Characteristics, management and outcomes of patients with acute liver failure admitted to Australasian intensive care units

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Acute liver failure (ALF), also referred to as fulminant hepatic failure, is an uncommon but devastating illness. It is defined by the onset of severe liver dysfunction within a period of less than 8 weeks in the setting of no previous known liver disease.[1] Regardless of the underlying cause of severe liver injury, a typical pattern of multiple organ failure generally ensues as hepatic function is lost. Severe metabolic disturbances, susceptibility to infection, vasodilatory shock and acute kidney injury are extremely common in severely affected patients.[2-5] Nearly all patients with ALF become critically ill and require admission to an intensive care unit (ICU).[6] While admissions for ALF account for less than 1% of patients cared for in Australian and New Zealand ICUs, it is an important condition because patients tend to be young, have few serious chronic illnesses and are at high risk of death.[7] The only intervention that demonstrably reduces mortality is emergency liver transplantation (ELT); however, this is a highly specialised service that is not available at most hospitals. In addition, ELT is limited by the availability of suitable organs for transplantation and necessitates lifelong immunosuppression. Despite the importance of this condition, little is known about the characteristics, treatment and outcomes of patients with ALF admitted to Australian and New Zealand liver transplantation centres. It is concerning that the incidence of ALF requiring ICU admission may be increasing and mortality may not have improved[7] despite increasing access to liver transplantation associated with better donation rates[8] and significant reductions in poor outcomes for other critically ill ICU patients.[9-11]

Accordingly, we conducted a detailed study of patients admitted to all Australian and New Zealand liver transplant centres. Our primary hypothesis was that patients with ALF admitted to ELT-capable Australian and New Zealand ICUs would have similar

ABSTRACT

Objective: Acute liver failure (ALF) leads to severe illness and usually requires admission to the intensive care unit (ICU). Despite its importance, little is known about patients with ALF in Australia and New Zealand.

Design: Binational observational study to evaluate the aetiology, baseline characteristics, patterns of illness, management, and outcomes for patients with ALF admitted to Australian and New Zealand ICUs.

Setting: All six Australian and New Zealand ICUs in liver transplant centres submitted de-identified data for ten or more consecutive patients with ALF. Data were obtained from the clinical record and included baseline characteristics, aetiology, mode of presentation, illness severity, markers of liver failure, critical care interventions, utilisation of transplantation, and hospital outcome.

Results: We studied 62 patients with ALF. Paracetamol overdose (POD) was the underlying cause of ALF in 53% of patients (33/62), with staggered ingestion in 42% of patients (14/33). Among patients with POD, 70% (23/33) were young women, most had psychiatric diagnoses, and most presented relatively early with overt liver failure. This group were transplanted in only 6% of cases (2/33) and had an overall mortality of 24% (8/33). The remaining patients with ALF had less common conditions, such as hepatitis B and non-paracetamol drug-induced ALF. These patients presented later and exhibited less extreme evidence of acute hepatic necrosis. Transplantation was performed in 38% of patients (11/29) in this subgroup. The mortality of non-transplanted non-POD patients was 56% (10/18). Illness severity at ICU admission, initial requirement for organ support therapies and length of hospital stay were similar between patients with POD and non-POD ALF.

Conclusion: POD is the major cause of ALF in Australian and New Zealand liver transplant centres and is a unique and separate form of ALF. It has a much lower associated mortality and treatment with liver transplantation than non-POD ALF. Non-POD patients have a poor prognosis in the absence of transplantation.

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Table 1. Patient characteristics prior to intensive care unit (ICU) admission at a liver transplant hospital

Variable	All	Paracetamol overdose	Non-paracetamol overdose	*P*
Total number of patients	62	33	29	
Age, median (IQR)	36 (28–47)	34 (28–44)	44 (29–52)	0.07
Female	36 (58%)	23 (70%)	13 (45%)	0.048
Any psychiatric or substance misuse	33 (53%)	27 (82%)	6 (21%)	< 0.0001
Depression/anxiety	20 (32%)	17 (52%)	3 (10%)	0.001
Schizophrenia	6 (10%)	6 (18%)	0 (0%)	0.026
Alcohol misuse	6 (10%)	4 (12%)	2 (7%)	0.68
Intravenous drug use	5 (8%)	4 (12%)	1 (3%)	0.36
Bipolar disorder	5 (8%)	4 (12%)	1 (3%)	0.36
Previous self-harm	4 (6%)	4 (12%)	0 (0%)	0.12
Personality disorder	2 (3%)	1 (3%)	1 (3%)	1.00
HBV carrier	5 (8%)	0 (0%)	5 (17%)	0.018
Hypertension	5 (8%)	1 (3%)	4 (14%)	0.18
Chronic pain syndrome	6 (10%)	5 (15%)	1 (3%)	0.20
Thyroid disease	5 (8%)	3 (9%)	2 (7%)	1.00
Asthma	5 (8%)	4 (12%)	1 (3%)	0.36
Diabetes	4 (6%)	3 (9%)	1 (3%)	0.62
Ischaemic heart disease	4 (6%)	3 (9%)	1 (3%)	0.62
Obesity	4 (6%)	1 (3%)	3 (10%)	0.33
Cancer	2 (3%)	2 (6%)	0 (0%)	0.49
HCV infection	1 (2%)	1 (3%)	0 (0%)	1.00
No documented comorbidities	17 (27%)	4 (12%)	13 (45%)	0.004
Contraindications to emergency liver transplantation	17 (27%)	11 (33%)	6 (21%)	0.26
Paracetamol overdose (all)	33 (53%)	-	-	
Paracetamol staggered	14 (23%)	14 (42%)	-	
Paracetamol single ingestion	19 (31%)	19 (58%)	-	
Paracetamol ingested dose known	-	29 (88%)	-	
Paracetamol ingested dose (g), median (IQR)	-	30 (8–42)	-	
Paracetamol level (mg/L)*, median (IQR)	-	40 (27–148)	-	
HBV new acquisition	5 (8%)	-	5 (17%)	
HBV flare of chronic	2 (3%)	-	2 (7%)	
Non-paracetamol drugs†	5 (8%)	-	5 (17%)	
Amanita poisoning	3 (5%)	-	3 (10%)	
Haemophagocytic lymphohistiocytosis syndrome	2 (3%)	-	2 (7%)	
Budd–Chiari syndrome	1 (2%)	-	1 (3%)	
Acute fatty liver of pregnancy	1 (2%)	-	1 (3%)	
Iatrogenic portal vein injury	1 (2%)	-	1 (3%)	
Leptospirosis	1 (2%)	-	1 (3%)	
Cryptogenic	7 (11%)	-	7 (24%)	
Presented to non-liver transplant unit hospital	45 (73%)	25 (76%)	20 (69%)	0.55
Presented to/transferred from tertiary hospital	37 (60%)	19 (58%)	18 (62%)	0.72
Transferred from community hospital	16 (26%)	8 (24%)	8 (28%)	0.76
Transferred from rural hospital	9 (14%)	6 (18%)	3 (10%)	0.48
Time from first presentation to admission to specialist transplant hospital ICU (h), median (IQR)	25 (8–49)	17 (6–34)	43 (19–112)	0.011

HBV = hepatitis B virus; HCV = hepatitis C virus, IQR = interquartile range. * Multiple by 6.62 to convert paracetamol units of measurement from mg/L to μmol/L. † Drugs involved include buprenorphine, agomelatine, infliximab, 3,4-methylenedioxymethamphetamine ("ecstasy" or MDMA) and methamphetamines.

Table 2. Clinical data and test results at the time of intensive care unit admission

Variable	All (median, IQR)	Paracetamol overdose (median, IQR)	Non-paracetamol overdose (median, IQR)	*P*
Total number of patients	62	33	29	
APACHE III score	77 (57–102)	73 (55–106)	81 (58–99)	0.64
APACHE III risk of death	0.32 (0.12–0.54)	0.26 (0.11–0.53)	0.40 (0.15–0.67)	0.23
Temperature (°C)	36.3 (35.6–36.9)	36.0 (35.3–36.9)	36.4 (36.0–36.9)	0.14
pH	7.41 (7.26–7.45)	7.35 (7.22–7.43)	7.43 (7.33–7.37)	0.01
CO_2 (mmHg)	31 (26–36)	30 (25–35)	32 (29–36)	0.18
Sodium (mmol/L)	137 (134–142)	138 (135–140)	137 (133–143)	0.83
Lactate (mmol/L)	4.9 (3.2–8.5)	7.2 (3.6–9.3)	4.1 (2.3–6.3)	0.03
Alanine aminotransferase (IU/L)	4020 (1800–6458)	5234 (3152–7569)	1987 (1217–5530)	0.005
γ-Glutamyltransferase (IU/L)	88 (55–180)	109 (59–188)	70 (55–145)	0.17
Alkaline phosphatase (IU/L)	129 (92–165)	119 (90–191)	137 (105–192)	0.26
Bilirubin (mmol/L)	75 (48–148)	61 (46–80)	148 (68–273)	0.001
Creatinine (μmol/L)	127 (68–231)	169 (93–266)	113 (56–189)	0.06
Urea (mmol/L)	6.5 (2.8–10.7)	7.8 (5.2–11.4)	3.4 (1.5–8.8)	0.034
INR	4.6 (3.2–6.8)	5.5 (3.8–9.2)	3.7 (2.5–5.5)	0.002
Activated partial thromboplastin time (s)	51 (43–66)	49 (40–64)	54 (46–68)	0.25
Fibrinogen (g/L)	1.4 (0.9–1.8)	1.4 (1.0–2.0)	1.3 (0.9–1.6)	0.60
Haemoglobin (g/L)	123 (100–137)	121 (100–130)	1240(100–140)	0.31
White cell count (10^9/L)	9.3 (6.8–15.0)	10.6 (7.0–15.9)	8.0 (6.6–14.6)	0.48
Platelets (10^9/L)	131 (82–194)	130 (84–206)	137 (80–157)	0.98
Ammonia (μmol/L)*	119 (82–170)	133 (84–187)	108 (81–141)	0.40

APACHE = Acute Physiology and Chronic Health Evaluation; INR = international normalised ratio. * Reference interval, 35–60 μmol/L.

causes, baseline characteristics, and patterns of critical illness to those described in studies from comparable regions. Our secondary hypothesis was that there would be less frequent utilisation of ELT in Australia and New Zealand, but that clinical outcomes would be similar to those of comparable settings where there is access to comprehensive critical care services and mature liver transplant programs. Finally, we hypothesised that ALF from paracetamol overdose (POD) would be common and would have a pattern of presentation, clinical course and outcome that is distinctly different from other causes of ALF.

Method

Study design

We conducted a binational observational study in which the ICUs from all six Australian and New Zealand hospitals that provide adult liver transplantation services were invited to submit detailed de-identified clinical data relating to a series of the last ten adult patients admitted to ICU for management of ALF, using a standardised collection tool. The six hospitals were: Austin Health (Melbourne, VIC, Australia), Sir Charles Gairdner Hospital (Perth, WA, Australia), Royal Prince Alfred Hospital (Sydney, NSW, Australia), Flinders Medical Centre (Adelaide, SA, Australia), Princess Alexandra Hospital (Brisbane, QLD, Australia) and Auckland City Hospital (Auckland, New Zealand). All are university-affiliated academic teaching hospitals that provide a statewide (or nationwide in the case of New Zealand) liver transplant service. Information for each patient was obtained from the patient's clinical record and only included data that were routinely documented as part of usual patient care. Local requirements governing the collection and collaborative sharing of de-identified clinical data for research purposes were adhered to at each participating site. Ethics approval from Austin Health was obtained (LNR/14/Austin/676) and, depending on local requirements, either a Memoranda of Understanding or a Clinical Trials Research Agreement was

implemented where required by participating sites to support the sharing of data with the principal investigator. Each ICU submitted ten or more consecutive patients coded as ALF in Acute Physiology and Chronic Health Evaluation (APACHE) III diagnostic code 301.01, with onset of overt liver failure over a period of less than 8 weeks in the absence of known pre-existing liver disease.

Variables collected included gender, age, comorbidities, cause of ALF, time to first presentation for medical care, time to ICU admission, APACHE III illness severity score, vital signs, key biochemical and haematological test results, provision of physiological support, fluid balance, blood product administration, duration of ICU stay and patient outcomes including death and ELT. A sample size of 60 patients was decided upon on the basis of convenience and feasibility. The selection of at least ten consecutive patients from each site, regardless of outcome or aetiology of ALF, was undertaken to achieve a representative sample of ALF presentations. The design and reporting of this study is aligned with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[12] A search of the MEDLINE database for observational studies of ALF in adults was undertaken to assist with the interpretation of findings from the analysis of Australasian data.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics for Macintosh, version 25 (IBM Corporation, Armonk, NY, USA). Continuous variables are expressed as medians with interquartile ranges (IQR); categorical variables are expressed as frequencies with percentages. Continuous data were compared using Mann–Whitney test. Categorical data were compared using χ^2 analysis or Fisher exact test where appropriate. Kaplan–Meier and Mantel–Cox log rank analyses were performed to assess differences in survival and utilisation of ELT between groups. A *P* value of less than 0.05 was considered significant.

Results

Patient characteristics before ICU admission

A total of 62 patients from across the six transplant centres over the period 2012–2016 were evaluated (Table 1). Most patients were women (36/62) and the median age was 36 years (IQR, 28–47 years). Overall, slightly more than half of patients (33/62) had a past history of psychiatric problems or substance misuse. Other important comorbidities included prior hepatitis B virus and hepatitis C virus infections. More than a quarter of patients (17/62) had no pre-existing chronic medical problems documented. Twenty-seven per cent of patients (17/62) were deemed ineligible for ELT by treating clinicians on the basis of comorbid conditions and/or extreme illness severity at presentation.

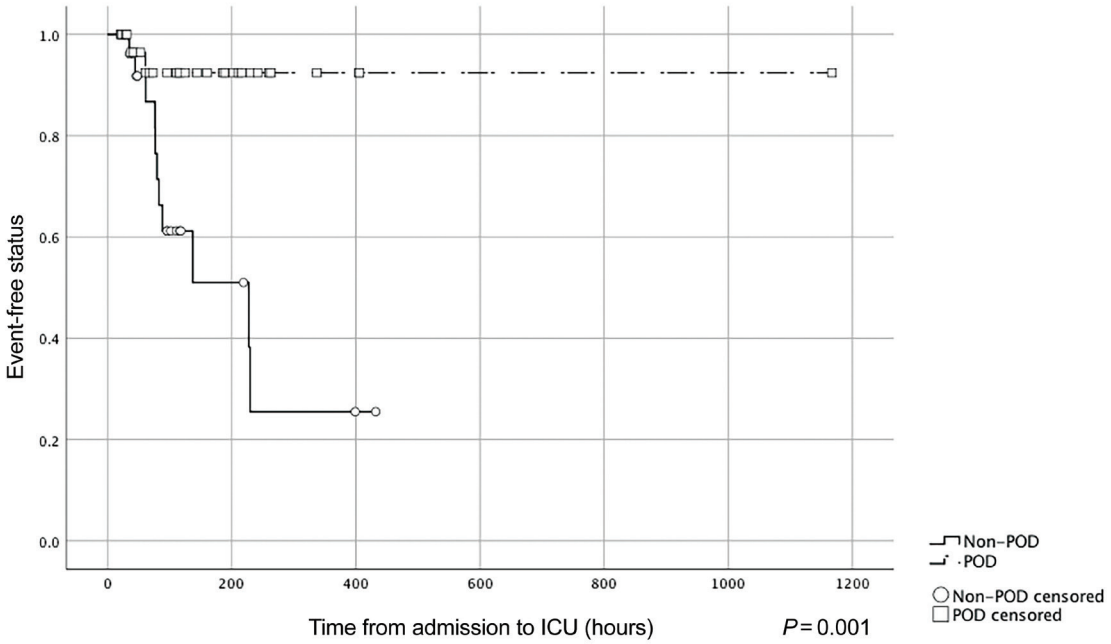
The cause of ALF was identified by treating clinicians in 89% of cases (55/62). Slightly more than half of ALF cases were due to POD (33/62), of which 58% (19/33) were from a single major overdose, while the remainder (14/19) were due to the ingestion of multiple supratherapeutic doses with an interval period of more than 8 hours ("staggered overdose").[13] The total ingested dose of paracetamol was known or reliably estimated in 88% of POD patients (29/33), with a median of 30 g (IQR, 8–42 g). At the time of admission to ICU, the median paracetamol concentration in blood of those with ALF secondary to paracetamol was 40 mg/L (265 μmol/L) (IQR, 27–148 mg/L). Hepatitis B virus infection caused ALF in 11% of patients (7/62), with most being newly acquired infections. Non-paracetamol drug-induced ALF was the next largest identified cause, accounting for 8% of cases (5/62). The drugs responsible and the other less common causes of ALF are listed in Table 1.

Nearly three-quarters of patients (45/62) initially presented to a hospital that did not have liver transplant capability. Sixty per cent of patients (37/62) presented to a tertiary referral hospital (including the ELT-capable reporting hospitals). In contrast, 26% (16/62) and 14% (9/62) of

Table 3. Critical care interventions at the time of intensive care unit admission

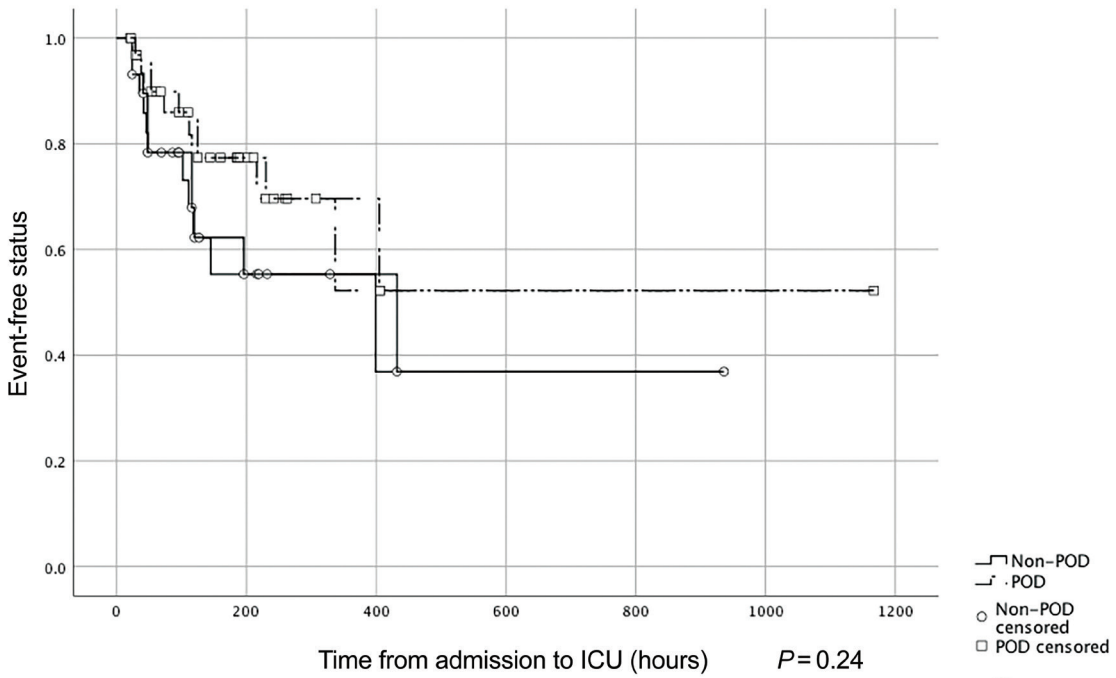
Variable	All	Paracetamol overdose	Non-paracetamol overdose	*P*
Total number of patients	62	33	29	
Intubation and mechanical ventilation	18 (29%)	9 (27%)	9 (31%)	0.74
Renal replacement therapy	17 (27%)	11 (33%)	6 (21%)	0.26
Active cooling	3 (5%)	1 (3%)	2 (7%)	0.59
Noradrenaline infusion	21 (34%)	11 (33%)	10 (34%)	0.92
Antibiotic use	40 (65%)	21 (64%)	19 (66%)	0.88
N-acetylcysteine infusion	39 (63%)	29 (88%)	10 (34%)	< 0.0001

Figure 1. Kaplan–Meier paracetamol overdose versus non-paracetamol overdose time to emergency liver transplantation



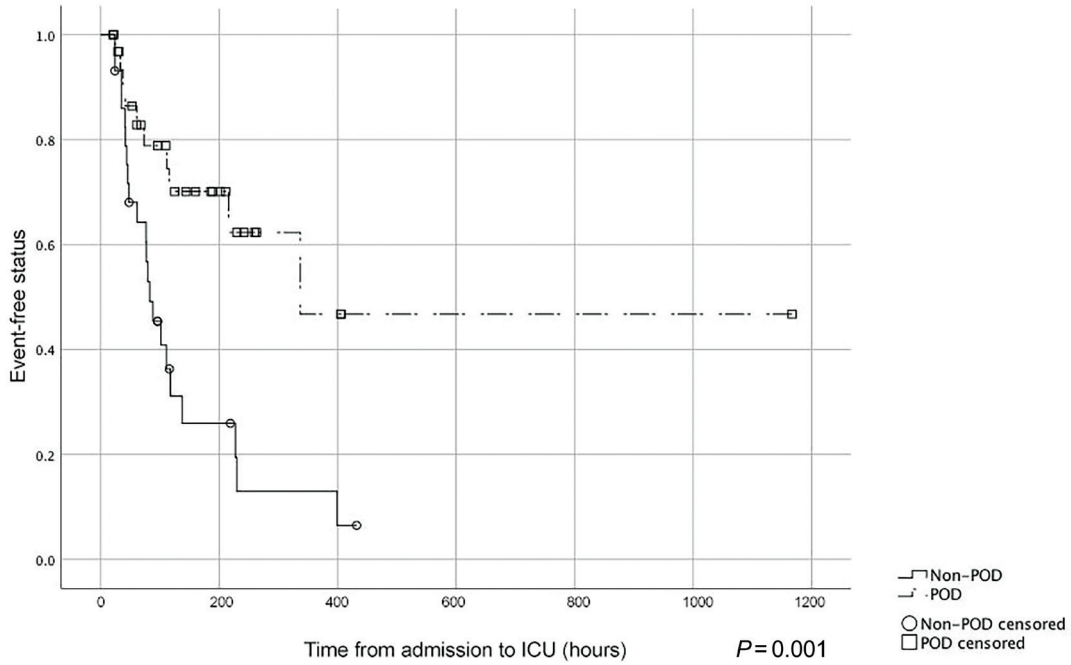
ICU = intensive care unit; POD = paracetamol overdose.

Figure 2. Kaplan–Meier analysis of survival by paracetamol overdose status



ICU = intensive care unit; POD = paracetamol overdose.

Figure 3. Kaplan–Meier analysis of time to either emergency liver transplant or death by paracetamol overdose status



ICU = intensive care unit; POD = paracetamol overdose.

patients first attended an outer metropolitan or rural hospital, respectively.

Several important differences between POD and non-POD patients were apparent. POD patients tended to be younger, were much more likely to be women and were nearly four times as likely to have psychiatric or substance misuse problems than patients with non-POD ALF. Most POD patients had at least one chronic comorbidity (inclusive of psychiatric and substance misuse problems), while nearly half of all non-POD patients had no documented long term health problems. POD patients were admitted to intensive care units at ELT-capable hospitals considerably earlier than non-POD patients.

Clinical findings and investigation results at time of ICU admission

On admission to intensive care, illness severity was high (Table 2), with an overall median APACHE III score of 77 (IQR, 57–102) and median APACHE III risk of death of 0.32 (IQR, 0.12–0.54). POD patients had a lower median

Table 4. Outcomes of study patients

Variable	All	Paracetamol overdose	Non-paracetamol overdose	*P*
Total number of patients	62	33	29	
ICU length of stay (h), median (IQR)	116 (48–217)	144 (61–230)	102 (48–96)	0.39
Hospital length of stay (days), median (IQR)	10.5 (4.8–18.3)	11.0 (4.8–17.6)	9.1 (4.0–18.2)	0.49
Emergency liver transplantation	13 (21%)	2 (6%)	11 (38%)	0.002
ICU mortality	19 (31%)	8 (24%)	11 (38%)	0.24
Hospital mortality	19 (31%)	8 (24%)	11 (38%)	0.24
Non-transplanted ICU mortality	18/49 (37%)	8/31 (26%)	10/18 (56%)	0.037
Non-transplanted hospital mortality	18/49 (37%)	8/31 (26%)	10/18 (56%)	0.037

ICU = intensive care unit; IQR = interquartile range.

Table 5. Observational studies of acute liver failure presentations (exclusive of paediatric only studies)

Study	Country/ region	Year	Type	Patients (*n*)	Population	Aetiology		Women	Age (years)	ELT			Mortality		
						POD	Non-POD			All	POD	Non-POD	All	POD	Non-POD
Bernal et al[14]	United Kingdom	1973–2008	Single centre	3305	ALF and ALI	65	35	60%	33	12%	7%	21%	43%	36%	56%
Shakil et al[15]	United States	1983–1995	Single centre	177	All ALF	19	81	63%	39	49%	30%	51%	37%	33%	38%
Bhatia et al[16]	India	1986–2006	Single centre	1015	All ALF	< 4*	96	58%	26	†	†	†	57%	nd	nd
Acharya et al[17]	India	1987–1993	Single centre	423	All ALF	0	100	53%	30	†	†	†	66%	nd	nd
Gow et al[18]	Australia	1988–2001	Single centre	80	All ALF	36	64	80%	38	33%	7%	47%	38%	28%	43%
Khuroo et al[19]	India	1989–1996	Single centre	180	All ALF	< 1*	> 99	62%	31	†	†	†	73%	nd	nd
Brandsaeter et al[20]	Scandina-via	1990–2001	Single centre	315	ALF listed for ELT	17	83	60%	-	73%	39%	79%	58%‡	31%	13%
Hiramatsu et al[21]	Japan	1990–2006	Single centre	50	All ALF	< 6*	> 94	34%	46	20%§	33%§	19%§	60%	nd	60%
Khuroo[22]	India	1992–1996	Single centre	119	All ALF	< 1*	> 99	61%	-	†	†	†	74%	nd	nd
Escorsell et al[23]	Spain	1992–2000	Multi-centre	267	All ALF	2	98	56%	37	56%	nd	nd	42%	nd	nd
Areia et al[24]	Portugal	1992–2006	Single centre	61	All ALF	2	98	57%	37	54%	nd	nd	31%	nd	nd
Marudanay-agam et al[25]	United Kingdom	1992–2008	Single centre	1237	All ALF	61	39	55%	37	21%	nd	nd	27%‡	nd	nd
Wei et al[26]	Sweden	1994–2003	Multi-centre	279	All ALF	42	58	61%	47	15%	5%		22%		
Yantorno et al[27]	Argen-tina	1995–2004	Single centre	64	All ALF¶	0	100	nd	35	66%	nd	nd	17%	nd	nd
Adukauskiene et al[28]	Lithuania	1996–2004	Single centre	28	All ALF	4	96	57%	44	4%	100%	0%	61%	0%	63%

(*Continues*)

Table 5. Continued

Study	Country/ region	Year	Type	Patients (*n*)	Population	Aetiology		Women	Age (years)	ELT			Mortality		
						POD	Non-POD			All	POD	Non-POD	All	POD	Non-POD
Fujiwara et al[29]	Japan	1998–2003	Multi-centre	634	All ALF	nd	nd	50%	47	21%	nd	nd	52%	nd	nd
Larson et al[30]	United States	1998–2003	Data-base	275	POD ALF	100	0	74%	37	na	8%	nd	29%	29%	na
Taylor et al[31]	United States	1998–2005	Database	29	HAV ALF	0	100	48%	48	31%	nd	nd	14%	nd	nd
Forde et al[32]	United States	1998–2006	Database	927	All ALF	47	53	32%	38	27%	nd	nd	31%	nd	nd
Reuben et al[33]	United States	1998–2007	Database	133	Non-POD DILI ALF	0	100	71%	44	42%			34%	na	
Reuben et al[34]	United States	1998–2013	Database	2070	All ALF	46	54	64%	39	22%	nd	nd	29%	nd	nd
Koskinas et al[35]	Greece	2000–2006	Multi-centre	40	All ALF	5	95	70%	37	45%	nd	nd	43%	nd	nd
Fábrega et al[36]	Spain	2000–2010	Single centre	17	All ALF	6	94	65%	45	65%			35%		
Reddy et al[37]	United States	2000–2013	Database	617	ALF listed for ELT	28	92	68%	39	64%	36%	74%	23%	24%	nd
Canbay et al[38]	Germany	2002–2008	Single centre	134	All ALF	16	84	63%	41	19%	nd	nd	19%	nd	nd
Warrillow et al[7]	Australia and New Zealand	2005–2014	Database	723	All ALF	nd	nd	60%	50	nd	nd	nd	39%	nd	nd
Hadem et al[39]	Germany	2008–2009	Multi-centre	109	All ALF	9	91	63%	46	47%	nd	nd	28%	nd	nd
Koch et al[40]	United States	2008–2013	Database	386	ALI only	50	50	61%	38	12%	2%	23%	5%	2%	8%
Sugawara et al[41]	Japan	2010	Multi-centre	220	All ALF	< 5*	> 95	nd	nd	13%	nd	nd	47%	nd	nd

ALF = acute liver failure; ALI = acute liver injury; DILI = drug-induced liver injury; ELT = emergency liver transplantation; HAV = hepatitis A virus; na = not applicable; nd = no data; POD = paracetamol overdose. * Combination of all drugs and toxins (specific agents not reported and may contain only a very small number or no paracetamol affected patients). † ELT not available. ‡ Non-ELT patient mortality. § Living donor ELT. ¶ Paediatric patients excluded.

pH and a greater lactate concentration compared with non-POD patients. The patterns of liver injury varied, with significantly higher alanine aminotransferase and international normalised ratio (INR) in POD patients, while bilirubin concentrations were more elevated in non-POD patients. Blood urea concentrations were greater in POD patients than in non-POD patients. The median fibrinogen concentration and platelet count were low for all patients, while the median blood ammonia level was high.

Critical care interventions

High level treatments were commonly required immediately on admission to the ICU, with treatment patterns broadly similar between patients with POD and non-POD ALF (Table 3). At the time of admission to ICU, 29% of all patients (18/62) were intubated and mechanically ventilated, 27% (17/62) received immediate renal replacement therapy, 34% (21/62) required noradrenaline infusion, and antimicrobial agents were administered to 65% of all patients (40/62). Most but not all POD patients were receiving an intravenous infusion of N-acetylcysteine (NAC) at the time of admission to the ICU (29/33, 88%), while only about a third (10/29) of non-POD patients were receiving this therapy on admission to ICU. Of the four POD patients who were not receiving NAC at the time of admission to ICU, two had it commenced during the subsequent 12 hours, one of these patients survived to hospital discharge without ELT, while the other died. Two POD patients did not receive NAC during their period of care within the ICU, with one of them surviving to hospital discharge without ELT and the other dying within a matter of hours from admission to the ICU.

Outcomes

Median ICU length of stay was just under 116 hours (IQR, 48–217 hours), while median hospital length of stay was 10.5 days (IQR, 4.8–18.3 days). ELT was performed in 21% of patients (13/62), with a median time from ICU admission to surgery of 78 hours (IQR, 61–83 hours). Ninety-two per cent (12/13) of the liver transplant recipients survived to hospital discharge. ELT was rarely used in POD patients, with only 6% (2/33) receiving a transplant (Figure 1). For non-POD patients without a contraindication to ELT, the transplantation rate was 48% (11/23) (Table 4).

Overall hospital mortality was 31% (19/62), with all deaths occurring within the ICU and no significant difference in mortality between POD and non-POD patients (Figure 2). Forty-seven per cent of patients (9/19) who died had a contraindication to ELT, six of these were POD patients, while another three were non-POD patients. One non-POD patient died after undergoing ELT. Two POD and seven non-POD patients who did not have contraindications to ELT died before potential transplantation. Transplant-free survival was far more common for POD patients (Figure 3), with non-POD patients having twice the mortality rate in the absence of ELT (Table 4).

The MEDLINE search for observational studies of ALF in adults identified 30 publications. These studies describe patients over a 40-year period from 1973 and report outcomes from North America, South America, Australasia, Asia, Western Europe, Eastern Europe, Scandinavia and India. Most studies were relatively small and single centre. There were also several publications from multicentre collaborations and registry databases. Key attributes of these studies with their reported outcomes are summarised in Table 5.

Discussion

Key findings

Patients with ALF admitted to the ICU of Australian and New Zealand liver transplant centres are young, have a high illness severity, require high level critical care interventions, and have a high overall mortality. Moreover, patients with POD-induced ALF differ considerably from those with ALF from other causes, with pre-existing mental health problems; higher lactate, alanine aminotransferase and INR levels at presentation; and higher survival rates despite low ELT rates. POD patients are a unique and substantial subset of those admitted to the ICU with ALF and have a different pattern of presentation, clinical course, and transplant-free survival outcomes from most other causes of ALF. Non-POD patients with ALF had a poor transplant-free survival, with more than half dying in the absence of ELT, while 90% of those transplanted survived to hospital discharge. Finally, nine patients who were potentially eligible for ELT died without undergoing this procedure.

Comparisons with previous studies

No multicentre data detailing the current characteristics, treatment or outcomes of critically ill patients with ALF admitted to liver transplant centres in Australia and New Zealand have been previously published. Compared with a 2004 single centre study from one of the participating transplant units,[18] the proportion of POD ALF has increased and the proportion of female patients has decreased, while patient age, utilisation of ELT, and survival outcomes appear similar. It is well recognised that the aetiology, the use of ELT and the outcome of ALF differ between countries[42] (Table 5). Paracetamol is the dominant cause of ALF in the United States,[34] Britain[14] and Australia,[18] with affected patients often surviving without ELT.[43] By contrast, studies from

elsewhere in Europe[24,28,36,38,44] as well as Asia[17,21,22,41] report a low incidence of POD, with hepatotropic viruses, non-paracetamol drugs, and toxins being the major causes of ALF. This current study confirms that Australia is similar to the northern hemisphere anglophone countries and suggests that New Zealand may be more like continental Europe and Asia in terms of ALF aetiology, with hepatitis B virus infection being quite common (70%) and POD relatively rare (10%). We found a higher proportion of POD patients affected by a staggered overdose than reported in previous studies. While this group are described as having poorer outcomes than those with ALF from a single major overdose,[13,43,45] overall survival and use of ELT for POD were similar to previous reports. Given that more than half of all ALF cases in Australasia are associated with paracetamol, the introduction of additional public health measures to reduce both deliberate and inadvertent POD warrants further consideration.

Access to ELT is a major determinant of outcome for ALF due to causes other than POD.[34] In some regions, ELT is provided to nearly half or more of all patients with ALF,[15,24,36,39] while it has limited utilisation[41] or is not available at all elsewhere.[16,17,19] Access to ELT has also varied over time[14] as transplant services become established and organ donation rates improve. Our findings regarding overall ELT and survival outcomes are consistent with previous data from Australia and New Zealand[18] and comparable to observational studies in the United States,[32,34] where the proportion of POD patients was very similar (Table 5). These findings suggest that, in a region where ELT is rarely used for POD patients and is used in less than half of non-POD ALF cases, outcomes are at least as good as previously reported[21,30,32,34] and are indeed similar to regions with substantially higher rates of transplantation.[15,24,33,36,39,44]

Strengths and limitations

All liver transplant-capable ICUs in Australia and New Zealand participated in this study and only patients with definite ALF were included. Highly complete and clinically relevant data were obtained, including aetiology of ALF, patient characteristics, comorbidities, illness severity, biochemical findings, haematological parameters, critical care interventions, ELT utilisation and survival outcomes for all patients. Data were collated by experienced clinical researchers at each centre using a consistent methodology to ensure accuracy and completeness. Given that the findings are remarkably consistent with a recent evaluation of ALF in Australia and New Zealand undertaken using a very large and entirely separate dataset, it seems likely that the findings of this study are representative and robust.[7]

While this study reports data from every liver transplant unit in Australia and New Zealand, only a relatively small number of patients with ALF were evaluated. As a convenience-based, fixed-size sample of ALF, there is the possibility that the patients studied were not truly representative of ALF patients overall, thus limiting the certainty of the findings. Nevertheless, participating ICUs selected ten or more sequential patients based solely on having ALF at the time of admission to ICU, limiting the potential for selection bias. Furthermore, many previous ALF studies are quite small and most are single centre reports, limiting the external validity of their findings. Another potential limitation of our study is the retrospective, chart-based nature of the review. The accuracy of documented findings and clinical data are sometimes uncertain, and it is possible that errors occurred during the process of clinical documentation. However, all patients were managed within large, experienced, university-affiliated ICUs with rigorous systems for clinical data collection. In addition, all diagnoses were carefully checked, and a comprehensive review of all data submitted was completed before the analysis.

Conclusion

In summary, more than half of all current patients with ALF admitted to Australian and New Zealand liver transplantation ICUs are related to POD. The majority of patients with POD survive without needing ELT, despite being extremely ill at ICU admission. Patients with non-POD ALF present with a different pattern of liver injury and have a much lower likelihood of survival in the absence of ELT. These findings strongly imply that POD- and non-POD-associated ALF are best considered as distinctly separate forms of ALF with specific implications for treatment and prognosis. Despite relatively low overall utilisation of ELT in Australia and New Zealand, outcomes are similar to most previous reports, including those from higher ELT use regions. While the survival benefit associated with ELT for non-POD ALF seems clear, the appropriateness of this intervention in patients with POD is unclear.

Competing interests

None declared.

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