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Diagnostic ability using fatty liver and metabolic markers for metabolic-associated fatty liver disease stratified by metabolic/glycemic abnormalities

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ABSTRACT

Aims/Introduction: Although several noninvasive predictive markers for fatty liver and metabolic markers have been used for fatty liver prediction, whether such markers can also predict metabolic-associated fatty liver disease (MAFLD) remains unclear. We aimed to examine the ability of existing fatty liver or metabolic markers to predict MAFLD.

Materials and Methods: Participants in a high-volume center in Tokyo were classified into groups with and without MAFLD, based on the presence of metabolic abnormalities and fatty liver diagnosed through abdominal ultrasonography, between 2008 and 2018. The diagnostic abilities of three fatty liver markers: fatty liver index (FLI), hepatic steatosis index (HSI), and lipid accumulation product (LAP), and three common metabolic markers: waist-to-height ratio (WHR), body mass index (BMI), and waist circumference (WC), for predicting MAFLD, were evaluated. Analyses stratified by MAFLD subtypes were performed.

Results: Of 92,374 individuals, 19,392 (36.1%) had MAFLD. The diagnostic performances for MAFLD prediction, measured as *c*-statistics, for FLI, HSI, LAP, WHR, BMI, and WC were 0.906, 0.892, 0.878, 0.844, 0.877, and 0.878, respectively. Optimal cutoff values for diagnosing MAFLD for FLI, HSI, LAP, WHR, BMI, and WC were 20.3, 32.7, 20.0, 0.49, 22.9, and 82.1, respectively. Analyses stratified by MAFLD subtypes, based on BMI and metabolic/glycemic abnormalities, suggested that FLI and HSI had acceptable (*c*-statistics >0.700) diagnostic abilities throughout all the analyses.

Conclusions: All six markers were excellent predictors of MAFLD in diagnosing among the general population, with FLI and HSI particularly useful among all sub-populations.

INTRODUCTION

Fatty liver disease affects approximately one-quarter of the global population, and nonalcoholic fatty liver disease (NAFLD) has attracted attention.[1] NAFLD is diagnosed by exclusion; it is defined as hepatic steatosis not secondary to specific causes such as viral infection, alcohol consumption, or drug-related liver damage, and its prevalence is increasing.[2] In contrast to NAFLD, metabolic-associated fatty liver disease (MAFLD) is defined more inclusively by focusing on the prognosis in relation to fatty liver disease (e.g., including those who regularly consume alcohol or have viral hepatitis).[3] The diagnostic value of MAFLD is reportedly superior to that of NAFLD; individuals with MAFLD are found to be at high risk not only for hepatic lesions such as hepatic fibrosis but also for extra-hepatic disease development such as cardiovascular disease, malignancy, and

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ultimately mortality.[3,4] In particular, among the Japanese population, comorbid MAFLD has recently been reported to be associated with atherosclerotic cardiovascular risk, colorectal adenoma, and reflux esophagitis.[5–7] Liver biopsy is the gold standard for the diagnosis of fatty liver. However, owing to the high disease prevalence and invasiveness of liver biopsy, predictive markers for either condition should be assessed.

Data on the diagnostic markers of MAFLD are limited. Meanwhile, markers for cases with fatty liver have been developed.[8–10] and validated;[8,11–15] these markers include the fatty liver index (FLI),[8] hepatic steatosis index (HSI),[9] and lipid accumulation product (LAP).[10] A previous study also assessed existing markers for obesity or metabolic abnormalities, such as waist-to-height ratio (WHR),[16] body mass index (BMI),[17] and waist circumference (WC), and reported their usefulness in predicting the presence of fatty liver.[15] All these markers utilize data such as physical measurements, common biochemical biomarkers correlated with liver function or lipid metabolism, and diabetes history.[8–10,18] The prediction of fatty liver disease is useful not only because it detects those at risk for fatty liver disease but also because predictive markers themselves enable the prediction of extrahepatic disease. For example, the fatty liver index is the most frequently used index for predicting the presence of fatty liver. This was developed in Europe and has been validated in several countries[8,11–15] and can predict cardiovascular diseases[19] and ultimately mortality,[20] as well as metabolic diseases including diabetes.[21] However, there have been no reports regarding the usefulness of such markers among individuals with each type of metabolic abnormality associated with MAFLD.

This observational study aimed to assess whether fatty liver and metabolic markers could be useful in predicting MAFLD in the Japanese population. At the same time, we evaluated the performance of the predictive models in terms of their discriminative ability and calibration. Further, we conducted stratified analyses according to the status of glycemic/metabolic abnormalities to reveal risks involved and the real-world prevalence of MAFLD in each stratum.

MATERIALS AND METHODS

Data source

This was a retrospective cross-sectional study that used data from individuals who participated in an annual health checkup program at the Center for Preventive Medicine at St Luke's International Hospital in Tokyo, Japan. Data collected from the database and used in this study have been described previously.[22] Approximately 70% of participants underwent the legally required checkups, which employers or insurers were obliged to provide for regular employees. The remaining participants voluntarily underwent checkups.

We included individuals aged 18–80 years who underwent health checkup examinations between January 2008 and December 2018. The inclusion criteria were as follows: (1) participants who underwent checkups using abdominal ultrasonography and (2) those with available laboratory data. Individuals who met any of the following criteria at baseline were excluded: (1) previous or current history of hormone replacement therapy, malignancy, or abdominal surgery; (2) renal replacement therapy; or (3) pregnancy. From those who satisfied the inclusion and who did not satisfy the exclusion criteria, the first observation for each individual was obtained to remove the effects of homogeneity in the same individual or those from health guidance. This guidance was performed by a team of trained registered nurses or physicians after prior checkups, particularly among those with abnormal results.[23]

This study was approved by the Institutional Review Board of the University of Tokyo (no. 2020264NI) and St Luke's International Hospital (no. 20-R184). The analyses performed in this study involved the secondary use of data obtained from the database of St Luke's Health Checkup, and the participants were provided with the option to withdraw consent for the use of their records for research.

Diagnostic ability of fatty liver and metabolic markers for prediction of MAFLD

We used several markers to examine their effectiveness in predicting MAFLD. As noninvasive diagnostic markers for fatty liver, we used FLI, HSI, and LAP.[8–10] Regarding metabolic markers, we used WHR, BMI, and WC for fatty liver prediction, as reported previously.[15] Details of these markers are presented in Table 1.

Variables and outcome

We obtained the following information from the medical checkup records: sex, age, BMI, blood pressure measurement, waist circumference, current illnesses and treatments, medical history, use of medications, and alcohol intake (grams per week), as described previously.[22] Moreover, data on complete blood cell counts and serum biochemistry from blood samples, including fasting blood glucose, serum albumin, creatinine, lipid markers (low- and high-density lipoprotein cholesterol and triglycerides), liver enzymes (aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase), and C-reactive protein (CRP) levels were collected.

An abnormal waist circumference was defined as ≥90 cm in women and ≥85 cm in men, based on the Japanese criteria for metabolic syndrome.[24] Moreover, alcohol overuse was defined as an ethanol level of ≥20 g/day in women and ≥30 g/day in men, as described in a previous study.[25] Dyslipidemia was defined as the presence of a history of dyslipidemia, fasting triglyceride levels of ≥150 mg/dL, or high-density lipoprotein cholesterol levels of <50 mg/dL in women or <40 mg/dL in men. Hypertension was defined as the presence of hypertension history, systolic blood pressure ≥130 mmHg, or diastolic blood pressure ≥85 mmHg, as described in a previous study.[26]

The primary outcome was the presence of MAFLD on abdominal ultrasonography. Participants were diagnosed with MAFLD based on the presence of fatty liver on

ultrasonography at each time based on the four criteria in a previous report (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring),[27] and the presence of metabolic abnormalities, which were as follows:[26]: (1) overweight/obesity (BMI ≥23 kg/m^2); (2) lean/normal weight (BMI of <23 kg/m^2) with the presence of at least two metabolic risk abnormalities, as listed in Table 2 and defined in a previous study,[28] except for the homeostasis model assessment of an insulin resistance score of ≥2.5, because this item was not available in our data; and (3) type 2 diabetes mellitus, defined as the presence or previous medical history of diabetes, or fasting glucose level of ≥126 mg/dL or HbA1c of ≥6.5%. The cutoff values for waist circumference that can determine metabolic abnormality were ≥90 cm in women and ≥85 cm in men according to the Japanese criteria for metabolic syndrome, which is based on a waist circumference corresponding to 100 cm^2 of visceral fat in Japanese individuals[24] and the measurement of waist circumference at the umbilical level, not at the midpoint between the lowest rib and iliac crest, as used worldwide.[29–31] We used CRP values by measuring the immunoagglutination assay with latex beads (IatroCRP-Ex, Mitsubishi Chemical Medience, Tokyo, Japan, and N-Assay LA CRP-T, Nittobo Medical Co., Ltd, Tokyo, Japan, before 2015 and in or after 2015, respectively). Both assays can detect a range of ≥0.01 mg/dL,[32] and an elevated CRP level measured using either assay was associated with the prognosis.[32–34] The latter has also been used to measure high-sensitivity CRP levels.[32,33]

Statistical analysis

Analysis of demographic characteristics

The background characteristics of people with and without MAFLD were summarized. Simultaneously, the prevalence of MAFLD was assessed because the dataset used mainly comprised information about the general population. Categorical and continuous variables were compared between participants

Table 1 | Markers examined in this study previously shown to be associated with metabolic abnormality or nonalcoholic fatty liver disease

Marker	Formula	Reference
Fatty liver index	$\frac{e^{0.953*\log(\text{triglycerides})+0.139*\text{BMI}+0.718*\ln(\text{GGT})+0.053*\text{waist circumference}-15.745}}{1+e^{0.953*\log(\text{triglycerides})+0.139*\text{BMI}+0.718*\ln(\text{GGT})+0.053*\text{waist circumference}-15.745}}$	8
Hepatic stenosis index	$8 * \frac{\text{ALT}}{\text{AST}}$ + BMI (+2 if having diabetes; +2 if female)	9
Lipid accumulation product	Waist circumference [cm] − 65 (+ 7 if female)] × (triglycerides [mmol/L])	10
Waist-to-height ratio	Waist circumference [cm]/height [cm]	16
Body mass index	$\frac{\text{Weight [kg]}}{(\text{Height [m]})^2}$	17
Waist circumference	Circumference measured at the umbilical level between the lowest rib and the iliac crest	24

BMI, GGT, AST, and ALT are body mass index, gamma-glutamyl transferase, aspartate aminotransferase, and alanine aminotransferase, respectively. Impaired fasting glucose was defined as a glucose level of ≥110 mg/dL.

Table 2 | Components of the criteria defining metabolic risk factors in individuals with lean or normal body mass index who did not present with diabetes

Metabolic risk factors	Definition of the international expert panels[3]	Definition in our study
Waist circumference	≥102/88 cm in Caucasian men and women or ≥90/80 cm in Asian men and women, measured at the midpoint between the lowest rib and the iliac crest	≥90 cm in women and ≥85 cm in men, measured at the umbilical level
Blood pressure	≥130/85 mmHg or specific drug treatment	≥130/85 mmHg or specific drug treatment
Plasma triglyceride levels	≥150 mg/dL or specific drug treatment	≥150 mg/dL or specific drug treatment
Plasma HDL-cholesterol level	<40 mg/dL for men and <50 mg/dL for women or specific drug treatment	<40 mg/dL for men and <50 mg/dL for women or specific drug treatment
Glucose metabolism	Prediabetes (fasting glucose levels of 100–125 mg/dL, or 2 h post-load glucose levels of 140–199 mg/dL or HbA1c of 5.7–6.4%)	Prediabetes (fasting glucose levels of 100–125 mg/dL, or HbA1c of 5.7–6.4%)
Insulin resistance	Homeostasis model assessment of insulin resistance score of ≥2.5	None
Systemic inflammation	Plasma high-sensitivity C-reactive protein level of >2 mg/L	Serum C-reactive protein level of >0.2 mg/L with assay capturing of >0.01 mg/dL

HbA1c, glycated hemoglobin; HDL, high-density lipoprotein.

with and without MAFLD using Pearson's chi-squared test and the Student's *t*-test, respectively.

Assessment of model performance: discriminative ability and calibration

The study participants were divided into a training group comprising 80% the total participants and a test set comprising the remaining 20% of participants. In the training set, models were created for each fatty liver or metabolic marker. In the test set, we calculated *c*-statistics expressed as the area under the receiver operating characteristic curve, comprising plots of sensitivity vs 1 minus specificity to assess the discriminative ability of each marker. *C*-statistics with ranges of 0.5 to <0.7, 0.7 to <0.8, 0.8 to <0.9, and 0.9 to <1.0 represented poor, acceptable, excellent, and outstanding discriminative ability, respectively, as described previously.[35]

Next, we evaluated the model performance using the test set in terms of calibration; calibration confirmed the consistency in the ability to predict the actual diagnosis along with the predicted probabilities. Visualization of the calibration was made possible using the pmcalplot command in Stata. Briefly, the command 'pmcalplot' makes a calibration plot of the observed against expected probabilities to assess the performance of predictive models. With this command, calibration was plotted in 10 groups across the risk spectrum, reporting the following components: (i) calibration in the large (CITL) index, describing the difference between the average predicted probabilities and the observed event frequencies, in which the ideal value should equal zero; (ii) the calibration slope, in which the ideal value should equal one; and (iii) the expected probability vs observed frequency (E:O) ratio, in which the ideal value should equal one. This method has been used in several studies describing calibration.[36–38]

Assessment of model performance: discriminative ability and calibration

Based on the best cutoff value of each predictor according to the Youden index,[39] we calculated the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratio, and kappa coefficient, which evaluates the agreement of categorization compared with the ultrasound-proven MAFLD. We also performed sex-stratified analysis. For each sex group, we assessed discriminative ability and calibration and calculated the cutoff values as in the primary analysis.

Subgroup analyses

We performed descriptive and subgroup analyses for MAFLD based on the three types of glycemic/metabolic abnormalities: BMI <23 kg/m^2 with at least two glycemic/metabolic risk factors; BMI ≥23 kg/m^2; and the presence of diabetes. We also performed an age-stratified analysis. We set the cutoff age to 50 years. For each subgroup, we assessed the discriminative ability and calibration and calculated the cutoff values, as performed in the primary analysis.

All hypothetical tests had a two-tailed significance level of 0.05, and all statistical analyses were performed using Stata version 17 software (StataCorp, College Station, TX, USA).

RESULTS

Study population and baseline characteristics

Of all the observations with health checkups, including abdominal ultrasonography (n = 413,714), 58,624 (14.2%) were excluded. Of the remaining 355,090 observations from 92,374 individuals, we used the initial checkup data of 92,374 individuals. Among the included 92,374 individuals, 19,392 (21.0%) presented with MAFLD on ultrasonography (Figure 1). Furthermore, among people with MAFLD (n = 19,392), 2,522 (13.0%) had a BMI of <23 kg/m^2 with at least two glycemic/metabolic risk factors; 16,777 (86.5%) had a BMI of ≥23 kg/m^2; and 2,713 (14.0%) had diabetes. Table 3 presents the demographic and clinical characteristics of the participants. We estimated the prevalence of MAFLD in the general population as 21.0%. Compared with individuals without MAFLD, those with MAFLD were significantly older and more likely to be men who had hypertension, dyslipidemia, or diabetes. Moreover, they had significantly higher WHR, BMI, WC, systolic/diastolic blood pressure, serum liver enzyme levels, and fatty liver predictive marker levels (FLI, HSI, and LAP). In addition, the MAFLD group had a higher proportion of current smokers and individuals with a history of cardiovascular disease and a lower estimated glomerular filtration rate (Table 3). However, there was no statistically significant difference in the proportion of individuals positive for hepatitis B virus s-antigen or hepatitis C virus antibody.

Diagnostic performance of fatty liver and metabolic markers for MAFLD

Table 4 shows the diagnostic performance of fatty liver markers and metabolic markers for MAFLD. The *c*-statistics of the FLI, HSI, and LAP for predicting MAFLD among all participants were 0.906 (95% confidence interval [CI]: 0.902–0.911), 0.892 (95% CI: 0.887–0.898), and 0.878 (95% CI: 0.873–0.884), respectively (Figure 2 and Table 4). Thus, the FLI had an outstanding discriminative ability for predicting MAFLD, whereas the HSI and LAP had excellent discriminative ability. WHR, BMI, and WC, representative of metabolic markers, were also good predictors for MAFLD, with *c*-statistics of 0.844 (95% CI: 0.837–0.850), 0.877 (95% CI: 0.871–0.882), and 0.878 (95% CI: 0.873–0.884), respectively; these markers had excellent discriminative abilities. The optimal cutoff values were 20.3, 32.7, 20.0, 0.49, 22.9, and 82.1, for FLI, HSI, LAP, WHR, BMI, and WC, respectively. The calibration of the markers used was generally good, with E:O ranging from 1.007 to 1.017, CITL ranging from −0.033 to −0.014, and the calibration slope ranging from 0.996 to 1.011 (Figure 2b, Figure S1a).

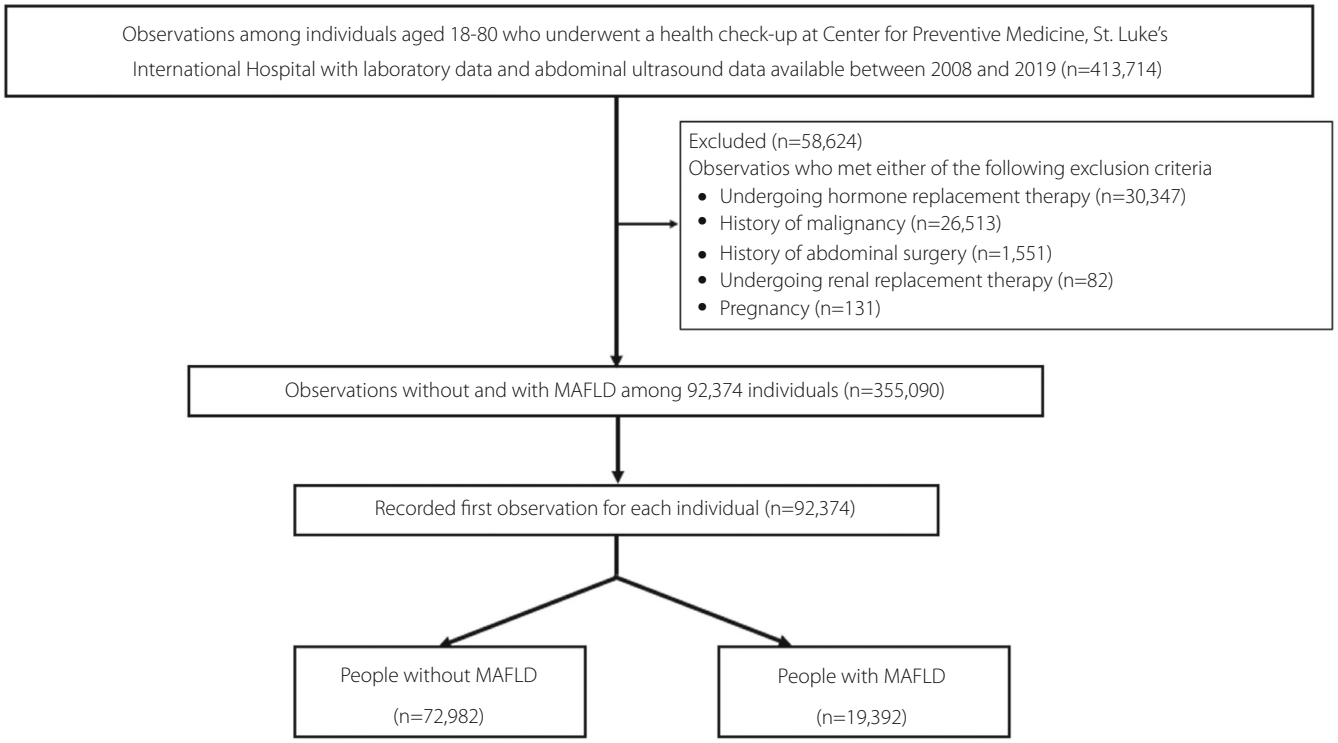

Figure 1 | Flow chart of selection of participants: MAFLD, metabolic-associated fatty liver disease.

Sex-stratified analyses yielded similar results (Figure 2c–f, Figure S1b,c). Among the 45,560 female participants, 3,761 had MAFLD (8.3%), while among the 46,814 male participants, 15,631 had MAFLD (33.4%). The c-statistics of prediction by each marker were generally higher in women than in men; thus, FLI, HSI, LAP, WHR, BMI, and WC had *c*-statistics of 0.948, 0.940, 0.925, 0.921, 0.917, and 0.913, respectively, in women and 0.845, 0.845, 0.829, 0.821, 0.815, and 0.817, respectively, in men (Table 4).

Subgroup analyses

Among the 92,374 individuals included in the primary analysis, 53,673 (58.1%) patients had metabolic abnormalities (i.e., at risk for MAFLD), among whom 16,993 (31.7%) had BMI <23 kg/m^2 with at least two glycemic/metabolic risk factors; 36,128 (67.3%) had BMI ≥23 kg/m^2; and 4,524 (8.4%) had diabetes (Figure S2, aggregated percentage exceeded 100% due to the overlapping). The descriptive summary of fatty liver and metabolic markers among each type of population at risk for MAFLD is shown in Table 5.

The discriminative abilities of the six markers among people with each glycemic/metabolic abnormality are listed in Table 6. Among individuals at risk for MAFLD, fatty liver and metabolic markers are most useful in the population with diabetes (Table 6). In the population with diabetes, two of the fatty liver markers, FLI and HSI, had excellent discriminative abilities for MAFLD prediction with *c*-statistics of 0.836 (95% CI: 0.809–0.862) and 0.845 (95% CI: 0.820–0.870), respectively. On the other hand, in this population, metabolic markers had acceptable discrimination ability. In comparison with the results analyzed in people with diabetes, the discrimination abilities decreased among the population with a BMI of <23 kg/m^2 and metabolic risks or population with a BMI of ≥23 kg/m^2. As for calibration, all markers yielded good results for calibration parameters among all the sub-populations, i.e., E:O, CITL, and calibration slope (Figure 3b). Calibration for fatty liver or metabolic markers was generally good among the individuals with BMI ≥23 kg/m^2 and with diabetes (Figure 3d,f, Figure S1e,f).

The age-stratified analyses also provided similar results (Figure 4, Figure S1g,h and Table 7). Among 59,089 participants aged <50 years, 10,120 had MAFLD (17.1%), while among 33,285 participants aged ≥50 years, 9,272 had MAFLD (27.9%). The c-statistics for each marker's prediction were generally higher in those aged <50 years than in those aged ≥50 years; FLI, HSI, LAP, WHR, BMI, and WC had *c*-statistics of 0.925, 0.913, 0.900, 0.871, 0.900, and 0.902, respectively, in those aged <50 years, while *c*-statistics of 0.869, 0.865, 0.832, 0.781, 0.839, and 0.829 were obtained in those aged ≥50 years, respectively.

Table 3 | Characteristics of eligible observations categorized based on the diagnosis of MAFLD among all participants

Variable	Category	All individuals n = 92,374	Individuals without MAFLD n = 72,982	Individuals with MAFLD n = 19,392	P value
Age (years)		46.4 (11.8)	45.6 (11.8)	49.6 (11.1)	<0.001
Male sex		46,814 (50.7%)	31,183 (42.7%)	15,631 (80.6%)	<0.001
Body mass index (kg/m^2)		22.4 (3.4)	21.4 (2.7)	26.1 (3.4)	<0.001
Waist circumference (cm)		79.6 (9.7)	76.8 (8.0)	90.0 (8.4)	<0.001
Abnormal waist circumference		22,071 (23.9%)	9,087 (12.5%)	12,984 (67.0%)	<0.001
Waist-to-height ratio		0.48 (0.05)	0.47 (0.05)	0.54 (0.05)	<0.001
Systolic blood pressure (mmHg)		117.9 (16.6)	115.3 (15.8)	127.9 (15.6)	<0.001
Diastolic blood pressure (mmHg)		72.1 (11.6)	70.3 (11.1)	79.3 (11.0)	<0.001
Anti-hypertensive treatment		7,824 (8.5%)	4,289 (5.9%)	3,535 (18.2%)	<0.001
Hypertension		25,783 (27.9%)	15,639 (21.4%)	10,144 (52.3%)	<0.001
Alcohol intake (g/day)		12.8 (22.5)	11.7 (21.2)	16.9 (26.3)	<0.001
Alcohol overuse		17,017 (18.4%)	12,545 (17.2%)	4,472 (23.1%)	<0.001
Smoking	Current	13,819 (15.0%)	9,783 (13.4%)	4,036 (20.8%)	<0.001
	Never	56,633 (61.3%)	47,645 (65.3%)	8,988 (46.3%)	
	Former	21,922 (23.7%)	15,554 (21.3%)	6,368 (32.8%)	
Hemoglobin level (g/dL)		13.9 (1.4)	13.6 (1.4)	14.8 (1.2)	<0.001
Platelet level (10^9/L)		233.2 (50.6)	232.0 (50.2)	237.8 (51.9)	<0.001
Serum albumin level (g/dL)		4.4 (0.2)	4.4 (0.2)	4.5 (0.2)	<0.001
Aspartate aminotransferase level (U/L)		21.8 (9.6)	20.4 (7.7)	26.9 (13.4)	<0.001
Alanine aminotransferase level (U/L)		22.6 (16.7)	18.8 (10.8)	37.0 (25.0)	<0.001
Gamma-glutamyl transferase level (U/L)		34.3 (44.7)	28.1 (36.2)	57.6 (62.5)	<0.001
Triglyceride level (mg/dL)		97.9 (79.4)	81.9 (54.4)	158.1 (119.5)	<0.001
High-density lipoprotein-cholesterol level (mg/dL)		62.4 (15.6)	65.3 (15.1)	51.5 (11.8)	<0.001
Low-density lipoprotein-cholesterol level (mg/dL)		116.5 (30.5)	112.8 (29.5)	130.2 (30.5)	<0.001
Anti-dyslipidemia treatment		5,511 (6.0%)	3,272 (4.5%)	2,239 (11.5%)	<0.001
Dyslipidemia		21,073 (22.8%)	10,917 (15.0%)	10,156 (52.4%)	<0.001
Fasting blood glucose level (mg/dL)		99.5 (15.0)	97.0 (11.5)	108.9 (21.4)	<0.001
HbA1c (%)		5.5 (0.5)	5.5 (0.4)	5.8 (0.8)	<0.001
Anti-diabetic drug treatment		2,572 (2.8%)	1,214 (1.7%)	1,358 (7.0%)	<0.001
Body mass index <23 kg/m^2 with metabolic risks		16,993 (18.4%)	14,471 (19.8%)	2,522 (13.0%)	<0.001
Body mass index ≥23 kg/m^2		36,128 (39.1%)	19,351 (26.5%)	16,777 (86.5%)	<0.001
Diabetes		4,524 (4.9%)	1,811 (2.5%)	2,713 (14.0%)	<0.001
Prediabetes		39,405 (42.7%)	26,785 (36.7%)	12,620 (65.1%)	<0.001
Metabolic syndrome		8,366 (9.1%)	2,243 (3.1%)	6,123 (31.6%)	<0.001
Estimated glomerular filtration rate (mL/min/1.73 m^2)		78.6 (14.6)	79.3 (14.6)	76.2 (14.2)	<0.001
C-reactive protein level (mg/dL)		0.10 (0.33)	0.09 (0.32)	0.15 (0.38)	<0.001
Positivity to HBV s-antigen		766 (0.8%)	587 (0.8%)	179 (0.9%)	0.11
Positivity to HCV antibody		412 (0.4%)	338 (0.5%)	74 (0.4%)	0.13
History of cardiovascular disease		1,187 (1.3%)	784 (1.1%)	403 (2.1%)	<0.001
Fatty liver index		21.1 (23.2)	13.4 (15.7)	49.7 (24.5)	<0.001
Hepatic steatosis index		31.5 (5.1)	29.9 (3.6)	37.4 (5.3)	<0.001
Liver accumulation product		22.4 (26.8)	15.7 (15.0)	47.5 (42.1)	<0.001

Data are presented as the mean (standard deviation) for continuous measures and as n (%) for categorical measures. HbA1c, glycated hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic-associated fatty liver disease.

DISCUSSION

This observational study used health checkup data obtained from individuals in a high-volume center. The results showed that all the six markers (FLI, HSI, LAP, WHR, BMI, and WC) had excellent discriminative ability in predicting MAFLD in the general population, and that the fatty liver index and the hepatic steatosis index had acceptable discriminative ability in all the sub-populations. Thus, FLI and HSI will be effective tools for predicting and screening MAFLD, both among the general population and individuals with metabolic risk.

The observation that the FLI and HSI had stable diagnostic abilities for MAFLD was in accordance with the results from previous validation studies performed in several countries on the diagnostic ability of the presence of FLI or HSI.[11–15,40]

Table 4 | Summary of discriminative parameters for metabolic-associated fatty liver disease in the main and sex-stratified analyses

Population	Marker	*C*-statistics	95% confidence interval	Optimal cut-off	Sensitivity (%)	Specificity (%)	LR+	LR−	DOR	PPV (%)	NPV (%)	κ
Whole	FLI	0.906	0.902–0.911	20.3	87.6	78.2	4.03	0.158	25.5	51.5	96.0	0.524
	HSI	0.892	0.887–0.898	32.7	82.2	80.0	4.10	0.223	18.4	52.0	94.4	0.512
	LAP	0.878	0.873–0.884	20.0	85.3	75.2	3.43	0.195	17.6	47.6	95.1	0.468
	WHR	0.844	0.837–0.850	0.49	83.4	70.0	2.78	0.237	11.8	42.3	94.1	0.394
	BMI	0.877	0.871–0.882	22.9	87.8	72.2	3.16	0.169	18.7	45.5	95.7	0.447
	WC	0.878	0.873–0.884	82.1	84.8	75.0	3.39	0.202	16.8	47.3	94.9	0.463
Female	FLI	0.948	0.942–0.954	14.5	88.7	88.0	7.40	0.129	57.4	40.4	98.8	0.497
	HSI	0.940	0.932–0.947	32.0	90.4	82.8	5.25	0.116	45.1	32.5	98.9	0.404
	LAP	0.925	0.916–0.933	19.9	88.8	82.0	4.93	0.137	36.0	31.1	98.8	0.384
	WHR	0.921	0.913–0.930	0.52	84.2	85.9	5.97	0.184	32.4	35.4	98.3	0.431
	BMI	0.917	0.907–0.926	22.9	85.1	84.9	5.62	0.176	32.0	34.0	98.4	0.416
	WC	0.913	0.903–0.922	80.0	87.1	80.4	4.44	0.161	27.6	28.9	98.5	0.352
Male	FLI	0.845	0.837–0.853	29.2	79.5	73.9	3.05	0.277	11.0	59.8	88.1	0.493
	HSI	0.845	0.837–0.853	33.1	79.1	73.4	2.97	0.286	10.4	59.2	87.7	0.483
	LAP	0.829	0.821–0.838	24.2	76.1	74.9	3.03	0.319	9.5	59.7	86.5	0.477
	WHR	0.821	0.812–0.829	0.49	80.7	68.3	2.54	0.283	9.0	55.4	87.8	0.438
	BMI	0.815	0.806–0.824	24.0	74.4	72.4	2.70	0.354	7.6	56.9	85.3	0.434
	WC	0.817	0.808–0.826	84.9	73.6	74.5	2.89	0.355	8.2	58.6	85.2	0.452

The optimal cut-off was calculated based on the best Youden index. BMI, body mass index; DOR, diagnostic odds ratio; FLI, fatty liver index; HSI, hepatic steatosis index; κ, kappa coefficient; LAP, lipid accumulation product; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; WC, waist circumference; WHR, waist-to-height ratio.

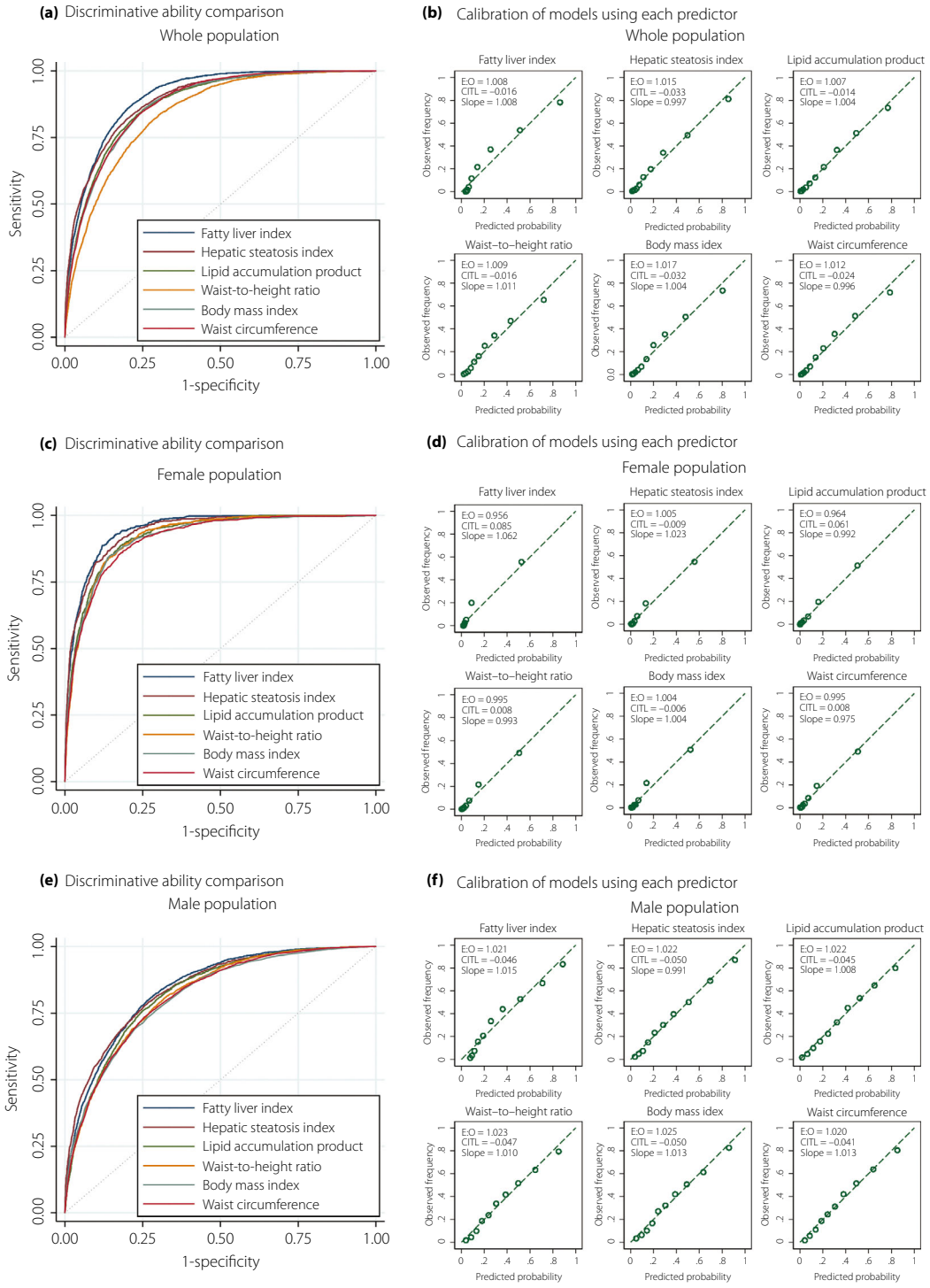

Figure 2 | Receiver operating characteristic curves and calibration plots of predictive models using the fatty liver index, hepatic steatosis index, lipid accumulation product, waist-to-height ratio, body mass index, and waist circumference for predicting MAFLD among all, female, and male participants. (a) Receiver operating characteristic curves showing discriminative abilities among whole population. (b) Calibration plots of the predictive models among whole population. (c) Receiver operating characteristic curves showing discriminative abilities among female population. (d) Calibration plots of the predictive models among female population. (e) Receiver operating characteristic curves showing discriminative abilities among male population. (f) Calibration plots of the predictive models among male population. CITL, calibration in the large index; E:O, expected probability vs observed frequency ratio; slope, calibration slope.

Table 5 | Summary of fatty liver and metabolic markers for each type of population at risk for MAFLD

Population	Marker	Individuals without MAFLD	Individuals with MAFLD	*P* value
Population with BMI <23 kg/m^2 and metabolic risks		*N* = 14,471	*N* = 2,522	
	FLI	14.1 (12.3)	26.2 (15.9)	<0.001
	HSI	29.1 (2.7)	31.8 (3.1)	<0.001
	LAP	16.3 (14.2)	28.8 (23.7)	<0.001
	WHR	0.46 (0.04)	0.48 (0.03)	<0.001
	BMI	21.0 (1.5)	21.8 (1.0)	<0.001
	WC	77.1 (5.5)	80.8 (4.4)	<0.001
Population with BMI ≥23 kg/m^2		*N* = 19,351	*N* = 16,777	
	FLI	29.5 (19.4)	53.4 (23.4)	<0.001
	HSI	33.8 (3.2)	38.3 (5.1)	<0.001
	LAP	27.2 (20.2)	50.5 (43.5)	<0.001
	WHR	0.51 (0.04)	0.54 (0.05)	<0.001
	BMI	24.9 (1.8)	26.8 (3.1)	<0.001
	WC	85.6 (6.0)	91.4 (8.0)	<0.001
Population with diabetes		*N* = 1,811	*N* = 2,713	
	FLI	24.1 (20.8)	57.5 (25.3)	<0.001
	HSI	33.1 (3.9)	39.9 (5.8)	<0.001
	LAP	23.6 (23.2)	56.8 (52.6)	<0.001
	WHR	0.50 (0.05)	0.55 (0.06)	<0.001
	BMI	22.8 (3.1)	27.0 (4.1)	<0.001
	WC	82.2 (8.6)	92.5 (9.9)	<0.001

Data are presented as mean (standard deviation). BMI, body mass index; FLI, fatty liver index; HSI, hepatic steatosis index; LAP, lipid accumulation product; MAFLD, metabolic-associated fatty liver disease; WC, waist circumference; WHR, waist-to-height ratio.

However, the FLI and HSI had a better performance in the current study than in previous studies regarding the diagnostic ability for fatty liver or NAFLD presence. This result can be attributed to the following. First, considering that fatty liver index can predict cardiovascular diseases[41] and that patients with MAFLD are more likely to develop these conditions,[3,4] FLI is presumably more effective in predicting MAFLD than in predicting NAFLD. Second, both markers have predictive ability for metabolic abnormalities, especially for glucose intolerance. The fatty liver index can predict the aggravation of glycemic status or metabolic syndrome,[42–44] while HSI can also reportedly predict gestational diabetes mellitus[45] or carotid atherosclerosis in patients with type 2 diabetes mellitus.[46] Hence, it can be inferred that FLI and HSI can predict the presence of fatty liver and glucose intolerance, that is MAFLD.

The other marker of fatty liver, lipid accumulation product, and metabolic markers, such as WHR, BMI, and WC, had diagnostic ability that was slightly inferior but almost comparable to FLI and HSI for MAFLD prediction. Although LAP was a good predictor of MAFLD, the confidence interval coverage suggests that LAP may be less useful than FLI in predicting MAFLD in our study, and this result was similar to that of NAFLD studies that compared the diagnostic performance of FLI and LAP in Europe.[11] The results of another previous study were also consistent with our findings, showing that the fatty liver index may have a higher diagnostic ability for fatty liver than BMI, WHR, or WC and that these three metabolic markers are also good predictors of fatty liver.[15]

Although results of diagnostic abilities and calibration among each subtype of MAFLD suggest that fatty liver and metabolic markers are useful as well, they differed in cut-off values among the three groups. Among the three groups, the population with BMI <23 kg/m^2 and metabolic risks had lower cut-off values than those of the other two groups in two fatty liver markers, FLI and LAP, for MAFLD diagnosis. This fact may remind us that interpreting FLI and LAP in association with MAFLD necessitates the presence/absence of overweight/obesity and diabetes.

Our results suggest that the *c*-statistics of markers predictive of the presence of fatty liver were lower in men than in women and lower in participants aged ≥50 years than in participants aged <50 years. These trends have also been confirmed in previous studies.[11,13,15] The exact reason for this remains unknown, but differences in the prevalence of MAFLD might affect these trends.[47]

The prevalence of MAFLD was relatively low in the general population compared with that in the cohort of a previous study in another country.[48] However, this result might be attributed to the fact that the prevalence of diabetes is higher in the USA than in Japan.[49,50] Meanwhile, the prevalence of NAFLD is comparable.[14,25] There is insufficient evidence regarding the prevalence and incidence of MAFLD because the term was only coined in 2020. Therefore, future studies should be conducted in other countries as well.

Our study has several strengths. First, we made a diagnosis of MAFLD in the general population using detailed information

Table 6 | Summary of discriminative parameters for metabolic-associated fatty liver disease in the analyses among each type of the population at risk for MAFLD: the population with body mass index <23 kg/m^2 and metabolic risks, the population with body mass index ≥23 kg/m^2, and the population with diabetes

Population	Marker	*C*-statistics	95% confidence interval	Optimal cut-off	Sensitivity (%)	Specificity (%)	LR+	LR−	DOR	PPV (%)	NPV (%)	Kappa
Population with BMI <23 kg/m^2 and metabolic risks	FLI	0.773	0.752–0.794	15.1	76.3	66.8	2.30	0.355	6.47	27.2	94.5	0.246
	HSI	0.760	0.737–0.783	30.2	74.0	68.6	2.36	0.378	6.24	27.8	94.2	0.251
	LAP	0.755	0.733–0.778	18.2	70.7	69.5	2.32	0.422	5.49	27.4	93.6	0.242
	WHR	0.684	0.660–0.707	0.46	78.8	50.7	1.60	0.419	3.81	20.6	93.6	0.135
	BMI	0.677	0.653–0.702	21.6	66.6	60.5	1.69	0.552	3.06	21.5	91.8	0.145
	WC	0.702	0.679–0.726	78.8	70.9	61.1	1.82	0.476	3.83	22.9	92.8	0.171
Population with BMI ≥23 kg/m^2	FLI	0.783	0.772–0.793	37.2	70.5	71.1	2.44	0.414	5.90	67.8	73.7	0.416
	HSI	0.781	0.770–0.791	36.1	62.2	80.3	3.16	0.471	6.71	73.1	71.1	0.429
	LAP	0.756	0.745–0.767	28.3	72.7	65.9	2.13	0.414	5.15	64.7	73.7	0.383
	WHR	0.687	0.675–0.699	0.52	67.5	60.4	1.71	0.538	3.17	59.5	68.3	0.277
	BMI	0.711	0.699–0.723	25.5	60.0	71.0	2.07	0.563	3.67	64.0	67.3	0.312
	WC	0.724	0.713–0.736	88.0	64.0	69.0	2.07	0.522	3.96	64.0	69.0	0.330
Population with diabetes	FLI	0.836	0.809–0.862	31.1	81.1	73.2	3.02	0.259	11.70	82.1	71.8	0.541
	HSI	0.845	0.820–0.870	35.9	74.3	79.0	3.54	0.325	10.90	84.3	67.0	0.517
	LAP	0.804	0.774–0.833	27.5	75.6	70.4	2.56	0.346	7.38	79.5	65.6	0.455
	WHR	0.757	0.725–0.789	0.50	79.6	60.2	2.00	0.339	5.91	75.2	66.1	0.404
	BMI	0.803	0.774–0.831	22.8	88.2	56.6	2.03	0.209	9.72	75.5	75.9	0.468
	WC	0.789	0.759–0.818	86.7	68.5	74.9	2.72	0.421	6.47	80.5	61.0	0.417

The optimal cut-off was calculated based on the best Youden index. BMI, body mass index; DOR, diagnostic odds ratio; FLI, fatty liver index; HSI, hepatic steatosis index; Kappa, kappa coefficient; LAP, lipid accumulation product; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; WC, waist circumference; WHR, waist-to-height ratio.

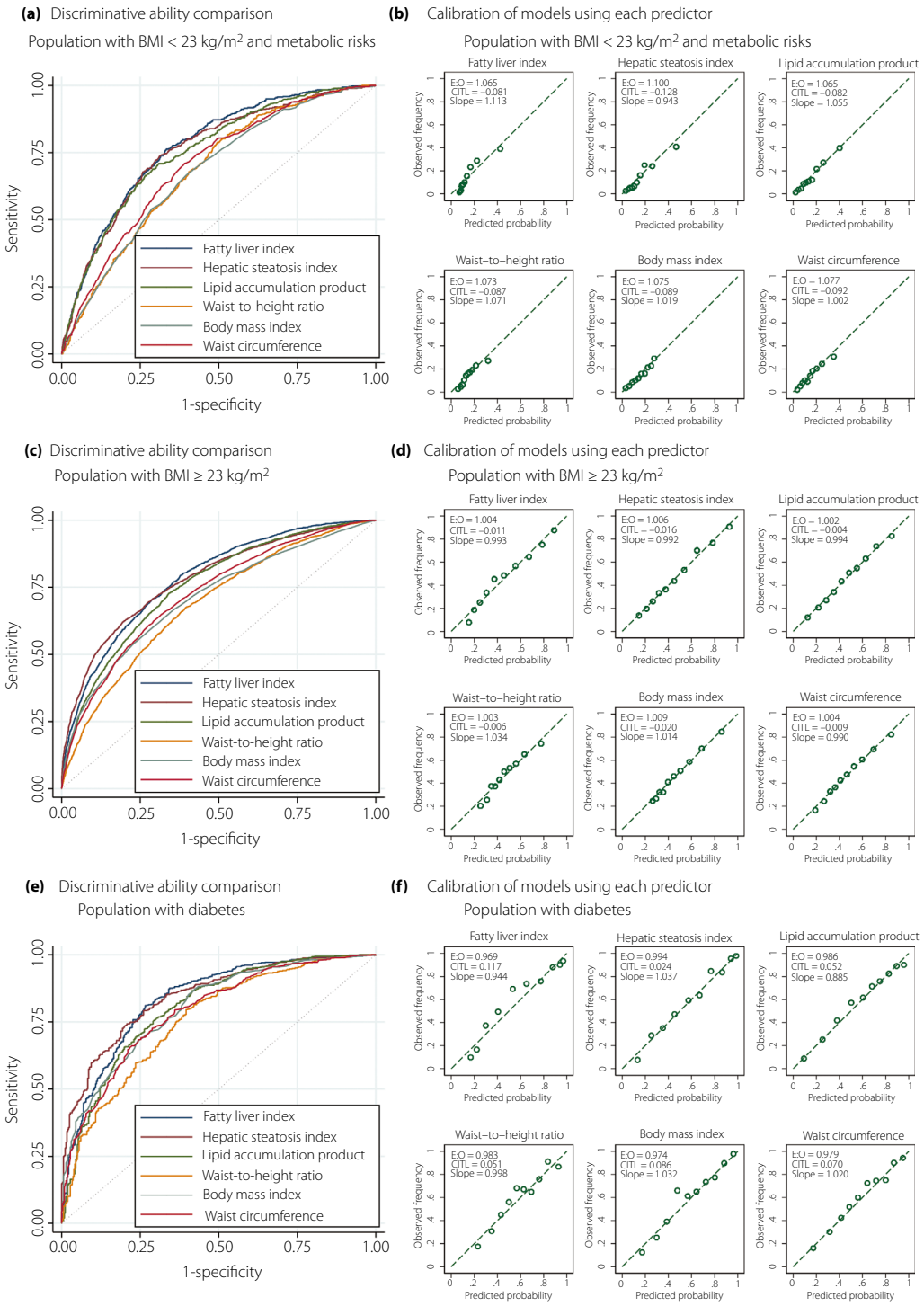

Figure 3 | Receiver operating characteristic curves and calibration plots of predictive models using the fatty liver index, hepatic steatosis index, lipid accumulation product, waist-to-height ratio, body mass index, and waist circumference for predicting MAFLD among each type of the population at risk for MAFLD: the population with body mass index <23 kg/m^2 and metabolic risks, the population with body mass index ≥23 kg/m^2, and the population with diabetes. (a) Receiver operating characteristic curves showing discriminative abilities among the population with body mass index <23 kg/m^2 and metabolic risks. (b) Calibration plots of the predictive models among the population with body mass index <23 kg/m^2 and metabolic risks. (c) Receiver operating characteristic curves showing discriminative abilities among the population with body mass index ≥23 kg/m^2. (d) Calibration plots of the predictive models among the population with body mass index ≥23 kg/m^2. (e) Receiver operating characteristic curves showing discriminative abilities among the population with diabetes. (f) Calibration plots of the predictive models among the population with diabetes. CITL, calibration in the large index; E:O, expected probability vs observed frequency ratio; slope, calibration slope.

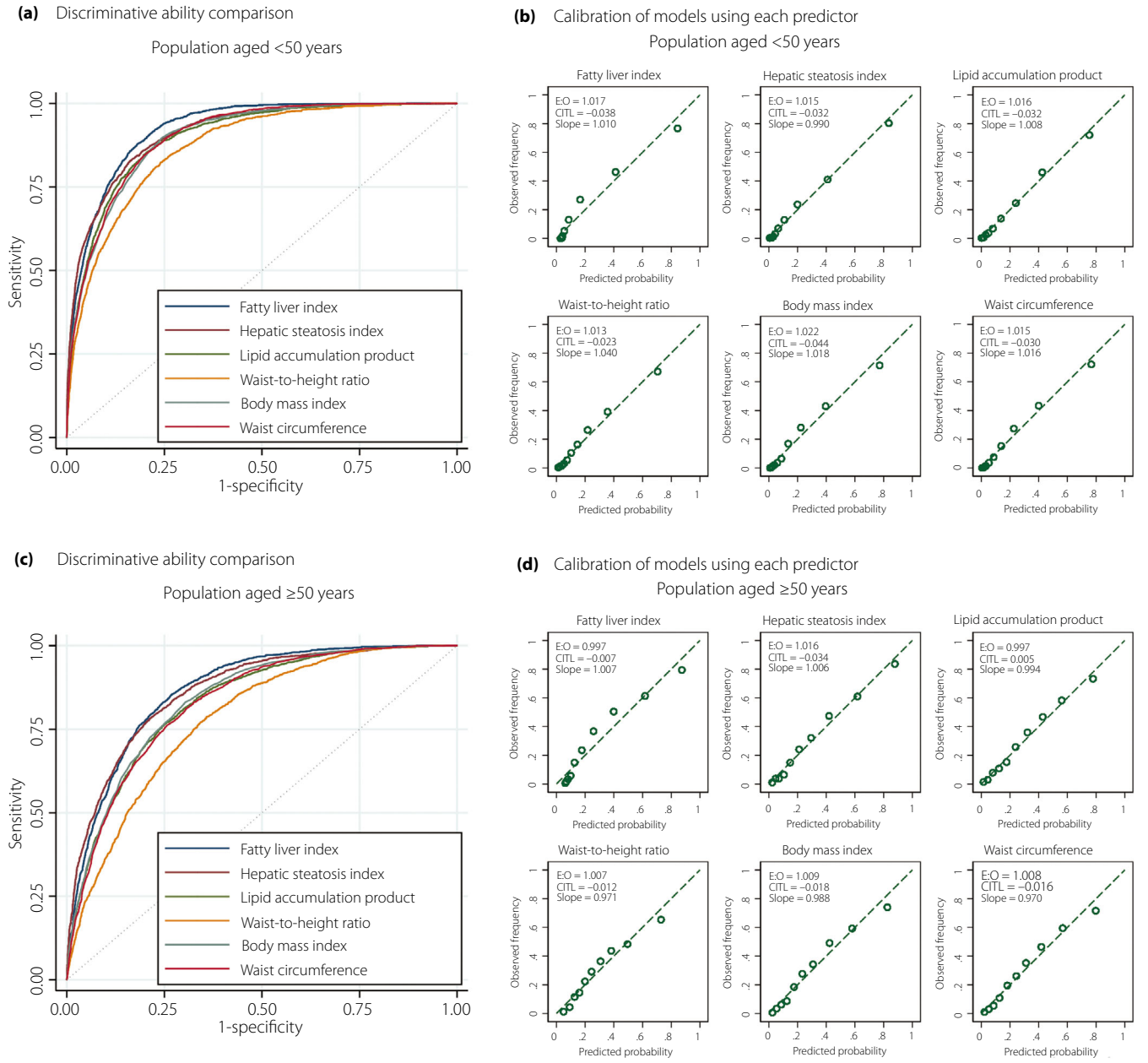

Figure 4 | Receiver operating characteristic curves and calibration plots of predictive models using the fatty liver index, hepatic steatosis index, lipid accumulation product, waist-to-height ratio, body mass index, and waist circumference for predicting MAFLD among participants aged <50 years or aged ≥50 years. (a) Receiver operating characteristic curves showing discriminative abilities among participants aged <50 years. (b) Calibration plots of the predictive models among participants aged <50 years. (c) Receiver operating characteristic curves showing discriminative abilities among participants aged ≥50 years. (d) Calibration plots of the predictive models among participants aged ≥50 years. CITL, calibration in the large index; E:O, expected probability vs observed frequency ratio; slope, calibration slope.

obtained during annual checkups, mostly consisting of individuals attending compulsory checkups that they are legally obliged to do in Japan. Thus, the population examined reflects the general population of Japan. Second, we described the diagnostic abilities of as many as six markers previously considered useful in diagnosing MAFLD. In addition, we used a dataset obtained from a large checkup center in Japan; therefore, the measurements from the sample assays were standardized.

Our study has several limitations. First, although ultrasonography is commonly used as a diagnostic method for MAFLD, liver pathology was not confirmed because data were not available. Furthermore, we did not assess the severity of hepatic

Table 7 | Summary of discriminative parameters for metabolic-associated fatty liver disease in an age-stratified analysis among whole people

Population	Marker	*C*-statistics	95% confidence interval	Optimal cut-off	Sensitivity (%)	Specificity (%)	LR+	LR−	DOR	PPV (%)	NPV (%)	Kappa
People aged <50 years	FLI	0.925	0.920–0.931	20.3	88.0	81.9	4.85	0.146	33.1	50.0	97.1	0.537
	HSI	0.913	0.907–0.920	33.4	82.8	84.0	5.16	0.205	25.1	51.5	95.9	0.538
	LAP	0.900	0.893–0.907	19.6	85.3	79.8	4.22	0.184	22.9	46.5	96.3	0.489
	WHR	0.871	0.864–0.879	0.48	82.4	76.0	3.44	0.232	14.8	41.4	95.4	0.420
	BMI	0.900	0.893–0.906	22.9	90.4	74.7	3.58	0.128	28.0	42.4	97.4	0.450
	WC	0.902	0.896–0.909	82.1	84.8	79.9	4.21	0.190	22.2	46.4	96.2	0.487
People aged ≥50 years	FLI	0.869	0.860–0.877	21.7	85.5	73.1	3.18	0.199	16.0	54.9	92.9	0.500
	HSI	0.865	0.855–0.874	32.6	78.8	78.2	3.61	0.271	13.3	58.0	90.6	0.513
	LAP	0.832	0.821–0.842	24.8	75.9	75.7	3.12	0.318	9.8	54.5	89.1	0.460
	WHR	0.781	0.770–0.793	0.50	78.7	64.3	2.20	0.332	6.6	45.8	88.7	0.352
	BMI	0.839	0.829–0.849	23.0	83.9	68.2	2.64	0.236	11.2	50.3	91.7	0.433
	WC	0.829	0.819–0.840	83.0	82.5	67.8	2.56	0.258	9.9	49.6	91.0	0.418

The optimal cut-off was calculated based on the best Youden index. BMI, body mass index; DOR, diagnostic odds ratio; FLI, fatty liver index; HSI, hepatic steatosis index; Kappa, kappa coefficient; LAP, lipid accumulation product; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; WC, waist circumference; WHR, waist-to-height ratio.

steatosis in patients with MAFLD because of a lack of histological data. Third, because there was no information about the homeostasis model assessment of the insulin resistance score, there might have been misclassifications. Finally, we did not perform preparation of a new predictive model using existing markers because our study aimed to examine the usefulness of existing markers for fatty liver in diagnosing MAFLD. Further studies should be conducted to address these issues.

In conclusion, this retrospective cross-sectional study, using data obtained from participants in a large-scale checkup center, revealed that all fatty liver and metabolic markers are excellent predictors for MAFLD among the general population, and that especially, FLI and HSI are stable predictors for MAFLD in all sub-population analyses. These markers may be useful for predicting the presence of MAFLD in daily clinical practice.

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DISCLOSURES

A.O., S.Y., K.I.K., and T.K. are members of the Department of Prevention of Diabetes and Lifestyle-related Diseases, a cooperative program between the University of Tokyo and the Asahi Mutual Life Insurance Company. K.I.K. was previously employed by Asahi Mutual Life Insurance Company. This affiliation has no role in the preparation of the manuscript.

Approval of the research protocol: This study was approved by the Institutional Review Board of the University of Tokyo (no. 2020264NI) and St. Luke's International Hospital (no. 20-R184).

Informed consent: The analyses performed in this study involved the secondary use of data obtained from the database of St Luke's Health Checkup, and the participants were provided with the option to withdraw consent for the use of their records for research.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Calibration curves with lowess smoothers.

Figure S2 | Flowchart for subgroup analysis.