Risk Stratification of Patients with Non-alcoholic Fatty Liver Disease in Primary Care

Short title: Risk Stratifying Non-alcoholic Fatty Liver Disease Patients.

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is a growing Canadian epidemic. However, identification of NAFLD patients with advanced liver fibrosis in primary care remains an unmet need. To address this we developed a shear wave elastography (SWE)-based case identification pathway in primary care to facilitate more appropriate and timely care of NAFLD patients at risk of advanced fibrosis.

Methods: A multi-disciplinary NAFLD clinical care pathway was co-developed by hepatologists, radiologists, and primary care physicians (PCP) to provide access to SWE-based screening of patients with NAFLD risk factors in primary care. NAFLD patients with liver stiffness by SWE ≥ 8.0 kPa (or inconclusive assessment) were referred to hepatology. A serum liver fibrosis score, FIB-4, was also measured and demographic, clinical, and laboratory characteristics of study groups compared.

Results: Between March- October 2018, 2,081 suspected NAFLD patients were evaluated. NAFLD was confirmed by ultrasound in 94%. Elevated liver biochemistry (52%) and obesity (60%) were prevalent in our cohort. The majority of NAFLD patients (91.5%) had SWE < 8.0 kPa and were not referred to hepatology, whereas 3.4% had a SWE ≥ 8.0 kPa and 5.1% had an inconclusive SWE (ie. total 8.5%) and were referred to hepatology. Using a FIB-4 score cut-off of 1.30 would have led to hepatology referral of 32% of patients.

Conclusions: Implementation of a primary care-accessible SWE pathway for NAFLD patients facilitated fibrosis risk-stratification and reduced hepatology referrals. Using serum fibrosis score FIB-4 alone would lead to higher referral rates of NAFLD patients.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is common in patients with diabetes, obesity, dyslipidemia, and metabolic syndrome and has become the leading cause of liver disease in North America.[1,2] Although awareness of NAFLD among primary care physicians is increasing, identifying high-risk NAFLD patients in primary care remains challenging[3-5] and resource-intensive.[6] Furthermore, a strategy to help primary care physicians better triage NAFLD patients for specialist care based on liver fibrosis is lacking.[7] In recent studies, primary care physicians found abnormal liver tests in 18-30% of patients, with 25-29% having NAFLD.[8,9] However, identifying patients with advanced fibrosis who may benefit from hepatology referral, amongst NAFLD population, remains a significant challenge.[6]

Non-invasive serum liver fibrosis scores, such as fibrosis-4 variable index (FIB-4), as well as ultrasound-based modalities including transient elastography (TE; Fibroscan®) and shear wave elastography (SWE) have been used to assess liver fibrosis severity in NAFLD patients.[10,11] Liver stiffness measurement (LSM) by TE and SWE are valid and reliable measures of liver fibrosis.[12,13] However, applying these tools in the primary care setting has not been explored.[11,13,14]

SWE technology can be applied to standard ultrasound machines and could potentially lead to assessment of more patients compared to TE (available mainly in tertiary care centers).[15] Moreover, SWE enables radiologists to directly assess patients for evidence of cirrhosis complications.[16]

Therefore, our primary objective was to implement a SWE-driven pathway to facilitate risk stratification of NAFLD patients within primary care, and evaluate whether SWE assessment could reduce low fibrosis risk NAFLD patient referrals to hepatology.

METHODS

Cohort development

The Calgary NAFLD clinical care pathway (CN-CCP) was developed by hepatologists, radiology, and primary care leadership in Calgary, Canada (population ~1.4 million). The CN-CCP was accessible to primary care physicians for patients with NAFLD risk factors or conditions including: diabetes, increased body mass index (BMI), dyslipidemia or metabolic syndrome, previous imaging evidence of fatty liver, and elevated liver biochemistry. Patients with other chronic liver diseases, including heavy alcohol consumption (> 2 standard alcohol drinks per day for men, >1 for women), viral hepatitis B or C, and immune-mediated liver disorders were excluded.

Patients with probable NAFLD, and no exclusion criteria, were referred by primary care to community-based radiology providers for SWE assessment. Based on SWE (threshold 8.0 kPa), patients were stratified as “at risk” or “low risk” for advanced fibrosis. “At risk” patients (SWE ≥ 8.0 kPa, or inconclusive SWE assessment) were recommended for hepatology referral through a single citywide central referral access point. Patients at “low risk” were managed within primary care using a standardized management plan that included lifestyle modifications. The Calgary NAFLD CCP is appended (Appendix 1).

NAFLD Pathway Evaluation

An evaluation period for the CN-CCP occurred October 2016 - February 2018, to ensure high-quality implementation.

Study Duration

Patients with a confirmed NAFLD diagnosis during SWE assessment (between March - November 2018) were included in our prospective cohort.

Data Source

The CN-CCP database was established, including all adult Calgary residents with suspected NAFLD referred by primary care physicians for SWE. The database contains patient demographics and SWE characteristics, comorbidities, laboratory data (complete blood count, lipid profile [triglycerides, cholesterol, high density lipoprotein (HDL), and low density lipoprotein (LDL)], hemoglobin A1c (HbA1c), international normalized ratio (INR), liver biochemistry (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, and gamma glutamyl transpeptidase (GGT), creatinine), medications for diabetes, dyslipidemia, and hypertension, and SWE findings (assessment date, reliable study [yes/no], median and interquartile range of speed based on 10 measurements [m/s], median elasticity [kPa], portal vein diameter, liver echogenicity and attenuation, liver contour and echotexture).

Covariates

We included the following variables from the CN-CCP database: age; sex; body mass index (BMI; weight in kg/ height in m^2); type 2 diabetes mellitus (T2DM) defined as: Hemoglobin A1c > 6.4%, a diagnosis code of T2DM by a physician, or patients using T2DM treatment; impaired fasting glucose (IFG) defined as HbA1c between 5.7-6.4%; hypertension defined by a physician diagnosis code or a drug treatment for hypertension; laboratory investigations.

Laboratory data were obtained at baseline (within 3 months of SWE). Patients had elevated liver enzymes if ALT values were $\geq$ ULN (ALT: male $\geq$ 30 U/L, female $\geq$ 25 U/L).[17] As AST was often not routinely ordered by primary care physicians, we described the patient characteristics of those with available AST and FIB-4 compared to patients with missing values (AST is required for FIB-4 calculation).

NAFLD case confirmation

All patients evaluated in the NAFLD CCP received an abdominal ultrasound and SWE. Patients with homogenous liver echotexture, normal echogenicity/ contour, and no signal attenuation were identified as not having fatty liver. Patients with liver steatosis were considered to have NAFLD.[15,16] Patients with failed SWE (n=3 patients) were excluded.

Liver stiffness assessment

SWE is a real-time ultrasound-based technique widely used to assess liver stiffness (ie. fibrosis) using an acoustic radiation force-induced (ARFI) pulse through tissue to create shear waves.[18].[15] SWE was performed using a 2D Canon Aplio i800 (Otawara-shi, Tochigi, Japan) ultrasound system. A standard abdominal ultrasound examination (fasting patient) was performed by a trained technologist (completed ≥100 supervised SWE exams) or a subspecialty body radiologist with SWE experience.[16,18] An inconclusive SWE reflected the inability to obtain a technically reliable shear wave (using IQR/median ≤ 15% for m/s or ≤ 30% for kPa).[16]

Statistical analyses

Patient characteristics according to SWE results were described. Chi squared (X^2) test and Wilcoxon rank-sum test or Kruskal-Wallis test were applied to study demographic, laboratory, and clinical differences between study groups at baseline according to LSM values. Logistic regression models identified independent predictors of SWE ≥ 8.0 kPa, or inconclusive SWE measurements. Logistic regression models were adjusted for age, sex, BMI, ALT at baseline, and comorbidities. All regression model estimates were reported as adjusted odds ratio (aOR) with accompanying 95% confidence intervals (CIs). Further analyses identified possible differences between patients with complete laboratory

investigations (for calculating FIB-4) and those lacking required tests. A published cut-off value of 1.30 for FIB-4 was used (cut-off has demonstrated high negative predictive value (NPV) for advanced fibrosis >90%).[11] All analyses were performed using Stata IC (version 15.1, Texas, USA).

RESULTS

Patient characteristics

2,081 suspected NAFLD patients were evaluated via the CN-CCP between March - November 2018 (Figure 1). NAFLD was diagnosed by ultrasound in 94.1% of patients (n=1,958). Diagnosis of NAFLD varied by BMI (97.1% for BMI ≥ 30 kg/m^2; 92.3% for BMI 25–30 kg/m^2, *P*<0.001). In our cohort, slightly more NAFLD patients were female (53.7%, n=1,052), with a median age of 55 years (IQR: 45–63). Baseline clinical and laboratory investigations are presented in Table 1. Median SWE was 4.4 kPa (IQR: 3.7–5.5 kPa), while median FIB-4 score was 0.99 (IQR: 0.69–1.48).

NAFLD patient classification by SWE in primary care

1,791 NAFLD patients (91.5%) had SWE < 8.0 kPa and were not referred to hepatology. However, 8.5% (n=167) NAFLD patients had SWE ≥ 8.0 kPa (3.4%) or inconclusive results (5.1%), and hepatology referral was recommended. Compared to non-referred patients, referred patients (SWE ≥ 8.0 kPa or inconclusive result) were older (median age 61, 57 vs. 54 years, *P*<0.01), had a higher BMI (median 37.2, 40.6 vs. 31.6, *P*<0.01), and were more likely to have IFG/DM (74.6%, 74.0% vs. 61.2%, *P*<0.01). NAFLD patients with SWE ≥ 8.0 kPa or inconclusive result had similar ALT and AST levels as those with SWE < 8.0 kPa. However, patients with SWE ≥ 8.0 kPa or inconclusive result had lower albumin levels (median 37, 37 vs.

39, *P*<0.01), higher GGT levels (median 87, 48 vs. 45, *P*<0.01), lower platelet count (median 214, 234 vs. 252, *P*<0.01), and higher FIB-4 scores (1.71, 1.19 vs. 0.96, *P*<0.01), compared to patients with SWE < 8.0 kPa (Table 1).

Cohort stratification based on different cut-offs of SWE

Using SWE cut-off points between 6.0 - 9.0 kPa led to different rates for recommended hepatology referral. Specifically, 67 patients (3.4%) had a SWE result ≥ 8.0 kPa, 106 (5.4%) had a SWE result ≥ 7.0 kPa and 44 (2.3%) had SWE ≥ 9.0 kPa (Supplementary Table 1).

Using the FIB-4 score for NAFLD cohort risk stratification

FIB-4 was modelled as a potential index test to classify NAFLD patients for being at risk for advanced fibrosis. Patient characteristics did not differ between patients with available FIB-4 scores (63.9%, n=1,251) and those without (Supplementary Table 2). Applying a FIB-4 cut-off of <1.30 as an index test would have classified 68.4% (n=855) of NAFLD patients as low-risk for advanced liver fibrosis but would have led to hepatology referral in 31.7% (n=396). However, in hepatology-referred patients with a FIB-4 cut-off > 1.30, only 34 (8.6%) would have SWE ≥ 8.0 kPa. Importantly, 21 patients (2.5%) had SWE ≥ 8.0 kPa within the FIB-4 <1.30 cohort (Figure 2). Therefore, agreement was observed in 69.4% of patients (n=868/1,250). Using a higher FIB-4 cut-off such as 2.24 would lead to referral of 10.2% of our cohort. However, only 29.1% (16/55) of NAFLD patients with SWE>8.0 kPa would be referred for assessment.

Which patient characteristics predict the need for hepatology referral?

In adjusted models for patient characteristics (including age, sex, obesity, diabetes, glucose intolerance, hypertension, and having either elevated ALT or AST at baseline), independent predictors of SWE ≥ 8.0 kPa were evaluated (Table 2).

Obesity (aOR 1.93: 1.01–3.75), T2DM (aOR 2.22: 1.13–4.36) and hypertension (aOR 2.18: 1.19–3.98) were the only independent predictors for a SWE ≥ 8.0 kPa. Independent predictors of need for hepatology referral (i.e., SWE ≥ 8.0 kPa or inconclusive results) were similar to our previous model. Specifically, obese patients had a three-fold higher risk of needing a hepatology referral (aOR 2.94: 1.85–4.69), while patients with T2DM and hypertension had two-fold higher risk (aOR 2.33: 1.50–3.63; and 2.38: 1.62–3.50, respectively) (Table 2).

DISCUSSION

We report findings from the largest North American primary care-based NAFLD patient cohort assessed for elevated LSM using a unique, Canadian primary care-based NAFLD clinical pathway implementing SWE to evaluate liver fibrosis risk. We used this pathway to differentiate those patients with low risk of advanced fibrosis, who do not require hepatology referral, from those who are "at risk" and could benefit from hepatology referral. 3.4% of NAFLD patients in our cohort had SWE ≥ 8.0 kPa, suggesting they were at risk for advanced liver fibrosis, and 5.1% had inconclusive SWE. The higher rate of inconclusive SWE was related mainly to morbid obesity (BMI ≥ 40). Therefore, the CN-CCP identified 8.5% of our total NAFLD cohort for specialist referral. Few studies have reported the prevalence of NAFLD-related elevated LSM in the general population.[19-22] Caballeria et al. found 5.8% of a Spanish population had LSM by TE > 8.0 kPa, with the majority of patients having NAFLD. In contrast, Koehler et al. reported a prevalence of 8.4% for the same LSM cut-off in a Dutch population.[19,21] However, all of these studies used TE measured LSM for estimating liver fibrosis.

Both SWE and TE (Fibroscan®) are ultrasound modalities commonly used to assess liver fibrosis.[6] These techniques are well validated in NAFLD patients.[12,23-25] A recent meta-analysis by Hermann et. al. showed that in 156 NAFLD patients, using liver biopsy as gold standard, performance of SWE was equivalent to TE, with a small gain in AUROC for all stages of fibrosis.[24] We used a SWE cut-off of 8.0 kPa, as this cut-off has previously shown excellent performance for *ruling out* advanced liver fibrosis (sensitivity of 91% and negative predictive value of >95%).[11,12,24] Therefore, we used this SWE cut-off to identify NAFLD patients at "low risk" for advanced liver fibrosis; allowing the pathway to direct further focused workup on at risk patients, recognizing that a SWE cut-off of > 8.0 kPa alone has a PPV >75% for identifying NAFLD patients with advanced fibrosis (which may be lower in a low prevalence community setting).[11]

In our cohort, obesity, T2DM, and hypertension, but not elevated liver enzymes, were the main independent predictors for SWE ≥ 8.0 kPa. These findings suggest that risk stratification of NAFLD patients for advanced liver fibrosis may benefit from targeting patients with these comorbidities.

31.7% of our patients had a FIB-4 score >1.30, previously shown to have a NPV >90 for ruling out advanced fibrosis.[11] Choosing higher cut-off values for FIB-4 would will lead to a higher PPV, but worse NPV.[11,26,27] Similar to our study, implementing FIB-4 scores in a British primary care setting found that 30% of NAFLD patients had a FIB-4 score >1.30.[28] While not the focus of this paper, a cost utility analysis could be conducted comparing SWE results to serum noninvasive fibrosis scores to risk stratify NAFLD patients.

There are multiple strengths to our study. We outline results from implementation of a novel primary care-based SWE-driven CCP to evaluate NAFLD

patients. Our pathway was widely accepted by primary care physicians due to its' simple algorithm and accessibility. Importantly, SWE technology is readily applied to most commonly used ultrasound machines. Our SWE-driven NAFLD pathway decreased primary care referral of at risk NAFLD patients to hepatology by >90% and enriched the referred population for advanced liver fibrosis. This type of NAFLD patient triaging within primary care, prior to specialist referral, will be critical for dealing with the huge and growing societal NAFLD patient burden, allowing streamlined specialist referral for patients at risk for advanced liver fibrosis who may benefit from aggressive intervention targeted at their liver disease. Importantly, our cohort is more representative of high-risk NAFLD patients in the general community, compared to previous studies focused on patient cohorts after tertiary care referral. Furthermore, our study provides essential data to answer uncertainties on performance of diagnostic tools for assessing NAFLD. Recent guidelines urged that studies like ours be undertaken to evaluate the feasibility of routine evaluation for NAFLD in primary care,[6,29] especially with anticipated availability of pharmacological treatment options for NAFLD patients with advanced fibrosis in the near future.

Our study has some limitations. To allow for easier implementation of the NAFLD pathway, we provided guidance to primary care physicians without strict criteria or incentives to assess only probable NAFLD patients. Therefore, most of our T2DM cohort had NAFLD, since primary care physicians often referred T2DM patients for SWE who had previous incidental findings of fatty liver. Similarly, we could calculate FIB-4 scores on ~ 2/3 of our cohort, as primary care physicians in Calgary historically have been discouraged from routinely ordering AST. However, this did not affect our results, as there were no significant differences between NAFLD patients with available FIB-4 scores and those without.

In summary, we demonstrate the feasibility of implementing a primary care-based NAFLD clinical care pathway using SWE that facilitates streamlining of specialist referral of NAFLD patients at risk of having advanced liver fibrosis. In our cohort, approximately 8.5% of NAFLD patients had elevated LSM (or inconclusive results), and were referred to hepatology. Using a noninvasive score like FIB-4 would lead to higher specialist referral rates of NAFLD patients with low risk for advanced liver fibrosis. Our findings are important to improve clinical care approaches for liver disease evaluation in NAFLD patients, and for directing NAFLD patient care based on fibrosis risk.

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Tables legends:

Table 1: NAFLD patient characteristics according to SWE ≥ 8 kPa.

Table 2: Independent predictors of SWE ≥ 8 kPa and need for hepatology referral.

Figure legends:

Figure 1: Study flow chart

Figure 2: Classification of NAFLD patients according to using FIB-4 as first step, then SWE as second step.

Table 1: NAFLD patient characteristics according to shear wave elastography ≥ 8 kPa.

Characteristic	Total NAFLD cohort N=1,958	Patients with SWE≥8 kPa N=67 (3.4%)	Patients with inconclusive results N=100 (5.1%)	Patients with SWE<8 kPa N=1,791 (91.5%)	P Value*
Age, yrs. (n=1,958)	55 (45-63)	61 (49-69)	57 (47-65)	54 (45-63)	0.004
Female sex (n=1,958)	53.7% (1,052)	65.7% (44)	55.0% (55)	53.2% (953)	0.129
BMI (Kg/Height in meter^2) (n=1,764)	32.0 (28.0-36.6)	37.2 (31.7-40.8)	40.6 (33.4-47.2)	31.6 (27.8-35.9)	<0.001
Baseline investigations					
ALT, U/L (n=1,944)	38 (25-60)	37 (21-63)	31 (20-52)	38 (25-61)	0.051
AST, U/L (n=1,273)	29 (21-42)	36 (23-56)	27 (19-50)	29 (21-41)	0.061
Albumin, g/L (n=1,473)	39 (37-41)	37 (36-39)	37 (34-39)	39 (37-41)	<0.001
ALP, U/L (n=1,667)	77 (64-94)	91 (68-107)	85 (71-118)	76 (63-93)	<0.001
GGT, U/L (n=1,627)	45 (27-87)	87 (36-133)	48 (29-138)	45 (27-82)	<0.001
INR (n=875)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (1.0-1.2)	1.0 (1.0-1.0)	<0.001
Platelets, 10E^9/L (n=1,922)	250 (209-294)	214 (169-255)	234 (179-295)	252 (211-295)	<0.001
Triglycerides, mmol/L (n=1,830)	1.80 (1.28-2.61)	1.79 (1.23-2.37)	1.71 (1.28-2.30)	1.81 (1.28-2.64)	0.170
Cholesterol, mmol/L (n=1,831)	4.75 (4.01-5.48)	4.04 (3.44-4.70)	4.01 (3.42-4.87)	4.81 (4.10-5.53)	<0.001
HDL, mmol/L (n=1,831)	1.16 (0.95-1.39)	1.11 (0.90-1.34)	1.10 (0.92-1.31)	1.16 (0.96-1.39)	0.087
LDL, mmol/L (n=1,831)	2.61 (1.95-3.27)	2.07 (1.57-2.55)	2.10 (1.62-2.71)	2.66 (2.03-3.33)	<0.001
Creatinine, mmol/L (n=1,895)	74 (60-87)	67 (51-79)	66 (54-79)	74 (61-88)	<0.001
HbA1c, % (n=1,810)	5.7 (5.5-6.2)	6.2 (5.6-7.2)	6.1 (5.6-7.1)	5.7 (5.4-6.2)	<0.001
Diabetes mellitus (n=1,958)	28.7% (562)	56.7% (38)	50.0% (50)	26.5% (474)	<0.001
Glucose intolerance (n=1,958)	33.6% (657)	17.9% (12)	24.0% (24)	34.7% (621)	0.002
Hypertension (n=1,958)	40.8% (798)	61.2% (41)	63.0% (63)	38.8% (694)	<0.001
FIB-4 (n=1,251)	0.99 (0.69-1.48)	1.71 (1.03-2.63)	1.19 (0.77-2.05)	0.96 (0.68-1.41)	<0.001

Distribution is expressed as median (interquartile range) or percentage (number).
* P value refer to comparison between cohort subgroups (3 groups).
SWE, shear wave elastography; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; INR, international normalized ration; HDL, high density lipoprotein; LDL, low density lipoprotein; HbA1c, hemoglobin A1c; FIB-4, fibrosis-4 variable index.

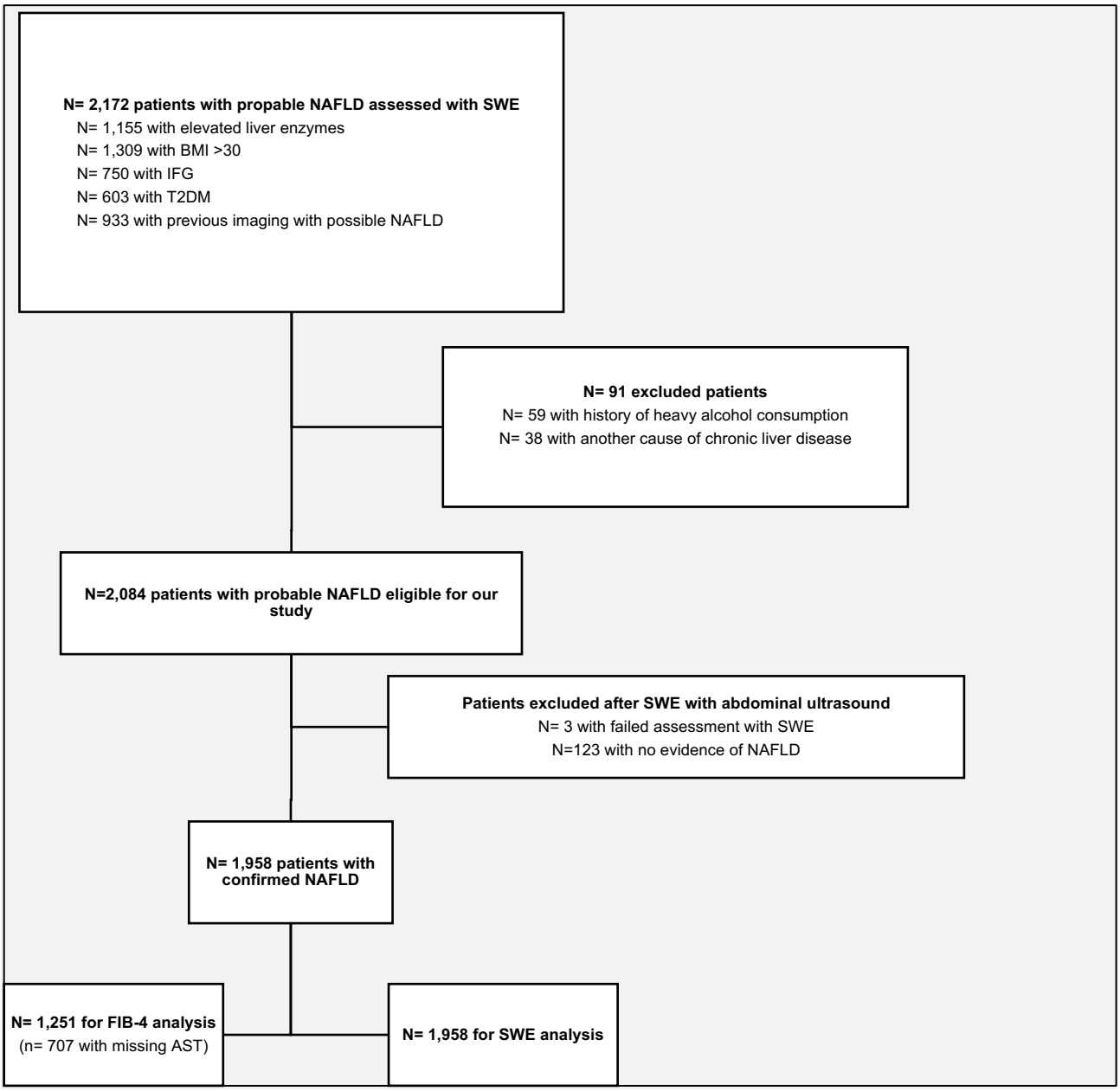
Table 2: Independent predictors of shear wave elastography ≥ 8 kPa and need for hepatology referral.

Characteristic	Predictors of SWE ≥8 kPa Odds Ratio (95% CI)		Predictors of inconclusive results or SWE ≥8 kPa Odds Ratio (95% CI)	
	Univariate analysis	Multivariate model	Univariate analysis	Multivariate model
Older patients (age >60 yr)	2.05 (1.26-3.34)	1.33 (0.75-2.37)	1.49 (1.08-2.05)	0.88 (0.60-1.31)
Female sex	1.68 (1.00-2.80)	1.40 (0.80-2.48)	1.28 (0.93-1.77)*	1.14 (0.79-1.64)
Elevated ALT or AST at baseline	1.61 (0.97-2.68)	NS	0.96 (0.70-1.32)	NS
Obesity (BMI >30)	2.11 (1.10-4.04)	1.93 (1.01-3.73)	3.19 (2.02-5.06)	2.94 (1.85-4.69)
Diabetes mellitus type 2	3.42 (2.09-5.60)	2.22 (1.13-4.36)	3.10 (2.24-4.27)	2.33 (1.50-3.63)
Impaired fasting glucose	0.42 (0.22-0.79)	0.75 (0.33-1.67)	0.52 (0.35-0.76)	0.91 (0.55-1.49)
Hypertension	2.36 (1.43-3.89)	2.18 (1.19-3.98)	2.61 (1.88-3.62)	2.38 (1.62-3.50)

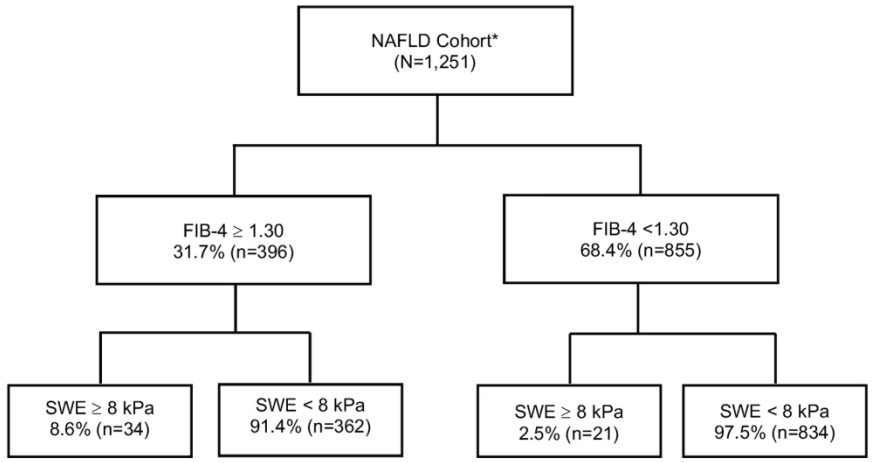
BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SWE, shear wave elastography; NS, not significant in univariate analysis.

* We adjusted for age and sex in our multivariate models even if either variable was not significant in univariate models.

Figure 1: Study flow chart



SWE, shear wave elastography; BMI, body mass index; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellites; FIB-4, fibrosis-4 variable index.



* Only 1251 NAFLD patients had data to calculate FIB-4 at baseline
FIB-4, fibrosis-4 variable index; SWE, shear wave elastography.

Figure 2

152x102mm (300 x 300 DPI)

Supplement Table 1: Performance of using different cut-offs of Shearwave Elastography (SWE) in classifying NAFLD patients (n=1,958)

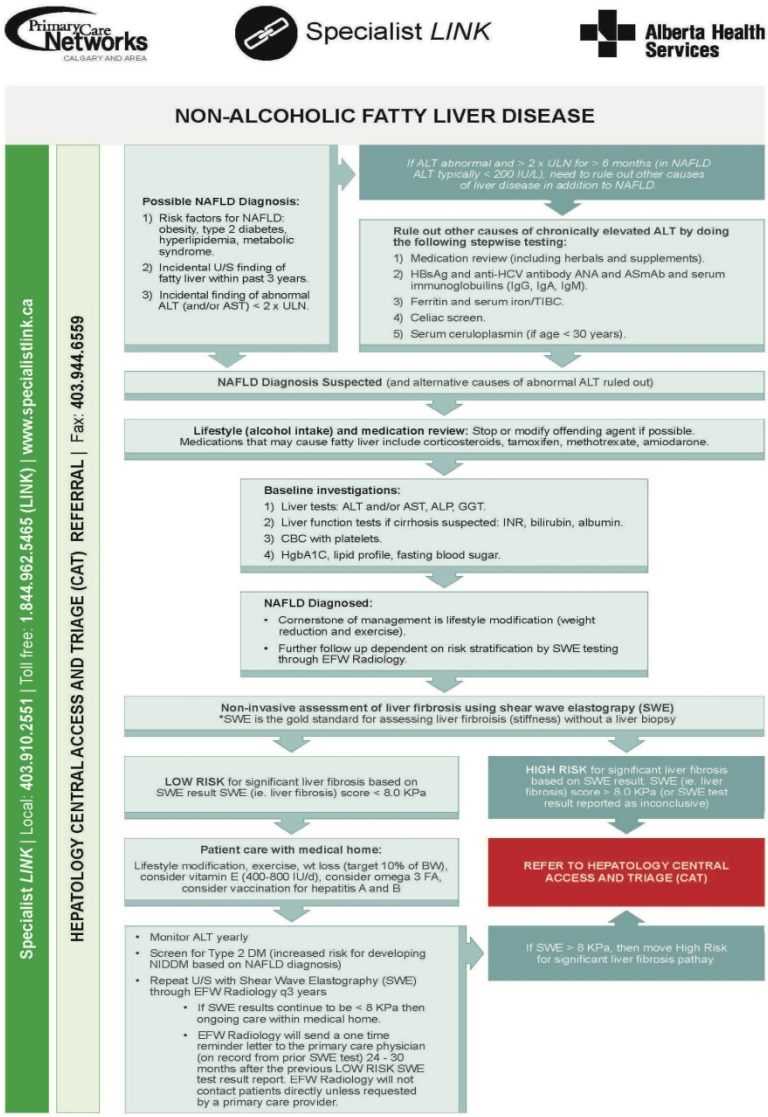
SWE cutoff	Number and (percentage) of patients at or above cut-off	Number and (percentage) of patients below cut-off
6.0 kPa	271 (13.8%)	1,687 (86.2%)
6.5 kPa	165 (8.4%)	1,793 (91.6%)
7.0 kPa	106 (5.4%)	1,852 (94.6%)
7.5 kPa	80 (4.1%)	1,878 (95.9%)
8.0 kPa	67 (3.4%)	1,891 (96.6%)
8.5 kPa	54 (2.8%)	1,904 (97.2%)
9.0 kPa	44 (2.3%)	1,914 (97.8%)

* There were 100 patients with inconclusive results.

Supplement Table 2: NAFLD Patients characteristics according to FIB-4 availability

Characteristic	Patients with available FIB-4 N=1,251 (63.9%)	Patients without FIB-4 N=707 (36.1%)	P Value
Age, yrs.	54 (44-63)	55 (46-63)	0.21
Female sex	54.3% (679)	52.8% (373)	0.52
BMI (Kg/Height in meter^2)	31.9 (27.8-36.4)	32.4 (28.4-36.8)	0.15
A1C at baseline, %	5.7 (5.4-6.3)	5.7 (5.5-6.2)	0.78
Diabetes mellitus	29.1% (364)	28.0% (198)	0.61
Glucose intolerance	32.1% (401)	36.2% (256)	0.06
Hypertension	42.1% (527)	38.3% (271)	0.10

Distribution is expressed as median (interquartile range) or percentage (number).
FIB-4, fibrosis-4 variable index; BMI, body mass index; HbA1c, hemoglobin A1c.


Primary Care Networks
CALGARY AND AREA
Specialist LINK
Alberta Health Services
NON-ALCOHOLIC FATTY LIVER DISEASE
Specialist LINK | Local: 403.910.2551 | Toll free: 1.844.962.5465 (LINK) | www.specialistlink.ca
HEPATOLOGY CENTRAL ACCESS AND TRIAGE (CAT) REFERRAL | Fax: 403.944.6559
Possible NAFLD Diagnosis:
1) Risk factors for NAFLD: obesity, type 2 diabetes, hyperlipidemia, metabolic syndrome.
2) Incidental U/S finding of fatty liver within past 3 years.
3) Incidental finding of abnormal ALT (and/or AST) < 2 x ULN.
If ALT abnormal and > 2 x ULN for > 6 months (in NAFLD ALT typically < 200 IU/L), need to rule out other causes of liver disease in addition to NAFLD.
Rule out other causes of chronically elevated ALT by doing the following stepwise testing:
1) Medication review (including herbals and supplements).
2) HBsAg and anti-HCV antibody ANA and ASmAb and serum immunoglobuilins (IgG, IgA, IgM).
3) Ferritin and serum iron/TIBC.
4) Celiac screen.
5) Serum ceruloplasmin (if age < 30 years).
NAFLD Diagnosis Suspected (and alternative causes of abnormal ALT ruled out)
Lifestyle (alcohol intake) and medication review: Stop or modify offending agent if possible.
Medications that may cause fatty liver include corticosteroids, tamoxifen, methotrexate, amiodarone.
Baseline investigations:
1) Liver tests: ALT and/or AST, ALP, GGT.
2) Liver function tests if cirrhosis suspected: INR, bilirubin, albumin.
3) CBC with platelets.
4) HgbA1C, lipid profile, fasting blood sugar.
NAFLD Diagnosed:
• Cornerstone of management is lifestyle modification (weight reduction and exercise).
• Further follow up dependent on risk stratification by SWE testing through EFW Radiology.
Non-invasive assessment of liver firbrosis using shear wave elastograpy (SWE)
*SWE is the gold standard for assessing liver firbroisis (stiffness) without a liver biopsy
LOW RISK for significant liver fibrosis based on SWE result SWE (ie. liver fibrosis) score < 8.0 KPa
HIGH RISK for significant liver fibrosis based on SWE result. SWE (ie. liver fibrosis) score > 8.0 KPa (or SWE test result reported as inconclusive)
Patient care with medical home:
Lifestyle modification, exercise, wt loss (target 10% of BW), consider vitamin E (400-800 IU/d), consider omega 3 FA, consider vaccination for hepatitis A and B
REFER TO HEPATOLOGY CENTRAL ACCESS AND TRIAGE (CAT)
• Monitor ALT yearly
• Screen for Type 2 DM (increased risk for developing NIDDM based on NAFLD diagnosis)
• Repeat U/S with Shear Wave Elastography (SWE) through EFW Radiology q3 years
• If SWE results continue to be < 8 KPa then ongoing care within medical home.
• EFW Radiology will send a one time reminder letter to the primary care physician (on record from prior SWE test) 24 - 30 months after the previous LOW RISK SWE test result report. EFW Radiology will not contact patients directly unless requested by a primary care provider.
If SWE > 8 KPa, then move High Risk for significant liver fibrosis pathay.