

THE ECONOMIC TSUNAMI OF LIVER DISEASE

AN EPIDEMIC THAT IS IMPACTING THE FINANCIAL
SOLVENCY OF THE U.S. HEALTHCARE SYSTEM

Author: Stephen A. Harrison, M.D., FACP, FAASLD, COL (ret.), USA,
MC, Visiting Professor of Hepatology, Radcliffe Department of Medicine,
University of Oxford, Medical Director, Pinnacle Clinical Research

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The Economic Tsunami of Liver Disease

An epidemic that is impacting the financial solvency of the U.S. healthcare system



A disease once considered uncommon in the 1980s is now a major epidemic poised to further growth escalating U.S. healthcare costs.

Traditionally a disease of hepatologists, nonalcoholic fatty liver disease (NAFLD) has recently become a major concern for a broad spectrum of health care providers. Primary care physicians (PCPs) and those caring for patients with obesity and type 2 diabetes mellitus (T2DM) are at center stage, as T2DM appears to worsen the course of NAFLD and the liver disease makes diabetes management more challenging.¹

Nevertheless, the nature of this relationship remains complicated. Although the increasing prevalence of NAFLD is frequently attributed to the epidemic of obesity and is often oversimplified as the “hepatic manifestation of the metabolic syndrome,” it is a much more complex disease process that may also be observed in nonobese individuals and in patients without clinical manifestations of the metabolic syndrome.²

It carries both metabolic and liver-specific complications that make its approach unique among medical conditions. Diabetes appears to promote the development of nonalcoholic steatohepatitis (NASH), the more severe form of the disease, and increases the risk of cirrhosis and hepatocellular carcinoma.³

Given its complexity, patients and physicians face a number of uncertainties, including challenges in the diagnosis of NASH, and few pharmacological agents with proven efficacy.

Furthermore, NAFLD, which affects roughly 100 million Americans, is costly to the U.S. healthcare system: **\$32 billion annually**, almost as much as the **\$34 billion annual** costs of stroke.⁴ The prevalence of NAFLD reflects the rising trend of obesity in the United States and is now the most common form of chronic liver disease.⁵ Identifying the economic burden of NAFLD underscores the need for readily available treatments and early detection to save money and lives.

The Economic Tsunami of Liver Disease

Continued

Fortunately, NAFLD can be reversed through diet and lifestyle modification if caught in the early stages, potentially avoiding progression to NASH or fibrosis. In fact, recent advances in diagnosis make it possible for PCPs to be more proactive in the screening of patients with T2DM and NAFLD.⁶ Keep in mind that a high level of evaluation is required by physicians to diagnose NAFLD in patients with T2DM, especially because liver enzymes alone are not reliable as markers of liver disease in patients with NAFLD.⁷

Screening and early detection, in particular, can help to identify patients at risk for more serious conditions. For this reason, it is critical to develop effective and efficient models to identify the subset of NAFLD patients with NASH earlier in the settings where they receive care.

Now clinicians, including PCPs, can utilize **FibroScan®**, a painless five-minute procedure as part of an overall workup to help diagnose NAFLD early on. This non-invasive test quickly provides a quantitative assessment of liver stiffness and fat at the point of care. With over 2,000 peer-reviewed research publications, this technology is the most widely studied tool for point-of-care liver assessment.

NASH Carries a Financial Whiplash

A challenging, high-volume and chronic condition that lacks a standardized care delivery model, NASH has created a global therapeutic treatment market projected to reach **\$21.5 billion** by 2025,⁸ with NASH being the leading cause of liver transplantation in the United States in the coming years. Although its progression rate may be slower than that of other types of liver disease, the incidence of NASH, and its interrelationship with hyperlipidemia, hypertension, Type 2 diabetes, obesity and metabolic syndrome, is increasing throughout the world.⁹

The High Costs of Liver Disease

In a recently published retrospective analysis of the Optum Database, claims for 108,420 patients diagnosed with NAFLD and 108,420 matched controls were evaluated both for peri-diagnosis period – one year pre-diagnosis through five years post diagnosis.¹⁰ For commercially insured patients diagnosed with NAFLD, the claims and costs prior to diagnosis were markedly higher than the controls, **\$4,547** and **\$2,298**, respectively. This was primarily driven by increased costs for imaging diagnostics and hospitalizations.

In this study, the costs in the year of diagnosis spiked by 72% or **\$3,257** (from \$4,547 to \$7,804) for patients covered by commercial insurance. The largest contributors to the cost increase were liver biopsies and hospitalizations. The study concluded that the costs associated with the care for NAFLD independent of its metabolic comorbidities are very high, especially at first diagnosis. Research efforts should focus on identification of underlying determinants of use, sources of excess cost, and development of cost-effective diagnostics.¹¹

The same study examined medical records during a 10-year period (2005-2015) and identified 4,569 patients diagnosed with NAFLD. Researchers analyzed the healthcare costs per patient and overall costs per year in both groups, and extrapolated costs to a national scale to determine an economic burden of **\$32 billion annually** for the United States.¹²

These results highlight a significant issue if healthcare leaders fail to address the causes of NAFLD or ignore preventive and effective screening methods.

This study also reveals the potential reduction in healthcare costs if screening and treatments are put into place. The key is to determine which patients are at a higher risk of developing liver damage due to the disease in order to get upstream of the problem at the population level.¹³

Clearly, the economic burden from NAFLD can be substantial, even without a definitive diagnosis.¹⁴

The High Costs of Liver Disease

Continued

While prospective studies are needed, the authors suggest that as the NAFLD burden continues to increase, solutions are needed to promote healthcare delivery platforms to reduce costs and provide PCPs to optimally manage this complex patient population. An interpretation of this data suggest that (1) undiagnosed disease may be more resource intensive than post diagnosis and (2) screening strategies that rule out patients with liver disease due to NAFLD in primary care may be cost-effective in reducing the number of patients subjected to specialist workup.

The Patient's Economic Burden

6.65 million adults (18+ years old) live with NASH in the U.S. Lifetime costs of all NASH patients in the U.S. in 2017 were **\$222.6 billion** and the cost of the advanced NASH population was **\$95.4 billion**. NASH, especially advanced NASH, is associated with a high lifetime economic burden. In the absence of treatment, the total direct costs of illness for these patients will continue to grow, keeping in mind that these costs would be even greater if the societal costs were included.¹⁵

Increased Risk of Mortality in NAFLD/NASH Patients

Data from a recently presented observational study suggested that NASH may affect up to 26.3 percent of patients with underlying NAFLD, or about 12.7 percent of the general population. In the population with NASH, over an eight-year period, increases in all-cause mortality were associated with increases in liver disease.¹⁶

Of the Medicare patients in this study, 2.4 percent had NAFLD-NASH. At the time of the first cirrhosis diagnosis, 93 percent were first identified with an event associated with decompensated cirrhosis. Furthermore, it is expected that by 2020, NASH will be the leading indication for liver transplant in the United States.¹⁷

Liver Disease and Diabetes

Diabetes appears to promote the development of NASH, leaving patients and physicians to face many challenges, including fragmented information on the natural history of the disease, diagnosis and treatment strategies. Recent advances in diagnosis and treatment, combined with the risk of serious consequences from inaction, call for health care providers to be more proactive in the management of patients with T2DM and NASH.¹⁸ The American Diabetes association just released recommendations that patients with T2DM and elevated ALT or fatty liver on ultrasound should be evaluated for the presence of NASH or liver fibrosis.¹⁹

This chart demonstrates that NAFLD increases the risk of all-cause mortality, while NASH compounds the problem by adding the risk of liver-related mortality.

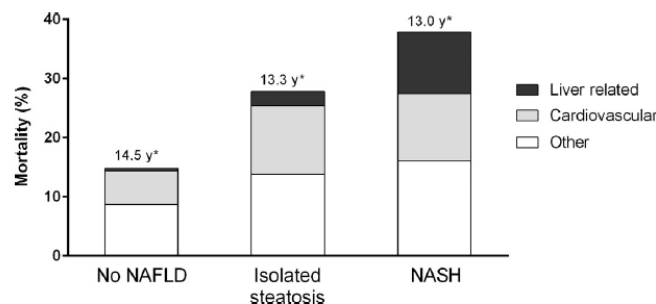


Fig. 1. All-cause mortality among patients without NAFLD by ultrasonography compared with patients with and without NASH by liver biopsy (liver related, cardiovascular, and other). * A weighted mean was performed to calculate time of follow-up. (Data from Refs. ^{10,11,28-31})

The High Costs of Cirrhosis

Cirrhosis is a worldwide problem that is associated with a substantial economic burden. Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcoholic liver disease are the main causes of cirrhosis, but cost-effective preventive strategies are only available for HBV infection.²⁰

Liver failure presents as NAFLD-related cirrhosis in **38–45 percent** of cases. In the early stages, the liver-related mortality rates are lower in NAFLD patients. Once cirrhosis decompensates, patients with NAFLD experience rapidly progressive hepatic deterioration, which leads to liver-related mortality as cirrhosis of other etiologies. In one study, the primary causes of death in patients with fibrotic NASH were infections and cirrhosis-related complications, mostly variceal hemorrhage, renal failure and hepatocellular carcinoma (HCC). The differentiator between the long-term prognosis of fibrotic NASH from the other etiologies of cirrhosis is the cardiovascular mortality, which was significantly higher in patients with NAFLD.

Because cirrhosis is a progressive disorder, prevention could significantly reduce the economic burden of the disease. Effectively managing underlying diseases in order to slow the progression of cirrhosis to liver failure would also help.²¹

- Increasing rates of NAFLD as indication for transplant (+140% over 10 years) vs 40-45% for HCV
- Heavier/sicker populations (metabolic syndrome) on the Transplant lists may lead to poorer outcomes and increased management expenses (medical costs for decomp & HCC management extremely high)
- Declining rates of donor organs due to sicker population overall

Impact of NAFLD on Pool of Potential Donors

Recent data based on expected demographic trends in the United States and past donor utilization indicate a further exacerbation of the donor shortage for liver transplantation. Older donor age, higher BMI and higher prevalence of diabetes were independent predictors for declining liver utilization in 21% of organ donors in United States in 2010. Assuming the actual trends in the prevalence of diabetes and obesity, it has been estimated that the overall liver graft utilization in 2030 will fall from 78% to 44%. As the prevalence of fatty liver is increasing, it is expected that a higher proportion of potential donors will have steatosis or steatohepatitis and might be declined for transplant use.²²

While most patients with NAFLD will not experience liver fibrosis or cirrhosis, it is critical to develop effective and efficient models to identify the subset of NAFLD patients with NASH with early stage disease.

The Value of Screening and Early Detection

NAFLD is reversible if caught in the early stages and accompanied by lifestyle changes. Screening and early detection can help to prevent more serious conditions such as end-stage liver disease or liver cancer.

While most patients are asymptomatic, NAFLD is sometimes associated with fatigue, weakness, loss of appetite, nausea, weight loss and abdominal pain. Increased liver enzymes may be associated with the disease but are not always a sign of liver disease.

Physicians can do a blood test to look for liver enzymes released after a liver cell dies, which may suggest inflammation. But today's standard approach is extracting a liver tissue sample (percutaneous liver biopsy), which allows doctors to see signs of scar tissue and ballooning under a microscope to determine how far the disease has progressed. This method, however, has been brought into question not only for its invasiveness, but also for its inaccuracy. In fact, scientists estimate that more than 30 percent of biopsy diagnoses may be wrong.²³

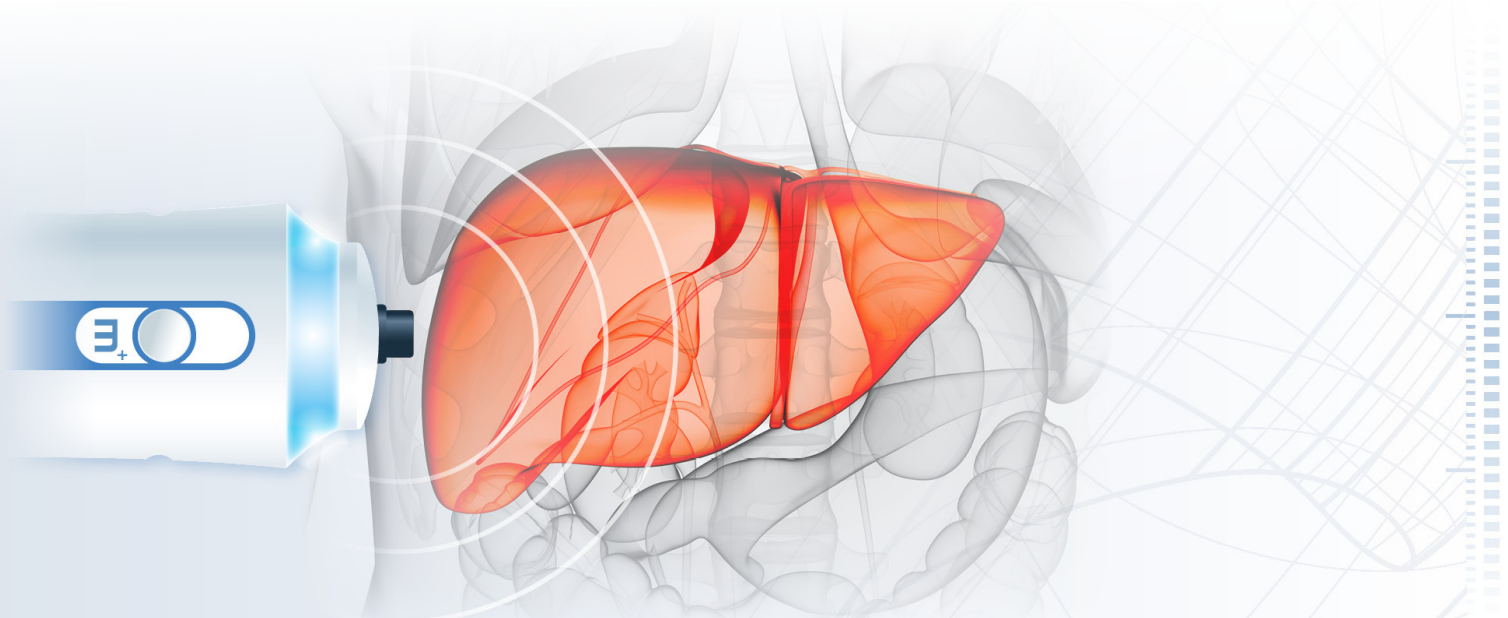
Echosens™ FibroScan® Selected by NASHNET for Rapid, Non-invasive Identification of NAFLD/NASH

Given the high prevalence and large number of drugs in the pipeline, building cost-effective models for NASH care model is critical.

NASH Network (NASHNet), a global Centers of Excellence Network represented by leading healthcare systems, has partnered with leading academic medical centers, who have expressed the importance of utilizing **Echosens™** FibroScan® system device as part of a standard workup in primary care to appropriately identify patients with progressive NAFLD.

The goal of the NASHNet pilot is to gather real world evidence to support cost-effective diagnosis strategies to identify at-risk patients where they seek care and identify cost-effective approaches for management. While patients with NAFLD may be at greater risk of cardiovascular mortality and morbidity, only about 20-30 percent will experience progressive liver disease.²⁴ Identifying and managing patients with advancing liver disease is critical for enhancing care for all patients with excessive liver fat, improving outcomes and reducing costs.

For those without progressive liver disease, the increased cardiovascular mortality risk should be assessed in their existing care plans.



FibroScan® Experience

FibroScan® is a non-invasive technology that quickly provides a quantitative assessment of liver stiffness and fat at the point of care. As part of an overall patient assessment, FibroScan®-based scores can be a tool to efficiently rule out the need for further assessment, like a painful liver biopsy, saving time and resources for people who do not require additional assessment for NASH.

FibroScan® is the most widely studied tool for quantitative liver assessment in point of care in the world, with over 2,000 peer-reviewed research publications. Over 1,200 FibroScan® systems have been placed in the United States, with the expectation that FibroScan® could eventually become an important component of point-of-care protocols in the doctor's office or other healthcare setting, performed as a part of patient management. FibroScan® is FDA-cleared for diagnosing and monitoring liver disease, is the non-invasive diagnostic reference in many clinical practice guidelines and utilized in many of the ongoing fatty liver drug clinical trials.



An interim look at an ongoing study of 10,000 patients with no history of liver disease was conducted in community-based endoscopy centers.

Using FibroScan® alone, 13% of patients were identified with elevated liver stiffness and only 43 percent of patients evaluated appeared to have what is considered normal levels of liver stiffness and fat, while the remainder had some form of liver abnormality, ranging from elevated liver fat to liver fibrosis. While definitive diagnosis is needed, this analysis of the first 5,000 patients suggests a significant rate of undiagnosed steatosis and steatohepatitis liver disease in the population studied. This high prevalence of disease, a dramatic rise from observations made in previous years, was indicative of the critical need for ongoing assessment and disease education²⁵.

These results underscore the importance of identifying asymptomatic patients who may be at risk for advancing disease for earlier intervention, while the high prevalence of disease – which saw a dramatic rise from observations made in previous years – demonstrated the critical need for ongoing assessment.



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Echosens, the developer of FibroScan®, is an innovative high-technology company offering a full range of products and services supporting physicians in their assessment and management of patients with chronic liver diseases. FibroScan® examinations are covered by Medicare, Medicaid and many insurance plans.

Echosens™ North America
950 Winter Street
Waltham, MA 02451
echosens.us

European Headquarters
30, PL d'Italie, 75013 Paris
echosens.com

