Original Article

Clinical cohort of nonalcoholic fatty liver disease in a primary care setting

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Abstract

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is increasingly common, and primary care physicians (PCPs) are often the first to diagnose NAFLD. While guidelines on NAFLD management in primary care exist, there are limited data on clinical practice patterns. **Approach:** We gathered data from over 370,000 patients with at least one PCP visit between July 2016 and September 2023. Using ICD-10 codes to identify patients with a diagnosis of NAFLD or Nonalcoholic Steatohepatitis (NASH), we extracted demographics, comorbidities, laboratory results, prescriptions, imaging orders, and referrals to describe their care. **Results:** We identified 10,334 patients with a diagnosis code of NAFLD (93.1%) and/or NASH (16.7%) during a PCP visit. Just over half (54.8%) were female, mean age was 52.8 years, and mean BMI was 33.2 kg/m^2 with 90% having overweight or obese. More than 50% had hypertension and hyperlipidemia, and 38% had diabetes. At the diagnosis visit, 2.7% had ultrasound elastography ordered, 2.7% liver biopsy, and less than 1% magnetic resonance elastography. During follow-up ranging from 0 to 7 years, patients had a mean of 15 encounters, during which 4% were diagnosed with fibrosis or cirrhosis. Only 24.2% of patients were referred to a nutritionist and 18% had an appointment, and only 0.7% were referred to hepatology and 3.8% saw a hepatologist. **Conclusion:** PCPs have not widely implemented clinical practice guidelines for NAFLD, resulting in suboptimal care including for the substantial minority with fibrosis or cirrhosis. Patients might benefit from targeted NAFLD education for PCPs and improved decision and management support.

Keywords: Metabolic syndrome, NAFLD, primary care

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a complex and increasingly common disease in the US and worldwide. Recent estimations indicate a prevalence of greater than 25% worldwide, and it is among the most common indications for liver transplantation in the Western world.[1] NAFLD is defined by the presence of hepatic steatosis on imaging or histology in a patient without other risk factors for fatty liver, including excessive alcohol use, exposure to steatogenic medication, or another underlying disorder which predisposes them to fat deposition.[2] NAFLD is now well understood as a component of metabolic syndrome and is associated with significant morbidity and mortality.[3] In spite of this, providers have demonstrated limited awareness of which patients are considered high risk and what medications may be useful to assist in treatment.[4]

Risk stratification NAFLD patients can help identify those at the highest risk for the development of nonalcoholic steatohepatitis

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or NASH, which involves hepatocellular damage secondary to fat deposition, fibrosis, or cirrhosis. High-risk patients include those with concomitant obesity, diabetes, hyperlipidemia, or cardiovascular disease, among others.[5] Scoring systems such as the NAFLD Fibrosis Score (NFS) and, in particular, the Fibrosis-4 index (FIB-4) have been recommended by the American Association for the Study of Liver Diseases (AASLD) as the first-line predictors of fibrosis but are largely underutilized.[5,6] Further, there are medications that have been shown to improve inflammation in patients who have progressed to NASH, including SGLT-2, GLP-1, glitazones, and vitamin E.[5] However, the frequency with which these are prescribed for patients with NASH is not known at this time.

NAFLD is most frequently diagnosed incidentally after patients receive abdominal imaging for various other indications.[7] Thus, the primary care physician (PCP) is often the first to suspect or make this diagnosis. As the main point of medical care, it is essential that these providers understand what steps to take when a patient is noted to have fatty liver to identify those most like to have or progress to advanced disease. However, many PCPs do not feel confident managing NAFLD at this time.[8]

One of the main goals when treating a patient with NAFLD or NASH is the prevention of progression. Lifestyle management alone can reduce and reverse liver steatosis, inflammation, and even fibrosis.[9] The treatment of comorbidities, including initiating glucose management for diabetes or starting antihypertensive medications, has been shown to lead to NASH improvement.[9] Meta-analyses of NASH treatment trials have demonstrated that even patients who received placebos had minimal progression of their disease.[10] Thus, NASH itself seems to have a slow progression rate, even without intervention. The mortality rate in this population, and the biggest risk for developing cirrhosis, is dependent on the presence and severity of fibrosis.[11] PCPs have the unique opportunity to reverse the process before their patients develop fibrosis and cirrhosis. Frequent check-ins with physicians, repeated nutritional counseling, addressing comorbidities, and patient education on fatty liver disease may be effective in slowing the progression of fibrosis. Given the high prevalence of NAFLD, gastroenterologists and hepatologists will not be able to care for all affected patients. Thus, PCPs will play an essential role in its diagnosis, staging, risk-stratification, and management moving forward.

Our goal was to examine the care of patients in primary care who had a NAFLD or NASH diagnosis to determine the percentage of patients receiving appropriate follow-up care including weight loss counseling, risk stratification, prescriptions for anti-inflammatory and weight loss medications, abdominal elastography, and/or referral to hepatology for those in whom advanced fibrosis is suspected. We hypothesized that most patients are not currently receiving the appropriate evaluation and follow-up to prevent the progression of NAFLD to NASH and cirrhosis and its complications.

Methods

We conducted a retrospective cohort study of adult (aged 18 years and older) patients who were identified from the Adult Primary Care Center of Excellence (APCCOE) patient registry at an academic medical center in Maryland. The APCCOE registry includes 370,700 patients who had completed at least one primary care encounter between July 1, 2016, and September 17, 2023. The institutional review board approved the formation of the registry and use of data for secondary research for this study (IRB00354153). Initial data extraction was provided by the Institute for Clinical and Translational Research through the Core for Clinical Research Data Acquisition. The analytic data set was extracted from the provided data projection using Microsoft SQL Server Management Studio, version 15.0.18424.0. Patient information was collected from medical records between July 1, 2016, and September 17, 2023. Extracted patient data consisted of demographics, comorbidities, vitals, medications, laboratory results, medical history, and imaging orders. During the study period, there were no protocols or practice standards in place for the diagnosis or management of NAFLD.

Patients were identified by searching each visit for the ICD-10 billing codes of K76.0 (fatty liver) and 75.81 (NAFLD/NASH). Descriptive data analyses were performed in RStudio 2022.12.0 Build 353. Data are presented as frequencies and percentages for categorical variables, means and standard deviations, or medians and interquartile ranges for continuous variables. We evaluated the subpopulation of patients with advanced fibrosis or cirrhosis using those who were also given an ICD-10 code of K74.6 (cirrhosis) or K74.02 (advanced fibrosis), as well as the subpopulation of patients with type-2 diabetes mellitus (E11). The institutional review board approved the formation of the registry and use of data for secondary research for this study (IRB00354153) on 11/13/2023.

Results

Our population included 10,334 patients (53.8% female) who had at least one visit to their PCP where the ICD diagnosis code for NAFLD (93.1%) and/or NASH (16.7%) was billed [Table 1]. Forty percent of those included were between 50 and 64 years of age, with an average age of 53 years. Sixty-three percent of included patients identified as white, 18% black, 9% Asian, and 8% other; 8.2% identified as Hispanic. The average weight and BMI were 210.6 pounds and 33.2 kg/m^2, respectively. More specifically, 26.6% were overweight (BMI 25–29.9), and 30.1% met criteria for class I obesity (BMI 30–34.9), 18.7% for class II obesity (BMI 35–39.9), and 14.9% for class III obesity (BMI >40). In terms of comorbidities, 67.8% of this population also carried a diagnosis of hypertension, 67.1% had hyperlipidemia, 38.3% had diabetes mellitus, and 15.5% had coronary artery disease.

Serum studies collected during the first appointment in which NAFLD was billed showed an average alanine transaminase (ALT) of 44.1 U/L, aspartate aminotransferase (AST) of 34.7 U/L,

Table 1: Patient demographics and comorbidities at the time of NAFLD diagnosis (*n*=10,334)

Characteristic	Percentage	Characteristic	Percentage
Diagnosis		Mean weight	210.6 lbs (SD 51)
NAFLD	93.1%		
NASH	16.7%		
Gender		Mean BMI	33.2 kg/m^2 (SD 7.07)
Female	53.8%		
Male	46.1%		
Nonbinary	<0.01%		
Other	<0.01%		
Age distribution		BMI category	
18–25	2.3%	Underweight	0.3%
26–35	9.9%	Normal weight	8.7%
36–49	27.1%	Overweight	26.6%
50–64	39.2%	Obesity Class I	30.1%
>65	21.4%	Obesity Class II	18.7%
		Obesity Class III	14.9%
		Unavailable	0.7%
Mean age	52.8 years (SD 13.7)	Substance use history	
		Current	3.7%
		Past	3.6%
		Never	86.2%
		Unknown	6.5%
Race		Alcohol use history	
White	63.3%	Current	49.0%
Black	17.6%	Past	11.9%
Asian	8.7%	Never	35.8%
Other	8.2%	Unknown	3.3%
Unknown	1.1%		
Not Disclosed	1.2%		
Ethnicity		Comorbidities	
Hispanic or Latino	8.2%	Hypertension	67.8%
Not Hispanic	88.2%	Diabetes mellitus	38.3%
Unknown	1.8%	Coronary artery disease	15.5%
Not Disclosed	1.5%	Hyperlipidemia	67.1%
Mean aspartate Aminotransferase (0–37)	34.7 U/L	Mean alanine aminotransferase (0–40)	44.1 U/L
Mean platelets (150–350)	260 K/cu mm	Mean total bilirubin (0–1.2)	0.58 mg/dL
Mean albumin (3.5–5.3)	5.87 g/dL	Mean INR (excluding those on Warfarin; 0.8–1.1)	1.91
Mean hemoglobin A1c (normal <5.6, prediabetes 5.7–6.4, diabetes >6.5)	6.22	Mean lipid panel results	
		Cholesterol (0–200)	186 mg/dL
		Triglycerides (0–150)	159 mg/dL
		HDL (>40)	48.9 mg/dL
		LDL (<70)	108 mg/dL

platelets of 260 K/cu mm, total bilirubin of 0.58 mg/dL, INR of 1.91 (excluding those on warfarin), hemoglobin A1c of 6.2%, total cholesterol of 186 mg/dL, triglycerides of 159 mg/dL, and LDL of 108 mg/dL. Nearly 15% of included patients with NAFLD were missing laboratory results for AST and ALT, 55% for platelets, 1.7% for total bilirubin, 61% for INR, 16.1% for hemoglobin A1c, and around 5% each for total cholesterol, triglycerides, and Low-Density Lipoprotein (LDL).

Prior to their first PCP visit for NAFLD, 53.1% of patients had undergone abdominal ultrasound, 33.8% abdominal CT, and 5.6% abdominal MRI. After the first visit, 30% had orders placed for an abdominal ultrasound, 30% for abdominal CT, and 5.7% for abdominal MRI [Figure 1]. During an average follow-up time ranging from 0 to 7 years (mean 1.4 ± 1.9), which included a mean of 15 visits to primary care for any reason, only 0.2% of patients completed ultrasound elastography, 0.9% had fibro scan, 0.2% had liver biopsy, and 0.1% had Magnetic Resonance Elastography (MRE) of the liver.

Prescriptions for medication to potentially treat NAFLD were relatively uncommon; 54% received a prescription for a statin, 36% for a thiazolidinedione, 21.5% for a Glucagon-like Peptide 1 (GLP-1), 10.5% for an Sodium-dependent Glucose Transporter 2 (SGLT-2), and 8.2% for Vitamin E. Additionally, 24% were referred to a nutritionist and 18.4% attended a nutrition appointment, whereas only 0.7% of patients were referred to a hepatologist by their PCP, though 3.8% were ultimately seen by hepatology.

Four hundred and seventeen patients (4%) in this population were diagnosed with advanced fibrosis or cirrhosis following

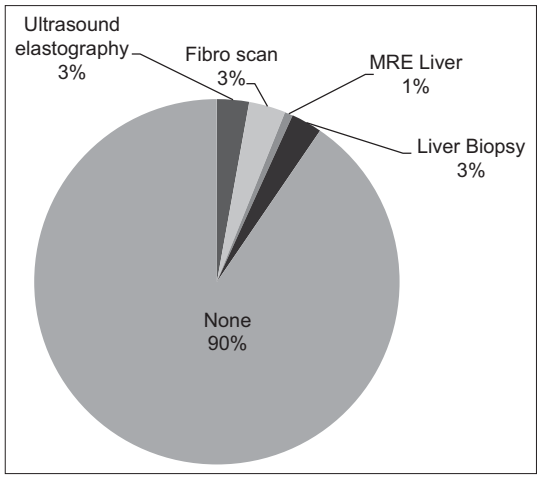

Figure 1: Imaging ordered for overall population

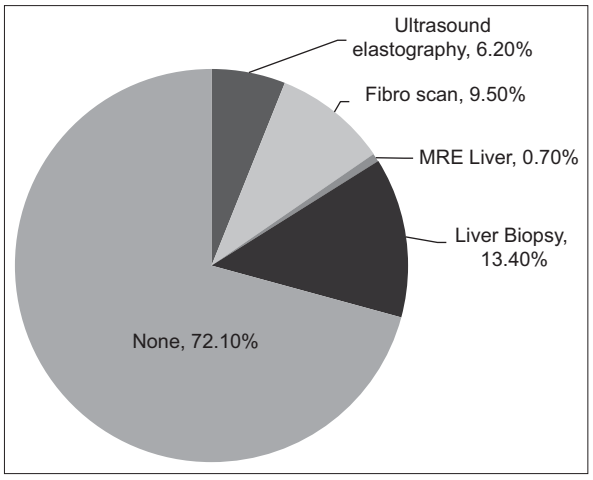

Figure 2: Imaging ordered for patients with fibrosis/cirrhosis

Table 2: Treatment and testing ordered for patients with diagnosed NAFLD

	Overall population (*n*=10,334)	Those with Type-2 Diabetes Mellitus (*n*=4,015)	Those with Advanced Fibrosis or Cirrhosis (*n*=417)
Prescriptions written			
SGLT-2	10.5%	27.9%	18%
GLP-1	21.5%	45%	26.1%
Vitamin E	8.2%	8.8%	18.0%
Statin	54.0%	79.6%	65.5%
Thiazolidinediones	35.6%	47.6%	44.6%
Referred to hepatology	0.7%	1.2%	12.2%
Seen by hepatologist	3.8%	4.1%	16.8%
Referred to nutrition	24.2%	37.1%	35.0%
Seen by nutritionist	18.4%	22.9%	15.6%
Imaging ordered at diagnosis			
Ultrasound elastography	2.7%	2.3%	6.2%
Fibro scan	3.1%	3.3%	9.1%
MRE liver	0.6%	0.5%	0.7%
Liver biopsy	2.7%	3.5%	13.4%
Repeat imaging			
Ultrasound elastography	0.2%	0.2%	0.5%
Fibro scan	0.9%	1.0%	1.4%
MRE liver	0.1%	0.1%	0.2%
Liver biopsy	0.2%	0.4%	1.7%

their primary NAFLD visit. Among this high-risk group, medication prescription was somewhat higher, with 65.5% receiving a prescription for a statin, 44.6% for a thiazolidinedione, 26.1% for a GLP-1, 18% for an SGLT-2, and 18% for Vitamin E [Table 2]. Thirty-five percent were referred to a nutritionist and 15.6% attended a nutrition appointment; 12.2% of these patients were referred to a hepatologist and 16.8% were ultimately seen by hepatology. Patients with a diagnosis of advanced fibrosis or cirrhosis were also more likely to have noninvasive fibrosis assessments ordered at their first NAFLD visit, including 6.2% with orders for ultrasound elastography, 9.1% for fibro scan, 0.7% for MRE liver, and 13.4% for liver biopsy [Figure 2].

Finally, four thousand fifteen patients in this population carried a diagnosis of type-2 diabetes mellitus. We chose to highlight this group as they are at high risk for developing advanced liver disease, and several medications are used for both NAFLD and diabetes. Among those with diabetes, 79.6% received a prescription for a statin, 47.6% for a thiazolidinedione, 45% for a GLP-1, 27.9% for an SGLT-2, and 8.8% for Vitamin E.

Discussion

Our study, using data from a large primary care network, demonstrates that most PCPs are not screening, risk stratifying, managing, or referring patients with NAFLD according to guidelines. Among our patients with a NAFLD diagnosis, less than half received referrals for nutrition services, recommended medications for weight loss or lipid control, or fibrosis assessment following diagnosis. While the Fib-4 score has been shown to be an excellent predictor of fibrosis within this population, 15% of PCPs did not order AST or ALT values, and nearly 55% did not order a platelet count at the time of diagnosis, which is required for score calculation. Perhaps most notably, among the 4% of included patients who carried a fibrosis or cirrhosis diagnosis, less than 20% overall were referred to or seen by a hepatologist.

Although not the focus of this study, only 2.8% of the patients within our database of over 300,000 had a diagnosis of NAFLD during this time period, which almost certainly reflects significant underdiagnosis. Further, approximately 38% of our study population had diabetes, and studies estimate that up to two-thirds of patients with diabetes also carry a diagnosis of NAFLD.[12] Given our findings on the management of patients with diagnosed NAFLD, it is almost certain that those without the diagnosis received less attention.

The prevalence of NAFLD in the United States continues to increase. It is quickly becoming the leading cause of cirrhosis and its complications, and a major economic burden within our

healthcare system.[13] Given its enormous and growing impact, helping PCPs feel confident caring for this population will likely have substantial benefits.

Many NAFLD patients have an elevated risk of progression to fibrosis given the presence of concomitant hypertension, diabetes, and hyperlipidemia.[2] However, fewer than 5% overall received follow-up scoring, imaging, or biopsies despite the recommendation for recurrent fibrosis screening every 1–3 years. While improved, medication prescriptions and imaging follow-up were still significantly below the current recommendations among those with diagnosed advanced fibrosis or cirrhosis. Patients with NAFLD and type-2 diabetes appeared more likely to be prescribed medications for weight loss, but less likely to receive liver-related care including imaging or referral to hepatology.

As an accepted component of the metabolic syndrome, NAFLD and its complications should be monitored regularly – akin to the management of diabetes or hypertension. Further, NAFLD patients with obesity (more than 90% in our sample) should all be offered effective weight management including intensive behavioral weight loss programs, antiobesity medications, or referral to obesity medicine or bariatric specialists. While there are known barriers including lack of insurance coverage, medication interactions, and affordability, our data show that SGLT-2 and GLP-1 are significantly underutilized in a way that is unlikely to be explained by medication restrictions alone. This was less of an issue among patients who also had a diagnosis of diabetes.

There are a few limitations to our work. Our data spans a nearly seven-year period (from July 2016 to September 2023). During these years, data on NAFLD management was evolving and recommendations were published at various points throughout this time. Notably, the AASLD first published NAFLD guidelines in 2012 but offered significant updates in 2018, 2021, and 2023.[2,6,14,15] We also used billing codes and ICD data as our sources for the diagnosis and did not access provider notes for further details on counseling, medication contraindications, or patient engagement in care for example. We are, therefore, unable to tell if providers were calculating Fib-4 or NFS, but the lack of appropriate labs ordered suggests they are not. Moreover, even when advanced fibrosis or cirrhosis were diagnosed, few were referred to hepatology. Lastly, data were available only for our healthcare system, and thus may underrepresent the proportions with referrals, laboratory values, imaging, or medications they may have received elsewhere.

Nonetheless, while there are published articles offering guidelines and flowsheets aimed at PCPs for managing NAFLD, to our knowledge, this study is one of the first to describe how PCPs are putting this information into practice. Our study includes a large sample size of PCPs at an academic center and uses EHR data on demographics, diagnosis codes, laboratory values, imaging and medication orders, and referrals to describe their management of patients with NAFLD.

Conclusions

Given that NAFLD is most often found incidentally, PCPs will play an essential role in screening, risk stratifying, and managing these patients, including arranging for appropriate follow-up. However, in our study, PCPs were not routinely following the published guidelines, and not referring patients for subspecialty care. There is a strong need to enhance education around NAFLD and its management particularly within the primary care and preventative settings. Furthermore, system level support, such as best practice advisories, automatic calculation of Fib-4 or other fibrosis estimating equations, and improved access to noninvasive fibrosis screening such as fibroscans in primary care settings, could significantly benefit patients with NAFLD and facilitate a clearer understanding of the natural history of NAFLD.

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Conflicts of interest

There are no conflicts of interest.

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