The Daffodil Centre

The Australian Prevention Partnership Centre

Preventing liver cancer: Assessing the benefits of risk assessment for patients with metabolic-associated fatty liver disease

Final report

30 June 2023

A partnership between

Cancer Council | The University of Sydney

daffodilcentre.org

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Contents

DEFINITIONS AND TERMINOLOGY **4**

EXECUTIVE SUMMARY **7**

Evidence reviews 8
Predictive modelling 9

1. BACKGROUND **10**

2. DISEASE PREVALENCE AND TRANSITIONS FOR MAFLD/MASH PATIENTS **11**

2.1 METHODS 11
2.1.1 Evidence Review Methods *11*
2.2 RESULTS 12
2.2.1 Evidence Review Results *12*

3. DIAGNOSTIC TECHNOLOGIES FOR THE DIAGNOSIS OF MASH IN MAFLD PATIENTS **14**

3.1 METHODS 14
3.1.1 Evidence Review Methods *14*
3.2 RESULTS 14
3.2.1 Evidence Review Results *14*

4. MODELLING DISEASE OUTCOMES AND COSTS FOR MASH AND MAFLD PATIENTS **15**

4.1 METHODS 16
4.2 RESULTS 17
4.2.1 Health outcomes in MAFLD vs MASH patients *17*
4.2.2 Routine HCC surveillance *18*
4.2.3 Cost-effectiveness of triaged HCC surveillance for MAFLD and MASH patients *20*
4.2.3 Potential HCC deaths averted in Australia *22*

5. DISCUSSION **22**

6. CONCLUSION **24**

7. REFERENCES **25**

Definitions and Terminology

ADAPT is a non-invasive test which detects liver fibrosis through a PRO-C3-based fibrosis algorithm which measures age, presence of diabetes, PRO-C3, and platelet count.(1)

Body mass index (BMI) is the ratio of a person's weight in kilograms (or pounds) to the square of their height in meters, used as a proxy measure for a person's body size. For most adults, the World Health Organization (WHO) defines a BMI (in kg/m^2) of: [18.5,25) as normal weight; [25,30) as overweight, and ≥30 as obese.

Cost-effectiveness ratio (CER) is the ratio of an intervention's cost to its effectiveness, typically measured in quality-adjusted life-years saved.

Compensated cirrhosis refers to asymptomatic build-up of scar tissue in the liver.

Decompensated cirrhosis refers to the build-up of scar tissue in the liver with at least one complication including ascites, jaundice, variceal haemorrhage, or hepatic encephalopathy.

Enhanced Liver Fibrosis (ELF) is a non-invasive test which detects liver fibrosis by assessing three markers: type III procollagen peptide (PIIINP), hyaluronic acid (HA), and tissue inhibitor of metalloproteinase-1 (TIMP1).(2)

Fibrosis refers to the formation of scar tissue in the liver. It can be further classified into stages: F0, there is no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis; F3, numerous septa without cirrhosis; F4, cirrhosis.

Fibrosis-4 (FIB-4) Index for Liver Fibrosis is a non-invasive test for steatosis or fibrosis based on a patient's platelet count and AST level.(3)

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer diagnosed in Australia.(4)

Incremental cost-effectiveness ratio (ICER) is the ratio of an intervention's cost to its effectiveness relative to the previously most cost-effective intervention.

Metabolic-associated fatty liver disease (MAFLD) is the presence of hepatic steatosis in combination with one or more of the following: overweight/obesity, T2DM, or two or more markers of metabolic dysregulation.

Metabolic-associated steatohepatitis (MASH) refers to the presence of hepatic steatosis with evidence of inflammation and hepatocellular injury the form of ballooning of the hepatocytes, with or without fibrosis, in patients with MAFLD.

Non-alcoholic fatty liver disease (NAFLD) encompasses the entire spectrum of fatty liver disease in individuals without other causes such as significant alcohol consumption, chronic viral hepatitis, hereditary disorders, or use of steatogenic medications.

Non-alcoholic fatty liver disease Fibrosis Score (NFS) is a non-invasive test which detects liver fibrosis in NAFLD patients by assessing a patient's age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio.(5)

Non-alcoholic steatohepatitis (NASH) refers to the presence of hepatic steatosis with evidence of inflammation and hepatocellular injury in the form of ballooning of the hepatocytes, with or without fibrosis, in patients with NAFLD.

Quality-adjusted life-expectancy (QALE) is the period a patient is expected to live, weighted by their expected quality of life.

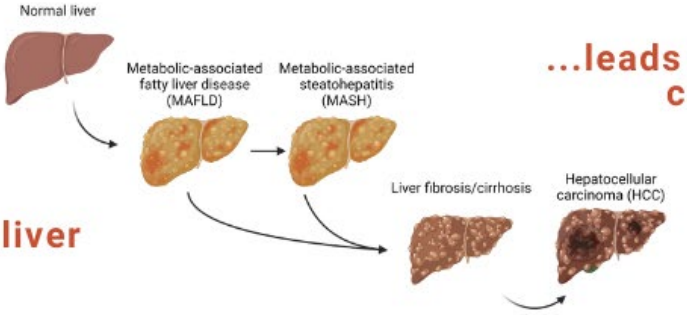
Quality-adjusted life-year (QALY) is a year of life lived by a patient, weighted to reflect the quality of life.

MAFLD and MASH

About **one in three** Australians have metabolic-associated fatty liver disease, or **MAFLD** - a liver disease common in people who are overweight, obese, or have other metabolic conditions.

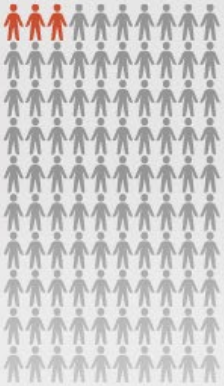
MAFLD can develop to metabolic-associated steatohepatitis, or **MASH**, through liver inflammation

MASH affects about **one in twenty** Australians and increases the likelihood of hepatocellular carcinoma (HCC), a common liver cancer



Worsening liver disease...

...leads to higher cancer risk



3% of people with MAFLD will develop HCC over their lifetime...

...but **17%** of people with MASH will develop HCC over their lifetime

Targeted routine liver surveillance can reduce the likelihood of HCC death by 27% in MASH patients while improving cost-effectiveness to $16,000 per life-year saved and reducing resource burden

Executive Summary

Background

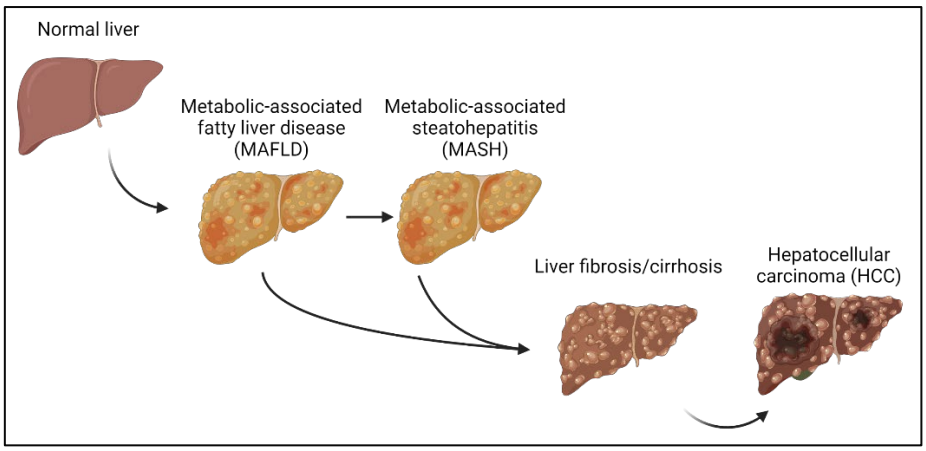
Liver cancer is one of the most rapidly growing cancer types in Australia in terms of both incidence and mortality.(6) Hepatocellular carcinoma (HCC), the most common type of liver cancer,(4) often develops in people with underlying liver disease caused by modifiable risk factors.(7)

Metabolic-associated fatty liver disease (MAFLD) is defined as a build-up of excess fat in the liver, linked to excess body fatness, type 2 diabetes mellitus and/or metabolic abnormalities. MAFLD is characterised by accumulation of fat in the liver without liver inflammation and is a major risk factor for the development of HCC.(8)

Recent Australian studies have shown that the incidence rate of MAFLD-related HCC has increased alongside increases in overweight and obesity rates,(9,10) and is likely to become the dominant cause of HCC in Australia over the next few decades. The diagnosis of MAFLD replaces the previous diagnosis of non-alcoholic fatty liver disease (NAFLD) and is intended to better reflect the role of metabolic factors in the development of liver disease.

Routine HCC surveillance, using technologies such as blood biomarker testing and ultrasound, can reduce HCC mortality through early detection.(11–13) Model estimates from a previous *Preventing Liver Cancer* report showed that routine HCC surveillance can reduce HCC mortality by 18% in MAFLD patients.(14) However, this would come at a cost of $58,000 per quality-adjusted life year (QALY) saved, above the usual $30,000 or $50,000 per QALY willingness-to-pay thresholds used in Australia. This is due to the large cohort of patients with early-stage liver disease who had a low risk of HCC and therefore were unlikely to benefit from surveillance. Targeting patients with later stage liver disease would improve the relative health benefits and cost-effectiveness of HCC surveillance.

Figure 1 – Progression of liver disease to MAFLD, MASH, fibrosis, cirrhosis, and HCC (created with biorender.com)



Metabolic-associated steatohepatitis (MASH) refers to the inflammation of the liver in patients with MAFLD and is a more advanced stage of liver disease (see Figure 1).[1] Patients

[1] We will refer to non-MASH MAFLD patients simply as MAFLD patients for convenience; terminology regarding the overlap between MAFLD and MASH patients differs across sources.

with MASH are likely to develop late-stage liver disease such as liver fibrosis, cirrhosis, and HCC compared to MAFLD patients(15) and may therefore be more likely to benefit from HCC surveillance compared to MAFLD patients. MASH replaces the previous classification of non-alcoholic steatohepatitis (NASH).

The aims of this report are to:

i. assess the recent evidence available on
    a. disease prevalence and transitions for MAFLD/MASH patients, and
    b. diagnostic technologies for the diagnosis of MASH in MAFLD patients, and
ii. identify the health benefits and cost-effectiveness of routine HCC surveillance for MASH patients in Australia, including the cost-effectiveness of triaging patients with MAFLD to HCC surveillance based on likelihood of having MASH.

Methods

Two evidence reviews were completed for this project, on the disease prevalence and transitions for MAFLD/MASH, and diagnostic technologies for the detection of MASH in MAFLD patients.

The first evidence review identified systematic reviews, meta-analyses, pooled analyses, and modelling studies on disease prevalence and transition rates for MAFLD/MASH patients, with a focus on recent and Australian studies. The second review assessed evidence on diagnostic technologies used to identify MASH in MAFLD patients. The most relevant and efficacious tests for the Australian setting were identified. Where data was not specifically available for MAFLD/MASH patients, data for NAFLD/NASH patients was extracted instead.

Based on the evidence reviews, predictive modelling estimates were generated using Policy1-Liver, a mathematical model of liver disease and HCC surveillance. Policy1-Liver was recalibrated to reflect health outcomes and costs MASH patients. The model was used to estimate the health impacts, costs, and cost-effectiveness of routine HCC surveillance for MASH vs MAFLD patients, including the use of a diagnostic tests to triage high-risk patients.

Results

Evidence reviews

The evidence review showed that NAFLD prevalence in the Australian population was estimated at 22.2% as of 2020 and is expected to continue to increase.(8) NASH prevalence was estimated to be 5.3% in 2020, and to increase to 6.2% by 2030, with MASH prevalence likely to be similar.(8) Overall, MASH patients had more advanced liver fibrosis, higher cirrhosis and HCC risk, and higher all-cause mortality risk compared to MAFLD patients.

The Fibrosis-4 (FIB-4) Index for Liver Fibrosis, the Enhanced Liver Fibrosis (ELF) Test, and the NAFLD Fibrosis Score (NFS) were identified as the most likely candidates for the identification of MASH in Australia based on effectiveness and clinician acceptability, while the ADAPT algorithm had the highest sensitivity of the identified technologies. FIB-4 is currently used in Australia to assess fibrosis in MAFLD patients; based on this, FIB-4 and ADAPT included in the predictive modelling exercise.

Predictive modelling

Over their lifetime, patients with MASH were at least six times more likely to develop HCC vs non-MASH MAFLD patients, had a 39% lower quality-adjusted life-expectancy (QALE), and 31% higher liver-disease related costs, including HCC treatment costs.

Policy1-Liver showed that HCC surveillance is unlikely to be cost-effective in the overall MAFLD cohort, with a cost-effectiveness ratio of $57,000/QALY, above the indicative willingness-to-pay thresholds of $30,000 or $50,000/QALY. However, stratification of MAFLD patients to HCC surveillance is likely to improve cost-effectiveness; with the use of FIB-4 for risk-stratified HCC surveillance cost-effective with a cost-effectiveness ratio of $16,000/QALY. Using the ADAPT tool for stratification would further reduce HCC deaths but could potentially lead to oversurveillance. Up to 100-143 HCC deaths in Australia would be preventable through risk-stratified surveillance annually.

Discussion

As the incidence rate of MAFLD-related HCC increases in Australia,(9,10) ongoing research into cancer control for high-risk patients. This study highlights the potential for preventing MAFLD-related HCC in Australia via risk assessment tools developed to diagnose MASH, improving efficiency and cost-effectiveness.

For patients with early-stage liver disease, behavioural changes may be a more effective way to manage HCC risk than surveillance. Weight loss can lead to a significantly improved prognosis for MAFLD patients with early-stage disease (see *Preventing Liver Cancer* report). For patients with later stage disease such as MASH, liver damage is less likely to be reversible and routine HCC surveillance is more likely to be effective.

As new biomarkers, tools, and algorithms for the assessment of liver disease become available,(16–18) work needs to be done to ensure that the health system prioritises the most promising technologies, both in terms of their health benefits as well as the cost burden and burden on patients.

Conclusion

By efficiently identifying high-risk patients with MASH, routine HCC surveillance can be made more effective and efficient while reducing patient burden. A quarter of MASH-related HCC deaths in Australia could be prevented through targeted surveillance.

As the burden of MAFLD in Australia continues to grow, targeted investment in cancer control and HCC surveillance can be guided by predictive economic modelling. The analyses in this report can form the foundations of a business case to advocate for efficient and effective targeted interventions to reduce the burden of HCC mortality in Australia.

1. Background

Liver cancer is one of the most rapidly growing cancer types in Australia in terms of both incidence and mortality.(6) Hepatocellular carcinoma (HCC), the most common type of liver cancer,(4) often develops in people with underlying liver disease caused by modifiable risk factors.(7)

Metabolic-associated fatty liver disease (MAFLD) is defined as a build-up of excess fat in the liver, linked to excess body fatness, type 2 diabetes mellitus and/or metabolic abnormalities. MAFLD is characterised by accumulation of fat in the liver without liver inflammation and is a major risk factor for the development of HCC.(8) Recent Australian studies have shown that the incidence rate of MAFLD-related HCC has increased alongside increases in overweight and obesity rates,(9,10) and is likely to become the dominant cause of HCC in Australia over the next few decades. Interventions to identify MAFLD patients and improve outcomes include routine liver surveillance and behavioural interventions,(19) though the potential impact of these interventions on health outcomes and health system costs is unclear.

Previously, patients with MAFLD were typically diagnosed with non-alcohol fatty liver disease (NAFLD) instead. From 2020, the MAFLD classification was introduced; proponents of the new classification argue that MAFLD better reflects the metabolic nature of the disease.(20) The majority of patients with MAFLD would also be diagnosed with NAFLD, and vice versa.

Routine HCC surveillance using technologies including blood biomarker testing and ultrasound can reduce HCC mortality through early detection.(11,16,17,21) Modelling from the previous *Preventing Liver Cancer* report showed that routine HCC surveillance can reduce HCC mortality by 18% in MAFLD patients.(14) However, this would come at a cost of $58,000 per quality-adjusted life-year (QALY) saved, above the usual $30,000 or $50,000 per QALY thresholds used in Australia. This result was primarily due to patients with early-stage liver disease who had a low risk of HCC and therefore were unlikely to benefit from HCC surveillance. Targeting patients with later stage liver disease would improve the relative health benefits and cost-effectiveness of HCC surveillance but requires accurate identification and stratification of these patients.

Whilst a benign condition in isolation, MAFLD can progress to metabolic-associated steatohepatitis (MASH), a more advanced stage of liver disease categorised by inflammation of the liver.(8) Patients with MASH are at higher risk of developing HCC and other liver complications than patients with non-MASH MAFLD, with previous research indicating a 10-times higher HCC incidence rate in NASH compared to NAFLD patients (5.29 vs. 0.44 per 1,000 person-years); these rates are likely to be similar in MASH and MAFLD patients.(15) MASH patients are therefore more likely to benefit from HCC surveillance compared to MAFLD patients. The progression of liver disease to MAFLD and MASH, as well as later stage disease such as fibrosis, cirrhosis, and HCC, are shown in Figure 1. As with MAFLD and NAFLD, the classification of MASH has been developed to replace the previous diagnosis of non-alcoholic steatohepatitis (NASH).

For the purposes of this report, we will refer to MAFLD patients as patients with metabolic associated liver disease who have not developed steatohepatitis, i.e., non-MASH MAFLD. The delineation between MASH and non-MASH patients differs across the literature.

Given the biological pathway of HCC through MAFLD and later MASH, there is potential for targeted liver cancer control interventions to reduce the disease burden at key stages in the development of liver disease. Risk assessments tools, which use imaging, biomarkers, and clinical characteristics to diagnose MASH/NASH, can allow patients at elevated risk of HCC to be identified and referred to appropriate HCC surveillance, simultaneously lessening the patient and resource burden of screening for those at lower risk. However, these technologies are very new, and the impact in the Australian setting such as health benefits, costs, and potential for harms is unknown.

The aims of this project were to:

i. assess the recent evidence available on
    a. disease prevalence and transitions for MAFLD/MASH patients, and
    b. diagnostic technologies for the diagnosis of MASH in MAFLD patients;
ii. identify the health benefits and cost-effectiveness of routine HCC surveillance for MASH patients in Australia, including the cost-effectiveness of triaging patients with MAFLD to HCC surveillance based on likelihood of having MASH.

This project is an extension of the *Preventing Liver Cancer* project,(14) which assessed the benefits of risk assessment for patients with MAFLD and alcohol-related liver disease.

2. Disease prevalence and transitions for MAFLD/MASH patients

2.1 Methods

2.1.1 Evidence Review Methods

This review identified evidence available on disease prevalence and transitions for MAFLD/MASH patients, with a focus on recent and/or Australian studies. The research aims were to determine:

1. What is known about the disease prevalence and transitions for patients with MAFLD, and/or MASH?
2. What are the prevalence and risk differences between patients diagnosed with MAFLD/MASH and patients diagnosed with NAFLD/NASH?

The search expanded upon a previous search on excess body fatness, the metabolic syndrome, and non-alcoholic fatty liver disease as part of the *Preventing Liver Cancer* project.(14)

Electronic literature searches were undertaken using the Ovid platform to search Embase and MEDLINE between January and May 2022. International evidence was assessed from systematic reviews, meta-analyses, pooled analyses and/or modelling studies published in the last ten years (2012 to 2022), as well as Australian studies of any type published to 2022. This was supplemented with later Australian studies from 2023 where available.

Based on this, key outputs such as fibrosis rates, fibrosis progression rates, and HCC/all-cause mortality risks by patient group were identified, with additional data relating to disease prevalence and/or disease transitions extracted from the original sources where necessary. Other relevant studies identified by study team members were also included. Complete

details are provided in the supplementary *Preventing Liver Cancer: scoping review on disease prevalence and transitions for MAFLD/MASH patients* report.

2.2 Results

2.2.1 Evidence Review Results

Prevalence of MAFLD/NAFLD (in Australia or similar contexts)

In Australia, the prevalence of NAFLD was estimated at 22.2% in 2020.(8) A similar proportion were reported in the Canadian population,(22) but estimates for North American were much higher at 38.47%.(23)

NAFLD-related HCC prevalence has dramatically increased over time in Australia,(9,10) with a New South Wales-based study reporting an increase in NAFLD/NASH-HCC from 13% in 2008 to 19% in 2016.(10) These trends have been driven by increases in overweight and obesity.(24)

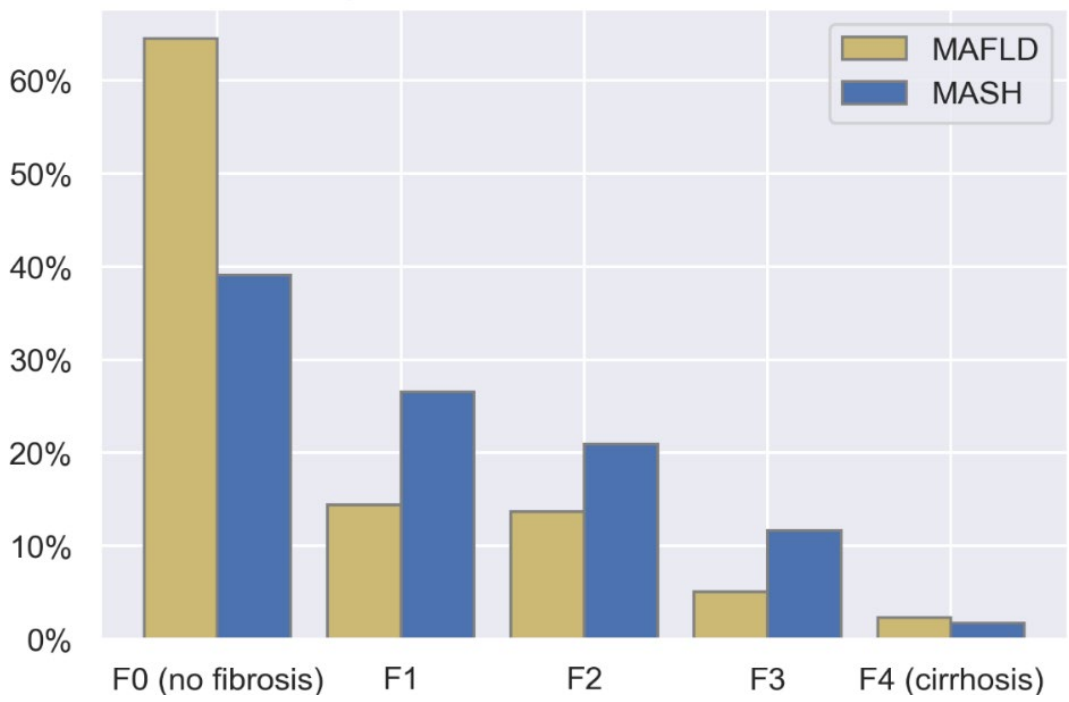
Prevalence of MASH/NASH in Australia or similar contexts

The prevalence of NASH in the Australian population was estimated at 5.3% in 2020, and is predicted to increase to 5.8% and 6.2% in 2025 and 2030, respectively. Similar estimates were reported in the Canadian population.(8,22)

Prevalence of MASH/NASH in MAFLD/NAFLD patients

The global prevalence of NASH among NAFLD patients was estimated at 16.02% in 2023,(23) and projected to reach 27% in the USA in 2030.(25) In contrast to these findings, Younossi et al.(15) reported an extremely high prevalence of NASH in NAFLD at 59.1%, though the authors acknowledged that this high estimate was likely a result of selection bias.

Figure 2 – Fibrosis stage distribution in patients with MAFLD and MASH



Prevalence of fibrosis in MAFLD/NAFLD patients

The prevalence of NAFLD with no fibrosis was estimated at 35.8% in the general NAFLD population.(26) The prevalence of NAFLD with stage F1 fibrosis was reported at 32.5% (or 14.89% and 13.84% in overweight and obese patients, respectively), and the prevalence of NAFLD at stage F2, F3 and F4 fibrosis was estimated at 16.7%, 9.3% and 5.7%, respectively.(27)

Prevalence of fibrosis in patients diagnosed with MASH/NASH

The prevalence of fibrosis within the overweight and obese NASH population was estimated at 26.55% (F1), 20.95% (F2), 11.6% (F3) and 1.71% (F4),(27) with MASH patients more likely to have advanced fibrosis than MAFLD patients. The distributions for each group are shown in Figure 2.

Risk of developing fibrosis in MAFLD/NAFLD patients

The risk of fibrosis progression within the NAFLD population was estimated at a progression rate of 0.13 stages per year,(26) and at an annual transition probability ranging from 0.0131 to 0.095 from F0 to F1, 0.023 to 0.14 from F1 to F2, and 0.018 to 0.07 from F2 to F3.(22,28)

Risk of developing fibrosis in MASH/NASH patients

The risk of fibrosis progression within the NASH population was estimated at a rate of 0.03-0.14 stages per year,(15,26,29) and at a transition probability from F0 (no fibrosis) to F1, F2 and F3 of 6.1%, 1.7% and 0.9% per year, respectively.(30) Notably, over 10% total body weight loss was associated with fibrosis regression in NASH patients.(31,32) Although both these studies had small sample sizes, these results indicate that weight loss is an effective treatment for the regression of fibrosis, even at advanced stages.

Risk of developing cirrhosis in MAFLD/NAFLD patients

The risk of cirrhosis within the NAFLD population was estimated at an annual transition probability of 0.04 to 0.118.(8,22,28)

Risk of developing cirrhosis in MASH/NASH patients

The risk of compensated cirrhosis within the NASH population was estimated at an annual transition probability of 0.9% in F0 patients, 0.3% in F1 patients, 1.8% in F2 patients, and 11% in F3 patients,(30) with F3 patients at a 22% risk of developing cirrhosis over a 29-month follow-up.(33)

Overlap between patients who would be diagnosed with MAFLD and patients who would be diagnosed with NAFLD

The overlap between NAFLD and MAFLD was estimated at a relative proportion of 73.2%.(34) High interrater reliability was reported between the two definitions, with a Cohen's kappa ranging from a 0.83 to 0.94.(34) Notably, the prevalence of MAFLD in Australian adults was estimated to be higher than NAFLD prevalence, at 37% in 2022,(35) aligning with other studies which have reported a higher overall prevalence of MAFLD vs NAFLD.(36)

3. Diagnostic technologies for the diagnosis of MASH in MAFLD patients

3.1 Methods

3.1.1 Evidence Review Methods

This evidence review identified evidence available from recently published international and national studies on diagnostic technologies for the diagnosis of MASH in MAFLD patients. Specifically, the research aims were to determine:

1. What diagnostic tests are available and in use for the diagnosis of MASH/NASH in Australia and internationally?
2. How effective are these diagnostic tests in the detection of MASH/NASH?

A preliminary scope of the literature was conducted to compile a list of current and emerging diagnostic tests for steatohepatitis. Expert opinion was sought from a gastroenterologist/hepatologist to identify the three tests most likely to be applied in the Australian context. An electronic literature search was performed in April 2023 using the MEDLINE database to search the national and international literature. Key terms relating to MASH/NASH were paired with terms relating to the selected tests.

Complete details, including the full study selection criteria, are provided in the supplementary *Preventing Liver Cancer: Scoping review on diagnostic technologies for the diagnosis of MASH in MAFLD patients* report.

3.2 Results

3.2.1 Evidence Review Results

The following studies were identified as potentially relevant for the Australian population, based on their acceptability and effectiveness:

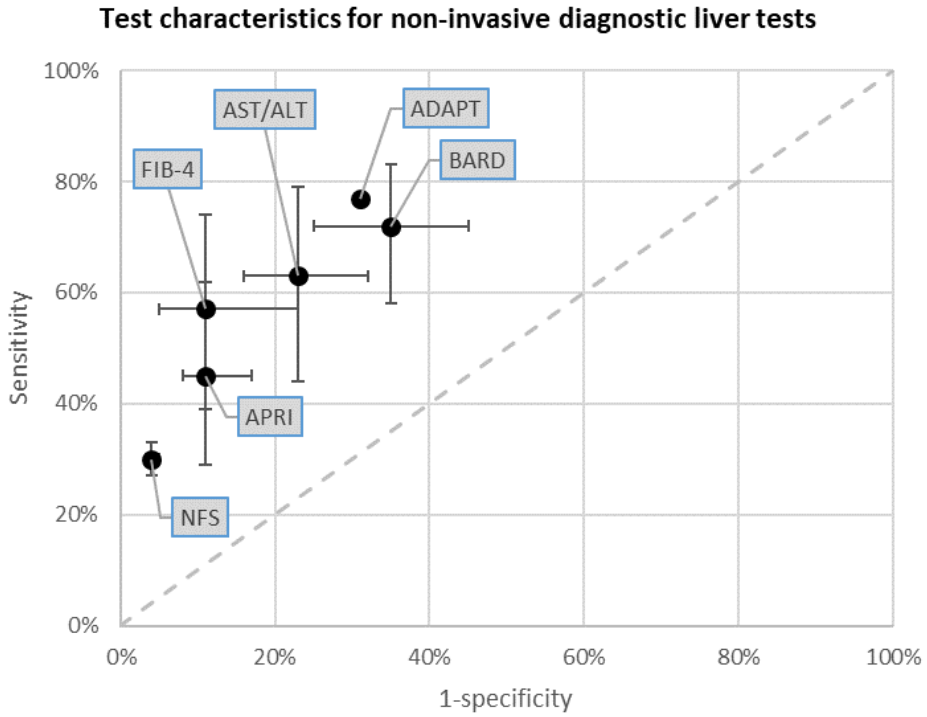
- Fibrosis-4 (FIB-4) Index for Liver Fibrosis
- NALFD Fibrosis Score (NFS)
- Enhanced Liver Fibrosis (ELF) Test
- PRO-C3-based fibrosis algorithm that included age, presence of diabetes, PRO-C3, and platelet count (ADAPT)

The test characteristics for each technology are illustrated in Figure 3. Details on each test, including the test thresholds used, are included in the supplementary report.

Of the diagnostic tests analysed, NFS had the highest specificity, with a 96% specificity at a 0.676 positivity cut-off, while ADAPT had the highest sensitivity at 77% at a 5.5 cut-off.

The Fibrosis-4 (FIB-4) Index for Liver Fibrosis, the NALFD Fibrosis Score (NFS) and Enhanced Liver Fibrosis (ELF) Test were identified as the most likely candidates for steatohepatitis screening, based on clinical acceptability and performance. FIB-4 and ADAPT were chosen for analysis in the modelling exercise (see Section 4), as they both had a strong balance of specificity and sensitivity; FIB-4 is also currently in use in Australia for the diagnosis of liver fibrosis and has a high degree of clinician acceptance.

Figure 3 – Test characteristics for non-invasive diagnostic liver tests.



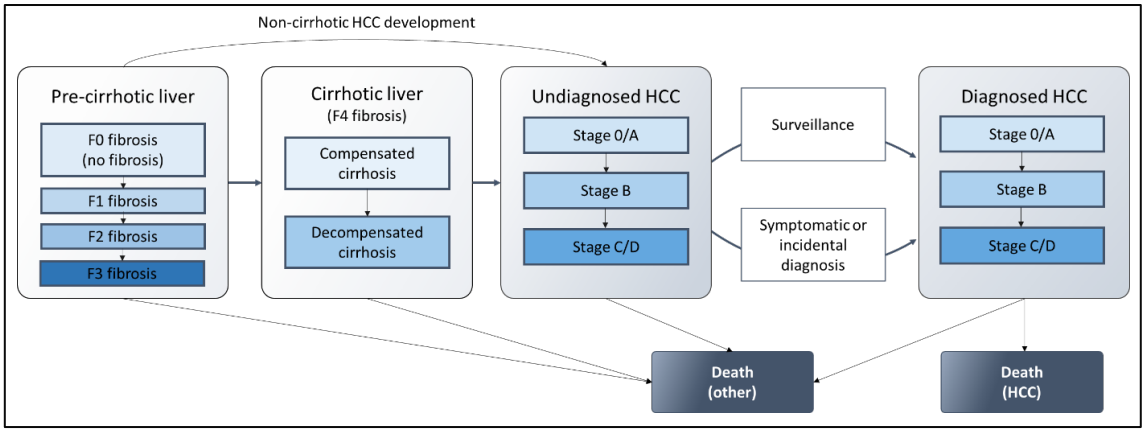
We also reviewed outcomes for each test for the detection of fibrosis in MASH patients; full outcomes are included in the supplementary report.

4. Modelling disease outcomes and costs for MASH and MAFLD patients

Based on the findings of the evidence reviews, the Policy1-Liver model of HCC and surveillance was recalibrated to capture differences in health outcomes and costs between MASH and MAFLD patients and the potential impact of MASH diagnostic tools and routine surveillance.

Policy1-Liver was developed for the *Roadmap to Liver Cancer Control*(13) and was subsequently expanded to capture pre-cirrhotic patients including those with MAFLD in the *Preventing Liver Cancer* project.(14) The model is designed to estimate liver disease progression and prevalence, including liver fibrosis progression, development of cirrhosis, onset and diagnosis of HCC, and HCC survival by stage in Australian MAFLD and MASH patients at risk of developing HCC. The main health states included in Policy1-Liver are shown in Figure 4. Further details about Policy1-Liver can be found in the supplementary modelling report *Preventing Liver Cancer: modelling estimates for diagnosis and surveillance of MASH and MAFLD patients*.

Figure 4 - A schematic of the health states and transitions captured in the Policy1-Liver model for MAFLD and MASH patients.



4.1 Methods

Policy1-Liver was recalibrated to capture specific all-cause mortality rates, HCC rates, and fibrosis transition rates in MAFLD and MASH patients. These calibration targets were identified based on findings of Section 2. Other parameters, such as those relevant for HCC diagnosis and treatment, were assumed to be the same in both sets of patients and were based on the previously reported calibration.(14)

The MAFLD and MASH patient cohorts were modelled with and without receiving routine HCC surveillance. For this analysis, the diagnosis of MAFLD or MASH was assumed to have already occurred, with complete accuracy; subsequent analysis incorporated the impact of diagnostic tools.

Based on the findings of Section 3, we modelled the technologies with the most favourable sensitivity and specificity; FIB-4 and ADAPT. This included the costs associated with administering a blood test and a GP visit. Other diagnostic technologies are likely to have similar efficacy and cost-effectiveness and may have advantages/disadvantages that could not be captured in this modelling exercise such as ease of use and patient acceptability.

Patients who had a positive diagnostic test were referred to routine HCC surveillance, as illustrated in Figure 5. This surveillance algorithm is based on recommendations by the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the Asian Pacific Association for the Study of the Liver, and expert consultation;(12,21,37) more details are included in the supplementary modelling report.(38)

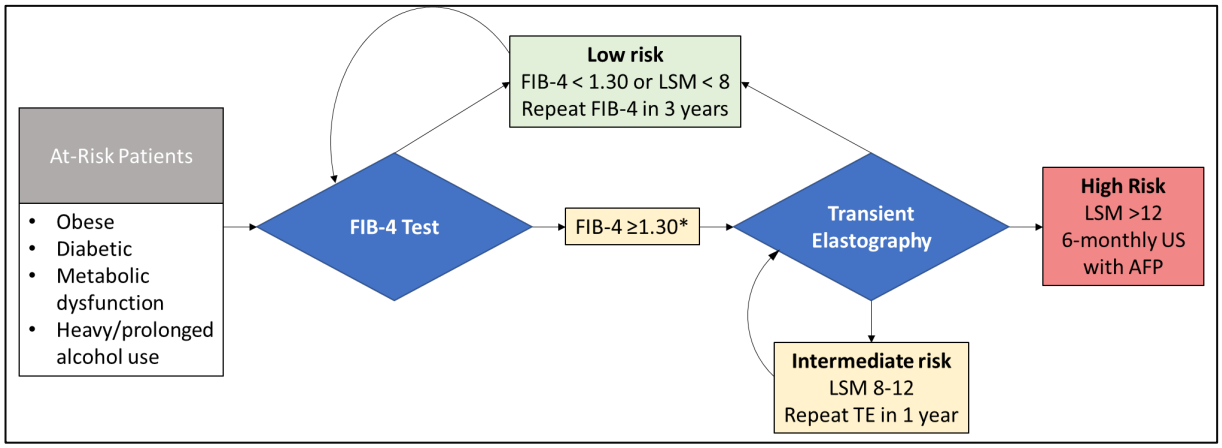
To assess the impact of a diagnostic test to triage patients, four scenarios were modelled:

- **No intervention:** No patients received routine HCC surveillance
- **FIB-4 stratified HCC surveillance**: patients with a positive FIB-4 (above the 3.25 threshold) received routine HCC surveillance
- **ADAPT stratified HCC surveillance**: patients with a positive ADAPT (above the 5.5 threshold) received routine HCC surveillance
- **HCC surveillance for all**: all MAFLD and MASH patients received routine HCC surveillance

Note that FIB-4 is used at a higher positivity threshold for the diagnosis of MASH, compared to the threshold used for routine HCC surveillance.

Patient costs were also modelled, including costs associated with ongoing cirrhosis care, costs related to the provision of HCC surveillance, costs associated with diagnosis of HCC (including cost associated with false positives in HCC surveillance), costs associated with HCC treatment, and end-of-life costs. A full list of the costs considered is included in the supplementary modelling report.(38) All costs use Australian sources and are presented in 2023 Australian dollars. The study took a *health system perspective*;(39) indirect costs such as productivity losses and travel costs were not included.

Figure 5 – Routine HCC surveillance algorithm for the at-risk patients



LSM: liver stiffness measurement. TE: transient elastography. US: ultrasound. LSM: liver stiffness measurement.

The cost-effectiveness ratio (CER) was calculated as the ratio of the costs associated with an intervention to the QALYs saved. Costs and QALYs were discounted using a 5% annual discount rate. To compare diagnostic technologies, the *incremental cost-effectiveness ratio* (ICER) was calculated. This is a health-economic method which allows for the comparison between multiple interventions. To calculate the ICER, the most cost-effective intervention is identified as the intervention with the lowest cost per QALY saved. The CER was then calculated for this intervention, then the process is repeated using that intervention as the new comparator. This is then continued until all incrementally cost-effective interventions have been identified.

4.2 Results

The results of the predictive modelling studies are included in the following sections. Note that "MAFLD patients" here refers to patients who have MAFLD at baseline and have not yet developed MASH i.e., outcomes for this group include patients who will subsequently develop MASH.

4.2.1 Health outcomes in MAFLD vs MASH patients

Predicted health outcomes for MAFLD and MASH patients are shown in Table 1. Patients who had been diagnosed with MASH were over 5 times more likely to develop HCC over their lifetime compared to MAFLD patients, and nearly 6 times more likely to die from HCC over their lifetime. The onset of HCC was more likely to occur sooner in patients with MASH vs those with MAFLD. Patients diagnosed with MASH also had lower life expectancies. These are illustrated in Figure 6.

Table 1 – Predicted health outcomes for MAFLD and MASH patients, with and without routine HCC surveillance

	MAFLD		MASH	
	No intervention	Routine HCC surveillance	No intervention	Routine HCC surveillance
Lifetime HCC incidence per 100,000	3,051	3,051	16,940	16,940
HCC stage at diagnosis (% early/intermediate/late)	46/24/30	70/14/16	48/25/27	83/11/7
Lifetime HCC mortality per 100,000	2,112	1,730	12,443	9,101
Reduction vs no intervention	-	18%	-	27%
Mean patient lifetime costs*	$42,105	$43,835	$55,096	$58,032

**Includes cirrhosis care costs, HCC diagnosis costs, HCC treatment costs, and end-of-life costs. Does not include non-HCC related costs or savings, or costs associated with identifying potential high-risk patients.*

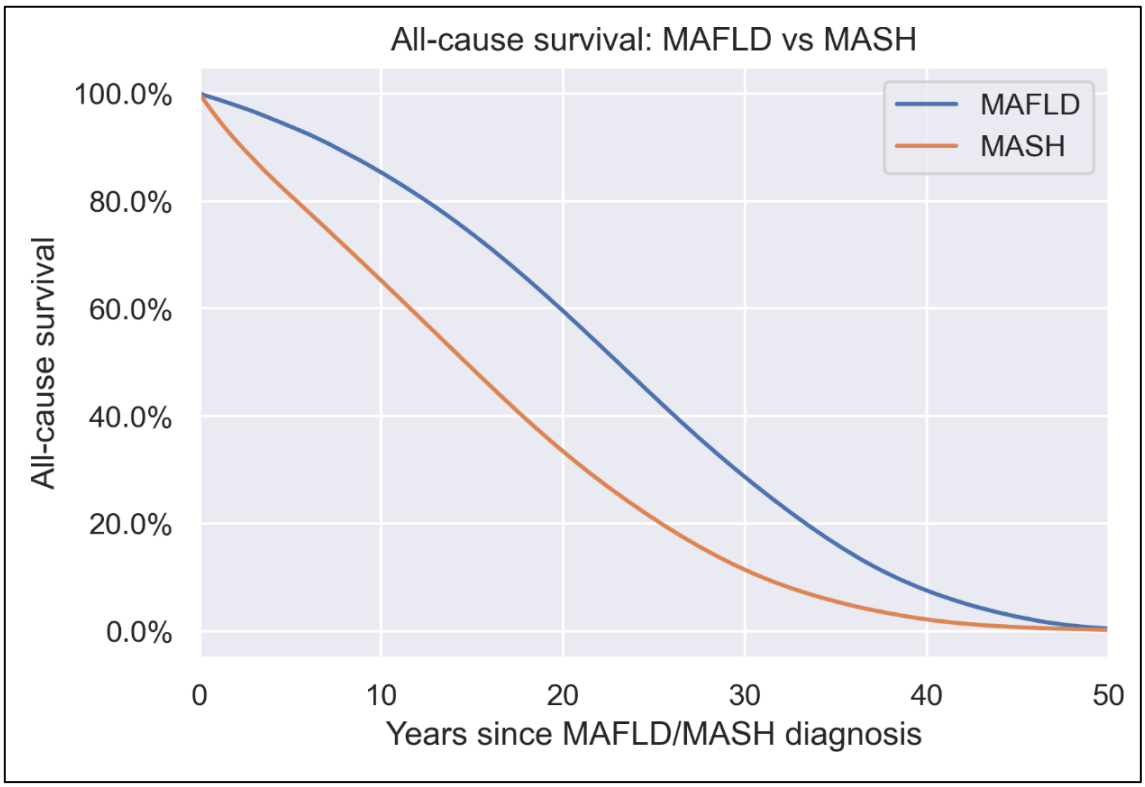
Routine HCC surveillance was estimated to be effective at detecting early-stage HCC, increasing the proportion of HCCs diagnosed at an early stage from 46% and 48% in MASH and MAFLD patients respectively to 70% and 83%. This would reduce mortality by 18% and 27% respectively, with a relatively limited impact on lifetime patient costs.

4.2.2 Routine HCC surveillance

The results of the cost-effectiveness analysis for routine HCC surveillance by subgroup are shown in Table 2. These results do not include the costs associated with diagnostic tools for MASH, nor the impact of false positive diagnoses of MASH.

As in previous studies,(14) routine HCC surveillance for all MAFLD patients had a cost-effectiveness ratio above the usually cited willingness-to-pay thresholds of $30,000 or $50,000 per QALY saved. However, HCC surveillance would be more cost-effective for MASH patients, with a CER of $11,487 per QALY saved. This would correspond to a 4% increase in quality-adjusted life expectancy (QALE) in the MASH cohort.

Figure 6 - All-cause survival curves (top) and annual HCC incidence (bottom) by years since MAFLD/MASH diagnosis



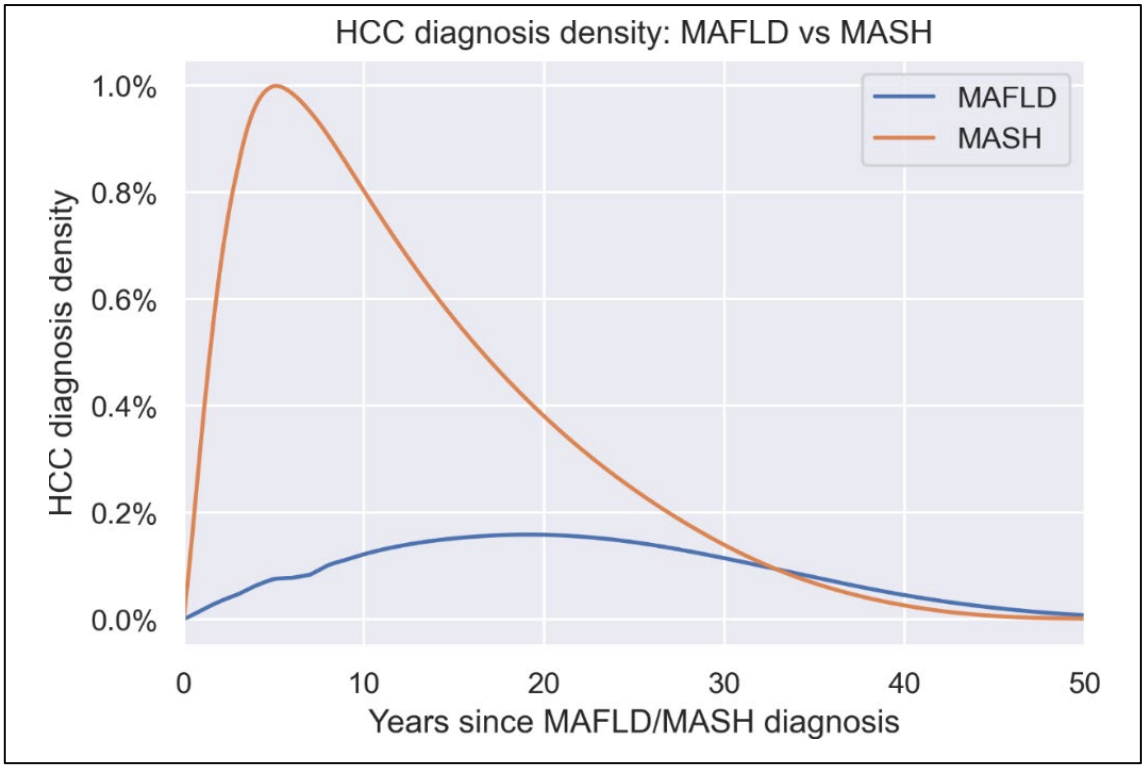


Table 2 – Predicted impact of routine HCC surveillance on quality-adjusted life expectancy (QALE, measured in quality-adjusted life-years or QALYs) and costs.

	MAFLD		MASH	
	No intervention	Routine HCC surveillance	No intervention	Routine HCC surveillance
Mean QALE (undiscounted)	27.2086	27.2738	16.5484	17.2401
Mean QALE (discounted)	14.0572	14.0743	10.1883	10.419
Additional discounted QALYs vs no intervention		0.0171		0.2307
Mean costs (undiscounted)	$42,105.43	$43,835.33	$55,096.20	$58,032.30
Mean costs (discounted)	$13,536.91	$14,509.65	$29,331.77	$31,982.04
Additional discounted costs vs no intervention		$972.74		$2,650.27
CER vs no intervention		$56,885.38		$11,487.95

Discounted values use a 5% annual discount rate. CER: cost-effectiveness ratio.

4.2.3 Cost-effectiveness of triaged HCC surveillance for MAFLD and MASH patients

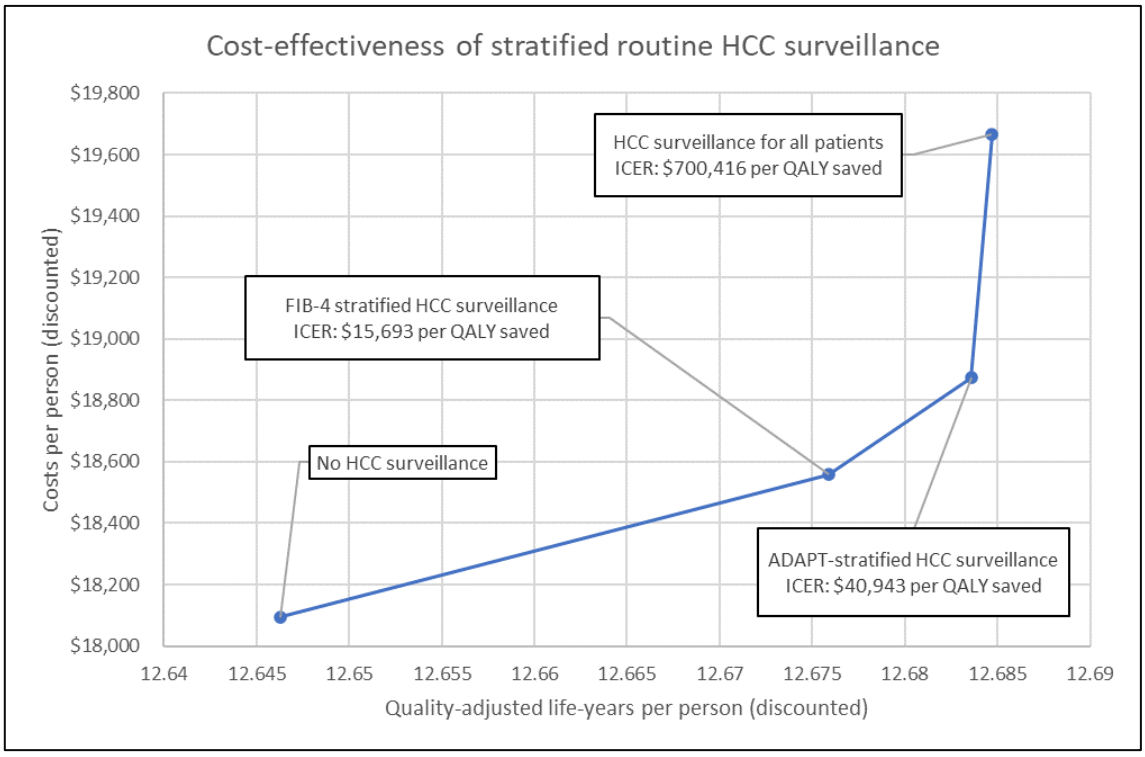
Recommending HCC surveillance for patients with a positive FIB-4 or ADAPT would significantly increase the cost-effectiveness of HCC surveillance compared to providing HCC surveillance to all MAFLD and MASH patients, as shown in Table 3. Stratified HCC surveillance using ADAPT, which has a high sensitivity, would increase the QALE by almost as much as HCC surveillance for all MAFLD and MASH patients. FIB-4 HCC surveillance has a lower sensitivity but a higher specificity, increasing the cost-effectiveness of HCC surveillance significantly through reduction of over-screening in patients who are unlikely to develop HCC. Compared to no intervention, all approaches would likely be cost-effective. However, when compared to stratified HCC surveillance, HCC surveillance for all MAFLD and MASH patients would be very cost-ineffective, with an incremental cost-effectiveness ratio of $700,416 per QALY saved. This reflects the marginal improvement in health benefits vs ADAPT or FIB-4 stratified screening and higher costs. This is illustrated in Figure 7.

Table 3 – Predicted impact of stratified HCC surveillance strategies for all MAFLD and MASH patients, including costs and false positive/negative diagnoses associated with the use of diagnostic tools.

	No intervention	FIB-4 stratification	ADAPT stratification	HCC surveillance for all
HCC mortality per 100,000	3,470	3,018	2,863	2,698
Reduction in HCC mortality vs no intervention		13.0%	17.5%	22.2%
Mean QALE (undiscounted)	22.8091	22.9003	22.9278	22.9467
Mean QALE (discounted)	12.6463	12.6759	12.6836	12.6847
Additional discounted QALYs vs no intervention		0.0296	0.0373	0.0384
Mean costs (undiscounted)	$46,702	$47,319	$47,855	$49,382
Mean costs (discounted)	$18,094	$18,558	$18,873	$19,666
Additional discounted costs vs no intervention		$464	$779	$1,572
CER vs no intervention		$15,693	$20,896	$40,943
ICER vs previous intervention		$15,693	$40,943	$700,416
Annual preventable HCC deaths vs no intervention*	-	100	134	150

**Total number of potentially preventable HCC deaths in Australia annually, based on implementation in 2023. QALE: quality-adjusted life expectancy. QALY: quality-adjusted life-years. CER: cost-effectiveness ratio. ICER: incremental cost-effectiveness ratio.*

Figure 7 - Cost-effectiveness plane for routine HCC surveillance for MAFLD and MASH patients, including FIB-4 or ADAPT stratified HCC surveillance.



ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life-year.

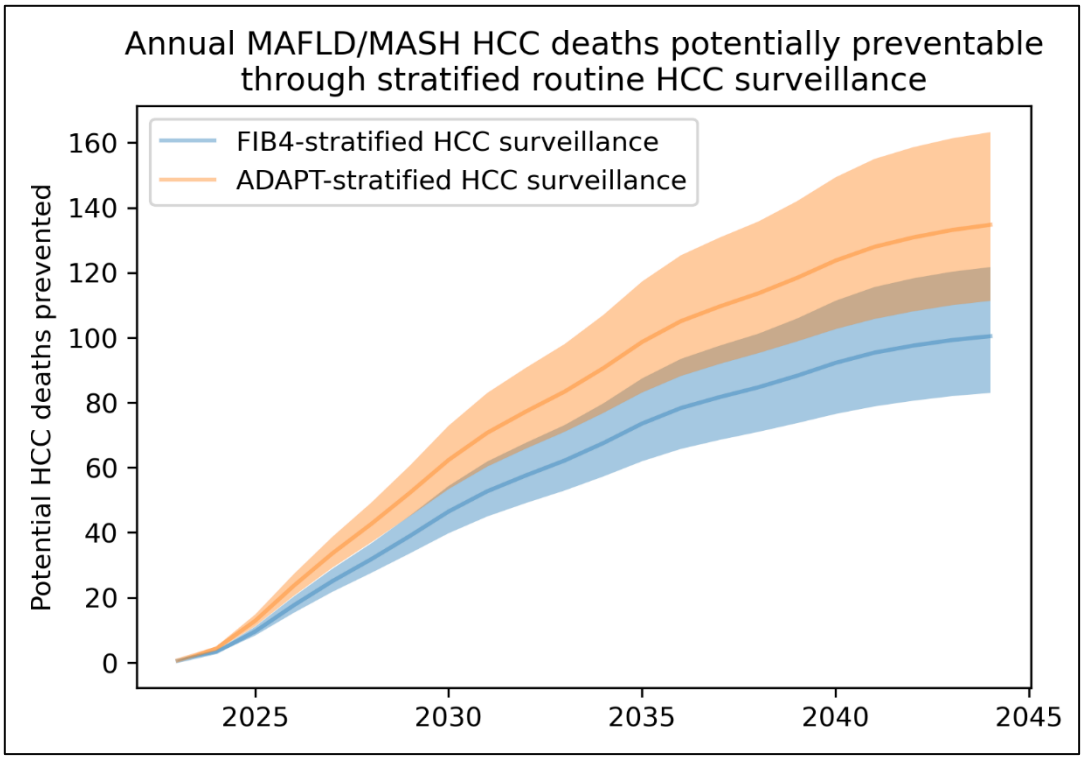
4.2.3 Potential HCC deaths averted in Australia

We estimated the number of HCC deaths that could be prevented through the stratified screening approaches described in the previous section of this report, with implementation from 2023. This was based on estimates of the prevalence of MASH and MAFLD in the Australian population and projections of liver cancer cases and deaths in Australia.(40)

For any HCC surveillance, the number of deaths prevented annually would increase gradually as the cumulative risk of HCC increases, then plateau around 2045 (Figure 8). It was estimated that approximately 100 HCC deaths could be prevented annually through FIB-4 stratified HCC surveillance by 2045, or 134 through ADAPT stratified HCC surveillance. Up to 150 HCC deaths could be prevented annually by providing routine HCC surveillance to all MAFLD patients.

Note that these outcomes are the estimated maximum number of preventable HCC deaths, and do not reflect difficulties associated with identifying MAFLD patients nor issues around compliance to HCC surveillance recommendations.

Figure 8 – Potentially preventable HCC deaths by implementing stratified HCC surveillance of MAFLD patients. Shaded area: 95% confidence interval, based on projections of liver cancer deaths in Australia.



5. Discussion

As the incidence rate of MAFLD-related HCC increases in Australia,(9,10) while the overall incidence rate of HCC decreases, ongoing research and a clearer understanding of MAFLD patient risks is crucial. This study highlights the potential for preventing MAFLD/NAFLD-related HCC in Australia through the use of risk assessment tools developed to diagnose MASH/NASH.

The evidence shows that the prevalence of NAFLD is high in Australia, estimated at just under a quarter (22.2%) of the population in 2020, while the prevalence of NASH is 5.3%. Our modeling demonstrates that routine HCC surveillance can alleviate this burden. However, without careful targeting, it can impose significant resource demands on an already strained health system. For instance, ultrasound services in Australia are currently understaffed due to the exponential growth in demand for imaging services over the past decade.(41)

For patients with early-stage liver disease who are not recommended for routine HCC surveillance, behavioural changes may be a more effective way to manage HCC risk. Weight loss can lead to a significantly improved prognosis for MAFLD patients with early-stage disease, as discussed in the *Preventing Liver Cancer* report.(14) For patients with later stage diseases such as those with MASH, liver damage is less likely to be reversible and routine HCC surveillance is more likely to be effective.

In reviewing the diagnostic tests there was a significant range of sensitivity and specificity observed across various cutoffs. This indicates the need for further research to determine the most appropriate cutoffs for specific settings and situations. No single diagnostic test was found to be unconditionally superior to others. Currently, FIB-4 is the most likely candidate for HCC surveillance in current practice due to its familiarity among general practitioners, while emerging algorithms like ADAPT may offer better performance. It is important to note that accumulating evidence suggests that combining multiple diagnostic tests may result in superior accuracy for diagnosing these conditions.(42,43) Therefore, future research should focus on analyzing the diagnostic accuracy of combinations of diagnostic tests

Numerous biomarkers and algorithms for assessing liver disease are currently in development, with some undergoing validation. For example, Cheng (17) examined the predictive value of biomarkers such as extracellular vesicles for HCC development, and Carter et al. (18) assessed the cost-effectiveness of a serum-based biomarker. Tools like the GALAD score incorporate these biomarkers along with other risk factors to calculate an overall HCC risk score.(16) As these algorithms continue to mature, it is necessary to ensure that the healthcare system prioritizes the most promising technologies based on their health benefits and the cost burden on patients.

The reviews and modelling conducted in this study were developed in collaboration with a practicing gastroenterologist/hepatologist based in Australia. Their expertise greatly enhanced our study by improving the search strategy for the review and ensuring the identification of the most prevalent diagnostic tools within the Australian context. Furthermore, they provided valuable feedback on the design of the Policy1-Liver model, ensuring that the essential aspects of HCC development and liver disease were effectively captured.

While a substantial amount of evidence was found regarding the NAFLD/NASH population, there was a scarcity of evidence for the MAFLD/MASH population due to the relatively recent introduction of these classifications. Sufficient time for large-scale data collection or studies has not yet elapsed. The term MAFLD was proposed through expert consensus in 2020(44,45) and has received endorsement from over 1,000 signatories, including professional bodies, specialist physicians, and primary care physicians.(20)However, the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver have yet to endorse the change in terminology, and there is still some controversy over the new

definition.(20) As the new definition becomes more widely accepted in standard practice, research utilizing these new classifications will be crucial in guiding the treatment and modelling of liver diseases.

It is imperative that efforts continue to understand the evolving risk profiles of MASH and MAFLD patients and the available diagnostic tools. This knowledge will facilitate the implementation of appropriate measures to reduce the future burden of liver disease and liver cancer in Australia.

6. Conclusion

By efficiently identifying high-risk patients with MASH, routine HCC surveillance can be made more effective and efficient while reducing patient burden. A quarter of MASH-related HCC deaths in Australia could be prevented through targeted surveillance.

As the burden of MAFLD in Australia continues to grow, targeted investment in cancer control and HCC surveillance can be guided by predictive economic modelling. The analyses in this report can form the foundations of a business case to advocate for efficient and effective targeted interventions to reduce the burden of HCC mortality in Australia.

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