

Modeling Longitudinal HCC Detection With Ultrasound Versus a Multi-Analyte Blood Test in Patients With Cirrhosis

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OVERVIEW

- Patients with cirrhosis require routine HCC surveillance, but ultrasound has limited sensitivity for small tumors and real-world adherence remains suboptimal.
- In the prospective CLiMB study¹, HelioLiver Dx demonstrated higher sensitivity than ultrasound, especially for lesions <3 cm, using multiphasic MRI as the reference standard.
- Because CLiMB evaluated test performance at a single time point, this study used Monte Carlo simulations to model how HelioLiver Dx and ultrasound may perform over repeated surveillance intervals.
- The simulations incorporated CLiMB-derived test sensitivities, different surveillance adherence rates, and tumor doubling times to evaluate cumulative detection and tumor size at diagnosis over 18 months.
- **The goal was to determine whether the higher cross-sectional sensitivity of HelioLiver Dx could translate into earlier HCC detection over time under clinically relevant surveillance scenarios.**

INTRODUCTION

Semi-annual ultrasound (US) is recommended for hepatocellular carcinoma (HCC) surveillance in patients with cirrhosis, but low adherence and suboptimal sensitivity for early-stage disease limits its effectiveness^{2,5,6}. Published US sensitivity estimates in literature generally reflect performance across repeated surveillance rounds rather than sensitivity at a single screening time point. At any individual surveillance visit, however, US sensitivity is substantially lower. In addition, in these surveillance studies, reported performance may also be inflated by verification bias, as US-negative patients are often not systematically confirmed with a uniform reference standard such as MRI or CT⁴. Recently, a cross-sectional multi-center, prospective, US-centric study called CLiMB compared the performance of a novel-blood based test, HelioLiver Dx, for detecting HCC in cirrhotic patients to ultrasound using multiphasic MRI as the reference standard. CLiMB demonstrated that the **HelioLiver Dx test significantly outperforms ultrasound, especially in the detection of lesions <3cm in size**. These CLiMB data provide a rigorous basis for modeling how differences in test sensitivity may accumulate across repeated surveillance rounds and influence when HCC is detected and the size of tumors at diagnosis.

AIM

Since the CLiMB study was cross-sectional in nature, longitudinal test performance was not reported. The PRIUS study⁷, in which concurrent MRIs were performed for each patient like in the CLiMB trial, reports nearly identical ultrasound performance as CLiMB. However, as most studies report ultrasound performance in a surveillance regimen, **in this study, we perform simulations to assess and compare the longitudinal performance of the HelioLiver Dx test and ultrasound**. The primary outcome was sensitivity for early-stage HCC detection, as defined by Milan Criteria - a single tumor ≤ 5 cm, or up to 3 tumors each ≤ 3 cm, with no major vessel involvement or extrahepatic metastases.

METHODS

- Patients diagnosed with HCC in the CLiMB study were binned into 4 groups :
 - 21 patients HCC <2cm
 - 13 with 2cm-3cm
 - 5 with 3cm-5cm
 - 7 with HCC >5cmSensitivity was calculated for both ultrasound and HelioLiver Dx based on the CLiMB trial results.
- Monte Carlo simulations were performed, using multiple surveillance adherence rates as well as binned test sensitivities described above, to compare the expected performance of ultrasound and HelioLiver Dx over time (at 6, 12 and 18 months).
- For each simulation, for each set of variables, 100 random trials were performed to calculate the mean/median cumulative sensitivity and its confidence intervals, assuming a cohort of 100 patients with baseline tumor size distribution as observed in the CLiMB study.
- A tumor doubling time of 6 months was used for the first set of simulations for all HCC patients. Additionally, tumor doubling times of 3 months for aggressive tumors, 6 months for average tumors and 12 months for indolent tumors were used to evaluate the impact of differential tumor growth rates on test performance over time. At each iteration, each patient/sample is assigned to one of the groups with probabilities - Aggressive=0.3, Average=0.4, Indolent=0.3. The groups are assigned independently.

RESULTS

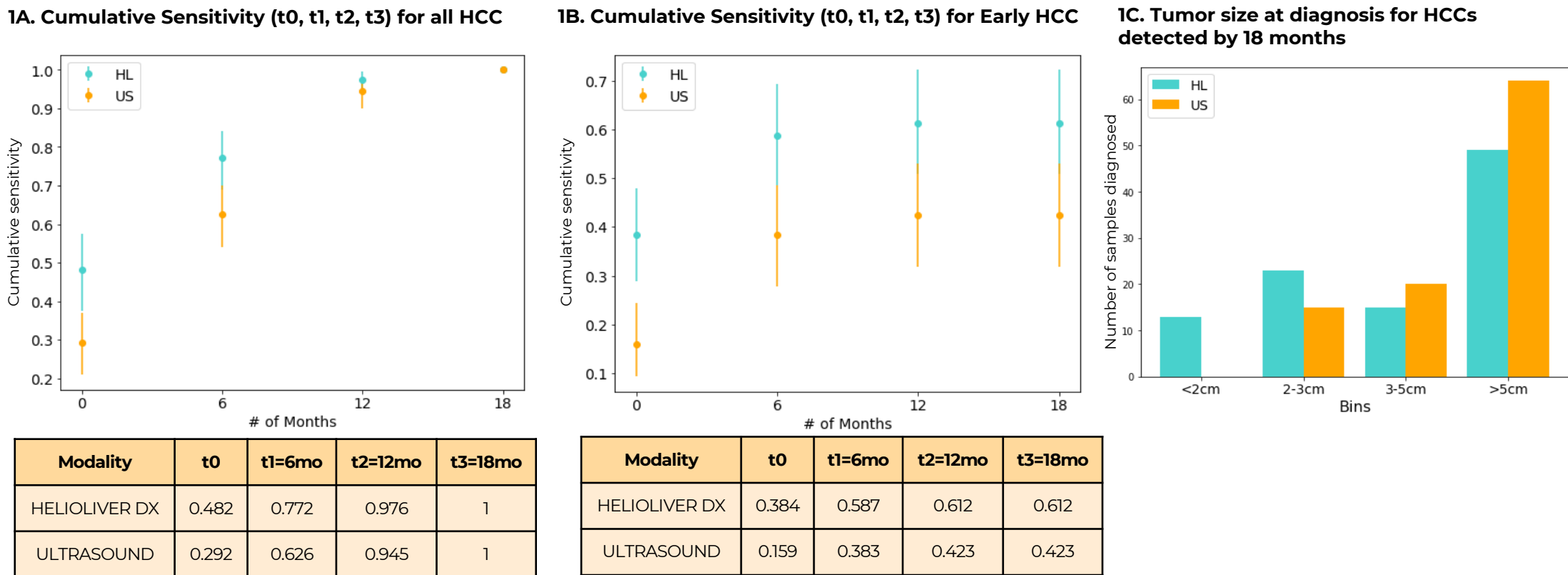


Figure 1. Baseline case assuming 100% adherence for both HelioLiver Dx (HL) and Ultrasound (US).

A) Cumulative sensitivities at t0, t1=6months, t2=12 months and t3=18 months. By 18 months, all HCCs were diagnosed by both modalities.

B) Cumulative sensitivities at each test time point for early-stage lesions. For each timepoint, sensitivity was calculated as the number of early-stage tumors detected divided by total number of early-stage tumors at the first timepoint.

C) Size distribution for when HCCs were diagnosed by each modality. HL detects tumors earlier than US.

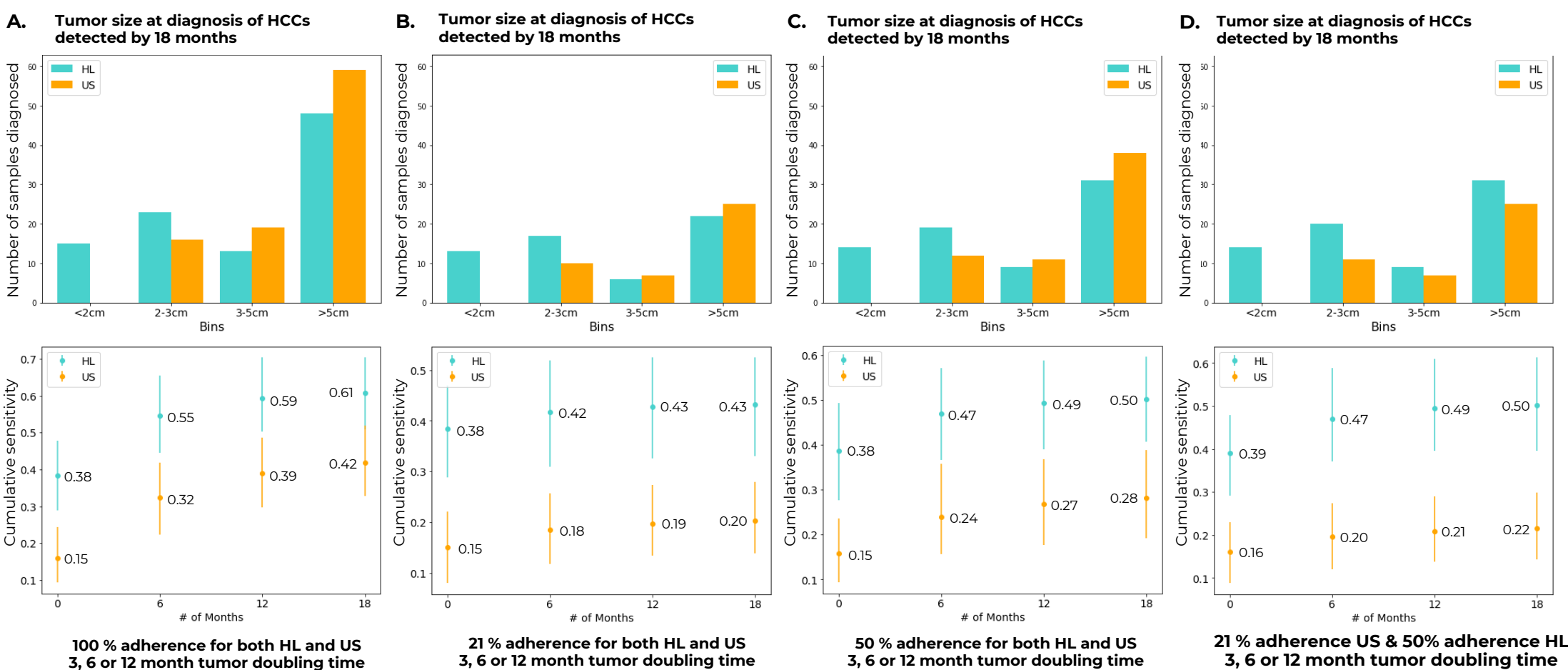


Figure 2. Sizes at which HCCs are detected by each testing modality and early-stage sensitivities for different adherence rates and tumor doubling times A,E) 100% adherence rate and 3, 6 or 12 month tumor doubling times B,F) 21 % adherence rate and 3, 6 or 12 month tumor doubling times C,G) 50% adherence rate and 3, 6 or 12 month tumor doubling times . D,H) 21% adherence rate for US as reported in literature^{2,4,5,6} and 50% adherence rate for HelioLiver Dx (based on a modest adherence rate for a blood-based test) and 3, 6 or 12 month tumor doubling times³

CONCLUSIONS

HelioLiver Dx increased the proportion of HCC detected within Milan criteria compared with ultrasound across all simulated longitudinal surveillance scenarios. These findings suggest that a blood-based surveillance strategy may shift detection toward earlier disease stages, when patients are more likely to remain eligible for curative treatment.

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