**Cost-effectiveness analysis of HCC screening in MASLD patients without cirrhosis**

**Background**

Currently, an estimated 25% of the global population has non-alcoholic fatty liver disease (NAFLD, now referred to as metabolic-dysfunction associated steatotic liver disease (MASLD)1. MASLD is becoming an increasingly prevalent cause of HCC globally and in the U.S. due to rising rates in obesity and metabolic disease.

Additionally, HCC incidence in patients without cirrhosis is higher for those with MASLD compared to other liver disease etiologies2. Over a quarter of MASLD-related HCC can occur in the absence of cirrhosis, making surveillance and early detection of HCC challenging in this population3-5. In the U.S. and Europe, HCC incidence in patients with non-cirrhotic NAFLD/NASH has been reported to be 0.1 to 1.3 per 1,000 patient-years2. Despite the relatively lower incidence of HCC among patients without cirrhosis compared to those with cirrhosis, the high prevalence of MASLD is likely to increase the number of HCC cases due to non-cirrhotic MASLD. In fact, in a Veterans Affairs cohort, the annual incidence of HCC among patients with NAFLD was projected to increase 122% by 20302. However, current AASLD guidelines do not recommend regular HCC screening in patients with non-cirrhotic MASLD/NAFLD. Due to the low incidence of HCC in MASLD patients without cirrhosis, it is not considered to be cost-effective to perform HCC surveillance in this cohort6.

Previous studies have shown overweight/obesity, diabetes, male sex, and White, Hispanic, and Asian race/ethnicity in combination with obesity to be associated with higher HCC incidence7. Additionally, studies report that 20-25% of patients with HCC cirrhosis were not aware of their cirrhosis prior to being diagnosed with HCC, especially among older patients and those with NAFLD8-11. Therefore, an underdiagnosis of cirrhosis could play a factor in reducing access to HCC surveillance among patients with MASLD. However, there are no cost effectiveness analyses (CEA) performed to further stratify the non-cirrhotic MASLD population to identify a group with higher risk of HCC in which HCC surveillance would be cost-effective.

We aim to perform a CEA to identify a high-risk population among patients with non-cirrhotic MASLD in which HCC surveillance would be cost-effective. The results of this study could help inform practice guidelines to improve the early detection and outcomes of HCC in patients with non-cirrhotic MASLD.

**Objectives**

1. **Primary objective:** Determine the cost-effectiveness of conducting HCC surveillance in patients with non-cirrhotic MASLD in the U.S.
2. **Secondary objectives:** Evaluate the impact of demographic (age, sex, race/ethnicity) and clinical variables (platelet, INR, FIB-4, diabetes, overweight/obesity) on HCC incidence in the non-cirrhotic MASLD population to determine a high-risk group in which HCC screening would be cost effective.

**Study Design and Methods**

**Population and setting**

Our study population will include adult patients (³18 years) in the U.S. who have non-cirrhotic MASLD. Sub-group analyses will be performed by demographic and clinical variables.

**Study Design**

The intervention arm will be patients with non-cirrhotic MASLD who receive regular HCC screening (biannual abdominal ultrasound and AFP). The control arm of this study will be all patients with non-cirrhotic MASLD who do not receive regular HCC screening.

We will conduct sub-group analyses to determine the cost effectiveness of conducting HCC screening in patients with various combinations of demographic and clinical characteristics that could impose higher HCC incidence. The cost-effectiveness of these groups will be compared to that of conducting HCC screening in all patients with non-cirrhotic MASLD.

**Time:** Utility and costs will be evaluated across a lifetime horizon.

**Discount rate:** 3% annual decrease in both cost and utility (as recommended by the Public Health Service Panel on Cost-Effectiveness in Medicine, Lipscomb et al., 1996)

**Measured outcomes:** The quality adjusted life years (QALYs) will be calculated using the estimated quality (quantified value ranging from 0-1) and length of life. The length of life will be estimated by the CEA model and will be validated using real-world data.

All costs will be determined from the payer’s perspective and will be converted to USD in 2024.

The incremental cost effectiveness ration (ICER) will be calculated for the intervention arms compared to the control and will be interpreted with reference to the contemporary willingness to pay threshold (WTP) of $100,000 or $150,000.

**Model and assumptions:**

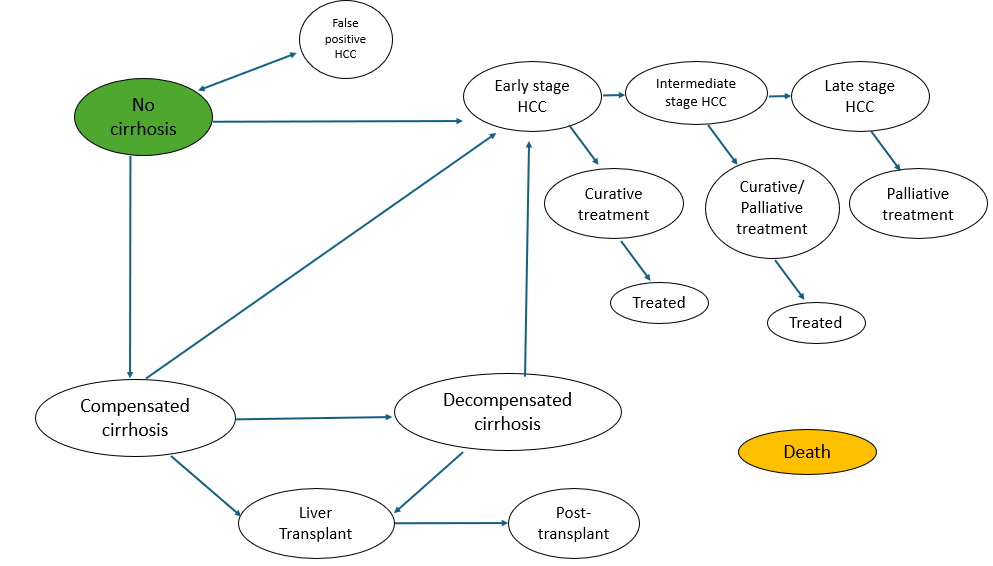
**Key Idea**

We want to measure the cost-effectiveness of screening MASLD non-cirrhosis patients. We assume that screening improves earlier detection and so lowers the death rate from HCC classes.

The graph represents the actual health states of patients and not what doctors know. So a false negative result should not affect the NC to HCC transition probability, the patients still develops HCC. However, earlier detection gives doctors more information so does reduce the death rate from HCC classes and there is an additional cost for false positive tests, which we process by creating a new node in the testing scenario.

Finally, we screen all people that we think do not have cirrhosis, we thus screen the NC and the CC groups.

**Figure 1:** Framework of the Markov Model representing the health state transitions of patients with non-cirrhotic MASLD.

Each health state above is independent of what is diagnosed or known by the patient/doctor. Therefore, we will account for the underdiagnosis of cirrhosis in MASLD patients by including patients with undiagnosed cirrhosis in our cohort. Based on literature, we will determine a certain proportion of our “non-cirrhotic” MASLD group to start in the compensated cirrhosis stage.

**Modelling Approach**

We generate 100,000 MASLD non-cirrhosis individuals, we conduct a simulation for each of the patients through the health states and collect a QUALY (utility) and a total cost (reward) value. This allows us to measure cost-effectiveness after running scenarios for each individual and then deduce group outcomes.

**Utility and Reward Definitions**

We calculate these values statically, not dynamically. If a health state sequence is [CC, HCC, HCC, D], then the utilities/rewards are based on values assigned to the states CC, HCC, HCC, D and not the transitions CC- HCC and HCC-HCC and HCC-D. We use uniform discounting.

**Subgroups Detection**

Based on our model, we can do the following:

* Analyze CE for the whole population
* Calculate CE for a given subgroup
* Deduce from the whole-population simulation which subgroups are most CE
* Derive mathematical parameterizations that are sufficient for a future subgroup to be CE (in expectation)

**Accounting for cirrhosis and HCC that are diagnosed vs undiagnosed**

In the Compensated Cirrhosis and the HCC states, whilst the health state is known in the Markov model, in the real world, the doctor may not know the true health state. We calculate a weighted average cost and death rate for these two groups. Better screening increases the proportion of “doctor knows” patients and thus improves the death rate but increases costs.

How we account for patients in the cirrhosis health state who are unaware of their cirrhosis. The % of patients who are aware vs unaware of their cirrhosis will be the same in both the intervention and the control arms. In the table below (example), we show how the weighted average of the cost and probabilities will be applied to determine the cost and probabilities of the overall cirrhosis population.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| % Patients | Health State | Cost | P(Death) | P(early stage HCC) |
| 70% | Compensated cirrhosis – doctor knows | $20,000 | 5% | 50% |
| 30% | Compensated cirrhosis – doctor doesn’t know | $0 | 10% | 100% |
| 100% | All cirrhosis patients | $14,000 | 6.5% | 65% |

We account for the difference in % of HCC patients who have HCC diagnosed by splitting the group into patients who has been diagnosed and those are unaware of the diagnosis. Then, in the overall HCC population, we assign costs and probabilities as the weighted average of the splitted groups.

Example: These are for patients in the HCC early health state, control group with a default 70% and 30% split.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| % Patients | Health State | Cost | P(Death) | P(intermediate stage HCC) |
| 70% | Early Stage HCC – doctor knows | $20,000 | 5% | 50% |
| 30% | Early Stage HCC – doctor doesn’t know | $0 | 10% | 100% |
| 100% | All population | $14,000 | 6.5% | 65% |

These are for patients in the HCC early health state, intervention group with a default 100% and 0% split. Here, the % of patients who knows the diagnosis goes up because they receive HCC screening.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| % Patients | Health State | Cost | P(Death) | P(intermediate stage HCC) |
| 100% | Early Stage HCC – doctor knows | $20,000 | 5% | 50% |
| 0% | Early Stage HCC – doctor doesn’t know | $0 | 10% | 100% |
| 100% | All population | $20,000 | 5% | 50% |

**Accounting for sensitivity and specificity of HCC surveillance...**

In our actual model, the split for the intervention group shown in the table above will be determined by the sensitivity of the HCC surveillance technique. For example, if sensitivity of US+AFP is 60% for example, then the split will be 60% and 40% for the intervention group.

Additionally, the specificity will be accounted for by considering false positive scenarios. If the specificity of HCC + AFP is 80% for example, then 20% of patients who were screened for HCC will incur an additional cost (while being in the no HCC health state) due to the additional testing and time lost that is a consequence of the false positive result.

The sensitivity and specificity will be difference depending on whether the HCC is early/intermediate/advanced stage.

**Data/Input parameters:** The input parameters for our model will be obtained from published literature when available. For data not found in published literature, we will use data from the Truven or NHANES (?) databases.

Characteristics of the base population (non-cirrhotic MASLD) which can be used to stratify the high-risk group:

|  |  |  |
| --- | --- | --- |
| **Parameters** | **Value** | **Reference** |
| Age >60 years |  |  |
| Male (%) |  |  |
| Diabetes (%) |  |  |
| Overweight or Obese (%) |  |  |
| Race/ethnicity |  |  |
| Platelet level distribution (categorical) |  |  |
| INR level distribution (categorical) |  |  |
| FIB-4 distribution (categorical) |  |  |

Population Characteristics

|  |  |  |
| --- | --- | --- |
| **Out of overall MASLD patients (non cirrhotic at MASLD diagnosis)** | | |
| Overall (N=) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |
| Undiagnosed cirrhosis (N=, %) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |
| Diagnosed cirrhosis (N=,%) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |
| **Out of patients who develop HCC** | | |
| Early stage HCC (N=) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |
| Intermediate Stage HCC (N=, %) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |
| Late stage HCC (N=,%) | Male | Female |
| Age <50 | N (%) | N (%) |
| Age >=50 | N (%) | N (%) |

Measures of health state transition (different subgroups may have different health state transition probabilities. Ex. Patients with higher FIB-4 will have higher rates of transitioning to cirrhosis and HCC):

|  |  |  |
| --- | --- | --- |
| **Annual incidence** | **Value** | **Reference** |
| No cirrhosis (NC) to: |  |  |
| (NC) | -- | -- |
| CC |  |  |
| HCC (early stage) |  |  |
| In males |  |  |
| In females |  |  |
| In age<50 |  |  |
| In age>=50 |  |  |
| Death |  |  |
| Compensated cirrhosis (CC) to: |  |  |
| (CC) | -- | -- |
| DC |  |  |
| HCC (early stage) |  |  |
| In males |  |  |
| In females |  |  |
| In age<50 |  |  |
| In age>=50 |  |  |
| Liver Transplant |  |  |
| Death |  |  |
| Decompensated cirrhosis (DC) to: |  |  |
| (DC) | -- | -- |
| HCC (early stage) |  |  |
| In males |  |  |
| In females |  |  |
| In age<50 |  |  |
| In age>=50 |  |  |
| Liver Transplant |  |  |
| Death |  |  |
| Early stage HCC to: |  |  |
| (Early stage HCC) | -- | -- |
| Intermediate stage HCC |  |  |
| Curative treatment |  |  |
| Death |  |  |
| In males |  |  |
| In females |  |  |
| In age<50 |  |  |
| In age>=50 |  |  |
| In treated |  |  |
| In untreated |  |  |
| Intermediate stage HCC to: |  |  |
| (Intermediate stage HCC) | -- | -- |
| Late stage HCC |  |  |
| Curative treatment |  |  |
| Palliative treatment |  |  |
| Death |  |  |
| In males |  |  |
| In females |  |  |
| In age<50 |  |  |
| In age>=50 |  |  |
| In treated |  |  |
| In untreated |  |  |
| Late stage HCC to: |  |  |
| (Late stage HCC) | -- | -- |
| Palliative treatment |  |  |
| Death |  |  |
| In males |  |  |
| In females |  |  |
| In age<50 |  |  |
| In age>=50 |  |  |
| In treated |  |  |
| In untreated |  |  |

Sensitivity/Specificity of HCC screening

|  |  |  |  |
| --- | --- | --- | --- |
| **Probability** | **Definition** | **Value** | **Reference** |
| Sensitivity of US/AFP | Used to account for false negative HCC screening. If patient receives false negative result, then they will incur an additional cost and decrease in utility due to time lost. |  |  |
| Specificity of US/AFP | Used to account for false positive HCC screening. If patient receives false positive result, then they will incur an additional cost and decrease in utility due to time lost. |  |  |

Quality of life by health state

|  |  |  |
| --- | --- | --- |
| **Health State** | **Utility** | **Reference** |
| No cirrhosis |  |  |
| Compensated cirrhosis |  |  |
| Decompensated cirrhosis |  |  |
| False positive HCC |  |  |
| Early stage HCC |  |  |
| Intermediate stage HCC |  |  |
| Late stage HCC |  |  |
| Death | 0 | -- |

Costs

|  |  |  |
| --- | --- | --- |
| **Cost** | **Value** | **Reference** |
| Repeat CT/MRI for false positive HCC |  |  |
| Cost of biannual US+AFP screening |  |  |
| Cost for medical care of patients with **non-cirrhotic MASLD** |  |  |
| Cost for medical care of patients with **MASLD and compensated cirrhosis** |  |  |
| Cost for medical care of patients with **MASLD and decompensated cirrhosis** |  |  |
| Cost for medical care of patients with **early stage HCC** |  |  |
| Cost for medical care of patients with **intermediate stage HCC** |  |  |
| Cost for medical care of patients with **late stage HCC** |  |  |
| Cost for **curative treatment for HCC** |  |  |
| Cost for **palliative treatment for HCC** |  |  |
| Cost for **terminally ill/additional costs associated with death** |  |  |

(For patients with undiagnosed cirrhosis, the cost will be same as that of the no cirrhosis state)

**Validation Approach**

Model will output survival curves, QUALYs and costs. Estimating from literature if these are reasonable are important.

**Tables and Figures**

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