Identification of Circulating MiR-4651 as Novel Biomarker for Metabolic Dysfunction–associated Steatotic Liver Disease

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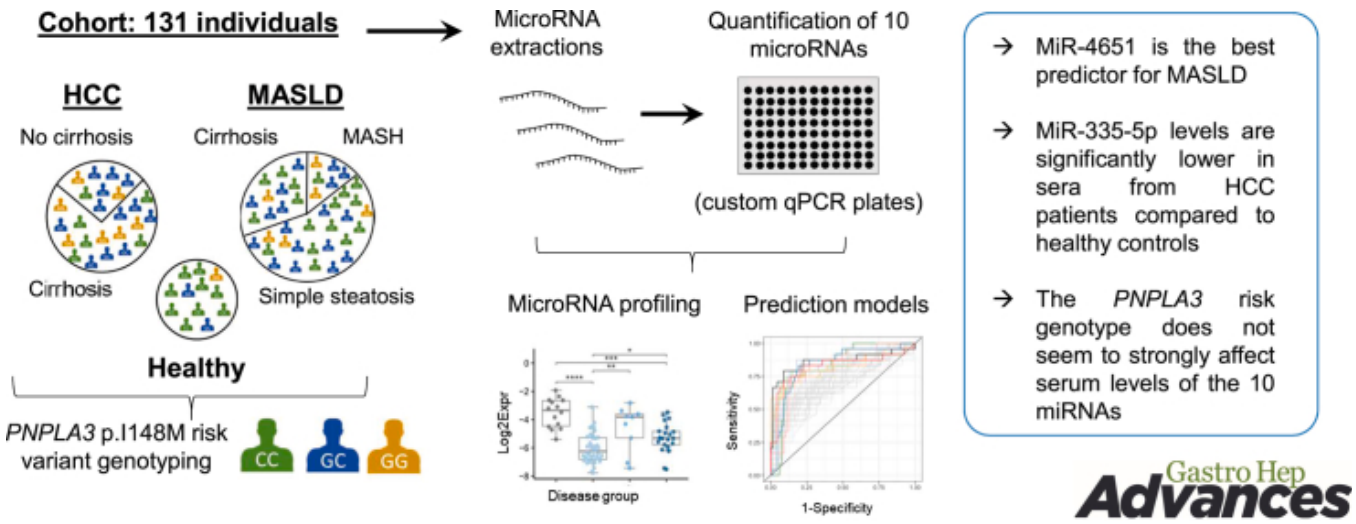
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Abstract

Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects >30% of adults and is becoming one of the leading causes of hepatocellular carcinoma (HCC). Reliable biomarkers are needed for the early diagnosis of HCC and detection of chronic liver diseases, like MASLD. Here we assessed the biomarker potential of circulating microRNAs in a cohort of patients genotyped for the risk allele of patatin-like phospholipase domain-containing protein 3 (PNPLA3), associated with increased susceptibility to chronic liver diseases.

Methods: The cohort comprised 70 MASLD patients (40 with simple steatosis, 9 with metabolic dysfunction-associated steatohepatitis (MASH), 21 with cirrhosis), 47 HCC patients (32 with cirrhosis), and 14 healthy controls. Serum levels of miR-122-5p, miR-146a-5p, miR-146b-5p, miR-21-5p, miR-335-5p, miR-433-3p, miR-4530, miR-4651, miR-526a2, and miR-873-5p were quantified using custom qPCR plates. Their suitability for prediction of MASLD (steatosis/MASH/cirrhosis) or HCC was assessed by receiver operating characteristic curve analyses.

Results: MiR-4651 and miR-21-5p were significantly reduced in sera from patients with MASLD, particularly in those with simple steatosis. Both microRNAs effectively distinguished MASLD patients with simple steatosis from healthy controls (area under the curve: 0.95 and 0.89, respectively). Moreover, miR-4651 emerged as the best predictor for differentiating "complicated" MASLD (i.e., MASH or cirrhosis) from simple steatosis; the predictive values could be increased by including additional parameters into the models (Fibroscan, thrombocytes, cytokines, or other miRNAs). miR-335-5p showed strong ability to differentiate HCC from healthy individuals (area under the curve: 0.86). The PNPLA3 p.I148M genotype was not associated with altered levels of microRNAs.

Conclusion: Serum microRNAs, in particular miR-4651, may serve as additional biomarkers in patients with steatotic liver disease.

Keywords: circulating microRNA; hepatocellular carcinoma; liver cirrhosis; patatin-like phospholipase domain-containing protein 3; receiver operating characteristic curve analysis.