# Diagnostic and prognostic biomarkers for the screening of patients with metabolic liver disease risk

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*Editor*

The increasing global prevalence of liver metabolic diseases associated with overweight, diabetes, high blood pressure and dyslipidemia has become a major public health problem. The spectrum of metabolic liver diseases – the non-alcoholic fatty liver disease (NAFLD) – parallels the prevalence of metabolic syndrome and is associated with the number of its components.[1-3]

NAFLD is characterized by excessive hepatic fat accumulation (steatosis) and it associates insulin resistance (IR) in the absence of secondary causes and in the absence of excessive alcohol intake (≥30 g for men and ≥20 g for women).[4-5] Patients who consume moderate amounts of alcohol may still have a predisposition towards NAFLD in the presence of metabolic risk factors. Steatosis is very common in developed countries (17-46%) and its prevalence is increasing with the body mass index: 67% with overweight and 94% with obesity.[6-7]

NAFLD could evolve to a more advanced condition [non-alcoholic steatohepatitis (NASH)] having different prognosis than isolated steatosis and a large spectrum of disease severity, including hepatic fibrosis, cirrhosis and hepatocellular carcinoma (HCC).

A recent study has assessed retrospectively a tertiary center cohort, and has shown that the 10-years comparative overall survival of patients with NAFLD was lower than that of patients with chronic hepatitis C (CHC), mainly explained by the fact that patients with NAFLD had older ages, and by the associated non-liver-related deaths.[8] NAFLD overall survival was lower than in chronic hepatitis B (CHB) and higher than in alcoholic liver diseases (ALD). It was known that cardiovascular disease has higher incidence and prevalence in patients with NAFLD than in matched controls[9] and in a recent prognostic study, it was observed that cardiovascular disease is a more frequent cause of death than liver disease in patients with NAFLD versus CHC, even in subjects younger than 50 years.[8] NAFLD is also associated with other extra-hepatic diseases as chronic kidney disease[10] and non-liver cancers (i.e., colorectal cancer).[11] A recent study highlighted age as being a key prognostic factor: patients with NAFLD who were 50 years of age or older had lower survivals than patients with CHC, mainly due to non-liver-related cancers, and cardiovascular-related deaths, despite a lower number of liver-related deaths.[8]

Clinical practice guidelines released by the European Associations for the Study of the Liver (EASL), of Diabetes (EASD) and of Obesity (EASO) recommend that patients with metabolic risk factors (particularly, obesity, metabolic syndrome or type 2 diabetes) undergo diagnostic procedures for NAFLD, specifically the demonstration of excessive liver fat by ultrasound or steatosis biomarkers.[1] The validated serum biomarkers for detecting ≥5% of hepatocytes steatosis that have been recommended are: Fatty Liver Index, SteatoTest (APHP-Sorbonne University Patent) and NAFLD Fat score. SteatoTest is the only serum biomarker that has demonstrated prognostic value in a cohort including patients with type 2 diabetes and dyslipidemia.[12] The presence of severe steatosis as per SteatoTest was associated with a twofold increased risk of all-cause mortality and of cardiovascular morbidity.

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SteatoTest is associated in the FibroMax panel with the FibroTest (APHP-Sorbonne University Patent), the pioneer quantitative marker for the severity of fibrosis, widely validated in subjects with the four most common chronic diseases: CHC and CHB,[13] ALD[14] and NAFLD.[15]

The European clinical practice diagnostic flow-chart to assess and monitor disease severity in the presence of suspected NAFLD recommended the use of serum fibrosis biomarkers in subjects having metabolic risk factors and steatosis even with normal liver enzymes. The recommended biomarkers are NAFLD Fibrosis Score, FIB-4, and three patented tests: FibroTest, FibroMeterV2G and ELF.[1] Prognostication with serum biomarkers in NAFLD, compared to other viral or alcoholic causes, is more difficult to demonstrate, probably because of the slower progression of fibrosis, because of the higher mortality of extra-hepatic origin and of a lower incidence of hepatic death, requiring larger cohorts and longer follow-ups. The review of the literature for liver-related mortality prognosis on the three patented tests found only FibroTest and FibroMeterV2G being validated on specific NAFLD populations with more than 5 years follow-up and enough events (deaths).[8,15,16] Only FibroTest has demonstrated higher cumulative probability of death in cirrhotic NAFLD patients according to cutoffs. In cirrhotic patients, the 10-years mortality was associated to liver-related deaths both in NAFLD and CHC and the prevalence of death related to primary liver cancer was 50% in NAFLD versus 38% in CHC.[8]

In a prospective study using FibroTest to screen diabetic patients without known liver disease, the prevalence of HCC was as high as six per thousand in type 2 diabetics 45 years older or more.[17] ALT does not exclude fibrosis in patients with risk of NAFLD and specific markers of fibrosis should be used. Despite the fact that increased ALT levels were associated with a fivefold higher risk of severe fibrosis in type 2 diabetic patients, physicians must be aware that ALT levels cannot be used to screen for severe fibrosis in diabetic patients, one third of them having normal ALT.[18] Moreover, FibroTest can improve the Framingham risk score in type-2 diabetes for the risk of cardiovascular-related death.[12]

Diabetes type 2 and age over 50 years are the best predictors of evolution towards NASH. NASH is defined as the presence of both steatosis (5% of hepatocytes or more) and lobular inflammation with hepatocyte injury (e.g., ballooning), with or without fibrosis.[4] The non-invasive assessment of inflammation in NASH lacks markers sufficiently validated, most of the existing markers being related to apoptosis or oxidative stress.[19] A new quantitative multi-analyte test, NashTest 2 (APHP-Sorbonne University Patent) was recently validated permitting to identify more cases of NASH with severe fibrosis compared to the histological definition (NASH-CRN).[20] NashTest 2 could be easily combined with FibroTest in order to identify clinically advanced diseases (activity A2 grade or fibrosis F2 stage). Moreover, for the first time, an activity marker, NashTest-2, has demonstrated significant prognostic values for survival without liver-related death, regardless of FibroTest.[8]

Liver biomarkers such as FibroTest, SteatoTest, and newly developed NashTest 2 are of particular utility in patients with metabolic liver disorders. FibroTest and SteatoTest have demonstrated prognostic value for predicting overall survival and allow a better assessment of both the hepatic risk and the cardiovascular risk.

Screening NAFLD risk subjects for metabolic liver diseases using biomarkers validated for both diagnosis and prognosis is possible today in order to make early diagnosis, identify the subjects most at risk, follow up longitudinally the liver lesions evolution and stratify patients according to the risk of major complications as HCC.

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