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The serum hepcidin and the hepcidin/ferritin ratio in NAFLD: a systematic review and meta-analysis

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Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is a spectrum of chronic liver diseases characterized by hepatic steatosis exceeding 5% in the absence of alcohol and other liver-damaging factors. Clinical studies have identified a potential link between abnormal iron metabolism and the high incidence of NAFLD; however, the results from clinical trials remain inconsistent. This meta-analysis aims to compare serum hepcidin levels and the hepcidin/ferritin ratio between adults with NAFLD and those without to explore their potential relationship with NAFLD.

Methods A systematic search was conducted across the Web of Science platform, Cochrane, Scopus, Embase, and PubMed databases from their inception until December 18, 2024. The analysis primarily focused on serum hepcidin levels and the hepcidin/ferritin ratio. Observational studies comparing serum hepcidin levels and the hepcidin/ferritin ratio between individuals with NAFLD and control groups were included. A random-effects model was employed to calculate effect estimates, and outcomes were reported as standardized mean differences (SMD) with 95% confidence intervals (95% CI).

Results Following the systematic review, a total of 19 studies, comprising 2216 patients and 2125 controls, were included. The findings revealed a statistically significant difference in both hepcidin levels (SMD = 1.03, 95% CI: 0.49 to 1.56, $p < 0.001$) and the hepcidin/ferritin ratio (SMD = -1.13, 95% CI: -1.79 to -0.46, $p < 0.001$) between NAFLD and controls. Significant heterogeneity was observed across studies for both hepcidin ($I^2 = 98.2\%$) and the hepcidin/ferritin ratio ($I^2 = 93.3\%$), and the limited number of studies on hepcidin/ferritin were acknowledged as key limitations. Subgroup analysis revealed that patients with obesity exhibited higher levels of hepcidin (SMD = 1.12, 95% CI: 0.40 to 1.97) than overweight (SMD = 0.88, 95% CI: 0.05 to 1.72). Meta-regression analysis identified the hepcidin measurement method ($p < 0.01$), male-to-female ratio ($p < 0.01$), and study quality ($p < 0.01$) as significant moderators of the observed heterogeneity.

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Conclusion This meta-analysis revealed a significant association between hepcidin levels, the hepcidin/ferritin ratio and NAFLD in adults. Further investigations are needed to fully elucidate the role of these variables in iron metabolism and their potential impact on the diagnosis, prevention, and management of NAFLD.

Keywords NAFLD, Hepcidin, Hepcidin/ferritin ratio, Meta-analysis

Background

Nonalcoholic fatty liver disease (NAFLD) is a group of chronic metabolic liver diseases associated with insulin resistance (IR) and genetic susceptibility. The disease spectrum primarily includes simple fatty liver, nonalcoholic steatohepatitis (NASH), and NASH related liver cirrhosis [1]. Given the critical role of metabolic mechanisms in the development of NAFLD, the condition has recently been renamed as metabolically associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD) to more accurately reflect its pathophysiology [2]. As obesity and metabolic syndrome continue to rise globally, NAFLD has become a significant public health challenge, affecting approximately 30.2% of the adult population worldwide [3]. Although the exact pathogenesis of NAFLD remains unclear, liver biopsy is still considered the gold standard for diagnosis; however, its invasive nature often leads to reservations among patients [4]. Consequently, early identification and intervention are critical for improving outcomes, with growing interest in serum biomarkers as potential tools for diagnosing NAFLD.

The liver plays a critical role in iron metabolism; numerous studies have reported that iron overload is considered one of the injury mechanisms of NAFLD [5]. Studies have shown that patients with simple fatty liver and NASH frequently exhibit iron overload, suggesting its role in the disease's development [6]. Research suggests that iron overload in the liver and adipose tissues may result from IR and contribute to NAFLD development by inducing oxidative stress, disrupting circadian rhythms, and elevating sex hormone-binding globulin levels [5]. As the primary iron reservoir in the body, the liver's excess iron accumulation can lead to cellular damage and inflammation. The complex interplay between hepatic iron levels and the emergence of NAFLD has ignited a growing interest in the intricacies of iron metabolism.

Iron is the most abundant essential trace element in the human body, primarily existing in the form of ferritin, and is regulated by hepcidin [7, 8]. Kowdley et al. [9] suggested that elevated serum ferritin levels, hepatic iron deposition and iron overload are closely correlated with NAFLD. Ferritin, the primary iron storage protein in the body, is found in high concentrations in liver cells and plays a crucial role in regulating iron homeostasis. It is also an acute-phase reactant, reflecting inflammatory states [10]. Increased ferritin synthesis is often induced by pro-inflammatory factors such as IL-1β and IL-18 [11]. In NAFLD, disruptions in carbohydrate, fat, and protein metabolism may promote the release of ferritin into the bloodstream, thereby further linking iron metabolism to disease severity [12]. Studies have established a significant correlation between serum ferritin levels and NAFLD risk [9, 13]. In addition to ferritin, hepcidin is pivotal in regulating systemic iron balance. Hepcidin exerts its effects by binding to iron transport proteins, inhibiting iron absorption in the duodenum, and limiting the release of iron from macrophages and hepatocytes [14]. Inflammation, a common feature of NAFLD, triggers elevated serum hepcidin levels, disrupting normal iron metabolism and exacerbating liver damage [15]. Chronic low-grade inflammation associated with obesity and NAFLD/NASH can further stimulate hepcidin expression, contributing to iron overload and liver injury [16]. Due to its central role in iron regulation, hepcidin has been suggested as a key factor in the pathogenesis of chronic liver diseases [17, 18]. Furthermore, recent studies suggest that the hepcidin/ferritin ratio may offer diagnostic value, particularly in monitoring fibrosis progression in chronic liver diseases [19].

Although hepatic iron overload is closely associated with NAFLD severity, the mechanisms by which hepcidin regulates circulating iron levels remain poorly understood. Findings on the relationship between serum hepcidin levels, the hepcidin/ferritin ratio, and NAFLD risk are inconsistent [20, 21]. While some studies report elevated hepcidin levels in NAFLD patients [21], others have failed to establish a clear link with disease severity or liver inflammation [22]. Additionally, the utility of the hepcidin/ferritin ratio in NAFLD remains inconclusive due to a lack of comprehensive pooled analyses. Although existing research has provided valuable insights, significant gaps remain in understanding the precise relationship between hepcidin, the hepcidin/ferritin ratio, and NAFLD. To date, most studies have been small or methodologically heterogeneous, and no meta-analysis has yet synthesized these results. Therefore, this meta-analysis systematically evaluates the available evidence to determine whether serum hepcidin levels and the hepcidin/ferritin ratio are associated with NAFLD risk in adults. By combining data from multiple studies, we aim to clarify these relationships and assess the potential of hepcidin as a biomarker for NAFLD risk.

Methods

Search strategies

This systematic review and meta-analysis were conducted following the PRISMA guideline [23] and registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42024500533). A comprehensive and systematic literature search was conducted on the Web of Science platform, Cochrane, Scopus, Embase, and PubMed databases from their inception to December 2024. We use the Boolean operator "OR, AND" to combine Medical Subject Headings (MESH) and free search terms related to NAFLD, MAFLD, MASLD, and hepcidin. The search formula is as follows ("Non alcoholic Fatty Liver Disease"[MeSH] OR "Non-alcoholic Fatty Liver Disease" OR "NAFLD" OR "Nonalcoholic Fatty Liver Disease" OR "Fatty Liver, Nonalcoholic" OR "Fatty Livers, Nonalcoholic" OR "Liver, Nonalcoholic Fatty" OR "Livers, Nonalcoholic Fatty" OR "Nonalcoholic Fatty Liver" OR "Nonalcoholic Fatty Livers" OR "Nonalcoholic Steatohepatitis" OR "Nonalcoholic Steatohepatitides" OR "Steatohepatitides, Nonalcoholic" OR "Steatohepatitis, Nonalcoholic" OR "metabolic dysfunction-associated fatty liver disease" OR "MAFLD" OR "metabolic dysfunction associated steatotic liver diseases" OR "MASLD") AND ("Hepcidins" [MeSH] OR "Hepcidin" OR "hepcidin" OR "Prohepcidin" OR "Pro-Hepcidin" OR "Pro Hepcidin" OR "Liver-Expressed Antimicrobial Peptide" OR "Antimicrobial Peptide, Liver-Expressed" OR "Liver Expressed Antimicrobial Peptide" OR "Peptide, Liver-Expressed Antimicrobial" OR "iron regulator" OR "membrane transport protein" OR "iron metabolism" OR "Antimicrobial Cationic Peptides" OR "HAMP protein, human"). Search strategies are shown in Supplementary Materials S1.

Inclusion and exclusion criteria

We employed the PICOS framework (Population, Intervention, Comparison, Outcome, and Study Design) to delineate the inclusion criteria for this review (Table 1) [24]. These criteria included: (1) studies published in English, (2) precise diagnosis of NAFLD, and (3) the hepcidin data presented in the study are in units that can be converted to ng/ml.

Exclusion criteria: (1) studies without data on the control group, (2) publications of other types (e.g., reviews, commentaries, individual case reports, conference presentations, study protocols, animal experiments, and duplicate publications), (3) patients with other liver diseases, include the viral (HBV or HCV) infection, autoimmune hepatitis, liver cancer.

Table 1 PICOS framework for eligibility criteria

PICOS Element	Description
Population (P)	Adults aged 18 years or older were diagnosed with NAFLD.
Intervention (I)	Studies measured one or more of the following biomarkers: serum Hepcidin levels and the Hepcidin/Ferritin ratio.
Comparison (C)	NAFLD patients compared with individuals exhibiting normal liver histology.
Outcome (O)	The association between NAFLD and serum Hepcidin levels or the Hepcidin/Ferritin ratio.
Study Design (S)	Observational studies.

Data extraction and literature quality evaluation

After removing duplicate studies, two reviewers independently reviewed abstracts based on the inclusion and exclusion criteria. Cohen's kappa coefficient (κ) was used to evaluate inter-rater agreement between the reviewers [25]. The full texts of the selected articles were retrieved for further evaluation. Data from the selected full texts were independently extracted and tabulated by the reviewers. Discrepancies in data extraction were resolved through discussion with a third reviewer until a consensus was reached. The extracted data included: (1) study characteristics (first author's name, study design, date of publication, and country of origin), (2) sample characteristics (sample size, sex, mean age of participants, BMI), (3) methodological features (methods used for diagnosis NAFLD, measurements of hepcidin), (4) outcome indicator (hepcidin, the hepcidin/ferritin ratio). Hepcidin levels reported in the included studies were in three different units: ng/ml, ug/l, and nmol/l. For calculation, hepcidin levels were converted to a uniform unit of ng/ml across all included studies. Two researchers assessed the quality of the included studies. The quality of case-control studies was evaluated using the Newcastle-Ottawa Scale (NOS), which consists of three categories and eight items, with a maximum score of 9 points. Studies with scores ≥ 6, $3 \leq$ score < 6, and scores < 3 were categorized as low-risk, moderate-risk, and high-risk, respectively [26]. Cross-sectional studies were evaluated using the Agency for Healthcare Research and Quality (AHRQ) tool, which includes 11 items. Based on the total score, studies were classified as low quality (0–3 points), medium quality (4–7 points), or high quality (8–11 points) [27].

Statistical analysis

For all included studies, the mean and standard deviation (SD) of hepcidin levels and the hepcidin/ferritin ratio for the two groups were extracted and managed using Excel. If studies did not report the mean and SD, we applied the methods described by Luo et al. [28] and Wan et al. [29] to convert medians, ranges, and interquartile ranges (IQR) into mean and SD. Subsequently, the meta-analysis was performed using the "metafor" package in RStudio (version 2023.09.1). The pooled Standardized Mean Difference (SMD) was calculated using

a random-effects model to compare hepcidin levels and the hepcidin/ferritin ratio between the two groups. The random-effects model was selected because it accommodates both within-study and between-study variability, providing a more accurate and generalizable estimate of the overall effect. Heterogeneity was evaluated by Q-statistic test and I-squared (I^2), with values exceeding 50% indicative of significant heterogeneity [30]. Subgroup and meta-regression analyses were conducted based on the Body Mass Index (BMI), hepcidin measurement method, region, male-to-female ratio (≤ 1.5 or > 1.5), development status of the country, study design, study quality, sample size (≤ 40 NAFLD patients, or > 40 NAFLD patients), and study period (before 2015 or after 2015). Sensitivity analysis was applied to test the stability of the pooled results by eliminating one study at a time and combining the effect sizes of the remaining studies. Finally, Begg's test, Egger bias tests, funnel plots and the Trim and fill Test were employed to assess the publication bias of the studies. $P < 0.05$ was considered statistically significant.

Grading of evidence

The quality and strength of the evidence for each outcome were independently assessed by two authors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method [31, 32]. GRADEpro software was used to generate evidence profiles and summarize the certainty of evidence in GRADE tables (Supplementary Materials S2).

Results

Search results

The literature screening process is presented in the PRISMA flow chart (Fig. 1). Initially, 1426 documents were retrieved, and 969 duplicates were removed. After excluding 111 documents of other types (e.g., reviews or commentaries), 457 studies were eliminated based on titles and abstracts for not meeting the inclusion criteria (e.g., studies on unrelated populations, pharmacological interventions, genetic research, or animal models). A full-text review of 82 articles resulted in the inclusion of 19 studies in the final analysis. All 19 studies provided specific data on hepcidin levels, but only 5 reported the hepcidin/ferritin ratio. All studies included in this systematic review and meta-analysis were published between 2011 and 2024. Detailed information on the included studies is provided in Table 1. The Cohen's kappa coefficient between the two reviewers was 0.702, indicating substantial agreement. The NOS assessment revealed that seven case-control studies were at low risk, and one was at moderate risk. The AHRQ assessment showed that seven cross-sectional studies were of high quality, and two were of moderate quality. The quality assessment of the included studies can be found in Table 2.

The association between serum hepcidin and hepcidin/ferritin ratio with the risk of NAFLD

The SMD of serum hepcidin levels between NAFLD patients and controls was compared across nineteen studies (Ncases = 2216, Ncontrols = 2125), demonstrating a statistically significant positive association with NAFLD risk (SMD = 1.03; 95% CI: 0.49 to 1.56, $p < 0.001$) (Fig. 2).

Five studies reported the hepcidin/ferritin ratio (Ncases = 587, Ncontrols = 718), and the pooled SMD demonstrated a significant negative correlation between the NAFLD groups (SMD = -1.13; 95% CI: -1.79 to -0.46, $p < 0.001$) (Fig. 3).

Subgroup analysis, meta-regression, and sensitivity analysis

Subgroup analyses were performed to explore the sources of heterogeneity based on BMI, hepcidin measurement method, region, male-to-female ratio (≤ 1.5 or > 1.5), development status of the country, study design, study quality, sample size (≤ 40 NAFLD patients or > 40 NAFLD patients), and study period (before 2015 or after 2015). The results are shown in Table 3. When considering different BMI groups, obesity (SMD = 1.12, 95% CI: 0.40 to 1.97) tended to showed a higher effect than overweight (SMD = 0.88, 95% CI: 0.05 to 1.72). The method of hepcidin measurement played a crucial role, with studies using ELISA showing a significant positive association (SMD = 1.01, 95% CI: 0.43 to 1.59), whereas studies using LC/MS/MS showed a weaker association, which was not statistically significant (SMD = 0.51, 95% CI: -0.57 to 1.60). Regional differences were also observed, with studies conducted in the Americas showing the most pronounced effect (SMD = 1.76, 95% CI: 0.45 to 3.08), whereas studies from Asia demonstrated a more modest effect (SMD = 0.65, 95% CI: -0.06 to 1.36). Regarding study quality, high-quality studies exhibited a stronger association (SMD = 1.07, 95% CI: 0.46 to 1.68), while low-quality studies showed a weaker effect (SMD = 0.92, 95% CI: -0.27 to 2.11).

Additionally, a subgroup analysis was conducted to evaluate the differences in serum hepcidin levels between the NASH and SS groups. Due to limited data availability, with only two studies meeting the inclusion criteria, the pooled effect size was calculated as SMD = -0.04 (95% CI: -0.49 to 0.41). This result suggests no significant difference in hepcidin levels between the two groups.

Meta-regression analysis revealed that the hepcidin measurement method ($p < 0.01$), male-to-female ratio ($p < 0.01$), and study quality ($p < 0.01$) appeared to be significant moderators of the observed heterogeneity. Neither the year of publication, age, region, nor study design accounted for the observed heterogeneity. The results are shown in Table 4.

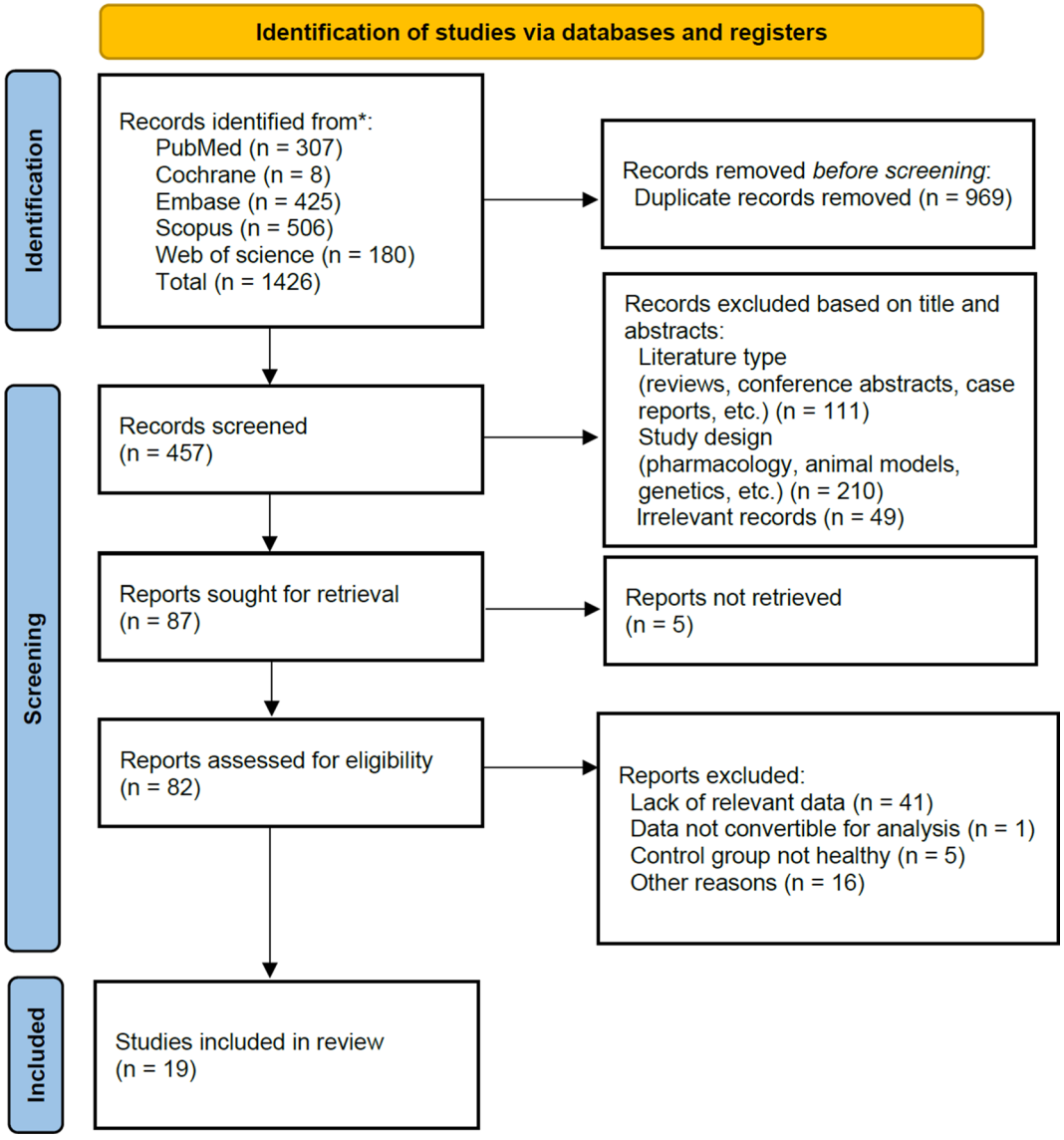

Fig. 1 Flow diagram showing the selection of studies for the meta-analysis

To verify the stability and reliability of the meta-analysis results, a leave-one-out sensitivity analysis was performed. This method systematically excludes one study at a time and recalculates the meta-analysis using the remaining data. The results before and after excluding each study were compared to evaluate the stability of the findings. As shown in Fig. 4, the pooled effect size remained stable across all iterations, with only minimal and non-significant fluctuation, supporting the robustness of the results.

Publication bias

Publication bias was assessed in the association of NAFLD with hepcidin and hepcidin/ferritin ratio. Begg's rank correlation test and Egger's regression test were performed to assess potential publication bias.

The results did not provide significant evidence of publication bias in the relationship between NAFLD and hepcidin (Begg's test: $p = 0.655$; Egger's: $p = 0.274$). Only five studies were available for the hepcidin/ferritin ratio, and Begg's test showed no significant evidence of publication bias ($p = 0.817$). A funnel plot was generated (Fig. 5), and a Trim-and-Fill analysis was conducted to assess potential publication bias between hepcidin levels and NAFLD. This analysis did not identify any missing studies from the funnel plot, suggesting no significant publication bias in the included studies.

The meta-analysis identified a significant difference in serum hepcidin levels between the NAFLD and control groups, with an overall effect size of SMD = 1.03 (95% CI: 0.49 to 1.56, $p < 0.001$).

Table 2 The basic information of studies included in the meta-analysis

Authors/year	Country	NAFLD		Control		NAFLD Diagnostic	Hepcidin Assay	Study Design	Quality score
		Mean Age	sample size (Males/Female)	Mean Age	sample size (Males/Female)				
Ali 2023	Egypt	38.28 ± 4.93	50(0/50)	35.87 ± 4.52	30(0/100)	Ultrasonography	ELISA	CCS	6
Auguet 2017	Spain	44.6–54.8	46(0/46)	34.6–53.5	49(0/100)	Liver biopsy	ELISA	CSS	6
Boga 2015	Turkey	44.4 ± 11.2	66(23/43)	43.0 ± 9.1	35(15/20)	Liver biopsy	ELISA	CCS	8
Floreani 2021	Italy	59(39–79)	17(7/10)	43(10–80)	150(56/94)	Ultrasonography	SELDI-TOF/MS	CSS	6
Hoki (SS) 2015	Japan	47.8 ± 17.8	15(7/8)	42 ± 8.6	9(4/5)	Liver biopsy	LC/MS/MS	CSS	6
Hoki (NASH) 2015	Japan	50.9 ± 13.7	25(12/13)	42 ± 8.6	9(4/5)	Liver biopsy	LC/MS/MS	CSS	6
Jamali 2016	Iran	34.5 ± 8.85	18(13/5)	30.44 ± 10.11	18(13/5)	Ultrasonography	ELISA	CCS	6
Lyberopoulou 2015	Greece	43.9 ± 16.1	32(16/16)	45.2 ± 15	17(10/7)	Liver biopsy	ELISA	CSS	8
Marmur 2018	Sweden	54 ± 16	22(8/14)	40 ± 10	34(19/15)	Liver biopsy	ELISA	CSS	8
Pan 2019	China	38–54	482(328/154)	39–54	490(331/159)	Ultrasonography	ELISA	CCS	8
Pan 2022	China	42.25	772(555/217)	41.31	766(579/187)	Ultrasonography	ELISA	CCS	7
Ravasi 2012	Italy	21–66	15(NA)	21-27.5	28(NA)	Liver biopsy	LC/MS/MS	CCS	5
Ryan 2018	UK	55 ± 12.7	51(32/19)	58 ± 10	20(8/12)	Liver biopsy	ELISA	CSS	8
Senates 2011	Turkey	44 ± 11	88(56/32)	43 ± 12	88(51/37)	Liver biopsy	ELISA	CCS	8
Shabana 2018	Egypt	44.23 ± 10.87	30(19/11)	39.20 ± 10.26	30(17/13)	Ultrasonography	ELISA	CCS	7
Uysal 2011	Turkey	47.7 ± 11.02	60(40/20)	48.1 ± 13.83	28(10/18)	Ultrasonography	ELISA	CSS	8
Vuppalanchi (SS) 2014	USA	46 ± 13	13(2/11)	51 ± 13	60(46/14)	Liver biopsy	ELISA	CSS	7
Vuppalanchi (NASH) 2014	USA	47 ± 9	44(5/39)	51 ± 13	60(46/14)	Liver biopsy	ELISA	CSS	7
Zhang 2024	China	47.6 ± 13.24	226(147/79)	43.80 ± 8.97	50(29/21)	Ultrasonography	ELISA	CSS	9
Zhou 2022	China	55.62 ± 7.22	119(65/54)	54.97 ± 8.15	100(59/41)	Ultrasonography	ELISA	CSS	8
Zimmermann 2011	Germany	51.8 ± 15.6	25(12/13)	52.3 ± 13.4	37(17/20)	Liver biopsy	ID-LC–MS/MS	CSS	5

ELISA, enzyme-linked immunosorbent assay; SELDI-TOF/MS, surface-enhanced laser-desorption ionization time-of-flight method; LC-MS/MS, Liquid Chromatography-Tandem Mass Spectrometry). ID-LC–MS/MS, isotope dilution liquid Chromatography–Tandem Mass Spectrometry. SS: hepatic steatosis; NASH: steatohepatitis. CCS: Case-control study; CSS: Cross-sectional study

Discussion

This meta-analysis highlights a significant association between serum hepcidin levels, the hepcidin/ferritin ratio and the risk of NAFLD. Our findings demonstrate that serum hepcidin levels are significantly elevated in NAFLD patients compared to controls, with an overall SMD of 1.03 (95% CI: 0.49 to 1.56, $p < 0.001$). In contrast, the hepcidin/ferritin ratio exhibited a significant negative association with NAFLD, with a pooled SMD of -1.13 (95% CI: -1.79 to -0.46, $p < 0.001$). Subgroup analyses revealed several factors contributing to heterogeneity, including BMI, hepcidin assay methods, geographic regions, sex distributions, study quality, and sample sizes. Meta-regression further identified hepcidin measurement methods, male-to-female ratios, and study quality as significant moderators. Sensitivity analyses also confirmed the robustness and consistency of these findings.

These results suggest that dysregulated iron metabolism, reflected by changes in serum hepcidin levels and hepcidin/ferritin ratio, may play a crucial role in the pathogenesis of NAFLD. Our findings align with prior studies [18, 21, 22, 33–37], which highlight the pivotal role of hepcidin in the development of NAFLD. Elevated serum hepcidin levels in NAFLD patients may reflect an adaptive response to hepatic iron overload, oxidative stress, and inflammation, all of which are known contributors to NAFLD pathophysiology. Notably, some studies reported no significant changes or reduced hepcidin levels in similar cohorts [20, 38–40]. These inconsistencies may be attributed to variations in sample sizes, study populations, and measurement methodologies. Furthermore, our meta-analysis revealed that the hepcidin/ferritin ratio was lower in NAFLD patients, corroborating the findings of previous studies [17, 20, 33, 36].

Putative mechanisms

The significant elevation of serum hepcidin levels observed in NAFLD patients suggests a multifaceted interplay between iron metabolism, inflammation, and metabolic dysregulation in the pathogenesis of the disease. Hepcidin, a central regulator of iron homeostasis, modulates iron absorption and distribution by binding

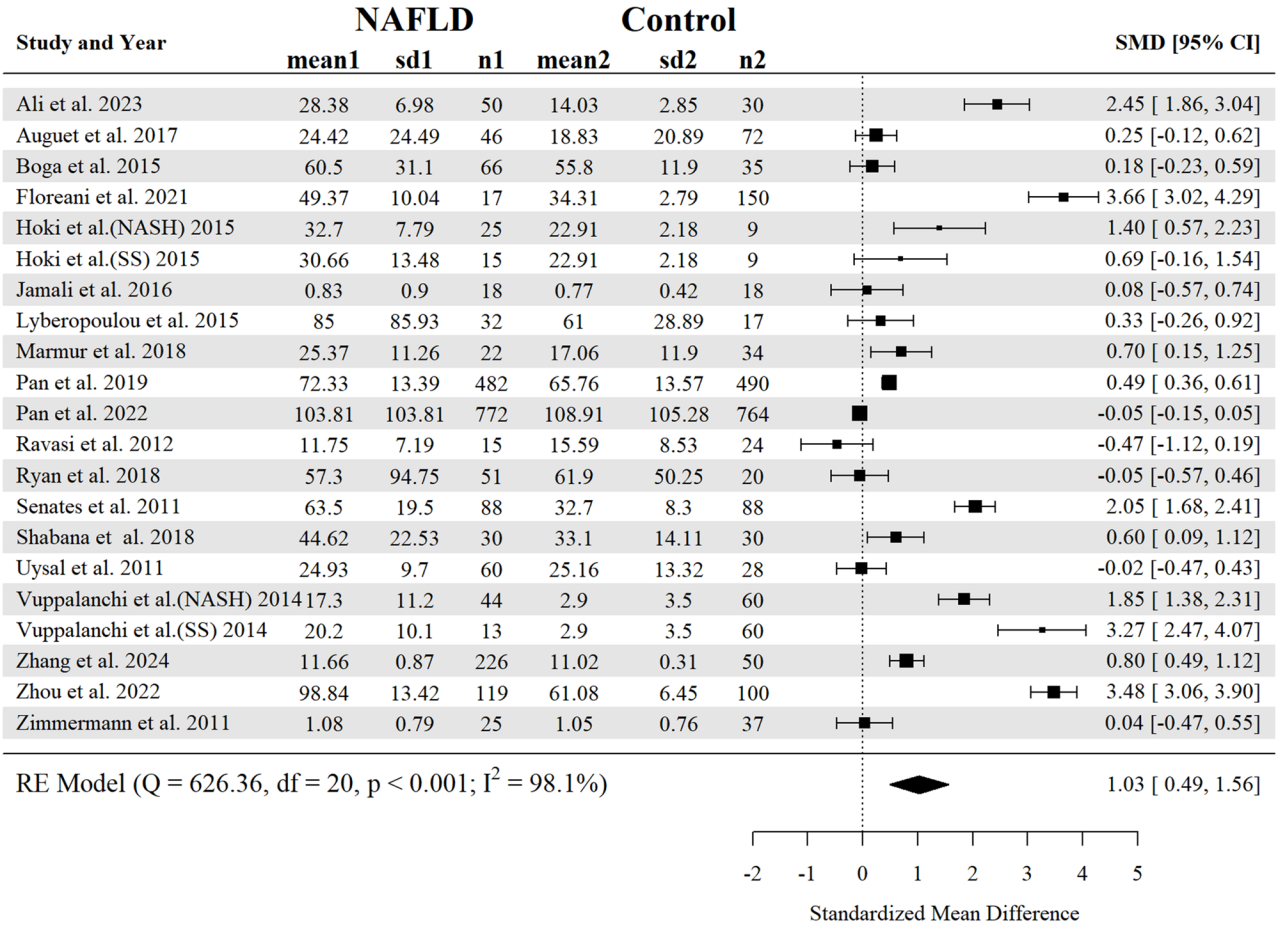

Fig. 2 Forest plot of the effect of the association between serum hepcidin level and NAFLD

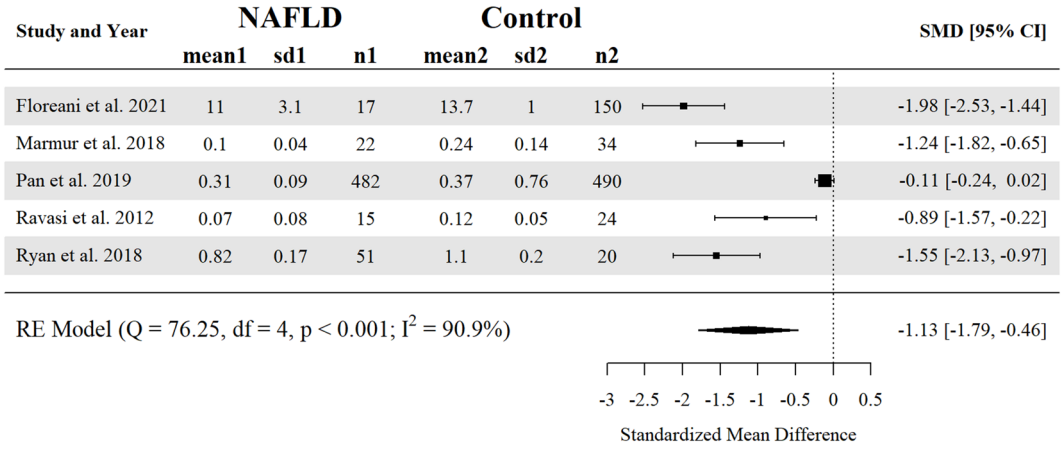

Fig. 3 Forest plot of the effect of the association between serum hepcidin/ferritin ratio and NAFLD. This meta-analysis focuses on the hepcidin/ferritin ratio, revealing a significant reduction in the NAFLD groups compared to the control groups, with an overall effect size of SMD = -1.13 (95% CI: -1.79 to -0.46, $p < 0.001$)

to the iron-exporter ferroprotein, leading to its internalization and degradation. In NAFLD, several mechanisms may contribute to the upregulation of hepcidin. First, NAFLD is often accompanied by systemic and hepatic inflammation, especially in patients with NASH [41, 42]. Inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) can directly promote hepcidin expression by activating the signal transducer and activator of the transcription 3 (STAT3) signalling pathway [43]. This inflammation-mediated

Table 3 Subgroup analysis of serum hepcidin levels in NAFLD

	Studies	NALFD patients	Controls	SMD (95% CI)	I^2 (%)
Overall	21	2216	2125	1.03 (0.49 to 1.56)	98.1
By BMI					
overweight	8	937	749	0.88 (0.05 to 1.72)	97.2
obesity	9	398	417	1.12 (0.40 to 1.97)	95.7
By hepcidin measurement method					
ELISA	16	2119	1896	1.01 (0.43 to 1.59)	98.3
LC/MS/MS	3	55	42	0.51 (-0.57 to 1.60)	83.1
By region					
Africa	2	80	60	1.52 (-0.29 to 3.33)	95.3
Europe	5	1339	1510	0.99 (-0.31 to 2.29)	99.5
America	4	205	236	1.76 (0.45 to 3.08)	96.7
Asia	10	592	319	0.65 (-0.06 to 1.36)	94.7
By Male/Female					
≤ 1.5	13	700	663	1.46 (0.73 to 2.19)	96.3
> 1.5	7	1501	1438	0.45 (-0.12 to 1.02)	97.4
By development status of the country					
Developed	11	303	505	1.07 (0.28 to 1.86)	95.4
Developing	10	1913	1620	0.98 (0.21 to 1.74)	98.8
By study design					
CCS	8	1521	1749	0.67 (-0.04 to 1.37)	98.4
CSS	13	695	646	1.25 (0.50 to 2.00)	96.5
By study quality					
High quality	15	2073	1824	1.07 (0.46 to 1.68)	98.4
Low quality	6	143	301	0.92 (-0.27 to 2.11)	95.9
By sample size					
≤ 40 NAFLD patients	11	331	488	1.25 (0.36 to 2.1)	95.8
> 40 NAFLD patients	10	1885	1637	0.78 (0.20 to 1.37)	98.1
By study period					
Before 2015	10	383	367	0.92 (0.20 to 1.64)	94.4
After 2015	11	1833	1758	1.12 (0.30 to 1.94)	99.0
By NASH/SS	2	69	28	-0.04 (-0.49, 0.41)	0.2

increase in hepcidin acts as a protective mechanism, to reduce further iron absorption and circulation, thus avoiding iron-catalyzed oxidative stress that could cause more severe liver damage. Second, the iron load frequently observed in NAFLD patients stimulate hepcidin production. Nicolas et al. [44] proposed that hepcidin functions as a critical signalling molecule reflecting systemic iron status across iron-transporting organs. Elevated hepatic hepcidin secretion in response to iron overload conditions decreases iron absorption in the gastrointestinal tract and limits iron release from the reticuloendothelial system, thereby maintaining iron balance. Moreover, obesity and metabolic syndrome, significant risk factors for NAFLD, are closely linked with IR and chronic inflammatory state [45]. IR may further disrupt iron metabolism by altering hepcidin regulation through pathways, including STAT3 [46]. Our meta-analysis demonstrates that elevated serum hepcidin levels are significantly associated with an increased risk of NAFLD, highlighting its potential as a biomarker for early detection and risk stratification. While our study did not establish specific diagnostic threshold levels for hepcidin, the findings support the need for further research to determine clinically relevant cutoff values. Establishing standardized threshold levels will be crucial for effectively integrating hepcidin measurements into routine clinical practice.

Ferritin, an acute-phase reactant, is often elevated in inflammatory states commonly observed in NAFLD, which can confound the interpretation of hepcidin level, as both are influenced by inflammation. Elevated ferritin may indicate not only iron storage but also underlying inflammation, masking the role of dysregulation of iron metabolism in NAFLD. To address this, we employed the hepcidin/ferritin ratio, which normalizes hepcidin levels relative to ferritin, accounting for inflammation. Our finding of lower hepcidin/ferritin ratios in NAFLD suggests disruptions in iron metabolism beyond inflammation. However, the limited number of studies on this ratio reduces the strength of this conclusion. In patients with NASH and Dysmetabolic Iron Overload Syndrome (DIOS), a reduced hepcidin/ferritin ratio reflects

Table 4 Meta-regression analysis of serum hepcidin levels in NAFLD

Variables	Number of studies	Meta-regression Coefficient (95% CI)	*P*-value	Tau^2	R^2 (%)
year	21	0.09 (0.04 to 0.22)	0.19	1.14	3.46
age	21	0.06 (-0.01 to 0.14)	0.07	1.34	10.31
BMI	17	0.04 (-0.04 to 0.12)	0.30	1.14	0.00
hepcidin measurement method				1.28	14.77
ELISA	16	1.01 (0.45 to 1.58)	0.00		
LC/MS/MS	3	-0.49 (-1.96 to 0.98)	0.51		
By region				1.55	0.00
Africa	2	1.52 (-0.25 to 3.29)	0.09		
Europe	5	-0.54 (-2.63 to 1.55)	0.61		
America	4	0.24 (-1.93 to 2.41)	0.83		
Asia	10	-0.87 (-2.81 to 1.07)	0.38		
By Male/Female				1.29	13.81
≤ 1.5c	13	1.46 (0.82 to 2.10)	0.00		
> 1.5	7	-1.01 (-2.08 to 0.06)	0.06		
By study design				1.50	0.19
CCS	8	0.67 (-0.20 to 1.53)	0.13		
CSS	13	0.58 (-0.52 to 1.68)	0.30		
By quality				1.58	0.00
High quality	15	1.07 (0.42 to 1.72)	0.00		
Low quality	6	-0.15 (-1.37 to 1.08)	0.81		

significant disruptions in iron metabolism. Studies indicate that IR is more pronounced in NASH compared to SS, and this IR is associated with decreased hepcidin levels [47]. This connection may arise from IR interfering with the normal regulatory mechanisms of hepcidin, leading to reduced hepcidin levels in NASH and subsequently affecting the hepcidin/ferritin ratio [48].

However, our study did not confirm this result because only two studies categorized NAFLD into SS and NASH. Although the combined effect size of serum hepcidin was − 0.04, the result was not statistically significant. Additionally, increased oxidative stress and mitochondrial dysfunction in NASH may exacerbate iron metabolism, leading to lower hepcidin/ferritin ratios in patients with severe hepatocellular damage [49, 50]. These mechanisms collectively highlight the pivotal role of hepcidin in regulating iron metabolism and its impact on the progression of NAFLD, emphasizing the need to target iron homeostasis and inflammatory pathways in therapeutic strategies.

Our meta-analysis indicated that obese groups exhibited higher levels of serum hepcidin compared to overweight groups. This difference is likely driven by chronic low-grade inflammation associated with obesity, which increases levels of inflammatory cytokines such as leptin, TNF-α, and IL-6 [6, 51–54]. These cytokines promote hepcidin synthesis through various signalling pathways, resulting in decreased iron absorption and increased iron storage [55, 56]. Consequently, this process helps reduce excessive iron release caused by inflammation, serving as a protective mechanism against inflammatory responses. However, inflammation related to obesity may confound the use of hepcidin as a biomarker for NAFLD, as elevated hepcidin levels could reflect both liver disease and inflammatory conditions associated with obesity. Future research should explore strategies to differentiate hepcidin elevations attributable to NAFLD from those caused by obesity-related inflammation.

Additionally, our analysis revealed that studies using ELISA reported higher hepcidin levels in NAFLD patients compared to those using LC/MS/MS. This can be attributed to the high sensitivity and low detection limits of ELISA, making it more effective in detecting significant associations between hepcidin and NAFLD. In contrast, mass spectrometry, while advantageous in terms of specificity and the ability to quantify multiple hepcidin subtypes, may result in weaker observed associations due to higher detection limits and more complex operational procedures [57].

Additionally, our meta-analysis demonstrated that the association between serum hepcidin levels and NAFLD varied significantly based on the male-to-female ratio within study populations. Specifically, studies with a male-to-female ratio of ≤ 1.5 in NAFLD participants demonstrated a strong positive association (SMD = 1.46; 95% CI: 0.73 to 2.19), whereas studies with a ratio > 1.5 exhibited a weaker and non-significant association (SMD = 0.45; 95% CI: -0.12 to 1.02). This disparity may arise from the modulatory effects of female sex hormones, particularly estrogen, on hepcidin expression. Estrogen upregulates hepcidin via the GPR30-BMP6 signalling pathway [58]. Consequently, studies with a more balanced or female-dominated population may exhibit stronger hepcidin-NAFLD associations due to higher baseline estrogen levels, while studies with a higher proportion of males may show attenuated associations.

Moreover, our findings revealed significant variations in the association between serum hepcidin levels and NAFLD risk across diverse geographic regions. This

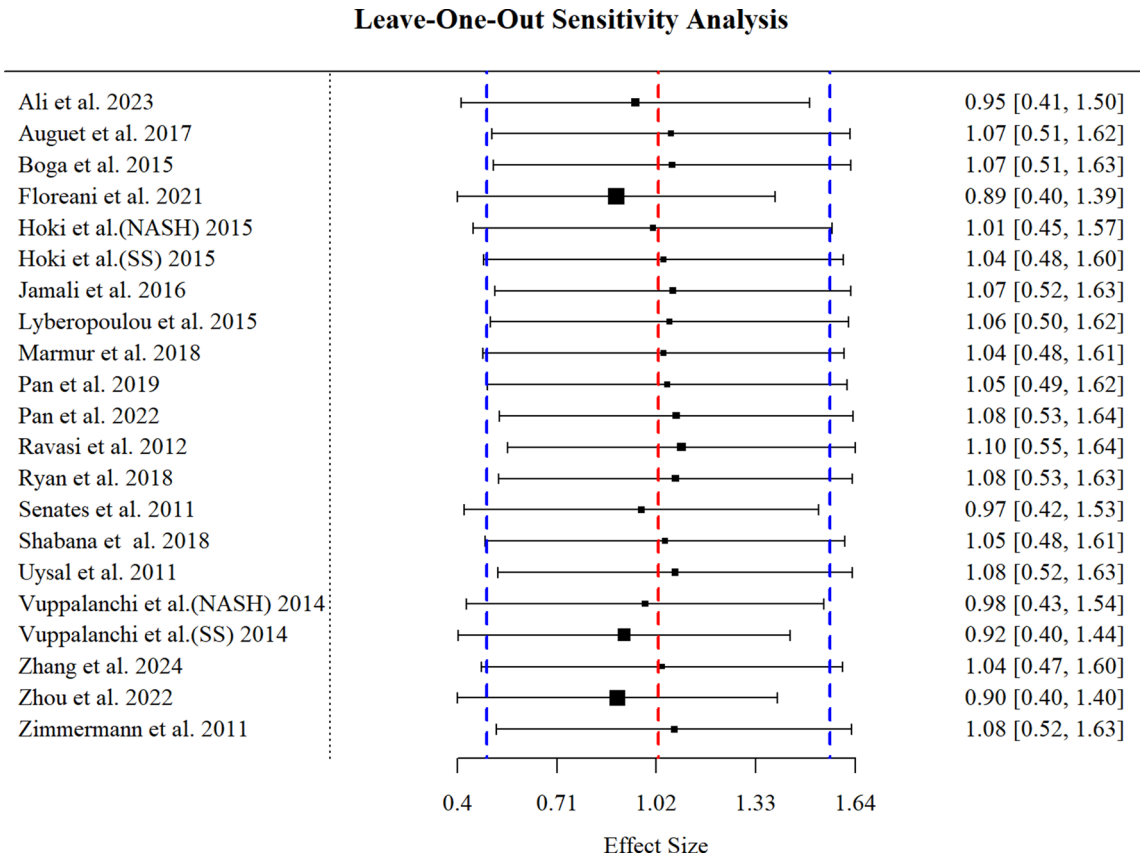

Fig. 4 Sensitivity analysis of the association between hepcidin and risk of NAFLD

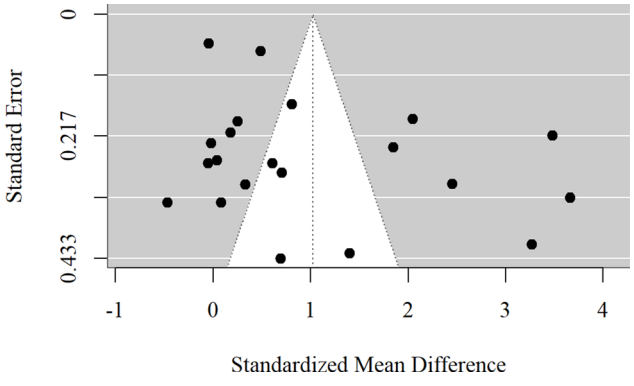

Fig. 5 Funnel plot of the association between hepcidin and risk of NAFLD

disparity can be attributed to differences in dietary habits, prevalence of obesity, IR, and metabolic syndrome across regions such as Africa, Europe, America, and Asia.

In conclusion, elevated hepcidin levels in NAFLD patients reflect a physiological response to iron metabolism disorders, underscoring the interplay between inflammation, iron overload, and metabolic factors in the disease's pathophysiology. Understanding these mechanisms is crucial for developing targeted therapeutic strategies for NAFLD, which could help regulate iron metabolism and reduce inflammation, thereby improving or halting the progression of the disease.

Limitations

The design and implementation of this study have several strengths that enhance the applicability and rigour of the analysis results. Firstly, the studies included in this analysis cover a broad geographical range, ensuring that the findings represent diverse populations and regions. Additionally, the study controlled for multiple potential confounding factors, ensuring the precision and comprehensiveness of the results. An additional strength of this study is its comprehensive literature search. The carefully designed search strategy covered five major databases, ensuring the completeness and breadth of the literature collection and significantly reducing the likelihood of missing key studies. Finally, the literature screening and selection process was conducted by two independent reviewers following a rigorous and transparent methodology. In conclusion, these measures form the core strengths of this study, providing highly reliable and practically meaningful analysis results.

Our meta-analysis has several limitations: (1) all of the included studies are cross-sectional in design, which results in a lower level of evidence; (2) due to the

cross-sectional nature of the studies, we were unable to assess the causal relationship between hepcidin, the hepcidin/ferritin ratio, and NAFLD; (3) additionally, there was significant heterogeneity across the included studies, which may affect the robustness and generalizability of our findings; (4) the methods used to measure hepcidin varied across the studies, potentially introducing variability in the results; (5) furthermore, due to the limited data available from the included studies, our meta-analysis was unable to fully explore the potential impact of the hepcidin/ferritin ratio on NAFLD; (6) although we controlled for several confounding factors, unidentified confounders may still exist, which could affect the accuracy of our findings.

Conclusion

In conclusion, our results indicate that patients with NAFLD may exhibit higher serum hepcidin levels and lower hepcidin/ferritin ratios. Furthermore, hepcidin levels appear modulated by multiple factors, highlighting the importance of considering variables such as the hepcidin/ferritin ratio and BMI in diagnosing, preventing, and managing NAFLD.

Future directions

Future research should prioritize the development and validation of standardized methods for measuring hepcidin to reduce variability across different laboratory techniques. Longitudinal cohort studies using standardized hepcidin assays are needed to explore the causal relationship between hepcidin dysregulation and the development of NAFLD. Additionally, further studies should investigate the potential of the hepcidin/ferritin ratio as a clinical tool for screening and assessing prognosis in NAFLD patients. Furthermore, it is essential to examine how factors like obesity and metabolic syndrome influence the relationship between hepcidin and NAFLD, as these conditions may modulate iron metabolism.

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
IR	Insulin resistance
NASH	Nonalcoholic steatohepatitis
MAFLD	Metabolically Associated Fatty Liver Disease
MASLD	Metabolic dysfunction associated steatotic liver disease
SD	Standard deviation
IQR	Interquartile ranges
SMD	Standardized Mean Difference
I^2	I-squared
ELISA	Enzyme-linked immunosorbent assay
SELDI-TOF/MS	Surface-enhanced laser-desorption ionization time-of-flight method
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
SS	Hepatic steatosis
CCS	Case-control study
CSS	Cross-sectional study
DIOS	Dysmetabolic Iron Overload Syndrome
TNF-α	Tumour Necrosis Factor-alpha
IL-6	Interleukin-6

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

J.S.: Conceptualization, methodology, software, validation, data curation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision, project administration.H.W.: Conceptualization, validation, investigation, writing – review & editing.X.G.: Conceptualization, formal analysis, resources, data curation, writing – review & editing, visualization, supervision, project administration, funding acquisition.F.Y.: methodology, validation.X.Z.: methodology, validation.G.Q.: methodology, validation.T.G.: methodology, validation.J.T.: investigation.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study adhered to ethical standards by following the PRISMA guidelines for systematic reviews and meta-analyses, ensuring transparency in methodology and the reporting of findings.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Fatty Liver Expert Committee CMDA. Guidelines of prevention and treatment for nonalcoholic fatty liver disease: a 2018 update. Zhonghua Gan Zang Bing Za Zhi Zhonghua Ganzangbing Zazhi. Chin J Hepatol. 2018;26(3):195–203.
2. >Eslam M, Sanyal AJ, George J, Sanyal A, Neuschwander-Tetri B, Tiribelli C, Kleiner DE, Brunt E, Bugianesi E, Yki-Järvinen H. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020;158(7):1999–2014. e1991.

3. Amini-Salehi E, Letafatkar N, Norouzi N, Joukar F, Habibi A, Javid M, Sattari N, Khorasani M, Farahmand A, Tavakoli S. Global prevalence of nonalcoholic fatty liver disease: an updated review Meta-analysis comprising a Population of 78 million from 38 countries. Arch Med Res. 2024;55(6):103043.
4. Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol. WJG2014;20(2):475.
5. Datz C, Müller E, Aigner E. Iron overload and non-alcoholic fatty liver disease. Minerva Endocrinologica. 2016;42(2):173–83.
6. Milic S, Mikolasevic I, Orlic L, Devcic E, Starcevic-Cizmarevic N, Stimac D, Kapovic M, Ristic S. The role of iron and iron overload in chronic liver disease. Med Sci Monit: Int Med J Exp Clin Res. 2016;22:2144.
7. Nemeth E. Ganz T. Hepcidin and iron in health and disease. Annual review of medicine 2023;74:261–77.
8. Nemeth E, Ganz, T. Hepcidin-ferroportin interaction controls systemic iron homeostasis. Int J Mol Sci. 2021;22(12):6493.
9. Kowdley KV, Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA, Chalasani N, Sanyal AJ, Nelson JE. Network NCR Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. Hepatology. 2012;55(1):77–85.
10. Means RT: Iron deficiency and iron deficiency anemia: implications and impact in pregnancy, fetal development, and early childhood parameters. Nutrients. 2020;12(2):447.
11. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014;6(4):748–73.
12. Lombardi R, Pisano G, Fargion S: Role of serum uric acid and ferritin in the development and progression of NAFLD. Int J Mol Sci. 2016;17(4):548.
13. Kim C-W, Chang Y, Sung E, Shin H, Ryu S: Serum ferritin levels predict incident non-alcoholic fatty liver disease in healthy Korean men. Metabolism. 2012;61(8):1182–88.
14. Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, Kaplan J. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. science. 2004;306(5704):2090–93.
15. Tussing-Humphreys L, Pustacioglu C, Nemeth E, Braunschweig, C. Rethinking iron regulation and assessment in iron deficiency, anemia of chronic disease, and obesity: introducing hepcidin. J Acad Nutr Diet. 2012;112(3):391–400.
16. Boga S, Alkim H, Alkim C, Koksal AR, Bayram M, Yilmaz Ozguven MB, Tekin Neijmann S. The relationship of serum hemojuvelin and hepcidin levels with iron overload in nonalcoholic fatty liver disease. J Gastrointestin Liver Dis. 2015;24(3):293–300.
17. Marmur J, Beshara S, Eggertsen G, Onelöv L, Albiin N, Danielsson O, Hultcrantz R. Stål P. Hepcidin levels correlate to liver iron content, but not steatohepatitis, in non-alcoholic fatty liver disease. BMC gastroenterol. 2018;18:1–10.
18. Lyberopoulou A, Chachami G, Gatselis NK, Kyratzopoulou E, Saitis A, Gabeta S, Eliades P, Paraskeva E, Zachou K, Koukoulis GK. Low serum hepcidin in patients with autoimmune liver diseases. PloS one. 2015;10(8):e0135486.
19. Tan TC, Crawford DH, Franklin ME, Jaskowski LA, Macdonald GA, Jonsson JR, Watson MJ, Taylor PJ, Fletcher LM. The serum hepcidin: ferritin ratio is a potential biomarker for cirrhosis. Liver Int. 2012;32(9):1391–99.
20. Ryan JD, Armitage AE, Cobbold JF, Banerjee R, Borsani O, Dongiovanni P, Neubauer S, Morovat R, Wang LM, Pasricha SR. Hepatic iron is the major determinant of serum ferritin in NAFLD patients. Liver Int. 2018;38(1):164–73.
21. Zimmermann A, Zimmermann T, Schattenberg J, Pöttgen S, Lotz J, Rossmann H, Roeddiger R, Biesterfeld S, Geiss H-C, Schuchmann M. Alterations in lipid, carbohydrate and iron metabolism in patients with non-alcoholic steatohepatitis (NASH) and metabolic syndrome. Eur J Intern Med. 2011;22(3):305–10.
22. Vuppalanchi R, Troutt JS, Konrad RJ, Ghabril M, Saxena R, Bell LN, Kowdley KV, Chalasani N. Serum hepcidin levels are associated with obesity but not liver disease. Obesity. 2014;22(3):836–41.
23. Moher D, Liberati A, Tetzlaff J, Altman DG. Group P: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–41.
24. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry. 1978;35(6):773–82.
25. Higgins J, Altman D, Gøtzsche P, Jüni P, Moher D, Oxman A, Savovic J, Schulz K, Weeks L, Sterne J. Cochrane bias methods group; cochrane statistical methods group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ 2011;343(7829):d5928.
26. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
27. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, Niu Y, Du L. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015;8(1):2–10.
28. Shi J, Luo D, Weng H, Zeng XT, Lin L, Chu H, Tong T. Optimally estimating the sample standard deviation from the five-number summary. Res Synth Methods. 2020;11(5):641–54.
29. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:1–13.
30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj 2003;327(7414):557–60.
31. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924–26.
32. Group GW: Grading quality of evidence and strength of recommendations. Bmj 2004, 328(7454):1490.
33. Floreani A, Navaglia F, Rizzotto ER, Basso D, Chiaramonte M, Padoan A, Petridis I, Cazzagon N, Testa R, Marra, M. Mass spectrometry measurement of plasma hepcidin for the prediction of iron overload. Clin Chem Lab Med. 2011;49(2):197–206.
34. Hoki T, Miyanishi K, Tanaka S, Takada K, Kawano Y, Sakurada A, Sato M, Kubo T, Sato T, Sato Y. Increased duodenal iron absorption through up-regulation of divalent metal transporter 1 from enhancement of iron regulatory protein 1 activity in patients with nonalcoholic steatohepatitis. Hepatology. 2015;62(3):751#x2013;761.
35. Jamali R, Hatami N, Kosari F. The correlation between serum adipokines and liver cell damage in non-alcoholic fatty liver disease. Hepat month. 2016;16(5).
36. Pan X, Chen B, Liu W, Li Y, Hu Z, Lin X, Xu S, Peng X-EJ. Circulating iron levels interaction with central obesity on the risk of nonalcoholic fatty liver disease: a case–control study in Southeast China. Ann Nutr Metab. 2019;74(3):207–14.
37. Senates E, Yilmaz Y, Colak Y, Ozturk O, Altunoz ME, Kurt R, Ozkara S, Aksaray S, Tuncer I, Ovunc. AOK: Serum levels of hepcidin in patients with biopsy-proven nonalcoholic fatty liver disease. Metabolic syndrome related disorders 2011;9(4):287–90.
38. Pan X, Peng H, Zhang J, Wu Y, Hu Z, Peng X-E. Genetic variants in promoter region of TFR2 is associated with the risk of non-alcoholic fatty liver disease in a Chinese Han population: a case–control study. Gastroenterology Report 2022;10:goac060.
39. Ravasi G, Pelucchi S, Trombini P, Mariani R, Tomosugi N, Modignani GL, Pozzi M, Nemeth E, Ganz T, Hayashi H. Hepcidin expression in iron overload diseases is variably modulated by circulating factors. PloS one. 2012;7(5):e36425.
40. Uysal S, Armutcu F, Aydogan T, Akin K, Ikizek M, Yigitoglu MR. Some inflammatory cytokine levels, iron metabolism and oxidan stress markers in subjects with nonalcoholic steatohepatitis. Clin Biochem. 2011;44(17-18):1375–9.
41. Farrell GC, Van Rooyen D, Gan L, Chitturi S. NASH is an inflammatory disorder: pathogenic, prognostic and therapeutic implications. Gut liver. 2012;6(2):149.
42. Gehrke N, Schattenberg JM: Metabolic inflammation—a role for hepatic inflammatory pathways as drivers of comorbidities in nonalcoholic fatty liver disease? Gastroenterology. 2020;158(7):1929–1947. e1926.
43. Huang Y-H, Chuang J-H, Yang Y-L, Huang C-C, Wu C-L, Chen C-.: Cholestasis Downregulate hepcidin expression through inhibiting IL-6-induced phosphorylation of signal transducer and activator of transcription 3 signaling. Lab Invest. 2009;89(10):1128–39.
44. Nicolas G, Bennoun M, Devaux I, Beaumont C, Grandchamp B, Kahn A, Vaulont S. Lack of hepcidin gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. Proc Natl Acad Sci. 2001;98(15):8780–5.
45. Jung UJ, Choi M-S. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014;15(4):6184–223.
46. Hilton C, Sabaratnam R, Drakesmith H, Karpe F. Iron, glucose and fat metabolism and obesity: an intertwined relationship. Int J Obes. 2023;47(7):554–63.
47. Mitsuyoshi H, Yasui K, Harano Y, Endo M, Tsuji K, Minami M, Itoh Y, Okanoue T, Yoshikawa T. Analysis of hepatic genes involved in the metabolism of fatty acids and iron in nonalcoholic fatty liver disease. Hepatol Res. 2009;39(4):366–73.

48. Barisani D, Pelucchi S, Mariani R, Galimberti S, Trombini P, Fumagalli D, Meneveri R, Nemeth E, Ganz T, Piperno A. Hepcidin and iron-related gene expression in subjects with dysmetabolic hepatic Iron overload. J Hepatol. 2008;49(1):123–33.
49. Le Guenno G, Chanséaume E, Ruivard M, Morio B, Mazur A. Study of iron metabolism disturbances in an animal model of insulin resistance. Diabetes Res Clin Pract. 2007;77(3):363–70.
50. Sam A, Busbridge M, Amin A, Webber L, White D, Franks S, Martin N, Sleeth M, Ismail N, Daud NM. Hepcidin levels in diabetes mellitus and polycystic ovary syndrome. Diabet Med. 2013;30(12):1495–99.
51. Fontes-Cal TC, Mattos RT, Medeiros NI, Pinto BF, Belchior-Bezerra M, Roque-Souza B, Dutra WO, Ferrari TC, Vidigal PV, Faria LC. Crosstalk between plasma cytokines, inflammation, and liver damage as a new strategy to monitoring NAFLD progression. Front Immunol. 2021;12:708959.
52. Schmidt PJ. Regulation of iron metabolism by hepcidin under conditions of inflammation. J Biol Chem. 2015;290(31):18975–83.
53. Chung B, Matak P, McKie AT, Sharp P. Leptin increases the expression of the iron regulatory hormone hepcidin in HuH7 human hepatoma cells. J Nutr. 2007;137(11):2366–70.
54. Aigner E, Theurl I, Theurl M, Lederer D, Haufe H, Dietze O, Strasser M, Datz C, Weiss G. Pathways underlying iron accumulation in human nonalcoholic fatty liver disease. Am J Clin Nutr. 2008;87(5):1374–83.
55. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz, T. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Investig. 2004;113(9):1271–76.
56. Lee P, Peng H, Gelbart T, Beutler, E. The IL-6-and lipopolysaccharide-induced transcription of hepcidin in HFE-, transferrin receptor 2-, and β2-microglobulin-deficient hepatocytes. Proc Natl Acad Sci. 2004;101(25):9263–5.
57. Rana S, Prabhakar N: Iron disorders and hepcidin. Clinica chimica acta; Int J Clin Chem Sci. 2021;523:454–68.
58. Ikeda Y, Tajima S, Izawa-Ishizawa Y, Kihira Y, Ishizawa K, Tomita S, Tsuchiya K, Tamaki T. Estrogen regulates hepcidin expression via GPR30-BMP6-dependent signaling in hepatocytes. PloS one. 2012;7(7):e40465.

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