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ORIGINAL ARTICLE

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Diagnosis, presentation and initial severity of Autoimmune Hepatitis (AIH) in patients attending 28 hospitals in the UK

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Abbreviations: AIH-PBC, AIH with Primary Biliary Cholangitis overlap; AIH-PSC, AIH with Primary Sclerosing Cholangitis overlap; ICD-10, International Classification of Disease-10.

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Abstract

Background & Aims: There is limited information regarding patients with AIH outside relatively few large centres. We describe here the presenting features of patients with AIH, collected as part of an audit involving 28 UK hospitals.

Methods: Patients (incident since 1/1/2007 or prevalent since 1/1/2000) were ≥18 years and either met 1999 International AIH Group (IAIHG) diagnostic criteria (n = 1164), or received immunosuppressive therapy for clinically diagnosed AIH (n = 103).

Results: Of 1267 patients (80% women, 91% Caucasian, age (median(range)) 55(8-86) years, 0.5% had acute viral hepatitis (CMV/EBV/HEV); 2% were taking Nitrofurantoin and 0.7% Khat. Twenty-one percent had clinical decompensation and/or a MELD score of >15. Time from first abnormal liver tests to diagnosis was ≥1 year in 19% and was longer in jaundiced vs non-jaundiced patients. HBV and HCV serology were undocumented in 4%, serum immunoglobulins in 31% and autoantibodies in 11%-27%. When documented, ≥1 antibody was present in 83%. LKM-1-positive and autoantibody-negative patients had more severe disease. Histological cirrhosis was reported in 23%, interface hepatitis 88%, predominant lymphocytes/plasma cells 75%, rosettes 19% and emperipolesis 0.4%. Only 65% of those meeting 1999 IAIHG criteria also met simplified IAIHG criteria. University Hospitals compared to District General Hospitals, were more likely to report histological features of AIH.

Conclusions: This cohort from across the UK is older than other multicentre AIH cohorts. One-fifth had decompensation or MELD >15. Diagnosis was delayed in 19%, diagnostic testing was incomplete in one-third and rosettes and emperipolesis were infrequently reported.

KEYWORDS
audit, autoimmune hepatitis, presentation, scoring system

1 | BACKGROUND AND AIMS

Autoimmune hepatitis (previously considered a disease of young women) is now recognised to affect people of all ages. Its prevalence in Europe and North America is 10-43/100 000,[1-5] but it is a worldwide disease, affecting all ethnic groups.

Although AIH is a clinical diagnosis, it can be characterised using diagnostic scores, which facilitate comparison between centres. The 1999 International Autoimmune Hepatitis Group (IAIHG) scoring system has been used in most published studies.[6] A later (2008) simplified score[7] was highly specific for AIH in single-centre validation studies,[8,9] but "missed" 5%-10% of cases defined by 1999 criteria.

Most reports on AIH have originated from single, large, usually tertiary centres, raising the possibility of referral bias. Reports describing presenting features of AIH have seldom included more than 250 patients. Exceptions include reports on epidemiology and initial presentation in 473 Swedish patients from 10 hospitals[3], 1313 patients from 31 Dutch centres[5], and a report including 1721 patients identified from Danish registries which reported on epidemiology and outcome (but not presenting features) of AIH.[1]

We conducted a multicentre audit of management and outcome of AIH in 28 UK centres of varying size. Here, we describe presenting features in this cohort.

Key points

- This UK multicentre audit identified an older cohort of patients than other reports.
- Diagnosis was delayed >12 months in one-fifth of cases.
- Reporting of rosettes and emperipolesis was less frequent than expected.
- The simplified scoring system as utilised failed to diagnose one-third of patients.
- AIH diagnosis might be improved by centralising histology reporting.

2 | METHODS

A network of Gastroenterologists and Hepatologists agreed to an audit of diagnosis, presentation and outcome of AIH, measuring against pre-agreed standards. Of 28 participating centres (Figure 1), 14 were University Hospitals (4 Transplant centres) and 14 District General Hospitals (DGHs). Sheffield was the coordinating centre. Standards relating to patients' AIH diagnosis were:

1. ≥100% tested for Hepatitis B (HBV) and Hepatitis C (HCV).
2. ≥80% undergo diagnostic liver biopsy.
3. ≥90% meet the 1999 IAIHG diagnostic criteria.
4. Time from first abnormal LFT's to diagnosis is <4 months (≥90%).

Patients were included if they met the following criteria:

1. Diagnosis of AIH based on either:
   a. meeting 1999 IAIHG criteria;[6] this was minimally modified; we did not subtract points if patients had a history of medication potentially relevant to disease onset, or score for autoantibodies other than ANA/ASMA/LKM-1 (few hospitals tested for these). If the patient scored ≥10, they have at least probable AIH.
   b. clinical diagnosis of AIH, treated with immunosuppressive therapy.
2. ≥18 years old at inclusion.
3. Absence of positive HBV/HCV serology

2.1 | Case capture

We developed a search strategy in Sheffield (Figure S1) by interrogating 3 overlapping electronic modalities from Jan 2007-Feb 2013; (a)

FIGURE 1 Participating centres

Histology database (liver biopsies): searched using 'SNOMED' codes for 'chronic' and 'acute inflammation'. (b) Electronic out-patient clinic letters (c) Hospital coding: departments, using ICD-10 codes (K45.5 (AIH), K73.2 (chronic active hepatitis) and K73.9 (chronic hepatitis unspecified)).

Cases from these sources underwent sequential diagnostic validation for AIH in 3 stages: (1) Excluding HBV/HCV patients. (2) Scoring diagnostic points by IAIHG criteria, based on electronic biopsy reports, immunological and biochemical data. (3) Awarding further diagnostic points (maximum 6) for other autoimmune diseases, alcohol history, treatment response and relapse. Unlike stages 1 and 2, this stage required patients' clinical records. Patients were excluded if diagnostic score was <4 after stage (2) or <10 after stage (3).

This search strategy was validated in the coordinating centre against a pre-existing patient monitoring database (N = 57) presenting from 2007-2013. The method identified all patients and 29 additional AIH patients not on the database. Letters search revealed 12 of these 29 patients (8 uniquely), histology search: 20 of 29, (9 uniquely) and coding search 4 of 29 (none uniquely). This underlines the value of searching all 3 modalities. We asked each centre to adopt this approach. Table S1 includes details of modalities searched in 22 centres, numbers and the centre's estimated percentage of patients from their centre .

Both **Incident cases** (AIH diagnosis after 1/1/2007 (regardless of whether still attending the hospital) and **Prevalent cases** (diagnosed with AIH between 1/1/2000-31/12/2006 and still attending hospital when data collected) were included. Patients with overlap syndromes (AIH-PBC or AIH-PSC) were included if they met 1999 IAIHG AIH criteria; the scoring system incorporates negative points for positive AMA and and/or histological features of PBC/PSC.

Cases were included retrospectively and prospectively. Three hospitals included only incident patients. Duplicate patient entry was prevented by centres stating whether patients had been managed elsewhere and cross checking. Information was collected between 1/1/2014 and 30/11/2015 using a bespoke encrypted web-based data collection system (FORMIC solutions). Patients were allocated a unique audit number and could only be identified by each participating centre, where a secure key was kept.

2.2 | Ethics

The project was approved by the University of Sheffield Ethics Board and was deemed an audit by the UK Health Research Authority. Living patients were sent an information letter, allowing them to opt out (2 did, and were excluded).

2.3 | Statistics

Data were analysed using Excel and SPSS. T-test analysis was used for comparison of groups and Chi-square test for categorical data comparisons.

3 | RESULTS

3.1 | Overall cohort

We included 1267 patients. Of these, 103 (8%) did not meet the 1999 IAIHG criteria but had received treatment for a clinical diagnosis of AIH. There were 1008 incident and 259 prevalent cases. Since there were only minor differences between all these categories, they were combined for the main analysis. Table 1 shows clinical and demographic information. Figure 2 shows age distribution at diagnosis; this was also similar in women and men.

3.1.1 | Clinical features

Nearly, a quarter were asymptomatic. The commonest presentation (Figure 3) was jaundice and/or itch (we did not distinguish between these), occurring in 42%. Of 537 patient with peak bilirubin values of <40 (and so, unlikely to be jaundiced), 81 (15%) had "jaundice and/or itch".

Time from first abnormal serum liver tests to diagnosis, was (median(range)) 3 (0-166) months. It exceeded 4 months in 543 of 1261 (43%) informative patients and 12 months in 237 (19%). Delay was shorter in patients presenting with jaundice/pruritus than others: 1 (0-106) vs 5 (0-166) months; ($P \leq .0001$).

Only 1.3% had a family history of AIH. A personal or family history of autoimmune disease was present in 546 patients (44%); (Table S2). Table S3 shows other comorbid conditions.

Twenty-three patients (6 with cirrhosis) were taking nitrofurantoin before presentation. AIH diagnostic score was 17 (12-23). With 5 points subtracted for "drug history", score was 12 (7-18); 13 patients still had at least "probable" AIH'. Nine male patients of African or Asian origin, were using Khat (AIH score 15 (8-20), 10 (3-15)) adjusted for drug history, with 4 still meeting probable AIH criteria. One patient was taking minocycline and none taking infliximab or interferon.

3.1.2 | Laboratory features (Tables 2 and 3)

HBV and HCV serology was negative in 1205 (95%) patients and undocumented in 56 (4%). The remaining 6 patients (0.5%) had negative HBV and HCV serology but had other hepatitis IgM antibodies (4 CMV, 1 EBV plus CMV, 1 HEV).

Table 2 shows laboratory values at presentation. Serum IgG values were recorded in 877 patients (69%). Serum IgG or globulin was raised in 78%. Table 3 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 1 was present in 83%. AMA was found in 9%, Anti-SLA was positive in 10 (24%) of 42 patients tested (in 3 centres), including 5 in whom ANA/ASMA and anti-LKM were negative.

TABLE 1 Demographics

Characteristic	
Age (y): 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 (2-15)
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 N (%)	
<22 units/wk	949 (75)
22-52 units/wk	289 (23)
>52 units/wk	29 (2)
BMI: median(range)[a]	27.5 (16-51)

[a]Available in 389 patients.

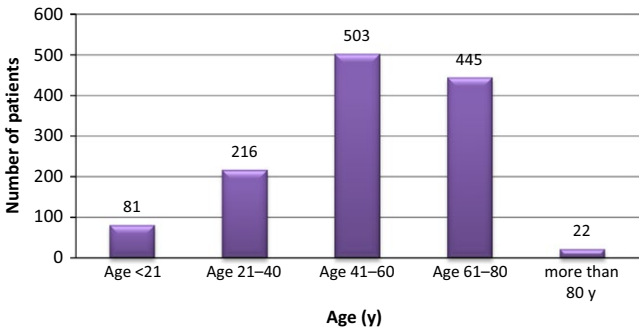

FIGURE 2 Age distribution at diagnosis

3.1.3 | Histology (Table 4)

Liver biopsy was performed in 1213 (96%) patients, with an accessible report in 1163 (92%). Most had interface hepatitis (IFH) and a predominantly lymphocyte or plasma cell infiltrate; however, only 19% had rosettes (range 0-63% amongst 28 centres). Emperipolesis was reported in only 5 patients (0.4%), from 3 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 7 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%; $P = .007$) but body weight and BMI values were similar, as was prevalence of interface hepatitis, plasma cells and rosettes.

Presence or absence of cirrhosis on biopsy was undocumented in 6%. Of 1124 informative patients, 254 (23%) had cirrhosis. Ishak

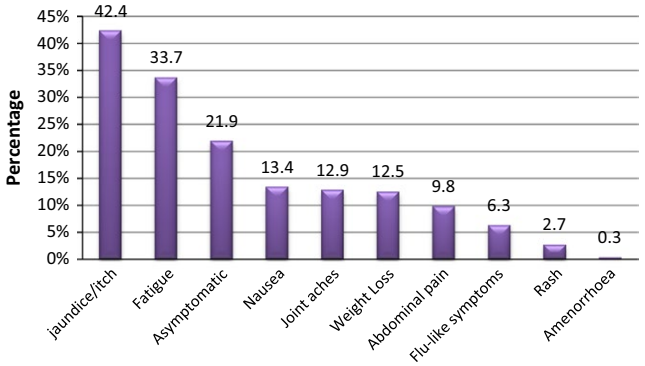

FIGURE 3 Presenting symptoms

TABLE 2 Serum parameters at presentation

Parameter	Value	No of patients with result
AST (IU/L), median(range)		
First AST	182 (13-3541)	348
Peak AST	333 (31-3785)	366
ALT (IU/L), median(range)		
First ALT	255 (10-3240)	1152
Peak ALT	488 (10-4181)	1110
ALP:Transaminase ratio, N (%)		
<1.5	1123 (89)	1267
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 at peak Transaminases	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 3 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%)

TABLE 4 Histological features on diagnostic liver biopsy

Histological feature	IAIHG Histology score	All patients (N = 1163)[a] 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 Necro-inflammatory 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)

[a]Where accessible.

fibrosis score (recorded in 539 patients) was zero in 62 (12%). 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. 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.

3.1.4 | Simplified diagnostic criteria

Of patients who met post-treatment 1999 AIH criteria (N = 1164), 758 also met the simplified 2008 diagnostic criteria for AIH and 406 (35%) had insufficient points. Information was missing in 183, but in only 67 patients did this preclude ascertainment regarding 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 not 1999 criteria; all received immunosuppressant therapy. Of these, 17 were AMA-positive (resulting in deduction of 4 diagnostic points by 1999 criteria), of 14 with accessible biopsies, 11 had bile duct changes.

3.1.5 | Disease severity

Overall, 318 patients (25%) had cirrhosis based either on liver biopsy (23%), Fibroscan®, presence of varices, ascites or encephalopathy. In only 8 patients was cirrhosis based solely on Fibroscan. One hundred and eight 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%)) and 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) .

3.2 | Subgroup comparisons

3.2.1 | Completeness of case capture

We performed 2 analyses to assess if our 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, in the ((52 vs 54 years; $P = .04$).

ii Comparing patients (n = 356) in 4 centres (Sheffield, Chesterfield, Nottingham and Coventry) where we were confident that the capture strategy described in METHODs was used, with the remaining centres (n = 911). Again, most parameters did not differ. However, proportion of patients undergoing diagnostic biopsy (98% vs 95%; $P = .01$) and prevalence of IFH (93% vs 86%; $P \leq .01$),

TABLE 5 Comparison by autoantibody[a]

	Group 1 (ANA or SMA+)	Group 2 (LKM+)	Group 3 (All negative)	*P* value (ANA/ASMA+ 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	.1	<.001	<.01
Gender F:M	522:132	14:3	52:176	<.01	.79	<.01
IgG elevated: N (%)	538 (82)	14 (82)	152 (67)	<.001	.99	.18
Histology: No biopsied	607	17	214			
IFH	534	14	186	.68	.48	.60
Lymphoplasmacytic predominance	473	13	145	.003	.89	.49
Rosettes	132	5	45	.85	.45	.43
Bile duct damage	65	0	25	.66	.15	.13
Cirrhosis: N (%)	166 (25)	8 (47)	52 (30)	.44	.04	.03
Decompensation at Presentation: N (%)	134 (20)	6 (35)	77 (34)	.01	.14	.89
NIS >3 vs ≤3	129:2	4:0	51:2	.34	.80	.69

[a]Comparisons only include patients where all autoantibodies were tested for.

lymphocyte/plasma cell predominance (76% vs 74%; *P* = .03) and rosettes 34% vs 13%; *P* ≤ .01) was higher in the centres with complete case capture.

3.2.2 | University hospitals and district general hospitals

Patients attending UH's (n = 830) were, compared to those attending DGHs (n = 437) more likely to have interface hepatitis (89% vs 86%; *P* = .01), lymphocyte/plasma cell predominant infiltrate (78% vs 69%; *P* ≤ .002) and rosettes (23% vs 11%; *P* ≤ .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* < .05). Mean age at diagnosis was significantly lower in UH's: 50 vs 56 years, (*P* = .0001).

3.2.3 | Autoantibody status (Table 5)

In patients who had undergone testing for all 3 autoantibodies, we 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 (Table 5). 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 had a pre-existing clinical diagnosis of PBC and 46 did not meet 1999 AIH criteria. Compared with patients who had at least 1 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* ≤ .0001) and mean ALT was lower (*P* = .002); (Table S4). Of AMA-positive patients, those with additional presence of AIH antibodies did not differ from those without; (Table S5).

3.2.4 | Caucasian and non-Caucasian patients

Caucasian patients (n = 101), compared to non-Caucasian patients): had more men (38% vs 19%; *P* < .01) (b) presented younger (41 years vs 54 years; *P* = .0001) (c) were more likely to be symptomatic (89% vs 79%), to be jaundiced (51% vs 33%; *P* = .0002; bilirubin 63 (3-702) vs 27 (2-789)), and to have clinical decompensation or MELD >15 (30% vs 21%; *P* = .046).

3.2.5 | Gender and age

Male patients (n = 257) presented younger (52 (8-83) vs 56 (8-86)) years; *P* ≤ .0001) and were more likely to be jaundiced (51% vs 35%: *P* ≤ .01) and to be decompensated (27% vs 20%; *P* = .03), than females. There were no other differences.

Those presenting aged over 55 years (n = 662) were more likely to be female (83% vs 77%; *P* = .007), asymptomatic (29% vs 14%: *P* ≤ .01) and cirrhotic (28% vs 21%; *P* = .005) and were less likely to be jaundiced (34% vs 44%; *P* = .0006), compared to those presenting younger.

4 | DISCUSSION

This large multicentre study affords several insights into the presenting features of AIH in the UK. The salient findings are as follows: firstly, that AIH in the UK affects an older population than

reported elsewhere. Secondly, there are often delays in diagnosis, incomplete diagnostic work-up and probable under-reporting of 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, our study may include 8%-16% of UK patients.

There are some weaknesses. As in other multicentre studies of AIH, there was probably incomplete case capture, resulting from the complex diagnostic criteria and from difficulties in searching data systems. We developed a three-pronged case finding strategy, which "captured" all patients with AIH on our "working" database and some that were not (though we had previously considered it to be comprehensive). However, despite repeated encouragement, we are confident that capture was complete in only 4 centres. We attempted to address this issue by performing subgroup comparisons. We found only trivial difference between (a) the 4 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.

Our cohort is similar in many respects to other multicentre[1,3,5,10] and large single-centre[11-15] cohorts. It has a similar gender balance. We confirm a prior observation[12] that men with AIH present younger than females. Most patients were Caucasian reflecting UK ethnic population distribution (87%).[16] This was similar in the Dutch cohort (89%)[5] and underlines the fact that AIH affects all major ethnic groups. Non-Caucasian groups had more severe disease, consistent with other reports.[17-19] Like the Dutch group, we report 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 4%. Only 1 patient had documented acute Hepatitis E virus (HEV) shortly before presenting with AIH. We did not ascertain the numbers tested for HEV. However, in a Dutch study of AIH, no patient had HEV viraemia and EBV antibody prevalence was not significantly higher than the general population.[20]

However, our cohort is older than other multicentre AIH cohorts[3,5,10] which have a median age at presentation of 43-48 years. It is also older than in some,[12,14] though not all single-centre studies.[13,21] Age at presentation was even older in patients presenting to DGHs than to University Hospitals. 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,[3,14,20] as is the 25% prevalence of cirrhosis,[3,14,21] and the 8.5% prevalence of clinical decompensation.[3] In our study, 17% had a MELD score >15, thus over one-fifth had serious liver dysfunction at presentation.

Of the 4 pre-agreed diagnostic standards, 2 were met; numbers having 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. The impact of such a delay on disease outcome is unknown.

Another potential concern is failure to document Hepatitis B and C serology in 4% of patients. 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.[22,23] It is associated with higher relapse rates and poorer outcomes.[24] 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%),[3] although contrasting with the Italian experience (23%).[14] 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.[25]

Another concern relates to histology reporting. We collected data from clinical reports, without central review. In 6% of cases, it was unclear whether there was fibrosis or cirrhosis on the biopsy. The prevalences reported here of interface hepatitis and of predominance of lymphocytes/plasma cells are similar to those previously reported (75%-98%).[3,26,27] However, the prevalence of rosettes (19%) is much lower than reported from single centres[27] and the wide variation in prevalence between the 28 centres (0%-63%) suggests widespread under-reporting. Prevalence of rosettes in the Dutch multicentre study was 16%.[5]

Emperipolesis was very rarely reported (0.4%). In single-centre studies, reported prevalence has been 65%-78%.[27,28] In a preliminary study in Sheffield,[29] 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).[30] Presence of rosettes contributes 1 diagnostic point to the 1999 IAIHG diagnostic system. Although there is lack of clarity in the original report,[7] both rosettes and emperipolesis appear necessary for "typical" histology, earning 2 diagnostic points by the 2008 simplified system. We 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.[29]

In calculating the simplified IAIHG score, we deemed the presence of interface hepatitis, lymphocyte/plasma cell predominance

and rosettes without a detracting finding (such as bile duct damage or >mild steatosis) amounted to "typical" AIH histology, thereby gaining 2 diagnostic points[7]. 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 multicentre study[5] was 18%. If we adopted the more stringent definition of typical histology and also required emperipolesis, then only 6 patients had "typical" histology. 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.

In conclusion, firstly, the results of this large multicentre Audit suggest that AIH in the UK may affect an older population than in previous multicentre studies. Secondly, they highlight delays in diagnosis, incomplete diagnostic work-up and probable under-reporting of important histological features, more so in district general hospitals. Thirdly, they call 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.

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CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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