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Epidemiology

Development and validation study of a non-alcoholic fatty liver disease risk scoring model among adults in China

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Abstract

Background. Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in China. It is usually asymptomatic and transabdominal ultrasound (USS) is the usual means for diagnosis, but it may not be feasible to have USS screening of the whole population.
Objective. To develop a risk scoring model for predicting the presence of NAFLD using parameters that can be easily obtain in clinical settings.
Methods. A retrospective study on the data of 672 adults who had general health check including a transabdominal ultrasound. Fractional polynomial and multivariable logistic regressions of sociodemographic and biochemical variables on NAFLD were used to identify the predictors. A risk score was assigned to each predictor using the scaled standardized β-coefficient to create a risk prediction algorithm. The accuracy for NAFLD detection by each cut-off score in the risk algorithm was evaluated.
Results. The prevalence of NAFLD in our study population was 33.0% (222/672). Six significant factors were selected in the final prediction model. The areas under the curve (AUC) was 0.82 (95% CI: 0.78–0.85). The optimal cut-off score, based on the ROC was 35, with a sensitivity of 76.58% (95% CI: 70.44–81.98%) and specificity of 74.89% (95% CI: 70.62–78.83%).
Conclusion. A NAFLD risk scoring model can be used to identify asymptomatic Chinese people who are at risk of NAFLD for further USS investigation.

Key words: Chronic disease, obesity, primary care, risk assessment, screening.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a liver disease that may progress to liver cirrhosis and hepatocellular carcinoma. In Asia, the prevalence of NAFLD ranges from 5% to 40% (1), with China being one of the high prevalence countries. With the changes in diet structure and lifestyle, the prevalence of NAFLD is increasing in developing countries including China, especially in big cities (2). Its threat to the health of the Chinese population is only second to hepatitis. NAFLD is associated with insulin resistance condition and can represent a hepatic manifestation of the metabolic syndrome (MS) which comprises obesity, dyslipidemia, hypertension and glucose intolerance (3). In recent years, studies show that simple hepatic

steatosis may progress to non-alcoholic steatohepatitis (NASH) and fibrosis if the weight and abdominal circumference increase. Weight loss may reduce the occurrence of hepatic complications (4). Early detection and treatment may reverse the progression of the disease. It is very important to detect NAFLD early so to control the risk factors through health education and lifestyle intervention to reduce the incidence of NAFLD and its complications.

Most NAFLD are asymptomatic in the early stage and are detected as an incidental finding during imaging examination for other diseases or health assessment. In many cases, the first sign of illness does not occur until significant liver damage has developed. Symptoms typically include fatigue, nausea, abdominal discomfort, jaundice, etc. The use of liver function tests such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) alone are not reliable. Studies in the United States revealed good associations between metabolic parameters and the presence of NAFLD (5,6).

Transabdominal ultrasound is a simple, widely available, acceptable and accurate for the diagnosis of fatty liver (7), but it may not be feasible or cost-effective for population screening. Therefore, it is useful to identify people at high risk of NAFLD base on metabolic risk factors and sociodemographic factors.

The aim of this study was to develop a risk scoring model for predicting the presence of NAFLD using parameters that can be easily obtain in clinical settings.

Methods

Study subjects

The study design was a retrospective analysis of data of anonymized adults collected in routine health assessments in the Health Assessment and Management Center of the University of Hong Kong-Shenzhen Hospital from 1 January 2014 and 31 March 2014. According to the guidelines for diagnosis of NAFLD in China (8), inclusion criteria were adults aged more than 18 years. Exclusion criteria were regular drinkers (alcohol intake ≥3 times per week) at any level (9), patients with history of viral hepatitis, including carriers hepatitis B or hepatitis C, drug-induced liver disease, total parenteral nutrition, hepatolenticular degeneration, and autoimmune liver disease.

Study methods

A comprehensive health assessment was conducted in all subjects as following: a questionnaire was used to obtain information on age, gender, frequency of alcohol intake (how many times per week), smoking status and medical history, when the subjects had difficulty completing the questionnaire, trained nurses provided assistance. Height and body weight were measured in subjects wearing light clothing without shoes, body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters. The measurement of waist circumference was done by trained nurses. The average of the blood pressure (BP) measurements was recorded after BP was measured twice on the right arm of the seated subjects with an electronic sphygmomanometer, BP included systolic blood pressure (SBP) and diastolic blood pressure (DBP). In addition to a transabdominal ultrasound of the liver, and tests on serum, uric acid (UA), total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), haemoglobin A1c (HbA1C), fasting glucose, ALT and AST were done. Venous blood samples were collected following an overnight 8 hours of fasting. UA, TC, TG, HDL, LDL, fasting glucose, ALT and AST levels were measured using the Roche Cobas 8000 chemistry analyzer. HbA1C was measured by the high performance liquid chromatography (HPLC) method using ADAMSTMA1c HA-8160.

Diagnosis of fatty liver

For the purpose of this study, the 'gold standard' for diagnosing fatty liver was transabdominal ultrasound. Fatty liver was diagnosed, if at least two of three abnormal findings were present on USS: diffusely increased echogenicity that is greater than the kidneys or spleen, vascular blurring, or deep attenuation of ultrasound signal (10). Ultrasound examination was done using PHILIPS HD15 equipped with a convex 3.5 MHz probe, performed by one of two experienced and professional ultrasound doctor in the University of Hong Kong-Shenzhen Hospital, who were blinded to patients' blood test results.

Risk factors

According to previous literatures (11–13), the NAFLD risk factors in this study were used as following: age, gender, metabolic risk factors including overweight (BMI ≥25 kg/m^2), central obesity (waist circumference ≥90 cm for men and ≥80 cm for women), raised blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg), hyperuricemia (UA >428 μmol/L for men and >357 μmol/L for women), hypertriglyceridemia (TG ≥1.7 mmol/L), reduced HDL (HDL <1.03 mmol/L for men and <1.29 mmol/L for women), raised fasting glucose (fasting glucose ≥6.1 mmol/L), Hyperglycemia (HbA1c ≥6.5%).

Table 1. Demographic and clinical characteristics of patients (*N* = 672)

Characteristics	Total samples (*n* = 672)
Sociodemographic	
Age (years), mean ± SD (range)	47.2 ± 9.6 (27.0–82.0)
Gender (%, n)	
Female	18.5% (124)
Male	81.5% (548)
Clinical parameters (%, *n*)	
BMI (kg/m^2)	
<25	62.8% (422)
≥25	37.2% (250)
Waist circumference (cm)	
Male <90, Female <80	59.7% (401)
Male ≥90, Female ≥80	40.3% (271)
Blood pressure (mmHg)	
SBP < 130 & DBP < 85	61.5% (413)
SBP ≥ 130 or DBP ≥ 85	38.5% (259)
Uric Acid (μmol/L)	
Male ≤428, Female ≤357	67.3% (452)
Male >428, Female >357	32.7% (220)
Triglyceride (mmol/L)	
<1.7	66.1% (444)
≥1.7	33.9% (228)
HDL (mmol/L)	
Male ≥ 1.03, Female ≥ 1.29	69.5% (467)
Male < 1.03, Female < 1.29	30.5% (205)
Fasting glucose (mmol/L)	
<6.1	90.9% (611)
≥6.1	9.1% (61)
HbA1c (%)	
<6.5	94.2% (633)
≥6.5	5.8% (39)
Fatty liver	
Absence	67.0% (450)
Presence	33.0% (222)

BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HDL, High Density Lipoprotein; HbA1c, Haemoglobin A1c.

Data analysis

All subjects with missing data were excluded from the analysis. The continuous variable was age; other collected data on the risk factors were transformed into categorical variable: gender (male and female), BMI (<25 and ≥25 kg/m^2), waist circumference (male <90 and ≥90 cm; female <80 and ≥80 cm), SBP (<130 and ≥130 mmHg), DBP (<85 and ≥85 mmHg), UA(male ≤428 and >428 μmol/L; female ≤357 and >357 μmol/L), TG (<1.7 and ≥1.7 mmol/L), HDL (male ≥1.03 and <1.03 mmol/L; female ≥1.29 and<1.29 mmol/L), fasting glucose (<6.1 and ≥6.1 mmol/L), HbA1c (<6.5 and ≥6.5%).

Descriptive data analysis and model development

Descriptive statistics were performed on the characteristics of subjects. Age was handled using fractional polynomial, other risk factors were entered into samples using stepwise logistic regression model. Significant risk factors with $P < 0.05$ were selected to produce a final assessment model. Both forward selection and backward selection were used to see if selected predictors were consistent. Each factor in the final model was assigned a weighted risk score using its β-coefficient divided by its standard error. All standardised scores were scaled up to construct a risk algorithm with a maximum of 100 points. Youden's J statistic (14) was used to determine the optimal cut-off point that yields the best sensitivity and specificity.

Model diagnostics

The discrimination of the risk algorithm was evaluated with the receiver operating characteristics (ROC) curve with 95% CI, calibration was assessed by Hosmer and Lemeshow statistic in which an insignificant value indicates a good fit. Calibration was also inspected via calibration plot.

Results

Characteristics of the study subjects

Data were collected on a total of 674 patients. Two patients with missing data were excluded from the analysis. The prevalence of overweight, central obesity, raised blood pressure, hyperuricemia, hypertriglyceridemia, reduced HDL, raised fasting glucose, hyperglycemia and fatty liver disease were 37.2% (250/672), 40.3% (271/672), 38.5% (259/672), 32.7% (220/672), 33.9% (228/672), 30.5% (205/672), 9.1% (61/672), 5.8% (39/672) and 33.0% (222/672), respectively (Table 1).

Multivariate analysis and model development

Based on the fractional polynomial comparisons testing the best fractional polynomial models for age, the effect of age was insignificant; therefore, age was left out in the list of predictors considered in regression model. Other factors were entered into stepwise logistic regression model. Fatty liver showed a correlation with overweight (OR: 2.31, 95% CI: 1.46–3.67), central obesity (OR: 3.43, 95% CI: 2.16–5.45), hyperuricemia (OR: 2.07, 95% CI: 1.39–3.08), hypertriglyceridemia (OR: 1.83, 95% CI: 1.18–2.82), reduced HDL (OR: 1.78, 95% CI: 1.15–2.76) and raised fasting glucose (OR: 3.24, 95% CI: 1.70–6.16) (Table 2). These significant factors were selected for the final prediction model. The risk score assigned to each predictor using the scaled standardised β-coefficient is shown in Table 2. The Youden's J statistics suggested an optimal cut-off of 35 points. The sensitivity was 76.58% (95% CI:70.44–81.98%) and the specificity was 74.89% (95% CI:70.62–78.83%) when patients with risk score ≤ 35 are classified as disease-free (Table 3). The cut-off scores below 35 had higher sensitivity but lower specificity. While the cut-off scores above 35 had lower sensitivity but higher specificity (Supplementary Table S1).

Model performance and internal validation

The AUC of the risk prediction model was 0.82 (95% CI: 0.78–0.85) (Figure 1), and the Hosmer and Lemeshow statistic was insignificant ($P = 0.77$). Diagnostics performance was comparable with the sensitivity and specificity at an acceptable level (Table 3). The calibration plot of prediction models also performed well (Figure 2).

Table 2. Significant risk factors for predicting non-alcoholic fatty liver disease in total samples ($N = 672$)

Risk factors	Odds ratio	95% CI	*P* value	β-coeff.	Standard error	Std. β-coeff.	Assigned score
BMI (kg/m^2)							
<25	1.00	—	—	—	—	—	0
≥25	2.31	1.46–3.67	<0.001*	0.84	0.24	3.50	17
Waist circumference (cm)							
Male <90, Female <80	1.00	—	—	—	—	—	0
Male ≥90, Female ≥80	3.43	2.16–5.45	<0.001*	1.23	0.24	5.13	24
Uric Acid (umol/L)							
Male ≤428, Female ≤357	1.00	—	—	—	—	—	0
Male >428, Female >357	2.07	1.39–3.08	<0.001*	0.73	0.20	3.65	17
Triglyceride (mmol/L)							
<1.7	1.00	—	—	—	—	—	0
≥1.7	1.83	1.18–2.82	0.006*	0.60	0.22	2.73	13
HDL (mmol/L)							
Male ≥1.03, Female ≥1.29	1.00	—	—	—	—	—	0
Male <1.03, Female <1.29	1.78	1.15–2.76	0.010*	0.58	0.22	2.64	12
Fasting glucose (mmol/L)							
<6.1	1.00	—	—	—	—	—	0
≥6.1	3.24	1.70–6.16	<0.001*	1.18	0.33	3.58	17

CI, Confidence interval; β-coeff., β-coefficient; Std. β-coeff., Standardised β-coefficient; BMI, Body mass index; HDL, High density lipoprotein.
*Significant with *P* value < 0.05.

Discussion

Main findings

Our results demonstrated that fatty liver was more likely among people with overweight, central obesity, hyperuricemia, hypertriglyceridemia, reduced HDL and raised fasting glucose. The combination of these easily measurable factors provides clinicians with a practical non-invasive tool to identify primary care patients at high risk of fatty liver, with adequate sensitivity and specificity of 76.58% and 74.89%, respectively. The sensitivity and specificity are comparable to many commonly used clinical tests. The prevalence of fatty liver in our study population was 33.0%, which was higher than those observed in previous local studies 30.75% (15). The prevalence of NAFLD reported in Guangzhou in 2003 and Shanghai in 2005 was 16.3% (16) and 15.4% (17), respectively, with an increasing prevalence of up to 20.5% in Guangzhou in 2008 (18), 27.3% in Hong Kong with the use of MRI in 2012 (19). The higher prevalence detected in this study may be related to the patients' selection criteria.

Table 3. Discrimination and accuracy of risk model

	Risk predication model (n = 672)
Accuracy (Using optimal cut-off value)	
Optimal cut-off score (range)	35 (0–100)
AUC (95% CI)	0.82 (0.78–0.85)
Sensitivity (95% CI)	76.58% (70.44–81.98%)
Specificity (95% CI)	74.89% (70.62–78.83%)
Positive predicted value (95% CI)	60.07% (55.80–64.19%)
Negative predicted value (95% CI)	86.63% (83.55–89.21%)
Positive likelihood ratio (95% CI)	3.05 (2.56–3.63)
Negative likelihood ratio (95% CI)	0.31 (0.25–0.40)
Discrimination	
Hosmer and Lemeshow Test	0.77

AUC, Area under the curve; CI, Confidence interval.

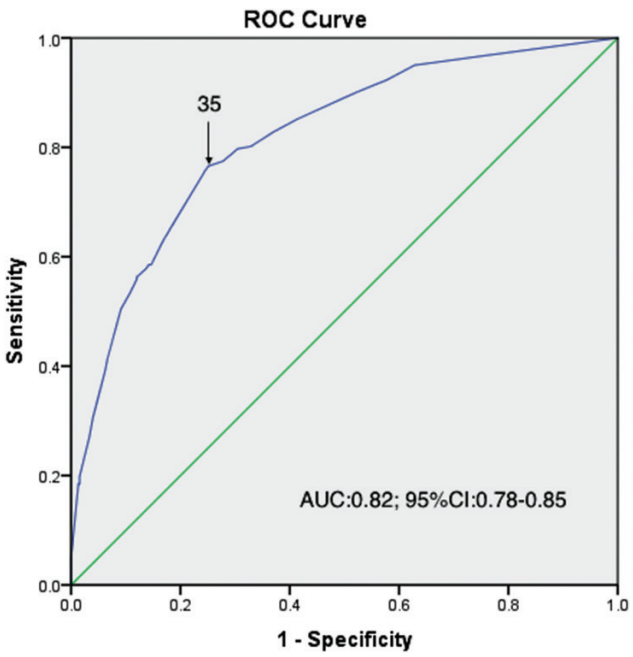

Figure 1. Receiver Operating characteristics curve of the risk scoring model (N = 672)

Firstly, people attending our Health Assessment and Management Center comprise mainly those who are more affluent in our society. Among our study subjects 37.2% were overweight and 40.3% were central obesity, thereby biasing towards a higher NAFLD prevalence in our study population. The factors associated with NAFLD found in this study are consistent with those reported in the literature. The 'two-hit' model suggests the development of steatohepatitis due to insulin resistance with subsequent hepatocellular inflammation and fibrosis. Obesity plays a role in insulin resistance and hence hyperinsulinaemia. Indeed, previous studies have a positive association between high fasting insulin levels and NAFLD. Insulin resistance also increases urate production (20) and excretion (21), explaining the positive relationship between hyperuricemia and increased NAFLD found in our study. Hypertriglyceridemia is an important factor in the development of NAFLD (22), since excessive triglyceride uptake can result in hepatocyte apoptosis. Hepatocellular injury from NAFLD inhibits hepatic glucose metabolism, which in turn raises serum glucose levels, contributing to the association between NAFLD and serum glucose (23).

A study of NAFLD scoring system development among adult medical check-up patients was held in Indonesia (24). Its prevalence of NAFLD was 51.0% higher than our study 33.0%. Its six independent risk factors for predicting fatty liver were male, age, BMI, triglyceride levels, HDL, and serum ALT levels which differed from our final predictors. In the USA, a study compared the performance of four NAFLD prediction scores: fatty liver index, hepatic steatosis index, lipid accumulation product, and NAFLD liver fat score (LFT). LFT included AST/ALT ratio, diabetes, fasting AST level, fasting insulin level, and metabolic syndrome. They found that LFT was the best non-invasive prediction score for NAFLD in the US population (6). Therefore, those two NAFLD prediction methods may not be suitable for the Chinese population. Another model for predicting NAFLD in a Chinese population named ZJU index was developed based on BMI, fasting serum glucose, TG and ALT/AST ratio (25). Its predictors were different from our risk scoring model and it performed better in subjects younger than 40 years old. ZJU index may also be helpful for distinguishing NASH from simple steatosis.

Implications for clinical practice

The screening tool derived from our results utilises six easily obtainable parameters (namely BMI, waist circumference, uric acid, triglyceride, HDL and fasting glucose) to predict the presence of NAFLD with good sensitivity and specificity. Various cut-off scores had different sensitivities and specificities. The optimal cut-off score was 35. The cut-off scores below 35 had higher sensitivity but lower specificity. While the cut-off scores above 35 had lower sensitivity but higher specificity. If a higher sensitivity is needed, we can choose a lower cut-off score for NAFLD prediction. Conversely, if a higher specificity is needed, a higher cut-off score can be chosen. Although our tool cannot diagnose NAFLD with absolute precision, its ease of use provides primary care physicians with a convenient and practical method for identifying patients at high risk for further investigation. At the same time, we can target personalised advice to patients who have high risk factors. For example, a 50-year old man, BMI = 25 kg/m^2, WC = 90 cm, UA = 410 μmol/L, TG = 2.0 mmol/L, HDL = 0.9 mmol/L, fasting glucose = 5.8 mmol/L. According to the risk scoring model, calculate the score of each factors, BMI = 17 points, WC = 24 points, UA = 0 points, TG = 13 points, HDL = 12 points. All scores were summed up to obtain the total score of 66 points which was more than the optimal cut-off score 35. So, we could consider that this man probably had NAFLD.

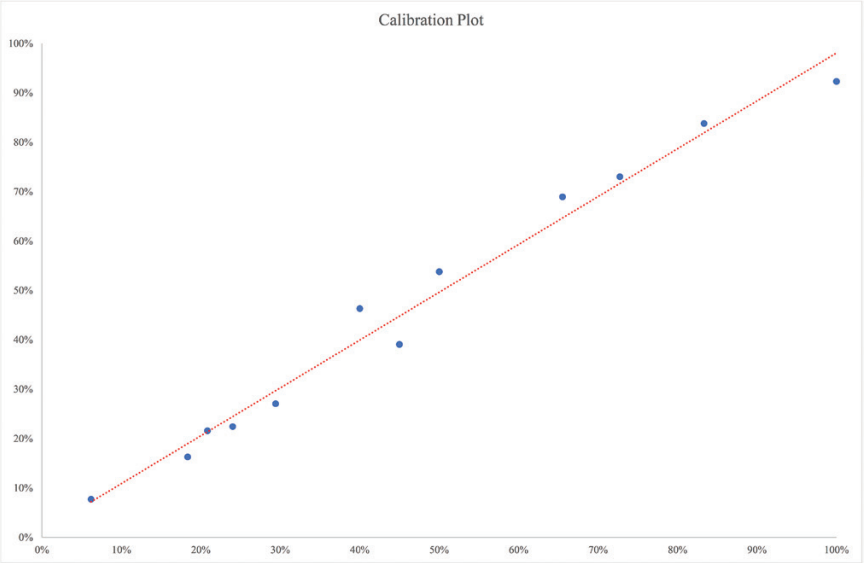

Figure 2. The calibration plot of the risk scoring model ($N = 672$)

Strengths and limitations

Patients were assessed using a uniform protocol with USS conducted by a restricted number of doctors to reduce reporting bias. Although USS is not the most accurate diagnostic tool for NAFLD and may not be able to detect very early stages of the diseases, we believe that it is adequate from a clinical perspective. Another limitation in this study is that we have not considered dietary factor (26), which may contribute to NAFLD. Nevertheless, quantifying diet and translating it into a screening tool may not be practical from a clinical perspective. The model is also susceptible to the issue of overfitting, as there is no cross-validation performed. The model will require validation with other dataset to ensure its validity. Finally, our results may not be generalizable to other populations in China since our subjects were healthy adults living in urban areas. Again, validation among other primary care populations will be required to confirm its accuracy.

Conclusion

In conclusion, a NAFLD risk prediction scoring model consisting of BMI, waist circumference, uric acid, triglyceride, HDL and fasting glucose can be used to identify people who are at high risk of NAFLD for further USS investigation, and it rare the resource for unnecessary tests in adults at low risk especially in primary care institutions. In this study, the results show that the model has good sensitivity and specificity for predicting NAFLD, it can be widely used in the future.

Supplementary Material

Supplementary data are available at *Family Practice* online.

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Declarations

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