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Cost-utility analysis of nonalcoholic steatohepatitis screening

Eric Zhang[1,5] · Claire Wartelle-Bladou[2] · Luigi Lepanto[1,3] · Jean Lachaine[4] · Guy Cloutier[1,5] · An Tang[1,5]

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Abstract
Objectives Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in Western countries. No studies have examined the cost-effectiveness of screening its advanced form, nonalcoholic steatohepatitis (NASH).
Methods We performed a cost-utility analysis of annual non-invasive screening strategies using third-party payer perspective in a general population in comparison to screening a high-risk obese or diabetic population. Screening algorithms involved well-studied techniques, including NAFLD fibrosis score, transient elastography (TE), and acoustic radiation force impulse (ARFI) imaging for detecting advanced fibrosis (≥ F3); and plasma cytokeratin (CK)-18 for NASH detection. Liver biopsy and magnetic resonance elastography (MRE) were compared as confirmation methods. Canadian dollar (CAD or C$) costs were adjusted for inflation and discounted at 5 %. Incremental cost-effectiveness ratio (ICER) of ≤C$ 50,000 was considered cost-effective.
Results Compared with no screening, screening with NAFLD fibrosis score/TE/CK-18 algorithm with MRE as confirmation for advanced fibrosis had an ICER of C$ 26,143 per quality-adjusted life year (QALY) gained. Screening in high-risk obese or diabetic populations was more cost-effective, with an ICER of C$ 9,051 and C$ 7,991 per quality-adjusted life-year (QALY) gained, respectively. Liver biopsy confirmation was not found to be cost-effective.
Conclusions Our model suggests that annual NASH screening in high-risk obese or diabetic populations can be cost-effective.
Key Points
- *This cost-utility analysis suggests that screening for nonalcoholic steatohepatitis may be cost-effective.*
- *In particular, screening of high-risk obese or diabetic populations is more cost-effective.*
- *Magnetic resonance elastography was more cost-effective to confirm disease compared to biopsy.*
- *More studies are needed to determine quality of life in nonalcoholic steatohepatitis.*
- *More management strategies for nonalcoholic steatohepatitis are also needed.*

Keywords Cost-effectiveness · Nonalcoholic fatty liver disease (NAFLD) · Fibrosis · Elastography · Screening

Abbreviations

ARFI	Acoustic radiation force impulse
CK-18	Cytokeratin-18

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✉ An Tang
an.tang@umontreal.ca

1 Department of Radiology, Radio-Oncology and Nuclear Medicine, University of Montreal, Saint-Luc Hospital, Montreal, Quebec, Canada

2 Department of Gastroenterology and Hepatology, University of Montreal, Saint-Luc Hospital, Montreal, Quebec, Canada

3 Health Technology Assessment Unit, University of Montreal, Saint-Luc Hospital, Montreal, Quebec, Canada

4 Faculty of Pharmacy and Pharmacoeconomics, University of Montreal, Montreal, Quebec, Canada

5 Laboratory of Biorheology and Medical Ultrasonics, University of Montreal Hospital Research Center (CRCHUM), Montreal, Quebec, Canada

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HCC	Hepatocellular carcinoma
ICER	Incremental cost-effectiveness ratio
MRE	Magnetic resonance elastography
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
QALY	Quality-adjusted life year
TE	Transient elastography

Introduction

Over the last decade, nonalcoholic fatty liver disease (NAFLD) has been recognized as the most prevalent liver disease in Western countries, due in large part to the high rates of obesity and type 2 diabetes [1]. It affects an estimated 20–30 % of the general adult population, and as much as 90 % of diabetic or obese patients [2–4]. The more advanced form, nonalcoholic steatohepatitis (NASH) may evolve to fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [5–9].

Although healthcare costs related to NASH have not been well studied, they are estimated to be significant due to potential progression to liver failure and HCC. NASH-related liver failure is predicted to become the main cause of liver transplantation within the next decade [10]. Current practice guidelines do not advocate screening of NAFLD or NASH at this time, in part due to a lack of knowledge regarding optimal noninvasive diagnostic strategies, long-term benefits, and the cost-effectiveness of screening [11, 12]. Although liver biopsy is the current reference standard for diagnosis of steatohepatitis and advanced fibrosis in patients with NAFLD [12], its invasiveness makes it an unlikely modality for large-scale screening [13]. To address this issue, noninvasive blood tests and elastography methods have been introduced for the detection of NASH or advanced fibrosis (≥ F3) [14–16]. Screening for this highly prevalent disease may be worthwhile [17], but as of yet, the value of screening strategies for NASH has not been studied.

Weight loss is currently the recommended standard of care for NASH [12, 18]. In more advanced disease, vitamin E has been recommended as pharmacotherapy in non-diabetic patients with histologically-proven NASH [11, 12]. Pioglitazone is another suggested pharmacotherapy based upon latest randomized-control trials and meta-analyses [19, 20]. A recent cost-utility study established the cost-effectiveness of pharmacological therapy for delaying the progression of NASH fibrosis using pioglitazone and vitamin E [21].

To our knowledge, there is currently no cost-utility study for NASH screening in the Western population. In this era of cost-containment, cost-effectiveness and opportunity cost of screening for NASH must be investigated. Thus, the primary aim of our study was to estimate the cost-effectiveness in a general population of different screening strategies for NASH or advanced fibrosis (≥ F3) detection, while incorporating currently recommended treatment practices. In order to determine the optimal population to target for screening, our secondary aim was to estimate the cost-effectiveness of these screening strategies in high-risk obese or type 2 diabetes populations.

Materials and methods

Markov model and assumptions

From a health-care system perspective, a decisional Markov model [22] was developed (TreeAge Software, Williamstown, MA) to estimate the expected lifetime costs and quality-adjusted life-years (QALYs) associated with screening strategies for NASH. This model was constructed to mirror the natural history of NAFLD disease progression through the histopathological continuum of simple steatosis, NASH, fibrosis stages, and cirrhosis [5]. Patients with cirrhosis may progress onto liver failure, and also have increased probability of developing HCC (Fig. 1) [23].

To address our research aims, we ran the simulation for a general population and for high-risk populations, either with obesity or type 2 diabetes. Patients began screening at the age of 30 years. At the beginning of the simulation, the population was divided among these mutually exclusive health states according to mean prevalence rates reported in developed countries for a general population, an obese population, and a type 2 diabetes population, respectively. The model assumed an annual cycle length. In each cycle, simulated populations could remain in their health states or progress according to transition probabilities derived from literature. Screening and treatment strategies were superimposed onto this life cycle model of NAFLD. Before screening began, the costs of specialist consultation and laboratory tests to rule out alternate causes of chronic liver injury were taken into account. For the purpose of developing this model, histological improvement was assumed a good correlate for clinical outcomes. Both all-cause and liver-related mortalities were taken into account at each stage of disease. The simulation ended once every member of the population died. A lifetime horizon was chosen for this model to better reflect NAFLD disease progression [24], as well as to better represent the magnitude of costs and utilities associated with the disease. Peer-reviewed guidelines for economic evaluations were followed in the creation of this model [22, 25].

Competing screening strategies

The competing screening strategies incorporated independently and widely studied noninvasive tests. Plasma cytokeratin-18 (CK-18) was assessed for the noninvasive detection of

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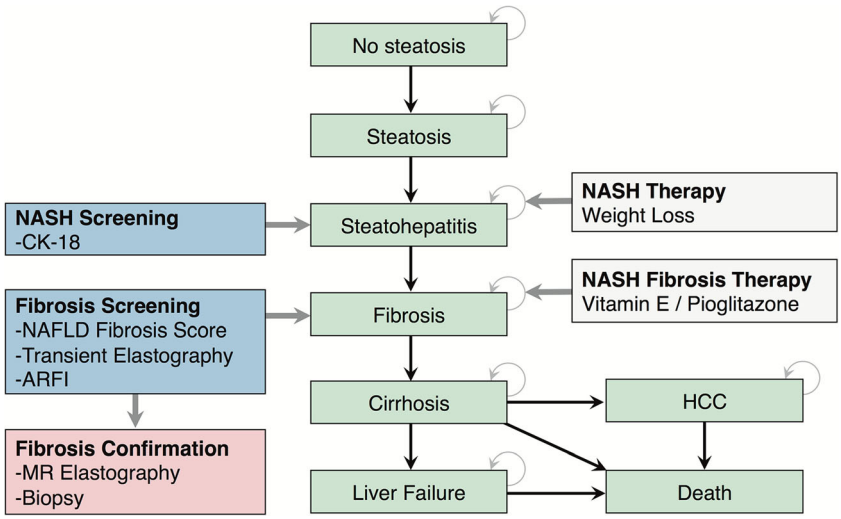

Fig. 1 Markov model illustrating the natural history of NAFLD, screening strategies, and therapies. Abbreviations: NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; TE = transient elastography; CK-18 = cytokeratin-18; ARFI = acoustic radiation force impulse; MRE = magnetic resonance elastography

NASH. NAFLD fibrosis score, ultrasound transient elastography (TE), and ultrasound acoustic radiation force impulse (ARFI) imaging were assessed for the detection of advanced fibrosis (≥ F3) [14, 16, 26]. We compared a sequential algorithm [14] that incorporates the NAFLD fibrosis score, transient elastography, and CK-18 with biopsy confirmation to no screening in our Markov model. The underlying assumption was that a strategy combining noninvasive methods for NASH and fibrosis detection would decrease the number of unnecessary liver biopsies [14, 16]. Given the similar sensitivity of ultrasound-based elastography for the detection of advanced fibrosis, we compared a variant of this sequential algorithm by substituting TE with ARFI [27]. In addition, considering the high diagnostic accuracy of magnetic resonance elastography (MRE) for fibrosis staging [26], we also compared MRE against liver biopsy for the confirmation of advanced fibrosis. The mortality risk associated with liver biopsy as well as the costs associated with severe bleeding complications were implemented in the model [28]. Figure 2 illustrates the various screening strategies compared in our study.

Treatment arms

Three treatment branches were implemented in the model. In accordance with international guidelines, NASH patients with no or mild fibrosis (F≤1) were treated with lifestyle intervention and weight loss, whereas patients with advanced fibrosis (F≥3) were treated pharmacologically [29]. Lifestyle intervention aimed to achieve an overall weight reduction of 7–10 % by combining regimented exercise, diet, and behaviour adjustments. The treatment effect on NASH progression was calculated from a randomized controlled trial looking at the histological improvements of a lifestyle intervention program versus standard of care [18]. The pharmacotherapies considered in our model included vitamin E and pioglitazone [19, 30]. Treatment effects on fibrosis progression were estimated by applying the relative risk for histological improvement used in a previous cost-utility analysis [21]. Pharmacotherapies were stopped in the event of liver decompensation development, in accordance with assumptions made previously [21].

Model parameter estimates

Prevalence, annual transition probabilities, and mortality risk for the Markov model were derived from a systematic literature review (Table 1). Annual transition probabilities were calculated based on the approach outlined by Miller and Homan for converting rates over time [31]. Screening test sensitivities were obtained from meta-analyses. Liver biopsy, as the accepted reference standard, was assumed to have 100 % accuracy.

Costs

Annual healthcare costs were derived from the Canadian Provincial Billing Guides [32]. Relevant costs include primary care follow-up, specialist consultation, and blood work panels to rule out alternative diagnoses of chronic liver disease. Screening tests were micro-costed from the Canadian Provincial Billing Guides, the Canadian Agency of Drugs and Technologies in Health, and related literature on micro-costing of elastography methods in Canada [33–35]. The cost of the cytokeratin-18 M30-apoptosense ELISA kit (PEVIVA, Bromma, Sweden) was obtained from the company website [36]. Annual patient care costs for liver decompensation were taken from the Canadian Institute of Health Information [37]. The costs of HCC management and liver transplantation were derived from published literature specific to the Canadian healthcare system [38, 39]. All costs incorporated into the model are in 2013 Canadian dollars (CAD or C$) (Table 2 and Supplementary Table 1). Costs were adjusted for inflation to 2013 when needed, using the national inflation index [40].

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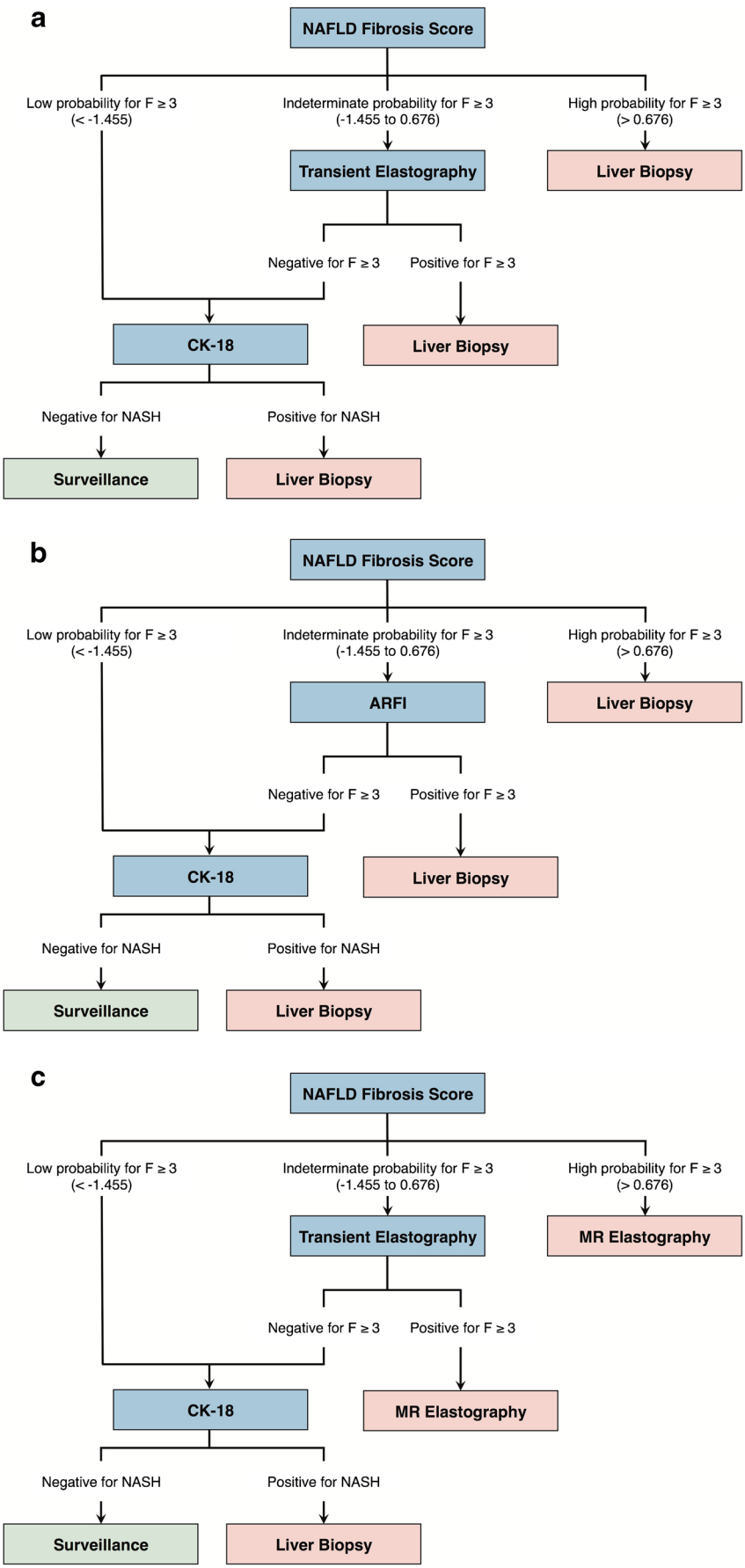

Fig. 2 Decision trees illustrating the 3 NASH screening algorithms investigated in cost-utility analysis. (**a**) Sequential algorithm with NAFLD fibrosis score/TE/CK-18 with liver biopsy confirmation. (**b**) Sequential algorithm with NAFLD fibrosis score/ARFI/CK-18 with liver biopsy confirmation. (**c**) Sequential algorithm with NAFL D fibrosis score/TE/CK-18 with MRE confirmation. Abbreviations: NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; TE = transient elastography; CK-18 = cytokeratin-18; ARFI = acoustic radiation force impulse; MRE = magnetic resonance elastography

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Table 1 Model parameters

Parameters	Base Estimate (Range)	References
Prevalence		
Prevalence of steatosis in general population	0.23 (0.16–0.30)	[4, 5, 69]
Prevalence of steatosis in type 2 diabetes population	0.70	[70]
Prevalence of steatosis in obese population	0.75 (0.64–0.90)	[5, 71–73]
Prevalence of NASH in general population	0.04 (0.02–0.122)	[2, 24, 74, 75]
Prevalence of NASH in type 2 diabetes population	0.25 (0.25–0.30)	[14, 76]
Prevalence of NASH in obese population	0.20 (0.19–0.50)	[5, 71–73]
Prevalence of NASH-cirrhosis in general population	0.0019 (0.0018–0.0020)	[77, 78]
Prevalence of NASH-cirrhosis in type 2 diabetes population	0.02 (0.02–0.03)	Author's assumptions
Prevalence of NASH-cirrhosis in obese population	0.02 (0.02–0.03)	[72]
Annual transition probabilities		
Probability of developing steatosis	0.029 (0.02–0.04)	[24, 79]
Probability of developing NASH	0.0084 (0.00029–0.088)	[24, 58, 80, 81]
Probability of NASH liver-related mortality	0.0038 (0.002–0.01)	[6, 59, 82]
Probability of developing fibrosis	0.089 (0.065–0.092)	[3, 24, 57, 83]
Probability of worsening fibrosis	0.11 (0.10–0.13)	[3, 24, 81, 84]
Probability of developing cirrhosis	0.02–0.06	[6, 85]
Probability of NASH-cirrhosis liver-related mortality	0.034 (0.015–0.049)	[59, 86–88]
Probability of developing decompensated cirrhosis	0.06 (0.04–0.16)	[6, 11, 57, 86, 87]
Probability of decompensated cirrhosis-related mortality	0.16 (0.15–0.38)	[8, 89]
Probability of developing HCC	0.029 (0.017–0.08)	[7, 8, 21, 23, 82, 87]
Probability of hepatoma mortality at year 1	0.52 (0.47–0.58)	[90–92]
Probability of hepatoma mortality in subsequent years	0.068 (0.068–0.23)	[92, 93]
Probability of liver transplantation	0.05 (0.05–0.25)	[21, 94]
Sensitivity for NASH detection		
Plasma cytokeratin-18 fragments	0.77 (0.64–0.92)	[14, 62, 95]
Sensitivity for advanced fibrosis (≥ F3)		
NAFLD fibrosis score	0.64 (0.5–0.70)	[14, 96]
Transient elastography (TE)	0.85 (0.58–0.95)	[14, 15, 48, 97, 98]
Acoustic radiation force impulse (ARFI)	0.89 (0.87–0.99)	[47, 48, 99, 100]
Magnetic resonance elastography (MRE)	0.92 (0.85–0.96)	[26]
Technical failure of elastography methods		
Rate of technical failure of TE	0.16	[101]
Rate of technical failure of ARFI	0.021	[48]
Treatment response		
Histological improvement to lifestyle changes	2.40	[18]
Histological improvement to pioglitazone	1.38 (1.01–1.89)	[19, 20]
Histological improvement to vitamin E	1.35 (0.87–2.09)	[19, 20]
Complications of liver biopsy		
Rate of mortality	0.002	[28]
Rate of major bleeding	0.0065	[28]

Abbreviations: NASH = nonalcoholic steatohepatitis; HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease

Health-related quality of life

For health-related quality of life data, we used the largest study performed in patients with NAFLD to date [41]. This study provided quality of life data on patients with NAFLD and NASH in the form of a SF-36 survey. The data from these surveys were then converted to utility estimates using the method described by Nichol et al. [42]. Further health-related quality

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Table 2 Health care costs (CAD, Canadian dollars)

Parameters	Base Estimate (Range)	References
Annual clinical care costs		
No care	77.20	[32]
Routine care and lifestyle changes	325.00	[32]
Routine care and pioglitazone	2106.20	[32]
Routine care and vitamin E	463.70	[32]
Compensated cirrhosis and pioglitazone	2183.40	[32]
Compensated cirrhosis and vitamin E	540.90	[32]
Decompensated cirrhosis	16,679.50 (10,884–22,475)	[32, 37]
Hepatocellular carcinoma (net over 5 years)	15,949.80	[38]
Liver transplant (1st year)	163,818.77	[39]
Itemized clinical care		
Specialist consultation (initial)	157.00	[32]
Specialist consultation (follow-up)	105.25	[32]
Primary care doctor consultation	77.20	[32]
Dietician/counselling	62.75	[32]
Laboratory		
Full blood count	11.03	[32]
Liver function tests	20.70	[32]
Lipids	21.31	[32]
Oral glucose tolerance test	15.68	[32]
Hepatitis C antibody	27.24	[32]
Hepatitis B surface antigen	36.30	[32]
Anti nuclear antibody	27.24	[32]
Screening methods		
NAFLD fibrosis score	12.95	[32]
Plasma cytokeratin-18 fragments (CK-18)	6.44	[36]
Transient elastography (TE)	99.44	[33, 35]
Ultrasound-based elastography (ARFI)	114.62	[33, 35]
Diagnostic method		
Magnetic resonance elastography	333.98 (250–400)	[34, 35]
Liver biopsy	595.60 (450–1300)	[102–104]
Complications		
Post-biopsy complication requiring hospitalization	4579	[105]
Treatment (yearly)		
Pioglitazone (Actos)	1084.05	[106]
Vitamin E (800 IU)	138.7	[106]

Abbreviations: NAFLD = nonalcoholic fatty liver disease

of life information on NASH-associated fibrosis, cirrhosis and hepatic decompensation were nonexistent. Therefore, we used utilities from health-related quality of life studies on other causes of chronic liver disease [43–46]. Given the benign nature of the disease, simple steatosis was assumed a utility estimate of 1. Utility values for each health state are reported in Table 3.

Outcomes

Outcomes were measured in terms of costs (CAD) and in terms of quality-adjusted life years gained (QALYs). The incremental cost-effectiveness ratio (ICER) of each strategy was calculated as the incremental difference in cost divided by the incremental difference in quality-adjusted life years of two consecutive strategies. In the Canadian heath care setting, ICERs of less than 50,000 CAD per QALY gained is usually considered cost-effective. The discount rate was set at 5 % in accordance with Canadian guidelines [25]. A strategy is *dominating* when it results in lower cost and higher QALYs in comparison to another and *dominated* when it results with higher cost and less QALYs in comparison to another.

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Table 3 Health-related quality of life

Parameters	Base Estimate (Range)	References
Well	1	Authors' assumption
Steatosis	1.0 (0.86–1)	[41], Author's assumption
NASH	0.85 (0.84–0.86)	[41]
Fibrosis	0.84 (0.83–0.85)	[41]
Cirrhosis	0.80 (0.65–0.89)	[21, 43, 44, 46]
Decompensated cirrhosis	0.60 (0.46–0.81)	[21, 43, 44, 46]
Hepatoma	0.73 (0.50–0.80)	[43]
Surgical resection (1st month)	0.73 (0.62–0.84)	[107]
Liver transplant (1st year)	0.69 (0.62–0.86)	[44, 45, 108]
Liver transplant (after transplant)	0.80 (0.79–0.83)	[108]

Abbreviations: NASH = nonalcoholic steatohepatitis

Sensitivity analyses

The robustness of our results was assessed in terms of one-way sensitivity analyses, in which all model parameters were varied across a range taken from published data or at 95 % confidence intervals. For the transition probability from simple steatosis to NASH, which was not readily available due to a paucity of data, we took a large range of plausible values [24]. Two-way sensitivity analyses were performed on select pairs of parameters that were influential in one-way sensitivity analyses. There were not enough published data to build probability distributions to undergo a probabilistic sensitivity analysis.

Results

Table 4 illustrates the results for the top three dominating screening strategies for the base case analysis for each population studied. In the general population, no surveillance as a baseline strategy costs C$ 6,561 per person with a total utility value of 42.04 QALYs gained over the lifetime of the patient. NAFLD fibrosis score/TE/CK-18 sequential strategy with MRE confirmation for advanced fibrosis and vitamin E treatment cost C$ 3,136 more per person, but also delivered incremental utility increase of 0.12 QALYs. This strategy was found to be cost-effective with an ICER of C$ 26,143/QALY gained according to a threshold of C$ 50,000/QALY gained. The same strategy with pioglitazone treatment was found to have an ICER of C$ 199,870/QALY gained.

Cost-utility in high-risk populations

In an obese population, the NAFLD fibrosis score/TE/CK-18 sequential strategy with MRE confirmation for advanced fibrosis and vitamin E treatment resulted in an ICER of C$ 9,051/QALY gained compared to no surveillance. In a type 2 diabetic population, the same screening strategy resulted in an ICER of C$ 7,991/QALY gained compared to no surveillance. The remaining screening strategies not seen in Table 4 were dominated and therefore not found to be cost-effective.

Sensitivity analyses

One-way sensitivity analysis results for the NAFLD fibrosis score/TE/CK-18 sequential algorithm with MRE confirmation and vitamin E treatment are summarized in Fig. 3. In this analysis, all parameters used during the simulations were varied through the range of values found in literature or by applying 95 % confidence intervals to test the robustness of our results, given the potential uncertainty of parameter values. The ICER for the base case scenario is delineated by the vertical line. The ICERs within the variable range tested move from the blue (lower range) to the red side (upper range).

Three variables were found to have the greatest effect on the ICER: the test cost for TE, the starting age for screening, and the annual transition probability of steatosis to NASH. If the cost of an individual TE test was assumed to be C$ 50, then the ICER was C$ 20,521/QALY gained. At an upper limit assumption of C$ 250 per test, then the ICER increased to C$ 43,040/QALY gained. If the starting age for screening began at 18 years of age, the ICER was found to be as low as C$ 17,535/QALY gained. However, if screening began at 43 years old or later, the ICER surpassed the C$ 50,000/QALY gained threshold. If the annual probability of developing steatohepatitis was 8.8 %, then the ICER would be C$ 11,164/QALY gained; however, if the annual incidence of steatohepatitis were as low as 0.03 %, then the ICER would increase to more than C$ 42,787/QALY gained.

In accordance with Canadian health technology assessment guidelines, the model was assessed using 0 % as well as 3 % discount rates for comparison purposes with other jurisdictions [25]. In general, lowering the discount rate resulted in more cost-effective strategies. At 0 % discount, all screening

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Table 4 Base case analysis of costs (CAD) and utilities of NASH screening strategies for general, high-risk obese, and high-risk type 2 diabetes populations

Population Type	Screening Strategies	Cost (CAD)	QALYs	Incremental Cost (CAD)	Incremental Benefits (QALYs)	$/QALY (ICER)
General Population	No Surveillance	$6,561	42.0422	—	—	—
	Screening* with MRE confirmation and vitamin E treatment	$9,697	42.1622	$3,136	0.1200	$26,143
	Screening* with MRE confirmation and pioglitazone treatment	$10,563	42.1665	$866	0.0043	$199,870
Obese Population	No Surveillance	$13,703	38.7285	—	—	—
	Screening* with MRE confirmation and vitamin E treatment	$17,197	39.1145	$3,494	0.3861	$9,051
	Screening* with MRE confirmation and pioglitazone treatment	$19,809	39.1289	$2,613	0.0143	$182,364
Type 2 Diabetes Population	No Surveillance	$15,049	38.1394	—	—	—
	Screening* with MRE confirmation and vitamin E treatment	$18,608	38.5848	$3,559	0.4454	$7,991
	Screening* with MRE confirmation and pioglitazone treatment	$21,576	38.6015	$2,968	0.0167	$178,210

*Screening algorithm involving NAFLD fibrosis score and transient elastography for fibrosis detection, and cytokeratin-18 for NASH detection

Abbreviations: NASH = nonalcoholic steatohepatitis; QALY = quality-adjusted life year; MRE = magnetic resonance elastography

strategies became more cost-effective. The NAFLD fibrosis score/TE/CK-18 sequential algorithm with MRE confirmation resulted in an ICER of C$ 15,493/QALY gained.

Two-way sensitivity analyses were conducted to examine the effect on ICER of varying pairs of influential variables simultaneously. This can help distinguish particular thresholds, whereby one strategy becomes more cost-effective than another assuming a C$ 50,000/QALY gained threshold. Two-way sensitivity analyses found that ARFI and TE were interchangeable in the sequential algorithm.

Discussion

We performed a cost-utility analysis to address the current knowledge gap regarding the cost-effectiveness of screening strategies for steatohepatitis and NASH-fibrosis, two advanced forms of NAFLD that may progress to end-stage liver disease. By combining the most widely studied noninvasive tests, we categorized patients according to their probability of having advanced disease and thus limited the total number of liver biopsies [14, 16]. To further decrease the invasiveness of a screening strategy for NASH, we examined the potential of MRE as an alternate reference standard to liver biopsy for liver fibrosis diagnosis, based on promising meta-analysis results [26]. Finally, we compared these screening algorithms in both general and high-risk populations to determine the most cost-effective population to screen.

Our model suggests that, in a general population, a sequential algorithm that includes the NAFLD fibrosis score/TE/CK-18, with MRE confirmation for advanced fibrosis, and vitamin E as treatment, can be a cost-effective surveillance strategy, with an ICER of C$ 26,143/QALY gained. In comparison, the same sequential algorithm with pioglitazone treatment had a higher ICER of C$ 199,870/QALY gained. The results indicate that the combination of noninvasive tests for detection of advanced fibrosis and NASH, with lifestyle changes and vitamin E as treatment, provides incremental gains of QALYs over no surveillance. By detecting earlier stages of NAFLD and by implementing treatment according to current guidelines, this surveillance strategy demonstrates the potential to limit the transition of patients towards liver cirrhosis and end-stage liver disease, and its associated quality-of-life and economic costs.

Our model suggests that MRE is more cost-effective than liver biopsy as a confirmation method in a screening program for advanced fibrosis (≥ F3). Strategies with liver biopsy as confirmation for advanced NASH-fibrosis were more costly for less QALYs gained. This result reflects both the potential of MRE as an alternative reference standard, as well as the mortality and morbidity associated with liver biopsy. In recent years, MRE has emerged as a highly accurate modality for the staging of liver fibrosis, with histopathology as the reference

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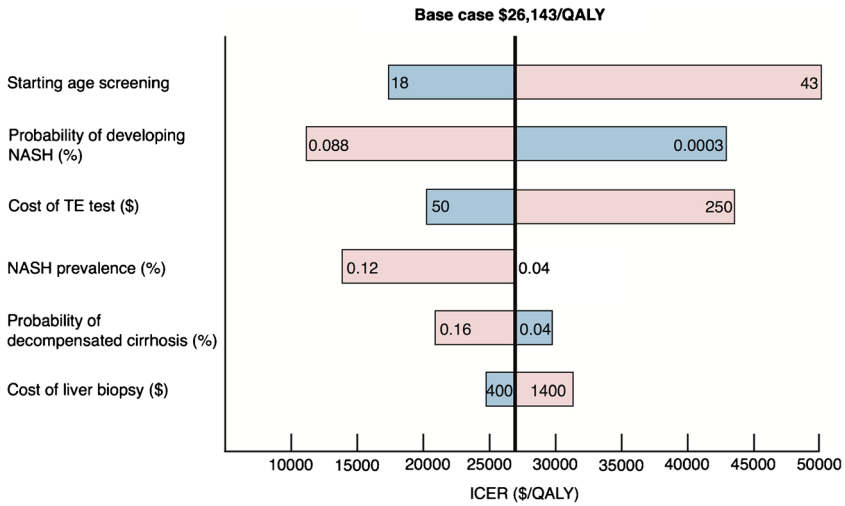

Fig. 3 One-way sensitivity analysis for the NAFLD fibrosis score/TE/CK-18 sequential strategy with MRE confirmation and vitamin E as treatment. Abbreviations: NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; TE = transient elastography; CK-18 = cytokeratin-18; ARFI = acoustic radiation force impulse; MRE = magnetic resonance elastography

standard [26]. From the point of view of a screening program, confirmation with MRE would likely be better accepted by the general population, given that it is noninvasive.

The key drivers of cost-effectiveness were the cost of TE, the starting age of surveillance, and the annual transitional probability from simple steatosis to NASH. In the base case scenario, the underlying assumption was that screening would begin at 30 years of age. Given that NASH and its complications are becoming an increasing problem among younger people [12], earlier screening could be a possibility. Ultrasound-based elastography methods, namely TE or ARFI, have similar sensitivities for detection of advanced fibrosis [27, 47, 48], and may be used interchangeably for fibrosis staging in the clinical workflow [16]. However, in our model, a sequential algorithm in which TE was substituted with ARFI was found to be dominated by the leading screening strategy with TE. This difference in cost/QALY gained may be explained by the higher cost of ARFI over TE in our micro-costing scenario. Since itemized costs for these elastography tests have yet to be established in the Canadian healthcare billing guides, the micro-costing relied on a series of assumptions. To address the inherent uncertainties surrounding our assumptions on costs for these exams, we performed a two-way sensitivity analysis, which suggested that ARFI and TE were close to equivalent in the sequential screening algorithm along the range of costs from C$ 50 to C$ 250.

While TE and ARFI appear to be similar in their sensitivity and cost-effectiveness, they do have unique advantages and disadvantages. For example, transient elastography devices (Fibroscan) may also detect liver steatosis using the Controlled Attenuation Parameter (CAP) [49, 50]. CAP represents a promising adjunct for the quantification of liver steatosis alongside fibrosis at the same time. However, TE suffers in the detection of fibrosis in obese patients, with failure rates and unreliable results that are higher than in non-obese patients. This disadvantage can be partially circumvented, however, by using the XL probe, although at an additional cost [51, 52]. On the other hand, ARFI technique is coupled with imaging and permits detection of liver fibrosis even in patients with a large body habitus. Some studies have thus far demonstrated that ARFI was feasible in obese patients and provided diagnostic accuracy similar to that of TE with the XL probe for the staging of liver fibrosis [53–55].

Our secondary aim was to examine the cost-effectiveness of these same screening strategies in high-risk obese and type 2 diabetes populations. We found that the most cost-effective screening strategy in a general population (C$ 26,143/QALY gained) was significantly more cost-effective in high-risk populations (C$ 9,051/QALY gained in an obese population and C$ 7,991/QALY gained in a type 2 diabetes population).

One of the principles of preventing over-diagnosis is to better differentiate between benign disease and progressive disease that will cause more harm [56]. Thus, in our model, we did not screen for simple steatosis, because without inflammation, it is considered a benign, non-progressive disease in the majority of patients and not likely to develop into advanced fibrosis during their lifetimes [57]. We have not included steatosis screening in our Markov model because only a small subset of patients with steatosis ever progress to NASH and cirrhosis [24, 58]. Also, patients with simple steatosis have a survival similar to that of the general population, whereas patients with NASH have a higher overall mortality [14, 59]. While simple steatosis is a hallmark feature of early NAFLD, it may be replaced by fibrosis in advanced disease [60, 61]. Finally, we based our cost-utility analysis on prior screening algorithms published in literature, which did not emphasize liver fat screening for these reasons [14].

Instead, we focused on the noninvasive detection of steatohepatitis and fibrosis, both of which are progressive stages of NAFLD and can lead to major complications if not found and treated. In our model, the noninvasive detection of NASH without advanced fibrosis depended on CK-18

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fragments, which has a fair accuracy for NASH screening [62], with confirmation by liver biopsy. The current challenge with CK-18 includes its limited availability and as such it has not been introduced in clinical practice in Canada. Alternatively, MRE has been proposed for detection of NASH [63]. However, this will require independent validation in the future before we can consider an entirely noninvasive screening algorithm.

There are limitations to our study. The relevance of screening relies on the assumption that effective long-term therapy for NASH exists. It is conceivable that the histological improvements observed in short-term randomized controlled trials on lifestyle modification [18], pioglitazone, and vitamin E [19, 20] may not be sustainable after discontinuation of therapy and over the lifetime horizon. Thus, longer-term studies on NASH and antifibrotic treatment are required. Nonetheless, current guidelines advocate pharmacotherapy (vitamin E and glitazones) with caution in specific patients with elevated risk of progression to cirrhosis who have failed lifestyle intervention [11].

Further, we did not model the potential side effects of pharmacotherapy. Glitazones have been implicated in long-term safety concerns regarding cardiovascular disease, bladder cancer, and bone loss, whereas vitamin E has been associated with a possible increase in all-cause mortality and risk of prostate cancer. However, given that there has been much controversy and conflicting results in the literature [64–68], and that it was not possible to model all complications for the purposes of an economic model, we decided not to implement them.

Our study has the following strengths. The algorithms studied in our model were derived from meta-analyses and compatible with current guidelines. The model parameters were based on a systematic literature review to identify prevalence, transition probabilities, costs, and utilities. These parameters represent a comprehensive simulation of NAFLD continuum. Where possible, we used utility estimates for steatohepatitis derived from a population with NASH [41].

In summary, our cost-utility model suggests that NASH screening is cost-effective with noninvasive screening methods for steatohepatitis and advanced fibrosis. Furthermore, screening in high-risk populations of obese or type 2 diabetes patients is more cost-effective than in a general Western population. Before decision-makers decide to implement a screening program, further studies should better establish the quality of life in NASH and the long-term effectiveness and safety of therapy.

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