WHITEPAPER

Prevalence and Characteristics of Nonalcoholic Fatty Liver Disease/ Nonalcoholic Steatohepatitis (NAFLD/ NASH) Patients in US Real-World Clinical Practice

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This paper by Veradigm presents a real-world evidence study on nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).

For information on NAFLD and NASH, please refer to the overview white paper by Veradigm included in this folder.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become a major public health concern in many parts of the world. A chronic and sometimes progressive condition, NAFLD is estimated to affect one-quarter of Americans (Younossi et al. 2018). Its increasing prevalence parallels rising rates of obesity and type 2 diabetes (Younossi et al. 2018).

NAFLD covers a wide range of hepatic pathology, from nonalcoholic fatty liver (NAFL) with uncomplicated steatosis to nonalcoholic steatohepatitis (NASH), a more aggressive form in which inflammation and hepatocyte injury or death are evident on histologic examination (Younossi et al. 2016). Patients with NASH may eventually develop liver fibrosis; decompensated cirrhosis and hepatocellular carcinoma are end-stage complications for a small fraction of patients (American Liver Foundation 2017).

An overview of NAFLD that includes discussion of cardiometabolic risk, screening, diagnosis, management, and clinical trials is available in a companion article.

REAL-WORLD STUDIES IN NAFLD/NASH

Real-world studies have evaluated diagnostic gaps, risk factors and clinical predictors, and long-term outcomes for NAFLD. The real-world evidence (RWE) obtained from these studies demonstrates an ongoing need for identifying individuals with NAFLD, stratifying risk, and referring patients to specialists.

- 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 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 retrospective analysis of patients diagnosed with NAFLD reported liver fibrosis was independently associated with future liver related events, liver transplantation, and overall mortality. Long-term prognosis depended less on a diagnosis of NASH than on whether fibrosis was evident on liver biopsy (Angulo et al. 2015).
- In a prospective observational study, patients with NAFLD had a greater than twofold increase and patients with NAFLD plus 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).

RETROSPECTIVE COHORT ANALYSIS

To generate insights into the clinical challenges and therapeutic opportunities associated with NAFLD/NAFL/NASH, we conducted a retrospective cohort analysis using de-identified real-world data sourced from a cloud-based, U.S. electronic health record (EHR) dataset offered by Veradigm® as part of its Health Insights database. The dataset includes ambulatory patients seen by primary care and specialty healthcare providers (practice size ranging from one to four clinicians).

The objectives of the analysis were to 1) establish the prevalence of NAFLD over a five-year period, 2) characterize the all-inclusive NAFLD cohort and NAFL and NASH subgroups, and 3) identify which provider types are seeing NAFLD patients. The NAFLD cohort and NAFL and NASH subgroups were characterized according to demographics, vital signs, laboratory values, cardiometabolic conditions and complications, and medication classes used to manage relevant cardiometabolic risk (i.e., pre-diabetes/type 2 diabetes, dyslipidemia, and hypertension).

Study Design

De-identified patients were included in the analysis if they met the following eligibility requirements:

- Any diagnosis code recorded during the five-year period between June 15, 2014–June 15, 2019 inclusive (Intake), with at least one office visit with a healthcare provider (HCP) ≥6 months prior to the most recent diagnosis;
- A diagnosis code for NASH, NAFL, or NAFLD recorded during Intake (Index);
- No diagnoses related to alcohol abuse, alcoholic steatosis, or alcoholic hepatitis;
- Eighteen (18) years of age or older at Index.

Additional study design details may be found in **Appendix A**.

Five-Year Period Prevalence of NAFLD/NASH

Of nearly 12 million patients who met entry criteria for any diagnosis and an HCP visit, 103,358 patients (<1%) met additional criteria for NAFLD/NAFL/NASH diagnosis, alcohol use/code restrictions, and age. Most patients (90.8%) in the NAFLD cohort had diagnosis codes that were specific for NAFL. Nearly six percent (5.9%) of NAFLD patients had NASH-specific diagnosis codes.

Patient Characteristics: Demographic and Vital Signs

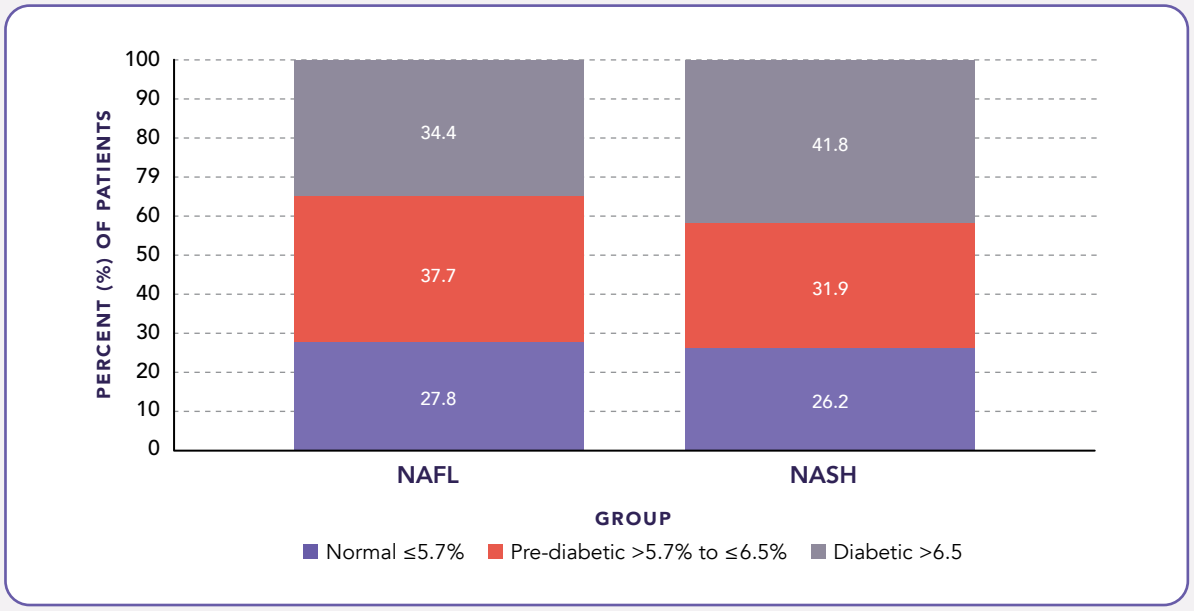
More than one-half of patients in the NAFLD cohort (56.8%), the NAFL subgroup (57.2%), and the NASH subgroup (55.9%) were aged 40 to 64 years. There were more females than males in each of the groups (NAFLD, 57.6% vs 42.2%; NAFL, 57.7% vs 42.1%; NASH, 58.6% vs 41.2%). No difference in the percentage of patients who smoked or had a history of smoking was noted between the NAFL and NASH subgroups (NAFL, 26.3% vs NASH, 26.9%) (P>0.05).

There were differences in the percentage of patients with BMI ≥30 (58.7% vs 60.8%) and systolic blood pressure ≥130 mmHg (42.5% vs 45.4%) between the NAFL and NASH subgroups, with higher percentages demonstrated for the NASH subgroup (both P≤0.001).

Laboratory Values: Glycosylated Hemoglobin and Lipids

HbA1c levels differed between the NAFL and NASH subgroups (P<0.001) (**Figure 1**). A higher percentage of patients in the NAFL than in the NASH subgroup had HbA1c levels suggestive of prediabetes (i.e., >5.7% and ≤6.4%) (37.3% vs 31.9%). Percentagewise, more patients in the NASH than in the NAFL subgroup had HbA1c levels ≥6.5% (41.8 vs 34.4%), the recommended cutoff for diagnosing type 2 diabetes, and fasting blood glucose levels >100mg/dL (27.7% vs 23.5%).

FIGURE 1 | **Percent (%) of Patients by Diagnostic Group: Glycosylated Hemaglobin**



Percentages of patients in the NAFL and NASH subgroups of the NAFLD cohort by HbA1c range. Laboratory values were those most recently recorded in the 12-month period prior to Index (or at Index). Nearly forty percent of patients in the NAFL (37.9%) and NASH (38.2%) subgroups had HbA1c values recorded. Abbreviations: NAFL=nonalcoholic fatty liver; NASH=nonalcoholic steatohepatitis; NAFLD=nonalcoholic fatty liver disease; HbA1c=glycosylated hemoglobin.

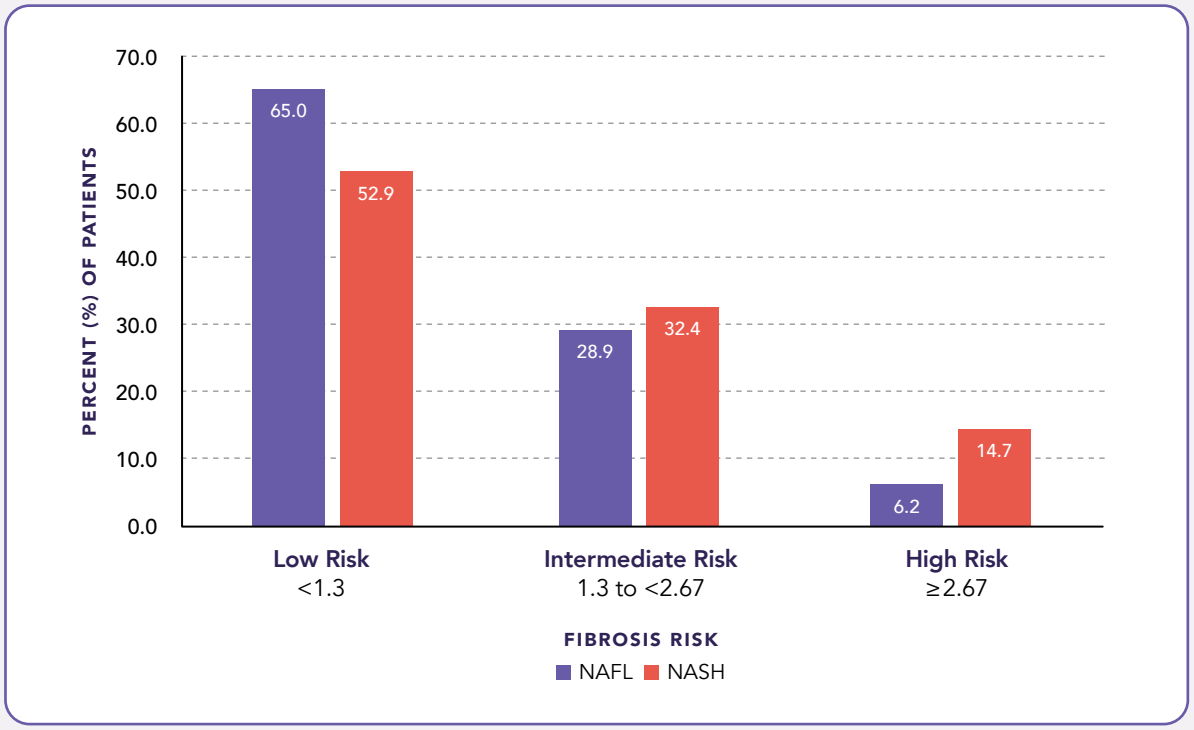
No differences were noted between the NAFL and NASH subgroups for triglyceride levels ≥175 mg/dL (14.8% vs 14.6%), LDL-C >160 mg/dL (3.4% vs 3.6%), and HDL-C <40 for males (11.0% vs 11.2%) (all P>0.05). Differences were observed between the NAFL and NASH subgroups for HDL-C <50 mg/dL for females (12.3% vs 10.8%) and total cholesterol (5.4% vs 4.7%) (both P≤0.01).

FIB-4 Scores

The extent of liver fibrosis was calculated using the FIB-4 Index, a non-invasive, validated test for detecting advanced fibrosis (Dyson et al. 2014; Chalasani et al. 2018).

A significant difference in the distribution of calculated risk scores was noted between the NAFL and NASH subgroups (P<0.001) (**Figure 2**). A higher percentage of patients in the NAFL subgroup than in the NASH subgroup had calculated FIB-4 scores corresponding to "low risk" (65.0% vs 52.9%). Conversely, higher percentages of patients in the NASH subgroup than in the NAFL subgroup had calculated FIB-4 scores corresponding to "intermediate risk" (32.4% vs 28.9%) and "high risk" (14.7% vs 6.2%).

FIGURE 2 | **Percent (%) of Patients by Diagnostic Group: FIB-4 Risk Assessment**



Percentages of patients in the NAFL and NASH subgroups of the NAFLD cohort according to FIB-4 Index. Fewer than one-half of patients in the NAFL (44.4%) and NASH (43.0%) subgroups had ALT, AST, and platelet values recorded in the 12-month period prior to Index (or at Index) to enable calculation of the FIB-4 Index. Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; FIB-4=Fibrosis-4 Index; NAFL=nonalcoholic fatty liver; NASH=nonalcoholic steatohepatitis; NAFLD=nonalcoholic fatty liver disease.

Cardiometabolic Comorbidities and Complications

NAFLD patients had additional diagnoses for one or more of six cardiometabolic conditions, with 228,398 diagnosis codes recorded in their histories. Of the 103,358 patients in the NAFLD cohort, 64.0% had a recorded diagnosis for dyslipidemia, 57.4% had a diagnosis for hypertension, 46.7% were overweight/obese, 35.1% had type 2 diabetes, 14.1% had pre-diabetes, and 3.6% had metabolic syndrome. A total of 11.7% had no recorded diagnoses for any of the six conditions.

While 3,708 (3.6%) patients in the NAFLD cohort had a diagnosis for metabolic syndrome, 44,045 NAFLD patients had evidence of metabolic syndrome based on individual risk factors (i.e., diagnosis codes for three or more of the following: prediabetes/insulin resistance, type 2 diabetes, overweight/obesity, dyslipidemia, and hypertension).

Higher percentages of NASH patients than NAFL patients had diagnoses codes for type 2 diabetes (44.1% vs 34.7%), hypertension (60.7% vs 57.2%), metabolic syndrome (4.8% vs 3.6%), and for three or more cardiometabolic risk factors (47.7% vs 42.8%) (all $P<0.001$). Percentagewise, more NASH patients than NAFL patients had recorded diagnoses for cirrhosis (11.1% vs 1.8%) and hepatocellular carcinoma (0.4% vs 0.1%) ($P<0.001$).

Medical Treatments for Cardiometabolic Conditions

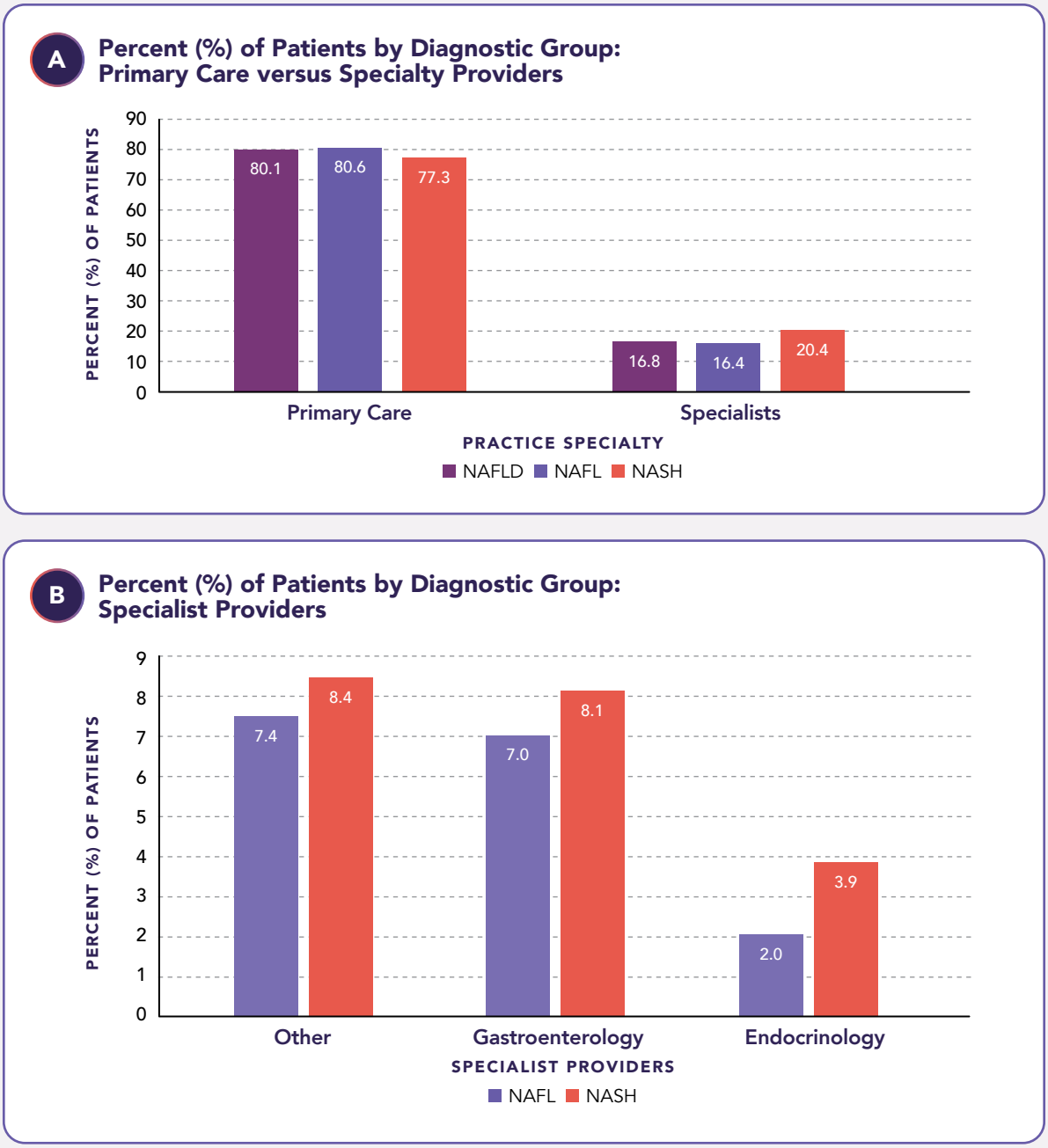
Of 36,327 NAFLD patients with a diagnosis for type 2 diabetes, 19.7% did not have prescriptions for or documented use of any antidiabetic medications/insulin sensitizers. Of 66,152 NAFLD patients with a diagnosis of dyslipidemia, 34.2% did not have prescriptions for or documented use of any antilipidemic medications.

Visits to Providers

Most patients in the NAFLD cohort (80.1%), the NAFL subgroup (80.6%), and NASH subgroup (77.3%) had one or more documented visits with primary care practitioners (i.e., family medicine, internal medicine, and general practice) (**Figure 3A**). Fewer than one-quarter of patients in the NAFLD cohort (16.8%), the NAFL subgroup (16.4%), and the NASH subgroup (20.4%) had documented visits with specialists, including gastroenterologists, endocrinologists, and hepatologists.

A higher percentage of patients in the NASH subgroup had documented visits with specialty providers than patients in the NAFL subgroup (gastroenterology, 8.1% vs 7.0% [$P=0.001$]; endocrinology, 3.9% vs 2.0% [$P<0.001$]; other, 8.4% vs 7.4% [$P=0.003$]) (**Figure 3B**). A total of sixty-nine patients had at least one documented visit with a hepatologist (included in "Other" provider category) during the five-year Intake.

FIGURE 3 | **Percent of Patients by Diagnostic Group: Primary Care versus Specialty Providers**



Percentages of patients in the NAFLD cohort (n=103,358) and the NAFL (n=93,862) and NASH (n=6,114) subgroups with one or more visits to a healthcare provider. Provider specialty was recorded anytime during Intake. Primary Care included Family Medicine, General Practice, and Internal Medicine. Specialty providers included Gastroenterology, Endocrinology, and Other. Provider types were not recorded for approximately 3% of patients. Panel A: Primary Care vs Specialty Providers. Panel B: Specialist Providers. Abbreviations: NALFD, nonalcoholic fatty liver disease; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis.

DISCUSSION

What clinical insights may be gained from the retrospective analysis?

Our analysis of de-identified patient data, sourced from a nationwide EHR available in the Veradigm Health Insights database, revealed potential underreporting of NAFLD-related diagnoses and care gaps across the NAFLD spectrum.

Prevalence

- Of nearly 12 million individuals meeting entry criteria for any diagnosis code and an HCP visit, fewer than 1% met additional criteria for a NAFLD, NAFL, or NASH diagnosis; alcohol use/code restrictions; and age. Of these patients, 6% had diagnosis codes for NASH, the more progressive inflammatory form of NAFLD.

In determining prevalence, our exclusive reliance on ICD-9-CM, ICD-10-CM, and SNOMED CT codes for identifying patients with NAFLD, NAFL, or NASH is a limitation of the analysis, as some diagnoses may have been added in narrative format to unstructured or semi-structured fields within the EHR platform. Such data could be identified, extracted, and presented in a structured format using natural language processing (NLP). Previously, we have used NLP to extract and supplement HbA1c levels (41%), left ventricular ejection fraction (100%), and DXA scores (81%) for patients with type 2 diabetes, heart failure with reduced ejection fraction, and osteoporosis, respectively.

The lower than expected prevalence of NAFLD and NASH obtained in this analysis is similar to that found in a real-world study of European primary care databases. That study captured NAFLD-related diagnosis codes in three of the databases and used text mining of diagnosis search terms in the fourth database in the absence of a diagnosis code for NALFD (Alexander et al. 2018). In our analysis and the European study, the lower than expected prevalence of NAFLD appears to reflect, in part, an underreporting of NAFLD-related diagnoses in primary care. Primary care comprised the largest physician specialty group in this US dataset (see below).

The diagnostic gaps observed in our analysis might be addressed by applying artificial intelligence capability (NLP and machine learning) and predictive analytics tools to the clinical records. Others have reported success in screening for NASH using a machine-learning–based approach that identified specific variables including laboratory values, BMI, and cardiometabolic conditions, deployed within the EHR, with subsequent determination of a diagnosis by the physician (Shattenberg 2020).

Cardiometabolic Risk

- Higher percentages of NASH than NAFL patients were obese (based on BMI), had hypertension (based on systolic blood pressure and diagnosis codes), diabetes (based on HbA1c levels and diagnosis codes), and had metabolic syndrome (based on three or more risk factors and diagnosis codes).
- Overall, nearly two-thirds of NAFLD patients had a diagnosis for dyslipidemia. Of these patients, more than one-third did not have prescriptions for or documented use of antilipidemic medications.

- Approximately one-third of patients had a diagnosis of type 2 diabetes. Of these patients, nearly 20% did not have prescriptions for or documented use of antidiabetic medications.

Cardiometabolic risk contributes substantially to the overall clinical burden of NAFLD. Our analysis suggests that not all patients are being managed for cardiometabolic conditions. Given that patients with NAFLD are at high risk of mortality from cardiovascular disease and that there exists a bidirectional relationship between NAFLD and type 2 diabetes (Chalasani et al. 2018; Gastaldelli and Cusi 2019), such cardiometabolic comorbidities should be treated according to the most recent medical guidance and taken into account when stratifying risk.

Provider Specialty

- Most patients with diagnoses for NAFLD, NAFL, or NASH were seeing primary care practitioners, with fewer than 10% of patients in each of these groups having documented visits with gastroenterologists and hepatologists.

There is a critical need for greater awareness and understanding of NAFLD and NASH among HCPs (Lim et al. 2017; Sumida and Yoneda 2018; Povsic et al. 2019). In a study that tracked understanding and practice patterns of primary care providers and non-gastroenterologic/non-hepatologic subspecialty providers, only a minority (31%) of survey respondents identified NAFLD as clinically important in their practice, with less than one-half (47%) of respondents being comfortable managing NAFLD and only one-third (33%) referring patients with suspected NAFLD to gastroenterologists or hepatologists (Wieland et al. 2013).

Another survey study suggested there are significant gaps in physician awareness of and familiarity with NAFLD and NASH; the authors concluded physician education regarding established practice guidelines is warranted for primary care providers who are likely to continue to diagnose and manage patients with NASH (Polanco-Briceno et al. 2016).

Fibrosis Scores

- FIB-4 scores indicated that over 380 patients with NASH and over 2,500 patients with NAFL were at high risk of fibrosis. Nevertheless, these NAFL patients had no recorded diagnoses codes for NASH.
- Percentagewise, significantly more NASH than NAFL patients had recorded diagnoses for cirrhosis (11.1% vs 1.8%) and hepatocellular carcinoma (0.4% vs 0.1%) ($P>0.001$).

Recent studies have reported that approximately one in five patients with high risk of fibrosis progresses to more advanced forms (compensated or decompensated cirrhosis) within a two-year period, a more compressed time course than previously reported (Sanyal et al. 2019). This finding suggests that up to 500 NAFL patients in our analysis may be at risk of progressing to decompensated liver disease absent timely confirmation of advancing liver fibrosis or intervention.

Liver biopsy, performed by limited numbers of specialists, is considered the best means of diagnosing and assessing NASH and stages of fibrosis. However, its invasive nature and associated morbidity and mortality risks limit its use. Identifying NAFLD patients at high risk of progressive liver disease is a major focus of clinical care (Younossi et al. 2018). Determining the extent of liver fibrosis is crucial, as fibrosis stage predicts overall outcomes and NAFLD-specific mortality (Ekstedt et al. 2015; Angulo et al. 2015; Rihki et al. 2020).

Practice guidelines do not currently provide well-defined screening recommendations or cost-effective means of monitoring NAFLD progression (Chalasani et al. 2012). Nevertheless, once a diagnosis of NAFLD has been established (or even prior to diagnosis), well-validated fibrosis calculators (such as the FIB-4 Index and the NAFLD Fibrosis Score, among others) that use clinical data collected as part of usual care may be of use in primary care and some specialist settings to noninvasively stage liver fibrosis and to predict worsening liver disease (Siddiqui et al. 2019; Rikhi et al. 2020).

Fibrosis scores and other clinical data from EHRs, patient registries, and transactional claims may be leveraged by life sciences stakeholders, including population health researchers and biopharma segments, to, for example, develop a deeper understanding of the NAFL-to-NASH-to-cirrhosis progression or to examine resource utilization by NAFLD patients according to cardiometabolic and hepatic risk. Currently, several potential pharmacotherapies targeted to NASH and fibrosis are in various stages of clinical development; successful candidates may help to slow or halt liver disease progression beyond that achievable with recommended lifestyle modification (i.e., exercise and weight control) and pharmacotherapies directed toward cardiometabolic comorbidities in these patient populations (Chalasani et al. 2018; Sumida and Yoneda 2018).

Medical Education

Availability of best-practice guidelines from within EHRs and registries may increase adoption of evidence-based care plans and, when warranted, support timely referrals from primary care providers to specialists to avoid complications and forestall end-stage liver disease in at-risk individuals. Additionally, medical educational materials may be shared by HCPs with their patients at the point of care or through patient-provider portals for the purpose of promoting health literacy, to enable shared decision-making and encourage patients to participate as partners in their own health and well-being.

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APPENDIX A. STUDY DESIGN

Nine diagnosis codes (ICD-9-CM [2], ICD-10-CM [2], SNOMED CT [5]) were used to establish the NAFLD cohort. From among these nine codes, codes specific for NAFL (ICD-10-CM [1], SNOMED CT [2]) and codes specific for NASH (ICD-10-CM [1], SNOMED CT [1]) were used to generate the NAFL and NASH subgroups, respectively (see **Appendix B** for codes). The last diagnosis code recorded during Intake was used to place a patient in the NAFL or NASH subgroup. Any patient with last diagnosis codes for NAFL and NASH recorded on the same date during Intake was included in the NASH subgroup.

Patient characteristics were those most recently recorded in the twelve-month period prior to Index (or at Index). Laboratory values were those most recently recorded in the 12-month period prior to Index (or at Index). Comorbidities and complications were recorded anytime in the patient history. Medications indicated for two of the cardiometabolic conditions were evaluated to determine whether care was consistent with recorded diagnoses in the medical records. Prescription orders for or documented use of medications were recorded within twelve months prior to Index or at Index. Provider specialty was recorded anytime during Intake.

Scores for the FIB-4 Index, a risk predictive fibrosis model, were calculated according to the formula,

FIB-4 score = Age (years) × AST (U/L) / [Platelet Count (10^9/L) × $ALT^{1/2}$ (U/L)], where AST and ALT refer to aspartate aminotransferase and alanine aminotransferase, respectively.

Summary statistics were tabulated and statistical analyses conducted. For continuous variables, differences between the NAFL and NASH groups were tested using single-factor analysis of variance. Chi-square tests were used to compare categorical variables. Statistical tests were two-sided, with an α-level of 0.05 for statistical significance.

APPENDIX B. DIAGNOSIS CODES

APPENDIX B | Diagnosis Codes to Establish Patient Cohorts and Complications

Terminology	Source Concept Code	Terminology String
INCLUSION CODES		
NAFLD		
ICD-9-CM	571.8	Chronic Liver Disease NEC; Other chronic nonalcoholic liver disease
ICD-9-CM	571.9	Unspecified chronic liver disease without mention of alcohol
SNOMED CT	197315008	Nonalcoholic fatty liver (disorder)
ICD-10-CM	K76.0	Fatty (change) of liver, NEC
ICD-10-CM	K75.8	Other specified inflammatory liver diseases
SNOMED CT	197321007	Steatosis of liver (disorder)
SNOMED CT	442191002	Steatohepatitis (disorder)
SNOMED CT	79720007	Chronic nonalcoholic liver disease
SNOMED CT	442685003	NASH-nonalcoholic steatohepatitis; Nonalcoholic steatohepatitis (disorder)
NAFL		
SNOMED CT	197315008	Nonalcoholic fatty liver (disorder)
ICD-10-CM	K76.0	Fatty (change) of liver, NEC
SNOMED CT	197321007	Steatosis of liver (disorder)
NASH		
ICD-10-CM	K75.81	Nonalcoholic steatohepatitis (NASH)
SNOMED CT	442685003	NASH-nonalcoholic steatohepatitis; Nonalcoholic steatohepatitis (disorder)
EXCLUSION CODES		
ICD-9-CM	571.0	Alcoholic fatty liver
ICD-9-CM	571.1	Acute alcoholic hepatitis
ICD-9-CM	571.2	Alcoholic cirrhosis of liver
ICD-9-CM	571.3	Alcoholic liver damage unspecified
ICD-9-CM	303	Alcohol dependence syndrome
ICD-10-CM	F10	Alcohol related disorders
SNOMED CT	7200002	Alcoholism (disorder)
SNOMED CT	66590003	Alcohol dependence
SNOMED CT	765482002	Alcoholic steatohepatitis

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APPENDIX B | Diagnosis Codes to Establish Patient Cohorts and Complications *Continued*

Terminology	Source Concept Code	Terminology String
COMPLICATIONS OF NAFLD/NAFL/NASH		
CIRRHOSIS		
ICD-9-CM	571.5	Cirrhosis of liver without mention of alcohol
ICD-10-CM	K74.6	Other and unspecified cirrhosis of liver
SNOMED CT	371139006	Early cirrhosis
SNOMED CT	266468003	Cirrhosis - non-alcoholic (disorder)
SNOMED CT	716203000	Decompensated cirrhosis of liver
HEPATOCELLULAR CARCINOMA (HCC)		
ICD-9-CM	155.0	Malignant neoplasm of liver, primary
ICD-10-CM	C22.0	Liver cell carcinoma
SNOMED CT	95214007	Primary malignant neoplasm of liver
SNOMED CT	109841003	Liver cell carcinoma

Abbreviations: NAFLD, nonalcoholic fatty liver disease; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; NEC, not elsewhere classified; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms; ICD-10-CM, International Classification of Disease, Tenth Revision, Clinical Modification; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis.

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