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Comparison of noninvasive scoring systems for the prediction of nonalcoholic fatty liver disease in metabolic syndrome patients

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Abstract

Over half of metabolic syndrome (MetS) patients have nonalcoholic fatty liver disease (NAFLD). To prevent its complications, standard routine screening is required, but the human-resource and budgetary implications need to be taken into consideration. This study compared the performances of 4 noninvasive scoring systems in predicting NAFLD in MetS patients. They were the fatty liver index, hepatic steatosis index, lipid accumulation product index, and nonalcoholic fatty liver disease in metabolic syndrome patients scoring system (NAFLD-MS).

Scores were determined for 499 MetS patients, including 249 patients in a type 2 diabetes mellitus (T2DM) subgroup. Ultrasonography was used to diagnose NAFLD. The accuracies and performance of the scoring systems were analyzed using published cutoff values, and comparisons were made of their areas under receiver operating characteristic curves, sensitivities, specificities, positive and negative predictive values, and likelihood ratios.

NAFLD was detected in 68% of the MetS patients and 77% of the MetS patients with T2DM. According to the areas under receiver operating characteristic curves, fatty liver index and hepatic steatosis index provided better performances in predicting NAFLD. NAFLD-MS provided the highest specificity of 99% among the MetS patients as a whole, and it provided even better accuracy with similar performance when applied to the subgroup of MetS patients with T2DM. The maximum cost avoidance from unnecessary ultrasonography was also reported by using NAFLD-MS. In terms of simplicity and ease of calculation, the lipid accumulation product index and NAFLD-MS are preferred.

All 4 scoring systems proved to be acceptable for predicting NAFLD among MetS and T2DM patients in settings where the availability of ultrasonography is limited. NAFLD-MS provided the highest specificity and cost avoidance, and it is simple to use. All 4 systems can help clinicians decide further investigations.

Abbreviations: AuROC = area under the receiver operating characteristic curve, BMI = body mass index, CI = confidence interval, FLI = fatty liver index, GGT = gamma-glutamyl transpeptidase, HSI = hepatic steatosis index, IFG = impaired fasting glucose, LAP = lipid accumulation product, MetS = metabolic syndrome, NAFLD = nonalcoholic fatty liver disease, NAFLD-MS = nonalcoholic fatty liver disease in metabolic syndrome patients scoring system, NPV = negative predictive value, PPV = positive predictive value, SD = standard deviation, T2DM = type 2 diabetes mellitus, USD = United States Dollar.

Keywords: metabolic syndrome, nonalcoholic fatty liver disease, noninvasive, risk score, sensitivity, type 2 diabetes mellitus

Editor: Xichan Hu.

This work was presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2019, Denmark on November 5, 2019.

The protocol for this study was approved by the Siriraj Institutional Review Board (SiRB) (COA no. Si 540/2011). Written consent was obtained from all participants in the study.

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

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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How to cite this article: Saokaew S, Kositamongkol C, Charatcharoenwitthaya P, Srivanichakorn W, Washirasaksiri C, Chaiyakunapruk N, Phisalprapa P. Comparison of noninvasive scoring systems for the prediction of nonalcoholic fatty liver disease in metabolic syndrome patients. Medicine 2020;99:50(e23619).

Received: 10 August 2020 / Received in final form: 3 November 2020 / Accepted: 10 November 2020

http://dx.doi.org/10.1097/MD.0000000000023619

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the common chronic diseases, with a prevalence in the general population of about 20% to 35%. The incidence of NAFLD is rising because of the increasing prevalence of metabolic syndrome (MetS).[1,2] However, its rates are not precisely defined because NAFLD patients may exhibit no clinical or laboratory abnormalities until the disease has progressed to more severe states, such as nonalcoholic steatohepatitis and cirrhosis.[1,3,4] The estimated liver-specific mortality incidence is higher for NAFLD patients than the general population. The reported incidence rate ratio was 1.94 [95% confidence intervals (CI): 1.28–2.92].[5] Hepatocellular carcinoma is one of the serious sequelae of NAFLD,[3,6] with an incidence among NAFLD patients of 0.44 per 1000 person-years.[5]

Currently, there is no recommendation for routine NAFLD screening in the general population via liver function tests, ultrasonography, or a scoring system.[6,7] NAFLD is more common among MetS and type 2 diabetes mellitus (T2DM) patients,[8,9] with a reported prevalence of up to 68% to 87%.[10,11] Recently, a panel of international experts from many countries raised the awareness of underdiagnosed liver disease associated with known metabolic dysfunction in real world practice. They have proposed a new and more specific term: "metabolic dysfunction-associated fatty liver disease." The diagnosis of metabolic dysfunction-associated fatty liver disease is based on evidence of hepatic steatosis (the recommended diagnostic method is ultrasonography), in addition to being overweight or obese, having T2DM, or evidence of metabolic dysregulation.[2,4] Awareness and early diagnosis of the disease are necessary to prevent complications, especially in high-risk groups. However, the financial and human-resource burdens of any screening strategy should be considered. Although a model-based study in Thailand reported that ultrasonography screening for NAFLD among MetS patients is cost-effective,[12] its real world application is still limited.

The European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity (EASL-EASD-EASO) 2016 guidelines recommend that high-risk patients (ie, those with obesity or MetS) should undergo routine screening for NAFLD by liver function test and/or ultrasound.[3] This contrasts with the 2018 guidance of the American Association for the Study of Liver Diseases (AASLD), which does not suggest routine screening for NAFLD in high-risk groups because of uncertainties surrounding the diagnostic tests and treatment options, along with a lack of knowledge of the long-term benefits and cost-effectiveness of screening.[7] Moreover, routine ultrasonography is still a burden to the healthcare systems of many countries.[6,8] Given this controversy, many algorithms have been developed to predict the presence of NAFLD as well as reduce the burden of disease investigation. Most of the algorithms are based on simple parameters that are commonly measured in general healthcare practice.[13,14] The outcome of each algorithm is reported as a score, with higher scores indicating a greater risk of having NAFLD. The fatty liver index (FLI), lipid accumulation product (LAP) index, and hepatic steatosis index (HSI) have been proposed as tools to predict NAFLD in the general population.[13] These 3 algorithms were originally developed in different parts of the world. Although they have been used in several different study populations,[13,14] there have been no reports on their accuracy and performance in detecting NAFLD among high-risk populations, such as MetS patients. Thus, this study aimed to compare the accuracy and performance of these noninvasive algorithms in the prediction of NAFLD among MetS patients. Additionally, the nonalcoholic fatty liver prediction scoring system disease in MetS patients, called nonalcoholic fatty liver disease in metabolic syndrome patients scoring system (NAFLD-MS), that had previously been developed to detect NAFLD in Thai MetS patients[11] was included to compare its accuracy with those of the 3 scoring systems.

2. Methods

2.1. Study population

The targeted population consisted of patients with MetS. We used the standard diagnostic criteria to identify MetS patients before including them in our study.[3,15] Between January and December 2011, MetS patients were enrolled at Siriraj Hospital, the largest university hospital in Thailand. The selected patients were subgrouped into a T2DM group to further evaluate the performance of the noninvasive scoring systems in predicting NAFLD for this specific group of patients. The T2DM group comprised patients who had been prescribed antidiabetic drugs and diagnosed using the American Diabetes Association criteria (a fasting plasma glucose level of $\geq$126 mg/dL, an HbA1c of $\geq$6.5%, or a 2-hour plasma glucose level of $\geq$200 mg/dL during a 75-gram oral glucose tolerance test).[16]

2.2. Data collection

Certificated research assistants collected details of the patients' demographics and all relevant clinical and laboratory data were reviewed from electronic medical charts within the period between before and after 3 months of NAFLD assessment. All laboratory procedures were performed using standard techniques. Physical examinations and laboratory result interpretations were undertaken by hepatologists. Those patients with any missing data that required for the score calculations were, then, excluded.

2.3. Assessment of nonalcoholic fatty liver disease

While the present gold standard for diagnosing NAFLD is a liver biopsy, it is an invasive and costly method which has the potential to lead to serious complications.[8,17] It is therefore not practical to use for NAFLD screening patients without clinical symptoms.[8] Thus, we used ultrasonography as the method for diagnosing NAFLD in our subjects. To differentiate NAFLD from other liver diseases, we first excluded patients with any etiology that identified diseases such as excessive alcohol consumption and viral hepatitis.[3] Ultrasonography was performed and independently interpreted by 2 radiologists. Each result was reported as a "bright liver score," which ranged from 0 to 3; NAFLD was considered absent in patients whose score was 0, whereas a score of 1 to 3 indicated the presence of NAFLD.[18,19] Any conflict in the results of the 2 radiologists was resolved through consensus-based discussion.

2.4. Noninvasive scores for predicting nonalcoholic fatty liver disease

Four, noninvasive scoring systems were utilized for the detection of NAFLD: FLI[20]; LAP index[21–23]; HSI[24]; and NAFLD-MS.[11]

Table 1

Noninvasive scores for the prediction of nonalcoholic fatty liver disease.

Scores	Formulas	Parameters (unit)	Cutoff values	References
Fatty liver index (FLI)	$(e^{0.953 * \text{Log}_e(\text{TG}) + 0.139 * \text{BMI} + 0.718 * \text{Log}_e(\text{GGT}) + 0.053 * \text{WC} - 15.745})/(1 + e^{0.953 * \text{Log}_e(\text{TG}) + 0.139 * \text{BMI} + 0.718 * \text{Log}_e(\text{GGT}) + 0.053 * \text{WC} - 15.745}) * 100$	BMI (kg/m^2) WC (cm) TG (mg/dL) GGT (U/L)	<30 absence of NAFLD ≥60 presence of NAFLD	Bedogni et al[20]
Lipid accumulation product (LAP) index	Male: (WC - 65) * TG Female: (WC - 58) * TG	Gender WC (cm) TG (mg/dL)	Male >30.5 presence of NAFLD Female >23.0 presence of NAFLD	Kahn et al[21] Bedogni et al[22] Dai et al[23]
Hepatic steatosis index (HSI)	8 * ALT/AST ratio + BMI + T2DM (yes = 2, no = 0) + female (yes = 2, no = 0)	Gender history of T2DM BMI (kg/m^2) AST (U/L) ALT (U/L)	<30 absence of NAFLD >36 presence of NAFLD	Lee et al[24]
NAFLD-MS score	ALT ≥ 40 U/L (yes = 2, no = 0) AST/ALT ratio ≥ 1 (yes = 1, no = 0) BMI ≥ 25 (yes = 1.5, no = 0) WHR (≥ 0.9 in male and ≥ 0.8 in female; yes = 1, no = 0) T2DM (yes = 1, no = 0)	Gender ALT (U/L) AST-to-ALT ratio BMI (kg/m^2) WHR history of T2DM	<3 absence of NAFLD ≥ 5 presence of NAFLD	Saokaew et al[11]

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = γ-glutamyl-transpeptidase, NAFLD = nonalcoholic fatty liver disease, T2DM = type 2 diabetes mellitus, TG = triglyceride, WC = waist circumference, WHR = waist-to-hip ratio.

The details of those scores and the cutoff values used to interpret the outcomes are presented in Table 1. As the FLI, HSI, and NAFLD-MS scores had 2 (high and low) cutoff values to identify the absence and presence of NAFLD, we calculated the predictive performances of the scores from both the high and low cutoff values. The accuracies of the scores were presented and compared by using area under the receiver operating characteristic (AuROC) curves. The higher AuROC curves indicated higher accuracies of the scores for NAFLD prediction. Since the calculations of the predictive scores were done after the bright liver scores obtained from ultrasonography were reported, we consider that the interpreters of the reference standard tests were blinded to the results of the predictive scores. Cost calculations were subsequently performed to compare the cost avoidance from unnecessary ultrasonography of each scoring system. All costs were based on Thai standard cost lists for Health Technology Assessment,[25] and they were reported in 2019 United States dollars (USD) using the consumer price index[26] (31 Thai Baht = 1 USD).

2.5. Statistical analysis

We conducted all statistical analyses using Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX). The categorical data are reported as number (percentage), while the continuous data are presented as mean ± standard deviation (SD). Continuous data that displayed a skewed distribution are reported as median (interquartile range). The performances of the scores are presented as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, along with 95% CI, and AuROC curve ± standard error. A statistically significant difference was set at $P < .05$ (2-tailed).

2.6. Ethics approval

Before the data collection process began, the study was approved by the Institutional Review Board of Siriraj Hospital where the study was conducted (certificate of approval: Si 540/2011). All participants received information on the study and informed-consent sheets were signed.

3. Results

3.1. General characteristics of patients

The study recruited 499 MetS patients who had all of the data required for the score calculations (see Figure S1, Supplemental Digital Content 1, http://links.lww.com/MD/F343, which illustrates STARD diagram reports flow of MetS patients through the study). Half of the patients had T2DM (n = 249) (see Figure S2, Supplemental Digital Content 2, http://links.lww.com/MD/F344, which illustrates STARD diagram reports flow of MetS patients with T2DM through the study). The proportion of patients with NAFLD among the T2DM subgroup (77%) was higher than the corresponding figure of 68% for the total MetS patients (ie, those with and without T2DM). The prevalence of NAFLD among male and female MetS patients was 66% and 69%, respectively. The general characteristics of the total MetS patients and the T2DM subgroup are listed in Table 2 and Table 3, respectively.

3.2. Predictive performance of scores for metabolic syndrome patients and T2DM subgroup

According to the AuROC curves, the most accurate prediction score for NAFLD among both the MetS patients and the T2DM subgroup was provided by HSI. The AuROC curves of HSI, FLI, LAP index, and NAFLD-MS for the prediction of NAFLD among the MetS patients were 0.7504, 0.7261, 0.7173, and 0.6818, respectively (see Table 4 and Figure S3, Supplemental Digital Content 3, http://links.lww.com/MD/F345, which illustrates ROC curves of the FLI, LAP, HSI, and NAFLD-MS scoring systems for the prediction of NAFLD among MetS patients, using ultrasonography as a reference). The only AuROC curves among MetS patients that showed statistical differences were between

Table 2

General characteristics of the metabolic syndrome patients.

Characteristics	All patients (n = 499)	No NAFLD (n = 161, 32.26%)	NAFLD (n = 338, 67.74%)
Age (years)	61.07 ± 10.83	64.34 ± 9.93	59.52 ± 10.91
Gender (female)	273 (54.71%)	84 (52.17%)	189 (55.92%)
Weight (kg)	70.01 ± 13.65	65.04 ± 11.77	72.37 ± 13.86
BMI (kg/m^2)	27.11 ± 4.36	25.42 ± 3.83	27.92 ± 4.38
BMI ≥ 25 kg/m^2	329 (65.93%)	76 (47.20%)	253 (74.85%)
Waist circumference (cm)	93.19 ± 10.57	89.16 ± 10.21	95.11 ± 10.21
Waist-to-hip ratio	0.93 ± 0.07	0.91 ± 0.08	0.94 ± 0.07
Central obesity	442 (88.58%)	127 (78.88%)	315 (93.20%)
WHR ≥ 0.9 in male	189 (83.63%)	56 (72.73%)	133 (89.26%)
WHR ≥ 0.8 in female	253 (92.67%)	71 (84.52%)	182 (96.30%)
FPG (mg/dL), mean ± SD	122.90 ± 40.80	111.92 ± 32.64	128.12 ± 43.24
Median (IQR)	111.00 (100.00–133.00)	104.00 (97.00–117.00)	114.00 (101.00–143.00)
HbA1c (%)	6.63 ± 1.71	6.31 ± 1.08	6.78 ± 1.18
IFG	156 (31.26%)	58 (36.02%)	98 (28.99%)
T2DM	249 (49.90%)	58 (36.02%)	191 (56.51%)
IFG or T2DM	405 (81.16%)	116 (72.05%)	289 (85.50%)
Total cholesterol (mg/dL)	179.24 ± 38.45	178.75 ± 39.00	179.48 ± 38.45
Triglyceride (mg/dL)	141.60 ± 93.60	116.76 ± 65.25	153.43 ± 102.42
HDL-C (mg/dL)	53.05 ± 14.52	57.02 ± 16.73	51.16 ± 12.95
Male	48.25 ± 12.41	49.10 ± 12.40	47.80 ± 12.43
Female	57.03 ± 15.00	64.27 ± 16.96	53.81 ± 12.76
LDL-C (mg/dL)	98.55 ± 33.57	98.92 ± 33.82	98.37 ± 33.50
Dyslipidemia	474 (94.99%)	154 (95.65%)	320 (94.67%)
Hypertension	450 (90.18%)	143 (88.82%)	307 (90.83%)
AST (U/L)	24.94 ± 12.17	21.84 ± 8.03	26.41 ± 13.47
ALT (U/L)	27.01 ± 20.21	18.85 ± 10.55	30.90 ± 22.44
ALT ≥ 40 U/L	78 (15.63%)	3 (1.86%)	75 (22.19%)
AST/ALT	1.09 ± 0.40	1.27 ± 0.40	1.00 ± 0.36
AST/ALT ≥ 1	280 (56.11%)	126 (78.26%)	154 (45.56%)
GGT (U/L)	45.20 ± 49.07	34.57 ± 39.17	50.27 ± 52.44

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = γ-glutamyl-transpeptidase, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, IFG = impaired fasting glucose, IQR = interquartile range, LDL-C = low-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, SD = standard deviation, T2DM = type 2 diabetes mellitus, WHR = waist-to-hip ratio.

Table 3

General characteristics of the type 2 diabetes mellitus subgroup patients.

Characteristics	T2DM (n = 249)	T2DM without NAFLD (n = 58, 23.29%)	T2DM with NAFLD (n = 191, 76.71%)
Age (years)	61.38 ± 11.14	67.30 ± 8.65	59.59 ± 11.21
Gender (female)	132 (53.01%)	26 (44.83%)	106 (55.50%)
Weight (kg)	71.19 ± 14.82	64.25 ± 11.54	73.29 ± 15.09
BMI (kg/m^2)	27.41 ± 4.65	25.21 ± 3.63	28.08 ± 4.72
BMI ≥ 25 kg/m^2	166 (66.67%)	24 (41.38%)	142 (74.35%)
Waist circumference (cm)	94.86 ± 10.62	90.40 ± 9.13	96.21 ± 10.69
Waist-to-hip ratio	0.94 ± 0.07	0.93 ± 0.08	0.95 ± 0.07
Central obesity	227 (91.16%)	48 (82.76%)	179 (93.72%)
WHR ≥ 0.9 in male	100 (85.46%)	24 (75.00%)	76 (89.41%)
WHR ≥ 0.8 in female	127 (96.21%)	24 (92.31%)	103 (97.17%)
FPG (mg/dL), mean ± SD	144.33 ± 48.46	130.45 ± 48.07	148.54 ± 47.90
Median (IQR)	133.00 (116.50–158.50)	119.00 (102.75–142.75)	137.00 (120.00–163.00)
HbA1c (%)	7.28 ± 1.34	7.00 ± 1.55	7.37 ± 1.26
Total cholesterol (mg/dL)	171.67 ± 34.78	166.50 ± 27.11	173.24 ± 36.71
Triglyceride (mg/dL)	146.80 ± 81.22	123.79 ± 81.19	153.79 ± 80.15
HDL-C (mg/dL)	51.49 ± 13.98	53.72 ± 16.11	50.81 ± 13.24
Male	48.74 ± 13.56	49.06 ± 13.46	48.62 ± 13.67
Female	53.92 ± 13.95	59.46 ± 17.47	52.57 ± 12.67
LDL-C (mg/dL)	91.18 ± 31.38	87.71 ± 21.74	92.24 ± 33.75
Dyslipidemia	238 (95.58%)	56 (96.55%)	182 (95.29%)
Hypertension	226 (90.76%)	52 (89.66%)	174 (91.10%)
AST (U/L)	25.42 ± 12.78	22.62 ± 11.45	26.27 ± 13.07
ALT (U/L)	29.12 ± 22.73	20.12 ± 14.82	31.85 ± 24.00
ALT ≥ 40 U/L	45 (18.07%)	2 (3.45%)	43 (22.51%)
AST/ALT	1.04 ± 0.39	1.25 ± 0.40	0.98 ± 0.37
AST/ALT ≥ 1	123 (49.40%)	41 (70.69%)	82 (42.93%)
GGT (U/L)	49.61 ± 53.99	33.17 ± 33.05	54.60 ± 58.04

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = γ-glutamyl-transpeptidase, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, IFG = impaired fasting glucose, IQR = interquartile range, LDL-C = low-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, SD = standard deviation, T2DM = type 2 diabetes mellitus, WHR = waist-to-hip ratio.

Table 4

Performance of the noninvasive scoring systems in predicting nonalcoholic fatty liver disease among the metabolic syndrome patients (n = 499), according to the systems' cutoff values.

Predictive performance	Scores' cutoff values	FLI (95% CI)	LAP index (95% CI)	HSI (95% CI)	NAFLD-MS (95% CI)
AuROC ± SE	—	0.726 ± 0.024	0.717 ± 0.025	0.750 ± 0.023	0.682 ± 0.024
Sensitivity (%)	Scores indicating low risk of NAFLD	47.2 (39.3–55.2)	40.4 (32.7–48.4)	19.9 (14.0–26.9)	46.0 (38.1–54.0)
Specificity (%)		82.8 (78.4–86.7)	88.5 (84.6–91.7)	96.2 (93.5–97.9)	69.8 (64.6–74.7)
PPV (%)		56.7 (47.9–65.2)	62.5 (52.5–71.8)	71.1 (55.7–83.6)	42.0 (34.7–49.7)
NPV (%)		76.7 (72.0–81.0)	75.7 (71.2–79.8)	71.6 (67.2–75.7)	73.1 (67.9–77.8)
Likelihood ratio (+)		2.75 (2.07–3.66)	3.50 (2.47–4.96)	5.17 (2.79–9.57)	1.52 (1.21–1.92)
Likelihood ratio (−)		0.64 (0.55–0.74)	0.67 (0.59–0.77)	0.83 (0.77–0.90)	0.77 (0.77–0.66)
Sensitivity (%)	Scores indicating high risk of NAFLD	48.2 (42.8–53.7)	88.5 (84.6–91.7)	67.8 (65.2–72.7)	13.3 (9.9–17.4)
Specificity (%)		80.7 (73.8–86.5)	40.4 (32.7–48.4)	70.2 (62.5–77.1)	99.4 (96.6–100.0)
PPV (%)		84.0 (78.1–88.9)	75.7 (71.2–79.8)	82.7 (77.7–86.9)	97.8 (88.5–99.9)
NPV (%)		42.6 (37.0–48.4)	62.5 (52.2–71.8)	50.9 (44.1–57.7)	35.3 (30.9–39.9)
Likelihood ratio (+)		2.50 (1.79–3.50)	1.48 (1.30–1.69)	2.27 (1.77–2.91)	21.43 (2.98–154.12)
Likelihood ratio (−)		0.64 (0.56–0.73)	0.29 (0.20–0.41)	0.46 (0.38–0.55)	0.87 (0.84–0.91)

AuROC = area the receiver operating characteristic curve, CI = confidence interval, FLI = fatty liver index, HSI = hepatic steatosis index, LAP = lipid accumulation product, NAFLD = nonalcoholic fatty liver disease, NPV = negative predictive value, PPV = positive predictive value, SE = standard error.

the HSI and NAFLD-MS scores ($P = .003$) (see Table S1, Supplemental Digital Content 5, http://links.lww.com/MD/F347, which illustrates pairwise comparison of the AuROC curves of the FLI, LAP, HSI, and NAFLD-MS scoring systems for the prediction of NAFLD among MetS patients). However, the NAFLD-MS score was the best for identifying a true-negative person: one whose score is below 5, which can be interpreted as an absence of NAFLD with a specificity of 99%. Patients with NAFLD were more likely to have scores of 5 or higher, with a positive likelihood ratio of 21.43. Cross-tabulation of the number of patients by the results of each scoring system and ultrasonography diagnosed NAFLD among MetS patients are shown in Supplemental Table S2 to S5 (see Supplemental Table S2–S5, Supplemental Digital Content 6, http://links.lww.com/MD/F348, which illustrates cross-tabulation of the number of patients by the results of each scoring system and ultrasonography diagnosed NAFLD among MetS patients).

Similar predictive performance results were obtained when the scoring systems were applied to the T2DM subgroup (Table 5). However, most of the scoring systems tended to have a higher accuracy in predicting NAFLD among the T2DM patients due to the higher prevalence of NAFLD in this group. The AuROC curves of HSI, FLI, LAP index, and NAFLD-MS for the prediction of NAFLD among the MetS patients with T2DM were 0.7709, 0.7454, 0.7171, and 0.6902, respectively (see Table 5 and Figure S4, Supplemental Digital Content 4, http://links.lww.com/MD/F346, which illustrates ROC curves of the FLI, LAP, HSI, and NAFLD-MS scoring systems for the prediction of NAFLD among MetS with T2DM, using ultrasonography as a reference). The only AuROC curves among T2DM subgroup that showed statistical differences were between the HSI and NAFLD-MS scores ($P = .017$) (see Table S6, Supplemental Digital Content 7, http://links.lww.com/MD/F349, which illustrates pairwise comparison of the AuROC curves of the FLI, LAP, HSI, and NAFLD-MS scoring systems for the prediction of NAFLD among MetS patients with T2DM). Moreover, the specificity of NAFLD-MS in detecting NAFLD remained the highest. Cross-tabulation of the number of patients by the results of each scoring system and ultrasonography diagnosed NAFLD among MetS patients with T2DM are shown

Table 5

Performance of the noninvasive scoring systems in predicting nonalcoholic fatty liver disease among the metabolic syndrome patients with type 2 diabetes mellitus (n = 249), according to the systems' cutoff values.

Predictive performance	Scores' cutoff values	FLI (95% CI)	LAP index (95% CI)	HSI (95% CI)	NAFLD-MS (95% CI)
AuROC ± SE	—	0.745 ± 0.035	0.717 ± 0.041	0.771 ± 0.034	0.690 ± 0.036
Sensitivity (%)	Scores indicating low risk of NAFLD	43.1 (30.2–56.8)	41.4 (28.6–55.1)	13.8 (6.1–25.4)	22.4 (12.5–35.3)
Specificity (%)		85.3 (79.5–90.0)	89.0 (83.7–93.1)	96.9 (93.3–98.8)	88.5 (83.1–92.6)
PPV (%)		47.2 (33.3–61.4)	53.3 (37.9–68.3)	57.1 (28.9–82.3)	37.1 (21.5–55.1)
NPV (%)		83.2 (77.2–88.1)	83.3 (77.5–88.2)	78.7 (72.9–83.8)	79.0 (72.9–84.2)
Likelihood ratio (+)		2.94 (1.87–4.62)	3.76 (2.27–6.25)	4.39 (1.59–12.14)	1.95 (1.05–3.62)
Likelihood ratio (−)		0.67 (0.53–0.84)	0.66 (0.53–0.82)	0.89 (0.80–0.99)	0.88 (0.76–1.02)
Sensitivity (%)	Scores indicating high risk of NAFLD	52.4 (45.0–59.6)	89.0 (83.7–93.1)	77.5 (70.9–83.2)	21.5 (15.9–28.0)
Specificity (%)		84.5 (72.6–92.7)	41.4 (28.6–55.1)	63.8 (50.1–76.0)	98.3 (90.8–100.0)
PPV (%)		91.7 (84.9–96.2)	83.3 (77.5–88.2)	87.6 (81.6–92.1)	97.6 (87.4–99.9)
NPV (%)		35.0 (27.1–43.5)	53.3 (37.9–68.3)	46.3 (35.0–57.8)	27.5 (21.6–34.2)
Likelihood ratio (+)		3.37 (1.82–6.24)	1.52 (1.22–1.90)	2.14 (1.51–3.04)	12.45 (1.75–88.55)
Likelihood ratio (−)		0.56 (0.47–0.68)	0.27 (0.16–0.44)	0.35 (0.25–0.49)	0.80 (0.74–0.87)

AuROC = area the receiver operating characteristic curve, CI = confidence interval, FLI = fatty liver index, HSI = hepatic steatosis index, LAP = lipid accumulation product, NAFLD = nonalcoholic fatty liver disease, NPV = negative predictive value, PPV = positive predictive value, SE = standard error.

in Supplemental Table S7 to S10 (see Supplemental Table S7–S10, Supplemental Digital Content 8, http://links.lww.com/MD/F350, which illustrates cross-tabulation of the number of patients by the results of each scoring system and ultrasonography diagnosed NAFLD among MetS patients with T2DM).

3.3. Cost comparison among scoring systems in unnecessary ultrasonography avoidance in metabolic syndrome patients

When the FLI, LAP index, HSI, and NAFLD-MS scores are used, ultrasonography could have been avoided in 61%, 21%, 44%, and 91% of the total cohort, respectively. In Thailand, the current unit cost of ultrasonography is approximately 33 USD, whereas the unit costs of aspartate aminotransferase, alanine aminotransferase, triglyceride, and gamma-glutamyl transpeptidase tests are 3, 3, 3, and 7 USD, respectively. If routine ultrasonography had been administered to all 499 MetS patients, the total cost would be 16,490 USD. After unnecessary ultrasonography is avoided, the total cost would be reduced to 11,225, 14,576, 11,673, and 4040 USD using the FLI, LAP index, HSI, and NAFLD-MS scores, respectively (see Table S11, Supplemental Digital Content 9, http://links.lww.com/MD/F351, which illustrates estimated number and costs of ultrasonography, with and without noninvasive scoring systems, to predict NAFLD).

4. Discussion

Our study established that all 4 scoring systems showed acceptable levels of accuracy for the detection of NAFLD in MetS patients. Moreover, the systems had an even better performance with the T2DM subgroup patients. Our findings indicated that the highest specificity was obtained with NAFLD-MS, which is a simple and inexpensive system. Nevertheless, the accuracies of all 4 scoring systems were lower than those reported by previous studies on the general population (an approximate AuROC value of 0.7 in the current study vs 0.8 in previous studies).[11,13,14] The parameters used to calculate the scores in the algorithms used by the 4 systems were waist circumference, body mass index (BMI), or both. In terms of central obesity, it is known that both waist circumference and BMI have ethnic-specific values.[27] The 2 parameters were included in the criteria for the diagnosis of MetS as well as the scoring systems' algorithms,[15] which might be the reason for the lower accuracy in detecting NAFLD among the Thai MetS patients. The LAP index was originally developed to predict cardiovascular risk in the US population.[21] However, it has since been additionally used to predict NAFLD in the Italian and Chinese general populations[22,23] and has been reported to be an acceptable algorithm for NAFLD prediction. In the case of FLI, it was first developed in Italy, and it has been subsequently used in several other populations.[14] As to HSI, it was originally developed using Korean subjects. The prevalence of NAFLD differs among ethnicities.[9] Thus, the eligible cutoff values should be reassessed when applying the scoring systems to different ethnic populations to optimize scoring performance.[24]

Although FLI might seem to provide a slightly higher accuracy than the LAP index and NAFLD-MS in predicting NAFLD, its algorithm is the most complex. Because of that complexity, FLI is not able to be calculated manually. Moreover, in addition to basic biochemistry laboratory results, calculation of the FLI requires the gamma-glutamyl transpeptidase value, which is expensive to obtain and uncommon in routine testing.[20] By comparison, the algorithm for the HSI draws on both continuous and categorical data, which are slightly more difficult to calculate.[24] As to the formula utilized by the LAP index, none of its parameters represents the liver function since the index was originally formulated to predict cardiovascular risk. Moreover, the formula and cutoff values are gender-specific, which may sometimes confuse users.[21]

A recent systematic review and meta-analysis reported that, in the general population, women had a lower risk of NAFLD than men [pooled risk ratio (RR), 0.81; 95% CI, 0.68–0.97; I^2, 97.5%].[28] According to our data, females had about a 3% higher prevalence of NAFLD than males. This correlated with the findings of a Thai population-based study which also found that the prevalence of NAFLD was higher among women than men.[29] In our present cohort, the patients had an average age of 61 years. This meant that most of the women were in the postmenopausal period, when there is a decline in estrogen and a resultant shift in adipose tissue deposition around the visceral organs. Several metabolic risk-associated sequelae, such as NAFLD, may have a greater effect among postmenopausal women.[30,31] In contrast, men tend to accumulate adipose tissue centrally throughout their lifetime.

Based on the differences in the AuROCs in the pairwise comparison analyses, statistical significance was noted only between the HSI and NAFLD-MS scores (see Table S1, Supplemental Digital Content 5, http://links.lww.com/MD/F347, and Table S6, Supplemental Digital Content 7, http://links.lww.com/MD/F349). The reason for the lower AuROC curve for NAFLD-MS might be associated with the characteristics of the algorithm. It consists of only binary variables, which results in a minimum difference between each score of 0.5 points and a maximum total score of 6.5 points. In comparison, the other scoring systems consist of continuous parameters; that feature results in more consecutive scores with no upper bounds. Nevertheless, NAFLD-MS yielded an acceptable AuROC and nearly a 100% specificity, and its simple binary variables made it easy to use. Other pairs of AuROC curves were not statistically different.

According to a previous population-based study in Khon Kaen in northeastern Thailand (the Cholangiocarcinoma Screening and Care Program), the reported prevalence of NAFLD was 21.9% (7584/34,709)[29]; this was much lower than the prevalence among the MetS patients in the current study. Also, the prevalence of NAFLD among the T2DM subgroup was lower in the previous research than in the current study (see Table S12, Supplemental Digital Content 10, http://links.lww.com/MD/F352, which illustrates participants' characteristics of both studies). This supports the fact that MetS patients have a higher risk of NAFLD than the general population. Still, our study was done at a university hospital, which might have influenced the apparent prevalence of NAFLD. As a result of using the calculated sensitivity and specificity to calculate the PPV and NPV in the Khon Kaen population, the values were dissimilar due to the differences in the prevalence of NAFLD (see Table S13 and Table S14, Supplemental Digital Content 10, http://links.lww.com/MD/F352, which illustrates calculated predictive performance among total participants and T2DM subgrouped patients, according to the scoring systems' cutoff values, indicating a high risk of NAFLD). Both the PPV and NPV of the NAFLD-MS scores in the overall Khon Kaen population exceeded 80%. In

that population, the highest PPV and NPV were revealed for NAFLD-MS and the LAP index, respectively. For the T2DM subgroup, however, the highest PPV and NPV values were delivered by the LAP index and NAFLD-MS, respectively.

Routine ultrasonography for NAFLD screening is not currently recommended for the general population, and its use within high-risk groups is still controversial because limited cost-effectiveness data are available.[3,7,8,32] Only 1 study from Thailand has demonstrated the cost-effectiveness of ultrasonography screening for NAFLD among MetS patients.[12] However, budgetary constraints, human resource limitations, and the high operator dependency of ultrasonography need to be taken into consideration. When the scoring systems are used, ultrasonography could be avoided for a number of patients, with the quantity depending on the particular scoring system. While NAFLD-MS appeared to have the highest cost avoidance, a full economic evaluation should be performed to confirm the findings. Moreover, liver function tests alone are insufficiently sensitive to detect NAFLD.[8] By applying any one of the 4 predictive scoring systems before sending patients for further investigation to confirm a diagnosis of NAFLD, 20% to 50% of MetS patients (depending on which scoring system is used) could avoid unnecessary ultrasonography. Thus, the overuse of ultrasonography would be reduced, and the number of individuals receiving early diagnosis and appropriate treatment would rise. This would benefit patients as well as reduce the financial burden for the healthcare system since the early detection of NAFLD prevents the development of more severe diseases and a consequential higher resource burden. Nowadays, lifestyle modification with significant weight reduction is the only evidence-based, management strategy for NAFLD.[8] Proper diet and exercise should therefore be recommended to patients in the early stages of NAFLD as the disease is reversible.[3,33]

Previous research has shown that NAFLD is more common among MetS and T2DM patients.[1,3,7,8] However, the investigation of the use of noninvasive scoring systems to predict NAFLD in MetS and T2DM patients has never been reported. The current study has several positive features. Firstly, as far as we know, it is the first to compare the accuracies and performance of the scoring systems when used with MetS patients and the T2DM subgroup. Furthermore, the study was undertaken at a well-known university hospital in Thailand which gathers patients from virtually throughout the nation. Moreover, all 4 scoring systems are practical for application in routine practice: their parameters are commonly collected, or are easy to collect, in most routine practice settings. This also means that the scoring systems do not require a large monetary investment. Lastly, this study estimated the cost of using each of the scoring systems to screen the cohort population. Even though the costing results need to be confirmed by a more complete economic evaluation, our costing information may still guide a clinician when selecting a cost-effective scoring system for an individual patient to avoid the cost of unnecessary ultrasonography.

However, there were some limitations to the present study. Firstly, an analysis of liver biopsy data—the gold standard for diagnosing NAFLD—was not undertaken; as with all healthcare institutions around the world, liver biopsies are not routinely performed at our hospital. Instead, we identified the presence of NAFLD in the subjects by using the ultrasonography results, a widely accepted method and recommended for NAFLD screening by the clinical practice guidelines of the European Association for the Study of the Liver.[3] In addition, we selected only scoring systems that could be used to assess the absence or presence of NAFLD, based on the parameters that would be collected from our included patients. Cytokeratin-18, which has been proposed as a serologic marker for the prediction of steatosis, was not included in this study[13] due to the absence of the related laboratory data. Another consideration is that the results from the 4 scoring systems should be interpreted with caution. Their scores can only be used to screen patients to identify those who need further investigation and early treatment.[11,14] Lastly, due to the scope of our study and the limited data, our subjects were limited to Asian MetS patients with an average BMI of 27 kg/m^2; the findings may therefore not be readily transferrable to the normal populations of other countries. However, given the variations in the prevalence of NAFLD in general populations, we attempted to represent the performance of each scoring system by calculating its PPV and NPV and using the prevalence from the population-based study undertaken in Khon Kaen, northeastern Thailand. The results proved acceptable.

In conclusion, even though a recommendation to routinely practice NAFLD screening in high-risk groups remains controversial, the cost and resource burdens on the healthcare system need to be considered. All 4 scoring systems were capable of predicting NAFLD among the MetS patients and the T2DM subgroup in settings where the availability of ultrasonography is limited. Our study results indicated that each scoring system had a higher degree of accuracy in predicting NAFLD for MetS patients with T2DM than for all MetS patients (ie, those with and without T2DM). NAFLD-MS, which is a simple system, provided the highest specificity and at the lowest cost, due to its avoidance of unnecessary ultrasonography. With appropriate cutoff values, all 4 scoring systems should help clinicians decide on the need for ultrasonography for MetS patients with suspected NAFLD. However, further work, including a cost-effectiveness analysis, is required to firmly conclude that there are indeed benefits through utilizing these scoring systems for NAFLD screening in routine practice.

Acknowledgments

The authors thank Miss Wimolrak Bandidniyamanon and Miss Pinyapat Ariyakunaphan, research assistants, for collecting the metabolic syndrome registry data. The authors gratefully thank David Park for language editing.

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References

[1] Fazel Y, Koenig AB, Sayiner M, et al. Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism 2016;65:1017–25.
[2] Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202–9.
[3] European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of ObesityEASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–402.
[4] Loomba R, Wong R, Fraysse J, et al. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. Aliment Pharmacol Ther 2020;51:1149–59.
[5] Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.
[6] Paul S, Davis AM. Diagnosis and management of nonalcoholic fatty liver disease. JAMA 2018;320:2474–5.
[7] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–57.
[8] Glen J, Floros L, Day C, et al. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance. BMJ 2016;354:i4428.
[9] Lonardo A, Bellentani S, et al. Non-alcoholic Fatty Liver Disease Study GroupEpidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups. Dig Liver Dis 2015;47:997–1006.
[10] Dai W, Ye L, Liu A, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a meta-analysis. Medicine (Baltimore) 2017;96:39(e8179).
[11] Saokaew S, Kanchanasuwan S, Apisarnthanarak P, et al. Clinical risk scoring for predicting non-alcoholic fatty liver disease in metabolic syndrome patients (NAFLD-MS score). Liver Int 2017;37:1535–43.
[12] Phisalprapa P, Supakankunti S, Charatcharoenwitthaya P, et al. Cost-effectiveness analysis of ultrasonography screening for nonalcoholic fatty liver disease in metabolic syndrome patients. Medicine 2017;96:17(e6585).
[13] Papagianni M, Sofogianni A, Tziomalos K. Non-invasive methods for the diagnosis of nonalcoholic fatty liver disease. World J Hepatol 2015;7:638–48.
[14] Machado MV, Cortez-Pinto H. Non-invasive diagnosis of non-alcoholic fatty liver disease. A critical appraisal. J Hepatol 2013;58:1007–19.
[15] Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.
[16] American Diabetes AssociationDiagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl 1):S62–9.
[17] Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA 2015;313:2263–73.
[18] Mathiesen UL, Franzen LE, Åselius H, et al. Increased liver echogenicity at ultrasound examination reflects degree of steatosis but not of fibrosis in asymptomatic patients with mild/moderate abnormalities of liver transaminases. Dig Liver Dis 2002;34:516–22.
[19] Catalano D, Trovato GM, Martines GF, et al. Bright liver, body composition and insulin resistance changes with nutritional intervention: a follow-up study. Liver Int 2008;28:1280–7.
[20] Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.
[21] Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. BMC Cardiovasc Disord 2005;5:26.
[22] Bedogni G, Kahn HS, Bellentani S, et al. A simple index of lipid overaccumulation is a good marker of liver steatosis. BMC Gastroenterol 2010;10:98.
[23] Dai H, Wang W, Chen R, et al. Lipid accumulation product is a powerful tool to predict non-alcoholic fatty liver disease in Chinese adults. Nutr Metab (Lond) 2017;14:49.
[24] Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42:503–8.
[25] Riewpaiboon A. Standard cost lists for health technology assessment. Nonthaburi: Health Intervention and Technology Assessment Program (HITAP); 2011. Available at: http://costingmenu.hitap.net/. Accessed May 16, 2019.
[26] Consumer Price index (CPI) of Thailand, Economic and Trade Indices Database (ETID) [Internet]. Bureau of Trade and Economic Indices, Ministry of Commerce 2017. Available at: http://www.price.moc.go.th. Accessed May 16, 2019.
[27] WHO Expert ConsultationAppropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
[28] Balakrishnan M, Patel P, Dunn-Valadez S, et al. Women have lower risk of nonalcoholic fatty liver disease but higher risk of progression vs men: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020; In press. doi: https://doi.org/10.1016/j.cgh.2020.04.067.
[29] Summart U, Thinkhamrop B, Chamadol N, et al. Gender differences in the prevalence of nonalcoholic fatty liver disease in the Northeast of Thailand: a population-based cross-sectional study. F1000Res 2017;6:1630. doi: 10.12688/f1000research.12417.2.
[30] Hallajzadeh J, Khoramdad M, Izadi N, et al. Metabolic syndrome and its components in premenopausal and postmenopausal women: a comprehensive systematic review and meta-analysis on observational studies. Menopause 2018;25:1155–64.
[31] Gurka MJ, Vishnu A, Santen RJ, et al. Progression of metabolic syndrome severity during the menopausal transition. J Am Heart Assoc 2016;5:e003609.
[32] Wieckowska A, Feldstein AE. Diagnosis of nonalcoholic fatty liver disease: invasive versus noninvasive. Semin Liver Dis 2008;28:386–95.
[33] Ofosu A, Ramai D, Reddy M. Non-alcoholic fatty liver disease: controlling an emerging epidemic, challenges, and future directions. Ann Gastroenterol 2018;31:288–95.