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Can advanced fibrosis be reliably excluded by simple non-invasive fibrosis scoring systems? Diagnostic performance of FIB-4 and NFS in Turkish patients with biopsy-proven non-alcoholic fatty liver disease

Eda Kaya[1], Alev Bakir[2], Yusuf Yilmaz[3]

[1]*Istanbul University-Cerrahpasa Cerrahpasa Faculty of Medicine, Turkey*
[2]*Halic University Department of Biostatistics and Medical Informatics, Turkey*
[3]*Marmara University Department of Gastroenterology, Turkey*

INTRODUCTION: Histopathological examination of a liver biopsy specimen is currently the reference standard for staging hepatic fibrosis. However, the invasive nature of liver biopsy – which portends a significant risk of sampling errors, complications, and costs – has led to a continuous quest for non-invasive diagnostic methods. Simple blood-based fibrosis scores based on routine parameters – including the FIB-4 and non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS) – can be easily obtained and thus are suitable for screening purposes. Several cutoffs for the identification of advanced fibrosis have been proposed. For example, FIB-4 scores of <1.3 and >2.67 or <1.45 and >3.25 have been used to identify patients with a low and high risk for advanced fibrosis, respectively. Similarly, NFS scores <-1.455 and >0.676 indicate a low and high risk for advanced fibrosis, respectively. In this study, we sought to investigate the diagnostic performances of FIB-4 and NFS in the detection of advanced fibrosis in patients with biopsy-proven NAFLD.

METHODS: This is a retrospective analysis of prospectively collected data. The study sample consisted of 463 consecutive patients with biopsy-proven NAFLD patients who were followed-up in our outpatient clinic over a 4-year period (between 2009–2010 and 2017–2018). The diagnostic performances of published cutoffs of FIB-4 and NFS in the detection of advanced fibrosis were compared with those reported in the literature. In addition, the optimal cutoff points in our population were determined.

RESULTS: The general characteristics of the study patients are summarized in Table 1. On histopathological examination, 34.1% of patients had an F0 fibrosis stage, 31.1% had F1, 17.3% had F2, 13.6% had F3, and 3.9% had F4. With regard to the FIB-4 cutoffs for low risk for advanced fibrosis, the sensitivity values were 64% and 48%, with positive predictive values (PPVs) of 0.342 and 0.358, respectively. A cutoff of 2.67 and 3.25 for high risk of advanced fibrosis had a negative predictive value (NPV) of 0.843 and 0.839, with specificity values of 97% and 98%, respectively. In our study population, the optimal cutoff for advanced fibrosis was 1.275 – which produced an area under ROC curve of 0.731 (95% confidence interval, 0.672–0.790) and was associated with a high kappa value. With regard to the NFS cutoff identifying low risk of advanced fibrosis, the sensitivity and the PPV were 71% and 0.291, respectively. Conversely, the NFS cutoff for high risk of advanced fibrosis had a specificity 96% and NPV of 0.842, respectively. In our sample, the optimal NFS cutoff for identifying patients with high risk of advanced fibrosis was -1.485 (Table 2).

CONCLUSION: Our results indicate that NFS and FIB-4 have an acceptable clinical usefulness for excluding advanced fibrosis, whereas their diagnostic utility for identifying patients with this condition remains suboptimal.

Keywords: Non-alcoholic fatty liver disease, noninvasive fibrosis scoring system, FIB-4, NFS

General characteristics of the 463 patients with NAFLD	
Age, mean±SD (years)	46.19±10.63
Sex (male/female)	243/220
Body mass index, mean±SD (kg/m2)	31.74±5.15
Lean/overweight/obese	6.5%/37.2%/60.8%
Metabolic syndrome	63.8%
Type 2 diabetes mellitus	34%
Systolic blood pressure, mmHg	127.78±17.38
Diastolic blood pressure, mmHg	82.29±10.86
Waist circumference, cm	104.16±10.54
AST, U/L	49.59±32.66
ALT, U/L	77.49±52.59
Total cholesterol, mg/dL	212.50±46.05
Triglycerides, mg/dL	190.29±109.0
HDL cholesterol, mg/dL	45.57±11.0
Platelets, × 10^3 per microliter	222±67
Hemoglobin, mg/dL	14.36±1.62
Uric acid, mg/dL	6.34±1.57
Glucose, mg/dL	108.96±30.25
HbA1c, %	6.11±2.86
HOMA-IR	4.39±2.97
HOMA-IR > 2.7	73.2%
FIB-4 score, mean±SD	1.24±0.86
FIB-4 score low/indeterminate/high risk (<1.3, >2.67)	67.2%/27.8%/5%
FIB-4 score low/indeterminate/high risk (<1.45, >3.25)	75.8%/20.7%/3.5%
NFS, mean±SD	-1.73±1.57
NFS low/indeterminate/high risk (<-1.455, >0.676)	57%/34.4%/5.6%
SAF algorithm classification, NASH/NAFL	90.3%/9.7%
Grade of activity (A) according to SAF score, A0 / A1 / A2 / A3 / A4	1.9%/6.9%/22.1%/34.2%/34.8%
Stage of fibrosis (F) according to SAF score, F0 / F1/ F2 / F3 / F4	34.1%/31.1%/17.3%/13.6%/3.9%
Significant fibrosis (≥F2)/advanced fibrosis (≥F3)/Cirrhosis (F4)	34.8%/17.5%/3.9%

Comparison of different cutoffs for FIB-4 and NFS in published studies

FIB-4 cut-off	Sensitivity (%)	Specificity (%)	Area under curve	95% CI	False negative	False positive	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Kappa
Yilmaz et al. (current study; n=463)											
<1.3	64	74	-	-	0.358	0.262	0.342	0.907	2.452	0.485	0.283
<1.45	48	81	-	-	0.519	0.191	0.358	0.880	2.52	0.641	0.252
>2.67	15	97	-	-	0.852	0.029	0.522	0.843	5.145	0.877	0.166
>3.25	11	98	-	-	0.889	0.018	0.563	0.839	6.063	0.905	0.136
>1.275	68	73	0.731	0.672-0.790	0.321	0.267	0.350	0.915	2.543	0.438	0.301
Shah et al. (n=541)											
<1.3	74	71	0.802	0.758-0.847	-	-	0.43	0.90	-	-	-
>2.67	33	98			-	-	0.80	0.83	-	-	-
McPherson et al. (n=145)											
<1.3	85	65	0.86	0.78-0.94	-	-	0.36	0.95	-	-	-
>3.25	26	98			-	-	0.75	0.85	-	-	-
Sterling et al. (n=555)*											
<1.45	67	71	-	-	-	-	0.38	0.89	-	-	-
>3.25	23	97	-	-	-	-	0.645	0.826	-	-	-
NFS cut-off	Sensitivity (%)	Specificity (%)	Area under curve	95% CI	False negative	False positive	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Kappa
Yilmaz et al. (current study; n=463)											
<-1.455	71	63	-	-	0.284	0.369	0.291	0.913	1.94	0.45	0.220
>0.676	15	96	-	-	0.852	0.037	0.462	0.842	4.042	0.884	0.152
>-1.485	74	62	0.715	0.652-0.777	0.259	0.377	0.294	0.919	1.965	0.416	0.228
Angulo et al. (n=480)											
<-1.455	82	77	0.88	0.85-0.92	-	-	0.56	0.93	3.567	0.229	-
>0.676	51	98			-	-	0.9	0.85	25.966	0.498	-

**This study included HCV/HIV coinfected patients.*