

Nonalcoholic Fatty Liver Disease: Interface Between Primary Care and Hepatology Clinics

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Primary care physicians (PCPs) have the primary role in the diagnosis and management of nonalcoholic fatty liver disease (NAFLD), and in selecting patients for referral to a hepatologist for further evaluation. This study aimed to characterize PCP referrals for patients diagnosed with NAFLD at a major referral hospital, and to determine the severity of liver disease and patient pathway following evaluation in secondary care. New patients seen in the hepatology outpatient clinic (HOC) with a secondary care diagnosis of NAFLD were identified from the HOC scheduling database. PCP referrals for these patients were retrieved from the electronic medical records and reviewed by study clinicians, along with the hepatologists' clinic notes and letters. Over a 14-month period, 234 new PCP referrals received a diagnosis of NAFLD, accounting for 20.4% of the total number of new cases (n = 1,147) seen in the HOC. The 234 referrals were received from 170 individual PCPs at 135 practices. Most patients with NAFLD (88.5%) were referred for investigation of abnormal liver enzymes or other clinical concerns, including abnormal iron studies, hepatomegaly, and abdominal pain. Only 27 (11.5%) referrals included an assessment of liver disease severity. Following evaluation in the liver clinic, 175 patients (74.8%) were found to have a low risk of advanced fibrosis, and most (n = 159; 90.9%) were discharged back to their PCP for ongoing follow-up in primary care. *Conclusion:* In addition to better access to noninvasive fibrosis tests, educational strategies to enhance awareness and recognition of NAFLD as a cause for many of the initial concerns prompting patient referral might improve risk stratification and increase the appropriateness of PCP referrals. (*Hepatology Communications* 2020;4:518-526).

Non-alcoholic fatty liver disease (NAFLD) associated with obesity and type 2 diabetes is an increasingly important chronic liver disease, due to its high prevalence (~25%) in the general population. Although overall less than 5% of people with NAFLD develop clinically significant liver disease,⁽¹⁾ its prevalence is such that the number of people with end-stage liver disease is predicted to more than double by 2030 in many regions globally,⁽²⁾ and it is increasing as an etiology for primary liver cancer.⁽³⁾ The most important predictor of mortality or liver-related clinical outcomes for NAFLD is the presence of advanced fibrosis, including bridging (stage 3) and cirrhosis (stage 4)⁽⁴⁾; these patients may benefit from specialist care and surveillance for liver cancer and liver decompensation. In contrast, patients

Abbreviations: BMI, body mass index; CI, confidence interval; ELF, enhanced liver fibrosis (test); FIB-4, fibrosis-4 (score); HOC, hepatology outpatient clinic; LFT, liver function test; LSM, liver stiffness measurements; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; OR, odds ratio; PCP, primary care physician.

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without clinically significant fibrosis may be managed in primary care with attention to cardiovascular risk factors and monitoring for progressive liver disease.

In Australia, primary care physicians (PCPs) are the first point of contact for people with health concerns, and coordinate care and referral to other specialists or hospital services. Due to the high proportion of affected individuals who largely have low-risk disease, it is essential that PCPs take an active role in the diagnosis and management of NAFLD and develop the awareness and skills to identify patients at risk of advanced fibrosis. Clinical guidance recommends a pragmatic approach to identify people with high-risk NAFLD using first-line, noninvasive tests, such as Fibrosis-4 (FIB-4)^(5,6) and NAFLD fibrosis score (NFS).⁽⁷⁾ These simple scoring systems combine routine biochemical tests with clinical risk factors for fibrosis such as age or diabetes, and low scores have high negative predictive values for excluding advanced fibrosis.⁽⁸⁾ People with indeterminate or high FIB-4/NFS scores require further assessment with second-line biomarkers such as the serum enhanced liver fibrosis (ELF) test⁽⁹⁾ or liver stiffness measurements (LSM),⁽¹⁰⁾ and may require referral to a hepatology clinic for investigation of liver disease.

We⁽¹¹⁾ and others⁽¹²⁾ have shown that PCPs often underestimate the prevalence of NAFLD, and this may contribute to many affected individuals remaining undiagnosed, in part because the condition is usually asymptomatic and associated with relatively normal or only mildly elevated liver enzyme levels. PCPs are often not familiar with the clinical spectrum of NAFLD and how this is assessed using fibrosis biomarkers and algorithms.^(11,13) Although it is hypothesized that this may lead to an inefficient or *ad hoc* approach to referrals,⁽¹⁴⁾ there are little

published data that describe the content or standard of hepatology referrals for patients with a secondary care diagnosis of NAFLD. This information is clearly important in developing strategies to increase the detection and referral of NAFLD patients with advanced fibrosis or cirrhosis, and to reduce the number of unnecessary referrals of patients with mild liver disease.

Therefore, the aim of this study was to characterize referrals for patients diagnosed with NAFLD at a major referral hospital. In addition, we determined the severity of liver disease following evaluation in secondary care, and whether patients were discharged to their PCP for management and follow-up in the community.

Methods

All new patients seen in the hepatology outpatient clinic (HOC) at the Princess Alexandra Hospital with a diagnosis of NAFLD between February 2017 and March 2018 were identified from the HOC scheduling database and review of the electronic medical records. A diagnosis of NAFLD was documented by the treating hepatologist and defined by demonstration of hepatic steatosis by liver ultrasound in the presence of metabolic risk factors and the exclusion of significant alcohol consumption (≥ 20 g/day) or other chronic liver diseases (including a prior history of alcohol-related liver disease).⁽¹⁵⁾

PCP referrals for these patients were retrieved from the medical records and were reviewed by the study clinicians, along with the hepatologists' clinic notes and letters. A template (available on request from

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the authors) was developed to collect written clinical information from the referrals and clinic notes/letters in a standardized form. The PCP's main reason for the patient's referral was coded as the "primary" reason. Additional queries or concerns documented in the referral letter were coded as "secondary" reasons for referral. Basic demographic and limited clinical information were available from the referral letter, and the NFS and/or FIB-4 tests were calculated using available clinical and laboratory data.

In the hepatology clinic, patients underwent a clinical assessment that included anthropometric measurements, laboratory tests (routine biochemical, hematological, and serological assays), transient elastography, and liver imaging (computed tomography, magnetic resonance imaging, and/or ultrasound). Transient elastography was performed using FibroScan technology (Echosens, Paris, France) as previously described.⁽¹⁶⁾ At our center, LSM ≥ 8.2 kPa are used to identify clinically significant fibrosis (LSM ≥ 9.5 kPa for advanced fibrosis, and >13 kPa to indicate cirrhosis).⁽¹⁶⁾ Evidence of cirrhosis on liver imaging was determined by liver surface nodularity or signs of portal hypertension, including portal vein dilatation, splenomegaly, portosystemic collaterals, and ascites. A liver biopsy was performed in a subset of patients for clinical indications. The diagnosis of definite or probable advanced fibrosis was based on the composite clinical judgement of the treating hepatologist using liver histology (if available), imaging, or a combination of noninvasive markers and clinical assessment.

The study was approved by the Metro South Health Human Research Ethics Committee (LNR/2018/QMS/44755).

DATA ANALYSIS

Data were analyzed using SPSS version 20.0 (IBM, Armonk, NY). Continuous data were assessed using the Shapiro-Wilk test. Normally distributed data are presented as mean \pm SD, and differences between groups were analyzed using the independent-samples *t* test. Nonparametric data are presented as median (interquartile range [Tukey's hinges]), and comparisons between groups were analyzed using the Mann-Whitney U test. Categorical data are presented as proportions (%), and differences between groups were assessed using the Pearson's χ^2 test (or Fisher's exact

test when expected cell counts were <5). Binary logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results

REFERRAL CHARACTERISTICS

Between February 2017 and March 2018 (14 months), 234 *new* PCP referrals seen in the HOC at the Princess Alexandra Hospital received a diagnosis of NAFLD, accounting for 20.4% of the total number of new cases ($n = 1,147$) seen in the HOC over this time period. The 234 referrals were received from 170 individual PCPs at 135 practices. A total of 131 PCPs referred 1 patient, 27 PCPs referred 2, and 12 PCPs referred 3 or more patients (3 PCPs referred 3 patients each, 7 referred 4 patients each, 1 referred 5 patients, and 1 referred 7 patients).

At the time of referral, the mean age of the patients was 52.6 ± 14.0 years, 53.0% were male, and 134 (57.3%) were born in Australia. The reasons for referral are outlined in Fig. 1. Overall, 143 referrals (61.1%) documented or requested an opinion regarding assessment and management of NAFLD, steatosis or fatty liver, although this was a "secondary" reason for referral in 88 (61.5%) of these cases. Only 27 patients (11.5%) were primarily referred for evaluation of NAFLD/steatosis and had no secondary reason for referral. The most common primary reason for referral was for investigation, diagnosis, or management of abnormal liver enzymes (108 referrals, 46.2%), although the indication for checking liver enzymes was not usually specified in the referral letter. Furthermore, a total of 114 referrals (48.7%) requested an opinion regarding at least one other issue, including abnormal iron studies (14.1%), hepatomegaly (10.3%), suspected advanced liver disease (11.5%), abdominal pain (6.8%), liver lesions (5.6%) or suspected other chronic liver diseases (5.1%). The average waiting time for an appointment was 9.2 ± 7.1 months.

Overall, the patient's body mass index (BMI) or weight was provided in 94 (40.2%) referrals. A comment about alcohol intake was provided in 99 (42.3%) referrals, although only qualitative descriptions were present in 31 (31.3%) of these. Information about diabetic status was provided in 104 (44.4%) referrals, dyslipidemia in 97 (41.5%) referrals, and hypertension

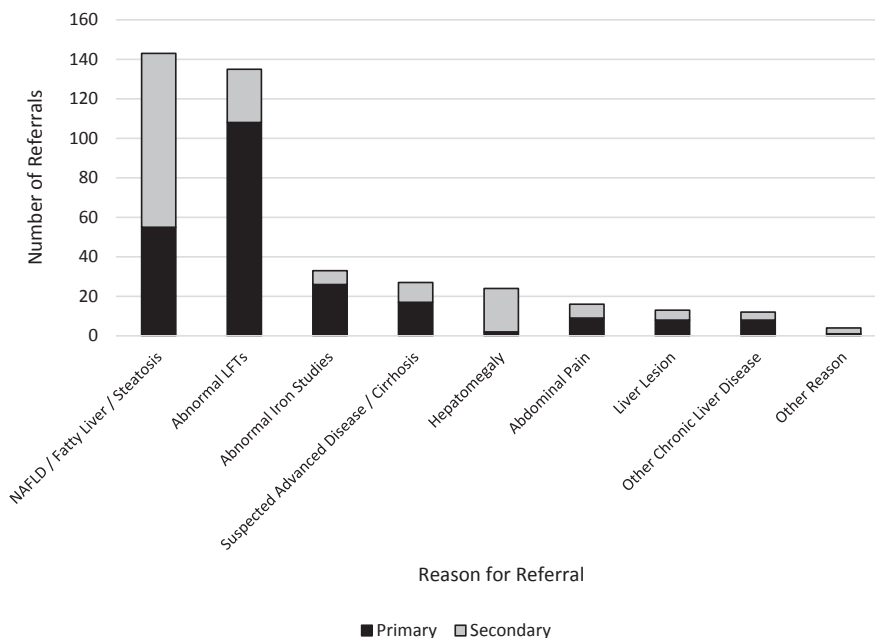


FIG. 1. Reason for referral of new patients seen in the HOC with a diagnosis of NAFLD. The PCP’s main reason for the patient’s referral was coded as the “primary” reason. Additional queries or concerns documented in the referral letter were coded as “secondary” reasons for referral.

in 80 (34.2%) referrals. A higher proportion of referrals documenting NAFLD included information about metabolic risk factors (Fig. 2).

LIVER DISEASE SEVERITY

Referrals with details regarding the assessment of disease severity were infrequent (n = 27, 11.5%). NFS was provided in 13 referrals, liver imaging reporting features suggestive of cirrhosis or portal hypertension was provided in 7 referrals, elastography was provided in 5 referrals, aspartate aminotransferase-to-platelet ratio index was provided in 1 referral, and ELF test was provided in 1 referral. There was a specific request for assessment of liver disease severity in 8 referrals (request for liver FibroScan in 6 referrals, for consideration of liver biopsy in 1 referral, and for assessment of gastroesophageal varices in 1 referral).

Most patients (n = 223, 95.3%) completed a fibrosis assessment in the HOC. A total of 51 (21.8%) patients were diagnosed as having advanced fibrosis following hepatology review, including 5 patients with “probable” advanced fibrosis based on elevated LSM in the absence of a liver biopsy, and without evidence of cirrhosis on liver imaging. Of the 11 patients who

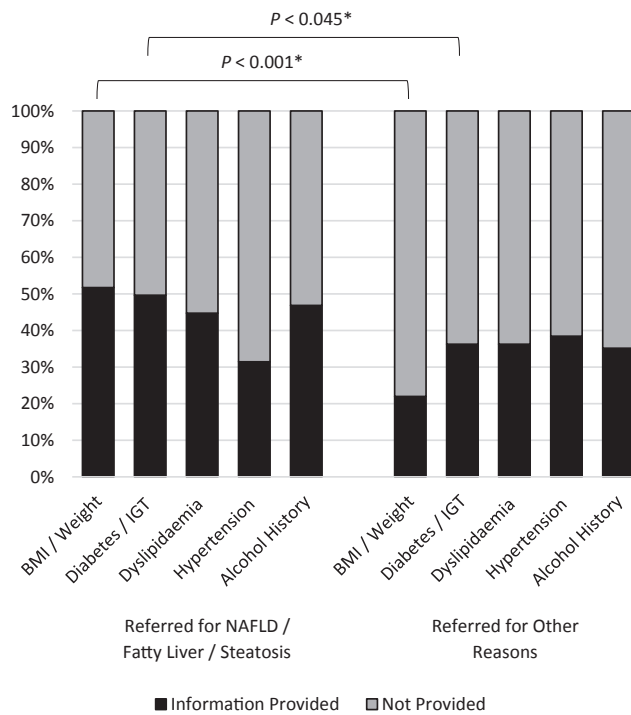


FIG. 2. Proportion of referrals providing information about alcohol consumption and metabolic risk factors. *Pearson’s χ^2 test. Abbreviation: IGT, impaired glucose tolerance.

did not complete a fibrosis assessment, 3 were considered to have nonadvanced disease (n = 2 scored “low” on both the NFS and FIB-4 tests, and n = 1 had an unsuccessful FibroScan but no evidence of cirrhosis or portal hypertension on imaging), and 8 patients failed to attend FibroScan and clinic appointments, and were thus discharged according to hospital policy (Fig. 3).

Among the 143 patients referred for NAFLD, steatosis or fatty liver, age-specific FIB-4 and NFS scores⁽¹⁷⁾ were provided or could be calculated using information in the referral for 54 (37.8%) patients. Twenty-one patients had concordant “low” scores⁽¹⁶⁾; the negative predictive value of NFS and FIB-4 in combination

for excluding definite/probable advanced fibrosis was 90.5%. Compared to those with concordant “low” scores at referral, patients with “indeterminate”/“high” FIB-4 and/or NFS scores were 5.7 (95% CI: 1.1-28.9; P = 0.036) times more likely to be diagnosed as having definite or probable advanced fibrosis.

PATIENT MANAGEMENT PATHWAY

Following hepatology consultation, 161 patients (68.8%) were discharged back to their PCP for ongoing management of NAFLD (Fig. 4), and 14 (6.0%)

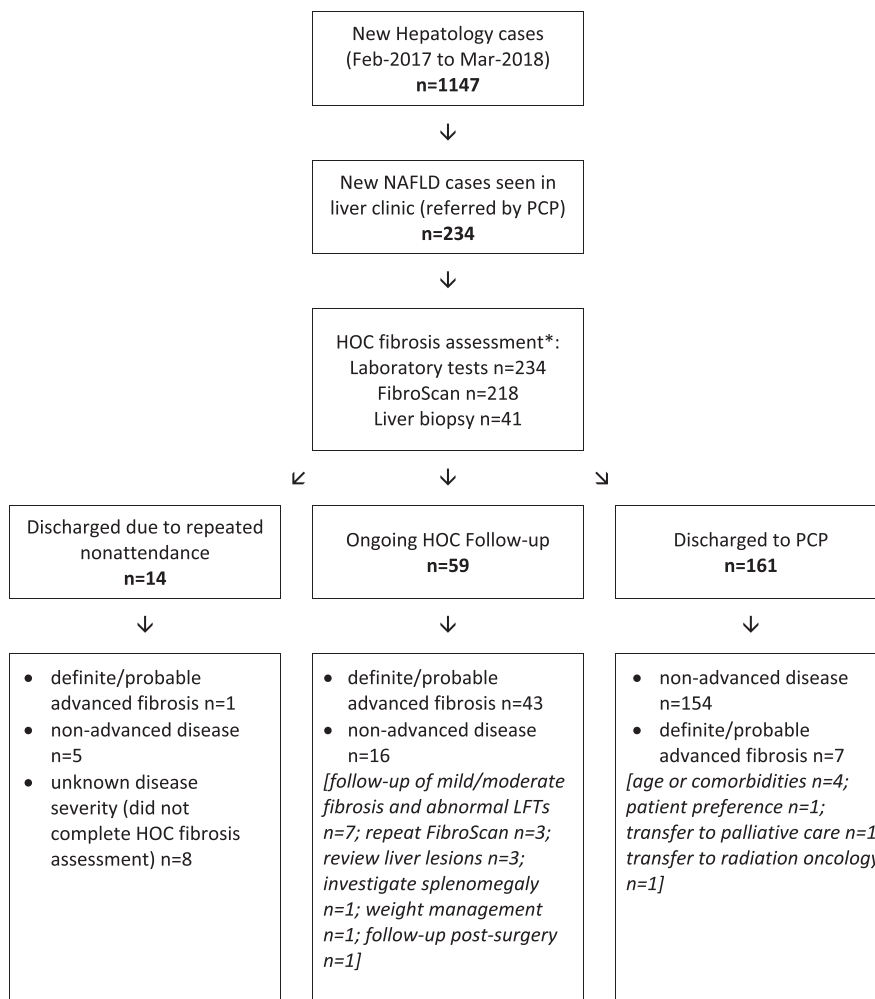


FIG. 3. Flow of patient referral, fibrosis risk assessment, and outcomes for patients diagnosed with NAFLD. *A total of 223 patients completed a fibrosis assessment in the HOC with FibroScan (n = 218) or had imaging consistent with cirrhosis (n = 5). Of the 11 patients who did not complete a fibrosis assessment, 2 patients scored “low” on both NFS and FIB-4 tests, 1 had an unsuccessful FibroScan due to body habitus but had no evidence of cirrhosis or portal hypertension on imaging, and 8 patients failed to attend fibrosis assessment and clinic appointments, and therefore were discharged according to hospital policy.

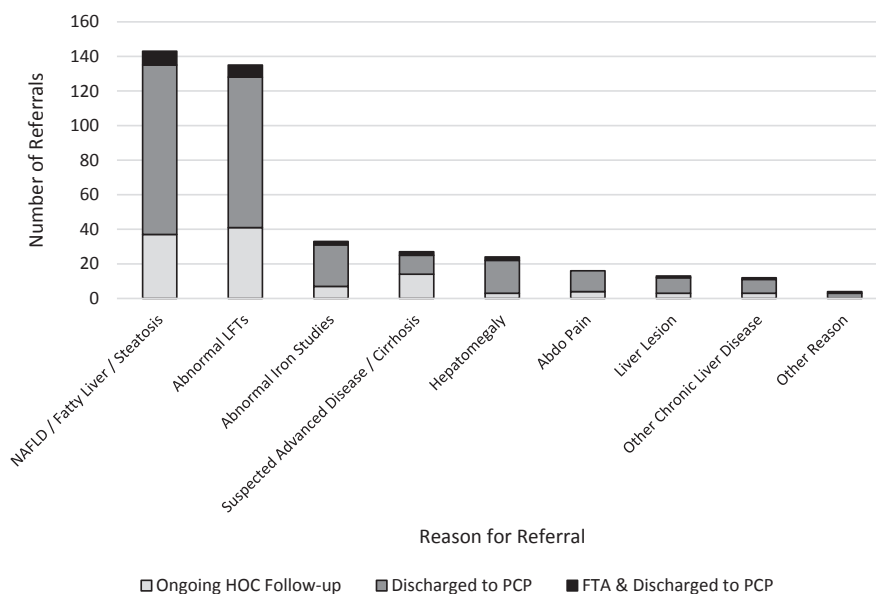


FIG. 4. Outcome for new patients diagnosed with NAFLD following hepatology review. Abbreviation: FTA, failed to attend.

patients repeatedly failed to attend follow-up investigations or hepatology reviews and were discharged from the clinic according to hospital policy. Table 1 summarizes the clinico-demographic characteristics of patients at the time of initial clinic appointment, according to whether they were subsequently scheduled for ongoing HOC follow-up or discharged back to their PCP. A higher proportion of patients scheduled for ongoing HOC follow-up were referred for suspected advanced liver disease (23.7%) compared with those discharged back to primary care (6.8%). Patients scheduled for ongoing hepatology follow-up had higher median LSM (11.8 [9.1-17.1] vs. 5.1 [4.4-6.3] for patients discharged back to primary care), higher median BMI (35.0 [32.0-44.0] vs. 33.0 [29.0-38.0]), and a higher proportion had diabetes or impaired glucose tolerance (57.6% vs. 34.8%).

Of the 51 patients diagnosed as having definite or probable advanced fibrosis, 43 (84.3%) were scheduled for ongoing follow-up in the liver clinic (Fig. 3). Eight patients with definite or probable advanced fibrosis were discharged back to their PCP for ongoing follow-up, due to patient preference ($n = 1$), age or comorbidities ($n = 4$), transfer of care to palliative ($n = 1$) or radiation oncology ($n = 1$) teams, or failure to attend appointments ($n = 1$). A further 16 patients *without* advanced fibrosis were scheduled for further review in the liver clinic for the following reasons:

follow-up of nonalcoholic steatohepatitis with mild/moderate fibrosis and abnormal liver enzymes ($n = 7$), repeat liver FibroScan ($n = 3$), review of liver lesions ($n = 3$), investigation of splenomegaly ($n = 1$), weight management ($n = 1$), follow-up after surgery ($n = 1$).

Discussion

PCPs have the primary role in the diagnosis and management of NAFLD, and in selecting patients for referral to a hepatologist for further evaluation of liver disease. There are little published data that describe the content or standard of hepatology referrals for patients with a secondary care diagnosis of NAFLD. The present study found that most patients with NAFLD (88.5%) were referred for investigation of abnormal liver enzymes or other clinical concerns, including abnormal iron studies, hepatomegaly, and abdominal pain. Only 11.5% of referrals included an assessment of liver disease severity, and following evaluation in the liver clinic, two-thirds of the patients were discharged back to their PCP for ongoing management of NAFLD.

Although clinical guidance recommends referral of patients with NAFLD at risk of advanced fibrosis or cirrhosis, our data demonstrate that PCPs do not consider their assessment of liver disease severity as

TABLE 1. CLINICO-DEMOGRAPHIC FEATURES OF PATIENTS AT THE TIME OF INITIAL HOC ASSESSMENT ACCORDING TO OUTCOME

	Ongoing HOC Follow-up (n = 59)	Discharged to PCP (n = 161)	P Value
Age, years (mean ± SD)	56.3 ± 13.4	52.9 ± 13.8	0.099*
Male gender	31 (52.5%)	87 (54.0%)	0.844 [‡]
Diabetes/IGT	34 (57.6%)	56 (34.8%)	0.002 [‡]
AST (median [IQR])	42 [30-58]	28 [20-39]	<0.001 [†]
ALT (median [IQR])	53 [35-72]	43 [28-66]	0.047 [†]
Albumin (median [IQR])	40 [38-43]	42 [40-45]	0.001 [†]
Platelets (median [IQR])	232 [184-279]	256 [216-304]	0.011 [†]
BMI (median [IQR])	35.0 [32.0-44.0]	33.0 [29.0-38.0]	0.001 [†]
Girth, cm (median [IQR])	120 [108-135]	109 [101-122]	<0.001 [†]
FibroScan LSM (median [IQR]) [§]	11.8 [9.1-17.1]	5.1 [4.4-6.3]	<0.001 [†]
FibroScan CAP (median [IQR]) [§]	339 [292-377]	333 [275-369]	0.578 [‡]
FIB-4 (median [IQR])	1.56 [0.87-2.32]	0.85 [0.59-1.21]	<0.001 [†]
NFS (mean ± SD)	-0.11 ± 1.96	-1.59 ± 1.46	<0.001*
Referred with NAFLD/fatty liver/steatosis	37 (62.7%)	98 (60.9%)	0.804 [‡]
Referred with suspected advanced disease	14 (23.7%)	11 (6.8%)	<0.001 [‡]
Hepatology diagnosis of definite or probable advanced fibrosis	43 (72.9%)	7 (4.3%)	<0.001 [‡]

Data not shown for n = 14 patients who were discharged due to nonattendance.

*Independent samples *t* test.

[†]Mann-Whitney U test.

[‡]Pearson's χ^2 test.

[§]FibroScan LSM results available for n = 57 patients undergoing HOC follow-up and n = 155 patients discharged back to PCP. FibroScan CAP available for n = 56 patients undergoing HOC follow-up and n = 153 patients discharged back to PCP.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IGT, impaired glucose tolerance; IQR, interquartile range.

important information to include in the referral letter. Furthermore, only 3% of referrals included a specific request for specialist assessment of liver disease severity. In Australia, most PCPs do not have direct access to FibroScan or the serum ELF test, and because these investigations are not reimbursed, they are usually only obtained following referral to secondary care. However, recent studies have shown that simple scoring systems (FIB-4, NFS), which are readily calculable in primary care, demonstrate acceptable diagnostic performance for excluding advanced fibrosis and identifying patients requiring further assessment for high-risk NAFLD.⁽⁸⁾

Of these new patients seen in the hepatology clinic with a diagnosis of NAFLD, most of the referrals appeared to be prompted by concerns about abnormal biochemistry or imaging, particularly abnormal liver enzymes. Although not usually specified in the referral letter, we presume that the presence of abnormal liver enzymes was identified during routine clinical investigations (i.e., monitoring of diabetes) or performed for a specific clinical indication (i.e., presence of steatosis or hepatomegaly on ultrasound or abdominal pain).

The findings support an earlier study in which most of the PCPs surveyed (70.6%) said they were unlikely to refer a patient with NAFLD for a hepatology opinion unless the liver function tests were abnormal.⁽¹¹⁾ This approach in selecting patients for referral based on elevated aminotransferases may fail to identify patients with significant liver disease, as most people with NAFLD have traditional normal-range liver blood tests, and liver enzyme levels do not reflect the presence or severity of fibrosis.⁽¹⁸⁻²⁰⁾ In fact, following evaluation in the liver clinic, 175 patients (74.8%) were found to have a low risk of advanced fibrosis, and most (n = 159; 90.9%) were discharged back to their PCP for ongoing follow-up in primary care.

Despite reports estimating that PCPs are likely to encounter more than 300 cases of NAFLD for every 1,000 patients that are seen,⁽²¹⁾ 77% of PCPs referred a single patient with NAFLD over the 14-month study period. In addition, the new PCP referrals seen in the liver clinics with a diagnosis of NAFLD accounted for only 20.4% of the total number of new cases seen over this time period. These data raise concerns that many patients in primary care with

likely NAFLD may not be evaluated for this condition. A current challenge for hepatologists is how best to support PCPs to better identify patients with NAFLD who are at risk of significant liver disease. Several programs to engage PCPs in the assessment of NAFLD are being examined, including referral and care pathways using a tiered approach to detect the presence of advanced fibrosis.^(22,23) With a rise in recognition of NAFLD, strategies to reduce pressure on secondary services and costs for the health care system will be crucial. A recent evaluation of a large data set (n = 6,295 participants) from Europe and Asia demonstrated that community-based screening for liver fibrosis with transient elastography was cost-effective through earlier identification of patients, and the authors suggested that it could represent a valuable public health strategy.⁽²⁴⁾ However, in the current cohort of patients with NAFLD, availability of transient elastography or the ELF test in primary care centers may not have avoided the need for hepatology referral, as most of the patients (88.5%) were referred with a request for an opinion regarding *other* clinical concerns. Interestingly, when NAFLD was recognized by PCPs, more relevant information about metabolic comorbidities was provided in the referral. These findings suggest that, in addition to better access to noninvasive fibrosis tests, educational strategies to enhance awareness and recognition of NAFLD as a cause for many of the initial concerns prompting patient referral might improve risk stratification and increase the appropriateness of referrals.

This retrospective study has a number of limitations. The study was conducted at a large hepatology center within a public hospital in Queensland, Australia. At the time of the study, the long waiting time for an appointment with a hepatologist may have been different from that of other countries or health districts, which may limit the generalizability of our findings. In addition, we were unable to determine how many PCPs within the catchment area did not refer any patients for suspected NAFLD. In the future it will be important to compare the PCP/office characteristics of those who did and did not refer patients with NAFLD. However, this comparison is beyond the scope of the current study.

In Australia there are likely to be a number of barriers to improving awareness and familiarity with care of liver disease in the community.⁽²⁵⁾ Chronic liver disease has not been considered a national health priority area,

and there are no incentives to develop primary care registers of patients with NAFLD that would facilitate recall for follow-up. To date, it is not standard practice to undertake an assessment for liver disease when patients with NAFLD risk factors are seen in secondary prevention programs for diabetes or metabolic syndrome. A recent survey of the public health response to NAFLD in Europe has highlighted the limited attention to NAFLD in current health care policies and clinical practice guidelines.⁽²⁶⁾ At a local level, our data highlight the need for a collaborative approach among hepatologists, primary health networks, and health service districts, to better engage PCPs in the use of locally available risk stratification tools and to improve awareness and familiarity with the care of liver disease.

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