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Preventing liver cancer: Modelling estimates for diagnosis and surveillance of MASH and MAFLD patients

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Contents

Purpose of this report

This report describes the predictive modelling completed to support the *Preventing Liver Cancer: Assessing the benefits of risk assessment for patients with metabolic-associated fatty liver disease* report. It is designed to be a supplement to be read in parallel to that report where further detail is required.

This report contains significant material previously included in the *Preventing Liver Cancer: Obesity and Alcohol Consumption* report, with adjustments and updates made where appropriate.[1]

Background and aims

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer[2] and is a significant public health issue worldwide.[3,4] Both the incidence and mortality burden of liver cancer are increasing in Australia.[5] HCC is a complex disease that requires multidisciplinary management and poses significant and emerging challenges in terms of diagnosis, treatment, and prevention.

One of the leading causes of hepatocellular carcinoma is metabolic-associated fatty liver disease (MAFLD), 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).[6]

Routine HCC surveillance of patients with high risk of advanced MAFLD for development of HCC can assist with early detection and increase the likelihood of curative treatment.[7,8] This monitoring typically uses biomarkers or non-invasive imaging. However, this would come at a cost of $58,000 per QALY saved,[1] above the usual $30,000 or $50,000 per QALY willingness-to-pay thresholds used in Australia. This was primarily driven by patients with early-stage liver disease, who had a low risk of HCC. Targeting patients with later stage liver disease would improve the relative health benefits and cost-effectiveness of HCC surveillance.

Metabolic-associated steatohepatitis (MASH) refers to the inflammation of the liver in patients with MAFLD, and is a more advanced stage of liver disease.[a] Patients with MASH are likely to develop late-stage liver disease, such as liver fibrosis and cirrhosis. NASH patients have a higher HCC incidence rate vs NAFLD patients (5.29 vs. 0.44 per 1,000 person-years)[9] and may therefore be more likely to benefit from HCC surveillance compared to MAFLD patients. 'MASH' replaces the previous classification of non-alcoholic steatohepatitis (NASH).

The aim of this study is to use predictive modelling to identify the health benefits and cost-effectiveness of routine HCC surveillance for MASH patients in Australia, including the cost-effectiveness of triaging patients with MAFLD to HCC surveillance based on likelihood of having MASH.

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

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 MASH and MAFLD patients at risk of developing HCC. The health states included in *Policy1-Liver* are shown in Figure 1.

Patients 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.[10] 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.[11] Although other measures of liver disease severity, such as inflammation/activity score,[12] fibrosis stage is a strong indicator of HCC risk with widely available patient data, making it an ideal proxy state for modelling.[13] Many MAFLD patients would subsequently be diagnosed with MASH – for simplicity, patients are modelled and referred to according to their primary diagnosis of MAFLD/MASH at model start time. Details of the distribution of initial fibrosis stage are included in Table 8, and differ between MAFLD and MASH patients.

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. Fibrosis progression rates and risk of HCC differ for MAFLD and MASH patients.

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 diagnosis of MASH, 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 10. All costs use Australian sources and are presented in 2023 Australian dollars. The study took a *health system perspective*;[14] indirect costs such as productivity losses and travel costs were not included.

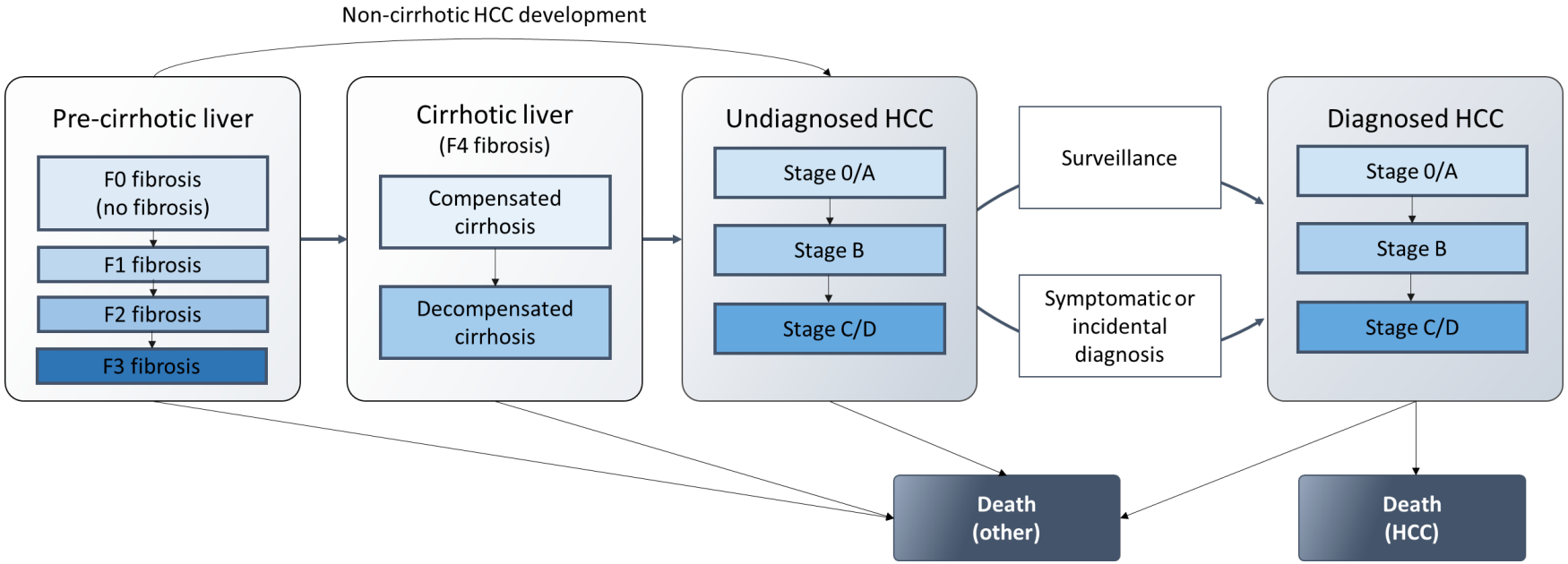
Health state utilities were also calculated for all patients. Health state utilities are used to capture a patient's *quality of life*, with patients with more severe/debilitating diseases experiencing lower quality of life. This is used to assess the health benefits associated with avoiding outcomes 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.[15] 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.[5] Combined with estimates of the proportion of liver cancers attributable to HCC,[16] the burden of MAFLD and MASH, and fibrosis stage among MAFLD and MASH patients,[10] this was used to generate projections of the number of MAFLD/MASH-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/MASH patients.*



MAFLD and MASH patients in Australia

Data sources for patient groups with confirmed MAFLD/MASH diagnoses are largely unavailable.[17] Positive diagnoses under MAFLD/MASH criterion vs NAFLD/NASH criterion was significantly associated with males, patients with higher BMI, and patients with higher fibrosis scores.[18] However, the majority of patients diagnosed with NAFLD/NASH would also receive a positive diagnosis for MAFLD/MASH, and vice versa. Further research is required to establish detailed prognostic differences between patients diagnosed with MAFLD/MASH and NAFLD/NASH.

For these reasons, we refer to patients in this section as MAFLD or MASH patients, though the majority of the relevant data sources were established in patients diagnosed with NAFLD and NASH. Unless noted, MAFLD/MASH patients are assumed to have the same risk of developing liver disease and HCC as NAFLD/NASH patients respectively.

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.[10] 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).

Routine HCC surveillance

Secondary prevention of HCC in MAFLD/MASH 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, international clinical practice guidelines recommend the use of non-invasive tests to stratify patients into risk categories,[19–21] with only those at high risk (typically with cirrhotic liver) recommended to progress to regular ultrasound surveillance.[22]

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.[13] 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,[23,24] 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.[25–27] 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.[28] Additionally, ultrasounds require trained sonographers, but Australia is experiencing a shortage of sonographers alongside an increase in demand.[29] By using more affordable and simple procedures to exclude patients with low risk, more effective and efficient surveillance can be provided.

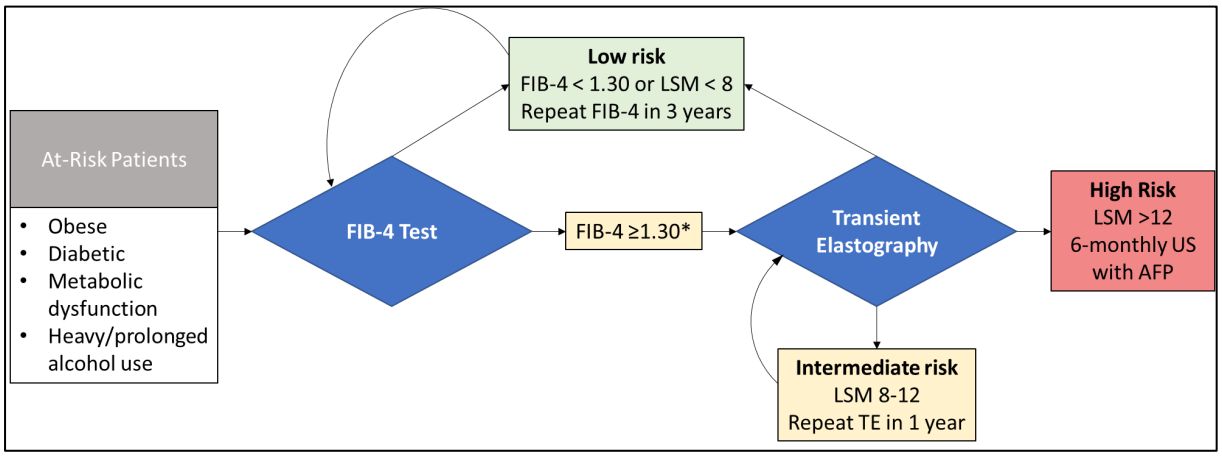
Surveillance was modelled via the following algorithm:

- FIB-4 testing every 3 years for all included 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.[19–21] Providing 6-monthly ultrasound for patients with likely cirrhotic liver is in line with GESA recommendations for cirrhotic patients[22] 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 4.

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.



Triaged HCC surveillance for MASH patients

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

Patients who had a positive diagnostic test were referred to routine HCC surveillance, as illustrated in Figure 2. 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;[20,21,30] more details are included in the supplementary modelling report.[31]

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

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

Note that FIB-4 is used at a higher positivity threshold for the diagnosis of MASH, compared to the threshold used for routine HCC surveillance. Test characteristics of the diagnostic tests used are shown in Table 7.

Results – MASH patients

Baseline health outcomes

Predicted health outcomes for MAFLD and MASH patients are shown in Table 1. Patients who had been diagnosed with MASH were over 5 times more likely to develop HCC over their lifetime compared to MAFLD patients, and nearly 6 times more likely to die from HCC over their lifetime. The onset of HCC was more likely to occur sooner in patients with MASH vs those with MAFLD. Patients diagnosed with MASH also had lower life expectancies. These are illustrated in Figure 3 and Figure 4

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

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

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

Without any intervention, in the MAFLD cohort estimated lifetime HCC incidence would be 3,051 per 100,000, and with an estimated lifetime HCC mortality of 2,112 per 100,000. In the MASH cohort this would be significantly higher at 16,940 and 12,443 respectively. Without intervention, 46% of HCC diagnoses in MAFLD patients 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). This would be similar in MASH patients, with 48% early and 25% intermediate.

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. In MASH patients this would be $55,096, due to higher costs associated with late-stage liver disease.

Figure 3 – All-cause survival by years since MAFLD/MASH diagnosis.

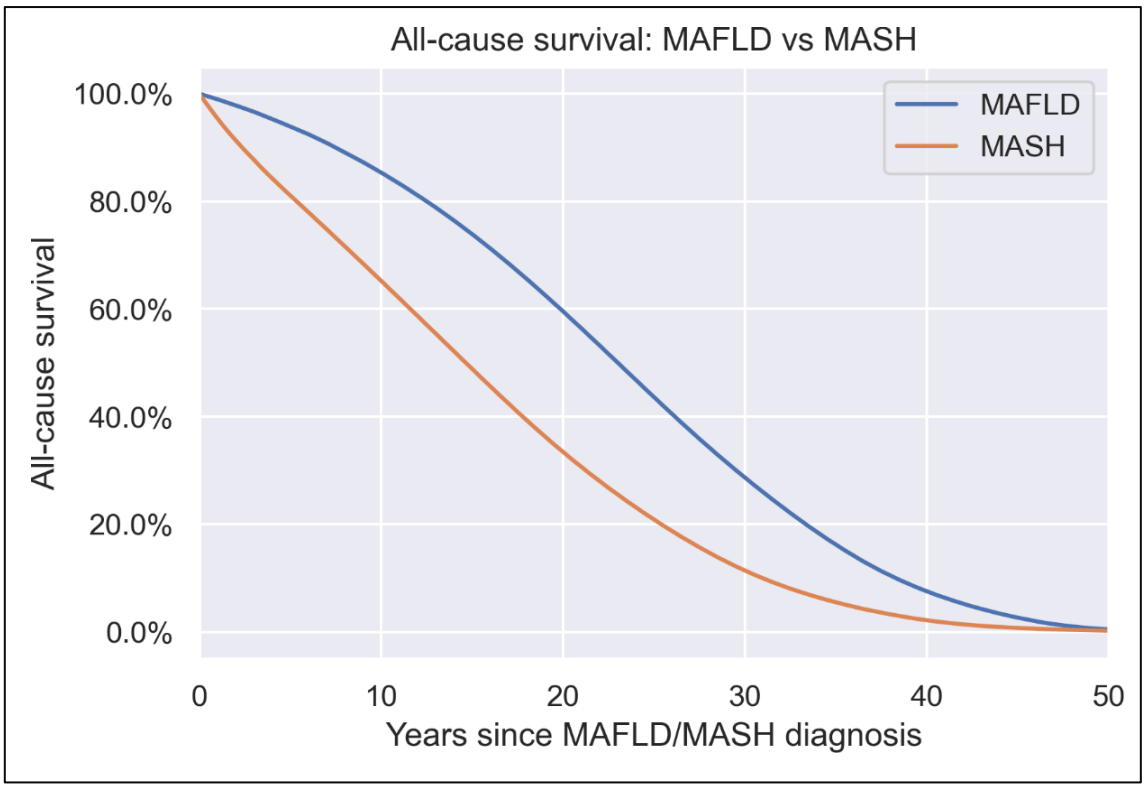
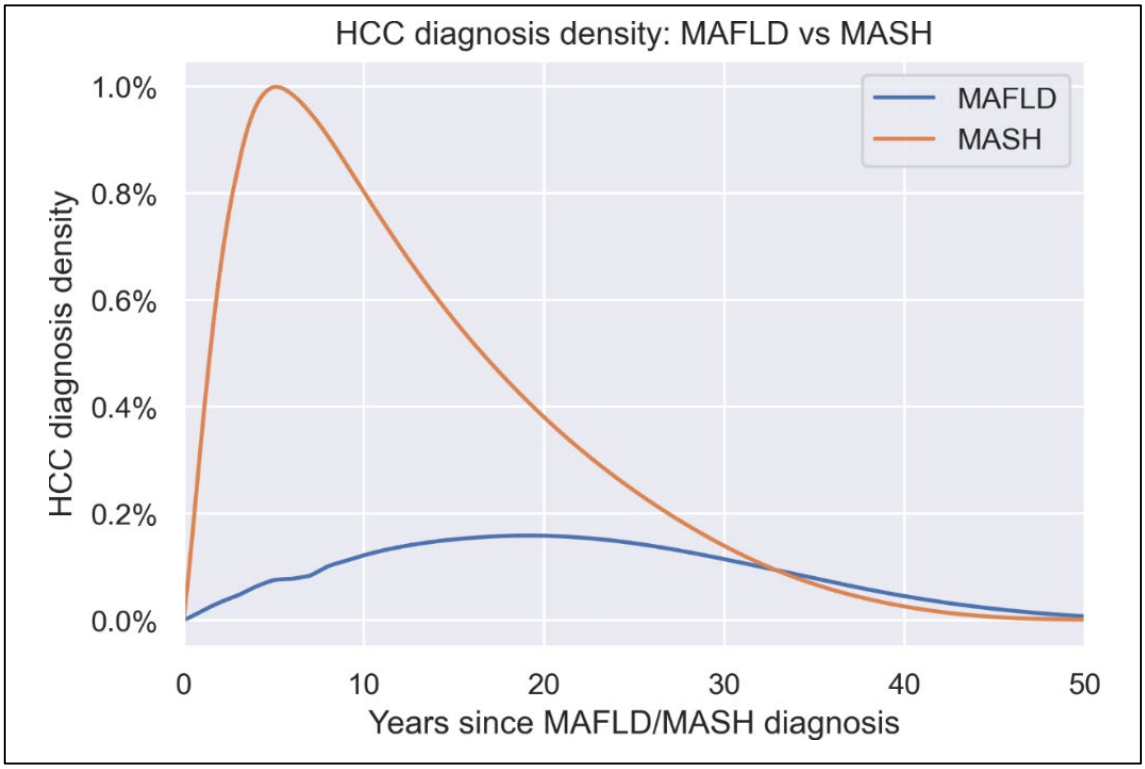


Figure 4 - Annual HCC incidence by years since MAFLD/MASH diagnosis.



Routine HCC surveillance

By providing routine HCC surveillance to MAFLD patients, lifetime HCC mortality risk can be reduced by 18% vs to the "no intervention" comparator to 1,730 per 100,000 in the modelled cohort (Table 1). This would be achieved through detection of HCC at earlier stages with higher chances of curative treatment. Overall, with routine HCC surveillance, 70% of HCC diagnoses would be at early stages. For MASH patients, this reduction would be 27%, and 83% of HCC diagnoses would be at early stage – a significant improvement over the MAFLD cohort.

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 represents a 4.1% increase in costs over the no intervention scenario. In the MASH cohort, this cost would be $58,032 – a 5.3% increase.

Cost-effectiveness of routine HCC surveillance MAFLD and MASH 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 - Predicted impact of routine HCC surveillance on quality-adjusted life expectancy (QALE, measured in quality-adjusted life-years or QALYs) and costs. Discounted values use a 5% annual discount rate. CER: cost-effectiveness ratio.

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

Providing routine HCC surveillance would save 0.0171 discounted QALYs per person in MAFLD patients, and 0.2307 in MASH patients. This increase reflects the higher likelihood of HCC development in MASH patients. However, the costs associated with surveillance would also be significantly higher in MASH patients, at $2,650 (discounted) vs $972 in MAFLD patients.

The cost-effectiveness ratio for providing routine HCC surveillance along would be $56,885/QALY saved for MAFLD patients – above the typically cited willingness-to-pay thresholds of $30,000 or $50,000 per QALY saved used in Australia. This implies that routine HCC surveillance would not be considered cost-effective in MAFLD patients. For MASH patients, this cost-effectiveness ratio would be $11,487/QALY saved – below the willingness to pay thresholds.

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 gain or loss. Overweight and obesity is a major

determinant of many health outcomes, not just liver disease, and is a key health concern in Australia.[32,33] The outcomes presented here are naturally through a narrow lens. Potential treatments for weight loss are likely to dramatically shift patient risk and costs.

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

Recommending HCC surveillance for patients with a positive FIB-4 or ADAPT would significantly increase the cost-effectiveness of HCC surveillance compared to providing HCC surveillance for all MAFLD and MASH patients, as shown in Table 3. Stratified HCC surveillance using ADAPT, which has a high sensitivity, would increase the QALE by almost as much as HCC surveillance for all MAFLD and MASH patients. FIB-4 HCC surveillance has a lower sensitivity but a higher specificity, increasing the cost-effectiveness of HCC surveillance significantly through reduction of over-screening in patients who are unlikely to develop HCC. Compared to no intervention, all HCC surveillance approaches would be cost-effective. However, when compared to stratified HCC surveillance, HCC surveillance for all MAFLD and MASH patients would be very cost-ineffective, with an incremental cost-effectiveness ratio of $700,416 per QALY saved. This reflects the marginal improvement in health benefits vs ADAPT or FIB-4 stratified screening at a higher cost and is illustrated in Figure 5.

Table 3 – Predicted impact of stratified HCC surveillance strategies for all MAFLD and MASH patients, including costs and false positive/negative diagnoses associated with the use of diagnostic tools. QALE: quality-adjusted life expectancy. QALY: quality-adjusted life-years. CER: cost-effectiveness ratio. ICER: incremental cost-effectiveness ratio.

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

*Total number of potentially preventable HCC deaths in Australia annually, based on implementation in 2023.

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. This analysis incorporated projections of liver cancer related cases and deaths in Australia to 2044.[5]

Figure 5 - Cost-effectiveness plane for routine HCC surveillance for MAFLD and MASH patients, including FIB-4 or ADAPT stratified HCC surveillance. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life-year.

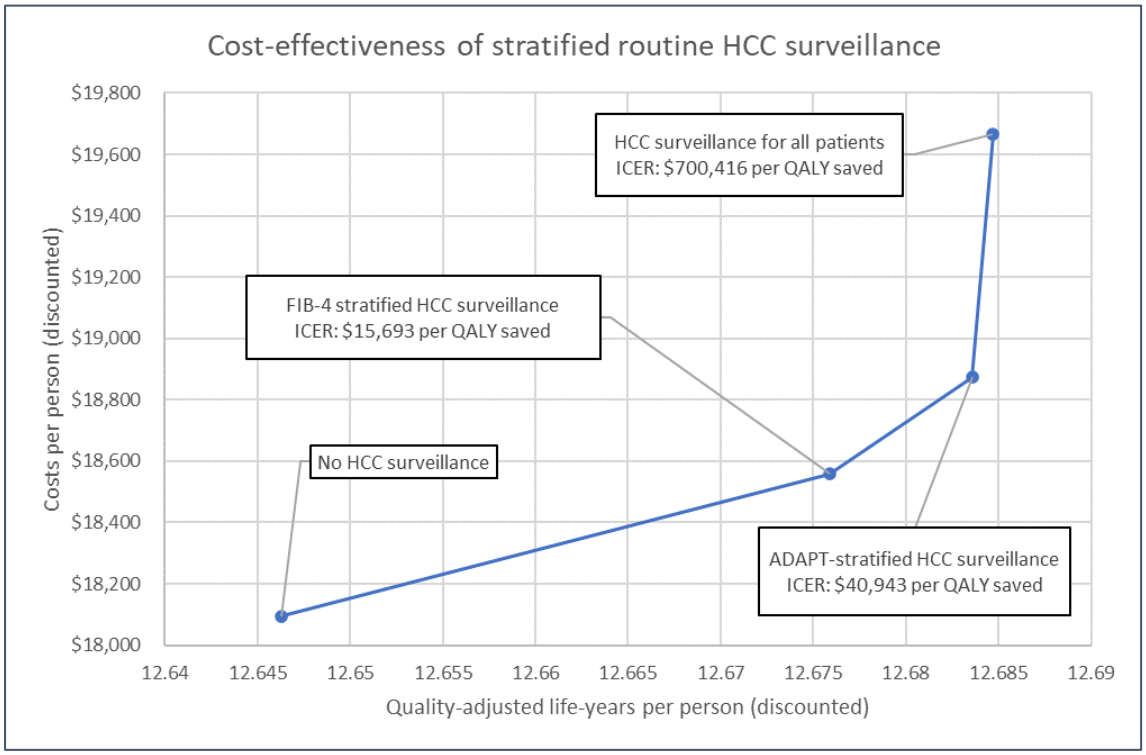
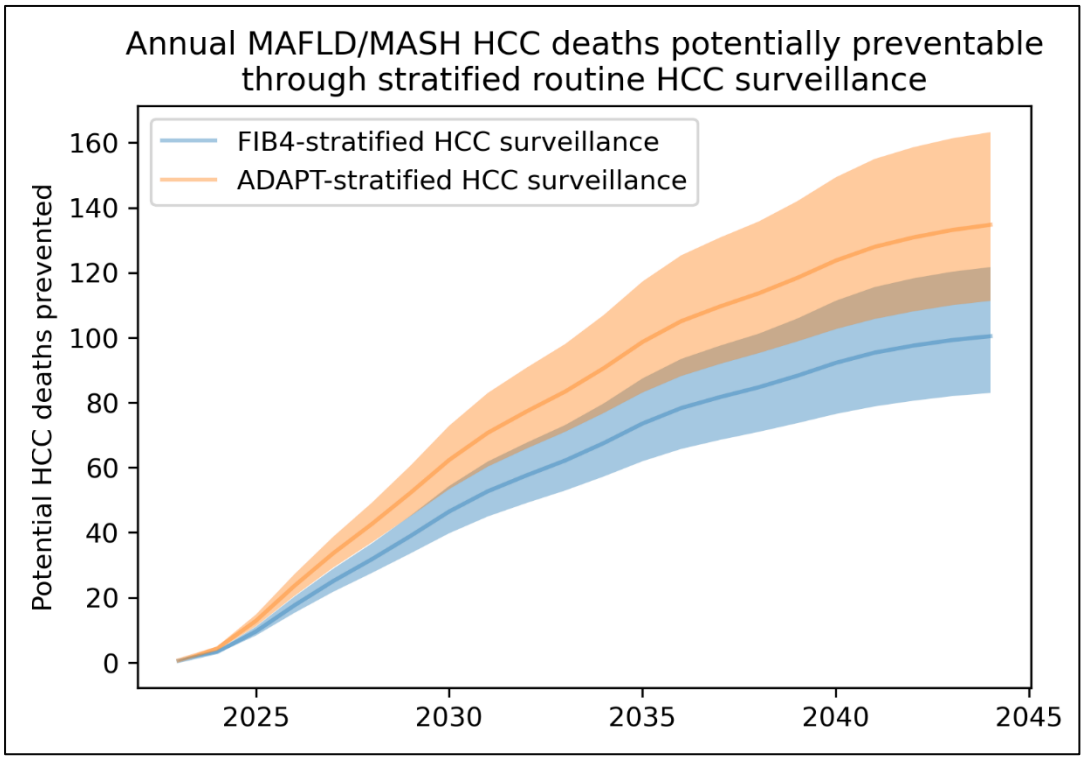


Figure 6 – Estimated maximum number of annual MAFLD- and MASH-related HCC deaths which could be prevented through providing routine HCC surveillance to all Australian MAFLD patients from 2023. Shaded area: 95% confidence interval, based on projections of liver cancer deaths in Australia.



By 2045, an estimated maximum 100 MAFLD-related HCC deaths could be prevented annually through FIB-4 stratified routine HCC surveillance in Australia, compared to 143 for ADAPT-stratified surveillance (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.

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

Discussion

This study highlighted the potential for preventing MAFLD--related HCC in Australia through surveillance, as well as the significant improvements to health system efficiency through risk-stratification to identify MASH patients. As MAFLD and HCC 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 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 and MASH population in Australia grows, identifying these patients will be key to keeping surveillance manageable and reducing the burden on ultrasonography services.[29]

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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 MAFLD/MASH. 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.

Five-year survival for HCC patients 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 [34] 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.[35] 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 8.

All costs are reported in 2022 Australian dollars, with the health CPI index used to inflate costs where necessary.[36] Costs for individual surveillance and diagnostic procedures were collated from MBS Online.[37] 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 10.

Routine HCC surveillance

The details of the algorithm used for HCC surveillance are given in Table 4 and illustrated in Figure 2. Parameter relating to surveillance (see algorithm in Table 4 and illustrated in Figure 2) are given in Table 6, including sensitivity, specificity, and positive rates for FIB-4, TE, and US by stage of disease. Costs associated with surveillance are given in Table 10.

Table 4 - Modelled surveillance algorithm for patients at risk of developing HCC.

Group	FIB-4 outcome	TE outcome	Recommendation
Low Risk	FIB-4<1.30	Not completed	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.

Diagnosis of MASH

In model scenarios where patients were initially provided with stratification to diagnose MASH, we modelled the sensitivity and specificity of the technology (FIB-4 or MAFLD). Patients who would receive a positive test, including false positives, were referred to routine HCC surveillance as described above. People who would receive a negative test, including false negatives, would receive no further surveillance and diagnosis was assumed to be symptomatic or incidental diagnosis. The test characteristics of the diagnostic tests are included in Table 7.

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 MAFLD/MASH patients, as identified in the evidence 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 5-14 and Figures 7-10. Further calibration outcomes have been reported previously, including rates relating to the development of cirrhosis, HCC, and cancer survival.[1,38]

Figure 7 – Fibrosis stage distribution for MAFLD and MASH patients.(top) and annual fibrosis upstage rates in MASH patients (bottom).[39,40]

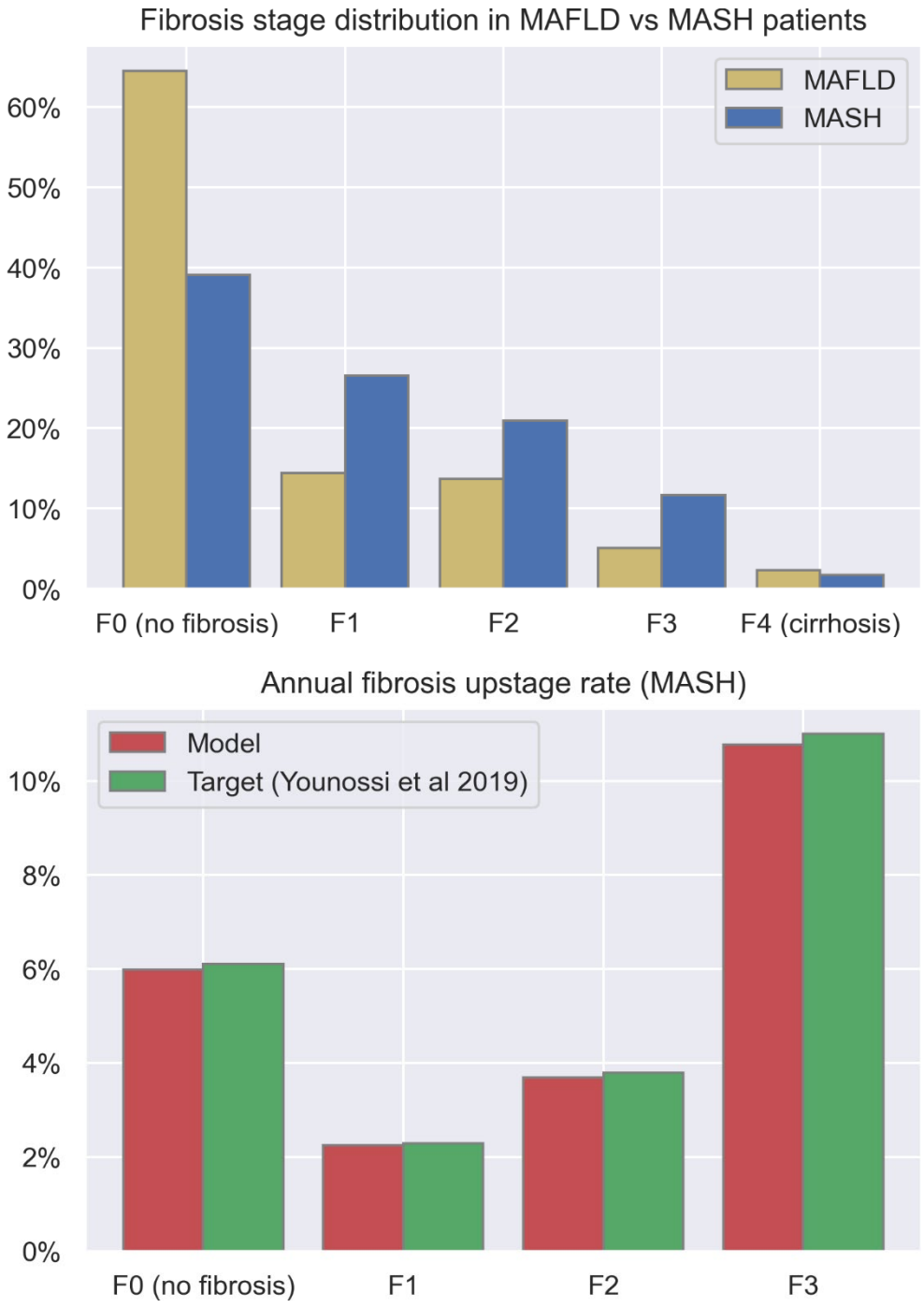


Figure 8 –Calibration targets for MAFLD/MASH patients. Top: cumulative HCC risk in MAFLD patients. Bottom: cumulative HCC risk in MASH patients.[41]

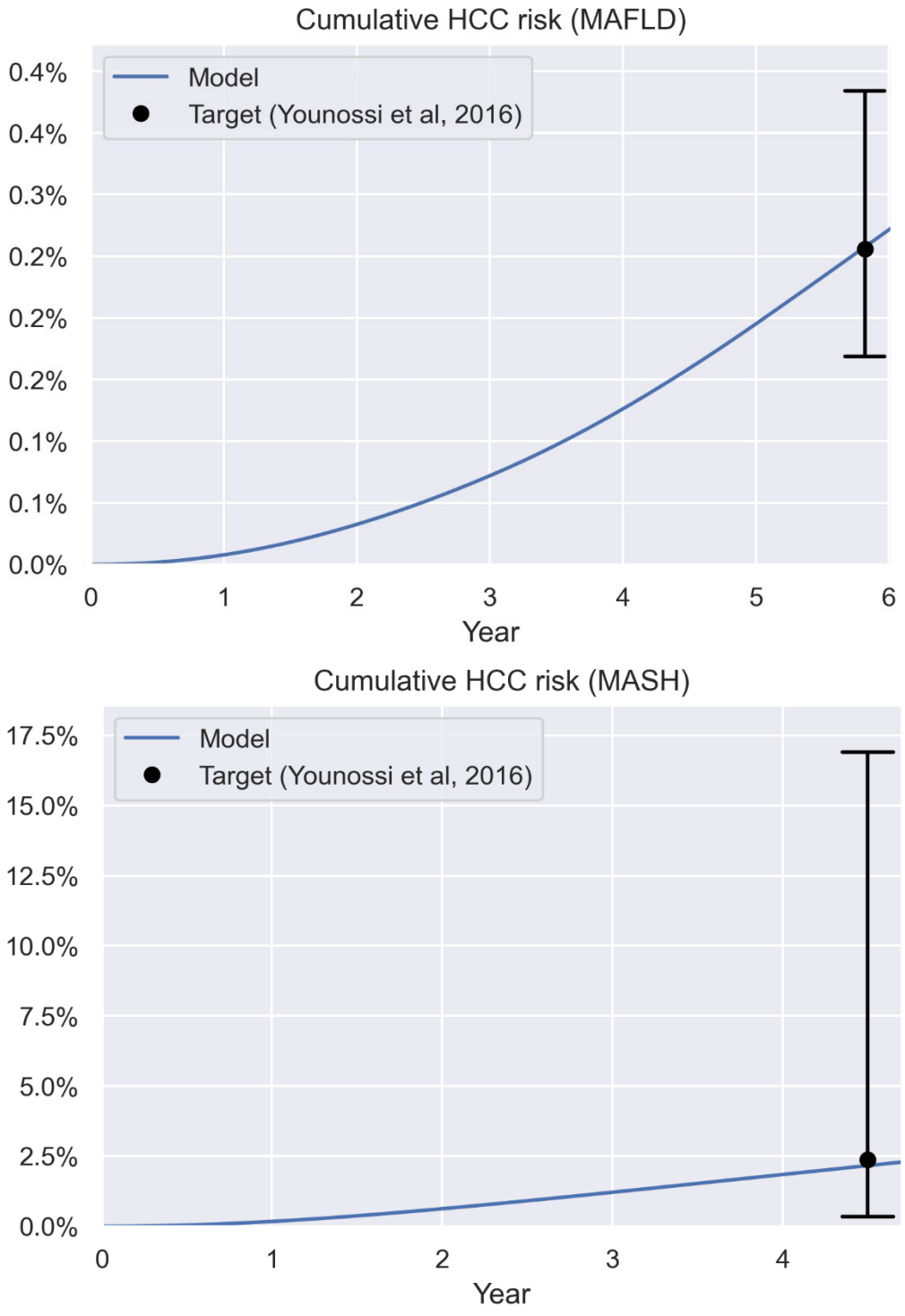


Figure 9 – Cumulative cirrhosis risk in MASH patients (top), mortality risk in MAFLD patients (middle), and mortality risk in MASH patients (bottom).[41,42]

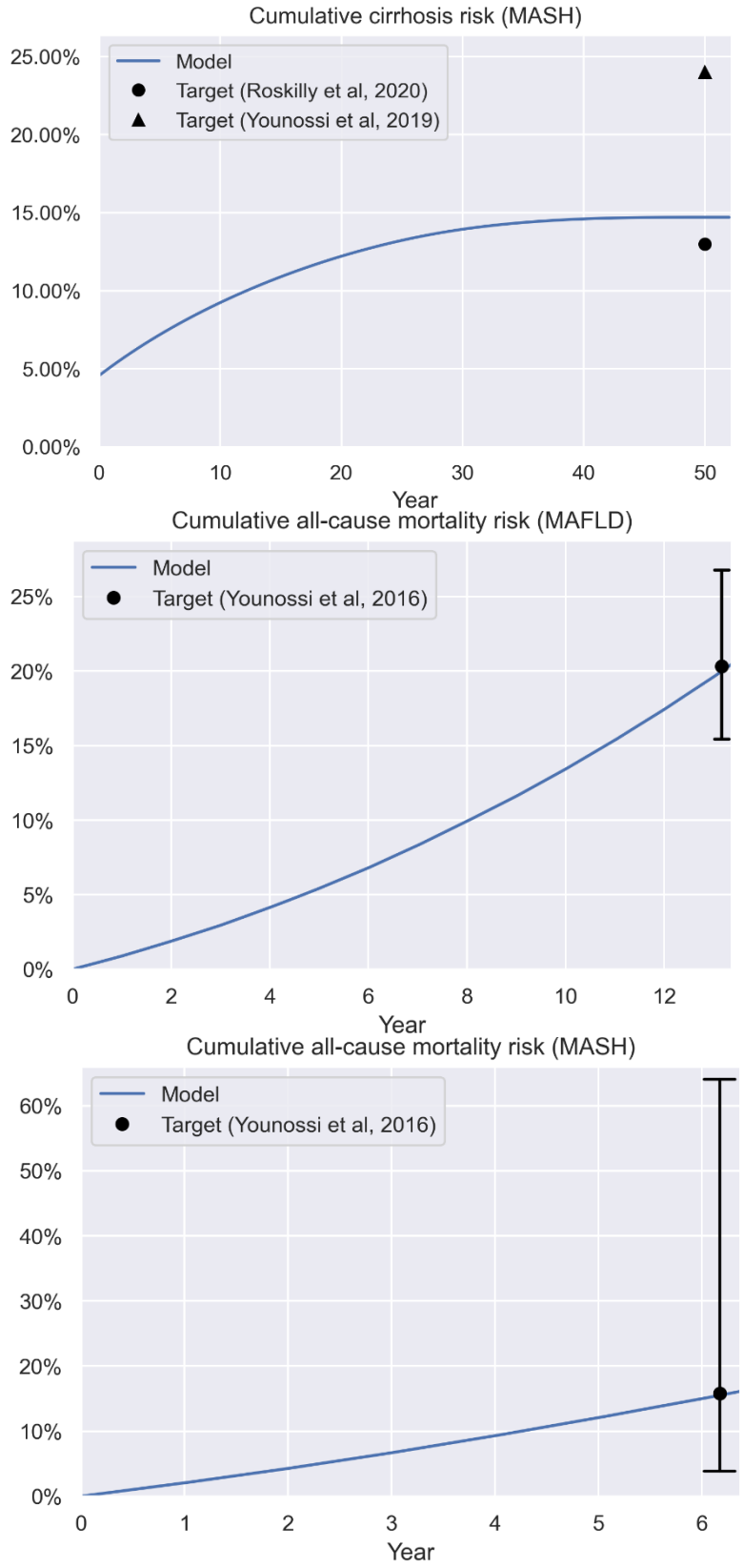
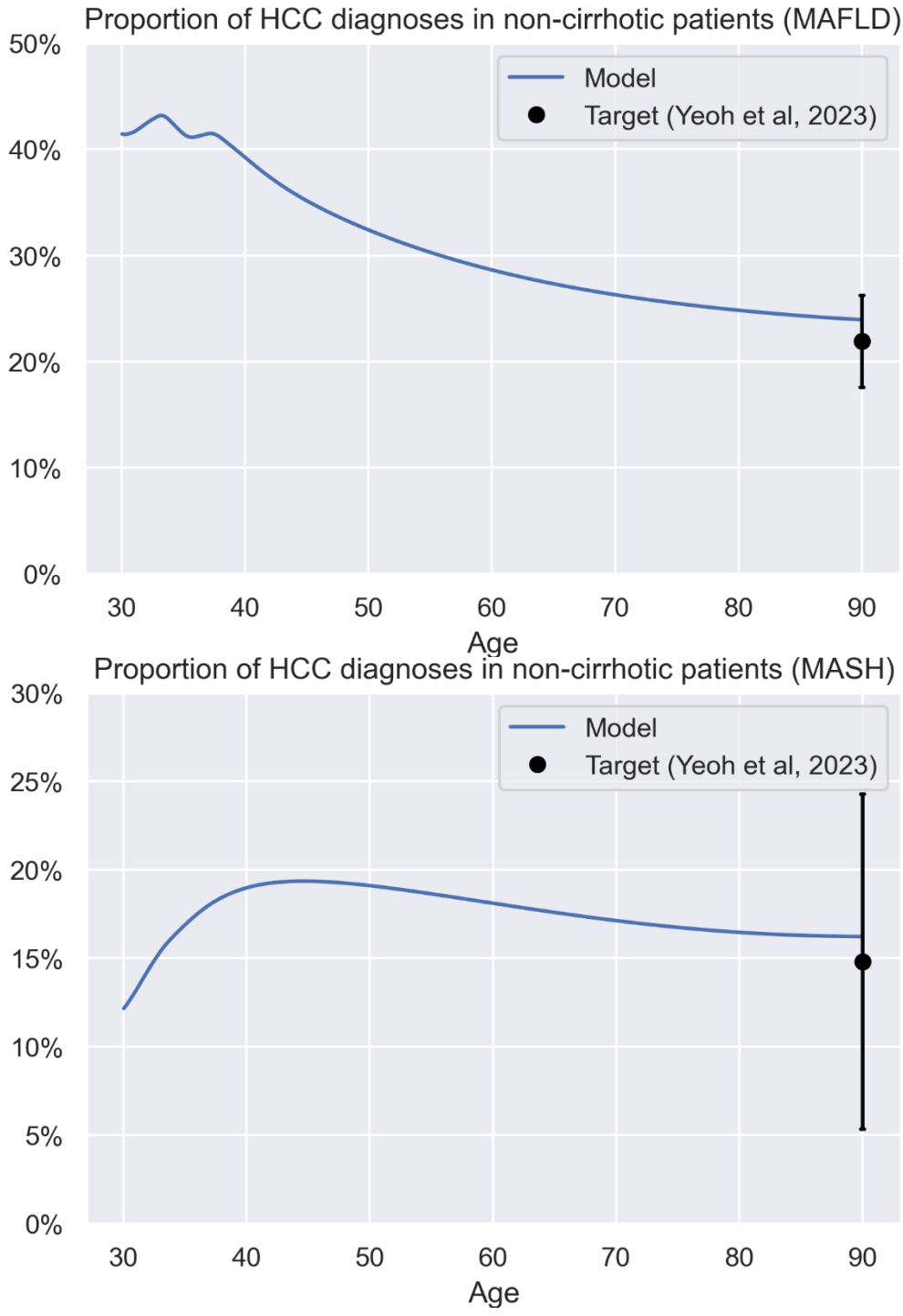


Figure 10 - Cumulative proportion of HCC diagnoses occurring in the absence of cirrhosis in MAFLD (top) and MASH (bottom) patients.[43]



Model parameters

Table 5 – Parameter table for liver disease progression.

Description	Value	Targets/source
MASH progression		
Upstaging hazard rate for F0 fibrosis	0.0628	[40]
Upstaging hazard rate for F1 fibrosis	0.0232	
Upstaging hazard rate for F2 fibrosis	0.0387	
Upstaging hazard rate for F3 fibrosis	0.1162	
Annual HCC rate	0.529%	[41]
Annual mortality rate	2.556%	
MAFLD progression		
Upstaging hazard rate for F0 fibrosis	0.0145	[10]
Upstaging hazard rate for F1/2 fibrosis	0.0884	
Upstaging hazard rate for F3 fibrosis	0.0661	
Annual HCC rate	0.044%	[41]
Annual mortality rate	1.544 %	

Table 6 – Test characteristics for surveillance technologies.

Description	Value	Targets/source
FIB-4		
Positive rate for patients with F0 fibrosis	23.5%	44
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%[2]	
Transient Elastography		
Inconclusive rate for patients with F0 fibrosis	12.6%	45
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%	46
Sensitivity (early-stage HCC)	63%	
Sensitivity (intermediate/late-stage HCC)	97%	

Table 7 – Test characteristics for the diagnosis of MASH in MAFLD patients.

Description	Value	Targets/source
FIB-4 sensitivity for detection of MASH in MAFLD patients	57%	47
FIB-4 specificity for detection of MASH in MAFLD patients	89%	
ADAPT sensitivity for detection of MASH in MAFLD patients	77%	48
ADAPT specificity for detection of MASH in MAFLD patients	69%	

Table 8 – Disease prevalence among MAFLD/MASH patients.

Description	Value	Targets/source
MASH		
Proportion of MASH with F0 fibrosis	39.13%	39
Proportion of MASH with F1 fibrosis	26.55%	
Proportion of MASH with F2 fibrosis	20.95%	
Proportion of MASH with F3 fibrosis	11.66%	
Proportion of MASH with F4 fibrosis (cirrhosis)	1.71%	
MASH prevalence in MAFLD patients	23.9%	10
MAFLD		
Proportion of MAFLD with F0 fibrosis	64.51%	39

[2] Based on expert advice.

Proportion of MAFLD with F1 fibrosis	14.42%	
Proportion of MAFLD with F2 fibrosis	13.69%	
Proportion of MAFLD with F3 fibrosis	5.11%	
Proportion of MAFLD with F4 fibrosis (cirrhosis)	2.28%	
Proportion of liver cancer deaths from HCC	57.6%	
Proportion of HCC deaths attributable to MAFLD	38.6%	[49]

Table 9 – Procedure utilisation for the detection and treatment of confirmed HCC.

Description	**Value**	**Targets/source**
Procedures for HCC diagnosis		
CT	80%	[50]
MRI	20%	
Biopsy	10%	
Early-stage (0/A) HCC treatment		
Transplant	19.0%	[51]
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%	[51]
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%	[51]
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 10 – Costs and disutilities used in the cost-effectiveness evaluation.

Item	Value	Range	Source
Annual cirrhosis care costs			
Compensated	$4,713	$1,108-8,772	[52]
Decompensated	$22,701	$10,464-34,939	
Surveillance-related costs			
Ultrasound	$115.75	-	[37] As of March 2023.
AFP	$24.35	-	
GP Visit	$39.75	-	
FIB4	$14.25	-	
ADAPT	$14.25	-	
TE	$161.90/81.0[3]	-	
CT (diagnostic)	$499.50	-	
MRI (diagnostic)	$558.80	-	
Liver biopsy (diagnostic)[4]	$377.2	-	
Treatment-related costs[5]			
Liver transplant	$320,107	-	[35]
Liver resection	$73,310	-	
Ablation (RFA/MWA/PEI)[6]	$94,611	-	
TACE[7]	$76,482	-	
Sorafenib	$42,338	-	
End-of-life costs			
Death from cancer	$44,945	$44,015-45,873	[53]
Death from other causes	$31,513	$30,767-32,259	
Disutilities (annual)			
Compensated cirrhosis	0.32	0.31-0.33	[54]
Decompensated cirrhosis	0.38	0.36-0.40	
HCC – Diagnostic Phase	0.288	0.193-0.399	[55]
HCC – Controlled Phase	0.049	0.031-0.072	
HCC – Terminal Phase	0.540	0.377-0.687	

[3] First event/subsequent events.
[4] Including anesthesia costs.
[5] Patient treatment costs are overall costs classified according to their primary treatment, following the methodology in Hong et al.[35] Patients may have further treatments -these costs are included in the figures presented.
[6] Proportion of patients allocated to RFA/MWA/PEI based on the proportions reported in Hong et al.[35]
[7] 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 [56] 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.[57]

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

$$\sum_{\mathrm{j}} \int_0^{\infty} f_{i,j}(0, \tau) + \sum_{\mathrm{k}} \int_0^{\mathrm{t}} f_{\mathrm{k,i}}(\mathrm{s}, 0)\mathrm{d\,s} - \sum_{\mathrm{j}} \int_0^{\mathrm{t}} f_{\mathrm{i,j}}(\mathrm{s}, 0)\mathrm{d\,s}.$$

In practice, this model is implemented by discretizing each transition distribution via a *finite difference method*.[58] 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.