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Original Article

Pretransplant coronary artery disease is a predictor for myocardial infarction and cardiac death after liver transplantation

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ABSTRACT

Background: Cardiovascular disease is a serious problem of liver transplant (LT) recipients because of increased cardiovascular risk due to immunosuppressive therapy, higher age, intraoperative risk and comorbidities (such as diabetes and nicotine abuse). Reported frequency of cardiovascular events after LT shows a high variability between different LT cohorts. Our aim was to analyze a cohort of LT recipients from a single center in Germany to evaluate frequency of the cardiovascular endpoints (CVE) myocardial infarction and/or cardiac death after LT and to investigate correlations of CVE post LT with pretransplant patient characteristics.

Patients: In total, data from 352 LT patients were analyzed. Patients were identified from an administrative transplant database, and all data were retrieved from patients' charts and reports.

Results: During the median follow-up of 4.0 (0 − 13) years, 10 cases of CVE were documented (six myocardial infarctions and four coronary deaths). The frequency of CVE did not differ according to classic cardiovascular risk factors such as body mass index ($p = 0.071$), total cholesterol ($p = 0.533$), hypertension ($p = 0.747$), smoking ($p = 1.000$) and pretransplant diabetes mellitus ($p = 0.146$). In patients with pretransplant coronary heart disease ($n = 24$; 6.8%) CVE were found more frequently ($p = 0.024$).

Conclusion: In summary, we found a rate of 2.8% CVE after LT in a German transplant cohort. Pretransplant CHD was the only risk factor for CVE, but showed no significant impact on overall survival.

1. Introduction

Liver transplantation (LT) is indicated for severe acute or advanced chronic liver disease when the limits of medical therapy have been reached [1]. Due to improvement in intensive care management, surgical technique and immunosuppression, the 5 year-survival rates increased to 71% [2]. As result of improved long-term survival, cardiovascular mortality became increasingly important because most cases of cardiovascular deaths (81.3%) occurred beyond 5 years after LT [3].

Coronary heart disease (CHD) is a major cause of mortality in the general population. Several factors, such as immunosuppression, weight gain or the development of diabetes mellitus (DM) contribute to an increased cardiovascular risk after LT [4]. In LT recipients who survived the first year post-transplant, cardiovascular mortality is the third leading cause of death [5].

To decrease cardiac mortality recent clinical practice guidelines recommend screening for CHD in all patients undergoing evaluation for LT in case of cardiovascular risk factors (chronic smokers, patients over the age of 50, personal or family history of heart disease or diabetes) [6]. Initial assessment should be made using dobutamine stress echocardiography, and positive test results should be confirmed with cardiac catheterization [1]. Although, there is a strong recommendation for the use of dobutamine stress echocardiography certified by Martin et al., several authors report limitations of stress echocardiography as screening test due to poor sensitivity, specificity, as well as poor positive predictive value [7,8].

Beside treatment of risk factors, a percutaneous coronary intervention is a safe intervention in order to reduce CVE [9,10].

Dual antiplatelet therapy after treatment with cardiac stents is associated with complications such as high rates of gastrointestinal bleeding. So it remains unclear, whether the cardiovascular benefits of cardiac stents outweigh the bleeding risk [11]. However, cardiac complications after LT are mainly pulmonary oedema and pleural effusion, whereas myocardial infarction is rare [12].

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LT recipients represent an inhomogeneous cohort (pretransplant obese patients with NASH, cachectic patients with alcohol-induced liver cirrhosis, patients with hepatocellular carcinoma, etc.) [13]. The cardiac risk of LT recipients can vary between centers and within one center over the years, due to different underlying diseases [8]. Because of increasing diagnoses of diabetes and fatty liver disease, an increase of cardiac risk and CVE is likely [14].

In literature, the reported incidence rate of CVE after LT was widely variable (0–31%) and predictable risk factors for cardiovascular events were inconsistent [15].

The aim of our analysis was to determine the frequency of CVE after LT and to determine possible risk factors for CVE.

2. Patients and methods

A total of 616 liver transplantations, performed at the University Medical Center of Mainz until June 1st, 2011, were evaluated. Patients were identified from an administrative transplant database, and all data were retrieved from patients' charts and reports to the cut-off date June 1st, 2011. Patients transplanted between December 1st, 2010 and June 1st, 2011 were excluded from analysis in order to achieve a follow-up of at least six months. The selection process of the study cohort is presented in Fig. 1.

In addition to commonly used patient demographics, we reviewed the etiology of liver failure, hepatocellular carcinoma (HCC) status, and prevalence of hypertension and CHD. Pretransplant data about patients' body mass index (BMI), arterial hypertension, total cholesterol, LDL, HDL and triglycerides were collected as a part of baseline information prior to LT. In case of persisting nicotine abuse after LT, patients were stated as smokers. Former nicotine abuse was not taken into account.

Cut off levels for cholesterol were > 200 mg/dl, for triglycerides > 150 mg/dl, for LDL-cholesterol > 160 mg/dl and for HDL-cholesterol < 40 mg/dl. Additionally we looked for statin treatment prior to LT.

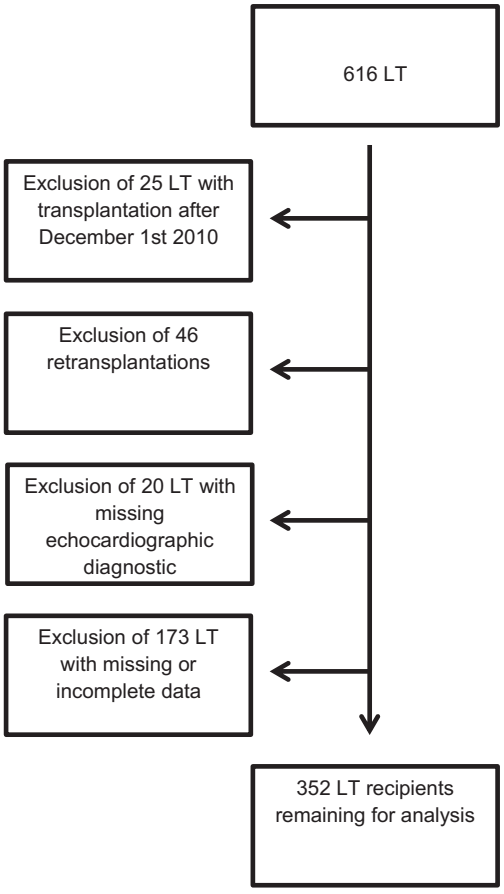

Fig. 1. Inclusion of patients.

According to World Health Organization guidelines [16] the presence of diabetes mellitus was based on self-reported usage of antidiabetic medication and/or fasting plasma glucose levels ≥ 7.0 mmol/l and/or postload plasma glucose levels ≥ 11.1 mmol/l. As the diagnosis was made before LT the diagnosis was called pretransplant diabetes.

We defined arterial hypertension as use of antihypertensive medication before LT [17] with the exception of non-selective beta-blockers, e.g. propranolol, given for prophylaxis in patients with esophageal varices [18].

During evaluation for LT, patients underwent a modified screening for cardiovascular diseases based on AASLD recommendations [1,6]: by electrocardiogram, echocardiography, pulmonary function testing, arterial blood gas, long-term blood pressure recordings, echocardiography and dobutamine stress echocardiography. In case of positive stress echocardiography, pathologic echocardiography, age > 60 years, diabetes mellitus for over 10 years or known coronary artery disease or nicotine abuse a left heart catheter with coronarangiography was performed. Patients transplanted before 2005 were screened with transthoracic echocardiography without additional stress echocardiography. Coronary heart disease was defined as manifestation of atherosclerosis in the coronary vessels with stenosis (of any degree) diagnosed by cardiac catheterization. Left ventricular ejection fraction was defined as normal (> 55%) or reduced (< 55%).

A common immunosuppressive regimen was the combination of a calcineurin inhibitor (tacrolimus or cyclosporine) with mycophenolate mofetil (MMF). Target trough levels were 5–7 ng/ml for tacrolimus during the first year and 3–5 ng/ml after one year. For cyclosporine target trough levels were 70–90 ng/ml during the first year and 50–70 ng/ml thereafter. Target trough levels were chosen by experience from our center in combination with reported data from other centers [19].

All patients were followed up at least every three to six months at our outpatient clinic. Follow-up and the primary endpoint cardiovascular event (CVE, defined as myocardial infarction and/or cardiac death) were documented. The observation period ended on December, 31th, 2011.

For descriptive analysis continuous variables were expressed as median (with inter quartile range (IQR)). Differences between groups were compared using the exact Fisher test for two categorical variables and the nonparametric Mann-Whitney-*U* test was calculated for differences in two groups for continuous outcome variables.

Additionally a univariate logistic regression analysis was performed with the binary outcome variable CVE and the independent variable preexisting CHD. Odds ratio, as well as the corresponding 95% confidence limits and *p* values are presented.

The survival time was estimated using the Kaplan-Meier method, and survival between groups was compared by the nonparametric log-rank test.

P-values < 0.05 were considered significant.

Statistical analysis was performed using IBM SPSS statistics version 22 (SPSS Inc., Chicago, IL, USA).

This research was approved by the local ethics committee of Rhineland-Palatinate and was conducted according to the ethical guidelines of the Declaration of Helsinki 1975 and Good Clinical Practice guidelines. Informed consent of patients was obtained during the evaluation process for liver transplantation, with general approval to use anonymous data in clinical studies.

3. Results

Three hundred and fifty-two patients who underwent LT for different reasons were included. Baseline patient characteristics are listed in Table 1.