

On kidney dysfunction in advanced liver disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i M106 K Isaksson, Medicinargatan 16, Göteborg, torsdagen den 1 december, klockan 13:00.

av

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Avhandlingen baseras på följande delarbeten

- I. Cederborg A, Widman L, Haraldsson B, Lindkvist B, Shang Y, Wester A, Marschall HU, Hagström H. Six-fold increased rate for chronic kidney disease after acute kidney injury: A population-based cohort study of 46,946 patients with cirrhosis. *Submitted*.
- II. Cederborg A, Lindkvist B, Haraldsson B, Kalaitzakis E, Björnsson ES, Marschall HU. Acute kidney injury in patients with liver disease is associated with increased mortality and later chronic kidney disease. *Submitted*.
- III. Cederborg A, Norén Å, Barten T, Lindkvist B, Bennet W, Herlenius G, Castedal M, Marschall HU, Åberg F. Renal function after liver transplantation: Real-world experience with basiliximab induction and delayed reduced-dose tacrolimus. *Digestive and liver disease* 2022; 54(8): 1076-1083.

**SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN**



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Abstract

Aims: The overall aim of this thesis was to characterize factors affecting kidney function in advanced liver disease as well as after liver transplantation and to further understand the complex interaction between acute and chronic kidney disease in cirrhosis. The aim of the first study was to investigate the association between acute kidney injury (AKI), including hepatorenal syndrome and subsequent chronic kidney disease (CKD) in patients with cirrhosis and to quantify the cumulative incidence of CKD in patients with cirrhosis, with or without prior AKI. The second study aimed to investigate the association between AKI in cirrhosis, AKI in acute-on-chronic liver failure (ACLF) and the impact on survival as well as the development of CKD. The aim of the third study was to evaluate the effect of basiliximab induction with delayed reduced-dose tacrolimus on kidney function, rejection episodes and survival rates after liver transplantation.

Methods: All three studies are retrospective cohort studies using different study cohorts. In studies I and II patients with liver cirrhosis were included from a national healthcare register (study I) and from a hospital-based register (study II). In study III, patients with advanced liver disease who were transplanted at Sahlgrenska University Hospital were included. Kidney function as well as dysfunction were evaluated using international classification of disease (ICD) codes in study I, serum creatinine and estimated glomerular filtration rate in studies II and III, as well as measured glomerular filtration rate in study III.

Results: Patients with cirrhosis and AKI had a more than six-fold increased rate of CKD compared to patients without, when adjusting for risk factors for CKD, such as age, hypertension, and diabetes. AKI in cirrhosis was associated with a high short-term mortality from both kidney and non-kidney sources. AKI progression further decreased survival, even after adjusting for ACLF and bacterial infections. Induction immunotherapy with interleukin-2 receptor antibodies and delayed reduced-dose tacrolimus did not increase the risk for rejection, graft loss or death and reduced kidney injury after liver transplantation.

Conclusions: This thesis shows that AKI constitutes a significant risk factor for CKD in cirrhosis. Also, that short-term survival in patients with cirrhosis and AKI is decreased due to both kidney and non-kidney related causes. These findings highlight the importance of an early diagnosis of AKI and distinct actions to prevent further progression and deterioration beyond kidney function. Furthermore, an updated immunosuppressive protocol with non-depleting induction therapy, allowing for a reduced early impact of calcineurin inhibitors is safe and can prevent kidney injury in liver transplanted patients, independent of pre-transplant kidney function.

Keywords: cirrhosis, acute on chronic liver failure, acute kidney injury, hepatorenal syndrome, chronic kidney disease, liver transplantation, immunosuppression