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Hepatic steatosis index: A simple screening tool reflecting nonalcoholic fatty liver disease

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ABSTRACT

Background/Aims: To optimize management of nonalcoholic fatty liver disease (NAFLD), a simple screening tool is necessary. In this study, we aimed to devise a simple index of NAFLD.
Study: A cross-sectional study with 10,724 health check-up subjects (5362 cases with NAFLD versus age- and sex-matched controls) was conducted. Study subjects were randomly assigned to a derivation cohort or a validation cohort.
Results: Multivariate analysis indicated that high serum alanine aminotransferase (ALT) to serum aspartate aminotransferase (AST) ratio, high body mass index (BMI), and diabetes mellitus were independent risk factors of NAFLD (all $P < 0.001$). Using these variables, a formula was derived by a logistic regression model: hepatic steatosis index (HSI) = $8 \times$ (ALT/AST ratio) + BMI (+2, if female; +2, if diabetes mellitus). HSI had an area under receiver-operating curve of 0.812 (95% confidence interval, 0.801–0.824). At values of <30.0 or >36.0, HSI ruled out NAFLD with a sensitivity of 93.1%, or detected NAFLD with a specificity of 92.4%, respectively. Of 2692 subjects with HSI <30.0 or >36.0 in the derivation cohort, 2305 (85.6%) were correctly classified. HSI was validated in the subsequent validation cohort.
Conclusion: HSI is a simple, efficient screening tool for NAFLD that may be utilized for selecting individuals for liver ultrasonography and for determining the need for lifestyle modifications.
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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is believed to be a feature of metabolic syndrome because it is closely associated with visceral obesity, dyslipidaemia, insulin resistance, and type 2 diabetes mellitus (DM) [1]. Due to the increased prevalence of obesity, about 30% of the adult population now has NAFLD in the United States [2]. In Korea, the prevalence of NAFLD has been reported to be 16.1–27.2% and continues to increase due to the adoption of a Westernized lifestyle [3–5]. This high prevalence of NAFLD is probably problematic because patients with NAFLD show higher all-cause mortality and increased risks for liver-related death and cardiovascular disease [6,7]. However, the screening of asymptomatic individuals using imaging modalities, such as ultrasonography (US) and computed tomography (CT), does not appear to be cost-effective because such studies are expensive for mass screening. Therefore, a simple, noninvasive test is required to identify patients at high risk of NAFLD and to establish an appropriate NAFLD screening programme. In this study, we aimed to derive a simple index based on standard laboratory tests and anthropometric parameters that can be used to determine the presence of NAFLD. In addition, we sought to validate this index in asymptomatic subjects.

2. Subjects and methods

2.1. Subjects

We performed a cross-sectional case–control study. A total of 21,130 adults who visited Seoul National University Hospital Gangnam Healthcare Center, Seoul, Korea for a routine health check-up between 1 January 2006 and 31 December 2006 participated in this study. NAFLD was defined as the presence of fatty liver disease by US in the absence of a potential cause of chronic liver disease, namely, (i) seropositivity for hepatitis B virus surface antigen

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(HBsAg) or anti-hepatitis C virus antibody (anti-HCV), (ii) excessive alcohol consumption (>20 g/day), (iii) medications known to precipitate fatty liver during the previous 6 months, and (iv) other causes of liver disease, such as Wilson's disease or haemochromatosis. The subjects that did not undergo the clinical, laboratory, and US assessments described below were excluded. Patients with the following conditions were also excluded from the study: prior or current malignancy; concomitant serious medical illness such as haematological disease, congestive heart failure, or chronic kidney disease; or active infection. The sampling frame for cases consisted of all subjects with a sonographically identified fatty liver.

To modify confounding factors, the same number of normal healthy controls with a normal hepatic US finding was randomly selected that matched the cases for age and sex. All cases and controls were randomly assigned to the derivation and validation cohorts.

2.2. Clinical, laboratory and US assessments

Each subject underwent laboratory tests, hepatic US, anthropometric assessment, and questionnaire assessment. Height and body weight were measured using a digital scale with examinees wearing a light gown and body mass index (BMI) was calculated using: BMI = body weight (kg)/height squared (m^2). Waist circumferences were measured using a tape measure to the nearest millimetre at the midpoint between the lower costal margin and anterior superior iliac spine by a trained examiner. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice during one day and mean values were used for analysis. Laboratory tests included: serum fasting glucose, haemoglobin A1c (HbA1c), total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), uric acid, and high sensitivity C-reactive protein (hs-CRP); HBsAg; anti-HCV; and prothrombin time. Low-density lipoprotein cholesterol levels (LDL-C) were calculated using the Friedewald equation. Venous blood samples were drawn from all subjects before 10:00 AM after a 12-h overnight fast. All biochemical determinations were performed in the same laboratory using standard laboratory methods. Those who had smoked regularly during the previous year were classified as current smokers [8]. The presence of DM was defined as a fasting glucose of $\geq$126 mg/dL or treatment with anti-diabetic medication. Hepatic US examinations were performed by experienced radiologists unaware of clinical data. The ACUSON Sequoia 512 system (Siemens, Mountain View, CA, USA) was used to diagnose fatty liver and to assess its degree. Semiquantitative grading of fatty liver was done as described by Saadeh et al. [9], as follows: grade 0, normal echogenicity; grade 1, slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders; grade 2, moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and the diaphragm; grade 3, marked increase in fine echoes with poor or no visualization of intrahepatic vessel borders, the diaphragm, and the posterior right lobe of the liver.

The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital.

2.3. Statistical analysis

During univariate analysis, continuous variables were compared using the Student's *t*-test or the Mann–Whitney *U*-test, and categorical variables were compared using the chi-square test or Fisher's exact test. Variables that were statistically significant by univariate analysis were added to a multiple logistic regression model to identify independent predictors of the presence of NAFLD after adjusting for other variables. When a significant correlation was found between two variables, the variable with the higher odds ratio (OR) was chosen as the representative variable. We performed stepwise multiple logistic regression analysis on 400 bootstrap samples (the conditional probabilities used for the stepwise entry and stepwise removal of a factor were 0.05 and 0.10, respectively) [10]. Based on the results of multiple logistic regression analysis, a simple index using representative variables was established to predict NAFLD. The predictive power of indices for detecting NAFLD were evaluated using areas under receiver-operating characteristic curves (AUROCs), sensitivities, specificities, positive likelihood ratios, and negative likelihood ratios. Effective cutoff values were determined using receiver-operating characteristics (ROC) curves. All analyses were conducted using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) and STATA version 10.0 (STATA Corp., College Station, TX, USA), and *P*-values of <0.05 were considered significant.

3. Results

3.1. Baseline characteristics

Of the 21,130 participants, 3591 participants with at least one potential cause of chronic liver disease were excluded: 975 with hepatitis B, 242 with hepatitis C, 1690 with excessive alcohol consumption (>20 g/day), 593 taking medications known to produce fatty liver (steroids, oestrogens, tamoxifen, valproate, diltiazem, amiodarone, methotrexate, and so on) and 91 participants with other causes (Wilson's disease, haemochromatosis, primary biliary cirrhosis, autoimmune hepatitis, and so on). Of the 17,539 subjects who meet inclusion criteria, 5769 participants (male, 73.6%) were diagnosed as having NAFLD according to the criteria described above. Among these 5769 subjects with NAFLD, 407 subjects (male, 97.0%) were missing in the course of age and sex matching mainly due to male predominance in NAFLD subjects. Finally, 5362 cases and the same number of age- and sex-matched controls without a fatty liver by US examination were included. A total of 5362 pairs (10,724 subjects) of cases and age- and sex-matched controls were randomly assigned to the derivation cohort (2680 pairs, 5360 subjects) and to the validation cohort (2682 pairs, 5364 subjects). No significant difference was found between these two cohorts in terms of baseline characteristics, except mean serum AST levels ($P = 0.022$; Table 1).

3.2. Derivation of a novel index for the presence of NAFLD

2680 subjects with NAFLD (cases) and 2680 age- and sex-matched subjects without NAFLD (controls) were included in the derivation cohort. Univariate analysis showed that BMI, the presence of DM, waist circumference, SBP, DBP, serum fasting glucose, HbA1c, total cholesterol, HDL-C, LDL-C, AST, ALT, GGT, hs-CRP, and uric acid, and ALT/AST ratio were significantly different between cases and controls (Table 2). Among these variables, significant interactions were found between BMI and waist circumference; between AST, ALT and ALT/AST ratio; between total cholesterol, TG, HDL-C, and LDL-C; and between fasting glucose, HbA1c, and the presence of DM. To avoid these interactions, we incorporated representative variables with highest ORs into the multivariate analysis, namely, BMI, ALT/AST ratio, TG, and the presence of DM. Multivariate analysis showed that BMI [OR, 1.349; 95% confidence interval (CI), 1.308–1.390; $P < 0.001$], the presence of DM (OR, 2.013; 95% CI, 1.575–2.574; $P < 0.001$), and ALT/AST ratio (OR, 10.999; 95% CI, 8.550–14.149; $P < 0.001$) were independent risk factors of NAFLD after adjusting for interactions between variables.

In multiple logistic regression model, the probability of having fatty liver was $e^{(0.315\times\text{BMI}+2.421\times\text{ALT-to-AST ratio}+0.630\times\text{DM}-9.960)}/$

Table 1
Baseline characteristics of the derivation and validation cohorts.

	Derivation cohort (n = 5360)	Validation cohort (n = 5364)	P-value
Age (years)	52.2 ± 10.7	52.2 ± 10.7	0.954
Male sex, n (%)	3750 (70.0%)	3756 (70.0%)	0.963
DM, n (%)	496 (9.3%)	495 (9.2%)	0.990
BMI (kg/m^2)	24.1 ± 2.8	24.1 ± 2.8	0.558
Waist circumference (cm)	87.1 ± 7.6	87.1 ± 7.6	0.629
Systolic BP (mmHg)	119.3 ± 16.0	119.8 ± 15.6	0.114
Diastolic BP (mmHg)	77.6 ± 11.7	77.8 ± 11.2	0.231
Fasting glucose (mg/dL)	100.1 ± 19.2	100.1 ± 18.6	0.987
HbA1c (%)	5.74 ± 0.64	5.73 ± 0.63	0.537
Total cholesterol (mg/dL)	194.4 ± 32.5	194.7 ± 33.1	0.651
Triglyceride (mg/dL)	121.0 ± 62.9	121.4 ± 62.1	0.776
HDL-C (mg/dL)	51.2 ± 12.4	51.2 ± 12.3	0.962
LDL-C[a] (mg/dL)	118.7 ± 29.4	118.8 ± 30.3	0.867
AST (IU/L)	23.7 ± 8.7	24.1 ± 10.6	0.022
ALT (IU/L)	26.3 ± 17.2	26.8 ± 19.5	0.108
ALT/AST ratio	1.07 ± 0.36	1.07 ± 0.36	0.836
GGT (IU/L)	27.7 ± 23.1	27.9 ± 24.0	0.717
hs-CRP (mg/dL)	0.145 ± 0.479	0.138 ± 0.378	0.459
Uric acid (mg/dL)	5.67 ± 1.37	5.71 ± 1.38	0.242
Current smoker, n (%)	1319 (24.6%)	1370 (25.5%)	0.275

Values are expressed as means ± SD or n (%). DM, diabetes mellitus; BMI, body mass index; BP, blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; hs-CRP, high sensitivity C-reactive protein.

[a] Calculated using the Friedewald equation: LDL-C = total cholesterol − triglyceride/5 − HDL-C.

$(1 + e^{(0.315 \times \text{BMI} + 2.421 \times \text{ALT-to-AST ratio} + 0.630 \times \text{DM} - 9.960)})$ (presence of DM, DM = 1; absence of DM, DM = 0). We utilized the exponent of this formula and changed the multiplicative factors into approximate integer by dividing by the multiplicative factor of BMI, 0.315. In addition, to adjust the difference of BMI between male and female subjects, we add 2 points to female. As a result, we derived an equation that could predict the presence of hepatic steatosis:

$$\text{hepatic steatosis index (HSI)} = 8 \times \text{ALT/AST ratio} + \text{BMI (+2, if DM; +2, if female)}$$

Median values of HSI were 30.8 (range, 20.2–47.5) in controls and 35.6 (range, 24.3–58.7) in cases. The AUROC of HSI for detecting NAFLD was 0.812 (95% CI, 0.801–0.824) (Fig. 1) and it was not different from that of the original formula, $e^{(0.315 \times \text{BMI} + 2.421 \times \text{ALT-to-AST ratio} + 0.630 \times \text{DM} - 9.960)}/(1 + e^{(0.315 \times \text{BMI} + 2.421 \times \text{ALT-to-AST ratio} + 0.630 \times \text{DM} - 9.960)})$ (P = 1.000). For males and females, the AUROCs of HSI were 0.816 (95% CI, 0.803–0.830) and 0.808 (95% CI, 0.787–0.829), respectively. At a value of <30.0, HSI could rule out NAFLD with a sensitivity of 92.5% (95% CI, 91.4–93.5) and a negative likelihood ratio of 0.186 (95% CI, 0.163–0.213), and at a value of >36.0, HSI could detect NAFLD with a specificity of 92.4% (95% CI, 91.3–93.4) and a positive likelihood ratio of 6.069 (95% CI, 5.284–6.970). In the derivation cohort, 1257 subjects (23.5%) had HSI <30.0 and 1435 subjects (26.8%) had HSI >36.0 (Table 3). According to these cutoff values, 2305 subjects (85.6% of subjects with HSI of <30.0 or >36.0) were correctly classified.

In subjects with normal serum ALT level (n = 4751), the predictive values of HSI were maintained. In those subjects or the derivation cohort, the AUROC of HSI was 0.768 (95% CI, 0.755–0.781). At a value of <30.0, HSI could rule out NAFLD with a sensitivity of 90.4% (95% CI, 89.1–91.7) and a negative like-

Table 2
Case and age- and sex-matched control data in the derivation cohort.

	Case (n = 2680)	Control (n = 2680)	Odds ratio (95% CI)	P-value
BMI (kg/m^2)	25.3 ± 2.7	22.9 ± 2.4	1.486 (1.446–1.527)	<0.001
DM, n (%)	355 (13.2%)	141 (5.3%)	2.747 (2.242–3.367)	<0.001
Waist circumference (cm)	90.2 ± 6.9	83.9 ± 6.9	1.148 (1.137–1.159)	<0.001
Systolic BP (mmHg)	121.7 ± 15.6	116.9 ± 16.1	1.019 (1.016–1.023)	<0.001
Diastolic BP (mmHg)	79.2 ± 11.5	75.8 ± 11.6	1.024 (1.019–1.029)	<0.001
Fasting glucose (mg/dL)	103.9 ± 22.2	96.2 ± 14.5	1.029 (1.025–1.034)	<0.001
HbA1c (%)	5.87 ± 0.75	5.60 ± 0.47	2.412 (2.131–2.730)	<0.001
Total cholesterol (mg/dL)	199.0 ± 33.5	189.8 ± 30.7	1.009 (1.007–1.011)	<0.001
Triglyceride (mg/dL)	143.3 ± 69.2	99.1 ± 46.5	1.014 (1.013–1.015)	<0.001
HDL-C (mg/dL)	48.0 ± 10.9	54.5 ± 13.0	0.955 (0.951–0.960)	<0.001
LDL-C[a] (mg/dL)	122.0 ± 30.6	115.5 ± 27.8	1.008 (1.006–1.010)	<0.001
AST (IU/L)	26.0 ± 10.9	21.3 ± 4.8	1.102 (1.091–1.113)	<0.001
ALT (IU/L)	32.8 ± 21.4	19.7 ± 6.8	1.106 (1.098–1.114)	<0.001
ALT/AST ratio	1.22 ± 0.40	0.93 ± 0.25	19.328 (15.587–23.967)	<0.001
GGT (IU/L)	34.5 ± 28.8	20.9 ± 12.1	1.041 (1.037–1.045)	<0.001
hs-CRP (mg/dL)	0.17 ± 0.45	0.12 ± 0.51	1.307 (1.087–1.572)	0.047
Uric acid (mg/dL)	5.91 ± 1.41	5.43 ± 1.29	1.299 (1.247–1.354)	<0.001
Current smoker, n (%)	683 (25.4%)	636 (23.8%)	1.099 (0.971–1.245)	0.144

Values are expressed as means ± SD or n (%). BMI, body mass index; DM, diabetes mellitus; BP, blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; hs-CRP, high sensitivity C-reactive protein.

[a] Calculated using the Friedewald equation: LDL-C = total cholesterol − triglyceride/5 − HDL-C.

Table 3
Predictive values of HSI in the derivation (n = 5360) and validation cohorts (n = 5364).

	Low cutoff point (<30.0)	Intermediate (30.0–36.0)	High cutoff point (>36.0)	Total
The derivation cohort				
Total, *n* (%)	1257 (23.5%)	2668 (49.8%)	1435 (26.8%)	5360
NAFLD, *n* (%)	196 (15.6%)	1252 (46.9%)	1232 (85.9%)	2680
Fatty liver grade[a], *n* (%)				
Grade 0	1061 (84.4%)	1416 (53.1%)	203 (14.1%)	2680
Grade 1	177 (14.1%)	959 (35.9%)	633 (44.1%)	1769
Grade 2	18 (1.4%)	290 (10.9%)	557 (38.8%)	865
Grade 3	1 (0.1%)	3 (0.1%)	42 (2.9%)	46
Sensitivity	92.5% (91.5–93.5)		46.0% (44.1–47.9)	
Specificity	40.0% (38.2–4.19)		92.4% (91.3–93.4)	
Positive likelihood ratio	1.543 (1.494–1.595)		6.069 (5.284–6.970)	
Negative likelihood ratio	0.186 (0.163–0.213)		0.585 (0.564–0.605)	
Negative predictive value	84.3% (82.1–86.2)		–	
Positive predictive value	–		85.9% (83.9–87.6)	
The validation cohort				
Total *n* (%)	1236 (23.0%)	2732 (50.9%)	1396 (26.0%)	5364
NAFLD, *n* (%)	183 (14.8%)	1289 (47.2%)	1210 (86.7%)	2682
Fatty liver grade[a], *n* (%)				
Grade 0	1053 (85.2%)	1443 (52.8%)	186 (13.3%)	2682
Grade 1	159 (12.9%)	986 (36.1%)	626 (44.8%)	1771
Grade 2	23 (1.9%)	296 (10.8%)	548 (39.3%)	867
Grade 3	1 (0.1%)	7 (0.3%)	36 (2.6%)	44
Sensitivity	93.1% (92.1–94.1)		45.1% (43.2–47.0)	
Specificity	39.6% (37.7–41.5)		93.1% (92.0–94.0)	
Positive likelihood ratio	1.542 (1.493–1.593)		6.505 (5.628–7.519)	
Negative likelihood ratio	0.173 (0.151–0.199)		0.590 (0.570–0.610)	
Negative predictive value	85.2% (83.1–87.1)		–	
Positive predictive value	–		86.7% (84.8–88.4)	
Interpretation	Absence of NAFLD		Presence of NAFLD	

Values are expressed as *n* (%) or values (95% confidence interval). NAFLD, nonalcoholic fatty liver disease.
[a] Semiquantitative sonographic grading of fatty liver according to the criteria described by Saadeh et al. [9].

lihood ratio of 0.238 (95% CI, 0.209–0.273), and at a value of >36.0, HSI could detect NAFLD with a specificity of 92.4% (95% CI, 91.3–93.4) and a positive likelihood ratio of 4.513 (95% CI, 3.903–5.218).

3.3. Validation of HSI

We next validated HSI using the validation cohort of 5364 subjects (2682 cases and 2682 controls). Median values of HSI were 30.9 (range, 21.6–43.4) in controls and 35.5 (range, 21.9–66.0) in cases. In the validation cohort, the AUROC of HSI for detecting NAFLD was 0.819 (95% CI, 0.808–0.830). At a value of <30.0, HSI could exclude NAFLD with a sensitivity of 93.1% (95% CI, 92.1–94.1) and a negative likelihood ratio of 0.173 (95% CI, 0.151–0.199); and at a value of >36.0, HSI could detect NAFLD with a specificity of 93.1% (95% CI, 92.0–94.0) and a positive likelihood ratio of 6.505 (95% CI, 5.628–7.519) (Table 3). These findings indicate that the predictive power of HSI was maintained at a similar accuracy in the validation cohort. In the validation cohort, 1236 subjects (23.0%) had HSI <30.0 and 1396 subjects (26.0%) had HSI >36.0. According to these cutoff values, 2272 subjects (86.3% of subjects with HSI of <30.0 or >36.0) were correctly classified.

In subjects having normal serum ALT level (n = 4720), the predictive values of HSI were also maintained. In those subjects or the derivation cohort, the AUROC of HSI was 0.776 (95% CI, 0.762–0.789). At a value of <30.0, HSI could rule out NAFLD with a sensitivity of 91.3% (95% CI, 89.9–92.4) and a negative likelihood ratio of 0.220 (95% CI, 0.191–0.254), and at a value of >36.0, HSI could detect NAFLD with a specificity of 93.1% (95% CI, 92.0–94.0) and a positive likelihood ratio of 4.804 (95% CI, 4.128–5.591).

3.4. Correlation between HSI and US fatty liver grade

Next, we evaluated whether HSI could predict fatty liver grade as measured by US. In the linear regression model, HSI showed a significant correlation with fatty liver grade (adjusted r^2 = 0.334, P < 0.001) (Fig. 2). This finding suggested that HSI reflects not only the presence of NAFLD but also its degree.

4. Discussion

In the present study, we devised a novel index to detect the presence of NAFLD using BMI and the results of routinely performed laboratory tests. Moreover, the performance of HSI for detecting NAFLD was confirmed in the validation cohort.

Many studies have attempted to devise noninvasive methods that can predict the presence of NAFLD. Conventional radiological imaging studies, such as US, CT, and magnetic resonance imaging, have been shown to be reasonably accurate [11–14]. For example, Hamaguchi et al. [11] used US to evaluate NAFLD and found that it had a specificity of 100% and a sensitivity of 92% using liver biopsy results as a standard. However, imaging studies are too expansive for mass screening test, and for this reason, a simple and noninvasive test is required to identify patients at high risk of having NAFLD and to establish an appropriate NAFLD screening programme. A fatty liver index (FLI), which incorporates the results of biochemical tests and anthropometric parameters, was proposed in Italy: fatty liver can be ruled out if FLI is <30 and fatty liver can be detected if FLI is ≥60 in Italian subjects [15]. However, FLI seems inappropriate in the Korean population because BMIs and waist circumferences are substantially lower than those in Caucasians. Indeed, more than half (58.2%) of subjects showed FLI <30 and the sensitivity was as low

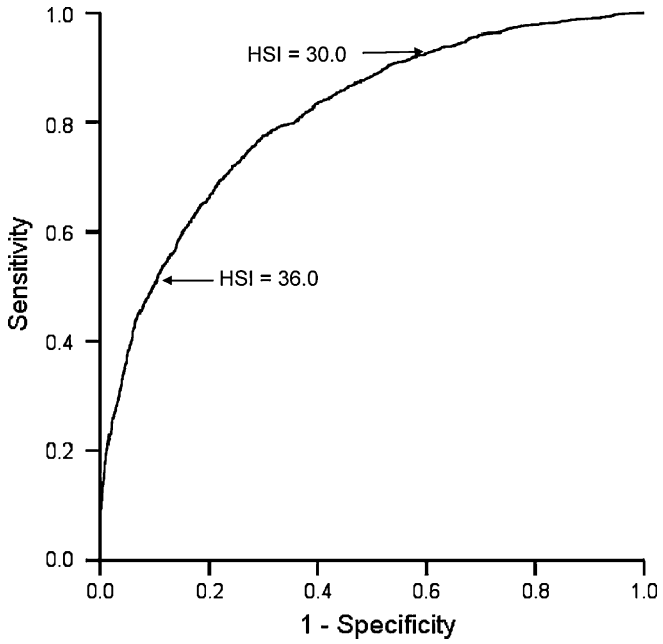

Fig. 1. Receiver-operating characteristic (ROC) curve of HSI for detecting nonalcoholic fatty liver disease. The area under ROC curve was 0.812. At a cutoff value of 30.0, sensitivity and specificity were 92.5% and 40.0%, respectively, and at cutoff value of 36.0, sensitivity and specificity were 46.0% and 92.4%, respectively.

as 63.1% (95% CI, 61.3–64.9) in the derivation cohort of our study. In the derivation and the validation cohort, the AUROCs of FLI predicting NAFLD were 0.783 (95% CI, 0.771–0.796) and 0.786 (95% CI, 0.774–0.798), respectively, which were significantly lower than those of HSI (both $P < 0.01$). Thus, we undertook to derive a simple index that reasonably reflects the presence of NAFLD in Korean population.

This study had several of attractive features. First, it was based on a large population-based cross-sectional study of 10,724 subjects, in which the prevalence of NAFLD was 27.3%, which concurs with previous studies [3–5]. Moreover, to strengthen the results

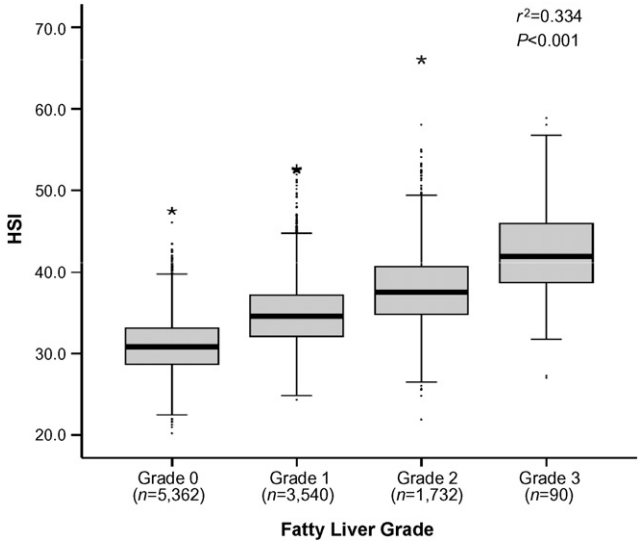

Fig. 2. Box plot of HSI versus ultrasonographically determined fatty liver grade. Fatty liver grade was determined using the criteria described by Saadeh et al. [9]. Boxes represent interquartile ranges, whiskers indicate highest values, dots represent outliers, asterisks represent extreme values, and horizontal lines within boxes indicate median values. HSI values were found to be significantly correlated with US fatty liver grade (adjusted $r^2 = 0.334$, $P < 0.001$).

of multiple logistic regression analysis, bootstrap methods were utilized. Second, to minimize confounding factors, we performed a case–control study using age- and sex-matched controls. Third, the derived index, HSI, can be calculated straightforwardly using routinely performed laboratory tests and anthropometric parameters (height and body weight). Fourth, the performance of HSI was validated using a large validation cohort. Fifth, the predictive values of HSI were also confirmed in the subjects with normal serum ALT level in which the risk of NAFLD is not significantly different from high ALT level [16].

US is an imperfect gold standard for diagnosis of fatty liver due to an imperfect sensitivity. This study was a large population-based cohort study and liver biopsy in asymptomatic individuals was usually unavailable. The diagnostic accuracy of US is reasonable (67–94%) [11,17,18]. Thus, we utilized the US result as a standard for the diagnosis of steatosis instead of histology in this study.

The AUROC of HSI is 0.812, which is far from perfect. However, it can be utilized to select eligible subjects for US screening and it is likely to improve the cost-effectiveness of screening. If a subject has a HSI of <30.0, one can omit sonographic screening because it is unlikely that the subject has NAFLD. On the other hand, if a subject has HSI of >36.0, then he or she can be considered to have NAFLD without US screening. Of the 10,724 subjects included in this study, 2537 subjects (23.7%) had HSI <30.0 and 2831 subjects (26.4%) had HSI >36.0. Therefore, we can expect that about 50% of US screening for HSI could be omitted if we had applied HSI to these subjects. Thus, we hope that HSI will be found to be a useful prescreening test for NAFLD in Korea.

Interestingly, HSI showed a significant correlation with US fatty liver grade. Since increased liver echogenicity at US has been shown to reflect degree of hepatic steatosis [19], it is possible that HSI also does so. However, we could not assess the HSI's predictability for nonalcoholic steatohepatitis due to lack of liver histology in this study. Therefore, further evaluation of the relation between HSI and histologically determined degree of hepatic steatosis or steatohepatitis is probably warranted.

In the present study, BMI, ALT/AST ratio, sex and DM were found to independently predict the presence of NAFLD, and were used to devise HSI. The average BMIs of Korean and non-Hispanic whites in the United States are quite different (23.2 versus 26.8) [20,21], and the susceptibility of Koreans to insulin resistance, which is suspected to underlie NAFLD development, is higher in Koreans than in Caucasians [22,23]. Moreover, there are evidences supporting different ethnic susceptibility for NAFLD [24]. Accordingly, if HSI is considered for use in other than the Korean population the cutoff value should be reassessed.

In conclusion, the derived HSI may offer an economical noninvasive means for predicting the presence of NAFLD with reasonable accuracy. Thus, we hope that HSI can be utilized to identify candidates for hepatic US and those requiring lifestyle modifications. External validation of HSI is warranted in other Asian population.

Conflict of interest statement

None declared.

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