Association between serum ferritin level and the various stages of non-alcoholic fatty liver disease: A systematic review

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Introduction: Non-alcoholic fatty liver disease (NAFLD) has become the most common liver disorder across the world, and non-invasive evaluation approaches are in need to assess NAFLD disease progression. Serum ferritin has been proposed as one of the biomarkers for NAFLD diagnosis in previous studies. This systematic review aims to identify, report, and synthesize studies that investigated the association of serum ferritin level with the various stages of NAFLD among the adult population.

Methods: Three databases – MEDLINE, EMBASE, and Scopus – were systematically searched to obtain potentially relevant publications before July 2022. No restrictions were applied to geographical region, study design, publication type and language. The association between serum ferritin level or different ferritin categories and the various stages of NAFLD was the primary outcome of interest. Title and abstract screenings, data extraction and coding, and quality assessment were independently completed by two authors with discrepancies resolved through discussion with a third author.

Results: Thirty-two studies were included and heterogeneity was considerable. The associations between serum ferritin level and the various stages of hepatic steatosis, fibrosis, inflammation and ballooning and the occurrence of non-alcoholic steatohepatitis (NASH) were investigated but inconsistent associations were reported. Most studies identified serum ferritin to be a predictor of advanced NAFLD, while several revealed the opposite end.

Conclusions: Serum ferritin could be considered to act as a non-invasive biomarker for assessing various stages of NAFLD. Nevertheless, further studies are still in need to confirm its predictive value since this study reported inconsistent associations based on the qualitative synthesis.

Systematic Review Registration: http://www.crd.york.ac.uk/PROSPERO, identifier: CRD42021275630.

Keywords: non-invasive predictor, clinical evaluation, hepatic fibrosis, hepatic steatosis, hepatic inflammation, non-alcoholic steatohepatitis
Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of hepatic pathology with fat excessively accumulating in the hepatic parenchyma in individuals who consume little or no alcohol (1, 2). It has become the most common liver disorder across the world, with a global prevalence estimated to be 25.24% (3) and still on the rise (4), heavy in both clinical and economic burdens. Noticeably, sex differences in NAFLD exist – NAFLD is more prevalent and more severe in men than in women during the reproductive age; the differences usually get smaller after menopause (5).

Generally, NAFLD consists of two subtypes: the first is simple steatosis (also termed as NAFL), which is nonprogressive; the second is non-alcoholic steatohepatitis (NASH), which has not only steatosis but also hepatocyte damage (6). NASH is progressive and may lead to end-stage liver diseases such as fibrosis, cirrhosis, and hepatocellular carcinoma, possibly resulting in liver-related mortality (Figure 1) (7, 8). In the United States, one of the major causes of adult cirrhosis is NASH, with NASH-related cirrhosis recognized as the second indication for liver transplantation (3). Hence, clinical evaluation of the disease progression in NAFLD patients is important for physicians to choose appropriate interventions and assess prognosis.

According to current clinical guidelines, liver biopsy is heavily relied upon for the clinical evaluation of NAFLD, especially for the diagnosis of NASH (9). However, liver biopsy is an invasive procedure and may be accompanied by complications such as bleeding (10), and there might be underestimation of the disease progression, which is caused by sampling bias, since a biopsy specimen represents only ~1/50,000 of the liver volume (11). Therefore, it is suggested to develop and utilize accurate non-invasive evaluation approaches such as imaging and biomarkers, either to combine with liver biopsy for higher validity and reliability, or replace it to avoid invasive diagnostic procedures.

Serum ferritin has been widely studied to assist with disease diagnosis and progression, since it is an acute-phase reactant and a pro-inflammatory cytokine whose concentration is elevated in both infectious and non-infectious inflammation (12). Elevated serum ferritin is reported in about 30% patients diagnosed with NAFLD (13) and it has been proposed as one of the biomarkers for NAFLD diagnosis in previous studies (11, 14). For instance, one Iranian study proposed that the ferritin values of 150 ng/ml in females and 248 ng/ml in males as potential diagnostic cut-off points (15). Studies have also identified it as a potential indicator for the evaluation of NAFLD progression and prognosis, e.g., predicting liver fibrosis in NAFLD patients (16).

To the best of our knowledge, few studies have synthesized existing evidence on the association between serum ferritin and disease progression of NAFLD. This systematic review aims to address the research gap by identifying, reporting, and synthesizing studies that investigated the association of serum ferritin with disease progression of NAFLD.
ferritin level or different ferritin categories with the various stages of NAFLD among the adult population.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (17), and was prospectively registered with PROSPERO (protocol number CRD42021275630; http://www.crd.york.ac.uk/PROSPERO).

Search strategy and eligibility criteria

Three databases – MEDLINE, EMBASE, and Scopus – were systematically searched using a combination of the key terms “ferritin,” “fatty liver,” “hepatic steatosis,” “non-alcoholic steatohepatitis” and related syntax (title/abstract/keywords/MeSH) to obtain potentially relevant publications before July 2022. No restrictions were applied to geographical region, study design, publication type and language. Full search strategies are presented in Supplementary Table 1.

The inclusion criteria were as follows: (1) original and empirical human studies; (2) observational studies including cross-sectional, case-control, and cohort studies; (3) studies that enrolled adult NAFLD patients diagnosed with any approach; (4) studies that explored the association between serum ferritin and disease progression of NAFLD, with confounding factors either adjusted or not.

The exclusion criteria were as follows: (1) review, case-report, abstract, protocol, letter, commentary, meta-analysis and proceeding articles; (2) interventional studies such as clinical trials; (3) experiments performed in vitro or in animals; (4) studies that included pediatric patients or patients diagnosed with other chronic liver diseases, e.g., hepatitis B and C, autoimmune hepatitis, etc.; (5) studies not analyzing the association between serum ferritin and disease progression of NAFLD.

Results identified from the search were imported into a citation manager (Zotero), and duplicates were removed. Two authors (HW and RS) independently extracted and coded the data. Disagreements between the two authors (HW and RS) were resolved through discussion with a third author (CY) until consensus was reached.

Data extraction and quality assessment

Data was extracted from the included studies using a purposive-built data collection form in Excel. The following data was extracted and coded into the form: (1) publication information including first author's name, article title, year of publication; (2) study design including study type, study location, sample size, target population, and selection criteria for participant recruitment; (3) socio-demographic status and medical history of study participants; (4) results of liver imageology (ultrasound, CT, or MRT) and liver biopsy, including grades of steatosis, ballooning, inflammation, fibrosis, cirrhosis, etc.; (5) serum ferritin level, together with its testing methods; (6) approaches or standards employed for NAFLD diagnosis and grading; (7) proven associations between serum ferritin level and the various stages of NAFLD. Two authors (HW and RS) independently extracted and coded the data. Discrepancies during this process were discussed with a third author (CY) until consensus was reached.

Quality of the included studies was assessed using the quality control criteria for proteomic studies reporting potential biomarkers (18). Quality assessment was independently completed by two authors (HW and RS), and disagreements were resolved through discussion with a third author (CY).

Results

A total of 3,234 records were returned from the literature search, of which 1,383 duplicates were removed and 1,707 citations were excluded during title/abstract screenings (Figure 2). We assessed 144 full-text articles, and 32 studies met the predefined inclusion criteria. Figure 3 presents the characteristics of all included studies, categorized by year of study, publication language, study design, study region (the World Health Organization (WHO) regions), and participants. Nearly half of the included studies were published after 2016 (n = 15, 46.9%; Figure 3). Most of the studies were published in English (n = 29, 90.6%), with another one study published in Chinese, one study published in Japanese, and one study published in Korean. Fifteen studies employed cross-sectional design, 10 studies were cohort studies, and seven studies were case-control studies. The included studies covered a total of 28,261 participants, of whom 27,028 were NAFLD patients, including 2,376 NASH patients; one study explored the association of ferritin and the various stages of NAFLD in patients with hypothyroidism (Table 1).

Most studies utilized liver biopsy for NAFLD diagnosis and grading. The studies of Brunt et al. (22) and Kleiner et al. (20) were often referred to as the criteria for grading NAFLD progression, e.g., the grading of steatosis, inflammation and fibrosis stages. As the primary outcome of interest, the association of ferritin and various stages of NAFLD was
proven by multivariate statistical analysis in 15 of the included studies, mostly adjusted for age, sex, BMI and other medical history variables. However, the other 17 studies only conducted univariate statistical analysis.

Serum ferritin level and hepatic steatosis stages

Altogether, 15 studies investigated the association of serum ferritin level and hepatic steatosis stages in NAFLD patients (25, 26, 28–30, 32–34, 39, 41, 45, 48, 49, 51, 53). Among the 15 studies, nine studies consistently reported that NAFLD patients with a higher serum ferritin level were more likely to have an advanced steatosis stage (25, 28–30, 33, 34, 41, 45, 49), usually analyzed by correlation analysis. An Indian study reported significant associations in both females and males (25). Three studies did not find any significant association between serum ferritin level and steatosis stage (32, 48, 53). The other three studies reported inconsistent associations: one Egyptian study identified ferritin as a predictor for steatosis among NAFLD patients with hepatic fibrosis, but the association was not significant among patients without fibrosis (26); one study from the UK reported ferritin to be a predictor in one
group of NAFLD patients, while it was not significantly related to steatosis progression in another group of NAFLD patients (39); the other study from China revealed that ferritin could distinguish Stage 2 or 3 steatosis from Stage 1, but not Stage 3 from Stage 1 or 2 (51). Almost all of the above results were tested by univariate statistical analysis without further exploration via multivariate analysis, except from two studies – one study reporting the predictive role of serum ferritin for steatosis progression that became non-significant in the multivariate analysis (34), and the other showed consistent non-significant associations in both univariate and multivariate analysis (53).

Serum ferritin level and the occurrence of steatohepatitis

The association of serum ferritin level and the occurrence of steatohepatitis among NAFLD patients were investigated in 11 studies (19, 21, 23, 27, 28, 33, 35, 37–39, 44). Nine of the 11 studies compared the serum ferritin level in NAFL patients with it in NASH patients, among which five studies identified it to be a predictor for the occurrence of NASH (23, 27, 28, 35, 38, 44) yet two studies showed non-significant associations (21, 39). Data in these studies were usually analyzed by ANOVA test or t-test. Only three studies further included ferritin into a multivariate model and their result remained the same as it was in the univariate analysis (21, 27) except that in one study, the significant difference ($p < 0.001$) became borderline ($p = 0.05$) (35). Interestingly, one Italian study set 160 and 380 ng/ml as ferritin cut-offs and found both of them were predictive for the occurrence of NASH, with the cut-off of 380 ng/ml having a higher odds ratio in both univariate and multiple logistic regression analyses (27).

An international study and a study from the US compared ferritin levels among patients with different NASH categories – no NASH, suspicious or borderline NASH and definitive NASH, and found a significant difference among the three groups of patients via $\chi^2$ test, but no further analysis was conducted to identify the trend of serum ferritin level in NASH progression (19, 33). Another Iranian study had similar results; there was a difference of serum ferritin levels among patients with mild, moderate and severe steatohepatitis, but no further comparison was made (37).

Five studies analyzed the accuracy of ferritin level for diagnosing NASH by conducting receiver operating characteristic (ROC) curve analysis (19, 28, 35, 38, 44) and reported inconsistent results (Table 2). Two suggested that ferritin had poor accuracy (19, 28), but three demonstrated the opposite end (35, 38, 44).

Serum ferritin level and hepatic fibrosis stages

There are 25 studies exploring the association of serum ferritin level and fibrosis stages in NAFLD patients (19, 21, 23, 26–29, 31–37, 39, 40, 43, 45–51, 53).

Ferritin and hepatic fibrosis stages graded from F0–F4 using Brunt et al.’s standards

Most of these studies employed the Brunt et al. (22) standards to grade fibrosis stages from F0 (absence of fibrosis) to F4 (cirrhosis). In an international study, ferritin was reported to be significantly different in NAFLD patients with different stages of fibrosis via $\chi^2$ test, and further identified that serum ferritin levels higher than the upper limit of normal (ULN, which
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different NAFLD gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | p-value were reported in Univariate analysis, OR (95% CI) and p-value were reported in Multivariate analysis, OR (95% CI) and p-value were reported in correlation analysis | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation analysis | Proven associations by multivariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation analysis | Confounders adjusted for | 
|--------------------------|--------------|---------|--------------|--------------------|---------------------|-------------------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------|
| Wang et al., 2014 (19)   | Retrospective cohort study | UK, Australia, Italy, US | Adult NAFLD patients | 1,014 (586 + 428) | 46.9 ± 6.4 | Liver biopsy | Liver biopsy | Presence of NASH was recorded on pattern and distribution of liver histologic lesions The stage of fibrosis [Kleiner et al. (21)] stage 0: absence of fibrosis-stage 1: perisinusoidal or portal stage 2: perisinusoidal and portal/periportal stage 3: septal or bridging fibrosis stage 4: cirrhosis Advanced fibrosis stage 3–4 fibrosis | 252 ± 9 | Normal ferritin: 485 patients Elevated ferritin level: 351 patients ULN: 200 ng/ml in females and 300 ng/ml in males | Ferritin and NASH category: p = 0.001 Ferritin and fibrosis stage: F0–F1 vs. F2: p = 0.024 Ferritin and fibrosis stage: F0–F1 vs. F3: p = 0.028 Ferritin and fibrosis stage: F2 vs. F3: p = 0.05 | Ferritin and the occurrence of NASH: p = 0.001 (t-test) Ferritin and the occurrence of NASH: p = 0.01 (logistic regression analysis) Ferritin and fibrosis stage (t-test): F0–F1 vs. F2: p = 0.05 F0–F1 vs. F3: p = 0.024 F0–F1 vs. F4: p = 0.028 F1 vs. F2: p = 0.05 | Age, sex, race, BMI, diabetes, ALT, and recruitment site | 
| Buzzetti, 2019 (22)     | Retrospective cohort study | UK, Italy | Adult NAFLD patients | 468 (291 + 177) | 47 ± 13 | Liver biopsy | Liver biopsy | NAFLD lesions were scored according to the NASH Clinical Research Network (CRN) NAS scoring system Hepatic fibrosis [Brunt et al. (22)] 0: absence of fibrosis 1: zone 3 perisinusoidal/peripoortal fibrosis 2: zone 3 and periporal fibrosis 3: septal/bridging fibrosis 4: cirrhosis Significant fibrosis stages (≥2) Advanced fibrosis stages (≥3) | 108 (range 41–314) | Ferritin > ULN: 122 (28%) patients ULN: 200 ng/ml in females and 300 ng/ml in males | Ferritin and the occurrence of NASH: p = 0.001 (t-test) Ferritin and the occurrence of NASH: p = 0.01 (logistic regression analysis) Ferritin and fibrosis stage (t-test): F0–F1 vs. F2: p = 0.05 F0–F1 vs. F3: p = 0.024 F0–F1 vs. F4: p = 0.028 F1 vs. F2: p = 0.05 | Ferritin and advanced fibrosis: p < 0.05 Ferritin and the occurrence of NASH: p < 0.05 | Age, sex, race, BMI, hypertension, diabetes, ALT, iron pattern, Ferritin and advanced fibrosis not reported | 

(Continued)
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD progress approach/tool | NAFLD diagnosis approach/tool | Serum ferritin level, mean ± SD (ng/ml) | Number of NAFLD patients with different gradings, n (%) | N/A | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Proven associations by multivariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|--------------|---------|--------------|-------------------|-------------------|----------------------------|----------------------------|----------------------------------|---------------------------------------------|--------|-----------------------------------------------|-----------------------------------------------|---------------------|
| Canbakan, 2007 (23)       | Prospective cohort study | Turkey | Adult NAFLD patients | 105 (54 + 51) | 46.6 ± 9.7 | Liver biopsy | Liver biopsy | NAFLD group: 71.2 ± 58.2 | N/A | Ferritin and the occurrence of NASH (p = 0.016, t-test) | Ferritin and fibrosis stage (r = 0.35, p < 0.001 (correlation analysis) | N/A |
| Chandok, 2012 (24)        | Prospective cohort study | Canada | Adult NAFLD patients | 482 (227 + 255) | 49.6 ± 3.1 | Liver biopsy or imaging (either liver ultrasound, CT, or MR) | Liver biopsy or imaging | NAFLD without cirrhosis or biopsy: 356 Non-NASH: 90 NASH: 28 Cirrhosis: 20 | N/A | ANOVA test: Ferritin among different groups (p = 0.34) | N/A |
| Chaturvedi, 2020 (25)     | Cross-sectional study | India | Adult patients with hypothyroidism, including NAFLD patients | 108 (35 + 73) | Not reported | Liver ultrasound | Liver ultrasound | Steatosis was graded according to Brunt et al. (22) | N/A | Correlation analysis: Ferritin and steatosis stage among males: r = -0.87%, p = 0.004 | Ferritin and steatosis stage among females: r = -0.87%, p = 0.043 | N/A |
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Proven associations by multivariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|--------------|---------|--------------|---------------------|---------------------|-------------------------------|-------------------------------|---------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------|
| El Nakeeb, 2017 (26)      | Cross-sectional study | Egypt  | Group 1: Healthy adults (control group) Group 2: adult NAFLD patients without hepatic fibrosis Group 3: adult NAFLD patients with hepatic fibrosis | 113 (Sex not reported) Group 1: 30 Group 2: 31 Group 3: 52 | Group 1: 28.03 ± 4.09 Group 2: 29.84 ± 9.27 Group 3: 32.82 ± 12.66 | Liver biopsy Serum and ferritin were graded according to Brunt et al. (22) | Liver biopsy | Liver biopsy Serum and ferritin were graded according to Brunt et al. (22) | Hepatic fibrosis: F1: 37 F2: 5 F3: 10 | Correlation analysis Ferritin and steatosis stage: r = 0.745, p < 0.001 Univariate logistic regression analysis: Ferritin and the occurrence of fibrosis: p = 0.330 | Multivariate logistic regression analysis: Ferritin and the occurrence of fibrosis: p = 0.018 | Referral center, gender, age, waist circumference, ALT, HOMA-IR, glucose tolerance, metabolic syndrome, steatosis stage or fibrosis stage |
| Fracanzani, 2011 (27)     | Cross-sectional study | Italy   | Adult NAFLD patients | 431 (360 + 71) Not reported | Liver biopsy | Liver biopsy Serum and ferritin were graded according to Kleiner et al. (20) | Liver biopsy | Liver biopsy Serum and ferritin were graded according to Kleiner et al. (20) | Steatosis: grade 1: 219 grade 2: 140 grade 3: 70 Fibrosis: 0–1: 301 Fibrosis: 2: 150 | Univariate logistic regression analysis: Ferritin and the occurrence of NASH: Ferritin < 160 ng/ml: Ref Ferritin 161–380 ng/ml: 1.14 (0.83–1.56) Ferritin > 380 ng/ml: 1.42 (1.07–1.89) | Ferritin and fibrosis stage: Ferritin < 160 ng/ml: Ref Ferritin 161–380 ng/ml: 1.42 (1.07–1.89) Ferritin > 380 ng/ml: 1.42 (1.07–1.89) | Referral center, gender, age, waist circumference, ALT, HOMA-IR, glucose tolerance, metabolic syndrome, steatosis stage or fibrosis stage |
| Goh, 2016 (28)            | Prospective cohort study | US      | Adult NAFLD patients | 405 (179 + 226) | Group 1: 48 ± 12 | Liver biopsy Stages of fibrosis, ballooning, steatosis and inflammation were diagnosed following the classification of Kleiner et al. (20) The degree of steatosis (0–3), lobular inflammation (0–3), and ballooning (0–2), made up the 8-point NAFLD activity score (NAS) | Liver biopsy | Liver biopsy Stages of fibrosis, ballooning, steatosis and inflammation were diagnosed following the classification of Kleiner et al. (20) The degree of steatosis (0–3), lobular inflammation (0–3), and ballooning (0–2), made up the 8-point NAFLD activity score (NAS) | NAFLD group: 114 (28) NASH group: 201 (72) | Correlation analysis: r = 0.15, p = 0.001 Correlation analysis: r = 0.15, p = 0.001 | Ferritin and ballooning stage: r = 0.11 (0.02, 0.21), p = 0.021 Ferritin and steatosis stage: r = 0.16 (0.06, 0.26), p = 0.001 | N/A | N/A |
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (ys) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|--------------|---------|--------------|--------------------|------------------|----------------------------|----------------------------|------------------------------------------------|--------------------------------|----------------------------------------------------------------------------------|----------------------------------|
| Hagstrom, 2016 (29)       | Prospective cohort study | Sweden | Adult NAFLD patients | 222 (134 + 88) | Not reported | Liver biopsy | Liver biopsy | The degree of steatosis (0–3), lobular inflammation (0–3), and ballooning (0–2), made up the 8-point NAFLD activity score (NAS) Portal inflammation was scored on a scale of 0–4. Fibrosis was scored according to METAVIR (0–4) | Steatosis grade: 1: 73; 2: 64; 3: 31; Lobular inflammation: 0: 13; 1: 78; 2: 99; 3: 32; Ballooning: 0: 61; 1: 78; 2: 93; 3: 20; 4: 9 | Normal ferritin level: 120 patients; High ferritin level: 89 patients, Cut-offs: 150 ng/ml in females and 350 ng/ml in males Correlation analysis: Ferritin and steatosis grade: r = 0.664, p < 0.001 Logistic regression analysis: Ferritin and the presence of significant fibrosis: OR = 4.64, p = 0.001 | - |
| Hanafy, 2019 (30)         | Case-control study | Egypt | Group 1: healthy adults (control group) | 455 (299 + 156) | Group 1: 38.2 ± 1.8 | Liver ultrasound | Liver ultrasound | The degree of steatosis was measured by controlled attenuation parameter (CAP) via ultrasound: S0: 212–265 dB/m; S1 (5–33% steatosis): 266–303 dB/m; S2 (34–66%): 304–320 dB/m; S3 (>66%): 321–400 dB/m | Steatosis: S0: 71; S1: 21; S2: 77; S3: 103; Fibrosis: F0: 66; F1: 26; F2: 26 | After adjusting for potential confounders, the hazard ratio remained essentially unchanged (HR = 1.10, 95% CI 1.10–1.21, p < 0.05) | Age at baseline (time for liver biopsy), time, the interaction between time and serum ferritin, sex, smoking, diabetes mellitus type 2, hypertension, BMI and fibrosis stage | - |
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|--------------------------|--------------|---------|--------------|--------------------|---------------------|-------------------------------|----------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------|---------------------------------|
| Kawanaka, 2012 [31]      | Prospective cohort study | Japan   | Adult NASH patients with stage 3 fibrosis | 33 (14 + 19) | 57.4 ± 14.4 | Liver biopsy | F3: 82  
F4: 72 | Changes in ferritin between follow-up and baseline:  
Deterioration group (F4) = 106  
Improvement group (F1,2) = 207 | N/A |
| Kim, 2013 [32]           | Prospective cohort study | South Korea | Adult NAFLD patients | 108 (75 + 35) | 39.0 ± 13.3 | Liver biopsy | NAFLD type 1: 1 (1)  
NAFLD type 2: 46 (37.0)  
NAFLD type 3: 39 (31.7)  
NAFLD type 4: 28 (25.9)  
NAS: 0–4 (60.7)  
Fibrosis stage: 0: 19  
F1: 34  
F2: 27  
F3: 30  
F4: 1 | Not reported | Changes in ferritin between follow-up and baseline:  
Deterioration group and improvement group p < 0.05 | N/A |
TABLE 1 Continued

| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin, mean ± SD (μg/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|--------------|---------|--------------|---------------------|---------------------|-----------------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------------------------------------------------------|-------------------------------|
| Kowdley, 2012 (33)        | Cross-sectional study | US Adult NAFLD patients | 628 (235 + 393) | 47.7 ± 11.8 | Liver biopsy | Liver biopsy | Histologic features of NAFLD were assessed by the Pathology Committee of the NAASH Clinical Research Network in a centralized consensus review format | Steatosis: S1: 252 S2: 214 S3: 162 Lobular inflammation <2 under 20x: 319 2–4 under 20x: 238 >4 under 20x: 71 Hepatocellular ballooning None: 198 Mild: 163 More than mild: 268 Fibrosis stage F0: 160 F1: 182 F2: 121 F3: 112 Cirrhosis: 49 NASH diagnosis category No NAASH 125 Insipicous/borderline: 119 | Ferritin <ULN: 418 patients Ferritin ≥ULN and ≤ 1.5 × ULN: 80 patients Ferritin >1.5 × ULN: 128 patients ULN: 200 ng/ml in females and 300 ng/ml in males | χ² test: Ferritin and steatosis grade: p < 0.0001 Ferritin and lobular inflammation: p = 0.026 Ferritin and hepaticlobular ballooning: p = 0.006 Ferritin and fibrosis stage: p < 0.001 Ferritin and NAASH diagnosis category: p = 0.013 | Multivariate logistic regression analysis: Ferritin >1.5 × ULN and the presence of advanced fibrosis (i.e., stage 3 or 4): OR = 1.67; p = 0.028 Ferritin >2.5 × ULN and the presence of advanced fibrosis: OR = 2.46; p = 0.005 | Age at biopsy, sex, presence of diabetes, BMI, ALT |
| Loguercio, 2004 (34)      | Cross-sectional study | Italy Adult NAFLD patients | 365 (230 + 135) | Not reported | Liver biopsy | Liver biopsy | Presence/absence and the entity of steatosis, intra-acinar and portal inflammation, pericellular, portal and perivenular fibrosis, and cirrhosis were semi-quantitatively assessed as follows: absent: 0; mild: ≥ 25%; moderate: ≥ 25–75%; severe: ≥ 75% | Steatosis: Absent: 0 Mild: 31.5% Moderate: 40.5% Severe: 14.8% Portal Fibrosis: Absent: 0 Mild: 32% Moderate: 6.1% Severe: 4.6% Lobular portal inflammation: | Elevated ferritin: approximately 35% of the included patients Cut-off: 150 ng/ml in females and 300 ng/ml in males | χ² test: Ferritin and steatosis stage: p = 0.011 Ferritin and inflammation stage: p = 0.011 Ferritin and fibrosis stage: p < 0.001 Ferritin and cirrhosis (combined with simple steatosis and inflammation/fibrosis): p = 0.01 | When data were processed with the multivariate analysis, ferritin was not found to be an independent predictor of hepatic lesions |

Histologic finding with stage 2 or above fibrosis were also defined as NASH. The stage of fibrosis was scored according to Brunt et al. (22).
| Study (first author, year) | Study design (country) | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|-----------------------|--------------|---------------------|---------------------|-------------------------------|-------------------------------|--------------------------------|-----------------------------|--------------------------------------------------------------------------------|------------------------------------------|
| Manousou, 2011 (35)      | Cross-sectional study (UK) | Adult NAFLD patients | 111 (71 + 40)       | 56 ± 14             | Liver biopsy Non-NASH: either NAFLD or those cases that were thought to be borderline NASH: having inflammation + / - fibrosis. Fibrosis: Group 1 (none or mild fibrosis): patients with fibrosis stages of 0 and 1A according to Kleiner et al. (20) Group 2 (moderate fibrosis to cirrhosis): patients with fibrosis stages of 1B, 1C, 2, 3 and 4 according to Kleiner et al. (20) Steatosis and fibrosis were assessed according to Kleiner et al. (20) Portal inflammation: 0: none to minimal 1: greater than minimal | 228 ± 100 | Abnormal ferritin: 27 (24.5%) patients T-test: Ferritin and the occurrence of NASH: p < 0.001 Ferritin between two fibrosis groups: p < 0.001 Multivariate logistic regression analysis: Ferritin and the occurrence of NASH: adjusted for BMI, DM, AST, Ferritin and fibrosis stage: adjusted for BMI; Ferritin and portal inflammation stage: adjusted for BMI; Ferritin and lobular inflammation stage: adjusted for BMI and DM. | Ferritin and the occurrence of NASH adjusted for BMI, DM, AST. Ferritin and fibrosis stage: adjusted for BMI. Ferritin and portal inflammation stage: adjusted for BMI. Ferritin and lobular inflammation stage: adjusted for BMI and DM. | |
| Moon, 2006 (36)          | Cross-sectional study (South Korea) | Adult NAFLD patients | 38 (35 + 6)         | 34.5 ± 13.7          | Liver biopsy Inflammation and fibrosis were staged according to Brunt et al. (22) | 250.5 ± 243.9 | Correlation analysis Ferritin and inflammation stage: r = 0.518, p = 0.001. Ferritin and fibrosis stage: r = 0.466, p = 0.005 Multivariate logistic regression analysis: Age and BMI | | | | |
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis, regression coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|--------------|---------|--------------|--------------------|-------------------|------------------------------|-----------------------------|--------------------------------------------------------|----------------------------------------|----------------------------------------------------------------|-----------------------------|
| Mousavi, 2018 (37)        | Cross-sectional study | Iran    | Adult NAFLD patients | 30 (17 + 13) | 37.93 ± 12.5 | Liver biopsy | Liver biopsy Staging and grading were performed according to the Brunt et al. (22) scoring | Fibrosis: Stage 0: 7 (37.0) Stage 1: 15 (38.3) Stage 2: 15 (38.3) Stage 3: 2 (5.1) Stage 4: 0 (0) | Ferritin levels above 200: 11 (36.7%) patients | Ferritin between patients without and with steatohepatitis: p > 0.05 (t-test) Ferritin among three grades of steatohepatitis: p = 0.058 (ANOVA test) Ferritin and fibrosis stage: p = 0.224 (correlation analysis) | N/A                          |
| Patilh, 2015 (38)         | Case-control study | India   | Group 1: healthy adults (control group) Group 2: adult NAFLD patients | 105 (77 + 28) Group 1: 50 (37 + 13) Group 2: 55 (40 + 15) | 41.6 ± 13.89 | Liver biopsy | Liver biopsy NAFLD: steatosis with or without inflammation; NASH: steatosis with either ballooning or Mallory Denk bodies, bridging fibrosis or cirrhosis | NAFLD: 35 NASH: 20 (all with fibrosis/cirrhosis) Group 1: 35.2 ± 18.5 Group 2: 31.2 ± 9.4 | Ferritin between NAFLD and NASH patients: p > 0.05 (t-test) Ferritin (cut off 48 ng/ml) between Brunt fibrosis stages 0–2 and 3/4: p = 0.052 (t-test) | N/A                          |

(Continued)
| Study (first author, year) | Study design | Country | Participants | Sample size (M+F) | Mean age±SD (yrs) | NAFLD approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin, level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis, and correlation coefficient (r) and p-value were reported in correlation analysis | Proven associations by multivariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|--------------|---------|---------------|-------------------|-----------------|-------------------|------------------------|--------------------------------|--------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------|
| Ryan, 2018 (39)          | Case-control study | UK       | Group 1: healthy adults (control group) Group 2: adult NAFLD patients Group 3: adult HBS or HCV infected patients Group 4: adult NAFLD patients (validation group) | 505 (396 + 107) Group 3: 30 (25 + 5) Group 4: 404 (333 + 71) | Group 1: 58 ± 10 Group 2: 55 ± 12.7 Liver biopsy and MRI Liver biopsy: Fibrosis and steatosis stage was determined as outlined by Brunt et al. (22) NAFLD: NA score ≥5 MRI: Steatosis was determined by hepatic lipid content (HLC) | MRI HLC in Group 2: 15.2 ±1.2% Fibrosis in Group 2: Mild: 17 (33.3%) Moderate: 16 (31.4%) Severe: 18 (35.3%) NAFLD in Group 4: 171 (49.3%) patients | Liver biopsy: Fibrosis and steatosis stage was determined as outlined by Brunt et al. (22) MRI: Steatosis was determined by hepatic lipid content (HLC) | Liver biopsy and MBS Liver biopsy: Fibrosis and steatosis stage was determined as outlined by Brunt et al. (22) NAFLD: NA score ≥5 MRI: Steatosis was determined by hepatic lipid content (HLC) | Group 2: 157 (age 1,944) Group 4: 2.5 (log10 ng/ml) Hyperferritinemia: 7 patients in Group 2 | Ferritin and MRI-proven steatosis stage (HLC value): r = 0.57, p < 0.0001 Ferritin and histological steatosis: r = 0.5, p < 0.0002 Ferritin and histological inflammatory grade: r = 0.07, p = 0.62 ANOVA test: Ferritin and fibrosis stages (F0/1, F2, F3, F4): p = 0.002 Ferritin and the occurrence of NAFLD: p = 0.12 Group 6: Ferritin and histological grade of steatosis: r = 0.08, p = 0.83 Ferritin and lobular necroinflammation: r = 0.03, p = 0.81 Ferritin and hepatocellular ballooning: r = 0.02, p = 0.71 Ferritin increased significantly from F0/F1 stage to F3 (p = 0.013), and then decreased (p = 0.048) in cirrhosis Linear regression analysis: Ferritin (log10 ng/ml) and steatosis: β = 0.03 (0.03), p = 0.33 Ferritin (log10 ng/ml) and inflammation: β = 0.07 (0.03), p = 0.42 Ferritin (log10 ng/ml) and fibrosis: β = 0.43 (0.02), p = 0.21 | Group 2: Multiple logistic regression analysis: Ferritin was an independent predictor of significant (F2) compared with early (F0/1) fibrosis stages (OR 95% CI): 1.01 (1.00–1.014), p = 0.048 Group 4: Linear regression analysis: Ferritin (log10 ng/ml) and inflammation: β = 0.08 (0.03), p = 0.002 | Group 2: adjusted for age, gender, weight, ALT, adiponectin, HOMA-IR, propeptide of Type III Procollagen (P3NP), hepcidin, and MR liver T2; Group 6: adjusted for age, sex, type 2 diabetes, and alcohol |
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum, ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Proven associations by multivariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|--------------------------|--------------|---------|--------------|-------------------|-------------------|-----------------------------|--------------------------------|----------------------------------------|------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------|
| Seyedian, 2017 (40)      | Cross-sectional study | Iran | Adult NAFLD patients | 284 (202 + 82) | Not reported | Not reported | Liver biopsy | Liver biopsy | NAFLD: 226 Advanced liver stiffness: 58 | High ferritin: 46 (26.2) patients, Low ferritin: 238 (83.8) patients | Ferritin and liver stiffness level | Ferritin and liver stiffness level | N/A | N/A |
| Uysal, 2011 (41)         | Case-control study | Turkey | Group 1: healthy adults (control group) | Group 1: 88 (47 + 41) | Group 1: 48 ± 11 | Group 2: 48 ± 14 | Liver ultrasound | Liver ultrasound | Minimal steatosis: 17 Moderate steatosis: 20 Marked steatosis: 23 | Ferritin between minimal and marked steatosis: p < 0.05 | N/A | N/A |
| Yao, 2019 (43)           | Cross-sectional study | China | Non-obese general population taking their annual health examination, including NAFLD patients | 1,020 (701 + 319) | 43.4 ± 7.4 | 25.4 ± 1.1 | Liver ultrasound | Liver ultrasound | NAFLD patients: 238.7 (415.6–786.6) Low risk fibrosis group: 238.0 (145.5–326.6) Advanced fibrosis group: 308.0 (104.4–786.6) | Ferritin betweenNAFLD/NASH patients: p = 0.006 | Multivariate logistic regression analysis: The ORs (95% CI) and p-values of the associations of ferritin and fibrosis stage are as follows: When adjusted for age, gender, and BMI, 1.194 (1.162–2.612), p < 0.001 | N/A | N/A |
| Yoneda, 2010 (44)        | Case-control study | Japan | Group 1: healthy adults (control group) | Group 1: 106 | Not reported | Not reported | Liver biopsy | Liver biopsy | NAFLD patients: 24 | Ferritin and NASH/NASH: p = 0.008 | N/A | N/A |
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Proven associations by multivariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|--------------------------|--------------|---------|--------------|--------------------|-------------------|-----------------------------|-------------------------------|-----------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------|
| Bugianesi, 2004 (45)     | Cross-sectional study | Italy | Adult NAFLD patients | 367 (sex not reported) | 41 ± 11 | Liver ultrasound | Liver ultrasound: steatotic, macroinflammation and fibrosis were graded according to Brunt et al. (22) with minor modifications. NASH was diagnosed based on the presence of fibrosis (grade 1 or higher) or macroinflammation (grade 2 or higher) | Steatosis: 1: 88 (52.7) 2: 47 (28.1) 3: 32 (19.2) 4: 1 (0.6) | 74 (44.3) | 2.5 (32.9) | 3.2 (37.5) | 2.0 (32.8) | 1.3 (18.0) | 3.2 (18.2) | 4.0 (18.6) | 1.0 (5.6) | 239 ± 235 Cut-off: 130 ng/ml | Univariate logistic regression analysis: Ferritin between mild fibrosis (stage 1–2) and no fibrosis (stage 0): OR (95% CI): 1.32 (1.06–1.67), p = 0.017 Ferritin between severe fibrosis (stage 3–4) and no fibrosis (stage 0): OR (95% CI): 1.49 (1.18–1.88), p = 0.001 Linear regression analysis: Ferritin and steatosis grade: r = 0.309, p < 0.0001 Ferritin and fibrosis grade: r = 0.311, p < 0.0001 Ferritin and inflammation grade: r = 0.041, p = 0.601 Mann-Whitney test: Ferritin between mild and severe fibrosis: p = 0.0001 |
| Shimada, 2002 (46)       | Cross-sectional study | Japan | Adult NASH patients | 81 (40 + 41) | 54 (range 21–82) | Liver biopsy | Liver biopsy: Steatosis and fibrosis were graded according to Brunt et al. (22). Fibrosis was also graded as mild (F0–2) or severe (F3–4) | Mild fibrosis: 58 Severe fibrosis: 23 | Severity of fibrosis: F0: 8 (10) | F1: 29 (36) | F2: 21 (26) | F3: 17 (21) | F4: 5 (7) | F4: 27 (25) | 120 (range 13–520) Cut-off: 200 ng/ml F0–2 fibrosis: 140 (127–520) F3–4 fibrosis: 67 (13–250) | Multivariate logistic regression analysis: Age, sex, and BMI Ferritin between mild fibrosis (stage 1–2) and no fibrosis (stage 0): OR (95% CI): 1.52 (1.06–2.15), p = 0.016 Ferritin between severe fibrosis (stage 3–4) and no fibrosis (stage 0): OR (95% CI): 1.69 (1.18–2.43), p = 0.0045 |

(Continued)
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD approach/tool | NAFLD diagnosis/approach/tool | Number of NAFLD patients with different grade, n (%) | Serum ferritin level, mean ± SD (μg/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Proven associations by multivariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|--------------|---------|--------------|---------------------|---------------------|---------------------|--------------------------|---------------------------------|------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------|
| Angulo, 1999 (47)         | Cross-sectional study | US | Adult NASH patients | 144 (47 + 97) | 50.5 (range 11–77) | Liver biopsy | Degree of fibrosis: 0 = none, normal connective tissue; 1 = mild, foci of pericellular fibrosis in zone 3; 2 = moderate, pericellular or pericellular fibrosis confluent to zone 3 and 2 regions, with or without portal/periportal fibrosis; 3 = severe, bridging or septal fibrosis | Degree of fibrosis: 0: 37 (24) 1: 55 (37) 2: 15 (18) 3: 14 (18) 4: 25 (17) Degree of steatosis: 1: 80 (56) 2: 85 (58) 3: 21 (15) | 221 (6–1,639) Elevated serum ferritin (≥200): 77 (53%) patients Cut-off: 20ng/dl Degree of fibrosis: 0: 228 (24–1,520) 1–2: 246 (6–1,639) 3–4: 194 (11–1,000) Degree of fat infiltration: 0: 187 (11–300) 1–2: 246 (11–1,639) 3–4: 149 (6–1,000) | --- | --- |
| Koruk, 2003 (48)         | Case-control study | Turkey | Group 1: healthy adults (control group) Group 2: adult NASH patients | 34 (24 + 10) | 34 (11 + 23) | Group 1: 40 ± 10.3 | Liver biopsy | Inflammation, fibrosis and steatosis were graded according to Brunt et al. (22) | Steatosis: 1: 11 (33.3) 2: 8 (25.0) 3: 3 (9.1) Inflammation: Minimal: 7 (38.8) Mild: 8 (44.4) Moderate: 3 (16.6) Severe: 0 Fibrosis: 0: 8 (44.4) 1: 7 (38.8) 2: 3 (16.6) 3: 0 4: 0 | There was no relationship between the serum concentrations of ferritin and the degree of hepatic steatosis, inflammation, and liver fibrosis in patients with NASH | --- | --- |
| Study (first author, year) | Study design, Country | Participants | Mean age ± SD (yrs) | NAFLD diagnosis approach/method | Number of NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---------------------------|----------------------|--------------|-------------------|-------------------------------|-----------------------------------------------|--------------------------------------|----------------------------------------------------------------------------------|-----------------------------|
| Qu, 2021 (49)             | Cross-sectional study, China Adult NAFLD patients | 167 (126 + 41) | 50.38 ± 5.56      | Liver biopsy                  | S0: 38.45 ± 9.34 S1: 41.97 ± 12.55 S2: 43.55 ± 12.45 S3: 38.09 ± 11.22 | Ferritin: 30.20 ± 169.83 S1 patients: 286.65 ± 158.80 S2 patients: 326.55 ± 214.71 S3 patients: 345.30 ± 184.95 | Ferritin and steatosis stage: p = 0.066 Ferritin and inflammation stage: p = 0.470 Ferritin and fibrosis stage: p = 0.234 | N/A                          |
| Trasolini, 2022 (50)      | Retrospective cohort study, Canada Adult NAFLD patients | 224 (112 + 112) | 52 (range 43–60) | Transient elastography        | No fibrosis (<8 kPa): 185 Fibrosis (≥8 kPa): 39 Steatosis: S0: 58 S1: 53 S2: 29 S3: 27 | Ferritin (cut-off of 300 ng/ml) and fibrosis stages: p = 0.099 Ferritin (cut-off of 450 ng/ml) and fibrosis stages: p = 0.92 | N/A                          | N/A                          |
| Wang, 2022 (51)           | Cross-sectional study, China Adult NAFLD patients | 136 (90 + 46) | 41.00 (range 33.00–57.75) | Liver biopsy                  | Steatosis: S1: 39 (28.7) S2: 55 (40.4) S3: 42 (30.9) | Ferritin between Steatosis 2–3 and Steatosis 1: p = 0.040 Ferritin between Steatosis 3 and Steatosis 1–2: p = 0.099 Ferritin between inflammation activity 3–4 and inflammation activity 1–2: p = 0.085 Ferritin between inflammation activity 4 and inflammation activity 1–3: p = 0.021 Ferritin between Fibrosis 2–4 and Fibrosis 1: p = 0.059 Ferritin between Fibrosis 3–4 and Fibrosis 1–2: p = 0.516 Ferritin between Fibrosis 4 and Fibrosis 1–3: p = 0.692 | N/A                          | N/A                          |
|                           |                      |              |                   |                               | Steatosis 2–3: 97 (73.3) Inflammation activity 1 point: 1 (1.5) 2 points: 24 (17.6) 3 points: 40 (29.4) 4 points: 70 (53.5) | Ferritin between Steatosis 2–3 and Steatosis 1: p = 0.040 Ferritin between Steatosis 3 and Steatosis 1–2: p = 0.099 Ferritin between inflammation activity 3–4 and inflammation activity 1–2: p = 0.085 Ferritin between inflammation activity 4 and inflammation activity 1–3: p = 0.021 Ferritin between Fibrosis 2–4 and Fibrosis 1: p = 0.059 Ferritin between Fibrosis 3–4 and Fibrosis 1–2: p = 0.516 Ferritin between Fibrosis 4 and Fibrosis 1–3: p = 0.692 | N/A                          | N/A                          |
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Yang, 2022 (53) | Cross-sectional study | US | Adult NAFLD patients | 1,604 (856 + 748) | 52.73 ± 16.26 | Vibration controlled and transient elastography | Steatosis: Severe steatosis (S3): CAP ≥ 302 dB/m Fibrosis: Significant fibrosis (≥ F2): LSM ≥ 8 kPa Advanced fibrosis (≥ F3): LSM ≥ 9.7 kPa Cirrhosis (F4): LSM ≥ 13.6 kPa | 0 point: 0 inflammatory cell foci per 20x; 1 point: ≤ 2 inflammatory cell foci per 20x; 2 points: > 2 inflammatory cell foci per 20x; Inflammation activity score: the sum of lobular inflammation and hepatocellular ballooning. The severity of fibrosis was graded according to Kleiner et al. (20) Vibration-controlled and transient elastographySteatosis: Severe steatosis (S3): CAP ≥ 302 dB/m Fibrosis: Significant fibrosis (≥ F2): LSM ≥ 8 kPa Advanced fibrosis (≥ F3): LSM ≥ 9.7 kPa Cirrhosis (F4): LSM ≥ 13.6 kPa | CAP: 322.20 ± 36.89 dB/m LSM: 6.37 ± 4.84 kPa | 106.41 ± 161.36 | Multivariate linear regression analysisDependent variable: serum ferritin levelsModel 1: age, gender, and race; Model 2: age, gender, race, BMI, diabetes, waist circumference, HDL-cholesterol, glycemia, ALT, AST, GGT, serum albumin, serum creatinine, and uric acid. | 0 point: 0 inflammatory cell foci per 20x; 1 point: ≤ 2 inflammatory cell foci per 20x; 2 points: > 2 inflammatory cell foci per 20x; Inflammation activity score: the sum of lobular inflammation and hepatocellular ballooning. The severity of fibrosis was graded according to Kleiner et al. (20) |
| Study (first author, year) | Study design | Country | Participants | Sample size (M + F) | Mean age ± SD (yrs) | NAFLD diagnosis approach/tool | NAFLD progression approach/tool | Number of NAFLD patients with different gradings, n (%) | Serum ferritin level, mean ± SD (ng/ml) | Proven associations by univariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Proven associations by multivariate analysis, OR (95% CI) and p-value were reported in logistic regression analysis and correlation coefficient (r) and p-value were reported in correlation analysis | Confounders adjusted for |
|--------------------------|--------------|---------|--------------|---------------------|---------------------|-----------------------------|-----------------------------|---------------------------------|---------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------|
| Yu, 2022 (54) Retrospective cohort study | US | Adult NAFLD patients | 18,569 (6,990 + 11,579) | At baseline Group 1: 66.1 ± 10.8 Group 2: 59.9 ± 12.0 | Not reported | Not reported | Group 1 (incident HCC during follow-up): 244 Group 2 (free of HCC during follow-up): 18,325 | Median (range: 5%−95%) Group 1: 85 (8–981) Group 2: 100 (9–700) Cut-offs: 200 ng/ml in females and 300 ng/ml in males | Wilcoxon rank sum test: Ferritin between Group 1 and Group 2 p = 0.445 | Cox proportional hazard regression: Independent variable serum ferritin level Dependent variable incident HCC Normal ferritin Reference ≤200 ng/ml in females ≤300 ng/ml in males | p = 0.368 |

SD, standard deviation; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; CI, confidence interval; NASH, non-alcoholic steatohepatitis; ULN, upper limit of normal; BMI, body mass index; ALT, Alanine aminotransferase; NAFL, non-alcoholic fatty liver; NAS, NAFLD activity score; HOMA-IR, homeostatic model assessment insulin resistance index; OGTT, oral glucose tolerance test; DM, diabetes mellitus; AST, aspartate aminotransferase; HR, hazards ratio; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; GGT, gamma glutamyl transpeptidase; HDL, high density lipoprotein; HCC, hepatocellular carcinoma.
was 200 ng/ml in females and 300 ng/ml in males), higher than 1.5 ULN and higher than 2 ULN were predictors of presence of fibrosis (F1–F4), severe fibrosis (F2–F4) and advanced fibrosis (F3/F4), respectively, through multiple logistic regressions (19). Similarly, a study from the US reported significant results in univariate analysis, and identified both 1.5 ULN and 2.5 ULN as predictors of presence of significant fibrosis (F2–F4), severe fibrosis; the associations remained significant when more variables were included, e.g., BMI, medical history of diabetes, waist circumference, laboratory analysis results including alanine aminotransferase (ALT), etc. (33).

**Different associations of ferritin and hepatic fibrosis stages**

Ten studies simply reported patients with more advanced fibrosis were more likely to have a higher serum ferritin level (23, 29, 32, 34, 35, 38, 40, 43, 45, 46), tested by univariate analysis. Four of the 10 studies further included ferritin into multivariate analysis models, and three studies had results that remained the same (35, 43, 45) yet one study showed non-significant association (36). One study only had results from multivariate analysis and reported the significant association that a higher ferritin level predicts the presence of significant fibrosis (30). Another seven studies showed non-significant results in univariate analysis (28, 37, 47–51). Further, one study found non-significant association between ferritin and the occurrence of fibrosis in NAFLD patients (26). Additionally, one study reported inconsistent results from two different groups of NAFLD patients (39), and one study reported that ferritin was higher in patients with cirrhosis when comparing with patients with simple steatosis and steatosis plus inflammation or fibrosis (34).

Interestingly, when ferritin cut-offs were set as 160 ng/ml and 380 ng/ml, the differences of ferritin levels among

| Study (first author, year) | Ferritin cut-off value (ng/ml) | Diagnostic aim | Sensitivity (%), Specificity (%) | AUROC (95% CI) | p-Value |
|---------------------------|-------------------------------|----------------|---------------------------------|----------------|---------|
| Angulo, 2014 (19)         | > ULN (200 ng/ml in females and 300 ng/ml in males) | Fibrosis stage 1–4 vs. stage 0 | 37, 76 | 0.57 (0.53–0.60) | Not reported |
|                          |                               | Fibrosis stage 2–4 vs. stage 0–1 | 39, 72 | 0.55 (0.52–0.59) | Not reported |
|                          |                               | Fibrosis stage 3–4 vs. stage 0–2 | 41, 70 | 0.55 (0.51–0.59) | Not reported |
|                          | > 1.5 ULN (300 ng/ml in females and 450 ng/ml in males) | Fibrosis stage 1–4 vs. stage 0 | 22, 89 | 0.55 (0.52–0.59) | Not reported |
|                          |                               | Fibrosis stage 2–4 vs. stage 0–1 | 25, 86 | 0.55 (0.52–0.59) | Not reported |
|                          |                               | Fibrosis stage 3–4 vs. stage 0–2 | 27, 84 | 0.56 (0.52–0.60) | Not reported |
|                          | > 2.0 ULN (400 ng/ml in females and 600 ng/ml in males) | Fibrosis stage 1–4 vs. stage 0 | 13, 95 | 0.54 (0.50–0.58) | Not reported |
|                          |                               | Fibrosis stage 2–4 vs. stage 0–1 | 14, 93 | 0.53 (0.50–0.57) | Not reported |
|                          |                               | Fibrosis stage 3–4 vs. stage 0–2 | 16, 92 | 0.54 (0.50–0.58) | Not reported |
|                          | > ULN (200 ng/ml in females and 300 ng/ml in males) | The occurrence of NASH | Not reported | No t reported | Not reported |
| El Nakeeb, 2017 (26)     | ≥ 51.95 ng/ml                | The occurrence of fibrosis | 65.4, 40 | Not reported | Not reported |
| Hanafi, 2019 (30)        | > 321 ng/ml                  | Fibrosis stage 3–4 vs. stage 0–2 | 95.8, 90 | 0.809 (0.77–0.85) | 0.001 |
| Manousou, 2011 (35)     | > 240 ng/ml                  | The occurrence of NASH | 91, 70 | 0.82 (0.73–0.90) | Not reported |
| Parikh, 2015 (38)       | ≥ 48 ng/ml                   | Fibrosis stage 3–4 vs. stage 0–2 | Not reported | 0.779 (95% CI not reported) | Not reported |
| Seyedian, 2017 (40)     | > 255 ng/ml (in males)       | Advanced liver stiffness vs. mild liver stiffness | 90, specificity not reported | 0.59 (0.489–0.697) | Non-significant |
|                          | > 135 ng/ml (in females)     | Not reported | | 0.79 (0.663–0.917) | Significant |
|                          | < 72.5 ng/ml (in males)      | Excluding advanced liver stiffness | 90, specificity not reported | Not reported | Not reported |
|                          | < 65.5 ng/ml (in females)    | 93, specificity not reported | Not reported | Not reported | Not reported |
| Yoneda, 2010 (44)       | 196 ng/ml                    | The occurrence of NASH | 64.2, 76.5 | 0.732 (0.596–0.856) | 0.005 |

**AUROC**, area under the ROC curve; CI, confidence interval; ULN, upper limit of normal; NASH, non-alcoholic steatohepatitis; NAFL, non-alcoholic fatty liver.
patients with different fibrosis were non-significant for both two cut-offs in univariate analysis, but the association of ferritin level and fibrosis stages became significant when ferritin cut-off was 380 ng/ml in multiple logistic regression (27).

Ferritin and hepatic fibrosis progression in longitudinal study

A Japanese study using longitudinal data followed a group of NAFLD patients with F3 fibrosis at baseline, and categorized them into deterioration group (F4), no-change group (F3) and improvement group (F1/F2) according to their fibrosis stage at follow-up after 1–10 year(s) (31). This study showed that changes of ferritin levels in these patients were significantly different among the three groups, with significant differences in both between no-change group and deterioration group and between no-change group and improvement group (31).

Accuracy of ferritin for predicting hepatic fibrosis

Three studies further explored the accuracy of ferritin for predicting fibrosis stages (19, 30, 40). One study suggested it had poor accuracy among males yet had high accuracy among females (40), one study reported poor accuracy generally (19), and one study demonstrated it was a good predictor (30).

Serum ferritin level and hepatic inflammation stages

Eleven studies explored the association serum ferritin level and inflammation stages among NAFLD patients (28, 29, 32–36, 39, 45, 48, 49). Ten of the 11 studies conducted univariate analysis: four studies demonstrated that NAFLD patients with a higher ferritin level were more likely to have more advanced hepatic inflammation (29, 33, 34, 36); five studies showed non-significant results (28, 32, 45, 48, 49); and one study reported inconsistent associations from two different groups of patients (39). Only three studies explored the association of ferritin and inflammation progression via multivariate analysis: one study identified ferritin as a predictor for more advanced portal and lobular inflammation status, with a significant cut-off value of 240 ng/ml (35); another study found non-significant associations of ferritin between patients with mild (Grade 0 and 1) and moderate (Grade 2 and 3) inflammation (36); the other study found significant association of ferritin (log 10 ng/ml) and inflammation stages by multiple linear regression analysis (39).

Serum ferritin level and hepatic ballooning stages

The association of serum ferritin level and hepatic ballooning were investigated in five studies (28, 29, 32, 33, 39), all tested by univariate analysis. Three of them suggested that NAFLD patients with higher ferritin were more likely to have a more advanced ballooning stage (28, 29, 33), and the other two reported non-significant results (32, 39).

Another one study from China combined inflammation and ballooning score as the inflammation activity score (1–4, the higher the more severe), and found that ferritin levels were different between patients with 4 points and 1–3 points, but not 3–4 points and 1–2 points (51).

Serum ferritin level and integrated NAFLD progression including incident HCC and mortality

Three studies reported that serum ferritin level was positively correlated with NAFLD activity score (NAS) (28, 29, 32).

One study from the US explored the role of ferritin in predicting future incident hepatocellular carcinoma (HCC), with an average follow-up of 4.34 years. The authors reported non-significant associations both in univariate analysis and multivariate Cox proportional hazard regression analysis (54).

There is one study investigating the association of serum ferritin level and mortality (29). It suggested that following 15 years after liver biopsy, patients with elevated ferritin (>350 ng/ml in males and >150 ng/ml in females) showed a significant and gradually steeper increase in mortality compared with those with normal ferritin levels at biopsy; following 30 years after biopsy, the hazard ratio increased 9% faster per year in patients with elevated ferritin, and the significance remained when potential confounders were adjusted.

Discussion

This systematic literature review identified 32 studies reporting the association between serum ferritin level or different ferritin categories and various stages of NAFLD, including the occurrence of NASH, hepatic steatosis stages, fibrosis stages, inflammation stages, ballooning stages, incident HCC and mortality. Most studies suggested that serum ferritin was a predictor for more advanced NAFLD and could relate to higher mortality. However, non-significant association was also reported by a few included studies. The accuracy of ferritin as a predictor for NAFLD progression was also reported inconsistently.
This study not only synthesized current evidence on the association of ferritin and NAFLD progressions, but also identified certain research gaps in this field. First, more than half of the included studies only employed univariate statistical analysis. Under these circumstances, the reliability of the association was not high due to the potential influences exerted by confounders such as age, sex, ATL levels, etc. Future studies should apply a rigorous study design. Second, although many studies employed a cohort design, only three of them used longitudinal data for analysis (29, 31, 54). Two of them investigated the association of ferritin and future incident HCC (54) and mortality (29), respectively; the other revealed the association of ferritin and changes of fibrosis stages (31). This calls for more studies to explore the predictive value of ferritin for NAFLD prognosis. Third, when categorizing the included studies according to the WHO regions, we found that none of the studies were from the African Region, indicating a research gap among African populations. Fourth, heterogeneity was high among the included studies and it prevented further data synthesis via meta-analysis. The included studies used different grading standards and various statistical analysis approaches. Future studies could apply consistent study design for better homogeneity to assist data synthesis on this topic. Fifth, many studies did not evaluate the diagnosis accuracy, specificity, or sensitivity of serum ferritin level, without which the predictive value of ferritin for evaluating various stages of NAFLD would not be clear. Sixth, many studies used the same ferritin cut-off values for all participants, thus failed to observe the potential sex differences in the associations of ferritin and NAFLD stages between the two populations, since in addition to the sex differences in NAFLD prevalence, there are also differences in ferritin cut-off values as a result of different iron status between females and males (55). Future studies are supposed to take sex differences into consideration.

Several previous reviews have narratively summarized existing evidence on this topic, which mostly elaborated the differences into consideration. The included studies used different grading standards and various statistical analysis approaches. Future studies could apply consistent study design for better homogeneity to assist data synthesis on this topic. Fifth, many studies did not evaluate the diagnosis accuracy, specificity, or sensitivity of serum ferritin level, without which the predictive value of ferritin for evaluating various stages of NAFLD would not be clear. Sixth, many studies used the same ferritin cut-off values for all participants, thus failed to observe the potential sex differences in the associations of ferritin and NAFLD stages between the two populations, since in addition to the sex differences in NAFLD prevalence, there are also differences in ferritin cut-off values as a result of different iron status between females and males (55). Future studies are supposed to take sex differences into consideration.

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to all the data and have approved the final version of the paper.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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