Characteristics and Long-term Outcome of 535 Patients with Histologically Confirmed Autoimmune Hepatitis (AIH) - A Single Center Experience of 18 Years

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Abstract

Introduction: Autoimmune hepatitis (AIH) is a rare liver disease with a favorable prognosis following immunosuppression. In this work-up, we present our long-term experience with this patient collective.

Patients and Methods: Overall, we were able to retrospectively evaluate data from 535 patients with histologically confirmed AIH over a period of 18 years between 2002 and 2020.

Results: As expected, almost ¾ of the patients were women (74.5 %) of middle age (47.0 ± 14.9 years). Type I AIH was diagnosed in almost all patients (97.5 %). However, 88 patients (16.4 %) revealed an overlap to primary biliary cholangitis (PBC). In contrast, overlap to primary sclerosing cholangitis (PSC) was detected in only 22 patients (3.7 %). Regarding auto-antibody profile, positivity for anti-nuclear antibodies (ANA) was found in 388 patients (72.5 %); smooth-muscle actin (SMA)-titer was positive in 90 patients (16.8 %), anti-mitochondrial antibodies (AMA) were detected in 43 individuals (8.0 %), and we found positive p-anti-neutrophil cytoplasmic antibodies (p-ANCA) in 12 patients (2.2 %). More than ¾ of the patients (n = 417 ≈ 77.9 %) were initially treated with corticosteroids (1 mg/kg/day) and this therapy was continued in almost all subjects (97.4 %) in low dose (5 - 7.5 mg/day) as maintenance therapy. Steroid-saving and remission-maintaining therapy with azathioprine was carried out in 380 patients (71.0 %). Mycophenolate mofetil (MMF) or calcineurin-inhibitors (CNI) were used as second- or third-line immunosuppression. Acute liver failure (ALF) - as the first manifestation of AIH - was diagnosed in 101 patients (18.8 %). Hepatocellular carcinoma (HCC) was detected in at least 6 patients (1.1 %). Liver transplantation (LT) was performed in 51 patients (9.5 %) who progressed to cirrhosis despite immunosuppression. Unfortunately, a total of 45 patients (8.4 %) died of cirrhosis-related complications (infected ascites, bleeding, encephalopathy) without chance for adequate organ offer.

Conclusion: We here present our long-term experience with a significant number of patients diagnosed with AIH over a long observation period of 18 years. In general, patients with AIH can adequately be managed with good clinical outcome at a liver center requiring immunosuppressive therapy. However, HCC-screening, acute-on-chronic (AOC) liver decompensation, or liver transplantation have to be taken into consideration carefully.

Introduction

Autoimmune hepatitis (AIH) is the result of disturbed immunologic homeostasis characterized by immune-mediated destruction of hepatic parenchyma, female gender bias, presence of auto-antibodies, hypergammaglobulinemia, association with other autoimmune conditions, and excellent response to corticosteroid or immunosuppressive treatment [1]. Genetic and environmental factors seem to play a crucial role. Despite being a rare liver disease with an estimated prevalence of 2–17 cases per 100’000 in Europe, we observe a notably increase in disease incidence within the last years [2]. In some cases, patients present an overlap to other hepato-biliary diseases such as primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC).

Despite being a chronic inflammatory liver disease, approximately 20 % of the patients reveal an acute presentation which may be induced by a triggering agent such as previous viral infections or treatment with immune-modifying drugs (DILI-AIH) [3]. Infectious triggers are commonly indicated as being involved in the induction of autoimmune diseases, with Epstein-Barr (EBV) or Cytomegalovirus (CMV) being implicated in several autoimmune liver disorders, such as type I AIH or PBC [4, 5]. A high proportion of patients with acute manifestation can even develop acute liver failure (ALF) as previously reported by our group, particularly in cases of delayed diagnosis or treatment [6, 7].

In the majority of patients clinical and biochemical remission can be induced following oral corticosteroid therapy with 1 mg/kg/day and a tapering-down scheme to 5-7.5 mg steroids per day within 3 months. Usually, steroid-sparing immunosuppression is performed with the use of azathioprine. In cases of azathioprine intolerance, drug toxicity or low-/non-response, other immunosuppressive agents, such as mycophenolate mofetil (MMF) or calcineurin-inhibitors (CNI) like cyclosporine A (CsA) or tacrolimus (FK 506) are used [8].

In addition to on-set and regular monitoring of their drug therapy, patients must also be monitored for liver-related complications. Fortunately, patients with AIH, among all other chronic liver diseases, are those who develop the least number of liver cancers (HCC) or who require liver transplantation (LT) due to progression to liver cirrhosis or fulminant course of the disease [9].

The aim of our current retrospective single center study was to investigate demographic characteristics, laboratory profiles, response to immunosuppressive therapy, clinical course, and outcome of especially these patients in order to share our experience as an excellence center for liver diseases with a total number of 535 patients with histologically-proven AIH over a long time period of 18 years.

Patients And Methods

Patient information, data collection, and ethical considerations

In this retrospective study between 07/2002 and 06/2020, a total of 535 consecutive patients with histologically confirmed AIH were analyzed. AIH was diagnosed according to the “Simplified Diagnostic Scoring System of the International Autoimmune Hepatitis Group” including the analysis of auto-antibodies, immunoglobulins, histological findings, and viral markers [10, 11]. Liver histology was available for all of our patients and was obtained either by percutaneous- or laparoscopy-guided biopsy (Figs. 1 and 2). The University Clinic of Essen ethics committee approved the retrospective, anonymous analysis of the data, and the study was conducted according to the principles expressed in the Declaration of Helsinki. All patients gave their written informed consent prior to study inclusion.

Laboratory parameters

At initial presentation, liver enzymes, total bilirubin, serum creatinine, INR, albumin, alpha-fetoprotein (AFP), IgG, -globulins, antibody profiles (ANA, AMA, ANCA, SMA, LKM, and SLA), viral markers, and finally, HLA-loci were analyzed in each included patient.

Ultrasound, FibroScan, and liver biopsy

Ultrasound examination (GE Healthcare, Solingen, Germany), FibroScan (Echosens, Paris, France), and liver biopsy (either percutaneous- or laparoscopy-guided) were performed in all patients.

Immunosuppressive therapy

After diagnosis of AIH, most of the patients received corticosteroid therapy (1 mg/kg body weight) with a consecutive down-tapering to 5-7.5 mg steroids daily as maintenance therapy. Further immunosuppressive therapy was conducted in dependence to steroid response and patient's clinical profile using predominantly azathioprine (1-1.5 mg/kg body weight/d), MMF (2 x 1'000 mg/d) or CNI (dose adapted to drug level), respectively.

Statistical analysis

Statistical analysis was performed using GraphPad Prism, version 6.00 for MacOsX (GraphPad Software, San Diego, USA). For descriptive statistics median and IQR were determined. All variables were tested for normal distribution with the Kolmogorov-Smirnov test, the Shapiro-Wilk test, and calculation of skew and kurtosis. The Mann-Whitney U test was used to compare differences between independent groups. Categorical data were tested with the chi-square test and the Kruskal-Wallis test was used for multiple comparisons. A p value < 0.05 was considered statistically significant.

Results

Patient demographics and laboratory data

As expected, most of our patients were female with 401 out of 535 patients (74.5 %). After all, 134 men (25.5 %) were diagnosed with AIH. Median age of our study population was 47.0 ± 14.9 years. Type I AIH was present in almost every patient (n = 522) reaching 97.5 % and type II AIH was detected in the remaining 13 patients (2.4 %). Interestingly, 101 patients (18.8 %) presented acute liver failure as their first manifestation of AIH. Overlap to PBC was present in 88 patients (16.4 %) and overlap to PSC was found in 22 patients (3.7 %). Biochemical and clinical remission following corticosteroid therapy could be achieved in the majority of our patients (n = 394 patients; 73.6 %) within the first year after initiation. During the follow-up controls within the observation period of 18 years, 45 patients (8.4 %) faced acute-on-chronic (AOC) hepatic decompensation like infected ascites (SBP), variceal bleeding, hepatic encephalopathy or hepato-renal syndrome (HRS) leading unfortunately to cirrhosis-related death. However, a small number of patients (n = 6; 1.1 %) developed hepatocellular carcinoma (HCC). Despite immunosuppressive therapy, a remarkable proportion of patients with AIH progressed to end-stage liver cirrhosis with the necessity of liver transplantation (LT). Finally, this procedure was performed in 51

patients (9.5 %) out of our cohort. Favorable course was documented in these transplanted patients during their out-clinic visits. Patients' demographics and further laboratory data are summarized in Table 1.

An overview of the crucial blood values at initial presentation is depicted in Table 2. Notably, patients with acute liver failure (ALF) as their first presentation of autoimmune hepatitis showed extremely high liver enzymes, partly in combination with severe jaundice and deterioration of the coagulation.

Antibody profiles and HLA-typing

Regarding auto-antibody profiles, ANA-titer was positive in 388 patients (72.5 %), SMA-titer was positive in 90 patients (16.8 %), AMA-titer was positive in 43 patients (8.0 %), SLA-titer was positive in 33 patients (6.1 %), LKM-titer was positive in 13 patients (2.4 %), and finally, p-ANCA-titer was positive in 12 patients (2.2 %). Data on HLA-loci demonstrated the following results: HLA-A1 positivity was present in 82 patients (15.3 %), HLA-B8 in 78 patients (14.5 %), HLA-DR3 in 86 patients (16.0 %), and last but not least, HLA-DR4 was detected in 74 (13.8 %) of our patients (Table 3).

Overlap to autoimmune diseases

In the next step, we examined which extra-hepatic autoimmune diseases were present in our collective. It should be emphasized that a total of 64 patients (11.9 %) suffered from autoimmune thyroiditis type Hashimoto - followed by patients with inflammatory bowel disease (IBD). There was a total of 26 patients (4.8 %) – 18 patients (3.3 %) suffering from ulcerative colitis (UC) and 8 patients (1.5 %) from Crohn's disease (MC). Rheumatoid arthritis (RA) was diagnosed in 22 patients (4.1 %). Furthermore, 16 patients (2.9 %) showed Sjogren's syndrome, 13 patients (2.4 %) were diagnosed with type A autoimmune gastritis, 9 patients (1.6 %) with systemic lupus erythematosus (SLE), and finally, additional 9 patients (1.6 %) with autoimmune hemolytic anemia (AIHA) (Fig. 1).

Viral hepatitis serology

Of course, virological status of our patients is also of clinical importance. Patients with active replicative viral disease were excluded from the study. Table 4 gives an overview of the virus infections with sero-prevalence in our study population. A previous hepatitis A-infection was present in 43 patients (8.0 %) with autoimmune hepatitis; followed by a previous hepatitis B-infection in 28 patients (5.2 %). After all, non-replicative hepatitis E was diagnosed in 17 (3.1 %) of our 535 patients. It is worth mentioning in this context that active hepatitis viruses can induce autoimmune phenomena or diseases such as type I and type II autoimmune hepatitis (12).

Liver histology

Liver biopsy (either percutaneous- or laparoscopy-guided) was performed in all of our patients (Fig. 2) and exemplarily demonstrated severe inflammation with typical interface-hepatitis. Furthermore, many plasma cells extending from the portal tract into the adjacent liver parenchyma were also detected in numerous AIH samples (Fig. 3).

Immunosuppressive therapy and survival analysis

Most of the patients (n = 417) were initially treated with corticosteroids and steroid therapy was continued to maintain remission in 97.4 % (n = 406 patients). Immunosuppression with azathioprine was preferentially used as first-line in 380 patients (71.0 %). However, due to drug intolerance or toxic hepatitis, therapy with azathioprine had to be stopped in 75 patients (14.0 %). Patients were switched to second or third-line immunosuppressive therapy with cyclosporine A (CsA), tacrolimus (FK 506) or mycophenolate mofetil (MMF), respectively. Remission of underlying AIH within the first year of diagnosis could be achieved in 394 patients (73.6 %). Moreover, 20-year cumulative survival was significantly improved in patients with AIH maintaining remission (91.6 vs. 56.0 %; $p < 0.0001$) (Fig. 4). In addition, liver-related complications and 20-year mortality was increased in patients without biochemical remission as compared to AIH patients with normal liver enzymes and remission (97.8 vs. 73.5 %; $p < 0.0001$) (Fig. 5).

Liver transplantation was indicated and performed in 51 patients (9.5 %) who presented acute liver failure or progressed to cirrhosis despite immunosuppression. Regrettably, a total of 45 patients (8.4 %) died of cirrhosis-related complications (infected ascites, bleeding, encephalopathy) without chance for adequate organ offer.

Discussion

This is a long-term observational study over a time period of 18 years in a German cohort with a significant number of patients (n = 535) diagnosed with AIH [13–15]. Moreover, liver histology as a hallmark of the “International AIH-Score” was gained in each included patient.

In daily clinical practice, AIH commonly presents as a chronic inflammatory liver disease. The majority of patients are diagnosed due to repeatedly elevated transaminases in check-up examinations without having any complaints. From the immunological perspective, disruption of the immune tolerance to autologous liver antigens may be a trigger for the induction of this rare autoimmune liver disease [16–18].

As expected, patients of our cohort were middle-aged and predominantly of female gender. In addition, type I AIH with ANA-positivity, was almost thoroughly observed in our study population. Overlap to other autoimmune liver diseases like PBC and PSC or to further extra-hepatic disorders were frequently observed [19]. Compared to other common liver diseases in Germany as viral or (non-) alcoholic steatohepatitis (NASH), patients diagnosed with autoimmune liver disease have fortunately a benign course under initial corticosteroid therapy followed by a sufficient immunosuppressive therapy using in general azathioprine with credible liver-related complications. As expected and demonstrated by us, clinical and biochemical remission in patients diagnosed with AIH is associated with a significantly improved overall-survival and reduced acute-on-chronic liver-related complications.

Compared to e.g. HCV- or alcohol-induced cirrhosis (ASH), development of HCC is not very common in AIH patients. Therefore, we did not focus on the different possibilities to treat HCC like the use of molecular-targeted therapies or selective internal radiation therapy (SIRT). Nevertheless, there is still a small group of AIH patients revealing low or even non-response to different immunosuppressive agents like mycophenolate mofetil, calcineurin inhibitors (tacrolimus/cyclosporine A), rituximab or plasmapheresis [20]. In these patients, liver inflammation with elevated transaminases progresses to fibrosis and in long-term course to end-stage liver cirrhosis with its sequela mentioned previously. In conclusion, liver transplantation is the only therapeutical option in these refractory patients - as we performed it in 51 patients.

In future, we should work on more potent immunosuppressive regimes and the goal should be to avoid the necessity of liver transplantation in patients with AIH because of its benign character. Risk factors for non-recovery among our patients in a sub-group analysis were increased age at AIH diagnosis, missing remission of liver enzymes following immunosuppression after 1 year, and a high MELD-score > 26 points [21].

Limitations of our study are of course the retrospective character and the case-by-case observational study at a single liver center. Nevertheless, we would like to emphasize that we were able to include a remarkable number of patients offering liver histology and a long-term follow-up with important data for the hepatologist. In summary, we do observe an increase in AIH incidence world-wide. Despite its benign character, some of the AIH patients need a close follow-up - on the one hand - to detect cirrhosis or HCC in early stages and - on the other hand - to escalate immunosuppressive therapy to induce and keep remission in disease activity.

Declarations

Ethics approval and consent to participate:

The University Clinic of Essen ethics committee approved the retrospective, anonymous analysis of the data, and the study was conducted according to the principles expressed in the Declaration of Helsinki. All patients gave their written informed consent prior to study inclusion.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets (raw data) used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

All authors have nothing to declare.

Funding:

No funding was obtained for this study.

Authors' contributions:

MB performed the liver biopsies. JK collected the raw data. BM did the statistical analyses. HAB examined the liver specimens. GG had the idea and reviewed the project. AK treated the patients.

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Authors' information:

Associate Professor Dr. Kahraman (MD) is the Head of the Department of Gastroenterology, Hepatology, and Infectious Diseases at the Max Grundig Clinic in Bühl/Baden, Germany.

References

1. Wang Q, Yang F, Miao Q, et al. The clinical phenotypes of autoimmune hepatitis: A comprehensive review. J. Autoimmun. 2016;66:98–107.
2. Lv T, Li M, Zeng N, Zhang J, et al. Systematic review and meta-analysis on the incidence and prevalence of autoimmune hepatitis in Asian, European, and American population. J Gastroenterol Hepatol. 2019 Oct;34(10):1676–1684
3. Kessler WR, Cummings OW, Eckert G, et al. Fulminant hepatic failure as the initial presentation of acute autoimmune hepatitis. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 2004;2:625–631.
4. Mendizabal M, Marciano S, Videla MG, et al. Fulminant presentation of autoimmune hepatitis: clinical features and early predictors of corticosteroid treatment failure. Eur. J. Gastroenterol. Hepatol. 2015;27:644–648.
5. Rigopoulou EI, Smyk DS, Matthews CE, et al. Epstein-barr virus as a trigger of autoimmune liver diseases. Adv. Virol. 2012;2012:987471.

6. Buechter M, Manka P, Heinemann FM, et al. Potential triggering factors of acute liver failure as a first manifestation of autoimmune hepatitis-a single center experience of 52 adult patients. World J Gastroenterol. 2018 Apr 7;24(13):1410–1418.
7. Bernal W, Wendon J. Acute liver failure. N. Engl. J. Med. 2013;369:2525–2534.
8. Anastasiou OE, Dogan-Cavus B, Kucukoglu O, et al. Corticosteroid Therapy Improves the Outcome of Autoimmune Hepatitis-Induced Acute Liver Failure. Digestion. 2018;98(2):104–111
9. Tansel A, Katz LH, El-Serag HB, et al. Incidence and Determinants of Hepatocellular Carcinoma in Autoimmune Hepatitis: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2017 Aug;15(8):1207–1217.
10. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. Hepatol. Baltim. Md. 2008;48:1540–1548.
11. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatol. Baltim. Md. 2008;48:169–176.
12. Thodou V, Buechter M, Manka P, et al. Course of hepatitis E infection in a patient with rheumatoid arthritis and autoimmune hepatitis: A case report. Medicine (Baltimore). 2017 Dec; 96(51): e9407.
13. Sebode M, Kloppenburg A, Aigner A, et al. Population-based study of autoimmune hepatitis and primary biliary cholangitis in Germany: rising prevalences based on ICD codes, yet deficits in medical treatment. Z Gastroenterol. 2020 May;58(5):431–438.
14. Lohse AW, Gerken G, Mohr H, et al. Relation between autoimmune liver diseases and viral hepatitis: clinical and serological characteristics in 859 patients. Z Gastroenterol. 1995 Sep;33(9):527–33.
15. Kanzler S, Löhr H, Gerken G, et al. Long-term management and prognosis of autoimmune hepatitis (AIH): a single center experience. Z Gastroenterol. 2001 May;39(5):339–41, 344–8.
16. Czaja AJ. Autoantibodies as prognostic markers in autoimmune liver disease. Dig. Dis. Sci. 2010;55:2144–2161.
17. Aizawa Y, Hokari A. Autoimmune hepatitis: current challenges and future prospects. Clin. Exp. Gastroenterol. 2017;10:9–18.
18. Lauletta G, Russi S, Pavone F, et al. Autoimmune Hepatitis: Factors Involved in Initiation and Methods of Diagnosis and Treatment. Crit. Rev. Immunol. 2016;36:407–428.
19. Arndtz K, Hirschfield GM. The Pathogenesis of Autoimmune Liver Disease. Dig. Dis. Basel Switz. 2016;34:327–333.
20. Yeoman AD, Westbrook RH, Zen Y, et al. Prognosis of acute severe autoimmune hepatitis (AS-AIH): the role of corticosteroids in modifying outcome. J. Hepatol. 2014;61:876–882.
21. Lleo A. Survival After Liver Transplantation for Autoimmune Hepatitis: Are We Messing With the Immune System? Liver Transpl. 2020 Jul;26(7):861–862.

Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

Figure 1

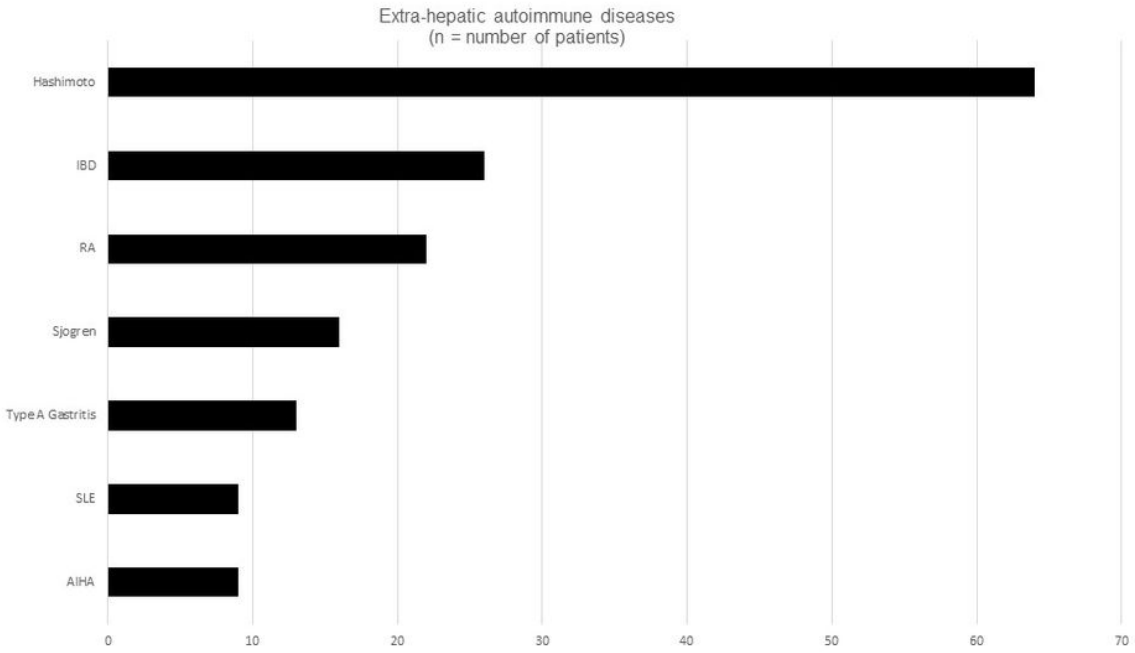

Figure 1

Overlap to extra-hepatic autoimmune disorders are shown.

Figure 2

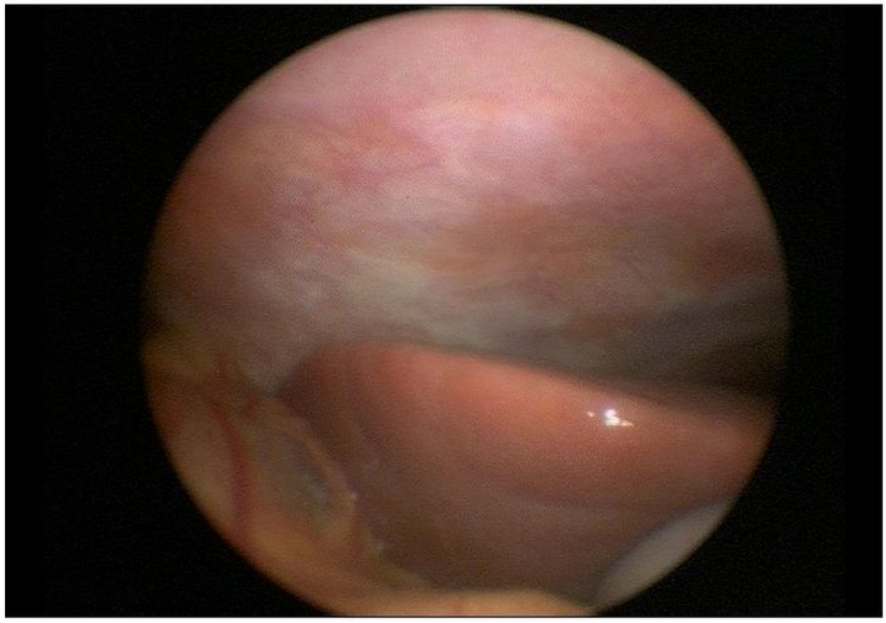

Figure 2

Exemplarily, mini laparoscopy of a patient with AIH demonstrating the right liver lobe with diffuse swelling, capsular fibrosis, and regenerative nodules.

Figure 3

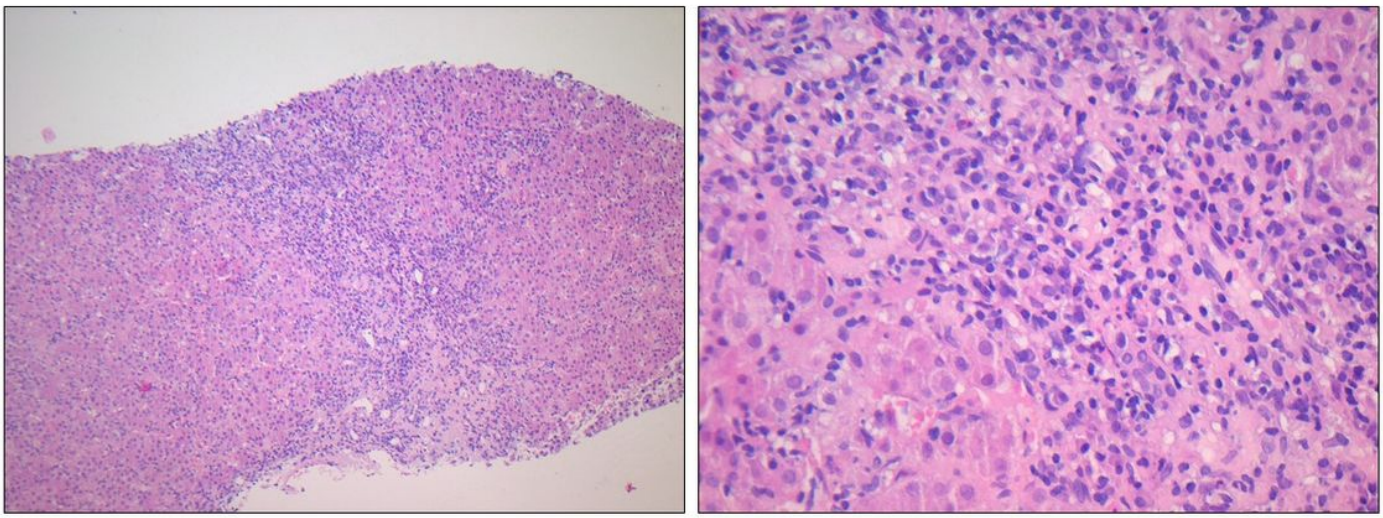

Figure 3

Left panel (magnification x100) showing severe inflammation with interface-hepatitis. Right panel (magnification x400) revealing many plasma cells extending from the portal tract into the adjacent liver parenchyma.

Figure 4

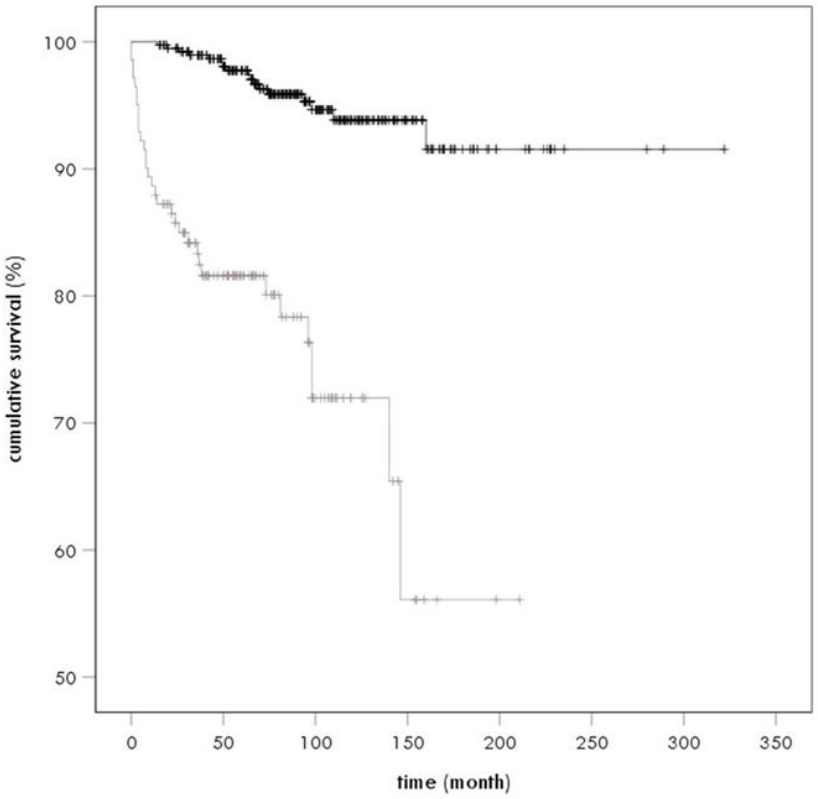

Figure 4

Cumulative survival is significantly improved in patients with AIH maintaining remission (black line).

Figure 5

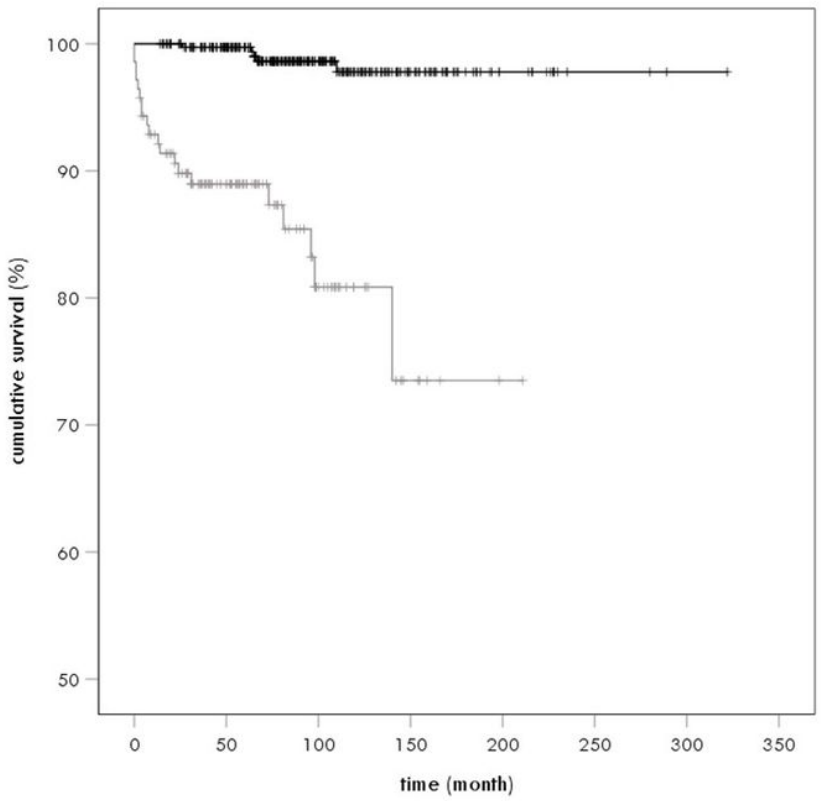

Figure 5

Liver-related complications and mortality is significantly decreased in patients presenting remission (black line).

Supplementary Files

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- Table1.jpg
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