Samenvatting proefschrift
S. Fu

'Biomarkers for the Risk Stratification and Detection of Early-Stage Hepatocellular Carcinoma'

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Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide. A major challenge in its management is that many cases are diagnosed at advanced stages, primarily due to the limited effectiveness of current early detection methods, such as ultrasound and alpha-fetoprotein (AFP) testing. This thesis investigates a range of novel biomarkers aimed at improving early HCC detection and risk stratification, including single nucleotide polymorphisms (SNPs), genetic risk scores (GRS), the GALAD and ASAP scores, and DNA methylation markers (DMMs).

For the risk stratification of MASLD-related HCC, we evaluated the performance of lipid metabolism-related genes—PNPLA3, MBOAT7, TM6SF2, and HSD17B13—and integrated these SNPs into a composite GRS. In the context of early HCC detection, we assessed the GALAD score, which incorporates age, gender, AFP, des-gamma-carboxy prothrombin (DCP), and AFP-L3%. We then developed a simplified version of this model, the ASAP score, by excluding AFP-L3%. Additionally, we examined the diagnostic utility of DNA methylation markers in both liver tissue and blood samples for detecting early-stage HCC.

Key findings of this study include:

- TLL1 SNPs were not associated with HCC risk in European and Latin American populations, highlighting geographic variability in genetic risk factors.
- A GRS combining four lipid-related SNPs enhanced risk prediction for MASLD-related HCC and was associated with immune microenvironment alterations.
- The ASAP score greatly outperforms AFP in detecting early HCC , and also outperformed GALAD in predicting HCC development within one year.
- DMMs showed promise for identifying HCC in non-cirrhotic patients but had limited discriminatory power between cirrhotic and cancerous tissues due to overlapping methylation patterns.

Aan de publicatie van dit proefschrift werd een financiële bijdrage geleverd door de Nederlandse Vereniging voor Hepatologie.

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- Combining DMMs with the ASAP score provided only marginal improvements in sensitivity for early detection among high-risk individuals.

Overall, the work described in this thesis contributes to a better understanding of novel biomarkers for the risk stratification and early detection of HCC. Current clinical biomarkers have a limited role in early HCC detection, underscoring the urgent need for new biomarkers to identify high-risk populations and detect early-stage HCC, as curative treatment options are available for patients diagnosed at earlier stages. Our findings provide an important step forward in guiding activities aimed at improving both the early-stage detection and risk stratification of HCC in clinical practice.

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