



## Samenvatting proefschrift Annarein J.C. Kerbert

**'Risk stratification in cirrhosis and acute-on-chronic liver failure – Exploration of invasive and non-invasive prognostic markers**

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Information on prognosis is essential for any physician for providing information to the patient and forms the basis for the decision-making process for therapy. Due to the heterogeneity of the disease, exploration of prognostic biomarkers in cirrhosis is a challenging, but important aspect of research in the field of chronic liver disease. Besides identifying patients who are at the highest risk of mortality, identification of reliable prognostic biomarkers may also help to improve treatment strategies. The aim of this thesis is to explore novel prognostic biomarkers throughout different stages of chronic liver disease and in acute-on-chronic liver failure (ACLF).

Chapter I provides a general overview on the pathogenesis and disease course of cirrhosis and ACLF. Furthermore, the hypothesis and aim of the thesis are described.

Advanced liver cirrhosis is associated with systemic hemodynamic derangement leading to the development of severe complications associated with increased mortality. Research on arginine vasopressin (AVP), a key-regulator in hemodynamic homeostasis, in cirrhosis has been complicated by the difficulty of measuring AVP levels accurately. Copeptin is a surrogate marker for AVP and could have a role as a prognostic biomarker in cirrhosis as it may reflect circulatory dysfunction. In chapter 2-5 of this thesis, we studied copeptin as a prognostic marker throughout different stages of cirrhosis. In an animal model, we showed that serum copeptin levels were significantly higher in cirrhotic rats as compared to healthy controls. Furthermore, serum copeptin was found to be negatively correlated to the mean arterial blood pressure. In humans, we found that serum copeptin levels at hospital admission independently predict outcome in populations with either compensated or decompensated cirrhosis and in patients with ACLF.

In chapter 6, we hypothesized that heterogeneity in the arginine vasopressin 1a receptor (AVP1aR) may affect the risk of developing renal and circulatory failure in cirrhotic patients. We studied the association between six single nucleotide polymorphisms (SNPs) of AVP1aR and the development of organ failure in 826 patients admitted for acute decompensation of liver cirrhosis or ACLF. Genetic variation in the vasopressin 1a receptor was found not to be associated with circulatory or renal failure.

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In chapter 7, the results are described of a meta-analysis assessing the potential clinical value of the implementation of hepatic venous pressure gradient (HVPG) measurements to monitor the efficacy of primary prophylactic therapy for variceal bleeding with non-selective beta-blockers (NSBBs). The results show that achieving a hemodynamic response to NSBB therapy (i.e., HVPG reduction  $<12$  mmHg or  $>10$ - $20\%$  from baseline) is associated with a significant lower risk of a first variceal bleeding episode as compared to a non-response.

In chapter 8, we outlined the results of a study exploring the impact of hepatic encephalopathy (HE) on mortality at the liver transplant waiting list in a Dutch cohort. We aimed to assess its prognostic significance independently of the Model for End-stage Liver Disease (MELD) score and presence of comorbidities related to HE development. The results show that HE is indeed an independent risk factor for mortality in patients awaiting liver transplantation. This was validated in a representative and independent Dutch cohort. In a second validation cohort from Spain, with significantly higher transplantation rates and a shorter waiting list, the prognostic impact of HE seemed to be attenuated.

Finally, chapter 9 summarizes the results of the studies described in this thesis and the results are discussed in a broader perspective.

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