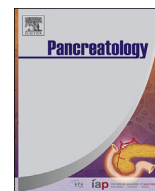




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Chronic pancreatitis in patients with liver cirrhosis negatively affects graft survival after liver transplantation

Malte H. Wehmeyer^{a, 1}, Werner Dammermann^{a, c, *, 1}, Oliver Seiz^{a, 1}, Madeleine E. Zinser^a, Antonio Galante^a, Ansgar W. Lohse^a, Martina Sterneck^a, Björn Nashan^b, Uta Herden^{b, 1}, Stefan Lüth^{a, c, 1}

^a 1. Department of Medicine, University Medical Center Hamburg-Eppendorf, Germany

^b Department of Hepatobiliary and Transplant Surgery, University Medical Center Hamburg-Eppendorf, Germany

^c Center of Internal Medicine II, Brandenburg Medical School Theodor Fontane, Germany

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ABSTRACT

Background: Limited data exists concerning the coincidence of chronic pancreatitis (CP) and liver cirrhosis with respect to the patient outcome after liver transplantation (LT). The aim of the study was to identify risk factors for graft loss after liver transplantation and to evaluate the impact of CP on graft survival.

Methods: We analyzed the data of 421 cirrhotic patients who underwent evaluation for primary liver transplantation from January 2007 to January 2014. Diagnosis of CP based on morphologic findings which were graded according to the Cambridge and Manchester classification. (Graft) survival after LT was analyzed by Cox regression analysis. Recipient- and donor-related risk factors for graft loss were evaluated using univariate and multivariate analysis.

Results: 40/421 cirrhotic patients suffered from CP (9.5%). 250/421 (59.4%) patients underwent LT between January 2007 and January 2014. In total, 89 patients died or were in need of a re-transplantation during follow-up until August 2017. Patients with CP (N = 26) were at increased risk for graft loss after LT (hazard ratio = 2.183; 95% confidence interval = 1.232–3.868). CP (P = 0.001), a MELD score ≥ 24 (P = 0.021), absence of esophageal or gastrical varices (P = 0.018), the age of the donor (P = 0.008) and infections after transplantation (P = 0.030) were independent risk factors for organ loss after transplantation in the multivariate Cox regression analysis.

Conclusion: Patients with chronic pancreatitis are at increased risk for graft loss after LT. A high MELD score, the absence of esophageal or gastrical varices, an advanced donor age and post-transplant infections negatively affect graft survival, too.

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Introduction

Liver transplantation is the only curative therapeutic option for patients with end stage liver disease. Because of the shortage of donor organs, allocation of grafts in Germany is based on disease severity as well as prognosis of the patient and organ after transplantation. The impact of recipient- and donor-related factors on

the post-transplant outcome of cirrhotic patients was investigated in various studies [1–3]. Surprisingly, data concerning the impact of chronic pancreatitis (CP) on the outcome after liver transplantation are limited [4]. Liver cirrhosis and CP can be caused by chronic alcohol abuse [5] and the coincidence of both diseases was demonstrated in post-mortem studies [6–8]. However, clinical data on the frequency of CP in cirrhotic patients are inconsistent, as some studies suggest a strong coincidence of cirrhosis and CP [9], while other authors describe only a low prevalence of CP in cirrhotic patients [4]. Moreover, most studies focussed solely on patients with chronic alcohol abuse [6–9] and data on the prevalence of CP in patients with liver cirrhosis of other origin than alcohol abuse are lacking. Our study aimed to describe the

* Corresponding author. Center of Internal Medicine II, University Hospital Brandenburg, Brandenburg Medical School, Hochstrasse 29, 14770 Brandenburg, Germany.

E-mail address: w.dammermann@klinikum-brandenburg.de (W. Dammermann).

¹ Contributed equally.

prevalence and impact of CP in cirrhotic patients of any origin. Furthermore, we evaluated the (graft) survival rates of cirrhotic patients with and without chronic pancreatitis after liver transplantation in long-term follow-up.

Methods

A retrospective cohort observational study was conducted in 438 consecutive adult patients (age 20 and up) with liver cirrhosis who were evaluated for liver transplantation between January 2007 and January 2014 at the I. Department of Medicine at the University Medical Center Hamburg-Eppendorf, Germany. Patients evaluated for retransplantation (N = 17) were excluded, thus 421 patients were included in the study. The diagnosis of CP was based on imaging studies according to the modified Cambridge criteria as recommended by the German S3-guidelines [10,11]. All 421 patients underwent thorough abdominal imaging with computed tomography (N = 361) and/or magnet resonance imaging (N = 153). Transabdominal ultrasound (N = 345) was assessed but not used for classification. The Child-Pugh score and the MELD score were calculated using the established formula [12,13]. The severity of CP was graded using the Manchester classification system [14].

Clinical and laboratory data of patients with CP were compared against the data of patients without CP (controls) to identify risk factors for CP in patients with liver cirrhosis using univariate Fisher's exact test, Mann-Whitney *U* test or *t*-test, each where applicable.

A total of 250 of the 421 evaluated patients were transplanted between January 2007 and January 2014. The patients were followed up until August 2017. The (graft) survival of patients with and without CP was compared by Cox regression analysis. Risk factors for organ loss during the follow-up period were evaluated using univariate and multivariate analysis (backward stepwise logistic regression with inclusion of variables with a *P*-Value ≤ 0.05 in the univariate analysis). Furthermore, variables which were associated with graft loss in the univariate analysis, were entered in a multivariate Cox regression model. All analyses were performed using SPSS Version 22. The figures were created with GraphPad Prism 4. For this retrospective, observational study neither informed consent nor approval of the ethics committee was needed according to the Professional Code of the German Medical Association (article B.III.,§15.1) and to the recommendations of our local ethics board. However, all patients provided written informed consent in their contract governing medical treatment for the use of their respective data for future retrospective analysis with regard to liver transplantation. This procedure has been approved by the Ethics Committee of the Hamburg Chamber of Physicians.

Results

Comparison of cirrhotic patients with and without CP

A total of 421 of 438 patients who were consecutively evaluated for liver transplantation were included in the study. 40 of 421 patients (9.5%) were diagnosed to have CP according to the Cambridge classification (Fig. 1A). Twenty patients had a mild CP (50%; Manchester grade 1) with typical imaging criteria and abdominal pain and 7 patients had a moderate CP (18%; Manchester grade 2) with additional endocrine (N = 6) or exocrine (N = 1) insufficiency of the pancreas. Finally, 13 patients who fulfilled imaging criteria for CP and had a (endocrine) pancreas insufficiency were defined to suffer from severe CP (33%; Manchester grade 3), because of additional signs of portal hypertension (N = 12) or a biliary stricture (N = 1) (Fig. 1B). The suspected etiology of the CP was alcohol abuse (with

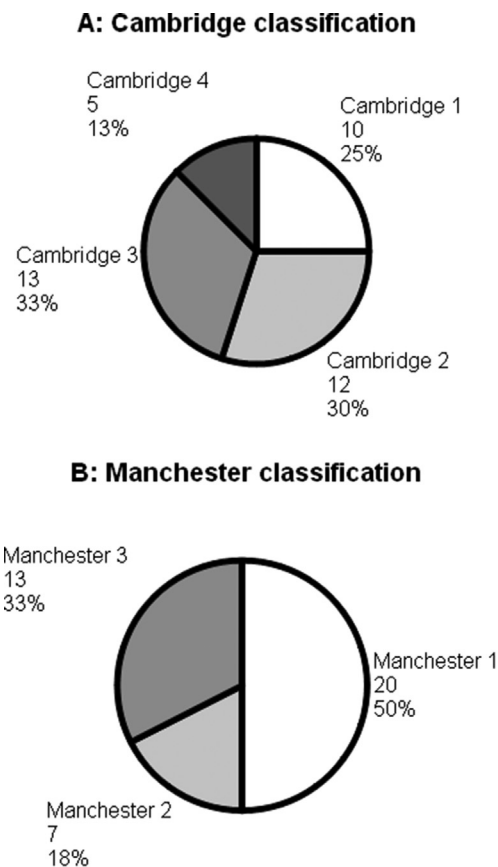


Fig. 1. Classification of cirrhotic patients with chronic pancreatitis according to the Cambridge (A) and Manchester (B) classification. Number and percentage of patients with the appropriate classification level are given, too. [CP = chronic pancreatitis].

or without concomitant nicotine abuse) in 22 patients (55%), the use of nicotine alone in 6 patients (15%) and unknown in 12 patients (30%). The univariate analysis revealed no significant differences between cirrhotic patients with and without CP, except a higher frequency of female patients and diabetes patients in the CP group ($P = 0.02$ and 0.01 , respectively), as well as an increased risk to suffer from hepatorenal syndrome or hepatic encephalopathy for patients with CP ($P = 0.01$ and 0.04 ; Supplementary table 1). Importantly, neither alcohol abuse nor smoking were associated with the occurrence of CP in our cohort ($P = 0.87$ and 0.73 , respectively). Nearly half of the patients with CP (18/40; 45%) had non-alcoholic cirrhosis (Supplementary table 1).

Intraductal papillary mucinous neoplasm (IPMN) from the side-branch type or pancreatic mucinous cystic neoplasm (MCN) was diagnosed in 1 patient, respectively (0.2%, each). One male patient was found to have pancreatic carcinoma (0.2%) during the evaluation for liver transplantation.

Comparison of cirrhotic patients with and without CP who underwent liver transplantation

Liver transplantation was performed in 250 of 421 (59.4%) of the patients between January 2007 and January 2014. CP was present in 10.4% (26/250) of the transplant recipients. The suspected etiology of CP was alcohol abuse (with or without nicotine abuse) in 13 patients (50%), nicotine abuse in 4 patients (15.4%) and unknown in 9 patients (34.6%). The only statistical significant difference between transplanted cirrhotic patients with and without CP was a predominance of the female gender in the CP group and increased

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