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Acute liver failure in Scotland between 1992 and 2009; incidence, aetiology and outcome

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Summary

Aim: To describe incidence, aetiology and outcome data for Scotland since the inception of the Scottish Liver Transplant Unit (SLTU) in 1992.

Background: Acute liver failure (ALF) is a rare but frequently fatal condition. Few studies have adequate patient numbers to draw convincing conclusions over demographic features, aetiology and outcome.

Design: Statistical analysis of prospectively collected data on aetiology, demographic, clinical and outcome of all admissions, including those with ALF, to the SLTU.

Methods: Incidence data presented for admissions and ALF. Descriptive frequencies for aetiology, clinical, demographic and outcome data presented; including split analysis for paracetamol and non-paracetamol aetiologies. Univariate and multivariate analysis of admission factors predictive of outcome is described.

Results: Nine hundred and forty-nine patients were admitted to the SLTU between 1992 and 2009. Five hundred and twenty-four patients had ALF. The annual incidence of ALF in the Scottish population is 0.62 per 100 000 and paracetamol overdose (POD) was the largest causative factor; responsible for 0.43 cases of ALF per 100 000 population per year. The odds ratio (OR) of transplantation or death was 0.47 in the POD group compared to other aetiologies; yet of not being a transplant candidate having met the Kings College Hospital poor prognostic criteria OR was 4.9. Of admissions listed for transplant 76.0% were transplanted. Of those listed and not transplanted mortality was approaching 100% and 76.1% of those transplanted survived to discharge.

Conclusions: This large, prospective, single centre study with a defined geographical area and well-recorded population provides accurate data regarding ALF between 1992 and 2009.

Introduction

Acute liver failure (ALF) occurs following the sudden extensive loss of liver cell mass resulting in hepatic encephalopathy and co-agulopathy in the absence of pre-existing symptomatic liver disease. This is sub-classified further according to speed of progression between jaundice and encephalopathy; into hyperacute, acute and sub-acute.[1] ALF is a rare condition, thought to affect ~2000 people per year in the USA[2] (US Population 257 million, 1 July 1993[3]) and demographic studies are invariably small. Paracetamol is a leading cause of ALF both in the UK,[4,5] USA[6,7] and Australia.[8] Paracetamol overdose has a clinical course distinct to other causes of ALF, characterized by a rapid deterioration but a relatively good prognosis.[1] Of importance to

the generalist, the small size of most studies previously published has limited the conclusions we are able to draw over the characterization of causes of other, non-paracetamol, ALF.

In this study, we present our experience in the Scottish Liver Transplant Unit (SLTU) of ALF, paracetamol overdose and liver transplantation (LT) in a geographically defined population between November 1992 and March 2009, in one of the largest single centre studies to date.

Methods

Patients

This study involved the analysis of prospectively collected data on 949 patients admitted to the SLTU in the Royal Infirmary of Edinburgh (RIE) between November 1992 and March 2009.

The SLTU is the tertiary referral centre for LT in Scotland and accepts patients on a national level (Scottish population, 2001 census, 5 million[9]). Data for all patients referred to the SLTU with ALF were prospectively collected and stored since its establishment in November 1992.

Definitions/Protocols

Throughout this study the definition of ALF is that defined by O'Grady *et al.*[1]—explicit in this definition is the speed of onset of the condition and presence of encephalopathy. Patients without hepatic encephalopathy were included and defined as severe acute liver injury. Patients with chronic liver failure were included under admissions but excluded from the acute liver injury/failure cohort. The criteria used for LT were the Kings College Hospital poor prognostic criteria (KCHPPC)[10,11] in conjunction with medical and psychological assessment. Medical and psychological contraindications to LT were similar to those used in other transplant centres across the UK[12] and previously published in Simpson *et al.*[5]

Patients admitted to the SLTU are managed using a standardized protocol. The protocol is reviewed on an annual basis but the goals of treatment remained unchanged throughout the study period. Contraindications to LT and the management protocol of patients admitted to the SLTU are summarized in Simpson *et al.*[5]

Paracetamol was considered to be the underlying aetiology when there was a history of paracetamol overdose (> 4 g of paracetamol/day within 7 days of presentation) whether or not there were elevated serum levels of paracetamol. Other aetiologies were confirmed through laboratory, pathological and/or radiological investigations. A diagnosis of seronegative hepatitis was only given as a diagnosis of exclusion.

Analysis was performed for the group as a whole and split by aetiology. Aetiology was split into 'paracetamol overdose' (POD) and 'other' aetiologies (non-POD).

Incidence data was calculated for complete years only.

Outcome was defined as one of four endpoints; survival to discharge without a transplant, survival to discharge with a transplant, death without a transplant, or death with a transplant.

Statistics

Statistical analysis of the database was undertaken and descriptive frequencies, univariate and multivariate analysis are presented. Results are presented as mean ± standard deviation (SD) followed by either range or percentage in parentheses, unless otherwise stated.

Statistics [Levene's test for equality of variances, independent sample (pooled–variances and separate–variances) *t*-test, one-sample *t*-test, χ^2-test, *z*-test using normal approximation of the binomial distribution with known population value, backward stepwise (likelihood ratio) logistic regression] were processed using SPSS 15.0 or Microsoft Excel 2003. All *P*-values are two-tailed. A $P < 0.05$ was considered statistically significant.

Results

Demographic/Clinical information

Between November 1992 and March 2009, 949 patients were admitted to the SLTU.

Five hundred and twenty-four patients were encephalopathic either on or during admission, excluding those with chronic liver failure, 515 patients had ALF.

The mean age of admissions was 38.1 ± 14.3 (2–79) years. The mean ages of men and women were similar, 38.6 ± 14.1 years and 37.9 ± 14.3 years, respectively (*t*-test $P = 0.48$). POD patients were significantly younger (35.9 ± 12.8 years, $n = 673$) than non-POD patients (43.5 ± 16.2 years, $n = 276$, *t*-test $P < 0.001$).

Patients with ALF were significantly older (39.7 ± 14.8 years, $n = 515$) than those with acute liver injury (35.22 ± 13.1 years, $n = 392$, *t*-test $P < 0.001$). This difference remained significant amongst POD patients (with ALF 38.1 ± 13.4 years, $n = 352$; with severe acute liver injury 33.4 ± 11.7, $n = 316$; *t*-test $P < 0.001$). However, among non-POD

patients there was no significant difference between the ages of those with ALF (43.1 ± 16.9 years, $n = 163$) and those with acute severe liver injury (43.0 ± 15.6 years, $n = 76$, t-test, $P = 0.53$).

The sex distribution (male: female) of admissions was 1:1.25 (n 420:527). Significantly different (z-test, $P = 0.02$) to the Scottish population in general (male: female 1:1.08, 2001 census data).[9] This difference remained significant for non-POD patients 1:1.73 (n 101:175) (z-test $P < 0.001$) but not for POD patients 1:1.10 (n 319:352, z-test $P = 0.79$). When analysed in isolation those with ALF showed a similar picture—total 1:1.34 (n 220:294, z-test $P = 0.02$), POD 1:1.24 (n 157:194, z-test $P = 0.21$), non-POD 1:1.59 (n 63:100, z-test $P = 0.02$).

The Carstairs score is a measure of social deprivation and has been linked with many other conditions (a higher score indicates more deprivation). The mean Carstairs score of patients admitted to the SLTU was 1.26 ± 3.97; 95% confidence interval (CI) 0.99–1.54, significantly higher than that of the Scottish population (mean 0) (one-sample t-test $P < 0.001$). The difference between POD and the general Scottish population remained significant (1.68 ± 4.05; 95% CI 1.34–2.01 one-sample t-test $P < 0.001$) but not between non-POD patients and the general population (0.28 ± 3.57; 95% CI −0.17 to – 0.74 one-sample t-test $P = 0.223$).

Most patients were admitted via other hospitals with only 21.6% (205/949) coming from within the Lothian region (Population ≈ 800 000)[9] and only 12.9% (122/949) being admitted directly to the RIE. No patients were admitted directly to the SLTU.

A total of 43.7% (399/913) of patients admitted were encephalopathic/ventilated at the point of admission. The most common hepatic encephalopathy grade on admission was grade I (Table 1).

A total of 56.6% (524/926) of patients were encephalopathic at some point during their admission. A total of 66.7% (172/258) of non-POD patients were encephalopathic during admission, significantly more than POD patients (52.7%, 352/668, $P < 0.001$, OR 1.79; 95% CI 1.33–2.42) (Table 1). A total of 12% (79/658) of POD and 9.8% (25/255) of non-POD were ventilated prior to transfer to the SLTU (χ^2 test; $P = 0.347$). A total of 40.7% (268/658) of POD and 51.4% (131/255) of non-POD patients were encephalopathic or ventilated on admission (χ^2 test; $P = 0.004$. OR 1.54 95% CI 1.15–2.06).

Table 2 summarizes the clinical parameters on admission to the referring hospital and the SLTU.

Incidence

The SLTU receives referrals from a geographically defined area with a population of 5 million (Scottish population 5064200 capita, 2001 census[9]).

The mean incidence of ALF was 0.62 per 100 000 population per year (31.56 cases per year). Of these 0.43 per 100 000 population per year (21.63 cases per year) were secondary to paracetamol overdose and 0.20 per 100 000 population per year (9.94 cases per year) were secondary to other causes. The mean number of admissions to the SLTU was 1.16 per 100 000 population per year (58.56 admission per year). Of these 0.82 per 100 000 population per year (41.56 admissions

Table 1 Encephalopathy grades

	POD	Non-POD	Total
Encephalopathy grade on admission			
Not encephalopathic	390 (59.3)	124 (48.6)	514 (56.3)
I	99 (15.0)	52 (20.4)	151 (16.5)
II	46 (7.0)	32 (12.5)	78 (8.5)
III	23 (3.5)	17 (6.7)	40 (4.4)
IV	21 (3.2)	5 (2.0)	26 (2.8)
Ventilated	79 (12.0)	25 (9.8)	104 (11.4)
Total	658 (100)	255 (100)	913 (100)
Encephalopathic during admission			
Yes	352 (38.0)	172 (18.6)	524 (56.6)
No	316 (34.1)	86 (9.3)	402 (43.4)
Total	668 (72.1)	258 (27.9)	926 (100)

Figures are number of patients (percent). Admission encephalopathy grade 36 missing data. Ever encephalopathic 23 missing data.

per year) were secondary to paracetamol overdose and 0.34 per 100 000 population per year (17 admissions per year) secondary to other causes (Figure 1).

Table 2 Clinical information

	N	Value
Referring hospital		
Encephalopathic (Y:N)	791	227 : 564
Haemoglobin (g/l)	774	145 ± 23
White cell count ($\times 10^9$/l)	776	14.5 ± 13.2
Platelets ($\times 10^9$/l)	763	192 ± 128
Prothrombin Time (s)	788	41 ± 30
Sodium (mmol/l)	814	137 ± 5
Potassium (mmol/l)	803	4.2 ± 0.9
Urea (mmol/l)	825	7.1 ± 6.2
Creatinine (μmol/l)	819	141 ± 112
Bilirubin (μmol/l)	756	125 ± 141
ALT (IU/l)	756	3551 ± 4673
ALP (IU/l)	746	257 ± 298
SLTU admission		
Encephalopathic (Y:N)	894	393 : 501
Haemoglobin (g/l)	914	127 ± 26
White cell count ($\times 10^9$/l)	912	12.3 ± 9.6
Platelets ($\times 10^9$/l)	908	146 ± 98
Prothrombin time (s)	911	51 ± 35
Sodium (mmol/l)	913	135 ± 5
Potassium (mmol/l)	908	4 ± 0.8
Urea (mmol/l)	914	8.3 ± 7.2
Creatinine (μmol/l)	912	176 ± 133
Bilirubin (μmol/l)	910	148 ± 157
ALT (IU/l)	911	6036 ± 4777
ALP (IU/l)	909	154 ± 165

n total = 920.
Chronic excluded. Mean ± SD unless otherwise stated
ALP: alkaline phosphatase; ALT: Alanine transferase.

Aetiology

Table 3 summarizes the responsible aetiology of admissions in the study. The most common, 73.9% (673/911), aetiology was paracetamol overdose. Of these the number of tablets taken was known in 530 (78.8%). The mean number of paracetamol tablets taken was 66 ± 43 (33 ± 21.5 g); range 4–300 tablets (2–150 g). Four patients in the study reported to have taken ⩽4 g of paracetamol; these cases have been discussed previously by Beer *et al.*[13] Of the 673 POD; type of overdose (staggered/single time point) was known in 618. 24.2% (163/673) were staggered and 67.6% (455/673) were single time point overdoses. Of the 455 with a single time point overdose the delay to presentation was known in 435. A total of 70.8% (322/455) had a delay to presentation of ⩾15 h. Of those with POD 36.7% (247/673) were known to have a past medical history of previous overdose.

Viral causes were thought to be responsible in 2.1% (19/911) of cases. There were 14 cases of hepatitis B, 2 cases of hepatitis A, 2 cases of hepatitis E and 1 case of coxsackie B4.

Idiosyncratic drug reactions were implicated in 42 cases (4.4%) of admissions. The likely drugs are listed in Table 4. Methylenedioxymethamphetamine (MDMA, 'ecstasy') was the most common causative drug, identified in five cases and the most frequently implicated group of drugs was antibiotics. A detailed analysis of data from 1992 to 2004 is given in Smith *et al.* (2005).[14]

Outcome

Outcome is summarized in Tables 5–7. Total mortality (of patients admitted to the SLTU) was 29.0% (275/949). A total of 31.8% (302/949) of

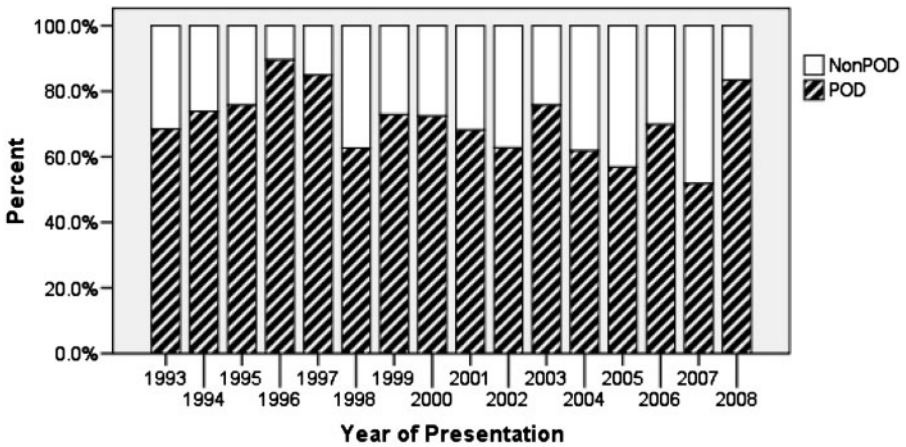

Figure 1. The proportion of yearly admissions attributable to paracetamol overdose. POD, paracetamol overdose; non-POD, aetiologies other than paracetamol overdose

Table 3 Aetiology data of admissions

Aetiology	Frequency	Percent
Paracetamol overdose	673	73.9
Non-A-E hepatitis	71	7.8
Idiosyncratic drug reaction	42	4.6
Ischaemia	23	2.5
Autoimmune hepatitis	22	2.4
Viral	19	2.1
Budd-Chiari	16	1.8
Malignancy	10	1.1
Pregnancy related	8	0.9
Other organ damage	7	0.8
Non-paracetamol overdose	7	0.8
Wilsons disease	7	0.8
Portal vein thrombosis	3	0.3
Sepsis	2	0.2
Liver trauma	1	0.1
Total	911	100
Alcoholic hepatitis	9	
Chronic liver disease	29	

Table 4 Idiosyncratic drug reactions

Medication	Frequency
Drugs of abuse	
Methylenedioxymethamphetamine (MDMA, 'ecstacy')	5
Antibiotics	
Rifampicin	3
Co-amoxiclav	2
Clarythromycin	2
Flucloxacillin	2
Nitrofurantoin	1
Anti-TB therapy, unspecified	2
Unspecified	3
Antivirals	
Stavudine	1
Chemotheraputic agents	
Unspecified	2
Antiemetics	
Ondansetron	1
Anti-inflamatories	
Diclofenac	3
Sulphasalazine	1
Antihistamines	
Terfenadine	1
Statins	
Pravastatin	1
Muscle relaxants	
Dantrolene	2
Antipsychotics	
Chlorpromazine	1
Contraceptives	
Oral contraceptive pill	1
Anti-androgens	
Cyproterone	1
Anti-convulsants	
Sodium valproate	1
Other	2
Unknown	4
Total	42

patients met the KCHPPC, 16.2% (154/949) were listed for transplant and 12.3% (117/949) were transplanted. Hence, of those considered transplant candidates, 76.0% (117/154) were transplanted. A total of 76.1% (89/117) of those transplanted survived to discharge. Of those transplanted 1-year survival was 72% (81/112), falling to 60% (50/84) at 5 years (Table 7). The Kaplan–Meier plot is shown in Figure 2. There were no significant differences identified between POD and non-POD patients during this analysis.

Of the transplant candidates not to receive a transplant, mortality was 97.2% (36/37), giving a total mortality rate amongst transplant candidates of 41.6% (64/154). There was no statistically significant difference between patients not transplanted that met KCHPPC when comparing outcome (died no transplant and survived no transplant) between those not listed for transplant and those that died on the transplant waiting list (χ^2 $P = 0.09$). Excluding chronic and those transplanted, KCHPPC had a specificity for death of 96% and a positive predictive value of 89%.

Mortality of patients with ALF (encephalopathic during admission, chronic liver failure excluded) admitted to the SLTU between 1993 and 2008 was 49.1% (248/505) with an annual mortality rate ranging from 36% (12/33) to 62% (23/37) (χ^2 $P = 0.73$).

The relative risk (RR) of transplantation or death (as opposed to survival, no transplant) was 0.65 (95% CI 0.55–0.76) among paracetamol overdose patients when compared to non-POD (excluding chronic liver disease), OR 0.47 (95% CI 0.35–0.64), χ^2 $P < 0.001$; (RR of survival 1.37; 95% CI 1.19–1.57). Among those that met KCHPPC, the RR of NOT being a transplant candidate was 2.51 (95% CI 1.74–3.61) amongst paracetamol overdose patients when compared to non-POD, odds ratio (OR) 4.90 (95% CI 2.86–8.42), χ^2 $P < 0.001$.Amongst those transplanted, the difference between POD and non-POD aetiologies in terms of survival was not statistically significant (χ^2 $P = 0.385$).

Table 8 shows both univariate and multivariate analysis of admission features (Table 2) at both admission to the referring hospital and admission to the SLTU as predictive of outcome. Transplant and death were considered together. Chronic liver

Table 5 Outcome by aetiology

	Aetiology		
	POD	Non-POD	Total
Outcome—All, *n* (%)			
No transplant survived	450 (66.9)	134 (14.1)	584 (61.5)
No transplant died	169 (25.1)	78 (8.2)	247 (26.0)
Transplant survived	38 (5.6)	51 (5.4)	89 (9.4)
Transplant died	15 (2.2)	13 (1.4)	28 (3.0)
Missing	1 (0.1)	0 (0)	1 (0.1)
Total	673 (70.9)	276 (29.1)	949 (100)
Outcome—patients that met KCHPPC, *n* (%)			
No transplant survived	17 (5.6)	3 (1.0)	20 (6.6)
No transplant died	134 (44.4)	32 (10.6)	166 (55.0)
Transplant survived	38 (12.6)	50 (16.6)	88 (29.1)
Transplant died	15 (5.0)	13 (4.3)	28 (9.3)
Total	204 (67.5)	98 (32.5)	302 (100)
Outcome—transplant candidates, *n* (%)			
No transplant survived	1 (1.3)	0 (0.0)	1 (0.6)
No transplant died	24 (30.8)	12 (7.8)	36 (23.4)
Transplant survived	38 (48.7)	51 (33.1)	89 (57.8)
Transplant died	15 (19.2)	13 (8.4)	28 (18.2)
Total	78 (50.6)	76 (49.4)	154 (100)

Table 6 KCHPPC and transplant candidacy by aetiology

	Aetiology		
	POD	Non-POD	Total
Met KCHPPC?, *n* (%)			
Yes	204 (21.5)	98 (10.3)	302 (31.8)
No	468 (49.3)	177 (18.7)	645 (68.0)
Missing	1 (0.1)	1 (0.1)	2 (0.2)
Total	673 (70.9)	276 (29.1)	949 (100)
Transplant candidate?, *n* (%)			
Yes	78 (11.6)	76 (8.0)	154 (16.2)
No	128 (19.0)	27 (2.8)	155 (16.3)
Not applicable	464 (69.0)	172 (18.1)	636 (67.0)
Missing	3 (0.5)	1 (0.1)	4 (0.4)
Total	673 (70.9)	276 (29.1)	949 (100)

disease excluded. Those factors significantly ($P<0.05$) associated with outcome were included in backward stepwise logistic regression analysis (likelihood ratio; P for removal >0.05; referring hospital and SLTU examined independently). On admission to the referring hospital encephalopathy, serum creatinine and bilirubin were found to be associated with outcome. On admission to the SLTU more variables were found to be associated with outcome; encephalopathy, haemoglobin concentration, white cell count, platelet count, prothrombin time and serum potassium, urea, creatinine, bilirubin and ALT concentrations.

Discussion

This study of 949 patients is one of the largest single centre studies with a defined geographical area of ALF to date and represents all admissions to the SLTU between November 1992 and March 2009.

Table 7 Survival analysis

Time	Survival		
	POD	Non-POD	Significance
1 year	71.4% (35/49)	73.0% (46/63)	NS
3 year	64.3% (27/42)	68.4% (39/57)	NS
5 year	55.0% (22/40)	63.6% (28/44)	NS
	Chi-square	Degrees of freedom	*P*-value
Log rank (Mantel-Cox):	0.997	1	0.318

See also Figure 2.
Result: survival percent (alive/total). NS: not significant.

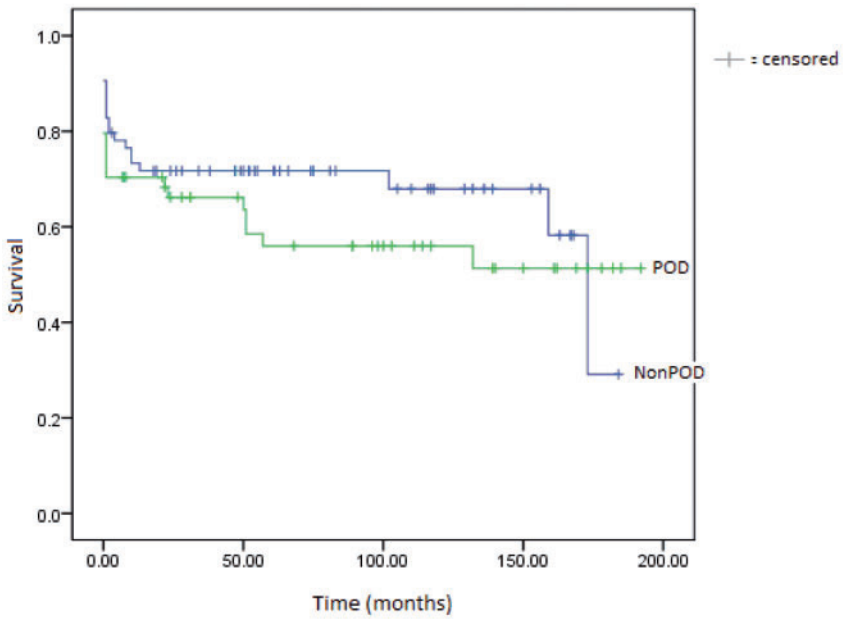

Figure 2. Kaplan–Meier plot of transplanted patients. POD, paracetamol overdose; non-POD, aetiologies other than paracetamol overdose.

The mean age of admissions to the SLTU was 38 years, consistent with previous studies,[7,8,15] and paracetamol overdose patients (mean 35.95 years) were on average 7.6 years younger than patients with other aetiologies.

Again, consistent with previous studies,[7,8,15–17] there was a slight female predominance in the sex distribution (male:female) of admissions to the SLTU (1:1.25, $P=0.02$) and in those with ALF (1:1.34, $P=0.02$). However, in contrast with other studies, this difference was more marked in those with non-POD aetiologies (1:1.73, admissions, $P<0.001$ and 1:1.59, ALF, $P=0.02$) when compared with POD which was not significantly different from the general population for admissions or ALF. The reasons for female predominance in ALF have not yet been fully elucidated. Female specific causes of ALF and aetiologies associated with higher incidence in females exist. Pregnancy-related complications (HELLP syndrome, acute fatty liver of pregnancy) and metastatic spread of breast cancer for example. However, these represent only a small proportion of patients in our study [pregnancy related complications 0.8% of admissions; malignancy (total) 1.1% of admissions]. The female predominance was not significant for admissions secondary to paracetamol overdose or in those who develop ALF secondary to paracetamol overdose ($P=0.79$ and $P=0.21$, respectively), this is in contrast with the typical sex distribution of

Table 8 Univariate and multivariate analysis

	Mean difference	*P*-value
Univariate analysis		
Referring hospital		
Haemoglobin (g/l)	−4.33 (95% CI −7.69 to −0.97)	0.01
White cell count ($\times 10^9$/l)	2.21 (95% CI 0.31 to 4.11)	0.02
Platelets ($\times 10^9$/l)	−6.71 (95% CI −26.15 to 12.73)	0.50
Prothrombin time (s)	13.37 (95% CI 8.85 to 17.88)	<0.01
Sodium (mmol/l)	−0.38 (95% CI −1.11 to 0.35)	0.31
Potassium (mmol/l)	0.34 (95% CI 0.21 to 0.47)	<0.01
Urea (mmol/l)	0.52 (95% CI −0.35 to 1.39)	0.24
Creatinine (μmol/l)	47.36 (95% CI 31 to 63.73)	<0.01
Bilirubin (μmol/l)	61.35 (95% CI 38.65 to 84.05)	<0.01
ALT (IU/l)	381.59 (95% CI −309.71 to 1072.88)	0.28
ALP (IU/l)	58.19 (95% CI 11.52 to 104.85)	0.01
SLTU		
Haemoglobin (g/l)	−16.5 (95% CI −19.81 to −13.19)	<0.01
White cell count ($\times 10^9$/l)	3.65 (95% CI 2.25 to 5.05)	<0.01
Platelets ($\times 10^9$/l)	−20.67 (95% CI −33.81 to −7.53)	<0.01
Prothrombin time (s)	23.06 (95% CI 17.92 to 28.2)	<0.01
Sodium (mmol/l)	−0.65 (95% CI −1.43 to 0.13)	0.10
Potassium (mmol/l)	0.56 (95% CI 0.45 to 0.68)	<0.01
Urea (mmol/l)	1.05 (95% CI 0.09 to 2)	0.03
Creatinine (μmol/l)	78.01 (95% CI 60.21 to 95.82)	<0.01
Bilirubin (μmol/l)	68.65 (95% CI 45.5 to 91.8)	<0.01
ALT (IU/l)	−2017.81 (95% CI −2631.84 to −1403.78)	<0.01
ALP (IU/l)	2.62 (95% CI −19.57 to 24.81)	0.82

	B	SE	exp(B)	*P*-value
Multivariate analysis				
Referring hospital				
ALF	1.279	0.227	3.592	0.00
White cell count ($\times 10^9$/l)	−0.017	0.009	0.983	0.07
Prothrombin time (s)	−0.008	0.004	0.992	0.05
Creatinine (μmol/l)	−0.002	0.001	0.998	0.02
Bilirubin (μmol/l)	−0.004	0.001	0.996	<0.01
SLTU				
ALF	1.542	0.201	4.673	<0.01
Haemoglobin (g/l)	0.016	0.005	1.016	<0.01
White cell count ($\times 10^9$/l)	−0.032	0.011	0.969	<0.01
Platelets ($\times 10^9$/l)	0.003	0.001	1.003	0.02
Prothrombin time (s)	−0.028	0.004	0.972	<0.01
Potassium (mmol/l)	−0.857	0.131	0.425	<0.01
Urea (mmol/l)	0.064	0.017	1.066	<0.01
Creatinine (μmol/l)	−0.003	0.001	0.997	<0.01
Bilirubin (μmol/l)	−0.005	0.001	0.995	<0.01
ALT (IU/l)	0.000	0.000	1.000[a]	0.02

OR of survival if encephalopathic (ALF) on admission to referring hospital 0.24 (95% CI 0.17 to 0.33; $P < 0.001$).
OR of survival if encephalopathic (ALF) on admission to the SLTU 0.14 (95% CI 0.11 to 0.20; $P < 0.001$)
[a]ALT exp(B) = 1.000066 (6.d.p)
Outcome: 'Died or Transplanted' compared to 'Survived'; multivariate coding = outcome: 0 = died or transplanted; 1 = survived no transplant; ALF: 0 = Encephalopathic; 1 = not encephalopathic.

patients presenting to Scottish emergency departments with deliberate self poisoning. Cook et al.[18] found the male: female ratio of patients presenting to the emergency department of Ninewells Hospital, Dundee, Scotland, with deliberate self-poisoning was 1:1.6 and Gorman *et al.*[19] demonstrated that paracetamol was a contributing factor in 30–40% of all poisonings admitted to Scottish hospitals at a rate of ~130 per 100 000 between 1995 and 2002.

The Carstairs score is a deprivation score, usually applied by postcode region, derived from census information. For the general population the mean Carstairs score is zero, a positive score indicates relative deprivation and a negative score relative affluence. The mean Carstairs score of all patients admitted to the SLTU was 1.26 ± 3.97 and of those admitted secondary to paracetamol overdose was 1.68 ± 4.05. The Carstairs score of those admitted secondary to POD (95% CI 1.34 – 2.01) was significantly higher than that of the general population ($P < 0.001$) and the population of patients admitted to the SLTU ($P < 0.001$), demonstrating a link between social deprivation and paracetamol overdose necessitating admission to the SLTU. Given the demographics of those presenting to Scottish emergency departments with self poisoning[18] this result is unsurprising and analysis of poisoning patients in Scotland reveals wide socio-economic disparity—the most deprived being over represented in frequency and mortality data.[19] The relationship between social deprivation and transplant candidacy has been previously investigated using the SLTU database and there was no relationship found between social deprivation and transplant candidacy.[20]

Hepatic encephalopathy is a cardinal feature of ALF and is commonly used in prognostic scoring criteria for ALF, for example KCHPPC[10] and Clichy.[21] There has been extensive research into the sensitivity and specificity of these various scoring criteria for identifying patients that are suitable for liver transplant. However, their remains a lack of robust criteria for identifying patient that require transfer to a specialist liver transplant unit. The need for such criteria is demonstrated by the grade of encephalopathy on admission to the SLTU. A total of 44/658 (6.7%) of paracetamol overdose patients and 22/255 (8.6%) of the non-POD aetiology group were admitted severely encephalopathic (grade III or IV) and were not yet ventilated, these patients should have been transferred earlier or ventilated prior to transfer.

Most patients admitted to the SLTU were not encephalopathic on admission. Schmidt and Larson[22] found that MELD score may be useful in the pre-encephalopathic assessment of paracetamol overdose as a screening indicator for identifying the subgroup of patients that are more likely to go on to develop ALF. Many admissions to the SLTU never developed encephalopathy.

Incidence data were calculated for admissions to the SLTU and for patients with ALF (encephalopathic during admission, chronic liver failure excluded).

A total of 56.6% of patients admitted were encephalopathic during admission, a cardinal feature of ALF. Therefore, 43.4% of admissions had severe liver injury but did not have ALF.

As ALF is a rare condition accurate yearly incidence figures are difficult to establish. From this study covering 16 complete years, a defined geographical area and accurately recorded population (5064200 capita, 2001 census[9]) the yearly incidence of ALF (encephalopathic during admission, chronic excluded) was 0.62 per 100 000 population. The yearly incidence of ALF secondary to paracetamol overdose was 0.43 per 100 000 population and the yearly incidence secondary to other causes 0.20 per 100 000 population. Lee (1993)[2] estimate that the yearly incidence of ALF in the USA is ~2000 people (US Population 257 million, 1 July 1993),[3] giving an incidence of 0.78 per 100 000 population per year, similar to our estimate in the Scottish population but higher that that of Gow et al., 2004[8] who estimate the incidence of ALF in the states of Victoria and Tasmania, Australia, as ~1 per million population (0.1 per 100 000 population). All three estimates demonstrate the low incidence of ALF and the consequent difficulties in studying this condition; requiring either a very large population or a long time to acquire sufficient data. One frequent proxy used to estimate the incidence is mortality. Annual variation of mortality of ALF patients in our study was not statistically significant ($P = 0.73$), but because of the very low incidence, using mortality as a proxy for incidence is likely to be inaccurate.

We accept that not all patients with ALF are transferred to the SLTU and it is worth noting that there may be a significant sub-population of patients with ALF that never get referred. However, there were also a significant number of patients that were admitted to the unit with 'ALF' but on further investigation their liver dysfunction transpired to be chronic (29 patients), or acute on chronic (alcoholic hepatitis, 9 patients). Evidently, the boundary between acute and chronic liver failure is not as clinically evident as initially expected.

Paracetamol overdose was by far the largest aetiological factor causing admission (responsible for 73.9% of cases) in this study. A total of 36.7%

of these patients had a past medical history of previous overdoses. Paracetamol has been identified as one of the main causes of ALF both in the UK,[4] the USA[6,7,23] and Australia.[8] Yet our data shows a far higher incidence than in previous US studies (20%;[6] 39%;[7] 19%[23]), Australian studies (36%)[8] and some other European studies [e.g. Areia *et al*. only identified 1 patient (2%) with paracetamol overdose as the causative aetiology in their study of 61 patients[15]].

Paracetamol is a well-recognized dose-dependant hepatotoxin. A total of 24.2% of POD admissions were staggered and 70.8% of single time-point overdoses were delayed ($\geqslant$15 h) presentations. This complicates the treatment of these patients as the treatment is normally based around the use of the Prescott nomogram, which is not applicable in staggered overdoses or delayed presentations. There is very little evidence for liver injury when paracetamol is used within recommended doses. In this study there were four patients included that reported having ingested $\leqslant$4 g paracetamol. This may represent interference by co-factors (e.g. chronic alcohol abuse, fasting or co-ingestion with cytochrome P450 inducers[24]).

Non-A–E hepatitis was the second largest causative aetiology, implicated in 7.8% of cases. In keeping with current evidence,[25] there were no cases of Hepatitis C-induced ALF. Given the longevity and large size of this study, this is good evidence that this condition alone does not cause ALF, or does so extremely infrequently. Interestingly, and in-keeping with evidence suggesting that hepatitis E is an increasingly recognized form of acute viral hepatitis,[26] ALF as a complication of hepatitis A was associated with a similar frequency as those associated with hepatitis E. Numbers with hepatitis E may be underestimated as routine testing has only recently been introduced.

While idiosyncratic drug reactions as a group were responsible for 4.6% of admissions, the third largest group, no individual drug was implicated for more than five cases and no therapeutically administered drug was responsible for more than three cases over the study period. Therefore, while catastrophic, cases of idiosyncratic drug reaction are very rare and our data does not implicate a drug hazard that a change in clinical practise could mitigate against.

Transplantation or death occurred much less frequently in the paracetamol overdose group (chronic liver disease excluded), the relative risk of transplantation or death was 0.64 (OR 0.47). This is in keeping with the clinical picture of paracetamol overdose of rapid deterioration but relatively good prognosis with medical management.[1] However, the relative risk of not being considered a transplant candidate despite having met KCHPPC was 2.51 amongst paracetamol overdose patients (OR 4.90) as previously discussed by Simpson *et al*. (2009),[5] where it was shown that the decreased survival to transplant in the POD group was due to an increased prevalence of psychiatric contraindications to transplantation and a decreased survival while on the transplant waiting list when compared to non-POD patients. It was demonstrated that most non-POD patients not listed despite meeting KCHPPC were excluded predominantly because of medical reasons. However, of the POD patients not listed despite meeting KCHPPC, only half were excluded because they were medically unsuitable for transplantation. Half were excluded due to psychiatric reasons; the most frequently cited reason (in two-thirds of cases) was 'active and resistant alcohol dependence', a factor that only featured in one case (5%) of non-POD patients not listed despite meeting KCHPPC. However, of those transplanted there were no significant differences identified between POD and non-POD patients with respect to 1- and 5-year survival.

Multivariate logistic regression revealed an association between encephalopathy, white cell count, PT time, creatinine and bilirubin at admission to the referring hospital. As expected those patients that were encephalopathic on admission had poorer outcomes as did those with higher white cell counts, prolonged PT times and higher serum creatinine and bilirubin—indicating worsening hepatic impairment and multi-organ dysfunction. At admission to the SLTU, the list of factors associated with outcome had expanded to include haemoglobin concentration, platelet count and serum potassium, urea and ALT. The larger list of associated factors is likely to be a product of worsening disease and physiological parameters in the time from admission to the referring hospital to transfer to the SLTU. As haemoglobin, platelet count, urea and ALT increased prognosis improved; as serum potassium increase prognosis worsened—again largely consistent with worsening organ dysfunction. However, increasing ALT and serum urea do not fit this pattern. We suggest that these are likely to be correlated with POD and therefore associated with an improved spontaneous survival as discussed above.

The liver transplantation rate amongst admissions was 12.4%; lower than in many other studies.[7,15] However, the survival to transplant rate of those listed for transplant (76.0%) was similar [Areia *et al*.[15]—82.5% (33/40) transplanted when criteria for transplant met and no contraindications; Ostapowicz *et al*.[7]—66% of those listed; Gow

et al.[8]—74% (26/35) of those listed]. This is likely a result of the increased prevalence of paracetamol overdose in our population.

16.2% of patients met KCHPPC. Of the transplant candidates not to receive a LT mortality was approaching 100%. There was not however any statistically significant difference in outcome between those that were not listed for transplant and those that died on the transplant waiting list. This uniformly bad prognosis is a good indicator that the specificity (96%) and positive predictive value (89%) of death given by the scoring criteria, in this case KCHPPC, is an effective clinical tool.

Survival amongst transplanted patients (76.1% to discharge and 72.3% at 1 year) were similar to previous studies (Areia *et al.*[15]—70% survival at 6 months; Ostapowicz *et al.*[7]—84% survival at 3 weeks of transplanted patients; Bernal *et al.*[12]—75% survival to discharge; Gow *et al.*[8]—77% of transplanted patient survival at 1 year). As was overall mortality—29% (Areia *et al.*[15]—31% overall mortality; Ostapowicz *et al.*[7]—33% mortality at 3 weeks).

Conclusion

This large, prospective, single centre study represents the Scottish experience of ALF since the inception of the SLTU in 1992. The annual incidence of ALF in the Scottish population is 0.62 per 100 000 population. Paracetamol overdose is by far the dominant aetiology requiring transfer to the SLTU. Transplant and death occurred much less frequently following paracetamol overdose than other aetiologies. However, despite therapeutic advances and liver transplantation, ALF remains a serious and frequently fatal condition.

Conflict of interest: None declared.

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