

Non-alcoholic fatty liver disease screening in type 2 diabetes mellitus: A cost-effectiveness and price threshold analysis

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ABSTRACT

Introduction: The cost-effectiveness of screening asymptomatic non-alcoholic fatty liver disease (NAFLD) patients remains debatable, with current studies assuming lifelong benefits of NAFLD screening while neglecting cardiovascular outcomes. This study aims to assess the cost-effectiveness of NAFLD screening among type 2 diabetes mellitus (T2DM) patients, and to establish a price threshold for NAFLD treatment, when it becomes available.

Method: A Markov model was constructed comparing 4 screening strategies (versus no screening) to identify NAFLD with advanced fibrosis among T2DM patients: fibrosis-4 (FIB-4), vibration-controlled transient elastography (VCTE), FIB-4 and VCTE (simultaneous), and FIB-4 and VCTE (sequential). Sensitivity analyses and price threshold analyses were performed to assess parameter uncertainties in the results.

Results: VCTE was the most cost-effective NAFLD screening strategy (USD24,727/quality-adjusted life year [QALY]), followed by FIB-4 (USD36,800/QALY), when compared to no screening. Probabilistic sensitivity analysis revealed a higher degree of certainty for VCTE as a cost-effective strategy compared to FIB-4 (90.7% versus 73.2%). The duration of expected screening benefit is the most influential variable based on incremental cost-effectiveness ratio tornado analysis. The minimum duration of screening benefit for NAFLD screening to be cost-effective was at least 2.6 years. The annual cost of NAFLD treatment should be less than USD751 for NAFLD screening to be cost-effective.

Conclusion: Both VCTE and FIB-4 are cost-effective NAFLD screening strategies among T2DM patients in Singapore. However, given the lack of access to VCTE at primary care and potential budget constraints, FIB-4 can also be considered for NAFLD screening among T2DM patients in Singapore.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a growing epidemic and has become a major cause of liver-related mortality and indication for liver transplantations globally. It is estimated that nearly 25% of the world's population and more than 60% of type 2 diabetes mellitus (T2DM) patients have NAFLD. A prior study demonstrated a high prevalence of NAFLD with

advanced fibrosis among T2DM patients in Singapore.¹ The disease burden of NAFLD in the Singapore population is projected to rise from 1,492,000 to 1,799,000 from 2019 to 2030.² This increasing burden of NAFLD is alarming because NAFLD can progress to liver cirrhosis, hepatocellular carcinoma (HCC), and death. Unfortunately, NAFLD is often under-recognised because most patients are either asymptomatic or do not

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CLINICAL IMPACT

What is New

- This study compares several non-invasive screening modalities including fibrosis-4 and vibration-controlled transient elastography to identify the most cost-effective strategy for risk stratifying non-alcoholic fatty liver disease (NAFLD) patients.
- The model also incorporates cardiovascular outcome and NAFLD-specific estimates from the latest literature.

Clinical Implications

- The annual cost of NAFLD treatment estimated will provide clinicians useful information when considering the cost-effectiveness of a screening strategy.
- Findings may aid in deciding the screening modality adopted for NAFLD screening in the primary care setting.

have elevated liver enzymes. Without screening, it is challenging to detect NAFLD patients with significant fibrosis or non-alcoholic steatohepatitis (NASH). Given the high NAFLD prevalence and higher risk of NAFLD progression among T2DM patients, risk stratification is crucial to stratifying patients for subsequent management, without overwhelming the tertiary care setting.

Growing evidence supports the use of fibrosis markers for risk-stratification of NAFLD and cirrhosis patients because fibrosis is the strongest predictor for mortality³ and long-term outcomes in NAFLD patients.⁴ Liver-related mortality increased exponentially with each fibrosis stage. While liver biopsy is currently the gold standard for diagnosis and fibrosis staging of NAFLD, it cannot be used as a screening tool due to its invasiveness and its variability in sampling and interpretation. Non-invasive tests are important for large-scale, population-based screening and risk stratification of NAFLD patients. A 2-tier screening strategy that combines different non-invasive tests has been shown to improve the risk stratification of Asian NAFLD patients.⁵ Proper risk stratification of NAFLD patients in the primary care setting has been shown to reduce unnecessary referrals to tertiary care.

Screening is important for identifying high-risk NAFLD patients for early interventions such as intensive

lifestyle modification, pharmacological therapy or bariatric surgery.⁶ While lifestyle modification alone may be sufficient for those without advanced fibrosis or NASH, NAFLD patients with advanced fibrosis should be referred to tertiary care and encouraged to consider clinical trials for new therapies or more aggressive interventions such as bariatric surgery. Non-invasive screening strategies using fibrosis-4 (FIB-4) scoring and vibration-controlled transient elastography (VCTE) have been proposed.⁷ While the cost-effectiveness of NAFLD screening has been explored, these studies had several shortcomings. First, cardiovascular complications such as ischaemic heart disease and stroke were not considered in the earlier models. Second, screening strategies were assumed to confer lifelong benefits, which may overestimate the benefits of NAFLD screening. Third, the health-state utilities (provides quantitative measures of how strongly a person values a certain health state, ranging from 0 to 1) and cost were often derived from studies conducted in other chronic liver diseases such as chronic hepatitis C or expert opinion. Meanwhile, current guidelines have conflicting views on the recommendations for NAFLD screening.⁸⁻¹⁰ To address these gaps, our primary aim was to compare the cost-effectiveness of different strategies for NAFLD screening in the primary care setting. Our secondary aim was to estimate the optimal cost of NAFLD treatment, at which it would be considered cost-effective in the setting of NAFLD screening.

METHOD

Overview

A cost-effectiveness analysis was undertaken to estimate the relevant costs and health outcomes of NAFLD screening to prevent further progression of NAFLD to liver cirrhosis or HCC compared with current care, defined as no screening. In the screening arm, all T2DM subjects were offered a once-off screening ultrasound at age 50 to diagnose NAFLD. Subjects diagnosed with NAFLD subsequently undergo fibrosis screening strategies, which include: (1) FIB-4 screening (FIB-4 > 3.25), (2) VCTE screening, (3) FIB-4 and VCTE simultaneous screening, and (4) FIB-4 and VCTE sequential screening. Both sequential and simultaneous testing using non-invasive tests were considered because they have been shown to improve the risk stratification and reduce the misclassification of NAFLD patients, when compared to single-step non-invasive testing.⁷ Advanced fibrosis was defined as FIB-4 > 3.25 or VCTE ≥ 15kPa based on published

literature.⁷ In sequential testing, patients were subjected to 2-tier testing, with those having a FIB-4 index beyond 3.25 subjected to further screening using VCTE. In simultaneous testing, patients were subjected to both FIB-4 and VCTE testing, with either test reflecting a positive result indicative of advanced fibrosis. Our model also accounted for the additional cost that resulted from misclassifying patients into advanced fibrosis during the first year of screening.

Following the diagnosis of advanced fibrosis, these subjects will undergo an intensive weight reduction and lifestyle programme, where evidence for hepatic fibrosis regression had been demonstrated in a prior study.⁶ The lifetime time horizon was chosen to model the long-term outcomes of NAFLD that included cardiovascular outcomes, cirrhosis, HCC and liver transplantation. This study was undertaken using the providers' perspective, where once-off screening is adopted for T2DM patients aged 50 years. The age cut-off of 50 years- was chosen for 2 reasons: this is the age threshold recommended by clinical practice guidelines,¹⁰ and recent study showing a threshold effect (where the vast majority of patients begin developing liver-related events such as cirrhosis after 50 years old) among T2DM patients with NAFLD.¹¹ Findings were reported using incremental cost-effectiveness ratios (ICERs) in US dollars (USD) per quality-adjusted life year (QALY) gained. The interpretation of the cost-effectiveness of the findings was based on the willingness to pay (WTP) of USD50,000/QALY. We extracted NAFLD-specific estimates and utility data, the prevalence of liver and cardiovascular events (acute myocardial infarction, congestive cardiac failure, transient ischaemic attack,

and stroke) and background mortality among diabetic patients aged 50 years and above from the SingHealth Diabetes Registry. The SingHealth Diabetes Registry is a comprehensive registry consisting of 208,102 T2DM patients from 8 healthcare sites within SingHealth, the largest health cluster in Singapore.¹²

Input parameters

All input parameters were summarised in the online Supplementary Table S1. The prevalence of liver and cardiovascular events and background mortality among diabetic patients aged 50 years and above were extracted from the SingHealth Diabetes Registry. The model was complemented with published literature on the: (1) prevalence and severity of NAFLD patients,^{1,13} (2) prevalence and utility of liver and cardiovascular events among NAFLD patients,¹⁴⁻¹⁸ (3) performance of FIB-4 and VCTE,^{7,19,20} (4) transition probability of NAFLD health states,^{2,7,15,21-24} and (5) NAFLD-specific health state utility.²² We obtained NAFLD-specific, direct medical costs for different health states from the data of SingHealth hospitals. The cost of liver transplantation and HCC was supplemented with published Singapore literature, adjusted for inflation at a rate of 3% per annum. A discount rate of 3% was used for both costs and health outcomes.

Economic model

A Markov model was developed with a 1-year cycle length to capture long-term health outcomes (Fig. 1). Patients with NAFLD with advanced fibrosis could either progress to liver cirrhosis, or regress to NAFLD with mild fibrosis (F0-F1). Fibrosis regression may

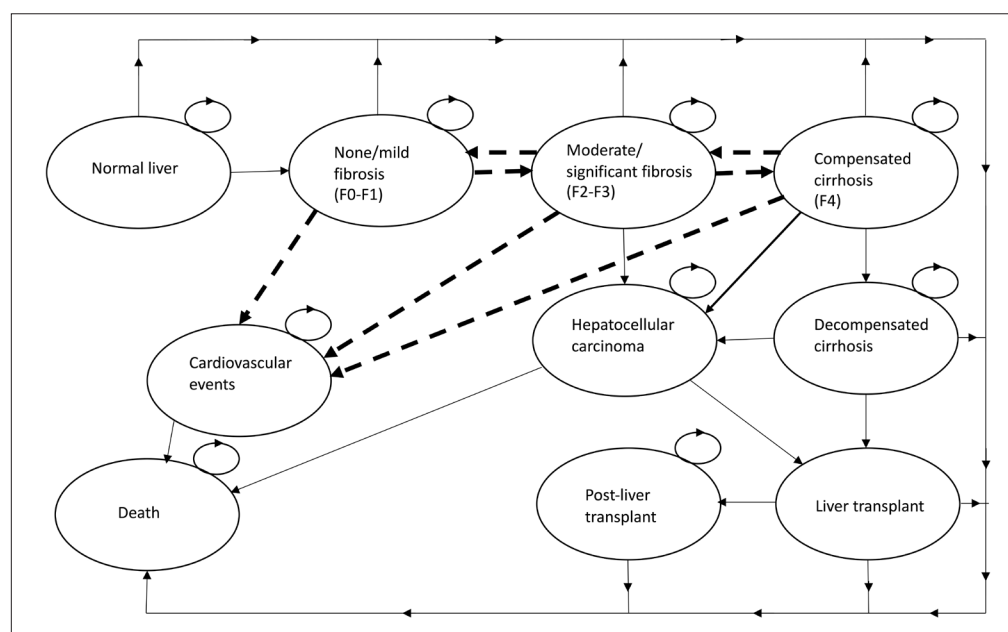


Fig. 1. Markov schematic capturing the main health states adopted in the model, with dotted arrows indicating the impact of screening, coupled with intensive weight loss and dieting on the respective progression and regression rates.

occur in patients with compensated NASH cirrhosis, and was associated with lower liver-related events, as shown in a recent study by Sanyal et al.²⁵ Patients beyond advanced fibrosis may progress to HCC. Those with HCC and decompensated cirrhosis may progress to having a liver transplant and subsequently remain in the post-liver transplant health state. Cardiovascular events may occur in all stages of NAFLD, except for patients with decompensated cirrhosis and HCC, where the risk of mortality is primarily driven by the underlying liver disease.²⁶ All health states could result in death through either progression of liver or cardiovascular disease.

Cost-effectiveness analysis

For base-case analysis, which is the baseline analysis without consideration of possible changes in variables adopted in the model, we calculated the expected clinical outcomes and lifetime costs of T2DM patients without NAFLD screening. The start age of 50 years was adopted as the base case of NAFLD screening to allow the potential demonstrable benefits of screening and a corresponding intensive weight reduction programme to take effect. We subsequently calculated the incremental costs, QALY gained, and the ICER of the various screening strategies as compared to no screening. A Tornado analysis was performed to identify the 3 most influential variables within the model. To determine the optimal price threshold of NAFLD treatment for NAFLD screening to remain cost-effective in Singapore, we performed a threshold analysis based on a pre-defined WTP threshold. We then performed a sensitivity analysis to determine the minimal duration of sustainable treatment effect for NAFLD screening to be cost-effective. A sensitivity analysis was also performed for the start age of screening to determine the optimal start age for NAFLD screening. Probabilistic

sensitivity analysis was performed to examine the effects of all parameter uncertainties using 10,000 sets of Monte Carlo simulations. A triangular distribution was applied by using the point estimate, minimal and maximal values as inputs. All analyses were performed using TreeAge Pro 2021 (TreeAge Software Inc, Williamstown, US).

Model assumptions

The assumptions adopted in this Markov model are the following. First, we assumed fibrosis regression is not possible in decompensated NASH cirrhosis. Second, we considered the additional unnecessary expenditure brought about by NAFLD screening, assuming that patients with a false positive diagnosis of NAFLD will incur an additional 1-year cost, which is equivalent to their prior fibrosis staging. Third, we assumed the annual rate of fibrosis progression to be constant, including subjects who experienced non-fatal cardiovascular complications. This assumption was made based on a recent study showing that most cardiovascular complications in NAFLD were non-fatal, and the risk of all-cause mortality was similar in NAFLD patients with or without cardiovascular complications.²⁷ We also assumed the direct medical cost derived from decompensated cirrhosis, HCC and liver transplantation to be similar, irrespective of the underlying aetiology of cirrhosis. Finally, we assumed the screening benefit of fibrosis regression and cardiovascular complications to cease after 5 years.

RESULTS

Base-case analysis

Base-case analysis of screening at age 50 years demonstrated that both VCTE and FIB-4 screenings were cost-effective, at USD24,727.23/QALY and USD36,799.87/

Table 1. Results of base-case analysis among 5 screening strategies: screening using FIB-4 or VCTE were considered cost-effective with ICER within the willingness to pay threshold (USD50,000)

Strategy	Cost (USD)	Effectiveness (QALY)	Incremental cost (USD)	Incremental effect (QALY)	ICER (USD/QALY)	Label
No screening	20,610.72	11.91	-	-	-	undominated
FIB-4 screening	22,957.79	11.97	2,347.07	0.0638	36,799.87	extendedly dominated
FIB-4+VCTE simultaneous screening	23,401.46	11.98	443.68	0.00692	64,102.01	extendedly dominated
VCTE screening	23,453.16	12.03	2,842.45	0.115	24,727.23	undominated
FIB-4+VCTE Sequential screening	28,735.91	11.98	5,282.75	-0.0461	-114,623.44	absolutely dominated

FIB-4: fibrosis-4; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VCTE: vibration-controlled transient elastography

QALY, respectively (Table 1). Meanwhile, screening that adopted either sequential or simultaneous testing (FIB-4 or VCTE) was considered not cost-effective in Singapore.

One-way sensitivity analysis

Based on one-way sensitivity analysis, the 3 most influential variables in the screening model were the duration of screening benefit, the effectiveness of NAFLD treatment in fibrosis regression within the first 5 years of screening, and the utility of no to mild fibrosis (F0–F1) health states (Fig. 2). For VCTE screening to be cost-effective, the minimum duration of screening benefit should be at least 2.69 years. Similarly, the minimum duration of screening benefit should be at least 3.86 years for FIB-4 screening to be cost-effective (Fig. 3). The screening benefit remains when sensitivity analysis was performed on ages 50 to 70 years, with most benefits observed when screening was started at the age of 50 (Fig. 4).

Based on multivariate probability sensitivity analysis performed in 10,000 Monte Carlo simulations, NAFLD

screening using VCTE or FIB-4, was cost-effective 90.7% and 73.2% of the time, respectively (Fig. 5). The cost-effective acceptability curve showed that NAFLD screening using either VCTE or FIB-4 was cost-effective when a WTP of USD50,000 was considered. Finally, price threshold analysis showed that for NAFLD screening to be cost-effective, the annual cost of NAFLD treatment should be less than USD751/annum.

Budget impact analysis

For the budget impact analysis, a total of 10,000 patients for this cohort was assumed (estimated for patients aged 50 years with diabetes for 2019). The current budget impact for the no-screening strategy would be approximately USD206.1 million when patients are tracked over the next 50 years. The budget impact of all patients who underwent a once-off VCTE or FIB-4 screening was USD234.5 million and USD229.6 million, respectively. Given that VCTE is not currently available in the primary care setting, the estimated budget to set up VCTE in all 23 polyclinics throughout Singapore would be approximately USD4.70 million.

DISCUSSION

NAFLD is a rapidly growing global pandemic. It is expected to be the driving cause of chronic liver disease, cirrhosis, HCC and liver transplantation in the near future.²⁸ Identifying NAFLD patients at greater risk of cirrhosis progression and death is important for early intervention. Despite an increased prevalence of NAFLD among high-risk populations such as T2DM, current guidelines were conflicting when recommending population-based NAFLD screening.^{9,10} In this study, we found that NAFLD screening is cost-effective among T2DM patients. For NAFLD screening to be considered cost-effective in Singapore, the benefits of treatment should last at least 2.6 years, and the cost of treatment should be less than USD751 per annum. To our best knowledge, this is the first study evaluating the cost-effectiveness of NAFLD screening among T2DM patients in Singapore. As there is no structured NAFLD screening programme in Singapore,¹⁰ our findings are important to inform policymakers on the cost-effectiveness of NAFLD screening to curb the upcoming “obesity tsunami”. With multiple novel NAFLD treatments in the pipeline, the price threshold analysis will be relevant globally when considering the price of NAFLD treatments when they are eventually available.²⁹

Our study found that NAFLD screening among high-risk populations such as T2DM patients is cost-effective when using either VCTE or FIB-4 alone. It is

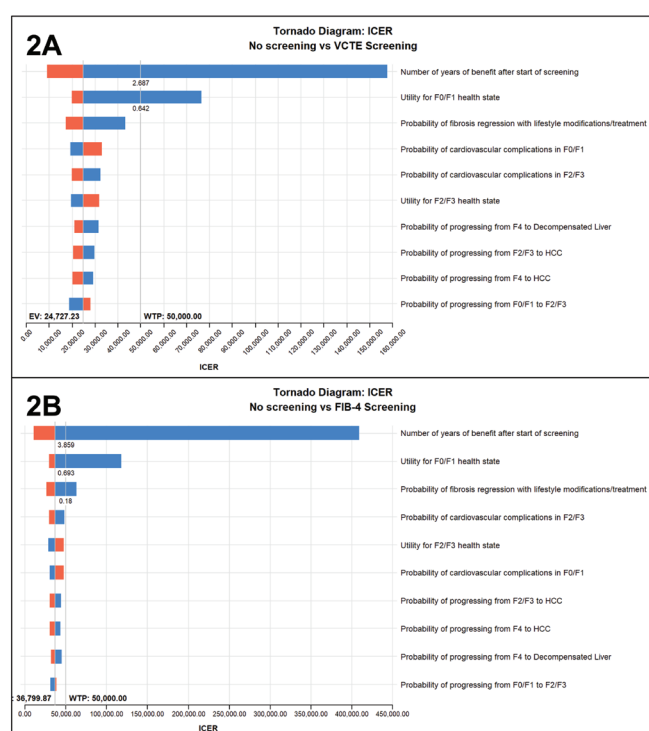


Fig. 2. Tornado diagram of base-case analysis. This model illustrates the result of one-way sensitivity analyses performed to study the effects of altering uncertainty parameters within the minimum-maximum ranges, including all clinical effects, costs and utilities on the incremental cost-effectiveness ratio in the model for (A) vibration-controlled transient elastography, and (B) fibrosis-4.

FIB-4: fibrosis-4; HCC: hepatocellular carcinoma; ICER: incremental cost-effectiveness ratio; VCTE: vibration-controlled transient elastography; WTP: willingness to pay

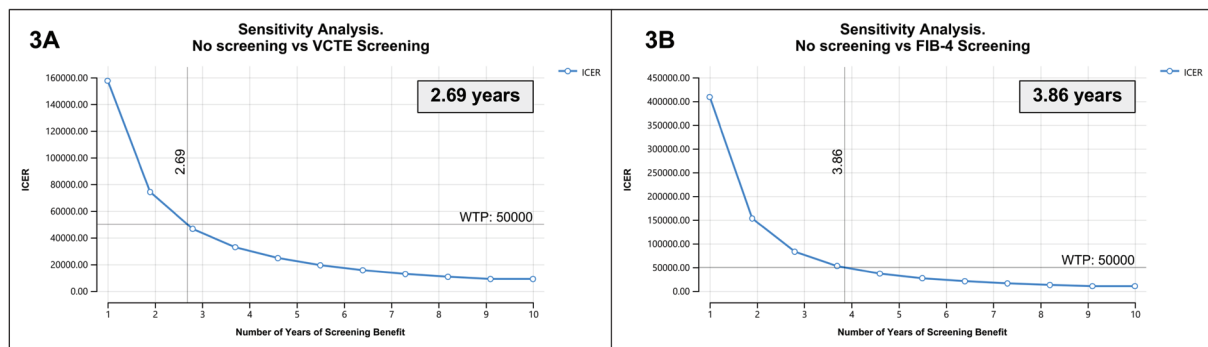


Fig. 3. Minimum duration of screening benefit for (A) vibration-controlled transient elastography and (B) fibrosis-4 to be cost-effective. FIB-4: fibrosis-4; ICER: incremental cost-effectiveness ratio; VCTE: vibration-controlled transient elastography; WTP: willingness to pay

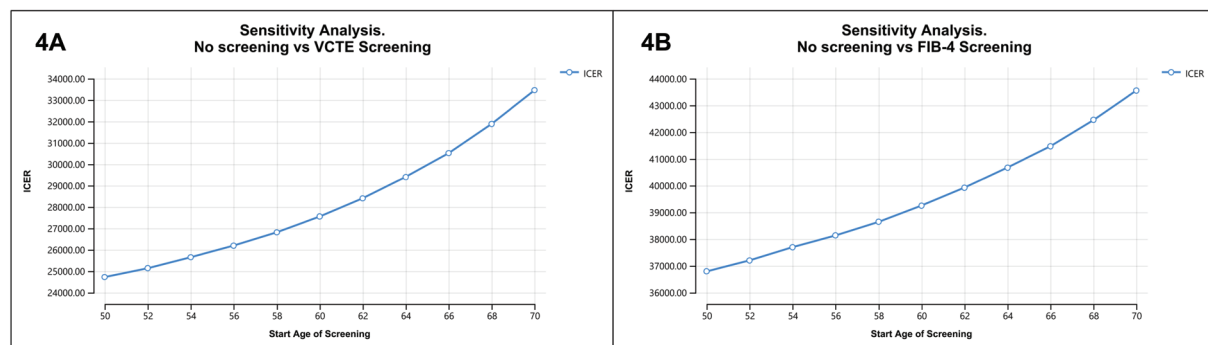


Fig. 4. One-way sensitivity analysis performed to study the effects of start age of screening for (A) vibration-controlled transient elastography and (B) fibrosis-4 to be cost-effective.

FIB-4: fibrosis-4; ICER: incremental cost-effectiveness ratio; VCTE: vibration-controlled transient elastography

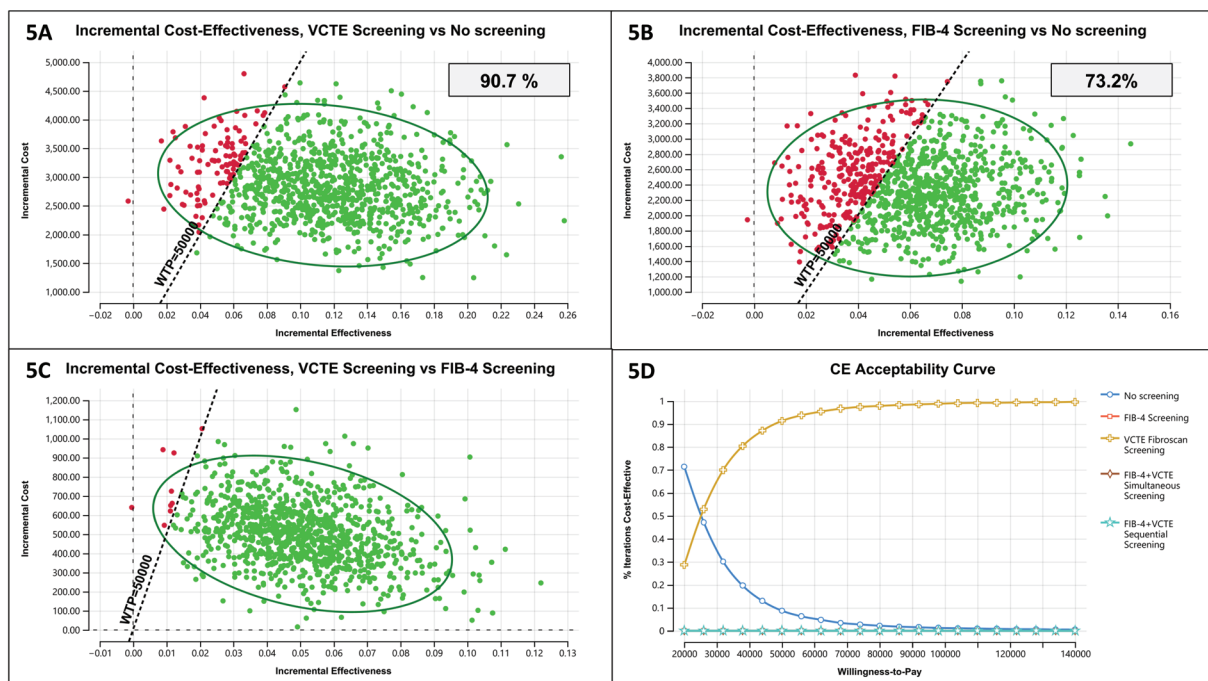


Fig. 5. Multivariate probabilistic sensitivity analysis, based on 10,000 Monte Carlo simulations. (A) Incremental cost-effectiveness scatterplot comparing vibration-controlled transient elastography (VCTE) screening versus no screening. (B) Incremental cost-effectiveness scatterplot comparing fibrosis-4 (FIB-4) screening versus no screening. (C) Incremental cost-effectiveness scatterplot comparing VCTE screening versus FIB-4 screening. (D) Cost-effectiveness acceptability curve.

CE: cost-effectiveness; FIB-4: fibrosis-4; ICER: incremental cost-effectiveness ratio; VCTE: vibration-controlled transient elastography

believed that the superiority of VCTE over FIB-4 was driven by VCTE's better accuracy in detecting NAFLD with advanced fibrosis, thus allowing more high-risk patients to receive early therapeutic intervention.⁷ However, the adoption of VCTE as the primary modality for population-based NAFLD screening should take into consideration the availability of VCTE machines and trained technicians, as the interpretation of VCTE is currently not available at the community level. Meanwhile, although FIB-4 is an extendedly dominated strategy (i.e. having a higher ICER yet less effective than VCTE) when compared with VCTE screening, it is also a cost-effective strategy within the WTP threshold when compared with no screening. Through our budget impact analysis, we demonstrated the significant cost and burden of NAFLD in our setting. The impact of the budget for both VCTE and FIB-4 was also included to provide policymakers with estimates for financial budgeting. Hence, FIB-4 can be considered in situations where the financial budget to set up the VCTE in the primary care setting is a constraint.

The high prevalence of T2DM observed in the SingHealth Diabetes Registry was consistent with other Asian studies.³⁰ While our model described a once-off screening strategy, repeated screening may be considered in 3–5 years' time, given that 50% of T2DM patients developed NAFLD in 3 years, even though few experienced fibrosis progressions within 3 years.³¹

Another important finding in our study is that the duration of screening benefit was identified as one of the key determinants in determining cost-effectiveness. While it is logical to expect screening benefits to gradually taper off with time, this was not considered in prior cost-effectiveness studies.^{21,22} We found that the benefits of screening should last at least 2.6 and 3.8 years for VCTE and FIB-4, respectively, for screening to remain cost-effective. It was also useful for determining the target population of interest, in which the screening benefit will be limited for patients with an expected life expectancy of less than 4 years from the point of NAFLD screening. Furthermore, the consideration of treatment pricing thresholds was crucial in the recommended treatment cost of USD751 per annum for cost-effectiveness to be maintained within the currently adopted WTP thresholds. These important considerations on the model structure and study design are useful and potentially transferable for future cost-effectiveness analysis on population-based NAFLD screening.

This study has several strengths. First, clinical data were derived from the SingHealth Diabetes Registry, comprising 208,102 individuals from 8 sites within SingHealth, the largest healthcare cluster in Singapore.¹² Second, due to increasing evidence available in the field of NAFLD research, we were able to incorporate NAFLD-specific cost and utility, as well as cardiovascular-related outcomes^{17,26} in our model. We model the impact of cardiovascular-related complications—the main cause of mortality in NAFLD patients.³² Third, to provide a more conservative estimate, our model also accounted for the duration of sustainable screening benefit for the findings to be rendered cost-effective. Fourth, the current strategies compared in our model is also in line with the latest recommendations from the American Association of Endocrinology Clinical Practice Guideline for the diagnosis and management of NAFLD in primary care and endocrinology in the clinical setting.³³ Finally, our price threshold analysis also provided a cost benchmark for NAFLD treatment, where NAFLD screening will remain cost-effective, as future NAFLD treatments become available.

We acknowledge that there are limitations to this study. First, even though VCTE is the most cost-effective strategy for NAFLD screening, the additional budget required to set up VCTE in the primary care setting was not included in this study. Meanwhile, FIB-4 as the alternative cost-effective option is more readily available, implementable, and scalable in the primary care setting. Second, the benefits of NAFLD treatment were assumed to be consistent in this study. To provide a more realistic and conservative estimate, we assumed the benefits of NAFLD treatment to last up to 5 years to avoid over-estimating the screening benefit. Third, we acknowledged the limitations on the performance of non-invasive markers selected in our model. For example, FIB-4 can be influenced by age, with decreasing accuracy beyond 70 years old.³⁴ Our model did not consider other serum-based biomarkers such as Enhanced Liver Fibrosis Test, FibroTest, Hepascore or PRO-C3 as they were not readily available in the local context. We also did not consider magnetic resonance imaging elastography for NAFLD screening given its long wait time and limited availability even in tertiary care, making it impractical as a population-based screening tool. The impact of NAFLD screening on non-hepatic cancers was not included in our model due to heterogeneity and wide ranges of prevalence and treatment costs of various cancers. We acknowledge that a structured programme may be required to ensure the continued adoption of lifestyle modifications in

NAFLD patients, which may increase the cost of the NAFLD screening programme. Because of differences in the healthcare system, decision-making criteria, and cost data, we acknowledge that our cost-effectiveness findings may not be directly extrapolated to other countries. Nevertheless, important considerations in the model structure (minimal duration of sustained screening benefit and cardiovascular-related complications) and study design (price threshold analysis) are useful factors that can be adapted for future cost-effectiveness analysis on population-based NAFLD screening. Finally, artificial intelligence and machine learning may present a new frontier for identifying NAFLD patients at high risk for fibrosis progression or liver-related complications.

In summary, NAFLD screening among T2DM patients is a cost-effective approach to reducing the disease burden of NAFLD in Singapore. Our findings complement our current understanding of NAFLD screening by estimating the minimal duration of screening benefit and incorporating cardiovascular outcomes into the existing NAFLD model. With an expanding treatment armamentarium for NAFLD, our findings are timely in providing a cost-effective threshold for NAFLD treatment in the setting of population-based NAFLD screening.

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