)	7.2 (5.7 - 8.0)	4.5 (3.2 - 6.5)	<0.001
Peak WCC, x 109/L	13 (10 - 17)	20 (15 - 28)	15 (10 - 22)	0.006
Peak Ammonia, µmol/L	112 (75 - 173)	166 (118 - 193)	130 (94 - 180)	0.02
Lowest pH	7.4 (7.3 - 7.4)	7.2 (7.1 - 7.3)	7.3 (7.3 - 7.4)	<0.001
Encephalopathy grade				0.008
Grade 0	9 (21.4)	0 (0.0)	9 (14.1)	
Grade 1	6 (14.3)	0 (0.0)	6 (9.4)	
Grade 2	3 (7.1)	1 (4.6)	4 (6.2)	
Grade 3	1 (2.4)	1 (4.6)	2 (3.1)	
Grade 4	23 (54.8)	20 (90.9)	43 (67.2)	
Complications				
Sepsis	8 (19.1)	16 (72.7)	24 (37.5)	<0.001
Bowel ischemia	0 (0.0)	3 (7.1)	3 (4.7)	0.54
Stroke / ICH	1 (2.4)	2 (9.1)	3 (4.7)	0.27
Major bleeding	7 (16.7)	10 (45.4)	17 (26.6)	0.01
Mortality				<0.001
Died	1 (2.4)	12 (54.6)	13 (20.3)	
Survived	41 (97.6)	10 (45.4)	51 (79.7)	

Values are presented as median (IQR) or n (%). APACHE: Acute Physiology And Chronic Health Evaluation; ANZROD: Australian and New Zealand Risk of Death mortality prediction model; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; ICH: Intracranial hemorrhage; ICU: Intensive Care Unit; LOS: Length of stay; INR: International Normalized Ratio; KCH: King's College Hospital; LT: Emergency liver transplantation; SOFA: Sequential Organ Failure Assessment; WCC: White cell count.



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