The role of noninvasive scoring systems for predicting cardiovascular disease risk in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis

Mengshi Yi[1], MD; Fei Teng[1], MD; Youyin Tang[2], MD; Qingyan Kong[1], MD; Zheyu Chen[1*], MD

Affiliations of authors:
[1]Department of Hepatic Surgery, West China Hospital, Sichuan University, Chengdu, 610041, China.
[2]Department of Vascular Surgery, West China Hospital, Sichuan University, Chengdu, 610041, China.

Correspondence:
[*]Prof. Zheyu Chen, Department of Hepatic Surgery, West China Hospital, Sichuan University, Chengdu, 37 Guoxue Road, Chengdu 610041, Sichuan Province, China.
Email: chenzheyu@scu.edu.cn

Legends.

Supplementary 1. Lists of excluded articles with specific reasons.

Supplementary 2. Detailed characteristics of included studies.

Supplementary 3. Detailed Newcastle-Ottawa Quality Assessment Scale (NOS) score for the cohort studies included in this meta-analysis.

Supplementary 4. Detailed Agency for Healthcare Research and Quality (AHRQ) assessment for the cross-sectional studies included in this meta-analysis.

Supplementary 5. Results of sensitivity analysis that eliminated each of included studies one at a time for the association between FIB-4 and CVD risk in patients with NAFLD.

Supplementary 6. Results of univariate meta regression analyses of comparison, country, NAFLD diagnosis, sample size, study design and risk of bias for the association between FIB-4 and CVD risk in patients with NAFLD.

Supplementary 1. Lists of excluded articles with specific reasons.

a. Not related to the topic:

1. Wu, T. et al. Apolipoproteins and liver parameters optimize cardiovascular disease risk-stratification in nonalcoholic fatty liver disease." Dig Liver Dis **53**(12): 1610-1619 (2021).

b. Included mixed populations:

1. Kwan, A. C. et al. Subclinical hepatic fibrosis is associated with coronary microvascular dysfunction by myocardial perfusion reserve index: a retrospective cohort study." Int J Cardiovasc Imaging (2022).
2. Tamaki, N. et al. Liver fibrosis and fatty liver as independent risk factors for cardiovascular disease. J Gastroenterol Hepatol **36**(10): 2960-2966 (2021).
3. Schonmann, Y. et al. Liver fibrosis marker is an independent predictor of cardiovascular morbidity and mortality in the general population. Dig Liver Dis **53**(1): 79-85 (2021).
4. Iwasaki, Y. et al. Correlation of the Fatty Liver Index with the Pathophysiological Abnormalities Associated with Cardiovascular Risk Markers in Japanese Men without any History of Cardiovascular Disease: Comparison with the Fibrosis-4 Score. J Atheroscler Thromb **28**(5): 524-534 (2021).
5. Fandler-Hofler, S. et al. Non-invasive markers of liver fibrosis and outcome in large vessel occlusion stroke. Ther Adv Neurol Disord **14**: 17562864211037239 (2021).
6. Chun, H. S. et al. Association between the severity of liver fibrosis and cardiovascular outcomes in patients with type 2 diabetes. J Gastroenterol Hepatol **36**(6): 1703-1713 (2021).
7. Turan, Y. The Nonalcoholic Fatty Liver Disease Fibrosis Score Is Related to Epicardial Fat Thickness and Complexity of Coronary Artery Disease. Angiology **71**(1): 77-82 (2020).
8. So-Armah, K. A. et al. FIB-4 stage of liver fibrosis is associated with incident heart failure with preserved, but not reduced, ejection fraction among people with and without HIV or hepatitis C. Prog Cardiovasc Dis **63**(2): 184-191(2020).
9. Sinn, D. H. et al. Non-alcoholic fatty liver disease and the incidence of myocardial infarction: A cohort study. J Gastroenterol Hepatol **35**(5): 833-839 (2020).
10. Lee, J. et al. Association between noninvasive assessment of liver fibrosis and coronary artery calcification progression in patients with nonalcoholic fatty liver disease. Sci Rep **10**(1): 18323 (2020).

11. Ciardullo, S. et al. Screening for non-alcoholic fatty liver disease in type 2 diabetes using non-invasive scores and association with diabetic complications. BMJ Open Diabetes Res Care **8**(1) (2020).
12. Chang, Y. et al. Alcoholic and Nonalcoholic Fatty Liver Disease and Incident Hospitalization for Liver and Cardiovascular Diseases. Clinical Gastroenterology and Hepatology **18**(1): 205-+ (2020).
13. Simon, T. G. et al. The nonalcoholic fatty liver disease (NAFLD) fibrosis score, cardiovascular risk stratification and a strategy for secondary prevention with ezetimibe. Int J Cardiol **270**: 245-252 (2018).
14. Lee, Y. H. et al. Association of non-alcoholic steatohepatitis with subclinical myocardial dysfunction in non-cirrhotic patients. J Hepatol **68**(4): 764-772 (2018).
15. So-Armah, K. A. et al. FIB-4 stage of liver fibrosis predicts incident heart failure among HIV-infected and uninfected patients. Hepatology **66**(4): 1286-1295 (2017).
16. Kirby, R. S. et al. Coronary artery disease and non-alcoholic fatty liver disease: Clinical correlation using computed tomography coronary calcium scans. JGH Open **5**(3): 390-395 (2021).

c. Failed to afford sufficient information for a data analysis:

1. Tutunchi, H. et al. The association of the steatosis severity, NAFLD fibrosis score and FIB-4 index with atherogenic dyslipidaemia in adult patients with NAFLD: A cross-sectional study. Int J Clin Pract **75**(6): e14131 (2021).
2. Gentili, A. et al. Non-alcoholic fatty liver disease fibrosis score and preclinical vascular damage in morbidly obese patients. Dig Liver Dis **48**(8): 904-908 (2016).

d. Letters, conference abstracts and posters:

1. Lai, M. et al. Association of FIB4 score with major cardiovascular events (MACE) in real-world populations diagnosed with NASH or NAFLD in US clinical practice. Gastroenterology **158**(6): S1269-S1270 (2020).

Supplementary 2. Detailed characteristics of included studies.

Study	Country	NAFLD diagnosis	Recruitment year	Outcome	Study design	Number of participants	Number of events	Age (mean)	Male/Female	Follow-up (years)	NSS	Metrics	Unadjusted ES (95%CI)	Adjusted ES (95%CI)	Adjustments
Barbosa et al. (2022)	USA	ICD code 9/10 OR NAFLD risk score	2015.7~2019.6	major cardiovascular events	cohort	67,273	9,112	62	not available	2.9	FIB-4 (>2.67 vs. ≤2.67)	HR	1.82 (1.63-2.04)	1.80 (1.61-2.02)	diagnostic group, FIB-4, sex, race/ethnicity, obesity, T2DM, hyperglycemia, high LDL, low HDL, hypertension, previous CVD
Akuta et al. (2021)	Japan	biopsy-proven	1976~2021	CVD	cohort	444	43	53	not available	5.9	FIB-4 (>2.67 vs. ≤2.67)	HR	3.14 (1.58-6.23)	2.73 (1.21-6.14)	body mass index, previous or current malignancies, CKD, comorbid hypertension, PNPLA3 genotype, FIB-4
Park et al. (2020)	Korea	ultrasound or ICD code 9/10	2003-2017	atrial fibrillation	cross-sectional	74,946	380	51	53,886/21,060	not available	FIB-4 (continuous variable)	OR	1.44 (1.33-1.55)	2.26 (1.74-2.92)	age, sex, body mass index, hypertension, diabetes, hypercholesterolemia, smoking, FIB-4
											APRI (continuous variable)	OR	1.22 (1.08-1.76)		

											APRI (>0.5 vs. ⩽0.5)	OR	1.27 (0.91-1.76)	1.08 (0.68-1.73)	age, sex, body mass index, hypertension, diabetes, hypercholesterolemia, smoking, FIB-4
Niederseer et al. (2020)	Austria	ultrasound or ICD code 9/10	2010~2014	CVD risk score (the Framingham risk score, Q4-FRS)	cross-sectional	975	322	60	556/419	not available	NFS (continuous variable)	OR	1.60 (1.41-1.83)	1.30 (1.09-1.54)	sex, age, concomitant diagnosis of metabolic syndrome, NFS
Henson et al. (2020)	USA	biopsy-proven	2011~2018	CVD	cohort	285	26	53	119/166	5.2	NFS (>0.676 vs. ≤0.676)	HR	4.61 (2.28-9.32)	3.16 (1.50-6.62)	FRS, high-risk FRS, atherosclerotic cardiovascular disease, NFS
											APRI (continuous variable)	HR	1.57 (0.95-2.59)		
Han et al. (2020)	Korea	a comprehensive NAFLD score ≥ 40 OR FLI ≥ 60	2008~2011	CVD risk score (ASCVD risk score, atherosclerotic cardiovascular disease)	cross-sectional	2,241	NA	54	1,118/1,123	not available	FIB-4 (>2.67 vs. ≤2.67)	OR		2.38 (1.48-3.84)	age, sex, exercise, current smoking, hypertension, diabetes, obesity, central obesity, HOMA-IR, CKD, hyper-LDL cholesterolaemia, hypo-HDL cholesterolaemia
Song et al. (2020)	Korea	ultrasound	2011.1~2015.12	coronary artery calcium score>100	cross-sectional	665	52	52	486/179	not available	FIB-4 (continuous variable)	OR	3.02 (1.76-5.18)		

											NFS (continuous variable)	OR	1.94 (1.49-2.54)		
											APRI (continuous variable)	OR	1.80 (0.32-10.12)		
Onnerhag et al. (2019)	Sweden	biopsy-proven	1978~2006	CVD	cohort	144	17	53	61/83	18.8	FIB-4 (>2.67 vs. ≤1.3)	HR		6.52 (3.07-13.86)	sex, BMI, CVD, diabetes, hypertension, fibrosis stage
											FIB-4 (1.3~2.67 vs. ≤1.3)	HR		2.67 (1.40-5.09)	sex, BMI, CVD, diabetes, hypertension, fibrosis stage
											NFS (>0.676 vs ≤-1.455)	HR		16.88 (5.68-50.23)	sex, CVD, hypertension, fibrosis stage
											NFS (1.455~0.676 vs. ≤-1.455)	HR		4.39 (2.39-8.07)	sex, CVD, hypertension, fibrosis stage
											APRI (0.5~1.0 vs. ≤0.5)	HR		1.05 (0.62-1.82)	age, sex, BMI>25, CVD, diabetes, hypertension, fibrosis stage
											APRI (>1.5 vs. ≤0.5)	HR		3.21 (1.40-7.37)	age, sex, BMI>26, CVD, diabetes, hypertension, fibrosis stage
Corey et al. (2016)	USA	ICD code 9/10	not available	CVD	cross-sectional	8,409	3,243	56	4,441/3,968	not available	NFS (>0.676 vs. ≤0.676)	OR	2.52 (1.79-3.55)		

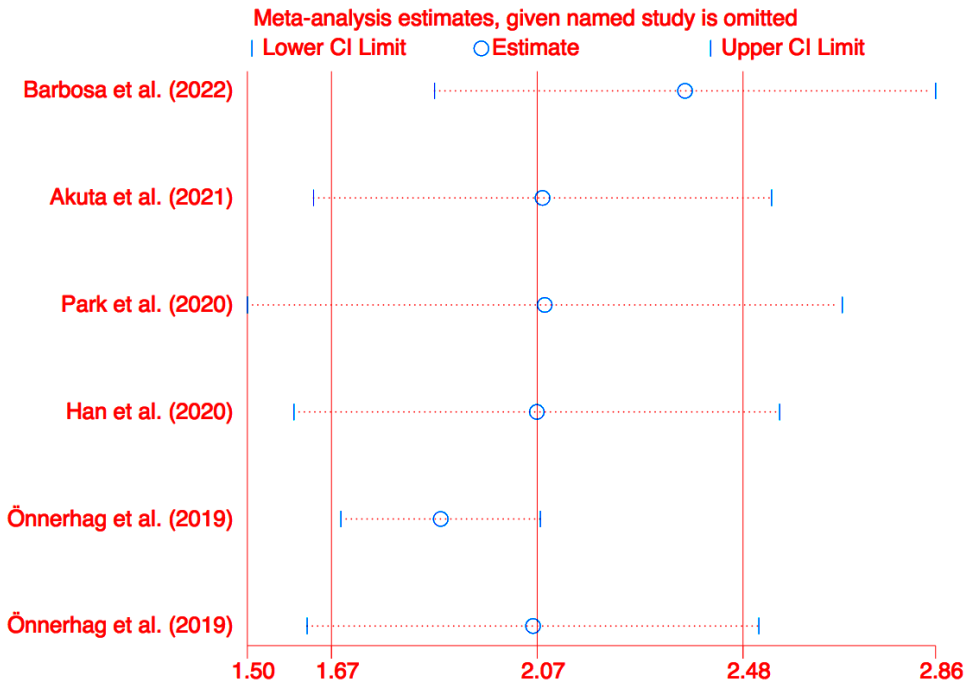
Supplementary 3. Detailed NOS score for the cohort studies included in this meta-analysis.

Study	Selection	Comparability	Outcome/Exposure
Barbosa et al. (2022)	****	**	***
Akuta et al. (2021)	****	*	***
Henson et al. (2020)	****	**	***
Onnerhag et al. (2019)	****	*	**

Supplementary 4. Detailed AHRQ assessment for the cross-sectional studies included in this meta-analysis.

Study	Define the source of information (survey, record review)	List inclusion and exclusion criteria for exposed and unexposed subjects (case and controls) or refer to previous publications	Indicate time period used for identifying patients	Indicate whether or not subjects were consecutive if not population-based	Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements	Explain any patient exclusions from analysis	Describe how confounding was assessed and/or controlled	If applicable, explain how missing data were handled in the analysis	Summarize patient response rates and completeness of data collection	Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained
Park et al. (2020)	yes	yes	yes	yes	unclear	yes	yes	yes	no	unclear	unclear
Niedeseer et al. (2020)	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	unclear	unclear
Han et al. (2020)	yes	yes	yes	yes	unclear	yes	yes	yes	unclear	yes	unclear
Song et al. (2019)	yes	yes	yes	yes	unclear	yes	yes	unclear	unclear	unclear	unclear
Corey et al. (2016)	yes	yes	no	yes	unclear	yes	no	unclear	unclear	yes	unclear

Supplementary 5. Results of sensitivity analysis that eliminated each of included studies one at a time for the association between FIB-4 and CVD risk in patients with NAFLD.



Supplementary 6. Results of univariate meta regression analyses of comparison, country, NAFLD diagnosis, sample size, study design and risk of bias for the association between FIB-4 and CVD risk in patients with NAFLD.

factors	Coef.	SE	t value	p value	95%CI
comparison	0.03	0.15	0.19	0.86	-0.39, 0.44
cons_	0.88	0.36	2.46	0.07	-0.11, 1.87
country	0.25	0.07	3.47	0.02	0.05, 0.45
cons_	0.34	0.11	3.13	0.04	0.04, 0.64
NAFLD diagnosis	0.57	0.27	2.11	0.10	-0.18, 1.31
cons_	0.13	0.33	0.40	0.71	-0.79, 1.06
study design	-0.16	0.37	-0.44	0.68	-1.20, 0.87
cons_	1.16	0.55	2.12	0.10	-0.36, 2.69
sample size	0.57	0.27	2.11	0.10	-0.18, 1.31
cons_	0.13	0.33	0.40	0.71	-0.79, 1.06
risk of bias	0.35	0.31	1.11	0.33	-0.52, 1.21
cons_	0.40	0.48	0.83	0.46	-0.94, 1.73