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Original Article

Impact of pancreatic comorbidities in patients with end-stage liver disease on outcome after liver transplantation

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ABSTRACT

Background: Diseases leading to end-stage liver disease (ESLD), especially alcoholic liver cirrhosis cause comorbidities of the pancreas, too. The aim of this retrospective study was to determine the impact of pancreatic alterations diagnosed pretransplant on the outcome after liver transplantation (LT).
Methods: In total, data from 372 LT patients were analyzed. Patients were followed up for a mean of 4.2 years. Incidence of chronic pancreatitis (CP), pancreatic cysts (PC) and intraductal papillary mucinous neoplasm (IPMN) was acquired retrospectively from patient's charts.
Results: CP, IPMN and PC were rarely diagnosed in LT-recipients [CP (3.8%), PC (1.6%) and IPMN (1.6%)]. There was no significant correlation of IPMN, CP, PC and other patient characteristics. The prevalence of CP (log rank: $p = 0.315$), PC (log rank: $p = 0.242$) and IPMN (log rank: $p = 0.491$) did not influence patient survival.
Conclusion: Frequency of radiological alterations of the pancreas in LT recipients (such as CP, PC, IPMN) diagnosed by sonography, CT scan or MRI is comparable to the non-transplant population. Short term survival of LT-recipients after transplantation is not reduced for patients with CP, PC and patients with branch-duct IPMN (with a low-risk for malignancy according to international consensus guidelines).

1. Introduction

Over the last decades liver transplantation (LT) was established as the last therapeutic option for patients suffering from end stage liver disease (ESLD). Related to reduction of perioperative complications comorbidities become increasingly important for long-term survival after LT. Increased mortality has been described for many diseases associated with liver cirrhosis, for example renal failure due to hepatorenal syndrome [1]. Due to the link between alcohol consumption and pancreatic pathologies (and common ethyltoxic etiology of liver cirrhosis) diseases of the pancreas must be considered as relevant comorbidities in LT recipients [2]. Pancreatic diseases in the general population are chronic pancreatitis (CP) (incidence 4.5/100 000 person years), pancreatic cysts (PC) (prevalence 1.2%) and intraductal papillary mucinous neoplasm (IPMN) (incidence 4.35/100 000 person years) [3–5].

Although alcohol consumption is the most common cause of chronic pancreatitis, surprisingly clinical co-incidence with liver cirrhosis is rarely reported (2.5%) [6]. In autopsy studies an association of the two diseases (35%) is suspected [7]. There are no reports on the frequency and impact of CP in LT cohorts. As complication of CP and as part of its diagnostic criteria (Cambridge classification) cystic alterations of the pancreas (pancreatic duct) can occur [8]. Cystic pancreatic pathologies are a heterogeneous disease entity, which is diagnosed increasingly frequent on the basis of widespread use of sonographic/radiologic imaging [9]. Non-malignant pancreatic cysts (such as true cysts, retention cysts, mucinous non-neoplastic cysts or lymphoepithelial cysts) must be distinguished from pancreatic cystic neoplasms (such as serous cystic tumors, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms and solid pseudopapillary neoplasms) [10]. In patients who underwent pancreatic resection for cystic pancreatic neoplasms the most frequent subtype was IPMN (38–49%) [11]. Optimal diagnosis and therapy of IPMN remain a challenge for the treating physician, as grade of dysplasia is not known until resection and clinical guidelines are "consensus" instead of "evidence based" due to low levels of evidence [12]. Surgical resection is recommended in the case of suspected malignancy due to high-risk stigmata in computed tomography or magnetic resonance imaging (obstructive jaundice in a patient with a cystic lesion of the pancreatic head, enhanced solid component, MPD size of ≥ 10 mm) [12]. Other cysts should undergo further testing or surveillance. Survival of non-LT recipients with invasive carcinoma is significantly decreased even after resection (5-year survival 60%) [13]. On the other hand the annual malignancy rate of IPMN without risk factors in non-LT is rather low. There are no data regarding prevalence or survival of LT-recipients with IPMN.

The aim of this study was to determine the clinical relevance of pancreatic alterations in LT recipients.

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2. Methods

A total of 616 liver transplantations (performed at the Clinic for General, Visceral and Transplantation Surgery of the University of Mainz until June 1, 2011) were evaluated. Patients were identified from an administrative transplant database. In this database all data were prospectively collected. Patients without at least six months of follow-up were excluded from the study. In the case of missing clinical data patients were also excluded from the study. In patients who underwent retransplantation only the first transplantation was included in the study. A total of 372 patients met the inclusion criteria. In addition to usual patient demographics, we reviewed the etiology of ESLD, prevalence of pretransplant diabetes mellitus, ascites, hepatocellular carcinoma (HCC) status, and prevalence of hypertension. Patients' body mass index (BMI), blood pressure, cholesterol and triglycerides were collected prior to transplant as a part of baseline information. Patients who had oral hypoglycemic agent and/or insulin requirement before transplantation were diagnosed as having pretransplant diabetes mellitus. Computed tomography (CT) and sonography were performed routinely in every patient before LT.

CP was diagnosed using imaging studies (either computed tomography/magnetic resonance cholangiopancreatography, transabdominal sonography, endosonography, or endoscopic retrograde cholangiopancreatography) according to the "Cambridge Classification" according to the German guidelines for diagnosis of chronic pancreatitis [8].

PC were diagnosed using imaging studies (either computed tomography/magnetic resonance cholangiopancreatography, transabdominal sonography, endosonography, or endoscopic retrograde cholangiopancreatography).

In the case of PC > 1 cm with suspected contact to the pancreatic duct further investigations were accomplished: either pancreatic protocol computed tomography or gadolinium-enhanced magnetic resonance imaging with magnetic resonance cholangiopancreatography, endosonography with cytology or endoscopic retrograde cholangiopancreatography according to the international consensus guidelines [12].

All patients were followed up at least every three to six months at our outpatient clinic. Radiologic controls were done on the basis of the individual findings and risk factors according to the guidelines [8,12].

Categorical variables were expressed as means (± standard deviations (SD)). Observations between groups were compared using chi-square test for categorical variables and the unpaired t-test for continuous variables. p-Values less than 0.05 were considered significant. Cumulative survival curves were generated using the Kaplan–Meier method, and survival between groups was compared by log-rank test. In this analysis, death was considered a censoring event. Cox regression was used for multivariate analysis of survival. All statistical analyses were performed using IBM SPSS statistics version 20 (SPSS Inc., Chicago, IL, USA).

3. Results

Mean (±SD) age of our 372 patient cohort was 54.8 (±10.1) years (Table 1). Most patients were male (68%). Nearly all patients were of Caucasian origin (98.4%). Nearly half of all patients (39.5%) were transplanted for alcohol related ESLD, other common causes for transplantation were hepatitis C (25.3%) and hepatitis B (13.7%). 39% of the patients had a history of HCC. Mean baseline BMI was 25.9 ± 5.1 kg/m^2, mean baseline cholesterol was 138.2 (±57.0) mg/dl, and mean baseline triglyceride was 105.25 (±73.2) mg/dl. 227 patients (61%) had a diagnosis of arterial hypertension. The majority (208 patients; 55.9%) received tacrolimus as their primary immunosuppressive drug, 99 (26.6%) were prescribed cyclosporine and 272 patients (73.1%) received mycophenolate mofetil. Pancreatic alterations (25/372 LT recipients, 6.7%) such as CP (3.8%), PC (1.6%) or IPMN (1.6%) were rarely found (Table 2). In one LT-recipient (0.3%) more than one pancreatic alteration was found (CP & IPMN). There was no statistically significant relation between IPMN, CP, PC and patient characteristics. CP was found more often in patients with alcoholic cirrhosis (p = 0.177) and cryptogenic cirrhosis (p = 0.143), however the difference was not significant. In 3/14 (21.4%) patients with chronic pancreatitis endocrine pancreatic insufficiency was diagnosed (while prevalence of diabetes mellitus in all LT-recipients was 26.6%). All diagnosed IPMN were classified as side branch type, no main duct type was found. All diagnosed IPMN showed no "high-risk stigmata" as thickened wall, intraductal mucin or mural nodules and no suspicious findings for malignancy in the imaging. One LT-recipient has already been treated by surgical left pancreatectomy in an extern hospital before being referred to our transplant center. In three out of six LT recipients with IPMN endosonography with fine-needle aspiration (FNA) was performed. We performed cytology of the cyst content, but we did not routinely perform tumor markers of the cyst fluid like carcinoembryonic antigen (CEA). In two out of three FNA no specific results were obtained,

Table 1
Demographic information on cohort (n = 372).

Follow-up (years), mean (±SD)	4.2 (±3.1)
Age (years), mean (±SD)	54.8 (±10.1)
Gender, % (n)	
- Male	68 (253)
- Female	32 (119)
Ethnicity, % (n)	
- Caucasian	98.4 (366)
- Others	1.6 (6)
Etiology of liver disease, % (n)	
- ETOH	39.5 (147)
- Hepatitis B	13.7 (51)
- Hepatitis C	25.3 (94)
- Autoimmune	7.3 (27)
- Amyloidosis	3.8 (14)
- Cryptogenic	4.8 (18)
- Other causes	5.7 (21)
- Acute liver injury	3.2 (12)
Hepatocellular carcinoma, % (n)	
- Yes	39 (145)
- No	61 (227)
Body height (cm), mean (±SD)	172 (±8.3)
Body weight (kg), mean (±SD)	77.7 (±16.6)
BMI (kg/m^2), mean (±SD)	25.9 (±5.1)
Baseline cholesterol (mg/dl), mean (±SD)	138.2 (±57.0)
Baseline triglycerides (mg/dl), mean (±SD)	105.25 (±73.2)
Hypertension, % (n)	
- Yes	61 (227)
- No	39 (145)
Immunosuppression, % (n)	
- Tacrolimus	55.9 (208)
- Advagraf	16.4 (61)
- Ciclosporin	26.6 (99)
- mTor inhibitor	18.8 (70)
- Mycophenolate mofetil	73.1 (272)
Nicotine, % (n)	
- Yes	21.2 (79)
- No	47.6 (177)
- Former smoker	31.2 (116)

Abbreviations: ETOH = ethyltoxic etiology of liver cirrhosis, BMI = body mass index.

Table 2
Prevalence of pancreatic pathologies in LT recipients.

No pathologies, % (n)	93.3 (347)
Pathologic findings, % (n)	6.7 (25)
- Chronic pancreatitis, % (n)	3.8 (14)
- Pancreatic cysts, % (n)	1.6 (6)
- IPMN, % (n)	1.6 (6)
- Multiple findings, % (n)	0.3 (1)

Abbreviations: IPMN = intraductal papillary mucinous neoplasm.