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ORIGINAL ARTICLE

Vascular events after liver transplantation: a long-term follow-up study

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Summary

Long-term follow-up studies on the impact of vascular events (VE) and risk factors of liver transplant recipients are scarce. In this study, 311 recipients of a first isolated liver transplant who survived at least 1 year were followed up from 1979 to 2002. The median follow-up duration was 6.2 (range1–22.7) years. Overall median survival was 18.7 [95% confidence interval (CI): 15.5–20.1] years and this was significantly lower compared with age- and sex-matched controls. Eleven (21%) of the patients had a vascular cause of death and VE were the third cause of death. VE occurred later compared with other causes of death (mean 10.3 years vs. 4.5 years, $P < 0.0001$, 95% CI: 2.7–8.9). Systolic hypertension, systolic blood pressure, smoking, renal failure, age, hypertriglyceridemia, serum total cholesterol levels and hypercholesterolemia at the 1-year follow-up visit were associated with the occurrence of VE, but renal failure and age at 1 year after transplantation were the only independent risk factors for vascular death (hazard ratio 0.06, 95% CI: 0.01–0.41 and hazard ratio 1.17, 95% CI: 1.02–1.34, respectively). Finally, it was shown that the adequate treatment of hypertension was associated with a significant reduced risk of vascular death. Therefore, vascular risk factors should be treated aggressively to prevent VE in the long term.

Introduction

Liver transplantation has become the established therapy for patients with acute or chronic liver failure. Currently, the 1-year patient survival in most centers ranges from 80 to 90%. The long-term prognosis of patients who survive the first postoperative year is considered excellent with 10-year survival rates as high as 84%. Nevertheless, the life expectancy of liver transplant recipients is lower compared with that of the general population.

In the Western population the main cause of death is vascular events (VE). In liver transplant recipients, hypertension, hypercholesterolemia, obesity, and diabetes mellitus are frequently observed [1–3]. As these are well known risk factors for VE [4], it can be anticipated that these patients have an increased risk of mortality caused by VE as well. Several studies on vascular morbidity and mortality of patients after liver transplantation have been published that indeed showed that VE are an important health hazard for liver transplant recipients [5–11]. Follow-up studies with a very long follow-up duration, however, are scarce.

The University Medical Center Groningen liver transplant program started in 1979 as the fourth program in the world. Meticulous adherence to protocols and strict follow up have been key features from the start as patients were seen at yearly follow-up visits by a small group of dedicated doctors and nurses and as patients in the small country of the Netherlands seldom emigrate and could be followed up easily. The result is a large

cohort of patients with a long-term follow up. We, therefore, were able to study the effect of age, gender and traditional vascular risk factors (VRF) on the occurrence of VE in patients in the long-term follow up after liver transplantation.

Patients and methods

All adult recipients of a liver transplant who received their first isolated orthotopic liver transplantation between April 1979 and January 2001 and survived at least 1 year after transplantation were included in this retrospective study. Patients with known vascular disease (VD) (a sudden cardiac death, myocardial infarction, angina pectoris, heart failure, peripheral and/or cerebral VD) at the time of transplantation were excluded. Medical records of all these patients were retrieved. The medical history concerning diabetes mellitus and hypertension was noted. Furthermore, medication, length, weight, body mass index, systolic and diastolic blood pressure, and smoking habits at the 1-year follow-up visit were noted. Finally, laboratory results 1 year after transplantation concerning full blood count, serum triglycerides, serum total cholesterol, serum creatinine, serum nonfasting glucose, proteinuria, and creatinine clearance were retrieved as well. Patients were followed up until death or until the first of January 2002. Occurrences of CE as well as causes of death were noted.

Vascular events were defined as the occurrence of an acute myocardial infarction, sudden cardiac death, angina pectoris (both stable and unstable), heart failure, a cerebral vascular accident, a transient ischemic attack or peripheral VD. Hypertension was defined as a systolic blood pressure above or equal to 140 mmHg and and/or a diastolic blood pressure above or equal to 90 mmHg [12] or when patients were using antihypertensive drugs irrespective of their blood pressure. Diabetes mellitus was defined as a nonfasting glucose above 11.0 mmol/l [13] or when patients were using oral blood glucose lowering drugs or insulin.

Obesity was defined as a body mass index above or equal to 30 kg/m^2 [14]. Hypertriglyceridemia was defined as a serum triglyceride level above 2.2 mmol/l [15] or when patients were using triglyceride-lowering drugs. Hypercholesterolemia was defined as a serum total cholesterol above 5.25 mmol/l [16] or when patients were using cholesterol-lowering drugs. Renal failure was defined as a serum creatinine above 120 μmol/l and 136 μmol/l, for females and males respectively [17]. Significant proteinuria was defined as proteinuria of more than 200 mg/l. Subjects were considered smokers if they had smoked within 2 years before liver transplantation.

For statistical analysis, the Statistical Package for the Social Sciences version 14 (SPSS Inc., Chicago, IL, USA) was used. The Student's *t*-test and Kruskal–Wallis test were used for parametric and nonparametric variables, respectively, to compare sex, age, follow-up duration and VRF in liver transplantation recipients with and without VE in the follow up. The relationship between VE and VRF was determined using the Cox multiple regression analysis method. Both univariate and multivariate models were used. *P*-values less then 0.05 were regarded as significant. Survival of patients was determined using the Kaplan–Meier method. The survival rate of the population was compared to the expected age- and sex-matched survival rate in the general Dutch population as provided by Statistic Netherlands (*'het Centraal Bureau voor de Statistiek')* (http://statline.cbs.nl/StatWeb). Statistic Netherlands is responsible for collecting, processing and publishing statistics for policymakers and scientists in the Netherlands.

Results

From 1979 to 2001, 314 of the 402 (78%) recipients of an isolated liver transplantation in the University Medical Center Groningen liver transplant program survived at least 1 year. Three of these patients were excluded from this study because of a history of VD. Therefore, a total of 311 patients (142 males and 169 females), were included in the analysis. The mean age of the patients at transplantation was 42.3 years (range 17.7–66.2 years). The indications for liver transplantation were: acute hepatic failure in 12 patients (4%), viral hepatitis in 36 patients (12%), autoimmune disease in 32 patients (10%), alcoholic liver disease in 26 patients (8%), primary biliary cirrhosis or primary sclerosing cholangitis in 106 patients (34%), cryptogenic cirrhosis in 36 patients (12%), and other reasons, including metabolic disease, large hemangiomas, polycystic liver disease, and veno-occlusive disease in 63 patients (20%).

The median follow-up duration was 6.2 years (range 1–22.7 years). In 43 patients, follow up in our center was ended for reasons other than death. The medical records of these patients concerning VE were analyzed until the last follow-up visit in our center. Survival rates for 5, 10, 15, and 20 years post-transplantation according to Kaplan–Meier calculations were 89%, 83%, 70%, and 50%, respectively (Fig. 1).

Overall, 52 of the 311 (17%) patients died during follow up, of which 11 (21%) had a vascular cause of death. Other causes of death were recurrence of liver disease in 16 patients (31%), infection in 14 patients (27%), malignancy in seven patients (13%) and other causes in four patients (8%). During the follow-up period, 33 VE- of which 11 were fatal- occurred in 24 patients. Eight of the

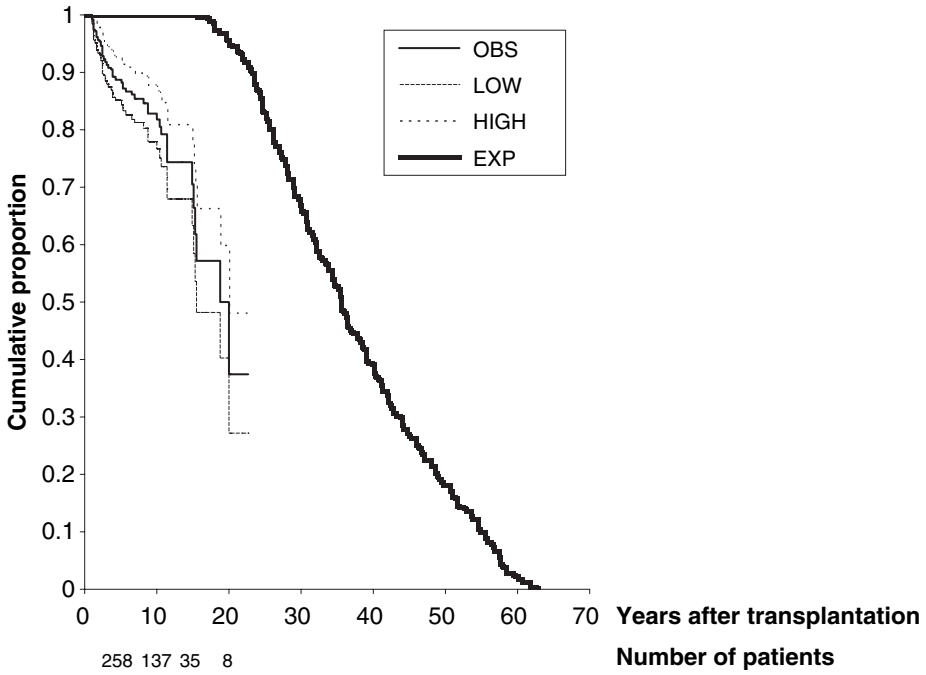

Figure 1 Overall survival rate of liver transplant recipients as compared to survival of the age- and sex-matched general Dutch population. Observed survival (OBS) rate with 95% confidence interval (Low–High) of the 311 patients surviving at least 1-year after liver transplantation when compared with the calculated expected (EXP) survival rate in the general Dutch population. $P < 0.05$. The observed median survival is 18.7 years.

11 fatal events had not been preceded by a nonfatal VE (Tables 1 and 2; Fig. 2). The mean time until the occurrence of a first VE was 7.6 years. The mean time until death caused by a VE was 10.3 years. The mean time of death caused by infection, malignancy, recurrence of liver disease and other causes was 6.5; 6.4; 2.5, and 2.1 years after liver transplantation, respectively. It was calculated that death caused by VE occurs significantly later than death because of other causes ($P < 0.0001$; log-rank test, $\chi^2 = 17.80$).

In Fig. 1 the survival rate of the patients is compared to the expected survival rate of the age- and sex-matched general Dutch population, showing a shorter survival rate after a liver transplantation compared with that in the general Dutch population.

Age at transplantation, systolic hypertension, systolic blood pressure, smoking, serum total cholesterol levels and hypercholesterolemia as measured at 1 year after transplantation were significantly higher in the group that developed VE in the follow-up (Table 3). Similarly, serum-creatinine and triglyceride-levels were significantly

Table 2. Distribution of the 33 vascular events and time until event after transplantation in 311 liver transplant recipients surviving at least 1 year after liver transplantation.

	Number of events	Time until event in years (mean, range)
Sudden cardiac death	2	17.8 (15.5–20.1)
Acute myocardial infarction	7	8.0 (2.5–12.4)
Unstable angina pectoris	7	5.9 (0.6–12.5)
Stable angina pectoris	3	5.6 (3.1–8.6)
Heart failure	3	14.9 (14.7–18.8)
Peripheral vascular disease	4	9.8 (2.6–16.4)
Hemorrhagic cerebral vascular accident	4	3.8 (1.6–8.8)
Ischemic cerebral vascular accident	1	6.6
Transient ischemic attack	2	5.1 (1.0–9.2)

Table 1. Distribution of the 11 vascular deaths, follow-up duration after transplantation until death and age at death in the 311 liver transplant recipients surviving at least 1 year after liver transplantation.

Cause of death	Number of events	Time until death in years	Age at death in years
Sudden cardiac death	2	15.5 and 20.1	70.9 and 73.6
Acute myocardial infarction	3	2.5; 9.9; and 11.4	53.5; 61.9; and 65.8
Heart failure	2	15.1 and 18.8	36.6 and 64.0
Mesenteric ischemia	1	2.6	55.4
Cerebral vascular accident	3	2.5; 5.5; and 8,8	57.0; 55.8; and 61.6

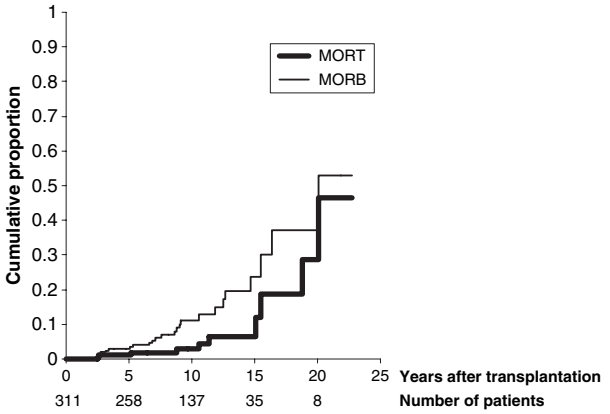

Figure 2 Cumulative incidence of vascular morbidity (MORB) and mortality (MORT) in patients surving at least 1 year after liver transplantation.

higher, but because of unequal variances, these parameters could not be further analyzed and instead of these variables, renal failure, and hypertriglyceridemia were used. Using the Cox multiple regression backward conditional analysis, systolic hypertension ($P = 0.179$), smoking ($P = 0.135$), age ($P = 0.067$), and hypertriglyceridemia ($P = 0.104$) were the only parameters remaining in the equation, but none of these parameters was a significant independent risk factor for VE, although a type II error cannot be excluded. Using the same method, we found that renal failure [$P = 0.004$; hazard ratio 0.06; 95% confidence interval (CI): 0.01–0.41] and age at transplantation ($P = 0.048$; hazard ratio 1.17; 95% CI: 1.02–1.34) were independent significant predictors of vascular mortality after liver transplantation.

Table 4. Risk of vascular morbidity and mortality for liver transplant recipients in relation to blood pressure (BP) and use of anti-hypertensive drugs. From 20 of the 311 patients data were missing and these patients are excluded from this analysis.

	Risk of morbidity	Risk of mortality
No use of anti-hypertensive drugs		
BP < 140/90 mmHg	2/112 (1.8%)*	2/112 (1.8%)†
BP ≥ 140/90 mmHg	3/66 (4.5%)*	4/66(6.1%)†
Use of antihypertensive drugs		
BP < 140/90 mmHg	2/55 (4%)‡	0/55 (0%)§
BP ≥ 140/90 mmHg	7/58 (12.1%)‡	4/58 (6.9%)§

*$P = 0.283$; †$P = 0.128$; ‡$P = 0.099$; §$P = 0.048$ using the Mann–Whitney test.

As systolic hypertension is a well known VRF [18,19], the effect of treatment of hypertension with anti-hypertensive drugs on VE and vascular mortality was analyzed separately. The results suggest that effective blood pressure reduction in liver transplant recipients with anti-hypertensive drugs results in a significant decreased risk of mortality caused by VE (Table 4). Fifty-eight percent (38/65) of the patients with diabetes mellitus were treated with glucose lowering drugs. Only 1% (2/167) of the patients with hypercholesterolemia were treated with cholesterol-lowering drugs and only 2% (1/69) of the patients with hypertriglyceridemia were treated with triglyceride-

Table 3. Distributions of sex, VRF and follow up in the liver transplantation recipients with and without occurrence of VE.

Baseline characteristics at 1 year after OLT	Patients with VE in follow up (n = 24)	Patients without VE in follow up (n = 287)
Males/females	8/16	134/153
Mean age at OLT in years** (range)	49.8 (17.8–64.6)	41.5 (17.7–66.2)
Mean follow up in years (range)	10.8 (2.5–20.1)	6.5 (1.0–22.7)
Smoking*	9/19 (47%)	62/266 (23%)
Mean Systolic blood pressure (mmHg, ±SE of mean)**	144.2 ± 3.2	131.5 ± 0.9
Mean diastolic blood pressure (mmHg ± SE of mean)	85.6 ± 1.5	81.8 ± 0.6
Systolic hypertension*	15/22(68%)	92/269(34%)
Hypertension	19/22 (86%)	157/273 (58%)
Diabetes mellitus	6/23 (26%)	59/271 (22%)
Mean body mass index (kg/m^2, ±SE of mean)	26.6 ± 0.8	24.9 ± 0.3
Mean total cholesterol (mmol/l, ±SE of mean)*	6.8 ± 0.5	5.7 ± 0.1
Hypercholesterolemia*	21/23 (91%)	146/279 (52%)
Mean proteinuria (mg/24U, ±SE of mean)	0.46 ± 0.19	0.30 ± 0.04
Significant proteinuria(>200mg/l)	7/20 (35%)	68/249 (28%)
Mean serum-creatinine *(μmol/l, ±SE of mean) NEV	123.6 ± 19.3	97.9 ± 1.6
Renal failure*	5/23 (22%)	22/278 (8%)
Mean creatinine-clearance (ml/min ±SE of mean)	76.8 ± 6.1	84.5 ± 2.1
Mean triglycerides *(mmol/l, ±SE of mean) NEV	4.6 ± 2.3	1.9 ± 0.1
Hypertriglyceridemia *	8/16(50%)	61/205(30%)

Significant differences are marked with an *($P < 0.05$) or **($P < 0.001$) using Kruskal–Wallis test and Student's t-test where appropriate.

lowering drugs. Finally, 11% (8/75) of the patients with proteinuria were treated with an angiotensin inhibitor.

With respect to immunosuppression, 21 patients were treated with high doses of prednisolon and azathioprine in the early days of transplantation and in this group five patients developed VD and four died because of VE. Two hundred eight patients were treated with a combination of prednisolon, cyclosporine, and azathioprine and in this group 19 patients developed VD and seven died because of a VE. Finally, since 1990, a combination of prednisolon and tacrolimus with or without azathioprine has been used and 82 patients were treated with this combination. In this group, so far, no patients developed VD or died of a VE.

Discussion

In this long term follow-up study, with a follow-up duration up to 22 years, it is shown that death because of VE is the third cause of death in liver transplant recipients. Several other studies have investigated the long-term survival of liver transplant recipients [5,9,11,20–23]. In this study, 5 and 10 years survival rates resemble those reported in other studies [5,11,20,23]. Although it must be acknowledged that our study population is not entirely comparable to in these studies, the study populations as there are a relative lower number of patients with alcohol-related liver disease and with viral disease in our population. As compared to these other studies, our study has the longest follow up. In most studies *de novo* malignancy, VD and recurrence of liver disease are the most important causes of death on the long term after liver transplantation [5,9,11,20–23]. As in our study, death caused by VD occurs later (mean 10.3 years) than death because of other causes (mean 4.5 years). It is suggested that, especially, in long term survivors, VE become an important health hazard; in 20 years after OLT, four out of eight patients (50%) had died because of a VE. This could have been anticipated as the patients who were included were those fit for major surgery and without VD at inclusion.

Our study is one of the few studies that extensively investigated the role of VRF and their association with VE. In our study, factors such as age, systolic hypertension, systolic blood pressure, smoking, renal failure, hypertriglyceridemia, serum total cholesterol levels, and hypercholesterolemia were associated with VE, although renal failure and age were the only independent risk factors for death because of VE. Therapondos *et al.* found age, gender and cholesterol levels to be independent predictors of VE [10]. Johnston *et al.* found that liver allograft recipients have a greater risk of vascular deaths and ischemic events than an age- and sex-matched population. Raised serum cholesterol and systolic hypertension were found in patients developing VE [1]. The fact that in our study hypertension, hypercholerolemia and smoking were not independently associated with VE may simply be related to sample size. Therefore, this study is in concordance with other studies.

It was shown, as expected, that older age is an independent predictor of death caused by VE. Nevertheless, when patients are compared to age- and sex-matched Dutch citizens, there still is an increased risk of vascular mortality. Although comparison with a matched population is somewhat misleading, the increased mortality in a population with an a priori lower risk of cardiovascular disease is striking. It can be suggested that this increased risk of mortality is partly unpreventable because of clinically not apparent vascular damage already present before liver transplantation was performed. However, the occurrence of VD in the long-term follow up of a population without VD at inclusion suggests that VD could be preventable. It was shown in this study that a partly preventable risk factor such as renal failure is an independent, significant risk factor for death caused by VE. Moreover, this study suggests that the effective treatment of hypertension results in a decreased risk of death caused by VE. A limitation of this study is the fact that our analysis was based on only one blood pressure measurement. Nevertheless, the observation in this study are in concordance with observations in nontransplant patients with hypertension [18,19]. Furthermore, although not shown in liver transplant recipients, it is known that refraining from smoking [24] and the treatment of hypercholesterolemia and hypertriglyceridemia [25–27] prevent the occurrence of vascular morbidity and mortality. Unfortunately, hypertension was not always treated optimally in our patients and neither were other risk factors such as hypercholesterolemia, hypertriglyceridemia, and proteinuria. The increased mortality as compared to the general population suggests that there is life expectancy to be gained and awareness of VRF and aggressive treatment of VRF could be advantageous and could prevent VE in liver transplant recipients. It is hoped that increased awareness of and treatment of VRF in our population will result in lower vascular mortality in our cohort.

Several studies emphasized the importance of the choice of the immunosuppressant drugs and the risk of VD [28–30]. In our patient population, a combination of high doses of prednisolon and azathioprine was used in the early years of liver transplantation, after the introduction of cyclosporine the combination of prednisolon, cyclosporine, and azathioprine was used, and since the 1990s, combination of prednisolon and tacrolimus with or without azathioprine was used. Comparisons between different immunosuppressive regimens were, therefore, not adequately possible in this study although the prevalence of VE was the highest in the early cohort, followed

by the cohort using cyclosporine. As the early cohort also had the longest follow up and VE did not yet occur in the 'youngest' group, a much longer follow up is needed to compare the influence of the immunosuppressive drugs on the risk of VE in our population. Nevertheless, as renal failure is an independent predictor of VE, it is suggested that the use of nonnephrotoxic immunosuppressant drugs may be advantageous.

In summary, although the long term prognosis of liver transplant recipients is considered 'excellent', this long term follow-up study shows that these patients live shorter than age and sex matched controls. Furthermore, it is suggested that in the patients with the longest follow up, VE become a more important health hazard. It was also shown that renal failure and age were independent risk factors for VE in liver transplant recipients and that classical risk factors are associated with VE. Finally, it was shown that the adequate treatment of hypertension reduces mortality caused by VE. Therefore, clinicians taking care of these patients should treat VRF aggressively. It is hoped that, this will result in a life-expectancy of liver transplant recipients becoming closer to that of age- and sex-matched controls.

Authorship

MAJPB: collected and analyzed data and wrote the paper. EJvdW: analyzed the data and wrote the paper. WJS: performed the statistical analysis. MJHS, EBH and APvdB: designed the study and wrote the paper.

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