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Current health status of patients who have survived for more than 15 years after liver transplantation

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ABSTRACT

Background: Liver transplantation was started in our centre as early as 1979. We have studied the clinical outcome of patients surviving longer than 15 years, with special interest for the broad range of comorbidity and the self-perceived quality of life.

Methods: All patients who underwent a liver transplantation at an adult age, between March 1979 and February 1991, and who had survived at least 15 years were eligible for the study. Data were collected from the medical records. Health-related quality of life was assessed using the Six-Dimensional EuroQol test.

Results: The five-year survival of patients alive 15 years after transplantation was 78%. Thirty-seven patients are currently alive with a median follow-up of 18.8 years (range 15.0 to 26.8) after transplantation. Comorbidity consists predominantly of overweight (57%), osteoporosis (49%), *de novo* cancer (38%, mainly skin cancer), hypertension (38%), cardiovascular events (19%), diabetes mellitus (22%), cataract (24%), and renal clearance <50 ml/min (11%). Eight patients (22%) underwent a retransplantation, and compensated cirrhosis is present in four patients (11%). The pattern of comorbidity seems to relate to the type of immunosuppression which consisted mainly of prednisolone and azathioprine. Quality of life was perceived as satisfactory (7 on a scale of 0 to 10). However, about half of the patients reported limitations in the domains mobility, usual activities and pain/discomfort. In addition a minority reported some anxiety or depression.

Conclusion. The outcome of liver transplantation in this early cohort of patients is fairly good. Improvements may be achieved by adaptations in the immunosuppressive regimen.

KEYWORDS

Comorbidity, EQ-6D, health status, liver transplantation, long-term survival, quality of life

INTRODUCTION

Liver transplantation has been the accepted therapeutic option for end-stage liver disease for more than 20 years. Over the years, survival rates have improved. A substantial number of patients now survive for more than one or even two decades. However, quality of life may be influenced by long-term side effects of immunosuppressive treatment and by the functional status of the liver graft as *de novo* liver disease or recurrent liver disease might develop. Most studies have focussed on single complications after liver transplantation, e.g. cardiovascular disease or renal disease, mainly in the first decade after the transplant, and are not concerned with the whole spectrum of comorbidity. Only two studies are known to us that report extensively on the health status in patients longer than ten years after liver transplant.[1,2] Patterns of comorbidity might differ between centres in relation to patient characteristics, duration of survival after liver transplantation, and the types of immunosuppressive drugs that are used.

The present study concerns the health status and quality of life of patients who received a liver transplant in our centre between 1979 and 1991 and were alive in February 2006.

PATIENTS AND METHODS

All patients who underwent a liver transplantation in our centre at an adult age (>17 years), between 1 March 1979 and 1 February 1991, and who survived at least 15 years were eligible for the present study.

Data collection

From the medical records the following basic data were collected: gender, age at transplant, present age, indication(s) for (re)transplant, date(s) of (re)transplant, date of death, and cause of death.

From all the patients who were alive in February 2006, the following data regarding the health status were collected: eye problems, ENT problems, neurological disease, lung disease, cardiovascular disease, hypertension, body mass index, diabetes, gastrointestinal disease, renal and urological disease, gynaecological disease, malignancies, and osteoporosis. The state of the liver was evaluated by the most recent liver pathology, radiology, and laboratory tests. Present medication, including the dosages of the immunosuppressive drugs, was noted. Most recent routine laboratory tests were noted, including haematological tests, liver tests, creatinine, creatinine clearance, and total cholesterol.

Immunosuppression

Basically, two immunosuppressive regimens have been used for long-term maintenance therapy since the start of our programme in 1979. Until 1986, immunosuppression consisted of azathioprine, 125 to 150 mg/day, and prednisolone in a starting dose of 200 mg/day, which was gradually tapered to a dose of 30 mg/day at six months, 20 mg/day at one year, and 10 mg/day at two years. In 1986 cyclosporine was added, which resulted in a triple drug regimen with lower prednisolone dosages. After the second year we aimed to taper and discontinue cyclosporine in patients with a triple drug regimen. Since 2000 we aim to reduce the prednisolone dose to 5 mg/day and the azathioprine dose to 50 mg/day in patients with long-term survival.

Quality of life

Health-related quality of life was assessed using the Six-Dimensional EuroQol test (EQ-6D).[3,4] The EQ-6D is a concise test which consists of six dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and cognitive functioning. Each dimension has three possible answers: no problems, some problems, and extreme problems. Three questions were added concerning a paid job (yes or no), paid help at home (yes or no), and a numerical expression of self-perceived health status (0 to 10, 0 = worst, 10 = best). The questionnaire was sent to the patients by post with the request to participate and to return the list by pre-paid post.

Charlson comorbidity index

The Charlson Comorbidity Index (CCI) gives a weighted score that takes into account both the number and the seriousness of a series of diseases. In addition weight is given to age.[5] We used the modified CCI according to Birim *et al.*[6] in which coronary heart disease is not limited to myocardial infarction alone. In short, one point is given for the conditions coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective pulmonary disease, peptic ulcer disease, mild liver disease, and diabetes. Two points are given for hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, any tumour in the last five years, leukaemia, and lymphoma. Three points are given for moderate or severe liver disease. Six points are given for metastatic solid tumour and AIDS. In addition, for each decade >40 years of age, one point is added.

In the absence of clear definitions, we defined moderate or severe renal disease as a creatinine clearance <50 ml/min, and moderate or severe liver disease as the presence of advanced fibrosis, cirrhosis, and/or portal hypertension.

Statistical analysis

The χ^2 or Fisher's exact test was used to analyse the categorical data. Survival was analysed by the Kaplan-Meier method. All data were analysed using the Statistical Package for Social Sciences 11.0 (SPSS Inc., Chicago, Illinois, USA). A two-tailed p value <0.05 was considered to indicate statistical significance. When not otherwise stated, the results are given in median and range.

RESULTS

Survival after the 15th year

Forty-nine (45.4%) of the 108 adult patients receiving a liver transplantation before 1 February 1991 survived for at least 15 years after the transplant. The median age at 15 years was 55.7 years (range 32.4 to 73.7). After the 15th year seven patients have died so far. Causes of death were cardiovascular in four patients, bacterial sepsis in relation to recurrent cholangitis and intra-abdominal abscess, respectively, in two patients, and colonic cancer in one patient.

The one- and five-year patient survival rates after the 15th year were 89 and 78%, respectively. In this respect there was no difference between patients older or younger than 55 years.

Health status of the currently alive patients

Patient characteristics

Five patients moved outside the Netherlands and are excluded from the study because of lack of detailed information. The patient characteristics of the 37 remaining patients are listed in *table 1*. Thirty patients are

Table 1. *Patient characteristics of 37 patients currently alive more than 15 years after liver transplantation (median and ranges)*

Number of patients	**37**
Gender (female/male)	30/7 (81%/19%)
Age at LT (years)	38.5 (17.3-58.7)
Diagnosis of liver disease:	
• Primary biliary cirrhosis	13 (35%)
• Primary sclerosing cholangitis	6 (16%)
• Autoimmune cirrhosis	5 (14%)
• Cryptogenic cirrhosis	4 (11%)
• Budd-Chiari	3 (8%)
• Miscellaneous	6 (16%)
Calendar year and month of LT	March 1987 (April 1979-January 1991)
Follow-up after first LT (years)	18.8 (15.0-26.8)
Re-LT:	
• Number of re-LTs	9 re-LTs in 8 patients (21.6%)
• First re-LT, years after LT	5.6 (0.0-12.9)
Reasons for re-LT:	
- HAT	2 (22%)
- De novo HCV	2 (22%)
- Chronic rejection	2 (22%)
- Acute rejection	1 (11%)
- ITBL	1 (11%)
- PNF	1 (11%)

LT = liver transplantation; HAT = hepatic artery thrombosis; HCV = hepatitis C virus; ITBL = ischaemic-type biliary lesions; PNF = primary non-function.

female. Present age is a median of 57.4 years (range 37.7 to 79.3). The median follow-up after liver transplantation is 18.8 years (range 15.0 to 26.8). Most patients were transplanted for autoimmune liver diseases. Eight patients (21.6 %) underwent retransplantations for different reasons.

Long-term medical complications after liver transplant

An overview is depicted in *figure 1*.

Eyes. Nine patients (24.3%) developed a cataract, for which five underwent surgery. One patient developed a glaucoma and one had Sjogren's disease.

ENT. Two patients (5.4%) needed ENT surgery for recurrent sinusitis.

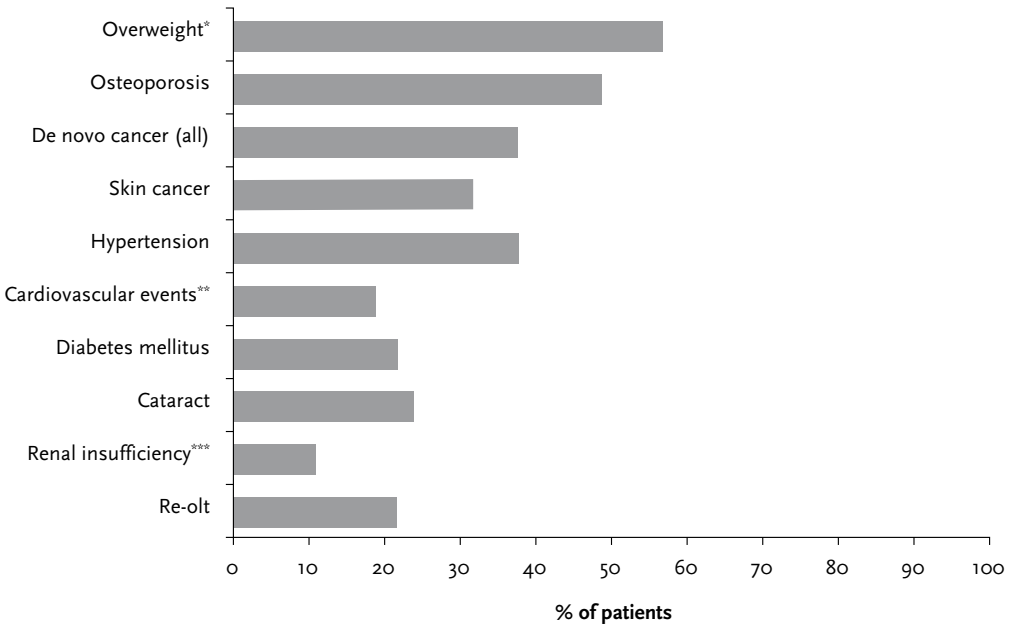
Oral cavity. None of the patients developed (pre)malignancy in the oral cavity.

Lungs. No major lung problems have occurred except that eight patients have had more than one episode of bacterial infection. One patient is suffering from COPD.

Breast. None of the patients developed breast cancer. In one patient a benign tumour was removed; and one patient underwent corrective surgery.

Neurological disorders. One patient suffered from a stroke, peroperatively, with minor long-term sequelae. Two patients had transient ischaemic attacks (TIA). One patient is being treated for epilepsy, after having developed a reversible coma associated with the use of cyclosporine in the first year after transplantation.

Figure 1. *Prevalence of the main comorbidity in 37 patients currently alive more than 15 years after liver transplantation*



***BMI ≥25; ****including myocardial infarction, angina, claudication and TIAs; *****creatinine clearance <50 ml/min.**

Cardiovascular system. Fourteen patients (37.8%) are receiving treatment for hypertension. Two patients suffered a myocardial infarction, after which one of them underwent coronary bypass surgery. Another two patients are being treated for angina pectoris. Two patients are being treated for intermittent claudication. Overall, including the patients with TIAs, 15 patients (40.5%) developed symptomatic cardiovascular disease. In addition one patient suffered from an episode of rheumatic pericarditis. Ten patients (27%) are receiving lipid-lowering drugs. The most recently measured serum cholesterol level is 5.31 mmol/l (3.30 to 9.60).

Body mass index. Overweight, defined as BMI ≥25, is currently present in 21 patients (56.8%). Seven patients (18.9%) are obese, with a BMI >30.

Diabetes mellitus. Six patients developed *de novo* diabetes mellitus type 2 after liver transplant. Including two patients who already had diabetes before the liver transplant, eight patients (21.6%) are currently being treated for diabetes mellitus.

Upper gastrointestinal tract. Two patients had peptic ulcers. Four patients developed recurrent asymptomatic oesophageal varices. Nineteen patients (51.4%) are taking proton-pump inhibitors or H2 blockers. One patient is being treated for exocrine pancreatic insufficiency.

Liver disease. See below, under liver graft.

Colon. One patient developed a colon cancer and underwent a hemicolectomy. Another eight patients had adenomatous polyps removed during screening colonoscopies. Four patients had documented inflammatory bowel disease before the transplant. One of them underwent colectomy after the liver transplant because of severe dysplasia.

Kidneys and urinary tract. Two patients developed a renal carcinoma (detected by routine ultrasound) for which a nephrectomy was performed. One patient with extensive uro-genital condylomata acuminata underwent a cystectomy with an uretero-ileostomy. Eight patients (21.6%) suffered from urinary tract stones. Ten patients were treated more than once for bacterial urinary tract infection.

The serum creatinine is 82 µmol/l (42 to 133), and the creatinine clearance 80 ml/min (24 to 148). Four patients have a clearance <50 ml/min.

Gynaecological disorders. Four of the 30 women had undergone a hysterectomy before liver transplantation. After the transplant, one patient who had surgery is still being monitored closely for extensive condylomata acuminata. Three patients were treated for meno-metrorrhagias. Another three patients were treated for cervical dysplasia. Three patients had successful pregnancies.

Haematological disorders. One patient developed a non-Hodgkin's lymphoma (Epstein-Barr virus negative), which was successfully treated with chemotherapy and anti-CD20. After five years this patient is doing well without signs of recurrence and on low-dose immunosuppression. One patient has anaemia in relation to erythropoietic protoporphyria. Recent laboratory tests show the following blood counts: haemoglobin 8.6 mmol/l (4.0 to 9.9), mean corpuscular volume 94.8 fl (70.9 to 102.1), leucocytes 7.7 10^3/l (range 2.2 to 12.7), platelets 224 10^9/l (61 to 504).

Bone disease. Overall 18 patients (48.6%) are suffering from osteoporosis, defined as a T value <2.5 SD, as measured by bone densitometry. Fifteen of these patients developed the osteoporosis after liver transplant. In 11 patients vertebral osteoporotic fractures occurred. Eight patients suffered from fractures of an arm or leg. Two patients have advanced arthrosis of the hip and ankle, respectively. One patient received a total hip arthroplasty.

Skin. Actinic keratosis is documented in 17 patients and Bowen's disease in five patients. Skin cancer developed in 12 patients (32.4%): basocellular in five patients, planocellular in four patients, and both in three patients. One patient is taking acetretine (Neotigason).

De novo cancer. Overall 16 *de novo* cancers developed in 14 of the 37 patients (37.8%). Excluding the patients who developed skin cancer, four of the 37 patients (10.8%) developed *de novo* cancer at other sites: renal cancer (two patients), colon cancer (one patient), and lymphoma (one patient).

The liver graft

Eight of the 37 patients were retransplanted for a variety of reasons (*table 1*). The current graft function in the 37 patients is as follows.

Most recent liver pathology shows cirrhosis in four patients (10.8%), and fibrosis in a greater or lesser degree in another ten patients (27.0%). Four patients (16.2%) have oesophageal varices. None of these patients, however, have decompensated liver disease, defined as the absence of ascites.

Recurrent disease is present in seven patients (18.9%). Recurrent primary biliary cirrhosis (PBC) in an early stage is present in four of the 13 PBC patients (30.7%), recurrent primary sclerosing cholangitis (PSC; non-anastomotic strictures; as judged by MRCP and histology) in two of the six PSC patients (33.3%), and one patient had signs of recurrent Budd-Chiari syndrome early after liver transplantation.

Three patients have hepatitis C infection; in all three the virus was acquired in the perioperative period either from the (first) donor liver or from blood products. Two patients have nonanastomotic strictures in the biliary tree.

Eight patients (21.6%) are on ursodeoxycholic acid.

Recent laboratory tests reflecting the function of the liver show the following: alkaline phosphatase 70 U/l (38 to 791), aspartate aminotransferase 30 U/l (15 to 105), alanine aminotransferase 22 Ul (8 to 88), γ-glutamyltransferase 49 U/l (9 to 742), bilirubin 13 µmol/l (6-44), total protein 69 g/l (58 to 83) and albumin 41 g/l (28 to 46).

Medication

At present, the medication includes a median of seven drugs (3 to 20) for a variety of conditions. Per patient a median of five conditions (2 to 12) are being treated with drugs. The immunosuppressive regimen consists of prednisolone/azathioprine in the majority of patients (31 patients, 83.8%). The other patients are taking prednisolone as monotherapy (one patient) or in combination with mycophenolate mofetil (one patient), cyclosporine (one patient), tacrolimus (one patient) or azathioprine/cyclosporine (two patients). The median dose of prednisolone is 10 mg (5 to 10), and of azathioprine 100 mg (50 to 125). The combination of prednisolone 5 mg and azathioprine 50 mg, which is currently the lowest dose we aim for after liver transplantation, is being taken by four patients (10.8%).

Other drugs are mainly for cardiovascular disorders and for the prevention or treatment of osteoporosis. See *figure 2* for an overview.

Quality of life

The interview on self-perceived quality of life was completed and returned by 35 patients (94.6%). The results of the EQ-6D are listed in *table 2*. It is shown that a large majority of patients have no problems with respect to self care, do not feel anxious or depressed, and have no cognitive symptoms. The majority of patients have no difficulties with their usual daily activities, but a substantial number do have problems. Most patients have some problems with mobility, and suffer from at least some pain and discomfort. Full inability to perform daily activities and serious pain is reported by 11 and 14% of the patients, respectively. Of the patients, 20% have a paid job and 20% make use of paid help at home.

On the scale of 0 to 10, the self-perceived health status was scored as 7 (4 to 10).

In all these aspects no differences were found between patients older or younger than 55 years, except that more younger patients had a paid job (37.5 *vs* 5.3 %) (p=0.032).

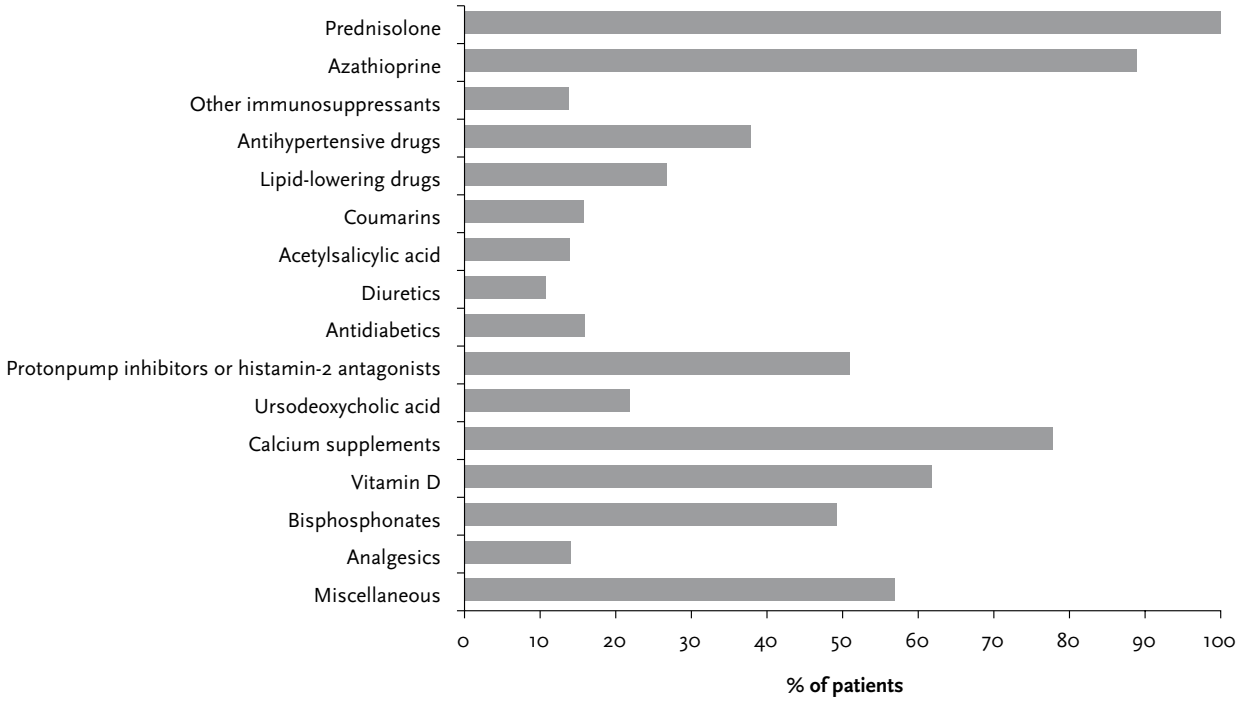
The Charlson Comorbidity index (CCI) in these 35 patients was 3 (0 to 7). No relation was found between the six

Table 2. *Quality of life as measured by the Six-Dimensional EuroQol in 35 patients (number of patients (%))*

	No problems	Some problems	Extreme problems
Mobility	15 (42.9)	19 (54.3)	1 (2.9)
Self-care*	29 (82.9)	4 (11.4)	1 (2.9)
Usual activities	19 (54.3)	12 (34.3)	4 (11.4)
Pain/ discomfort	13 (37.1)	17 (48.6)	5 (14.3)
Anxiety/ depression	27 (77.1)	8 (22.9)	0
Cognition	25 (71.4)	10 (28.6)	0

*Result from one patient is missing.

Figure 2. *Medication use in 37 patients currently alive more than 15 years after liver transplantation*



domains of the EQ-6D and the CCI. Usual activities and the need for help at home tended to relate to the presence of osteoporosis ($0.05 < p < 0.10$).

DISCUSSION

Liver transplantations are usually performed in chronically ill patients. As a result of cirrhosis, the use of drugs (e.g. prednisolone) or the cause of the disease (e.g. alcohol), many patients are already biologically old and suffer from more extrahepatic disease than age controls at the time of transplant. After transplantation, the continuous use of immunosuppressive drugs adds especially to cardiovascular and cancer risk. Although the aim of liver transplantation is to reach long-term survival well beyond 15 years, especially in the younger age group, many do not reach this goal. On the other hand, taking into account all the risks for hepatic and extrahepatic disease one might fear that the quality of life and the overall health status of the long-term survivors is much less than optimal. Liver transplantation was started in our centre as early as 1979 as the fourth regular programme in the world. We evaluated the clinical outcome of patients surviving longer than 15 years, with special interest for the broad range of comorbidity and the self-perceived quality of life. Reports on this subject have been scarce so far.[1,2]

The five-year survival of patients still alive 15 years after transplantation was 78%, with cardiovascular disease as the principle cause of death. It is interesting to note that even after 15 years, age was still not a prognostic marker for survival, and death was determined by comorbidity.

Comorbidity in the currently surviving patients, as listed in *figure 1*, consisted mainly of overweight, hypertension, cardiovascular disease, diabetes mellitus, osteoporosis, and *de novo* cancer. Renal insufficiency defined as clearance <50 ml/min was present in 11% of patients. Looking at this spectrum, two things are remarkable. First, although we did not compare the patient group with a gender- and age-matched control group, comparison with prevalence data in the Dutch population shows lower percentages in the general population.[7-10] From other studies, which focussed on one particular complication, we know that cardiovascular disease and cancer occur more often in organ transplant recipients than in controls.[11-15] Second, the spectrum of comorbidity we found appears to differ from that reported in the studies of Kisilisik *et al.*[1] and Cicarelli *et al.*[2] in patients surviving more than ten years after transplantation. Our patients more often suffered from osteoporosis (prevalence 49 *vs* 4 and 9%, respectively), skin cancer (32 *vs* 4 and 7%), overweight (56 *vs* 49 and 13%), and cataract (24 *vs* unknown and 8%). However, we less often observed hypertension (38 *vs* 64 and 48%), and end-stage renal disease for which haemodialysis or renal transplantation was indicated (0 *vs* 4 and 9%), and serum creatinine levels were significantly lower in our patient group.

Most likely, these differences in comorbid conditions reflect the different immunosuppressive regimens that were used in these patient cohorts. In the early years of our programme, patients were only taking prednisolone and azathioprine. Prednisolone was given in dosages that are, by today's standards, excessively high. A minority of patients started on cyclosporine-based triple therapy, but cyclosporine was tapered and discontinued after the second or third year in most patients. As a result, most of our long-term survivors are still being treated with prednisolone and azathioprine. In contrast, Kizilisik *et al.*[1] used cyclosporine, in combination with low-dose steroids, in most patients, and azathioprine in a minority of them. Cicarelli *et al.*[2] have used cyclosporine or tacrolimus in almost all patients, with prednisolone and/or azathioprine in some patients. The high prevalence of osteoporosis, cataract and overweight in our patients may well be the result of the continued use and high cumulative doses of steroids. Skin cancer might relate to the long-term use of especially azathioprine.[16-18] On the other hand, the limited and short-term use of calcineurin blockers in our patients seems to have led to a lower rate of hypertension and a virtual absence of renal insufficiency in comparison to the other groups. This underscores the importance of the immunosuppressive regimen as a determinant of future complications.

In earlier studies, including the patients presented in this study, we have shown that bone loss occurred mainly in the first year after transplantation, despite the preventive use of daily 1-alpha-hydroxycholecalciferol and 1 gram calcium, with no significant deterioration or even improvement afterwards.[19,20] In the present era development of osteoporosis before and after transplantation is a less serious problem due to preventive strategies with biphosphonates, which became available in the 1990s, in combination with calcium and vitamin D.[21]

A second important finding concerns the graft. In total, 22% of our patients received a retransplant. We have previously reported that the cumulative retransplantation rate rises from 10% at one year to 22% at 15 years after the first transplantation. This figure does not differ from that of most centres.[22] It shows that retransplantation is feasible with good outcome. Currently, compensated cirrhosis is present in 11% of patients, but overall liver function is good. Recurrence of disease without major consequences as yet was found in a minority of patients transplanted for primary biliary cirrhosis, primary sclerosing cholangitis, and hepatitis C, as expected.

A third important finding concerns quality of life. We found that the patients were generally satisfied with their present health status, rating it on average as 7 on a scale of 0 to 10 (with 0 as lowest and 10 as optimal). However, as measured by the EQ-6D, about half of the patients reported limitations in the domains mobility, usual activities, and pain/discomfort. In addition a minority report some anxiety or depression. In a study by Hoeymans *et al.*[23] Dutch adults in the general population scored better on all

EQ-6D domains. Our findings seem to be in agreement with those from other centres. In general, quality of life has been shown to improve after a successful transplantation, but in the long run remains lower than that of the general population.[24-28] Kizilisik *et al.*[1] report an equal or even better quality of life in comparison with age-matched controls, but they restricted their questionnaire to a self-perceived health score, satisfaction with life, self care, and activity level. Also our patients scored high on satisfaction and self care, but probably lower on activity level.

Quality of life as measured by the EQ-6D did not relate to the level of comorbidity as measured by the CCI. However, caution is warranted here because the CCI and its variants were originally developed and used for prediction of outcome after breast cancer,[5] lung cancer,[6] peritoneal dialysis,[29] kidney transplantation,[30] and other.[31,32] Caution is also called for with respect to the value of these self-assessments. Having been chronically ill, patients may accept physical problems without complaining. Many patients are grateful that they received this opportunity for survival, and tend to regard remaining problems as 'minor'.

To conclude, our data show that patients ultimately have to pay a price for long-term immunosuppression. Several strategies may be useful to keep this price as low as possible. Nowadays, the availability of a wide spectrum of immunosuppressive agents allows individualised selection of drugs, thereby avoiding specific side effects. Knowledge of regimen-specific long-term toxicities should prompt adequate monitoring for side effects and timely adaptation of the regimen, and the use of prophylactic measures (e.g. biphosphonates, lipid lowering drugs). In this way, we may achieve a better long-term health status in future patients.

REFERENCES

1. Kizilisik AT, Grewal HP, Shokouh-Amiri MH, Vera SR, Hathaway DK, Gaber AO. Impact of long-term immunosuppressive therapy on psychosocial and physical well being in liver transplant recipients. Prog Transplant 2003;13:278-83.
2. Ciccarelli O, Kaczmarek B, Roggen F, et al. Long-term medical complications and quality of life in adult recipients surviving 10 years or more after liver transplantation. Acta Gastroenterol Belg 2005;68:323-30.
3. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
4. Krabbe PFM, Stouthard MEA, Essink-Bot ML, Bonsel GJ. The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system. J Clin Epidemiol 1999;52:292-301.
5. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Disease 1987;40:373-83.
6. Birim O, Kappetein AP, Bogers AJJC. Charlson comorbidity index as a predictor of long-term outcome after surgery of non small cell lung cancer. Eur J Cardiothorac Surg 2005;28:759-62.
7. Website CBS (Central Bureau for Statistics): http://statline.cbs.nl.
8. Website MLD (Maag Lever Darm Stichting): http://www.mlds.nl.
9. Website RIVM Nationaal Kompas Volksgezondheid: http://www.nationaalkompas.nl.
10. Website College voor Zorgverzekeringen – GIPdatabank (Drug Information System of the Health Care Insurance Board): http://www.gipdatabank.nl.
11. Therapondos G, Flapan A, Plevris J, Hayes P. Cardiac morbidity and mortality related to orthotopic liver transplantation. Liver Transpl 2004;10:1441-53.
12. Guckelberger O, Bechstein W, Neuhaus R, et al. Cardiovascular risk factors in long-term follow-up after orthotopic liver transplantation. Clin Transplant 1997;11:60-5.
13. Johnston S, Morris J, Cramb R, Gunson B, Neuberger J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. Transplantation 2002;73:901-6.
14. Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation. Crit Rev Oncol Hematol 2005;56:87-99.
15. Haagsma EB, Hagens VE, Schaapveld M, et al. Increased cancer risk after liver transplantation: a population-based study. J Hepatol 2001;34:84-91.
16. Otley CC, Pittelkow MR. Skin cancer in liver transplant recipients. Liver Transpl 2000;6:253-62.
17. Parrish JA. Immunosuppression, skin cancer, and ultraviolet A radiation. N Engl J Med 2005;353:2712-3.
18. Kelley GE, Meikle W, Sheil AG. Effects of immunosuppressive therapy on the induction of skin tumors by ultraviolet irradiation in hairless mice. Transplantation 1987;44:429-34.
19. Haagsma EB, Thijn CJP, Post JG, Slooff MJH, Gips CH. Bone disease after orthotopic liver transplantation. J Hepatol 1988;6:94-100.
20. Hamburg SM, Piers DA, Van den Berg AP, Slooff MJH, Haagsma EB. Bone mineral density in the long term after liver transplantation. Osteoporos Int 2000;11:600-6.
21. Millonig G, Graziadei IW, Eichker D, et al. Alendronate in combination with calcium and vitamin D prevents bone loss after orthotopic liver transplantation: a prospective single-center study. Liver Transpl 2005;11:960-6.
22. Postma R, Haagsma EB, Peeters PM, van den Berg AP, Slooff MJH. Retransplantation of the liver in adults: outcome and predictive factors for survival. Transpl Int 2004;17:234-40.
23. Hoeymans N, van Lindert H, Westert GP. The health status of the Dutch population as assessed by the EQ-6D. Qual Life Res 2005;14:655-63.
24. Taylor R, Franck LA, Fibson F, Ddhwan A. A critical review of the health-related quality of life of children and adolescents after liver transplantation. Liver Transpl 2005;11:51-60.
25. Lewis MB, Howdle PD. Cognitive dysfunction and health-related quality of life in long-term liver transplant survivors. Liver Transpl 2003;9:1145-8.
26. Aadahl M, Hansen BA, Kirkegaard P, Groenvold M. Fatigue and physical function after orthotopic liver transplantation. Liver Transpl 2002;8:251-9.
27. Bryan S, Ratcliffe J, Neuberger JM, Burroughs AK, Gunson BK, Buxton MJ. Health-related quality of life following liver transplantation. Qual Life Res 1998;7:115-20.
28. Hellgren A, Berglund B, Gunnarsson U, Hansson K, Norberg U, Bäckman L. Health-related quality of life after liver transplantation. Liver Transpl Surg 1998;4:215-21.
29. Fried L, Bernadini J, Piranoino B. Charlson comorbidity index as a predictor of outcomes in incidental peritoneal dialysis patients. Am J Kidney Disease 2001;37:337-42.
30. Wu C, Evans I, Joseph R, et al. Comorbid conditions in kidney transplantation: association with graft and patient survival. J Am Soc Nephrol 2005;16:3437-44.
31. Nuttall M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. J Clin Epidemiology 2006;59:265-73.
32. Schroeder RA, Marroquin CE, Bute BP, et al. Predictive indices of morbidity and mortality after liver resection. Ann Surg 2006; 243: 373-9.