The Daffodil Centre

The Australian Prevention Partnership Centre

Preventing liver cancer: Obesity and alcohol consumption

Final report

April **2023**

A partnership between

Cancer Council | THE UNIVERSITY OF SYDNEY

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Executive summary

Introduction

Liver cancer is one of the most rapidly growing cancer types in Australia in terms of both incidence and mortality. The most common type of liver cancer, hepatocellular carcinoma (HCC), often develops in people with underlying liver disease caused by modifiable risk factors, including excessive alcohol consumption, excess body fatness and the metabolic syndrome.

Prolonged excess alcohol consumption can cause liver damage and may lead to alcohol related liver disease (ARLD), while excess body fatness and the metabolic syndrome are associated with an increased risk of non-alcoholic fatty liver disease (NAFLD; now also referred to as metabolic-associated fatty liver disease: MAFLD).

Given the biological pathway of HCC through these groups, there is potential for targeted primary and secondary prevention interventions to reduce the disease burden – namely through alcohol cessation, weight loss interventions and HCC surveillance.

The Preventing Liver Cancer Project looked at (a) excessive alcohol consumption and ARLD, and (b) excess body fatness and the metabolic syndrome to NAFLD and/or MAFLD, to:

i. assess the recent evidence on changes in risk factor prevalence and progression to advanced liver disease and liver cancer, and
ii. provide estimates of the proportion HCC deaths in Australia which could be averted through HCC surveillance and other public health interventions.

Methods

An evidence review and predictive modelling were conducted in the two areas of: excessive alcohol consumption and ARLD, and excess body fatness and the metabolic syndrome to NAFLD and/or MAFLD.

The evidence reviews covered risk factor and liver disease prevalence in Australia, research on the association between the risk factors and the risk of liver disease and liver cancer, and finally the natural history progression from liver disease to death. Electronic literature searches were undertaken between January and May 2022 to identify international systematic review evidence from 2012 to 2022 and Australian studies of any type.

The predictive modelling was completed using *Policy1-Liver*, a mathematical model of liver disease and HCC surveillance. *Policy1-Liver* is designed to estimate liver disease progression and prevalence, including liver steatosis, steatohepatitis, and fibrosis progression, and development of cirrhosis in those at risk of developing HCC, as well as onset and diagnosis of HCC, and HCC survival by BCLC stage. *Policy1-Liver* also estimated healthcare costs related to liver disease and HCC, patient quality of life in terms of *quality-adjusted life expectancy* (QALE, measured in *quality-adjusted life years*), the *cost-effectiveness ratio* (CER) and the projected number of HCC deaths to 2045 related to ARLD and MAFLD.

These modelled outcomes are reported in terms of no intervention, primary prevention intervention and secondary prevention intervention.

Results

Excessive alcohol consumption, alcohol related liver disease and prevention

Approximately eight in ten (78.8%) Australian adults drank, and 6.3% consumed on average more than four alcoholic drinks per day. The estimated prevalence of ARLD ranged from 4-9%. An estimated 3%, 10% and 8% of heavy drinkers with histologically confirmed steatosis, steatohepatitis and fibrosis developed alcohol-related cirrhosis each year. The relationship between excessive alcohol consumption and increased risk of liver disease is well established, though not exclusively related to ARLD, and there is strong evidence of the association with heavy alcohol consumption and liver cancer.

Without any intervention, estimated lifetime HCC incidence and mortality would be 9,881 and 7,883 per 100,000 ARLD patients, respectively. By providing routine HCC surveillance to ARLD patients, lifetime HCC mortality could be reduced by 18.6% by increasing the number of HCC diagnoses at an early stage. Providing HCC surveillance for ARLD patients would have a cost-effectiveness ratio of $11,809 per quality-adjusted life-year saved, indicating it would be highly cost-effective.

To estimate the impact of alcohol cessation, we calculated the all-cause survival in ARLD patients with and without active alcohol use. For patients with current or previous ARLD but with no active alcohol use, 10-year all-cause survival was 61.8%, a significant increase compared to the 10-year all-cause survival of 37.6% in patients with active alcohol use.

By 2045, an estimated maximum 108 ARLD-related HCC deaths could be prevented annually through routine HCC surveillance in Australia. 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.

Excess body fatness, the metabolic syndrome, metabolic-associated fatty liver disease and prevention

Seven in ten (67.0%) carried excess body weight with 35.6% of Australian adults classified as overweight and 31.3% classified as obese according to their body mass index (BMI). Prevalence of excess body weight is projected to increase, contributing to the growing liver cancer burden in Australia. International meta-analyses estimated the prevalence of MAFLD to be 39.2%, and the prevalence of NAFLD, 33.9%. Existing evidence shows an increased risk of NAFLD, NAFLD-related cirrhosis and liver cancer with excess body weight. There was limited published evidence for MAFLD. Australian projections suggest there will be a 75% increase in the number of incident primary liver cancer cases from 2019-30.

Without any intervention, estimated lifetime HCC incidence and mortality would be 3,051 and 2,112 per 100,000 MAFLD patient, respectively. By providing routine HCC surveillance to MAFLD patients, lifetime HCC mortality can be reduced by 23.6% by detecting HCC at an earlier stage. After a once-off weight loss intervention, lifetime HCC mortality would be reduced by 25.9%. By additionally providing HCC surveillance after a once-off weight loss, HCC mortality would be reduced by 38.2% vs no intervention. Providing HCC surveillance for MAFLD patients without weight loss interventions would be unlikely to be cost-effective;

however, combining weight loss interventions with HCC surveillance would be cost-effective or cost-saving.

By 2045, up to an estimated 150 MAFLD-related HCC deaths could be prevented annually through routine HCC surveillance in Australia. A once-off 10% weight reduction intervention in 2023 or at age 40, whichever occurs first, would prevent to an estimated maximum 417 MAFLD-related HCC deaths. If the weight loss intervention was combined with routine HCC surveillance, this would further increase to 485.

Discussion

Alcohol consumption in Australia remains common and excess body fatness continues to increase. The evidence shows a strong association between excessive alcohol consumption and excess body fatness and the risk of liver disease and liver cancer. The evidence is less clear for moderate alcohol consumption and the metabolic syndrome and MAFLD. However, interventions designed to reduce the prevalence of alcohol consumption and excess body fatness have the potential to reduce the liver cancer burden, particularly when targeted at high-risk patients with reversible, early-stage liver disease.

Predictive modelling estimated that evidence-based interventions could reduce HCC deaths in Australia by 100-500 deaths annually, with the most reductions resulting from the combination of primary and secondary prevention activities are combined. Currently, routine HCC surveillance is more commonly used for patients with chronic hepatitis B or cirrhotic patients. Its use and application are relatively new for patients with suspected MAFLD or ARLD. 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 HCC surveillance in preventing HCC deaths while being more affordable and less burdensome for patients.

This analysis focused on HCC and does not capture any costs, savings, or additional health benefits associated with weight loss. Overweight and obesity and alcohol consumption are major determinants of many other health outcomes in addition to liver disease, and are key health concerns in Australia. The outcomes presented here are through a narrow lens but weight loss and alcohol cessation would likely be of broader benefit if other disease types were considered.

Future reviews could seek to identify evidence regarding the interplay between the risk factors for chronic liver disease and primary liver cancer and extend the predictive modelling platform. In future work, predictive modelling can be extended to identify whether non-invasive testing can be used to identify patients with metabolic-associated steatohepatitis (MASH), a more developed form of MAFLD, and whether routine HCC surveillance would be more cost-effective for MASH patients compared to MAFLD patients.

Conclusion

It is important that efforts are taken to understand the impact of modifiable risk factors so that action can be taken to reduce the future burden of liver cancer in Australia. This study highlighted the potential for preventing MAFLD- and ARLD-related HCC in Australia through primary and secondary prevention. As liver cancer rates continue to rise in Australia, ongoing research and clearer understanding in these areas is crucial. Using current evidence and predictive modelling, recommendations can be developed for those with liver disease

associated with modifiable risk factors including alcohol consumption and excess body weight. Not only do the findings of this project illustrate the extent to which liver cancer outcomes can be improved, it also demonstrates both the cost and cost-effectiveness of primary and secondary prevention interventions in emerging high-risk groups to build the case for policy and practice change. This would guide future investment in liver cancer control and reduce the burden in Australia.

1. Introduction

Liver cancer is one of the most rapidly growing cancer types in Australia in terms of both incidence and mortality (1). The most common type of liver cancer, hepatocellular carcinoma (HCC), often develops in people with underlying liver disease caused by modifiable risk factors (2). These include infection-related risk factors, predominantly chronic viral hepatitis, behavioural risk factors such as excessive alcohol consumption and metabolic risk factors including excess body fatness and the metabolic syndrome (2). It has been estimated that 58.1% of liver cancer cases will be attributed to these modifiable risk factors in Australia (3).

While rates of liver cancer burden have historically been driven by viral hepatitis infections, the burden is shifting in developed countries such as Australia to non-viral aetiologies (4). Two key non-viral, pre-cirrhotic groups are patients with alcohol-related liver disease (ARLD) and non-alcoholic fatty liver disease (NAFLD). Prolonged excess alcohol consumption can cause liver damage and may lead to ARLD, while excess body fatness and the metabolic syndrome are associated with an increased risk of NAFLD (now also referred to as metabolic-associated fatty liver disease: MAFLD). Although ARLD and MAFLD are distinguished as distinct liver disease aetiologies, patients often present with multiple conditions and their comorbidity can led to liver scarring (fibrosis to cirrhosis) and increase the risk of liver cancer. Given the biological pathway of HCC through these groups, there is potential for targeted liver cancer control interventions to reduce the disease burden.

Public health interventions to reduce alcohol consumption and/or excess body weight may also contribute to reducing the liver cancer burden in Australia. Alcohol cessation, through either abstinence or alcohol withdrawal, has been associated with fibrosis regression, HCC risk and survival in patients with ARLD (5–8). Weight loss interventions (including behavioural programs, pharmacotherapy and bariatric surgery) have not been conclusively associated with reduced HCC risk (9,10) but can improve markers associated with fibrosis progression in NAFLD (11,12). However, there have been clinically demonstrated instances of significant reductions in fibrosis severity following weight loss (13).

Additionally, routine HCC surveillance of people at high-risk is one possible intervention which would enable the early identification of HCC when curative treatment may be possible (14). A recent review of the literature found promising evidence to support the effectiveness and cost-effectiveness of 6-monthly ultrasound HCC surveillance for patients with liver cirrhosis (15). This review has informed the development of a predictive simulation model (*Policy1-Liver*) for the Australian context. *Policy1-Liver* mathematically maps health outcomes for cirrhotic patients.

The Preventing Liver Cancer Project looked at (a) excessive alcohol consumption and ARLD, and (b) excess body fatness and the metabolic syndrome to NAFLD and/or MAFLD, to:

iii. assess the recent evidence on changes in risk factor prevalence and progression to advanced liver disease and liver cancer, and
iv. provide estimates of the proportion HCC deaths in Australia which could be averted through HCC surveillance and other public health interventions.

The methodology and results are presented below separately by risk factor.

2. Excessive alcohol consumption and alcohol related liver disease

2.1 Methods

2.1.1 Evidence review methods

The evidence review was designed to:

1. Determine the Australian prevalence of excessive alcohol consumption and ARLD using data from the Australian Bureau of Statistics, and
2. Report the association between alcohol consumption and risk of liver disease and liver cancer, and
3. Quantify the progression from ARLD to liver fibrosis, cirrhosis, liver cancer and death.

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.

In addition, the Cochrane Library of Systematic Reviews, the ANZCTR online registry of clinical trials being undertaken in Australia, New Zealand and elsewhere, and the International Prospective Register of Systematic Reviews (PROSPERO) databases were searched. Reference lists of all included papers were scanned manually for other relevant studies.

Due to limited availability of literature relating specifically to ARLD, we reviewed studies relating to alcohol consumption and risk of liver disease of any aetiology.

2.1.2 Predictive modelling methods

The predictive modelling analysis was completed with *Policy1-Liver*, a mathematical model of liver disease and HCC surveillance. *Policy1-Liver* is designed to estimate liver disease progression and prevalence, including liver steatosis, steatohepatitis, and fibrosis progression, development of cirrhosis, onset and diagnosis of HCC, and HCC survival by stage in Australian ARLD patients at risk of developing HCC. The modelling used a *time-to-event distribution modelling* approach, a multistate model capturing competing and evolving risks across a patient lifetime. *Policy1-Liver* was previously developed to assess the costs and health benefits of ultrasound HCC surveillance for patients with cirrhotic liver (16); for this project it has been extended to capture patients with pre-cirrhotic liver disease and disease-specific rates for ARLD and MAFLD patients. More details on *Policy1-Liver* are included in the provided modelling report (*Preventing liver cancer: modelling estimates for MAFLD and ARLD patients*).

Patients with ARLD were modelled from 2023 until patient death from HCC or other causes. The distribution of age and severity of liver disease is based on an indicative cohort with of ARLD with active alcohol use according to Huang et al and Delacote et al (17,18). These outcomes assume all patients continue to continue active alcohol use unless otherwise noted. In the model, patients with fibrosis can progress through the stages of liver disease and cancer to death and those who survive five years past the diagnosis of HCC transition to "survivors" and have no further elevated likelihood of HCC death.

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 HCC

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. The study took a *health system perspective* (19); indirect societal costs such as productivity losses and travel costs were not included.

Health state utilities were calculated and capture a patient's *quality of life*. Combined with estimates of the likelihood of patient survival, this is used the calculate the *quality-adjusted life expectancy* (QALE), which is measured in *quality-adjusted life-years* (QALYs). The *cost-effectiveness ratio* (CER) associated with interventions such as routine HCC surveillance was calculated. The CER can be compared between interventions and compared to indicative *willingness-to-pay* (WTP) thresholds of $30,000/QALY and $50,000/QALY which are used to identify potentially beneficial health investments. For all costs and quality-adjusted life-expectancies, 2023 Australian dollars are used with a 5% annual discount rate was applied from 2023.

To generate population-level estimates, we used projections developed by Luo et al of liver cancer burden in Australia to 2045 (20). Combined with estimates of the proportion of liver cancers attributable to HCC (21), the burden of ARLD, and fibrosis stage among ARLD patients (22), this was used to generate projections of the number of ARLD-related HCC deaths to 2045.

Modelled interventions

Primary prevention: Alcohol cessation intervention

Primary prevention was modelled in ARLD patients as alcohol cessation, and the resulting impact on liver disease and patient mortality rates. For our modelling, alcohol cessation implies no active alcohol use,(6) compared to patients with continuing alcohol use. Fibrosis regression was modelled in patients who were abstinent from alcohol use,(5) as well as lower decompensation and all-cause mortality rates in cirrhotic patients (23). 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) (23–25). Long-term outcomes were compared with patients who continued alcohol use.

Secondary prevention: HCC surveillance

Alongside primary prevention, secondary prevention can be provided through routine HCC surveillance where cancers can be detected at earlier disease stages, when there is a higher possibility of curative treatment (14). Currently, for patients with ARLD, Australian clinical practice guidelines recommend the use of non-invasive tests to stratify patients into risk categories, with only those at high risk recommended to progress to HCC surveillance (16,26).

For patients without cirrhosis, previous modelling studies have found that regular HCC surveillance using ultrasound would not be cost-effective in most circumstances.(27) By using simpler and more affordable procedures to exclude patients with low risk, more effective and efficient surveillance can be provided.

HCC surveillance for ARLD patients was modelled via an algorithm based on international guidelines (28–30) and expert consultation to manage costs and resources as well as avoiding unnecessary surveillance. The algorithm included the use of non-invasive testing to stratify patients by estimated liver disease severity through FIB-4 every 3 years or annual transient elastography (TE); patients at high risk were recommended to 6-monthly ultrasound (US) with

alpha-fetoprotein (AFP) testing. Inferred fibrosis/cirrhosis stage based on test results is used as an indicator of patient risk level.

2.2 Results

2.2.1 Evidence review results

The evidence relating to excessive alcohol consumption, ARLD and progression is summarised in Figure 1 and the association between alcohol consumption and risk of liver disease and liver cancer is summarised in Figure 2.

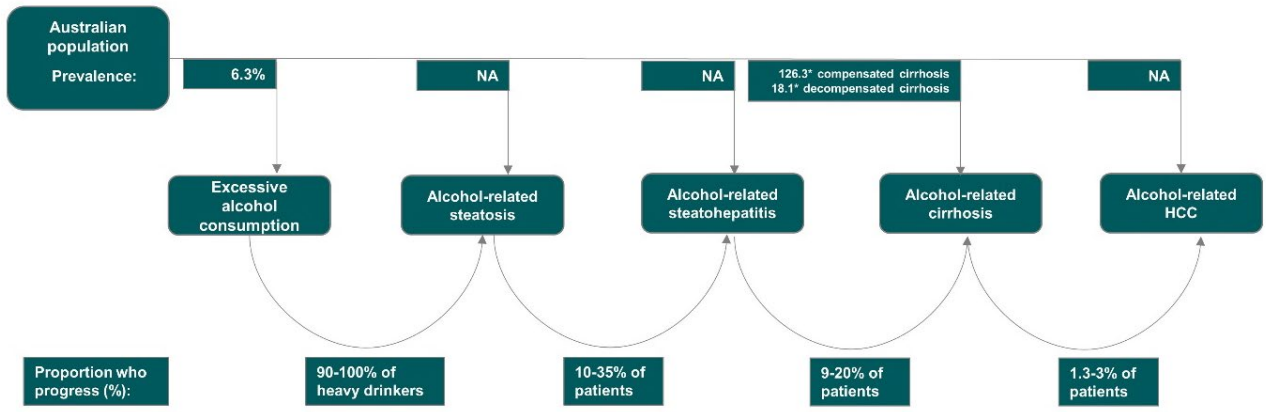
Australian prevalence

Alcohol consumption is common in Australia according to most recent data collected over 2017-18. Approximately eight in ten (78.8%) of Australian adults drank and 6.3% consumed on average more than four alcoholic drinks per day (31). The estimated prevalence of ARLD ranged from 4-9% based on a systematic review of population-based studies (32).

Progression of ARLD

A recent systematic review estimated rates of disease progression in patients with ARLD based on observational studies (32). An estimated 3%, 10% and 8% of heavy drinkers with histologically confirmed steatosis, steatohepatitis and fibrosis developed alcohol-related cirrhosis each year (32). Among those patients with alcohol-related cirrhosis, the rate of all-cause mortality was 8% each year (6% liver-related, 2% non-liver related) (32).

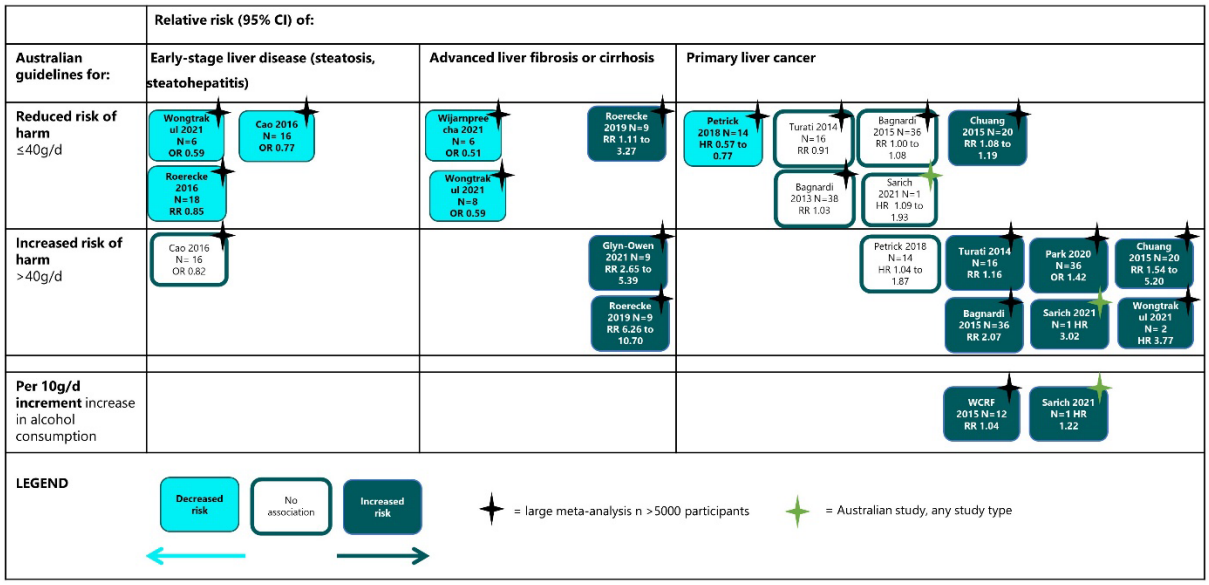
Figure 1 – Alcohol consumption and alcohol related liver disease prevalence and progression



**Age-standardised prevalence rate per 100,000; NA; not available.*

Sources: ABS 2017-18. National Health Survey, alcohol consumption 2017-18 (31); Sepanlou et al Lancet Gastroenterol Hepatol. 2020 (33); Seitz et al. Nat Rev Dis Primers. 2018 (34).

Figure 2 – Alcohol consumption and risk of liver disease and liver cancer



No association was reported if the confidence interval crossed over one. Some of the included studies reported on alcohol consumption in terms of grams of alcohol consumed per week or the number of standard drinks consumed. Where necessary, these values were converted into grams per day using the NHMRC definition of 10 grams alcohol as a standard drink. Australian guidelines for reduced risk of alcohol-related harm recommend drinking ≤4 drinks per on any one day and ≤10 drinks per week. As we have collected data in terms of g/d we have grouped studies according to the former. The relative risk estimates were odds, risk or hazards ratios and these are reported as a range where several estimates were available. This diagram only provides a crude indication of the relative risk as reference groups were different between each study (e.g., some studies used current non-drinkers whilst other used lifetime abstainers or light drinkers as the reference group participants). The meta-analyses by Park et al. (2020) did not fit into either category as the authors reported on the relative risk due to consuming >12.5g/d for men and >25g/d for women, this study has been placed in the increased risk of harm category. CI; confidence interval, F3-4; fibrosis stage 3-4, g/d; grams per day, g/w; grams per week, HR; hazards ratio, N; number of studies included in the meta-analysis, n; number of participants, OR; odds ratio, RR; risk ratio, WCRF; World Cancer Research Fund.

Impact of alcohol consumption and excess body weight on risk of liver disease

The relationship between excessive alcohol consumption and increased risk of liver disease is well established, though not exclusively related to ARLD (35–40). A recent meta-analysis found that among participants who drank, 10 grams per day (g/d), 20g/d, 30-40g/d, 50-60g/d and ≥70g/d compared to lifetime abstainers, the relative risk of alcohol or non-alcohol related liver cirrhosis increased stepwise from 1.11 (95% confidence interval (CI) 0.77-1.59) to 10.70 (95% CI 2.95-38.78) (35). These estimates were highly heterogenous (I^2 values ranged from 71 to 99%) (35).

Impact of alcohol on risk of primary liver cancer

The World Cancer Research fund (WCRF) report found strong evidence that alcohol consumption greater than 45g/d was a convincing cause of liver cancer (41). Dose-response meta-analyses showed that per every 10g/d increment alcohol consumed, the relative risks of liver cancer was 1.04 (95% CI 1.02-1.06), I^2 =64% (41). Among people who consumed on average more than four drinks per day, the relative risk of liver cancer ranged from 1.04 (95% CI 0.79-1.38) to 5.20 (95% CI 3.25-8.29) (42–44). It appeared that moderate drinking showed no significant association with the relative risk of liver cancer, except in patients with underlying liver diseases such as NAFLD. In these patients with NAFLD, the relative risk of HCC was 3.77 (95% CI 1.75-8.15) (38).

2.2.2 Predictive modelling results

Based on the findings of the review above, *Policy1-Liver* was calibrated to accurately reflect the prevalence of liver disease in the ARLD patient population, the risk of worsening liver disease and HCC, the impact of HCC surveillance, and the potential impact of alcohol cessation. Further details are available in the provided modelling report (*Preventing liver cancer: modelling estimates for MAFLD and ARLD patients*).

Health outcomes and costs

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 1, Figure 3). 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 4).

Table 1 – Summary of key outputs for ARLD patients with and without routine HCC surveillance

	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 associated with identifying potential high-risk patients.*

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 costs associated with alcohol use or cessation.

HCC surveillance alone

By providing routine HCC surveillance to ARLD patients, lifetime HCC mortality can be reduced by 18.6% vs to the "no intervention" comparator to 6,415 per 100,000 in the modelled cohort (Figure 3). Overall, with routine HCC surveillance, 62% of HCC diagnoses would be at early stages (Figure 4).

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 HCC 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 3 – Estimated HCC mortality per 100,000 ARLD patients over patient lifetime

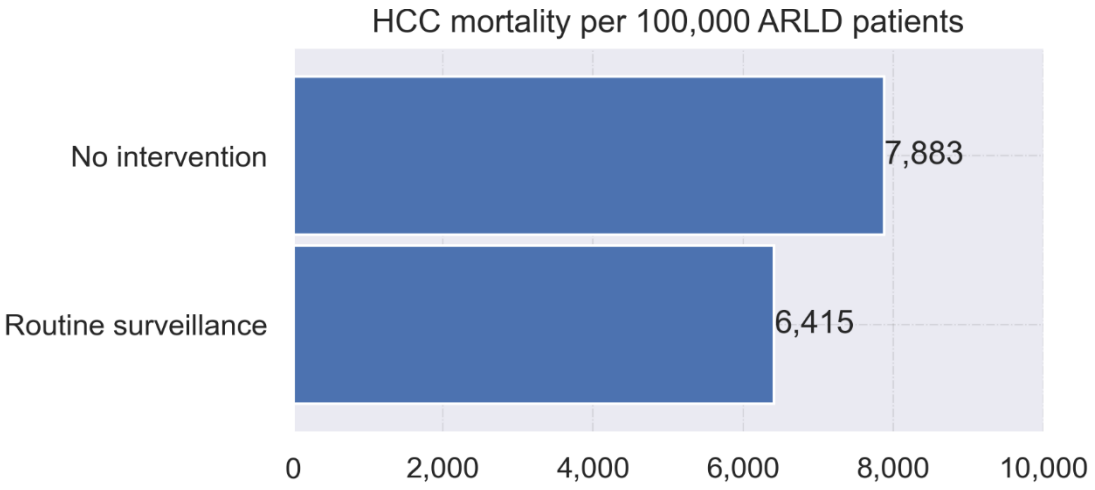
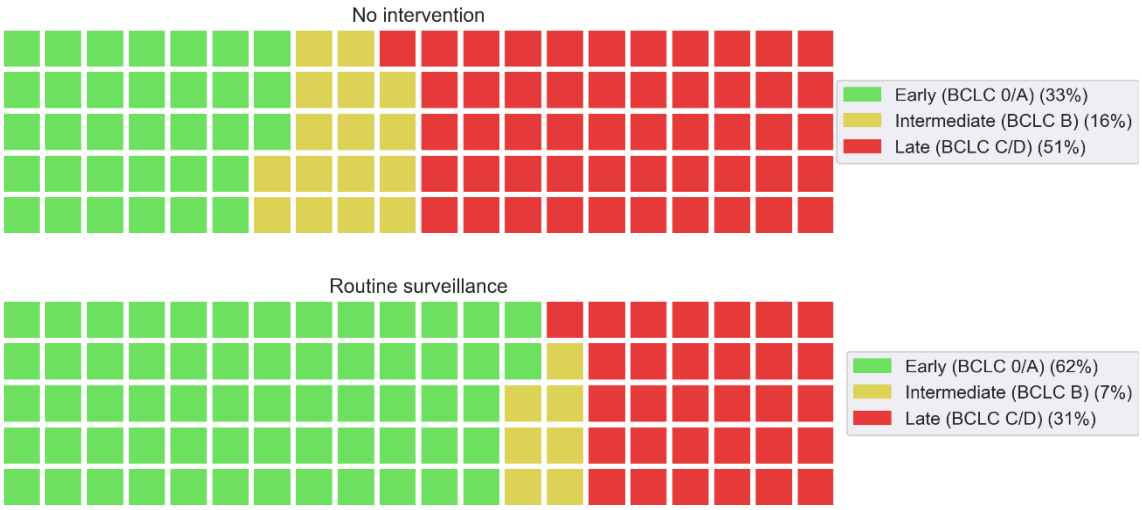


Figure 4 – Stage at diagnosis among ARLD patients diagnosed with HCC. Top: no intervention. Bottom: routine HCC surveillance



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 2.

Table 2 – Cost-effectiveness of HCC 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/QALY

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 indicative willingness-to-pay thresholds used.

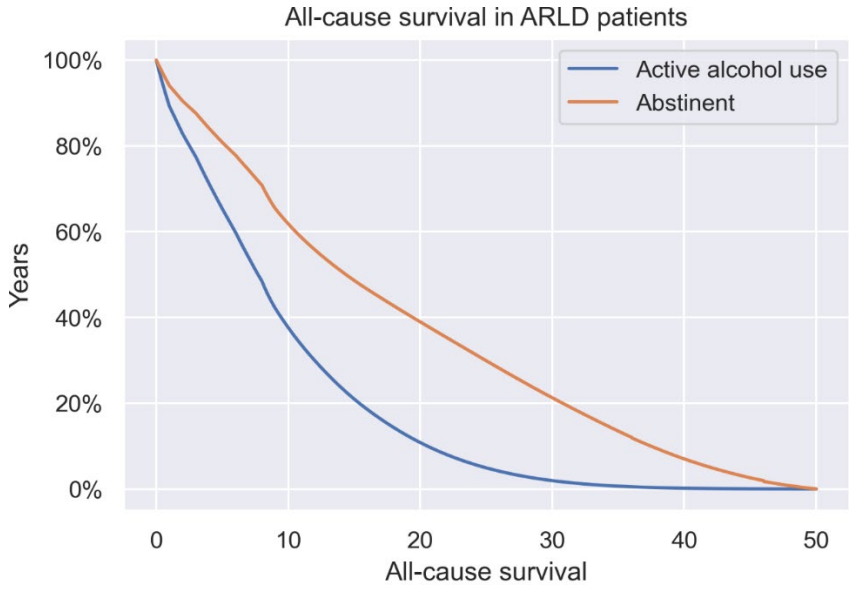
The cost-effectiveness was similar in all ARLD patients without decompensation regardless of stage of fibrosis at baseline, likely due to the quick onset of serious liver disease in ARLD patients (Figure XX). The CER was least favourable for patients with F0 fibrosis ($14,337/QALY saved), and most favourable for patients with compensated cirrhosis ($10,854/QALY saved), though HCC surveillance was less than the $30,000/QALY saved for all patients.

Impact of alcohol cessation on all-cause mortality in ARLD patients

To estimate the impact of alcohol cessation on ARLD patient outcomes, we calculate the all-cause survival in patients with and without active alcohol use. Unlike weight loss in MAFLD patients (see below), HCC mortality was not used as a primary outcome of interest for this analysis as current evidence found no statistically significant link between alcohol cessation and long-term HCC incidence or mortality.(23) We therefore focus on modelling all-cause mortality changes after cessation, for which there was a clearer and more established evidence base.

In a weighted cohort (including patients with fibrosis, compensated cirrhosis, and decompensated cirrhosis(17)) 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 5). Alcohol cessation would nearly double the QALYs in the modelled cohort from 8.630 QALYs to 17.110 QALYs. 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 and be cost-effective with a cost-effectiveness ratio of $9,606/QALY saved. Providing ongoing HCC surveillance to patients without cirrhosis who are abstinent would likely have little benefit, as their liver disease is unlikely to progress.

Figure 5 – All-cause survival in ARLD patients with and without continuing alcohol use

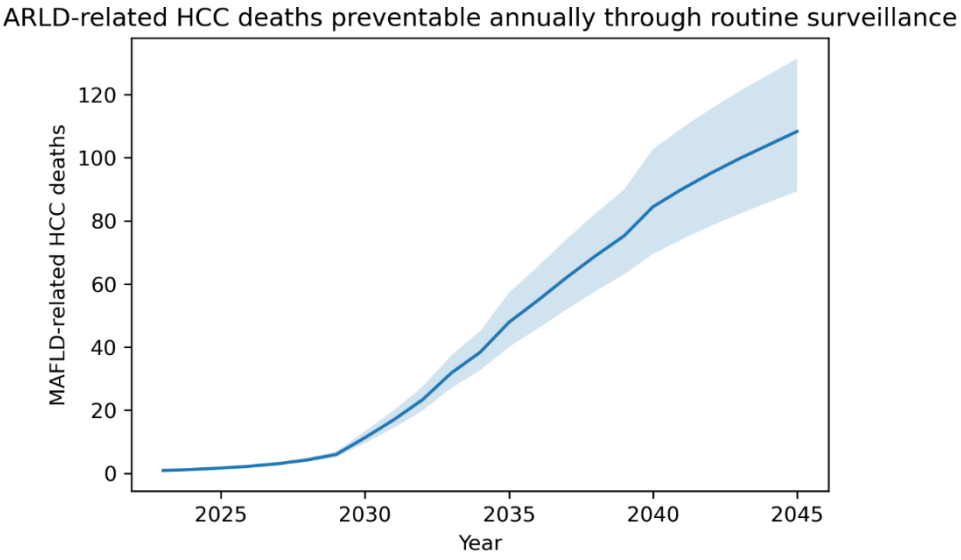


Preventable ARLD-related HCC deaths in Australia

By 2045, an estimated maximum 108 ARLD-related HCC deaths could be prevented annually through routine HCC surveillance in Australia (Figure 6). 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.

Unlike weight loss in MAFLD patients (see below), we could not estimate the number of HCC deaths preventable by alcohol cessation in the Australian population, as current evidence did not find a statistically significant effect on HCC mortality after cessation. The all-cause survival (as distinct from HCC-free survival) estimates calculated above could not be used to estimate deaths averted in the Australian population, as the scope of the modelling does not capture competing risks of death in the ARLD (or former ARLD) population and so we cannot capture overall deaths averted or delayed in this population.

Figure 6 – 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



3. Excess body fatness, the metabolic syndrome and non-alcoholic fatty liver disease

3.1 Methods

3.1.1 Evidence review methods

The evidence review was designed to:

1. Determine the Australian prevalence of excess body fatness, metabolic syndrome and NAFLD and/or MAFLD using data from the Australian Bureau of Statistics, and
2. Report the association between excess body fatness, metabolic syndrome, and risk of NAFLD, MAFLD and liver cancer, and
3. Quantify the progression from NAFLD and/or MAFLD to liver fibrosis, cirrhosis, liver cancer, and death.

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.

In addition, the Cochrane Library of Systematic Reviews, the ANZCTR online registry of clinical trials being undertaken in Australia, New Zealand and elsewhere, and the International Prospective Register of Systematic Reviews (PROSPERO) databases were searched. Reference lists of all included papers were scanned manually for other relevant studies.

3.1.2 Predictive modelling methods

The predictive modelling was completed with *Policy1-Liver*, a model of liver disease and HCC 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 patients at risk of developing HCC. The modelling used a *time-to-event distribution modelling* approach, a multistate model capturing competing and evolving risks across a patient lifetime. *Policy1-Liver* was previously developed to assess the costs and health benefits of ultrasound HCC surveillance for patients with cirrhotic liver (16); for this project it has been extended to capture patients with pre-cirrhotic liver disease. More details on *Policy1-Liver* are included in the provided modelling report (*Preventing liver cancer: modelling estimates for MAFLD and ARLD patients*).

Patients with MAFLD 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 (22). In the model, patients with fibrosis can progress through the stages of liver disease and cancer to death and those who survive five years past the diagnosis of HCC transition to "survivors" and have no further elevated likelihood of HCC death.

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 HCC 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. The study took a *health system perspective*;(19) indirect costs such as productivity losses and travel costs were not included.

Health state utilities were calculated and capture a patient's *quality of life*. Combined with estimates of the likelihood of patient survival, this is used the calculate the *quality-adjusted life expectancy* (QALE), which is measured in *quality-adjusted life-years* (QALYs). The *cost-effectiveness ratio* (CER) associated with interventions such as routine HCC surveillance was calculated. The CER can be compared between interventions and compared to indicative *willingness-to-pay* (WTP) thresholds of $30,000/QALY and $50,000/QALY which are used to identify potentially beneficial health investments. For all costs and quality-adjusted life-expectancies, 2023 Australian dollars are used with a 5% annual discount rate was applied from 2023.

To generate population-level estimates, we used projections developed by Luo et al of liver cancer burden in Australia to 2045 (20). Combined with estimates of the proportion of liver cancers attributable to HCC,(21) the burden of NAFLD, and fibrosis stage among NAFLD patients (22), and the overlap between NAFLD and MAFLD diagnoses, this was used to generate projections of the number of MAFLD-related HCC deaths to 2045.

Modelled interventions

Primary prevention: Weight loss intervention

Primary prevention was modelled in terms of the likelihood of HCC developing with fibrosis reductions due to weight loss, based on Vilar-Gomez et al (13). As there was no data to inform the ongoing impact, "weight loss" was modelled as a once-off intervention corresponding to patients who lose over 10% of their body mass, which would lead to a regression in liver damage severity in most patients.

In the absence of further longitudinal data, 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 subsequently increase in weight.

Secondary prevention: HCC surveillance

Alongside primary prevention, secondary prevention can be provided through routine HCC surveillance where cancers can be detected at earlier disease stages, when there is a higher possibility of curative treatment (14). Currently, for patients with MAFLD, Australian clinical practice guidelines recommend the use of non-invasive tests to stratify patients into risk categories, with only those at high risk recommended to progress to HCC surveillance (16,26).

For patients without cirrhosis, previous modelling studies have found that regular HCC surveillance using ultrasound would not be cost-effective in most circumstances.(27) By using more affordable and simple procedures to exclude patients with low risk, more effective and efficient surveillance can be provided.

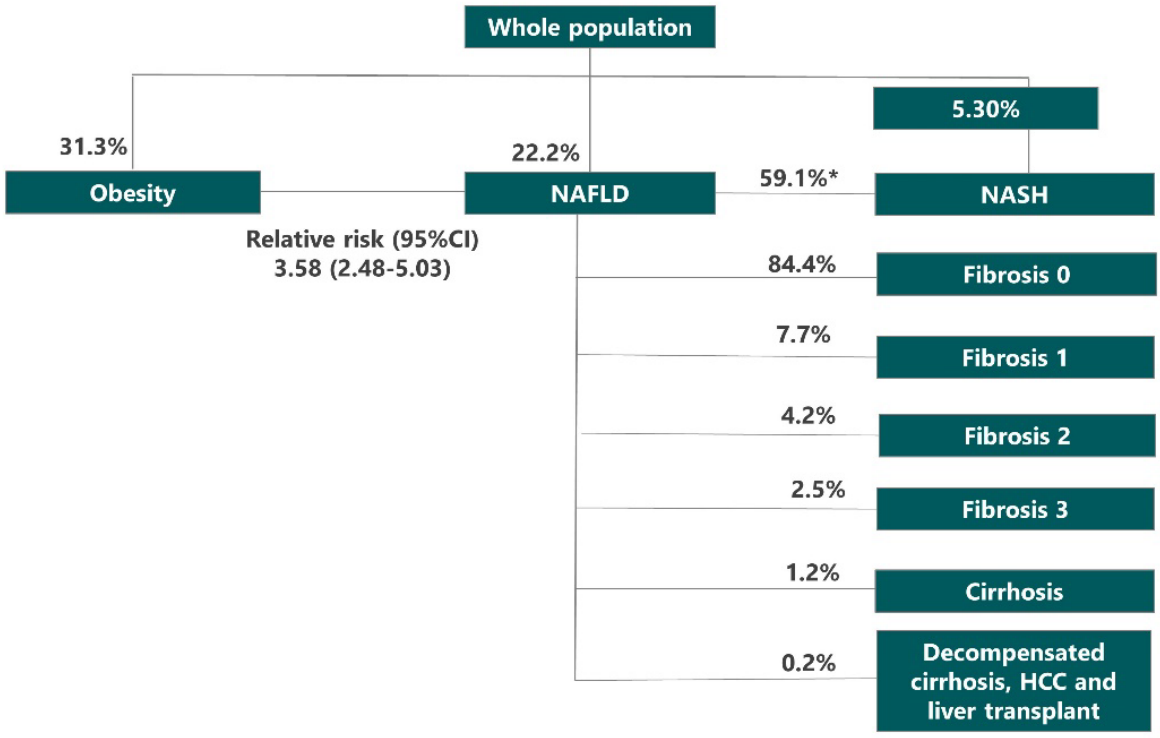
HCC surveillance for MAFLD patients was modelled via an algorithm based on international guidelines (28–30) and expert consultation to manage costs and resources as well as avoiding unnecessary surveillance. The algorithm included the use of non-invasive testing to stratify patients by estimated liver disease severity through FIB-4 every 3 years or annual transient elastography (TE); patients at high risk were recommended to 6-monthly ultrasound (US) with alpha-fetoprotein (AFP) testing. Inferred fibrosis/cirrhosis stage based on test results is used as an indicator of patient risk level.

3.2 Results

3.2.1 Evidence review results

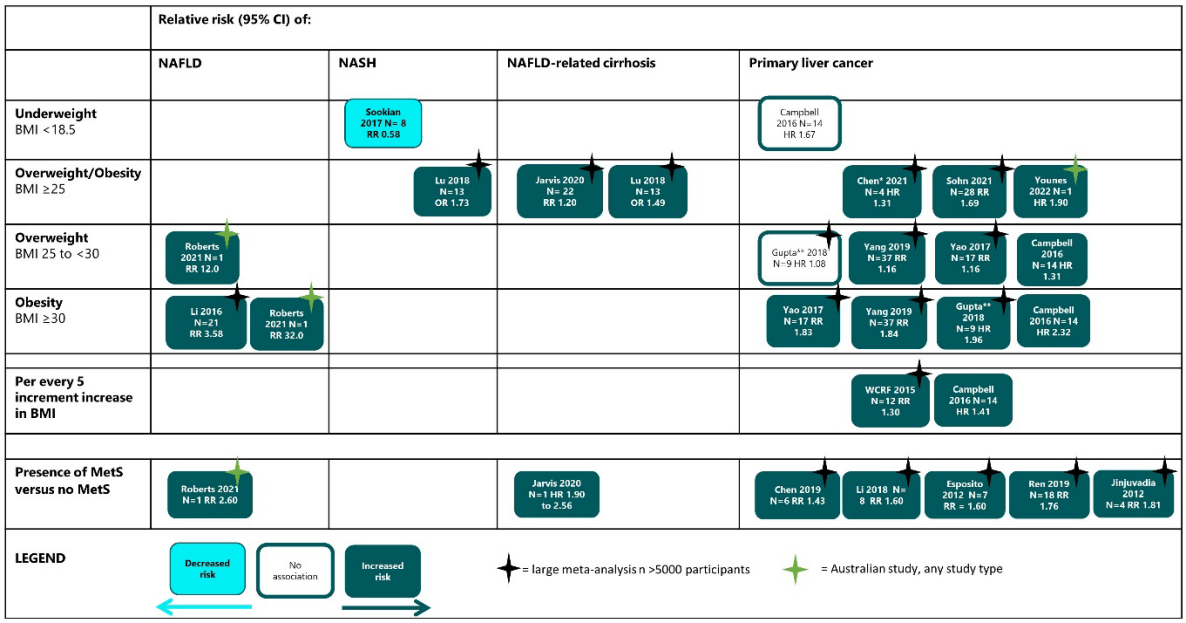
The evidence relating to excess body fatness, NAFLD/MAFLD and progression is summarised in Figure 7 and the association between excess body fatness, metabolic syndrome and risk of NALFD and liver cancer is summarised in Figure 8.

Figure 7 – Excess body fatness and non-alcoholic fatty liver disease prevalence and progression



Sources: Australian Bureau of Statistics National Health Survey Data 2017-2018 (45)*; Li et al Obese Rev. 2016* (46)*; Adams LA et al J Gastroenterol Hepatol. 2020* (22)*; Younossi ZM et al Hepatology. 2016* (47).

Figure 8 - Excess body weight, metabolic syndrome and risk of NAFLD and liver cancer



**The study by Chen et al. (2021) examined risk of HCC incidence among NAFLD patients. **The study by Gupta et al. (2018) examined risk of primary liver cancer mortality, all other studies related to risk of NAFLD or liver cancer incidence. No studies were identified that related to MAFLD. BMI; body mass index, CI; confidence interval, F3-4; fibrosis stage 3-4, HR; hazards ratio, N; number of studies included in the meta-analysis, n; number of participants, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, MAFLD; metabolic associated fatty liver disease, OR; odds ratio, RR; risk ratio, WCRF; World Cancer Research Fund*

Australian prevalence

Excess body fatness was common in Australia according to most recent data collected over 2017-18. Seven in ten (67.0%) carried excess body weight with 35.6% of Australian adults classified as overweight and 31.3% classified as obese according to their body mass index (BMI) (45). Estimates of the prevalence of the metabolic syndrome in Australia ranged from 13.4% to 35.8% (48,49).

The estimated global prevalence of NAFLD was 32.4% based on a global meta-analysis (50). In Australia, the prevalence of NAFLD was estimated as 22.2% in 2019 and forecast to increase to 23.6% by 2030 (22). Taking into account the recent shift away from NAFLD , global meta-analyses estimated that almost 20% more patients would meet the diagnostic criteria for MAFLD resulting in a higher prevalence compared to NAFLD (51).

Impact of excess body weight and the metabolic syndrome on risk of liver disease

There is clear association between excess body weight and risk of NAFLD. Among participants who carry excess weight, the relative risk of NAFLD and NAFLD-related cirrhosis ranged from 1.20 (95% CI 1.12-1.28) to 3.58 (95% CI 1.12-1.28) (46,52,53). Estimates from studies in the Australian context were varied with the relative risk of NAFLD estimated at 12.0 (95% CI 4.6-33.0) in those who are overweight and 32.0 (95% CI 12.0-86.0) in those who are obese (54). Evidence on the metabolic syndrome was limited to increasing risk found for NAFLD-related cirrhosis (55).

Impact of excess body weight and the metabolic syndrome on risk of primary liver cancer

The World Cancer Research fund (WCRF) report found strong evidence that body fatness was convincing causes of liver cancer (41). Dose-response meta-analyses showed that per every 5 increment increase in BMI the relative risks of liver cancer was 1.30 (95% CI 1.16-1.46), I^2 =78.3% (41). Among people who carried excess body weight, the relative risk of liver cancer ranged from 1.16 (95% CI 1.09-1.23) to 2.32 (95% CI 1.95-2.77) (56–58) and liver cancer-related mortality 1.08 (95% CI 0.97-1.21) to 1.96 (95% CI 1.17-5.05) (59). Meta-analyses also found that the metabolic syndrome increased HCC risk (RR 1.76 (1.33-2.33), I^2=88%) (60–64).

Progression of MAFLD and NAFLD

No studies were identified relating to MAFLD. Several recent systematic reviews with meta-analyses have characterised rates of disease progression in patients with NAFLD (47,65–68). The fibrosis progression rate among NASH patients ranged from 0.00 (95% CI -0.05-0.06) to 0.13 (95% CI 0.07-0.18) stages per year, indicating that some patients experienced disease regression. Of patients with NAFLD-related cirrhosis, the incidence rate of HCC was estimated to be 3.78 (95% CI 2.47-5.78) per 100 person-years (67). Rates of liver- and non-liver- related mortality increased in parallel to advancing NAFLD fibrosis stage, with the annual rate of all-cause mortality estimated at 1.5%, 1.7%, 2.8%, 3.6% and 4.6% among patients with NAFLD-related fibrosis stage 0, 1, 2, 3 and 4 respectively (68).

3.2.2 Predictive modelling results

Based on the findings of the review above, *Policy1-Liver* was calibrated to accurately reflect the prevalence of liver disease in the MAFLD patient population, the risk of worsening liver disease and HCC, the impact of HCC surveillance, and the potential impact of weight loss. Further details are available in the provided modelling report (Preventing liver cancer: modelling estimates for MAFLD and ARLD patients).

Health outcomes and costs

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 3, Figure 9). 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 10).

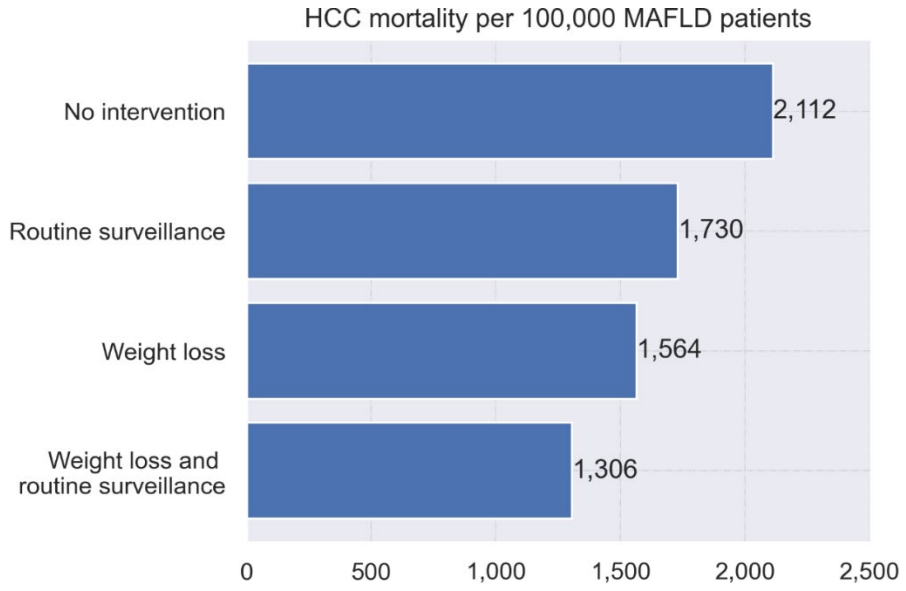
Over the lifetime of the modelled cohort, the average liver-disease and HCC-related cost per MAFLD patient would be $42,105, including potential ongoing cirrhosis care costs, HCC diagnosis costs, HCC treatment costs, and end-of-life costs.

Table 3 – Summary of key outputs for MAFLD patients with and without routine HCC surveillance and/or once-off weight loss

	No intervention	*HCC surveillance*	*Weight loss*	*Weight loss and 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.*

Figure 9 - Estimated HCC mortality per 100,000 MAFLD patients over patient lifetime



HCC surveillance alone

By providing routine HCC surveillance to MAFLD patients, lifetime HCC mortality can be reduced by 23.6% vs to the "no intervention" comparator to 1,730 per 100,000 in the modelled cohort (Figure 9). Overall, with routine HCC surveillance, 69% of HCC diagnoses would be at early stages (Figure 10).

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 HCC 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 and HCC surveillance interventions

After a once-off weight loss intervention, lifetime HCC mortality in the modelled MAFLD cohort would be reduced by 25.9% vs to the "no intervention" comparator to 1,564 per 100,000 (Figure 9) through both HCC prevention and diagnosis at earlier stages (Figure 10). By additionally providing HCC surveillance to the cohort after once-off weight loss, lifetime HCC mortality would be reduced further to 1,306 per 100,000 (Figure 9), a 38.2% reduction vs the comparator.

Figure 10 - Stage at diagnosis among MAFLD patients diagnosed with HCC. "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 in the "no intervention" scenario

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

To determine the budget impact of providing routine HCC surveillance with or without weight loss interventions, the costs associated with saving a quality-adjusted life-year in the modelled cohort were calculated (Table 4). Providing routine HCC surveillance would save 0.0171 QALYs per person, with a relatively small additional cost of $992 per patient –

primarily caused by the additional cost of providing HCC surveillance, as well as differences in HCC treatment costs for patients diagnosed at earlier stages.

Table 4 - Cost-effectiveness of HCC 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	-	$58,027 per QALY	Cost-saving	Cost-saving

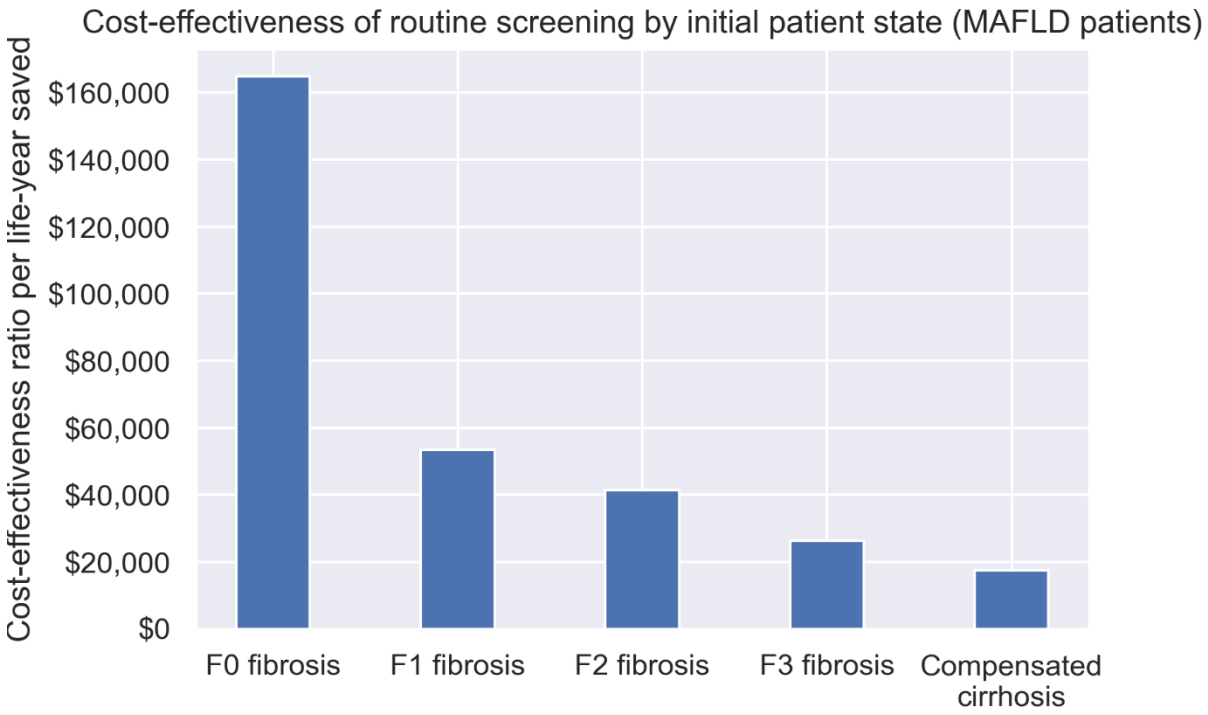
QALE: Quality-adjusted life expectancy. QALY: Quality-adjusted life year. CER: Cost-effectiveness ratio. Discounting at 5% rate.

Once-off weight loss intervention would increase patients' QALE by 0.1622 and reduce liver-disease related costs by $3,972 compared to no intervention; if this were combined with HCC surveillance, patient costs would still be $678 lower than no intervention.

The CER for providing routine HCC surveillance along would be $58,027 per QALY saved – above the indicative willingness-to-pay thresholds used in Australia of $30,000 or $50,000 per QALY saved. 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.

For MAFLD patients with underlying F0 fibrosis, the cost-effectiveness ratio associated with routine HCC surveillance was very high ($164,851 /QALY saved), likely as these patients are less likely to progress to HCC (Figure 11). HCC surveillance was under the indicative $50,000/QALY WTP threshold for patients with F2 fibrosis, F3 fibrosis, and cirrhotic patients, and under the indicative $30,000/QALY threshold for F3 fibrosis and cirrhotic patients.

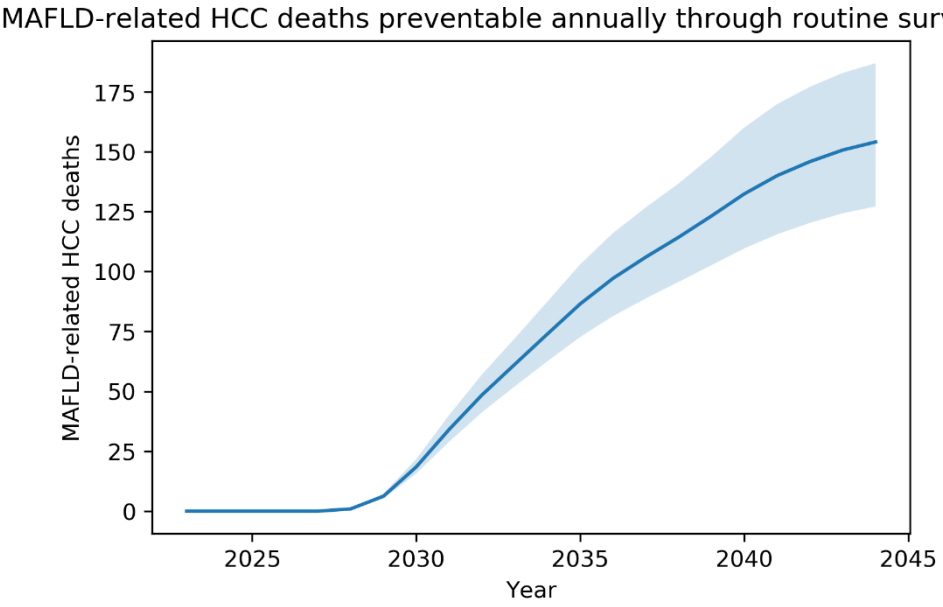
Figure 11 - Cost-effectiveness of routine HCC surveillance in MAFLD patients, stratified by liver disease at baseline



Preventable MAFLD-related HCC deaths in Australia

By 2045, an estimated maximum 150 MAFLD-related HCC deaths could be prevented annually through routine HCC surveillance in Australia (Figure 12). By 2045, an estimated maximum 417 MAFLD-related HCC deaths could be prevented annually in Australia (Figure 12) 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.

Figure 12 – 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



4. Discussion

Alcohol consumption in Australia remains common and excess body fatness continues to increase (over 2017-18, 78.8% of Australian adults drank with 6.3% consuming excessive amounts of alcohol and 67.0% carried excess body weight). This study highlighted the potential for preventing MAFLD- and ARLD-related HCC in Australia, through primary and secondary prevention. As liver cancer rates continue to rise in Australia, ongoing research and clearer understanding in these areas is crucial.

The evidence shows a strong association between excessive alcohol consumption and the risk of liver disease and liver cancer although evidence relating to moderate alcohol consumption is less clear. Excess body weight similarly shows a strong association with risk of NAFLD and primary liver cancer. There are limited studies available relating to the metabolic syndrome and MAFLD. However, local evidence was limited in the Australian context identified.

Interventions designed to reduce the prevalence of alcohol consumption and excess body fatness have the potential to reduce the liver cancer burden, particularly when targeted at high-risk patients with reversible, early-stage liver disease. It should be noted that it may take an extended time for prevention interventions to affect liver cancer outcomes. For example, it has been estimated that it would take a washout period of 23 years for former drinkers to reach the same risk level as never drinkers following abstinence from alcohol (25). In addition, HCC surveillance is effective in diagnosing liver cancer at an earlier stage (15).

Predictive modelling has been used to estimate the impact of evidence-based interventions on the prevention of liver disease. In ARLD patients, HCC surveillance would reduce HCC deaths by 18.6% and prevent an estimated 108 ARLD-related HCC deaths in Australia annually. For patients with current or previous ARLD but with no active alcohol use, 10-year all-cause survival was 61.8%, compared to a 10-year all-cause survival of 37.6% in patients with active alcohol use. In MAFLD patients, HCC surveillance would reduce HCC deaths by 18.1% and 38.2% in combination with weight loss. An estimated 150 MAFLD-related HCC deaths in Australia annually through HCC surveillance alone, up to 417 HCC deaths through once-off weight loss and up to 485 when these interventions are used in combination.

The use of routine HCC surveillance for 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 (16,26). 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 HCC 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 HCC surveillance is successfully identifying low-risk patients who have little to no need for short-term HCC surveillance. As the MAFLD population in Australia grows, identifying these patients will be key to keeping HCC surveillance manageable and reducing the burden on ultrasonography services (69).

Our modelling found that HCC surveillance is unlikely to be cost-effective for MAFLD patients in the early stages of liver disease, such as F0 and F1 fibrosis, as these patients have a lower risk of developing HCC. Patients with later stage disease, such as F2 and F3 fibrosis or compensated cirrhosis, are more likely to benefit from routine HCC surveillance. However, tests such as FIB-4 have poorer sensitivity and specificity for patients with early liver disease, and so cannot be used to reliably exclude patients from HCC surveillance.

A strength of evidence review is the comprehensive nature of the search and appraisal of studies. The included meta-analyses were conducted on a large scale, involving participants from a wide range of geographical locations and various ethnicities. However, results from the included meta-analyses frequently had high heterogeneity, with wide confidence intervals for estimates of the relative risk. This was particularly in relation to studies relating alcohol consumption and risk of liver disease.

Though NAFLD may occur in patients who are lean or not obese (approximately 19% of NAFLD patients are lean) (70) we only included studies relating to excess body weight and the metabolic syndrome. Additionally, this review did not investigate the role of type 2 diabetes mellitus (T2DM). T2DM has been identified as an important predictive, although not necessarily causative, risk factor for NAFLD (52). Understanding the interplay between excess body weight, metabolic syndrome and T2DM will be important to capture and account for in future research.

This analysis focuses on HCC and 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 (71,72). The outcomes presented here are through a narrow lens. Note that we also cannot capture any potential expenses associated with weight loss, such as the use of medication.

It should be emphasised that this analysis only provides an estimate of how many HCC deaths are potentially preventable in Australia through primary prevention or routine HCC surveillance. There are significant difficulties associated with both identifying patients with MAFLD or ARLD and implementing HCC surveillance, weight loss, or alcohol cessation interventions. The numbers included here should be interpreted with caution and proper context.

Future reviews could seek to identify evidence regarding the interplay between risk factors chronic liver disease and primary liver cancer. While the key risk factors chronic viral hepatitis, ARLD and NAFLD each have distinct pathways of disease progression, evidence increasingly shows that there is overlap and possible synergism between different risk factors. Presence of high BMI and metabolic syndrome can exacerbate disease progression in ARLD, for example, putting patients at heightened risk of primary liver cancer and mortality (73,74). Additionally, the change in terminology to MAFLD facilitates research in patients with concomitant liver disease as the exclusion of significant alcohol intake or other chronic liver disease is no longer a pre-requisite for its diagnosis (75). In future work, predictive modelling can be extended to identify whether non-invasive testing can be used to identify patients with metabolic-associated steatohepatitis (MASH), a more developed form of MAFLD, and whether routine HCC surveillance would be more cost-effective for MASH patients compared to MAFLD patients.

5. Conclusion

It is important that efforts are taken to understand the impact of modifiable risk factors so that action can be taken to reduce the future burden of liver cancer in Australia. Using current evidence and predictive modelling, recommendations can be developed for those with liver disease associated with modifiable risk factors including alcohol consumption and excess boy weight. Not only do the findings of this project illustrate the extent to which liver cancer outcomes can be improved, it also demonstrates both the cost and cost-effectiveness of primary and secondary prevention interventions in emerging high-risk groups to build the case for policy and practice change. This would guide future investment in liver cancer control and reduce the burden in Australia.

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