The Daffodil Centre

The Australian Prevention Partnership Centre

Preventing liver cancer: modelling estimates for MAFLD and ARLD patients

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A partnership between

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Contents

Summary

Background and aims

- The burden of liver cancer is increasing in Australia, both in terms of cases and deaths.
- Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Most HCC deaths in Australia are caused by metabolic associated fatty liver disease (MAFLD) and/or alcohol-related fatty liver disease (ARLD), which are associated with overweight/obesity and alcohol use respectively.
- As overweight and obesity rates continue to rise, rising MAFLD rates in particular are a key driver of liver cancer rates.
- HCC risk in MAFLD and ARLD patients can be managed through routine HCC surveillance, weight loss, and alcohol abstinence. Routine HCC surveillance increases the likelihood that HCC is detected at an early, treatable stage, while weight loss and alcohol abstinence reduce the likelihood of developing HCC.
- To estimate the impact of prevention activities on HCC, we used a model of HCC development and surveillance, *Policy1-Liver*, to calculate patient outcomes and costs.

MAFLD prevention

- Without intervention, over the lifetime of 100,000 MAFLD patients we estimated there would be 3,051 HCC cases and 2,112 HCC deaths.
- Routine HCC surveillance using FIB-4 biomarker testing, transient elastography imaging, and ultrasound would reduce HCC deaths by 18.1% to 1,730 per 100,000 MAFLD patients and be associated with additional costs of $1,774 per patient.
- Weight loss interventions (once-off weight loss of 10% of patient body mass) could reduce HCC death rates by 25.9% compared to no intervention, to 1,564 HCC deaths per 100,000 MAFLD patients. If weight loss were combined with routine HCC surveillance, this would be further reduced to 1,306 HCC deaths per 100,000.
- By 2045, an estimated 150 MAFLD-related HCC deaths in Australia could be prevented annually by routine HCC surveillance interventions alone. Up to 417 HCC deaths would be preventable annually through once-off weight loss.

ARLD prevention

- Without intervention, over the lifetime of 100,000 ARLD patients we estimated there would be 9,881 HCC cases and 7,883 HCC deaths.
- Routine HCC surveillance using FIB-4 biomarker testing, transient elastography imaging, and ultrasound would reduce HCC deaths by 18.6% to 6,415 per 100,000 ARLD patients and be associated with additional costs of $3,099 per patient.
- By 2045, an estimated 108 ARLD-related HCC deaths in Australia could be prevented annually by routine HCC surveillance interventions alone.

Background and aims

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer[1] and is a significant public health issue worldwide.[2,3] Both the incidence and mortality burden of liver cancer are increasing in Australia.[4] HCC is a complex disease that requires multidisciplinary management and poses significant and emerging challenges in terms of diagnosis, treatment, and prevention.

Two of the leading causes of hepatocellular carcinoma are metabolic-associated fatty liver disease (MAFLD) and alcohol-related liver disease (ARLD, sometimes referred to as ALD). These conditions are both characterised by the accumulation of fat in the liver, which can progress to liver fibrosis and cirrhosis and potentially HCC. MAFLD patients are characterised by the presence of 2 diabetes mellitus (T2DM) and overweight/obesity, regardless of alcohol intake or other liver diseases (as distinct from the previously preferred diagnosis of non-alcoholic fatty liver disease, NAFLD, where diagnosis required the exclusion of other aetiologies).[5] ARLD patients have liver damage caused by ongoing excess alcohol intake, sometimes classified as alcohol use disorder (AUD).[6,7] In Australia, most HCC cases are attributable to one or both of these, with the remaining HCC cases attributable to viral hepatitis B or C.[8,9] Patients with both MAFLD and ARLD are sometimes referred to as "both alcohol and fatty liver disease" or BAFLD patients.[10]

Routine HCC surveillance of patients with high risk of advanced MAFLD or ARLD for development of HCC can assist with early detection and increase the likelihood of curative treatment.[11,12] This monitoring typically uses biomarkers or non-invasive imaging. Another key method of prevention for the development of HCC in MAFLD or ARLD patients is behavioural change – primarily weight loss in MAFLD patients,[13–15] and alcohol abstinence in ARLD patients.[16]

The aim of this study was to provide estimates of the proportion of MAFLD- and/or ARLD-related HCC deaths in Australia which could be averted through routine HCC surveillance, weight loss, and alcohol abstinence. To accomplish this, the Policy1-Liver model was employed, which provides a detailed simulation of liver disease progression in patients with MAFLD or ARLD. The model tracks development of fibrosis and/or cirrhosis in the liver, the onset and diagnosis of HCC, and the patient's survival outcomes based on the cancer stage at diagnosis. Using this model, we estimated the effects of regular surveillance for early detection of liver disease, as well as interventions such as weight loss and abstinence of alcohol use, on reducing the incidence and mortality of liver cancer.

Methods and modelled scenarios

Policy1-Liver model of liver disease and HCC

For this study, modelling was completed with *Policy1-Liver*, a model of liver disease and surveillance. *Policy1-Liver* 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 ARLD patients at risk of developing HCC. The health states included in *Policy1-Liver* are shown in Figure 1.

Patients with MAFLD and ARLD were modelled from 2023, with the distribution of age and severity of liver disease in the cohort based on the most recent available Australian estimates.[17] The extent of liver disease in pre-cancer patients is stratified by METAVIR fibrosis/cirrhosis staging, from F0 (no fibrosis) through F1, F2, F3, to F4 (cirrhosis), which is further delineated into compensated and decompensated cirrhosis.[18] Patients with ARLD were also modelled in "normal liver" and "steatosis, no fibrosis" states. Although other measures of liver disease severity, such as inflammation/activity score,[19] fibrosis stage is a strong indicator of HCC risk with widely available patient data, making it an ideal proxy state for modelling.[20] Patients were modelled according to their primary diagnosis; patients with BAFLD were not explicitly modelled. Details of the distribution of initial fibrosis stage are included in Table 12.

In the model, patients with fibrosis can progress to each successive stage, i.e., F0 to F1, F1 to F2, etc, as well as compensated cirrhosis to decompensated cirrhosis. Patients can also progress to other-cause death (i.e., death not from HCC), with patients at more advanced fibrosis or cirrhosis having higher other-cause death rates vs patients with little or no fibrosis. Patients with F3 fibrosis or cirrhosis could also progress to undiagnosed HCC, with decompensated cirrhosis patients progressing to later stage HCC.

HCC was modelled as early (Stage 0/A), intermediate (Stage B), or late (Stage C/D), consistent with reporting from primary data sources such as Australian Institute of Health and Welfare and New South Wales Cancer Institute. Patients with undiagnosed HCC begin as early stage unless they have already developed liver decompensation. Patients with undiagnosed HCC can progress to a later stage, to diagnosed HCC, or to death.

Patients with diagnosed HCC have an elevated likelihood of HCC death based on their stage at diagnosis, with later stages having lower survival rates. Note that this includes patients whose HCC progresses to a later stage within this five-year period, as well as patients with recurrent HCC; these groups are captured in the original data sources and are classified by their stage at diagnosis here for consistency. Patients who survive five years past the diagnosis of HCC transition to "survivors" and have no further elevated likelihood of HCC death.

In addition to tracking patient health states, *Policy1-Liver* also tracks relevant healthcare costs related to liver disease and HCC, including costs associated with ongoing cirrhosis care, costs related to the provision of surveillance, costs associated with diagnosis of HCC (including negative diagnoses after false positives from surveillance), costs associated with HCC treatment, and end-of-life costs. A full list of the costs considered is included in Table 15. All costs use Australian sources and are presented in 2023 Australian dollars. The study took a *health system perspective*;[21] indirect costs such as productivity losses and travel costs were not included.

Health state utilities were also calculated for all patients. Health state utilities are used to capture a patient's *quality of life*, with patients with more severe/debilitating diseases

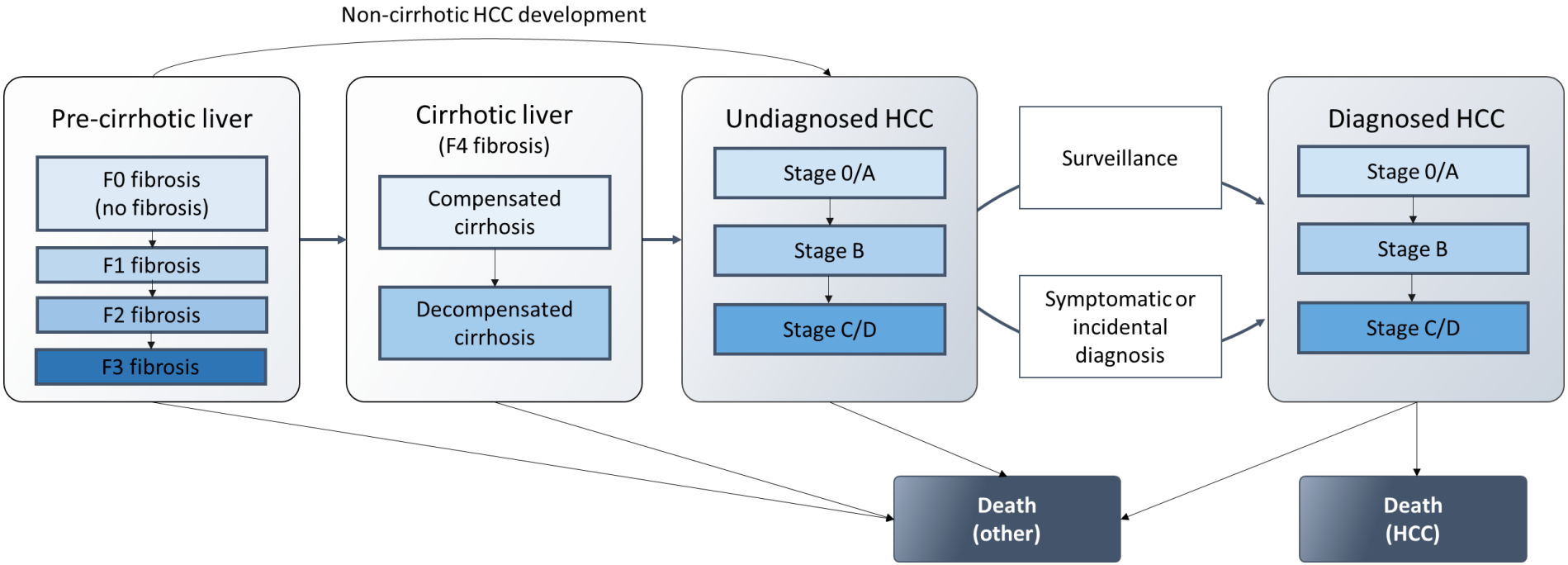
experiencing lower quality of life. This is used to assess the health benefits associated with avoiding outcomes such as decompensated liver cirrhosis, which is associated with a low quality of life. Combined with estimates of the likelihood of patient survival, this is used the calculate the *quality-adjusted life expectancy* (QALE), which captures both the impact of preventing premature death and avoiding health states with a low quality of life.

The *cost-effectiveness ratio* (CER) associated with interventions such as routine HCC surveillance was calculated. This is the ratio of the costs associated with an intervention to the *quality-adjusted life-years saved*, i.e., the difference between the QALE with and without the intervention. Lower values for the CER indicate more health benefits for the same expenditure. The CER can be compared between interventions and compared to common *willingness-to-pay* (WTP) thresholds which are used to identify potentially beneficial health investments. For all costs and quality-adjusted life-expectancies, a 5% annual discount rate was applied from 2023. This is a standard methodology in health economics used to ensure that short-term costs and benefits are valued higher than long-term costs and benefits – this allows the analysis to reflect both the lower certainty around long-term outcomes and the preference for upfront benefits.

The modelling used a *time-to-event distribution modelling* approach, a multistate model capturing competing and evolving risks across a patient lifetime. This is key to accurately capturing the evolution of liver disease, and the potential impact of surveillance.[22] The mathematical framework is described in *Appendix 2 - Time-to-event distribution modelling*, and relies on tracking the likelihood an individual is in a particular health state at any given time. All transition rates were calibrated to the best available data, prioritising data sources for Australian populations, recent studies, and large cohort sizes. Calibration data is included in *Appendix 1 – Additional* Policy1-Liver *model details*.

To generate population-level estimates of the number of preventable cancers, we used projections developed by Luo et al of liver cancer burden in Australia to 2045.[4] Combined with estimates of the proportion of liver cancers attributable to HCC,[23] the burden of MAFLD/ARLD, and fibrosis stage among MAFLD/ARLD patients,[17] this was used to generate projections of the number of MAFLD- or ARLD-related HCC deaths to 2045. Data informing these estimates are included in Appendix 1.

Figure 1 – A schematic of the health states and transitions captured in the Policy1-Liver *model for MAFLD/ARLD patients. Patients with ARLD may also have a "normal" (pre-steatosis) liver state.*



MAFLD and NAFLD patients in Australia

Data sources for patient groups with confirmed MAFLD diagnoses are largely unavailable.[24] Positive diagnoses under MAFLD criterion vs NAFLD criterion was significantly associated males, patients with higher BMI, and patients with higher fibrosis scores.[25] However, the majority of patients diagnosed with NAFLD would also receive a positive diagnosis for MAFLD, and vice versa. Further research is required to establish detailed prognostic differences between patients diagnosed with MAFLD and NAFLD.

For these reasons, we refer to patients in this section as MAFLD patients, though the majority of the relevant data sources were established in patients diagnosed with NAFLD. Unless noted, these patients populations are assumed to have the same risk of developing liver disease and HCC. Further discussion of differences between these patient populations is included below.

The patient populations were modelled from index age which was drawn from a distribution with mean age 55 and standard deviation of approximately 10 years (except where otherwise noted), based on the Australian NAFLD patient population described in Adams et al.[17] Fibrosis stage and presences of compensated or decompensated cirrhosis was simulated to reproduce reported proportions. For the comparator, no intervention was modelled: all HCC cases were assumed to be detected symptomatically or incidentally (i.e., outside of routine HCC surveillance), and liver disease progressed per average-risk MAFLD patients.

Weight loss interventions in MAFLD patients

The association between weight loss in MAFLD patients and HCC risk has not been clinically verified.[15] However, there have been clinically demonstrated instances of significant reductions in fibrosis severity following weight loss.[13] Based on this, we modelled the likelihood of HCC developing with fibrosis reductions due to weight loss. As there was not data to inform the ongoing impact after the studies on weight loss and fibrosis, we modelled "*weight loss*" as a one-off intervention corresponding to patients who lose over 10% of their body mass based on a study of fibrosis severity by Vilar-Gomez et al.[13] This weight loss would lead to a regression in liver damage severity in the majority of patients.

In the absence of further longitudinal data, our modelling assumed that after the initial liver disease regression attributable to weight loss, any further liver disease/HCC development would progress at usual rates. This is expected to correspond to patients who maintain their current weight or increase in weight. Additional exploratory modelling was completed which assumed no further progression in liver disease severity, which may correspond to further and ongoing weight loss. However, there is little data to suggest that this is a possible outcome in real-world MAFLD patients; the analysis included here is indicative only.

ARLD patients in Australia

Data to inform ARLD modelling was limited compared to data to inform MAFLD modelling. The primary Australian sources used were Huang et al and Yeoh et al.[8,12] International sources were used where data was not available; details of all data sources are included in *Appendix 1 – Additional* Policy1-Liver *model details*.

The use of fibrosis staging is controversial in ARLD patients; although some sources discourage the use of the METAVIR scoring in ARLD patients and propose a seven stage system,[26] we here use the METAVIR system for consistency in both the modelling and with the data sources used.[27] For modelling purposes, the METAVIR staging acts as a proxy of a patient's risk of developing F3 fibrosis or cirrhosis and subsequently HCC.[28]

Alcohol cessation and risk of severe ARLD and HCC

For ARLD patients, we modelled primary prevention via alcohol cessation, and the resulting impact on liver disease and patient mortality rates. Fibrosis regression was modelled in patients who were abstinent from alcohol use,[29] as well as lower decompensation and all-cause mortality rates in cirrhotic patients.[30] Changes to HCC incidence, decompensation regression, and mortality rates post-alcohol cessation were not modelled due to lack of evidence, with studies showing no significant effect (likely due to lack of statistical power and ongoing follow-up).[30,31] Long-term outcomes were compared with patients who continued alcohol use.

Routine HCC surveillance for patients at risk of HCC

Alongside primary prevention of HCC cases by avoiding and mitigating risk factors, secondary prevention of HCC in MAFLD and ARLD patients can be provided through routine HCC surveillance of at-risk patients with liver disease. Routine HCC surveillance means that any cancers that develop can be detected at earlier disease stages, when there is a higher possibility of curative treatment. Currently, for patients with MAFLD and/or ARLD, international clinical practice guidelines recommend the use of non-invasive tests to stratify patients into risk categories,[32–34] with only those at high risk (typically with cirrhotic liver) recommended to progress to regular ultrasound surveillance.[35]

This surveillance algorithm relies on three technologies: FIB-4, transient elastography (TE), and ultrasound. FIB-4 is a non-invasive blood test used to assess the degree of liver fibrosis in patients with liver disease.[20] It is based on four factors: age, platelet count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). FIB-4 testing is a simple and inexpensive way to monitor the progression of liver disease over time, with higher scores indicating a higher likelihood of liver disease. Although it was originally designed for HCC patients, it is now used for all patients at risk of liver disease.

TE is a non-invasive imaging technique that is used to measure liver stiffness,[36,37] which is an indicator of liver fibrosis. It uses a FibroScan device to send a low-frequency vibrations through the liver to determine liver stiffness. A higher liver stiffness measurement (LSM) indicates a higher likelihood of liver disease. Finally, ultrasound is the standard for regular monitoring of patients at highest risk of developing HCC, typically those with cirrhotic liver.[38–40] Ultrasound is used as frontline imaging test for liver cancers. FIB-4, TE, and ultrasound are used in series to stratify patients, with a positive result in each test referring patients to further testing as shown in Figure 2.

For patients without cirrhosis, previous modelling studies have found that regular surveillance using ultrasound would not be cost-effective in most circumstances.[41] Additionally, ultrasounds require trained sonographers, but Australia is experiencing a

shortage of sonographers alongside an increase in demand. By using more affordable and simple procedures to exclude patients with low risk, more effective and efficient surveillance can be provided.

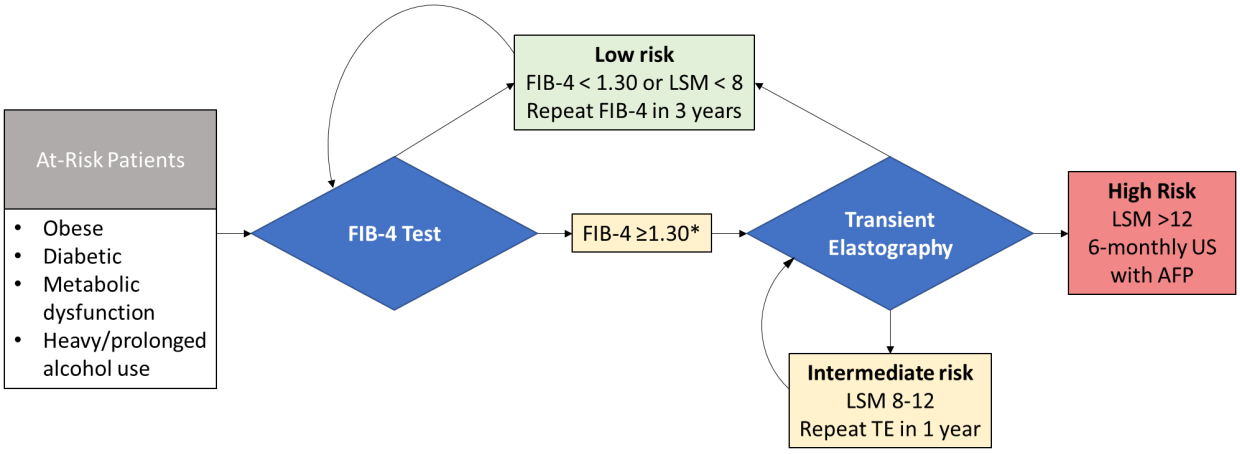
Surveillance for MAFLD and ARLD patients was modelled via the following algorithm:

- FIB-4 testing every 3 years for patients identified as high-risk (i.e. likely MAFLD patients)
- annual TE for patients with a positive FIB4 test, with patients with a negative test returning to 3-yearly FIB4 and patients with an inconclusive test returning to TE annually;
- 6-monthly ultrasound surveillance with alpha-fetoprotein (AFP) testing for patients with positive TE, until age 80 or death (whichever occurs first).

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.[32–34] Providing 6-monthly ultrasound for patients with likely cirrhotic liver is in line with GESA recommendations for cirrhotic patients[35] and the recently developed liver cancer guidelines. By triaging surveillance in this way, costs and resources can be managed and patients can be spared unnecessary surveillance burden, and inferred fibrosis/cirrhosis stage is used as an indicator of patient risk level. This will be referred to as "routine HCC surveillance" throughout, or "FIB4-stratified surveillance" where the distinction is necessary. This is illustrated in Figure 2 and Table 5.

As a supplementary analysis, we also estimated the differing cost-effectiveness of routine HCC surveillance by age of surveillance initiation, and by surveillance stop age.

Figure 2 – Modelled surveillance algorithm for patients at risk of developing hepatocellular carcinoma (HCC). LSM: liver stiffness measurement. TE: transient elastography. US: ultrasound. LSM: liver stiffness measurement.



Results – MAFLD patients

Baseline health outcomes

Table 1 – Summary of key outputs for MAFLD patients with and without routine HCC surveillance (FIB-4 stratified) and/or once-off weight loss.

	No intervention	Routine HCC surveillance	Weight loss	Weight loss and routine HCC surveillance
Lifetime HCC incidence per 100,000	3,051	3,051	2,298	2,298
Reduction vs no intervention	-	0%	24.7%	24.7%
HCC stage at diagnosis (% early/intermediate/late)	46/24/29	69/14/16	46/24/29	67/15/17
Lifetime HCC mortality per 100,000	2,112	1,730	1,564	1,306
Reduction vs no intervention	-	18.1%	25.9%	38.2%
Mean patient lifetime costs*	$42,105	$43,879	$39,373	$40,864

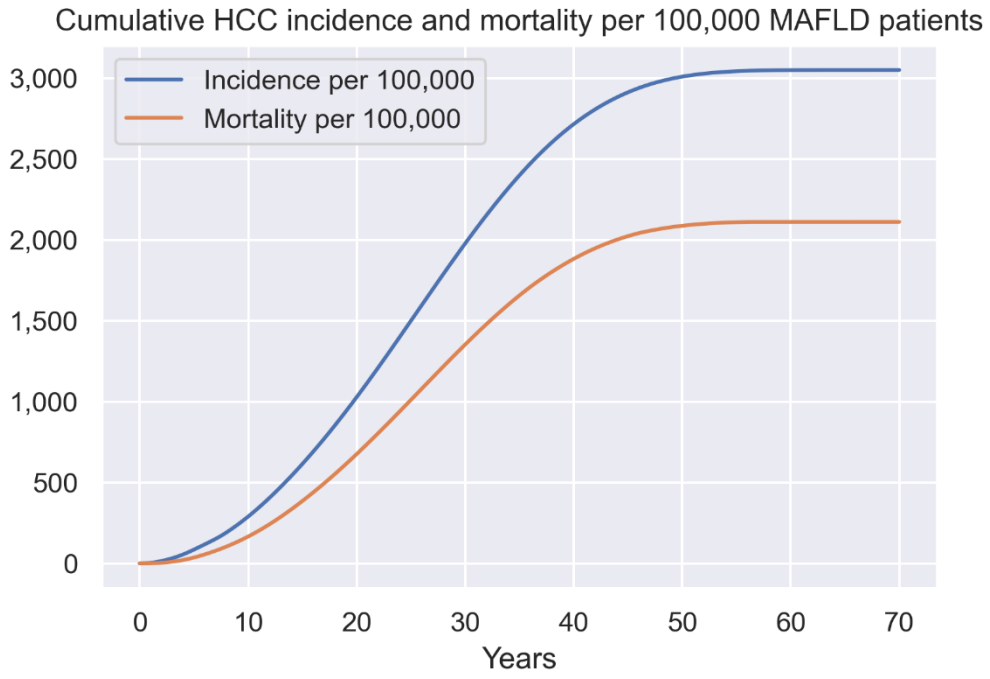
**Including cirrhosis care costs, HCC diagnosis costs, HCC treatment costs, and end-of-life costs. Does not including costs or non-HCC related savings associated with weight loss, or costs associated with identifying potential high-risk patients.*

Without any intervention, estimated lifetime HCC incidence would be 3,051 per 100,000 MAFLD patients in the modelled cohort, and with an estimated lifetime HCC mortality of 2,112 per 100,000 (

Table *1*, Figure 3). Without intervention, 46% of HCC diagnoses would be early stage cancers (BCLC stage 0/A), where curative treatment is significantly more likely, and 24% would be at the intermediate stage (BCLC stage B), with the remainder late stage cancers (BCLC stage C/D) (Figure 4).

Over the lifetime of the modelled cohort, the average liver-disease and HCC-related cost per MAFLD patient would be $42,105, including potential ongoing cirrhosis care costs, HCC diagnosis costs, HCC treatment costs, and end-of-life costs.

Figure 3 – Cumulative HCC incidence and mortality per 100,000 MAFLD patients in the modelled cohort with no intervention.



Routine HCC surveillance

By providing routine HCC surveillance to MAFLD patients, lifetime HCC mortality risk can be reduced by 23.6% vs to the "no intervention" comparator to 1,730 per 100,000 in the modelled cohort (Figure 5). This would be achieved through detection of HCC at earlier stages with higher chances of curative treatment. Overall, with routine HCC surveillance, 69% of HCC diagnoses would be at early stages (Figure 4).

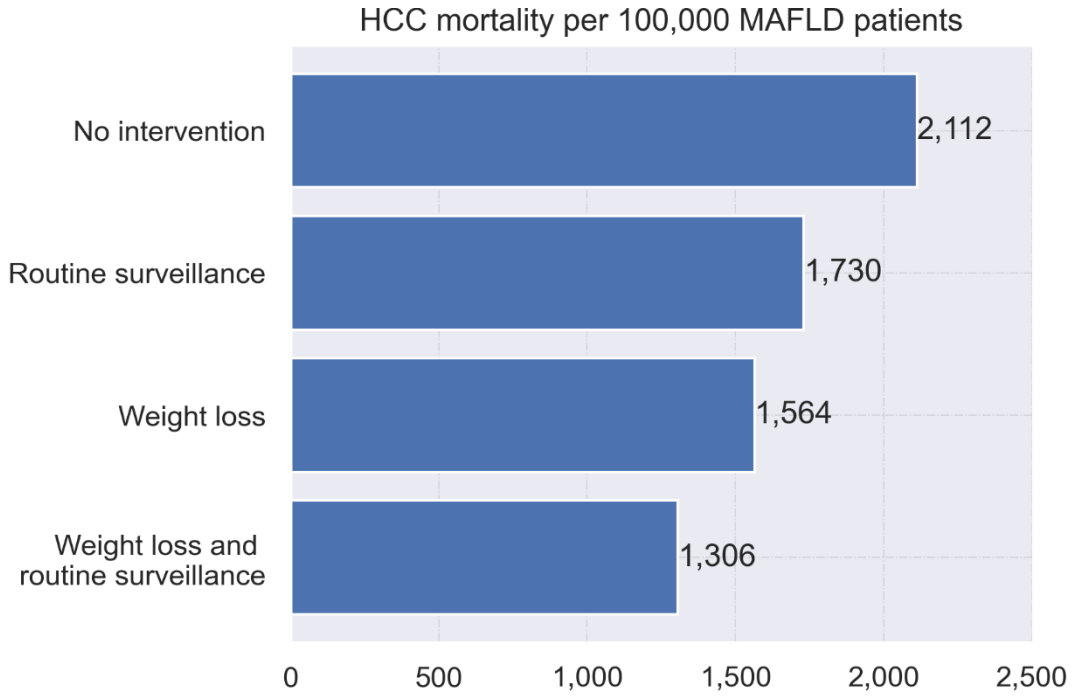
Over the lifetime of the modelled MAFLD cohort receiving routine HCC surveillance, the average cost per patient would be $43,879, including ongoing potential ongoing cirrhosis care costs, HCC diagnosis costs, HCC treatment costs, end-of-life costs, and the cost of surveillance including FIB4, TE, and ultrasound testing, and associated GP and specialist visit costs. This is an 4.2% increase vs the no surveillance scenario.

Weight loss

In the once-off weight loss scenario described above, lifetime HCC mortality risk in the modelled MAFLD cohort would be reduced by 25.9% vs to the "no intervention" comparator to 1,564 per 100,000 (Figure 5), through both HCC prevention and diagnosis at earlier stages (Figure 4). By additionally providing routine HCC surveillance to the cohort after once-off weight loss, HCC mortality risk would be reduced further to 1,209 per 100,000 (Figure 5), a 42.7% reduction vs the comparator.

Figure 4 - Stage at diagnosis among MAFLD patients diagnosed with HCC. Top to bottom: no intervention, routine HCC surveillance, weight loss, weight loss and routine HCC surveillance. "Weight loss" refers to temporary liver disease regression due to once-off weight loss of ≥10% patient weight. "HCC averted" refers to HCC cases that would have occurred in the absence of weight loss (i.e. in the "no intervention" scenario).

Figure 5 - Estimated HCC mortality per 100,000 MAFLD patients over patient lifetime. "Weight loss" refers to once-off weight loss of at least 10% of body mass.



Cost-effectiveness of routine HCC surveillance and/or weight loss in MAFLD patients

To determine the budget impact of providing routine HCC surveillance with and without weight loss interventions, we completed a cost-effectiveness analysis. This analysis calculated the costs associated with saving a quality-adjusted life-year in the modelled cohort. The main results are shown in Table 2.

Table 2 - Cost-effectiveness of surveillance and weight loss interventions in the modelled MAFLD cohort.

	No intervention	Routine HCC surveillance	Weight loss	Weight loss and routine HCC surveillance
Mean QALE (undiscounted)	27.2086	27.2738	27.653	27.6954
Mean QALE (discounted)	14.0572	14.0743	14.2194	14.2298
Additional discounted QALYs vs no intervention	-	0.0171	0.1622	0.1726
Mean costs (undiscounted)	$42,105	$43,878	$39,373	$40,864
Mean costs (discounted)	$13,537	$14,529	$12,050	$12,858
Additional discounted costs vs no intervention	-	$992	-$3,972	-$678
CER vs no intervention	-	$58,026.90	Cost-saving	Cost-saving

QALE: Quality-adjusted life expectancy. QALY: Quality-adjusted life year. CER: Cost-effectiveness ratio. Discounting at 5% rate.

Providing routine HCC surveillance to MAFLD patients would save 0.0171 QALYs per person. Although this may seem like a small benefit, the proportion of MAFLD patients who would develop HCC is relatively small, and in patients who do not develop HCC there is no benefit to surveillance. This is reflected in the relatively small additional cost associated with routine HCC surveillance of $992 per patient – primarily caused by the additional cost of providing surveillance, as well as differences in HCC treatment costs for patients diagnosed at earlier stages (where curative treatment is more likely).

Once-off weight loss interventions, where patients lose 10% of their body mass at time of MAFLD diagnosis and have no further weight loss activities, would increase patients' QALE by 0.1622. This is a significant increase, primarily driven by the immediate impact of weight loss interventions on health outcomes (unlike surveillance interventions, where the impact is only actualised upon diagnosis of HCC). Once-off weight loss would reduce liver-disease related costs by $3,972 compared to no intervention; if this were combined with routine HCC surveillance, patient costs would still be $678 lower than no intervention.

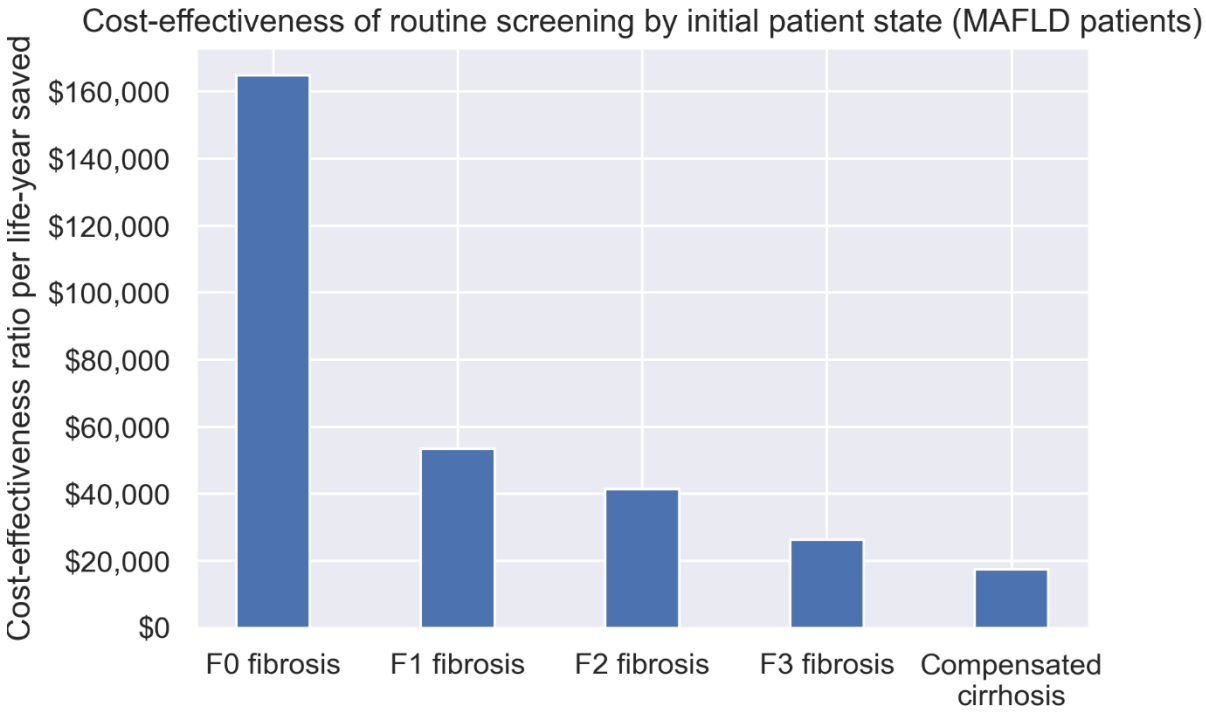
As this analysis focuses on HCC, it should be noted that this does not capture any costs, savings, or additional health benefits associated with weight loss. Overweight and obesity is a major determinant of many health outcomes, not just liver disease, and is a key health concern in Australia.[42,43] The outcomes presented here are naturally through a narrow lens. Note that we also cannot capture any potential expenses associated with weight loss, such as the use of medication.

The cost-effectiveness ratio for providing routine HCC surveillance along would be $58,027 per QALY saved – above the typically cited willingness-to-pay thresholds of $30,000 or $50,000 per QALY saved used in Australia. This implies that, in isolation, routine HCC surveillance would not be considered cost-effective. However, paired with even limited weight loss interventions, routine HCC surveillance would likely be cost-effective. In fact, if investment of up to $5,856 per MAFLD patient was made to assist with weight loss, routine HCC surveillance would remain under the $30,000/QALY saved threshold used for prevention interventions in Australia.

Cost-effectiveness of routine HCC surveillance in MAFLD by liver disease status

To determine the relative benefit of routine HCC surveillance by initial liver disease state (fibrosis/cirrhosis), the cost-effectiveness ratio was calculated for patients in each state at initial surveillance event. The results are shown in Figure 6. The cost-effectiveness ratio was very high for patients with F0 fibrosis ($164,851 /QALY saved), likely as these patients are less likely to progress to HCC. Surveillance was under the $50,000/QALY saved willingness-to-pay threshold for F2 fibrosis, F3 fibrosis, and cirrhotic patients, and under the $30,000/QALY saved threshold for F3 fibrosis and cirrhotic patients. This indicates that surveillance is likely to be more cost-effective if surveillance is not recommended for patients with no fibrosis or low levels of fibrosis, or delayed until more significant fibrosis has developed. However, affordable tests such as FIB4 cannot accurately discriminate between early stages of fibrosis, so patients cannot be safely excluded.

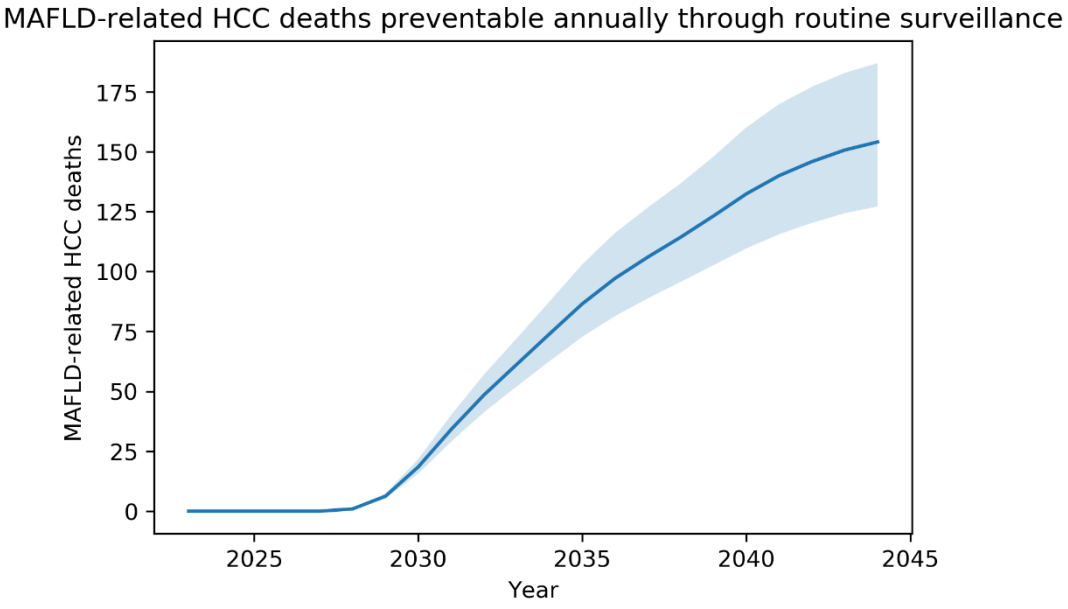
Figure 6 - Cost-effectiveness of routine HCC surveillance (FIB4 stratified) in MAFLD patients, stratified by the patient's liver disease at baseline.



Preventable MAFLD-related HCC deaths in Australia

By combining the above estimates of the impact of surveillance and/or weight loss with estimates of the prevalence of MAFLD and projections of MAFLD-related HCC deaths, we estimated the number of MAFLD-related HCC deaths in Australia that could potentially be prevented in Australia by prevention measures implemented from 2023.

Figure 7 – Estimated maximum number of annual MAFLD-related HCC deaths which could be prevented through providing routine HCC surveillance to all Australian MAFLD patients from 2023. Shaded area: 95% confidence interval, based on projections of liver cancer deaths in Australia.



By 2045, an estimated maximum 150 MAFLD-related HCC deaths could be prevented annually through routine HCC surveillance in Australia (Figure 7) – this is likely to continue to increase past 2045, as long-term participation in routine HCC surveillance increases the likelihood of early detection of HCC (see *Appendix 3 - Additional analyses*).

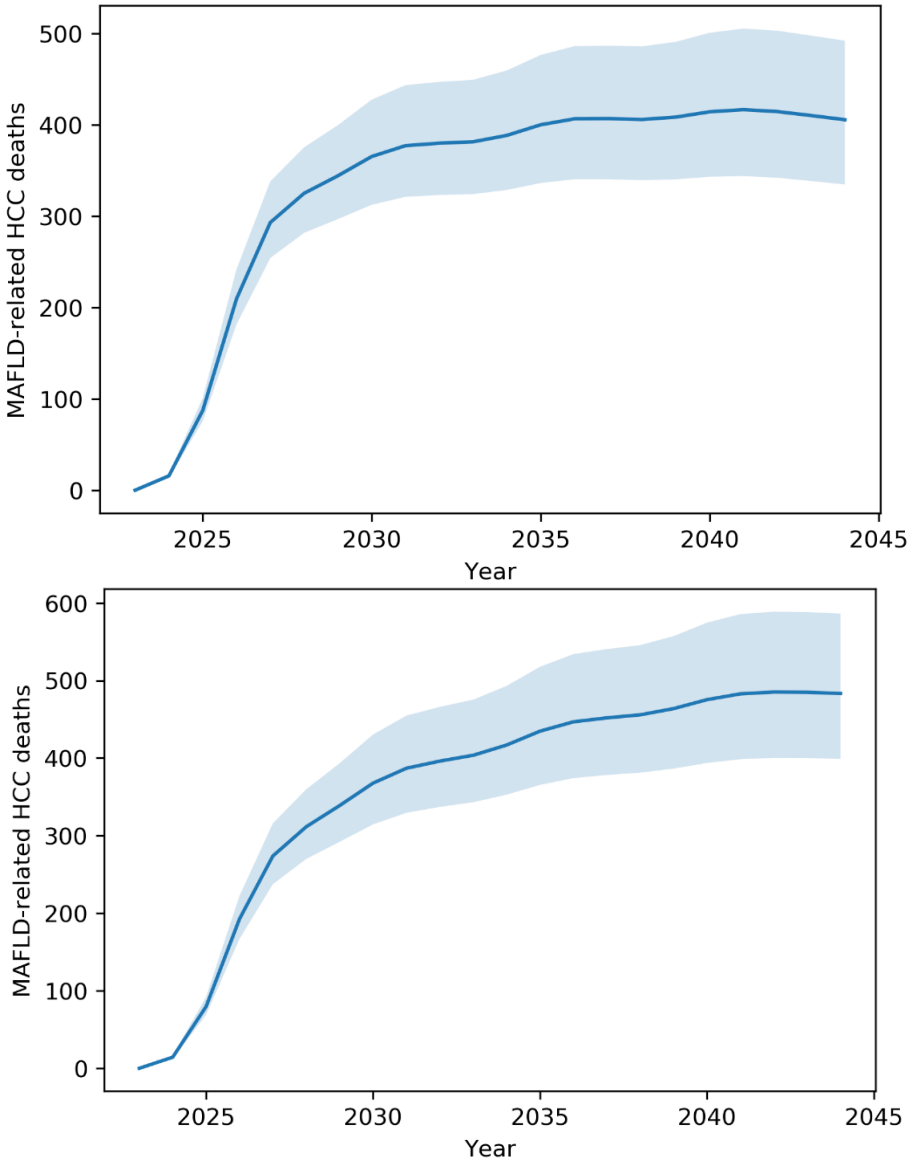
By 2045, an estimated maximum 417 MAFLD-related HCC deaths could be prevented annually in Australia (Figure 8) if all MAFLD-patients undergo a 10% weight reduction in 2023 or at age 40, whichever occurs first. If this was combined with routine HCC surveillance, this would increase to 485. Weight loss would have a faster short-term impact than routine HCC surveillance, as it delays or prevents patient progression to HCC; the benefits of routine HCC surveillance only manifest when the patient develops HCC.

It should be emphasised that this analysis only provides an estimate of how many HCC deaths are potentially preventable in Australia through weight loss or routine HCC surveillance. There are significant difficulties associated with not only identifying patients with MAFLD but also implementing surveillance and/or weight loss interventions. The numbers included here should be interpreted with caution and proper context.

Additional analyses

Further analysis for the MAFLD cohort were completed and are detailed in Appendix 3. In short, these analyses found that surveillance was more effective if started at younger ages, and that surveillance was most cost-effective if it stopped after age 80, due to lower life-expectancies past this age. Six-monthly ultrasound surveillance was found to have similar health impact as stratified FIB-4 surveillance but would have much higher costs and be highly inefficient.

Figure 8 - Estimated maximum number of annual MAFLD-related HCC deaths which could be prevented through once off 10% weight loss in all Australian MAFLD patients in 2023. Top: without additional routine HCC surveillance. Bottom: with additional routine HCC surveillance. Shaded area: 95% confidence interval, based on projections of liver cancer deaths in Australia.



Results –ARLD Patients

The results in this section refer to an indicative cohort with AUD, with distribution of liver status according to Huang et al and Delacote et. al. (see Appendix 1 for specific weightings).[12,44] These outcomes assume all patients continue to have AUD unless otherwise stated.

Baseline health outcomes

Table 3 – Summary of key outputs for ARLD patients with and without routine HCC surveillance (FIB-4 stratified).

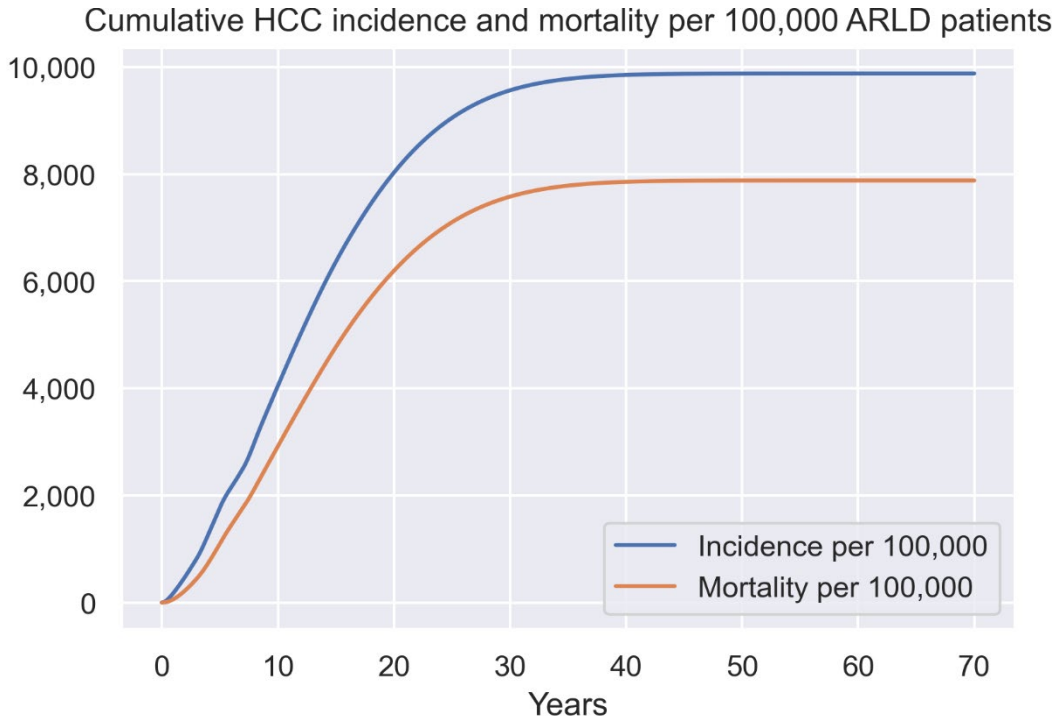
	No intervention	Routine HCC surveillance
Lifetime HCC incidence per 100,000	9,881	9,881
HCC stage at diagnosis (% early/intermediate/late)	33.6/15.6/50.9%	62.0/7.0/31.0%
Lifetime HCC mortality per 100,000	7,883	6,415
Reduction vs no intervention	-	18.6%
Mean patient lifetime costs*	$113,930	$115,981

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

Without any intervention, estimated lifetime HCC incidence would be 9,881 per 100,000 ARLD patients in the modelled cohort, and with an estimated lifetime HCC mortality of 7,883 per 100,000 (Table 3, Figure 9). Without intervention, 33.6% of HCC diagnoses would be early-stage cancers (BCLC stage 0/A), where curative treatment is significantly more likely, and 15.6% would be at the intermediate stage (BCLC stage B), with the remainder late-stage cancers (BCLC stage C/D) (Figure 10).

Over the lifetime of the modelled cohort, the average liver-disease and HCC-related cost per ARLD patient would be $113,930, including potential ongoing cirrhosis care costs, HCC diagnosis costs, HCC treatment costs, and end-of-life costs. Note that this does not include other AUD-related costs.

Figure 9 - Cumulative HCC incidence and mortality per 100,000 ARLD patients in the modelled cohort with no intervention.



Routine HCC surveillance

By providing routine HCC surveillance to ARLD patients, lifetime HCC mortality risk can be reduced by 18.6% vs to the "no intervention" comparator to 6,415 per 100,000 in the modelled cohort (Figure 11). This would be achieved through detection of HCC at earlier stages with higher chances of curative treatment. Overall, with routine HCC surveillance, 62% of HCC diagnoses would be at early stages (Figure 10). Note that the modelled cohort includes a significant proportion (32%) of patients with decompensated cirrhosis,[12] for whom surveillance is not recommended.[35]

Over the lifetime of the modelled ARLD cohort receiving routine HCC surveillance, the average cost per patient would be $113,930; this is primarily ongoing cirrhosis care costs, as well as HCC diagnosis costs, HCC treatment costs, end-of-life costs, and the cost of surveillance including FIB4, TE, and ultrasound testing, and associated GP and specialist visit costs. This is an 1.8% increase compared to the no surveillance scenario.

Figure 10 - Stage at diagnosis among ARLD patients diagnosed with HCC. Top: no intervention. Bottom: routine HCC surveillance.

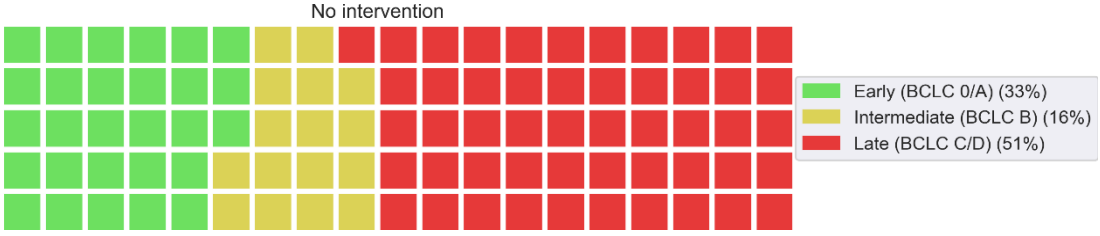
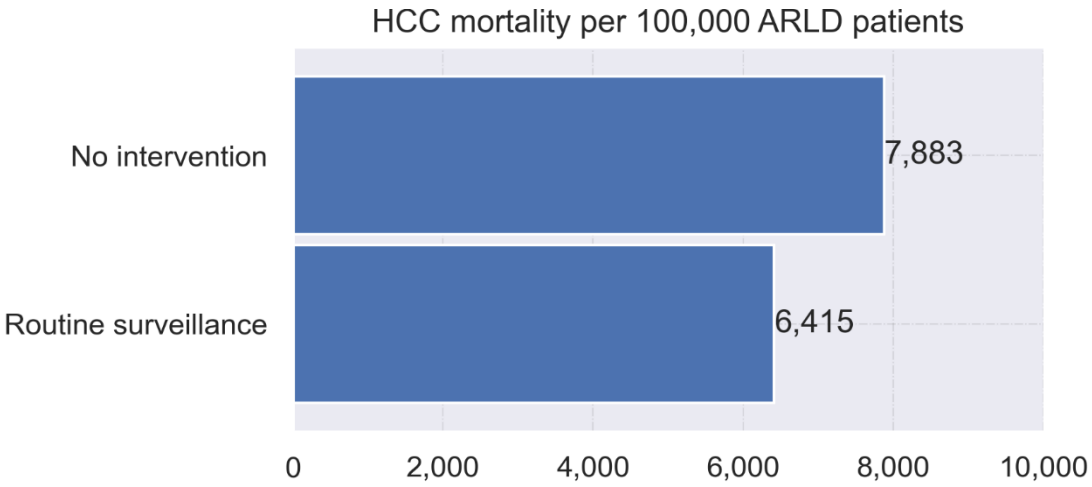


Figure 11 - Estimated HCC mortality per 100,000 ARLD patients over patient lifetime.



Cost-effectiveness of routine HCC surveillance in ARLD patients

To determine the budget impact of providing routine HCC surveillance to ARLD patients, we completed a cost-effectiveness analysis. The main results are shown in Table 4.

Table 4 - Cost-effectiveness of surveillance in the modelled ARLD cohort.

	No intervention	Routine HCC surveillance
Mean QALE (undiscounted)	8.6295	9.5831
Mean QALE (discounted)	5.5637	5.7271
Additional discounted QALYs vs no intervention	-	0.1634
Mean costs (undiscounted)	$113,930	$115,981
Mean costs (discounted)	$76,925	$78,854
Additional discounted costs vs no intervention		$1,929
CER vs no intervention		$11,809

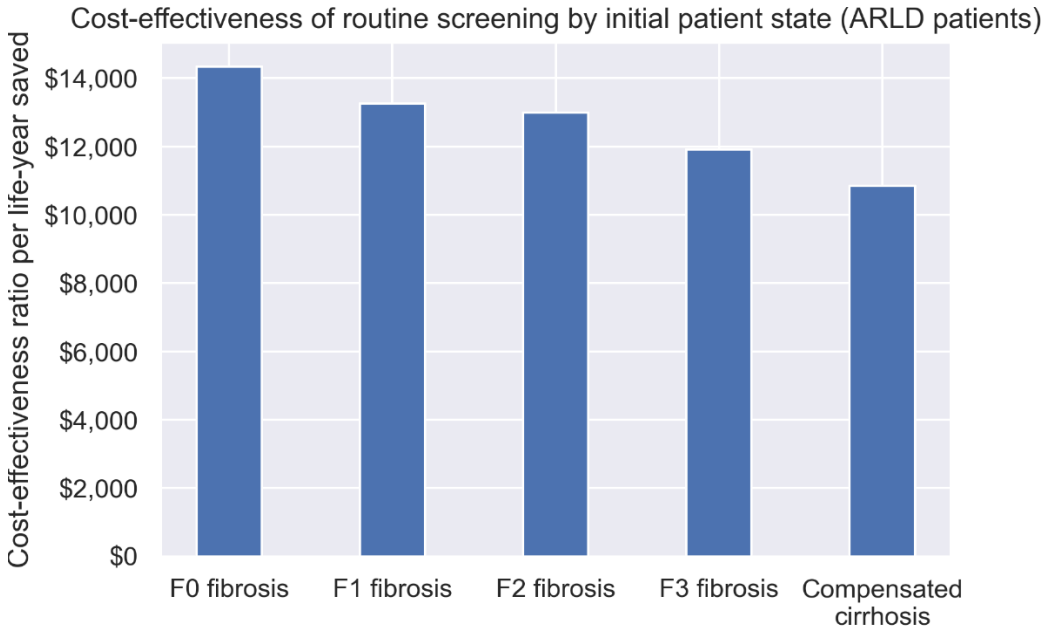
QALE: Quality-adjusted life expectancy. QALY: Quality-adjusted life year. CER: Cost-effectiveness ratio. Discounting at 5% rate.

Providing routine HCC surveillance to ARLD patients would save 0.1634 discounted QALYs per person with an additional discounted cost of $1,929 per patient. The cost-effectiveness ratio for providing routine HCC surveillance along would be $11,809 per QALY saved, below the typical $30,000/QALY and $50,000/QALY willingness-to-pay thresholds used.

Cost-effectiveness of routine HCC surveillance in ARLD patients by initial liver disease state

To determine the relative benefit of routine HCC surveillance by initial liver disease state (fibrosis/cirrhosis), the cost-effectiveness ratio was calculated for patients in each state at initial surveillance event. The results are shown in Figure 12. The cost-effectiveness was similar in all patients, likely due to the quick onset of serious liver disease in ARLD patients. The cost-effectiveness ratio was least favourable for patients with F0 fibrosis ($14,337/QALY saved), and most favourable for patients with compensated cirrhosis ($10,854/QALY saved), though surveillance was less than the $30,000/QALY saved willingness-to-pay threshold for all modelled patients.

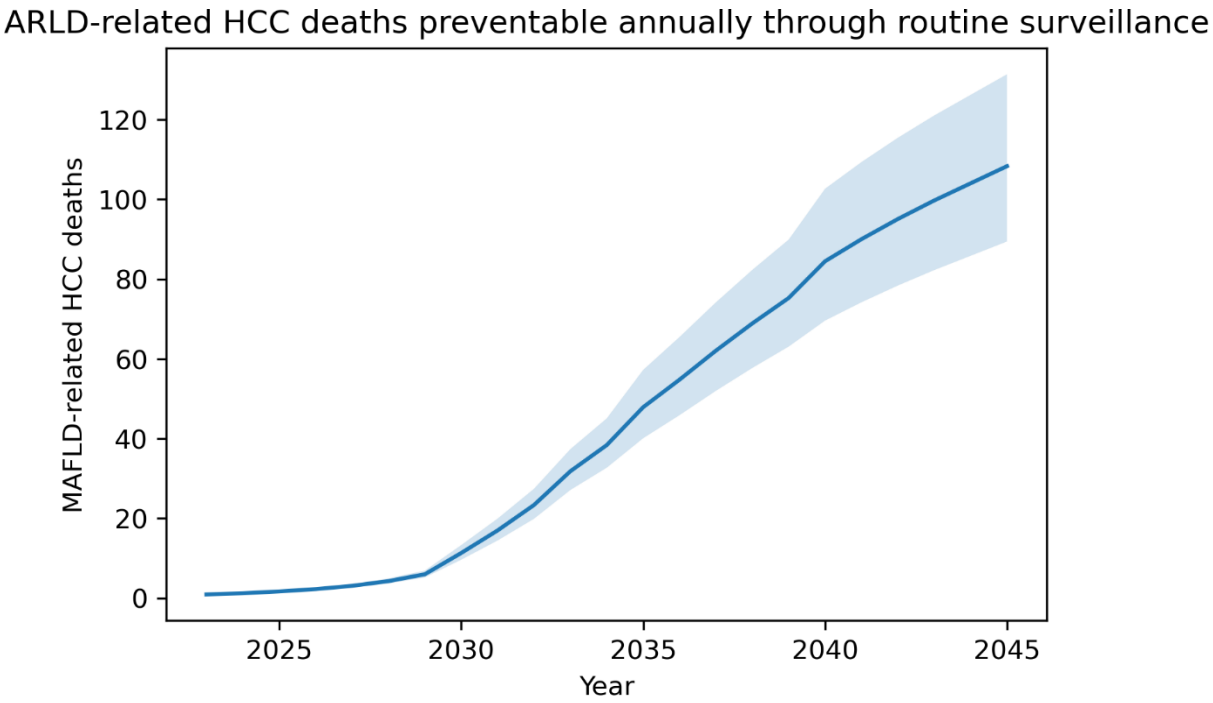
Figure 12 – Cost-effectiveness of routine (FIB4 stratified) screening in ARLD patients, stratified by the patient's liver disease at baseline.



ARLD-related HCC Deaths preventable through surveillance

By combining the above estimates of the impact of surveillance with projections of ARLD-related HCC deaths, we estimated the number of ARLD-related HCC deaths in Australia that could potentially be prevented in Australia by routine HCC surveillance implemented from 2023.

Figure 13 - Estimated maximum number of annual ARLD-related HCC deaths which could be prevented through providing routine HCC surveillance to all Australian ARLD patients from 2023. Shaded area: 95% confidence interval, based on projections of liver cancer deaths in Australia.



By 2045, an estimated maximum 108 ARLD-related HCC deaths could be prevented annually through routine HCC surveillance in Australia (Figure 13) – this is likely to continue to increase past 2045, as long-term participation in routine HCC surveillance increases the likelihood of early detection of HCC.

Alcohol abstinence and mortality rates in ARLD patients

Based on the available literature, we completed an exploratory analysis of the potential impact of alcohol abstinence on mortality rates in ARLD patients, and the use of surveillance in a cohort of ARLD patients who are abstinent from alcohol use. However, data regarding these cohorts are sparse, and so the analysis is limited and must be interpreted with caution.

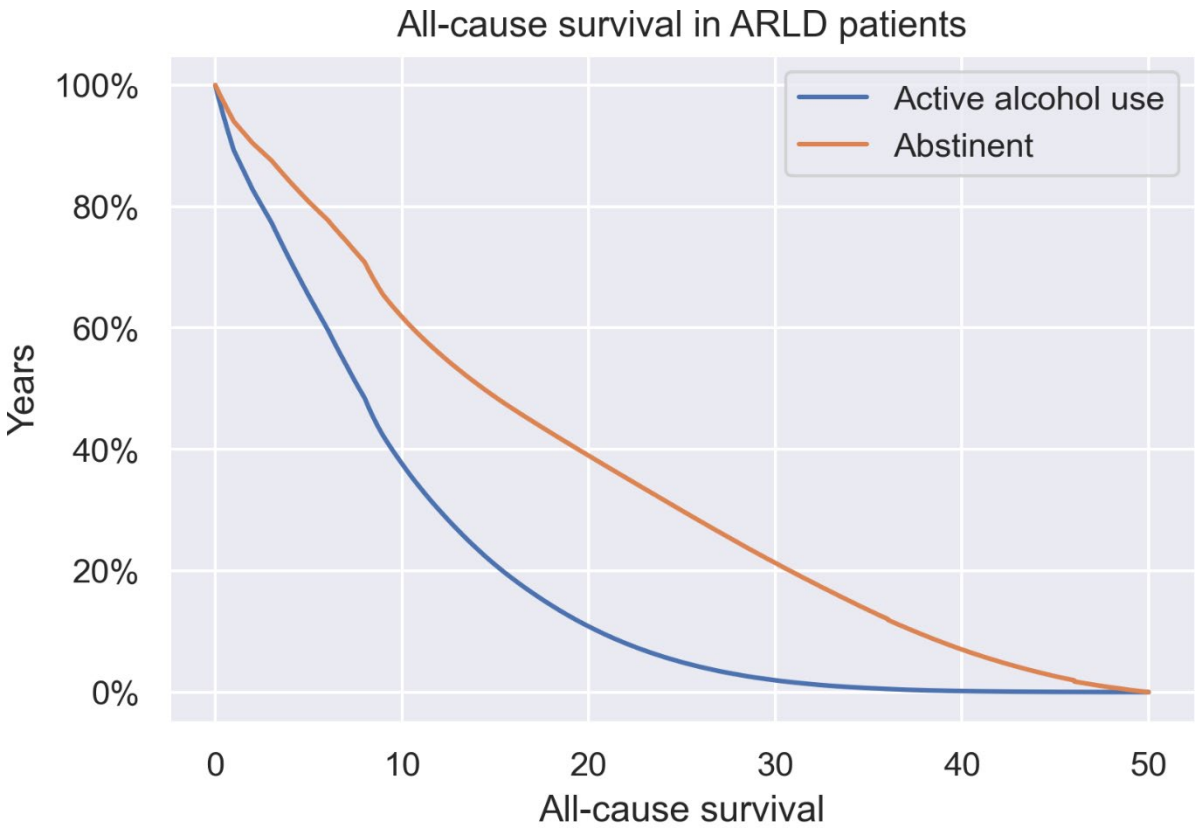
It is widely considered that most fibrosis will regress quickly after alcohol cessation, with (for example) 58.6% of F2 fibrosis regressing to F0 (no fibrosis) or F1 within seven days of sobriety.[29] For this reason, our analysis assumed that total cessation of alcohol use led to total regression of all pre-cirrhotic fibrosis.

Currently, there is limited evidence to support the regression of cirrhotic liver, even after alcohol cessation, though this is a controversial point.[45] However, decompensation rates are known to significantly slow after alcohol cessation, as well as all-cause mortality rates in cirrhotic patients.[46] Unfortunately, there was no change to HCC rates recorded in cirrhotic patients after alcohol cessation, though there are no sufficiently large studies to be confident of this. The improvements in decompensation rates and all-cause mortality in cirrhotic patients after alcohol cessation were incorporated into our modelling.

In a weighted cohort (including patients with fibrosis, compensated cirrhosis, and decompensated cirrhosis) with current or previous ARLD but with no active alcohol use, 10-

year all-cause survival was 61.8%, vs a 10-year all-cause survival of 37.6% in patients with active alcohol use (Figure 14). Abstinence from alcohol would nearly double the quality-adjusted life expectancy in the modelled cohort from 8.630 QALYs to 17.110 QALYs.

Figure 14 – All-cause survival in ARLD patients with and without continuing alcohol use.



Providing routine HCC surveillance to cirrhotic patients in the cohort with no active drinking would increase the quality-adjusted life expected by a further 5.24% to 18.008 years. This would have a cost-effectiveness ratio of $9,606/QALY saved, and would be cost-effective using the $30,000/QALY saved willingness-to-pay threshold. Providing ongoing surveillance to patients who without cirrhosis who are abstinent would likely have little benefit, as their liver disease is unlikely to progress.

As these survival improvements are not HCC deaths prevented but other mortality causes (according to the available data), it is not possible within the scope of this project to estimate these changes at a population level for Australia. However, decreases in alcohol use are likely to lead to widespread increases in both life expectancy and quality of life,[47] as well as the improvements in liver-related deaths estimated above.

Discussion

This study highlighted the potential for preventing MAFLD- and ARLD-related HCC in Australia, through primary and secondary prevention. As liver cancer rates and overweight and obesity rates continue to rise in Australia, ongoing research and clearer understanding in these areas is crucial.

The use of routine HCC surveillance for high-risk patients with suspected MAFLD or ARLD is a relatively new field, with Australian GPs and hepatologists primarily working to guidelines developed for other contexts and cohorts. This study demonstrates that the use of non-invasive technologies to monitor for HCC can be effective in Australian patients and would be nearly as effective as ultrasound surveillance in preventing HCC deaths while being more affordable and less burdensome for patients. As new technologies to stratify high- and low-risk patients are developed, we can assess their optimal use in diagnosis. A key component of the acceptability and cost-effectiveness of surveillance is successfully identifying low-risk patients who have little to no need for short-term surveillance. As the MAFLD population in Australia grows, identifying these patients will be key to keeping surveillance manageable and reducing the burden on ultrasonography services.[48]

A key finding of our study is on the importance of identifying high-risk patients as early as possible; our study found that the earlier patients enter routine HCC surveillance, the more cost-effective it would be. Conversely, we found that providing surveillance past age 80 would be less cost-effective and is unlikely to be a good use of resources.

We found that once-off weight loss of 10% of body mass would significantly reduce HCC risk in the MAFLD population. It is likely that ongoing weight loss would further reduce HCC risk; however, there is not currently sufficient data to inform this. Current Australian government targets aim to halt the increase in obesity and overweight rates in Australia;[49] this would correspondingly limit increasing trends in MAFLD rates.

As weight loss affects many dimensions of health, not just liver disease, the findings of this study could be used in a broader context to study the overall impact of weight loss, including increases in life expectancy and quality of life, as well as the associated economic impact.[42,43] Similarly, the impact of alcohol abstinence on ARLD patients are a small piece of the extensive evidence on the benefits of sobriety. Alcohol use trends are decreasing in Australia;[47] however, the COVID-19 significantly shifted drinking patterns in many Australian.[50] Ongoing monitoring of alcohol use and ARLD prevalence in the Australian population is crucial.

In the two groups studied, mean costs were higher in ARLD patients than MAFLD patients. This reflects higher rates of cirrhotic liver in ARLD patients. Surveillance was more cost-effective in ARLD patients, due to the higher likelihood of HCC. Ideally, future studies would analyse patients with alcohol use and metabolic factors – however, data for subgroups with overlapping aetiologies are difficult to obtain.

Our analysis found that surveillance was most effective and cost-effective in patients with more advanced fibrosis or cirrhosis, as these patients are at the highest risk of developing

HCC. Future studies must investigate potential strategies to exclude low-risk patients from surveillance,[51] or increase the interval between surveillance events. Additionally, lifestyle interventions such as weight loss and alcohol abstinence may lessen the need for surveillance; further research is required.

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Appendix 1 – Additional *Policy1-Liver* model details

Additional model information

We simulated the development of fibrosis, compensated cirrhosis, decompensated cirrhosis and/or HCC in patients with ARLD or MAFLD. Transitions between these states are illustrated in Figure 1, and parameters governing the rates of these transitions are listed in Table 6. Mortality rates for patients by liver disease state are given in Table 7.

Patient classification ("fibrosis", "compensated cirrhosis" etc) were based on the definitions used in the original studies, as noted in the parameter tables. For example, in Vilar-Gomez et al,(2) cirrhosis (F4 fibrosis) was confirmed by an independent histologic assessment upon trial recruitment, and a sample of the cohort were selected to assess the agreement of pathology diagnosis.

Progression and symptomatic detection rates for undiagnosed HCC are given in Table 8. Stage at diagnosis is given in Table 9. Patients with diagnosed HCC have their treatments, costs, and survival rates determined based on their stage at diagnosis. These are shown in Table 10, Table 14, and Table 15. Five-year survival is based on data from the NSW Cancer Registry (NSWCR), as this data is provided for a large local dataset and is relatively complete. For detailed survival, including survival by stage, year since diagnosis, and surveillance, reference data from Haq et al [52] was used for hazard ratios between groups.

Treatment costs include both primary treatment and any secondary follow-up procedures. The "primary" treatment is used to classify costs for each; these data were chosen as they are both locally relevant and based on real-world observations, rather than ideal treatment recommendations which may not reflect the complexities in practice. The primary treatments identified were liver transplant, liver resection, ablation (including RFA, MWA and PEI), TACE (including TACE with cisplantin, TACE with doxorubicin, and SIRT), and palliation/best supportive care. Costs relating to HCC treatment were classified according to the primary form of treatment, following the methodology from Hong et al.[53] This approach was chosen as these costs are the most inclusive of all additional costs during a patient's HCC treatment.

Patients who survive for five years after cancer diagnosis are then classified as HCC survivors and have no additional risk of developing HCC. For modelling purposes, recurrent HCC is assumed to occur within five years from the initial HCC diagnosis.

The characteristics of the modelled cohorts, including mean age and distribution of liver disease state at index are given in Table 12. The impact of weight loss or alcohol cessation are shown in Table 13.

All costs are reported in 2022 Australian dollars, with the health CPI index used to inflate costs where necessary.[54] Costs for individual surveillance and diagnostic procedures were collated from MBS Online.[55] For all costs and health state utilities, 5% annual discounting was applied. This reflects preference for short-term benefits over long-term benefits and is standard practice in health economic evaluations. Other costs include annual costs of cirrhosis care for patients with and without decompensation, and end-of-life costs for cancer

patients and non-cancer patients. To ensure relevance, all costs were identified from Australian sources.

The quality-adjusted life expectancy (QALE) was calculated for all patients. Disutilities were identified for patients with compensated and decompensated cirrhosis, and HCC patients. Disutilities for HCC patients were classified according to their phase of care: diagnostic/initial phase (first year post diagnosis), terminal phase (final year before death), and ongoing phase (any time between diagnostic phase and terminal phase/recovery). Data on disutilities are given in Table 15.

Routine HCC surveillance

The details of the algorithm used for HCC surveillance are given in Table 5 and illustrated in Figure 2. Parameter relating to surveillance (see algorithm in Table 5 and illustrated in Figure 2) are given in Table 11, including sensitivity, specificity, and positive rates for FIB-4, TE, and US by stage of disease. Costs associated with surveillance are given in Table 15.

Table 5 - Modelled surveillance algorithm for patients at risk of developing HCC.

Group	FIB-4 outcome	TE outcome	Recommendation
Low risk	FIB-4<1.30	Not recommended	Repeat FIB-4 in 3 years
	FIB-4≥1.30	LSM<8	
Intermediate risk	FIB-4≥1.30	8≤LSM≤12	Repeat TE in 1 year
High risk	FIB-4≥1.30	LSM≥12	Ultrasound with AFP every six months

FIB-4: Fibrosis-4. LSM: liver stiffness measurement. TE: Transient elastography.

Model calibration

Calibration is an essential step in developing epidemiological models to ensure the model accurately reflects the real-world data and can make reliable predictions. Calibration involves adjusting the model parameters to fit the observed data, such as the number of cases, deaths, and other relevant outcomes. This calibrated model can then be used to analyse the impact of changes to the calibrated baseline, such as modifications of risk factors or surveillance.

Policy1-Liver was calibrated to the best available data relating to liver disease, HCC outcomes, and surveillance in ARLD and MAFLD patients, as identified in the literature reviews describe in the main report. This ensure that estimates generated by *Policy1-Liver* are as accurate as possible. Calibrated model parameters are shown in Tables 6-15 and illustrated in Figures 15-22.

Figure 15 – Modelled likelihood of fibrosis progression in MAFLD patients by initial fibrosis stage and age. Targets shown are from Adams et al, 2020.[17] Note the increasing impact of the competing risk of all-cause mortality at older ages.

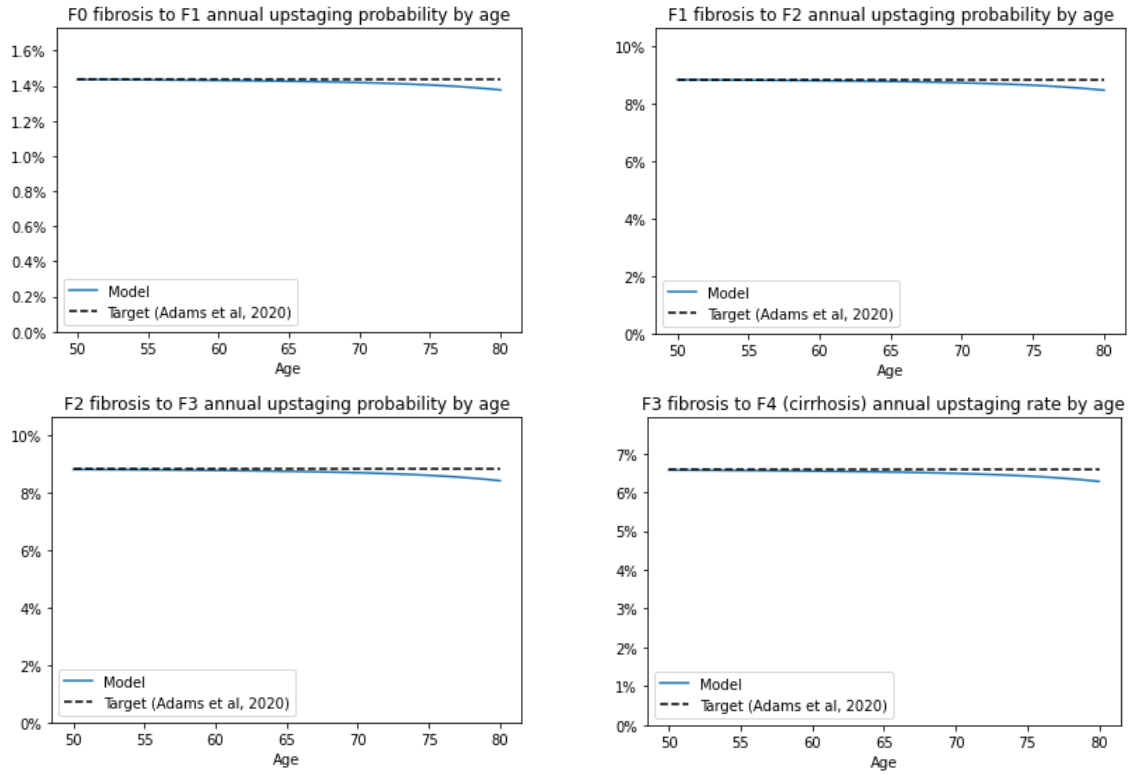


Figure 16 –Calibration targets for non-cirrhotic MAFLD patients. Top left: cumulative HCC risk in all MAFLD patients (including patients with and without fibrosis and/or cirrhosis in a cohort undergoing routine ultrasound surveillance).[12] Top right: cumulative risk of HCC in patients with stage F3 fibrosis.[56] Bottom left: cumulative all-cause mortality in MAFLD patients with fibrosis.[12] Bottom right: cumulative all-cause survival in MAFLD patients who had a low (< 1.3) FIB4 level at baseline.[57]

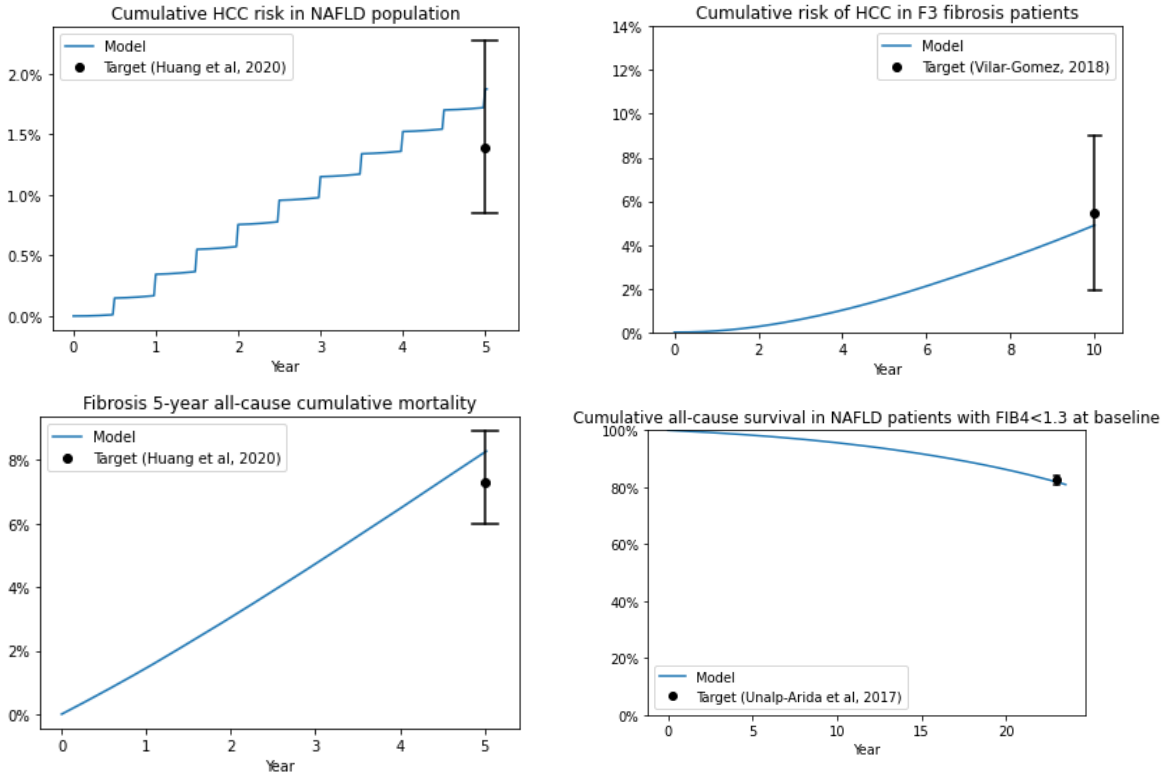


Figure 17 – Calibration targets relating to cirrhotic patients with MAFLD. Top left: cumulative HCC incidence in patients with cirrhotic MAFLD.[58] Top right: cumulative incidence of decompensation events in patients with cirrhotic liver.[56] Bottom: all-cause survival in patients with compensated (left) and decompensated (right) liver.[59]

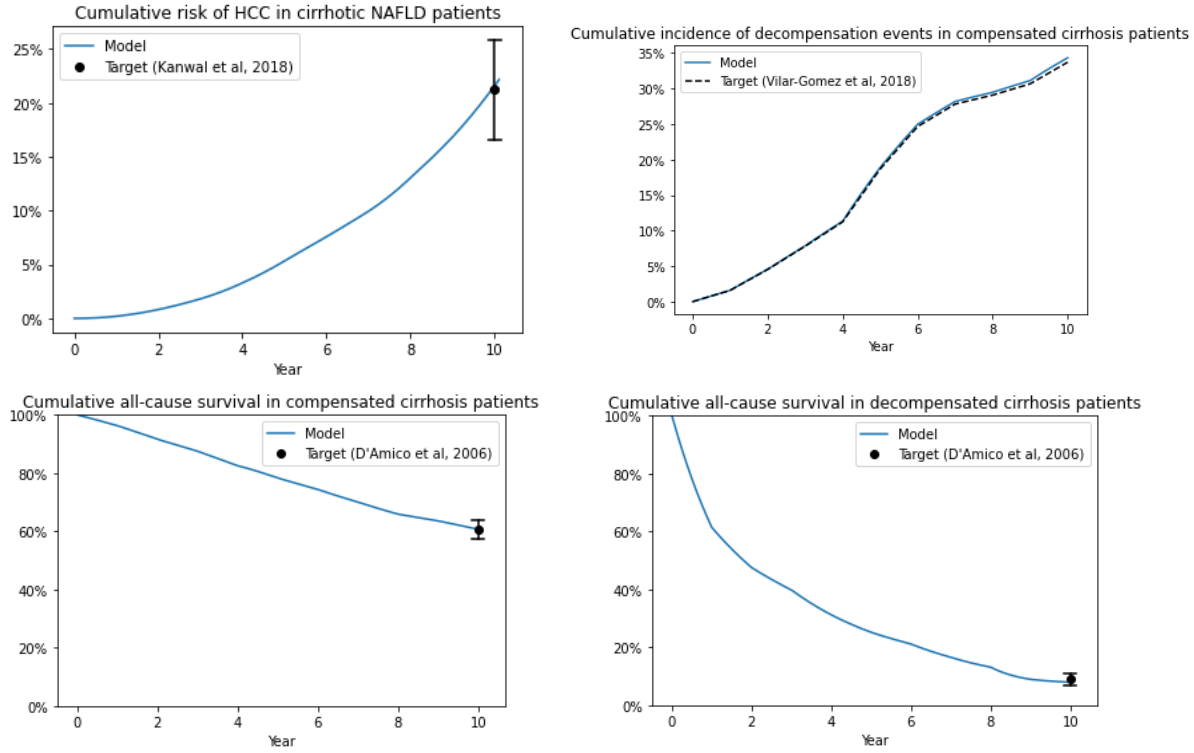


Figure 18 - Calibration targets relating to HCC diagnoses in MAFLD patients. Top left: cumulative proportion of HCC diagnoses occurring in the absence of cirrhosis.[8] Top right: cumulative incidence of HCC in all fibrosis patients, including patients with and without fibrosis and/or cirrhosis.[58] Bottom: HCC stage at diagnosis in MAFLD patients without (left) and with (right) regular ultrasound surveillance.[11]

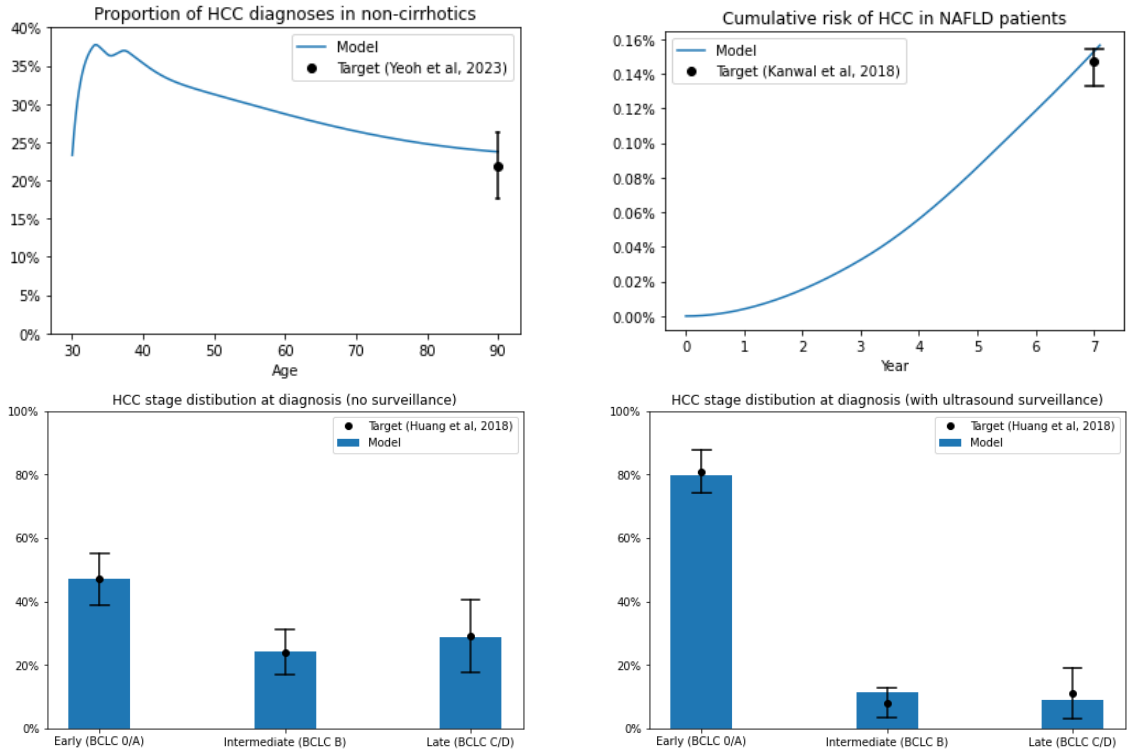


Figure 19 - Calibration targets relating to HCC diagnoses in ARLD patients - primary targets from Australian sources (Huang et al and Yeoh et al).[8,12] Top: five-year all-cause mortality (left) and HCC incidence (right) in Australian ARLD population (including patients with no fibrosis, fibrosis, and cirrhotic liver).[12] Bottom left: proportion of HCC diagnoses occurring in the absence of liver cirrhosis in ARLD patients.[8] Bottom right: HCC BCLC stage at diagnosis in ARLD patients.[8]

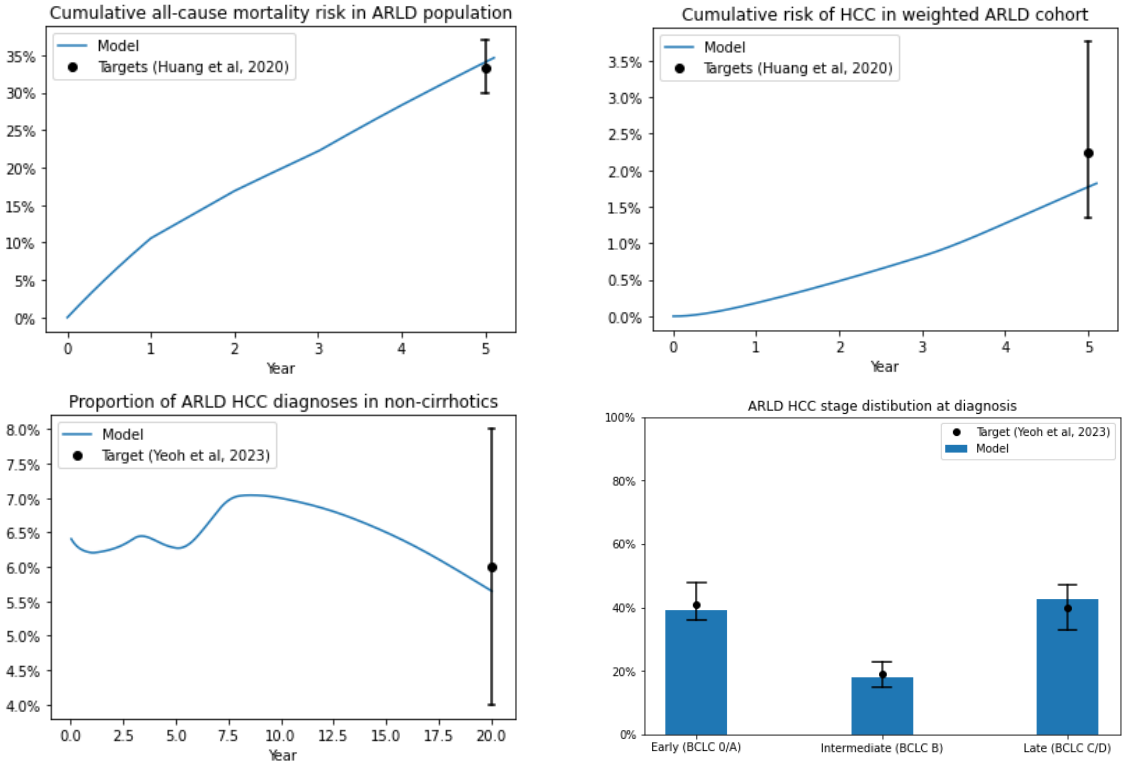


Figure 20 - Calibration targets relating to worsening liver disease in ARLD patients. Top left: cumulative incidence of cirrhosis in patients with no steatosis.[60] Top right: cumulative incidence of cirrhosis in patients with steatosis.[61] Bottom left: cumulative incidence of cirrhosis in patients with F1-F3 fibrosis.[60,62] Bottom right: cumulative incidence of decompensation events in patients with compensated cirrhosis.[12,62,63]

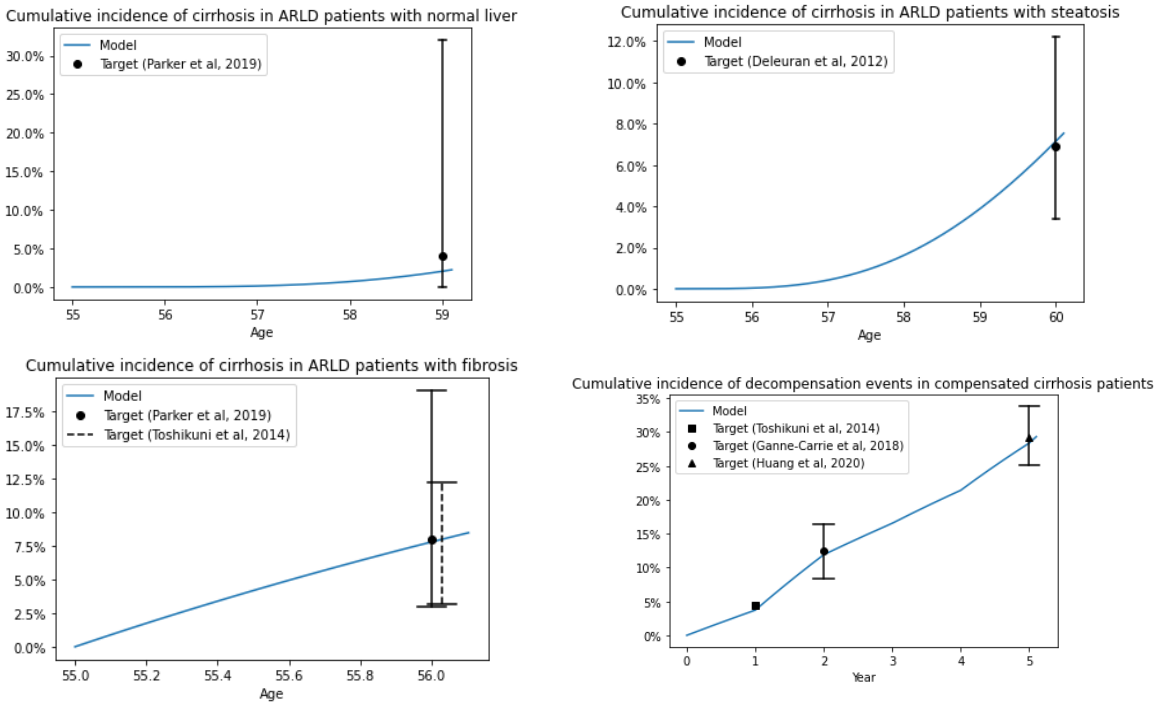


Figure 21 - Calibration targets relating to all-cause mortality in ARLD patients.[64] Top left: in patients with normal liver (no steatosis) at baseline. Top right: in patients with steatosis at baseline. Bottom left: in patients with fibrosis at baseline. Bottom right: in patients with cirrhosis at baseline (including compensated and decompensated – note this is five-year survival).

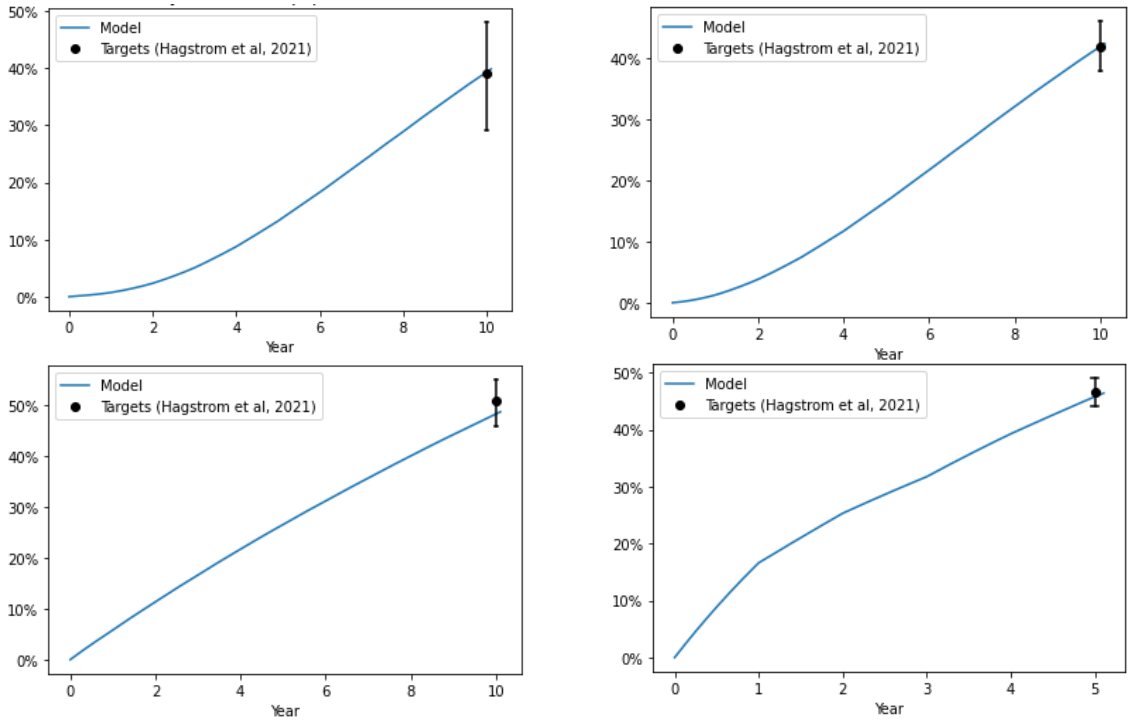
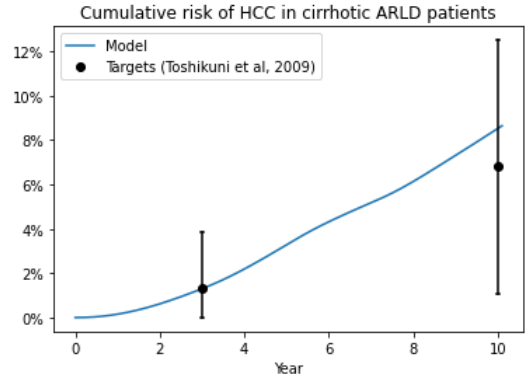
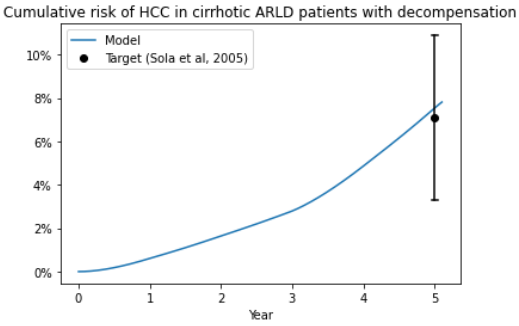


Figure 22 – Calibration targets for cumulative risk of HCC in all cirrhotic ARLD patients (left; includes patients with compensated and decompensated cirrhosis)[65] and compensated cirrhotic ARLD patients (right).[66]





Model parameters

Table 6 – Parameter table for liver disease progression.

Description	Value	Targets/source
ARLD progression		
Upstaging hazard rate for F0 fibrosis	0.217-0.290[1]	44,64
Upstaging hazard rate for F1-3 fibrosis	0.229-0.344	
5-year risk of decompensation for cirrhotic patients	28%	12,62,63
Hazard rate for progression from F3 fibrosis to HCC	0.00258	8
10-year risk of HCC for cirrhotic patients	8.4%	62
5-year risk of HCC for cirrhotic patients with decompensation	7.2%	66
MAFLD progression		
Upstaging hazard rate for F0 fibrosis	0.0145	17
Upstaging hazard rate for F1/2 fibrosis	0.0884	
Upstaging hazard rate for F3 fibrosis	0.0661	
10-year decompensation risk in patients with cirrhosis	34.20%	56
Hazard rate for progression from F3 fibrosis to HCC	0.0067	8
Incidence rate of HCC per 1,000 person-years	0.21	58

Table 7 – Parameter table for mortality rates for pre-cancer ARLD and MAFLD patients.

Description	Value	Targets/source
ARLD		
Relative risk of all-cause mortality in patients with fibrosis	11.3[2]	64
5-year risk of all-cause mortality for cirrhotic patients	46%	
MAFLD		
Relative mortality with F0-2 fibrosis	1[2]	11
Relative mortality with F3 fibrosis	1.15[2]	
Annual mortality with compensated cirrhosis	1.26%	59
Annual mortality with decompensated cirrhosis	9.44%	

[1] Varies by patient age.

[2] Reference group: general population with matched age.[67]

Table 8 – Parameter table for undiagnosed HCC.

Description	Value	Source
ARLD		
Upstaging hazard rate for undiagnosed early (BCLC 0/A) HCC in ARLD patients	0.254	Calibrated to targets[12]
Upstaging hazard rate for undiagnosed intermediate (BCLC B) HCC in ARLD patients	1.88	
Annual symptomatic/incidental detection rate for ARLD patients with undiagnosed early stage HCC	0.209	
Annual symptomatic/incidental detection rate for ARLD patients with undiagnosed intermediate stage HCC	1.17	
Annual symptomatic/incidental detection rate for ARLD patients with undiagnosed late stage HCC	1.49	
MAFLD		
Upstaging hazard rate for undiagnosed early (BCLC 0/A) HCC in MAFLD patients	0.225	Calibrated to targets[12]
Upstaging hazard rate for undiagnosed intermediate (BCLC B) HCC in MAFLD patients	1.23	
Annual symptomatic/incidental detection rate for MAFLD patients with undiagnosed early stage HCC	0.209	
Annual symptomatic/incidental detection rate for MAFLD patients with undiagnosed intermediate stage HCC	1.17	
Annual symptomatic/incidental detection rate for MAFLD patients with undiagnosed late stage HCC	1.49	

Table 9 – Parameter table for HCC stage at diagnosis

Description	Value	Targets/source
ARLD		
Proportion of ARLD HCC diagnosed at early stage	41%	[8]
Proportion of ARLD HCC diagnosed at intermediate stage	19%	
Proportion of ARLD HCC diagnosed at late stage	40%	
MAFLD		
Proportion of MAFLD HCC diagnosed at early stage	47%	[11]
Proportion of MAFLD HCC diagnosed at intermediate stage	24%	
Proportion of MAFLD HCC diagnosed at late stage	29%	

Table 10 – Parameter table for HCC survival rates

Description	Value	Targets/source
ARLD and MAFLD[3]		
Five-yearly HCC survival rates for patients with early or intermediate stage HCC at diagnosis	47.0%	Privately provided data from Australian Institute of Health and Welfare [52]
Five-yearly HCC survival rates for patients with late stage HCC at diagnosis	17.7%	
Hazard ratio for five-year survival for intermediate vs early stage disease	0.508	

[3] No statistically significant difference in survival by aetiology in stage-matched patients.[68]

Table 11 – Test characteristics for surveillance technologies.

Description	Value	Targets/source
FIB-4		
Positive rate for patients with F0 fibrosis	23.5%	69
Positive rate for patients with F1 fibrosis	33.8%	
Positive rate for patients with F2 fibrosis	60.4%	
Positive rate for patients with F3 fibrosis	79.0%	
Positive rate for patients with compensated cirrhosis	88.1%	
Positive rate for patients with decompensated cirrhosis	88.1%	
Positive rate for patients with HCC	100.0%[4]	
Transient Elastography		
Inconclusive rate for patients with F0 fibrosis	12.6%	70
Inconclusive rate for patients with F1 fibrosis	25.9%	
Inconclusive rate for patients with F2 fibrosis	12.5%	
Inconclusive rate for patients with F3 fibrosis	18.2%	
Inconclusive rate for patients with cirrhosis or HCC	7.6%	
Positive rate for patients with F0 fibrosis	0.3%	
Positive rate for patients with F1 fibrosis	7.5%	
Positive rate for patients with F2 fibrosis	36.2%	
Positive rate for patients with F3 fibrosis	49.5%	
Positive rate for patients with cirrhosis	74.0%	
Positive rate for patients with HCC	92.4%	
Ultrasound and alpha-fetoprotein		
Specificity (for detection of HCC)	84%	71
Sensitivity (early-stage HCC)	63%	
Sensitivity (intermediate/late-stage HCC)	97%	

Table 12 – Disease prevalence among MAFLD and ARLD patients.

Description	Value	Targets/source
ARLD		
Mean age of ARLD patients (SD)	54.6 (12.3)	12
Proportion of ARLD with no steatosis ("normal liver")	9.2%	
Proportion of ARLD with F0 fibrosis	12.4%	
Proportion of ARLD with F1 fibrosis	5.0%	
Proportion of ARLD with F2 fibrosis	3.5%	
Proportion of ARLD with F3 fibrosis	2.9%	
Proportion of ARLD with compensated cirrhosis	26%	
Proportion of ARLD with decompensated cirrhosis	32%	
Proportion of liver cancer deaths from HCC	57.6%	1,72
Proportion of HCC deaths attributable to ARLD	31.5%	9
MAFLD		
Mean age of MAFLD patients	53.2 (13.6)	11

[4] Based on expert advice.

Proportion of MAFLD with F0 fibrosis	85.6%	[17]
Proportion of MAFLD with F1 fibrosis	7.3%	
Proportion of MAFLD with F2 fibrosis	2.8%	
Proportion of MAFLD with F3 fibrosis	2.1%	
Proportion of MAFLD with compensated cirrhosis	0.97%	
Proportion of MAFLD with decompensated cirrhosis	0.13%	
Proportion of liver cancer deaths from HCC	57.6%	
Proportion of HCC deaths attributable to MAFLD	38.6%	[9]

Table 13 – Parameters relating to MAFLD and ARLD after weight loss and alcohol cessation respectively.

Description	Value	Source
ARLD – Alcohol cessation		
Proportion of ARLD with complete regression after alcohol cessation	42%	[29]
Proportion of ARLD with compensated cirrhosis after alcohol cessation	26%	
Proportion of ARLD with decompensated cirrhosis after alcohol cessation	32%	
Hazard ratio for decompensation events after alcohol cessation	0.482	[30]
Hazard ratio for all-cause mortality in cirrhotic patients after alcohol cessation	0.524	
MAFLD – Once-off weight loss		
Proportion of MAFLD with F0 fibrosis after once-off weight loss	91.5%	[13]
Proportion of MAFLD with F1 fibrosis after once-off weight loss	4.46%	
Proportion of MAFLD with F2 fibrosis after once-off weight loss	2.45%	
Proportion of MAFLD with F3 fibrosis after once-off weight loss	1.19%	
Proportion of MAFLD with compensated cirrhosis after once-off weight loss	0.19%	
Proportion of MAFLD with decompensated cirrhosis after once-off weight loss	0.13%	

Table 14 – Procedure utilisation for the detection and treatment of confirmed HCC.

Description	Value	Targets/source
Procedures for HCC diagnosis		
CT	80%	[73]
MRI	20%	
Biopsy	10%	
Early-stage (0/A) HCC treatment		
Transplant	19.0%	[74]
Resection	13.8%	
Ablation	25.6%	
TACE	34.8%	
Resection, Ablation/TACE, then sorafenib	3.4%	
Ablation, then sorafenib	1.5%	
TACE, then sorafenib	2.0%	
Intermediate-stage (B) HCC treatment		
Transplant	8.3%	[74]
Resection	8.3%	
Ablation	17.7%	
TACE	24.0%	
Ablation, then sorafenib	14.1%	
TACE, then sorafenib	19.2%	
Resection, then sorafenib	8.3%	
Late-stage (C/D) HCC treatment		
Ablation	3.4%	[74]
TACE	4.6%	
Ablation, then sorafenib	6.8%	
TACE, then sorafenib	9.2%	
Ablation, then palliation	11.9%	
TACE, then palliation	16.1%	
Sorafenib, then palliation	16.0%	
Palliation	32.0%	

Table 15 – Costs and disutilities used in the cost-effectiveness evaluation.

Item	Value	Range	Source
Annual cirrhosis care costs			
Compensated	$4,713	$1,108-8,772	[75]
Decompensated	$22,701	$10,464-34,939	
Surveillance-related costs			
Ultrasound	$115.75	-	[55] As of March 2023.
AFP	$24.35	-	
GP Visit	$39.75	-	
FIB4	$14.25		
TE	$161.90/81.0[5]		
CT (diagnostic)	$499.50	-	
MRI (diagnostic)	$558.80	-	
Liver biopsy (diagnostic)[6]	$377.2	-	
Treatment-related costs[7]			
Liver transplant	$320,107	-	[53]
Liver resection	$73,310	-	
Ablation (RFA/MWA/PEI)[8]	$94,611	-	
TACE[9]	$76,482	-	
Sorafenib	$42,338	-	
End-of-life costs			
Death from cancer	$44,945	$44,015-45,873	[76]
Death from other causes	$31,513	$30,767-32,259	
Disutilities (annual)			
Compensated cirrhosis	0.32	0.31-0.33	[77]
Decompensated cirrhosis	0.38	0.36-0.40	
HCC – Diagnostic Phase	0.288	0.193-0.399	[78]
HCC – Controlled Phase	0.049	0.031-0.072	
HCC – Terminal Phase	0.540	0.377-0.687	

[5] First event/subsequent events.
[6] Including anesthesia costs.
[7] Patient treatment costs are overall costs classified according to their primary treatment, following the methodology in Hong et al.[53] Patients may have further treatments -these costs are included in the figures presented.
[8] Proportion of patients allocated to RFA/MWA/PEI based on the proportions reported in Hong et al.[53]
[9] Including TACE with cisplantin, TACE with doxorubicin, and SIRT.

Appendix 2 - Time-to-event distribution modelling

Policy1-Liver was developed based on a **time-to-event distribution model**. This modelling framework allows us to realistically model the distribution of time an individual spends in an individual health state, while also capturing competing risks and sequential evolution of liver disease.

The time-to-event distribution framework is based around a set of health states, S_i, and the transitions between these health states, represented by the distribution $f_{i,j}(t,\tau)$ defined by:

$$P\big(\text{an individual is in state } S_i \text{ at time } t \text{ and will enter state } S_j \text{before time } t+\tau\big) = \int_0^\tau f_{i,j}(t,s)\mathrm{d}\,s.$$

These distributions are in turn generated by the time-to-event functions $d_{i,j}(\tau)$, the distribution of times for an individual to transition from state S_i to state S_j. These are then related by:

$$\frac{\partial}{\partial t} f_{i,j}(t,\tau) = \frac{\partial}{\partial \tau} f_{i,j}(t,\tau) + \sum_k f_{k,i}(t,0) d_{i,j}(\tau).$$

The first two terms of this equation are a transport equation, indicating that as time t progresses, the distribution $f_{i,j}(t,\tau)$ concurrently shifts towards the "terminus" $\tau = 0$. The third term shows progression between one state and another – when the distribution reaches $\tau = 0$, the distribution is moved to the next states according to the function $d_{i,j}(\tau)$.

The distributions $d_{i,j}(\tau)$ are determined by the relevant data for the problem being analysed. In the simplest example, for a state $\mathrm{S_i}$ with a single transition to a state $\mathrm{S_j}$ at a constant hazard rate of $\lambda_{\mathrm{i,j}}$, the time-to-event distribution is given by the probability distribution function corresponding to the survival function for remaining in that state, $d_{i,j}(\tau) = \lambda_{i,j} \mathrm{e}^{-\lambda_{i,j}\tau}$.

More generally, for states with more than one possible transition and/or non-constant hazard rates, these distributions are given by:

$$\mathrm{d_{i,j}}(\tau) = \lambda_{i,j}(\tau)\widehat{S_i(\tau)}$$

where $\hat{\mathrm{S}}_i(\tau)$ is the *all-cause survival function* for people entering state S_i defined by:

$$\hat{\mathrm{S}}_i(\tau) = \mathrm{e}^{-\Lambda_\mathrm{i}(\tau)}$$

and $\Lambda_\mathrm{i}(\tau)$ is the *cumulative hazard function* for individuals in state S_i

$$\Lambda_\mathrm{i}(\tau) = \sum_\mathrm{j} \left(\int_0^\tau \lambda_{\mathrm{i,j}}(\mathrm{s})\mathrm{ds} \right).$$

See e.g. Austin et al [79] for a full derivation of the above. The hazard rates $\lambda_{\mathrm{i,j}}(\tau)$ can also be made to depend on covariates X like $\lambda_{\mathrm{i,j}}(\tau|X)$ as per Cox proportional hazards models, or in the case of more than one competing risk, a Fine-Gray subdistribution hazard model.[80]

The distributions $d_{i,j}(\tau)$ satisfy:

$$\sum_{k} \int_{0}^{\infty} d_{i,k}(\tau) \mathrm{d}\,\tau \leq 1.$$

If a state S_i is a terminal state (i.e., death), this sum will be zero as $d_{i,j}(\tau) = 0$ for all j – there are no subsequent states. Otherwise, this sum would usually be 1, as all individuals would eventually reach a terminal state.

The initial conditions for the distribution $f_{i,j}(0,\tau)$ must be specified, based on the setting. Typically for some i one selects $f_{i,j}(0,\tau) = d_{i,j}(\tau)$ for all j as an initial condition, and $f_{k,l}(0,\tau) = 0$ for all $k \neq i$.

The number of individuals in a state S_i at a given time t can be calculated by:

$$\sum_{\mathrm{j}} \int_{0}^{\infty} f_{i,j}(0,\tau) + \sum_{\mathrm{k}} \int_{0}^{\mathrm{t}} f_{\mathrm{k,i}}(\mathrm{s},0) \mathrm{d}\,\mathrm{s} - \sum_{\mathrm{j}} \int_{0}^{\mathrm{t}} f_{\mathrm{i,j}}(\mathrm{s},0) \mathrm{d}\,\mathrm{s}.$$

In practice, this model is implemented by discretizing each transition distribution via a *finite difference method*.[81] By selecting a sufficiently small timestep size κ and defining $\mathrm{f}_{i,j}^{a,b} \approx \mathrm{f}_{i,j}(\kappa a, \kappa b)$ as a discrete approximation, one can develop the first-order numerical scheme

$$f_{i,j}^{a+1,b} = f_{i,j}^{a,b+1} + \sum \left(f_{k,i}^{a,0} \int_{\kappa b}^{\kappa(b+1)} d_{i,j}(\tau) d\tau \right).$$

As these are convergent in an epidemiological context (due to terminal death states), first order numerical accuracy is usually high; otherwise, higher-order approximations can be developed.

Further technical details of time-to-event distribution modelling will be published in an upcoming manuscript.

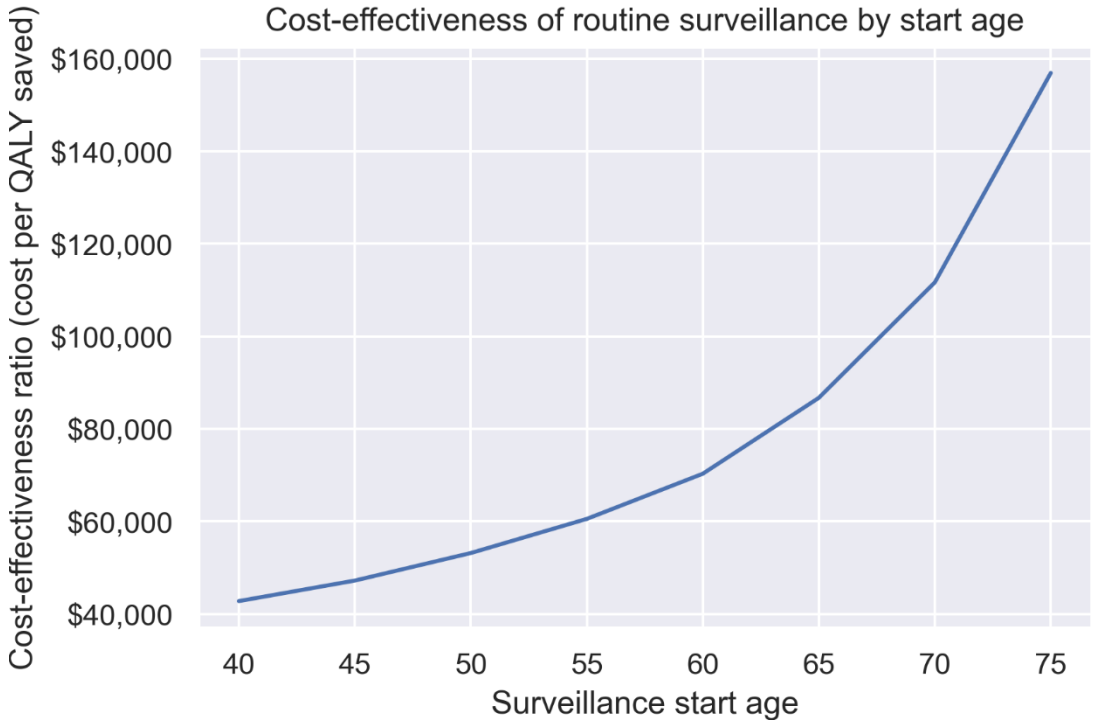
Appendix 3 - Additional analyses

Impact of surveillance start age in MAFLD cohort

In our main analyses, the modelled cohort is based on estimates of the actual cohort of Australian MAFLD patients, who vary in age. To explore the relative cost-effectiveness of routine HCC surveillance by patient age, we calculated outcomes in cohorts where MAFLD was identified, and routine HCC surveillance was commenced from differing start ages. The results are shown in Figure 23.

The results show that routine HCC surveillance is more cost-effective when commenced from earlier ages. This is primarily due to two factors – the low frequency of surveillance with frontline FIB-4 testing, and the lower life expectancy for patients at older ages. As FIB-4 testing is infrequent and has significant false negative rates, patients at younger ages have more opportunities to detect severe liver disease and progress to more frequent and more accurate diagnostic modalities, increasing the efficacy of surveillance. Additionally, disease which is caught at an early age naturally saves more life years as the patient will have a higher overall life expectancy (including from non-liver related causes).

Figure 23 – Estimated impact of the starting age of routine HCC surveillance on cost-effectiveness.

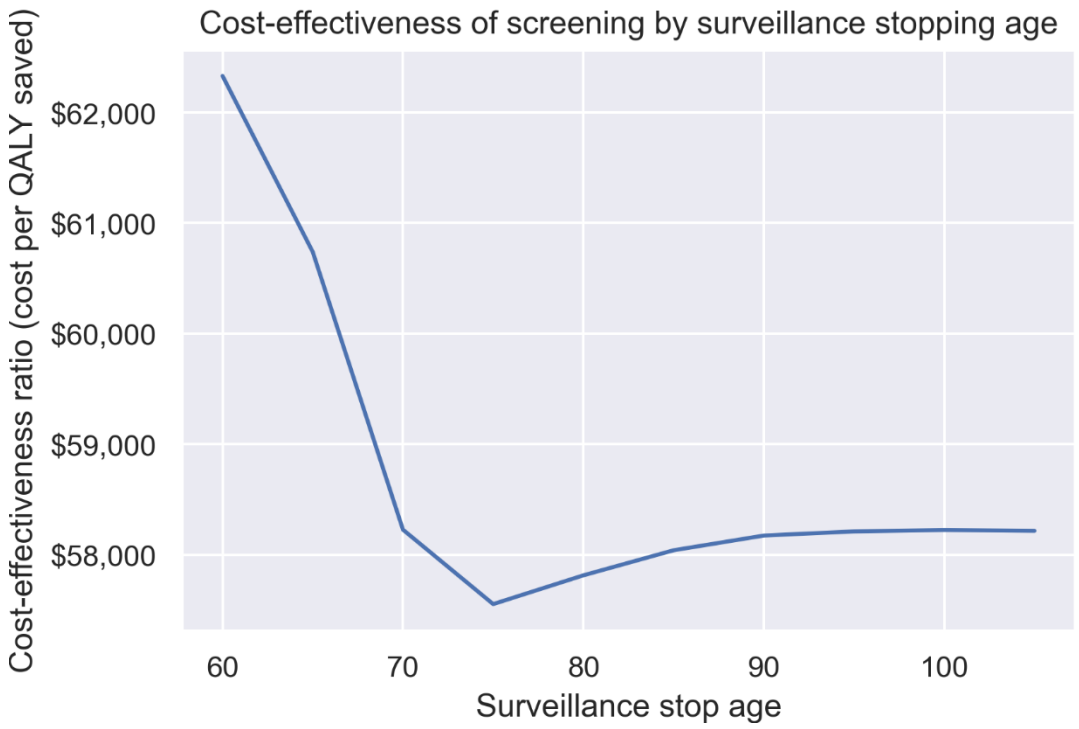


Impact of surveillance stop age in MAFLD cohort

To identify the most appropriate age to cease screening, we completed an analysis of the cost-effectiveness of screening stratified by screening stop age. As mentioned above, surveillance is less effective at older ages, when comorbidities are likely to lead to a reduced life expectancy, and the costs and harms of surveillance (including the potential of a dangerous biopsy from false positive HCC diagnoses) outweigh the potential benefits.

This analysis was completed in the Australian MAFLD cohort, i.e., with a mean age of 55. The results are shown in Figure 24. This analysis found that the optimal stopping age was between 70 and 80. Combined with expert consultation, we decided to use 80 as the screening stop age in this analysis.

Figure 24 – Impact of stopping age for routine HCC surveillance on cost-effectiveness of routine HCC surveillance in the modelled MAFLD patient cohort.



Ultrasound surveillance in MAFLD cohort

Currently, only patients with cirrhotic liver are recommended to receive routine ultrasound surveillance, with or without parallel AFP testing.[35] To demonstrate the benefits of the stratified routine HCC surveillance algorithm modelled here (Figure 2), we also compared outcomes for 6-monthly US surveillance with AFP for all MAFLD patients. In this analysis, providing six-monthly ultrasound surveillance would reduce HCC mortality by 19.3% vs no intervention, compared to an 18.1% reduction for patients in surveillance using the stratified algorithm. This limited increase in effectiveness would require patients to undergo up to 56 ultrasounds over their lifetime and would increase costs 6.03 times more than stratified surveillance. The cost-effectiveness of US surveillance for all MAFLD patients would be approximately $311,777/QALY saved, well over the $50,000/QALY saved threshold typically used.