WHITEPAPER

Real-World Complexity of NAFLD and NASH: Identifying and Addressing Gaps in Diagnosis and Disease Management

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This paper by Veradigm provides an overview of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).

To access a real-world study of NAFLD/NASH by Veradigm, please refer to the real-world evidence white paper included in this folder.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has been described as an "epidemic of the 21st century." (Medscape Medical News 2020). The most common liver disease in industrialized countries, NAFLD occurs in the absence of excessive alcohol consumption, viral hepatitis, genetic causes, autoimmune diseases, or drug-induced hepatotoxicity. Its increasing prevalence parallels rising rates of obesity and diabetes (Younossi et al. 2018). Approximately one-quarter of the United States population—currently, over 80 million Americans—may have NAFLD (Younossi et al. 2016a; Younossi et al. 2018).

NASH PROGRESSION

As a chronic and sometimes progressive condition, NAFLD encompasses a wide range of hepatic pathology (Chalasani et al. 2012). All patients with NAFLD have evidence of excessive lipid storage in the liver, or simple steatosis. Up to 30% of individuals with nonalcoholic fatty liver (NAFL) and uncomplicated steatosis may develop nonalcoholic steatohepatitis (NASH), a more aggressive form of NAFLD.

The NAFLD to NASH progression is characterized by inflammation and cell injury or death evident on tissue biopsy (Younossi et al. 2016a). NASH can lead to liver scarring or fibrosis, with the potential for developing end-stage liver disease (American Liver Foundation 2017). NASH is on track to replace hepatitis C as the most common reason for liver transplantation (Zezos et al. 2014; Younossi et al. 2018).

CARDIOMETABOLIC RISK

For patients with NAFLD, cardiometabolic risk contributes substantially to overall clinical burden.

- Conditions that underlie metabolic syndrome—central obesity, insulin resistance, fasting hyperglycemia, hypertension, and dyslipidemia—are risk factors for NAFLD (Kanwar and Kowdley 2016). Metabolic syndrome in NAFLD is independently associated with all-cause, liver-related, and cardiovascular mortality (Younossi et al. 2013).

- There appears to be a bi-directional relationship between NAFLD and type 2 diabetes (Chalasani et al. 2018; Gastaldelli and Cusi 2019). Patients with type 2 diabetes have double the risk of developing chronic NAFLD and hepatocellular carcinoma compared with patients without diabetes (El-Serag et al. 2004). Diabetes and obesity strongly predict advanced fibrosis (stage 3 or higher) (Wong et al. 2017), and diabetes is an independent predictor of overall mortality in NAFLD patients (Stepanova et al. 2010).
- The association between NAFLD and cardiovascular disease appears to be independent of shared risk factors (Sao and Aronow 2018). Patients with NAFLD are more likely to die from cardiovascular disease than from liver disease (Chalasani et al. 2018).

ECONOMIC BURDEN

Economic costs associated with NAFLD are substantial.

- In the United States, annual direct medical costs attributable to NAFLD/NASH are estimated to exceed $100 billion, with the highest costs related to care of individuals aged 45 to 64 years (Younossi et al. 2016b).
- A study that examined real-world data from a large medical claims database showed long-term cumulative healthcare costs were significantly higher (80%) for patients with NAFLD than for patients without NAFLD (Allen et al. 2018).

NAFLD/NASH DIAGNOSIS AND SCREENING

A diagnosis of steatosis or simple fatty liver is often made incidentally following imaging procedures or standard blood testing that reveals elevated liver enzymes. Liver biopsy, performed by limited numbers of specialists, is considered the best means of diagnosing and assessing NASH and stages of fibrosis. However, sampling errors, high cost, invasiveness, and associated morbidity and mortality risks limit its use.

Other methods used to assess fibrosis levels include non-invasive imaging procedures that measure liver stiffness or elasticity (Dyson et al. 2014; Lim et al. 2017). Risk-predictive fibrosis models that use patient characteristics and/or laboratory values collected as part of usual care may be useful in primary care settings (Siddiqui et al. 2019; Rikhi et al. 2020).

Determining the extent of fibrosis following a NAFLD diagnosis is important, as fibrosis stage predicts overall outcomes and disease-specific mortality (Rikhi et al. 2020; Ekstedt et al. 2015; Angulo et al. 2015).

NAFLD/NASH MANAGEMENT

Currently, management of NAFLD focuses on lifestyle modifications such as exercise and gradual weight loss (Chalasani et al. 2012). However, these measures may fall short for some patients, especially for those struggling with advanced disease.

Guideline-recommended pharmacotherapy is limited to the use of pioglitazone and vitamin E in patients with biopsy proven NASH with and without diabetes. Concurrently, physicians should be treating cardiometabolic comorbidities with glucose-lowering, lipid-lowering, and anti-hypertensive medications (Chalasani et al. 2012; Chalasani et al. 2018; Sumida and Yoneda 2018).

NASH CLINICAL TRIALS

No drug has yet received approval from the US Food and Drug Administration for slowing, halting, or reversing the progression of NASH. However, several innovative pharmacotherapies are currently in various stages of clinical development.

The number of potential therapeutic agents in development targeting myriad molecular pathways—fibrosis, inflammation, oxidative stress, apoptosis, and metabolic homeostasis—speaks to the complexity of NAFLD/NASH.

Drug candidates for NASH have been evaluated in past and ongoing clinical trial programs as stand-alone or combination therapies. These potential treatments have included

- Farnesoid X receptor agonists
- Peroxisome proliferator-activated receptor agonists
- Apoptosis signal regulating kinase 1 inhibitors
- Acetyl-CoA carboxylase inhibitors
- Dual chemokine receptor antagonists
- Fibroblast growth factor analogues
- Bile acid analogues
- Pan-caspase inhibitors
- Thyroid hormone receptor agonists
- Stearoyl coenzyme A desaturase inhibitor
- Fatty acid synthase inhibitor
- Anti-diabetic agents

REAL-WORLD STUDIES IN NAFLD

Real-world studies have evaluated, among other topics, diagnostic gaps, clinical predictors and risk factors, and long-term outcomes for NAFLD.

- In a study that combined real-world data from four European primary-care electronic databases, less than 2% of patients had coded diagnoses for NAFLD, a prevalence much lower than that previously established global estimates (20%-30%) based on defined cohorts (Alexander et al. 2018).
- In another study that evaluated pooled data from these four European primary-care databases, type 2 diabetes was an independent predictor of advanced liver disease. In addition, a recorded diagnosis for NAFLD/NASH increased the risk of life-threatening liver outcomes (Alexander et al. 2019).
- A meta-analysis of large observational cohort studies reported a two-fold increased risk of incident type 2 diabetes for individuals with NAFLD compared with those without NAFLD. The risk for developing diabetes was greatest for NAFLD patients who had advanced fibrosis scores (Mantovani et al. 2018).
- A prospective, observational study that assessed the progression of liver damage and cardiometabolic disorders in nearly 900 outpatients demonstrated patients with NAFLD had a greater than twofold increase and patients with NAFLD and liver fibrosis had a fourfold increase in risk of ischemic stroke, myocardial infarction, and other cardiovascular events compared with patients without NAFLD (Baratta et al. 2019).
- A retrospective analysis of over 700 patients diagnosed with NAFLD reported fibrosis stage, but no other histologic features of steatohepatitis, was independently associated with liver-related events, liver transplantation, and overall mortality over the long term (Angulo et al. 2015).

These studies demonstrate an ongoing need for identifying individuals with NAFLD, stratifying risk, and referring patients for specialized care. To generate real-world insights into the clinical challenges and therapeutic opportunities associated with NAFLD, including its more progressive, inflammatory forms, Veradigm® conducted a retrospective cohort analysis using de-identified real-world data sourced from one of its large, cloud-based US electronic health record datasets. The analysis establishes prevalence of NAFLD over a five-year period, characterizes the all-inclusive NAFLD cohort and the NAFL and NASH subgroups, identifies which provider types are seeing NAFLD patients, and discusses potential solutions for current gaps in diagnosis and disease management.

Please go to the complete report:
Prevalence and Characteristics of NAFLD/NASH Patients

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