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Article type : Original Articles

Title page

# Role of autoimmunity in patients transplanted for acute liver failure of unknown origin: a clinical and graft-biopsy analysis

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/lt.25729

Key words: Liver transplantation, autoimmune hepatitis, protocol liver biopsy, HLA, autoimmune disease

Footnote page

## Abbreviations

AIH, autoimmune hepatitis; ALF, acute liver failure, AMA; Antimitochondrial antibodies, ANA; antinuclear antibodies; cANCA, cytoplasmic antineutrophil cytoplasmic antibodies; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; HLA, human leukocyte antigen; LKM, Liver and kidney microsomal antibodies; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; SCD-AIH, simplified criteria for the diagnosis of autoimmune hepatitis; SMA, smooth muscle antibodies

## Grants

This study was supported by Sigrid Juselius Foundation and The Finnish Transplantation Surgery Association.

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# Abstract

## Background

The etiology and prognosis of acute liver failure (ALF) remains unknown in a significant proportion of cases. Signs of autoimmunity may be present, but no consistent pattern has been observed. We aimed to analyse if pretransplant immunological findings, HLA haplotypes and clinical features among patients with unknown etiology differ from those of autoimmune or other known etiology. We also analysed whether such signs impact post-transplant biopsy findings or complications.

## Methods

All adult ALF patients undergoing liver transplantation (LT) in Finland during 1987-2015 were followed to 2016. Data were from the LT registry, pathology database and patient records. 124 patients were included in the analysis. Study subgroups were acute autoimmune hepatitis (AIH) (n=25), known non-AIH etiology (n=54), and unknown etiology (n=45).

## Results

The unknown etiology group differed from the known non-AIH group with regard to the following pretransplant autoimmunity-associated features: positive pANCA (35% vs 8%; P=0.02), higher mean IgA (3.2±1.7 vs 2.1±1.4, P=0.006) and IgG (12.7±4.3 vs 8.5±3.6, P=0.001). AIH-associated HLA haplotypes B8, DR3 and B8DR3 were more common in the AIH group (40%, 44% and 36%) and in the unknown group (29%, 33% and 29%) than in the known non-AIH group (11%, 17% and 11%) or in the Finnish general population (17%, 18% and 8%). However, these findings had no association with protocol biopsies, extrahepatic autoimmune diseases or survival. Patients with ≥1 rejection episode had higher pretransplant IgA (3.7±2.3 vs 2.6±1.2, P=0.02) and IgG (16.4±10.2 vs 12.4±6.8, P=0.03) than those without rejections.

## Conclusions

Autoimmunity-associated pretransplant laboratory findings and HLA haplotypes were common in ALF of unknown etiology, but showed minimal predictive value for post-transplant biopsy findings, clinical complications or survival.

# Main body text

## Introduction

Acute liver failure (ALF) is a severe clinical syndrome characterized by impaired liver function, coagulopathy and encephalopathy (1) without pre-existing liver disease. ALF accounts for 8% of all liver transplantations in Europe (ELTR 2018) and 3% in United States (OPTN 2017 annual report).

ALF can be caused by various etiologies. Still, despite careful evaluation, the etiology of acute liver failure remains unknown in a significant proportion of patients. Studies have so far failed to identify novel viral etiology (2,3). Association of ALF of unknown etiology with specific HLA-haplotypes, female predominance and unspecific autoantibodies may suggest autoimmune etiology (4-7). Autoimmune hepatitis (AIH) can manifest as acute liver failure (8-10), and autoimmune hepatitis may be the cause in some of these previously unknown ALFs (11). However, diagnosis in this setting is difficult as there are no established diagnostic criteria for AIH-ALF.

It is unclear whether the unspecific elevations of autoantibodies and immunoglobulins observed in many patients with ALF (6) indicate autoimmune etiology or if they are just an epiphenome of the immunologic processes triggered by ALF (12). AIH is known to recur after liver transplantation in 17-33% of patients depending on the duration of follow-up and diagnostic criteria, and recurrent AIH may lead to graft loss (13). If ALF of unknown etiology has autoimmune background, disease recurrence would be expected after transplantation in a significant proportion of patients. Some studies have demonstrated an increased prevalence of chronic hepatitis at one year in the group with unknown etiology compared to known non-autoimmune etiologies, but few studies with protocol biopsies exist (5,11,14).

The aim of the present study was to analyze whether signs of autoimmunity (autoimmune serology, HLA-haplotype, and clinical history) differ between ALF of known and unknown cause, and whether such signs of autoimmunity predict post-transplant liver protocol biopsy findings, rejections or survival. We reviewed all adult patients transplanted for ALF in Finland (since the start of our transplant program).

## Materials and methods

### Patients

All liver transplantations in Finland are performed at Helsinki University Hospital. We identified all adult patients who had been transplanted for ALF in Finland between 1987 and 2015 (N = 152) from the liver transplant registry. Data were collected from the transplant registry and patient records. All patients included had ALF with encephalopathy and coagulopathy and were transplanted within 26 weeks of diagnosis.

The etiology of ALF was determined based on patient's medical history, laboratory and histology data, including the histology of the explanted liver. Patients were considered to have AIH-ALF if they fulfilled criteria for probable or definite AIH according to simplified criteria for the diagnosis of AIH (SCD-AIH) (15).

### Clinical data

Patient records were reviewed for possible extra-hepatic autoimmune diseases in the medical history or during the follow-up. We recorded laboratory values and immunosuppressive medication at annual visits and at the time of liver biopsy.

All patients received calcineurin inhibitor (CNI)-based immunosuppression; cyclosporin (CYA) was slightly more common than tacrolimus (TAC) (latest immunosuppression used). CNI was combined with an antimetabolite, azathioprine (AZA) or mycophenolate mofetil (MMF) in most cases. All patients received methylprednisolone (MP), which was usually tapered off after the first post-transplant year. There were no significant differences in immunosuppression between etiological groups at 1, 5 or 10 years (Supplement table 1).

### Laboratory data

Laboratory testing to evaluate the etiology of ALF at the transplantation center included hepatitis A IgM and IgG antibodies, hepatitis B surface antigen, core antibody and DNA, hepatitis C virus antibodies and RNA, hepatitis E IgM and IgG antibodies, cytomegalovirus IgM and IgG antibodies and DNA, Ebstein-Barr virus IgM and IgG antibodies and DNA , antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (cANCA and pANCA), smooth muscle antibodies

(SMA), anti-mitochondrial antibodies (AMA), liver and kidney microsomal antibodies (LKM), immunoglobulins A, M and G (IgA, IgM, IgG) and human immunodeficiency virus antigen and antibodies. Diagnostic tests for Wilson's disease were made with a low threshold on clinical suspicion.

HLA haplotypes B8, DR3, DR4 and DR13 are associated with autoimmune hepatitis in Northern Europe (16,17) and homozygosity for B8-DR3 and A1-B8-DR3 have been associated with non-A, non-B ALF (4). We evaluated the presence of these HLA haplotypes in our patients and compared this to that reported in the Finnish general population (18). The prevalence of HLA B8-DR3 was received from the Finnish Red Cross Blood Service (unpublished).

## Histological data

Data of possible pretransplant biopsy and histology of the explanted liver were used to evaluate the etiology of ALF. Post-transplant histological data comprised evaluation of all post-transplantation liver biopsies. Biopsies are routinely reviewed at multidisciplinary meetings by an experienced liver pathologist and reported structurally. Portal inflammation (graded 0-3), lobular inflammation (graded 0-2), interface inflammation (graded 0-3) and fibrosis (graded 0-4) were graded according to METAVIR (19). Indication biopsies were performed following unclear abnormalities in liver biochemistry after transplantation. All rejections were biopsy-confirmed according to Banff criteria (20). Protocol biopsies were started at 2009: at 1 year and 5 years post-transplant and every 5 years thereafter. Protocol biopsies were performed in all patients after 2009, also on those transplanted before 2009.

Graft hepatitis was diagnosed in the presence of portal inflammation combined with lobular or interface inflammation without characteristics of other defined pathologies (acute or chronic rejection, viral infection or steatohepatitis) (21). The diagnosis of *de novo* or recurrent AIH was based on liver histology typical to AIH with plasma cell-rich hepatitis. Autoantibodies or immunoglobulins were not routinely monitored after transplantation.

## Statistical analysis

Statistical analysis was performed using SPSS (version 24). Categorical variables were analyzed with Fisher's exact test and continuous variables with Mann-Whitney U-test or Kruskal-Wallis

test. Survival was analyzed using Kaplan Meier method and compared with log rank test. P values < 0.05 were considered significant.

# Results

## Pre-transplant findings

Patient characteristics and baseline laboratory data are presented in Table 1. Etiologies comprised 25 AIH, 54 known non-AIH and 45 patients with unknown etiology. Patients with incomplete data to confirm the diagnosis (N = 28) were excluded from the analysis.

Known non-AIH etiologies included Budd Chiari syndrome (n = 11), acetaminophen over-dose (n = 5), non-acetaminophen drug-induced liver injury (n = 19), acute hepatitis B (n = 5), amanita poisoning (n = 5) and miscellaneous (n = 9; trauma, post-operative, lymphoma, EBV, pregnancy-induced rupture). In case of non-acetaminophen drug-induced liver injury only a definite or very likely association was considered as known etiology.

Patients with SCD-AIH score ≥ 6 were classified as AIH. AIH patients had positive ANA titers ≥ 1:80 (23/25) and/or SMA titers ≥ 1:40 (11/25), elevated IgG > 15 g/l (23/25), negative viral serology and no other evident etiology. Only eight of these patients were considered to have histology typical to AIH and most had only unspecific histology. Unknown etiology included all the patients without a defined etiology.

Compared to patients with known non-AIH etiology, patients with unknown etiology had more often pANCA titres ≥ 1:10 (36% vs 8%, P = 0.02), IgA above ULN (27% vs 7%, P = 0.04), IgG above ULN (20% vs 0%, P = 0.04). Unknown group had also higher SCD-AIH scores (3.1 ± 1.0 vs 2.4 ± 1.0, P = 0.005), higher IgA (3.2 ± 1.7 vs 2.1 ± 1.4, P = 0.001) and higher IgG (12.7 ± 4.3 vs 8.5 ± 3.6, P = 0.001). The known non-AIH group had more often hyperacute presentation and they were transplanted faster (22 ± 24 days) than AIH patients (38 ± 36 days) and unknown patients (32 ± 35 days), P = 0.02.

We compared hyperacute, acute and subacute patients in the unknown group and they had similar autoantibodies, HLA haplotypes, rejections and survival (data not shown). Patients with subacute presentation had higher IgG than acute or hyperacute patients (14.7 ± 3.7 vs 12.1 ± 4.4 vs 9.7 ± 2.9, P = 0.04).

Pretransplantion liver biopsy was available in 48/124 (39%) patients. Four biopsies showed histology typical to AIH and most biopsies (26/48, 54%) revealed only unspecific inflammation and necrosis. Histology of the explanted liver was available in all patients. Nine patients showed histology typical to AIH and again, unspecific necrosis (mean level of necrosis 73%, no difference between groups) was the most common histological finding (83/124, 67%). Histological evaluation of the explanted livers is presented in Supplement table 2.

### HLA

There were significant differences in the presence of HLA haplotypes B8, DR3 and B8DR3 between different etiology groups and the Finnish general population (Table 2). These haplotypes were common in the AIH group (B8 40%, DR3 44% and B8DR3 36%) and in the unknown group (B8 29%, DR3 33%, B8DR3 29%). The unknown group had these haplotypes significantly more often than known non-AIH group (B8 29% vs 11%, P = 0.04; B8DR3 29% vs 11%, P = 0.04) or the Finnish general population (B8 29% vs 17%, P = 0.04; DR3 33% vs 18%, P = 0.02; B8DR3 29% vs 8%, P = 0.001). However, only the difference between the presence of B8DR3 in the unknown group and the Finnish general population remained statistically significant when Bonferroni correction was applied. Haplotypes DR4 and DR13 were equally distributed among groups. No haplotype differed between the known non-AIH group and the Finnish general population.

We compared these HLA haplotypes with pretransplant laboratory test and found that DR4 was associated with higher IgM (1.6 ± 0.7 vs 1.4 ± 1.0, P = 0.03) and DR3 was associated with higher IgA (3.9 ± 2.0 vs 2.9 ± 2.0, P = 0.01) and IgG (16.7 ± 9.4 vs 13.6 ± 8.7, P = 0.051 (not significant)).

### Extrahepatic autoimmune diseases

There were no significant differences in the rates of extra-hepatic autoimmune diseases between groups before or after transplantation (Table 1). Twenty-nine patients (19%) had extra-hepatic autoimmune disease before the transplantation: autoimmune thyroiditis (n = 14), rheumatic conditions (n = 8) and others (n = 12; type 1 diabetes, ulcerative colitis, celiac disease, multiple sclerosis, immune thrombocytopenic purpura). Ten patients (7%) were diagnosed with extra-hepatic autoimmune disease after transplantation: autoimmune thyroiditis (n = 5) and one each of

Grave's disease, sarcoidosis, lupus erythematosus disseminatus, polymyalgia rheumatica, immune thrombocytopenic purpura and ulcerative colitis; n = 1 for all.

### Biopsies after transplantation

Protocol-biopsy results are displayed in Table 3. Of 104 protocol biopsies available, 31 (30%) showed no pathology. Mild portal inflammation (grade 1) occurred in 40 (39%), whereas any lobular or interface inflammation were seen in 15 (14%) and 10 (10%), respectively. Fibrosis grade 1 was seen in 25 (24%) and grade 2-4 in 5 (5%). Mild cholangitis was present in 5 biopsies; 3 of these also showed graft hepatitis and one had also co-existent anastomotic biliary stricture.

There was less fibrosis in biopsies ≥10 years post-transplant in the AIH group (0%) compared to the known non-AIH group (F1 31%, F2+ 15%) and the unknown group (F1 45%, F2+ 5%), P = 0.01.

Idiopathic graft hepatitis was found in 10 protocol biopsies: 1 in the AIH group (4%), 2 in the known non-AIH group (5%) and 6 in the unknown group (14%) (P = 0.48). Only one graft hepatitis was diagnosed under corticosteroid treatment (3% vs 13%; P = 0.16). Only one recurrent AIH was observed in protocol biopsies in the AIH group. All patients with graft hepatitis diagnosed by protocol biopsy were alive at the end of study period and without significant graft dysfunction.

Complete protocol biopsy data was available from all patients transplanted since 2008 (N = 42). In this group, two patients with AIH (2/9, 22%) developed post-transplant disease recurrence, and three (two in the unknown group and one in the known non-AIH group) were diagnosed with mild idiopathic graft hepatitis. No *de novo* AIH was detected in the unknown or the known non-AIH groups.

## Rejections

At least one episode of rejection occurred in 68% of AIH patients, 46% of known non-AIH patients and 53% of unknown patients (P = 0.73). Patients with at least one episode of rejection had higher pretransplant IgA (3.7 ± 2.3 vs 2.6 ± 1.2, P = 0.02) and IgG (16.4 ± 10.2 vs 12.4 ± 6.8, P = 0.03) than patients without rejections. Other baseline data or HLA haplotypes did not correlate with rejection episodes.

## Survival

Patient survival at 1, 5 and 10 years was 90%, 84% and 81% and graft survival 85%, 74% and 73%, respectively. There were no significant differences between etiology groups in either patient or graft survival (Figure 1 and Figure 2). Re-transplantation rates were similar: 8% in the AIH group, 13% in the known non-AIH group and 9% in the unknown group (P = 0.8). No pre-transplant laboratory test or recipient HLA haplotype had any effect on patient or graft survival in univariate analysis (data not shown). Indications for re-transplantation were acute or chronic rejection (n = 6), biliary complication (n = 4), primary non-function (n = 1) and arterial thrombosis (n = 2).

## Discussion

Our study found that features suggesting autoimmunity occurs in some patients transplanted for ALF of unknown etiology with more frequent positive pANCA and higher IgA and IgG than in the known non-AIH group. No patient in the known non-AIH group had elevated IgG. AIH-associated HLA haplotypes were equally common in the AIH and unknown groups.

The diagnosis of AIH-ALF has remained difficult as there are no acknowledged diagnostic criteria. Diagnostic criteria used in different studies differ markedly and show poor concordance (Table 4). Due to these differences, comparing findings from different studies is difficult. Our study is in line with previous ones showing features compatible with autoimmune etiology in the unknown group (4,11,22).

pANCA is frequently present in type 1 AIH (23), and in UC and PSC. We observed high prevalence of pANCA in our AIH group (74%) and also in the unknown group (36%). We had no patients diagnosed with AIH-PSC overlap and only two patients had ulcerative colitis. We have found no previous studies reporting the prevalence of pANCA in the setting of ALF, only a single patient report where pANCA was initially the only detectable antibody in acute-onset AIH (24). Our results indicate a role for pANCA in the diagnostic evaluation of AIH-ALF.

The unknown group had a similar prevalence of AIH-associated HLA haplotypes as the AIH group, which further supports the hypothesis of autoimmune pathogenesis in some patients in the unknown group. Previously Gow et al (4) reported higher prevalence of homozygosity of HLA

B8-DR3 and A1-B8-DR3 in ALF patients of unknown etiology, but could not conclude if these haplotypes predispose patients to ALF per se or if they are specific to unknown etiology only. Our results suggest that certain HLA haplotypes predispose patients only to ALF of unknown and autoimmune etiology, not to other etiologies. Interestingly, these haplotypes still showed only subtle correlation with pretransplant IgG and no correlation with clinical outcomes. HLA haplotypes DR3 and DR4 are associated with greater risk of AIH recurrence after transplantation for AIH (13), but as we found only a few cases of recurrent disease in the follow-up, we cannot conclude if this also applies to AIH-ALF.

Classical AIH responds well to corticosteroid treatment (25), but results are less encouraging in the context of AIH-ALF (26). Recognizing these patients early enough may be key to success as patients who reach high MELD-scores may no longer benefit from corticosteroid treatment (8,27). Our findings may help to recognize patients who are likely to have an autoimmune etiology of ALF and might benefit from a trial of corticosteroid treatment. However, as EASL recommends, a trial of corticosteroids should not last for more than seven days if response is not observed (28).

As reported earlier, only a minority of protocol biopsies were completely "normal" (21). Mild portal inflammation and fibrosis were frequent, but high inflammatory activity and fibrosis were rare. Biopsy results were fairly similar among the etiology groups, and protocol biopsies did not reveal any signs of original etiology of unknown ALF. We observed a low incidence of graft hepatitis in our ALF patients compared to previous reports, which noted graft hepatitis incidences up to 53-71% in the unknown ALF group (5,14). Differences in immunosuppression regimens and post-transplantation biopsy interpretation may explain these differences (21,29).

The etiology of ALF did not affect patient or graft survival. Patients received different type of immunosuppression according to etiology, rejections and biopsy findings, and it is impossible to evaluate how this might have affected survival. Still, it appears that signs of autoimmunity do not have an influence on prognosis after ALF.

Strengths of our study include a ~~large~~ single center experience of all 152 patients transplanted for ALF in an entire country, uniform diagnostic methods and perioperative and post-transplantation care including protocol biopsies. Coverage of post-transplantation follow-up was ~~nearly~~ almost complete with only one patient lost to follow-up. Still, lack of statistical power may explain some "non-significant" findings.

The retrospective setting is the main weakness of our study. However, due to rarity of ALF leading to liver transplantation, prospective studies are practically non-existent. We did not re-evaluate liver biopsies for this study, but they were originally reviewed by an experienced liver pathologist in multidisciplinary meetings. Applying the SCD-AIH criteria, we found high prevalence of AIH in our patients (20%), compared to 5% reported in the US and Spain (30,31). This is probably due to few acetaminophen intoxications and viral hepatitis leading to transplantation, which is in contrast to many centres where these are the most common causes of ALF. Recent study showed that prevalence of "classic" AIH in Finland (14 / 100 000) is comparable with other European countries (32).

In conclusion, we found some features compatible with autoimmune etiology in the unknown ALF group. These features had still only minor effect on post-transplant biopsy findings and complications, and no effect on survival. As we found no clear-cut cases of AIH in the grafts of patients transplanted due to unknown etiology, these patients will probably not benefit from AIH-targeted post-transplantation immunosuppressive regimens.

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Table 1. Clinical and laboratory data of the patients

| | Etiology | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Autoimmune | | Known | | Unknown | | P All | P Known vs Unknown |
| Patients (N) | 25 | | 54 | | 45 | | | |
| SCD-AIH-score, mean ±SD | 6.2 | ± 0.9 | 2.4 | ± 1.0 | 3.1 | ± 1.0 | **0.001** | 0.14 |
| Female | 21 | 84 % | 34 | 63 % | 31 | 69 % | 0.17 | 0.67 |
| Age at Tday, years, mean ±SD | 51 | ± 13 | 43 | ± 14 | 46 | ± 12 | **0.04** | 0.40 |
| Diagnosis-Tday (days) | 38 | ± 36 | 22 | ± 24 | 32 | ± 35 | **0.02** | **0.04** |
| MELD at Tday | 29.8 | ± 7.5 | 29.1 | ± 7.8 | 29.2 | ± 7.3 | 0.81 | 0.86 |
| S-ANA positive (≥ 1:80) (n) | 23 | 92 % | 10 | 26 % | 14 | 31 % | **0.001** | 0.63 |
| S-pANCA positive (≥ 1:10) (n) | 14 | 74 % | 2 | 8 % | 11 | 36 % | **0.001** | **0.02** |
| S-cANCA positive (≥ 1:10) (n) | 6 | 30 % | 5 | 19 % | 2 | 6 % | 0.06 | 0.22 |
| P-IgA above ULN[1] (n) | 13 | 52 % | 2 | 7 % | 12 | 27 % | **0.001** | **0.001** |
| P-IgA (mean), g/l, ±SD | 4.7 | ± 2.3 | 2.1 | ± 1.4 | 3.2 | ± 1.7 | **0.001** | **0.006** |
| P-IgM above ULN[2] (n) | 2 | 8 % | 1 | 3 % | 5 | 11 % | 0.57 | 0.39 |
| P-IgM (mean), g/l, ±SD | 1.7 | ± 1.2 | 1.0 | ± 0.6 | 1.6 | ± 0.8 | **0.001** | **0.001** |
| P-IgG above ULN[3] (n) | 23 | 92 % | 0 | 0 % | 9 | 20 % | **0.001** | **0.04** |
| P-IgG (mean), g/l, ±SD | 25.7 | ± 10.2 | 8.5 | ± 3.6 | 12.7 | ± 4.3 | **0.001** | **0.001** |
| S-SMA positive (≥ 1:40) (n) | 11 | 44 % | 5 | 14 % | 3 | 7 % | **0.001** | 0.46 |
| S-AMA positive (n) | 0 | 0 % | 2 | 5 % | 5 | 11 % | 0.18 | 0.45 |
| Extrahepatic autoimmune disease diagnosed before Tday, (n) | 5 | 20 % | 11 | 20 % | 10 | 22 % | >0.99 | >0.99 |
| Extrahepatic autoimmune disease diagnosed after Tday (n) | 4 | 16 % | 3 | 6 % | 2 | 4 % | 0.19 | >0.99 |
| ALF presentation | | | | | | | | |
| Hyperacute (0-7d) | 1 | 4 % | 18 | 33 % | 6 | 13 % | | |
| Acute (1-4w) | 14 | 56 % | 22 | 41 % | 23 | 51 % | **0.02** | 0.07 |
| Subacute (1-6m) | 10 | 40 % | 14 | 26 % | 16 | 36 % | | |

[1] ULN: 4.84g/l for men, 4.02g/l for women

[2] ULN: 2.59g/l for men, 2.84g/l for women

[3] ULN: 15g/l

Abbreviations: SCD-AIH, simplified criteria for the diagnosis of autoimmune hepatitis; Tday, transplantation day; ANA, antinuclear antibodies; S-pANCA, perinuclear antineutrophil cytoplasmic antibodies; S-cANCA, cytoplasmic antineutrophil cytoplasmic antibodies; P-Ig, immunoglobulin; S-SMA, smooth muscle antibodies; S-AMA, antimitochondrial antibodies

Table 2. HLA analysis of the study population

| | ALF | AIH | Known | Unknown | Population | P all | P U vs K [1] | P U vs K [2] | P U vs P [3] | P U vs P [4] |
|---|---|---|---|---|---|---|---|---|---|---|
| B8 | 23 % | 40 % | 11 % | 29 % | 17 % | **0.001** | **0.04** | 0.23 | **0.04** | 0.25 |
| DR3 | 28 % | 44 % | 17 % | 33 % | 18 % | **0.001** | 0.06 | 0.38 | **0.02** | 0.11 |
| B8DR3 | 23 % | 36 % | 11 % | 29 % | 8 % | **0.001** | **0.04** | 0.23 | **0.001** | **0.001** |
| A1B8DR3 | 15 % | 24 % | 7 % | 20 % | - | 0.16 | 0.08 | 0.47 | - | - |
| DR4 | 25 % | 28 % | 22 % | 25 % | 27 % | 0.98 | 0.86 | > 0.99 | 0.64 | > 0.99 |
| DR13 | 18 % | 8 % | 17 % | 24 % | 23 % | 0.22 | 0.45 | > 0.99 | 0.72 | > 0.99 |

[1] Unknown vs known non-AIH

[2] Unknown vs known non-AIH, Bonferroni correction

[3] Unknown vs general population

[4] Unknown vs general population, Bonferroni correction

Table 3. Protocol biopsies

| | | 1 year (N = 22) | | | 5 year (N = 34) | | | 10+ year (N = 48) | | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AIH | Known | Unknown | AIH | Known | Unknown | AIH | Known | Unknown | |
| Portal | 0 | 1 (25%) | 2 (22%) | 3 (38%) | 4 (57%) | 8 (62%) | 5 (42%) | 8 (67%) | 7 (50%) | 11 (52%) | P = 0.72 for 1 year |
| Inflammation | 1 | 2 (50%) | 5 (56%) | 5 (63%) | 3 (43%) | 4 (31%) | 6 (50%) | 4 (33%) | 6 (43%) | 5 (24%) | P = 0.89 for 5 year |
| | 2+ | 1 (25%) | 2 (22%) | 0 (0%) | 0 (0%) | 1 (8%) | 1 (8%) | 0 (0%) | 1 (7%) | 5 (24%) | P = 0.33 for 10+ year |
| Lobular | 0 | 2 (50%) | 6 (75%) | 7 (88%) | 6 (100%) | 12 (92%) | 9 (75%) | 11 (92%) | 13 (93%) | 17 (81%) | P = 0.46 for 1 year |
| Inflammation | 1 | 2 (50%) | 1 (13%) | 1 (13%) | 0 (0%) | 1 (85) | 3 (25%) | 1 (8%) | 1 (7%) | 3 (14%) | P = 0.39 for 5 year |
| | 2+ | 0 (0%) | 1 (13%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) | P = 0.93 for 10+ year |
| Interface | 0 | 3 (75%) | 8 (89%) | 7 (88%) | 7 (100%) | 12 (92%) | 11 (92%) | 11 (92%) | 13 (93%) | 18 (86%) | P = 0.73 for 1 year |
| Inflammation | 1 | 0 (0%) | 0 (0%) | 1 (13%) | 0 (0%) | 1 (8%) | 0 (0%) | 1 (85) | 1 (7%) | 3 (14%) | P > 0.99 for 5 year |
| | 2+ | 1 (25%) | 1 (11%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | P = 0.85 for 10+ year |
| Fibrosis | 0 | 2 (50%) | 8 (89%) | 4 (50%) | 5 (71%) | 11 (85%) | 9 (75%) | 12 (100%) | 7 (54%) | 10 (50%) | P = 0.25 for 1 year |
| | 1 | 2 (50%) | 1 (11%) | 3 (38%) | 2 (29%) | 2 (15%) | 2 (17%) | 0 (0%) | 4 (31%) | 9 (45%) | P = 0.78 for 5 year |

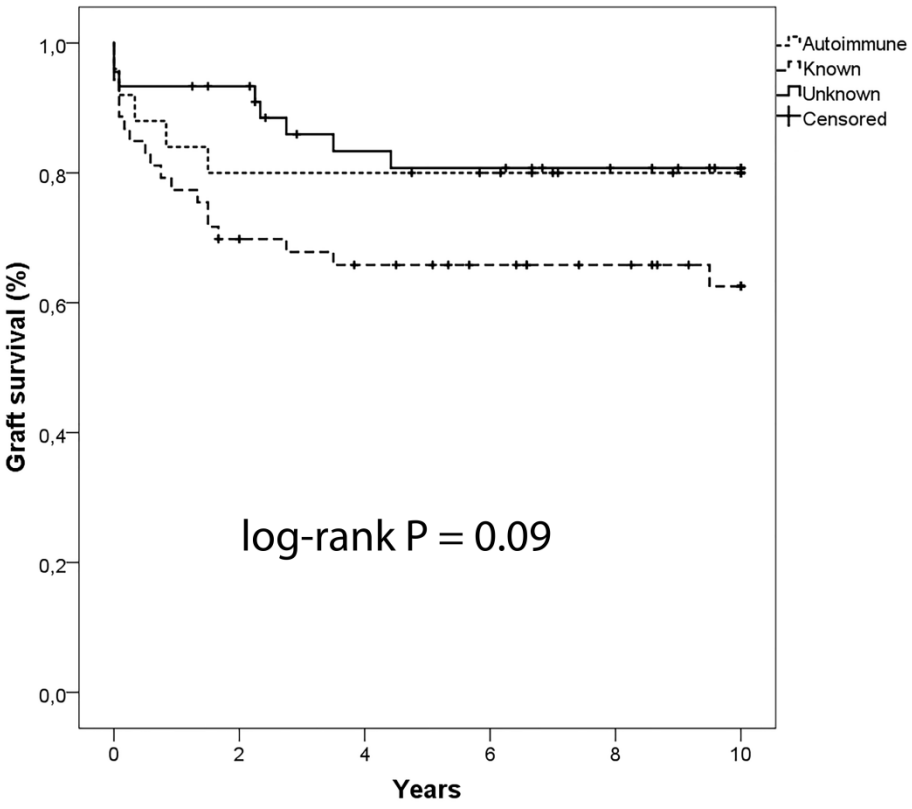
Table 4. Diagnostic criteria for AIH-ALF in different studies.

| Study | AIH-ALF diagnostic criteria | Patients (n) | Considerations |
|---|---|---|---|
| Kessler et al 2004 | IAIHG 1999 | 10 AIH-ALF | AIH-ALF patients have poor corticosteroid response compared to non-ALF AIH patients |
| Wigg et al 2005 | Exclusion: No history of AIH, absence of strongly positive autoantibodies (≥ 1:100) or a marked IgG elevation and the lack of characteristic histological findings | 110 seronegative ALF | More chronic hepatitis in 1-year biopsies in the seronegative group (53% vs 15%) compared to known non-AIH etiologies |
| Bernal et al 2007 | IAIHG 1999 | 14 cryptogenic ALF | 50% of cryptogenic patients classified as probable or definite AIH |
| Ichai et al 2007 | 2 / 3 of : 1) autoantibodies at significant titers; 2) gamma globulin levels above 20 gm/L; or 3) liver biopsy revealing features compatible with chronic hepatitis | 16 AIH-ALF | Corticosteroids usually ineffective in the setting of AIH-ALF |
| Yeoman et al 2009 | IAIHG 1999 and IAIHG SDC | 70 ALF | Concordance of the IAIHG 1999 criteria and the simplified criteria only 46% in ALF patients. Patients with AI by clinical perceptions, 50% identified as AIH by the IAIHG SDC and 60% by the IAIHG 1999 criteria |
| Stravitz et al 2011 | IAIHG SDC with novel histologic scoring | 72 indeterminate ALF | Histologic score combined with positive autoantobodies (but not the IAIHG SDC) associated with increased prevalence of chronic hepatitis. 42% of patients had histology compatible with AIH-ALF and positive autoantibodies |

| | | | |
|---|---|---|---|
| Karkhanis et al 2014 | By histology (when available) and ANA and anti- smooth muscle antibody | 361 ALF | Reassigment according to Stravitz et al : 12% of AIH classified as indeterminate. 16% of indeterminate classified as AIH. Corticosteroids not beneficial regardless of the etiology |

IAIHG 1999: review of criteria for diagnosis of autoimmune hepatitis (33)

IAIHG SDC: simplified diagnostic criteria for the diagnosis of autoimmune hepatitis (15)

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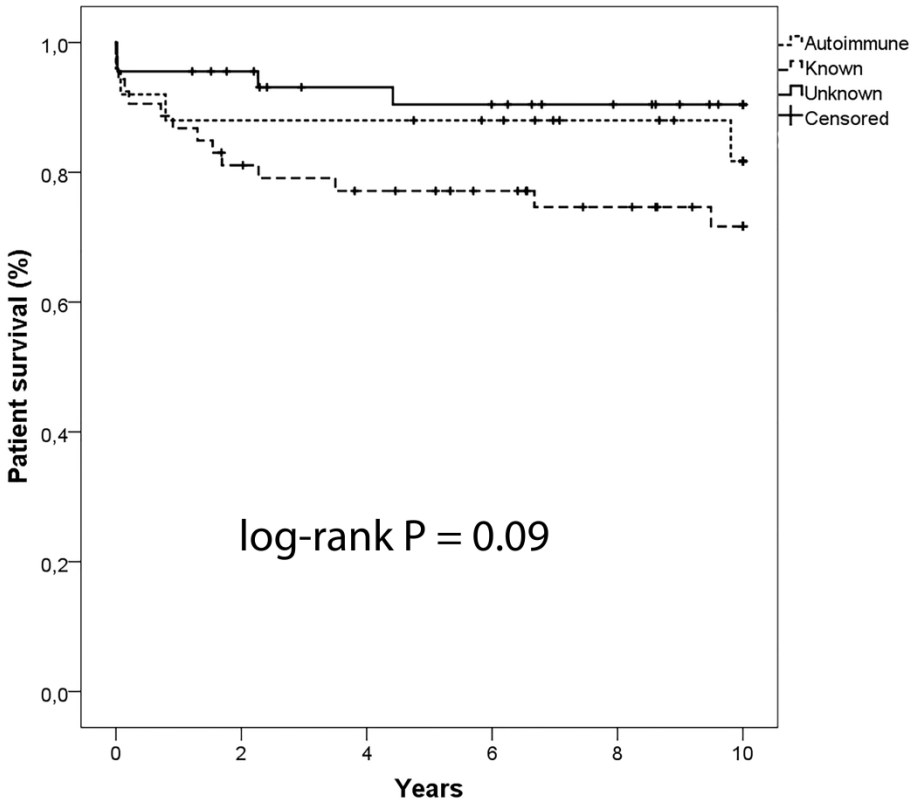


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