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Prevalence, severity, duration and resolution of cholestasis after acute liver failure

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ABSTRACT

Objective Persistent cholestasis may follow acute liver failure (ALF), but its course remains unknown. We aimed to describe the prevalence, onset, severity, duration and resolution of post-ALF cholestasis.

Design Cohort of 127 adult patients with ALF at a liver transplantation centre identified using electronic databases. We obtained laboratory data every 6 hours for the first week, daily until day 30 and weekly, when documented, until day 180.

Results Median age was 40.7 (IQR 31.0–52.4) years, median peak alanine aminotransferase level was 5494 (2521–8819) U/L and 87 (68.5%) cases had paracetamol toxicity. Overall, 12.6% underwent transplantation (3.4% for paracetamol vs 32.5% for non-paracetamol; p<0.001). Ninety-day mortality was 20.7% for paracetamol versus 30.0% for non-paracetamol patients. All non-transplanted survivors reached a bilirubin level>50 µmol/L, which peaked 3.5 (1.0–10.1) days after admission at 169.0 (80.0–302.0) µmol/L. At hospital discharge, 18.8% of patients had normal bilirubin levels and, at a median follow-up time from admission to last measurement of 16 (10-30) days, 46.9% had normal levels. Similarly, there was an increase in alkaline phosphatase (ALP) (207.0 (148.0–292.5) U/L) and gamma-glutamyl transferase (GGT) (336.0 (209.5–554.5) U/L) peaking at 4.5 days, with normalised values in 40.3% and 8.3% at hospital discharge.

Conclusion Post-ALF cholestasis is ubiquitous. Bilirubin, ALP and GGT peak at 3 to 5 days and, return to baseline in the minority of patients at median follow-up of 16 days. These data inform clinical expectations of the natural course of this condition.

Summary box

What is already known on this topic

- Following major injury, liver recovery is complex and can be slow.
- No studies have provided prolonged detailed assessment of post-ALF cholestasis.

what this study adds

- We have described the prevalence, severity, duration and time to normalisation of markers of blood purification of factors that lead to jaundice (cholestasis) in such patients admitted to intensive care.
- Only a minority of patients achieve normal cholestasis markers by hospital discharge, and some even fail to return to normal at subsequent longer follow-up.
- how this study might affect research, practice and/or policy
- These findings inform clinical expectations of the natural course of this condition and help with both diagnosis and prognosis.
- Importantly, they can be of assistance during conversations with patients and families regarding realistic expectations post-ALF jaundice and its likely duration.

INTRODUCTION

Acute liver failure (ALF) is a rapidly progressive severe illness typically leading to intensive care unit (ICU) admission.[1] ALF carries a high mortality without emergency liver transplantation (ELT).[2 3] Nonetheless, with intensive supportive care, some patients (especially after paracetamol overdose) recover sufficient function without transplantation.[3] However, in all cases, in the absence of transplantation, improvement can be slow and may be associated with several biochemical abnormalities.

Almost all studies of the biochemical abnormalities associated with ALF have focused on aminotransferase levels on admission to hospital[3–12] and/or have followed biochemical recovery for just 1 week from admission.[13–16] No studies have provided a prolonged detailed assessment of markers of ALF cholestasis (bilirubin, alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT)). This is unfortunate because prolonged postinjury jaundice may be of concern to patients, families and clinicians. Moreover, knowledge of the typical course of postinjury cholestasis would provide useful diagnostic and prognostic information.

Table 1 Baseline characteristics of the included patients considering only survivors and patients who did not undergo transplantation

	Overall (n=85)	Type of liver failure		P value
		Paracetamol (n=67)	Non-paracetamol (n=18)	
Age, years	38.6 (28.3–51.2)	38.6 (29.5–51.6)	38.7 (27.3–46.8)	0.906
Male gender, n (%)	11 (12.9)	6 (9.0)	5 (27.8)	0.050
Body mass index, kg/m^2	24.8 (21.6–27.8)	24.6 (22.2–28.0)	25.2 (21.3–27.1)	0.451
Severity of illness				
APACHE II	14.0 (10.0–18.0)	14.0 (9.5–18.0)	15.5 (10.0–20.8)	0.438
APACHE III	61.0 (46.0–80.0)	59.0 (45.5–78.0)	63.5 (50.2–81.8)	0.788
ANZROD	0.09 (0.04–0.26)	0.09 (0.04–0.26)	0.09 (0.05–0.22)	0.974
MET call admission, n (%)	3 (3.5)	1 (1.5)	2 (11.1)	0.112
Acute liver failure aetiology, n (%)				< 0.001
Paracetamol	67 (78.8)	67 (100.0)	0 (0.0)	
Unknown	6 (7.1)	0 (0.0)	6 (33.3)	
Other drugs	2 (2.4)	0 (0.0)	2 (11.1)	
Vascular	1 (1.2)	0 (0.0)	1 (5.6)	
Amanita phalloides	3 (3.5)	0 (0.0)	3 (16.7)	
Viral	2 (2.4)	0 (0.0)	2 (11.1)	
Alcohol	2 (2.4)	0 (0.0)	2 (11.1)	
Autoimmune	1 (1.2)	0 (0.0)	1 (5.6)	
NAFLD of pregnancy	1 (1.2)	0 (0.0)	1 (5.6)	
Other	–	–	–	
ICU source of admission, n (%)				0.104
Other hospital	63 (74.1)	52 (77.6)	11 (61.1)	
ICU from other hospital	15 (17.6)	10 (14.9)	5 (27.8)	
Emergency department	4 (4.7)	4 (6.0)	0 (0.0)	
Ward	3 (3.5)	1 (1.5)	2 (11.1)	
Hospital source of admission, n (%)				0.425
Other hospital	63 (74.1)	50 (74.6)	13 (72.2)	
ICU from other hospital	13 (15.3)	8 (11.9)	5 (27.8)	
Home	5 (5.9)	5 (7.5)	0 (0.0)	
Emergency department from other hospital	3 (3.5)	3 (4.5)	0 (0.0)	
Nursing home	1 (1.2)	1 (1.5)	0 (0.0)	
Hepatic encephalopathy, n (%)	56 (65.9)	45 (67.2)	11 (61.1)	0.780
1	26 (30.6)	20 (29.9)	6 (33.3)	0.968
2	15 (17.6)	13 (19.4)	2 (11.1)	
3	9 (10.6)	7 (10.4)	2 (11.1)	
4	6 (7.1)	5 (7.5)	1 (5.6)	
Acute kidney injury at ICU admission, n (%)	22 (25.9)	18 (26.9)	4 (22.2)	0.772
Organ support at ICU admission, n (%)				
Renal replacement therapy	56 (86.2)	43 (86.0)	13 (86.7)	0.999
Mechanical ventilation	37 (43.5)	29 (43.3)	8 (44.4)	0.999
Coexisting disorders, n (%)				
Chronic respiratory disease	0 (0.0)	0 (0.0)	0 (0.0)	---
Chronic cardiovascular disease	0 (0.0)	0 (0.0)	0 (0.0)	---
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	---
Immune disease	1 (1.2)	1 (1.5)	0 (0.0)	0.999

Continued

Table 1 Continued

	Overall (n=85)	Type of liver failure		P value
		Paracetamol (n=67)	Non-paracetamol (n=18)	
Immunosuppression	3 (3.5)	3 (4.5)	0 (0.0)	0.999
Leukaemia	0 (0.0)	0 (0.0)	0 (0.0)	---
Vital signs at ICU admission				
Highest temperature, °C	37.0 (36.5–37.5)	37.0 (36.5–37.5)	37.0 (36.5–37.3)	0.293
Highest heart rate, bpm	115 (100–130)	112 (101–130)	117 (101–134)	0.901
Lowest mean arterial pressure, mm Hg	67 (62–75)	67 (62–75)	70 (63–78)	0.401
Highest respiratory rate, breaths/min	22 (18–28)	22 (16–28)	21 (18–27)	0.816
Urine output, mL	1247 (369–1824)	1070 (323–1650)	1650 (1102–2150)	0.061
Laboratory tests at ICU admission				
Lowest albumin, g/L	27 (24–29)	26 (23–29)	27 (25–29)	0.267
pH	7.41 (7.30–7.46)	7.43 (7.30–7.46)	7.39 (7.31–7.41)	0.242
PaO_2/FiO_2	424 (293–533)	414 (300–537)	443 (221–500)	0.839
$PaCO_2$, mm Hg	33 (29–37)	33 (28–37)	33 (30–39)	0.546
Bilirubin, µmol/L	81 (50–127)	81 (50–127)	85 (50–143)	0.683
Highest creatinine, µmol/L	132 (75–257)	129 (76–186)	182 (69–348.2)	0.444
Lowest glucose, mmol/L	5.3 (4.6–6.5)	5.3 (4.7–6.3)	5.3 (4.2–6.8)	0.743
Lowest haemoglobin, g/L	102 (87–114)	102 (87–112)	103 (86–121)	0.519
Highest white blood cell count, $\times 10^9$/L	10.8 (6.7–16.0)	10.8 (6.6–15.3)	11.9 (7.1–18.6)	0.543
Lactate, mmol/L	4.1 (3.2–5.9)	4.1 (3.4–5.8)	4.1 (2.9–8.9)	0.826
Lowest platelets, $\times 10^9$/L	107 (70–162)	100 (70–162)	126 (70–165)	0.607
Urea, mmol/L	5.4 (3.3–9.9)	5.0 (3.2–9.9)	6.3 (4.5–17.0)	0.202

Data are median (IQR) or N (%).
ANZROD, Australian and New Zealand risk of death; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; MET, medical emergency team; NAFLD, non-alcoholic fatty liver disease.

Accordingly, in order to define the natural course of such cholestasis in the absence of liver transplantation, we aimed to study the prevalence, severity, duration and resolution of postinjury cholestasis in ALF patients overall and according to the aetiology of ALF (paracetamol vs non-paracetamol).

METHODS

Study design

We performed a single-centre retrospective observational study in an academic tertiary teaching hospital referral centre for liver transplantation (Austin Hospital, Heidelberg, Australia).

Patients

All adult patients (age>16 years) with an ICU admission diagnosis of ALF were eligible for inclusion. We excluded patients with chronic liver disease (either on historical, clinical, laboratory, radiographic and/or histopathologic results) based on agreement between two investigators (SW and CM). For patients who were readmitted to the ICU, only the first admission was included.

Data collection and definitions

We used the Australian and New Zealand Intensive Care Society Adult Patient database[17] for patient screening and selection, and retrieval of patient demographics and biochemical and in-hospital outcomes. We obtained additional data, including aetiology of hepatic insult, hepatic encephalopathy scores on admission according to West Haven criteria (independently assessed by two investigators), 30-day and 90-day survival, vital signs, supportive therapies (including sedation, mechanical ventilation, renal replacement therapy) and laboratory test results from the hospital's electronic medical records. Laboratory data were obtained every 6 hours for 7 days while in ICU, daily (when available) until day 30 and weekly (when available) until day 180, or until time of death or ELT. Day 1 was the first day of ICU admission.

We defined normalisation of laboratory tests as two consecutive measurements within the normal laboratory range: alanine aminotransferase (ALT)≤40 U/L, an aspartate aminotransferase (AST)≤35 U/L, a GGT≤50 U/L, an ALP≤110 U/L and bilirubin≤21 µmol/L.

We defined time to normalisation as the number of days between ICU admission and the normalisation of

Table 2 Laboratory tests in the included patients considering only survivors and patients who did not undergo transplantation

	Overall (n=85)	Type of liver failure		P value
		Paracetamol (n=67)	Non-paracetamol (n=18)	
Transaminases				
Alanine aminotransferase				
Peak, U/L	5594 (3463–8868)	6529 (3862–9356)	4468 (2314–5992)	0.018
Days between ICU admission and peak	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.6)	0.004
Days until normalisation*	21.5 (17.5–29.5)	20.0 (18.0–26.5)	45.0 (29.0–80.0)	0.373
Patients with normalisation at latest follow-up	18/62 (29.0)	15/46 (32.6)	3/16 (18.8)	0.355
Median time until last measurements, days	16.0 (10.0–30.0)	15.0 (9.0–29.0)	19.0 (12.0–30.8)	0.438
Number of measurements after hospital DC	1.6±2.7	1.4±2.2	2.5±4.2	0.133
Patients with normalisation until hospital DC	12/85 (14.1)	11/67 (16.4)	1/18 (5.6)	0.446
Aspartate aminotransferase				
Peak, U/L	7343 (3808–11 010)	7711 (4987–11 010)	5984 (2594–11 160)	0.407
Days between ICU admission and peak	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.5)	0.034
Days until normalisation*	12.0 (11.0–14.0)	12.0 (11.0–14.0)	13.0 (11.0–15.0)	0.999
Patients with normalisation at latest follow-up	13/50 (26.0)	9/37 (24.3)	4/13 (30.8)	0.719
Median time until last measurements, days	13.0 (8.2–22.8)	13.5 (8.2–23.0)	13.0 (10.0–19.0)	0.625
Number of measurements after hospital DC	0.8±1.0	0.7±0.9	1.1±1.3	0.139
atients with normalisation until hospital DC	9/78 (11.5)	7/62 (11.3)	2/16 (12.5)	0.999
Coagulation				
APTT				
Peak, s	44.0 (38.0–60.0)	44.0 (38.0–55.0)	57.5 (40.2–69.5)	0.177
Days between ICU admission and peak	0.6 (0.0–4.6)	0.6 (0.0–4.6)	2.0 (0.1–4.6)	0.444
INR				
Peak	4.5 (3.1–5.8)	4.6 (3.2–5.9)	3.7 (2.3–4.7)	0.090
Days between ICU admission and peak	0.0 (0.0–0.5)	0.0 (0.0–0.0)	0.0 (0.0–0.6)	0.245
Days until normalisation*	7.5 (6.0–11.0)	9.0 (5.8–13.2)	7.0 (6.0–7.0)	0.090
Patients with normalisation at latest follow-up	42/68 (61.8)	32/52 (61.5)	10/16 (62.5)	0.999
Median time until last measurements, days	13.0 (9.0–27.0)	15.0 (8.0–27.5)	12.5 (10.2–18.5)	0.539
Number of measurements after hospital DC	1.0±1.4	1.0±1.5	0.9±0.9	0.846
Patients with normalisation until hospital DC	36/85 (42.4)	27/67 (40.3)	9/18 (50.0)	0.592
Renal				
Creatinine				
Peak, µmol/L	210.0 (111.0–451.0)	200.0 (106.5–450.0)	295.0 (139.2–476.5)	0.423
Days between ICU admission and peak	4.5 (0.0–9.6)	4.6 (0.0–10.1)	3.5 (0.1–9.3)	0.952
Days until normalisation*	1.0 (1.0–3.0)	1.0 (1.0–3.0)	2.0 (1.0–5.0)	0.160
Patients with normalisation at latest follow-up	69/81 (85.2)	56/63 (88.9)	13/18 (72.2)	0.126
Median time until last measurements, days	15.0 (9.0–31.0)	15.0 (9.0–30.5)	16.0 (11.2–30.8)	0.698
Number of measurements after hospital DC	1.6±2.9	1.4±2.3	2.5±4.4	0.158
Patients with normalisation until hospital DC	66/85 (77.6)	54/67 (80.6)	12/18 (66.7)	0.217
Urea				
Peak, mmol/L	12.5 (7.6–18.5)	11.6 (7.4–17.6)	14.0 (10.0–22.2)	0.280
Days between ICU admission and peak	6.5 (0.5–10.5)	6.5 (0.6–11.5)	5.6 (0.1–8.3)	0.491
Others				
Ammonia				
Peak, L	123.0 (92.0–178.0)	123.0 (96.0–184.5)	119.0 (75.8–143.2)	0.346

Continued

Table 2 Continued

	Overall (n=85)	Type of liver failure		
		Paracetamol (n=67)	Non-paracetamol (n=18)	P value
Days between ICU admission and peak	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.5 (0.0–1.6)	0.031
Days until normalisation*	8.5 (5.5–12.0)	10.0 (6.5–13.0)	6.0 (4.0–7.0)	0.153
Patients with normalisation at latest follow-up	24/27 (88.9)	19/20 (95.0)	5/7 (71.4)	0.156
Median time until last measurements, days	7.0 (4.0–11.0)	7.0 (4.0–12.0)	6.5 (4.0–8.0)	0.406
Number of measurements after hospital DC	0.0±0.2	0.0±0.1	0.1±0.3	0.050
Patients with normalisation until hospital DC	24/81 (29.6)	19/63 (30.2)	5/18 (27.8)	0.999
Lactate				
Peak, mmol/L	5.7 (3.7–7.9)	6.4 (4.7–9.5)	5.7 (3.1–6.5)	0.624
Days between ICU admission and peak	1.5 (0.0–1.6)	0.0 (0.0–0.4)	1.6 (1.5–1.6)	0.071
Days until normalisation*	2.5 (1.2–4.5)	5.0 (5.0–5.0)	2.0 (1.0–3.0)	0.373
Patients with normalisation at latest follow-up	6/6 (100.0)	1/1 (100.0)	5/5 (100.0)	---
Median time until last measurements, days	9.0 (6.0–10.0)	11.5 (4.2–20.2)	9.0 (6.0–10.0)	0.999
Number of measurements after hospital DC	0	0	0	---
Patients with normalisation until hospital DC	6/9 (66.7)	1/4 (25.0)	5/5 (100.0)	0.048

Data are median (IQR) or N (%).
*Days to normalisation refers only to those patients where normalisation documented at the time of longest follow-up.
†Normalisation was defined as two consecutive measurements with alanine aminotransferase≤40 U/L or aspartate aminotransferase≤35 U/L or INR≤1.1 or creatinine≤115 µmol/L or ammonia≤35 µmol/L or lactate≤2 mmol/L.
APTT, activated partial thromboplastin time; DC, discharge; ICU, intensive care unit; INR, international normalised ratio.

the test, as described above. The peak value was defined as the highest value within the follow-up period.

Statistical analysis

Continuous variables are reported as median (quartile 25% to quartile 75%) or means with 95% CIs as appropriate and categorical variables as number (percentage). We divided patients according to the aetiology of ALF into paracetamol or non-paracetamol-related ALF. We compared continuous variables using the Wilcoxon rank-sum test and, for categorical variables, using Fisher's exact test.

We plotted laboratory tests (when performed) over time after excluding measurements after ELT, stratified according to aetiology and presented as mean with 95% CI. We compared groups using mixed-effect linear models with the group, time (as a continuous variable) and interaction between group×time included as fixed effect, with patients included as random effect to account for repeated measurements. Two p values are reported: (1) p value for the group difference, reflecting the overall test for differences between groups across the follow-up; and (2) p values for the group×time interaction, evaluating whether change over time differed by group. All analyses were performed using the software R (R Core Team, 2016, Vienna, Austria), and, given the multiplicity of comparisons and variables, a p value<0.01 was considered statistically significant.

RESULTS

Patients

We studied 127 ALF patients admitted to the study ICU between 1 January 2010 and 30 June 2020. Their baseline characteristics are reported in online supplemental etable 1. Median age was 40.7 (31–52) years, 84.3% were women, and the most frequent ALF aetiology was paracetamol overdose (68.5%). Patients in the paracetamol group were more often women, had higher ALT and AST and more prolonged international normalised ratio (INR) values, but lower bilirubin levels at ICU admission. All other laboratory tests and vital signs were similar. On the day of ICU admission, 90.3% were treated with continuous renal replacement therapy and 55.1% with mechanical ventilation. ALT, bilirubin and ALP differed between transplanted patients, non-transplanted survivors and non-transplanted non-survivors at presentation (online supplemental etable 2).

Clinical outcomes

Overall, 12.6% of patients underwent ELT, with fewer patients receiving ELT in the paracetamol group (3.4% vs 32.5%; p<0.001). Overall, 30-day mortality was 20.5% (18.4% paracetamol vs 25% non-paracetamol; p=0.478) and 90-day mortality was 23.6% (20.7% paracetamol vs 30% non-paracetamol; p=0.268) (online supplemental etable 3). After excluding transplantation and non-survivors, 85 non-transplanted survivors remained for analysis of post-ALF cholestasis (table 1). The duration of stay in ICU and hospital for such survivors is presented in online supplemental etable 4

Laboratory tests

Laboratory tests for markers of organ injury including time to peak level and time to normalisation in survivors

Table 3 Laboratory tests results for markers of cholestasis considering only survivors and patients who did not undergo transplantation

	Overall (n=85)	Type of liver failure		P value
		Paracetamol (n=67)	Non-paracetamol (n=18)	
Cholestatic markers				
Alkaline phosphatase				
Peak, U/L	183.0 (140.0–243.0)	179.0 (134.5–244.5)	207.0 (167.0–225.8)	0.501
Days between ICU admission and peak	4.5 (1.5–8.5)	4.5 (1.5–8.6)	5.1 (2.1–8.3)	0.666
Days until normalisation*†	6.0 (4.5–12.5)	6.0 (4.2–12.0)	12.0 (10.0–13.0)	0.306
Patients with normalisation at latest follow-up	31 / 69 (44.9)	26 / 52 (50.0)	5 / 17 (29.4)	0.168
Median time until last measurements, days	16.0 (10.0–30.0)	15.0 (9.0–29.0)	19.0 (12.0–30.8)	0.438
Number of measurements after hospital DC	1.6±2.7	1.4±2.2	2.4±4.2	0.154
Patients with normalisation until hospital DC	29 / 72 (40.3)	26 / 56 (46.4)	3 / 16 (18.8)	0.081
Gamma-glutamyl transferase				
Peak, U/L	341.0 (223.0–492.0)	338.0 (228.0–500.5)	354.0 (195.5–473.8)	0.936
Days between ICU admission and peak	4.6 (3.5–8.6)	4.5 (3.5–8.6)	5.6 (4.5–9.0)	0.511
Days until normalisation*†	15.0 (8.5–40.0)	12.5 (4.8–24.2)	28.0 (24.0–43.5)	0.153
Patients with normalisation at latest follow-up	11 / 62 (17.7)	8 / 45 (17.8)	3 / 17 (17.6)	0.999
Median time until last measurements, days	16.0 (10.0–30.0)	15.0 (9.0–29.0)	19.0 (12.0–30.8)	0.438
Number of measurements after hospital DC	1.6±2.7	1.4±2.2	2.4±4.2	0.154
Patients with normalisation until hospital DC	7 / 84 (8.3)	6 / 67 (9.0)	1 / 17 (5.9)	0.999
Bilirubin				
Peak, µmol/L	169.0 (80.0–320.0)	181.0 (78.0–313.5)	136.5 (88.8–396.5)	0.855
Days between ICU admission and peak	3.5 (1.5–10.6)	3.6 (1.0–10.6)	2.5 (1.5–8.1)	0.553
Days until normalisation*†	14.0 (5.0–50.5)	17.0 (5.0–66.0)	11.0 (8.5–14.8)	0.541
Patients with normalisation at latest follow-up	30 / 64 (46.9)	22 / 48 (45.8)	8 / 16 (50.0)	0.781
Median time until last measurements, days	16.0 (10.0–30.0)	15.0 (9.0–29.0)	19.0 (12.0–30.8)	0.438
Number of measurements after hospital DC	1.6±2.7	1.4±2.2	2.4±4.2	0.153
Patients with normalisation until hospital DC	16 / 85 (18.8)	13 / 67 (19.4)	3 / 18 (16.7)	0.999

Data are median (IQR) or N (%).
*Days until normalisation applies only to those patients who achieved normalisation. Normalisation was defined as two consecutive measurements with alkaline phosphatase<110 U/L or gamma-glutamyl transferase<50 35 U/L or bilirubin≤21 µmol/L.
†Considering the time after the first abnormal value until normalisation.
DC, discharge; ICU, intensive care unit.

are presented in table 2. Patients exhibited major abnormalities of coagulation, ammonia, lactate and renal function tests, with greater abnormalities of ALT and AST and earlier onset of abnormalities for paracetamol overdose. Overall, ALT levels returned to normal in 14.1% of patients (16.4% paracetamol vs 5.6% non-paracetamol) with a similar pattern for AST. At hospital discharge, the INR had normalised in approximately half of ALF patients, and the serum creatinine in three-quarters of patients.

Cholestasis markers

Among non-transplanted survivors, the peak level, days to peak level after ICU admission and days to normalisation and number and percentage of patients achieving normalisation are presented in table 3. The median peak bilirubin level was 169 µmol/L, peaking at day 3.5 days. Although the bilirubin level was lower at baseline for paracetamol, it rapidly increased to equivalent levels to non-paracetamol ALF by day 4 (figure 1). In the patients where normalisation occurred at last follow-up (n=30), the median number of days to normalisation was 14.

Changes in bilirubin were accompanied by an ALP increase to a median peak of 183 U/L after a median of 4.5 days, and GGT to 341 U/L by 4.5 days (table 3). The courses of ALT, ALP, GGT and bilirubin levels in the week

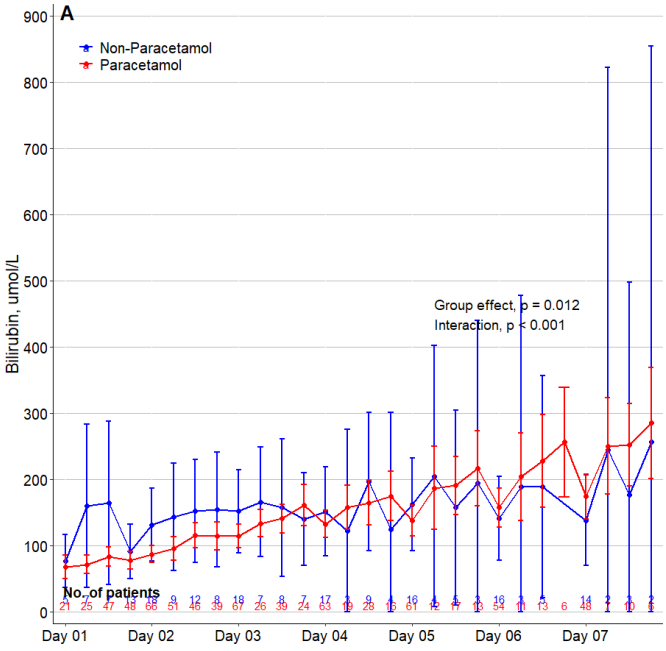

Figure 1 Trend of bilirubin over 7 days. Trend of serum bilirubin (µmol/L) over 7 days using all available measurements. Data are mean and 95% CI. Each timepoint represents 6 hours. All figures stratified by aetiology: paracetamol group (red), non-paracetamol group (blue). Number of patient values for each timepoint documented for paracetamol (red) and non-paracetamol groups (blue). P values reported for group difference and for group×time interaction.

following ICU admission are shown in figure 2. When followed to 30, 60, 90 and 180 days, as shown in figure 3, ALT levels were essentially down to normal levels by day 15. In contrast, all markers of cholestasis remained abnormal for much longer (table 4). Patients with follow-up measurement of bilirubin after hospital discharge did not appear to differ from those without such follow-up (table 5).

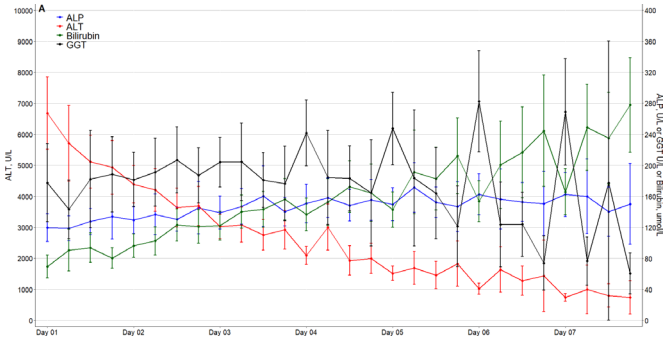

Figure 2 Trend of alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin over the first 7 days. ALT (red), plotted against left y-axis (U/L). ALP (blue) and bilirubin (green) plotted against right y-axis in U/L and µmol/L, respectively. Each timepoint represents mean and 95% CI 6-hourly for first 7 days.

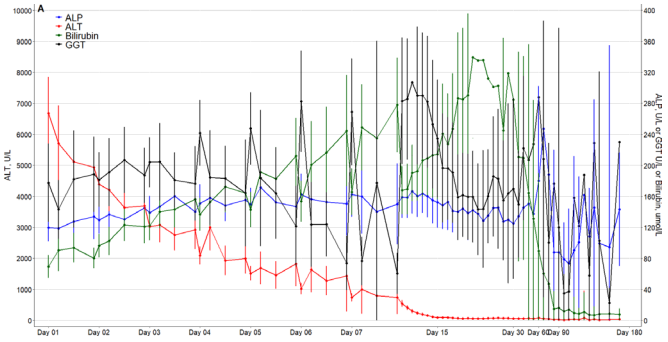

Figure 3 Trend of alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin over 180 days. ALT (red), plotted against left y-axis (U/L). ALP (blue) and bilirubin (green) plotted against right y-axis in U/L and µmol/L, respectively. Each timepoint represents mean and 95% CI 6-hourly for first 7 days, daily until 30 days, then weekly until 180 days, where all available measurements were used.

DISCUSSION

Key findings

We studied the prevalence, severity, duration and time to normalisation of biochemical markers of cholestasis (bilirubin, ALP, GGT) after ALF in patients who survived without liver transplantation. We found that all patients developed biochemical evidence of cholestasis, which peaked between 3 and 5 days after ICU admission. Moreover, at hospital discharge, only one in five patients had achieved normal bilirubin levels and, at last follow-up, despite ALT levels returning to normal measurement at a median of 16 days, less than half had normal bilirubin levels. Finally, similarly, patterns of failed normalisation at hospital discharge or last follow-up also applied to ALP and GGT levels.

Relationship to previous studies

To the best of our knowledge, this is the only study detailing changes in bilirubin and liver enzymes in critically ill patients with ALF until hospital discharge and subsequent follow-up. In particular, it is the only one to report changes in biochemical markers of cholestasis over such an extended period. Previous studies have documented laboratory results in ALF patients, but typically only at the time of ICU admission or peak values.[3–12] Kumar *et al* found predictive value in combined assessment of binary trends of ammonia, bilirubin and INR (elevated, increased or decreased) but only over the first 3 days.[13] Only three studies, extended their observations to 1 week. Kim *et al* noted that a raised bilirubin and activated partial thromboplastin time were associated with mortality after poisonous mushroom ingestion, but of 93 study patients, only 23 had ALF and 10 died.[14] Koch *et al* reported lower bilirubin and ALP levels in 7 patients with ALF secondary to paracetamol versus 16 non-paracetamol patients but no laboratory follow-up beyond 7 days.[15] Finally, Li *et al* grouped 380 paediatric patients with indeterminate liver failure (only 48 had severe disease) according to biochemical (INR, bilirubin) and

Table 4 Liver enzyme levels at different follow up periods

	Overall (n=85)	Paracetamol (n=67)	Non-paracetamol (n=18)	P value
Follow-up time	16.0 (10.0–31.0)	15.0 (9.0–30.5)	19.0 (12.0–30.8)	0.491
Day 7				
Alanine aminotransferase	701.6 (455.5–1013.0)	701.6 (455.5–1009.9)	680.4 (476.5–1230.8)	0.799
Aspartate aminotransferase	85.3 (68.8–116.6)	83.8 (68.5–115.2)	97.2 (75.2–214.0)	0.212
Alkaline phosphatase	134.8 (108.2–181.3)	133.0 (103.7–182.2)	151.3 (118.8–175.0)	0.566
Gamma-glutamyl transferase	210.3 (135.9–340.9)	218.8 (135.9–320.9)	204.9 (161.8–449.4)	0.524
Bilirubin	119.2 (43.9–231.8)	134.7 (56.5–238.0)	75.8 (38.3–201.5)	0.448
Day 15				
Alanine aminotransferase	89.8 (61.1–121.4)	88.7 (70.3–116.3)	104.3 (52.2–130.2)	0.986
Aspartate aminotransferase	56.5 (37.4–77.8)	56.5 (37.9–73.2)	59.7 (35.4–85.7)	0.909
Alkaline phosphatase	118.0 (105.0–160.4)	116.7 (105.0–171.7)	120.0 (108.8–145.7)	0.901
Gamma-glutamyl transferase	129.3 (74.5–303.4)	126.7 (75.0–269.0)	253.7 (75.2–469.5)	0.682
Bilirubin	213.6 (27.9–300.8)	242.7 (60.0–291.3)	24.0 (18.5–212.3)	0.130
Day 30				
Alanine aminotransferase	40.4 (30.0–59.5)	51.7 (35.2–99.0)	32.0 (20.0–32.0)	0.061
Aspartate aminotransferase	86.0 (68.1–113.2)	86.0 (68.1–113.2)	---	---
Alkaline phosphatase	123.8 (78.2–150.8)	138.0 (110.7–175.8)	67.0 (64.0–117.0)	0.079
Gamma-glutamyl transferase	115.3 (65.2–173.2)	146.5 (84.8–278.8)	72.0 (39.0–80.0)	0.157
Bilirubin	130.0 (14.2–364.1)	203.5 (74.0–373.8)	9.0 (8.0–14.0)	0.047
Day 60				
Alanine aminotransferase	61.0 (39.5–100.0)	72.0 (52.8–108.5)	23.0 (23.0–23.0)	0.134
Aspartate aminotransferase	95.0 (52.0–144.8)	95.0 (52.0–144.8)	---	---
Alkaline phosphatase	177.0 (86.5–202.0)	179.0 (128.2–212.5)	61.0 (61.0–61.0)	0.207
Gamma-glutamyl transferase	196.0 (96.0–514.5)	341.0 (157.0–528.8)	44.0 (44.0–44.0)	0.134
Bilirubin	42.0 (19.5–123.0)	50.0 (27.0–155.5)	8.0 (8.0–8.0)	0.134
Day 90				
Alanine aminotransferase	18.0 (12.0–19.9)	18.0 (16.0–18.6)	20.8 (14.9–26.6)	0.999
Aspartate aminotransferase	---	---	---	---
Alkaline phosphatase	81.2 (69.5–103.9)	81.2 (64.6–105.6)	88.5 (78.8–98.2)	0.999
Gamma-glutamyl transferase	35.5 (25.2–57.2)	51.2 (37.2–146.9)	19.5 (17.8–21.2)	0.064
Bilirubin	9.3 (5.6–17.0)	15.6 (11.0–21.4)	4.8 (4.4–5.1)	0.064
Day 180				
Alanine aminotransferase	20.0 (13.5–40.8)	30.5 (14.5–48.0)	17.5 (13.8–21.2)	0.355
Aspartate aminotransferase	52.0 (52.0–52.0)	52.0 (52.0–52.0)	---	---
Alkaline phosphatase	140.5 (103.5–166.2)	160.5 (144.8–184.8)	86.0 (82.0–90.0)	0.064
Gamma-glutamyl transferase	133.5 (22.5–360.8)	320.5 (186.8–418.8)	18.5 (17.2–19.8)	0.064
Bilirubin	7.0 (3.2–11.5)	6.5 (3.0–11.5)	8.0 (6.0–10.0)	0.639

Data are median (IQR).
Definitions: day 7 (between day 6 and 8); day 15 (between day 14 and 16); day 30 (between day 29 and 31); day 60 (between day 55 and 65); day 90 (between day 80 and 100); day 180 (between day 160 and 200).

clinical data in the first 7 days of enrolment into common subgroups. However, only three or more laboratory values of any one measurement were required, missing data points were imputed based on observed data and linear trajectories in biochemical changes were assumed.[16]

Implications

Our findings imply that, in ALF patients, cholestasis is ubiquitous at presentation and peaks between 3 and 5 days. Moreover, they indicate that the cholestatic phase of injury is long. Finally, they demonstrate that less than one

Table 5 Baseline characteristics of the included patients according to the measurement or not of bilirubin after hospital discharge considering only survivors and patients who did not undergo transplantation

	Measurement of bilirubin after discharge		
	Yes (n=57)	No (n=28)	P value
Age, years	38.6 (31.1–48.0)	39.0 (24.1–55.2)	0.844
Male gender, n (%)	8 (14.0)	3 (10.7)	0.999
Body mass index, kg/m_2	24.2 (21.3–27.1)	25.7 (22.9–29.4)	0.284
Severity of illness			
APACHE II	14.0 (9.0–18.0)	14.0 (10.0–19.2)	0.650
APACHE III	59.0 (45.0–78.0)	63.0 (46.0–82.0)	0.397
ANZROD	0.1 (0.0–0.2)	0.1 (0.0–0.3)	0.466
MET call admission, n (%)	1 (1.8)	2 (7.1)	0.251
Acute liver failure aetiology, n (%)			0.211
Paracetamol	41 (71.9)	26 (92.9)	
Unknown	6 (10.5)	0 (0.0)	
Other drugs	1 (1.8)	1 (3.6)	
Vascular	1 (1.8)	0 (0.0)	
Amanita phalloides	3 (5.3)	0 (0.0)	
Viral	2 (3.5)	0 (0.0)	
Alcohol	2 (3.5)	0 (0.0)	
Autoimmune	1 (1.8)	0 (0.0)	
NAFLD of pregnancy	0 (0.0)	1 (3.6)	
ICU source of admission, n (%)			0.338
Other hospital	45 (78.9)	18 (64.3)	
ICU from other hospital	9 (15.8)	6 (21.4)	
Emergency department	2 (3.5)	2 (7.1)	
Ward	1 (1.8)	2 (7.1)	
Hospital source of admission, n (%)			0.110
Other hospital	46 (80.7)	17 (60.7)	
ICU from other hospital	8 (14.0)	5 (17.9)	
Home	2 (3.5)	3 (10.7)	
Emergency department from other hospital	1 (1.8)	2 (7.1)	
Nursing home	0 (0.0)	1 (3.6)	
Hepatic encephalopathy, n (%)	36 (63.2)	20 (71.4)	0.478
1	17 (29.8)	9 (32.1)	0.578
2	10 (17.5)	5 (17.9)	
3	4 (7.0)	5 (17.9)	
4	5 (8.8)	1 (3.6)	
Acute kidney injury at ICU admission, n (%)	14 (24.6)	8 (28.6)	0.793
Organ support at ICU admission, n (%)			
Renal replacement therapy	37 (86.0)	19 (86.4)	0.999
Mechanical ventilation	22 (38.6)	15 (53.6)	0.246
Coexisting disorders, n (%)			
Chronic respiratory disease	0 (0.0)	0 (0.0)	---
Chronic cardiovascular disease	0 (0.0)	0 (0.0)	---
Chronic kidney disease	1 (1.8)	1 (3.6)	0.999
Immune disease	1 (1.8)	0 (0.0)	0.999

Continued

Table 5 Continued

	Measurement of bilirubin after discharge		
	Yes (n=57)	No (n=28)	P value
Immunosuppression	3 (5.3)	0 (0.0)	0.548
Leukaemia	0 (0.0)	0 (0.0)	---
Vital signs at ICU admission			
Highest temperature, °C	37.1 (36.5–37.5)	37.0 (36.5–37.1)	0.203
Highest heart rate, bpm	110.0 (100.0–130.0)	124.0 (109.5–140.0)	0.064
Lowest mean arterial pressure, mm Hg	67.0 (62.0–77.2)	67.0 (59.8–72.5)	0.326
Highest respiratory rate, breaths/min	22.0 (18.0–28.0)	20.0 (15.8–25.0)	0.480
Urine output, mL	1150.0 (330.0–1932.5)	1343.5 (431.8–1631.2)	0.896
Laboratory tests at ICU admission			
Lowest albumin, g/L	27.0 (24.0–29.0)	26.0 (22.2–29.8)	0.974
pH	7.4 (7.3–7.5)	7.4 (7.3–7.5)	0.918
PaO_2/FiO_2	423.8 (269.6–533.3)	426.7 (359.5–532.1)	0.630
$PaCO_2$, mm Hg	31.0 (29.0–36.5)	34.5 (30.2–38.5)	0.152
Bilirubin, µmol/L	84.0 (54.0–127.5)	81.0 (44.8–121.2)	0.730
Highest creatinine, µmol/L	134.0 (75.5–265.5)	124.0 (75.0–160.8)	0.413
Lowest glucose, mmol/L	5.2 (4.6–6.5)	5.4 (4.6–6.5)	0.532
Lowest haemoglobin, g/L	102 (83–117)	103 (89–111)	0.907
Highest white blood cell count, $\times 10^9$/L	9.6 (6.2–15.8)	12.3 (8.2–15.7)	0.470
Lactate, mmol/L	4.1 (3.4–6.5)	4.6 (2.4–5.6)	0.568
Lowest platelets, $\times 10^9$/L	100.0 (68.5–165.5)	120.5 (76.2–159.2)	0.927
Urea, mmol/L	6.3 (3.8–11.4)	4.8 (3.2–9.3)	0.299
Clinical outcomes			
ICU length of stay, days	6.2 (2.6–8.6)	10.0 (4.4–19.8)	0.027
Hospital length of stay, day	11.6 (8.1–18.0)	15.5 (8.6–6.9)	0.051

Data are median (IQR) or N (%)
ANZROD, Australian and New Zealand risk of death; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; MET, medical emergency team; NAFLD, non-alcoholic fatty liver disease.

in five patients will normalise their cholestatic markers at hospital discharge and less than one in two patients will achieve recovery from cholestasis at last follow-up within 180 days. This implies that the true time to normalisation could not be determined in the majority of patients.

Strengths and limitations

This is the only study to report the changes in laboratory measurements over time after ALF. We have reported data on critically ill ALF survivors, in what is one of the largest reported cohorts of ALF patients in the literature. Additionally, for the first time we address the issue of post-ALF cholestasis, which has, to date, remained unexplored. Furthermore, for the first time, we provide granular biochemical information for a median follow of 16 days after ICU admission.

We acknowledge several limitations. This is a single-centre study with all the limitations inherent to such a study design. However, our ICU and transplantation centre has all the typical features of other similar centres in resource-rich countries, and our findings are likely generalisable to such centres. As the study is retrospective in nature, biochemical data collection was not protocolised. Thus, after discharge from the ICU, the measurement of blood biochemistry decreased with time and patients were discharged prior to normalisation of blood tests. As subsequent measurements were only dictated by clinical need and/or may have occurred outside of our electronic medical record system, our ability to report on biochemical variables beyond 30 days is limited. However, no data exist in the literature beyond day 7, making our report the most detailed representation of changes over time to date.

CONCLUSION

In summary, in ALF patients, postinjury cholestasis is ubiquitous and peaks after 3–5 days. This cholestatic phase of injury is prolonged, with only a minority of patients achieving normal cholestatic markers at hospital discharge and a median follow-up of 16 days, and, in some patients, failing to return to normal even at subsequent

follow-up. These findings inform clinical expectations of the natural course of this condition and help with both diagnosis and prognosis. Importantly, they can be of assistance during conversations with patients and families regarding realistic expectations post-ALF jaundice and its likely duration. Further studies are needed to ascertain whether normalisation of post-ALF cholestasis does eventually occur in all survivors and, if so, when and to understand the impact of long-term cholestasis on future liver function and outcomes.

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