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Treatment and Outcome of Autoimmune Hepatitis (AIH): Audit of 28 UK centres.

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ABSTRACT

Background: With few data regarding treatment and outcome of patients with AIH outside of large centres we present such a study of patients with AIH in 28 UK hospitals of varying size and facilities.

Methods: Patients with AIH were identified in 14 University and 14 District General hospitals; incident cases during 2007-2015 and prevalent cases, presenting 2000-2015. Treatment and outcomes were analysed.

Results: In 1267 patients with AIH, followed-up for 3.8(0-15) years, 5- and 10-year death/transplant rates were 7.1±0.8% and 10.1±1.3% (all-cause) and 4.0±0.6% and 5.9±1% (liver-related) respectively. Baseline parameters independently associated with death/transplantation for all-causes were: older age, vascular/respiratory co-morbidity, cirrhosis, decompensation, platelet count, attending transplant centre and for liver-related: the last four of these and peak bilirubin

All-cause and liver-related death/transplantation was independently associated with: non-treatment with corticosteroids, non-treatment with a steroid-sparing agent (SSA), non-treatment of asymptomatic or non-cirrhotic patients and initial dose of

Prednisolone >35mg/0.5mg/kg/day (all-cause only), but not with type of steroid (Prednisolone versus Budesonide) or steroid duration beyond 12-months.

Subsequent all-cause and liver-death/transplant rates showed independent associations with smaller percentage fall in serum ALT after 1 and 3-months, but not with failure to normalise levels over 12-months.

Conclusions: We observed higher death/transplant rates in patients with AIH who were untreated with steroids (including asymptomatic or non-cirrhotic sub-groups), those receiving higher Prednisolone doses and those who did not receive an SSA. Similar death/transplant rates were seen in those receiving Prednisolone or Budesonide, those continuing steroids after 12-months and patients attaining normal ALT within 12-months versus not.

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Key words: Autoimmune hepatitis, treatment, Prednisolone, Budesonide, outcome

Key Points

In patients with AIH attending 28 hospitals across the UK, we demonstrate increased mortality/transplant rates are independently associated with:

- Non-treatment with steroids, both overall, and in asymptomatic and also non-cirrhotic subgroups stressing the importance of considering treatment in all patients with AIH.
- Initial doses of Prednisolone >35 mg and >0.5 mg/kg/day highlighting the need for caution when using higher doses.
- Non-treatment with steroid sparing agents (20% of patients).

We also found that when treating AIH:

- Steroid treatment beyond 6 months or for >3 months after serum ALT normalisation may not be of benefit.
- Budesonide may be as effective as Prednisolone over the first 5 years.

Lay summary

We established the personal and baseline disease factors associated with death and the need for liver transplantation in this large UK multicentre study of treatment and

outcome in patients with AIH. Higher steroid doses are independently linked with poorer outcome. We show that even those patients with AIH without symptoms or without cirrhosis should be considered for steroid treatment, as they have higher mortality without treatment.

INTRODUCTION

The mortality of Autoimmune Hepatitis (AIH) over 2-10 years was reduced dramatically by Prednisolone (+/- the steroid sparing agent Azathioprine) in randomized controlled trials (RCTs) performed 40-50 years ago.[1] However, even with treatment, mortality of AIH over 10-20 years remains excessive, with Standard Mortality Ratio (SMR) values of 1.4-2.3 reported;[2] this excess mortality results from liver disease.

Whilst steroids plus Azathioprine remain standard therapy of AIH,[1] it remains unclear whether they are always necessary, or what is the optimal dose or duration of steroid therapy. UK guidelines recommend initiating Prednisolone 30 mg/day (plus Azathioprine) and continuing 5-10 mg/day for 2 years. EASL guidelines recommend a higher dosage range of Prednisolone (0.5-1mg/kg/day),[1,3] but make no recommendations regarding duration. Another steroid, Budesonide has similar short-term efficacy to Prednisolone but fewer cosmetic side effects in a large RCT. However, data are lacking on its longer-term efficacy.[4]

Given this uncertainty regarding optimal treatment, it is unsurprising that AIH treatment regimens vary widely across the UK, as shown by a recent survey.[5]

Parameters of early response to AIH treatment (such as fall or normalisation of serum ALT), if predictive of longer-term outcome, would facilitate evaluation of novel treatments for AIH. However, no predictive early response parameter has been established conclusively. Serum ALT response to treatment is highly variable: with the percentage of patients achieving normal values within 6 months of starting treatment varying between 10-90%.[6] Various studies have, however, supported the predictive value of serum ALT normalisation after 6 [7] and after 12 months [8,9] and, recently, the percentage fall in serum AST after 8-weeks.[10]

Most information about outcome in AIH has originated from single tertiary referral centres with potential selection bias towards younger patients with more severe disease.[1,11-13] In multicentre studies from Scandinavia[9] and the Netherlands,[14] most patients came from academic centres. A study of a Danish national AIH database indicated higher mortality than other studies but did not include information on baseline severity, treatment and early response.[15]

We established a longitudinal cohort of patients with AIH, attending 28 UK hospitals of varying size, for an audit of management and outcome over the period 2000-2015. Explicitly pre-stated aims included establishing the relationship between outcome (especially death/liver transplantation rate) and type, dose and duration of drug treatment. We report here the main study results.

1. METHODS

The study was categorised as an Audit by the UK Health Research Authority (HRA) and was approved by the University of Sheffield Research Ethics board (reference no: 009662).

We asked the 28 participant centres, including 4 transplant centres[16] to identify all prevalent AIH cases presenting since 2000 still under follow-up, and all incident cases since 2007 by interrogating 3 overlapping electronic sources: electronic patient letters (key-word searching), histology databases using SNOMED codes for 'chronic' and 'acute inflammation' and hospital coding using ICD-10 codes. Patient lists generated from these sources underwent a sequential diagnostic case validation for AIH ensuring they met minimally modified 1999 International AIH group diagnostic criteria. This strategy and process have been detailed previously.[16] Information regarding treatment, response of serum parameters to treatment and outcome, including death and its cause, was entered into a bespoke web-based, data collection system between January 2014-November 2015. Study size was not pre-calculated.

Normal serum ALT was defined as the normal range for each individual centre (upper limit of normal (ULN) ranged from 30-56 IU/L). Decompensated liver disease at baseline presentation was defined as ascites, oedema, encephalopathy, variceal bleed or MELD >15. As previously reported, [16] cirrhosis was defined by liver biopsy,

presence of varices, ascites, or Fibroscan®. Relapse was defined as elevation of one of the transaminases (ALT or AST) above two times ULN, having previously returned to normal. Follow-up time was defined as time from diagnosis to last recorded out-patient appointment, liver transplantation or death. Vascular or respiratory co-morbidity (V-R Co-M) was defined as either documented ischaemic/non-ischaemic heart disease, cerebrovascular disease or chronic lung disease. Where data was missing in some patients: numbers of informative patients are given in tables and figures.

SPSS and GraphPad software were used to analyse data. Survival analysis was performed by generating Kaplan-Meier plots and comparing groups using Log-rank testing.

We performed Cox analysis separately for the time-dependent outcomes: all-cause and liver-related death or liver transplant. Baseline variables associated ($p<0.10$) with these outcomes in univariate analysis were then assessed in stepwise multivariate Cox regression analysis to ascertain the variables independently associated ($p<0.05$) with each outcome. We then assessed parameters of steroid and SSA treatment and of response of serum ALT to treatment, first alone and then with significantly associated baseline variables in stepwise regression analysis to ascertain which of the treatment or response parameters remained independently significantly associated with outcome ($p<0.05$).

For time-dependent variables, including duration of steroid treatment and relapse number (where an association with time dependent outcomes might be artefactual), we performed regression analysis considering death/transplant as a dependent variable, and considering follow-up time as a covariate.

Chi-square or Z-test was used to calculate differences between proportions and t-test to assess inter-group differences where appropriate. Medians (with ranges) were used to describe continuous data and means (with standard deviations) were used for normally distributed data.

To assess consistency of results, we performed separate analyses in the following subgroups (a) incident cases: overall and considering separately those presenting over 2007-10 and 2011-15, (b) patients attending the four centres where we were

sure of complete case capture because of documented adherence to the detailed recommended strategy and (c) those who met 1999 criteria only.

Patients were invited to the initial planning meeting and to the first presentation of the final results but not involved in the design or conduct of the study.

3. RESULTS

3.1 Baseline characteristics, treatment, and initial response

Table 1 shows the demographic, clinical and laboratory characteristics of all 1267 patients at diagnosis. Overall, 1186 (94%) of patients were treated. Table 1 details initial treatments received for AIH.

Serum ALT had fallen to within normal range in 34% (n=892), 56% (n=904), 69% (n=860) and 76% (n=830) of patients after 1, 3, 6 and 12-months respectively. Of patients followed for $\geq$12 months 148/930 (16%) failed to attain any normal serum ALT value over that time and was independently associated with younger age ($p<0.001$) and with presence of cirrhosis ($p=0.001$).

Serum IgG fell from peak pre-treatment values of (mean$\pm$SD) 24.9±10 to 14.1±5.8 (n=235), 13.5±5.0 (n=228) and 13.3±5.5 g/L (n=242) after 3, 6 and 12 months respectively. Peak pre-treatment serum IgG values were higher in patients with baseline cirrhosis than those without (28.7±11.3 vs 23.7±9.6 g/L; $p<0.001$) and these differences persisted after 1 and 3-months but not after 6 and 12-months.

Among treated patients,1098/1186 (93%) eventually achieved normal serum ALT values after median (range) 2(0-135) months. Subsequently, 354 (32%) had at least one relapse (median 1(1-6)). Relapse rate was 17±1% and 37±2% after 1 and 5 years respectively. Younger age ($p<0.001$) and absence of cirrhosis ($p=0.001$) were independently associated with initial relapse rate and with number of relapses.

3.2 Overall Outcome and baseline predictors of mortality

Follow-up time was 3.8(0-15) years, after which 46 patients died (15 from liver disease) and 29 received liver transplantation. Five- and 10-year death/transplant rates were 7.1$\pm$0.8% and 10.1$\pm$1.3% (all-cause) and 4.0$\pm$0.6% and 5.9$\pm$1% (liver-related) respectively.

On multivariate analysis (Table 2), all-cause death/transplantation rate was independently associated with the following baseline variables: older age, vascular/respiratory co-morbidity,platelet count <150, cirrhosis (Fig 1a), decompensation and attending a transplant centre. Liver-related mortality showed independent associations with cirrhosis, decompensation, platelet count (Supplementary Fig 1a), and attending a transplant centre (Table 2). Several other baseline parameters (Table 2) showed no association with death/transplantation.

Of the 951 patients without cirrhosis at diagnosis, 72 (8%) subsequently developed cirrhosis after median(range)16(1-140) months follow-up. New cirrhosis development showed negative independent associations with serum albumin and platelet count but not with other baseline parameters. Those who developed de-novo cirrhosis had an increased risk of all-cause (Fig 1b) and liver-related death/transplantation (Supplementary Fig 1b), persisting in Cox regression analysis (HR=2.40 (1.03-5.55); p=0.042 and 9.37 (CI 2.76-31.8); p=<0.001) respectively.

3.3 Effects of corticosteroids

(a) Received versus not

Overall, 1169 patients received Corticosteroids (Table 1) within the first 3 months and 1175 at any stage. Delay between diagnosis and starting treatment was 0 (0-135) months. Reasons for non-treatment with steroids are shown in Supplementary Fig 2a; the reason was unclear in 37/92 (40%).

Patients who did not receive corticosteroids (n=92) had a similar prevalence of cirrhosis and of decompensation but likely to be older, female, and not jaundiced (Supplementary Table 1) compared to those who did. They had lower pre-treatment serum ALT values than steroid-treated patients but similar values after 3 and 6-months.

Despite this, patients not receiving steroids had higher all-cause (Fig 2a) and liver-related (Supplementary Fig 2b) death/transplant rates and independently predicted both all-cause and liver-related (4-fold and 8-fold more likely) death/transplantation (Table 3). This remained an independent predictor of all-cause mortality in patients without cirrhosis and in asymptomatic patients but not in patients with mildly active disease, defined as peak serum ALT<150 IU/L, pre-treatment ALT <50 IU/L or baseline necro-inflammatory score <9 (Table 3).

(b) Initial Prednisolone dose

The initial starting dose of 30(2-60)mg/day Prednisolone (or equivalent; Table 1 footnote) was positively associated with higher pre-treatment serum ALT ($p<0.001$) on multivariate analysis. However, neither subsequent serum ALT values nor the percentage of patients attaining normal values after 3, 6 and 12-months showed links with initial dose.

Rate of new onset Diabetes Mellitus (NODM) was 4.4% overall, after 5(1-94) months, and was higher in those initially receiving >35mg Prednisolone/day (n=434) compared to those (n=655) receiving ≤35 mg/day (6.5% vs 3.5% $p=0.03$ Chi2).

Patients initially receiving >35 mg/day Prednisolone (Fig 2b) or >0.5mg/kg/day had higher all-cause death/transplant rate than those receiving lower doses, remaining significant on multivariate analysis for all-cause death/transplant only (Table 3). Both of these sub-groups of patients were significantly younger, had a higher peak bilirubin and ALT values. Patients receiving >35mg/day also had a higher prevalence of cirrhosis and decompensation than those receiving lower doses.

(c) Duration of Corticosteroid treatment

Initial duration of steroid treatment was 18 (1-241) months, this showed no association with death/transplantation in regression analysis when corrected for follow-up time.

Patients followed up for at least 6 months, receiving steroids for more than 6 months (compared to ≤6), had lower subsequent liver-related but not all-cause death/transplant rates (Table 3, Fig 2c, Supplementary Fig 2c). Similar analyses comparing steroid treatment for less versus greater than 1 and 2-years showed no associations with subsequent outcome. Nor did subsequent death/transplant rates differ between patients who continued steroids for more than 3 months after serum ALT normalisation or those who stopped steroids within 3 months of normalisation (Table 3).

(d) Type of Corticosteroid

Budesonide (9 (3-9)mg/day) was the initial steroid given in the first 3 months of treatment in 58 patients (Supplementary Table 2). Compared to the 1111 Prednisolone/Methylprednisolone-treated patients, they were more likely to be

female and have less severe liver disease. However, 16/58 (28%) of the Budesonide treated patients had cirrhosis at diagnosis (three had a prior diagnosis of diabetes).

Serum ALT values after 1, 3 and 12-months were lower in Budesonide (compared to Prednisolone) treated patients; however, these differences disappeared if pre-treatment serum ALT was included as a covariate (higher in those receiving Prednisolone). Percentage fall in serum ALT after 1, 3,6 and 12-months was similar in Budesonide and Prednisolone-treated patients.

Compared with Prednisolone, patients receiving Budesonide had significantly less reported side effects (13% vs 3%: p=0.02) with just two patients reporting side effects (weight gain and “generally unwell”), and no development of NODM, low trauma fractures or psychosis. One non-cirrhotic patient receiving Budesonide developed portal vein thrombosis.

There was no difference in all-cause or liver-related death/transplantation rate between patient initially receiving Budesonide and those receiving Prednisolone (Table 3, Fig 2d, Supplementary Fig 2d).

3.4 Steroid-sparing agents (SSA’s)

Addition of a SSA to steroid treatment was associated with reduced rates of both all-cause and liver-related death/transplantation (Fig 3, Supplementary Fig 3). These associations remained significant in multivariate analysis incorporating baseline factors; HR 0.25(0.13-0.46) and 0.17(0.08-0.38) respectively. The differences seemed confined to early deaths, as when limiting analysis to patients with >6months follow-up, they disappeared. Outcomes were unrelated to delay in starting SSA and were similar in those initially receiving Mycophenolate (n=32) compared to Azathioprine.

Data on duration of SSA treatment was complete in only one-third of patients, so we could not assess whether this was associated with outcome.

3.5 Association of outcomes with serum ALT response to treatment

Death/transplant rates were independently associated with lower percentage fall in serum ALT after 3 and 6-months (all-cause and liver-related) and after 1-month (all-cause), see Table 4.

Death/transplantation rates were higher in patients with a ≤80% fall in serum ALT after 1, 3, 6 and 12-months (all-cause) and after 3 and 6-months (liver-related) though mainly due to higher death rates in those with no ALT fall at all (Table 4, Fig. 4a, Supplementary Fig 4a). Differences between those with >80% and 1-80% fall over 3-months were not significant.

We observed associations on univariate analysis between subsequent liver-related death/transplantation and failure to normalise serum ALT after 3 and 6-months (Table 4) and additionally (in 218 informative patients) with failure to normalise both serum ALT and IgG after 6 months; however, these did not persist on multivariate analysis. All-cause or liver related death/transplant rate showed no association with failure to achieve any normal serum ALT within 12 months in patients followed for >12 months (Table 4,Fig 4b, Supplementary Fig 4b).

New cirrhosis development showed independent associations with higher serum ALT values after 12 months (HR=1.003 (1.0-1.005): p=0.037), with serum ALT above normal after 3-months (HR=1.01 (1.00-1.02): p=0.042) and after 12-months (HR=1.07 (1.01-1.14): p=0.019), and lastly, with number of relapses (HR=1.28 (1.03-1.59): p=0.029).

3.6 Subgroup analyses and outcome (Supplementary Tables 3 and 4)

With analysis confined to the 1009 incident patients and to the 1164 patients who met the 1999 IAIHG diagnostic criteria, cirrhosis, decompensation, low platelet count and (for all-cause death) older age, remained independent baseline predictors of death/transplantation. Non-treatment with Steroids, or SSA and those with initial Prednisolone >35mg/day and >0.5mg/kg/day, were still independently associated with both all-cause and liver-related death/transplantation.

When death/transplant rates were analysed separately in incident patients presenting 2007-10 and those presenting 2011-2015, the relationships with not receiving an SSA persisted, as did those with not receiving steroids and also with initial Prednisolone dose (though only in univariate analysis for >35mg/day in the 2010-15 cohort).

Patients attending a transplant centre (compared to those who did not) were younger, had less co-morbidity, but also had more severe disease; higher proportion

with cirrhosis, decompensation, higher peak bilirubin and lower serum albumin (Supplementary Table 4). However, the death/transplantation associations found between steroid treatment, initial steroid dose and SSA treatment were observed in both transplant and non-transplant centres.

Finally, in the 356 patients from centres with complete case capture, relationships with steroid and SSA use remained, but that with initial Prednisolone dose was no longer significant.

4. DISCUSSION

Our study, from a large multi-centre real-world cohort, provides a comprehensive description of treatment, medium-term outcome and their associations in patients with AIH from a wide variety of hospitals in the UK. First, we confirm several previously reported baseline predictors of death/transplantation. Second, we confirm (in the overall cohort and in defined subgroups) that patients receiving both steroids and SSAs have a better outcome than those receiving only one (or neither) of these. Third, we observe a novel association between mortality and higher initial doses of Prednisolone. Fourth, we do not demonstrate benefits from (a) continuing steroid therapy after 12 months or after achieving normal serum ALT and (b) use of Prednisolone over Budesonide.

The strengths of our study include its size, being one of the largest clinical cohorts of patients of AIH reported. A recent UK primary care based epidemiological study[17] found an AIH prevalence of 9.1/100,000, suggesting our cohort may comprise about 11% of the total UK AIH population. Second, it included patients presenting with AIH to several hospitals of varying size, facilities and expertise and thus, is more likely to represent AIH outcome in the real world than most other studies from single, or a small number of larger centres. As we have reported,[16] our patients were similar to those in other multi-centre and larger single-centre studies, apart from being slightly older.

There are, however, weaknesses. As is very likely in other multi-centre studies of AIH,[9,18] there was probably incomplete case capture, resulting from the complex diagnostic criteria for AIH and from difficulties in searching data systems. We developed a detailed case-finding strategy, previously described,[16] however, despite

repeated encouragement, we are confident that capture was complete in only four centres. To mitigate this, we attempted to address the impact of case selection on our main results by subgroup analysis. The significant relationships with steroid and SSA use and with initial Prednisolone dose were also seen in the incident case subgroup and in those meeting 1999 IAIHG criteria, We previously demonstrated only minor differences at presentation between incident patients diagnosed between 2007-10 and 2011-15.[16] The relationship of outcome with SSA use and with initial Prednisolone dose remained at or near significance levels in both cohorts, but the relationship with steroid use was not demonstrated in the post-2011 cohort.

The overall 10-year death/transplantation rate of 10% (all-cause) and 6% (liver-related) is similar to the median rate of 12% (7% liver) in a review of 10 large (>100 patients) studies, most from single centres.[2] It is also, similar to two multicentre studies from the Netherlands and Scandinavia, [9,18] although these had lower mean ages at diagnosis (39 and 46 versus 55 years in the current study). However, 10-year mortality in our study was lower than those quoted in recent UK (31.9% (10.5% liver-related)) and Danish (26% (10% liver-related)) studies based on national databases.[15,17] Whilst these lower rates in the present study might represent patient selection, based on incomplete case capture, mortality of patients attending centres with complete case-capture, was not different than other centres.

We confirm previously documented associations of death/transplantation with older age, with cirrhosis [8,12,18,19] and decompensation [8] and with low platelet count [9] at diagnosis. We observed that patients attending transplant centres were younger, had less co-morbidity but presented with more severe disease, which likely contributed to, but did not entirely explain the higher death/transplantation rate. However, we could not confirm previously reported associations between outcome and gender,[11] lower baseline peak serum ALT,[20] concurrent PBC[21] and with younger age at diagnosis (for liver-related death),[12] possibly due to our relatively short period of follow-up (median 3.8 years).

UK, EASL and AASLD management guidelines recommend Prednisolone plus Azathioprine as initial treatment for AIH.[1,3,22] However, in our audit, thirteen regimens were used as first-line treatment.

We found that non-treatment with steroids was associated with a 4-fold all-cause and 8-fold liver-related increase in death/transplant rates, substantiating observations initially made in RCTs nearly 50 years ago. Some patients had severe liver disease and either died or underwent liver transplantation shortly after diagnosis. In these, steroid use may have been futile and likely to increase the risk from infection. However, many patients who did not receive steroids survived for several months, and sometimes years. In many patients the reason for non-treatment was unclear. Our results underline that in the absence of active contraindications (such as sepsis or uncontrolled diabetes) steroids should be offered to patients with all but the mildest forms of AIH.

We also provide novel evidence for a mortality-lowering effect of steroids in two subgroups: asymptomatic patients (who may be reluctant to accept treatment) and patients without cirrhosis.

Initial doses of Prednisolone used in the early RCTs in AIH ranged from 15-60 mg/day with initial dosing of up to 1 mg/kg/day advocated in EASL guidelines.[3] In an International AIH group survey of experts' management practices, initial doses of Prednisolone varied from 20-100mg/day.[23] In the current audit, initial doses of 2.5-60 mg/day were used. Higher doses were associated with higher pre-treatment serum ALT levels and were probably influenced by perception of disease severity.

However, we found that higher initial doses of Prednisolone were not associated either with more rapid normalisation of serum ALT, confirming results of a recent study,[24] or with lower liver-related mortality. However, there appeared to be a tendency to use higher initial doses of prednisolone in more severe liver injury, and a reluctance to use higher doses in older patients. Furthermore, that initial Prednisolone doses of >35 mg/day were associated firstly, with a higher risk of developing NODM. Secondly, Prednisolone doses >35 mg/day (or >0.5mg/kg/day) were independently associated with increased all-cause death/transplant rates possibly resulting from the effects of steroids on the risks of infection and cardiovascular disease. Whilst this result needs confirmation, it suggests the need for caution in employing higher initial Prednisolone doses in AIH.

Consensus is lacking about the optimal duration of corticosteroid treatment and in particular, whether they should be continued beyond attainment of normal serum transaminases. Continuation has been justified because histological remission lags behind biochemical remission and is not always achieved despite serum ALT normalisation.[25] Also, that Azathioprine alone (often continued after steroid withdrawal) is no more effective than placebo in inducing remission in AIH.[1]

However, we show here that continuing steroid treatment for ≥12 months and after serum ALT normalisation, was not associated with a better outcome. Although it remains possible that longer duration of steroid treatment (e.g. more than 2 years or until histological remission) might be associated with better longer-term outcomes if patients were followed-up for longer.

In recent trials, Budesonide achieved a higher rate of serum ALT normalisation than Prednisolone in adults but not in children,[4,26] with a lower incidence of cosmetic side effects. There are few data on its longer-term efficacy and none on histological remission or on medium/long-term survival. We observed that patients receiving Budesonide as initial steroid treatment had less severe, less active liver disease. Notably a quarter of patients receiving Budesonide in our cohort had cirrhosis at treatment outset. Cirrhosis is a contraindication to Budesonide use because the associated portosystemic shunting reduces its first-pass hepatic metabolism, increasing side effects and has associations with portal venous thrombosis.

Patients initially receiving Budesonide had similar rates of ALT normalisation after 6 and 12-months, less side-effects than Prednisolone-treated patients and similar 5-year death/transplantation rates. This supports the use of Budesonide as an initial treatment (with a steroid-sparing agent), in non-cirrhotic patients with milder disease and in whom steroid-related side effects might be particularly problematic.

Treatment with steroid-sparing agents (SSA's) allows a reduction in steroid dose with maintained efficacy and SSA's (as monotherapy) reduce the rate of relapse after steroids discontinuation.[27,28] However, long-term continued use of SSA's has not been associated with lower mortality.[2,8]

We found that use of a SSA was independently associated with reduced all-cause and liver-related death/transplantation although this appeared to be an early effect, disappearing when patients with <3 months follow-up were excluded from analysis.

Published percentages of patients with AIH who achieve normal serum ALT on treatment have varied widely; 65 (10-95)% (median(range)) after 6 months and 83 (46-100)% after 12 months.[2,6] The percentages in our study fall within these ranges. We confirm previous observations of failure of serum transaminases to normalise being associated with younger age and with the presence of cirrhosis.[29]

Identifying early response parameters which reliably predict long-term-outcome, would aid evaluation of novel treatments for AIH. Single-centre studies have reported that failure to achieve normal serum ALT within 6-months, [7,9] 12-months.[8,9] or at times unspecified [18] are associated with higher death/transplant rates. However, in these studies, some deaths occur early, within the first 6-12 months. Patients who die or are transplanted early may not have been followed for long enough to allow normalisation of serum ALT. It does not follow that failure to achieve serum ALT normalisation at a given time point (which implies follow-up to that time point) might in itself, be predictive of subsequent death/transplantation.

We observed independent associations between subsequent death/transplant rate and percentage change in serum ALT from pre-treatment values (after 1-6 months). Notably, a >80% fall in serum ALT after 3 months predicted lower death/transplantation rates, consistent with another study reporting associations with fall in serum AST (after 2 months). [10] However, in our study, this relationship arose mainly from a high death/transplant rate in patients whose serum ALT had risen over the first 3 months.

Attaining normal serum ALT over the first 12 months (at any stage or at specific time points) either in isolation or combined with IgG normalisation, showed no independent association with death/transplantation; but the limited data on serum IgG prohibits firm conclusions.

Thus, these results do not support the common perception that attaining normal serum ALT within the first 6 or 12 months of treatment is a reliable surrogate marker of subsequent death/transplantation outcome over the subsequent 5-10 years.

However, we found associations between failure to achieve normal serum ALT at any time within 12 months and de-novo cirrhosis development, which is itself, is independently associated with death/transplantation. [8] Hence, failure to attain normal serum ALT might still predict mortality in the longer term.

In conclusion and notwithstanding the study's limitations, our results have some implications for the clinical management of AIH. Firstly, confirming, that both steroids and a steroid-sparing agent are needed for optimal outcome. Secondly, that initial doses of Prednisolone of >35 mg (or >0.5 mg/kg)/day are not associated with higher remission rates and may be harmful. Third, that routine continuation of steroids beyond 12 months (or after serum transaminase normalisation) may not be beneficial. Although such observations should ideally be confirmed by clinical trials, such trials are unlikely in the foreseeable future. Lastly, our results cast some doubt on the proposed goal of serum ALT normalisation over the first year of treatment, and warrant further studies with longer follow-up time, to characterise better short-term markers of medium and long-term prognosis in AIH.

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Table 1: Baseline features of the 1267 patients and initial treatment given

Patient Characteristics	All patients (n=1267)
Age (Years): median (range)	55 (8-86)
Gender: Female: Male N (%)	1010 (80): 257 (20)
Ethnicity stated: N (%)	1180 (93)
Caucasian	1079 (91)
Asian	79 (7)
Afro-Caribbean	15 (1.3)
Chinese	1 (0.1)
Other groups	6 (0.5)
Personal History of other autoimmune disease: N (%)	546 (44)
Immunoglobulin G/ Globulin raised: N (%)	991 (78)
Autoantibody positive (ANA/ASMA/LKM): N (%)	1012 (80)
Peak ALT (IU/L): median (range)	488 (10-4181)
IAIHG Score: median (range)	17 (2-25)
Definite AIH: N (%)	596 (47)
Probable AIH: N (%)	568 (45)
Did not meet criteria: N (%)	103 (8)
Cirrhosis: N (%)	316 (25)
MELD >15: N (%)	216 (17)
Clinically decompensated: N (%)	108 (9)
Clinically decompensated or MELD >15 (%)	272 (21)
Initial treatment in 1st 3 months	
Corticosteroids given: N	1169†
• **Prednisolone‡: N**	1111
• **Budesonide: N**	58
Patients given steroids at any time point: N	1175
Steroid monotherapy throughout: N	132
Combination therapy at any time during follow-up: N	1043
Non-Steroid immunosuppressant monotherapy first§	19
• **Azathioprine**	17
• **6-Mercaptopurine**	2
First non-steroid immunosuppressant given	1056
• **Azathioprine/ 6-Mercaptopurine**	1011
• **Mycophenolate (MMF)**	32
• **Tacrolimus**	10
• **Cyclophosphamide¶**	1
• **Cyclosporin††**	1
• **Methotrexate‡‡**	1

† 6 patients were subsequently given steroids after the first 3 months, ‡in patients initially given Methylprednisolone (n=19) or Hydrocortisone (1 with concurrent coeliac disease) were pooled with those initially given Prednisolone (n=1091, as all received Prednisolone shortly afterwards. §There were 2 patients initiated on non-steroid monotherapy for 2 months who then received corticosteroids, ¶ Received for SLE therapy and AIH then MMF,††for SLE and AIH, ‡‡Received for polyarthritis and AIH, then Azathioprine started.

Table 2: Demographic and baseline parameters independently associated with outcome.

Parameter (No of patients)	All-cause death/transplantation		Liver-related death/transplantation	
	Univariate P value	Multivariate P Value (HR (CI))	Univariate P value	Multivariate P Value (HR (CI))
Age (1267)	0.001	0.001 (1.03 (1.01-1.05))	0.002	ns
V-R Co-M (1267)	0.001	0.032 (1.84 (1.06-3.21))	0.65	ns
Cirrhosis‡ (1267)	<0.001	0.015 (1.90 (1.13-3.18))	<0.001	<0.001 (3.64 (1.70-7.68))
Decompensation‡ (1267)	<0.001	0.001 (2.70 (1.64-4.45))	<0.001	0.011 (2.58 (1.24-5.34))
Low platelets§ (1202)	<0.001	<0.001(0.993 (0.991-0.995)	<0.001	0.001 (0.995(0.990-0.998)
Transplant centre (1267)	<0.001	0.003 (2.30 (1.32-4.03))	0.001	0.019 (2.28 (1.44-4.59))
Peak Bilirubin (1218)	<0.001	ns	<0.001	0.002 (1.003 (1.001-1.005))
Albumin at peak bilirubin (1047)	<0.002	ns	<0.001	ns
Black Ethnicity (1180)	0.004	ns	0.011	ns
Sex (1267)	0.33	ns	0.72	ns
PBC coexistence (1267)	0.28	ns	0.31	ns
PSC coexistence (1267)	0.94	ns	0.93	ns
Diabetes coexistence (1262)	0.32	ns	0.88	ns
Autoantibody negative (1160)	0.60	ns	0.06	ns
LKM positive (924)	0.39	ns	0.70	ns
Delay in diagnosis (1259)	0.87	ns	1.0	ns
Delay in treatment (1187)	0.64	ns	0.37	ns
Asymptomatic (1267)	0.99	ns	0.21	ns
Did not meet 1999 criteria (1267)	0.14	ns	0.52	ns

†V-R Co-M is Vascular/respiratory comorbidity ‡At presentation, §at start of treatment

Table 3: Steroid treatment parameters associated with death/transplantation (multivariate analysis).

Parameter (No of informative patients)	All-cause death/transplantation		Liver-related death/transplantation	
	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)
Steroids yes/no:				
All patients (1267)	<0.001	0.25 (0.14-0.45)	<0.001	0.11 (0.05-0.22)
Patient sub-groups:				
Asymptomatic (278)	0.001	0.13 (0.04-0.42)	0.065	0.18 (0.03-1.12)
No cirrhosis (951)	0.007	0.29 (0.13-0.65)	0.001	0.13 (0.04-0.43)
Peak serum ALT<150 U/L (213)	ns	-	ns	-
Pre-treatment ALT <50 U/L (154)	ns	-	ns	-
Necro-inflammatory score<9 (34)	ns	-	ns	-
Age >75 years (207)	ns	-	ns	-
Initial prednisolone dose				
≤ or >35 mg/day† (1084)	0.005	2.22 (1.48-3.31)	ns	-
≤ or >0.5 mg/kg/day† (710)	0.001	2.59 (1.39-4.84)	ns	-
Duration of steroid therapy‡				
> 6 months Y/N (896/181)	0.064	0.51 (0.25-1.07)	0.016	0.32 (0.12-0.81)
>12 months Y/N (696/299)	ns		ns	-
>24 months Y/N (472/375)	ns		ns	-
Stopped vs continued steroids after 1st normal serum ALT (120/835)	ns		ns	-
Prednisolone vs Budesonide (1111/58)	ns		ns	-

†Prednisolone or Prednisolone equivalent if Methylprednisolone/Hydrocortisone treated. Not including Budesonide treated patients. ‡Patients followed up for at least this time.

Table 4: Serum ALT treatment response parameters independently associated with death/transplantation†

Parameter (No of patients)		Time after treatment started	All-cause		Liver-related	
			p value	Hazard ratio (95%CI)	p value	Hazard ratio (95%CI)
% change ALT‡	(858)	1 month	0.007	1.24§ (1.06-1.45)	ns	-
	(875)	3 months	<0.001	1.42 (1.19-1.69)	<0.001	1.53 (1.26-1.86)
	(821)	6 months	0.09	1.14 (0.98-1.32)	0.001	1.22 (1.04-1.44)
	(782)	12 months	ns	-	ns	-
% fall ALT>80% (or not)	(838)	1 month	0.041	0.45 (0.21-0.97)	ns	-
	(865)	3 months	0.012	0.36 (0.16-0.80)	0.024	0.24 (0.07-0.86)
	(811)	6 months	0.005	0.34 (0.16-0.72)	0.030	0.28 (0.09-0.88)
	(778)	12 months	0.038	0.31 (0.21-0.95)	ns	-
ALT raised	(863)	1 month	ns	-	ns	-
	(885)	3 months	ns	-	ns	-
	(839)	6 months	ns	-	ns	-
	(807)	12 months	ns	-	ns	-
ALT failed to ever normalise	(930)	12 months	ns	-	ns	-

† Analysis was performed in the 1169 patients receiving steroids within the 1st 3 months; numbers indicate those in whom serum ALT values were available at each time point. ‡from value prior to starting treatment. §relationship with mortality is positive, thus a larger negative change (ie fall) associated with lower mortality

Figure 1 Kaplan-Meier graphs showing associations between all-cause death/transplantation and: 1a: Baseline cirrhosis and 1b: Development of de-novo cirrhosis

Figure 2 (a-d) Kaplan-Meier graphs showing associations between steroid treatment parameters and all-cause death or transplantation:

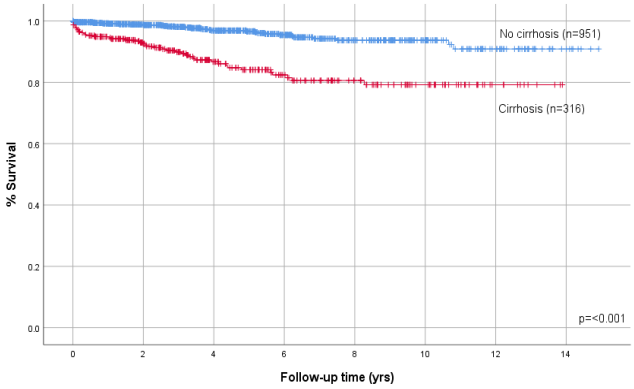
2a: Whether or not received steroids
2b: Initial Prednisolone* dose > or ≤35mg/day (Budesonide-treated patients excluded).
2c: Initial steroid treatment duration >6 months versus ≤6 months (follow-up for at least 6 months
2d: Patients initially receiving Budesonide versus Prednisolone (or Methylprednisolone or Hydrocortisone)

Figure 3. Kaplan-Meier graphs showing associations between all-cause death or transplantation rate in steroid-treated patients by whether (or not) steroid-sparing agent (SSA) was also used.

Figure 4. Kaplan-Meier graphs showing associations between all-cause death or transplantation and serum ALT response parameters.
4a: by Percentage change in ALT from baseline values over the 1st 3 months of treatment. †
4b: by whether or not at least one normal serum ALT value was achieved within the 1st 12 months.‡

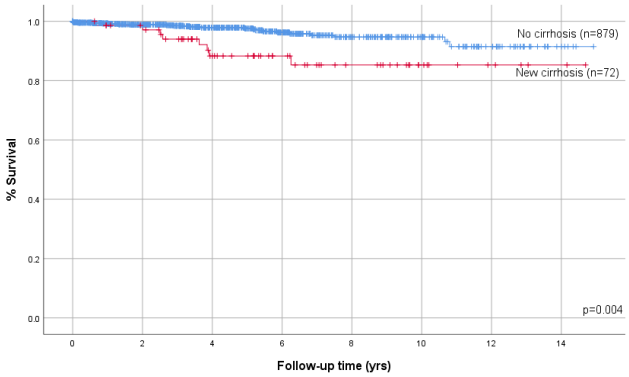
Figure 1. Kaplan-Meier graphs showing associations between all-cause death/transplantation and:

1a: Baseline cirrhosis



Yes	316	221	143	92	62	35	43	0
No	951	684	465	276	161	88	41	8

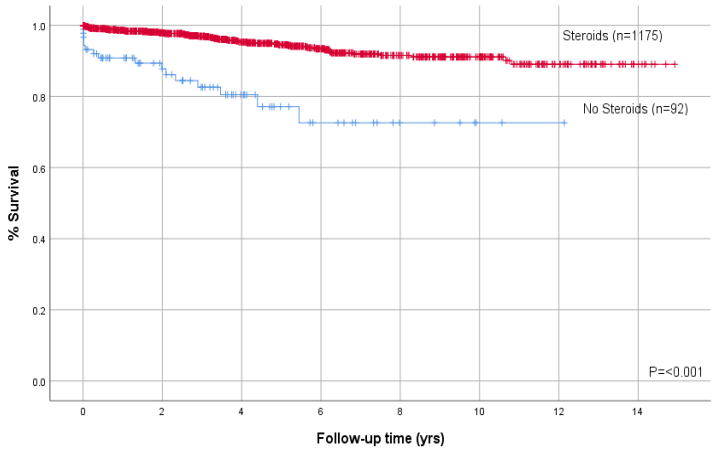
1b: Development of de-novo cirrhosis



Yes	72	66	45	31	20	10	5	2
No	879	618	420	245	141	78	36	6

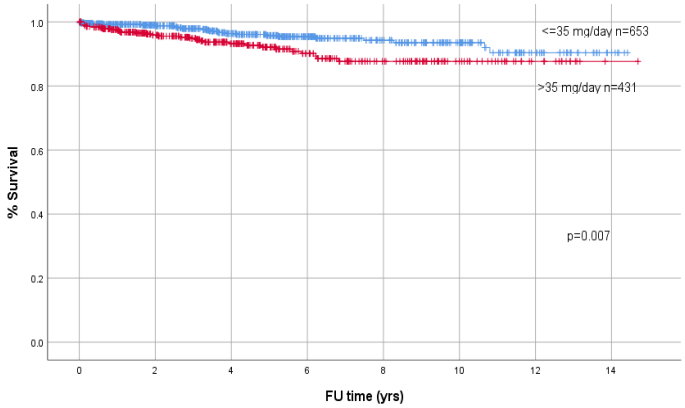
Figure 2 (a-d) Kaplan-Meier graphs showing associations between steroid treatment parameters and all-cause death or transplantation:

2a: Whether or not received steroids



Yes	1175	851	579	354	217	121	50	8
No	92	54	29	14	6	2	0	0

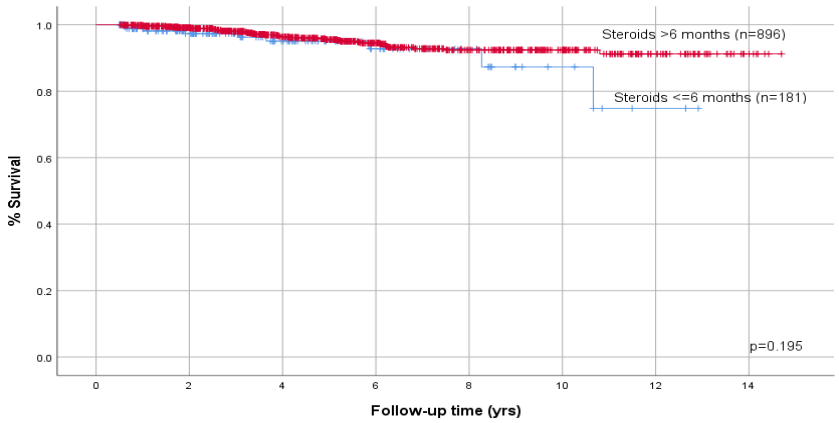
2b: Initial Prednisolone* dose > or ≤35mg/day (Budesonide-treated patients excluded).



>	431	301	198	122	73	35	14	1
>=	653	483	345	211	136	82	34	6

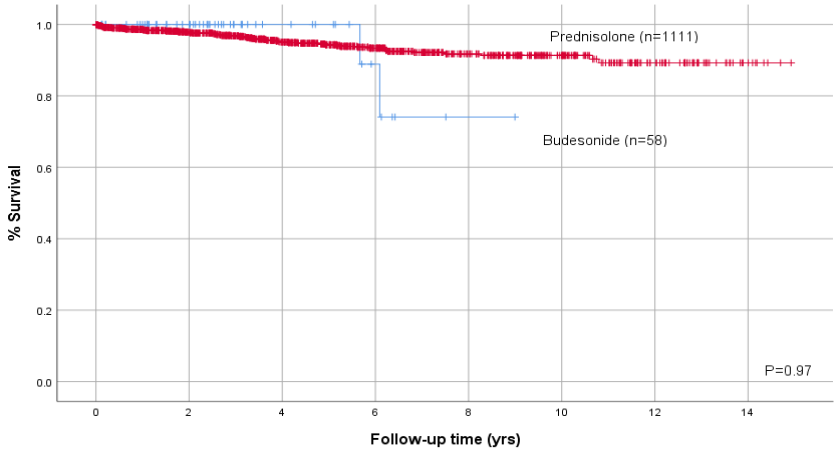
*Included 19 patients initially receiving methylprednisolone and one receiving hydrocortisone (converted to Prednisolone equivalent dose)

2c: Initial steroid treatment duration >6 months versus ≤6 months (follow-up for at least 6 months



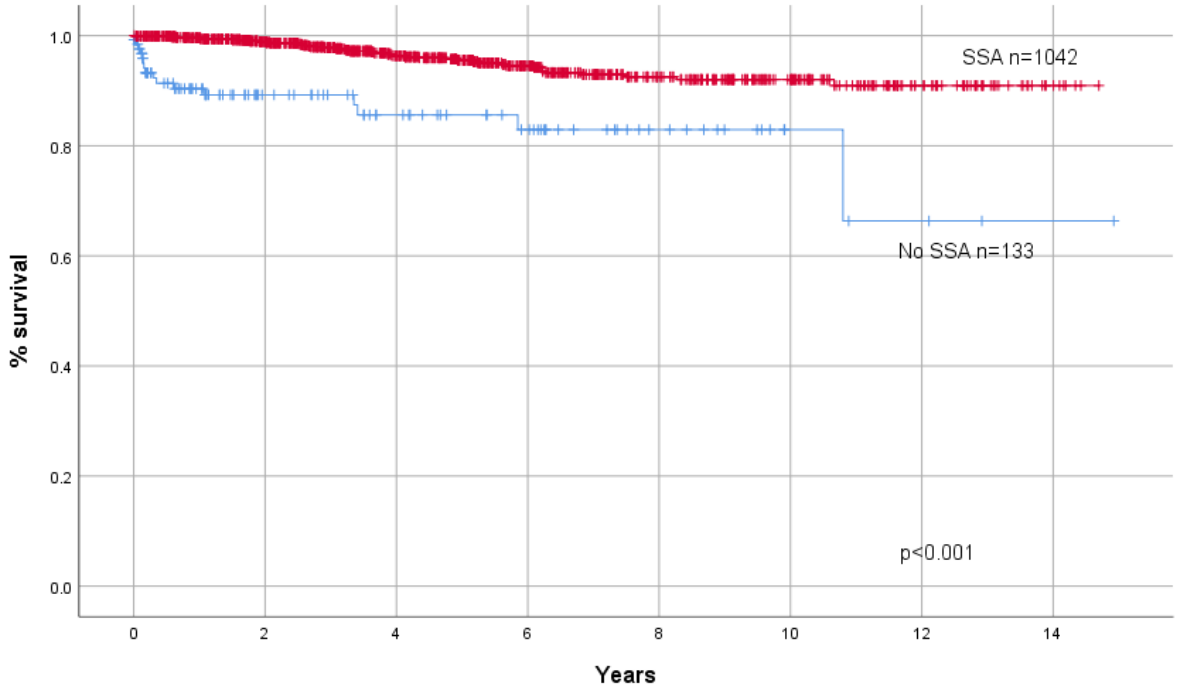
<6mo	181	120	74	38	18	8	3	0
>=6m0	896	722	499	311	198	112	46	7

2d: Patients initially receiving Budesonide or Prednisolone (or Methylprednisolone/Hydrocortisone)



Yes	58	38	15	6	1	0	0	0
No	1111	867	559	344	216	121	49	7

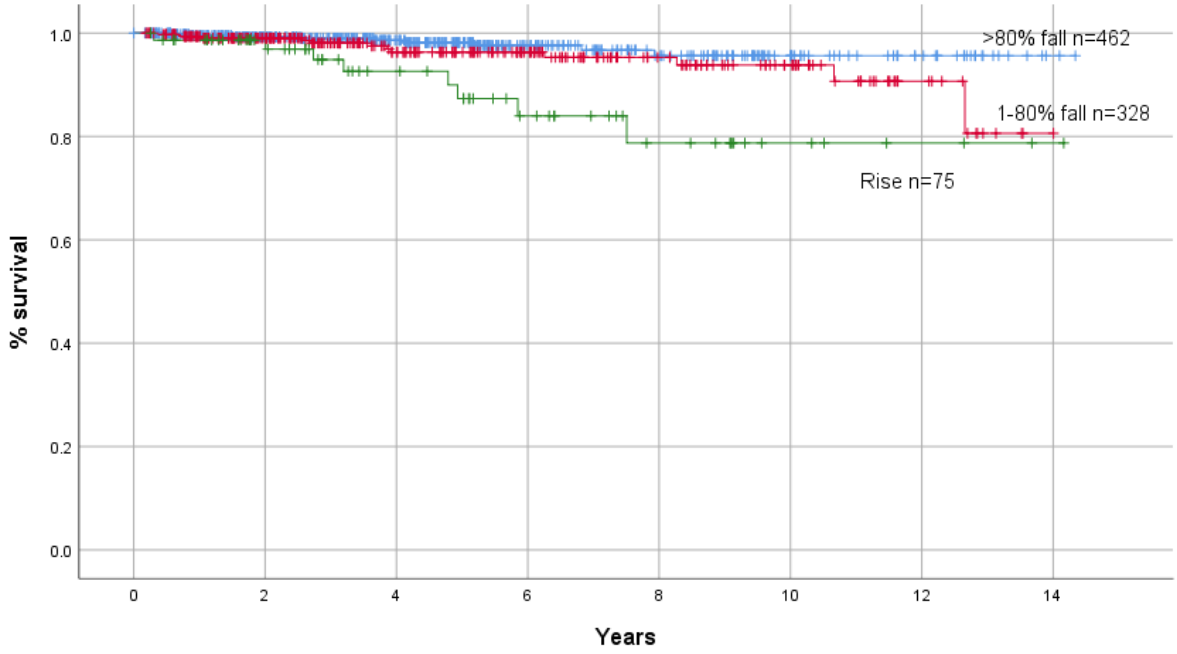
Figure 3. Kaplan-Meier graphs showing associations between all-cause death or transplantation rate in steroid-treated patients by whether (or not) steroid-sparing agent (SSA) was also used.



No SSA	133	59	42	30	15	5	3	1
SSA	1042	792	537	324	202	116	47	7

Figure 4. Kaplan-Meier graphs showing associations between all-cause death/transplantation and serum ALT response parameters.

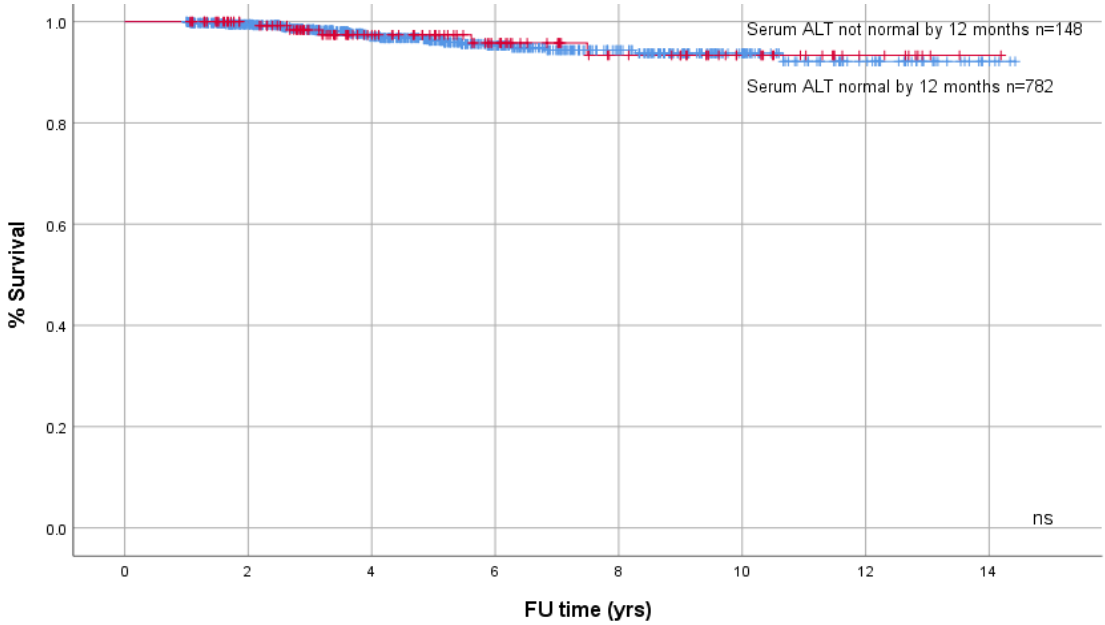
4a: by Percentage change in ALT from baseline values over the 1st 3 months of treatment.†



>80%	462	352	243	131	85	40	21	2
1-80%	328	240	157	106	65	38	12	1
Rise	75	56	36	23	14	6	3	1

†Differences between those >80% and 1-80% fall not significant .

4b: by whether or not at least one normal serum ALT value was achieved within the 1st 12 months (in patients with ≥12 months follow-up).



Not normal	148	118	79	54	34	22	9	1
normal	782	632	417	247	156	79	35	5