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Clinical predictive score for detecting nonalcoholic fatty liver disease with significant fibrosis in patients with metabolic syndrome

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Abstract

Patients with metabolic syndrome are at a higher risk of nonalcoholic fatty liver disease (NAFLD) and liver fibrosis than the general population. Still, accessibility of screening method for NAFLD with significant fibrosis, such as transient elastography (FibroScan) are limited in some settings. This study aimed to develop a simple clinical predictive score for detecting NAFLD with significant fibrosis in patients with metabolic syndrome.

A cross-sectional study was designed to obtain the data from medical records of all relevant patients who underwent transient elastography between January 2011 and December 2020 at Siriraj Hospital, Thailand. A liver stiffness cutoff value of 7.0 kilopascal was used to define the presence of significant liver fibrosis. To examine potential predictors, medical history and clinical data commonly assessed in routine practice were selected by following expert opinions and univariable statistical analysis. Backward and forward stepwise logistic regression was performed to acquire a final prediction model. To simplify the model, a weighted score was assigned for each categorized predictor. In addition, eligible cutoff values of the score and their predictive performances were determined.

A total of 745 medical records were reviewed. The prevalence of NAFLD with significant fibrosis in patients with metabolic syndrome was 12.6%. Most clinical characteristics of patients with NAFLD with significant fibrosis and those non-NAFLD and NAFLD with no/mild fibrosis were quite disparate. The most practical model comprised globulin, aspartate transaminase, platelet count, and type 2 diabetes. It provided a good predictive performance with an area under the receiver operating characteristic curve of 0.828 (95% confidence interval [CI]: 0.782, 0.874). At the proper cutoff value, sensitivity and specificity were 76.6% (95% CI: 66.7%, 84.7%) and 72.4% (95% CI: 68.7%, 75.8%), respectively. The likelihood ratio of testing positive for NAFLD with significant fibrosis was 2.8 (95% CI: 2.34, 3.27) among patients with scores above the cutoff value.

The first score for detecting of NAFLD with significant fibrosis in patients with metabolic syndrome was developed. This practical score, providing a good predictive performance, should be useful to help clinicians prioritize needs for further investigations among high-risk patients, especially in resource-limited settings.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, AuROC = area under the receiver operating characteristic curve, BMI = body mass index, CI = confidence interval, GGT = gamma-glutamyl transferase, kPa = kilopascal, NAFLD = nonalcoholic fatty liver disease.

Keywords: liver fibrosis, metabolic syndrome, nonalcoholic fatty liver disease, predictive score

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This study was approved by the Institutional Review Board of Siriraj Hospital, Faculty of Medicine Siriraj Hospital, Mahidol University (CoA number: Si 102/2021) and the Human Research Ethics Committee of Thammasat University (Medicine) (CoA number: 039/2021).

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

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most underdiagnosed conditions which leads to not only severe chronic liver disease but also non-liver related diseases.[1,2] It is the most common cause of chronic liver disease in western countries.[3] In Asian countries, a study from Korea reported the NAFLD prevalence of 31% in overall population versus 64% in patients with metabolic syndrome. Additionally, they indicated the NAFLD with metabolic risk factors incidence rate of 70 to 77 per 1000 person-years.[2] A strong association between NAFLD and metabolic syndrome is known, patients with metabolic syndrome are at a higher risk of NAFLD as well as liver fibrosis.[4–7] While patients with significant liver fibrosis were encountering a higher rate of long-term unfavorable clinical outcomes, such as overall mortality, liver transplantation, and liver-related events, than those without fibrosis,[8] most of them were asymptomatic.[9] Recently, the systematic review by Harris et al reported that liver fibrosis was detected in 1% to 26% of general population, depended on diagnostic method and criteria used.[9] Despite the increasing incidence of NAFLD and liver fibrosis, the best strategy for screening in a high-risk group of population is yet to be a consensus among international guidelines, mainly because of the varieties in healthcare system characteristic around the world and natural history of the disease itself.[3,5,6]

Besides, liver biopsy which is the gold standard procedure for NAFLD and liver fibrosis diagnosis, transient elastography is a promising noninvasive tool that provides benefit in detecting both hepatic steatosis and fibrosis in population at risk.[5,6] Unfortunately, transient elastography is not appropriate as a tool for systematic screening in large population. Not only because of its limited availability—not every healthcare provider has this medical device, but it also requires trained personnel to operate the device. Moreover, the evidence-based study about the long-term benefit of NAFLD and liver fibrosis screening as well as their treatment options is still limited.[6,10] In resource-limited settings, accessibility of transient elastography is the main barrier of being a method of choice for NAFLD and liver fibrosis screening, even in high-risk population, such those with metabolic syndrome. Solely liver function test is not sensitive enough to detect these spectrums of liver abnormalities.[9,11] Numbers of noninvasive clinical scoring systems which cooperate clinical parameters for enhancing the predictive performance of liver fibrosis in NAFLD patients had been developed.[11,12] However, some of them are not practical for adopting in countries with different contexts as some parameters are not routinely assessed. For example, in Thailand, hyaluronic acid, procollagen III amino-terminal propeptide, and tissue inhibitor of matrix metalloproteinase 1 which are required to calculate Enhanced Liver Fibrosis blood test, the algorithm for liver fibrosis evaluation that recommended in National Institute for Health and Care Excellence guidelines[3] are not commonly measured in general practice. Also, the predictive performances of scores tended to vary when applied in different populations.[13] Interestingly, none of the existing scoring systems was developed particularly for patients with metabolic syndrome. Target populations of previously published scores for detecting liver fibrosis are patients with known NAFLD and suspected ones identified from abnormal liver function tests or those with severely obesity. However, about half of the patients with these liver-related conditions manifested normal hepatic enzymes.[1,2,9] Moreover, there was an evidence showed that about 29% of nonobese NAFLD patients were diagnosed with significant fibrosis.[14] Thus, a simple yet proficient scoring system for predicting significant fibrosis is still required to prioritize needs for further investigation among patients with metabolic syndrome. This study aimed to develop a simple clinical predictive score for detecting NAFLD with significant fibrosis in patients with metabolic syndrome.

2. Methods

This study complied with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis[15] and standards for the reporting of diagnostic accuracy studies.[16,17]

2.1. Study population

A cross-sectional study was designed to obtain the data that required to develop a predictive model for a diagnostic outcome of having NAFLD with significant fibrosis among patients with metabolic syndrome. Medical records of all adult patients (age ≥18 years) with metabolic syndrome who underwent transient elastography (FibroScan: Echosens, Paris, France) between January 2011 and December 2020 at Siriraj Hospital (a 2061-bed university hospital), Thailand,[18] were retrospectively reviewed. Data of all patients who passed the eligibility criteria were included in the model development process, regardless of diagnosis results from transient elastography. Metabolic syndrome was identified followed to National Cholesterol Education Program Adult Treatment Panel III 2005[19,20] and American Heart Association/National Heart Lung and Blood Institute 2005 criteria.[21] We used the waist circumference criteria for Asian population (i.e., ≥90 cm in male and ≥80 cm in female),[20] other details were described elsewhere.[19–21] Additionally, those with exclusion criteria for NAFLD diagnosis which were secondary causes of liver fat accumulation, including

(1) a daily alcohol consumption of ≥30 g for male and ≥20 g for female,
(2) viral hepatitis, and
(3) drug-induced hepatitis were excluded from the analysis.[5,6]

2.2. Assessment of NAFLD with significant fibrosis and sample size

In spite of liver biopsy being the reference standard procedure for diagnosis and confirmatory of NAFLD and liver fibrosis, all guidelines agree that it is not an appropriate method used for diagnosis among population without explicit risks of the disease due to its invasive characteristic and sampling variation.[3,5,6] Therefore, this study adopted transient elastography as a reference test to identify NAFLD with significant fibrosis (fibrosis stage ≥2) which was the purposed diagnostic outcome of a predictive model that we intended to develop. Transient elastography is a popular noninvasive medical tool that was purposively developed for the measurement of liver fat accumulation and liver stiffness.[22,23] It was developed based on an ultrasonography technique and it is one of the accurate and reliable methods that could be used to quantify liver fibrosis.[5,6,22] A liver stiffness cutoff value of 7.0 kilopascal (kPa) was used to define the presence of outcome of interest among the included patients.[11]

We calculated the sample size based on 10 events per variable.[24] Since previous scoring systems for the prediction of significant fibrosis comprise a maximum of 7 predictors and a simple scoring system should not compose of too many predictors, the sample size should consist of at least 70 patients with the outcome. The previously reported prevalence of NAFLD with significant fibrosis among patients with metabolic syndrome in Thailand was 11%.[25] Thus, the least amount of sample eligible for developing a model was 637. However, a larger sample size with more outcomes is more preferred, especially when the potential predictors were not prespecified.[26,27] We, therefore, reviewed and included all relevant patients with a transient elastography result during the above-mentioned time period.

2.3. Data collection and data imputation

Patient demographic and clinical parameters that tended to be potential predictors according to the literature review and hepatologist opinions were retrospectively reviewed from patients' electronic medical records. The values of those potential predictors that had been assessed on the date of transient elastography were collected. If it was not available, the data that had been measured closet to the date and lay within a 6-month period apart from the date of transient elastography were collected. In case of no recorded data during the mentioned time period, we considered that the data was missing. All clinical and laboratory data reported in electronic medical records had been measured by standard technique. To avoid any bias from complete case analysis as well as insufficient sample size, the missing data were handled with a single imputation method. The predicted values from regression analyses were applied.[26,28]

2.4. Model development

To preliminary determined the candidate predictors, patients' medical history and clinical data that are regularly assessed in routine practice were selected by following opinions of a hepatologist, proper univariable statistical analysis (including unpaired *t*-test, Man–Whitney *U t*-test, and Fisher exact test), and their power of discrimination (*c*-statistic). The significant difference of univariable statistical analysis was defined when *P*-value $< .1$. Whenever the univariable statistical analyses showed the same significant level of two or more similar parameters that tended to be correlated with each other, the one that provided better discriminative ability was selected (i.e., the one with *c*-index equaled to the value that was furthest from 0.5). To simplified the model, all continuous data were categorized by standard cutoff values that are clinically meaningful and commonly use in clinical practice. After that, backward and forward stepwise logistic regression was performed to acquire a final prediction model, predictors with *P*-value $< .1$ would be considered to be left in the final model. Weighted scores which calculated based on the regression coefficient were, then, assigned for all predictors to make the model easier for using in practice. Two cutoff values for the model were defined: one was set at the score which provided the least number of patients with misdiagnosis, according to Liu method (a lower cutoff value), and the other was set at the score which provided a specificity of more than 90% (a higher cutoff value), aimed to identify those patients who would be in the urgent need for further investigation.

2.5. Statistical analysis and model validation

Continuous data, with normal distribution, were reported as mean ± standard deviation. Those with non-normal distribution were presented as median (interquartile range). Categorical data were demonstrated as frequency (percentage). The internal validity of the developed model was evaluated in terms of both discrimination and calibration. The discriminative ability of the model was determined using Man–Whitney *U* test. The predictive accuracy, according to the proper cutoff values, were presented through area under the receiver operating characteristic (AuROC) curves, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, along with 95% confidence intervals. The calibration plot was illustrated and Hosmer–Lemeshow test was also conducted to demonstrate the results of model calibration. All statistical analyses and figures were performed and created using Stata Statistical Software: Release 15 (StataCorp LP, College Station, TX). A statistically significant difference was set at *P*-value $< .05$ (2-tailed).

2.6. Ethics approval

This study was approved by the Institutional Review Board of Siriraj Hospital, Faculty of Medicine Siriraj Hospital, Mahidol University (CoA number: Si 102/2021) and the Human Research Ethics Committee of Thammasat University (Medicine) (CoA number: 039/2021).

3. Results

3.1. Patient characteristic

A total of 969 patients' medical records with transient elastography results between January 2011 and December 2020 were identified. Of which 224 were excluded from the analysis adhered to the exclusion criteria. NAFLD with significant fibrosis was detected in 94 of 745 patients; this implied the prevalence of NAFLD with significant fibrosis in patients with metabolic syndrome of 12.6%. Average age of the patients was 61.2 ± 10.2 years. More than half were female (58.4%). About 60% of patients had body mass index (BMI) $\geq 25\,kg/m^2$. Dyslipidemia, hypertension, and type 2 diabetes mellitus had been diagnosed in 96.9%, 86.9%, and 46.3% of the patients, respectively. Most clinical characteristics of patients with NAFLD with significant fibrosis and those non-NAFLD and NAFLD with no/mild fibrosis were quite disparate. However, average age and proportion of males in both groups were not different. The characteristics of patients were demonstrated in Table 1. The data imputation process was described in Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A622.

3.2. Model development

The candidate predictors, which were identified by following expert opinions together with univariable statistical analysis and power of discrimination of each predictor, included BMI, type 2 diabetes mellitus, triglycerides, aspartate transaminase (AST), globulin, gamma-glutamyl transferase (GGT), and platelet count. The cutoff values which commonly used to indicate clinical abnormalities in routine practice of continuous data were BMI $\geq 25\,kg/m^2$, triglycerides ≥ 150 mg/dL, AST ≥ 30 IU/L, globulin ≥ 3.5 g/dL, GGT ≥ 50 IU/L, and platelet count $< 150{,}000$/

Table 1

Clinical characteristics, evidence of difference (*P-value*), and area under receiver operating characteristic (AuROC) curve along with 95% confidence interval (CI).

Characteristic	n	Non-NAFLD and NAFLD with no/mild fibrosis (n = 651) mean ± SD	NAFLD with significant fibrosis (n = 94) mean ± SD	*P-value*	AUROC (95% CI)
Age (yr)	745	61.1 ± 9.8	62.2 ± 12.7	.337	0.526 (0.490, 0.563)
Gender: male (n, %)	745	266 (40.9)	44 (46.8)	.314	0.530 (0.494, 0.567)
Weight (kg)	745	67.5 ± 13.0	74.3 ± 16.0	<.001	0.620 (0.584, 0.655)
BMI (kg/m^2)	745	26.2 ± 4.0	28.5 ± 5.5	<.001	0.629 (0.592, 0.663)
Obesity* (n, %)	745	391 (60.1)	67 (71.3)	.041	0.556 (0.519, 0.592)
Waist circumference (cm)	646	91.0 ± 10.5	98.1 ± 10.2	<.001	0.695 (0.658, 0.730)
Hypertension (n, %)	745	560 (86.0)	87 (92.6)	.101	0.533 (0.496, 0.569)
T2DM (n, %)	745	275 (42.2)	70 (74.5)	<.001	0.661 (0.627, 0.696)
Dyslipidemia (n, %)	745	630 (96.8)	92 (97.9)	.756	0.506 (0.470, 0.543)
Total cholesterol (mg/dL)	745	176.3 ± 37.6	168.3 ± 32.8	.051	0.442 (0.406, 0.478)
Triglycerides (mg/dL) median (IQR)	745	115.0 (83.0, 156.0)	134.0 (112.0, 166.0)	.002	0.601 (0.565, 0.637)
HDL-C (mg/dL)	745	54.6 ± 14.0	51.3 ± 13.6	.031	0.428 (0.392, 0.465)
LDL-C (mg/dL)	745	96.3 ± 32.2	86.6 ± 29.0	.006	0.415 (0.379, 0.451)
AST (IU/L)	745	22.0	34.0	<.001	0.801
median (IQR)		(18.0, 27.0)	(25.0, 45.0)		(0.771, 0.829)
AST ≥30 IU/L (n, %)		106 (16.3)	59 (62.8)	<.001	0.732 (0.700, 0.764)
ALT (IU/L) median (IQR)	745	20.0 (16.0, 29.0)	34.0 (25.0, 53.0)	<.001	0.748 (0.715, 0.778)
AST/ALT ratio	745	1.1 ± 0.4	1.1 ± 0.4	.443	0.468 (0.431, 0.504)
GGT (IU/L)	745	30.0	52.0	<.001	0.745 (0.712, 0.776)
median (IQR)		(21.0, 46.0)	(36.0, 80.0)		
GGT ≥50 IU/L (n, %)		136 (20.9)	49 (52.1)	<.001	0.656 (0.621, 0.690)
Globulin (g/dL)	745	3.3 ± 0.4	3.5 ± 0.5	<.001	0.615 (0.580, 0.651)
Globulin ≥3.5 g/dL (n, %)	745	182 (28.0)	46 (48.9)	<.001	0.605 (0.569, 0.641)
Albumin (g/dL)	661	4.4 ± 0.3	4.4 ± 0.4	.045	0.464 (0.426, 0.503)
Platelets (10^3/μL)	745	264.9 ± 67.4	226.5 ± 77.1	<.001	0.346 (0.312, 0.382)
Platelets <150,000 /μL (n, %)	745	18 (2.8)	13 (13.8)	<.001	0.555 (0.519, 0.592)

/μL = per microliter, ALT = alanine aminotransferase, AST = aspartate transaminase, AuROC = area under receiver operating characteristic curve, BMI = body mass index, cm = centimeter, g/dL = gram per deciliter, GGT = gamma-glutamyl transferase, HDL-C = high-density lipoprotein cholesterol, IQR = interquartile range, IU/L = international unit per liter, kg = kilogram, kg/m^2 = kilogram per square meter, LDL-C = low-density lipoprotein cholesterol, mg/dL = milligram per deciliter, NAFLD = nonalcoholic fatty liver disease, SD = standard deviation, T2DM = type 2 diabetes mellitus.

* Obesity defined when BMI ≥25 kg/m^2.

μL.[10,19,29–32] Once stepwise logistic regression was analyzed to acquire a final prediction model, 5 potential predictors remained in the model (i.e., AST ≥30 IU/L, globulin ≥3.5 g/dL, GGT ≥50 IU/L, platelet count <150,000/μL, and type 2 diabetes mellitus). Both backward stepwise and forward stepwise selection approaches resulted in the same final prediction models. However, when considered the application of the model in general practice, other than in university hospitals, GGT might not be commonly assessed in primary, secondary, and some tertiary healthcare settings. Therefore, in this study, we decided to demonstrate 2 predictive models:

(1) "NAFLD-fibrosis metabolic syndrome (MS) plus GGT," which included GGT as one of the predictors and
(2) "NAFLD-fibrosis MS" which GGT were excluded from the final model.

The results of multivariable logistic regression, regression coefficients, odds ratios, and assigned scores of both models were demonstrated in Table 2. For NAFLD-fibrosis MS plus GGT, the cutoff value defined according to Liu method was at the score of 2.5 and the cutoff value which gave the specificity of more than 90% was at the score of 3.5. For NAFLD-fibrosis MS, the proper cutoff values were 2 and 3.5 according to Liu method and specificity of more than 90%, respectively.

3.3. Model validation

Despite the significant *P*-value from the likelihood-ratio test (*P*-value = .003) which meant that NAFLD-fibrosis MS plus GGT was likely to be a better predictive model, both NAFLD-fibrosis MS plus GGT and NAFLD-fibrosis MS showed good and clinically similar discriminative power. The parametric AuROC of NAFLD-fibrosis MS plus GGT and of NAFLD-fibrosis MS were 0.834 (95% confidence interval [CI]: 0.789, 0.879) and 0.828 (95% CI: 0.782, 0.874), respectively (Fig. 1). The average NAFLD-fibrosis MS plus GGT scores of patients with NAFLD with significant fibrosis and those without significant fibrosis were 3.59 ± 1.68 and 1.49 ± 1.31, respectively (*P*-value < .001). Additionally, the average NAFLD-fibrosis MS scores were 3.38 ± 1.66 and 1.36 ± 1.31, respectively (*P*-value < .001). The distributions of metabolic syndrome patients with and without NAFLD with significant fibrosis stratified by the scores were demonstrated in Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A623.

Table 2

Multivariable clinical predictors, regression coefficients, odds ratios, 95% confidence intervals, and assigned scores.

Predictors	Coefficient	Odds ratio	95% CI of odds ratio	*P-value*	Assigned score
NAFLD-fibrosis MS plus GGT					
GGT ≥50 IU/L	0.83	2.28	1.34, 3.89	.002	1
Globulin ≥3.5 g/dL	0.92	2.52	1.51, 4.19	<.001	1
T2DM	1.23	3.43	2.01, 5.86	<.001	1.5
Platelets <150,000 /μL	1.35	3.87	1.51, 9.94	.005	1.5
AST ≥30 IU/L	1.79	5.98	3.54, 10.08	<.001	2
NAFLD-fibrosis MS					
Globulin ≥3.5 g/dL	0.85	2.33	1.41, 3.83	.001	1
T2DM	1.29	3.65	2.15, 6.19	<.001	1.5
Platelets <150,000 /μL	1.36	3.91	1.57, 9.76	.003	1.5
AST ≥30 IU/L	2.05	7.79	4.76, 12.76	<.001	2.5

AST = aspartate transaminase, GGT = gamma-glutamyl transferase, g/dL = gram per deciliter, IU/L = international unit per liter, nonalcoholic fatty liver disease, MS = metabolic syndrome, T2DM = type 2 diabetes mellitus, /μL = per microliter.

At the lower cutoff values, sensitivity and specificity of NAFLD-fibrosis MS plus GGT were 75.5% (95% CI: 65.6%, 83.8%) and 70.2% (95% CI: 66.5%, 73.7%). The sensitivity and specificity NAFLD-fibrosis MS were 76.6% (95% CI: 66.7%, 84.7%) and 72.4% (95% CI: 68.7%, 75.8%), respectively. At the higher cutoff values, sensitivities of both models were reduced to around 60% and the positive likelihood ratio was increased to approximately 6. The details of predictive performances were shown in Table 3.

NAFLD-fibrosis MS plus GGT and NAFLD-fibrosis MS were well-calibrated scoring systems, given that the Hosmer–Lemeshow goodness-of-fit test produced the *P*-value of .493 and .717, respectively. The calibration plots of both models were illustrated in Figure 2.

4. Discussion

Liver fibrosis is one of the strong predictors of clinical outcomes in patients with NAFLD.[33,34] Recently, a systematic review claimed that liver fibrosis could also be found in general population with the prevalence of 1% to as high as 26%.[9] Metabolic risk factor is another strong predictor of fatty liver, patients with metabolic syndrome are associated with a higher risk of NAFLD and liver fibrosis.[6,7,35] We found that the prevalence of NAFLD with significant fibrosis in patients with metabolic syndrome was 12.6% and the prevalence of advanced fibrosis was 9.8% (determined at the liver stiffness cutoff value of ≥8.7 kPa[11,13]). The evidence showed that these clinical conditions were one of the most underdiagnosed liver-related diseases, since numbers of patients were asymptomatic and about half of them also presented with normal hepatic enzymes.[1,2,9] Currently, the systematic screening for NAFLD and liver fibrosis in general population is not recommended by international guidelines, also, in high-risk groups such as patients with metabolic syndrome is debatable, because of the limited information about its cost-effectiveness and the variation in healthcare systems across the globe.[3,6] The accessibility of the screening test should also be considered, especially in resource-limited setting. This study, therefore, brought up 2 new clinical predictive scores for detecting NAFLD with significant fibrosis. These scoring systems were purposively developed to help clinicians prioritized the needs for further investigation among patients with metabolic syndrome.

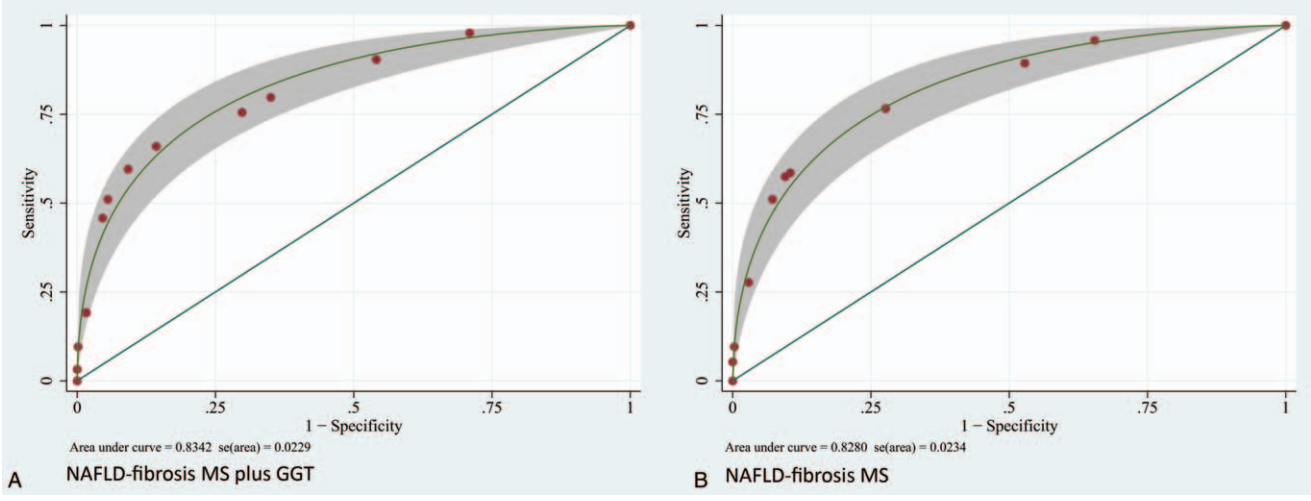

Figure 1. Receiver operating characteristic curves of (A) NAFLD-fibrosis MS plus GGT (B) NAFLD-fibrosis MS. GGT = gamma-glutamyl transferase, NAFLD = nonalcoholic fatty liver disease.

Table 3

Predictive performances of NAFLD-fibrosis MS plus GGT and NAFLD-fibrosis MS scores.

	NAFLD-fibrosis MS plus GGT		NAFLD-fibrosis MS	
Predictive performance (95% CI)	**≥2.5 (n = 265)**	**≥3.5 (n = 116)**	**≥2 (n = 252)**	**≥3.5 (n = 116)**
AuROC	0.729 (0.682, 0.776)	0.752 (0.701, 0.803)	0.745 (0.698, 0.791)	0.740 (0.688, 0.791)
Sensitivity	75.5% (65.6%, 83.8%)	59.6% (49.0%, 69.6%)	76.6% (66.7%, 84.7%)	57.4% (46.8%, 67.6%)
Specificity	70.2% (66.5%, 73.7%)	90.8% (88.3%, 92.9%)	72.4% (68.7%, 75.8%)	90.5% (88.0%, 92.6%)
Likelihood ratio (+)	2.53 (2.15, 2.99)	6.46 (4.82, 8.66)	2.77 (2.34, 3.27)	6.03 (4.50, 8.09)
Likelihood ratio (−)	0.35 (0.24, 0.50)	0.45 (0.35, 0.57)	0.32 (0.22, 0.47)	0.47 (0.37, 0.60)
Positive predictive value	26.8% (21.6%, 32.6%)	48.3% (38.9%, 57.7%)	28.6% (23.1%, 34.6%)	46.6% (37.2%, 56.0%)
Negative predictive value	95.2% (92.9%, 96.9%)	94.0% (91.8%, 95.7%)	95.5% (93.3%, 97.2%)	93.6% (91.4%, 95.4%)

AuROC = area under receiver operating characteristic curve, Likelihood ratio (+) = positive likelihood ratio, Likelihood ratio (−) = negative likelihood ratio, MS = metabolic syndrome.

Statistically significant difference was observed in most clinical characteristics of patients with and without NAFLD with significant fibrosis. Many clinical variables tended to be potential predictors. However, after considered various aspects such as predictive performance, simplicity, and practicability; NAFLD-fibrosis MS plus GGT and NAFLD-fibrosis MS were introduced. Both of them are simple, still they provide good predictive performances. The internal validation showed the AuROC curves of above 0.8 and the models were well-calibrated. Two proper cutoff values were defined for each scoring system. Those patients whose scores were above the lower cutoff values should be suggested about a lifestyle modification (such as diet control, exercise, and weight reduction), since this is currently the best therapeutic strategy for patients with NAFLD, recommended in all guidelines.[3–7] Moreover, those whose scores were above the higher cutoff values, besides the suggestion about lifestyle modification, they should be offered additional investigations, such as transient elastography, to confirm the diagnosis. The higher cutoff values were defined to increase specificities of the scoring systems which would reduce the rate of false-positive results that might lead to overutilization of transient elastography. When the higher cutoff values were applied to determine which patients should undergo transient elastography, we could avoid the overutilization in about 20% of patients who were non-NAFLD and NAFLD with no/mild fibrosis. In the current context of Thailand which the availability and accessibility of transient elastography are still limited as well as the best therapeutic strategy of NAFLD with significant fibrosis is a lifestyle modification, the higher cutoff values may be more reasonable.

To our knowledge, NAFLD-fibrosis MS plus GGT and NAFLD-fibrosis MS scoring systems are the first predictive scores that had been developed for detecting NAFLD with significant fibrosis among patients with metabolic syndrome. The other previously published validated models and scoring systems such as NAFLD fibrosis score; fibrosis-4; AST/platelet ratio index; BMI, AST/ALT ratio, diabetes; BMI, age at liver biopsy, ALT, and serum triglyceride; Gholam's model; original European liver fibrosis score; simplified enhanced liver fibrosis; FibroTest; and Fibrometer had been developed to predict liver fibrosis among NAFLD patients and suspected ones.[11,12] Majority of the models and scoring systems, including our newly developed scores, have similar predictors such as age, platelet count, BMI, liver enzymes, type 2 diabetes mellitus, and other metabolic risk factors. In this study, we found that there was no difference

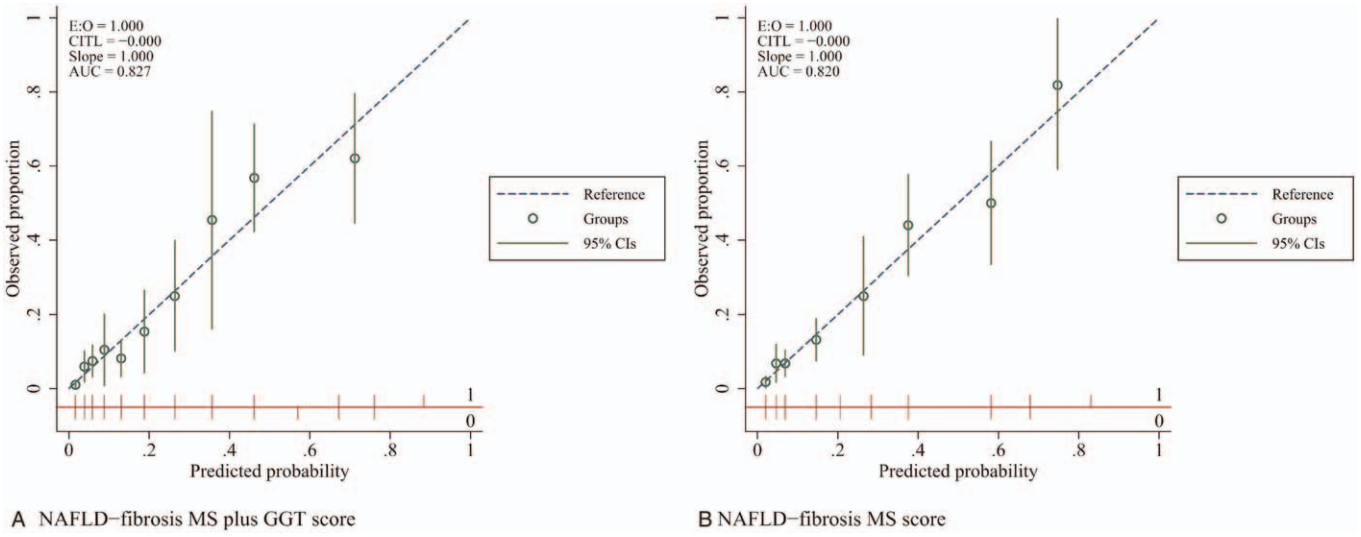

Figure 2. Calibration plots of (A) NAFLD-fibrosis MS plus GGT (B) NAFLD-fibrosis MS. GGT = gamma-glutamyl transferase, NAFLD = nonalcoholic fatty liver disease.

between average age of the patients with and without NAFLD with significant fibrosis. Additionally, BMI, in terms of obesity (BMI $\geq$25 kg/m^2), was not one of the predictors in our models. This might be associated with our cohort that we used to develop the predictive models. Having metabolic syndrome was one of the inclusion criteria for our study, even BMI was not one of the criteria for metabolic syndrome that we used, but waist circumference was, and these 2 variables seemed to be correlated.[19–21] Moreover, a meta-analysis conducted by Ye et al also reported that 25% to 50% of general population were nonobese NAFLD.[7,14] Since, our predictive scores and other models/scoring systems have a different target of use, we could not directly compare their predictive performances. We could only describe that all models, including ours, provided good predictive accuracy represented by AuROC curves of about 0.7 to 0.9.[11,12] NAFLD-fibrosis MS plus GGT and NAFLD-fibrosis MS scoring systems may not be the most accurate ones, but it is the most practical in our context because they are simple and composes of only commonly assessed parameters in routine practice. Some of the previous models, such as simplified enhanced liver fibrosis and FibroTest required specific laboratory parameters to calculate the risk of liver fibrosis. Cost of the models is one of the issues that should be concerned when applies the scores in general practice. If a model required uncommon laboratory parameters to predict the risk, its cost will rise and may economically burden healthcare systems in the future.

Our study has several drawbacks. First, we did not use liver biopsy as a reference standard procedure for diagnosis of NAFLD with significant fibrosis. Nevertheless, transient elastography is a reliable method for quantifying liver fibrosis and it is also a more appropriate method to use to detect the risk of significant liver fibrosis among those patients without certain risks of NAFLD and liver fibrosis. Although all eligible patients with metabolic syndrome who underwent transient elastography in our center within 10-year period (2011–2020) were included in the analysis, the sample size was still considered small for non-prespecified model development.[27] Second, the liver stiffness threshold for significant fibrosis of transient elastography is still varied, but we did apply the most common cutoff values in our study.[11,13] Third, we traded some of the predictive performances of our models off to increase the ease of use as we aimed to develop simple scoring systems which minimized the burden for users. In the future, if possible, predictive scores may be developed along with a tool, such as an application in smartphones, which helps users to calculate the risks to avoid this limitation. Fourth, when applies the scoring systems in different situations or when the context of healthcare system changes, for example, the availability of transient elastography is increased, the proper cutoff values and recommended management strategies for patients with different scores should be re-evaluated, since the cutoff values that we proposed had been set based on the current situation of Thai healthcare system. Fifth, even if the internal validity of the scoring systems was quite appreciated, external validations especially those carried out using prospectively collected data are needed before adopting the score in routine practice.

To conclude, NAFLD-fibrosis MS plus GGT and NAFLD-fibrosis MS scores which were developed in our study were appropriate and practical. In the healthcare setting where GGT is not routinely assessed, NAFLD-fibrosis MS score can be used instead of NAFLD-fibrosis MS plus GGT. Both of them provided good predictive performances and should be useful to help clinicians in general settings prioritize needs for further investigations among patients with metabolic syndrome, especially in resource-limited settings.

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