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Evaluation of current practice and outcome in autoimmune hepatitis (AIH)

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Declaration

I declare that this work is my own and that Chapter 6 contains a large portion of work that has already been published. I have gained the correct permissions from Wiley and Sons and co-authors that contributed to this work, for its use in this thesis, as was agreed at the outset of this Audit.

Abbreviations

General

BSG	British Society of Gastroenterology
DGH	District General Hospital
HQIP	Health Quality Improvement Partnership
IAIHG	International Autoimmune Hepatitis Group
NGH	Northern General Hospital (Sheffield)
RHH	Royal Hallamshire Hospital (Sheffield)
UH	University Hospital

Conditions

AIH	Autoimmune Hepatitis
ALF	Acute Liver failure
CAH	Chronic Active Hepatitis
CMV	Cytomegalovirus
DIAIH	Drug-induced autoimmune hepatitis
DILI	Drug-induced liver injury
EBV	Epstein-Bar virus
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IBD	Inflammatory Bowel Disease
PBC	Primary Biliary Cirrhosis
PSC	Primary Sclerosing Cholangitis

Liver Enzymes

ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
GGT	Gamma- Glutamyl Transferase

Immunology

AMA	Anti-mitochondrial Antibody
ANA	Anti-nuclear Antibody
Anti-LKM-1	Anti-Liver Kidney Microsomal -1 Antibodies
Anti-SLA-LP Ab	Soluble liver antigen/liver pancreas antigen antibody
Anti-SLA-LP	Soluble liver antigen/liver pancreas antigen
cANCA	Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies
HBsAg	Hepatitis B Surface Antigen
HLA	Human Leukocyte Antigen
IgG	Immunoglobulin G
pANCA	Perinuclear Anti-Neutrophil Cytoplasmic Antibodies
SMA	Anti-smooth muscle antibody
Tregs	Regulatory T Cells

Investigations

MRCP	Magnetic Resonance Cholangiopancreatography
ERCP	Endoscopic Retrograde Cholangiopancreatography

Treatments

Anti-TNF	Anti-tumour necrosis factor
MMF	Mycophenolate Mofetil
SSA	Steroid-sparing agent

Terminology

ACD	All-cause death
LRD	Liver-related death
EC	European Caucasoid
ULN	Upper limit of normal
NIS	Necroinflammatory score

Summary

Although practice guidelines[1,2] for the management of AIH exist, they are based on data from many years ago and may not be reflective of actual current practice. Therefore, this study investigated current practice and outcome in the UK's first large-scale multicentre audit involving 28 hospitals. This has characterised 1267 patients presenting to hospitals of varying size, expertise and facilities across several regional areas.

Major findings were:

- Patients were older than those from other multicentre studies overseas and some single-centre studies, indicating that AIH may affect older people in the UK and should be considered in older patients more readily.

- One-fifth of cases had ≥12-month diagnostic delay, though this study did not demonstrate worse overall outcome, one does not know the impact of this delay on longer-term outcome highlighting inefficiency in diagnosing this rare condition.

- There is under-reporting of key histological features, especially in DGH's. The effect of this on diagnosis is emphasised by findings that simplified-criteria, as utilised, failed to diagnose one-third of patients.

- Independent baseline predictors of all-cause mortality/transplantation were age, cardiac/respiratory co-morbidity, black ethnicity, cirrhosis, decompensation, low platelets and peak bilirubin.

- Independent baseline predictors of liver-related mortality/transplantation were cirrhosis, decompensation, low platelets and peak bilirubin.

- Failure to receive corticosteroids or SSA's are independently associated with adverse outcome underlining the importance of always offering patients treatment in the absence of contraindications.

- Higher dosages of prednisolone have a 2-fold increased risk of all-cause death/transplantation urging use of caution when considering dosing regimens. Type of steroid used does not affect overall outcome.

- Serum ALT at 1 and 3-months was an independent predictor of outcome of LRD/transplantation and could be used as a useful prognosticator.

- There is variability in service provision between hospitals, with better provision of specialist clinician's and nurses at UH's, with AIH often managed by a larger number of clinicians than necessary. Liver blood test monitoring was inadequate and referral to/discussion with transplant teams were not done in all decompensated patients potentially eligible for transplantation. This supports the case for AIH to be managed by a smaller number of designated clinicians, improving patient monitoring and the rate of transplant referral.

- Histopathologists with a specialist-interest in liver disease improved reporting of at least some histopathological findings of AIH calling for the expansion of Histopathologist numbers, improved liaison between centres, sharing clinical experience and encouraging adherence to guidelines to improve patient care.

Chapter 1: Introduction

In the 1940's, the term Chronic active hepatitis was initially ascribed to patients with symptoms presumed to be of a persistent viral hepatitis, that did not settle. In those who were asymptomatic but whose laboratory features continued, were said to have chronic inactive hepatitis. In these times, autoimmunity was not a commonly recognised clinical phenomenon and the lack of availability of testing of autoantibodies and liver sampling would hamper recognition of this. Later, there were suspicions that these clinical episodes pertained to a separate clinical entity of chronic hepatitis.

In 1950, both Swedish physician Jan Waldenström and American physician Henry Kunkel separately described the clinical phenotype of young females with chronic liver disease who had hypergammaglobulinaemia. [3,4] They described symptoms of fever, arthralgia and demonstrated plasma cell infiltration on liver biopsy in these patients. The patients were often referred to as 'Kunkel-Waldenström girls' by followers of their work. It was later described that "altered liver proteins" stimulated the formation of "anti-liver antibodies" which in turn produced liver injury, perpetuating more altered protein release thereby causing further hepatic necrosis. [5]

Appropriately, the term autoimmune hepatitis (AIH) was eventually adopted after the earliest meeting of the International Autoimmune Hepatitis Group in 1992 where the diagnostic criterion was codified. We now recognise the collection of characteristics of raised serum transaminases, hypergammaglobulinaemia, positive autoantibodies, and representative histological changes on liver biopsy with steroid responsiveness to be classical AIH.

AIH is recognised to be a chronic unremitting autoimmune inflammatory parenchymal liver disease of undetermined aetiology. However, there is increasing evidence of its association with other autoimmune diseases, HLA associations,[6,7] evidence of immune over activity and typically responds to immunosuppression.[1] Left untreated this condition can progress to cirrhosis, liver failure and death.

1.1 Epidemiology

There are no published data on the incidence and prevalence of AIH in the UK.
The European annual incidence of AIH is between 0.8-1.9 cases per 100,000 per annum,[8-10] and it has been suggested that it is increasing perhaps because of the 'hygienist theory' (improved hygiene leading to reduced infections).[11]

Prevalence data from Spain, Scandinavia and New Zealand indicate ranges from 10-24/100,000.[8,9,12-14] Interestingly, in one homogenous population of Native Alaskans, the point prevalence was reported as 42.9 per 100,000. [15]

Females are affected 3-4 times more commonly than men in type 1 AIH but in type 2 AIH this sharply increases to a 10:1 ratio. [16] Type 1 and type 2 AIH are denoted by their antibody profile; which is discussed in more detail later in this review.

AIH can affect all ages and ethnic groups worldwide. [17-22] Age appears important because older patients have a higher all-cause death/transplant,[23,24] but in some reports younger age was associated with liver-related death/transplant. [25,26]

Ethnicity has been associated with variations in disease severity and outcome. African-Americans are more likely to be cirrhotic at index presentation (56%-85%) versus 38% in patients from Northern Europe. [21,27] One retrospective single-centre UK study found non-Caucasian patients; specifically African, Asian and Arabian presented at earlier age ($p<0.05$), were more likely to have cholestatic biochemical features ($p=0.014$) and were also less treatment responsive ($p<0.0005$) than white (European Caucasoid; EC) patients. [18] This small study had only 12 patients who were non-EC as compared to 180 of EC origin and thus the former were a relatively small representation of all their AIH patients. Such diverse presentations and features may signify different genetic predispositions, environmental exposure, cultural and socio-economic circumstances. [28]

Several viruses (hepatitis A, Hepatitis E, CMV and EBV), use of medications and even herbal medicines have been reported to precede cases of AIH. [1]

Drug-induced AIH (DIAIH)

Up to 9% of AIH cases could be drug-induced; with Nitrofurantoin and Minocycline being the most frequently associated. [29] A chronic active hepatitis of varying degrees has been shown to be induced by Nitrofurantoin but there is no consistent correlation with dose or duration of therapy, which is unlike an 'ordinary' drug-induced liver injury (DILI).[30] Often histological patterns seen with Minocycline, Nitrofurantoin, Statins and Khat are indistinguishable from AIH. [31,32]

A large retrospective study of consecutive AIH patients (n=237) made a comparison with DIAIH (n=24) and found they had similarly raised antinuclear antibodies (70% versus 83%) and smooth muscle antibodies (45% versus 50%). [29]

The complexity of the relationship between drugs and AIH can be seen with Anti-TNF agents (Infliximab and Adalimumab). This is demonstrated by the fact they have been successfully used in treatment-refractory AIH patients [33] but they have also been implicated in causing both drug-induced liver injury (DILI) and DIAIH. [34] In practice, it is often difficult to distinguish between DILI and DIAIH. Unlike DIAIH, usually, a DILI will usually resolve and not recur.

Reported associations between AIH and many other drugs such as Methydopa [35] and Clometacin (Non-steroidal anti-inflammatory) [36] are based on single or small case series may just be coincidental.

1.2 Genetics

Studies of major histocompatability complex (MHC) genes which are located on the short arm of chromosome 6, have given insight into the genetics of AIH because they mediate interactions with leucocytes, in particular, those that code for human leucocyte antigen (HLA) are present in higher frequency. The MHC is divided into Class I, II and III with different genes belonging to each. It is variations in the MHC region that are important.

In Type 1 AIH susceptibility has been linked to HLA class II genes, which are highly polymorphic, and mapped to the HLA-DRB1 region. [37] In particular associated with DRB1∗03, DRB1∗04, and DRB3 alleles in White-European and North-American patients. HLA-DRB1∗0405 and DRB1∗1301 alleles are seen in Latin America, with DRB1∗04 in Japan and DRB1∗03 or DRB1∗13 in Brazil. [38]

A genome-wide association study was performed in the Netherlands and it has further corroborated that type 1 AIH has strong links to the MHC region, in particular, association to the amino acid lysine at position 71 in the HLA DR β chain (which is encoded by HLA-DRB1*0301 and HLA-DRB1*0401) and also found a non-HLA gene; SH2B3 to be a risk factor. [39] HLA-DRB1*04:01 or *03:01 positive patients are recognised in revised International Autoimmune Hepatitis Group diagnostic scoring (IAIHGS) systems and produce higher mean diagnostic scores and may be considered as ‘risk alleles’, indicating phenotypic significance. [7,40]

Few studies have focussed on type 2 AIH because of its low prevalence. HLA-DQB1∗0201 and HLA-DRB1∗07 alleles have been associated thus far. [6,41] Tumour necrosis factor-alpha (TNF-α) gene promoter (-308A allele) has been associated with a higher risk of developing AIH (OR=1.67). [42]

1.3 Pathogenesis

The pathogenesis of AIH has not been clearly delineated. It is postulated that genetically vulnerable individuals are exposed to an environmental insult which sparks an immune response; aptly named the 'hit-and-run phenomenon'. This possible infectious agent triggers the immune system, potentially many years before being clinically or biochemically evident. [43] A T-cell mediated response engages against liver antigens causing necroinflammatory activity within the liver, which is then chronically destructive.

Immunopathogenesis

It is thought that autoantigens initiate 'molecular mimicry' or auto-reactivity in AIH as they possess similar epitopes, which activate CD4+ T cells causing liver cell injury, which in turn cause plasma cells to produce more autoantibodies which perpetuates a vicious cycle. Such autoantigens are identified as soluble liver antigen (Anti-SLA) in type 1 disease and Microsomal antibody Anti-LKM-1 can be detected in the serum of AIH patients with type 2 disease and the latter are directed against Cytochrome P450 more specifically CYP2D6. [44,45]

Regulatory T cells (Tregs) normally regulate CD4, CD8 and B cells. If Tregs are reduced in numbers or alternatively defective versions are allowed to proliferate, the liver-specific effectors become 'unchecked'. These effector cells attract monocytes, macrophages and natural killer cells causing hepatocyte damage by releasing signals such as interleukins. Hepatocytes themselves become antigen presenting cells utilising HLA class II molecules thus directing or 'sign-posting', allowing amplification propagating liver damage. T helper 17 (Th17) cells form part of the host defence by suppressing Treg cells [46], and higher Th17 levels are associated with the degree of inflammation and fibrosis in AIH. [47] Activated T helper cells express C-X-C motif chemokine receptor-3 (CXCR3) which in turn binds to ligands such as CXCL10. [48] CXCL10 has been postulated as a biomarker of hepatic inflammation and fibrosis. A reduction in serum levels have been said to correlate with reduced hepatic inflammation and transaminases following treatment of AIH.[49] Treatment aims to restore a balance between regulatory T cells and effector cells (T and B cells).

1.4 Diagnosis

A combination of clinical, biochemical, immunological and histological features lead to a diagnosis of AIH. Biochemistry usually reveals a pattern of elevated transaminases; Alanine aminotransferase (ALT) and Aspartate aminotransaminase (AST) compared to the alkaline phosphatase (ALP). The degree of elevation does not necessarily indicate disease severity as even minor rises can be related to significant histological inflammation. [50]

1.4.1 Clinical Presentation:

AIH is a heterogeneous disease with presentations reflective of this, therefore, ranging from patients with asymptomatic abnormal liver tests to those with acute liver failure (ALF) or end-stage liver disease. Around one-quarter of patients will be asymptomatic at presentation. [12,22,51] Jaundice is seen in about 30%, but only a small proportion of these will develop ALF. [41,52]

Delayed diagnosis can arise because of the non-specific nature of presenting symptoms. These include fatigue, anorexia, nausea, itching, amenorrhoea, arthralgia or abdominal pain. Macular-papular rash and fever are less common manifestations.

1.4.2 Immunology

(i) Immunoglobulin G

Elevated immunoglobulin G (IgG) in patients with AIH was originally described in 1973 when one group tested levels in AIH patients and compared it to those with other causes of liver disease. [53] They discovered the mean level was almost three times higher than controls. Levels can be elevated in both type 1 and type 2 AIH but in 25% of the latter, they can be normal. [54] It is also of note that the range considered to be normal varies widely and may explain why some patients appear to have normal IgG at presentation but when they are subjected to treatment this level falls. [2] An isolated elevation of IgG without cirrhosis with compatibly elevated transaminases would be typical of AIH.

Antibody isotype immunoglobulin G is normally responsible for binding to, and incapacitating pathogens, allowing their recognition and eventual destruction via phagocytic immune cells. Elevated IgG is one of the most important parameters to look for when diagnosing AIH [40], and will be elevated in up to 90% of cases. [55-57] IgG has also been used for monitoring response to immunosuppression and determination of remission.

(ii) Autoantibodies

Several autoantibodies are associated, but not exclusive to AIH including anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA) and type-1 liver kidney microsomal antibody (Anti-LKM-1). They form a key part of the diagnostic scoring system. The Antibodies against Soluble Liver Antigen and Liver pancreas (Anti-SLA-LP) are linked with severe AIH and adverse outcome and is the only disease-specific autoantibody. [58,59] Fifteen to twenty-five per cent of patients have no detectable autoantibodies at diagnosis. [41,60]

No particular ANA pattern is specific to AIH and staining can be similarly seen in chronic viral hepatitis and drug-induced hepatitis. [29,61] Around 35% of patients with type 1 AIH are SMA positive and between 55-60% have both ANA and SMA positivity.

Anti-LKM-1 and Anti-liver cytosol (anti-LC-1) are associated type 2 AIH which originally was thought to be more severe and more prevalent in children. However, a recent study in adults indicates that patients with type 1 and type 2 AIH do not appear to behave differently in presentation or follow-up. [62] Type 2 disease appears to be geographically more common in Southern Europe. [63]

Anti-mitochondrial antibodies (AMA) can be positive in patients with AIH, but usually occur at low titres and do not necessarily indicate PBC overlap but could represent a clinical variant. Czaja et al demonstrated that AMA was detectable in 5% of patients with AIH using Eliza.[64]

Studies have found neither the titre or reduction in level has been definitively associated with clinical or histological activity. [65-67] Although, more recently it has been shown that after treatment the presence of SMA >1:80 was significantly associated with the biochemical and histological activity ($p<0.001$). [68]

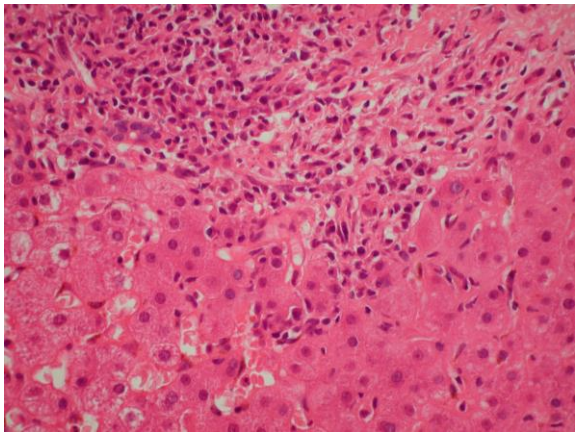
1.4.3 Histological Findings

Liver biopsy sampling is useful to confirm diagnosis, stage, inflammation and fibrosis. There is no single pathognomonic feature of AIH on histology. However there are classical histological features in AIH including interface hepatitis (75-87%)[12,69] (shown in Figure 1.1); with inflammatory cells spreading from the portal tracts permeating into the parenchyma and rosetting (49%)[1,69] of peri-portal hepatocytes, clustering like a ball, in response to lobular injury, representing hepatocyte regeneration. There is often mixed inflammatory infiltrate but with a predominance of lymphocytes and plasma cells (75-98%). [1,41,69] There are exceptions to this, when AIH presents acutely and can have hepatocellular necrosis and cholestasis superimposed on chronic hepatitis. [70] Centrilobular

injury with significant hepatocellular necrosis has been observed as a prominent finding in 29% of biopsies with AIH and the only feature in 2-3% of cases. [71]

Figure 1.1: Interface Hepatitis

(Image kindly provided by Dr A. McGregor (University Hospitals of Leicester)



Another histological finding has been associated with AIH, namely emperipolesis, which describes an intact cell penetrating another cell for example a lymphocyte infiltrating a hepatocyte, although the significance of this is not certain, it has been included in diagnostic criteria as a corroborating feature and occurs in approximately 75-80% of AIH cases. [1,69,72-76] One postulated relevance of its presence is the theory that it may induce hepatocyte apoptosis and thus an additional mechanism to autoimmune hepatocyte injury. [77,78]

Both rosettes and emperipolesis have been shown to be superior to plasma cells and interface hepatitis as independent predictors of AIH.[69]

1.4.4 Diagnostic Scoring Systems

There have been developments of the diagnostic criteria over time; in 1992 the International Autoimmune Hepatitis Group (IAIHG) formulated an initial comprehensive scoring system which was revised in 1999 (Table 1.1). This defined probable AIH (pre-treatment score 10-15 or post-treatment ≥12) or definite AIH (pre-treatment score >15 and post-treatment >17). [40,60] At first glance it can seem daunting and complex but is a useful aid where there is clinical uncertainty. This was developed primarily for research purposes to compare populations within clinical trials but is undoubtedly useful in clinical practice.

Table 1.1: International Autoimmune Hepatitis Group Modified Diagnostic Criteria

(Adapted from Alvarez[40])

Parameter/ Feature	Score	Parameter/Feature	Score
Female sex	+2	Drug history	
		Positive	-4
		Negative	+1
ALP:AST(ALT) ratio<1.5	+2	Average alcohol intake	
1.5-3.0	0	<25g/day (equiv to <3 units in UK)	+2
>3.0	-2	>60g/day (equiv to >7.5 units in UK)	-2
Serum globulins or IgG		Other autoimmune disease(s)	
>2.0 above ULN	+3	In either patient or first degree relative	+2
1.5-2.0	+2		
1.0-1.5	+1		
<1.0	0		
ANA, SMA or LKM-1		Liver Histology	
>1:80	+3	Interface hepatitis	+3
1:80	+2	Predominantly lymphoplasmacytic infiltrate	+1
1:40	+1	Rosetting of hepatocytes	+1
<1:40	0	None of the above	-5
		Biliary changes	-3
AMA positive	-4	Atypical features	-3
Hepatitis Viral markers		Optional additional parameters	
Positive	-3	Seropositivity for other defined antibodies	+2
Negative	+3	HLA DR3 or DR4	+1
Response to therapy		Interpretation of aggregate scores:	
Remission alone	+2	**Pre-treatment**	
Remission with relapse	+3	Definite AIH	>15
		Probable AIH	10-15
		Post Treatment	
		Definite AIH	>17
		Probable AIH	12-17

There also exists a 'simplified criteria' for diagnosis [72] based on autoantibodies, immunoglobulins, liver histology and negative hepatitis virology where ≥6 is probable AIH and ≥7 is definite AIH (Table 1.2). Potential problems can be identified with this approach as there is heavy emphasis on titres of antibodies which may not be available in all centres and one of the histological criterion to allocate a patients biopsy as 'typical AIH' is emperipolesis which does not appear to be a validated diagnostic feature, both of which are weighted heavily in this scoring system. The simplified criteria are less sensitive than the 1999 criteria and consequently 16% of patients would no longer be diagnosed with AIH and might be denied effective treatment. [79] A study from Greece similarly found that the 1999 criteria was more sensitive in diagnosing AIH [80] There have been other validation studies comparing simplified and 1999 criteria; and found both to have high sensitivity and specificity in Chinese patients[75] and children in the US. [81]

Table 1.2: Simplified Diagnostic Criteria for the diagnosis of Autoimmune Hepatitis

(Adapted from Hennes [72])

Tests	Cut off	Points allocated
ANA or SMA+	≥1:40	1
ANA or SMA+	≥1:80	2*
Or LKM+	≥1:40	
Or SLA+	Positive	
IgG	>ULN	1
	>1.1 times ULN	2
Liver histology (evidence of hepatitis is necessary)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2

*maximum of 2 points for all antibodies.

≥6: probable AIH

≥7: definite AIH

Despite the presence of diagnostic criteria, diagnosing AIH requires clinical judgement. In atypical cases not meeting the required diagnostic criteria for AIH in these scoring systems, it may still be appropriate to treat and monitor response.

1.4.5 Overlap syndromes

Overlap syndromes are also referred to as variant syndromes and are said to be present when a patient displays two concurrent or sequential autoimmune liver diseases such as AIH and Primary Biliary Cirrhosis (PBC) and are denoted AIH/PBC overlap or in the case of overlap with Primary Sclerosing Cholangitis (PSC) as AIH/PSC. There is also the possibility of small duct PSC when patients have a cholestatic blood profile but typical changes of the large bile ducts on Magnetic Resonance Cholangiopancreatography (MRCP) or Endoscopic Retrograde Cholangiopancreatography (ERCP) are not seen but there are changes present on liver biopsy consistent with degeneration or paucity of the bile ducts.

Variant syndromes with biliary features present the clinician with the problem of determining which is the predominant disease and be willing to change treatment approach when the disease courses changes. [82] In particular up to 50% of children with AIH in one study had biliary features.[83]

1.5 Management of AIH

Characteristically AIH responds well to steroid therapy and is included in the diagnostic repertoire for this reason. The purpose of treatment is to suppress the autoimmune inflammatory process affecting the liver. Consequences of failing to treat AIH can include progression to cirrhosis, liver failure and death.

The benefits of Prednisolone and Azathioprine in AIH were first demonstrated by controlled trials 40 years ago and have been included in management guidelines ever since. [84,85] There are now 3 recent management guidelines for AIH which have been produced by the European Association for the Study of Liver Diseases (EASL), the British Society of Gastroenterology (BSG) and American Association for Study of the Liver (AASLD). [1,2,86] These are based on limited 'high quality' data. This is because there are only 11 randomised controlled trials in AIH (7 of initial treatment and 4 of maintenance therapy), and all but one performed 25-45 years ago. Thus, many questions remain to be answered with regard to the application of "standard" therapy of prednisolone with or without azathioprine. As such, no formal standards of care have been proposed or validated against clinical outcomes.

1.5.1 Which patients should be treated?

Patients with raised ALT and or AST levels that are more than 5 times the upper limit of normal (ULN) who have elevated IgG and/or histological evidence of AIH should be treated. Trials performed in the 1970's and 80's showed the clear survival benefit in such patients. In the placebo arms of these trials; 3-year mortality was 50%, rising to 90% after 10 years. [84,87,88] 82% would become cirrhotic if they were not treated. [89] Treatment should also be considered in those with symptoms, have cirrhosis and in younger patients with the intention of preventing progression to cirrhosis. [90-92] Presence of symptoms is not obligatory to guide the decision to treat because 26% of asymptomatic patients can progress on to cirrhosis. [50]

Clinical judgement should be exercised in older patients where there is only mild interface hepatitis (equivalent to an Ishak necroinflammatory score 4-6) and the presence of relative contraindications to steroid therapy. Evidence suggests that in untreated mild disease there is between a 67-90% ten-year survival. [93-95] In those who have only mild necroinflammation on liver biopsy, normal transaminases and serum globulins or IgG, treatment would not be advocated, as spontaneous improvement may occur. Such patients should be monitored.

1.5.2 Standard Initial Treatment

Prednisolone and Azathioprine

By the 1950's, it was evident that the outlook of untreated AIH was poor, with 5-year survival rates of only 30%. Thus the primary aim of the initial controlled trials of immunosuppression therapy completed in the early 1970's [84,85,87,96] was to reduce this high mortality rate.

The earliest trials of induction treatment for AIH from the 1970's, showed the efficacy of prednisolone (15-20mg) over placebo and azathioprine monotherapy. Improvement of transaminases and serum globulins were shown along with a 2-4 year survival advantage. [84,87,88] The superiority of corticosteroids comes from their ability to act rapidly, inhibiting lymphocyte activation and limiting cytokine production, whereas azathioprine takes months to act. This is because azathioprine inhibits maturation of lymphocyte precursors at their origin; inside the bone marrow, instead of acting on the numerous circulating lymphocytes. [41]

Two key studies from the Mayo Clinic investigated treatment regimens; the first compared prednisolone monotherapy (starting at 60mg/day and tapering to a maintenance dose of 20mg over 4 weeks) versus the combination of 30mg prednisolone with azathioprine 50mg/day versus placebo and also versus azathioprine monotherapy. Investigators found that steroid containing groups were associated with improvement in serum parameters, histology and survival. The combination of azathioprine and prednisolone were accompanied by fewer side effects than prednisolone alone. [85] In their second controlled follow-up study, they added an additional treatment group (with a starting dose of 60mg prednisolone) where the dose was tapered and then titrated dependant on the serum transaminases, aiming to keep them less than twice the ULN. The latter strategy was associated with fewer side effects with the maintenance dosage being just 10mg/day, but unfortunately histological remission was significantly less in this group. [85,97]

Of note, some of the above studies found between 4-14% of patients were Hepatitis B surface antigen (HBsAg) positive and none of the previous studies tested for Hepatitis C virus (HCV) as the discovery of HCV was not until the 1980's. In a study from the United States; 8 patients from 105 'established' AIH patients tested positive HBV and HCV. 4% had HBV 4% were also found to have positive readings on initial testing with a first generation immunoassay for HCV although this was not seen on second testing and probably represents false positivity. [98] It is now common practice to attain negative viral hepatitis serology before diagnosing AIH apart from in exceptional circumstances.

Standard initial treatment in the UK is prednisolone 30mg/day with azathioprine 1mg/kg/day. Those who develop initial severe steroid side effects can be switched to Budesonide 9mg/day which is discussed later in this review. [1]

Other regimens are seen in the American 2010 AASLD guidelines which suggest 60mg prednisolone initial monotherapy. [86] This regimen is not used in the UK due to the likelihood of significant steroid side effects. Although this strategy can lead to rapid normalisation of transaminases in non-cirrhotic patients, there is no evidence of any overall prognostic benefit. [1,86]

Steroid side effects include the development of cushingoid features, diabetes,[99] psychosis, hypertension, reduction in bone density, osteoporosis and cataracts. Weight-gain from steroids can also often be sustained, even after withdrawal. [100] Corticosteroids can have other unintended side effects which can occur such as hastening incidence and progression of atheromatous cardiovascular events. [101] In unpublished data from Sheffield, presented at EASL in 2016, showed that hepatic steatosis can occur; as seen on 126 paired biopsies at diagnosis (25% at baseline) and increased on follow-up to 52%. The grade of steatosis worsened in 37%, but progression in fibrosis was not related to steatosis. [102] These side effects can be limited by the addition of azathioprine (combination treatment) which has a 'steroid-sparing' effect, allowing lower doses of prednisolone. Approximately 5% of patients on azathioprine develop early adverse severe reactions with arthralgia, fever and skin rash [103]. Around 10-20% gets nausea and anorexia which often resolves with persistence of the medication. Other side effects include pancreatitis, rash and cholestatic hepatitis. Myelosuppression is the most worrisome side effect and therefore monitoring of full blood count is warranted. Thiopurine methyltransferase (TPMT) testing can be helpful in identifying patients more likely to get myelosuppression as this enzyme is involved in the metabolism of azathioprine into inactive products. [104] One in 300 patients are homozygous for the deficiency in enzyme activity and thus severe toxicity will commonly occur, this is where alternatives such as Mycophenolate (MMF) should be used.

1.5.3 Alternative induction therapy for AIH

Budesonide

Recently, Budesonide 9mg/day in addition to azathioprine 1-2mg/kg/day has been proposed in non-cirrhotic patients for 6 months. Investigators convincingly demonstrated that budesonide when compared to those on prednisolone (both with azathioprine) showed more rapid normalisation of transaminases (60% versus 38.8%; P= 0.001) and lesser side effects (28% versus 53.4%; p<0.001) [105] Compared to previous trials this was however a surprisingly low biochemical remission rate in the

prednisolone group. This was a large multi-centre randomised controlled trial (208 patients) where viral hepatitis was excluded but unfortunately, no post-intervention histology data was examined and as yet there are no long-term data for this treatment regime.

The 90% first-pass metabolism of budesonide lends the advantage of low side effects, but in cirrhosis this process is reduced because of haemodynamic factors resulting in shunting of portal blood away from the liver and also bypassing effective metabolism and thus not recommended in these patients. Its use is in those with significant fibrosis is linked to treatment failure and side effects [106] and also potentially increases the risk of portal vein thrombosis.[107] Current UK guidelines reflect this and therefore offer budesonide as an option for non-cirrhotic patients who have severe or predictable steroid side effects.[1]

There is probably insufficient evidence to advocate its use in steroid intolerant or steroid dependant patients. In one study of its use in such patients, 25% discontinued Budesonide due to side-effects.[108]

1.6 Outcomes of Treatment

Studies have given rise to a widespread perception that the long-term outlook of treated AIH is good. Previously, studies from the US suggested the 10-year survival was 90%. [109,110] However, recent studies from the UK showed that when patients are followed up for longer (20-years) survival rates fall to 50-70%. [23,111] One older UK study suggested a 5-year survival of 60%, although this was partly explained by older age at diagnosis of AIH. [112] This is however, not simply due to ageing because it has been established that patients with treated AIH have excessive mortality compared to the general population, with standardised mortality ratio of 2-4. [23,113] There is an excess of deaths in patients presenting under the age of 45 years, and after more than 10 years of follow-up it appears entirely due to liver disease, being only modestly reduced by liver transplantation.
Such a “late” excess of deaths is probably a consequence of ongoing low-grade inflammatory damage and slow progression of fibrosis to cirrhosis. Whilst overall severity of fibrosis stabilises or improves on follow up biopsy in treated AIH, such improvement is not achieved in about 25% of patients. [114] New development of cirrhosis, which is now uncommon in treated chronic viral hepatitis, is eventually seen in 30-50% of patients with treated AIH, a striking indictment of the limited efficacy of standard treatment. Even though its significance has previously been questioned, cirrhosis development is important as it is an independent risk factor for long-term mortality. [23,115]

Early studies focused on survival rates. Later, endpoints of treatment focussed on biochemical responses taken as ALT<2 times ULN. However, things are changing yet again because many observational studies suggest those that fail to normalise ALT do worse than those that do.
One study assessed whether ALT, IgG or γ-globulins correlate with the degree of ongoing histological activity on follow up liver biopsy. They found that ALT and IgG were related to histological activity indices ($p<0.0075$) and that if ALT and IgG parameters were both raised this was associated with high histological inflammatory activity. [116] If both serum IgG and ALT were normal this was predictive of either no (or minimal) inflammation (Ishak necroinflammatory score (NIS) 0-3) or only low-level inflammation (NIS 4 or 5). The authors concluded that such low-level inflammation was an acceptable endpoint as they did not observe fibrosis progression in this group. However, others suggest that even low-level activity is predictive of long-term mortality. [117] Thus the validity of a normal serum IgG as an adequate treatment endpoint needs further evaluation.

Patients who are treated to normalisation of their transaminases, bilirubin and ϒ-globulin levels are far more likely to attain histological resolution, but it does not necessarily guarantee it. [118] A recent study by Hartl et al demonstrated complete biochemical remission was a surrogate of low histological disease activity and was the only independent predictor for histological fibrosis regression (relative risk 3.66; 95% CI 1.54–10.2; $p = 0.001$). They also showed that serial measurements of transient elastography were reliable for monitoring disease course. [119]

The UK, American and European guidelines agree that normalisation should be the aim of treatment because withdrawing treatment before this is associated with relapse and poor outcome. [1,2,86]

There are some useful phrases that describe the response to treatment (Table 1.3). The definitions are important as they provide aims, guide management and allow comparison in the literature. One always hopes to achieve a 'complete response' when treating AIH which equates to marked improvements in symptoms, normalisation of serum transaminases and γ-globulins within one year and sustained for 6 months. There is initial non-response in 5-20% of patients. [1,86,120]

Table 1.3: Definitions of Response

Response	Definition
'Biochemical Remission'	Serum Transaminases (ALT and AST) and γ-globulins normalise.
'Clinical Remission'	Symptom dissolution.
'Histological Remission'	Liver biopsy shows only minimal hepatitis or is normal.
'Complete Response'*	Either or both: Marked improvement in **symptoms** with ≥50% of all liver tests within month 1 and **transaminases** continue to fall below twice ULN within 6 months during any reductions toward maintenance therapy. OR Minimal activity on **liver biopsy** within 1 yr.
'Treatment Failure'	No clinical or biochemical response within 6 months of starting treatment.

*Definition of complete response taken and adapted from [40]. Other definitions are from [121,122].

1.7 Relapse of AIH

Relapse has been defined as serum ALT >3 times the ULN and occurs in 50-90% of patients within 12 months of ceasing treatment. [115,123,124] Relapses are important as they cause ill health, can precipitate liver failure, even death, and require reinstitution of corticosteroid therapy with its associated side effects. It is perhaps unsurprising then that multiple relapses constitute an independent risk factor for development of cirrhosis and long-term mortality.[23,125,126]
A retrospective review of 117 patients in the Netherlands found relapse is almost universal on treatment withdrawal. [127] This group defined relapse as ALT >3 times ULN and loss of remission as rising ALT requiring reintroduction of drug therapy. 89% either relapsed or had loss of remission (47% and 42% respectively). 73% had treatment reinstated within 2 years of drug withdrawal and 81% within 3 years.

The relapse rate may be reduced by continuing treatment. As demonstrated in one controlled trial, relapse rate was 32% after 1 year following azathioprine withdrawal (but continuing prednisolone alone). [128] Relapse rate is reduced to 17% over 5 years if azathioprine is continued in the higher dose of 2 mg/kg/day.[129] However, there are concerns about increased cancer risk related to long-term immunosuppressive treatment in AIH. A recent report from Sheffield found that the hazard ratio for those patients on non-steroidal immunosuppression for less than 4 weeks compared with those receiving therapy for more than 10 years compared was 8.7, and was 2.5 when comparing with those on therapy for between 4 weeks to 10 years. [130]

Even normalisation of the biochemical and histological tests does not confer protection against relapse; one study showed 60% of patients who relapsed had a prior resolution of inflammation on these tests. [118]

Preventing relapse using combination maintenance treatment in those with confirmed initial histological remission has been shown to be successful; one group found that only 8% relapsed in year 1 but increased to 32% when azathioprine was stopped and prednisolone continued. [128] A further study compared continuing combination treatment with phasing out prednisolone and increasing azathioprine dose from 1mg to 2mg/kg/day in the other group. [129] Reduction in steroid side effects was seen in the latter group and relapse did not occur. In a follow-up study, 83% remained in remission for a median of 67 months follow-up. [100]

The factors found to be associated with relapse of AIH are longer time to biochemical remission, presence of other autoimmune diseases and presence of an initial identifiable disease trigger. [131]

1.8 Other treatments for AIH

Mycophenolate Mofetil (MMF)

Mycophenolate (MMF) is a pro-drug of mycophenolic acid and shows potential as an alternative agent to azathioprine. Importantly, it has been used comprehensively in the treatment of liver, heart and kidney transplant recipients without reported hepatotoxicity. [132-134]

Advantages over azathioprine are that it inhibits inosine monophosphate dehydrogenase exerting anti-proliferative effects which are more lymphocyte specific. [135] Mycophenolate is generally well tolerated with leucopenia and diarrhoea being the main side effects. Unlike calcineurin inhibitors (such as cyclosporine or FK-506), MMF has no neurotoxic or nephrotoxic side effects but is highly teratogenic and thus should be used with great caution in women of child-bearing age. [136] MMF is also around 10-15 times more expensive than azathioprine. [137]

There are a small number of studies that use MMF first-line with an average of 85% achieving remission. [138-140] MMF thus far has been shown to be an effective first-line agent but is not currently recommended due to its relative expense. Exceptions would include the 0.3% of patients with severe TPMT deficiency and those on Allopurinol. A dose of 2g daily is proposed in the AASLD practice guidelines. The CAMARO trial (ClinicalTrials.gov) is currently on-going comparing standard therapy (steroid plus azathioprine) versus steroid plus MMF for treatment naïve patients.

The vast majority of experience with MMF for AIH is where it has been used in patients who are either intolerant or unresponsive to azathioprine. When given for azathioprine intolerance the chance of remission is between 43-88% [139,141-146] with the bulk of studies quoting towards the higher end of the spectrum percentage remission rates. A UK study showed that MMF plus prednisolone induced and maintained biochemical and histological remission in 13 patients who had azathioprine intolerance, and they also achieved similar or better rates of fibrosis regression than patients receiving azathioprine plus prednisolone. [147]

However, when MMF is given in those refractory to standard treatment, the success has been variable; studies with only very small numbers of patients quoting between 0-100% remission rates [139,142,143] but larger case series reporting between 0-64%, [96,141,144,145] with a further small study in children quoting a 67% remission rate. [146] One of these recent studies from the Netherlands showed that of those in the azathioprine refractory group 27% responded to MMF and only 13% went into remission. In contrast, in the AZA intolerant group, 67% went into remission on MMF. [141]

In summary, of azathioprine intolerant patients given MMF, many will attain disease remission. In contrast, azathioprine non-response usually predicts MMF non-response. This probably reflects the fact that these patients are likely to have a phenotypically more severe disease and thus a more difficult group to treat successfully. MMF does seem to reduce steroid dose and improves biochemistry even in these patients. Due to its relative expense, teratogenicity, lack of follow up histology, and lack of data on its long-term efficacy and prevention of relapse, MMF cannot be recommended as a first-line treatment for AIH.

1.9 Salvage therapies in non-responsive patients

When treatment fails, an alternative diagnosis should be considered (such as a variant syndrome or in the acute setting; Hepatitis E) and adherence to treatment should be reviewed.

In those not responding to conventional treatment, increased dosages of steroids, and calcineurin inhibitors such as cyclosporine A or Tacrolimus can be used successfully [148,149]. Rituximab has also been used in non-responders to standard therapy[150] and in second-line therapy. [151] The B-cell depleting properties reduce T cell activation via reducing B-cell help for T cell activation. There are other pharmacological agents in development which focus on alteration of gut microbiota, B cell modulation and expansion of intrahepatic Tregs by IL-2 or administration, modification, expansion or induction of autologous immune cells (adoptive Treg cell transfer). It is not the intention of the review to focus on this area in detail.

Of course, any patient who does not respond to treatment and progresses to liver failure should be referred for liver transplantation and will have a 75% five-year survival with such treatment, with a 20% recurrence rate. [152]

1.10 Pregnancy

Pregnancy is normally uneventful in patients with AIH but has been associated with lower live birth rate, maternal death, hepatic decompensation and an increased requirement for transplant if the patient has cirrhosis.

Autoimmune conditions, including autoimmune liver disease, may improve during pregnancy because elevation in oestrogen levels produces anti-inflammatory cytokine effects, protecting the foetus preventing immunological rejection. [153] This is the antitheses of what happens in AIH where immunological imbalance stimulates cell-mediated autoimmunity. Thus it follows that women are more likely to have problems post-partum and may be in part, related to the fall in oestrogen after pregnancy. [154]

Early data regarding pregnancy in AIH patients come from very small retrospective studies in the late 1960-1970's. The earliest included just 8 patients and 4 of these showed deterioration during pregnancy; 2 with toxaemia, one with bleeding varices and one with hepatic ascites. 3 mothers died within 2.6 years of pregnancy. [155] Another study suggested a high foetal loss rate (33%) and prematurity (23%). [156] The latter study did not provide any data on disease flares post-partum but did state that 12 of 16 women survived for a mean period of eight years after pregnancy.

More recently, a large single-centre cohort (53 patients and 81 pregnancies) found 33% of patients had a relapse of AIH and 78% of these happened post-partum. 11% had serious maternal events, defined as death or liver transplant during pregnancy (or within 12 months of delivery) or hepatic decompensation during pregnancy (or within 3 months of delivery). [157]

Most recently a Danish nationwide AIH cohort (179 births in 103 patients) was studied with population controls (1623 births in 1051 age-matched women). They found that fertility in AIH patients was unaffected but that they were at increased risk of pre-term birth (OR 3.19 (95% CI 1.53-6.64) and smaller babies for gestational age (OR 3.20 (95% CI 0.33-31.29). There was no evidence of an increase in congenital malformations or stillbirths. [158] This data is comparable to a population study from Sweden quoting a pre-term odds ratio of 3.21 but did not find smaller children for

gestational age.[159] Further studies are needed and a population-based data registry may help clarify this and also examine the effect of immunosuppression during pregnancy.

Patients are more likely to flare off immunosuppression and can be reassured that azathioprine is safe during pregnancy by experience shared so far in patients with AIH, IBD and rheumatoid arthritis. [157,160,161] Recent data suggest an 11-52% chance of relapse post-partum. [162,163] This wide variation reflects the lack of national or international consensus on the risk of relapse post-partum.

1.11 Predictors of liver transplantation and mortality

It is known that AIH, especially if untreated, can lead to cirrhosis, liver failure, require liver transplantation and cause death. It is imperative to know which features may be associated with poor outcome.

The presence of cirrhosis or decompensation has been associated with liver transplantation/death in the majority of studies [23,90,111,115,164,165] but not in all. [110,166]

The relationship of age to outcome is complex because in some studies younger age has been associated with liver death/transplantation [25,26] but in others older age is linked to all-cause death/liver transplantation. [23,24,167]

Prolonged International Normalised Ratio (INR), failure to respond to initial treatment (or normalise transaminases) [26,168] and unimproved day 7 UKELD (end stage liver disease) score (in icteric presentations of AIH) have been found to be predictors of poor outcome.[169] However one study demonstrated that patients who presented with serum AST above 10 times the ULN had a lower risk of cirrhosis and had improved long-term outcome.[170] Multiple disease relapses, but not single relapses, have also previously been identified as a predictor of liver-related mortality. [23,171,172]

1.12 Summary and overall aims of this thesis

Given that data from studies in Europe and New Zealand have found the incidence of AIH is between 10 to 24/100,000, this would suggest that between 6-15,000 people in the UK have AIH. Thus, a District General Hospital (DGH) in the UK serving a population of a quarter of a million would likely have between 24 to 60 patients attending and an estimated 96 to 240 patients for a University Hospital serving 1 million patients. These numbers highlight a significant workload for clinicians to diagnose, initiate treatment and employ intense monitoring, especially in the early phase of treatment of this chronic disease.

There are limited data from multi-centre experiences from one country or whole geographical areas reporting on AIH. To date the largest collection of AIH cases have come from three multi-centre cohorts of 473 Swedish patients which included 10 hospitals [12] and 1313 patients from 31 centres collected from the Dutch AIH group;[10] focusing on initial presentation, and one further study from Denmark including 1721 AIH patients; [14] which presents data on incidence and prognosis but did not focus on individual characteristics pertaining to presentation. These cohorts have, however, given great insight into the Scandinavian population. This is something we wanted to define further in the United Kingdom, but from a wide variety of centres to gain more representative 'real life' data. Similarly, there are only 11 randomised controlled trials regarding the treatment of AIH and thus there are limited data regarding the most efficacious management strategy. Most studies reporting the outcome of AIH are from larger specialist units who are more likely to have younger patients and patients with more severe disease, because of inherent referral bias, likely because of centre expertise and access to liver transplantation.

This literature review highlights several areas that need further study and exploration with regard to disease prevalence, optimal management and outcome of patients with varying treatment regimens. A significant barrier to answering questions about optimal treatment is that it would be difficult to perform large multi-centre randomised controlled trials pertaining to optimal regimens of just prednisolone and azathioprine, as funding would be difficult to attain, as we already know these medications are effective. However, one admires the success of multi-centre audits and the insight they can offer. For example, the Royal College of Physicians led National Inflammatory Bowel disease (IBD) and the National Upper Gastrointestinal bleeding audits have been shown to be beneficial in information gathering with regards to current practice and disease outcome and can be used as leverage to change guidelines and practice. [173,174]

To the author's knowledge, there are no UK multi-centre audits of AIH, but there has been some insight into care for patients with AIH from a 2012 nationwide questionnaire-based survey which was designed to give an overview of service provision for liver disease in the UK.[175] It found that (of 106 responding hospitals) DGH's had fewer Hepatologists than tertiary hospitals (0(0-1) versus 1(0-10)), and 41/71 (58%) versus 26/35 (74%) respectively had a specialist liver nurse (although this was not statistically significant) implying some disparity in staffing. They also found that all hospitals used standard therapy as first-line treatment for AIH but when patients were unresponsive or intolerant of this, the majority were then referred to a liver unit (74% in DGH's). Follow-up liver biopsies are not frequently performed (in 25% of cases). This indicates some variation in the management of this

rare condition. This wide variation in approach to managing AIH was also demonstrated by another UK-wide survey of 228 Gastroenterologists and Hepatologists in the same year, with half of the respondents indicating that all consultants looked after patients with AIH, Hepatologists were more likely to always perform diagnostic liver biopsies than Gastroenterologists (82 vs 58%) and 65% continued prednisolone treatment only until transaminases normalised or for up to 6 months, whilst others continued for more than 2 years. [176] Given the persistent uncertainty regarding the optimal management of AIH, such variation might be expected but whether this affects the outcome is unclear.

Although liver disease has been highlighted as a health priority, resources remain inadequate in many hospitals. In 2011, a census of the UK medical workforce[164] highlighted few Hepatologists in District General hospitals (DGH's) compared to University hospitals (UH's). Of 146 responding hospitals; 103 (71%) did not have a Hepatologist and 23 (16%) had no Hepatologist nor Gastroenterologist with a specialist interest in Hepatology (GIH). In a 2018 survey of 88 UK Trusts by the BSG Clinical Services and Standards committee; 37 of 63 DGH's (compared to 1 of 27 UH's) had no Hepatologist.[177]

Networks have been developed for management of patients with Hepatitis C across the UK, with similar recent developments in respect to second-line treatments for Primary Biliary Cholangitis. These links facilitate provision of specialist advice and when needed, direct care, adherence to nationally agreed management guidelines, sharing of scarce facilities, such as transient elastography, training for doctors and specialist nurses and finally involvement in research and audit. There are no comparable systems for the management of AIH.

At present, there are no formally validated current agreed standards of care that serve as a benchmark to compare a Hospital's performance to, but there are American, European and UK practice guidelines[1,2,86] which provide some assistance when drawing up standards pertaining to the diagnosis, treatment and outcome.

In general, the overall aim of this work to emulate the success of previous audits with our own multi-centre large-scale audit by deliberately including centres of varying size and facilities. It will firstly build a picture of the current numbers of cases of AIH that hospitals are responsible for caring for. Secondly it will define current 'real-life' practice (diagnosis and treatment) and its relationship with the short and longer-term outcome of patients with AIH in the UK. Collecting data on management

and outcome from multiple centres allows an analysis of this relationship and should help define and validate clinically relevant standards of care for management in AIH. With this work, the aspiration is to improve current practice and establish more robust evidence-based guidelines. Chapter 2 shows the audit design.

1.13 Study Aims

Methods chapters:

- Chapter 3 Aim: To produce a user-friendly modified diagnostic tool to validate cases of AIH in a step-wise fashion to be used in a multi-centre audit.
- Chapter 4 Aim: To develop a strategy for retrospectively identifying patients with AIH.
- Chapter 5 Aim: To produce a robust and secure data collection tool.

Results chapters:

- Chapter 6 will address the following aims:
  i. To report the number of cases of AIH whom hospitals are managing across Yorkshire (12 hospitals) and from 16 other hospitals further afield participating in this multicentre audit.
  ii. To report information on diagnosis, presenting features and initial severity of AIH across the UK.
  iii. To assess hospitals performance against agreed audit standards below.

Audit Standards pertaining to diagnosis:

i. 100% of patients will be tested for Hepatitis B (HBV) and Hepatitis C (HCV).
ii. ≥80% of patients will undergo diagnostic liver biopsy.
iii. ≥90% of patients will meet the 1999 International Autoimmune Hepatitis Group (IAIHG) diagnostic criteria.
iv. Time from first abnormal LFT's to diagnosis is <4 months (≥90%).

- Chapter 7 Aims:
  i. To report the overall outcome (liver deaths, all-cause death and liver transplantation rate).
  ii. To determine any baseline predictors of all-cause death or requirement for liver transplantation.
  iii. To determine any baseline predictors of Liver-related death or requirement for liver transplantation.
  iv. To determine any relationship between treatment and outcome.
  v. To report initial treatment response and determine any predictors of incomplete response to treatment.

vi. To report drug toxicity

vii. To report the proportion of patients maintaining normal ALT, relapse rate and its effect on all-cause or liver-related outcome.

viii. Report disease progression; the development of cirrhosis and determine baseline factors associated with its development, new clinical decompensation and Hepatocellular carcinoma (HCC).

- Chapter 8 will address the adherence to:

Audit Standards pertaining to treatment and outcome:

i. ≥90% of symptomatic patients will receive prednisolone within 4 months of diagnosis.

ii. ≥90% will continue Prednisolone for at least 12 months.

iii. ≥80% will have liver blood tests measured 3 monthly.

iv. ≥90% will attain normal serum ALT within 12 months after the start of treatment.

v. ≥80% of those with clinical decompensation should be discussed with a transplant centre or state a reason why not.

vi. ≥60% of those re-biopsied (liver biopsy) will attain histological remission.

vii. ≥75% will not develop de-novo cirrhosis.

viii. <21% will not clinical decompensation (defined as ascites, encephalopathy or variceal bleed)

Chapter 2: Overview of Study Design

2.1 Audit Background and Conduct

The original idea to pursue an audit was presented at a meeting held near Sheffield in 2012, attended by approximately 45 receptive Gastroenterologists and Hepatologists, mainly from Yorkshire and the North of England, to discuss the prospect of gathering information on diagnosis, presentation, and outcome of AIH and its associations. There was universal support for this endeavour. The venture was also open to centres outside of Yorkshire and interested centres were contacted and invited to attend a satellite meeting at the British Society of Gastroenterology (BSG) Conference in 2013 in Glasgow. A protocol was designed in Sheffield (the coordinating centre), then reviewed by centre coordinators and revised accordingly. Standards were generated by consulting current practice guidelines (BSG and AASLD) and by consensus of consultants at participant centres.

The audit was intended to be conducted both retrospectively (mainly) and prospectively to allow for sufficient follow-up time, to provide meaningful results and to allow an overall shorter completion time for the project. This meant including both incident and prevalent cases. Prevalent cases with a diagnosis prior to 1/1/2000 were excluded firstly because the criterion for diagnosis was codified finally in 1999, and secondly obtaining details about diagnosis and response would be challenging prior to this date due to difficulties in viewing medical records from this time period. Lastly, that given the earlier diagnosis of these prevalent cases, the fact they had survived may mean these cases would be less representative of patients with AIH in terms of outcome.

It was important to try to capture all cases attending each centre otherwise the project would suffer from survival bias. The capture strategy is briefly summarised below but the methodology of developing this is discussed in detail in Chapter 2. This ensured an approach that did not rely on centres own pre-existing lists or databases of patients but allowed an approach that could identify patients regardless.

Given the complexities of AIH diagnosis, which is reliant upon clinical, serological and histological data, this meant that case validation was needed and a minimally modified version of the 1999 International AIH group (IAIHG) diagnostic criteria were used.

2.2 Participant centres

Initially, 29 centres agreed to participate but one later dropped out, leaving 28 centres of varying sizes and amenities; there were 14 District General Hospitals and 14 University Hospitals (4 were transplant centres):

[1] Sheffield Teaching Hospitals NHS Trust (coordinating centre), [2]Calderdale Royal Hospital, [3]Bradford teaching Hospitals Foundation Trust, [4]Addenbrooks, Cambridge, [5]University Hospitals Leicester, [6]Airedale NHS Foundation Trust, [7]Chesterfield Royal Hospital, [8]Freeman Hospital, Newcastle, [9]Rotherham Foundation NHS Trust, [10]Royal Derby Hospital, [11]York Teaching Hospital NHS Foundation Trust, [12]St James's University Hospital, Leeds,[13]Doncaster Royal Infirmary, [14]Nottingham Digestive Diseases Centre, National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre at the Nottingham University Hospitals NHS Trust and University of Nottingham,[15]North Tees University Hospital,[16]Scarborough Hospital,[17]Darlington Memorial Hospital, [18]Manchester Royal Infirmary,[19]Singleton Hospital, Swansea,[20]Barnsley District General Hospital,[21]Kettering General Hospital, [22]Kings College Hospital, London,[23]University Hospital North Durham, [24]Hull Royal Infirmary, [25]Mid-Yorkshire Hospital [26]Royal Gwent Hospital; Newport, [27]Stepping Hill Hospital, Stockport, [28]University Hospitals Coventry and Warwickshire.

Each centre had a 'local centre coordinator' (LCC) who enrolled clinical effective audit workers (CE's) to identify patients and enter data. The LCC was also required to register the audit with the Trust and liaise with their local information governance team about data transfer.

2.3 Ethics and Governance

The project, specifically the strategy used to identify patients and subsequent multi-centre audit of practice and outcome has been discussed in full with our local hospital Caldicott Guardian and with the research and development department at Sheffield Teaching Hospitals, who determined that this was an audit as opposed to research and as such did not require formal ethical approval. The project was registered with our local audit department. It was also sought to discuss this more widely with the Health Research Authority (HRA) who evaluated our protocol and answered our questions about reporting the outcomes of our audit. The HRA was happy that this whole project was encapsulated within the remit of the audit and it was possible to fully report clinical outcomes. The study was approved by the Health Quality Improvement Partnership (HQIP). This study was also reviewed and endorsed by the University of Sheffield ethics department (ref 009662).

Patients who were alive, were also sent a letter informing them about the audit and that they could ask for more information, with a telephone number to ring (of LCC or Specialist Nurse) if they required more information or could opt out if they wished (only two patients subsequently did this and they were removed from the audit).

2.4 Funding

A competitive application was made to Health Quality Improvement Partnership (HQIP) and to the British Society of Gastroenterology (BSG) for funding, a total of £50,000 was received. This was mainly used to remunerate CE's time to gather relevant data and to purchase a web-based data collection system.

2.5 Design and Informatics

Centres were asked to identify and include both incident and prevalent cases by utilising a pre-validated search technique which included searching electronic clinical records, histology databases and hospital coding as well as any pre-existing databases of patients. This is described in more detail in Chapter 4. Patient lists were generated from the search, and cases were then validated using a 3-stage sequential diagnostic validation form which formed the first part of the web-based data collection proforma (see Appendix A). This part of the proforma used a minimally modified 1999 IAIHG diagnostic score to make this as uniform and comparable as possible across centres for reasons described in detail in Chapter 3. Thus, if the patient scores ≥10 they have at least probable AIH. This was only for ease of use of the proforma. (see Appendix A and 1999 IAIHGS in Table 1.1: Chapter 1). However, to avoid confusion, scores have then been converted for comparison to other studies and discussion in this thesis.

Anonymised details relating to diagnosis, management and outcome of patients with AIH were then entered into a password protected web-based electronic proforma. Duplication of patient entry was prevented by centres stating whether patients had been managed at other centres or not and cross-checking between them, where appropriate. No control group was included and thus incidence and prevalence data are not calculated. It is also of note that some hospitals only included incident patients (Manchester, Cambridge and Mid-Yorkshire). Information pertaining to individual centre infrastructure was competed by centre coordinators and collected on a separate web-based proforma.

This information was entered into a custom-built encrypted web-based data collection tool (FORMIC solutions), this data was held on an N-3 server and downloaded centrally at Sheffield Teaching

Hospitals. There were no identifiable patient details entered; each patient was allocated an audit number which only the centre entering the details possessed the key to. In addition, each centre had a unique encrypted username and password to access the system.

Cases were both retrospectively and prospectively captured as per the inclusion criteria. All data were collected between 1/1/14 to 30/11/15.

2.6 Inclusion criteria

1. Meet minimally modified 1999 IAIHG score criteria or have a clinical diagnosis of AIH and are receiving treatment with immunosuppressive therapy.
2. ≥18 years old at inclusion.
3. An absence of positive HBV/HCV serology but can include those in whom the result was undocumented.
4. Include patients with overlap/variant syndromes (AIH/PBC or AIH/PSC); as the scoring system itself has negative adjustments for positive anti-mitochondrial antibody and biopsy changes.
5. Presented between 2000 and 2015, defined as:
    a) Prevalent cases; those presenting from 01/01/2000 to 31/12/2006 and are still being followed up, or
    b) Incident cases; those presenting from 01/01/2007 to date whether they were still alive or not.

Chapter 3: Creating a user-friendly modified diagnostic tool to validate cases of AIH.

3.1 Background:

Although the 1999 IAIHG diagnostic scoring system is lengthy, complex and involves using information from a number of sources to complete in order to denote the likelihood of AIH, it is the most inclusive of scoring systems.

For ease of use, researchers developed a simplified scoring system (simplified criteria) which utilises fewer parameters. However, this approach loses some of the integrity of the 1999 system; considering less parameters and because of its descriptive histological criterion, which includes emperipolesis, that is not usually commented upon in liver biopsy reports. It was found in a small study from Sheffield, that 83 of 84 (99%) biopsy specimens had emperipolesis present on second histological review, when none of the primary reports including this finding.[178] The published prevalence from other studies is between 32-65%. [72,179-181] The histological parameters (Interface hepatitis, lymphoplasmacytic infiltration, rosettes and also emperipolesis) as used in the simplified criteria to determine 'typical' features of AIH as described and utilised may inadvertently exclude around one-sixth of patients it was felt that it was not a feasible tool for use in the audit. [79]

Studies from other centres have not always been completely 'inclusive' when identifying patients: 2008 simplified criteria,[182] 1999 'definite' cases only,[111] 1999 with 'early deaths' excluded[171] and one solely reliant on clinical codes for selection.[14] This poses the problem of case selection bias of more 'pure' AIH and causes difficulty in comparing studies. Others have used full IAIHG 1999 criteria (definite and probable). [12,23,26,109,172] By taking a broader approach one can perform sub-group analysis to compare like for like.

Thus, a minimally modified version of the IAHG diagnostic scoring system is described here for use within our multi-centre audit to identify patients with AIH.

3.2 Aim

To produce a user-friendly modified diagnostic tool to validate cases of AIH in a step-wise fashion to be used in a multi-centre audit.

3.3 Methodology

A minimally modified 1999 International AIH diagnostic scoring (IAIHGS) system was used. They are referred to as Case Validation Proforma part one (Figure 3.1) and part two (Figure 3.2), to be used for patient cases identified by Histology, Electronic Letters or Hospital Coding search. The latter proforma includes a list of autoimmune diseases for user reference.

Figure 3.1: Modified IAHGS used in the Multi-Centre Audit – Part 1 case validation

AUTOIMMUNE HEPATITIS CASE VALIDATION

	Points Awarded
HBV sAg and HCV (also HAV, HEV or acute CMV/EBV)	
1 is Positive	Exclude
Both Negative	3
Results not available for either HBV/HCV (please tick if HAV/HEV/CMV/EBV IgM positive ☐)	0
Female	2
Histology (Biopsy on which diagnosis based if >1)	
Not done	0
Done but result inaccessible	0
Interface Hepatitis	3
Mainly lymphocytes and/or plasma cells	1
Rosettes	1
None of the above	-5
Bile duct changes	-3
Granuloma	-3
More than mild steatosis (fat); pre-treatment only	-3
Other Changes (other *prominent* feature suggesting alternate aetiology)	-3
Immunology (please use your own hospital parameters)	
Highest serum IgG (or globulin if no IgG):	
>2x upper limit of normal (ULN)	3
1.5-2.0 x ULN	2
1.0-1.5 x ULN	1
<ULN or not done	0
Anti-nuclear, anti-smooth muscle or anti-LKM-1 Ab titre	
>1:80	3
1:80	2
Titre unspecified or 1:40	1
Not done, weak +ve or <1:40, negative	0
Anti-mitochondrial Ab Negative or not done	0
Weak +ve or >1:40	-4
Biochemistry (first available within 1 yr biopsy) – **only if abnormal enzymes:**	
(Alk Phos (divided by ULN)) /(ALT* (divided by ULN)) ratio:	
<1.5	2
1.5-3.0 **/ or normal enzymes**	0
>3.0	-2
TOTAL POINTS <4	**Exclude**

***use AST if no ALT**

Figure 3.2: Modified IAHGS used in the Multi-Centre Audit – Part 2 case validation

CLINICAL RECORDS REVIEW (HOPEFULLY ELECTRONIC)

Score carried forward from previous page =

Alcohol consumption pre-diagnosis	
<22 Units/wk	2
22-52 Units/wk or not recorded	0
>52 units/week	-2
Autoimmune diseases (see list below and tick all that apply)	
Past History or Family Hx of autoimmune disease	2
No such recorded history	0
Drug History (everyone awarded 1 point regardless)	1
Treatment	
Failure to normalise serum ALT or AST with treatment	-2
Not treated	0
Normalised on treatment	0
Relapse (serum ALT or AST >2 times ULN) after prior normal value	1
TOTAL POINTS FROM HISTO SEARCH+ CLIN RECORDS	**=**
Include	**≥10**
Exclude	**<10**

Adapted from Alvarez et al 1999 J Hepatology

Patients/Family Hx Other Autoimmune Diseases

Primary Biliary Cirrhosis (PBC)		Polymyositis	
Autoimmune Hepatitis (family Hx)		Primary Sclerosing Cholangitis (PSC)	
Antiphospholipid syndrome (APS)		Psoriasis	
Coeliac Disease		Rheumatoid Arthritis (RA)	
Diabetes (type 1)		Sarcoidosis	
Fibrosing alveolitis		Sjogrens	
Glomerulonephritis		Systemic Lupus Erythematosus (SLE)	
Haemolytic Anaemia		Temporal Arteritis	
Thyroiditis/Hypothyroidism		Thrombocytopenia	
Inflammatory Bowel Disease (IBD)		Uveitis	
Mixed connective tissue disease		Vitiligo	
Mononeuritis multiplex		Other AI disease (specify):	
Multiple sclerosis (MS)			

The rationale for modifying the current IAHG diagnostic criteria is that some parameters are not commonly used or may be unavailable in some hospitals and thus may not 'include' patients who may otherwise have been labelled with AIH. This adjustment refers to the removal of 'other antibodies' and 'HLA' testing from initial scoring. Although this information was collected, if tested for, in the subsequent data collection electronic clinical proforma which follows the initial case validation (see Appendix A). This would ensure scores were comparable across centres.

The order in which the modified AIH diagnostic tool appears has been chosen specifically to minimise wasted time entering further data than necessary. Any patients with HBV or HCV were excluded to protect the integrity of our audit, thus if a patient had positive serology for either we asked that the case is excluded immediately and no further data should be entered. Although it is possible to have both HBV or HCV and AIH one would never be clear on whether the clinical picture was because of the former or the latter and their management would be different to a patient with isolated AIH. Those with acute IgM positive CMV, EBV or HEV were included, for later consideration, given that these viruses have been thought to trigger AIH.

The histology section was enhanced slightly to clarify that those with more than mild steatosis (a common finding in liver biopsies), may suggest an alternate aetiology and thus should score -3 which is the same as allocated by the 'other changes' category which signifies another prominent feature suggesting an alternate aetiology. There was also an option to indicate 'biopsy not done' (scores 0) so the user does not incorrectly allocate none of the above (score -5) and penalise scores.

If the patient has not reached a score of 4 by the end of part one, then it is not possible to achieve the points needed to make a diagnosis of AIH by completing part two and thus needless to carry on. In part 2 of case validation required the patients' clinical records (unlike part 1 where this data can be obtained from electronic laboratory and histology systems). The alcohol section was adapted to accommodate the alcohol unit system used in the UK, rather than grams, to simplify the process for the user. The drug history section has been changed; awarding every patient 1 point to avoid the data handler (who may be non-clinical) from having to decide whether a drug could be causative, but drugs history was requested to be documented. Specifically, whether the patient was on Nitrofurantoin, minocycline, Infliximab or had a history of Khat ingestion was recorded. The rationale for this lies with the fact there remains difficulty in deciding whether a drug is to blame for a serological, clinical and histological picture presenting itself, particularly in the shorter term. Recent evidence suggests that up to 9% of AIH is drug-induced. [29] For this reason, it was the intention to be inclusive of patients rather than exclusive.

The original 1999 IAIHG diagnostic scoring system (see Table 1.1, Chapter 1) indicates that scores between ≥10-15 pre-treatment or ≥12-17 post-treatment is indicative of probable AIH, and scoring >15 pre-treatment or >17 post-treatment indicates definite AIH. The overall weighting of responses was changed to accommodate alterations made. Thus, a score ≥10 with our modified version

denotes inclusion into our audit as a case of AIH. The maximal points available are 24 compared to 29 in the original IAIHG scoring.

3.4 Conclusion

A minimally modified IAIHG diagnostic scoring system has been developed here to serve as a practical, time efficient tool for use within our multi-centre audit to validate cases of AIH. This tool was employed to score patients on our prospective AIH database and cases identified by the capture strategy described in Chapter 4. This has been successfully transposed into an electronic format to be completed as the initial screening of cases, before sequentially moving on to further detailed data entry involving demographics, initial severity, serum parameter values and drug treatment.

Chapter 4: Methods for developing a strategy to identify patients with AIH.

4.1 Introduction

Being able to accurately identify as many patients as possible with AIH is essential to the integrity of a multi-centre audit evaluating management and outcome to ensure meaningful results. Anecdotally; in the meeting with approximately 45 Gastroenterologists from the UK, it was established that most hospitals do not have a saved list of monitored patients (or database) with AIH. Such a list is not only helpful for monitoring patients but also enables review of practice. Additionally, there is potential to compare data with other centres and can possibly be utilised for research purposes, with appropriate approval. Generating such a list would certainly not be instant because diagnosing AIH relies on evaluating clinical information, compatible blood tests and histology, thus requiring information gathering from different sources to reach a diagnosis.

There was a need to develop a robust, accurate strategy for identifying patients who have AIH. The proposed strategy would hopefully 'cast a net', allowing retrospective identification of patients who potentially had AIH. This would then allow case confirmation by application of the modified version of the IAIHG diagnostic scoring system for AIH ,[40] shown in Chapter 3 (Figure 3.1 and 3.2), acting as a sieve to retain only those who met the criteria for AIH.

At Sheffield Teaching Hospitals; since the year 2000, one of our dedicated specialist Hepatology nurses has diligently kept a prospective list of patients with AIH. The main function of which was to keep a record of patients who were on treatment and aid monitoring of blood tests.

One wanted to see if it was possible to identify all patients on the database with a proposed search strategy and proceeded to first test this strategy within our own centre (Sheffield) and validate it against our prospective database. The resultant cohort of patients from the time frame chosen would represent the incident cases of AIH from 1st January 2007 to February 2013. Once validated, this capture strategy could then be utilised by all participating centres involved in the audit.

4.2 Aim

To develop a strategy for retrospectively identifying patients with AIH.

4.3 Methods:

A retrospective search was performed interrogating three facets; histology database, electronic letters and hospital coding (for patients admitted with a diagnosis of AIH). The search period was 1st January 2007 to February 2013 as follows:

1. Histology Search

Sheffield Teaching Hospitals histology database was searched using histological 'SNOMED' codes used to denote different histological descriptions and indicate diagnoses. After discussion with our local Histopathologist, a list of liver biopsies (code T-62000) performed was generated. The terms 'chronic inflammation' (code M-43000), 'acute inflammation' (code M-41000) and 'acute hepatitis NOS' (code D5-80140) were used. This is because our histology database was not reliably searchable for 'autoimmune hepatitis' as a diagnostic code, so these more general terms had to be used. The list generated from the database included the hospital number, name and date of biopsy and then case validation was performed in three stages:

(i) Patients who were Hepatitis B (HBV) and Hepatitis C (HCV) positive were excluded immediately to prevent unnecessary time spent collecting further information. (Figure 3.1, Chapter 3)

(ii) The list was then reduced by cross-referencing with histological, immunological and biochemical data from the hospital results reporting system depicted in the first part of the scoring system used to determine if a case meets initial criteria for AIH. If the patient scored <4 they were excluded. (Figure 3.1, Chapter 3)

(iii) If the case scored ≥4 then the second part of the case validation proforma was used with reference to the electronic letters system. Of note the maximal number of points that can be allocated in this second part of the form is 6; this should be added to the score carried from the first part of the form. Thus, patients with a score of ≥10 meet the criteria for AIH (see Figure 3.2, Chapter 3). This process took approximately 5 working days to complete for our data sample of 1470 patients initially identified by the search.

2. Electronic letters Search

In Sheffield there is a departmental 'S' drive within our hard drive which can be accessed to view typed letters containing up-to-date information about patient's hepatology clinic appointments. This system was started in 2006 and all letters were searched and not restricted by date.

The search terms 'autoimmune hepatitis', 'auto immune hepatitis', 'chronic active hepatitis' and 'AIH' were usedusing the 'search-term' function available on the windows system. The patients'

hospital number, name, approximate date of diagnosis was entered into an Excel spreadsheet. This took approximately two working days to complete. These cases were then verified by utilising the case validation tool. This process took approximately another 3 working days to complete.

3. Hospital Coding Search

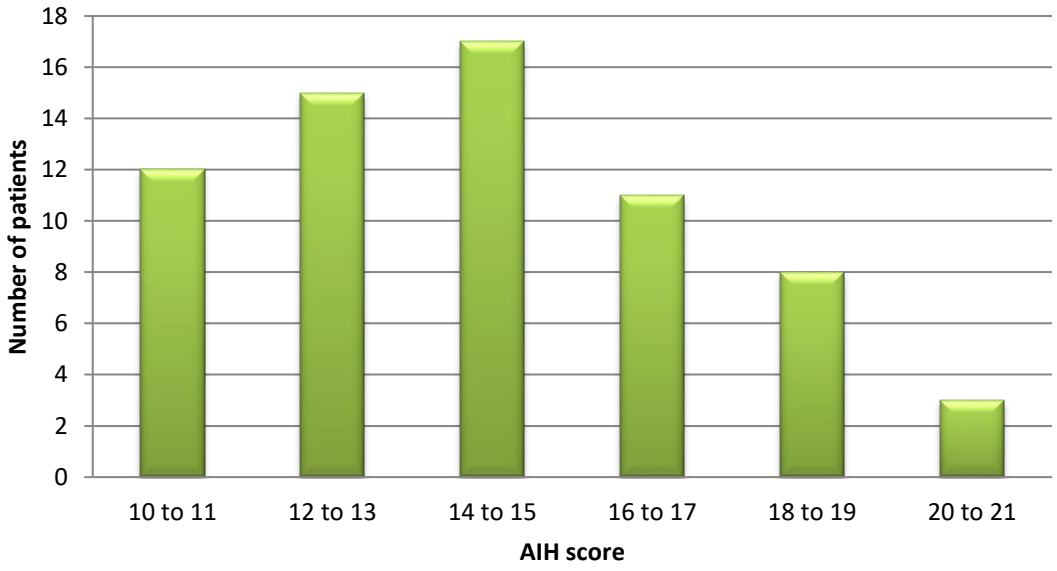
The coding department was contacted and were requested to search their records for the ICD-10 codes K45.4 (AIH), K73.2 (chronic active hepatitis) and K73.9 (chronic hepatitis unspecified) pertaining to AIH patients. They provided us with a list of hospital episodes between the dates of 1/1/07 to 28/2/13; these were in-patient admissions or attendance for day case procedures such as liver biopsies. Duplicate patients were removed. This list was then subjected to the case verification process as described above. The whole process took approximately 2 working days to complete. The same case validation tool was then applied to our own prospective database.

4.4 Results

Our Prospective database (our gold standard):

As of mid-February 2013, this database contained a total of 242 patients. 66 of these patients presented after from 2007 onwards. When scored with the case validation tool these cases all scored 10 or more, meaning they all met the criteria for AIH as per the modified 1999 AIH score. The average score was 14 (range 10-21). The number of patients and scores are shown in Figure 4.1.

Figure 4.1: Range of AIH diagnostic scores for patients on the AIH database



Anticipated capture rates:

After examining the AIH database, it was evident that 4 patients did not have biopsies performed in Sheffield (or did not have biopsies) and 9 patients presented after the search strategy was applied and thus have not been found by this search. Hence, 53 patients remain that should be captured by a histology search. One would expect that most patients should be identified by an out-patient letter search unless admitted acutely and transferred elsewhere. From the 66, 4 patients presented after our search was performed and thus our expectation would be that all the remaining 62 patients should be identified. It is not possible to say how many should be identified in the coding search as not all patients are admitted with this condition.

Histology:

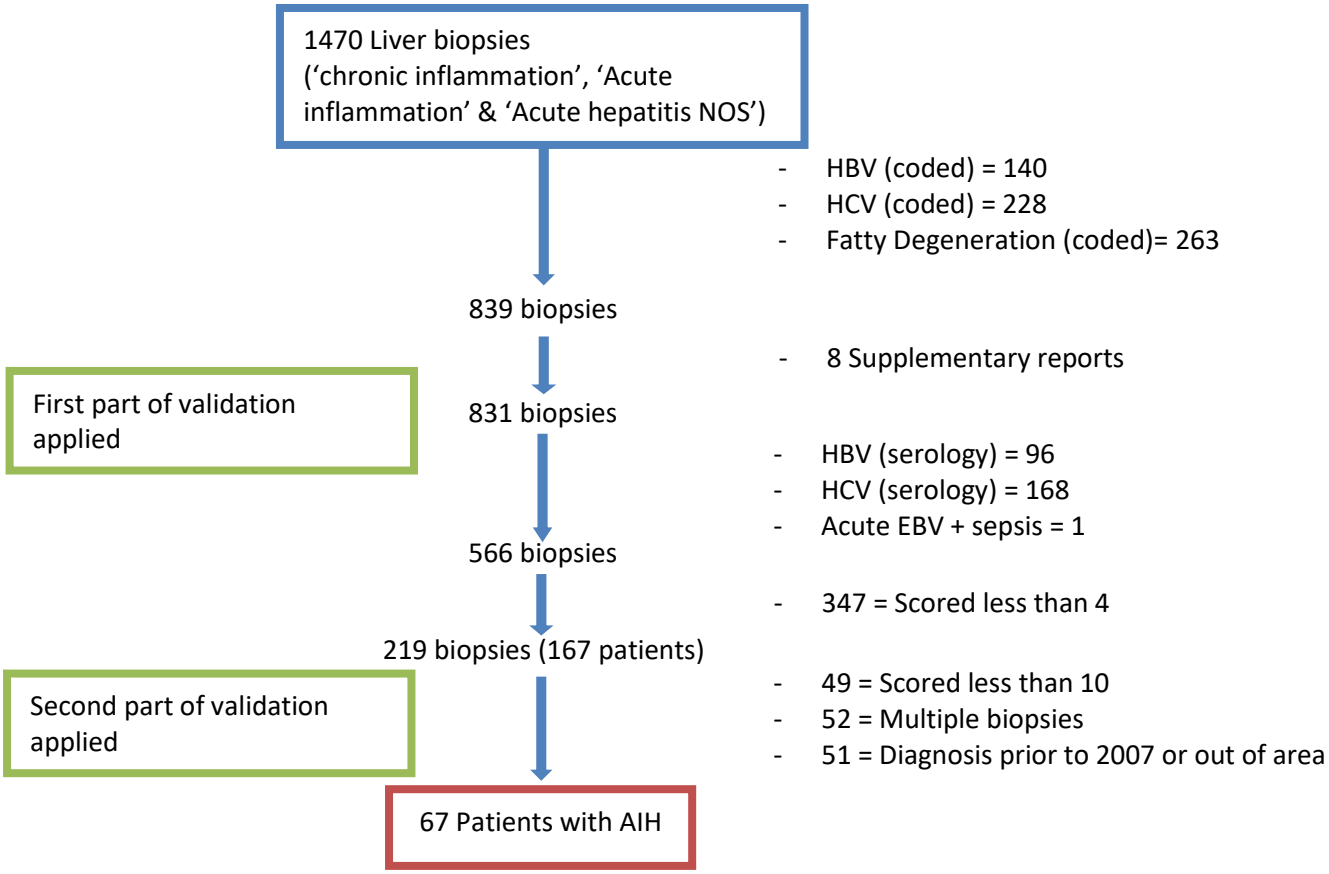
The histology coding for liver biopsies with chronic inflammation yielded 1470 patients. A separate search using 'acute inflammation' and 'acute hepatitis NOS' search terms only yielded total of 4 patients; 2 were AIH cases diagnosed prior to 2007 (and also duplicates of those found in the 'chronic inflammation' search), therefore excluded. The remaining 2 cases had an alternate diagnosis on review of their liver histology meeting documentation and letters. Thus, no additional AIH patients from those identified in the chronic inflammation search were identified. So overall this meant 1470 patients were our starting point prior to case validation.

A total of 633 patients were excluded because their viral markers were positive (HCV; 396, HBV; 236, 1 patient was excluded for EBV positivity, sepsis and an implicated causative drug). 263 patients were excluded as their only histological diagnosis was fatty degeneration.

After the initial phase of case validation (found to score 4 points or more), there were 167 patients were found to score 4 points or more on the initial phase of case validation using the terms 'chronic inflammation'. 49 cases were excluded by the second phase of scoring and 51 were found to have been diagnosed prior to the year 2007 (n=47) or were from out of area (n=4) and therefore excluded (See Figure 4.2).

This left 67 patients who had liver biopsies (all in the chronic inflammation group), all scoring 10 or more in the case validation, thereby indicating a diagnosis of AIH. There were 12 other patients who did attain 10 or more points but had been given another diagnosis following review of their clinical case notes, histology and discussion at the liver histology meeting. In all of these cases, another diagnosis was evident and thus were excluded.

Figure 4.2: Histology capture flow chart



Of 67 the patients who were diagnosed after 2007; 47 matched our pre-existing database. 20 patients identified did not match our list of known patients (Table 4.1). Of these, 9 patients were not found by any other modality and thus found unique to this facet of the capture strategy (Table 4.2).

Table 4.1: Histology search

Snomed search	No of overall cases identified	No of known Pt's on AIH database identified	Not on known AIH Database
Chronic inflammation	67	47	20
Acute inflammation	0	0	0

Table 4.2: Additional Histology patients identified and number found by other sources

	Not on known AIH Database	Found in 'Letters Search'	Found in 'Coding Search'	Uniquely found by 'Histology search'
Chronic inflammation	20	5	7 (2 also in letters)	9
Acute inflammation	0	0	0	0

Overall, 47 (88.7%) patients were identified from 53 patients with liver histology on the database. There were 6 (11.3%) patients recorded in the AIH database that were not found in the histology

search. The reasons why this was not complete capture via the histology search were investigated. Direct search of the histology database for the 6 remaining patients not identified by the search revealed the reason for their absence in our results was a discrepancy or incomplete coding (Table 4.3).

Table 4.3: Histological codes given to patients who were missed

Coding	Number of Patients
'Cirrhosis'	2
'PBC'	1
'Necrosis'	1
'Deposition of iron and metaplasia'	1
Liver biopsy was incorrectly coded as 'pancreas biopsy'	1

Realistically, learning from this process it seems that it would not be practical to include searches for cirrhosis, necrosis or deposition of iron and metaplasia as these would presumably lead to a huge number of patients being identified who are unlikely to have AIH. The liver biopsy coded as pancreas is an error, which cannot be foreseen. There would perhaps be an argument for including PBC as this is sometimes seen concurrently with AIH and is a rare disease thus shouldn't produce copious numbers of cases.

Of the 20 patients not included in the prospective database between 2007 and 2013 (Table 4.4); 11 were found by another facet of the search strategy (letters or coding). Of the 9 patients were unique to the histology search: 2 were Nitrofurantoin-induced and settled without treatment, 4 were considered mild (not treated), 2 under the care of Gastroenterologists at the Northern General Hospital (NGH); thus, not monitored on a hepatology database, and 1 was initially treated and has not relapsed but not labelled with a diagnosis of AIH.

Table 4.4: Patients identified by histology search but not in database (n=20)

Details of those not on database	No of patients
Not treated	8
Treated*	8
Nitrofurantoin-induced (not treated)	3
Defaulted	1

*3 of these patients were under the general gastroenterologists at NGH.

A further breakdown of those who underwent treatment, who were not in the database, is shown in Table 4.5. There are two hospitals in Sheffield (Royal Hallamshire Hospital (RHH) and NGH) that receive liver patients, 3 patients came under the latter hospital and therefore not on the AIH

database used in conjunction with the liver unit at the RHH. The AIH database was originally created to monitor those on treatment and therefore it is unsurprising that the 4 people not on maintenance treatment (patients 1-4) are not included on the database. One other patient not on the database (patient 5) had defaulted at the time the database was viewed.

Table 4.5: Treatment and current status of the 8 patients who met AIH criteria and were treated who were not in the prospective database.

	AIH score	Initial treatment received	Current treatment	Status
Patient 1	11	Yes	not on treatment	discharged
Patient 2	12	Yes, but diagnosis uncertain	weaning off steroids	current
Patient 3	12	Yes, then defaulted	not on treatment	defaulted
Patient 4	10	Yes, (Khat-induced)	unknown	defaulted
Patient 5	13	Yes	on maintenance treatment	defaulted
Patient 6	16	Yes, under NGH care	on maintenance treatment	current
Patient 7	11	Yes, under NGH care	on maintenance treatment	current
Patient 8	14	Yes, under NGH care	on maintenance treatment	current

Electronic letters

277 patient letters were identified using the search terms mentioned in the methods. 189 were excluded because 70 were diagnosed prior to 2000, 95 presented from 2000-2007 and 24 patient cases originated from other sites seeking opinion. This left 88 possible AIH patients presenting from 2007-2013 which were then subjected to the case validation. 11 patients were subsequently excluded by scoring and 3 excluded because they developed AIH after transplantation. 74 patients met the criteria for AIH; 62 of these matched our prospective list of patients and thus 12 were potential extra patients (Table 4.6). Therefore, all patients in the prospective database were detected by the electronic letters search when it was performed.

Table 4.6: Electronic letters: Patients subjected to case validation and outcome

No of known Patients in the Database	No of patients identified by letters	Excluded by modified IAIHG score	Developed AIH post-transplant (excluded)	Identified by Letters search in the database	Not in known Database (Extra patients)
62	88	11	3	62	12

Out of 12 potentially new patients; 5 were also found by other sources (histology, coding and 1 by both) leaving a total of 7 unique patients found by this method alone (Table 4.7). Of these 7 patients; 1 was acutely transplanted, 5 did not receive treatment for AIH and 1 patient who was treated but there was diagnostic uncertainty.

Table 4.7: Electronic letters: Additional patients found and other search modality performance

Not in AIH Database	Also found in Histology Search	Also found in Coding Search	Uniquely found in letters search
12	4	2 (1 found in histology also)	7*

*3 patients did not have biopsies performed or were not performed in Sheffield.

Hospital Coding Search

The number of hospital episodes generated by the coding department was 194, from 106 different patients, presenting to Sheffield teaching hospitals with a coded diagnosis compatible with AIH between January 1st 2007 and February 2013.

After reviewing patients' records, 21 patients were excluded as they were coded incorrectly and had obvious alternative diagnoses. This left 85 patients who had a hospital episode during the search period. 48 patients were diagnosed prior to 2007 or lived out of area, and a further 6 did not meet diagnostic scoring via case validation and thus excluded. This left 31 patients meeting the criteria for AIH identified by this method. 27 (40.9% matched the database of AIH patients and 4 patients did not. However, all 4 were also found in the electronic letters search and 2 of these were also found in the histology search. Therefore, there were no new AIH patients identified by this method alone.
A summary of overall case capture for each search modality is shown in Figure 4.3 and then Figure 4.4 compares these findings to the database already kept.

Figure 4.3: Summary of overall capture

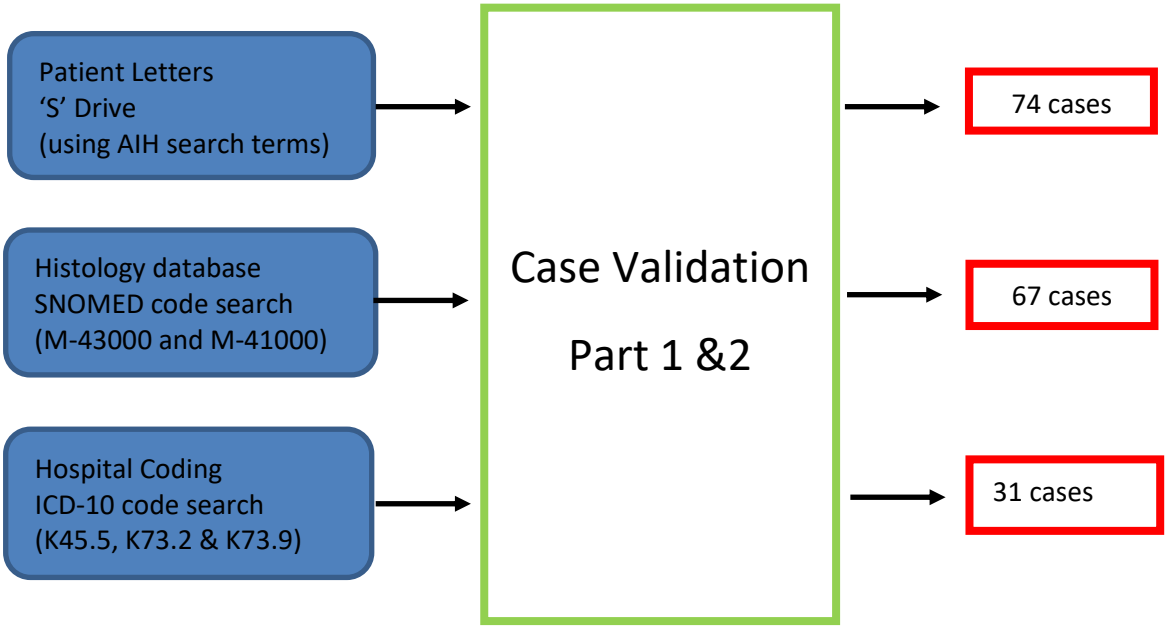
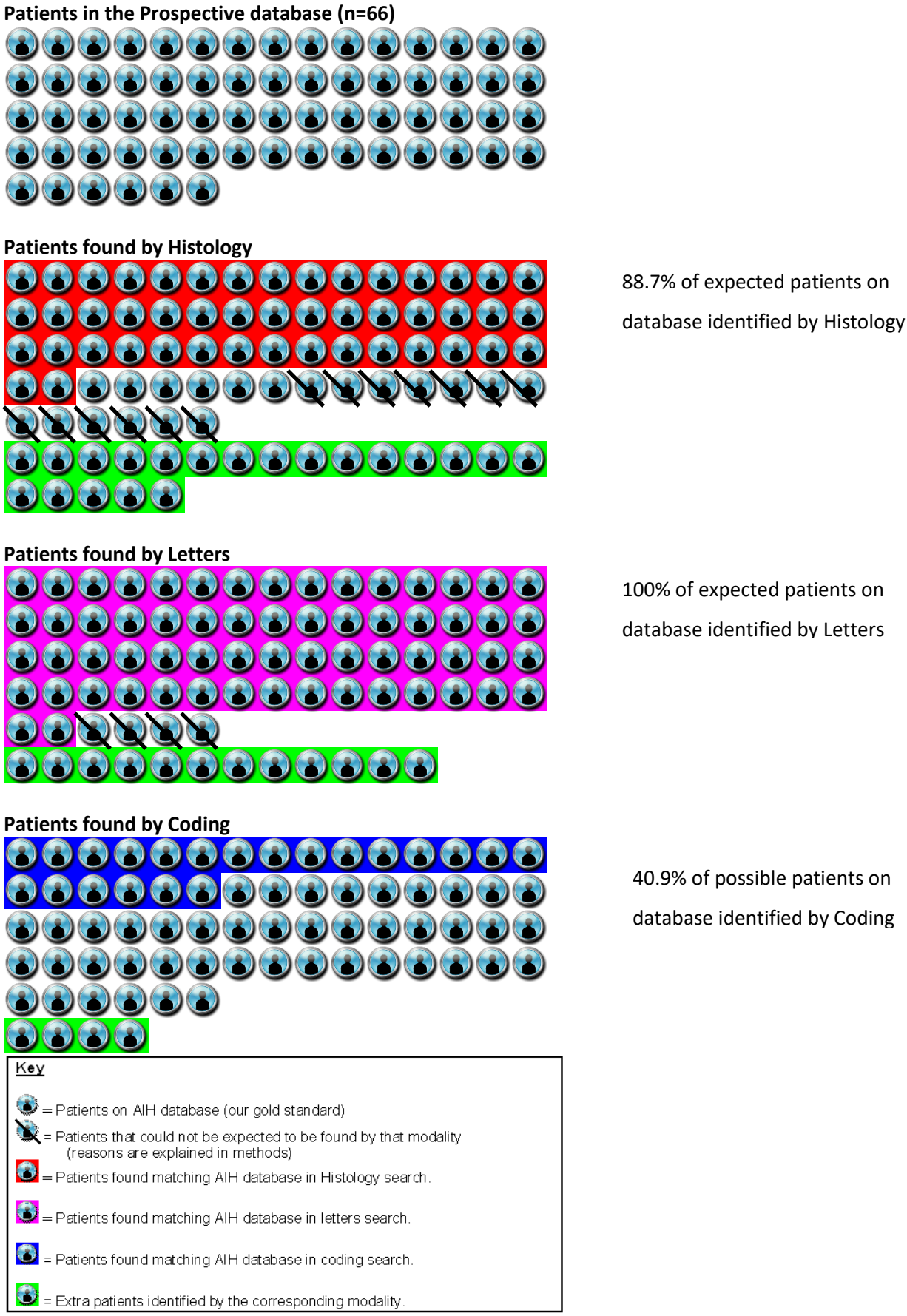


Figure 4.4: Actual case capture of search modalities compared with prospective AIH database



4.5 Discussion

Overall, the entire multi-stage capture process took 12 full working days to complete but successfully identified all patients on the prospective monitoring database.

Our search for patients using the histology search was hampered by the generalised diagnostic codes used and thus prolonged the time taken to identify patients. Searching the histology database would have been far simpler had there been coding employed specifically for AIH. However, any histological diagnosis needs to be matched with relevant clinical information to reach an overall diagnosis in AIH. Perhaps a solution would be to code liver histology following a multidisciplinary meeting, rather than prior.

The electronic letters system at Sheffield Teaching Hospitals was not introduced until 2006 and therefore this aspect would not useful for identifying patients who presented before this and who are no longer under follow up. No patients were identified using the search term 'chronic active hepatitis'; this may well reflect that terminology can be very individual to a particular Hepatologist or Gastroenterologist, and may now be considered out-dated. Searching electronic letters was the most productive and accurate modality for finding all known patients with AIH and also useful for identifying extra patients. However, one of the potential limitations of our search of electronic letters was not performing a search of the 'Gastroenterology drive' as they have separate drives to the Hepatologist's. These patients were, however, identified by the histology search and thus captured by the other facets of the strategy.

The coding modality for identifying patients seems only to be corroborative of patients already labelled with a diagnosis, rather than being additive to our prospective database. This is inevitable, as those being admitted for investigation, such as liver biopsy, may not yet have a diagnosis and thus would lack a diagnostic code.

4.6 Conclusions

This multi-stage capture process is lengthy but proved to be a productive, robust all-inclusive capture strategy for Sheffield patients. If utilised, where possible, by other centres then there could be the capture of large numbers of AIH patients whose cases can be studied and outcomes could be meaningfully compared. It is acknowledged that some hospitals may be limited by how electronically advanced each of the respective systems is for searching for patients.

Chapter 5: Creating a clinical proforma and a central data collection tool.

5.1 Introduction

It has been shown that in some instances a central system for data entry has been successfully utilised. Examples of this are the direct electronic data entry for the Inflammatory Bowel Disease Audit (IBD) and registry, [183] and electronic questionnaire scanning for the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) audits. [184] It was decided to see if it would be possible for our project to use a web-based data collection tool. Alternative options included using Microsoft Excel spreadsheet or Microsoft Access database for data entry but this requires knowledge to use this software.

It was decided that it would be prudent to avoid duplication of tasks by potentially using an electronic data collection tool whereby data-collection and entry could occur together. The majority of information needed to complete a clinical audit proforma could also be completed utilising electronic sources in hospitals that hold blood results and liver biopsy reports and electronic letters, accessible via a computer.

There are many benefits of collecting data from multiple centres via an electronic method thereby allowing secure, password protected entry and would ideally use the secure and reliable NHS-N3 (National Broadband) server to host the system. Data entered would have any patient identifiers stripped before entry and only the centre inputting data would have the key for the attributed unique audit ID. This avoids the need for copious paper records containing clinical information and also their transportation either physically or by other less safe electronic transfer such as email after entry into a spreadsheet to a coordinating centre. The process of exploring the options available to us is described.

5.2 Aim

To produce a robust and secure data collection tool.

5.3 Methods

A clinical proforma was produced initially in a draft format which was built from the aims of the multi-centre audit described in the study design (Chapter 1). Since UK AIH cohorts have come from a few large centres, one was keen to establish the age, gender and ethnic demographic parameters of AIH across a broader and more representative section of the population. Therefore, the proforma

incorporates questions about the diagnosis and demographics. The main outcome measurement of the audit is death (all-cause and liver-related) and liver transplantation, and one wanted to explore the associations between these outcomes and (a) drug treatment (drug type, delay in starting and duration) and (b) type of centre. In order to achieve this, it was necessary to also collect information on (a) presenting features, (b) severity of liver disease and (c) co-morbidity.

Potential surrogate markers of outcome including (a) liver blood test (bilirubin, albumin and ALT) response to treatment and (b) development of cirrhosis were also of interest.

The proforma asks for details of drug treatment and provision of blood results on starting treatment, monitoring and relapses. Finally, one also had questions pertaining to follow-up liver biopsy, pregnancy, complications, admissions, other liver diseases, outcome and transplantation.

The paper clinical proforma is shown in Appendix B. This then went through a peer review process receiving input from other centres involved in the audit and where it was felt appropriate, changes were incorporated.

To develop a strategy for collecting data from 28 centres onto a single platform, different options were considered. Firstly, a meeting with the local audit team provided some advice and they recommended that a Microsoft Access database would be the most powerful tool, especially for analysis. However, this requires in-depth knowledge to design such a database and our local audit office did not have the manpower to achieve this for us. One was also not confident that every hospital would have Microsoft Access software available for use. In addition, separate databases would have to be created for each centre to use and then merge to analyse all the data; this seemed a large task and may introduce error. The audit team considered that a Microsoft Excel spreadsheet may or may not be powerful enough to deal with the amount of data being collected. After consideration, and a trial with designing a preliminary spreadsheet in Excel for this purpose it was found that it looked extremely cumbersome, and if the person entering data were to just make one error in one row, for one patient ID, the entire spreadsheet could fail.
My supervisor Professor Gleeson and I also liaised with the Royal College of Physicians and British Society of Gastroenterology audit teams to seek advice on audit tools they used to complete national projects. They provided us with names of companies that may be able to help and we liaised with them; communicating via email, telephone and in person and in addition with several colleagues in other centres about their experiences with different systems.

This audit was financially constrained and one needed to find an affordable option that could be tailored to our specific project. Several options were explored; including a system provided by 'Web-Logik' – but the cost of such a system was prohibitive: £11,050 minus VAT plus additional 'hosting' fees (£16,830 plus VAT) and a company called 'Net-Solving' (£9000 plus VAT and £2,400 for hosting and £100 for certificates) but they could not offer us secure hosting on the NHS-N3 network which would potentially make our data less safe.

Finally, one contacted a company called 'FORMIC' which I had heard of whilst working for the University Hospitals Leicester NHS trust and we were quoted an overall cost of £12,000 (including VAT) plus £2000/year maintenance costs. References were retrieved from others who used the system and considered their experiences to be positive. The main advantages were that they allowed secure hosting on N3-NHS server and had a proven track record of working with hospitals. The system also offered an option of filling other facets out on paper and scanning them in which could be considered for any patient questionnaires at a later date or on future projects. All data entered into this system could then finally be converted into an Excel spreadsheet output file.

A meeting with a FORMIC representative was arranged and one outlined exactly what needed to be achieved. It was then necessary to liaise with our local IT department also via email, telephone calls and meetings in person to assess the feasibility to install. They advised us to fill out a 'non-standard request' and advised us it would be possible to install.

However, there were some glitches with the process of instalment and persistence was needed whilst being cognisant of the fact that the hospitals IT department had other priorities to attend to. Several meetings took place with IT representatives and clinical informatics to resolve installing the system. After several months, the head of IT was contacted who finally facilitated the work for us. The system was installed and one day of training learning on how to design, process forms and export data was undertaken. The clinical proforma was then transposed over to the FORMIC fusion system and drop-down boxes were programmed containing lists or choices, so that data was uniform and could be analysed without difficulty. The proforma as it appears for those entering data is seen in Appendix A. Its usability and functionality were tested by entering Sheffield's anonymous data, which allowed small improvements to be made. Data entry for the audit was then 'open' to other centres, once each hospital obtained permission from their respective Caldicott Guardian.

5.4 Conclusion

It is shown here the value of researching others experience of multi-centre data collection. This process, as described here demonstrates that it is possible to individually design an electronic web-based data collection system, with limited funds, without the need to pay an external company to complete. Although this took more time than expected, this process produced an efficient, robust and secure portal for data entry.

Chapter 6: Diagnosis, presenting features and initial severity of Autoimmune Hepatitis: A Multi-Centre Audit of AIH

6.1 Aims:

i. To report the number of cases of AIH whom hospitals are managing across Yorkshire (12 hospitals) and from 16 other hospitals further afield participating in this audit.
ii. To report information on diagnosis, presenting features and initial severity of AIH across the UK.
iii. To assess hospitals performance against agreed audit standards outlined below.

6.2 Audit Standards pertaining to diagnosis:

i. 100% of patients will be tested for Hepatitis B (HBV) and Hepatitis C (HCV).
ii. ≥80% of patients will undergo diagnostic liver biopsy.
iii. ≥90% of patients will meet the 1999 International Autoimmune Hepatitis Group (IAIHG) diagnostic criteria.[40]
iv. Time from first abnormal LFT's to diagnosis is <4 months (≥90%).

6.3 Statistics

Software used to analyse data included Excel, SPSS and GraphPad. A t-test analysis was used for comparison of groups and when comparing categorical data then chi-square testing was utilised. A p-value of 0.05 was considered statistically significant.

6.4 Results

6.4.1 Overall cohort

1267 patients were included; 80% were female with 103 (8%) not meeting the scoring criteria (score <10) but did receive immunosuppressive therapy for AIH. These patients were from 28 participating centres (Figure 6.1). There were 1008 (80%) incident and 259 (20%) prevalent cases. Clinical and demographic data are presented in Table 6.1.

Figure 6.1: **Participating Centres**

Table 6.1: **Demographics**

Characteristic	
Age (Years): median(range)	55 (8-86)
Female Gender N (%)	1010 (80)
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)
IAIHG Score: median(range)	17 (2-25)
Definite AIH: N (%)	596 (47)
Probable AIH: N (%)	568 (45)
Did not meet criteria: N (%)	103 (8)
Smoking History stated N (%)	916 (72)
Smoker	162 (18)
Ex-smoker	168 (18)
Never smoked	586 (64)
Alcohol History stated N (%)	1267 (100)
<22 units/week	949 (75)
22-52 units/week	289 (23)
>52 units/week	29 (2)
BMI in kg/m^2: median(range)[¥]	27.5 (16-51)

¥Available in 389 patients

Age distribution is shown in Figure 6.2 and was similar in women (n=1010) and men (n=257); shown in Figure 6.3, but between Caucasian (n=1079) and non-Caucasian (n=101) patients there was a small peak between 41-80yrs in Caucasian patients and only a small peak between ages 21-40yrs old in non-Caucasian patients (shown in Figure 6.4).

Median weight at presentation was 72kg (n= 791) with a mean BMI of 28 and median 27.5 kg/m^2 (n=389 with a documented observation).

Figure 6.2: Age Distribution at Diagnosis

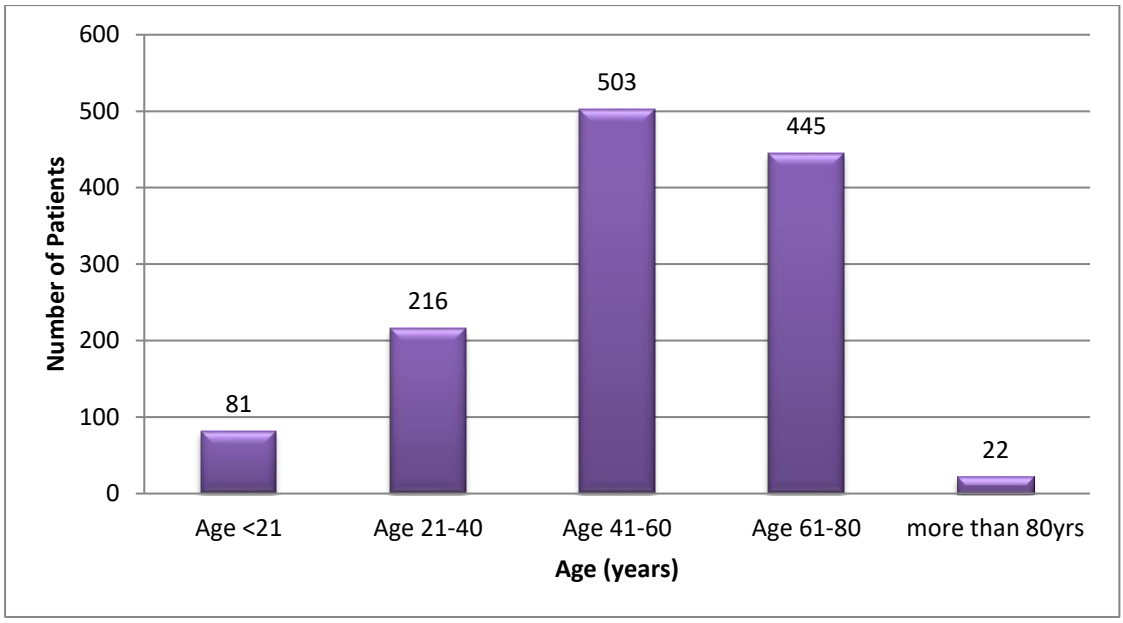


Figure 6.3: Age Distribution at Diagnosis by Gender

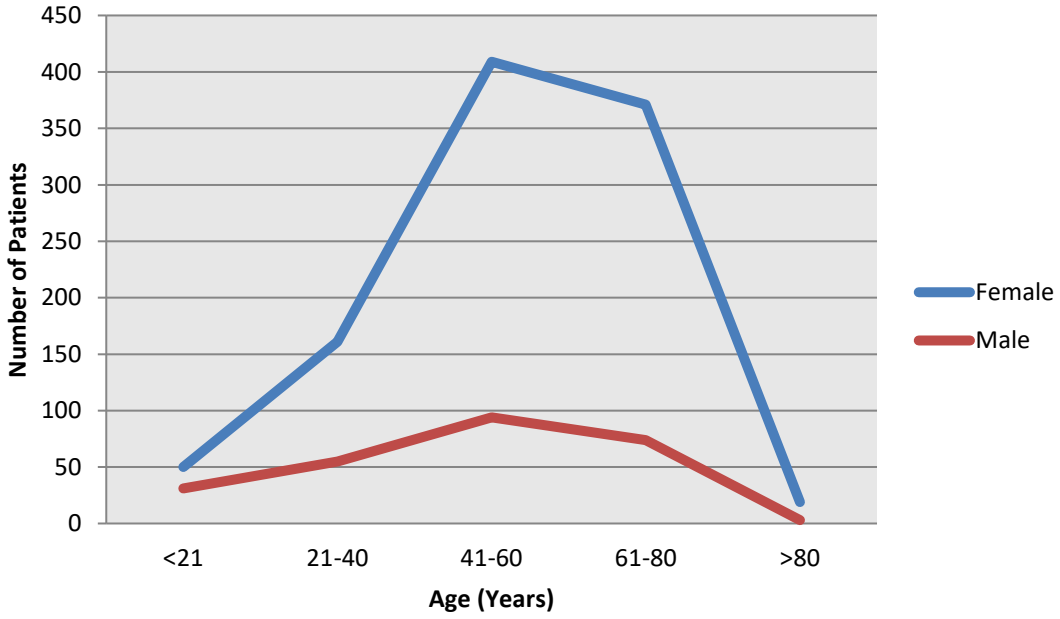
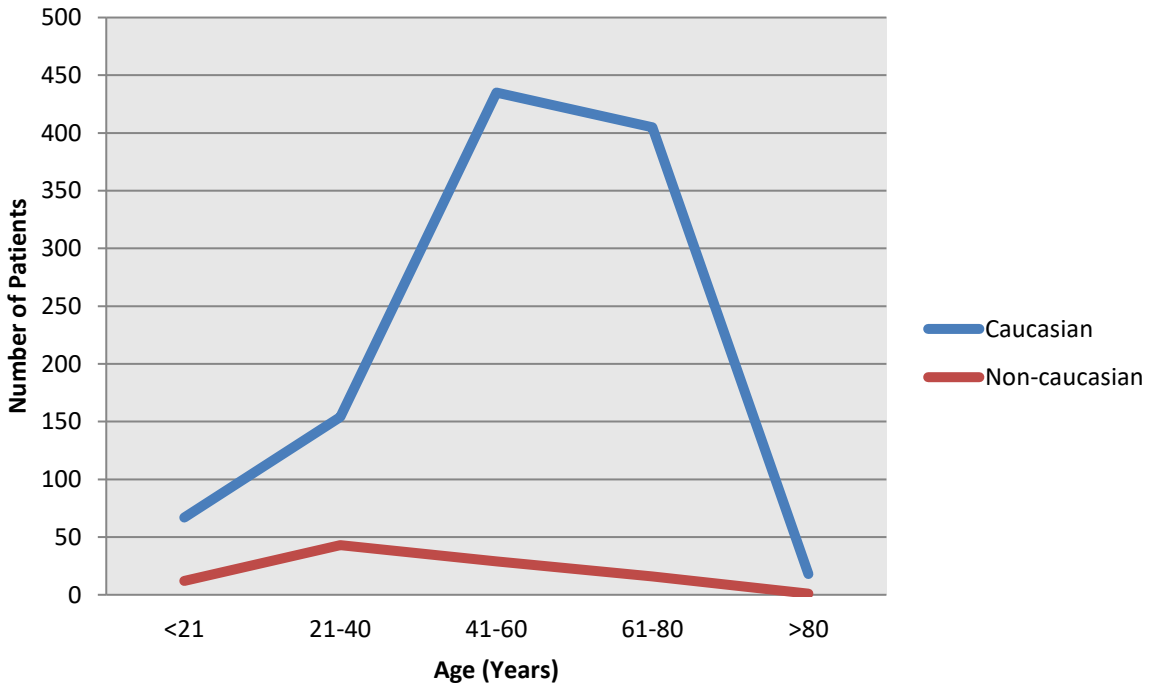


Figure 6.4: Age Distribution and Ethnicity



6.4.2 Clinical features

Presenting symptoms are shown in Figure 6.5. Although 42% of patients reported jaundice or pruritus at presentation, the proportion actually jaundiced (bilirubin >50µmol/L) according to first abnormal liver blood tests was 31% (376 of 1196 values recorded) but more so on 'peak' bloods which was 38% (488 of 1218 values). Nearly one-quarter was asymptomatic.
Time from first abnormal liver blood tests to diagnosis (defined as date of start of treatment or date of diagnostic liver biopsy) was 3 (0-166) months. Time exceeded 4 months in 46% (583 of 1260 informative patients) and 12 months in 19% (243/1260). The time to diagnosis was shorter in patients who presented with jaundice or pruritus than those who did not: 1(0-106) vs 5(0-166) months; (p=<0.0001).

There were 546 (44%) patients who had a personal or family history of autoimmune disease, with the commonest being thyroiditis/hypothyroidism (15%) and PBC (9%); based on positive AMA (see Table 6.2 for a full list of autoimmune conditions at presentation, in order of frequency). Just over 1% had a family history of AIH. Major co-morbid conditions patients had prior to presentation were recorded (see Table 6.3).

Twenty-three patients (6 with cirrhosis), had taken nitrofurantoin before presentation. Median AIH diagnostic score in these patients was 17(12-23). Adjustment for 'drug history', with five points

subtracted the score then was 12(7-18); and 13 patients still had at least “probable” AIH’. Nine male patients of African or Asian origin, had used Khat (AIH score was 15(8-20) and 10(3-15)) when adjusted for drug history, with four still meeting criteria for probable AIH. One patient was taking minocycline and no patient had taken infliximab or interferon therapy either prior to diagnosis.

Figure 6.5: Presenting features

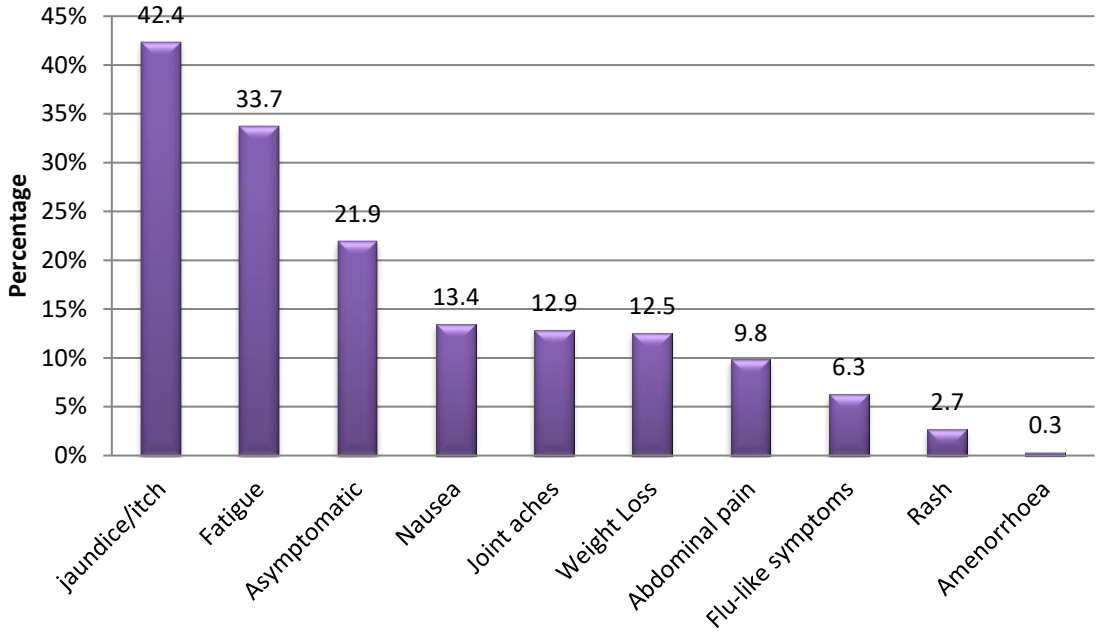


Table 6.2: **Personal or family history of Autoimmune conditions**

Autoimmune Condition	Personal or Family History N (%) of patients
Thyroiditis/hypothyroidism	191 (15)
Primary Biliary Cholangitis	115 (9.1)
Inflammatory Bowel Disease	58 (4.6)
Rheumatoid Arthritis	55 (4.3)
Systemic Lupus Erythematosus	43 (3.4)
Coeliac Disease	39 (3.1)
Diabetes (Type 1)	30 (2.4)
Psoriasis	30 (2.4)
Sjogrens	26 (2.1)
Mixed Connective Tissue Disease	13 (1.0)
Primary Sclerosing Cholangitis	11 (0.9)
Vitiligo	11 (0.9)
Multiple Sclerosis (MS)	7 (0.6)
Antiphospholipid Syndrome	6 (0.5)
Haemolytic Anaemia	6 (0.5)
Thrombocytopenia (AI)	6 (0.5)
Fibrosing Alveolitis	3 (0.2)
Mononeuritis Multiplex	2 (0.2)
Temporal Arteritis	2 (0.2)
Uveitis	2 (0.2)
Glomerulonephritis	1 (0.1)
Polymyositis	1 (0.1)
Sarcoidosis	0 (0)
Family history of AIH	16 (1.3)
Personal/family history of Autoimmune disease	546 (44)

N=1267

Table 6.3: **Co-morbidity Patients had prior to Diagnosis**

Condition	All Patients No (%)
Cancer	68 (5.4)
Cerebrovascular disease	32 (2.5)
Chronic Lung disease	46 (3.6)
Diabetes	128 (10.1)
Ischaemic Heart Disease	91 (7.2)
Non-ischaemic heart disease	34 (2.7)

N=1267

6.4.3 Serum Parameters

Hepatitis B (HBV) and hepatitis C (HCV) viral serology were negative in 1205 (95%) patients and undocumented in 56 (4%). The remaining six patients (0.5%) had negative HBV and HCV serology but had other hepatitis IgM antibodies (4 CMV, 1 EBV plus CMV, 1 HEV).

Table 6.4 shows laboratory values at presentation. Serum IgG values were recorded in 877 patients (69%). Serum IgG or globulin was raised in 78%.
Table 6.5 shows serum autoantibody data; these were not tested for, or not recorded in 11% (ASMA), 12% (ANA) and 27% (LKM-1). Where tested, ANA was present in 57%, ASMA in 47% and Anti-LKM-1 in 2%; at least one was present in 83%. AMA was found in 9%, Anti-SLA was positive in 10 (24%) of 42 patients tested (in 3 centres); including five in whom ANA/ASMA and anti-LKM were negative.

Very few other autoantibodies were tested for: Anti-LP: 1/13 (8%), Anti-LC1: 1/14 (7%) and Anti-ASGPR: 0/7 (0%). Human leukocyte antigens were rarely tested for; HLADR3: 3/7 (43%), and HLADR4: 1/7(14%). pANCA testing was more commonly tested for and where performed: 91/169 (54%) were positive. Of those with pANCA positive, only 7/91 (8%) had either a prior diagnosis of PSC (n=2 (2%)) or developed it during follow-up (n=5 (6%)).

Table 6.4: **Serum Parameters at presentation**

Parameter	Value	No of patients with result
ALT (IU/L), median(range)		
First ALT	255 (10-3240)	1152
Peak ALT	488 (10-4181)	1110
AST (IU/L), median(range)		
First AST	182 (13-3541)	348
Peak AST	333 (31-3785)	366
ALP:Transaminase ratio, N (%)		1267
<1.5	1123 (89)	
1.5-3.0	135 (11)	
>3.0	7 (0.6)	
Bilirubin (µmol/L), median(range)		
First Bili	19 (2-625)	1196
Bili at peak ALT/AST	28 (2-789)	1102
Albumin (g/L), median(range) at peak transaminases	36 (15-70)	1047
Immunoglobulin G (g/L), Median(range)		
Peak IgG	23 (5.8-66.5)	657
Globulin (g/L) at peak Transaminases, Median (range)	43 (10-95)	566
AST:ALT ratio		
Median	0.87	307
No with ratio >1 (%)	114 (37)	307
MELD >15, number (%)	216 (17%)	1267

Table 6.5: **Autoantibody titres**

Autoantibody	Not done/ recorded	Negative	1:40/Weak positive	1:80	≥1:80	Positive but unknown Titre
ANA	154 (12%)	484 (43%)	109 (10%)	71 (6.4%)	237 (21%)	212 (19%)
SMA	137 (11%)	593 (52.5%)	75 (6.6%)	45 (4.0%)	188 (16.6%)	229 (20.3%)
LKM-1	343 (27%)	904 (98%)	3 (0.3%)	0 (0%)	6 (0.6)	11 (1.2%)

n=1267

6.4.4 Histological findings (Table 6.6)

Liver biopsy was performed in 1213 (96%) patients, and of which 1163 (92%) had an accessible report. Most had interface hepatitis and a predominantly lymphocyte or plasma cell infiltrate; however, only 19% had rosettes (range 0-63%, amongst 28 centres) reported. Emperipolesis was reported in only 5 patients (0.4%), from three individual centres. Histology score (1999 IAIHG

histological criteria) was 3(-5 to 5). In 12 patients (1%), all treated as AIH, histology score was -5, implying very atypical histology, with seven not meeting 1999 criteria.
Bile duct abnormalities were reported in 147 (13%) patients; compared to patients without such abnormalities, these were more likely to have granulomas (6% vs 1.8%), be AMA positive (28% vs 6%), and not to meet 1999 criteria (22% vs 6%).

Moderate or severe steatosis was present in 27 patients (2%). In these, diabetes was commoner than in those without or with only mild steatosis (26% vs 9%; p=0.007) but body weight and BMI values were similar, as was the prevalence of interface hepatitis, plasma cells and rosettes.

The presence or absence of cirrhosis on liver biopsy was undocumented in 6%. Of 1124 informative patients, 254 (23%) had cirrhosis. Ishak fibrosis score (recorded in 539 patients) was zero in 62 (12%). The prevalence of cirrhosis did not differ between those diagnosed less than or >4 months after first abnormal serum liver tests, nor when 12 months was used as a cut-off. Cirrhosis was associated with increased age (p=0.049) but the proportion of those with cirrhosis is shown in different age ranges in Figure 6.6 and demonstrates that the relationship is not linear. Ishak necro-inflammatory score (NIS; range 0-18 or denoted as minimal, mild, moderate and severe) was recorded in 688 (59%) patients.

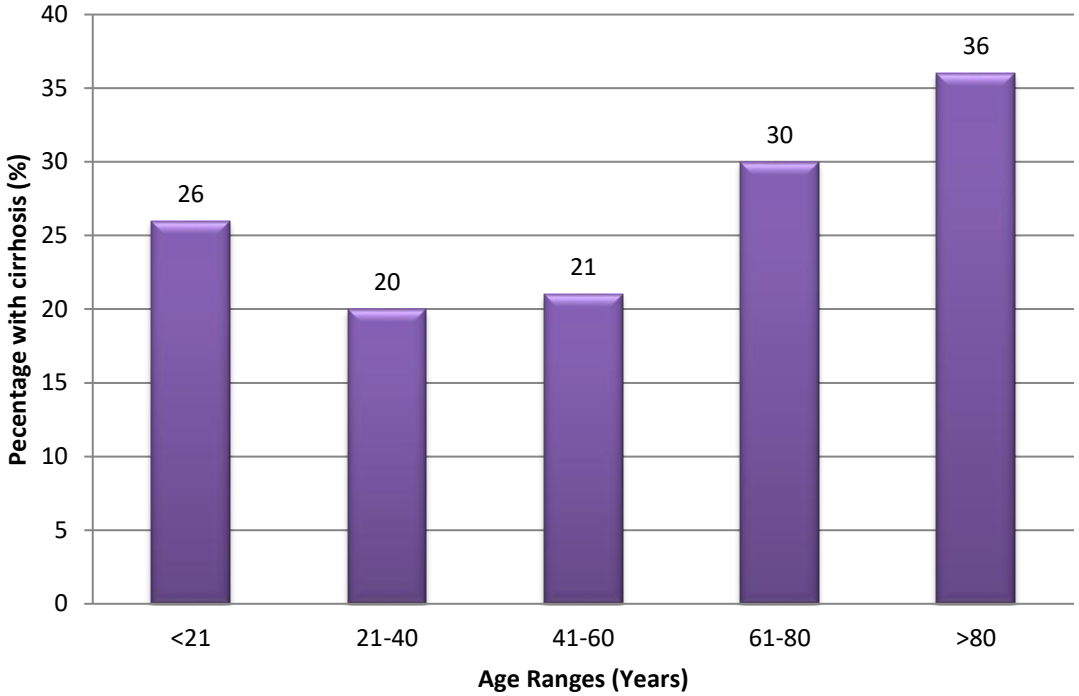
Of the 1086 treated patients whose date of biopsy was known, 246 (23%) were already receiving treatment when biopsied. These did not differ significantly from those biopsied before treatment in regard to histological features.

Table 6.6: **Histological features on diagnostic liver biopsy**

Histological Feature	IAIHG Histology Score	All Patients (N=1163*) No of patients (%)
Interface Hepatitis	3	1023 (88)
Lymphocyte/plasma cell predominance	1	869 (75)
Rosettes	1	222 (19)
Emperipolesis	0	5 (0.4)
None of Above	-5	9 (0.8)
Bile duct changes	-3	147 (13)
Granuloma	-3	28 (2.4)
More than mild steatosis	-3	27 (2.3)
Other predominant pathology	-3	16 (1.4)
Ishak Necroinflammatory score stated		688
Minimal (1-3)		44 (6)
Mild (4-8)		225 (33)
Moderate (9-12)		283 (41)
Severe (≥13)		135 (20)
Ishak Fibrosis Score stated		539
F0		62 (12)
F1		59 (11)
F2		102 (19)
F3		123 (23)
F4		62 (12)
F5		70 (13)
F6		61 (11)
Median score		3 (0-6)

*In whom report accessible

Figure 6.6: Proportion with cirrhosis by age range



6.4.5 *Simplified Diagnostic Criteria*

Of patients who met post-treatment 1999 IAIHGS criteria (N=1164), 758 met the simplified 2008 diagnostic criteria for AIH[72] and 406 (35%) had insufficient points. Information was missing in 183, but in only 67 patients did this preclude ascertainment of meeting the criteria. After excluding these, there remained 339 (31%) of 1097 patients who met 1999 criteria but did not meet the simplified criteria. Of these patients, cirrhosis was present in 18%, and 18% had either clinical decompensation or a MELD score of >15.

There were only 26 (2%) patients who met simplified criteria but did not meet 1999 criteria; all received immunosuppressant therapy. Of these, 17 were AMA positive (resulting in a deduction of 4 diagnostic points by 1999 criteria), of 14 with accessible biopsies, 11 had bile duct changes.

6.4.6 *Disease Severity*

Overall, 318 patients (25%) had cirrhosis at diagnosis, based either on liver biopsy (23%), Fibroscan®, presence of varices, ascites or encephalopathy. In only 8 patients was cirrhosis based solely on Fibroscan. The factors found to be significantly associated with cirrhosis at presentation on cox regression univariate analysis were age, peak ALT, bilirubin at peak transaminases (>150), serum IgG, albumin and low platelets (Table 6.7). On multivariate analysis (Table 6.8) bilirubin at peak transaminases (>150), serum IgG, albumin and low platelets were found to be associated with

cirrhosis. In particular those with bilirubin levels of >150g/L had an associated 89% increase in cirrhosis at baseline OR 1.89 (CI 1.12-3.23, p=0.018).

Table 6.7: Factors associated with cirrhosis at baseline presentation (univariate analysis)

Parameter	No of values	OR	95% CI	P value
Age	1267	1.008	1.00-1.015	**0.049**
Gender	1267	0.92	0.83-1.71	0.832
Ethnicity	1180			0.459
PBC	1267	1.038	0.63-1.71	0.882
Symptomatic	1267	0.96	0.703-1.3	0.78
Peak ALT	1110	1.00	0.99-1.000	**0.001**
Peak ALT/AST >350	1141	1.043	0.79-1.38	0.76
Peak Bilirubin	1218	0.99	0.99-1.001	0.334
Peak Bilirubin >150	1218	0.72	0.529-0.96	**0.029**
IgG >16g/L	877	2.3	1.49-3.56	**<0.0001**
Platelets <150U/L*	1205	4.07	3.01-5.49	**<0.0001**
Albumin at peak ALT <35g/L	1047	3.05	2.29-4.01	**0.003**

*At start of treatment

Table 6.8: Factors associated with cirrhosis at presentation (multivariate analysis)

Parameter	No of values	OR	95% CI	P value
Age	1267	1.01	0.99-1.02	NS
Peak ALT	1110	1.00	0.99-1.00	NS
Bilirubin >150	1218	1.89	1.12-3.23	**0.018**
IgG >16g/L	877	0.55	0.32-0.95	**0.030**
Platelets <150U/L*	1205	0.31	0.206-0.47	**<0.001**
Albumin at peak ALT <35g/L	1047	0.30	0.21-0.45	**<0.001**

108 patients (8.5%) had clinical decompensation at presentation; defined as ≥1 of ascites (n=57 (4.5%)), oedema (n=70 (5.5%)), encephalopathy (n=22 (1.7%)), variceal bleeding (n=9 (0.7%)). MELD score at presentation was >15 in 17% (N=216). In total 272 (21%) patients had either clinical decompensation or a MELD >15. Overall; 74 (6%) patients had varices (on imaging or endoscopy) and no patient had Hepatocellular Carcinoma (HCC) at presentation.

6.5 Sub-group Comparisons

6.5.1 Completeness of case capture

Centres were asked after data collection was complete to state whether they had utilised the full capture strategy as intended and the responses are shown in Table 6.9.

Table 6.9: Actual modalities searched from 22 responding centres

Centre	No of Patients	% included	All modalities	Departmental DB	Histology	Electronic clinic letters	Coding
Barnsley	33	80-90	×	×	×	✓	✓
Calderdale	40	>95	×	✓	✓	×	✓
Cambridge	45	majority' (incident only)	×	✓	✓	✓	×
Chesterfield	37	**100**	✓	✓	✓	✓	✓
Coventry	58	**100**	✓	✓	✓	✓	✓
Darlington	14	30	×	×	✓	×	✓
Derby	106	93	✓	✓	✓	✓	✓
Doncaster	61	90 incident, <50 prevalent	×	×	✓	×	✓
Durham	53	Unsure	×	✓	✓	×	✓
Hull	35	Unsure	×	×	×	✓	✓
Kettering	15	70	×	✓	×	✓	×
Kings	44	40	×	✓	×	×	✓
Leicester	51	90	×	✓	✓	×	×
Manchester	24	95 incident only	×	✓	×	✓	×
Mid Yorks	17	>75	×	×	✓	✓	×
Newport	45	30 (45/140 known)	✓	✓	✓	✓	✓
North Tees	29	Majority	×	✓	×	✓	✓
Nottingham	100	**100**	✓	✓	✓	✓	✓
Rotherham	65	>95	×	✓	✓	×	✓
Sheffield	161	**100**	✓	✓	✓	✓	✓
Swansea	11	10	×	✓	✓	×	×
York	16	>90	×	✓	✓	✓	×

Two further analyses were performed to assess if results were distorted by incomplete case capture:

i) Comparing incident patients presenting between 1/1/2007 to 30/12/2010 (n=488) with those between 1/1/2011 to 1/11/2015 (n=520). The only parameter which differed was lower mean age at diagnosis;52 vs 54yrs; p=0.04.

ii) Comparing patients (n=356) in four centres (Sheffield, Chesterfield, Nottingham and Coventry) where were confident that the capture strategy described in Chapter 4 was used, with the remaining centres (n=911). Again, most parameters did not differ. However, proportion of patients undergoing diagnostic biopsy (98% vs 95%; p=0.01) and prevalence of

IFH (93% vs 86%; p=<0.01), lymphocyte/plasma cell predominance (76% vs 74%; p=0.03) and rosettes 34% vs 13%; p=<0.01) was higher in the centres with complete case capture.

6.5.2 University Hospitals (UH's) and District General Hospitals (DGH's).

Patients attending UH's (n=830) were, compared to those attending DGHs (n=437) more likely to have interface hepatitis (89% vs 86%; p=0.01), lymphocyte/plasma cell predominant infiltrate (78% vs 69%; p=<0.002) and rosettes (23% vs 11%; p=<0.001) recorded. There was also more complete testing in UH's for ASMA, ANA and LKM-1 (92%, 90% and 75% vs 84%, 84% and 69% respectively; p<0.05). Mean age at diagnosis was significantly lower in UH's: 50 vs 56yrs, (p=0.0001).

6.5.3 Autoantibody status (Table 6.10)

Patients who had undergone testing for all three autoantibodies were compared; patients who were ANA/ASMA positive (n=654), LKM positive alone (n=17) and autoantibody negative (n=228) (although some were AMA positive).

Those who were LKM positive (n=17) compared to ANA/ASMA positive (n=654) or to autoantibody negative (n=228) patients, were younger and more likely to have cirrhosis at presentation.

Compared to ANA/ASMA positive patients, those who were antibody negative were more likely to be male and to have decompensation at presentation. There were no other differences.

Of AMA positive patients (n=119 (9.4%)), 41 (39%) of 106 accessible biopsies had bile duct changes, 59 (50%) had a pre-existing clinical diagnosis of PBC and 46 (39%) did not meet 1999 AIH criteria.

Table 6.10: Comparison by Autoantibody*

	Group 1 (ANA or SMA+)	Group 2 (LKM+)	Group 3 (All negative)	P value (ANA/SMA+ vs All neg)	P value (ANA/SMA+ vs LKM)	P value (LKM vs all neg)
No of Patients	654	17	228			
Age <50: ≥50	236:418	13:4	96:132	0.1	**<0.001**	**<0.01**
Gender F:M	522:132	14:3	52:176	**<0.01**	0.79	**<0.01**
IgG elevated: N (%)	538 (82)	14 (82)	152 (67)	**<0.001**	0.99	0.18
Histology: No biopsied	607	17	214			
IFH	534	14	186	0.68	0.48	0.60
LPC~ predominance	473	13	145	**0.003**	0.89	0.49
Rosettes	132	5	45	0.85	0.45	0.43
Bile duct damage	65	0	25	0.66	0.15	0.13
Cirrhosis: N (%)	166 (25)	8 (47)	52 (30)	0.44	**0.04**	**0.03**
Decompensation¥: N (%)	134 (20)	6 (35)	77 (34)	**0.01**	0.14	0.89
NIS >3 versus ≤3	129:2	4:0	51:2	0.34	0.80	0.69

*Comparisons only include patients where all autoantibodies were tested for.
~LPC is lymphoplasmacytic predominance

Compared with patients who had at least one AIH autoantibody (ANA/ASMA/LKM-1) but were AMA negative (n=816), bile duct changes were commoner in AMA positive patients (39% vs 10%; P=<0.0001 and mean ALT was lower (p=0.002); (Table 6.11). Of AMA positive patients, those with the additional presence of AIH antibodies did not differ from those without; (Table 6.12).

Table 6.11: Anti-mitochondrial positive (AMA) patients with other autoantibodies present compared

	AMA positive	AMA negative (≥AIH Autoantibody +ve)*	P value
No of patients	119	816	-
Bile duct changes: N (%)	41/106 (39) ¥	73/749 (10) ¥	**<0.0001**
Female: N (%)	103 (87)	645 (79)	0.055
Age <55:≥55	55:64	383:433	0.92
Asymptomatic: N (%)	29 (24)	180 (22)	0.55
Mean peak Bilirubin µmol/L	56.4	87.97	0.039
Jaundiced: peak bili >50µmol/L: N (%)	24 (20)	321 (39)	**<0.0001**
Mean peak ALT U/L (SD)	471 (478)	733 (653)	**0.002**
Cirrhosis at presentation: N (%)	26 (22)	213 (26)	0.32
Decompensation at presentation: N (%)	15 (13)	168 (21)	**0.047**
Pre-treatment score >10: N (%)	58 (49)	771 (94)	-
Median pre-treatment score N (range)	10 (1-18)	16 (2-22)	-
Score excluding AMA	14 (5-22)	-	-

* ASMA/ANA/LKM positive, ¥ Denominator is number of accessible liver biopsies

Table 6.12: AMA positive patients without other autoantibodies present compared

	AMA positive (At least one AIH Ab +ve)*	AMA positive (All AIH Ab's -ve)**	P value
No of patients	66	32	-
Bile duct changes¥: N (%)	24 (45)^	10 (31)	0.25
Female: N (%)	58 (88)	28 (88)	1
Age <55:≥55	30:36	15:17	1
Asymptomatic: N (%)	20 (30)	6 (26)	0.33
Mean peak Bilirubin µmol/L (SD)	54.6 (101)	49.2 (74)	0.09
Jaundiced: peak Bili >50µmol/L: N (%)	11 (16)	7 (22)	0.58
Mean peak ALT U/L (SD)	398	487	0.32
Cirrhosis at presentation: N (%)	13 (20)	7 (22)	0.80
Decompensation at presentation: N (%)	8 (12)	6 (19)	0.38
Pre-treatment score >10: N (%)	38 (58)	14 (44)	-
Median pre-treatment score N (range)	11 (3-16)	10 (1-14)	-
Score excluding AMA	15 (7-20)	14 (5-18)	-

* ASMA/ANA/LKM positive, **patients only included if all tested for, ¥ found on liver biopsy ^53 patients had biopsy with available report

6.5.4 Caucasian and non-Caucasian patients

Non-Caucasian patients (n=101), compared to Caucasian patients (1079): (i) had more men (38 vs 19%; p<0.01), (ii) presented younger (41yrs vs 54yrs; p=0.0001), (iii) were more likely to be

symptomatic (89% vs 79%; p=0.006), to be jaundiced (51% vs 33%; p=0.0002; bilirubin 63(3-702) vs 27(2-789); p=0.009), and to have clinical decompensation or MELD >15 (30% vs 21%; p=0.046).

6.5.5 Gender and age

Male patients (n=257) presented younger (52(8-83) vs 56(8-86)) years; p=<0.0001) and were more likely to be jaundiced (51% vs 35%: p=<0.01) and to be decompensated (27% vs 20%; p=0.03), than females. Twenty-eight percent of males versus 24% of females complained of jaundice at presentation but this was not significant (p=0.3). There were no other differences.

Those presenting aged over 55yrs (n=662) were more likely to be female (83% vs 77%; p=0.007), asymptomatic (29% vs 14%: p=<0.01) and cirrhotic (28% vs 21%; p=0.005) and were less likely to be jaundiced (34% vs 44%; p=0.0006), compared to those presenting younger.

6.5.6 IAIHG Score

Sub-analysis of only those meeting IAIHG scoring for AIH, we found that gender, age and ethnic distribution was not different from the entire cohort.

However, patients not meeting IAIHG criteria had significantly lower peak serum IgG: 18 vs 23g/L; p=0.004 and a significantly higher albumin at peak transaminases 37 vs 36g/L; p=0.03. There were no other significant differences between presenting serum parameters.

6.5.7 Audit standards:

Each of the four audit standards pertaining to diagnosis has been assessed and results are shown in Table 6.13. Centre-specific figures can be seen in Table 6.14.

Testing for viral hepatitis was recorded as having been undertaken in nearly all patients. However, it was not recorded as being performed in less than 80% of cases in 4 individual centres, but these were hospitals that were looking after few patients.

Only one centre did not meet the pre-defined minimum of 80% of patients having a diagnostic liver biopsy but again this centre contributed very few patients. Overall, those who performed fewer liver biopsies had fewer patients meeting diagnostic criteria.

Most notably there was a significant delay between the first abnormal LFT's and diagnosis, with no individual centre meeting the pre-defined minimum of 90% of patients being diagnosed within 4 months.

Table 6.13: Audit standards summary table

Audit Standard	Pre-defined minimum (%)	Actual overall no. (%)	% in individual centres (median(range))	Centres meeting pre-defined minimum No. (%)
Tested for HBV and HCV	100	1211 (96)	98 (50-100)	22 (79)
Had diagnostic liver biopsy+	80	1213 (96)	97 (71-100)	27 (96)
Met 1999 IAIHG diagnostic criteria¥	90	1179 (93)	94 (65-100)	22 (79)
Time from 1st abnormal LFTs to diagnosis is <4 months	90	54	55 (12-82)	0 (0)

+performed >90 days after the start of treatment in 42 patients, ¥ Pre- or post-treatment score

Table 6.14: Comparison of centre specific data for diagnostic standards

Hospital	Number of Patients (n=1267)	Diagnostic Biopsy performed (%)	Tested for Viral Hepatitis (%)	Meet IAIHGS (%)	Diagnosis <4 months (%)
Airedale	15	100%	93%	93%	60%
Barnsley	33	97%	97%	85%	27%
Bradford	47	91%	100%	89%	66%
Calderdale	40	98%	98%	90%	28%
Cambridge	45	100%	98%	98%	82%
Chesterfield	37	97%	100%	100%	58%
Coventry	58	98%	100%	95%	47%
Darlington	14	71%	50%	50%	38%
Derby	106	97%	100%	84%	44%
Doncaster	61	98%	98%	95%	49%
Durham	53	89%	96%	98%	58%
Hull	35	94%	97%	97%	49%
Kettering	15	100%	93%	93%	23%
Kings	44	95%	100%	100%	68%
Leeds	77	95%	100%	91%	71%
Leicester	51	80%	98%	94%	65%
Manchester	24	100%	79%	88%	43%
Mid-Yorks	17	94%	100%	94%	41%
Newcastle	37	92%	73%	65%	54%
Newport	45	96%	96%	100%	60%
North Tees	29	100%	97%	90%	28%
Nottingham	100	100%	87%	95%	62%
Rotherham	65	100%	100%	97%	55%
Scarborough	14	100%	79%	100%	71%
Sheffield	161	97%	99%	98%	58%
Stockport	17	100%	76%	100%	12%
Swansea	11	91%	100%	91%	45%
York	16	81%	100%	100%	75%
Average	45	95%	93%	92%	51%

6.6 Discussion

This large multi-centre study affords several insights into the presenting features of AIH in the UK. The salient findings are first, that AIH in the UK affects an older population than reported elsewhere. Second, there are often delays in diagnosis, incomplete diagnostic work-up and probable under-reporting of key diagnostic histological features. Our findings also call into question, the utility in clinical practice of the simplified IAIHG Diagnostic Criteria.

One of the study's strengths is that it characterises patients presenting with AIH to several hospitals of varying size, facilities and expertise. This is one of the largest clinical cohorts of patients of AIH reported. There are approximately 170 Acute Trusts in the UK and based on epidemiological studies elsewhere, an estimated 8-15,000 patient's with AIH. Therefore, this study may include 8-16% of UK patients.

There are some weaknesses. As in other multi-centre studies of AIH, there was probably incomplete case capture, resulting from the complex diagnostic criteria and from difficulties in searching data systems. Despite the presence of a multi-faceted case discovery strategy which found all patients with AIH on our prospective database, and some that were not (although this had previously been considered to be comprehensive), one can be assured that capture was complete in only four centres. Attempts to address this issue were made by performing subgroup comparisons. This study found only trivial difference between (a) the four centres with complete capture and the rest and (b) patients recruited 2007-10 and 2011-1/11/15. Thus, this seems to be a homogenous group and probably representative of UK patients with AIH.

This cohort is similar in many respects to other multicentre[10,12,14,185] and large single-centre[22,23,26,51,111] cohorts. It has a similar gender balance (71-82%). It confirms a prior observation[111] that men with AIH present younger than females. Most patients were Caucasian, reflecting UK ethnic population distribution (87%).[186] This was similar to the Dutch cohort (89%)[10] and underlines the fact that AIH affects all major ethnic groups. Non-Caucasian groups had more severe disease, consistent with other reports.[18,21,28]

Like the Dutch group, this study reports very few patients with a family history of AIH (1.3%) suggesting that environmental triggers may play a more important role, although a likely viral or drug precipitant was identified in only 3%. Only one patient had documented acute Hepatitis E virus (HEV) shortly before presenting with AIH. The numbers tested for HEV were not ascertained. However, in a Dutch study of AIH, no patient had HEV viraemia and EBV antibody prevalence was not significantly higher than the general population.[187]

As with the IAIHG score, this study did not differentiate between personal and family history of autoimmune disease. Our figure of 44% was similar to the Swedish group (49% had a personal history alone).[12] The data collected on the prevalence of specific autoimmune diseases were comparable to the review presented in the BSG guidelines. [1]

However, this cohort is older than other multi-centre AIH cohorts from other countries[10,12,185] which have a median age at presentation of 43-48 years. It is also older than in some,[51,111] though not all single centre studies.[13,23] Age at presentation was even older in patients presenting to DGHs than to University Hospitals. This may mean that AIH might affect older people in the UK than in other countries. Alternatively, because DGH's are less subject to tertiary referral bias, this might more accurately reflect the "true" age distribution of AIH, which might be older than suggested by most published studies (usually coming from large centres).

The varied clinical presentations of AIH reported here are similar to those reported elsewhere,[12,22,51] as is the 25% prevalence of cirrhosis,[12,26,51] and the 8.5% prevalence of clinical decompensation.[12] In this study, 17% had a MELD score >15, thus over one fifth had serious liver dysfunction at presentation.

Of the four pre-agreed diagnostic standards, two were met; numbers having a diagnostic liver biopsy and meeting 1999 IAIHG diagnostic criteria. However, our standard for diagnostic delay was not met, with over 40% waiting over 4 months and 19% at least 1 year. Delay was longer in non-jaundiced patients. This could imply that the relatively non-specific symptoms of AIH may not alert the physician to this diagnosis. The other postulated reasons for delay could lie with a delay in referral, a delay between referral and being seen or delay in obtaining or reporting of liver biopsy sampling. The impact of such a delay on disease outcome is unknown. These percentages are open to type two errors because some centres had very few patient cases, this may culminate in an exaggerated pattern.

Another potential concern is the failure to document Hepatitis B and C serology in 4% of patients, this may be because it was performed in primary care, with results often held on separate systems. There were also undocumented results for serum autoantibodies commonly associated with AIH in 12-27% of patients. Other autoantibodies associated with AIH (Anti-SLA/LP, -ASGPR, -LC-1) and similarly HLA antigens were uncommonly tested for. Anti-SLA antibody was found in 24% of patients tested and in 10 of 12 patients who were negative for other autoantibodies. In other studies, SLA was found in 43-53% of patients who were negative for conventional autoantibodies. [188,189] It is associated with higher relapse rates and poorer outcomes. [182] SLA should be tested for in 'antibody negative' patients.

Only 2% of tested patients were positive for LKM-1 antibody AIH (Type 2 disease), similar to in the Scandinavian report (5%),[12] although contrasting with the Italian experience (23%).[51] Differences in presentation parameters between ANA/SMA positive, LKM-1 positive and autoantibody-negative patients were minor. The 109 AMA positive patients were more likely (41%) to have bile duct abnormalities on biopsy, but many did not, and had otherwise typical AIH, as has previously been described.[190]

Another concern relates to histology reporting. Data was collected from clinical reports, without central review. In 6% of cases, it was unclear whether there was fibrosis or cirrhosis on the biopsy. The prevalence's reported here of interface hepatitis and a predominance of lymphocytes/plasma cells are similar to those previously reported (75-98%).[1,12,191] However, the prevalence of rosettes (19%) is much lower than reported from single centres (49%)[191] and the wide variation in prevalence between the 28 centres (0-63%) suggests widespread under-reporting. Similarly, the prevalence of rosettes in the Dutch multi-centre study was 16%.[10]

Emperipolesis was very rarely reported (0.4%). In single-centre studies, reported prevalence has been 65%-78%.[191-193] In a preliminary study in Sheffield,[178] emperipolesis was seen in 83 of 84 of patients already known to have AIH but took the Histopathologist 6-10 minutes to assess. Presence of rosettes and/or emperipolesis can help distinguish AIH from viral hepatitis and from drug-induced liver injury (DILI).[193] Presence of rosettes contributes one diagnostic point to the 1999 IAIHG diagnostic scoring system. It is thought that rosettes represent hepatocyte regeneration after lobular injury, and in paediatric patients, has been shown to be the most significant predictor of AIH in biopsies with chronic hepatitis.[179] Although there is a lack of clarity in the original report,[72] both rosettes and emperipolesis appear necessary for "typical" histology, earning 2 diagnostic points by the 2008 simplified system. It has been previously observed that 37% of patients with AIH by 1999 criteria would have been excluded by simplified score if emperipolesis was unreported, but only 15% would be excluded if reported.[178]

In calculating the simplified IAIHG score, it was deemed the presence of interface hepatitis, lymphocyte/plasma cell predominance and rosettes without a detracting finding (such as bile duct damage or more than mild steatosis) amounted to "typical" AIH histology, thereby gaining 2 diagnostic points[72]. Even with this "liberal" interpretation, 31% of patients meeting the 1999 criteria and with sufficient diagnostic information (one-fifth with severe disease), failed to meet the simplified criteria. The equivalent figure in the Dutch multi-centre study[10] was 18%. If the study had

adopted the more stringent definition of typical histology and also required emperipolesis, then only six patients had "typical" histology. The simplified criteria have been shown to be highly specific for AIH in single-centre validation studies,[79,80] but missed 5-10% of cases as defined by the 1999 criteria. Thus, the simplified system may be too strict to be useful in clinical practice and its rigid application may result in non-diagnosis of serious and potentially treatable disease. Indeed, the low prevalence of rosettes, and the rarity of emperipolesis (together with the incomplete testing for Immunoglobulins and autoantibodies) in this study raise the possibility of under-diagnosis of AIH in the UK.

6.7 Conclusions

The results of this large multicentre Audit suggest that AIH in the UK may affect an older population than in previous multi-centre studies. It highlights delays in diagnosis, incomplete diagnostic work-up and probable under-reporting of important histological features, more so in district general hospitals. It calls into question the utility of the simplified IAIHG diagnostic criteria in clinical practice. One way of achieving more complete, more accurate, and probably earlier diagnosis of AIH might be central corroboration of liver histology in a few larger centres and more explicit guidelines for Histopathologists. Histopathological meetings with clinicians and Histopathologists discussing cases with relevant information could optimise patient management.

6.8 Future Work

The ultimate aspiration of this work was to characterise AIH in the UK and the fulfilment of this depends on continuing to collect prospective cases but also to extend this audit to all hospitals in the UK. With appropriate patient consent, for example, they could then be offered entry into appropriate research studies pertaining to the treatment of AIH.

Please note

Parts of this work have also been presented orally and in abstract form at National (Digestive Diseases Federation (DDF); London, England) and International (European Association of Study of Liver disease (EASL) in Vienna, Austria) conferences. An edited version of this chapter has been published in Liver International, full permissions have been received.

Chapter 7: Management of Autoimmune Hepatitis in multiple regions in the UK: Treatment and Outcomes

7.1 Aims

To perform a comprehensive study of treatment and outcome of AIH in 28 UK centres, including hospitals in Yorkshire, and several hospitals located in Wales, Trent and the North East. Given the sizable cohort of patients included from a number of centres of varied size, there is an opportunity to see whether the outcome predictors reported by UK single-centres, often tertiary centres, often with only 100-250 patients, are a true reflection of patients across the UK with AIH.

It is hypothesised that there will be baseline demographic, clinical features, serum markers, treatment factors, disease relapses and type of hospital will be associated with outcome. It is speculated that there will be varied treatment strategies between different types of hospital and that this will affect outcome.

Therefore specifically, the study describes:

i. Overall outcome (liver disease related mortality, all-cause death and liver transplantation rate).
ii. Baseline predictors of all-cause death or requirement for liver transplantation.
iii. Baseline predictors of liver-related death or requirement for transplantation.
iv. The relationship between treatment and outcome
v. Initial treatment response and predictors of incomplete response to treatment.
vi. Drug toxicity.
vii. The proportion of patients subsequently maintaining a normal ALT, relapse rate and its effect on all-cause or liver-related outcome.
viii. Disease progression; the development of de-novo cirrhosis and determine baseline factors associated with its development, new clinical decompensation and Hepatocellular Carcinoma (HCC).
ix. Type of centre (District General Hospitals and University Hospitals) and association with outcome.

7.2 Methods

Participant centres were asked to identify and validate retrospective and prospective cases using the detailed methodology described in Chapter 3 and 4. Information pertaining to treatment and outcome was entered into a web-based, bespoke data collection system between January 2014 and November 2015 (see Chapter 5).

The primary outcome studied was death or liver transplantation. This was further subdivided into all-cause mortality or transplantation and liver-related mortality or transplantation.

Decompensated liver disease at presentation was defined as ascites, oedema, encephalopathy, variceal bleed or Meld>15. Cirrhosis was defined by liver biopsy, presence of varices, ascites, encephalopathy or Fibroscan®. Treatment response was defined at normalisation of ALT by 6 months. Relapse was defined as two times the upper limit of normal transaminases (ALT and/or AST), having previously returned to normal. Follow-up time was defined as time from diagnosis to last out-patient appointment, liver transplantation or death.

7.3 Statistics

SPSS (version 21) and GraphPad software were used to analyse data. Kaplan-Meier survival analysis compared sub-groups using the Log-rank test and survival tables were used to calculate overall survival. Variables associated with outcome (all-cause death/ transplantation and liver death/transplantation) were ascertained by looking at each variable in univariable analysis and those with $p<0.10$ were then assessed using a backward stepwise multivariate Cox regression analysis to elucidate which may be independently associated with outcome. Binary logistic regression was used to calculate odd ratio's. Chi square test was used to calculate differences between proportions and t-test was used for non-parametric data with means and standard deviations quoted. Medians were used to describe continuous data with ranges. $P<0.05$ was considered statistically significant.

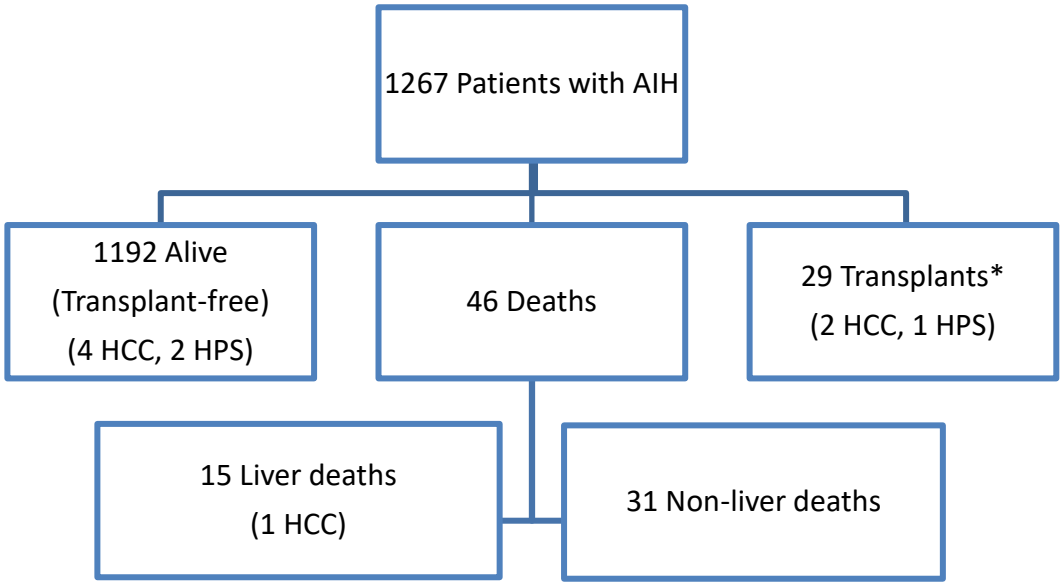
7.4 Results:

7.4.1 Overall Outcome

Of 1267 patients; 1110 (80%) were female, the median (range) age at diagnosis was 55(8-86) years and follow-up was 3.8(0-15) years. At diagnosis, 318 (25%) patients had cirrhosis and 74 (6%) had clinical decompensation. There were 272 (21.5%) overall who were decompensated (clinical decompensation or MELD >15).

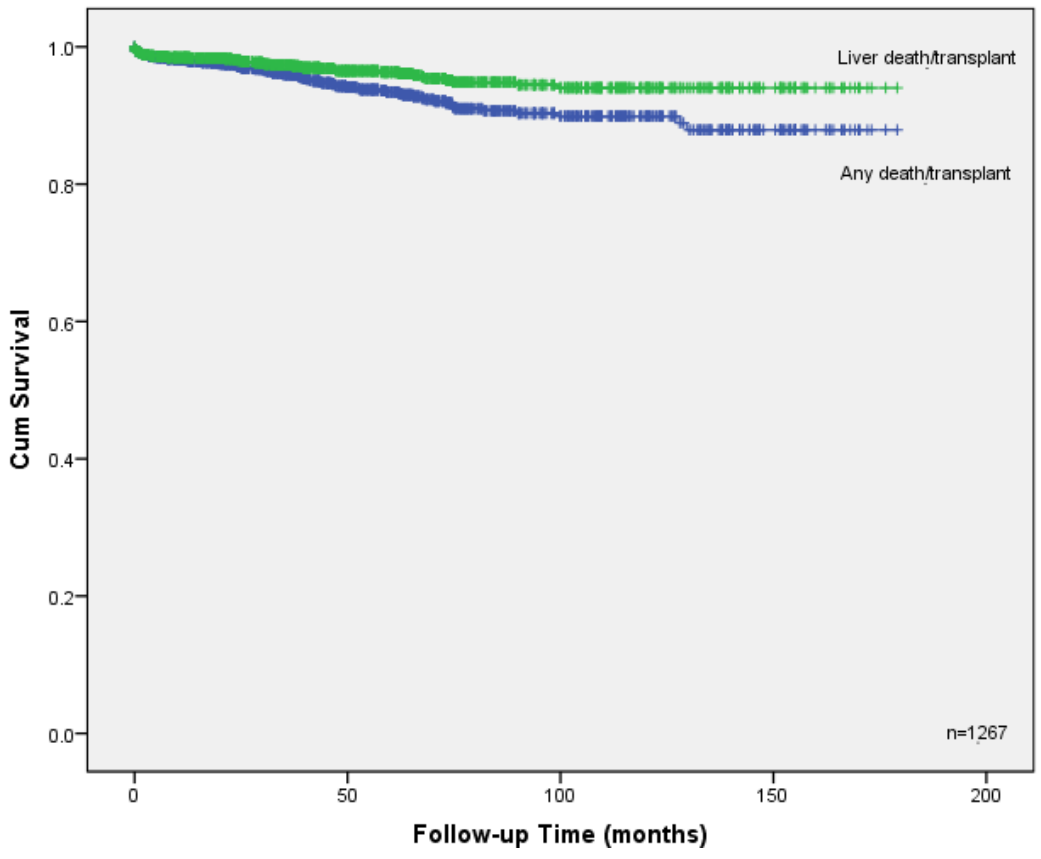
Overall 1.2% patients died from liver disease, 2.3% underwent liver transplantation and 2.4% died of liver-unrelated causes (see Figure 7.1). Five- and 10-year death/transplant rates were 7.1±0.8% and 10.1±1.3% (all-cause) and 4.0±0.6% and 5.9±1% (liver-related) respectively, illustrated in Figure 7.2.

Figure 7.1: Overall outcome Flow chart



*All alive at the end of follow-up, HCC is Hepatocellular Carcinoma and HPS is Hepatopulmonary Syndrome.

Figure 7.2: Overall Survival



7.4.2 *Baseline predictors of all-cause death (ACD) or transplantation*

There are several baseline characteristics that found to be associated with all-cause death (ACD) or transplant rate on univariate cox proportional hazard regression analysis which is shown in Table 7.1. These include age, cardiac or respiratory co-morbidity, black ethnicity (see Figure 7.3), history of cancer, cirrhosis and decompensation at presentation. Serum parameters identified were bilirubin, platelets at the start of treatment and albumin at peak transaminases. Delay in diagnosis was not associated with ACD.

On multivariate analysis (see Table 7.2) black ethnicity was associated with a 4-fold increased risk of AC death or transplantation. A history of cardiac or respiratory disease, cirrhosis or decompensation at presentation were all independently associated with a 2-fold increase in ACD or transplantation. Low platelets at the start of treatment were associated with reduced survival and higher bilirubin at peak transaminases was linked with adverse all-cause outcome. History of cancer and serum albumin were no longer significant on multivariate analysis.

Table 7.1: Baseline parameters associated with all-cause death or transplantation (univariate analysis)

Parameter	No of values	HR	95% CI	P value
Age	1267	1.03	1.01-1.05	**<0.0001**
Cardiac/Respiratory disease	1267	2.28	1.37-3.81	**0.002**
Cirrhosis*	1267	4.06	2.57-6.42	**<0.0001**
Decompensation*	1267	4.10	2.64-6.55	**<0.0001**
Gender	1267	0.88	0.677-1.13	0.33
Ethnic group	1180			0.054
Asian	79	0.59	0.187-1.89	0.31
Black	15	4.49	1.42-14.45	**0.011**
Chinese	1	0	0	0.98
Other	6	0	0	0.96
White	1079	1		
Diabetes	1267	0.65	0.353-1.21	0.32
PBC	1267	0.67	0.32-1.39	0.28
Symptomatic	1267	0.99	0.57-1.73	0.99
Cancer	1267	0.39	0.20-0.77	**0.007**
AMA positive	1267	1.03	0.48-2.25	0.93
Peak ALT	1110	1	0.99-1	0.218
Bilirubin at peak transaminases	1218	1	1.001-1.004	**0.004**
IgG >16g/L	877	1.02	0.544-1.95	0.931
Low Platelets **	1205	0.993	0.99-0.995	**<0.0001**
Albumin at peak transaminases	1047	0.92	0.88-0.949	**<0.0001**
Time to diagnosis	1267	1	0.99-1.02	0.89

*at presentation, **at start of treatment

Figure 7.3: Cumulative survival estimation for all-cause death or transplantation for different ethnicities

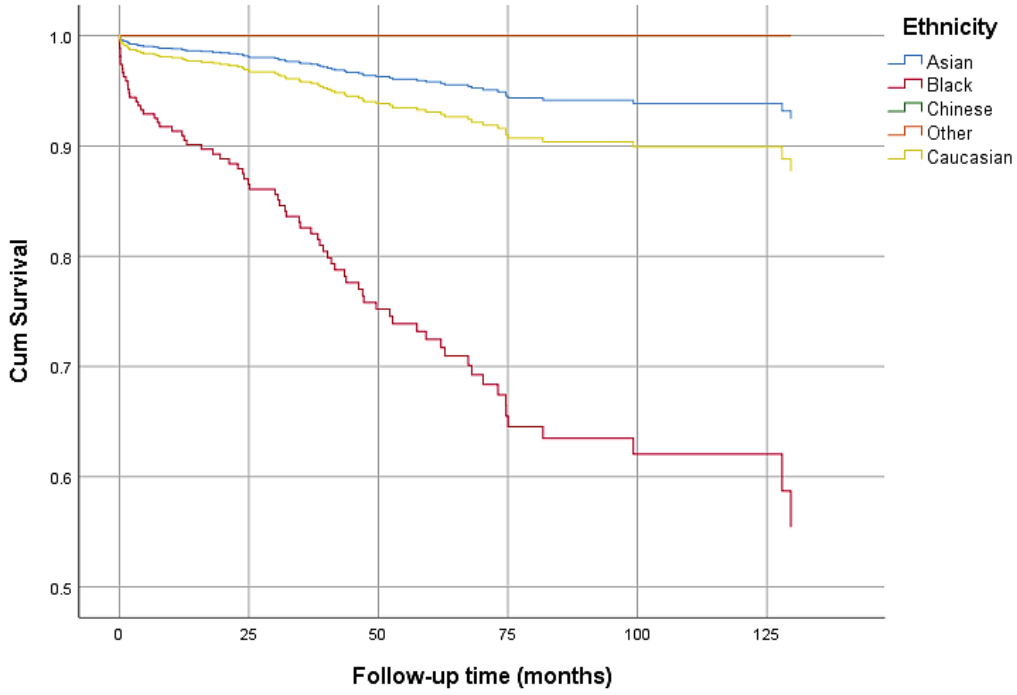


Table 7.2: Baseline parameters associated with all-cause death or transplantation (multivariate analysis)

Parameter (no of values)	HR	95% CI	P value
Age	1.03	1.01-1.05	**0.002**
Cardiac/Respiratory disease	2.07	1.15-3.73	**0.015**
Black ethnicity	4.37	1.17-16.25	**0.028**
Cirrhosis*	2.01	1.17-3.47	**0.012**
Decompensation*	2.23	1.28-3.88	**0.005**
Bilirubin at peak transaminases	1.002	1.00-1.004	**0.022**
Low Platelets **	0.99	0.989-0.996	**<0.0001**

*at presentation, **at start of treatment

7.4.3 Baseline predictors of liver-related death (LRD) or transplantation

Those factors found to be associated with liver-death or transplantation on univariate analysis (see Table 7.3) were black ethnicity, cirrhosis and decompensation at presentation. Serum parameters associated were low platelets at the start of treatment, high bilirubin and low albumin at peak transaminases.

The factors independently associated (see Table 7.4) with liver-related death and transplantation were cirrhosis and decompensation at presentation; with a more than 3-fold and more than 2-fold increased risk respectively. Serum parameters associated with poor outcome were bilirubin at peak transaminases and low platelets at the start of treatment. Black ethnicity nor bilirubin were

independently associated with LRD or transplantation. Importantly delay in diagnosis was not associated with LRD or transplantation.

Table 7.3: Baseline parameters associated with Liver-death and transplantation (Univariate analysis)

Parameter	No of values	HR	95% CI	P value
Age	1267	1.01	0.987-1.02	0.60
Cardiac/Respiratory disease	1267	0.8	0.32-2.05	0.65
Cirrhosis*	1267	8.04	4.14-15.6	**<0.0001**
Decompensation*	1267	7.11	3.81-13.26	**<0.0001**
Gender	1267	0.98	0.66-1.33	0.72
Ethnic group	1180			0.145
Asian	79	0.72	0.17-2.99	0.65
Black	15	5.082	1.22-21.54	**0.025**
Chinese	1	0	0	0.98
Other	6	0	0	0.96
White	1079	1	-	-
Diabetes	1267	0.95	0.37-2.39	0.88
PBC	1267	0.62	0.25-1.58	0.32
Symptomatic	1267	0.58	0.25-1.37	0.99
Cancer	1267	0.82	0.25-2.65	0.74
AMA positive	1267	0.99	0.35-2.76	0.98
Peak ALT	1110	1.00	1.0-1.001	0.68
Peak Bilirubin	1218	1.004	1.002-1.006	**<0.0001**
IgG >16g/L	877	1.02	0.544-1.95	0.931
Low Platelets **	1205	0.993	0.99-0.995	**<0.0001**
Albumin at peak ALT	1047	0.88	0.842-0.921	**<0.0001**
Time to diagnosis	1267	0.98	0.98-1.01	0.19

*at presentation, **at start of treatment

Table 7.4: Baseline parameters associated with Liver death and transplantation (multivariate analysis)

Parameter (no of values)	HR	95% CI	P value
Cirrhosis*	3.82	1.82-8.01	**<0.0001**
Decompensation*	2.65	1.28-5.46	**0.008**
Peak Bilirubin	1.00	1.001-1.005	**0.002**
Low Platelets **	0.99	0.990-0.997	**0.001**

*at presentation, **at start of treatment

7.4.4 Treatment and outcome

There was a wide variation of different treatment regimens initiated at the start of treatment; these are shown in Table 7.5.

Table 7.5: Initial treatment regimens

Initial Treatment	N (%)	Treatment details	N
Corticosteroids	1167	Corticosteroid monotherapy (%)	148
• Prednisolone	(98)	Corticosteroids + other agent (started ≤ 90 days)	(12)
• Budesonide	1089	Corticosteroids + other agent (started >90 days-6 mo)	729
• Methylprednisolone	(86)	Corticosteroids + other agent (started >6 mo)	157
• Hydrocortisone	58 (4.6)		133
	19 (1.5)	**All other agents included:**	
	1 (0.07)	• Azathioprine	998
		• 6-Mercaptopurine	76
		• Mycophenolate	145
		• Tacrolimus	52
		• Cyclophosphamide*	2
		• Cyclosporine	1
		• Methotrexate~	1
Thiopurine monotherapy	19 (1.6)	Azathioprine	17
		6-Mercaptopurine	2

7.4.4.1 Untreated

There were 81 patients who did not receive drug therapy; 18 (22%) of these did achieve normalisation of their transaminases. Untreated patients had worse all-cause and liver related outcomes on univariate and multivariate analysis (all p=<0.001). This was still maintained even when those who had less than 3 months follow-up for ACD (univariate p=0.001 and multivariate p=0.03 and for LRD (univariate p=0.018, on multivariate p=0.01) or transplantation. If the analysis was further restricted to those with >3 months follow-up and to those who were not decompensated at baseline, then all-cause death was significant (p=0.017) on univariate but not multivariate analysis (p=0.053) but not LRD (p=0.53 (univariate analysis)).

Compared to treated patients (n=1186), untreated patients had lower mean (±SD) peak ALT levels; 417±469 vs 711±646 (p=<0.001) and were less likely to be jaundiced (defined here as Bilirubin >50 IU/L); 17(21%) vs 449(38%); p=0.002.

7.4.4.2 Corticosteroid treatment

Compared to those patients who received steroids (n=1175) at some point in clinical course, those that did not (n=92) were older: 58 vs 52 years (p=<0.001) but had similar prevalence of cardio-respiratory comorbidity, cirrhosis and decompensation at presentation.

Steroid treatment conferred significant survival benefit (p=<0.001) for both all-cause and liver-related death/transplantation (Figure 7.4 and Figure 7.5), this is also significant on multivariate analysis (p=<0.001) in Table 7.6 and Table 7.7. There was a 79% reduced risk of AC-death or

transplantation and an 82% reduced risk of liver-related death or transplantation if patients were treated with steroids.

Figure 7.4: All-cause death/transplantation and steroid therapy

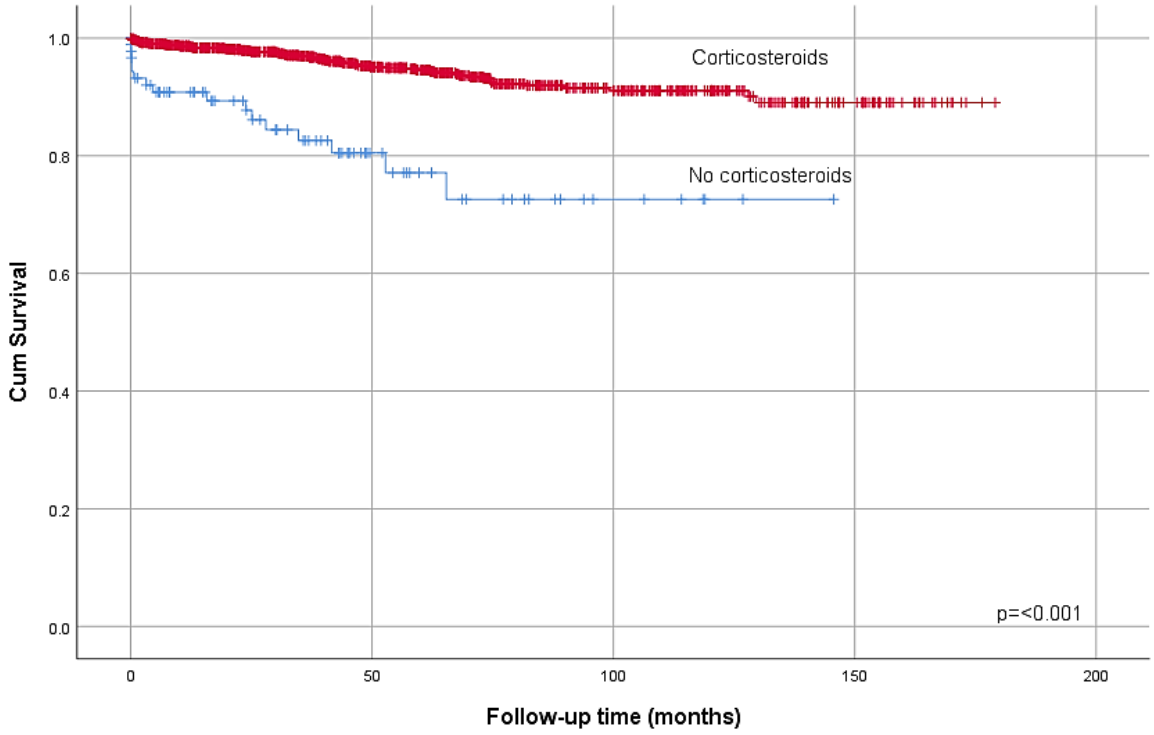


Figure 7.5: Liver death/transplantation and steroid therapy

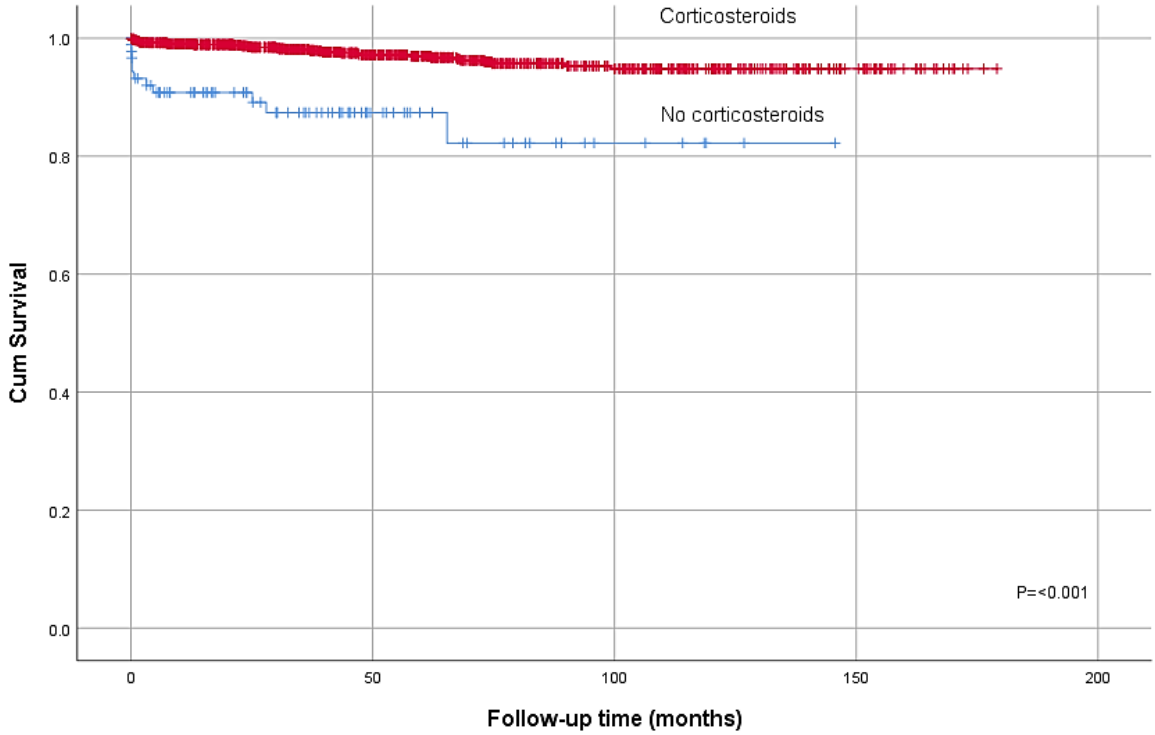


Table 7.6: Basic treatment factors and all-cause death or transplantation

Parameter (no of values)	Univariate		Multivariate	
	HR (95% CI)	AC-deaths/ transplantation P-value	HR (95%CI)	AC-deaths/ transplantation P-value
Steroids vs no steroids (1267)	0.21 (0.12-0.37)	**<0.001**	0.26 (0.13-0.49)	**<0.001**
Time to treatment *** (1186)	0.97 (0.9-1.0)	0.34	-	-
Age (1267)	1.03 (1.01-1.05)	**<0.001**	1.02 (1.0-1.04)	**0.01**
Cardiac/Respiratory ~(1267)	2.28 (1.4-3.8)	**0.002**	2.25 (1.24-4.05)	**0.007**
Black Ethnicity (1180)	4.49 (1.42-14.4)	**0.01**	3.32 (0.88-12.5)	**0.076**
Cirrhosis* (1267)	4.06 (2.6-6.4)	**<0.001**	2.20 (1.15-3.49)	**0.013**
Decompensation* (1267)	4.10 (2.6-6.6)	**<0.001**	2.17 (1.25-3.78)	**0.006**
Peak Bilirubin (1218)	1 (1.001-1.004)	**0.004**	1.003 (1.001-1.004)	**0.004**
Low Platelets**(1205)	0.92 (0.88-0.95)	**<0.001**	0.99 (0.99-0.996)	**<0.001**

*at presentation **start of treatment ***from diagnosis ~co-morbidity

Table 7.7: Basic treatment factors and liver-related death or transplantation

Parameter (no of values)	Univariate		Multivariate	
	HR (95% CI)	Liver-deaths/ transplantation P-value	HR (95%CI)	Liver-deaths/ transplantation P-value
Steroids vs no steroids (1267)	0.18 (0.91-0.36)	**<0.001**	0.12 (0.58-0.26)	**<0.001**
Time to treatment*** (1186)	0.97 (0.88-1.06)	0.46	-	-
Cirrhosis* (1267)	8.04 (4.14-15.6)	**<0.001**	4.07 (1.91-8.65)	**<0.001**
Decompensation* (1267)	7.11 (3.81-13.26)	**<0.001**	2.17 (1.04-4.5)	**0.038**
Peak Bilirubin (1218)	1.004 (1.002-1.006)	**<0.001**	1.0 (1.002-1.006)	**<0.001**
Low Platelets** (1205)	0.993 (0.99-0.995)	**<0.001**	0.99 (0.99-0.998)	**0.002**

*at presentation **start of treatment ***from diagnosis

This significance persisted even after removal of patients who had less than 3 months follow-up for liver-related: p=0.006 but not all-cause (p=0.08) death/ transplantation. Time to treatment from diagnosis did not impact on liver-related survival.

7.4.4.3 Type of Corticosteroid

A comparison of type of steroid initially given and the baseline presenting features and outcome is shown in Table 7.8 (n=1169). Budesonide was used in 5% of patients at a median dose of 9mg (3-9mg/day); 47 (81%) of these patients were initiated by University Hospital's. Those patients receiving Methylprednisolone or Hydrocortisone (patient with coeliac disease) were pooled with Prednisolone as all were given prednisolone shortly afterwards. Those receiving prednisolone (or equivalent) had significantly higher serum ALT, more likely to be jaundiced, have cirrhosis and have decompensation at baseline (all p=<0.01). There were a similar proportion of patients with cirrhosis in both groups, of note 28% in the Budesonide group. Whilst median treatment duration was longer in the prednisolone group compared to Budesonide, there were only 8 (of 61) patients who were given Budesonide before 2010 and only 3 of these were prevalent patients.

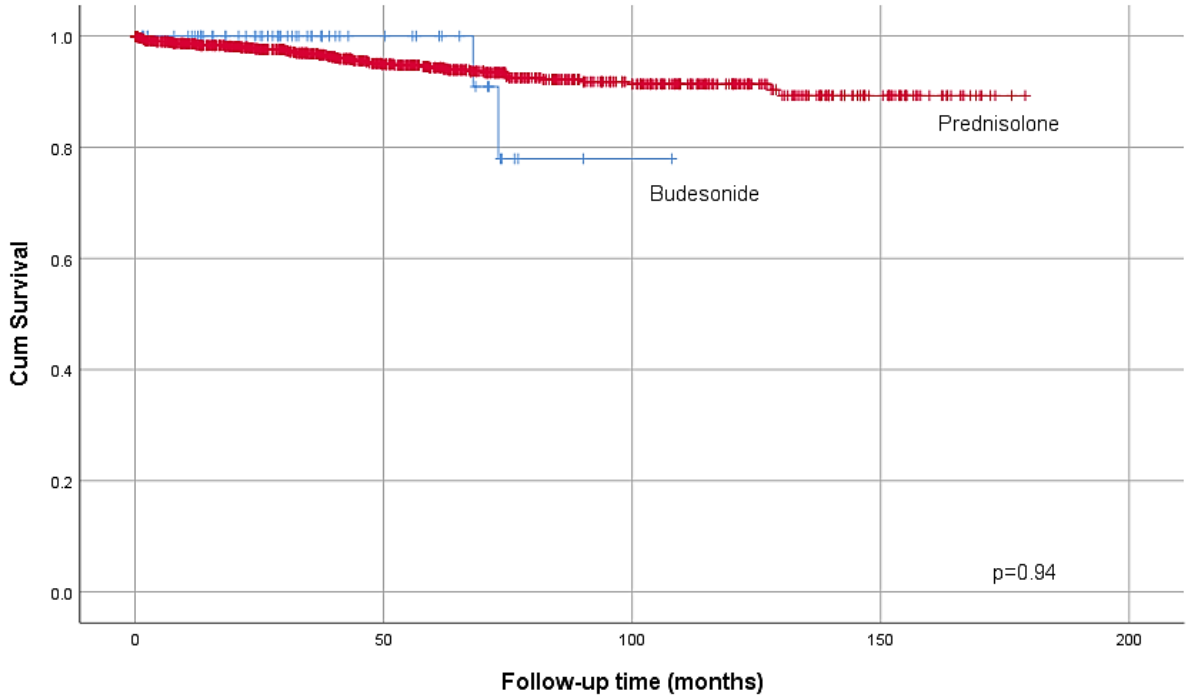
Table 7.8: Baseline characteristics and outcome of patients receiving Prednisolone or Budesonide in the first 3 months

Parameter	Prednisolone* n=1111	Budesonide n=58	P value
At Baseline			
ALT (IU/L); mean ±SD at start of treatment	451±509[f]	182±199[ff]	**<0.001**
Jaundice (bilirubin >50µmol/L): N (%)	369 (35)[€]	4 (7)[€€]	**<0.001**
Cirrhosis: N (%)	276 (25)	16 (28)	0.64
Decompensated at presentation: N (%)	245 (22)	4 (7)	**0.006**
Pre-treatment IAIHGS: median(range)	15(1-22)	14(5-22)	0.47
Moderate/severe Necroinflammation on biopsy: N (%)	370 (63)[^]	18 (55)[^^]	0.36
Dose at start of treatment (mg): median (range)	30 (2-60)[+]	9 (3-9)[++]	-
Outcome			
Follow-up time: median(range), months	37 (0-179)	29 (1-108)	**<0.0001**
Treatment duration: median(range), months	19 (1-241)[¥]	10 (1-144)[¥¥]	**0.004**
Conversion of Bud to Pred N (%)	-	11 (19)	-
Conversion of Pred to Bud N (%)	61 (5.5)	-	-
Transplantation N (%)	17 (1.5)	2 (3)	0.24
Any Death/transplant	54 (4.8)	2 (3)	1

*there were 20 patients; given Hydrocortisone (1) or Methylprednisolone (19) prior to prednisolone).
[f]Available in 1043 and [ff]56 patients. [€]Available in 1062, and [€€]56 patients.
[^]Available in 591 patients, [^^]Available in 33 patients. [+]Dose unknown in 21, and [++] Dose unknown in 2 patients.
[¥]Available in 1100 patents, and [¥¥] available in all patients.

Overall outcome (ACD and LRD and transplantation) was not different between the two groups (p=0.94 and 0.5 respectively). The Kaplan Meier plot for all-cause survival and transplantation is shown in Figure 7.6. The Kaplan Meier survival analysis of those with and without cirrhosis in the Budesonide group was not statistically significant (p=0.08) but it is note that both the patients that required liver transplantation had cirrhosis at presentation. Of those in the Budesonide group with cirrhosis with ALT values available; 10/15 (67%) patients compared to those without cirrhosis 29/32 (91%); (p=0.04) had normal ALT at 6 months (male <35 and female <30 IU/L).

Figure 7.6: All-cause death and transplantation and type of steroid used



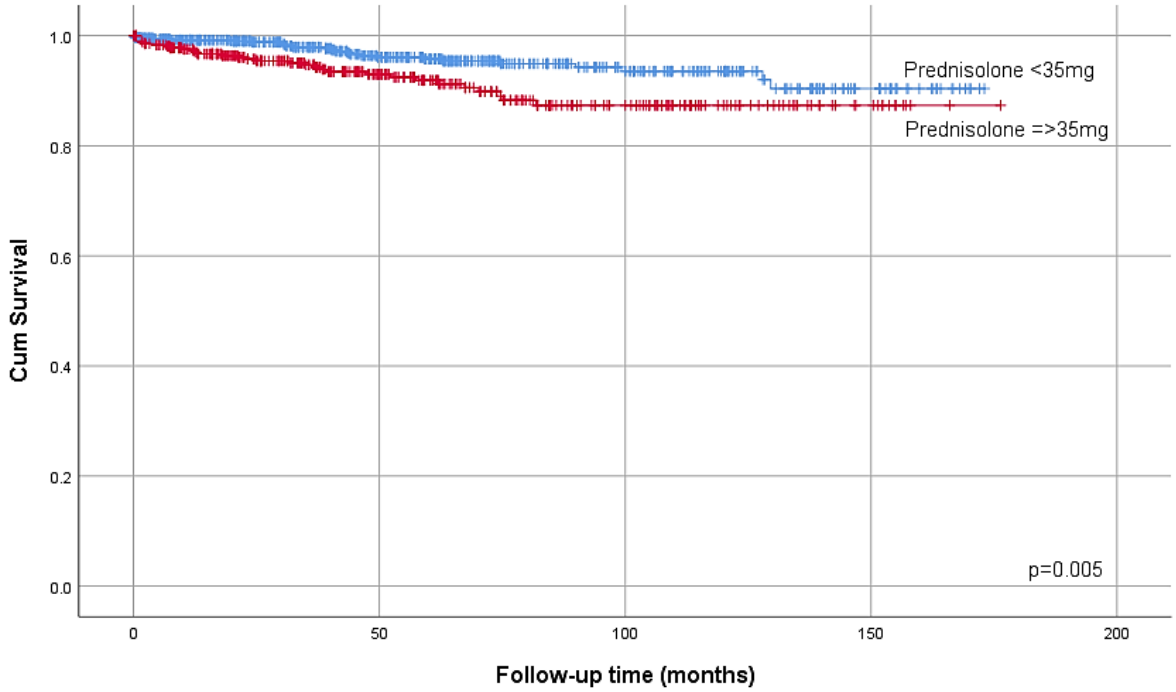
After treatment initiation, the mean 6 month serum ALT was lower in the prednisolone group (56 ±114 vs 91±280; p=0.001), but the median ALT at 6 and 12 months for prednisolone group versus Budesonide was no different: 31(5-2161) vs 31(13-1824) and 25(7-1149) vs 27(11-73) IU/L (p=0.08 and p=0.3 respectively) despite higher baseline ALT levels in the prednisolone group. There was a similar proportion of patients achieving normal serum ALT values after 6 (69 vs 70%; p=1) and 12 months (85 vs 75%; p=0.2) of treatment. Three percent (2/58) of patients receiving Budesonide had a follow-up biopsy had new cirrhosis found in both patients (100%) versus 7% (22/316) of those receiving prednisolone (28% of which biopsied (316/1111)) and NIS was moderate or severe in 50% vs 23% respectively.

7.4.4.4 Dose of corticosteroid

An initial dose of prednisolone (or equivalent (methylprednisolone or hydrocortisone)) of 35mg or more (n=416) compared to those receiving less (n=653) was found to negatively impact and survival for both ACD (see Figure 7.7) and LRD and transplantation (HR 2.1 (1.24-3.55);p=0.005 and HR 2.87 (CI 1.37-6.04); p=0.005 respectively) on univariate analysis. On multivariate analysis a dose of 35mg prednisolone or above was found to be an independent predictor for all-cause (HR 2.25 (CI 1.24-4.05); p=0.007) but not for liver-related death and transplantation HR 1.99 (CI 0.90-4.43); p=0.089. Higher doses of prednisolone (≥35mg) were used in those with higher ALT (943 ±694 vs 580±557 IU;p=<0.001) and higher Bilirubin (128±143 vs 65±97 µmol/L; p=<0.001) levels. There was no

difference in time to normalisation of ALT associated with higher doses of steroids (4.7 ±12 vs 4.6 ±11 months; p=0.92).

Figure 7.7: Cumulative AC survival/transplantation and association with initial dose of prednisone



7.4.4.5 Duration of corticosteroid

Median length of steroid treatment for all follow-up times was 18(1-241) months but in those with at least 4 years follow-up, this increased to 31(1-241) months. Shorter duration of steroid treatment for all periods of follow-up was found to be an independent predictor of all-cause and liver-related death and transplantation (all p=<0.001). However, when restricted to the 995 patients who had more than one year of follow-up, it was found that continuing steroids for more than one year when compared to those who did not continue for one year was not detrimental to all-cause or liver death and transplantation (p=0.98 and 0.99 respectively). Nor did death/transplant rates differ between patients who continued.

7.4.4.6 Steroid-Sparing agents (SSA's)

Overall, 1053 patients received an SSA during follow-up. Patients taking steroid-sparing agents had improved both all-cause and liver related (LD) outcome on univariate and multivariate analysis (both p=<0.001). However, when removing those who had less than 6 months follow-up there was only a significantly improved all-cause survival (p=0.017) on univariate but not on multivariate cox regression analysis (p=0.95). Liver-related outcome was not significantly affected by treatment with SSA's when limited to those with more than 6 months follow-up (p=0.58 on univariate analysis).

When comparing those patients who were initially given steroids alone (n=148) compared to SSA alone (n=19) and also with SSA plus steroids (n=1019), there was a significant improvement in both all-cause and liver related survival and transplantation in the combined therapy group as shown in Figure 7.8 and Figure 7.9 (p=<0.001 and p=0.001 respectively).

Figure 7.8: SSA and steroid groups and association with all-cause death/transplant

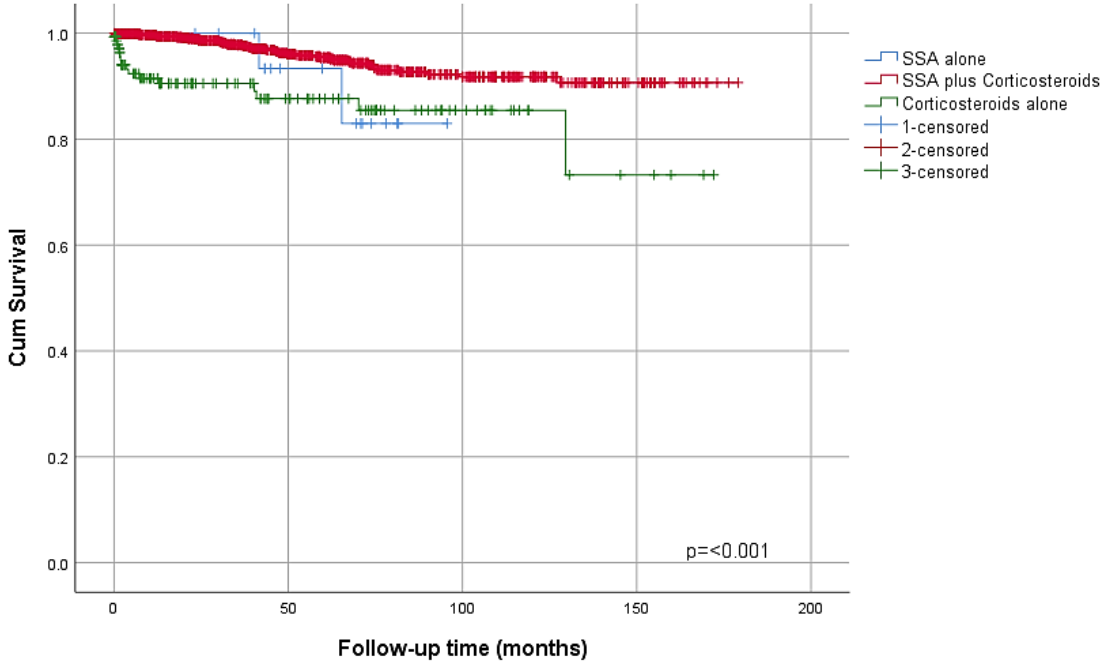
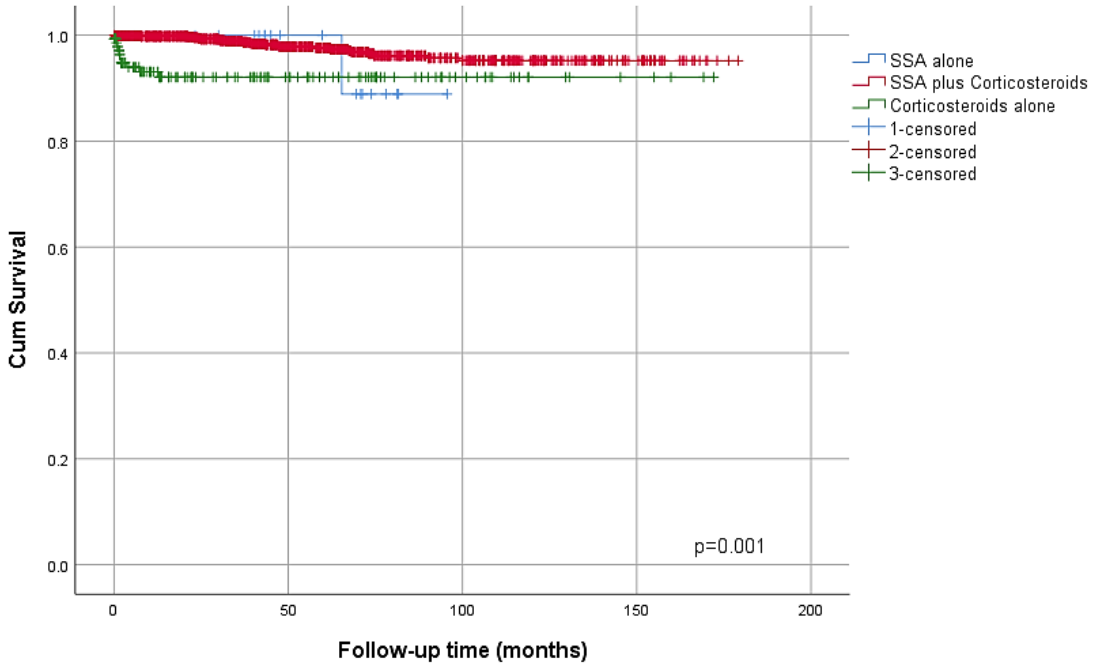


Figure 7.9: SSA and steroid groups and association with Liver-related death/ transplant

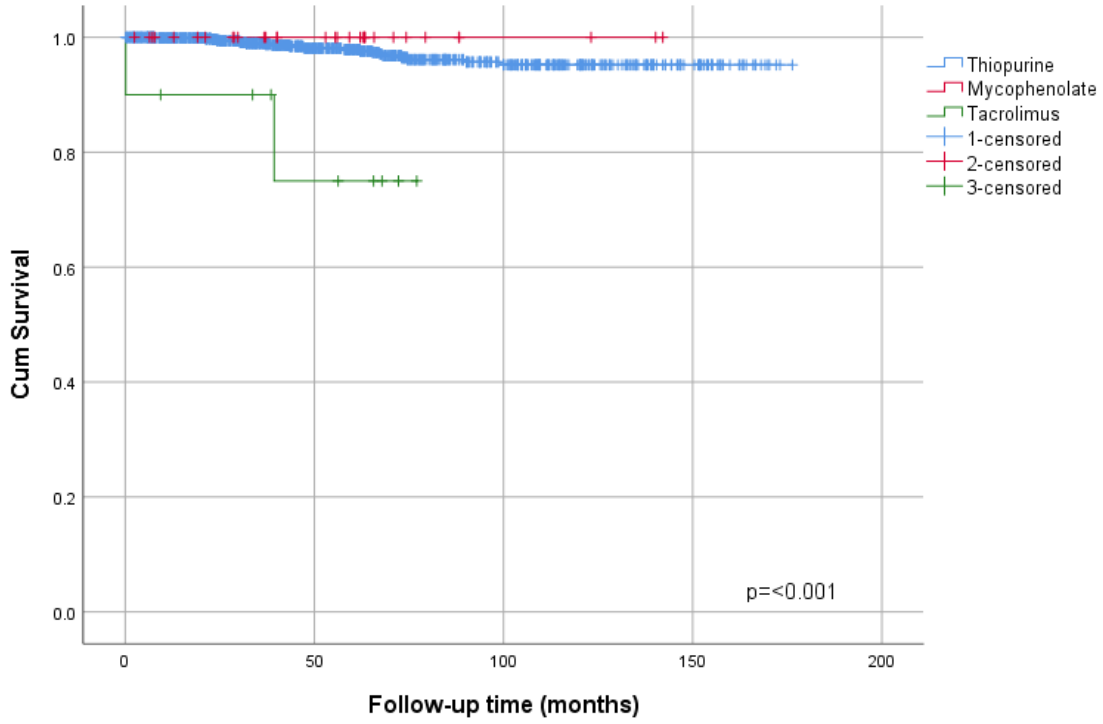


On multivariate analysis there was a more than 3-fold increased risk of death between the steroid alone group compared with the combined therapy group for both AC and LRD or transplantation (HR

3.09 (CI 1.69-5.66):p=<0.001 and HR 3.59 (CI1.61-7.98); p=0.002 respectively). However, when those with less than 3 months follow-up were excluded, this relationship was lost (p=0.16 and p-=0.68 on univariate analysis). The median timing of SSA initiation was 1.4 (0-132) months and delay in receiving an SSA did not affect outcome (ACD; p=0.472 and LRD; p=0.609).

Of the three main types of SSA given first; Mycophenolate (n=32) had significantly superior survival compared to Tacrolimus (n=10) for LRD (see Figure 7.10; p=<0.001) and ACD and transplant (p=0.014), but not when compared to Thiopurines alone (LRD: p=0.43and ACD: p=0.26). Cyclosporine, Cyclophosphamide and Methotrexate were given to a total of only 3 patients, thus were excluded from this analysis. Tacrolimus was compared to other SSA's used in younger patients (40(±16) vs 51(±17); p=0.028, with more severe disease; mean (±SD) bilirubin 230(±232) vs 86(±116); p=0.0003, and in those with cirrhosis 7/10(70%) vs 263/1043(25%); p=0.0012. Eight of these ten patients did go on to normalise their transaminases but one died from liver failure and one underwent liver transplantation. However, on multivariate analysis with baseline predictors of outcome, the type of SSA was no longer significantly associated with either LRD or ACD or transplant (p=0.21 and 0.65 respectively). When those with less than 3 months of follow-up were excluded then significance on univariate analysis was also lost for both LRD and ACD or transplant.

Figure 7.10: Type of SSA and association with liver-related death and transplant



7.4.5 Treatment response

Of all 1186 treated patients; 1098 (93%) eventually achieved normalisation of their transaminases. The median time to normalise transaminases was 2 (0-135) months (the number of patients where the time was known was 1025). There were 1013 treated patients who had more than 6 months follow-up and had dates of ALT normalisation, with 34 of these normalising prior to the start of treatment. There were 818 (of 979 (84%)) who normalised ALT by 6 months.

Failure to normalise transaminases for the duration of follow-up was found to be significantly associated with death (AC and LD) and decompensation occurring at presentation (all p=<0.001). In contrast, failure to achieve ALT normalisation at specific time points (at 28 days, 6 months and at 12 months) showed no association with ACD or LRD /transplantation (all p=>0.05), with or without treatment. However, the value of ALT at 28 days and 3 months (significant on univariate analysis in Table 7.9) was found to be an independent predictor of outcome for LRD or transplantation on multivariate analysis with baseline predictors (HR 1.002 (CI 1.001-1.004); p=0.003 and HR 1.003 (CI 1.001-1.005); p=0.009 respectively) and also at 28 days a predictor for ACD (HR1.002 (CI 1.001-1.003); p=0.003).

Table 7.9: ALT value at specific time points and outcome (univariate analysis)

ALT at Time (no of values)	Any death/transplant HR (95% CI)	p-value	Liver death/transplant HR (95% CI)	p-value
7 days (n=649)	0.99 (0.997-1.001)	0.19	1.000 (0.988-1.001)	0.84
28 days (n=860)	1.001 (1.000-1.002)	**0.045**	1.002 (1.001-1.002)	**0.001**
3 mo (n=846)	1.002 (0.99-1.003)	0.28	1.002 (1.000-1.004)	**0.049**
6 mo (n=840)	1.0 (0.99-1.003)	0.91	1.001 (0.99-1.003)	0.47
12 mo (n=817)	0.99 (0.993-1.005)	0.71	1.000 (0.997-1.003)	0.99

Of the patients who received treatment and achieved normal transaminases (n=1098); 306 (28%) had a follow-up liver biopsy. There were 97 (39%) had no or minimal inflammation on Ishak scoring (251 had necroinflammatory scores).

7.4.6 Drug Toxicity

Corticosteroids

Of those treated with corticosteroids (n=1175); 151 (13%) patients suffered ≥1 more steroid side effects. Specifically, steroid psychosis occurred in 14 (1%) after a median (range) of 2(1-16) months on treatment, receiving a median initial dose of 30(20-40mg) Prednisolone. Low trauma fracture was reported in 5 (0.4%) at a median of 30(1-72) months. Diabetes was diagnosed in 53 (4.5%) patients during treatment; receiving a median initial dose of 40(20-60mg) Prednisolone with median length

of treatment of 5(1-94) months. Where dose was known, those who were given a prednisolone dose of 35mg or more (n=416) were found to have a higher incidence of diabetes development during follow-up (27 (6.5%) vs 23 (3.5%)); p=0.025 on chi square) than those who received less (n=653). Compared with Prednisolone, Budesonide had less reported side effects (13% vs 3%: p=0.02), with no steroid psychosis, diabetes or low trauma fracture, and only two patients (3%) having any documented side effects (weight gain and 'generally unwell').

Steroid-Sparing agents (SSA's)

Of 1053 patients receiving a SSA; 31% (316/1015) patients reported Azathioprine side effects; the commonest being leucopenia (white cell count <2.5 and fall of >1.0) in 64 (6%) patients at median of 8 (1-96) months) and 3 (0.3%) patients got pancreatitis (all Azathioprine) at a median of 2 (1-18) months. 15 of 76 (20%) patients and 7 of 145 (5%) had side effects related to 6MP and MMF respectively.

Tacrolimus

Of a total of 52 patients receiving Tacrolimus; 5 (10%) patients had side effects including headaches, tremor, pneumonia and diarrhoea.

7.4.7 Maintenance of normal transaminases, relapse and association with outcome

Of those who achieved normal transaminases, 538 (49%) maintained normal values throughout follow-up.

Of 1098 patients who were treated and achieved normal transaminases there were 354 (32%) patients who relapsed (transaminases >2 times the upper limit of normal (ULN)), of which 61 had cirrhosis. During the first relapse there were 316 where ALT was known (the rest had a documented AST instead) and 138/316 (44%) had ALT ≥5 times the ULN (35IU/L defined as ULN for ALT) and 18 (5%) (of 342 where values known) were jaundiced (bilirubin >40). The first relapse occurred a median of 12 (0-138) months from date of first normalisation. There were 134 (12) who had 2 relapses and 54 (5%) who had ≥3 relapses.

The baseline parameters associated with relapse were age, cirrhosis and decompensation at presentation on univariate binary logistic regression analysis (see Table 7.10). On multivariate analysis (see Table 7.11) the patients are less likely to have a relapse if they are of older age at

diagnosis and patients are 42% less likely to have a relapse if they have cirrhosis at baseline (OR 0.58 (CI 0.42-0.80); p=0.001).

Having a one or more relapses was found to improve AC-survival and transplantation (HR 0.27 (CI 0.09-0.88); p=0.03) on univariate analysis but not on multivariate analysis HR 0.55 (0.17-1.82); p=0.33. However, one or more relapses had no effect on liver-related mortality or transplantation on univariate analysis (p=0.08 and p=0.09 respectively). When those with less than 6 months of follow-up are removed, then there is no significant association on ACD or LRD on univariate analysis with number of relapses (all p=>0.05).

Table 7.10: Baseline Parameters and association to relapse (univariate analysis)

Baseline Parameter	OR (95% CI)	P Value
Female gender	0.95 (0.8-1.1)	0.48
Age at diagnosis	0.98 (0.97-0.99)	**<0.001**
Black ethnicity	0.61 (0.13-2.9)	0.54
Cardiac/Respiratory comorbidity	0.99 (0.69-1.41)	0.95
Peak ALT	1.0	0.21
Albumin (<35g/L)	1.002 (0.75-1.33)	0.99
IgG at peak ALT (>16g/L)	0.74 (0.52-1.04)	0.084
Bilirubin (>150µmol/L)	1.08 (0.81-1.43)	0.62
Platelets <150U/L)	0.74 (0.52-1.04)	0.084
Cirrhosis at presentation	0.54 (0.39-0.74)	**<0.001**
Subsequent cirrhosis	1.24 (0.74-2.06)	0.41
Decompensation at presentation	1.53 (0.79-2.96)	**0.025**
Prednisolone initial dose ≥35mg	0.98 (0.75-1.23)	0.88

Table 7.11: Baseline Parameters and association to relapse (multivariate analysis)

Baseline Parameter	OR (95% CI)	P Value
Age at diagnosis	0.98 (0.977-0.992)	**<0.001**
Cirrhosis at presentation	0.58 (0.42-0.80)	**0.001**

7.4.8 Disease Progression

During clinical follow-up; de-novo cirrhosis developed in 76 of 949 (8%). This was confirmed histologically in 25 (33%), and by the presence of varices or variceal bleed, encephalopathy, ascites/oedema, on imaging or Fibroscan scores consistent with cirrhosis (7 by fibroscan alone). Median time to de-novo cirrhosis was 15 (1-140) months. All but one of these patients had a prior baseline biopsy and all but one (not clear) of these reports stated they did not have cirrhosis (Ishak fibrosis score was available in 39 (all ≤4)).

The baseline parameters associated with de-novo cirrhosis are shown in Table 7.12. Multiple relapses compared to those with just one relapse were associated with a 3-fold increased likelihood of developing cirrhosis. Low platelets and low serum albumin at baseline were associated with a 6-fold and two and a half-fold increase risk of developing cirrhosis during follow-up (Table 7.13).

Table 7.12: Baseline factors associated with subsequent development of cirrhosis during follow-up

Parameter	No of values	OR	95% CI	P value
Age	949	1.008	0.99-1.02	0.26
Gender (Female)	949	0.68	0.53-0.88	0.003
Black ethnicity	949	0	-	0.99
AMA positive	949	0.77	0.33-1.83	0.56
Symptomatic	949	1.75	0.90-3.3	0.97
Peak ALT	829	1.00	1.0-1.0	0.88
Peak Bilirubin >150µmol/L	906	1.39	0.85-2.28	NS
IgG >16g/L	651	1.63	0.80-3.29	0.18
Platelets <150U/L*	899	3.59	2.11-6.12	**<0.0001**
Albumin at peak ALT <35g/L	779	3.83	2.28-6.46	**<0.001**
Transaminase normalisation	949	0.91	0.38-2.17	0.83
Relapse	949	1.05	0.64-1.76	0.83
Multiple versus one relapse	304	3.04	1.3-7.12	0.011

Table 7.13: Baseline factors associated with de-novo cirrhosis during follow-up (multivariate analysis)

Parameter	OR (95% CI)	P Value
Gender	0.87 (0.51-1.49)	0.158
Platelets <150U/L	6.43 (2.36-17.52)	**<0.001**
Albumin at peak ALT <35g/L	2.61 (1.04-6.58)	**0.042**
Multiple versus one relapse	3.19 (1.24-8.21)	**0.016**

There was also an increased risk of adverse outcome if cirrhosis developed during follow-up ($p<0.001$ for ACD and LRD or transplantation). Those who developed de-novo cirrhosis during follow up had a 2-fold increase risk of ACD or transplantation (HR 2.40 (1.03-5.55); p=0.042) and a 9-fold increased risk of LRD or transplantation on multivariate analysis (HR 9.37 (CI 2.76-31.8); p= <0.001).

Development of new clinical decompensation (Ascites/oedema, variceal bleed or encephalopathy) or hepatopulmonary syndrome developed in 49 (3.9%) patients at a median time of 33(1-137) months. The total number with clinical decompensation at any time was 150 (12%). Variceal bleeding occurred in 18 (1.4%) at a median of 6(0-11) months during follow-up.

Hepatocellular carcinoma occurred in 7 (0.6%) patients at 43(15-128) months after diagnosis; one died, 2 patients underwent liver transplantation, four were still alive and transplant free (all 79 yrs old or older) and underwent resection or palliative treatment.

Hepatopulmonary syndrome occurred in 3 patients at 46(7-52) months; one patient underwent transplantation, one was being assessed at time of data collection.

7.4.9 *Type of Hospital and outcome*

There were 437 patients attending DGH's and 830 patients attending UH's. Compared to DGH's patients attending UH's were more likely to be treated with steroids 393 (90%) vs 782 (94%); p=0.005, and more likely to receive Budesonide 12/392 (3%) vs 49/780 (6%); p=0.019.

Patients were more likely to receive an SSA 719 (87%) vs 334 (76%);p=<0.001 and less of a delay in initiating an SSA (<3months) 177 (25%) vs 124 (37%) if attending UH's compared to DGH's.

Patients attending UH's also had lower mean serum ALT levels at 3 months (65 ±104 vs 100±181; p=<0.001) and were more likely to attain normal levels at 3 months (41% vs 34%; p=0.03), 6 months (54% vs 45%; p=0.019) and 12 months (64% vs 55%; p=0.02) than those attending DGH's.

Whether patients attended District General hospitals (DGH's) or University Hospitals (UH's) did not affect overall outcome; for AC: p=0.13 and LRD: p=0.017 death/transplantation on univariate analysis. On multivariate analysis (Table 7.14) DGH/UH status was not significantly associated with LRD or transplantation (p=0.09).

Table 7.14: Type of Hospital and liver death or transplantation (multivariate analysis)

Parameter	HR	95% CI	P value
Cirrhosis*	3.72	1.76-7.88	**0.001**
Decompensation*	0.38	0.18-0.77	**0.008**
Peak Bilirubin	1.00	1.00-1.005	**0.004**
Low Platelets **	0.99	0.989-0.99	**0.002**
UH vs DGH	0.51	0.23-1.11	0.09

7.5 Discussion

In this study we found that overall 10-year all-cause survival of 90% is slightly better than expected when compared to single centre UK cohorts (83-85%), [23,111] but not dissimilar to other multi-centre cohorts from Denmark, Sweden and Holland (74-88%), [12,14,172] although one factor that may account for this is that the median follow-up time in our study was shorter than others (3.8 years compared to 5.9-18.7). We also have to accept that not every centre may have been able to fully utilise the capture strategy as described. The 6% 10-year liver-related deaths and transplantation rate found in this study were slightly less than in other multicentre studies (7-10%)[12,14,172] and other UK cohorts [23,111] but matched a study of a whole geographical area of Canterbury, in New Zealand. [26]

Other studies, like this one have found factors found to be linked to all-cause mortality have included age.[14,23,111] Cirrhosis or decompensation at presentation has also been linked to both adverse all-cause and liver-related mortality,[109,111,168,172,182] and this is corroborated in the present study. Cardiac or respiratory comorbidity was found to increase all-cause outcome 2-fold, and other groups have factored this in using co-morbidity indices (HR 1.6 (CI 1.34-1.82).[14]

Black ethnicity has been shown by one other group to be linked to poor all-cause outcome. [21] Two other groups have investigated whether black ethnicity affected liver-related outcome, the first found outcome to be similar, [194] but the second collaborative study found poorer outcome (HR 2.4 (CI 1.4-4.0; $P < 0.001$).[195] Although this study found that black race was an independent predictor of all-cause death, it was found that adverse liver-related outcome and incomplete normalisation was more likely in black patients compared to non-blacks on univariate but not multivariate analysis.

Serum markers at baseline that were associated with both all-cause and liver related adverse outcome were found to be bilirubin at peak transaminases and low platelets at the start of treatment, with bilirubin being a surrogate marker of disease severity and the latter likely marker of underlying cirrhosis. Important non-associations were established, being that neither gender, presence of symptoms, coexistence of PBC, delay nor time to diagnosis were related to ACD or LRD or transplantation.

Those who remained untreated had reduced survival. An analysis of the proportion of patients with jaundice and mean ALT in treated group compared to the untreated group reveal that the clinicians' decision to treat may have been based influenced by these parameters. However, the untreated group seemed to harbour some patients who were entering acute or sub-acute liver failure, in whom it may be contentious to immunosuppress, and appropriately underwent early liver transplantation. The sub-analysis excluding early deaths showed that those left untreated still had reduced all-cause and liver-related survival which indicates that these patients would have benefited from treatment. Even with further sub-analysis, in those with more than 3 months follow-up and those decompensated at baseline were removed, this was still significant for AC survival, but unsurprisingly not for liver-deaths underlining the potential advantage of treatment.

Our results show that patient's not receiving corticosteroid therapy had inferior ACD and LRD or transplantation outcome. The decision not to treat may have been influenced by older age. The sub-analysis confined to patients who had more than 3 months follow-up (thereby excluding early

deaths) still showed an adverse outcome in patients not treated with steroids indicating that leaving these patients untreated is not justified.

There appeared to be wide variation of length of steroid treatment and our observation that shorter duration was linked to adverse outcome is probably related to follow-up time, which of course itself is interrelated with outcome, thus may be an artefactual finding. When restricting analysis to those with more than 12 months follow-up, outcomes were similar in those continuing treatment for more than 12 months compared to those who did not. This means this study could not confirm that duration of steroid treatment is related to improved outcome. Although, because of the median follow-up time it was not possible to analyse longer-term outcomes effectively but there remains the possibility that histological remission may be more likely achieved with longer durations of steroid therapy.

Whether patients initially received Prednisolone or Budesonide was not associated with ACD or LRD or transplantation. Although Budesonide has been shown in randomised controlled trials to achieve a greater rate of ALT normalisation [105,196-198] than Prednisolone there are few data on its longer-term efficacy, with only one study reporting up to 2-year remission rates[199] and none on histological remission or 5- and 10-year survival. This study shows here that despite this, Budesonide is being used in secondary care as a first line treatment for AIH in 5% of patients. Compared to those initially receiving Prednisolone, those receiving Budesonide had similar age and gender distribution but had less severe liver dysfunction and more likely to be attending University Hospitals. Interestingly, there were a similar proportion of patients with cirrhosis in each group. Of concern 28% of patients who received Budesonide had cirrhosis, including the two patients who later required liver transplantation. This is somewhat surprising when the presence of cirrhosis is a contraindication for Budesonide use given the 90% reduced hepatic metabolism and portosystemic shunting giving rise to side effects and also its association with venous thrombosis. [200] This is especially important given that Budesonide is also associated with reduced efficacy in cirrhosis.[201] This may explain why the overall mean 6 month ALT (but not median) was lower in the patients given Prednisolone rather than Budesonide and why those with cirrhosis in the Budesonide group compared to those without had a significantly lower proportion achieving ALT normalisation at 6 months despite the higher baseline serum ALT. However, it is accepted that there were fewer patients in the Budesonide group to make comparisons. Treatment duration was longer in the prednisolone group, this probably relates to Budesonide not being used frequently before 2010, this coincides with the publication of the largest randomised control trial in AIH (Published in October 2010), comparing Budesonide and

prednisolone, with the primary endpoint being biochemical remission without side effects.[105] Contrary to this study and others[196-198] this study found no difference in ability to normalise ALT at 6 months, although our study is an audit, it is an important observation that these patients appear to have similar biochemical outcomes. Only two patients receiving Budesonide had a follow-up biopsy but both patients had developed cirrhosis during follow-up, these are too few to draw any conclusions but does perhaps highlight that there are no data published on histological remission rates or cirrhosis development in these patients. It is well known that Budesonide has a superior side effect profile which is echoed here. [105,199]

Dosage of corticosteroids equal to or above 35mg of prednisolone was fascinatingly linked to reduced all-cause survival, presumably due to their metabolic effects and increased risk of ischaemic heart disease. This is analogous to a recent study in patients with Rheumatoid arthritis where there was found to be a dose-dependent increase in all-cause mortality.[202] New onset diabetes during follow-up was 5% and was significantly associated with the higher dosage of steroids (≥35mg), which also must be more commonly prescribed by our European and American counterparts, given their dosing guidance. [2,86] Selecting a higher dose of steroids appeared to be linked to the degree of ALT and bilirubin elevation.

Treatment with steroid-sparing agents have been found to allow reduction in corticosteroid dosage, maintain remission and prevent relapse.[100,129] SSA's were only shown to reduce all-cause and liver related outcomes when considering all periods of follow-up, but do not significantly affect ACD or LRD or transplantation outcomes when early follow-up events are removed, implying an 'early effect' on mortality only. Although there was a wide variation in timing of SSA initiation, this did not affect outcome. This study observed superior outcome in those initially receiving mycophenolate compared to other agents, it is well known that this is the preferred agent in those intolerant but not unresponsive to azathioprine.[141] Azathioprine was associated with side effects in approximately one-third of patients but only 5% had adverse effects with mycophenolate. Despite its cost still it is established as a good option for the approximately 16% of patients that discontinue Azathioprine,[203] but there is importantly the currently on-going CAMARO trial (ClinicalTrials.gov) comparing standard therapy (steroid plus azathioprine) versus steroid plus MMF for treatment naïve patients and anticipate that this will formally answer this question.

Those receiving tacrolimus first-line were younger patients with more severe disease, and although had a high proportion of early deaths, longer-term outcome was not affected. The incidence of side

effects with tacrolimus in other studies of AIH are between 16-30%,[204,205] which is higher than in our cohort.

As well as increased age, the factors associated with treatment response at 6 months were low platelet level and cirrhosis at presentation, whilst this study found a 57% and 48% reduced likelihood of having a normal ALT by 6 months, this is contrary to a report from one single centre; where no significant relationship was found, but there was an association with low platelet level. [26] However, a more recent study, including more patients also found, like this study, that cirrhosis was associated with attainment of remission.[167]

Only just over one-third of patients were in histological remission on follow-up biopsy despite normalising transaminases. It is perhaps relevant that time in remission and serum ALT on the day of biopsy was not evaluated, which may have influenced interpretation histological remission lags behind biochemical remission as. Histological remission is however, important because it has been linked with both all-cause and liver related adverse outcome. [117]

Like some, [127,182,206] but not all,[206] this study found younger age to be linked to relapse. However, the present study found cirrhosis at presentation was associated with a reduced likelihood of relapse but other studies have found no association but many of these were in the context of treatment withdrawal. [127,207,208] It is unclear why this is the case but adherence to treatment specifically was not assessed and one postulates that this could be a confounding factor in these groups. Multiple relapses compared to patients having one or zero relapses was associated with the development of de-novo cirrhosis corroborating others findings, although this data did not observe an effect on mortality as others have found, which may be due to this cohorts median follow-up time.[23,172]

Subsequent cirrhosis development during follow-up independently predicted poor outcome (all-cause and liver-related) was similar to others findings.[23,172] Male gender, low platelets and low serum albumin at diagnosis were associated with an increased risk of developing de-novo cirrhosis. The latter two parameters are unsurprising but raise the question as to whether the patients had cirrhosis at baseline, despite reassuring liver biopsies. The impact of gender on overall outcome has been investigated by one other UK centre but they did not examine whether gender had any association with de-novo cirrhosis. [111]

Although there was an observed variation in treatment strategies for patients attending DGH's, namely a reduced likelihood of receiving corticosteroid therapy, less likely to receive Budesonide or SSA's and a delay in SSA initiation, there was no impact on overall mortality.

7.6 Conclusions

In this considerably large cohort of patients with AIH, which is probably representative of AIH, demographics which were independent predictors of all-cause mortality include age, black ethnicity and co-morbidity. Serum bilirubin and platelets and markers of disease severity such as cirrhosis or decompensation at presentation predicted both all-cause and liver-related mortality or transplantation. This can be taken into consideration when clinically treating these patients. Overall all-cause and liver-related outcome is marginally better than might be expected in this large multi-centre cohort with the only limitations of this data being the probable incomplete capture and the shorter median length of follow-up than other studies.

Failure to receive corticosteroids and failure to receive SSA are independently associated with adverse outcome which underlines their usefulness in the clinical treatment of AIH. Given the finding that even when early events are excluded those not receiving steroids had a higher risk of liver-related mortality and transplantation, where reasoning is unclear, these results underline the point that in the absence of contraindications (sepsis or uncontrolled diabetes; which are treatable and usually temporary) corticosteroids should always be offered to patients with AIH.

Initially high dosages of prednisolone used in treatment of AIH have a 2-fold increased risk of all-cause death or transplantation and is associated with development of diabetes, therefore caution should be used when considering dosing regimens.

Type of steroid used does not affect overall outcome, although needs to be carefully interpreted in this cohort as it tended to be used in less severe disease. Budesonide was used in 5% of patients receiving steroids and was commonly used in patients with cirrhosis and although numbers were small, these patients did not achieve normal ALT's at 6 months as often which supports its reduced efficacy in this cohort and thus emphasises the lack of evidence for its use in these patients.

Increased age was positively associated with achieving normal ALT at 6 months, whereas cirrhosis and low platelets at baseline associated with reduced likelihood of attaining complete biochemical remission. Unlike other studies relapse was not an independent predictor of outcome. [23,171,172] De-

novo cirrhosis independently predicted poor outcome but another new finding was that male gender, as well as low platelets and low albumin were associated with its development.

Serum ALT at 28 days and at 3 months was independently predictive of LRD or transplant and for ACD/transplant only 28 day ALT, so this could be used as a prognosticator in clinical practice. Despite guidelines suggesting that steroids should continue for one to two years we found there to be a lack of evidence for long duration of steroids.

We observed differences in treatment strategies between those attending DGH's and UH's and although patients have similar outcome they appear to be treated less often with steroids and SSA's and do not normalise ALT levels as quickly. The impact of this on longer-term outcome is at this point unknown but one hopes that dissemination of this information will lead to improvement in standards of care in these hospitals.

Chapter 8: Provision and standards of care for treatment and follow-up of patients with Autoimmune Hepatitis- UK multicentre Audit

8.1 Introduction

Although considered a rare disease, AIH has a prevalence and incidence in Western Europe of 24/100,000 and 1.7/100,000 respectively, [8,12,14] equivalent to a UK District General Hospital serving approximately 250,000 people, having about 60 patients with AIH attending it, and seeing 4-5 new patients per year. AIH is usually a life-long disease, which even with standard treatment can result in progressive liver disease and excess mortality.[23,112,113] AIH is thus a substantial health burden in the UK but there is variation in care, facilities and in opinion regarding management. [164,175,209]
Here, we report on the available resources and on adherence to the pre-agreed management standards in participating centres.

8.2 Aim

To undertake an Audit of service provision for and care of AIH in 28 UK hospitals.

8.3 Methods:

We arrived at our audit standards based on the 2012 meeting and on the (then) recently published AASLD and BSG Guidelines,[1,86] and these are detailed in Chapter 1 and in Table 1.2.

Audit design, conduct, case capture and validation are discussed in detail in earlier chapters (Chapters 2, 3, 4 and 5). Centres provided information about staffing, infrastructure and patient management via the encrypted web-based data collection tool (See Appendix A and C).

Results, unless stated otherwise, are expressed as median (range). Z test was used to calculate proportional differences and Mann-Whitney U test used for non-parametric independent samples. $p<0.05$ was considered statistically significant.

Hepatologists were defined as consultants with >70% of their workload being liver disease. Gastroenterologists with an interest in hepatology (GIH) were defined as 40-70% of workload being liver disease.

8.4 Results

8.4.1 Resources

Of 28 centres, 14 classified themselves as District General Hospitals (DGH's); 9 with >500 beds, and 14 as University Hospitals (UH's); all with >500 beds. Sixteen hospitals accepted Hepatology referrals from other hospitals.

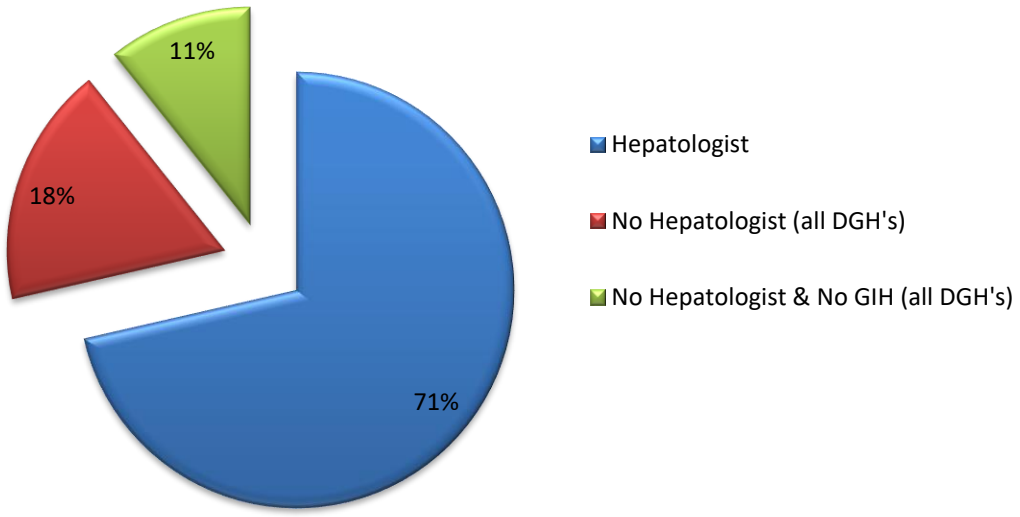
Hospitals had a median (range) of 8(3-23) Consultant Gastroenterologists. Of these, 3(0-10) were Hepatologists, and more prevalent in UH's than DGH's (Table 8.1). There were 0(0-4) Gastroenterologists per hospital who had an interest in Hepatology (GIH) and these were more prevalent in DGH's.

Table 8.1: Staffing and infrastructure

	No of Hepatologists	No of GIH	No of specialist nurses	No of liver specialist nurses	Histopathologist with Liver specialist interest %	Clinical Histopathology meeting %
	Median (range)					
DGH (n=14)	0(0-2)	1(0-4)	2(0-4)	0.5(0-3)	35	57
UH (n=14)	3(1-10)	0(0-3)	6(2-16)	2.5(0-7)	86	86
P value	**<0.001**	**0.04**	**<0.001**	**0.002**	**0.006**	**0.09**

Eight hospitals (29%), all DGHs, had no Hepatologist and three (11%) had neither a Hepatologist nor a GIH (Figure 8.1). Across all hospitals, the number of Consultant Gastroenterologists who managed patients with AIH per hospital was 3(0-10) with only 30% having an interest in Hepatology, and the number of Hepatologists managing AIH was 2(0-10). Overall, 18% (n=234) of patients were being managed in a hospital without a Hepatologist.

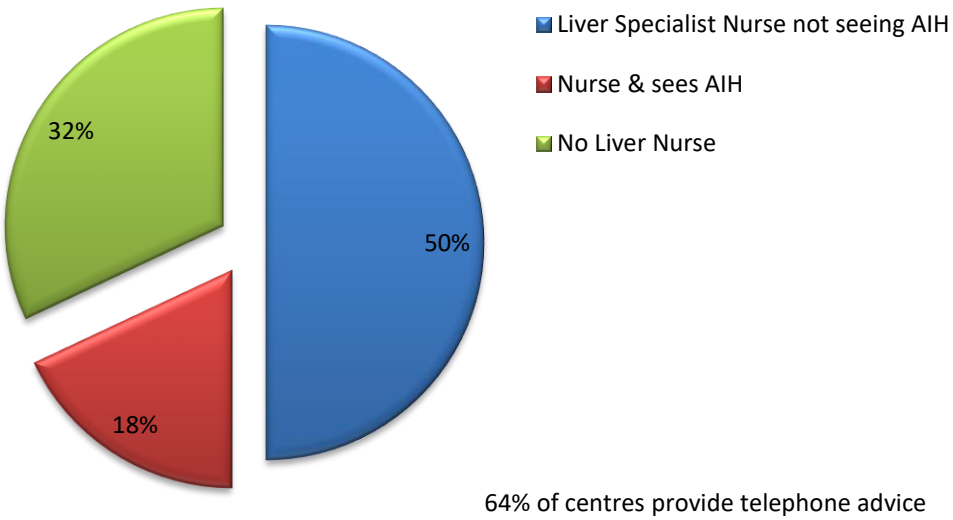
Figure 8.1: Number of Hepatologists



The percentage of all the Consultants in each hospital who managed AIH was 50(18-100%). This was higher in DGH's than in UH's: 92(20-100%) vs 46(17-100%); p=0.051 (two-tailed Mann-Whitney U test). In eight hospitals all of the resident Gastroenterologists and Hepatologists managed AIH.

Nineteen hospitals (68%) had 1(1-7) specialist nurse's managing mainly liver disease and 9 hospitals (7 were DGH's) had no liver nurses (Figure 8.2). However, in only five (18%) hospitals (2 DGH's) did specialist nurses see patients with AIH.

Figure 8.2: Specialist nurse provision



64% of centres provide telephone advice

Seventeen hospitals (61%) had at least one Histopathologist with an interest in liver disease. There was a significantly higher proportion of these in UH's (Table 8.1). These specialists were more likely to report rosettes on liver biopsy (172/834 (21%) versus 50/378 (13%); p=0.002). 20 hospitals (71%) had a joint clinical-pathological meeting, with a higher proportion of meetings occurring in UH's (Table 8.1).

Thirteen hospitals (46%) indicated that they provided hospital patient information sheets and four (14%) had departmental guidelines for the management of AIH. Ten (36%) had a pre-existing database of patients with AIH prior to the Audit.

8.4.2 Standards

8.4.2.1 Overall cohort

We included 1267 patient cases of AIH, with a median follow-up of 3.8(0-15) years. A summary of the results of performance against agreed audit standards (a-h) are shown in Table 8.2.

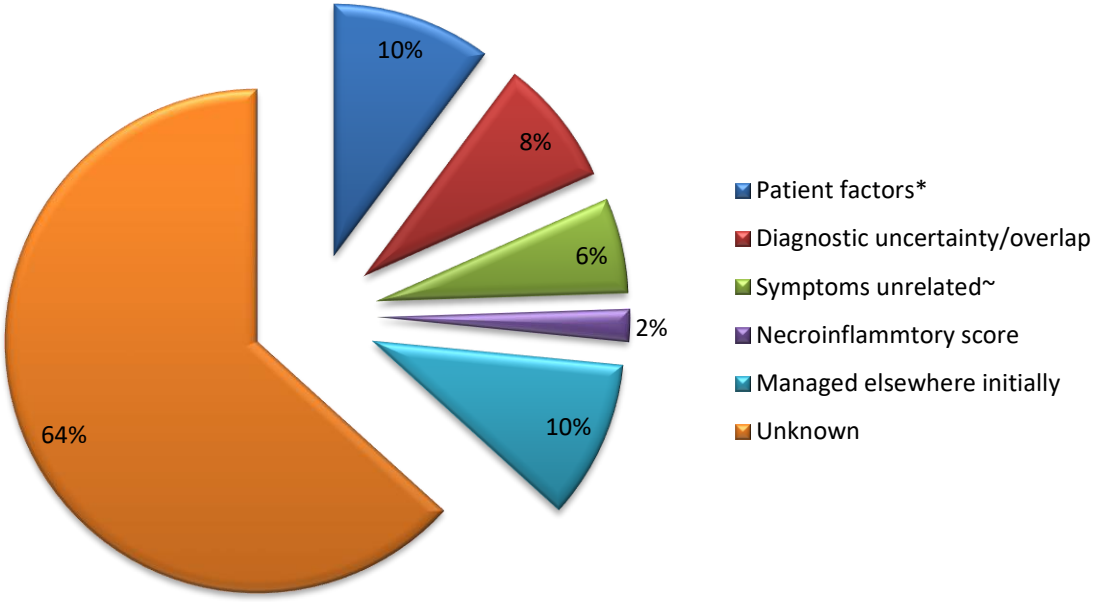
Table 8.2: Performance against standards in the overall cohort

Audit Standard	All cases %	Standard met	% in individual centres (median(range)	No of Centres meeting standard (%)
Treatment				
a) ≥90% of symptomatic patients start prednisolone~ within 4 months of diagnosis	92	✓	92 (33-100)	19 (68)
b) ≥90% steroids continued ≥1 year	73	×	78 (33-92)	3 (11)
c) ≥80% appropriate blood monitoring+	74	×	79 (3-100)	14 (50)
d) ≥90% attain normal serum ALT by 1 year after start of treatment**	86	×	89 (33-98)	10 (36)
e) ≥80% clinically decompensated patients¥ who did not improve on treatment were discussed with a transplant team	95	✓	100 (0-100)	24 (96)^
Follow-up				
f) ≥60% of those re-biopsied attain histological remission	37	×	35 (0-70)	2 (8)^
g) ≥75% do not develop de-novo cirrhosis	92	✓	96 (80-100)	28 (100)
h) <21% new decompensation¥	7	✓	3 (0-10)	28 (100)

~or equivalent (Budesonide/methylprednisolone or hydrocortisone).
+Liver Blood tests documented at 3, 6 & 12 months adjusted for length of follow-up for the first year.
**In those with ≥12months follow up after treatment started & date of first normal ALT is known.
¥Ascites, encephalopathy or variceal bleed.
^25 of 28 centres had decompensated patients or performed follow-up liver biopsies.

The median time to treatment from diagnosis (defined as date of liver biopsy) in patients symptomatic at presentation was 0(0-92) months. Fifty-nine of 877 (7%) symptomatic patients were not treated with prednisolone or its equivalent, within four months (Standard a). The reasons why are shown in Figure 8.3.

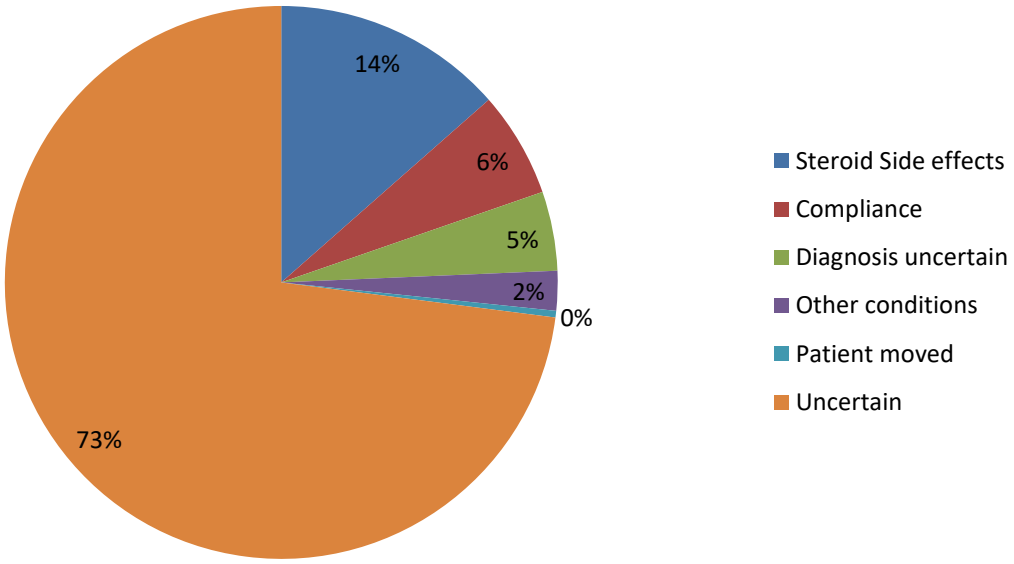
Figure 8.3: Reasons why patients were not treated within 4 months of presenting symptoms



*Patient wishes or obesity, ~clinician determined

Of the 955 patients who received steroids (duration known) and who were followed up for at least 12 months, steroids were continued for less than 12 months in 259 patients (failing to meet Standard b). The reasons are shown in Figure 8.4. In those patients stopping steroids for uncertain reasons; 138 of 189 (73%) had normalised transaminases within a median 1(0-9) months. Of 236 cases (where steroid duration known), 49 (21%) had not normalised their ALT prior to stopping.

Figure 8.4: Reasons why Prednisolone stopped before one year



Monitoring of liver blood tests (defined as checked and recorded after 3, 6 and 12 months on treatment was inadequate in 26% of patients (failing to meet Standard c), with 50% of hospitals failing to meet the standard of ≥80% of patients with adequate monitoring, and three hospitals achieving adequate monitoring in less than 10% of their patients.

Of 973 patients followed up for at least 12 months, and in whom date of first normal ALT was known, 134 (14%) did not achieve normal serum ALT by 1 year after starting treatment (failing to meet Standard d). Only 10 of the 28 centres met the 90% standard and in 2 (7%) centres the percentage was less than 50%.

Standard e: 'Decompensated cases were discussed with transplant team, where appropriate', was met in the cohort as a whole. Of 150 (12%) patients who were clinically decompensated (ascites/oedema, variceal bleed or encephalopathy) either at presentation, or during follow-up; 45 (30%) cases were discussed with or referred to a transplant team. A total of 105 cases were not discussed and there are additional data presented in Table 8.3 which demonstrate the demographic details of patients; 57 (38%) had significant co-morbidities and 6 (4%) were non-compliant or had excess alcohol consumption. There were 42 (28%) in whom there was no stated reason for non-referral. Of these, seven patients did not improve on treatment: One of whom who had decompensation at presentation died of liver failure and a further six developed decompensation whilst on treatment; one of whom died from liver failure. Of the remaining 35 patients, one patient died from non-liver causes and four did not achieve normal serum transaminases (although serum but bilirubin normalised and albumin was normal or increasing on treatment) and the remaining 30 remaining patients normalised transaminases (only one patient had minimally elevated bilirubin at 47) indicating improvement on treatment.

Table 8.3: Characteristics of patients not referred to transplant team (n=105)

Category	Age >70 years	Co-morbidities	Non-compliant	Alcohol excess	Reason unknown
Not referred	26	31	4	2	42

Of 333 patients who underwent a follow-up liver biopsy, 103 (37%) of 282 patient cases (where necroinflammatory score recorded) were in remission (NIS ≤ 3) with wide variation between centres median 35% (0-70) rates of remission (Standard f).

Only 8% of patients developed new cirrhosis during follow-up, with all centres meeting standard h. Only 7 percent of patients developed liver decompensation during follow-up, meeting standard in all centres (Standard g).

8.4.2.2 Sub-group comparisons and attainment of standards:

Patients were more likely to receive SSAs for >2 years in the 14 UHs, compared to those attending the 14 DGHs (Table 8.4). This difference was also seen in hospitals with a Specialist Liver Nurse (n=23), in those with a Hepatologist (n=19), and those hospitals with complete case capture (n=4) achieved[14] (compared to those without) (Table 8.5, Table 8.6 and Table 8.7 respectively). Patients attending a hospital with a Specialist Liver nurse also received steroids for longer; (82 vs 77%; p=0.001) (Table 8.5). Hospitals without a Hepatologist and those without complete case capture were less likely to have blood monitoring (69% vs 75%; p=0.04 and 69% vs 86%; p=<0.001. However, there were no other differences between these different types of hospitals in regard to meeting of standards.

Table 8.4: Standards in University hospitals (n=830 cases) versus District General Hospitals (n=437 cases)

Standard	UH's n (%)	Standard met	DGH's n (%)	Standard met	p value
a) ≥90% of symptomatic patients start prednisolone~ within 4 months of diagnosis	540/593 (95)	✓	258/284 (91)	✓	0.9
b) ≥90% Steroids continued ≥1 year*	495/658 (75)	✗	250/341 (73)	✗	0.51
c) ≥80% adequate blood monitoring[++]	560/744 (75)	✗	280/389 (72)	✗	0.23
d) ≥90% attain normal serum ALT at 1 year treatment**	598/716 (84)	✗	281/360 (78)	✗	0.02
e) ≥80% clinically decompensated patients[¥] who did not improve on treatment were discussed with a transplant team	103/108 (95)	✓	40/42 (95)	✓	0.97
f) ≥60% of those re-biopsied attain histological remission***	69/195 (35)	✗	34/74 (46)	✗	0.11
g) ≥75% do not develop de-novo cirrhosis	571/617 (93)	✓	308/334 (92)	✓	0.89
h) ≤21% new clinical decompensation	32/754 (4)	✓	10/405 (2.5)	✓	0.12

~or equivalent (Budesonide/methylprednisolone/hydrocortisone) as proportion of symptomatic patients.
*In those followed up ≥1 year.
[+]Liver Blood tests documented at 3 months, 6 months & 12 months adjusted for length of follow-up.
***In those with ≥12months follow up after treatment started & date of first normal ALT is known.
Follow-up biopsy NIS available in 74 (of 86) and 195 (of 247) DGH and UH biopsies respectively.

Table 8.5: Centres with specialist nurses seeing patients (n=5) versus those without (n=23).

	Sp Nurse sees pts n=400 n (%)	Standard met	No Sp nurse seeing pts n=1148 n (%)	Standard met	p value
a) ≥90% of symptomatic patients start prednisolone˜ within 4 months of diagnosis	275/291 (95)	✓	543/586 (93)	✓	0.3
b) ≥90% Steroids continued ≥1 year*	239/293 (83)	×	506/707 (77)	×	0.001
c) ≥80% had appropriate blood monitoring++	239/347 (69)	×	601/786 (76)	×	0.007
d) ≥90% attain normal serum ALT at 1 year treatment***	250/298 (84)	×	589/693 (85)	×	0.66
e) ≥80% clinically decompensated patients¥ who did not improve on treatment were discussed with a transplant team	45/48 (94)	✓	96/102 (94)	✓	0.93
f) ≥60% of those re-biopsied attain histological remission	49/123 (40)	×	54/148 (36)	×	0.6
g) ≥75% do not develop de-novo cirrhosis	276/302 (91)	✓	596/648 (92)	✓	0.76
h) New decompensation during follow-up (<21%)	30/400 (8)	✓	57/867 (7)	✓	0.54

˜or equivalent (Budesonide/methylprednisolone/hydrocortisone) as proportion of symptomatic patients.
*In those followed up ≥1 year.
++Liver Blood tests documented at 3 months, 6 months & 12 months adjusted for length of follow-up.
***In those with ≥12months follow up after treatment started & date of first normal ALT is known.

Table 8.6: Centres with a Hepatologist (n=20) versus those without a Hepatologist (n=8)

	Hepatologist n=1033 patients n (%)	Standard met	No Hepatologist n=234 patients n (%)	Standard met	p value
a) ≥90% of symptomatic patients start prednisolone˜ within 4 months of diagnosis	675/722 (93)	✓	143/155 (92)	✓	0.58
b) ≥90% Steroids continued ≥1 year*	712/820 (75)	×	133/180 (74)	×	0.83
c) ≥80% had appropriate blood monitoring⁺⁺	694/920 (75)	×	146/213 (69)	×	0.04
d) ≥90% attain normal serum ALT at 1 year treatment***	684/794 (86)	×	155/179 (87)	×	0.87
e) ≥80% clinically decompensated patients¥ who did not improve on treatment were discussed with a transplant team	122/130 (94)	✓	19/20 (95)	✓	0.84
f) ≥60% of those re-biopsied attain histological remission	78/230 (34)	×	25/53 (47)	×	0.07
g) ≥75% do not develop de-novo cirrhosis	694/761 (91)	✓	178/189 (94)	✓	0.18
h) New decompensation during follow-up (<21%)	66/1033	✓	21/234 (9)	✓	0.27

˜or equivalent (Budesonide/methylprednisolone/hydrocortisone) as proportion of symptomatic patients.
*In those followed up ≥1 year.
⁺⁺Liver Blood tests documented at 3 months, 6 months & 12 months adjusted for length of follow-up.
***In those with ≥12months follow up after treatment started & date of first normal ALT is known.

Table 8.7: Those attending hospitals with complete capture (n=4) versus those with likely incomplete capture (n=24)

	Complete capture n=356 n (%)	Standard met	Incomplete capture n=911 n (%)	Standard met	p value
a) ≥90% of symptomatic patients start prednisolone˜ within 4 months of diagnosis	228/238 (96)	✓	590/639 (92)	✓	0.07
b) ≥90% Steroids continued ≥1 year*	218/281 (78)	×	527/719 (73)	×	0.16
c) ≥80% had appropriate blood monitoring++	272/316 (86)	✓	568/817 (69)	×	<0.001
d) ≥90% attain normal serum ALT at 1 year treatment***	253/275 (92)	✓	586/698 (84)	×	0.001
e) ≥80% clinically decompensated patients¥ who did not improve on treatment were discussed with a transplant team	34/37 (92)	✓	107/113 (95)	✓	0.53
f) ≥60% of those re-biopsied attain histological remission^	52/130 (40)	×	51/151 (33)	×	0.28
g) ≥75% do not develop de-novo cirrhosis	252/274 (92)	✓	620/676 (92)	✓	0.89
h) New decompensation during follow-up (<21%)	19/356 (5)	✓	68/911 (7.5)	✓	0.17

˜or equivalent (Budesonide/methylprednisolone/hydrocortisone) as proportion of symptomatic patients.
*In those followed up ≥1 year.
++Liver Blood tests documented at 3 months, 6 months & 12 months adjusted for length of follow-up.
***In those with ≥12months follow up after treatment started & date of first normal ALT is known.

8.5 Discussion

This is the first multicentre audit of both resources and of adherence to pre-defined standards regarding management of AIH.

Only limited development of sub-specialisation amongst Gastroenterology and Hepatology physicians and nurses in regard to management of AIH was found. Nearly one-third of centres did not employ a Hepatologist. In half of centres (all DGH's), at least half of the Consultants managed AIH, a median of 92% did so. One-third of centres have no Specialist liver nurse and less than 20% have a nurse reviewing patients with AIH. Finally, most hospitals do not have departmental guidelines for AIH. This situation contrasts with that for chronic viral hepatitis. Indeed, the lack of Nurses may result from the lack of funding of Specialist Liver Nurses, which for Hepatitis C has

sometimes been sourced from Pharmaceutical Companies aiming to facilitate drug treatment. Business cases to develop such posts are challenging for rarer diseases such as AIH alone.

Approximately 40% of hospitals did not have a Histopathologist with a specialist interest in liver disease and that these centres were less likely to report rosettes on the liver biopsy report. This underlines our earlier impression[210] that histopathological AIH findings may have been under-reported, which may lead to diagnostic uncertainty.

The majority of hospitals do not have departmental guidelines for AIH, such guidelines might be of benefit, especially to those not coming across cases frequently.

Of the eight pre-defined management standards, five (Table 8.2, standards a,e,g,h were met in the overall patient population; however two of these (a and e) were met only in only 68% and 70% respectively of the individual centres. For Standard (a): 8% of symptomatic patients whose commencement of treatment was delayed by >4 months, it is likely that patient's quality of life was reduced for this period. In most cases the reason for the delay wasn't clear. Standard (e) is based on UK guidelines which state that clinically decompensated patients should be discussed with a transplant teams unless there is a clear contraindication, as this is associated with poor outcome. [1,23,26] Although the pre-defined standard of 80% was met, it is still of concern that 7 of 150 with decompensation, which did not apparently improve with treatment, were not discussed with a transplant centre, despite being apparently eligible (based on age and absence of stated comorbidity).

The other four pre-defined standards (Table 8.2: b-d and f) were not met in the overall patient cohort and in 14-26 of the 28 centres. In one-quarter of cases, steroids were discontinued after less than 12 months; reasons provided included side effects, compliance and uncertain diagnosis but in over 70% of patients, the reason was unclear. The case for continuing steroid therapy for more than 1 year is based on fact that histological remission lags behind biochemical remission by about six months and is achieved by only half of patients after a year.[1] Histological activity may persist even in patients who achieve biochemical normalisation and is associated with failure of fibrosis regression and reduced long-term survival. [117] However, it remains unproven that longer duration of corticosteroid therapy is associated with improved longer-term outcome.[23,207] Therefore it is debatable that this should be accounted for when considering treatment withdrawal.

Patients on Thiopurines and other immunosuppressive drugs need to have blood tests monitored at least every three months.[1] This is because of their often narrow therapeutic index and the potential of haematological, renal and hepatic impairment, especially in those with pre-existing dysfunction, and in elderly patients. Our results suggest that 50% of centres fall short of this with a wide variation in monitoring practice shown by the range of percentages (3-100%) with adequate liver test monitoring. We did not ascertain whether patients not having liver tests checked had renal function and full blood count monitoring was not examined, but this seems unlikely.

Recently published data suggest that remission rates were poorer in non-transplant centres (55% versus 62%). [211] However, when we compared DGH's to UH's we did not find significantly reduced rates of biochemical remission at 1 year (both 86%, p=0.73).

A greater percentage of patient cases met minimum standards in centres we believe to have full capture compared to those who did not search all modalities (coding, histology, electronic databases and clinical letters). However, the presence of complete case capture did not have any overall impact on attainment of standards apart from blood monitoring, arguing against any case selection bias by centres.

8.6 Conclusions

This study shows that there is wide variability in service provision for AIH across hospitals in the UK, with better staffing of specialist Physicians, Histopathologists and nurses at University Hospitals than DGH's. In many hospitals, AIH is managed by a larger number of Physicians than seems necessary and there is a case for having patients with AIH under the care of a limited number of designated Physicians (either Gastroenterologists or Hepatologists).

Furthermore, several of our pre-defined management standards were not met; either in the overall cohort of patients or in most of the individual centres. Whilst the importance of some of the standards in regard to patient outcome could be debated (for example, duration of steroid therapy), the >4 month delay in starting treatment (albeit only in 7% of patients, widespread failure to meet blood monitoring standards and the failure to discuss some apparently eligible patients with liver decompensation with transplant teams, are of some concern. This study was unable to show widespread differences between different types of hospital regarding meeting standards. Finally, we show that Histopathologists with a specialist interest in liver disease improve reporting at least some histological findings associated with AIH.

These findings support the case for improved liaison between services, such as monthly histopathology review (ideally via hospital link/teleconference); which would encourage discussion of clinical cases, pool experience, provide training and encourage adherence to guidelines. All of which are likely to improve patient care.

Finally, it is hoped that participation in this audit will encourage improvements in care for patients with AIH, who will likely benefit from being part of an audit database in their home centre, which will allow monitoring of their case (such a database pre-existed in only 10 of the 28 centres). The database should also assist in business case planning for more resource provision.

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Appendix A: Electronic data-entry proforma used on Formic platform

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

MULTI-CENTRE AUDIT OF MANAGEMENT AND OUTCOME OF AUTOIMMUNE HEPATITIS

Please allocate your patient a unique audit number and keep a record of this number with patients name and hospital number in a safe place (as you will be the only person with the key to this).

Unique Patient audit number:

Todays Date

D	D	/	M	M	/	Y	Y	Y	Y
		/			/				

Autoimmune Hepatitis Case Validation

HBVsAg and HCV

- ☐ One is Positive **(Exclude immediately if HBV or HCV positive)**
- ☐ Both negative **(score 3)**
- ☐ Results not available for either HBV/HCV **(score 0)**
- ☐ (If acute HAV, HEV,EBV or CMV (IGM) positive) **(score minus 3)**
  - pls record which at end of form

Score for Virology ☐

Female ☐ Yes **(score 2)** ☐ No **(score zero)**

Score for Gender ☐

Date of Initial Liver Biopsy

D D / M M / Y Y Y Y

Liver Biopsy

- ☐ Not Done **(score zero)**
- ☐ Done but result inaccessible **(score zero)**
- ☐ Interface Hepatitis or piecemeal necrosis **(score 3)**
- ☐ Mainly lymphocytes and/or plasma cells **(score 1)**
- ☐ Rosettes **(score 1)**
- ☐ Emperipolesis (intact cell within the cytoplasm of another cell **(no score added)**
- ☐ None of the above **(score minus 5)**
- ☐ Bile duct changes **(score minus 3)**
- ☐ Granuloma **(score minus 3)**
- ☐ More than mild steatosis (fat):pre treatment only **(score minus 3)**
- ☐ Other changes (other *prominent* feature suggesting alternate aetiology) **(score minus 3)**

Score for Biopsy ☐☐

Ishak fibrosis score (0-6) ☐ **Ishak Necroinflammatory Score (0-18)** ☐ OR

- ☐ Minimal
- ☐ Mild
- ☐ Moderate
- ☐ Severe

Cirrhosis ☐ Yes ☐ No

Highest Serum IgG (or Globulin if no IgG)

- ☐ >2 times upper limit of normal (ULN) **(score 3)**
- ☐ 1.5-2.0 times ULN **(score 2)**
- ☐ 1.0-1.5 times ULN **(score 1)**
- ☐ < ULN or not done **(score zero)**

Score for IgG/Globulins ☐

Anti-nuclear,anti-smooth muscle or anti-LKM-1 Ab titre

- ☐ >1:80 **(score 3)**
- ☐ 1:80 **(score 2)**
- ☐ Titre unspecified or 1:40 **(score 1)**
- ☐ Not done, weak positive or <1:40, negative **(score zero)**

Score for Autoantibodies ☐

Anti-mitochondrial Antibody

- ☐ Negative or not done **(score zero)**
- ☐ Weak Positive or >1:40 **(score minus 4)**

Score for AMA ☐☐

Alkaline Phosphatase to ALT ratio: which is ((ALP/ULN ALP) divided by (ALT/ALT ULN)

- ☐ <1.5 **(score 2)**
- ☐ 1.5-3.0/normal enzymes **(score zero)**
- ☐ >3.0 **(score minus 2)**

Score for ALP:ALT ratio ☐

Subtotal ☐☐

Alcohol Consumption pre-diagnosis (units/Week)

- ☐ <22 units **(score 2)**
- ☐ 22-52 units or not recorded **(score zero)**
- ☐ >52 units **(score minus 2)**

Score for Alcohol ☐☐

Autoimmune Diseases (see list below and tick all that apply)

- ☐ Past Personal History or Family History of autoimmune disease **(score 2)**
- ☐ No such recorded history **(score zero)**

Score for Autoimmune diseases ☐

Does the Patient have (or their family) a history of autoimmune diseases?

Primary Biliary Cirrhosis (PBC)	☐	Polymyositis	☐
Anti-phospholipid syndrome (APS)	☐	Primary Sclerosing Cholangitis	☐
Coeliac Disease	☐	Psoriasis	☐
Diabetes (type 1)	☐	Rheumatoid Arthritis	☐
Fibrosing alveolitis	☐	Sarcoidosis	☐
Glomerulonephritis	☐	Sjogrens	☐
Haemolytic anaemia	☐	Systemic Lupus Erythematosis (SLE)	☐
Thyroiditis/hypothyroidism	☐	Temporal Arteritis	☐
Inflammatory Bowel Disease	☐	Thombocytopenia	☐
Mixed connective tissue disease	☐	Uveitis	☐
Mononeuritis muliplex	☐	Vitiligo	☐
Muliple Sclerosis (MS)	☐	Family Hx of AIH	☐

Other Autoimmune Disease - please state: ☐

Drug History

- ☐ For the purpose of this scoring system regardless of drug history please tick **(score 1)**

Score for Drug history ☐

Treatment

- ☐ Failure to normalise serum ALT or AST with treatment **(score minus 2)**
- ☐ Not treated **(score zero)**
- ☐ Normalised on treatment **(score zero)**

Score for treatment ☐☐

Relapse

- ☐ Serum ALT or AST >2 times ULN after a prior normal value **(score 1)**
- ☐ No relapse **(score zero)**

Score for Relapse ☐

OVERALL SCORE: ☐☐

If 10 or more please proceed with rest of data entry.
If less than 10 but being treated as AIH then also proceed.
If less than 10 otherwise please exclude

Drugs patient on at time of diagnosis - please tick all that apply - please record other drugs patient is on in free text at the end of the whole web-form

	Y	N
Nitrofurantoin	☐	☐
Minocycline	☐	☐
Infliximab	☐	☐
Interferon	☐	☐
Khat or Qat	☐	☐

Other Autoantibodies

	Positive	Negative	Not done
Anti-SLA	☐	☐	☐
Anti-ASGPR	☐	☐	☐
Anti-LP	☐	☐	☐
Anti-sulfatide	☐	☐	☐
Anti-LC1	☐	☐	☐
HLA-DR3	☐	☐	☐
HLA-DR4	☐	☐	☐
p-ANCA	☐	☐	☐

Date Of Diagnosis
(Defined as: Date of diagnostic Biopsy or if no biopsy then date of commencing steroids; if no biopsy and no treatment then discuss with coordinator)

D D / M M / Y Y Y Y

Ethnic Group

Also managed at another centre ☐ **Enter which centre here**

1. DEMOGRAPHICS and CO-MORBIDITY (give year of diagnosis if known)

Age at diagnosis

Height (cm)
(Any documented height after age 20ys if pt is over this age)

Weight at diagnosis (Kg) . **Smoker** Yes ☐ Ex ☐ Never ☐ Not documented ☐

	Y	N	Year diagnosed
Diabetes	☐	☐	
Chronic Lung Disease	☐	☐	
Cerebrovascular Disease	☐	☐	

	Y	N	Year diagnosed
PBC	☐	☐	
PSC	☐	☐	
Cancer	☐	☐	
Heart Disease (ischaemic)	☐	☐	
Heart Disease (not ischaemic)	☐	☐	

2. PRESENTING FEATURES

☐ Jaundice/itching ☐ Joint aches ☐ Amenorrhoea

☐ Weight loss ☐ Rash ☐ Flu-like symptoms

☐ Nausea ☐ Fatigue ☐ Asymptomatic

Other:

Date of First Abnormal LFT's: / /

3. SEVERITY INDICES (at presentation) : tick N if not evident or not assessed

Cirrhosis/Portal Hypertension

	Y	N
Varices on imaging	☐	☐
Varices on endoscopy	☐	☐
Fibroscan score cirrhotic	☐	☐

Other evidence:

	Y	N
Ascites	☐	☐
Oedema	☐	☐
Encephalopathy	☐	☐
MELD >15 (calculator available - click on right)	☐	☐
Variceal Bleed	☐	☐
Hepatocellular Carcinoma	☐	☐

4. FOLLOW-UP BIOPSY

Follow-up Biopsy Done? ☐ Y ☐ N

1st follow-up biopsy date: / /

Ishak Necroinflammatory Score (0-18)

OR ☐ Minimal ☐ Mild ☐ Moderate ☐ Severe

Ishak fibrosis score (0-6)

2nd follow-up biopsy date: / /

Ishak Necroinflammatory Score (0-18)

OR ☐ Minimal ☐ Mild ☐ Moderate ☐ Severe

Ishak fibrosis score (0-6)

5. PREGNANCY

Number of Pregnancies

Relapse during pregnancy ☐ Y ☐ N **Date:** / /

Number of births

Relapse after pregnancy ☐ Y ☐ N **Date:** / /

6. SUBSEQUENT FIRST DEVELOPMENT OF COMPLICATIONS

	Y	N	Month/Year		Y	N	Month/Year
New Cirrhosis	☐	☐	/	Variceal Bleed	☐	☐	/
Follow-up liver biopsy indicates cirrhosis	☐	☐	/	Ascites/Oedema	☐	☐	/
Varices (on imaging or endoscopy)	☐	☐	/	Encephalopathy	☐	☐	/
Fibroscan score indicates cirrhosis	☐	☐	/	MELD >15	☐	☐	/
other evidence of cirrhosis				Albumin <30 g/L for >4 weeks	☐	☐	/
				Hepatoma	☐	☐	/
Portal vein thrombosis ☐ Y ☐ N			Month/Year /	Hepatopulmonary Syndrome	☐	☐	/

7. SUBSEQUENT HOSPITAL EPISODES RELATED TO LIVER DISEASE (please also record if admitted at index presentation and why)

Number	Dates	Reasons
☐☐	☐☐/☐☐/☐☐☐☐	
☐☐	☐☐/☐☐/☐☐☐☐	
☐☐	☐☐/☐☐/☐☐☐☐	
☐☐	☐☐/☐☐/☐☐☐☐	

8. DEVELOPMENT OF OTHER LIVER DISEASE

PBC Y ☐ N ☐ **PBC Basis** AMA Positive ☐ Biopsy ☐ Month/Year ☐☐/☐☐

NAFLD Y ☐ N ☐ **NAFLD Basis** Imaging ☐ Biopsy ☐ Month/Year ☐☐/☐☐

PSC Y ☐ N ☐ **PSC Basis** Imaging ☐ Biopsy ☐ ☐☐/☐☐

Other liver disease and basis

9. LATEST RECORDED STATUS

Died: Y ☐ N ☐ Date Died ☐☐/☐☐/☐☐☐☐

If Cancer specify type here:

Cause of death:

- Liver failure ☐
- Variceal bleed ☐
- Hepatoma ☐
- Extra Hepatic Cancer ☐
- Other cause ☐

If other cause of death specify here:

	Y	N	Date last known to have attended or had bld test
Still attending	☐	☐	☐☐/☐☐/☐☐☐☐
Moved or defaulted	☐	☐	☐☐/☐☐/☐☐☐☐
Discharged	☐	☐	☐☐/☐☐/☐☐☐☐

10. REFERRAL FOR TRANSPLANTATION?

Not referred ☐

Reason why not referred (tick all that apply)

- Not needed ☐
- Co-morbidity ☐
- Not stated ☐

Referred ☐

	Y	N
Documented discussion with transplant centre	☐	☐
Assessment pending	☐	☐
Accepted/awaiting/done	☐	☐
Not accepted	☐	☐

Reason not accepted

- Not needed ☐
- Co-morbidity ☐
- Not stated ☐

Please enter transplant date at end of form.

FLOW CHART FOR LIVER TESTS

Date treatment started ☐☐/☐☐/☐☐☐☐ **tick if not NOT treated** ☐

BASELINE BLOOD TESTS

	Month/Year	ALT	AST	Bili	Alb (g/L)	Creat	Glob (g/L)	IgG	PT	INR
First Available	☐☐/☐☐							☐☐.☐	☐☐.☐	☐☐.☐
Peak Values (ALT/AST)	☐☐/☐☐							☐☐.☐	☐☐.☐	☐☐.☐

	Month/Year	**ALT**	**AST**	**Bili**	**platelets**	**Smooth Musc Ab**	**ANA**	**LKM-1 Ab**
Values at start of treatment	☐☐/☐☐							

(or last values recorded if not treated)

Date of First normal (ALT and/or AST) ☐☐/☐☐/☐☐ **ALT** **AST** **Bili**

tick if Tranaminases DID NOT normalise ☐

ONGOING MONITORING *** = nearest date possibly within reason**

	Month/Year	ALT	AST	Bili	Alb	Glob	IgG	PT	INR
Day 7*	☐☐/☐☐						☐☐.☐	☐☐.☐	☐☐.☐
Day 28*	☐☐/☐☐						☐☐.☐	☐☐.☐	☐☐.☐
Month 3	☐☐/☐☐						☐☐.☐	☐☐.☐	☐☐.☐
Month 6	☐☐/☐☐						☐☐.☐	☐☐.☐	☐☐.☐
1 year	☐☐/☐☐						☐☐.☐	☐☐.☐	☐☐.☐

For each parameter tick if abnormal at least once during year

	Month/Year	ALT	AST	Glob	IgG	PT	INR
2nd Year	☐☐/☐☐	☐	☐	☐	☐	☐	☐
3rd Year	☐☐/☐☐	☐	☐	☐	☐	☐	☐
4th Year	☐☐/☐☐	☐	☐	☐	☐	☐	☐
5th Year	☐☐/☐☐	☐	☐	☐	☐	☐	☐
6th Year	☐☐/☐☐	☐	☐	☐	☐	☐	☐
7th Year	☐☐/☐☐	☐	☐	☐	☐	☐	☐
8th Year	☐☐/☐☐	☐	☐	☐	☐	☐	☐

RELAPSES:
Document all relapses as ALT or AST rising to > twice upper normal limit from prior normal. Date of relapse = date of first abnormal AST or ALT

	Month/Year	First abnom ALT or AST	Peak ALT	Peak AST	Bili	IgG
Relapse 1	☐☐/☐☐					☐☐.☐
Relapse 2	☐☐/☐☐					☐☐.☐
Relapse 3	☐☐/☐☐					☐☐.☐
Relapse 4	☐☐/☐☐					☐☐.☐
Relapse 5	☐☐/☐☐					☐☐.☐

FLOW CHART FOR DRUG THERAPY

Date started or dose changed	STEROID	Dose (mg)	Steroid sparing or other agent	Dose (mg)	Patient weight (nearest Kg)
/ /					

Overall length of steroid treatment since intially starting (in months)
Put zero if not treated

DRUG TOXICITY **(tick if occurred and state month after starting when side effect occurred).**

STEROIDS

	Month
☐ Psychosis	
☐ Diabetes (onset during treatment	
☐ low trauma fracture	
☐ Other	

Please specify if other:

☐ **Azathioprine** ☐ **6MP** ☐ **MMF**

	Month
☐ White cell count <2.5 (and fall of >1.0)	
☐ Pancreatitis	
☐ Other	

Please specify if other:

1. Please enter the **drugs patients were on** at the time of diagnosis (no doses necessary)
2. You can add any other **clinically relevant information** which has not previously been included.
3. Please record here any problems with **compliance.**

Appendix B: Initial Paper Clinical Proforma

Please fill **all** fields; tick for yes and cross for no (or circle)

Date of Diagnosis: **Ethnic Group:**

(Defined as: Date of diagnostic biopsy or if no biopsy then date of commencing steroids; if no biopsy and no treatment, discuss with coordinator)

Also managed at another centre ☐ enter which centre here…… Please still enter all info below

1. DEMOGRAPHICS and CO-MORBIDITY (give year of diagnosis if known)

Age at diagnosis:	Height:
Weight at diagnosis:	Smoker: Yes ☐ Ex- ☐ or Never☐

	Y	N	Year		Y	N	Year
Diabetes				PBC or PSC (specify):			
Chronic lung disease				Cancer (specify):			
Cerebrovascular disease				Heart disease: • Ischaemic • Other (specify):			

2. PRESENTING FEATURES:

Jaundice/itching		Rash		Asymptomatic	
Weight Loss		Fatigue		Other:	
Nausea		Amenorrhoea		Date 1st abnormal LFTs:	
Joint aches		'Flu' like symptoms			

3. SEVERITY INDICES (at presentation)

	Y	N		Y	N
Cirrhosis/Portal hypertension: • Varices on imaging • Varices on endoscopy • Fibroscan Score			• Ascites • Oedema • Encephalopathy • MELD>15 • Variceal bleed • Hepatocellular carcinoma		
Other evidence (specify):					

4. FOLLOW-UP BIOPSY

Follow up Biopsy done?	Y/N		
Follow-up biopsy 1 done (date)		Follow-up biopsy 2 done (date)	
Iskak necroinflammatory score: OR Minimal Mild Mod/severe		Ishak necroinflammatory score: OR Minimal Mild Mod/severe	
Ishak fibrosis score:		Ishak fibrosis score:	

5. PREGNANCY (since diagnosis of AIH)

Number of pregnancies		Relapse during pregnancy	Y ☐ N ☐ Date:

Number of births		Relapse after pregnancy	Y ☐ N ☐ Date:
And Dates if known:			

6. SUBSEQUENT *FIRST* DEVELOPMENT OF COMPLICATIONS (please circle which and state mo and yr)

	Y	Mo/Yr		Y	Mo/Yr
New cirrhosis:	☐		Decompensation:		
• Follow-up liver biopsy (not cirrhotic on prev. biopsy)	☐		• Variceal bleed	☐	
			• Ascites/oedema	☐	
• Varices (imaging/endoscopy)	☐		• Encephalopathy	☐	
• Fibroscan score	☐		• MELD score >15	☐	
			• Albumin<30 g/L for >4 wks	☐	
			Hepatoma	☐	
Other evidence of cirrhosis (specify):			Hepatopulmonary syndrome	☐	
Portal vein thrombosis ☐			Other Cancers (specify sites):		

7. SUBSEQUENT HOSPITAL EPISODES RELATED TO LIVER DISEASE (excluding day case admissions for liver biopsy)

Number	Dates	Reasons:

8. DEVELOPMENT OF OTHER LIVER DISEASE (please circle and date)

PBC	Basis: AMA +ve or Biopsy	NAFLD	Basis: Imaging/Biopsy
PSC	Basis: Imaging/Biopsy	Other	Basis:

9. LATEST RECORDED STATUS

Died: Y/N date:		If Cancer specify type here:	
Cause of death:		If other cause of death specify:	
• Liver failure	☐		
• Variceal bleed	☐		
• Hepatoma	☐		
• Extra Hepatic cancer	☐		
• Other cause	☐		
		Still attending ☐	Date:
		Moved/defaulted ☐	Date:

10. REFERRAL FOR TRANSPLANTATION? (Please tick appropriate box)

Not referred	☐	Documented discussion with transplant centre	☐
Referred Y ☐ N ☐ date:		Assessment pending	☐
Reason why not referred (tick all that apply):		Accepted, awaiting	☐
• Not needed	Y ☐	Not accepted	☐
• Co-morbidity	Y ☐	Reason not accepted:	
• Not stated	Y ☐	• Not needed	☐
		• Co-morbidity	☐
		• Not stated	☐

FLOW CHART FOR LIVER TESTS

Date treatment started:_____

BASELINE BLOOD TESTS

	Date	ALT	AST	Bili	Alb	Creat	Glob	IgG	PT /INR
First available									
Peak values (ALT/AST)									
Values at start of treatment									
First Normal (ALT and/or AST)									

ONGOING MONITORING
(Give first available *value* within time period)

	Date	ALT	AST	Bili	Alb	Glob	IgG
Day 7*							
D. 28*							
Month 3							
Month 6							
1 year							

*or nearest day

***For each parameter, tick* box if all normal during year; *cross* if at least one abnormal value:**

	Start Date	ALT	AST	Glob	IgG
2nd year					
3rd year					
4th year					
5th year					
6th year					
7th year					
8th year					

RELAPSES

Document all relapses, defined as ALT or AST rising to *> twice upper normal* limit from prior normal values. Date of relapse =date first abnormal AST or ALT

Relapse Number	Date	First abnorm ALT/AST	Peak ALT	Peak AST	Bili	IgG	Date of first normal ALT/AST
1							
2							
3							
4							
5							

FLOW CHART FOR DRUG THERAPY

- **State drug and total daily dose in mg: thus, prednisolone 40mg od = pred 40; Budesonide 9mg od = Bud 9; Azathioprine 125mg od = Aza 125**
- **Other drugs: Mycophenolate (MMF), Cyclosporine (CYC), Tacrolimus (Tac)**
- **Please add rows if needed.**

DATE started or dose changed	STEROID (pred/Bud/ methyl pred)	Steroid Sparing agent (Aza/6MP)	Other Drug MMF/Tac/Cyc/ Biological agent	Patient Weight (Kg)

DRUG TOXICITY (tick if occurred and state month after starting when SE occurred)

STEROIDS			AZATHIOPRINE/6MP/MMF		
	Y	month		Y	month
Psychosis			White cell count <2.5 (and fall of >1.0)		
Diabetes (onset during treatment)			Pancreatitis		
Low trauma fracture			Other (specify):		
Other (specify):					

Free text; please add any clinically relevant information which has not previously been included:

Appendix C: Centre Infrastructure

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

HQIP
Healthcare Quality Improvement Partnership

Information about your centre for AIH Audit

You obviously only have to fill this in once - if you are unsure about any of the answers you should ask the consultant leading the project

Todays Date

d d / m m / y y y y

Hospital Name _____

Type of Hospital
- ☐ DGH
- ☐ University Hospital

Approx number of beds
- ☐ <500
- ☐ >500

No. of Gastroenterologists ☐☐

No. of Gastroenterologists with a "liver interest" (>40% of workload liver disease) ☐☐

No. of Gastroenterologists who manage AIH ☐☐

No. of Hepatologists (>70% of workload liver disease) ☐☐

No. of Specialists nurses ☐☐

No. of Specialists nurses with >50% workload liver disease ☐☐

Does your centre....

Accept liver referrals from other hospitals? ☐ Yes ☐ No

Have the facility for patients to phone a specialist nurse? ☐ Yes ☐ No

Departmental electronic database for AIH patients ☐ Yes ☐ No

Have written departmental guidelines for AIH ☐ Yes ☐ No

Have biopsies discussed at a joint clinico-pathological meeting at least once a month ☐ Yes ☐ No

Have information sheets for AIH in the department ☐ Yes ☐ No

Have a specialist nurse seeing AIH patients in clinic ☐ Yes ☐ No

Have a histopathologist with a special interest in liver disease ☐ Yes ☐ No

Please specify the normal serum ranges for AST and ALT in the free text boxes below (if this has changed at all since 2000 to present please state the ranges for each date range - you can easily find this information out on your computer system or from patients notes if they have hard copy results within their notes. If you are not sure just enter the current values and email me when you have the information.

AST (please specify minimum and maximum and the units) _____

ALT (please specify minimum and maximum and the units) _____

Thank you