Cardiovascular Risk 10 Years After Liver Transplant

Olivier Guillaud,1 Olivier Boillot,1,2 Laurent Sebbag,3 Thomas Walter,1,2 Yves Bouffard,1 Jérôme Dumortier1,2

Abstract

Objectives: We sought to evaluate the frequency of cardiovascular risk factors in a cohort of patients 10 years after a liver transplant, and to assess their 10-year risk of fatal cardiovascular disease using Systematic COronary Risk Evaluation charts.

Materials and Methods: Between January 1990 and June 1996, one hundred eighty-nine adults underwent a first liver transplant in our center. Fifty-nine patients (31%) died before reaching their tenth year, and 115 patients were available with complete clinical data at 10 years.

Results: The main indications for liver transplant were alcoholic (38%) and viral cirrhosis (40%). The median age of patients was 56 (range, 29-73 y), 80% were men, 23% were obese, 16% were active smokers, 18% were diabetic, 40% had hypercholesterolemia, and 77% had hypertension. Before the 10th year after transplant, 6 deaths were because of cardiovascular diseases, which represents the third cause of late death (> 1 year after liver transplant). After liver transplant, 5% of the surviving patients underwent ischemic cardiovascular events during the first decade. At a 10-year assessment, the median estimated 10-year risk of fatal cardiovascular disease was 1% (range, 0%-9%) and 10% of the patients had a high risk (ie, SCORE ≥ 5%).

Conclusions: Our results suggest that the frequency of cardiovascular events is relatively low after a liver transplant, even if most of the patients had 1 or more cardiovascular risk factors. Nevertheless, clinicians should perform a similar evaluation 15 or 20 years after the liver transplant because cardiovascular risk exponentially increases with age.

Key words: Cardiovascular risk, Liver transplant, Outcome

Introduction

Immunosuppressive therapies expose transplant recipients to systemic complications (eg, hypertension, diabetes, dyslipidemia), which are well-known cardiovascular risk factors, and consequently, to cardiovascular complications.1 Patients with previous coronary artery disease undergoing a liver transplant have an increased intraoperative and postoperative risk when a liver transplant is performed. This should be considered when determining the candidacy of these patients.2 Therefore, the potential for perioperative and late cardiovascular complications in liver transplant candidates makes careful preoperative risk assessment imperative, especially in patients with typical anginal symptoms and low-density lipoprotein cholesterol levels.3 Even if the increased relative risk of cardiovascular events compared with a standard population remains controversial, it is widely accepted that cardiovascular disease is a leading cause of late (> 1 year) postliver transplant mortality in liver transplant recipients.4 Currently, liver allograft recipients live longer going to significant advances in posttransplant medical management and surgical techniques. Improvements in posttransplant care, along with older recipients at transplant and increased comorbidities, have made cardiovascular complications a key issue for long-term survival.

Because the combination of modest risk factors may result in a higher risk than a raised single factor,
several risk estimation models can help clinicians to assess the effects of cardiovascular risk factor combinations in planning management strategies. Many risk estimation systems can estimate the long-term cardiovascular risk. The best known are probably the Framingham risk score, the SCORE system (Systematic COronary Risk Evaluation), and the PROCAM system (PROspective CArdiovascular Münster). The SCORE risk chart is an easy-to-use tool with 4 basic data (sex, smoking status, systolic blood pressure, and total cholesterol [or total/high-density lipoprotein cholesterol ratio]), which allows prediction of the 10-year risk of fatal cardiovascular events (both coronary and cerebral). The SCORE system is based on a pooled data from 12 European prospective studies that contains > 205,000 persons, which represents 2.1 million person-years of observation; it recently has been validated in a German liver transplant cohort.

This study sought to investigate the prevalence of conventional risk factors for ischemic heart disease late (10 y) after a liver transplant and to determine the 10-year risk of fatal cardiovascular event using the SCORE model.

Materials and Methods

Study population
The study is a retrospective review of patients transplanted in our program. Between October 1990 and June 1996, one hundred eighty-nine adult patients underwent a first liver transplant. Multiorgan transplant recipients (at the time of first liver transplant) were not included. From these 189 patients, 13 were lost to follow-up, and 59 died during the first decade after the transplant: 6 patients died (10%) from cardiovascular diseases, and cardiovascular death was the third cause (16%) of late mortality (> 1 year after the liver transplant) behind recurrence of the initial disease (32%), and de novo malignancies (27%). The study group included 115 patients who survived 10 years after a liver transplant and with complete available data: 80 were men; the age at the time of liver transplant ranged from 19 to 63 years (median 46 y). Table 1 shows the indications for liver transplant.

The prevalence of cardiovascular risk factors (i.e., smoking status, hypertension, diabetes mellitus, hypercholesterolemia) was determined during the scheduled visit 10 years after the liver transplant.

Arterial hypertension was defined as a systolic blood pressure greater than 139 mm Hg, or a diastolic blood pressure greater than 89 mm Hg, or if an antihypertensive treatment already had been given. Diabetes mellitus was defined as fasting plasma glucose > 7.7 mmol/L, or if antidiabetic treatment already had been given. Hypercholesterolemia was defined as a total cholesterol > 5 mmol/L, or if a cholesterol-lowering drug already had been given.

Assessment of cardiovascular risk was calculated using the SCORE system. Calculation of risk is based on age, sex, smoking habit, total cholesterol, systolic blood pressure. The age limits were 40 to 65 years. Cardiovascular relative risk compared with a population of the same age without a no ny cardiovascular risk factors was assessed using a specific chart.

Statistical analyses
The chi-square, Fisher exact test, and Mann-Whitney U test were used, as appropriate. A P value < .05 was considered statistically significant. Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 13.0, IBM Corporation, Armonk, NY, USA).

Results

Immunosuppression
At the time of the evaluation, all the patients were on calcineurin inhibitors for immunosuppression: tacrolimus (n=28) or cyclosporine (n=87), associated with mycophenolate mofetil (n=60) or azathioprine (n=4), and/or low-dose of corticosteroids (n=24). In sum, 37 patients were on calcineurin inhibitor monotherapy, 65 on dual therapy mostly with mycophenolate mofetil, and 12 patients on triple therapy with steroids.
Nonfatal cardiovascular events
Of 115 patients, 8 underwent cardiovascular events during the first decade after the liver transplant. Ischemic events occurred in 6 patients (cerebral ischemia in 4 and myocardial ischemia in 2). Nonischemic events were recorded in 2 cases (arrhythmias: atrial fibrillation=1 and junctional tachycardia=1).

Prevalence of cardiovascular risk factors
Prevalence of the usual cardiovascular risk factors is shown in Figure 1 and detailed in Table 2, according to the indications for liver transplant. Hypertension was the most-common risk factors and was found in 88 patients (77%): 15 of 88 were not treated, 23 of 88 were treated with a controlled blood pressure, and 50 of 88 had persistently elevated blood pressure despite treatment (reported in 11 patients above 160 mm Hg). 65 patients were on antihypertensive monotherapy (mostly with calcium channel blockers), 12 on dual therapy, and 1 on triple therapy. Obesity (defined as a body mass index > 30) was present in 27 patients (23%).

Mean estimated calculated glomerular filtration rate (Cockroft and Gault) was 70 (± 28) mL/minute: 41 of 115 had calculated glomerular filtration rate < 60 mL/minute, and 10 of 115 calculated glomerular filtration rate < 30 mL/minute, 4 patients were on hemodialysis, and 1 patient had received a kidney transplant.

The prevalence of the 4 usual cardiovascular risk factors was different according to the underlying disease, and ex-alcoholic patients had the highest prevalence for all (hypertension 91%, smoking 30%, diabetes mellitus 25% and hypercholesterolemia 55%).

Regarding the number of risk factors per patient (either hypertension, smoking, diabetes, and hypercholesterolemia)—15 patients (13%) had no risk factors, 42 patients (36.5%) had 1 risk factor, 42 patients (36.5%) had 2 risk factors, 16 patients (14%) had 3 risk factors, and no patients (0%) had 4 risk factors. There was no difference in the prevalence of each cardiovascular risk factor according to the type of calcineurin inhibitor (Table 3). Repartition of these cardiovascular from an open risk factors was different according to the indication for liver transplant and ex-alcoholic patients cumulated these cardiovascular risk factors: 77% of ex-alcoholic patients, 43% of patients with hepatitis C virus, and only 29% of the others patients had 2 or more risk factors ($P < .05$).

Estimation of the 10-year risk of fatal cardiovascular event using the SCORE model
From our 115 patients, only 82 were eligible for SCORE analysis according to age. Median SCORE
was 1 (range 0-7), which corresponds to a low (1%) 10-year risk of a fatal cardiovascular event. In addition, 90% of the patients had a low risk (SCORE < 5), and 10% had a high risk (SCORE ≥ 5). Considering the relative risk (RR) compared with a sex- and age-matched ideal population (nonsmoking, normal blood pressure, and cholesterol), the median RR in our population was 2 (range, 1-7). In addition, 37 patients had a RR=1, twenty-five patients had a RR=2, and 20 patients had a RR ≥ 3. For the 21 patients between 40 and 50 years whose absolute SCORE was low (whatever their other associated cardiovascular risk factors were), the median RR compared with normal population was 2 (range, 1-5). One third of these patients had a RR=1, and two thirds had an increased RR (7 patients had a RR=2 and 7 patients had a RR ≥ 3).

The high SCORE was present in 18%, 15%, and 0% of patients transplanted for alcoholic cirrhosis, hepatitis C virus-cirrhosis, and other indications (P = .04). Among the different determinants of SCORE, age > 55 years was the most significant factor associated with a high SCORE. There was no difference between the prevalence of man, smoker, diabetes mellitus, hypercholesterolemia, hyper-tension between both groups (Table 4). Cardiovascular risk also was not different respecting the type of calcineurin inhibitor. In sum, 18% of ex-alcoholic patients, 15% of hepatitis C virus patients had high cardiovascular risk, whereas none of the patients transplanted for other indications had an increased risk.

### Table 4. Comparison of Cardiovascular Risk Factors Between Low and High SCORE Groups

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Low SCORE (&lt; 5)</th>
<th>High SCORE (≥ 5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 55 yrs</td>
<td>32 (43%)</td>
<td>8 (100%)</td>
<td>.03</td>
</tr>
<tr>
<td>Male</td>
<td>52 (70%)</td>
<td>8 (100%)</td>
<td>.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>54 (73%)</td>
<td>8 (100%)</td>
<td>.19</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (18%)</td>
<td>3 (37.5%)</td>
<td>.18</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (12%)</td>
<td>2 (25%)</td>
<td>.29</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>26 (35%)</td>
<td>4 (50%)</td>
<td>.42</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>19 (26%)</td>
<td>1 (12.5%)</td>
<td>.67</td>
</tr>
</tbody>
</table>

**Discussion**

Because immunosuppressive therapies induce metabolic disorders and, therefore, cardiovascular complications, long-term assessment of cardiovascular risk in transplant patients is relevant. However, few data are available in the literature, particularly for liver transplant recipients. This study sought to focus only on long-term survivors (ie, ≥ 10 years after liver transplant), to analyze the prevalence of the well-recognized cardiovascular risk factors (ie, hypertension, smoking, diabetes, and hyper-cholesterolemia), and estimate their 10-year risk of cardiovascular events.

Our study confirms the high prevalence of cardiovascular risk factors in the long term after a liver transplant. Only 13% of long-term survivors had none of these risk factors, and half of our patients had 2 or more risk factors. In a recent report, 92% of patients transplanted for acute liver failure had at least 1 cardiovascular risk factor 5 years after an orthotopic liver transplant.7 In our experience, patients transplanted for alcoholic cirrhosis are particularly exposed and cumulate most of these risk factors compared with other patients. Hypertension was the most common risk factor, encountered in 77% of our patients, which is close to the 86% found by Guckelberger and associates in their cohort of liver recipients who were 10 years postorthotopic liver transplant.8 It is well-acknowledged that hypertension after liver transplant is multifactorial: calcineurin inhibitor toxicity with prerenal vasoconstriction, obesity, and renal impairment.9 Interestingly, we found that despite active medical management (> 80% of our patients were treated), the control of the blood pressure was only achieved in one-third of our treated patients has recommended.10 In another recent report,11 only 15% of kidney transplants had controlled hypertension, which also stresses the importance of close monitoring of blood pressure for these patients, with probably more-aggressive management. Most of our treated patients were only on calcium channel blocker monotherapy, but it has been shown that the need for multiple antihypertensive doubles after 10 years of follow-up.8 If possible, reduction of calcineurin inhibitor dosage is also recommended, as the risk of rejection for most patients decreases with time after transplant.

Hypercholesterolemia was found in 40% of our patients. In the literature, the prevalence of hypercholesterolemia varies from 27% to 64 %,8,12-15 The variation in prevalence among the different studies may be explained by some difference in the definition of hypercholesterolemia, the difference in the prevalence of obesity, the difference in immunosuppressive regimes (the long-period use of corticosteroid has a deleterious effect), and the
timing after a liver transplant. Diabetes mellitus was found in 18% of our patients, mostly new-onset diabetes mellitus (NODM). In a French multicentre study, the overall incidence of NODM was similar (22.7%). The risk for NODM was higher in patient with hepatitis C virus (41.7% vs 18.9%), especially when they received tacrolimus (46.7% vs 19.3%). Other independent pretransplant risk factors for NODM included impaired fasting glucose and a maximum lifetime body mass index exceeding 25 kg/m². New-onset diabetes mellitus is associated with an increase in cardiovascular morbidity and mortality, impaired graft survival and function, more infections, and overall reductions in the quality of life and survival of the patients. Finally, active smoking was found in 16% of our patients, which appears to be similar to the recent report of Van der Heide. Smokers are at risk for both de novo malignancies and cardiovascular events. Ceasing smoking before undergoing a liver transplant is important and a challenge. Despite evidence that tobacco use is a serious problem in liver transplant patients, transplant centers do not require liver transplant patients to stop smoking, and there are no available studies of tobacco cessation in liver transplant candidates or recipients, although protocols to assist in smoking cessation have been proposed.

The question whether this increase in exposure to cardiovascular risk factors, translates into higher incidence of cardiovascular events compared with the general population is controversial. In the Birmingham’s study, liver transplant recipients had a significant increased relative risk of ischemic cardiac events and deaths of 3.07 and 2.56 compared with an age-matched nontransplant population, whereas the incidence ratios for myocardial infarction in liver transplant candidates or recipients, although protocols to assist in smoking cessation have been proposed. At the individual level, it is important to identify patients at risk of developing cardiovascular events to adapt the medical management, either by establishing a closer surveillance or changing medications. Most of the current systems of cardiovascular risk estimation include the “conventional” cardiovascular risk factors (age, sex, smoking, blood pressure, and lipids levels). The addition of extra factors has resulted in minor improvements. The application of these systems that have been developed in the general population to the transplant patients is challenging, because few data exist in the transplant population and these systems are not systematically transposable in other populations than the validation cohorts. In kidney transplants, 2 different studies have demonstrated that the Framingham model, which estimates the 10-year risk of fatal and nonfatal coronary event, did not predict absolute ischemic heart disease in the transplant population, particularly in high-risk patients. In liver transplant, only 1 study from Germany has performed an external validation of 3 different scores and has demonstrated that SCORE and PROCAM can discriminate liver transplant recipients for their individual risk of cardiovascular events, whereas the Framingham score did not.

Neal and associates reported that the predicted 10-year risk of coronary heart disease according to Framingham equation increased from 6.9% before transplant to 11.5% at 1 year after transplant, whereas that of a matched local population was 7%. In the study of Johnston and associates evaluating 110 consecutive adult liver transplant patients, the median calculated 10-year risk of ischemic heart disease in the 110 liver transplant patients was 7.9%,
and the median calculated relative risk for ischemic heart disease was 10% lower compared with a standard Framingham population. However, given the previous results, it is not clear if using the Framingham score is relevant in the transplant population. In our study, even if transplant recipients presented with an increased relative risk of cardiovascular fatal event compared with a sex- and age-matched population, with no other risk factors, we found that their overall 10-year fatal cardiovascular risk assessed by SCORE model was low in 90% of the patients.

Cardiovascular risk was higher in ex-alcoholic patients who cumulated cardiovascular risk factors and in hepatitis C patients who were significantly older. Interestingly, we found no difference in the degree of cardiovascular risk between tacrolimus and cyclosporine groups, as well as in prevalence for each cardiovascular risk factors (hypertension, diabetes, and hypercholesterolemia). Calcineurin inhibitors, which represent the cornerstone of postliver transplant immunosuppressive therapy, are clearly linked to nephrotoxicity, hypertension, hyperlipidemia, and new-onset diabetes. Tacrolimus and cyclosporine are known to have different toxicity profile, and some studies with short or intermediate follow-up demonstrate that tacrolimus may expose patients to a lower cardiovascular risk after liver or kidney transplant. However, this initial difference between the 2 drugs may disappear with a longer follow-up.

Why the absolute cardiovascular risk, taken as a whole, was so low in our cohort? Several explanations could be proposed. First, the young age of the population. The median age at the time of the evaluation was 56 years. Age, which is not per se a risk factor but a measure of exposure time to cardiovascular risk factors, is one of the major components of all the cardiovascular risk estimation systems. For example, in SCORE system, patients under 50 years old would have a low risk, whatever the number of associated risk factors. Second, even if a nonnegligible number of patients still presented with nonoptimal control, either of their blood pressure, their glycemia, or their lipid profile, regular follow-up of our patients (at least twice yearly), associated with early treatment of modifiable risk factors, has probably helped minimize global cardiovascular risk. Third, it is not sure whether the SCORE system was applicable and pertinent in our cohort. As several authors, we have used a cardiovascular model without an external validation in our population of liver transplant recipients. If the model is not valid, this may explain controversial results in evaluation of cardiovascular risk compared with the standard population. We believe that a scoring system would be helpful for clinicians and advocate for external multicentre validation of the preexisting systems.

However, even validated, all scoring systems have limitations. Given they have been developed in the general population, they underestimate the real risk in high-risk groups such as diabetic patients, patients with advanced chronic renal failure, and patients with prior history of cardiovascular events. Besides, they are not validated in young and/or older populations. For instance, the SCORE system is only recommended for use in a 40- to 65-year age range, so 29% patients of our cohort were not eligible. An extension of the SCORE system is currently being developed for an older population. All these limitations urge the finding of alternative solutions to assess cardiovascular risk. Measuring carotid intima-media thickness can be a useful tool to reflect the vascular age.

In the nontransplant population with established atherosclerosis in at least 1 territory, carotid intima-media thickness correlates with the number of involved arterial territories and the risk of adverse cardiovascular events, a carotid intima-media thickness value ≥ 1.25 mm being an important prognostic marker. In young renal transplant recipients, noninvasive monitoring of carotid intima-media thickness is useful in detecting early vascular lesions and may represent a cardiovascular risk.

In conclusion, our results suggest that the absolute 10-year risk of fatal cardiovascular events according to SCORE is relatively low in long-term (10 years) liver transplant survivors, even when the majority of these patients had 1 or more cardiovascular risk factors. Active medical follow-up, early treatment before complication and the relatively young age of our population could explain this paradox. An external validation of SCORE model in French transplant recipients is mandatory and a new assessment of our cohort should probably be done after 15 or 20 years of follow-up because cardiovascular risk exponentially increases with age.
References