Comparison of clinical features and liver histology in liver failure caused by autoimmune hepatitis with different prognosis

Huili Wu[1], Hongbo Shi[2], Hui Liu[3], Yanmin Liu[4], Zhongping Duan[1,5]

[1]Complicated Liver Diseases and Artificial Liver Center, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China;
[2]Institute of Liver Diseases, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China;
[3]Department of Pathology, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China;
[4]Department of Hepatology Immunology, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China;
[5]Beijing Municipal Key Laboratory of Liver Failure and Artificial Liver Treatment Research, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China.

To the Editor: Autoimmune hepatitis (AIH) is a type of liver parenchymal inflammation mediated by the autoimmune response of liver cells. AIH was previously considered to be a chronic liver disease, but recent observers have confirmed that AIH patients can have acute onset or even liver failure (AIH-LF).[1] The incidence of AIH-LF has also increased. Once LF occurs, the mortality rate within 90 days could reach >40%.[2] Therefore, the occurrence of LF has a major impact on the prognosis of AIH. Although AIH-LF has a low incidence and a high mortality rate, some cases can still be cured by treatment. The clinical characteristics that may affect the prognosis of patients with AIH-LF are still unclear. To clarify the factors affecting the prognosis of AIH-LF, we compared the clinical characteristics of two groups of AIH-LF patients with different prognosis.

This study was approved by the Ethics Committee of the Beijing YouAn Hospital, Capital Medical University. Written informed consent was obtained from all participants.

We enrolled 53 patients with AIH-LF, who were treated at our center from October 2009 to October 2019. Of the 53 patients, there were four males and 49 females with a mean age of 48.7 ± 14.7 years (range: 11–84 years). All patients were scored according to the scoring system of the International Autoimmune Hepatitis Group in 1999 or simplified AIH score.[3] Diagnosis of LF was according to the Chinese guidelines for diagnosis and treatment of LF.[4] Patients were divided into improvement (I) group ($n = 26$) and deterioration (D) group ($n = 27$). Improvement was defined as clinical cure or amelioration without liver transplantation within 6 months. Deterioration was defined as worse condition than that at admission or death from LF. Routine serological indices, such as liver function, blood cell analysis, circulating autoantibodies, serum immunoglobulin, serum a-fetoprotein (AFP), and hepatotropic virus, were performed in all patients and detected at the first visit before therapy. Histological specimens were available in 23 patients and were reviewed retrospectively and blindly by two pathologists in our facility. The first-line treatment was defined as the standardized treatment with corticosteroids and/or azathioprine drugs. Data on mortality, improvement periods, and outcomes were available from stored medical records and consultations with the patients' physicians or follow-up of the patients and their family members, which ended on the date of death, liver transplantation, or the end of the study. In all patients who underwent transplantation, their organs were available from voluntary donations.

We found that gender and age structure in the two groups were similar and the peak age of onset was 41 to 60 years. Twenty (76.9%) patients were cured and six (23.1%) patients were improved in the I group, while 11 (40.7%) patients survived because of liver transplantation and 16 (59.3%) patients died (one after liver transplantation) in the D group. About 59.2% (16/27) of patients who had been diagnosed with AIH for >6 months in the D group were higher than 34.6% (9/26) in the I group ($P = 0.039$), and the average interval from diagnosis of AIH to occurrence of liver failure in the D group was 26.5 months, which was longer than 13.0 months in the I group ($P = 0.009$). Patients in the I group were more likely to have subacute liver failure (SALF) (46.2% *vs.* 14.8%, $P = 0.004$) and early-stage LF on admission (73.1% *vs.* 40.7%, $P = 0.018$), but less acute-on-chronic liver failure or subacute acute-on-chronic liver failure (ACLF/SACLF) (50.0% *vs.* 74.1%, $P = 0.035$), end-stage LF (3.8% *vs.*

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001677

Correspondence to: Dr. Zhongping Duan, Complicated Liver Diseases and Artificial Liver Center, Beijing YouAn Hospital, Capital Medical University, 8 Xitoutiao, Youwai Street, Beijing 100069, China
E-Mail: duan@ccmu.edu.cn

Chinese Medical Journal 2022;135(6)

Received: 27-08-2021; **Online:** 05-10-2021 **Edited by:** Yanjie Yin and Xiuyuan Hao

25.9%, $P = 0.018$), or cirrhosis (30.8% *vs.* 43.7%, $P = 0.033$) than in the D group. More patients in the I group received steroids or immunosuppressive drugs (80.8% *vs.* 44.4%, $P = 0.018$). Patients in the D group had more symptoms and complications, such as anorexia, bacterial infection, renal insufficiency ($P < 0.050$). The laboratory tests of the two groups were similar, but the AFP level and the former infection of hepatitis B virus and parvovirus B19 in the I group were significantly higher ($P = 0.016$ and 0.024, respectively). In addition, the detection of autoantibodies in the two groups was similar. Severe interface hepatitis was more common in the I group ($P = 0.033$), but the stage of liver fibrosis and bile duct injury were more severe in the D group ($P = 0.033$ and 0.002, respectively) [Table 1].

In our study, about 59.2% of the AIH-LF patients in the D group were diagnosed with AIH before the occurrence of LF and had started treatment with steroids or immunosuppressant drugs. In contrast, only 34.6% of the patients in the I group were diagnosed with AIH. About 74.1% of AIH-LF patients in the D group were diagnosed with ALF/SALF, compared with 50.0% in the I group. This indicated that some patients had indistinguishable AIH (undiagnosed chronic AIH before the occurrence of LF) and always had worse prognosis. We found that there were at least two reasons. On the one hand, chronic AIH patients with long-term use of steroids or immunosup-pressant drugs were more likely to develop infection and serious complications because of the continuous immuno-suppression, which affected the continued use of steroids or

Table 1: Comparison of clinical characteristics between improvement and deterioration LF-AIH patients.

Characteristics	I group ($n = 26$)	D group ($n = 27$)	P
Sex (M/F)	2/24	2/25	NS
Age at onset (years)	49.5 (24.0–84.0)	47.9 (19.0–71.0)	NS
AIH diagnosed >6 months	9 (34.6)	16 (59.2)	0.039
Interval from diagnosis of AIH to LF (months)	13.0 (0.5–72.0)	26.5 (0.5–120.0)	0.009
Classification of LF			
(Sub) Acute	13 (50.0)	6 (26.9)	0.035
Acute	1 (3.8)	3 (11.1)	NS
Subacute	12 (46.2)	3 (14.8)	0.004
(Sub) Acute-on-chronic	13 (50.0)	21 (74.1)	0.035
Acute-on-chronic	2 (7.7)	6 (22.2)	NS
Subacute-on-chronic	11 (42.3)	15 (51.9)	NS
Stage of LF on admission			
Early (30% <PTA ≤40%)	19 (73.1)	11 (40.7)	0.018
Middle (20% <PTA ≤30%)	6 (23.1)	9 (33.3)	NS
End (PTA ≤20%)	1 (3.8)	7 (25.9)	0.018
MELD scores	20.3 (17.9–26.6)	23.8 (18.3–35.3)	NS
Classification of AIH			
Idiopathic AIH	13 (50.0)	18 (66.7)	NS
drug-induced AIH	9 (34.6)	5 (18.5)	NS
Overlap syndrome	4 (15.4)	4 (14.8)	NS
Cirrhosis	8 (30.8)	14 (43.7)	0.033
Other autoimmune diseases*	8 (30.8)	10 (37.4)	NS
Therapy after LF			
Steroids	21 (80.8)	12 (44.4)	0.006
Steroids and azathioprine	2 (7.7)	1 (3.7)	NS
Artificial liver plasma exchange	8 (30.8)	9 (33.3)	NS
Symptoms			
Anorexia	8 (30.8)	16 (59.3)	0.020
Bacterial infection	13 (50.0)	21 (77.8)	0.035
Renal insufficiency	1 (3.8)	7 (25.9)	0.018
Melena or Hematemesis	0	6 (22.2)	0.023
Laboratory data			
AFP (ng/mL)	109 (1–576)	53 (2–468)	0.017
HBcAb positive	7 (30.4)	14 (66.7)	0.016
PVB19-IgG positive	1 (10.0)	6 (54.5)	0.024
Histological features			
Liver biopsy	15 (57.7)	8 (29.6)	0.039
Severe interface hepatitis	14 (93.3)	4 (50.0)	0.033
Bridging and fusion necrosis	12 (80.0)	7 (87.5)	NS
Portal inflammation	13 (86.7)	8 (100)	NS
Plasma cell infiltration	8 (86.7)	5 (86.7)	NS
Rosette formation	2 (13.3)	3 (12.5)	NS
Bile duct injury	1 (6.7)	6 (75.0)	0.002
Ductular reaction	13 (86.7)	6 (75.0)	NS
Centrilobular necrosis	15 (100.0)	8 (100.0)	NS
Fibrosis	6 (40.0)	3 (37.5)	NS
Stage F0–2	5 (33.3)	1 (12.5)	NS
Stage F3–4	1 (6.7)	4 (50.0)	0.033

Values are presented as median (interquartile range) or *n* (%). *Extrahepatic autoimmune diseases include: Hashimoto thyroiditis, Sjogren syndrome, systemic lupus erythematosus. AFP: Alpha fetoprotein; AIH: Autoimmune hepatitis; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DI-AIH: Drug-induced autoimmune hepatitis; GGT: Glutamyl transpeptidase; HBcAb: Hepatitis B core antibody; IgG: Immunoglobulin G; LF: Liver failure; NS: Not significant; PTA: Prothrombin activity; PVB19: Parvovirus B 19; TBiL: Total bilirubin.

immunosuppressant drugs, resulting in deterioration of the disease. On the contrary, acute AIH patients who had not been treated with steroids or immunosuppressant drugs tended to have better efficacy, because the initial use of steroids or immunosuppressant drugs could quickly alleviate the immune liver injury. On the other hand, decompensated cirrhosis was more common in chronic AIH, which had poor liver tissue regeneration and recovery ability; therefore, LF based on chronic AIH had worse prognosis than that based on acute AIH. We also found that 33.3% of the patients in the D group had reached the middle stage and 25.9% had reached the end stage, However, 73.1% of the patients in the I group were in the early stage. These findings suggested that the stage of LF was associated with prognosis.

The average value of AFP in the I group was 109 ng/mL within 3 days after admission, which was significantly higher than that of the D group (53 ng/mL). Although previous studies have shown that AFP is a tumor marker, it might also be associated with liver regeneration due to the discovery of AFP. Therefore, elevated AFP in patients with LF often indicates an active liver regeneration after exclusion of hepatocellular carcinoma or other tumors, which shows favorable hepatic self-recovery ability and better prognosis. Studies have suggested that AFP could enhance the ability to predict the short-term survival of patients with LF, especially when it is between 76.0 and 252.2 ng/mL.[5]

As part of the pathogenesis of AIH, virus infection can destroy immunotolerance and induce non-specific activation and proliferation of resting T cells and lead to AIH.[6] Our study also suggested that the virus infection rate, especially the former infection rate of HBV and parvovirus B19 in the D group, was higher than that in the I group. However, it was interesting to find that the current infection rate of hepatophilic virus in the two groups was not high. We speculate that immune disorder might occur at the time of previous hepatophilic virus infection, which might be one of the factors promoting disease progression.

The pathological difference between the two groups was that severe interface inflammation was more common in the I group (93.3%), and bridging and fusion necrosis, bile duct injury, and grade 3/4 liver fibrosis were more obvious in the D group. Although plasma cell interface inflammation is a typical pathological feature of AIH, its severity is associated with immune injury and indicates a better response to steroid therapy. However, bridging and fusion necrosis and bile duct injury are the main features of LF, and their severity is related to prognosis.[2] In addition, liver fibrosis was more obvious in the D group, which was related to previous chronic injury or rapid progression of fibrosis caused by acute injury. The specific mechanism of liver fibrosis is still unclear.

In summary, although the incidence of AIH-LF is not high, it can cause high mortality. Different clinical characteristics predict different prognosis, which is important for clinical work. This allows us to detect patients with poor prognosis as early as possible, thereby reducing mortality and improving prognosis. Fortunately, these clinical phenomena have been observed, although the overall number of patients involved in this study was small and from a single-center retrospective study. Therefore, we need more observation and discussion to gain more understanding in the future.

Funding

This study was supported by grants from the National Key R&D Program of China (No. 2017YFA0103000), the National Science and Technology Key Project on "Major Infectious Diseases such as HIV/AIDS, Viral Hepatitis Prevention and Treatment" (Nos. 2012ZX10002004-006, 2017ZX10203201-005, 2017ZX10201201-001-001, 2017ZX10201201-002-002, 2017ZX10201201-004-002, 2017ZX10202203-006-001, 2017ZX10302201-004-002), the "Beijing Municipal Administration of Hospitals" Ascent Plan (No. DFL20151601), the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. ZYLX201806), the Science and Technology Innovation Service Capacity Building-high-precision Discipline Construction Project (No. 11920703) and the Open research project of Key Laboratory of Capital Medical University (No. BJYAHKF2017008).

Conflicts of interest

None.

References

1. Manns MP, Lohse AW, Vergani D. Autoimmune hepatitis-update 2015. J Hepatol 2015;62:S100–S111. doi: 10.1016/j.jhep.2015.03.005.
2. Anand L, Choudhury A, Bihari C, Sharma BC, Kumar M, Maiwall R, *et al*. Flare of autoimmune hepatitis causing acute on chronic liver failure: diagnosis and response to corticosteroid therapy. Hepatology 2019;70:587–596. doi: 10.1002/hep.30205.
3. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, *et al*. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169–176. doi: 10.1002/hep.22322.
4. Liver Failure and Artificial Liver Group CSo ID, Chinese Medical Association; Severe Liver Disease and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. Guideline for diagnosis and treatment of liver failure. Zhonghua Gan Zang Bing Za Zhi 2019;27:18–26. doi: 10.3760/cma.j.issn.1007-3418.2019.01.006.
5. Huang GQ, Xie YY, Zhu PW, Wang XD, Lin Z, Wang Y, *et al*. Stratified alpha-fetoprotein pattern accurately predicts mortality in patients with acute-on-chronic hepatitis B liver failure. Expert Rev Gastroenterol Hepatol 2018;12:295–302. doi: 10.1080/17474124.2018.1424540.
6. Buechter M, Manka P, Heinemann FM, Lindemann M, Baba HA, Schlattjan M, *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;24:1410–1418. doi: 10.3748/wjg.v24.i13.1410.

How to cite this article: Wu H, Shi H, Liu H, Liu Y, Duan Z. Comparison of clinical features and liver histology in liver failure caused by autoimmune hepatitis with different prognosis. Chin Med J 2022;135:735–737. doi: 10.1097/CM9.0000000000001677