Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Early detection is crucial for improving treatment outcomes and prognosis. In this multicenter prospective study (ASCEND-Hep, NCT04835675), we aimed to investigate the potential of multi-omics analysis, including cfDNA methylation, ctDNA mutation, and AFP, for early detection of HCC.

**METHODS**

Blood samples were prospectively collected from patients with HCC and benign liver diseases (including liver cirrhosis) across multiple centers, which were then randomly split into training and validation sets. Age-matched healthy controls were obtained from a previous study. Methylation analysis was performed using ELSA-seq, targeting 161,984 sites at a depth of 1,000X. Mutation analysis was performed using targeted enrichment sequencing aided by machine learning. Nat Biomed Eng 5:586-599, 2021 for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021. 71(3): p. 209-249.

**RESULTS**

Three models were developed and validated. In both the training and validation sets, the cfDNA methylation model exhibited a higher area under the curve (AUC) compared to AFP and cfDNA mutation alone (Figure 2). In the validation set, the methylation model yielded an overall sensitivity of 92.3% (95% CI, 89.9%-96.4%) at a specificity of 95.0% (90.0%-98.0%). Meanwhile, AFP >400 ng/mL had a sensitivity of 27.3% (18.8%-37.2%) with a specificity of 100.0% (96.5%-100.0%). Combining cfDNA methylation and AFP showed a better performance with a sensitivity of 94.0% (88.1%-97.6%) and a specificity of 95.0% (90.0%-98.0%), while the addition of mutation did not further improve the performance. Consistent findings were observed in the independent validation set (Table 2).

**CONCLUSION**

cfDNA methylation yielded superior performance than AFP and mutation alone. Our study highlights a potential clinical utility of combining cfDNA methylation and AFP for HCC early detection. Better modeling algorithms are still being explored and optimized. At the same time, the performance of the model in high-risk populations of liver cancer still need to be verified.

**REFERENCE**


**CONTACT**

Mingxin Pan: pannmx@smu.edu.cn