

News Release

Title

Utility and Limitation of serum-based non-invasive tests to predict liver fibrosis in Asian patients with non-alcoholic fatty liver disease - multicenter multinational clinical study-

Key Points

- Liver fibrosis is the most important factor associated with in the prognosis in patients with nonalcoholic fatty liver disease (NAFLD), and noninvasive fibrosis markers (NITs) have been developed and used to predict liver fibrosis.
- In this multinational study, serum-based NITs, FIB-4 index, NAFLD fibrosis score (NFS), and Hepamet fibrosis (HFS), were evaluated in 1,489 Asian patients with NAFLD, and FIB-4 index showed the highest prediction ability for liver fibrosis among these NITs.
- However, the predictive abilities of these NITs were found to be widely reduced with younger age, obesity, and the presence of diabetes.
- Young NAFLD patients with obesity and type 2 diabetes should be evaluated for fibrosis by the other methods (i.e. elastography) in addition to these serum-based NITs.

Summary

Liver fibrosis is the key driver of long-term mortality in patients with non-alcoholic fatty liver disease (NAFLD). Several non-invasive tests (NITs) for liver fibrosis based on blood tests and simple factors such as age and body mass index have been developed and determined to be reasonably accurate in the overall population of patients with NAFLD. Our multinational study of 1,489 NAFLD patients with liver biopsy found that the performance of some of these well-known tests (namely FIB-4, NFS, and HFS) varied greatly by age, presence of obesity, and diabetes. Even with the FIB-4 index as the best performing test overall, the ability of the FIB-4 index to detect advanced fibrosis was unacceptably poor (accuracy rate ~60%) in young (≤ 60 years) or obese diabetic patients. This study indicated that young obese diabetic patients with NAFLD should be assessed for fibrosis by other methods.

Research Background

Non-alcoholic fatty liver disease (NAFLD) is rapidly increasing in Asia, including Japan, and the frequency of NAFLD in the general population in Japan is expected to increase to approximately 40% by 2030 and 45% by 2040. The most prognostic risk factor in patients with NAFLD is known to be liver fibrosis. Currently, liver biopsy is still the gold standard for assessing liver fibrosis in NAFLD; however, it is associated with sampling error in pathological assessment, high cost, and rare but lethal complications such as hemorrhage. Therefore, various non-invasive tests (NITs) have been developed, such as serum-based markers and imaging for measuring liver stiffness and fibrosis. The FIB-4 index and NAFLD fibrosis score (NFS) are serum-based NITs that are calculated by combining clinical data such as age, liver enzymes, and metabolic factors, especially before referral to a hepatologist. The NAFLD guidelines recommend a diagnostic algorithm based on these markers, but it has been pointed out that the diagnostic performance of these markers can vary depending on the components of the NITs, such as age and presence of type2 diabetes mellitus (T2DM). Therefore, we aimed to compare the predictive utility of FIB-4, NFS, and the newly proposed Hepamet fibrosis score (HFS) in determining the presence of significant and advanced liver fibrosis among biopsy-proven patients who have NAFLD by age, BMI, and the presence of T2DM.

Research Results

Using clinical data from 1,489 Asian patients with NAFLD confirmed by liver biopsy (6 centers: Japan (n=821), Taiwan (n=341), Korea (n=327)), we investigated the predictive ability of three NITs: FIB-4 index, NFS, and HFS, for liver fibrosis. By histology, 44.0% (655/1489) of the overall cohort had F2-4 and 20.6% (307/1489) had F3-4 fibrosis. The results of ROC analysis showed that the FIB-4 index, which is calculated by the simplest formula among these NITs, had the highest predictive ability for liver fibrosis (Figure. 1).

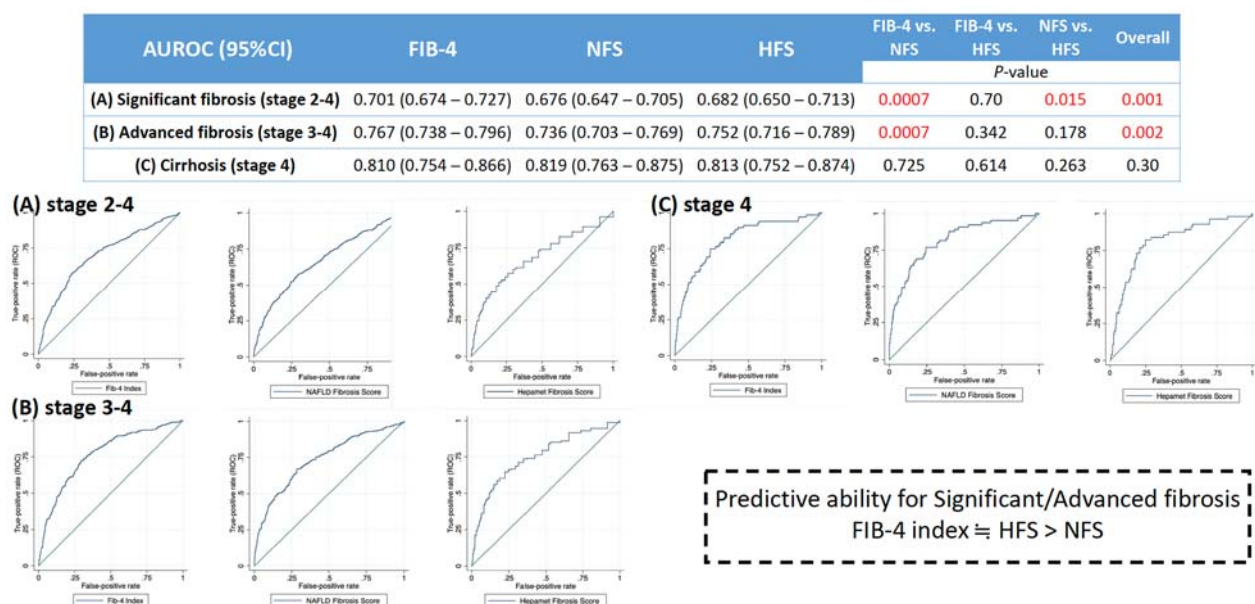


Figure.1 Predictive accuracy of NITs for predicting fibrosis with ROC analysis

When examined by age, BMI, and presence of type 2 diabetes, we found that the AUROCs of all 3 NITs were generally higher in older (> 60 years), nonobese (BMI < 25 kg/m²), and non-diabetic patients, though overall the best performance was observed with FIB-4 among nonobese (BMI<25) diabetic patients (AUROC 0.92). The worst performance was observed in younger patients with T2DM for all NITs including FIB-4 (AUROC 0.63-0.66) (Figure 2).

AUROC (95%CI)	FIB-4 index	NFS	HFS	P-value		
				(FIB-4 vs. NFS)	(FIB-4 vs. HFS)	(NFS vs. HFS)
Age > 60	0.74 (0.69 – 0.79)	0.72 (0.66 – 0.77)	0.72 (0.66 – 0.78)	0.64	0.84	0.9
Age ≤ 60	0.72 (0.68 – 0.76)	0.67 (0.62 – 0.72)	0.69 (0.64 – 0.74)	0.0004	0.3	0.3
BMI < 25	0.83 (0.76 – 0.88)	0.80 (0.72 – 0.86)	0.80 (0.71 – 0.87)	0.03	0.1	0.9
BMI ≥ 25	0.76 (0.73 – 0.79)	0.72 (0.68 – 0.76)	0.75 (0.70 – 0.79)	0.0001	0.2	0.2
No T2DM	0.78 (0.74 – 0.82)	0.74 (0.69 – 0.78)	0.75 (0.70 – 0.79)	<0.0001	0.04	0.5
T2DM	0.72 (0.67 – 0.77)	0.70 (0.64 – 0.76)	0.69 (0.63 – 0.76)	0.09	0.8	0.5

The ability of NITs to detect advanced fibrosis was unacceptably poor in young or obese diabetic patients.

AUROC (95%CI)	FIB-4 index		NFS		HFS	
	No T2DM	T2DM	No T2DM	T2DM	No T2DM	T2DM
Age > 60	0.75 (0.69 – 0.82)	0.73 (0.65 – 0.81)	0.73 (0.66 – 0.81)	0.73 (0.64 – 0.81)	0.74 (0.65 – 0.81)	0.70 (0.61 – 0.79)
Age ≤ 60	0.74 (0.68 – 0.79)	0.66 (0.59 – 0.74)	0.64 (0.58 – 0.71)	0.64 (0.56 – 0.72)	0.65 (0.57 – 0.73)	0.63 (0.54 – 0.71)
BMI < 25	0.78 (0.69 – 0.85)	0.92 (0.85 – 0.97)	0.76 (0.64 – 0.84)	0.87 (0.75 – 0.95)	0.70 (0.56 – 0.82)	0.87 (0.77 – 0.94)
BMI ≥ 25	0.79 (0.75 – 0.84)	0.67 (0.60 – 0.74)	0.73 (0.68 – 0.78)	0.65 (0.58 – 0.71)	0.75 (0.69 – 0.81)	0.66 (0.58 – 0.73)

The diagnostic performance for each NIT was lowest in young adults with type 2 diabetes. Conversely, non-obese NAFLD with type 2 diabetes showed the highest diagnostic performance.

Figure.2 Comparison of AUROCs for advanced fibrosis (F3-4) of non-invasive tests by age, BMI, and T2DM

Research Summary and Future Perspective

The results of this study indicated that young NAFLD patients with obesity and T2DM should be evaluated for liver fibrosis by additional methods other than these serum-based NITs. We believe it is important for the physicians in primary care to understand the utilities and limitations of these NITs, especially when referring patients to hepatologists in tertiary centers. Future multicenter international studies, including non-Asian NAFLD, will be needed to determine what additional tests are suitable to predict liver fibrosis in these populations.

Publication

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