Aus der Klinik für Allgemein-, Viszeral- und Transplantationschirurgie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Zwanzig-Jahres Follow-up nach orthotoper Lebertransplantation an der Charité – 313 konsekutive Fälle

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

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INHALTSVERZEICHNIS

Abstrakt

Hintergrund: Die Lebertransplantation (LT) ist mit mehr als je 5000 Eingriffen pro Jahr in Europa und in den USA inzwischen die Standardtherapie für Patienten mit terminaler Leberinsuffizienz, akutem Leberversagen und bestimmten primären Lebertumoren. Mit einer wachsenden und alternden Population Lebertransplantierter und mit kaum weiter verbesserbaren Ein-Jahres-Überlebensraten, liegt der Fokus mittlerweile auf der Optimierung des Langzeitüberlebens und der Minimierung von Spätkomplikationen nach LT. Daten zu Langzeitergebnissen über 15 Jahre hinaus sind jedoch in der Literatur nur spärlich zu finden. In dieser Arbeit präsentieren wir die ersten monozentrischen 20-Jahres-Überlebensdaten aus Europa.

Methoden: An unserem Zentrum wurden zwischen 1988 und 1992 insgesamt 337 LT an 313 Patienten durchgeführt. In den darauffolgenden 20 Jahren wurden regelmäßig Nachuntersuchungen aller Patienten realisiert. Für diese Studie wurden das Patienten- und Transplantatüberleben evaluiert, das Überleben mit dem der Normalpopulation verglichen, Einflussfaktoren auf das Langzeitüberleben analysiert, und individuelle Vorhersageparameter bezüglich des Überlebens identifiziert. Darüber hinaus werden die Prävalenz und Entwicklung von Übergewicht, Hypertonie, Fettstoffwechselstörung und eingeschränkter Nierenfunktion im Verlauf von 20 Jahren Nachsorge präsentiert.

Ergebnisse: Die 1-, 5-, 10- und 20-Jahres-Überlebensrate der Patienten betrug 88,4%, 81,0%, 72,7% bzw. 52,5%, die Überlebensrate der Transplantate 83,7%, 73,8%, 64,7% bzw. 46,6%. Ohne Berücksichtigung der 1-Jahres Mortalität glich das Überleben der älteren Transplantatempfänger (> 55 Jahre) annähernd dem der Normalbevölkerung. Signifikanten Einfluss auf das Langzeitüberleben hatten Primärindikation zur LT ($p<0,001$), Empfängeralter bei LT ($p<0,001$), Empfängergeschlecht ($p=0,017$), Notwendigkeit zur Retransplantation ($p=0,034$) und Einschränkung der Nierenfunktion sechs Monate nach LT ($p<0,001$). In der multivariaten Analyse erwiesen sich folgende Faktoren als negative Prädiktoren für das Langzeitüberleben: Patientenalter > 30 (HR 2,56; 95% CI 1,32-4,94; $p=0,005$), Cholangiokarzinome (HR 3,77; 95% CI 1,81-7,84; $p<0,001$), Hepatozelluläre Karzinome (HR 2,04; 95% CI 1,26-3,29; $p=0,004$) und Retransplantation (HR 1,76; 95% CI 1,15-2,70; $p=0,010$). Die Prävalenz von Übergewicht stieg signifikant während des Beobachtungszeitraums (33,2% auf 45%, $p=0,014$), ebenso die Prävalenz von Hypertonie (57,3 auf 85,2%, $p<0,001$) und eingeschränkter Nierenfunktion (41,8 auf 55,2%, $p=0,01$), während die Prävalenz von Fettstoffwechselstörungen abfiel (78,0 auf 47,6%, $p<0,001$). Wiederauftreten der Grunderkrankung (21,3%), Infektionen (20,6 %) und de-novo Malignome (19,9%) waren die häufigsten Todesursachen.

Fazit: Mit dieser Arbeit präsentieren wir die ersten europäischen 20-Jahres-Überlebensdaten, gleichzeitig die bisher besten Langzeitergebnisse weltweit. Die Therapie durch Lebertransplantation hat viele Hürden überwunden und exzellente Langzeitergebnisse sind realisierbar, solange der Empfänger und das multidisziplinäre Transplantationsteam zeitlebens zusammenarbeiten. Dennoch müssen auch weiterhin insbesondere das Wiederauftreten der Grunderkrankungen verhindert und Nebenwirkungen der Immunsuppression minimiert werden.

Abstract

Background: With more than 5000 liver transplantations (LT) being performed every year, each in the United States and in Europe, LT has emerged as a standard therapeutic procedure for patients with end-stage liver disease, acute liver failure, and certain liver tumors. With a growing and aging posttransplant population, and first year survival rates almost at a pinnacle, the focus has shifted to optimizing long-term outcome and minimizing late complications after LT. However, few authors have published survival data of ≥15 years of follow-up. This study reports the first European single-center 20-year survival data.

Methods: 337 consecutive LT were performed in 313 patients between 1988 und 1992. Over the next 20 years regular follow-up examinations took place. In this study, patient and graft survival was evaluated, factors affecting survival were analyzed, independent predictors of survival were identified, and a comparison to the life expectancy of a matched normal population was performed. Furthermore, the prevalence and influence on outcome of overweight, hypertension, diabetes, dyslipidemia, and moderately or severely impaired renal function during 20 years of follow-up are presented.

Results: Overall 1-, 5-, 10-, and 20-year patient and graft survival estimates were 88.4%, 81.0%, 72.7%, 52.5%, and 83.7%, 73.8%, 64.7%, 46.6%, respectively. Excluding one-year mortality, survival in the elderly LT recipients was similar to normal population. Etiology of liver disease ($p<0.001$), recipient age ($p<0.001$), gender ($p=0.017$), necessity of retransplantation ($p=0.034$), and impaired renal function at six months after LT ($p<0.001$) had significant impact on patient survival. In a multivariate analysis, patient age > 30 (HR 2,56; 95% CI 1,32-4,94; p=0,005), biliary malignancy (HR 3,77; 95% CI 1,81-7,84; p<0,001), hepatocellular carcinoma (HR 2,04; 95% CI 1,26-3,29; p=0,004), and retransplantation (HR 1,76; 95% CI 1,15-2,70; p=0,010) again emerged as significant negative predictors of long-term survival. Prevalence of overweight increased throughout follow-up (33.2% to 45%, $p=0.014$), as well as prevalence of hypertension (57.3 to 85.2%, $p<0.001$) and impaired renal function (41.8 to 55.2%, $p=0.01$), while prevalence of dyslipidemia (78.0 to 47.6%, $p<0.001$) declined. Recurrent disease (21.3%), infection (20.6%), and de-novo malignancy (19.9%) were the most common causes of death.

Conclusion: We present the first European 20-year survival data from a single institution, at the same time the most promising long-term results published, so far. LT has conquered many barriers to achieve long-lasting survival benefits. If a lifelong commitment between both the recipient and the members of the multidisciplinary transplant team is ensured, excellent long-term results are feasible. However, much work is needed to combat recurrent disease and inhibit side effects of immunosuppression.

Eidesstattliche Versicherung

„Ich, Niklas Büscher, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Zwanzig-Jahres Follow-up nach orthotoper Lebertransplantation an der Charité – 313 konsekutive Fälle“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Ausführliche Anteilserklärung an der erfolgten Publikation

Publikation:
Schoening WN*, **Buescher N***, Rademacher S, Andreou A, Kuehn S, Neuhaus R, Guckelberger O, Puhl G, Seehofer D, Neuhaus P. Twenty-Year Longitudinal Follow-Up After Othotopic Liver Transplantation: A Single-Center Experience of 313 Consecutive Cases. American Journal of Transplantation, 2013;13(9):2384-94

*geteilte Erstautorenschaft

Alle Lebertransplantierten der Charité kommen in regelmäßigen Abständen zu Nachuntersuchungen in die Lebertransplantationsambulanz.
Die Nachuntersuchungsdaten zum Zeitpunkt 6 Monate und 20 Jahre nach Lebertransplantation der ersten 313 Patienten, die an der Charité eine neue Leber erhalten haben, bilden die Grundlage dieser Publikation. Die erforderlichen Daten für die Veröffentlichung entnahm ich den Patientenakten und trug sie in eine eigenständig erstelle Datenbank ein. Neuere Patientendaten fand ich im Aktenarchiv in der Transplantationsambulanz vor. Ältere Daten und Informationen zur Evaluation vor Transplantation konnte ich im Altarchiv der Charité finden. Fehlende Daten wurden durch mich durch Nachuntersuchungen oder telefonische Anfragen, soweit möglich, ermittelt. Die Erstellung der SPSS-Datenbank, die anschließende Datenauswertung und statistische Analyse erfolgte selbstständig durch mich nach Einarbeitung in das Statistikprogramm durch Dr. Andreou und Dr. Schöning. Das erste Manuskript der Publikation inklusive aller Tabellen und Abbildungen habe ich selbst erstellt. Korrekturen und Nachbearbeitungen erfolgten durch Dr. Schöning und Dr. Seehofer.
Zusätzlich erstellte ich einen Kongressbeitrag in Form einer Posterpräsentation für den European Student Congress 2013.

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Twenty-Year Longitudinal Follow-Up After Orthotopic Liver Transplantation: A Single-Center Experience of 313 Consecutive Cases

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With excellent short-term survival in liver transplantation (LT), we now focus on long-term outcome and report the first European single-center 20-year survival data. Three hundred thirty-seven LT were performed in 313 patients (09/88–12/92). Impact on long-term outcome was studied and a comparison to life expectancy of matched normal population was performed. A detailed analysis of 20-years follow-up concerning overweight (HBMI), hypertension (HTN), diabetes (HGL), hyperlipidemia (HLIP) and moderately or severely impaired renal function (MIRF, SIRF) is presented. Patient and graft survival at 1, 10, 20 years were 88.4%, 72.7%, 52.5% and 83.7%, 64.7% and 46.6%, respectively. Excluding 1-year mortality, survival in the elderly LT recipients was similar to normal population. Primary indication ($p < 0.001$), age ($p < 0.001$), gender ($p = 0.017$), impaired renal function at 6 months ($p < 0.001$) and retransplantation ($p = 0.034$) had significant impact on patient survival. Recurrent disease (21.3%), infection (20.6%) and *de novo* malignancy (19.9%) were the most common causes of death. Prevalence of HTN (57.3–85.2%, $p < 0.001$), MIRF (41.8–55.2%, $p = 0.01$) and HBMI (33.2–45%, $p = 0.014$) increased throughout follow-up, while prevalence of HLIP (78.0–47.6%, $p < 0.001$) declined. LT has conquered many barriers to achieve these outstanding long-term results. However, much work is needed to combat recurrent disease and side effects of immunosuppression (IS).

Key words: Liver transplantation, long-term outcome

Abbreviations: ALD, alcoholic liver disease; ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCC, cholangiocellular carcinoma; CI, cerebral infarction; CIT, cold ischemia time; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CSA, cyclosporin A; CVK, Campus Virchow-Klinikum; dBP, diastolic blood pressure; ECD, extended criteria donor; eGFR, estimated glomerular filtration rate; ELTR, European Liver Transplant Registry; F, female gender; Gluc, blood glucose level; HBMI, overweight; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HGLY, diabetes; HLIP, hyperlipidemia; HTN, hypertension; IRI, ischemia reperfusion injury; IS, immunosuppression; LT, liver transplantation; M, male gender; MELD, model for end-stage liver disease; MI, myocardial infarction; MIRF, moderately impaired renal function; MMF, mycophenolate mofetil; MOSF, multiorgan system failure; NEC, neuroendocrine carcinoma; PBC, primary biliary cirrhosis; PCP, pneumocystis carinii pneumonia; PSC, primary sclerosing cholangitis; PTLD, posttransplant lymphoproliferative disorder; RD, recurrent disease; Re-LT, (liver) re–transplantation; SBC, secondary biliary cirrhosis; sBP, systolic blood pressure; SIRF, severely impaired renal function; SSC, secondary sclerosing cholangitis; TAC, tacrolimus; tBili, total bilirubin.

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Introduction

Since the first liver transplantation (LT) in 1963 (1), short-term survival has improved rapidly (2,3). However, long-term attrition rates have not changed similar (4). The liver transplant community now completes the second decade of follow-up. Patients who survived 10 or 15 years are at different risks than most of the patients we usually meet in the outpatient LT department. Many of them are elderly and all of them have experienced a very long period of IS. There is no doubt that patients who require long-term IS are at risk of cardiovascular disease (2,5–9), *de novo* malignancy (7,10) infections and renal dysfunction (2,11,12). Furthermore, long-term complications include recurrence of primary disease (RD) (2,13–15). At least some of our long-term patients will not have died of the above-mentioned reasons but of decrepitude or associated phenomena.

This is the first publication of European single-center 20-year survival data. Object of this study was to evaluate patient and graft survival and allograft function longitudinally for two decades after LT in more than 300 consecutive

cases. Survival patterns in relation to age, gender and primary diagnosis were analyzed. Furthermore, the rate of retransplantations (Re-LT), maintenance IS, liver function by means of laboratory values, and (co-)morbidities (kidney function, overweight, hypertension, hyperlipidemia and diabetes) were examined and causes and time of deaths analyzed. Additionally we compared the survival of the presented cohort to life expectancy of gender and age matched normal population controls.

Patients and Methods

A longitudinal single-institution study was performed to evaluate 20-year outcome after LT.

Patients

This retrospective study was approved by the Institutions Review Board. Three hundred thirteen patients underwent primary LT at the Charité, Campus Virchow-Klinikum (CVK) between 1988 and 1992. Those patients received in total 365 livers including 54 Re-LTs. Of the Re-LTs 46 were first, 7 second and 1 third Re-LT.

Male to female ratio was 1.3:1. At primary LT, mean patient age was 45 ± 11 years. Two patients were minors (age 14 and 16). Indications for primary transplants are presented in Table 1. Virus-related cirrhosis (25.2%), alcoholic cirrhosis (16.0%), cholestatic disease (16.7%), cryptogenic cirrhosis (9.3%) and hepatocellular carcinoma (HCC) (8.6%) were the most common indications for primary LT. Seven of the 27 included HCCs were beyond the later on defined Milan criteria (16).

Table 1: Recipient characteristics

Characteristic	Variable	No.
Total no. of recipients		313
Recipient age (year)	Mean	45 (±11)
	Median	47 (14–66)
Gender	Male	178 (57%)
	Female	135 (43%)
Primary indication for LT	Alcoholic cirrhosis	50 (16.0%)
	Hepatitis B	47 (15.0%)
	Hepatitis C	32 (10.2%)
	PBC	29 (9.3%)
	Cryptogenic cirrhosis	29 (9.3%)
	Hepatocellular carcinoma	27 (8.6%)
	Acute liver failure	23 (7.3%)
	PSC	19 (6.1%)
	Autoimmune hepatitis	12 (3.8%)
	Hepatitis B and D	10 (3.2%)
	Morbus Wilson	5 (1.6%)
	CCC	5 (1.6%)
	Klatskin tumor	4 (1.3%)
	Polycystic liver disease	4 (1.3%)
	Budd–Chiari syndrome	3 (1.0%)
	Hepatitis B and C	3 (1.0%)
	SSC	3 (1.0%)
	Alpha 1-antitrypsin deficiency	2 (0.6%)
	Hemochromatosis	2 (0.6%)
	Neuroendocrine carcinoma	1 (0.3%)
	Biliary atresia	1 (0.3%)
	Porphyria	1 (0.3%)
	SBC	1 (0.3%)

For Kaplan–Meier estimates, all 313 patients were analyzed (except renal function at T1 (6 months after primary LT), which includes only patients with complete data concerning renal function at T1, n = 226). All patients were prospectively observed over 20 years. Regular follow-up examinations were performed at 6 months, 1, 3, 5, 7, 10, 13, 15, 17, and 20 years after LT. In addition, we performed a detailed analysis of the 20 years (T2) follow-up concerning (co-)morbidities. All analyses comparing T1 and T2 were carried out with 286 patients that completed a minimum follow-up of 6 months post-LT (T1).

Clinical assessment of the patients' height, weight and arterial blood pressure was performed and actual medication was recorded. Patients that failed to attend their assigned date for follow-up and did not respond to our attempts to reach them by phone or letter were considered lost.

Comparison of life expectancy/survival with normal population

To compare survival data of LT recipients with life expectancy of normal population we retrieved life expectancy data of gender and age matched controls (n = 313) in the time frame 1988 to 1992 from the official database of the German ''Statistisches Bundesamt'' (https://www.destatis.de/).

Laboratory parameters

Laboratory parameters (total cholesterol, triglycerides, creatinine, total bilirubin (tBili), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and glucose) were obtained after a fasting period of at least 12 h.

Variables

Overweight (HBMI) was defined according to WHO as body mass index (BMI = weight/height^2) above 25. Systolic blood pressure (sBP) higher than 139 mmHg, diastolic blood pressure (dBP) above 89 mmHg, or anti–hypertensive treatment (except single diuretic therapy) was considered ''arterial hypertension'' (HTN) (17). Blood glucose levels (Gluc) >120 mg/dL, or oral anti–diabetic treatment and insulin dependency were defined as ''hyperglycemia'' (HGLY) (18). Cholesterol levels >200 mg/dL, triglyceride levels >175 mg/dL, or statin treatment were considered ''hyperlipidemia'' (HLIP). Glomerular filtration rate (eGFR) was estimated using the MDRD formula. eGFR <60 mL/min/1.73 m^2 was considered moderately impaired renal function (MIRF), rates <30 mL/min/1.73 m^2 were defined severely impaired renal function (SIRF) (19).

Statistical analysis

Data are expressed as median and range (x, y–z), or mean ± standard deviation. Categorical variables were compared by the χ^2-test. Kaplan–Meier estimates were used to calculate survival curves. Differences in survival curves were compared using log-rank statistics. Multivariate logistic regression modeling with stepwise backward covariable selection was performed to determine the association between different variables and long-term outcome. Variables with a significant impact in univariate analysis ($p < 0.05$) were entered in the regression models. All calculations were done using the SPSS software package (version 21.0 for Macintosh, SPSS, Inc., Chicago, IL).

Results

After a median follow-up of 233 months (0–260), 157 patients were alive (141 complete data sets, 16 incomplete)

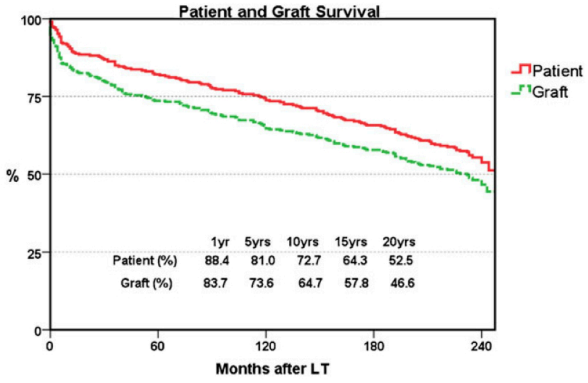


Figure 1: Patient and graft survival.

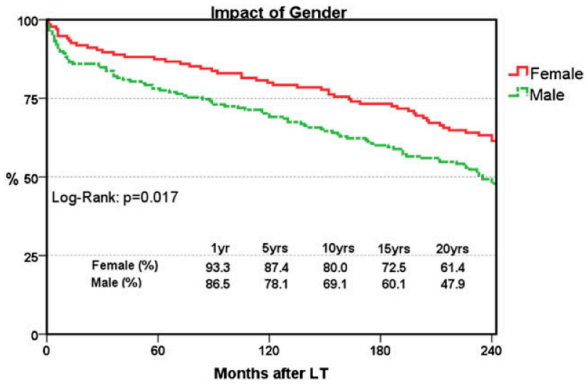


Figure 2: Impact of gender.

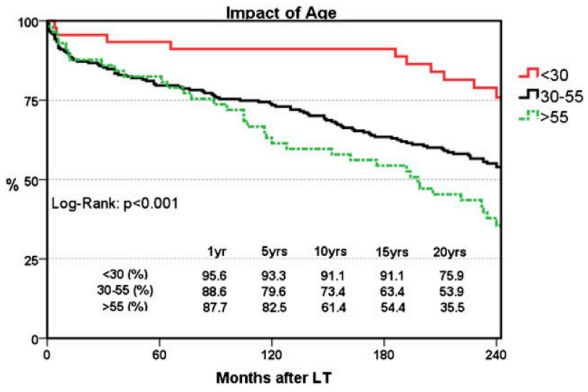


Figure 3: Impact of age.

and 141 had died while 15 had to be considered lost 99–243 months after LT.

Patient survival

The overall actuarial patient survival at 1, 10 and 20 years was 88.4%, 72.7% and 52.5% (Figure 1). Considering only patients who survived beyond 6 months, patient survival at 1, 10 and 20 years was 97.6%, 80.8% and 58.8%.

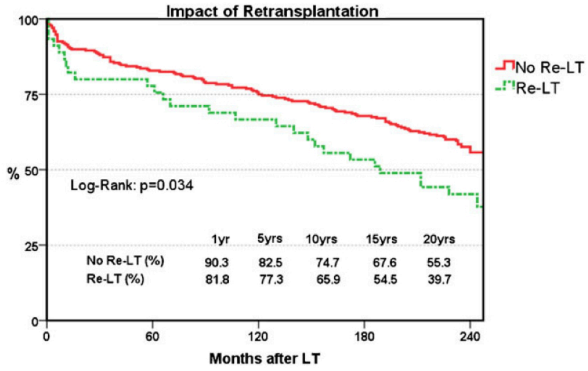


Figure 4: Impact of retransplantation.

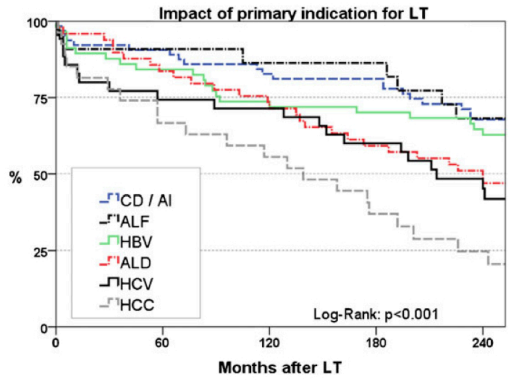


Figure 5: Impact of primary indication.

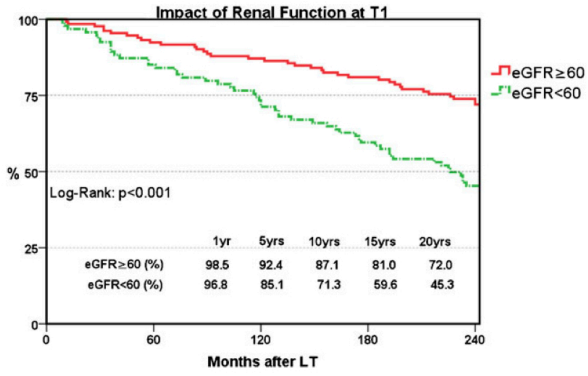


Figure 6: Impact of renal function at T1.

Gender ($p = 0.017$) (Figure 2), age ($p < 0.001$) (Figure 3), Re-LT ($p = 0.034$) (Figure 4), etiology of liver disease ($p < 0.001$) (Figure 5) and impaired renal function at T1 ($p < 0.001$) (Figure 6) had significant impact on patient

survival. Regarding the etiology of disease, patients were separated into seven different groups (Table 2). Patients diagnosed with biliary malignancy and HCC showed significantly worse 20-year survival rates ($p < 0.001$), while patients with autoimmune liver disease or cholestatic disease had significantly better survival ($p = 0.012$). For age analyses patients were split into three groups: Aged <30 ($n = 45$), 30–55 ($n = 211$) and >55 ($n = 57$). Patients <30 demonstrated significantly better survival than those aged 30–55 ($p = 0.007$) and >55 ($p < 0.001$), whereas patients >55 showed significantly worse outcome ($p = 0.005$) than patients aged 30–55. Impaired renal function at T1 (eGFR < 60) had significant impact on long-term survival ($p < 0.001$). In Figure 6 survival appears much better than overall actuarial survival, because for this analysis only 226 patients were eligible.

Cold ischemia time (CIT) >10 h ($p = 0.889$) did not significantly impact patient survival. Neither did CIT >12 h ($p = 0.826$) or >14 h ($p = 0.380$). Graft survival was also not significantly affected by CIT >10 h ($p = 0.687$), >12 h ($p = 0.676$), or >14 h ($p = 0.587$). Mean CIT was 10.7 ± 4.0 h (10, 3.2–26.8 h). Mean donor age was 31.4 ± 12.4 years (29, 9–64) pointing to excellent donor quality.

Initial IS ($p = 0.818$) did not significantly impact long-term survival. Neither did HBMI ($p = 0.066$), HTN ($p = 0.272$), HGLY ($p = 0.228$) or HLIP ($p = 0.643$) at T1. Mean death rate was 2.9%/a, after 6 months it decreased to 2.4%/a.

In a multivariate model patients >30 years (HR 2.56; 95% CI: 1.32–4.94; $p = 0.005$), biliary malignancy (HR 3.77; 95% CI: 1.81–7.84; $p < 0.001$), HCC (HR 2.04; 95% CI: 1.26–3.29; $p = 0.004$) and Re-LT (HR 1.76; 95% CI: 1.15–2.70; $p = 0.010$) again emerged as significant negative predictors of long-term survival, whereas patient gender was no longer significant ($p = 0.199$).

Causes of death

Causes and time of all deaths are listed in Table 3. Moreover, Figure 7 gives a detailed analysis of cumulative deaths sorted by most common causes and year after LT. RD, infection and *de novo* malignancy were the most common causes of death, representing 21.3% ($n = 30$), 20.6% ($n = 29$) and 19.9% ($n = 28$). Cardiovascular events represented 14.9% ($n = 21$) of deaths. The prevalence of cardiovascular events was significantly higher in male patients, than in female patients ($p = 0.012$). 59.6% ($n = 84$) of all deaths occurred within the first decade after LT, mostly due to RD (32.1%; $n = 27$), infection (20.2%; $n = 17$) and *de novo* malignancy (15.5%; $n = 13$). 40.4% ($n = 57$) of the patients died within the second decade after LT, caused by *de novo* malignancy (26.3%; $n = 15$), infection (21.1%; $n = 12$), and cardiovascular events (12.3%; $n = 7$).

To further characterize the high rate of late lethal infections and SEPSIS we analyzed those 12 patients more detailed: They were six females and six males. Primary diagnoses were ALD ($n = 2$), PBC ($n = 3$), PSC ($n = 1$), HCV ($n = 2$), acute Budd Chiari ($n = 1$) and cryptogen ($n = 3$). Mean age at first LT was 49 ± 12 (53, 25–63). Three of these patients received a Re-LT (two within 6 months after first LT and one 227 months after first LT, postoperatively he developed septic MOSF). Five had MIRF at T1 and one SIRF, this patient later on had to be put on dialysis. Mean age at death was 65 ± 12 (68, 43–80). Seven patients died to pneumonia or septic MOSF because of pneumonia. Their mean age was 73 ± 5 (71, 66 to 80). Two patients experienced non–fatal CVEs during follow-up.

Graft survival

Patient death and Re-LT were considered as graft loss. Graft survival rates were 83.7%, 64.7% and 46.6% after 1, 10, and 20 years (Figure 1). Fifty-four Re-LTs had to be performed in our cohort. The first Re-LT affected 46 patients (14.7%), 7 patients received a third and 1 patient received a fourth transplant. 44.4% ($n = 24$) of Re-LTs were performed within 12 months after primary LT, 27.8% ($n = 15$) within 2–5 years, 13% ($n = 7$) within 6–10 years and 14.8% ($n = 8$) beyond 10 years. Mean time interval between primary LT and Re-LT was 42 ± 57 (14, 0–248) months. Reasons for Re-LT are summarized in Table 4. Table 5 shows reasons for late Re-LT.

Table 2: Long-term survival rates of the most common indications for LT

		Survival rate (%)				
Primary indication for LT	n	1 year	5 years	10 years	15 years	20 years
Cholestatic/autoimmune	64	92.2	90.6	82.8	81.2	67.5
Acute liver failure	23	91.3	91.3	82.6	82.6	65.2
HBV/HBV + HDV	57	89.5	84.2	71.9	70.1	62.4
Alcoholic cirrhosis	49	95.9	83.7	71.4	59.2	46.9
HCV/HCV + HBV	35	82.9	74.3	71.4	60.0	44.7
Hepatocellular carcinoma	27	81.5	66.7	55.6	37.0	24.7
Cryptogen	29	96.6	86.2	82.8	65.5	54.6

Table 3: Causes and time of death

		Number of patients at time after LT			
Cause of death	n (%)	0–3 months (n)	4–12 months (n)	1–10 years (n)	10–20 years (n)
Total	141 (100 %)	13	22	49	57
Recurrent disease	30 (21.3%)				
Hepatitis B	8	1	4	2	1
HCC	7	0	2	4	1
Hepatitis C	5	0	2	2	1
CCC	4	0	2	2	0
Alcoholism	4	0	0	4	0
NEC	1	0	0	1	0
PBC	1	0	0	1	0
Infection	29 (20.6%)				
Sepsis/MOSF	13	3	1	3	6
Pneumonia	9	1	1	1	6
PCP	4	1	2	1	0
Pneumonitis, CMV	3	0	3	0	0
De novo malignancy	28 (19.9%)				
Lung[1]	12	0	0	5	7
Other solid organ[2]	8	0	0	4	4
Skin[3]	5	0	0	2	3
Lymphatic[4]	3	0	1	1	1
Cardiovascular	21 (14.9%)				
MI	11	0	0	6	5
CI	4	0	1	1	2
Pulmonary embolism	3	0	0	0	3
Intraoperative (LT) ventricular failure	2	2	0	0	0
Postoperative (non-LT) ventricular failure	1	0	0	1	0
Others	33 (23.4%)	5	3	8	17

HCC, hepatocellular carcinoma; CCC, cholangiocellular carcinoma; NEC, neuroendocrine carcinoma; PBC, primary biliary cirrhosis; MOSF, multiorgan system failure; PCP, pneumocystis carinii pneumonia; CMV, cytomegalovirus; MI, myocardial infarction; CI, cerebral infarction.
Note: One hundred forty-one patients of 313 adult survivors after liver transplantation (LT) died during 20-year follow-up. Cause and time of death are given.
[1]n = 12 are: malignant mesothelioma (n = 1), non–small cell lung carcinoma (n = 2), small cell lung carcinoma (n = 9).
[2]n = 8 are: urinary bladder carcinoma (n = 1), glioblastoma (n = 1), carcinoma of the esophagus (n = 1), HCC (n = 1), oropharyngeal cancer (n = 2), gastric cancer (n = 1), thyroid cancer (n = 1).
[3]n = 5 are: malignant melanoma (n = 1), squamous cell carcinoma (n = 4).
[4]n = 3 are: AML (n = 1), lymphoma (n = 2).

Immunosuppression

At T1, 75.0% (n = 204) of the patients were on cyclosporin A (CSA) and 25.0% (n = 68) on tacrolimus (TAC). Mean dosages of CSA and TAC were 337 ± 114 (median, 320) mg/day and 7.2 ± 2.1 (median, 6) mg/day. 2.2% (n = 6) of the patients were steroid free, while 56.2% (n = 176) were treated with azathioprine as adjunctive IS.

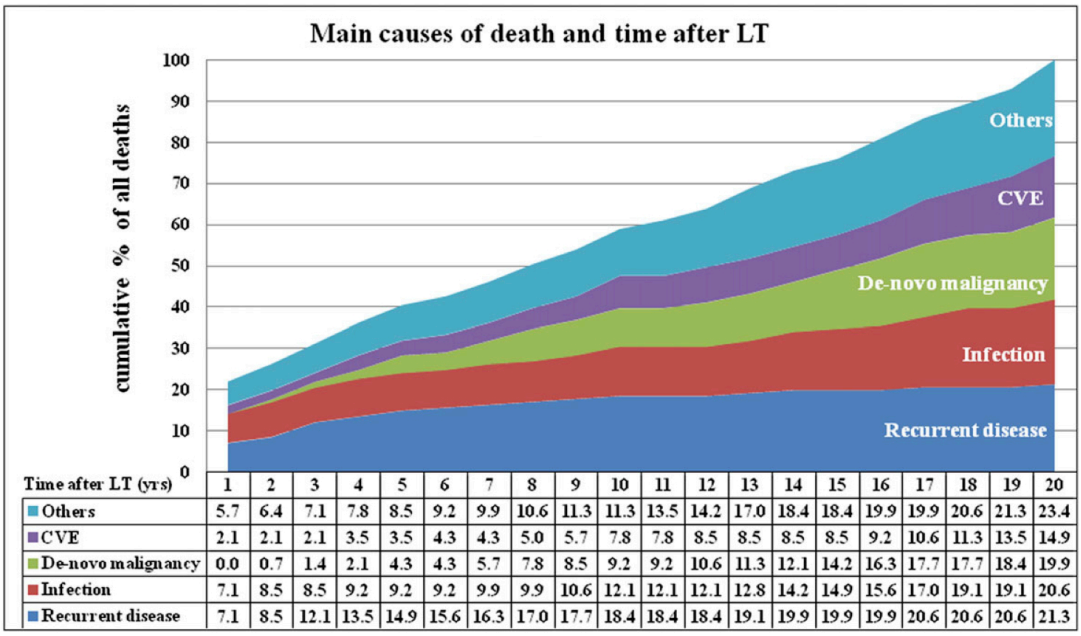
At the last follow-up, 17.2% (n = 27) of survivors were on CSA monotherapy and 9.6% (n = 15) were on a combined treatment with mycophenolate mofetil (MMF). The mean dose of CSA was 115 ± 60 (median, 100) mg/day. Fifty patients (31.8%) took TAC for IS and 30 patients (19.1%) were on TAC and MMF. Mean TAC dose was 2.3 ± 1.3 (median, 2.0) mg/day. Six patients (3.9%) were on sirolimus. 17.8% (n = 28) of the patients were on MMF monotherapy. One patient was off IS altogether and had normal liver functions. At T2 146 (94.2%) survivors were steroid-free and three patients (2%) were on azathioprine as adjunctive therapy.

Liver function

At T1, mean tBili was 1.6 ± 3.2 mg/dL (0.8, 0.2–33.3). Mean tBili at T2 was 0.7 ± 0.7 (0.6, 0.2–6.3) mg/dL. Mean AST was 54.5 ± 74.5 (26, 7–620) U/L (T1) and 31.7 ± 22 (27, 9–178) U/L (T2); mean ALT was 107.2 ± 245.8 (37, 6–2910) U/L (T1) and 40.4 ± 73.9 (25, 8–805) U/L (T2).

Overweight

Mean BMI in patients increased from 23.8 ± 3.4 kg/m^2 at T1 to 24.8 ± 3.9 kg/m^2 at T2. 33.2% (n = 74) and 45% (n = 68) of the patients had overweight at T1 and T2, respectively (p = 0.014). Prevalence of HBMI at T1 and T2 was higher in male (37.0% and 51.3%) than in female (28.1% and 38.4%) patients, but not significantly (male vs. female at T1 p = 0.105; at T2 p = 0.076).



Time after LT (yrs)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Others	5.7	6.4	7.1	7.8	8.5	9.2	9.9	10.6	11.3	11.3	13.5	14.2	17.0	18.4	18.4	19.9	19.9	20.6	21.3	23.4
CVE	2.1	2.1	2.1	3.5	3.5	4.3	4.3	5.0	5.7	7.8	7.8	8.5	8.5	8.5	8.5	9.2	10.6	11.3	13.5	14.9
De-novo malignancy	0.0	0.7	1.4	2.1	4.3	4.3	5.7	7.8	8.5	9.2	9.2	10.6	11.3	12.1	14.2	16.3	17.7	17.7	18.4	19.9
Infection	7.1	8.5	8.5	9.2	9.2	9.2	9.9	9.9	10.6	12.1	12.1	12.1	12.8	14.2	14.9	15.6	17.0	19.1	19.1	20.6
Recurrent disease	7.1	8.5	12.1	13.5	14.9	15.6	16.3	17.0	17.7	18.4	18.4	18.4	19.1	19.9	19.9	19.9	20.6	20.6	20.6	21.3

Figure 7: Causes and time of death. Cumulative deaths (%) over time (years) after LT.

Hypertension

Median sBP rose from 135 (90–200) to 142 (83–195) mmHg at T1 and T2, respectively, while dBP dropped from 85 (60–140) to 82 (56–116) mmHg. At T1, 20.1% (n = 55) of the patients were on antihypertensive therapy and 63.4% (n = 144) had hypertension. At T2, 68.2% of the patients (n = 105) took antihypertensive medication and 63.3% (n = 95) had hypertension. The number of patients with HTN increased from 57.3% (n = 157) to 85.2% (n = 132) ($p < 0.001$). Prevalence of HTN at T1 and T2 was higher in male (60.3% and 91.0%) than in female patients (53.7 and 79.2%), the latter being significant ($p = 0.039$).

Diabetes

At T1, mean blood glucose level was 105 ± 38 mg/dL. This number increased to 115 ± 56 mg/dL at T2. 2.6% (n = 7) and 11.2% (n = 17) of the patients took oral antidiabetic medication while 7.3% (n = 20) and 11.8% (n = 18) were on insulin at T1 and T2. The number of patients with HGLY increased from 23.0% (n = 63) to 28.4% (n = 44) at T1 and T2 ($p = 0.215$). At T1 and again at T2, HGLY was prevalent significantly more often in male (30.5% and 43.0%) than in female (13.8% and 13.2%) recipients ($p = 0.001$).

Dislipidemia

Mean total cholesterol was 235 ± 59 mg/dL at T1 and 188 ± 46 mg/dL at T2. One hundred fifty-seven (69.2%) and 54 (36.7%) had hypercholesterolemia at T1 and T2 ($p < 0.001$). The decline was also shown in the number of patients with hypertriglyceridemia, which was 95 (41.5%) and 18 (12.4%) at T1 and T2, ($p < 0.001$). The overall number of people with HLIP decreased from 78.0%

Table 4: Reasons for retransplantation

	Number of patients			
Reason	1st Re-LT	2nd Re-LT	3rd Re-LT	Total
Recurrence of primary disease	14	1	0	15 (27.8%)
Rejection	11	4	0	15 (27.8%)
Hepatic artery thrombosis	7	2	0	9 (16.7%)
Primary nonfunction	6	0	1	7 (13%)
Ischemic type biliary lesion	5	0	0	5 (9.3%)
Others	3	0	0	3 (5.6%)
Total	46	7	1	54 (100.0%)

Table 5: Reasons for late hepatic graft loss

Age at Re-LT	Sex	Primary indication for LT	Indication for Re-LT	Months after LT	No. of Re-LT	Alive
50	F	PSC	Chronic rejection	125	2nd	n
52	F	Cryptogenic cirrhosis	Thrombosis of hepatic artery	144	1st	n
42	F	Morbus Wilson	Chronic rejection	149	1st	y
43	F	ALF (cryptogen)	Chronic rejection	184	1st	n
62	F	ALF (Budd–Chiari)	Thrombosis of hepatic artery	190	1st	y
39	F	Morbus Wilson	Chronic rejection	216	1st	n
44	M	PSC	PSC recurrence	227	1st	n
41	M	Autoimmune hepatitis	*De novo* PBC	248	1st	y

(n = 177) to 47.6% (n = 70) ($p < 0.001$) with no difference concerning the recipients' gender. Nineteen patients (12.6%) were on statins at T2.

Renal impairment

At T1 mean eGFR was 69.4 ± 28.2 mL/min/1.73 m^2, at T2 61.7 ± 26.5 mL/min/1.73 m^2. The number of patients with MIRF increased significantly from 41.8% (n = 94) to 55.2% (n = 85), ($p = 0.01$). 3.1% (n = 7) and 6.5% (n = 10) had SIRF at T1 and T2 ($p = 0.118$). Prevalence of MIRF was significantly higher in male patients both at T1 ($p < 0.001$) and T2 ($p < 0.001$). At T1, the number of patients with SIRF was more common in male patients ($p = 0.019$), whereas the gender difference at T2 was not significant ($p = 0.569$).

Concerning renal replacement therapy, two of the surviving patients needed intermittently peri–operative dialysis. During follow-up five of the surviving patients developed SIRF with need for chronic hemodialysis and two received kidney transplantation.

De novo *malignancy*

A posttransplant lymphoproliferative disease (PTLD) occurred in 2.9% (n = 9) of the patients. Overall, 77 *de novo* malignancies occurred in 58 patients. Skin squamous cell carcinoma made up the largest portion of all malignancies, representing 39.5% (n = 30). Further details on lethal *de novo* malignancies can be obtained from Table 3 and Figure 7, displaying the cumulative deaths in % of all deaths over time after LT. The per-year rate of deathly *de novo* malignancies is higher in the second decade than in the first. Late (beyond 10 years) lethal *de novo* malignancies were: lung (n = 7; SCLC: 6, NSCLC: 1); AML, HCC, glioblastoma, oropharyngeal cancer, urinary bladder carcinoma, (each n = 1); and squamous cell carcinoma (n = 3).

Comparison of live expectancy/survival to normal population

Overall survival rates of the gender and age matched cohort were: 1-year (99.5%), 5 years (97.6%), 10 years (93.2%), 15 years (87.2%) and 20 years (78.9%). Concerning LT patients aged <30 years compared to the gender and aged matched controls survival seems worse (Figure 8A). The same is true for patients aged 30–55 (Figure 8B). Most interestingly, patients aged >55 (Figure 8C), especially those who survived more than 1 year (Figure 8D) seem to have a survival similar to the matched cohort. Since the gender and age matched control is only ''virtual'' we did not perform Kaplan–Meier estimates or statistical tests.

Discussion

This study reports the first European single-center 20-year survival data. It is helpful for informing patients about their survival chances, and for improving long-term results by identifying factors that relate to late graft loss and complications from IS.

Worldwide only two other single centers have published such long-term survival data: Jain et al. (20) reported 20-year actuarial patient and graft survival of 35.8% and 32.6%, whereas Duffy et al. (21) presented 52% and 42%. The European Liver Transplant Registry (ELTR) has recently published 20-year survival of 43% and 36% (22).

Interestingly these cohorts mentioned (20,21) included a large amount of minors or pediatric recipients. Mean ages at LT were 42.6 ± 20.2 years (16.6% of the patients <18) (20) and 28 ± 21 years (44% <18) (21), compared to our mean age of 45 ± 11 (0.6% <18). Considering this, long-term outcome of our cohort seems outstanding, since more than 50% of the patients live 20 years and longer. Our data, as well as Duffys' et al. (21) show that many transplanted livers function satisfactorily for 20 years or longer.

In our cohort 8.6% of the patients were transplanted for HCC. Implementation of model-for-end-stage-liver-disease (MELD) allocation, allowing priority scores to patients with limited stage HCC, resulted in a sixfold rise in the proportion of HCC recipients (23,24). With respect to reduced patient survival of HCC (24), and significant lower 20-year survival data for HCC patients in the presented cohort we doubt that future reports will be able to present comparable long-term outcomes.

Main causes of death in our patients were RD, infections, *de novo* malignancies, and cardiovascular disease. These

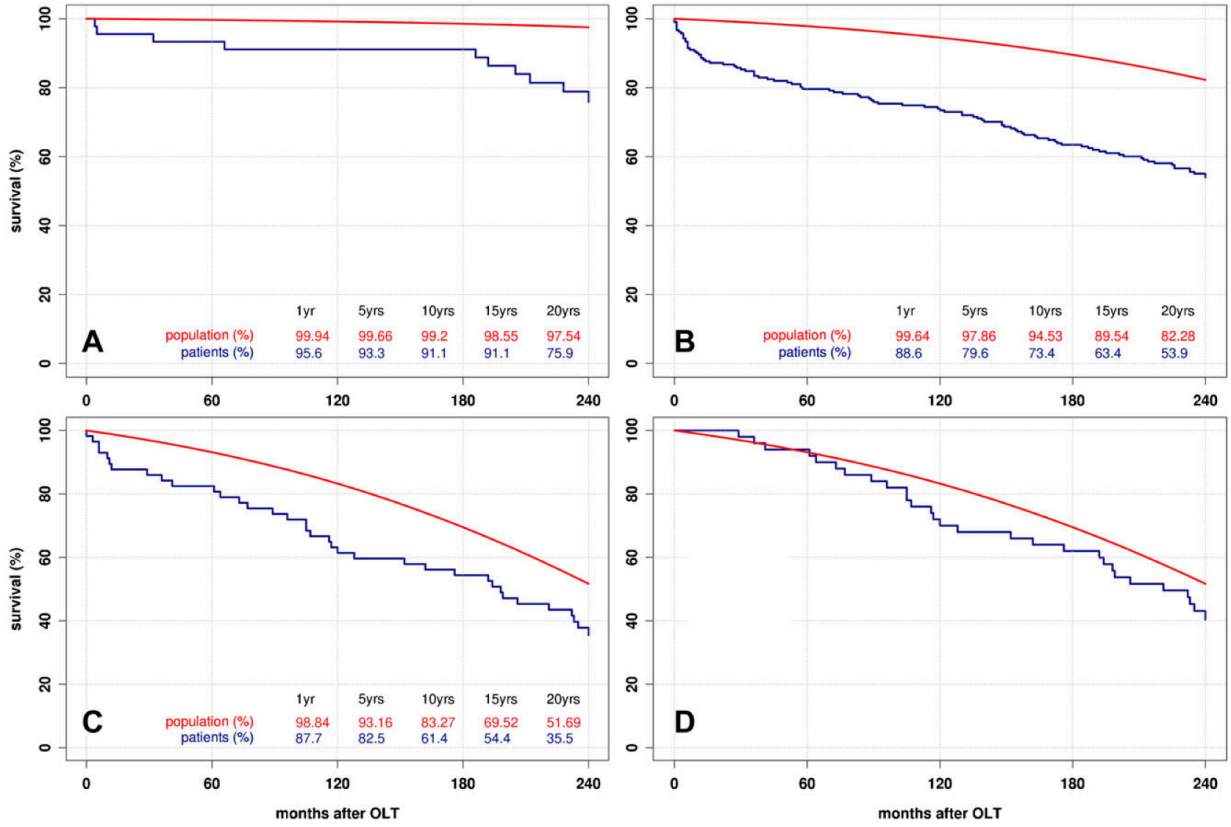


Figure 8: Survival of LT recipients (Kaplan–Meier estimate) vs. life expectancy of normal population (smooth line). (A) Age <30 years; (B) age 30–55 years; (C) age >55 years; (D) age >55 years, excluding 1-year mortality.

variables are consistent with the findings in other cohorts (5,7,10,14,15,20,25–34). As for RD certain malignancies (HCC beyond Milan (35) and advanced cholangiocarcinomas (36)) are no longer indications for LT. Concerning alcoholism, psychometric tools and assessments are not able to predict a relapse post-LT accurately (37). Over 10 years ago our center published that patient selection is a major issue and established criteria should be strictly adhered to (38). Risk factors for alcoholism relapse were identified as sobriety less than 6 months before LT, divorced marital status, poor psychosomatic prognosis in pretransplant evaluation and the presence of underage children (39).

HCV recurrence was shown to depend on graft quality as several ECD factors, such as age (40), steatosis (41), CIT and ischemia-reperfusion injury (42), have been reported to significantly increase recurrence and decrease patient and graft survival (23). Again, matching of donors and recipients proves to be crucial for long-term success. Although RD is responsible for the major part of deaths and graft loss during the first decade, one would not simply abandon such transplantation. In the future it would be advisable to establish a more differentiated donor-recipient matching and individualized IS to overcome some of the above-mentioned problems of RD.

The rate of Re-LT (17.3%) in our cohort is slightly higher than in other series; for example, Duffy et al. (21) presented 9%, whereas Jain et al. (43) reported 13.4% in their third era (1991–1998). Interestingly, the 15-year survival (54.5%) after Re-LT in our cohort is higher than the 10-year survival in the latter cohort (32% (43)). Reasons for Re-LT differ substantially in our series from those presented by Jain et al. with RD being the most frequent cause.

20.6% of deaths were attributed to early or late infections in our cohort. This is similar to the published 15-year follow-up data of our center (2), as well as comparable to long-term data of Jain et al. (43), who report 28.4% of deaths caused by infections. CMV and PCP infection associated deaths seem to occur more often in the early phase after transplantation (0–12 months), whereas lethal pneumonia and Sepsis/MOSF were observed predominantly in the late phase. Our findings are partially in line with the ''timeline of infection after organ transplantation'' proposed by

Fishman (44). Accordingly ''the main determinants of infections are the dose, duration, and sequence of IS.''

We found a high rate of late lethal infection and SEPSIS/MOSF. More than 50% of these patients succumbed to pneumonia. The mean age of these patients was 73 ± 5 (71, 61–80). Those patients might therefore rather be interpreted to have had a successful course after LT.

In our cohort a slightly higher PTLD rate (2.9%) than in the literature (1–2%) was detected (45). The rate of skin squamous cell carcinomas in our cohort is in line with rates reported in the literature, showing nonmelanoma skin cancers to be the most common *de novo* malignancies after LT (46). The most common cause of death in *de novo* malignancies was lung cancer (42.9% of all lethal *de novo* malignancies). Lung cancers occur at higher rates in LT patients compared to the general population. This underscores the need for aggressive interventions for smoking cessation (47), especially as lung cancer occurred most commonly in patients with a history of smoking (previous or active) and ALD (48,49).

The major part (81.3%) of cardiovascular deaths occurred beyond 5 years after LT. The cardiovascular risk of LT patients is increased and strict surveillance is required. Male long-term (10 years) survivors after LT presented with an increased prevalence of cardiovascular risk factors and corresponding numbers of coronary events (5). Risk stratification of LT recipients is well described (50) and primary and secondary prevention measures include early steroid withdrawal, CNI-sparing IS, conversion of CSA to TAC and statin intervention. Prevalence of HBMI, HTN and HGLY has increased throughout follow-up, while the prevalence of HLIP has shown a decline. Interestingly, prevalence of HTN, HGLY and impaired renal function was significantly higher in male than in female patients at both described follow-ups. In univariate analysis, male patients had worse overall survival than female. Even though HBMI, HTN, HGLY did not have significant impact on survival, the combination of those risk factors, the higher prevalence of impaired renal function, and the elevated prevalence of cardiovascular events might explain the differences in gender-specific survival rates.

Although prevention measures are applied, HBMI, HGLY, HLIP and HTN rates at 20 years were 45%, 28.4%, 47.6% and 85.2%, indicating that there is still space for improvement, especially for male recipients who show higher rates of cardiovascular risk factors.

Concerning the survival comparison of LT recipients to life expectancy of normal population the findings for the whole cohort as well as age groups <30 and 30–55 were expected and need no further comment. Most interestingly, patients aged >55 seem to have a survival similar to the normal population, especially those who survived more than 1 year after LT. This finding has to be interpreted cautiously. One explanation might be the strict medical surveillance that those patients experience.

In our cohort renal impairment significantly increased over the 20-year follow-up. While most authors described renal function after LT by serum creatinine levels (20,51), few have looked at the eGFR. Patients who showed deteriorated renal function were either switched to CNI-sparing IS protocols or MMF monotherapy, which has shown to cause less nephrotoxicity (11,52,53). As impaired renal function has turned out to be an independent risk factor for long-term survival after LT, the prognostic value of low eGFR for long-term outcome needs to be further evaluated. Several authors have reported the importance of assessing pre- and posttransplant renal functions (54,55).

The sequential (T1, T2) laboratory data presented are liable to selection bias and should be interpreted having this in mind.

In almost all studies on outcome after LT, CIT affects both short- and long-term survival. Interestingly in our cohort this was not the case. This finding should be interpreted cautiously. The median donor age in this cohort was low (31 years). Moreover, almost all of the grafts were self-procured (regionally allocated). Taken together, this points to a very good graft quality and we assume this might have diminished the influence of CIT.

We are herewith able to present the most promising LT survival data that have been published so far. In conclusion, LT offers excellent long-term results given a lifelong commitment between both the recipient and the members of the multidisciplinary transplant team is ensured. In the 1980s and 1990s, many centers started their LT program, thus one can expect an immense increase of 20-year LT survivors over the next decade, helping further elucidate the analysis of factors associated with long-term survival.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Liste eigener Publikationen

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