Non-Invasive Assessment Of Liver Fibrosis, Inflammation And Steatosis

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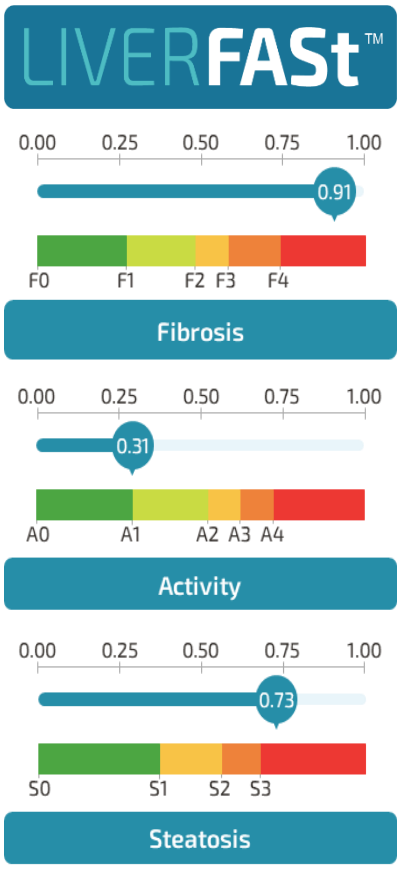
LIVER DISEASE: CAUSE AND PREVALENCE

Chronic liver diseases (CLDs), such as chronic viral hepatitis, non-alcoholic fatty liver diseases (NAFLD) and non-alcoholic steatohepatitis (NASH), are leading causes of morbidity and mortality globally and usually develops over many years. The prevalence of NAFLD has increased in recent years (15% in 2005 to 25% in 2010)[1]. As approximately 20% of NAFLD cases develop NASH, the associated increase in NASH during the same period is to be expected (33% in 2005 to 59.1% in 2010)1. Indeed, NAFLD now represents the most common cause of abnormal liver blood tests and chronic liver disease in the Western world[2]. Non-alcoholic steatohepatitis (NASH) is currently the second leading cause of liver disease among those awaiting liver transplantation in the United States[2]. Numerous clinical practice guidelines including AASLD, EASL-EASD-EASO, APASL, and WHO recommend non-invasive biomarker-based diagnostic modalities to diagnose liver diseases[3–7].



LIVERFASt™ is a blood based diagnostic test that combines 10 biomarkers and algorithm technology to determine the fibrosis, activity and steatosis stages of the liver.

LIVERFASt™ utilizes the following biomarkers:

- Alpha-2-Macroglobulin
- Haptoglobin
- Apolipoprotein A1
- Total Bilirubin
- GGT
- ALT (P5P)
- AST (P5P)
- Fasting Glucose
- Triglyceride
- Total Cholesterol

DIAGNOSIS AND STAGING OF LIVER DISEASE

A challenging element of the diagnostic workup of patients with NAFLD is the determination of disease severity. The goal here is to identify patients with more advanced disease at increased risk for morbidity and mortality.

Percutaneous liver biopsy remains the gold standard for making a precise diagnosis of NAFLD with specification categorization and is necessary to assess the histopathologic criteria essential to making a diagnosis of NASH[8,9]. Biopsy allows for confirmation of steatosis as well as determining the degree of lobular inflammation, ballooning, and fibrosis. Commonly used scoring systems for evaluating the severity of NAFLD include the NAFLD Activity Score, which evaluates and assigns scores to 4 domains: steatosis (0-3), lobular inflammation (0-3), hepatocyte ballooning (0-2), and liver fibrosis (0-4) 10. The first 3 elements can be summed to generate an aggregate value whereas fibrosis staging is kept separate.

NASH is diagnosed based on an overall assessment by a pathologist using scoring systems such as the Steatosis, Activity, and Fibrosis (SAF) score, which evaluates for the presence and extent of each individual component of steatosis, inflammation, and ballooning[10].

LIVERFASt™: AN ADVANCED BLOOD BASED TEST FOR LIVER DISEASE

LIVERFASt™ is a non-invasive clinical and staging tool for staging and grading fatty liver disease that utilizes a combination of basic blood biomarkers and algorithm technology to generate a report for providers use and it has been developed as an alternative to liver biopsy[8,11–13]. It is a reliable, and reproducible tool which provides grading or staging of the three liver lesions: fibrosis, activity and steatosis[11].

LIVERFASt™ DEVICE COMPONENTS

The LIVERFASt™ system is comprised of two parts:

1. Biomarker digital assays for the non-invasive diagnostic test.

2. Software containing a proprietary algorithm to generate the LIVERFASt™ biomarker digital assay scores from the serum biochemical markers, adjusted for patient demographics.

The serum biomarker assays are conducted by a lab using FDA cleared assays. Those results are then inputted into the LIVERFASt™ cloud-based physician portal in order to calculate the LIVERFASt™ scores using the LIVERFASt™ algorithm.

Fibrosis

SCORE	STAGE	INTERPRETATION
0.75 - 1.00	F4	Severe fibrosis (Cirrhosis)
0.59 - 0.74	F3	Significant fibrosis
0.49 - 0.58	F2	Moderate fibrosis
0.28 - 0.48	F1	Minimal fibrosis
0.00 - 0.27	F0	No fibrosis

Activity

SCORE	STAGE	INTERPRETATION
0.73 - 1.00	A4	Severe activity
0.63 - 0.72	A3	Significant activity
0.53 - 0.62	A2	Moderate activity
0.30 - 0.52	A1	Minimal activity
0.00 - 0.29	A0	No activity

Steatosis

SCORE	STAGE	INTERPRETATION
0.69 - 1.00	S3	Severe steatosis (>32%)
0.57 - 0.68	S2	Moderate steatosis (6-32%)
0.38 - 0.56	S1	Minimal steatosis (1-5%)
0.00 - 0.37	S0	No steatosis (<1%)

CLINICAL BIOMARKERS: LIVERFASt™

The LIVERFASt™ machine learning based algorithm uses a combination of anthropometric and serum biomarkers that are individually used to provide general assessments of various bodily functions. The required LIVERFASt™ platform serum biomarkers are:

- Alpha-2-Macroglobulin
- Apolipoprotein A1
- Haptoglobin
- Total Bilirubin
- GGT
- AST
- ALT
- Fasting Cholesterol (Total)
- Fasting Triglycerides
- Fasting Glucose

These biomarkers are obtained from a CLIA certified lab and the results are entered into the LIVERFASt™ platform. Those individual serum biomarkers have been identified as appropriate biomarkers for liver disease evaluation[14–19]. Each serum biomarker results from FDA cleared assays, in addition to patient characteristics including age, gender, height and weight, are used in the LIVERFASt™ algorithm for scoring the three liver histological features, as described below. A LIVERFASt™ report is generated with all three non-invasive test scores, for the healthcare provider to use.

1. Fibrosis score to detect the degree of fibrosis. The result is provided as a score from 0 to 1, proportional to the severity of the fibrosis, with a conversion to the SAF scoring system (from F0 to F4). The five scores of histological scoring system are: F0 (no fibrosis), F1 (minimal fibrosis), F2 (moderate fibrosis), F3 (significant fibrosis), and F4 (severe fibrosis /cirrhosis).

2. Activity score to detect the degree of ballooning and lobular inflammation. The result is provided as a score of 0 to 1, proportional to the significance of the activity, with a conversion to the SAF scoring system (from A0 to A4). The five scores of histological scoring system are: A0 (no activity), A1 (minimal activity), A2 (moderate activity), A3 (significant activity), and A4 (severe activity).

3. Steatosis score to detect the degree of steatosis. The result is provided as a score from 0 to 1, proportional to the severity of steatosis, with a conversion to the SAF scoring system (from S0 to S3). The four scores of histological scoring system are: S0 (no steatosis), S1 (minimal steatosis), S2 (moderate steatosis), and S3 (steatosis activity).

To generate the Fibrosis, Activity, and Steatosis scores, the software analyzes the results of 10 biochemical markers, including alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, gamma glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, cholesterol (total) and fasting glucose in the combination with age, gender, height, and weight.

In order to obtain a LIVERFASt™ digital assay test report, a healthcare provider must prescribe the LIVERFASt™ digital assay test from the web portal, where LIVERFASt™ ordering is integrated with laboratory ordering systems.

PERFORMING LIVERFASt™ EVALUATION

A simple blood draw will be performed to obtain the laboratory panel results so the LIVERFASt™ machine learning technology can be applied. The final report with patient's stage of liver fibrosis, activity and steatosis will be revised by the physician and communicated appropriately to the patient.

SUGGESTED USE USING LIVERFASt™ IN PATIENTS WITH NAFLD/NASH IN COMPARISON WITH OTHER PRODUCTS

From the patient and clinician perspective, current diagnostic techniques are expensive, invasive and may display inter-observer variations[11,20]. The modified SAF score and stage generated by LIVERFASt™ provides a simple and convenient staging of NAFLD and NASH.

Non-invasive diagnostic tools such as LIVERFASt™ are easy to perform, less expensive, and readily available and aid to the early diagnosis and better prognosis in patients with NAFLD and NASH.

Staging/Grading of three lesions – Fibrosis Activity & Steatosis

	LIVERFASt™	Transient Elastography	MRI	Ultrasound	APRI	ELF	FIB-4
Fibrosis	YES	YES	YES	NO	YES	YES	YES
Activity	YES	NO	NO	NO	NO	NO	NO
Steatosis	YES	YES	YES	YES	NO	NO	NO
# Biomarkers	10	NA	NA	NA	2	3	4

LIVERFASt™ provides complete evaluation and staging of fibrosis, activity and steatosis

(MRI = Magnetic Resonance Imaging, APRI = AST-to-Platelet Ratio Index,

ELF = Enhanced Liver Fibrosis, FIB-4 = Index for Liver fibrosis)

WORLDWIDE USE OF LIVERFASt™

The LIVERFASt™ system has been successfully used worldwide as an advanced algorithm using the combination of serum biomarkers and patient demographics for staging of fibrosis, inflammatory activity, and steatosis of liver disease in adult non-alcoholic fatty liver disease (NAFLD) patients from asymptomatic early stage through non-malignant late stage. In a recent study, we analyzed the real-world data of biomarker-based diagnosis of NAFLD in approximately 13000 subjects from South-East Asia. These patients underwent the LIVERFASt™ test for diagnosis of fatty liver disease revealing 14.03% of the patients exhibited significant fibrosis with fibrosis scores ranging between 0.6-1.00. Approx. 6.13% of the patients had severe hepatic inflammation. Steatosis (74.58%) was observed in most patients within this dataset. Severe steatosis was observed in 28.73% of the patients. NAFL and NASH were diagnosed in 8.92% of the patients using modified SAF scores obtained using LIVERFASt™. Approx. 4.49% of the patients had NAFL only while 1.91% of the patients had either NAFL or NASH (manuscript submitted for publication). Early liver disease detection allows patients treatment options for a healthier and productive life. Once liver disease progresses to cirrhosis or cancer, treatment options are limited and expensive. Reducing the almost US$2 Billion liver disease economic burden to the United States, requires a breakthrough technology, which brings diagnosis to the patient Current liver disease diagnosis devices are dependent on fixed facilities, which utilize ultrasound, computerized tomography scan (CT), Magnetic resonance imaging (MRI) or biopsy sampling with pathology analysis. The dependency on fixed facility clinical procedures introduces barriers to patients receiving early detection. While it is known that early detection, wellness and cost effectiveness mitigate these realities, and many trends today in clinicals are pushing greater early access to the patients, providers limit screening and detection to patients for which the procedure meets the cost-benefit in the ever-evolving value-based healthcare system. Additionally, requiring patients to travel to radiology or laboratory facilities introduces adherence issues.

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