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Synergistic impact of serum uric acid and ferritin on MAFLD risk: A comprehensive cohort analysis

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The characterization of Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) underscores metabolic anomalies as critical in fatty liver disease progression. Serum uric acid is increasingly recognized as a determinant for fatty liver diseases due to its association with metabolic disorders. Ferritin, in parallel, serves as an inflammatory marker closely tied to metabolic syndrome and insulin resistance. Our study explores the combined influence of serum uric acid and ferritin on MAFLD prevalence. We conducted a retrospective cohort analysis at Samsung Changwon Hospital's Health Screening Center (2011–2018), encompassing 7,818 individuals post-exclusion criteria. Participants were stratified into gender-specific quartiles based on serum uric acid and ferritin levels. Utilizing multivariable Cox proportional hazard models alongside Kaplan-Meier analysis, we assessed the incidence of MAFLD and its relationship with these serum biomarkers, also performing subgroup assessments by gender, age, and BMI. Over 41,819 person-years with an average observation period of 5.35 ± 2.06 years, 1,073 incident cases of MAFLD were recorded. The risk of MAFLD was notably higher within the upper quartiles of serum uric acid (HR: 2.17, 95% CI: 1.70–2.78). Each increment in natural logarithmic serum uric acid level correlated with an increased risk (HR: 3.65, 95% CI: 2.32–5.74). Serum ferritin also indicated an enhanced risk, albeit less pronounced. The simultaneous presence of elevated levels of both uric acid and ferritin correlated with the highest MAFLD risk (HR: 3.89, 95% CI: 2.41–6.28). Our findings affirm that high serum uric acid levels significantly escalate the risk of MAFLD, with serum ferritin levels contributing to a lesser yet substantial degree. The concurrent elevation of both biomarkers magnifies MAFLD risk, reinforcing the need for their combined assessment in MAFLD risk evaluation.

Keywords Hepatic steatosis, Serum uric acid, Serum ferritin, Risk factors

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) has been recently characterized as a form of fatty liver disease that underscores the significant influence of metabolic dysfunction on the onset, progression, and clinical outcomes of hepatic steatosis[1].

This term reflects a broader understanding of the disease, which, unlike its predecessor Non-Alcoholic Fatty Liver Disease (NAFLD), incorporates a spectrum of metabolic abnormalities beyond the exclusion of alcohol consumption, viral hepatitis, and medication effects[2]While NAFLD is diagnosed based on the presence of fat in over 5% of liver cells in the absence of secondary causes of hepatic fat accumulation[3], MAFLD includes patients with coexisting metabolic diseases or two of the other metabolic risk abnormalities specified in the consensus definition, thereby acknowledging the complexity of metabolic interactions within this spectrum[4].

Epidemiological studies have demonstrated that NAFLD affects approximately 25% of the global population, with a notably higher prevalence of 30% in Korea[5], stablishing it as a significant public health concern. The condition carries substantial health implications, as patients with NAFLD experience a 1.6-fold increased risk of cardiovascular disease, a 2.2-fold increased risk of type 2 diabetes, and a 1.2-fold increased risk of chronic kidney disease compared to the general population[6–8] These elevated risks, coupled with the complex interplay between metabolic factors and liver disease progression, underscore the critical need for reliable biomarkers for early detection and risk stratification[9,10] Serum uric acid, the end-product of purine metabolism, is implicated in

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several metabolic disorders[11,12] It has been identified as an independent risk factor for NAFLD, with each 1 mg/dL increment associated with a 21% increased risk for the disease[13,14] Ferritin, an iron-storage protein complex, doubles as an inflammation indicator and has been associated with insulin resistance and metabolic syndrome, conditions often concurrent in patients with NAFLD and MAFLD[15,16] Elevated ferritin levels have also been predictive of NAFLD in asymptomatic populations, suggesting its utility as a prognostic biomarker[17,18] Although serum uric acid and ferritin are individually linked to hepatic steatosis and liver damage, the intersection of these biomarkers in MAFLD pathogenesis is not well-defined. Our study seeks to elucidate the incidence of MAFLD in relation to serum uric acid and ferritin levels, employing a retrospective cohort design to unravel the intricacies of their interaction. By delving into the confluence of these metabolic factors, we aim to shed light on their collective impact on MAFLD, which may inform future research directions and contribute to the refinement of management practices.

Results

Baseline characteristics by serum uric acid levels

Table 1 delineates the baseline characteristics of participants stratified by gender-specific serum uric acid quartiles. Quartiles for men are set as: ≤5.00 mg/dL (Q1), 5.10–5.70 mg/dL (Q2), 5.80–6.40 mg/dL (Q3), and ≥6.50 mg/dL (Q4); and for women: ≤3.50 mg/dL (Q1), 3.60–4.10 mg/dL (Q2), 4.20–4.60 mg/dL (Q3), and ≥4.70 mg/dL (Q4). Statistically significant differences were observed across quartiles in TG, HbA1c, hs-CRP, AST, ALT, GGT, FIB-4, and FLI. Higher serum uric acid levels were significantly associated with increased BMI, WC, blood pressure, TG, TC, LDL-C, and FPG, and correlated with smoking status and physical activity levels. Furthermore, higher serum uric acid was linked to younger age and varied levels of FPG, HDL-C, and NFS.

Baseline characteristics by serum ferritin levels

Table 2 summarizes the baseline characteristics of participants stratified by gender-specific serum ferritin quartiles. For men, the quartiles are established as: ≤88.73 ng/mL (Q1), 88.78–123.80 ng/mL (Q2), 123.90–169.10 ng/mL (Q3), and ≥169.20 ng/mL (Q4); for women: ≤16.00 ng/mL (Q1), 16.02–34.26 ng/mL (Q2), 34.27–60.27 ng/mL (Q3), and ≥60.36 ng/mL (Q4). Notable associations with serum ferritin quartiles were found for age, BMI, WC, TG, TC, HbA1c, HOMA-IR, hs-CRP, AST, NFS, and APRI scores. Higher serum ferritin levels were positively correlated with increased LDL-C, alcohol intake, ALT, GGT, FIB-4 scores, and FLI.

Incidence rate of MAFLD by serum uric acid and ferritin quartiles

During an average follow-up of 5.35 ± 2.06 years, participants had health examinations approximately 6.35 ± 2.06 times. Over 41,819 person-years, 1,073 new MAFLD cases were identified. Table 3 presents the incidence rates of MAFLD by quartiles of serum uric acid and ferritin levels. In the fully adjusted Cox proportional hazards models (Model 4), considering age, sex, smoking status, alcohol consumption, physical activity, and log-transformed serum ferritin levels (for uric acid analysis) or log-transformed serum uric acid levels (for ferritin analysis), the hazard ratios (HRs) and 95% confidence intervals (CIs) for developing MAFLD across the serum uric acid quartiles were 1.15 (0.88–1.50), 1.28 (0.98–1.67), and 2.17 (1.70–2.78), respectively, with the highest quartile showing a 2.17-fold increased risk compared to the lowest quartile ($P < 0.001$). For each unit increase in the log-transformed serum uric acid, the risk of MAFLD rose substantially with an HR of 3.65 (95% CI, 2.32–5.74). In contrast, the HRs and 95% CIs for developing MAFLD across the serum ferritin quartiles were 1.04 (0.75–1.44), 0.99 (0.66–1.48), and 1.43 (0.88–2.34), respectively ($P = 0.096$), not demonstrating a statistically significant difference across the baseline quartiles. However, each one-unit increase in the natural log of serum ferritin (ln[ng/mL]) was associated with a fully adjusted hazard ratio of 1.33 (95% CI, 1.16–1.53) for the development of MAFLD.

Kaplan-Meier curves illustrated significant differences in the cumulative incidence of MAFLD across the uric acid quartiles (Fig. 2), with higher quartiles correlating with increased risk, although the inter-quartile comparison between Q2 and Q3 did not yield a statistically significant difference ($P = 0.212$). For serum ferritin quartiles, cumulative risk assessments for incident MAFLD depicted using Kaplan-Meier curves (Fig. 3) highlighted that only participant in the highest ferritin quartile (Q4) had a significantly greater cumulative risk of developing MAFLD compared to those in the lower quartiles (Q1 vs. Q4: $P < 0.01$; Q2 vs. Q4: $P < 0.01$; Q3 vs. Q4: $P = 0.01$).

Combined associations of serum uric acid and serum ferritin levels with incident MAFLD

In investigating the conjoint influence of serum uric acid and ferritin on the occurrence of MAFLD, fully adjusted quartiles for both biomarkers were scrutinized. Table 4 illustrates the specific associations between these quartiles and the incidence of MAFLD. A discernible trend suggests a dose-response effect, where higher quartiles of both uric acid and ferritin correspond to an escalating risk of MAFLD onset. Although the interaction between uric acid and ferritin levels did not achieve statistical significance (P_interaction = 0.170), the composite evaluation revealed biologically meaningful combined effects, with participants occupying the highest quartiles for both biomarkers showing the most substantial risk for MAFLD development. They had a hazard ratio of 3.89 (95% CI, 2.41–6.28) when juxtaposed with counterparts in the lowest quartiles for both measures, suggesting potential synergistic effects even in the absence of statistical interaction. They had a hazard ratio of 3.89 (95% CI, 2.41–6.28) when juxtaposed with counterparts in the lowest quartiles for both measures. This points to a plausible synergistic impact of elevated levels of these biomarkers on MAFLD incidence.

Subgroup analyses based on demographic and physical variables

Subgroup analyses explored the interaction between serum uric acid and serum ferritin levels with MAFLD incidence across various demographics, categorized by gender, age (below 40 years and 40 years and above), and

		Quartile of serum uric acid				
		Q1 (lowest) (*n* = 1,977)	Q2 (*n* = 2,100)	Q3 (*n* = 1,880)	Q4 (highest) (*n* = 1,861)	*P*-value
Age, years (mean ± SD)	41.53 ± 6.45	42.17 ± 6.29	41.58 ± 6.15	41.36 ± 6.62	40.99 ± 6.71	< 0.001
Sex (n, %)						0.017
Female	4,744 (60.68)	1,206 (61.00)	1,328 (63.24)	1,102 (58.62)	1,108 (59.54)	
Male	3,074 (39.32)	771 (39.00)	772 (36.76)	778 (41.38)	753 (40.46)	
Abdominal obesity (mean ± SD)						
BMI (kg/m^2)	22.19 ± 2.15	21.82 ± 2.12	22.10 ± 2.13	22.27 ± 2.11	22.60 ± 2.16	< 0.001
WC (cm)	78.14 ± 5.72	77.12 ± 5.73	77.80 ± 5.63	78.35 ± 5.60	79.38 ± 5.67	< 0.001
Obesity (n, %)	769 (9.84)	135 (6.83)	186 (8.86)	208 (11.06)	240 (12.90)	< 0.001
Blood pressure (mean ± SD)						
SBP (mmHg)	115.75 ± 11.34	114.95 ± 10.99	115.11 ± 11.05	116.09 ± 11.58	117.00 ± 11.68	< 0.001
DBP (mmHg)	70.10 ± 9.39	69.48 ± 9.23	69.77 ± 9.25	70.30 ± 9.29	70.94 ± 9.76	< 0.001
Lipid profile (mean ± SD)						
TG (mg/dL)	82.27 ± 35.38	80.97 ± 34.53	80.40 ± 34.05	82.54 ± 34.40	85.52 ± 38.40	< 0.001
TC (mg/dL)	192.96 ± 32.20	190.55 ± 31.94	190.87 ± 31.73	194.13 ± 32.05	196.72 ± 32.77	< 0.001
HDL-C (mg/dL)	65.49 ± 14.33	66.78 ± 14.29	65.59 ± 13.95	65.09 ± 14.47	64.42 ± 14.55	< 0.001
LDL-C (mg/dL)	120.64 ± 30.03	117.12 ± 29.62	118.77 ± 29.25	122.08 ± 29.86	125.02 ± 30.86	< 0.001
Glucose intolerance index (mean ± SD)						
$HbA1_c$ (%)	5.40 ± 0.42	5.44 ± 0.59	5.39 ± 0.34	5.39 ± 0.35	5.38 ± 0.31	< 0.001
FPG (mg/dL)	87.61 ± 11.78	88.99 ± 16.37	87.56 ± 10.34	87.31 ± 9.04	86.50 ± 9.58	< 0.001
HOMA-IR score	0.88 ± 0.73	0.87 ± 0.52	0.90 ± 0.71	0.89 ± 1.06	0.87 ± 0.53	0.822
Prediabetes (n, %)	1,588 (20.31)	421 (21.29)	416 (19.81)	387 (20.59)	364 (19.56)	0.523
Alcohol consumption (g/day) (mean ± SD) (*n* = 4,155)	13.18 ± 17.65	12.39 ± 16.18	13.51 ± 18.13	13.41 ± 17.82	13.34 ± 18.30	0.281
Smoking status (n, %) (*n* = 4,677)						0.011
Non-smoker	2,727 (61.12)	653 (60.41)	778 (63.46)	660 (60.11)	636 (60.17)	
Ex-smoker	719 (16.11)	173 (16.00)	166 (13.54)	176 (16.03)	204 (19.30)	
Current smoker	1,016 (22.77)	255 (23.59)	282 (23.00)	262 (23.86)	217 (20.53)	
Physical activity (n, %) (*n* = 6,286)						0.408
Inactive	3,070 (48.84)	754 (49.67)	834 (48.63)	743 (48.28)	739 (48.81)	
Moderately active	1,808 (28.76)	412 (27.14)	481 (28.05)	469 (30.47)	446 (29.46)	
HEPA active	1,408 (22.40)	352 (23.19)	400 (23.32)	327 (21.25)	329 (21.73)	
Inflammatory marker (mean ± SD)						
hs-CRP (mg/L)	0.59 ± 1.05	0.56 ± 1.11	0.54 ± 1.01	0.59 ± 1.02	0.68 ± 1.05	< 0.001
AST, IU/L (mean ± SD)	21.27 ± 9.09	21.13 ± 10.32	20.89 ± 8.49	21.30 ± 8.50	21.82 ± 8.89	0.007
ALT, IU/L (mean ± SD)	17.87 ± 9.98	17.53 ± 10.66	17.26 ± 9.57	18.19 ± 9.72	18.58 ± 9.88	< 0.001
GGT, IU/L (mean ± SD)	18.15 ± 12.35	17.09 ± 10.85	16.97 ± 10.94	18.66 ± 13.05	20.07 ± 14.22	< 0.001
Hepatic fibrosis scores (mean ± SD)						
FIB-4 score	0.94 ± 0.53	0.98 ± 0.80	0.94 ± 0.37	0.92 ± 0.35	0.92 ± 0.45	< 0.001
NFS	−2.82 ± 0.92	−2.76 ± 1.02	−2.80 ± 0.89	−2.85 ± 0.88	−2.89 ± 0.88	< 0.001
APRI score	0.09 ± 0.06	0.10 ± 0.08	0.09 ± 0.05	0.09 ± 0.05	0.10 ± 0.06	0.723
FLI (mean ± SD)	10.52 ± 7.46	9.21 ± 6.88	9.74 ± 7.15	10.82 ± 7.39	12.47 ± 8.02	< 0.001

Table 1. Baseline characteristics of the study participants by quartiles of serum uric acid. Data are presented as means ± standard deviations or frequencies, percentages, following descriptive and frequency analyses. Statistical significance was evaluated using one-way ANOVA or the chi-square test, as appropriate. It should be noted that the sample size for each variable might vary due to missing data. The stratification of serum ferritin levels into quartiles for men and women was established based on the following cut-off values: for men, Quartile 1, Q1, ≤ 88.73 ng/mL; Quartile 2, Q2, 88.78–123.80 ng/mL; Quartile 3, Q3, 123.90–169.10 ng/mL; and Quartile 4, Q4, ≥ 169.20 ng/mL; for women, Q1 ≤ 16.00 ng/mL, Q2 16.02–34.26 ng/mL, Q3 34.27–60.27 ng/mL, and Q4 ≥ 60.36 ng/mL, respectively. ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

	Overall (*n* = 7,818)	Quartile of ferritin				*P*-value
		Q1 (lowest) (*n* = 1,995)	Q2 (*n* = 1,995)	Q3 (*n* = 1,995)	Q4 (highest) (*n* = 1,953)	
Age, years (mean ± SD)	41.53 ± 6.45	41.65 ± 5.80	41.19 ± 6.03	41.23 ± 6.50	42.07 ± 7.33	0.045
Sex (n, %)						0.492
Female	4,744 (60.68)	1,186 (60.66)	1,186 (60.66)	1,187 (60.72)	1,185 (60.68)	
Male	3,074 (39.32)	769 (39.34)	769 (39.34)	768 (39.28)	768 (39.32)	
Abdominal obesity (mean ± SD)						
BMI (kg/m^2)	22.19 ± 2.15	22.20 ± 2.17	22.03 ± 2.14	22.17 ± 2.13	22.35 ± 2.15	0.006
WC (cm)	78.14 ± 5.72	77.94 ± 5.74	77.72 ± 5.71	78.13 ± 5.66	78.77 ± 5.70	< 0.001
Obesity (n, %)	769 (9.84)	194 (9.92)	167 (8.54)	192 (9.82)	216 (11.06)	0.072
Blood pressure (mean ± SD)						
SBP (mmHg)	115.75 ± 11.34	115.92 ± 11.27	115.39 ± 11.31	115.56 ± 11.48	116.14 ± 11.30	0.470
DBP (mmHg)	70.10 ± 9.39	70.15 ± 9.33	70.08 ± 9.44	69.84 ± 9.36	70.35 ± 9.43	0.710
Lipid profile (mean ± SD)						
TG (mg/dL)	82.27 ± 35.38	81.41 ± 35.39	82.02 ± 34.71	81.84 ± 34.79	83.83 ± 36.56	0.048
TC (mg/dL)	192.96 ± 32.20	191.70 ± 31.49	192.31 ± 31.13	192.26 ± 32.72	195.59 ± 33.32	< 0.001
HDL-C (mg/dL)	65.49 ± 14.33	65.59 ± 13.98	66.09 ± 14.45	65.42 ± 14.17	64.87 ± 14.68	0.052
LDL-C (mg/dL)	120.64 ± 30.03	119.20 ± 28.83	119.37 ± 28.95	119.98 ± 30.59	124.04 ± 31.42	< 0.001
Glucose intolerance index (mean ± SD)						
$HbA1_C$ (%)	5.40 ± 0.42	5.48 ± 0.42	5.36 ± 0.36	5.36 ± 0.42	5.39 ± 0.45	< 0.001
FPG (mg/dL)	87.61 ± 11.78	87.74 ± 11.25	87.44 ± 10.41	87.46 ± 10.54	87.81 ± 14.46	0.845
HOMA-IR score	0.88 ± 0.73	0.92 ± 0.56	0.88 ± 1.04	0.85 ± 0.69	0.88 ± 0.52	0.044
Prediabetes (n, %)	1,588 (20.31)	512 (26.19)	368 (18.82)	323 (16.52)	385 (19.71)	< 0.001
Alcohol consumption (g/day) (mean ± SD) (*n* = 4,115)	13.18 ± 17.65	11.91 ± 17.56	12.79 ± 16.93	13.43 ± 18.41	14.51 ± 17.61	0.001
Smoking status (n, %) (*n* = 4,677)						0.323
Non-smoker	2,727 (61.12)	664 (60.69)	685 (61.22)	656 (59.26)	722 (63.22)	
Ex-smoker	719 (16.11)	178 (16.27)	174 (15.55)	178 (16.08)	189 (16.55)	
Current smoker	1,016 (22.77)	252 (23.03)	260 (23.24)	273 (24.66)	231 (20.23)	
Physical activity (n, %) (*n* = 6,286)						0.304
Inactive	3,070 (48.84)	796 (50.54)	760 (47.86)	755 (48.09)	759 (48.87)	
Moderately active	1,808 (28.76)	424 (26.92)	471 (29.66)	445 (28.34)	468 (30.14)	
HEPA active	1,408 (22.40)	355 (22.54)	357 (22.48)	370 (23.57)	326 (20.99)	
Inflammatory marker (mean ± SD)						
hs-CRP (mg/L)	0.59 ± 1.05	0.49 ± 0.84	0.63 ± 1.14	0.62 ± 1.11	0.63 ± 1.08	< 0.001
AST, IU/L (mean ± SD)	21.27 ± 9.09	20.58 ± 7.86	20.58 ± 7.17	21.21 ± 9.26	22.71 ± 11.33	< 0.001
ALT, IU/L (mean ± SD)	17.87 ± 9.98	16.34 ± 7.86	17.16 ± 8.67	18.01 ± 9.73	19.95 ± 12.63	< 0.001
GGT, IU/L (mean ± SD)	18.15 ± 12.35	16.25 ± 9.96	17.25 ± 10.47	18.76 ± 12.99	20.33 ± 14.94	< 0.001
Hepatic fibrosis scores (mean ± SD)						
FIB-4 score	0.94 ± 0.53	0.91 ± 0.40	0.93 ± 0.43	0.95 ± 0.77	0.98 ± 0.41	< 0.001
NFS	−2.82 ± 0.92	−2.90 ± 1.04	−2.79 ± 0.87	−2.82 ± 0.86	−2.78 ± 0.90	< 0.001
APRI score	0.09 ± 0.06	0.09 ± 0.04	0.09 ± 0.05	0.10 ± 0.07	0.10 ± 0.06	< 0.001
FLI (mean ± SD)	10.52 ± 7.46	9.84 ± 7.29	9.93 ± 7.29	10.57 ± 7.37	11.73 ± 7.73	< 0.001

Table 2. Baseline characteristics of the study participants by quartiles of serum ferritin. Values are expressed as mean ± standard deviation or number (%) by descriptive analysis and frequency analysis. P-values were calculated using one-way ANOVA or chi-square test. The number of subjects in each variable may differ due to missing study values. Cut-offs for quartiles 1–4 of serum ferritin levels are as follows: ≤ 88.73 ng/mL, 88.78–123.80 ng/mL, 123.90–169.10 ng/mL, and ≥ 169.20 ng/mL in men; and ≤ 16.00 ng/mL, 16.02–34.26 ng/mL, 34.27–60.27 ng/mL, and ≥ 60.36 ng/mL in women, respectively. Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

	Quartile of uric acid				*P*-value	1 unit increase in ln (uric acid)
	Q1 (lowest)	Q2	Q3	Q4 (highest)		
N	1,977	2,100	1,880	1,861		
Person-years	10,890	11,487	10,042	9,401		
Incident cases (n)	204	255	248	366		
Incidence rates per 1,000 person-years	18.73 (16.33–21.49)	22.20 (19.63–25.10)	24.70 (21.81–27.97)	38.93 (35.14–43.13)		
Model 1 ($n = 7,818$)	Reference	1.19 (0.99–1.43)	1.33 (1.10–1.60)	2.12 (1.78–2.51)	< 0.001	4.41 (3.49–5.57)
Model 2 ($n = 7,818$)	Reference	1.23 (1.02–1.47)	1.33 (1.11–1.61)	2.14 (1.81–2.55)	< 0.001	3.71 (2.73–5.05)
Model 3 ($n = 3,472$)	Reference	1.15 (0.88–1.50)	1.31 (1.01–1.70)	2.25 (1.76–2.88)	< 0.001	3.94 (2.50–6.20)
Model 4 ($n = 3,472$)	Reference	1.15 (0.88–1.50)	1.28 (0.98–1.67)	2.17 (1.70–2.78)	< 0.001	3.65 (2.32–5.74)
	Quartile of ferritin				***P*** -value	1 unit increase in ***ln*** (ferritin)
	Q1 (lowest)	Q2	Q3	Q4 (highest)		
N	1,955	1,955	1,955	1,953		
Person-years	10,909	10,617	10,446	9,847		
Incident cases (n)	238	258	257	320		
Incidence rates per 1,000 person-years	21.82 (19.21–24.77)	24.30 (21.51–27.45)	24.60 (21.77–27.80)	32.50 (29.12–36.26)		
Model 1 ($n = 7,818$)	Reference	1.11 (0.93–1.33)	1.15 (0.97–1.38)	1.54 (1.30–1.82)	< 0.001	1.38 (1.29–1.47)
Model 2 ($n = 7,818$)	Reference	1.12 (0.94–1.34)	1.17 (0.98–1.39)	1.54 (1.30–1.82)	< 0.001	1.23 (1.13–1.33)
Model 3 ($n = 3,472$)	Reference	1.14 (0.89–1.48)	1.14 (0.88–1.47)	1.75 (1.38–2.22)	< 0.001	1.33 (1.16–1.53)
Model 4 ($n = 3,472$)	Reference	1.04 (0.75–1.44)	0.99 (0.66–1.48)	1.43 (0.88–2.34)	0.096	1.33 (1.16–1.53)

Table 3. Incidence of MAFLD according to quartiles of serum uric acid and ferritin levels. Incidence rates per 1,000 person-years are reported as values with 95% confidence intervals (CI). Hazard ratios (HR) for the risk of incident MAFLD are shown for Models 1–4 with their respective 95% CIs. Serum uric acid level quartiles for men are defined as ≤ 5.00 mg/dL for Quartile 1, 5.10–5.70 mg/dL for Quartile 2, 5.80–6.40 mg/dL for Quartile 3, and ≥ 6.50 mg/dL for Quartile 4; for women, the quartiles are defined as ≤ 3.50 mg/dL for Quartile 1, 3.60–4.10 mg/dL for Quartile 2, 4.20–4.60 mg/dL for Quartile 3, and ≥ 4.70 mg/dL for Quartile 4. Serum ferritin level quartiles for men are set at ≤ 88.73 ng/mL for Quartile 1, 88.78–123.80 ng/mL for Quartile 2, 123.90–169.10 ng/mL for Quartile 3, and ≥ 169.20 ng/mL for Quartile 4; for women, the levels are ≤ 16.00 ng/mL for Quartile 1, 16.02–34.26 ng/mL for Quartile 2, 34.27–60.27 ng/mL for Quartile 3, and ≥ 60.36 ng/mL for Quartile 4. Model 1 is unadjusted; Model 2 is adjusted for age and sex; Model 3 is further adjusted for smoking status (categorized as never, former, or current smokers), alcohol consumption (categorized as never, moderate, or heavy drinkers), and physical activity levels (classified as inactive, moderately active, or HEPA active); Model 4 includes additional adjustments for log-transformed serum ferritin levels in the serum uric acid analysis and for log-transformed serum uric acid levels in the serum ferritin analysis. Abbreviations: Q, quartile.

BMI (below 23 kg/m² and 23 kg/m² and above). Notably, a consistent increase in MAFLD incidence was evident within higher quartiles of serum uric acid across all subgroups.

During the study, 18.90% of male participants (581 of 3,074) developed MAFLD, while the figure was 10.4% for females (492 of 4,744), as reported in Table 5. The combined associations of serum uric acid and serum ferritin with incident MAFLD, stratified by gender, age, and BMI, are detailed in Table 6. In males, the hazard ratio for those in the highest quartiles of both uric acid and ferritin was 3.67 (95% CI, 2.07–6.50), and in females, it was 4.28 (95% CI, 1.78–10.26). For males, particularly those with elevated levels of both uric acid and ferritin, the risk of developing MAFLD increased incrementally with higher concentrations of these variables, a pattern that was not as evident in females. As serum uric acid quartiles rose, both genders exhibited a significant uptick in MAFLD incidence (Supplementary Table 1). However, increments in ferritin quartiles did not correspond with a significant change in MAFLD incidence (Supplementary Table 2). Age subgroups showed that individuals below 40 years had a cumulative MAFLD incidence of 11.5%, whereas those 40 and older had a higher incidence at 15.0%. In the highest quartile for both serum uric acid and ferritin, the hazard ratio for MAFLD was 7.51 (95% CI, 2.66–21.21) for those under 40, and 2.99 (95% CI, 1.69–5.28) for the older group. Increases in uric acid quartiles corresponded with higher MAFLD incidence in both age groups (Supplementary Table 3), while changes in ferritin quartiles were not statistically significant (Supplementary Table 4). When stratified by BMI, individuals with a BMI below 23 kg/m² had a 7.4% incidence of MAFLD. In contrast, for those with BMI 23 kg/

		Quartile of uric acid			
		Q1 (lowest)	Q2	Q3	Q4 (highest)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Quartile of ferritin	Q1 (lowest)	Reference	1.35 (0.77–2.37)	1.08 (0.59–1.98)	1.81 (1.03–3.16)
	Q2	1.46 (0.86–2.48)	1.63 (0.95–2.80)	1.06 (0.59–1.92)	1.78 (1.03–3.06)
	Q3	1.54 (0.88–2.70)	1.50 (0.87–2.59)	1.36 (0.77–2.39)	2.36 (1.41–3.95)
	Q4 (highest)	1.87 (1.06–3.29)	2.17 (1.27–3.70)	3.28 (2.00–5.40)	3.89 (2.41–6.28)

Table 4. Combined associations of serum uric acid and serum ferritin levels with incident MAFLD. Cut-offs for quartiles 1–4 of serum uric acid levels are as follows: ≤5.00 mg/dL, 5.10–5.70 mg/dL, 5.80–6.40 mg/dL and ≥6.50 mg/dL in men; ≤3.50 mg/dL, 3.60–4.10 mg/dL, 4.20–4.60 mg/dL and ≥4.70 mg/dL in women respectively. Cut-offs for quartiles 1–4 of serum ferritin levels are as follows: ≤88.73 ng/mL, 88.78–123.80 ng/mL, 123.90–169.10 ng/mL and ≥169.20 ng/mL in men; ≤16.00 ng/mL, 16.02–34.26 ng/mL, 34.27–60.27 ng/mL and ≥60.36 ng/mL in women respectively. Individuals in the lowest quartile of serum uric acid and ferritin levels are used as the reference group. The model is adjusted for sex, age, smoking status (never, past, or current), alcohol intake (never, moderate, and heavy drinkers), physical activity (inactive, moderately active, and HEPA active). Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quartile.

subgroup		*N*	Person-years	Incident cases (*n*,%)	Incidence rates per 1,000 person-years
Stratified by gender	Males	3,074	16,433	581 (18.90)	35.35 (32.59–38.35)
	Females	4,744	25,385	492 (10.37)	19.38 (17.74–21.17)
Stratified by age	Age of < 40 years	2,897	16,012	333 (11.49)	20.80 (18.68–23.15)
	Age of ≥ 40 years	4,921	25,807	740 (15.04)	28.67 (26.68–30.82)
Stratified by BMI	BMI < 23 kg/m ^{2}	5,028	27,937	374 (7.44)	13.39 (12.10–14.82)
	BMI ≥ 23 kg/m ^{2}	2,790	13,882	699 (25.05)	51.22 (49.01–53.52)

Table 5. Incidence of MAFLD according to subgroups. Incidence rates per 1,000 person-years are reported with their 95% confidence intervals (CI). Abbreviations: BMI, body mass index.

m² or above, the incidence was 25.1%. The subgroup with lower BMI saw a marked rise in MAFLD incidence in line with increasing uric acid and ferritin quartiles (HR 6.76, 95% CI 2.92–15.64). This pattern did not hold statistically for the higher BMI category (HR 1.76, 95% CI 0.98–3.15). Across both BMI categories, ascending uric acid quartiles were associated with a higher MAFLD incidence (Supplementary Table 5), while variations in ferritin quartiles did not yield a significant difference (Supplementary Table 6).

Sensitivity analysis

A sensitivity analysis, prompted by literature suggesting a lower FLI threshold for the Korean population compared to Western counterparts, was performed using a revised FLI cut-off of 30[19] This analysis reinforced the principal findings, yielding more statistically significant results, as displayed in **Supplementary Tables 7**, **8 and 9**. The analysis confirmed that the incidence of MAFLD rose in tandem with increases in serum uric acid and progressed through ferritin quartiles. Importantly, those in the highest quartiles for both uric acid and ferritin faced a 3.23 times greater incidence of developing MAFLD than those in the lowest quartiles (HR: 3.23, 95% CI: 2.31–4.51), endorsing the robustness of the primary analysis outcomes.

Discussion

This retrospective cohort study, with an average follow-up duration of 5.35 years, sought to explore the interrelated impact of serum uric acid and ferritin levels on MAFLD incidence. The data revealed that each unit increase in the natural logarithm of serum uric acid was associated with a 3.65-fold rise in MAFLD occurrence, while a similar increase in serum ferritin corresponded to a 1.33-fold increase in incidence. Recent evidence has further demonstrated its complex metabolic interactions, particularly in the context of endocrine system activation and metabolic regulation[20] Notably, when both serum uric acid and ferritin levels were elevated, there was a heightened risk for the future development of MAFLD. The underlying biological processes linking uric acid and ferritin to MAFLD development, although not fully understood, could be postulated through several potential pathways. A plausible mechanism may involve the exacerbation of oxidative stress from the combined elevation of uric acid and ferritin levels. Uric acid, as an end product of purine catabolism, is known to instigate reactive oxygen species (ROS) formation, thus amplifying oxidative stress[21] Concurrently, high ferritin levels may precipitate iron accumulation, catalyzing further ROS generation via lipid peroxidation[22] The convergent impact of these pathways could potentially amplify oxidative stress within hepatocytes, triggering inflammation and accelerating the pathogenesis of MAFLD. Furthermore, insulin resistance is posited as another mechanism that may elucidate the intricate relationship between uric acid and ferritin in MAFLD incidence. Uric acid's role in disrupting insulin signaling and its contribution to the development of insulin resistance is well-documented,

Quartile of ferritin	Quartile of uric acid			
	Q1 (lowest)	Q2	Q3	Q4 (highest)
Male (n = 3,074)				
Q1 (lowest)	Reference	1.47 (0.77–2.81)	1.31 (0.66–2.57)	1.62 (0.83–3.16)
Q2	1.34 (0.71–2.53)	1.61 (0.84–3.06)	1.07 (0.53–2.14)	1.93 (1.02–3.65)
Q3	1.47 (0.75–2.88)	1.56 (0.82–2.96)	1.30 (0.66–2.54)	2.22 (1.20–4.11)
Q4 (highest)	1.94 (1.01–3.75)	2.15 (1.15–4.04)	3.05 (1.67–5.56)	3.67 (2.07–6.50)
Female (n = 4,744)				
Q1 (lowest)	Reference	0.97 (0.28–3.31)	0.26 (0.03–2.08)	2.49 (0.90–6.89)
Q2	1.86 (0.72–4.79)	1.72 (0.64–4.63)	0.98 (0.31–3.12)	1.20 (0.40–3.58)
Q3	1.66 (0.58–4.75)	1.22 (0.41–3.65)	1.50 (0.53–4.29)	2.49 (0.94–6.57)
Q4 (highest)	1.54 (0.49–4.84)	2.01 (0.70–5.73)	3.92 (1.61–9.56)	4.28 (1.78–10.26)
Age of < 40 years (n = 2,897)				
Q1 (lowest)	Reference	1.29 (0.68–2.45)	0.86 (0.42–1.75)	1.38 (0.70–2.71)
Q2	0.99 (0.52–1.88)	1.24 (0.65–2.39)	0.83 (0.41–1.70)	1.64 (0.89–3.05)
Q3	1.28 (0.67–2.47)	1.47 (0.80–2.72)	0.99 (0.49–2.03)	2.23 (1.22–4.05)
Q4 (highest)	1.53 (0.80–2.95)	1.67 (0.88–3.16)	2.91 (1.63–5.19)	2.99 (1.69–5.28)
Age of ≥ 40 years (n = 4,921)				
Q1 (lowest)	Reference	1.29 (0.68–2.45)	0.86 (0.42–1.75)	1.38 (0.70–2.71)
Q2	0.99 (0.52–1.88)	1.24 (0.65–2.39)	0.83 (0.41–1.70)	1.64 (0.89–3.05)
Q3	1.28 (0.67–2.47)	1.47 (0.80–2.72)	0.99 (0.49–2.03)	2.23 (1.22–4.05)
Q4 (highest)	1.53 (0.80–2.95)	1.67 (0.88–3.16)	2.91 (1.63–5.19)	2.99 (1.69–5.28)
BMI < 23 kg/m^2 (n = 5,028)				
Q1 (lowest)	Reference	2.04 (0.81–5.11)	1.86 (0.72–4.80)	1.96 (0.71–5.43)
Q2	2.50 (1.03–6.03)	2.01 (0.79–5.10)	1.38 (0.51–3.71)	2.61 (1.05–6.47)
Q3	2.12 (0.79–5.71)	1.64 (0.63–4.25)	1.39 (0.50–3.84)	3.74 (1.57–8.91)
Q4 (highest)	2.10 (0.73–5.98)	3.01 (1.18–7.67)	5.57 (2.36–13.15)	6.76 (2.92–15.64)
BMI ≥ 23 kg/m^2 (n = 2,790)				
Q1 (lowest)	Reference	0.98 (0.47–2.04)	0.70 (0.31–1.61)	1.32 (0.68–2.58)
Q2	0.82 (0.42–1.61)	1.35 (0.69–2.62)	0.82 (0.39–1.72)	1.14 (0.57–2.26)
Q3	0.88 (0.44–1.75)	1.34 (0.69–2.63)	1.28 (0.65–2.53)	1.44 (0.75–2.77)
Q4 (highest)	1.13 (0.58–2.21)	1.28 (0.66–2.46)	1.65 (0.89–3.05)	1.76 (0.98–3.15)

Table 6. Combined associations of serum uric acid and serum ferritin levels with incident MAFLD stratified by gender, age, and BMI. Data are presented as hazard ratios (HRs) for incident MAFLD with 95% confidence intervals (CIs) across quartiles of serum uric acid and ferritin levels. Cut-offs for quartiles 1–4 of serum uric acid levels are as follows: ≤5.00 mg/dL, 5.10–5.70 mg/dL, 5.80–6.40 mg/dL and ≥ 6.50 mg/dL in men; ≤3.50 mg/dL, 3.60–4.10 mg/dL, 4.20–4.60 mg/dL and ≥ 4.70 mg/dL in women respectively. Cut-offs for quartiles 1–4 of serum ferritin levels are as follows: ≤88.73 ng/mL, 88.78–123.80 ng/mL, 123.90–169.10 ng/mL and ≥ 169.20 ng/mL in men; ≤16.00 ng/mL, 16.02–34.26 ng/mL, 34.27–60.27 ng/mL and ≥ 60.36 ng/mL in women respectively. Individuals in the lowest quartile of both serum uric acid and ferritin levels are used as the reference group. The model is adjusted for smoking status (never, past, or current), alcohol intake (never, moderate, and heavy drinkers), physical activity (inactive, moderately active, and HEPA active). In subgroup analyses stratified by gender and age, the model is additionally adjusted for the other variable (age or gender). Abbreviations: BMI, body mass index; Q, quartile.

implicating it as a significant factor in the pathogenesis of MAFLD[23] Ferritin, traditionally involved in iron storage, is now understood to influence insulin signaling as well[24] Recent insights suggest that ferritin plays a more complex role in cellular functions than previously recognized[25] The simultaneous elevation of uric acid and ferritin appears to exacerbate insulin resistance, potentially accelerating the onset and progression of MAFLD. These findings indicate that both biomarkers are part of a shared pathophysiological framework involving oxidative stress, chronic inflammation, and insulin resistance, which are key contributors to MAFLD[26] Although these biological connections provide an insightful framework, further detailed studies are necessary to comprehensively dissect these mechanisms. MAFLD is characterized by significant heterogeneity, potentially resulting in varied clinical manifestations across its different subtypes[1] Gender-based analyses have shown that elevated levels of both uric acid and ferritin are associated with a higher incidence of MAFLD, regardless of gender. Among males, particularly those with the highest concentrations of both biomarkers, there is an observed gradient increase in MAFLD risk. This suggests a cumulative effect of high levels of uric acid and ferritin in this subgroup. However, in females, this correlation is not as distinctly evident[5].

Age-based division in this study highlighted a significantly higher risk for developing MAFLD in individuals under 40 with elevated levels of both uric acid and ferritin compared to those over 40. Among the younger cohort, those in the highest quartiles for both markers faced a 7.51-fold increase in the incidence of MAFLD, while in the older group, the risk increase was 2.99-fold. Pinpointing the precise reasons for the differential impact of uric acid and ferritin across age groups remains challenging, yet it may relate to the intrinsic health characteristics of those over 40. Typically, this group presents with increased levels of oxidative stress, inflammation, and insulin resistance, which may mitigate the additional risk imposed by uric acid and ferritin levels[27] In individuals under the age of 40, the absence of chronic health conditions commonly seen in older adults may render this subgroup more susceptible to the effects of uric acid and ferritin on MAFLD risk. In particular, our findings indicate that without elevated ferritin, uric acid alone does not significantly increase MAFLD risk. However, the co-elevation of ferritin appears to establish a context in which uric acid levels are positively correlated with an escalating risk of MAFLD. This pattern points to a potential synergistic threshold effect, where the presence of high ferritin levels is a prerequisite for uric acid to exert its influence on MAFLD risk. The evidence thus highlights the critical need to consider the combined impact of uric acid and ferritin when evaluating the risk for MAFLD, particularly in the presence of raised ferritin. To fully discern the complexity of this relationship, future research must delve into the molecular mechanisms and pathways that govern this interaction, offering a holistic view of the factors that drive MAFLD pathogenesis. When BMI is considered, a stark increase in MAFLD incidence—6.47 times higher—was noted in individuals with the highest quartile levels of both uric acid and ferritin, provided their BMI was below 23 kg/m^2. This significant association suggests that in leaner individuals, the risks posed by uric acid and ferritin may have a cumulative effect, leading to a greater likelihood of developing MAFLD. However, in the group classified as overweight or obese (BMI ≥ 23 kg/m^2), such a clear correlation was not established, and no statistically significant difference was observed in the incidence of MAFLD across the quartiles of uric acid and ferritin. This could imply that among individuals with a higher BMI, factors beyond uric acid and ferritin levels might play more substantial roles in the risk of developing MAFLD.

The differential influence of uric acid and serum ferritin on the incidence of MAFLD in varying BMI categories may stem from the complex baseline health profiles present in overweight or obese individuals. For those with a BMI above 23 kg/m^2, the effects of uric acid and ferritin are potentially less discernible due to pre-existing elevated levels of oxidative stress, inflammation, and insulin resistance, factors that are pervasive in this demographic[28–30] This interplay of metabolic conditions could mask the specific impacts of uric acid and ferritin. Hence, in the context of overweight or obesity, the development of MAFLD could be driven by a constellation of factors beyond these biomarkers. Conversely, for individuals with a BMI under 23 kg/m^2, the absence of such pronounced metabolic disturbances may render the contributions of uric acid and ferritin more significant, underlining their role in the risk assessment of MAFLD in this leaner subgroup.

This study acknowledges certain limitations. Firstly, the Fatty Liver Index (FLI) was utilized as a surrogate for liver steatosis in the absence of ultrasound results, which might have affected the precision of the assessments. However, it's important to note that FLI is commonly employed in the clinical setting for this purpose. To enhance diagnostic accuracy, this study applied a more conservative FLI threshold of 60 for defining steatosis, as opposed to the lower cut-off of 30 that is sometimes recommended for Korean populations, potentially addressing some concerns about the accuracy of steatosis estimation. Secondly, as a single-center study, the baseline characteristics of participants, who were selected from those undergoing routine health check-ups at one center, may not represent the broader population. While our large sample size ($n = 7{,}818$) and comprehensive health screening data provide valuable insights into the relationship between serum biomarkers and MAFLD development, we acknowledge that health screening participants may differ from the general population in terms of health consciousness and socioeconomic status. These factors should be considered when interpreting the applicability of these results to diverse populations. However, our extended follow-up period (average 5.35 ± 2.06 years) and comprehensive assessment of multiple risk factors strengthen the internal validity of our findings regarding the temporal relationships between serum biomarkers and MAFLD development. Additionally, while our analyses adjusted for major established risk factors, we acknowledge that some potential confounders, such as detailed dietary habits and genetic predisposition, were not available in our health screening dataset. However, several aspects of our study design help minimize the impact of these unmeasured variables. Our use of repeated measurements over the extended follow-up period allows for observation of temporal relationships while accounting for within-person variations in unmeasured factors. Furthermore, the consistency of our findings across various subgroup analyses suggests that the observed associations between serum biomarkers and MAFLD development are robust and unlikely to be solely attributable to unmeasured confounding. Nevertheless, future studies incorporating detailed dietary information and genetic factors could provide additional insights into these relationships.

Despite these limitations, it is notable that this study is among the initial efforts to conduct a population-based cohort analysis exploring the cumulative effects of serum uric acid and ferritin levels on MAFLD incidence over time. By examining these relationships through carefully adjusted models and extensive subgroup analyses, the study contributes to the foundational knowledge necessary for identifying potential risk factors for MAFLD and underscores the importance of these biomarkers in predicting the likelihood of disease development.

Conclusion

Our study establishes a significant correlation between elevated serum uric acid levels and the increased risk of MAFLD, with serum ferritin showing a subtler yet relevant association. The coexistence of high levels of both uric acid and ferritin compounds the risk, underscoring the importance of joint assessment of these markers in the accurate appraisal of MAFLD risk. The exploration of the complex biological mechanisms involved, including oxidative stress, inflammation, and insulin resistance, not only deepens our comprehension of the pathogenesis of MAFLD but also paves the way for the development of future interventions and treatments.

Methods

Study design and study participants

We conducted a retrospective cohort study at the Health Screening Center of Samsung Changwon Hospital, South Korea, from 2011 to 2018. From the initial pool of 254,930 individuals screened, we focused on 78,270 individuals who had their first check-up in 2011. To ensure accurate assessment of MAFLD development and maintain methodological rigor, we established comprehensive exclusion criteria.

The study required complete data sets for each participant; therefore, we first excluded 63,674 individuals for the absence of essential variables: (1) serum uric acid, (2) serum ferritin, (3) components for the Fatty Liver Index (FLI) calculation including body mass index (BMI), waist circumference (WC), triglycerides (TG), and gamma-glutamyl transferase (GGT), and (4) criteria necessary to characterize MAFLD, including but not limited to BMI, WC, blood pressure, TG, GGT, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), and fasting insulin.

Further exclusion criteria were applied to ensure a clear assessment of MAFLD development and minimize confounding factors. We excluded individuals (n = 6,778) with the following conditions: (1) younger than 20 years, (2) absent follow-up post-2011, (3) initial diagnosis of fatty liver via abdominal ultrasound, (4) cancer diagnosis of any type, (5) gout or history of gout medication, (6) an FLI score of 30 or higher, (7) high-sensitivity C-reactive protein (hs-CRP) levels exceeding 10 mg/L, and (8) serum ferritin above 300 ng/mL. Additionally, we excluded participants with pre-existing liver diseases including viral hepatitis, autoimmune liver diseases, and drug-induced liver injury, as well as those with metabolic disorders requiring ongoing medication, to minimize potential confounding effects.

The final cohort for analysis consisted of 7,818 individuals who were monitored through to 2018 (Fig. 1). This careful selection process helped ensure the validity of our findings while maintaining a substantial and representative study population.

Variables and measurements

Anthropometric and physiological measurements were precisely obtained. Height, weight, and waist circumference (WC) were measured using a calibrated body composition analyzer (InBody 770, Inbody Inc., Seoul, Korea). Body mass index (BMI) was computed by dividing weight in kilograms by the square of height in meters. Blood pressure, both systolic (SBP) and diastolic (DBP), was measured after a five-minute seated rest with an automatic oscillometric sphygmomanometer.

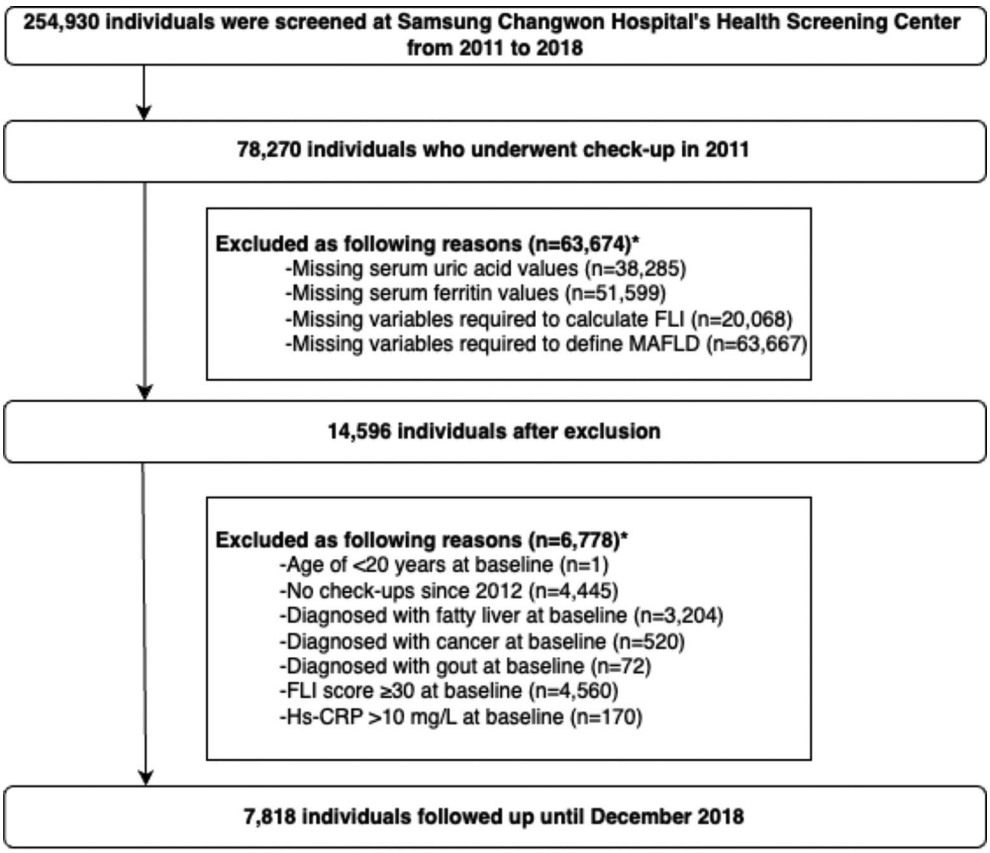

Fig. 1. Flow diagram of the study population selection *There may be an overlap in the detailed counts of targets. Abbreviations: FLI, fatty liver index; MAFLD, metabolic associated fatty liver disease.

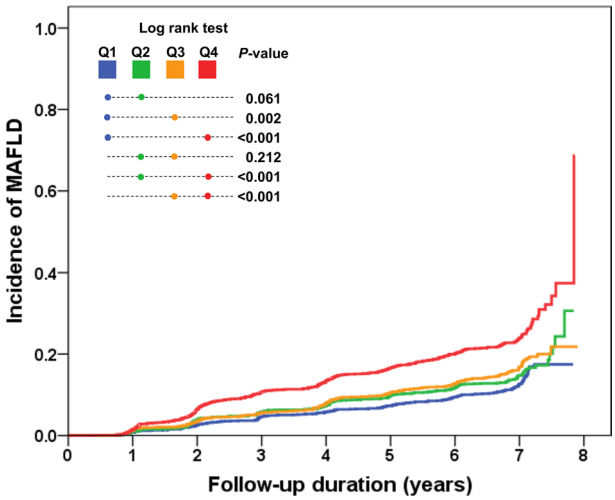

Fig. 2. Kaplan-Meier analysis of MAFLD incidence according to serum uric acid quartiles. Cut-offs for quartiles 1–4 of serum uric acid levels are as follows: ≤5.00 mg/dL, 5.10–5.70 mg/dL, 5.80–6.40 mg/dL and ≥6.50 mg/dL in men; ≤3.50 mg/dL, 3.60–4.10 mg/dL, 4.20–4.60 mg/dL and ≥4.70 mg/dL in women respectively. Abbreviations: Q, quartile.

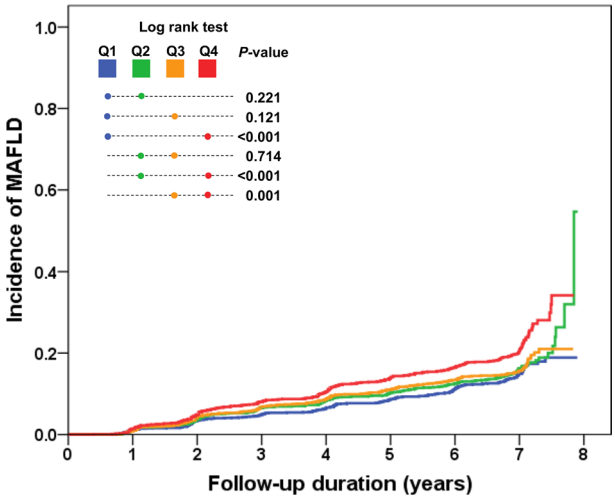

Fig. 3. Kaplan-Meier analysis of MAFLD incidence according to serum ferritin quartiles Cut-offs for quartiles 1–4 of serum ferritin levels are as follows: ≤88.73 ng/mL, 88.78–123.80 ng/mL, 123.90–169.10 ng/mL and ≥169.20 ng/mL in men; ≤16.00 ng/mL, 16.02–34.26 ng/mL, 34.27–60.27 ng/mL and ≥60.36 ng/mL in women respectively. Abbreviations: Q, quartile.

Health behaviors were self-reported through a standardized questionnaire capturing details on alcohol consumption, smoking status, and physical activity patterns. Smoking categories were defined as non-smoker, ex-smoker, or current smoker. Physical activity levels were stratified according to the International Physical Activity Questionnaires (IPAQ)[31], dividing into vigorous-intensity activities, moderate-intensity activities, and walking. Metabolic equivalent tasks (METs) were calculated thus: vigorous MET (minutes/week) = 8.0 * minutes of vigorous activity per week * days engaged; moderate MET (minutes/week) = 4.0 * minutes of moderate activity per week * days engaged; walking MET (minutes/week) = 3.3 * minutes spent walking per week * days engaged. These were summed to obtain a total MET score, classifying individuals as inactive (Category 1), moderately active (Category 2), or health-enhancing physical activity (HEPA) active (Category 3) based on the accumulated MET-minutes per week.

Biochemical and metabolic markers were assessed from blood samples taken after an 8-hour fast. Assays included aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Glycated hemoglobin (HbA1c) was measured with an HLC-723 G11 analyzer (Tosho, Inc.). Serum insulin was determined using a commercial kit and an electrochemiluminescence assay (Cobas e 602, Roche Diagnostics). Insulin resistance was gauged using

the Homeostatic Model Assessment (HOMA) index: HOMA-IR = fasting insulin (μIU/mL) * fasting glucose (mmol/L)/22.5, with FPG levels of 100–125 mg/dL or HbA1c levels of 5.7–6.4% designating prediabetes[32] Liver fibrosis indices were computed: the Fibrosis-4 (FIB-4) score, the Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS), and the AST to Platelet Ratio Index (APRI). The FIB-4 score = age (years) * AST (U/L)/(platelet count [×10^9/L] * √ALT [U/L]), with a score ≥ 2.67 suggesting a high likelihood of significant fibrosis, and < 1.30 a low likelihood[33] The NFS = − 1.675 + 0.037 * age (years) + 0.094 * BMI (kg/m^2) + 1.13 * impaired fasting glucose/diabetes + 0.99 * AST/ALT ratio − 0.013 * platelet count (×10^9/L) − 0.66 * albumin (g/dL), with values < − 1.455 ruling out, and > 0.676 indicating, advanced fibrosis[34] APRI = (AST/upper limit of normal)/platelet count (×10^9/L) * 100, with > 1 reflecting advanced fibrosis[35] The Fatty Liver Index (FLI) was employed as a non-invasive marker for fatty liver disease, derived from BMI, TG, GGT, and WC. The formula: FLI = e^y/(1 + e^y) * 100, where y = 0.953 * ln(TG) + 0.139 * BMI + 0.718 * ln(GGT) + 0.053 * WC − 15.745, categorizes scores as follows: <30 indicating no fatty liver, 30–60 as indeterminate, and > 60 signifying the presence of fatty liver[36] While some studies suggest a lower FLI cut-off of 30 for Asian populations, we chose the more conservative threshold of 60 to maximize specificity in MAFLD diagnosis. This decision was based on validation studies showing that this higher threshold reduces false-positive rates while maintaining good diagnostic accuracy.

Diagnostic criteria of MAFLD

MAFLD was identified based on the presence of hepatic steatosis alongside one or more of the following conditions: overweight/obesity, type 2 diabetes mellitus (T2DM), or signs of metabolic dysregulation[4] Hepatic steatosis was confirmed via abdominal ultrasound or a Fatty Liver Index (FLI) score ≥ 60. Overweight was delineated as a BMI ≥ 23 kg/m² and obesity as BMI ≥ 25 kg/m² following the Korean Society for the Study of Obesity 2022 guidelines[37] Diabetes was established with a hemoglobin A1c level ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or a self-reported diabetes diagnosis or treatment from the pre-screening questionnaire[38].

Metabolic dysregulation was characterized by the presence of at least two of the following seven criteria: (1) WC ≥ 90 cm for men and ≥ 80 cm for women; (2) prediabetes (HbA1c between 5.7 − 6.4%, or FPG 100–125 mg/dL); (3) blood pressure ≥ 130/85 mmHg or current use of antihypertensive medication; (4) HDL-C < 40 mg/dL for men and < 50 mg/dL for women; (5) TG ≥ 150 mg/dL or on drug therapy for elevated triglycerides; (6) a HOMA-IR score ≥ 2.5; and (7) hs-CRP > 2 mg/L.

Statistical analysis

In our analysis, we utilized available complete data for all included variables. Given our large sample size and comprehensive health screening data, we believe our complete case analysis approach provided reliable results for examining the associations between serum biomarkers and MAFLD development.

Baseline characteristics of participants were categorized by serum uric acid and ferritin levels. Categorical data were examined using the Chi-square test, while continuous data employed the independent t-test. Due to their skewed distributions, serum uric acid and ferritin levels underwent logarithmic transformation for continuous variable analysis. Data are presented as means ± standard deviation for continuous variables and as numbers (percentages) for categorical variables, analyzed using descriptive and frequency statistics. P-values were derived via One-way ANOVA or the Chi-square test, as appropriate.

We employed multivariable Cox proportional hazard models to estimate the prospective risk for MAFLD, adjusting for various covariates across four models: Model 1 (unadjusted); Model 2 (adjusted for age and sex); Model 3 (further adjusted for smoking status, alcohol intake, and physical activity levels); and Model 4 (inclusive of adjustments in Model 3 plus log-transformed serum uric acid or ferritin levels). The combined impact of serum uric acid and ferritin on MAFLD incidence was examined by classifying participants into quartiles of these biomarkers. Participants' follow-up was censored at the last visit date or upon MAFLD confirmation. We explored potential interactions between the two biomarkers using a multiplicative approach and integrating interaction terms (log-transformed serum uric acid * log-transformed serum ferritin) into the fully adjusted models, with the lowest quartiles serving as reference. Kaplan–Meier analysis delineated the time to MAFLD onset, while subgroup analyses assessed the relationship of serum uric acid and ferritin with MAFLD incidence across gender, age (< 40 and ≥ 40 years), and BMI (< 23 and ≥ 23 kg/m²) strata. The selection of covariates in our models was based on established risk factors for MAFLD and potential confounders identified from previous literature. Our stepwise modeling approach allowed evaluation of how different sets of covariates influenced the associations of interest. Sensitivity analysis tested the stability of our findings by applying an alternative steatosis criterion, an FLI score of 30, acknowledging that the threshold for the Korean population might differ from Western counterparts[39] Statistical analyses were executed using STATA, version 14.0 (StataCorp, College Station, TX, USA), and R, version 3.4.4 (Vienna, Austria; http://www.R-project.org/).

Data availability

The datasets generated and analyzed during this study are not publicly available due to restrictions pertaining to patient consent and institutional guidelines for data sharing. However, the datasets are available from the corresponding author upon reasonable request.

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Author contributions

Conceptualization: Jeong-Hyun Yoon, Kwang Min Kim Data curation: Mi Hyeon Jin, MiyeongBae Formal analysis: Miyeong Bae, Mi Hyeon Jin Methodology: Jeong-Hyun Yoon, Kwang Min Kim Writing - original draft: Miyeong Bae Writing - review & editing: Jeong-Hyun Yoon, Kwang Min Kim Final approval of the manuscript: All authors.

Declarations

Competing interests
The authors declare no competing interests.

Ethical considerations and data approval
The Institutional Review Board (IRB) of Samsung Changwon Hospital approved this study (approval number SCMC 2023-05-019), which proceeded in line with the tenets of the Declaration of Helsinki. The retrospective design, utilizing de-identified administrative and clinical data, obviated the need for individual informed consent, a waiver for which was sanctioned by the IRB.

Additional information
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