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A multi-analyte liquid biopsy assay integrating cfDNA methylation and protein biomarkers for liver cancer diagnosis

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BACKGROUND

Liver cancer is the third leading cause of cancer-related death worldwide and nearly half of deaths occur in China. The major histological types are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Serum marker alpha-fetoprotein (AFP) and ultrasound have been widely used in liver cancer high-risk population surveillance programs, but both methods have unsatisfactory sensitivities for early stage of the disease and sub-optimal specificities. AFP also has much lower sensitivity for ICC compared to HCC. Circulating tumor DNA (ctDNA) provides new opportunity for non-invasive detection of liver cancer. Here we intended to develop a blood-based liquid biopsy assay for liver cancer diagnosis by detecting abnormal methylation of cell-free DNA (cfDNA) as well as serum protein biomarkers.

METHODS

Blood samples were collected from 333 liver cancer patients and 157 non-cancer age-matched control subjects (including 33 benign liver tumor patients, 105 liver cirrhosis patients, and 19 healthy individuals) in this multi-center study in China. cfDNA methylation and protein biomarker levels were analyzed.

RESULTS

We identified a panel of 2 cfDNA methylation markers and 2 protein markers, AFP and des-gamma-carboxyprothrombin (DCP). Methylation markers were measured by quantitative real-time PCR (qPCR) and protein markers were measured by chemiluminescent enzyme immunoassay (CLEIA).

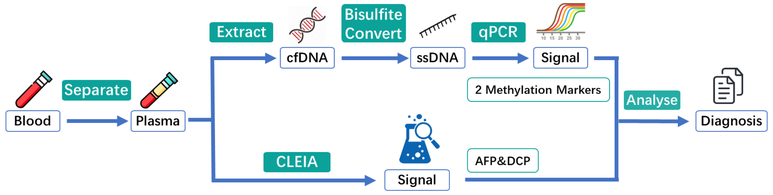
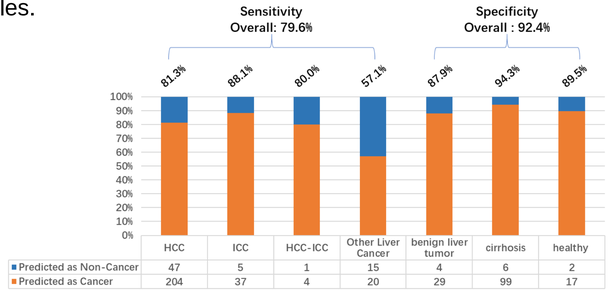


Fig 1. The multi-analyte liquid biopsy assay integrating cfDNA methylation and protein biomarkers.

We found that cfDNA methylation markers alone achieved a sensitivity of 81.3% for HCC and 88.1% for ICC, and a specificity of 92.4% in control samples.



	HCC	ICC	HCC-ICC	Other Liver Cancer	benign liver tumor	cirrhosis	healthy
Predicted as Non-Cancer	47	5	1	15	4	6	2
Predicted as Cancer	204	37	4	20	29	99	17

Fig 2. The qPCR assay achieved a sensitivity of 79.6% and a specificity of 92.4%.

For BCLC stage 0-C HCC, the sensitivities were 58.8%, 70.9%, 94.6%, and 97.9%, respectively.

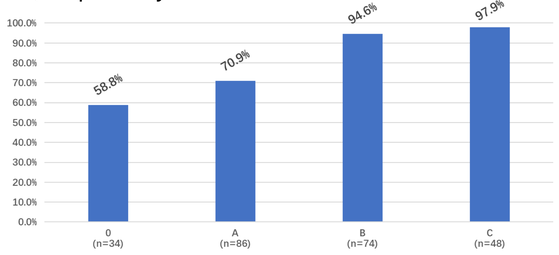
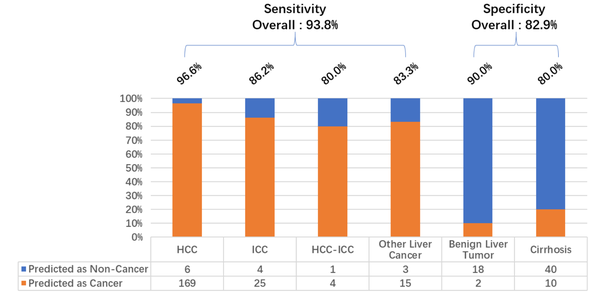


Fig 3. The sensitivities of the qPCR assay for BCLC stage 0-C HCC.

When combined with AFP and DCP, sensitivities further improved to 96.6% for HCC and 86.2% for ICC.



	HCC	ICC	HCC-ICC	Other Liver Cancer	Benign Liver Tumor	Cirrhosis
Predicted as Non-Cancer	6	4	1	3	18	40
Predicted as Cancer	169	25	4	15	2	10

Fig 4. The multi-analyte assay achieved a sensitivity of 93.8% and a specificity of 82.9%.

The integrated panel achieved sensitivities of 81.0%, 98.0%, 100.0%, and 97.5% for stage 0-C HCC respectively.

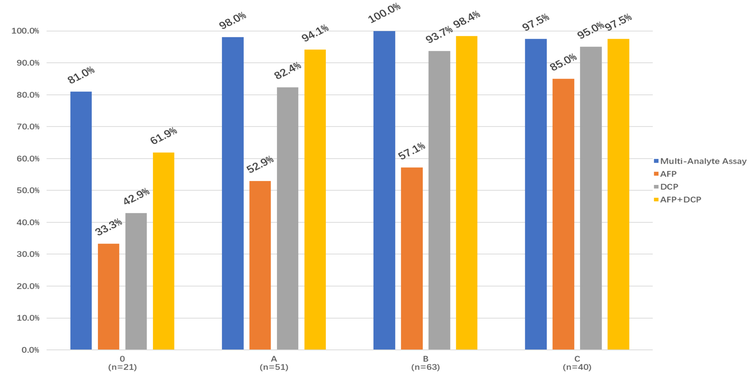


Fig 5. The sensitivities of the multi-analyte assay, AFP, and DCP for stage 0-C.

CONCLUSIONS

We developed a blood-based liquid biopsy with a panel of 2 cfDNA methylation markers and 2 protein markers for liver cancer diagnosis. It achieved high sensitivity for both HCC and ICC. The assay also showed high sensitivity for early stage HCC (stage 0 + A). These results highlighted the potential for multi-analyte liquid biopsy assay for early detection of liver cancer.

DISCLOSURE

The first and presenting author, Dr Guo, declares that there is no conflict of interest.

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