CORRESPONDENCE

Open Access

No association of serum ferritin levels with advanced liver fibrosis in untreated German patients with autoimmune hepatitis

Bastian Engel[1,2]* , Elmar Jaeckel[1,2,3] and Richard Taubert[1,2]

Abstract

In the January 2022 issue of BMC Gastroenterology, Chen et al. report an association between serum ferritin levels and the presence of advanced liver fibrosis in patients with treatment-naïve autoimmune hepatitis (AIH). The odds ratio for ferritin in this study was marginally above 1.0. We analyzed our own published data from a German cohort for an association between ferritin levels and the presence of advanced fibrosis in treatment-naïve AIH and were not able to validate the findings of Cheng et al.

Keywords: Biochemical remission, Incomplete response, AIH, Iron, Treatment response

To the editor,

We read with greatest interest the recent work by Chen et al. in BMC Gastroenterology [1] that reported a correlation of parameters of iron metabolism with advanced fibrosis in patients with untreated autoimmune hepatitis (AIH). Chen and colleagues identified ferritin levels above 199 µg/L as a non-invasive predictor of advanced fibrosis (≥ F3) in baseline biopsies from pre-treatment AIH patients in a Chinese retrospective single-center study (n = 97). Although ferritin was slightly associated with advanced fibrosis according to the odds ratio (OR) (95% confidence interval (95%-CI) 1.001–1.004), the association according to the area under the curve was moderate (AUC = 0.738, 95%-CI 0.639–0.822).

We analyzed parameters of iron homeostasis in a similarly sized retrospective single-center cohort of untreated German AIH patients [2]. As we did not investigate an association between ferritin and advanced fibrosis in the initial publication, we reanalyzed our data

to investigate the findings of Chen et al. in our cohort. A detailed histological scoring of fibrosis was available from 85 of 109 patients in our cohort (Table 1). We defined advanced fibrosis as F4–F6 according to Ishak et al. [3], which should correspond to fibrosis stages F3–F4 according to Batts/Ludwig [4] as applied by Chen et al. We replicated univariate binary logistic regression ("Enter"-method, IBM SPSS Statistics 27) but found no predictive capacity of ferritin for advanced fibrosis (ferritin normalized to the upper limit of normal (ULN) OR: 1.917; 95%-CI 0.943–1.096; $p = 0.665$ or ferritin as absolute values in µg/L: OR: 1.000; 95%-CI 1.000–1.000; $p = 0.963$). This was reflected in the ROC analysis with AUCs of 0.574 (95%-CI 0.441–0.708; $p = 0.253$; absolute ferritin values) and 0.556 (95%-CI 0.424–0.689; $p = 0.386$; ferritin values normalized to the ULN) respectively in our German cohort (Fig. 1).We generally prefer to use ferritin values normalized to the upper limit of normal as this approach corrects for differences in the normal range related to sex and age which Chen et al. accounted for by including these parameters in the logistic regression analysis. To allow comparison and fair validation, we present both absolute and normalized ferritin values. Of note, AIH has different genetic and
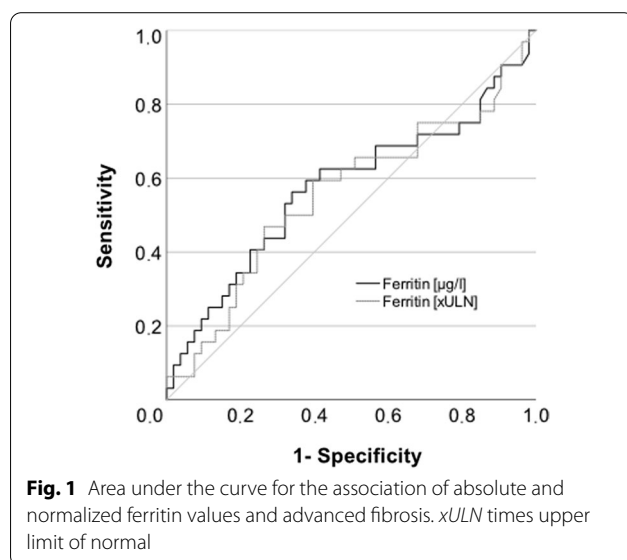
*Correspondence: Engel.Bastian@mh-hannover.de

[1] Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Carl-Neuberg-Street 1, 30625 Hannover, Germany
Full list of author information is available at the end of the article

Engel *et al. BMC Gastroenterology* (2022) 22:528

Page 2 of 4

Table 1 Clinical parameters of patients with or without significant liver fibrosis

	F0-3	F4-6	*p*-value
Patient number	53	32	
Female sex	37 (69.8)	19 (59.4)	0.353
Age [years]	52 (17–78)	59 (20–83)	0.231
Ferritin [µg/l]	423 (15–5869)	755.0 (25.0–7892.0)	0.253
Ferritin [xULN]	1.3 (0.1–16.1)	2.5 (0.1–21.6)	0.386
TIBC [µmol/l]	67 (42–378) (n = 39)	50.0 (24.0–97.0) (n = 24)	**< 0.001**
Transferrinsaturation [%]	35.5 (16.0–100.0) (n = 40)	45.5 (16.0–100.0) (n = 24)	0.282
Iron [xULN]	1.1 (0.5–3.7) (n = 42)	1.0 (0.2–2.3) (n = 26)	0.767
IgG [xULN]	1.2 (0.5–3.6)	1.7 (0.6–4.6)	**< 0.001**
CRP [mg/l]	5.0 (1.0–38.0) (n = 51)	11.5 (1.0–77.0) (n = 28)	0.066
Hb [g/dl]	13.6 (11.4–16.5)	13.1 (9.8–15.8)	0.091
ANA	44 (84.6) (n = 52)	31 (96.9)	0.143
SMA	44 (83.0)	23 (79.3) (n = 29)	0.768
SLA	2 (3.8)	2 (6.3)	0.630
LKM	1 (1.9)	0 (0)	1.0
AIH Score	13 (10–21)	14 (10–21)	0.728
ALT [xULN]	20.8 (0.7–68.5)	15.9 (1.9–118.4)	0.207
AST [xULN]	19.1 (1.2–45.1)	17.2 (2.1–113.2)	0.964
gGT [xULN]	3.6 (0.8–23.9)	5.5 (0.5–34.1)	0.113
ALP [xULN]	1.2 (0.3–5.5)	1.4 (0.5–5.7) (n = 31)	0.131
Bilirubin [xULN]	2.1 (0.3–27.8) (n = 51)	3.7 (0.3–45.2) (n = 31)	0.207
PT [%]	78 (44–112)	63 (39–100) (n = 31)	**0.002**
mHAI	9 (4–15) (n = 49)	8 (3–15) (n = 24)	0.214
Ishak F	1 (0–3)	5 (4–6)	**< 0.001**

Fisher's Exact test was used to compare categorical variables and the Mann–Whitney-U test was used to compare continuous variables. Results are displayed as n (%) or median (range) as appropriate. *xULN* times upper limit of normal; *TIBC* total iron binding capacity; *IgG* immunoglobulin G; *CRP* C-reactive protein; *Hb* hemoglobin; *ANA* antinuclear antibodies; *anti-SMA* anti-smooth muscle actin antibodies; *anti-SLA* anti-soluble liver antigen antibodies; *anti-LKM* anti-liver kidney microsomal antibodies; *ALT* alanine aminotransferase; *AST* asparatate aminotransferase; *gGT* gamma-glutamyl transferase; *ALP* alkaline phosphatase; *PT* prothrombin time; *mHAI* modified histologic activity index; *Ishak F* Fibrosis staging according to Ishak et al

p-values < 0.05 were regarded as significant and are designated in bold

Fig. 1 Area under the curve for the association of absolute and normalized ferritin values and advanced fibrosis. *xULN* times upper limit of normal

environmental risk factors in different age groups and different parts of the world, which could explain differences in clinical presentation at the time point of diagnosis of AIH, i.e. in terms of severity which may affect ferritin levels, too [5–7].

Next, we applied the cut-off value for ferritin of 199 µg/l from Chen et al. to divide our cohort into two groups. Remarkably, the parameters of iron metabolism were significantly different between both groups. In addition, parameters of general (C-reactive protein) and liver-specific inflammation (transaminases, cholestasis parameters) were higher in patients with higher ferritin levels. However, the histological fibrosis stages were not significantly different with regard to patients' ferritin levels (Additional file 1: Table S1). The OR for advanced fibrosis using absolute ferritin levels with

Engel *et al. BMC Gastroenterology*   (2022) 22:528

Page 3 of 4

a cut-off of 199 µg/l as published by Chen et al. was 1.444 (95%-CI 0.571–3.653) (calculated using a cross-tab). Overall, as the findings of Chen et al. and ours contradict each other, further analysis in other cohorts is needed to clarify the relevance of ferritin levels in terms of fibrosis prediction in AIH patients.

The main finding of our analysis of iron homeostasis in untreated AIH patients was the association of elevated ferritin levels ($> 2.09 \times$ ULN) with achieving biochemical remission after initiation of immunosuppressive therapy. In addition to elevated ferritin levels, hypergammaglobulinemia below 1.89 xULN was independently associated with achievement of biochemical remission. Finally, we could develop a treatment response score for AIH using both baseline parameters (ferritin and immunoglobulin G (IgG)). This treatment-response score was significantly associated with the achievement of biochemical remission in a training (AUC: 0.75; 95% CI 0.64–0.86) and validation cohort (AUC: 0.74; 95% CI 0.56–0.92). While almost all patients with a score < 1 achieved biochemical remission to standard of care, 20–40% of patients with a score ≥ 1 did not achieve biochemical remission. The advantage of this treatment-response score is its ability at baseline to predict achievement of biochemical remission, while a more recent treatment response score developed in a European retrospective multicenter study used the 80% decline of aspartate aminotransferase after eight weeks of therapy as predictor of biochemical remission at six and twelve months after diagnosis[8]. Interestingly, the predictive capacity of the 80% AST decline was comparable to our treatment response score (AUC (80% AST decline) = 0.65; 95%-CI 0.59–0.71).

Many centers do not measure parameters of iron homeostasis in the initial assessment of acute hepatitis, including AIH, which explains why our treatment response score has not yet been validated. Unfortunately, Chen et al. did not analyze predictors of treatment response in their Chinese cohort. Although we could not replicate the findings by Chen et al., we would be very interested to see if the prediction of treatment response in AIH by baseline ferritin and baseline IgG before starting therapy could be validated in their Chinese cohort.

Abbreviations
AIH: Autoimmune hepatitis; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; ANA: Antinuclear antibodies; anti-LKM: Anti-liver kidney microsomal antibodies; anti-SLA: Anti-soluble liver antigen antibodies; anti-SMA: Anti-smooth muscle actin antibodies; AST: Aspartate aminotransferase; CI: Confidence interval; CRP: C-reactive protein; gGT: Gamma-glutamyl transferase; Hb: Hemoglobin; IgG: Immunoglobulin G; Ishak F: Fibrosis staging according to Ishak et al.; mHAI: Modified histologic activity index; OR: Odds ratio; PT: Prothrombin time; TIBC: Total iron binding capacity; xULN: Times upper limit of normal.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12876-022-02588-0.

> **Additional file 1. Table S1** Patients' characteristics stratified by ferritin levels

Editor's note
The Editors attempted to invite the authors of the published article to which this letter refers to submit a response; however, we did not receive a response from the corresponding email address provided on the original article, and no reply has been submitted at the time of publication of this letter.

Author contributions
BE and RT designed the study, provided administrative, technical or material support, obtained funding, acquired data and performed statistical analyses. BE and RT drafted the manuscript. RT supervised the study. EJ revised the manuscript, supervised the study and provided important intellectual content. EJ provided administrative, technical or material support. All authors read and approved the final manuscript.

Availability of data and materials
The datasets supporting this article are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The use of retained samples from our clinical laboratories from patients with liver diseases was approved by the local ethical committee (approval number 2817-2015). The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in an a priori approval by the institution's human research committee.

Consent for publication
Not applicable.

Competing interests
The authors report no conflicts of interest regarding this work.

Author details
[1]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Carl-Neuberg-Street 1, 30625 Hannover, Germany. [2]Member of the European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Hannover, Germany. [3]Present Address: Ajmera Transplant Center, Toronto General Hospital, United Health Network, University of Toronto, Toronto, Canada.

Engel *et al. BMC Gastroenterology*   (2022) 22:528

Page 4 of 4

References

1. Chen Q, Gao M, Yang H, Mei L, Zhong R, Han P, Liu P, Zhao L, Wang J, Li J. Serum ferritin levels are associated with advanced liver fibrosis in treatment-naive autoimmune hepatitis. BMC Gastroenterol. 2022;22(1):23.
2. Taubert R, Hardtke-Wolenski M, Noyan F, Lalanne C, Jonigk D, Schlue J, Krech T, Lichtinghagen R, Falk CS, Schlaphoff V, et al. Hyperferritinemia and hypergammaglobulinemia predict the treatment response to standard therapy in autoimmune hepatitis. PLoS One. 2017;12(6): e0179074.
3. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22(6):696–9.
4. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol. 1995;19(12):1409–17.
5. Taubert R, Diestelhorst J, Junge N, Kirstein MM, Pischke S, Vogel A, Bantel H, Baumann U, Manns MP, Wedemeyer H, et al. Increased seroprevalence of HAV and parvovirus B19 in children and of HEV in adults at diagnosis of autoimmune hepatitis. Sci Rep. 2018;8(1):17452.
6. Engel B, Laschtowitz A, Janik MK, Junge N, Baumann U, Milkiewicz P, Taubert R, Sebode M. Genetic aspects of adult and pediatric autoimmune hepatitis: a concise review. Eur J Med Genet. 2021;64(6): 104214.
7. Webb GJ, Hirschfield GM, Krawitt EL, Gershwin ME. Cellular and molecular mechanisms of autoimmune hepatitis. Annu Rev Pathol. 2018;13:247–92.
8. Pape S, Gevers TJG, Vrolijk JM, van Hoek B, Bouma G, van Nieuwkerk CMJ, Taubert R, Jaeckel E, Manns MP, Papp M, et al. Rapid response to treatment of autoimmune hepatitis associated with remission at 6 and 12 months. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2020;18(7):1609–17.