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Specific author contributions:

RP developed the idea for this study, collected data, analaysed data, drafted and submitted manuscript

JC, JA, JPA, MV-C, AS, AD, MA, AM, IAR, BS, PM, DS, JJGA, MRL, GG-T, EV, RSB, FB-P, VV, APH, RB collected/supervised data collection , reviewed draft manuscript and approved final submission

APH and RB guided the development of the study, reviewed draft manuscripts and approved the final submission

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Abstract

Background and aims Alcoholic hepatitis (AH) is a severe condition with poor short-term prognosis. Specific treatment with corticosteroids slightly improves short-term survival but is associated with infection and is not used in many centers. A reliable method to identify patients who will recover spontaneously will minimise the numbers of patients who experience side effects of available treatments.

Methods We analysed the trajectory of serum bilirubin concentration over the course of hospital admissions in patients with AH to predict spontaneous survival and the need for treatment.

Results data from 426 patients were analysed. Based on bilirubin trajectory, patients were categorized into three groups: 'fast fallers' (bilirubin <0.8 x admission value at day 7), 'static' (bilirubin of >0.9 – <1.2 x admission value) and 'rapid risers' (bilirubin of ≥1.2 x admission bilirubin). Fast fallers had significantly better 90-day survival compared to other groups (log rank p<0.001), and showed no benefit of corticosteroid therapy (OR for survival at 28 days of treatment, 0.94, 95% CI 0.06 - 8.41). These findings remained even amongst patients with severe disease based on initial DF, GAHS or MELD scores.

Conclusions We present an intuitive method of classifying patients with AH based on the trajectory of bilirubin over the first week of admission. It is complimentary to existing scores that identify candidates for corticosteroid treatment or assess response to treatment. This method identifies a group of patients with AH who recover spontaneously and can avoid corticosteroid therapy.

Keywords

1. Alcoholic hepatitis

2. Outcomes

3. Corticosteroid

Alcoholic hepatitis (AH) is a severe clinical entity characterized by acute onset of jaundice and coagulopathy in patients with alcohol use disorder [1]. The incidence of AH is increasing over recent years [2]. Short-term mortality of AH remains very high globally [3,4]: 15-40% of patients with AH die within 30 days of admission to hospital [5].

The medical management of AH has not evolved substantially in the last two decades, with multiple potential therapeutic agents tested without a great deal of success [6]. Corticosteroids remain the only established treatment for AH. Although the largest randomised controlled trial of corticosteroids showed only a modest short-term (28-day) survival benefit [5], a recent network meta-analysis showed a survival benefit [7] but this comes at the cost of a greater risk of infection [5]. There is considerable heterogeneity regarding corticosteroid use amongst physicians with a recent survey of practice showing that a quarter of clinicians did not use corticosteroids in patients with AH [8].

In contrast to effective treatments, methods to predict prognosis in AH are legion and all perform with a roughly similar degree of accuracy [9–11]. Some of these scores have been used to identify the sub-group of patients who will benefit from corticosteroid therapy, most commonly the discriminant function (DF) [12], the model for end-stage liver disease (MELD) score and the Glasgow alcoholic hepatitis score (GAHS) [13]. Baseline bilirubin concentration is an important indicator of severity of AH and prognosis in patients with AH, and is included in all scoring systems. The dynamic change in bilirubin over the first days of admission has been identified as an important prognostic indicator [14] and a marker of response to corticosteroid treatment [15]. The Lille model uses change in bilirubin after initiation of prednisolone to gauge response to therapy and guide ongoing treatment and is conventionally applied after seven days of therapy [16] but is also useful after shorter duration of treatment. [17].

We used computer-aided analysis to study how the trajectory of bilirubin concentration during admission might be useful to identify clinical phenotypes, stratify the probability of short-term survival and guide treatment in a real-world, multi-national observational cohort of patients with AH.

Patients and Methods

Study Population, Data Collection and Definitions

Data from consecutive patients were collected prospectively from 3 centers in the UK (University Hospitals Birmingham NHS Foundation Trust (UHB), Birmingham; University Hospitals Bristol NHS Foundation Trust, Bristol; Plymouth Hospital NHS Trust, Plymouth) and from the InTeam consortium (details of participating centers are included in the supplementary material). These cohorts were observational only; no patients underwent treatments or procedures outside the standard of care in each institution.

All patients included had alcoholic hepatitis, defined as a) alcohol use of at least 60 g/d in men and >40 g/d in women for >5 years, b) last drink within four weeks of admission, c) serum bilirubin > 3 mg/dL, d) elevated transaminases >50 and <400 IU/L, e) aspartate transaminase to alanine transaminase ratio >2:1, and f) exclusion of other concomitant liver disease [18]. Liver biopsy was performed only in cases of diagnostic uncertainty, consistent with recent NIAAA guidance for trialists [18]. When biopsy was performed, the histological diagnosis of AH was defined by the presence of hepatocellular damage (hepatocellular ballooning and presence of Mallory bodies), inflammatory infiltrate (predominantly polymorphonuclear cells), and pericellular fibrosis. These criteria are consistent with the INTEAM project inclusion/exclusion criteria (detailed in supplementary data). Baseline (i.e. earliest recorded data after admission to first admitting hospital) clinical and biochemical characteristics, specific treatments for AH and presence of complications during admission (infection or acute kidney injury, AKI) were collected. Clinical complications during admission such as ascites, spontaneous bacterial peritonitis, renal dysfunction, hepatic encephalopathy or gastrointestinal bleeding were treated according to current international guidelines in effect at the time of admission [19–21].

Bilirubin trajectory across 28 days of admission was analysed in patients who did not receive corticosteroid therapy, using Traj software (http://www.andrew.cmu.edu/user/bjones/) in Stata version 15 (StataCorp LLC, Texas, USA). Distinct trajectories were identified that categorised patients into three groups. All other statistical analyses were done in SPSS version 24 (IBM, New York USA).

Statistical Analysis

The accuracy of predicting bilirubin trajectory at various points within an individual's hospital admission was tested with Kappa values. Groups were compared with t-tests (two group comparisons) or one-way analysis of variance (ANOVA) (for multiple groups). The odds of spontaneous survival at 90 days after admission, i.e. without corticosteroid therapy were calculated for each group and odds ratios calculated based on fast fallers as a reference group. Survival was analysed with Kaplan Meier univariate analysis, and multivariate Cox Proportional hazard analysis to control for multiple factors. Scoring systems (DF, MELD, GAHS, Lille) were calculated as per published data.

To examine the efficacy of corticosteroid use in each group, patients were included if they received corticosteroids after seven or more days of admission to allow for bilirubin trajectory early in admission to be analysed, or if they did not receive corticosteroid therapy. As differences existed between treated and non-treated patients, propensity score matching was used to assemble a comparable cohort. Patients were matched for age, bilirubin concentration, creatinine concentration and albumin concentration, using the SPSS propensity score matching function (**supplementary table 1**). To analyse the value of using bilirubin trajectory to predict patient who may not require treatment, risk ratios for survival at 28 days (as per standard outcomes in therapeutic studies) was calculated with or without corticosteroid therapy.

Results

In total data from 426 patients with AH were collected of whom 317 had a DF above 32 at admission to hospital, and 105 received corticosteroid therapy. The demographic and biochemical characteristics of included patients are depicted in **table 1**.

Identification of bilirubin trajectories

Patients who did not receive corticosteroids (n=321) were used as a modelling group to identify and analyse bilirubin trajectories. Sequential bilirubin values up to 28 days after admission revealed three groups with distinct trajectories of bilirubin concentration over time (**figure 1**): patients with a rapid decrease in bilirubin concentrations ('fast fallers'), patients with bilirubin concentration that remained elevated but without obvious improvement or deterioration ('static') and patients that showed a bilirubin concentration rising inexorably after admission ('rapid risers').

To allow for clinical application of this classification system, the accuracy of using bilirubin observed trajectory at 3 or 7 days after admission to predict subsequent bilirubin trajectory was examined using Kappa values. Groups could not be identified with accuracy at day 3 (Kappa 0.39) but by day 7 bilirubin trajectory over the course of 28 days could be accurately predicted (Kappa 0.92). Accordingly, bilirubin trajectory as assessed at seven days after admission was used for all analyses of clinical utility. Fast fallers had a bilirubin of less than 0.9 x admission value at day 7, the static group had a bilirubin of ≥0.9 – ≤1.2 x admission value and rapid risers had a bilirubin >1.3 x admission value. Importantly, in published trials of corticosteroid therapy in AH the median delay from admission to treatment is 8 days with no association between treatment delay and survival (**supplementary figure 1**), suggesting that a seven day evaluation period is acceptable in hospitalised cases.

The characteristics of each trajectory group are shown in **table 1.** A statistically non-significant difference in bilirubin concentration between groups was observed (one-way ANOVA p=0.098), where the highest bilirubin concentration was observed in the static group, with lower bilirubin concentrations in fast faller and rapid risers groups.

Fast-falling bilirubin trajectory is associated with spontaneous recovery

Spontaneous recovery, i.e. survival without corticosteroid therapy at 90-days varied between groups: fast fallers were more likely to recover than patients with static or rising bilirubin concentration (OR 0.54, 95% CI 0.31 – 0.94, and OR 0.39, 95% CI 0.19 – 0.76 respectively) (**table 2, figure 2A**). This remained when severe alcoholic hepatitis was considered defined by GAHS, MELD or DF: in each case, patients with severe disease who had a fast fall in bilirubin had rates of spontaneous recovery comparable to those without severe disease (**figure 2B-D**). After controlling for baseline differences in bilirubin and prothrombin time between groups with Cox proportional hazard analysis, bilirubin trajectory was independently associated with mortality at 90-days (p=0.042). Dynamic changes in MELD score between day 1 and day 7, and the Lille score were also predictors of spontaneous recovery.

Use of bilirubin trajectory to stratify treatment in alcoholic hepatitis

To investigate the utility of using bilirubin trajectory to guide treatment, we examined patients who received corticosteroid (CS) treatment *after* seven days of admission, allowing for bilirubin trajectory to be assessed at day 7 before CS therapy. Patients who received corticosteroid therapy after 7 days differed from those who did not (**table 1**), so propensity score matching was used to identify comparable groups. After removing patients who received corticosteroid therapy before seven days of admission and doing propensity score matching, 180 patients were analysed, of whom 90 received corticosteroids and 90 did not.

Corticosteroid therapy had no survival benefit in fast fallers (OR for survival at 28 days of treatment, 0.94, 95% CI 0.06 - 8.41, p=0.879). When analysis was limited to patients with severe disease (defined as DF >32, GAHS >8 or MELD >20) this remained the case, with no benefit of corticosteroids observed in each case (**table 3, supplementary figure 2**). Corticosteroid therapy in rapid risers showed a trend towards benefit without reaching statistical significance (OR 4.82, 95% CI 0.85 - 24.4, p=0.079). The use of bilirubin trajectory to allow patients with severe disease but a fast falling bilirubin to be managed without corticosteroids would have excluded many patients from treatment: 43% of patients with a DF >32, 45% of patients with a MELD >20 and 45% of patients with a GAHS >8 (**table 1, figure 3)**.

Discussion

This large multi-center, multinational study of patients with AH used computer-assisted analysis of bilirubin trajectory to identify three groups of patients, with distinct clinical phenotypes. A 'fast falling' bilirubin trajectory indicated a group of patients who had a greater chance of spontaneous survival and who did not benefit from corticosteroid therapy, even amongst patients with severe disease. Identification of this group of 'fast fallers' with a better outcome can allow clinicians confidence to avoid treatment with prednisolone and may facilitate earlier discharge from hospital.

Bilirubin long been identified as important dynamic measure in AH in terms of prognostication [14] and assessing response to treatment [15]. Our data confirm the value of observing this indicator in AH both as a guide to outcome and a guide to therapy. The use of more complex scores – MELD or Lille – over the same seven-day period also gave prognostic information with accuracy comparable to bilirubin alone. This does not detract from the simple observation of the maxim that if patients are getting better, they are likely to continue to improve and liver-specific treatment might be avoided, beyond standard supportive measures.

Importantly the trajectory system is different to the Lille score, as trajectory identifies individuals likely to do well *before* starting treatment with corticosteroids, whereas the Lille score is designed to assess response *after* starting treatment. Indeed, the two scores could be used sequentially in the same patient before and after starting therapy to further minimise futile exposure to corticosteroids. Several scores exist that predict mortality in patients with AH. Bilirubin trajectory does not replace these as a means of prognostication but it can serve as an additional means of identifying patients who may not require corticosteroid therapy despite severe disease. Liver transplantation (LT) for patients who fail to respond to corticosteroid therapy has been shown to be effective in AH [23,24]. 'Fast fallers' who are likely to improve without specific treatment are less likely to require LT, and this may influence decision making around patients with severe disease at admission but who display a favourable trajectory of bilirubin.

The observed trajectories of bilirubin concentration that we describe are from the point of hospital admission, rather than from the onset of jaundice. Whilst there are few data to illustrate this, anecdotally there is significant variation in the delay between the onset of jaundice and admission to hospital. The impact of this on observed trajectories of bilirubin can only be speculated about, but it is conceivable that it is more individuals who become sicker outside of hospital eventually present to medical services, whereas those who improve do not. This variation in presentation may be further complicated by transfer of patients with AH between centers that is common in some health systems, principally in the US. The data used for this study were the earliest available values. The observed trajectories therefore are from the time of admission or very close to it. This may introduce a bias to the observed trajectories when considering AH as a whole, but our findings remain relevant to patients who are admitted to hospital. Further research will illustrate the impact of 'jaundice to door time' and it's impact on outcome and observed bilirubin trajectory.

The study has limitations. The research cohort is observational such that the question of the clinical utility of using bilirubin trajectory to guide treatment was not tested specifically. This is a similar technique to derivation of existing scoring systems in AH, and also represents a 'real world' sample where there is known to be marked heterogeneity regarding use of corticosteroids. There may be reasons why certain patients received corticosteroid therapy that were not have been captured and thus introduced bias to the dataset despite propensity score matching. Clinicians eager to start specific therapies may baulk at the requirement to observe patients for seven days before patients can be allocated to a group. However, in practice a period of seven days allows for time exclusion of infection, other liver diseases and biopsy if this is felt necessary. We note that the median delay from admission to treatment in the STOPAH trial was 6.7 days, and overall delay in various trials of corticosteroids over the years is more than a week (**supplementary figure 1**). Validation of these observations is key and it is obvious that propensity score matching resulted in a much smaller group than the initial, large cohort.

We used the NIAAA criteria to identify a coherent group of patients to study. These criteria use a bilirubin threshold of 3mg/dL, whereas clinical criteria and histological concordance has only previously been established for higher levels of bilirubin. However in this cohort only a few patients had a bilirubin below 5mg/dL (10 of 321 in the group not treated with corticosteroids and used for model building). Removing this group from the analysis did not result in any meaningful differences in the observations regarding likelihood of survival (data not shown). Lower bilirubin concentrations would make it difficult to understand what small fluctuations may mean, but this group of patients are unlikely to be considered for corticosteroid therapy in practice.

We present a novel, intuitive method of classifying patients with AH based on the trajectory of bilirubin over the first week of an admission. This system aids in prognostication, but most importantly identifies a group of patients who are likely to have better outcomes and do not benefit from corticosteroid therapy.

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Table 1: characteristics of included patients. Data are presented as mean and standard error of mean except for ^median and interquartile range.

	Entire cohort n=426		Patients without corticosteroid use									
			Modelling cohort n=321		Fast fallers n=150 (47%)		Static n=99 (31%)		Rapid risers n=72 (22%)		p ANOVA
	Average	variance	Average	variance	Average	variance	Average	variance	Average	variance	
Age^ (years)	49.3	10.0	48.5	10.1	47.0	1.0	49.2	1.0	50.3	1.6	0.161
Bilirubin (μ mol/L)	271	143	269	139	271	14	296	16	240	19	0.098
Prothrombin time (seconds)	24.2	8.8	23.4	8.38	21.1	0.7	26.1	0.9	25.1	1.4	**<0.001****
White Cell Count ($x10^9$/L)	10.9	6.1	10.9	6.0	10.6	0.6	12.0	0.9	10.3	0.9	0.300
Creatinine (mmol/L)	91.7	78.5	90.2	80.0	88.2	6.3	91.4	8.3	109	0.9	0.378
Sodium (mmol/L)	131	7.1	131	7.6	131	1	131	1	132	1	0.723
Urea (mmol/L)	5.56	13.4	5.56	13.3	7.56	2.30	4.66	0.50	5.20	0.98	0.400

Albumin (g/L)	26.7	6.2	26.9	6.4	26.1	0.8	27.3	0.6	27.5	1.0	0.318
Platelets (x10^9/L)	132	82	131	81	149	13	129	8	115	12	0.128
DF >32 n (%)	324 (75%)		243 (75%)		103		85		53		
MELD >20 n (%)	317 (73%)		191 (59%)		86		61		42		
GAHS ≥ 9n (%)	238 (56%)		187 (58%)		84		59		43		

Table 2: odds of spontaneous recovery in each trajectory group, analysed with Fisher's exact test

	Odds of spontaneous recovery	Odds ratio	95% CI	p
Fast faller	3.16	1 (reference)		
Static	1.68	0.54	0.30 - 0.93	0.028
Rapid riser	1.32	0.39	0.19 - 0.76	0.005
All non-fast faller	1.61	0.48	0.29 – 0.80	0.005
Improved MELD	3.22	1 (reference)		
Stable MELD	2.20	0.68	0.37 – 1.27	0.2
Deteriorating MELD	1.21	0.38	0.20 – 0.69	0.002
Lille response	9.29	1 (reference)		
Lille partial	2.12	0.23	0.09 – 0.53	0.001
Lille null response	1.02	0.10	0.04 – 0.25	<0.001

Table 3: propensity matched analysis of patients treated with or without corticosteroids

	28 day survival				
	Corticosteroids	No corticosteroids	OR	95% CI	p (fishers)
Fast faller	96%	96%	0.94	0.060 - 8.41	0.999
GAHS >8 and fast faller	95%	83%	3.60	0.411 - 31.6	0.416
MELD > 20 and fast faller	91%	88%	1.37	0.208 - 9.02	0.999
DF> 32 and fast faller	96%	96%	1.00	0.086 - 11.6	0.999
	90 day survival				
	Corticosteroids	No corticosteroids	OR	95% CI	p (fishers)
Fast faller	79%	79%	0.99	0.317 - 3.10	0.988
GAHS >8 and fast faller	56%	50%	0.80	0.173 - 3.71	0.776
MELD > 20 and fast faller	62%	65%	1.16	0.352 - 3.84	0.805
DF> 32 and fast faller	76%	75%	0.94	0.292 - 3.01	0.914

Figure legends

Figure 1: differing trajectories of change in serum bilirubin concentration over time after admission with alcoholic hepatitis

Figure 2 Kaplan Meier analysis of survival after admission to hospital with AH: **A** survival differs between bilirubin trajectory categories (log rank $p < 0.01$). Patients with 'fast falling' bilirubin concentration but with severe disease defined as **B** GAHS above 8, **C** MELD above 20 or **D** discriminant function above 32, have outcomes comparable to non-severe disease (log rank p value: ns, non-significant, *** $p<0.001$)

Figure 3: Identification of patients for with severe disease: bilirubin trajectory analysis identifies a different group of patients with compared to the DF, the GAHS or MELD.