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ORIGINAL ARTICLE

Evaluation of domino liver transplantations in Germany

Fabian Johannes Bolte,[1] Hartmut H.-J. Schmidt,[1] Thomas Becker,[2] Felix Braun,[2] Andreas Pascher,[3] Jürgen Klempnauer,[4] Jan Schmidt,[5] Silvio Nadalin,[6] Gerd Otto[7] and Ana Paula Barreiros[8]

1 Klinik für Transplantationsmedizin, Universitätsklinikum Münster, Münster, Germany
2 Klinik für Allgemeine Chirurgie und Thoraxchirurgie, Universitätsklinikum Schleswig-Holstein, Schleswig-Holstein, Germany
3 Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Charité - Universitätsmedizin Berlin, Berlin, Germany
4 Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Medizinische Hochschule Hannover, Hannover, Germany
5 Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsklinikum Heidelberg, Heidelberg, Germany
6 Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsklinikum Tübingen, Tübingen, Germany
7 Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany
8 I. Medizinische Klinik und Poliklinik, Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany

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Correspondence
Univ.-Prof. Dr. med. Hartmut Schmidt, Klinik für Transplantationsmedizin, Universitätsklinikum Münster, Albert-Schweitzer-Campus 1, Gebäude: A14, Münster 48149, Germany.
Tel.: +49 251 83 57935;
fax: +49 251 83 57771;
e-mail: hepar@ukmuenster.de

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Summary

A retrospective multicenter study has been conducted to evaluate domino liver transplantations (DLTs) in Germany. The study provides insight into survival and features having an impact on the assessment of neuropathy after DLT. In addition, a neurologic follow-up program with a scheme to estimate the likelihood of *de novo* amyloidosis is presented. A series of 61 DLTs at seven transplant centers in Germany was enrolled. The mean age of domino recipients at the time of transplantation was 58 years, 46 of them being men, and 15 being women. The median follow-up was 46 months. The overall 1-, 3-, and 5-year survival of domino recipients was 81.6%, 70.8% and 68.8%, respectively. Causes of death were primarily not related to familial amyloidosis. The main indication of DLT was hepatocellular carcinoma. Two of the reported domino recipients developed symptoms and signs of *de novo* amyloidosis within 10 years after transplantation. A total of 30 domino graft recipients (49.18%) presented with diabetes post transplantation. In conclusion, an advanced follow-up program is crucial to evaluate the risk of transmitting familial amyloidosis by DLT and to establish more strict selection criteria for domino recipients.

Introduction

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant inherited disease caused by specific mutations within the transthyretin (TTR) gene [1,2]. It has been discovered in more than 30 countries with large foci in Portugal, Japan, and Sweden [3]. The first case was reported by Andrade *et al.* in Portugal in 1952 [4]. In contrast to these endemic areas, cases with FAP have been less commonly reported in Germany.

Familial amyloidotic polyneuropathy is primarily characterized by sensory, motor and autonomic neuropathy and or cardiomyopathy [3]. The age at the onset of first symptoms varies depending on genotype and endemic region with a mean age of 35 years in Portugal and Japan [3]. A later mean age of onset has been described in Swedish patients [5]. The course of the disease is progressive and in all symptomatic cases ultimately fatal [6]. In several studies, orthotopic liver transplantation is highlighted as an effective and curative treatment [7–11].

The first patient with FAP underwent liver transplantation in 1990 [12,13].

A valuable consequence of performing liver transplantation in patients with FAP in the time of organ shortage is the possibility to use the removed liver for transplantation into another patient, a well established procedure called domino liver transplantation (DLT) [6,14]. There are several points emphasizing FAP to be an excellent condition to perform a DLT. Firstly, the explanted liver is morphologically and functionally normal apart from the genetic defect that leads to production of the TTR variant within some decades [15]. Secondly, the donor is comparatively young and the cold ischemia time would be short if the amyloidotic liver was used for DLT in the same transplant center. Finally, FAP inherently requires 18–83 years to develop disease symptoms [3,16]. A period of approximately 20 years was assumed in domino recipients before the onset of FAP-related symptoms when DLT was first performed by Furtado and his team in Portugal in 1995 [13,17,18]. In Germany, the first DLT was performed in Hannover in 1997 [19]. The Domino Liver Transplant Registry reports more than 1000 DLTs performed worldwide by December of 2011 [20].

This study has been conducted to evaluate DLTs in Germany. It provides insight into survival and features like diabetes and immunosuppression having an impact on the assessment of FAP symptoms after DLT. In addition, a neurologic follow-up program with a scheme to estimate the likelihood of *de novo* amyloidosis is presented for the first time in literature. Finally, the results lead to the discussion of consistent selection criteria for domino recipients.

Methods

A retrospective multicenter study including 61 DLTs between January 1997 and November 2010 has been performed. Transplant centers in Berlin ($n = 6$), Hannover ($n = 15$), Heidelberg ($n = 11$), Kiel ($n = 2$), Mainz ($n = 19$), Münster ($n = 5$) and Tübingen ($n = 3$) participated.

All domino donors with FAP proven by genetic testing were eligible for study inclusion. The following donor parameters were recorded: age, sex and type of TTR mutation. The main focus was to gather information about the recipients including age, sex, nationality, height and weight for body mass index (BMI) as well as modified BMI (mBMI = serum albumin [g/l] × BMI), preoperative diagnosis of liver disease, Child-Pugh-Score, MELD-Score (calculated according to the following formula: MELD = 3.8 [Ln serum bilirubin (mg/dl)] + 11.2[Ln INR] + 9.6[Ln serum creatinine (mg/dl)] + 6.4) [21], date of DLT, operation time, cold ischemia time, outcome, recurrence of primary disease, immunosuppression referred to the last visit of post-transplant medical care, graft rejection, retransplantation, comorbidities like alcohol, diabetes and arterial hypertension as well as symptoms of neuropathy. In patients with hepatocellular carcinoma (HCC), data about bridging therapy, TNM-stage according to the American Joint Committee on Cancer were gathered. In addition, the number and maximal diameter of tumor noduli for the Milan criteria (defined as single lesion ≤ 5 cm or up to three separate lesions, none larger than 3 cm) [22] was obtained. The retrospective evaluation of Milan criteria was consistently based on pathologic findings in the explanted liver. Comorbidities like arterial hypertension and diabetes were assessed twice: prior to DLT and in post-transplant follow-up. The diagnosis of diabetes mellitus was based on the criteria of the World Health Organization (hemoglobin $A_{1C} \geq 6.5\%$, fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l), random elevated glucose >200 mg/dl (11.1 mmol/l) with symptoms, or abnormal oral glucose tolerance test ≥ 200 mg/dl (11.1 mmol/l). To evaluate symptoms and signs of neuropathy in domino recipients, observations and examinations during follow-up were retrieved.

Statistics

All data entered into a Microsoft Excel database were processed by using the statistical package PASW Statistics 18 (version 18.0.0; SPSS Inc., an IBM company, Chicago, IL, USA). The results were expressed as mean values and standard deviation for normally distributed continuous data, as median values and interquartile ranges for not normally distributed continuous data and as percentages for qualitative data. The actuarial survival was calculated by the Kaplan–Meier method from the date of DLT until death from any cause. Survival curves were compared by the log-rank test. A P-value < 0.05 was regarded as statistically significant.

Approval

The study has been approved by the local institutional review board in Münster.

Results

The patient population consisted of 37 male and 24 female domino donors with a mean age of 45 (±11.29, range 28–68) years at the time of transplantation. The majority of them carried the p.Val30Met ($n = 28$, 45,90%) mutation. Their livers were sequentially transplanted into 46 male and 15 female domino recipients. No split graft was used. At the time of transplantation, the mean recipient age was 58 ± 6.76 years. It ranged from 43 to 74 years; 49.20%

($n = 30$) of the domino recipients were younger than 60 years of age. The mean BMI was 25.91 (±3.63) kg/m²; the mean modified BMI was 873.38 (±238.95). The characteristics of domino liver transplant donors and recipients are summarized in Tables 1 and 2.

The most common indication for DLT was HCC ($n = 46$, 75.40%). The underlying liver diseases primarily were hepatitis C related liver cirrhosis (19/61, 31.1%), alcoholic liver cirrhosis (11/61, 18.0%) and hepatitis B related liver cirrhosis (10/61, 16.4%). In total, 32 out of 46 HCC patients (69.6%) fulfilled the Milan criteria. However, many patients were submitted to adjuvant cancer therapy such as arterial chemoembolization as bridging concept. In a small number of patients, hepatitis C liver (2/61, 3.3%) cirrhosis, alcoholic liver cirrhosis (2/61, 3.3%), alpha-1 antitrypsin deficiency related liver cirrhosis (1/61, 1.6%), hereditary hemochromatosis related liver cirrhosis (1/61, 1.6%), and cryptogenic cirrhosis (1/61, 1.6%) were an indication for DLT. The Model for End Stage Liver Disease (MELD) predicting three- month survival ranged from 6 to 30. The median value was 9 (interquartile range 6–13). Regarding the Child Turcotte classification, 25 (41.0%) patients could be classified as Child A liver cirrhosis, 19 (31.1%) patients as Child B liver cirrhosis, and 9 (14.8%) patients as Child C liver cirrhosis prior to liver transplantation.

Table 1. Characteristics of the donors.

Age at the time of transplantation (years)	
Mean ± SD	45.02 ± 11.29
Gender	
Male	*n* = 37 (60.7%)
Female	*n* = 24 (39.3%)
TTR mutation	
p.Ala97Gly (c.290C>G)	*n* = 1 (1.6%)
p.Asp38Val (c.113A>T)	*n* = 1 (1.6%)
p.Glu89Lys (c.265G>A)	*n* = 2 (3.3%)
p.Gly47Ala (c.140G>C)	*n* = 4 (6.6%)
p.Gly47Glu (c.140G>A)	*n* = 2 (3.3%)
p.Gly53Ala (c.158G>C)	*n* = 1 (1.6%)
p.Gly53Glu (c.158G>A)	*n* = 1 (1.6%)
p.Ile107Met (c.321T>G)	*n* = 1 (1.6%)
p.Ile107Val (c.319A>G)	*n* = 1 (1.6%)
p.Leu12Pro (c.35T>C)	*n* = 2 (3.3%)
p.Leu55Arg (c.164T>G)	*n* = 1 (1.6%)
p.Leu58His (c.173T>A)	*n* = 1 (1.6%)
p.Phe33Leu (c.97T>C)	*n* = 1 (1.6%)
p.Ser50Arg (c.148A>G)	*n* = 4 (6.6%)
p.Thr49Ala (c.145A>G)	*n* = 2 (3.3%)
p.Thr49Ile (c.146C>T)	*n* = 1 (1.6%)
p.Thr59Lys (c.176C>A)	*n* = 1 (1.6%)
p.Val30Met (c.88G>A)	*n* = 28 (45.9%)
Unknown	*n* = 6 (9.8%)

SD, Standard deviation; TTR, Transthyretin.

Table 2. Characteristics of the recipients.

Age at the time of transplantation (years)	
Mean ± SD	58.31 ± 6.76
Gender	
Male	*n* = 46 (75.4%)
Female	*n* = 15 (24.6%)
Body mass index (kg/m²)	
Mean ± SD	25.91 ± 3.63
DLTs	*n* = 61
Median operation time (min)	344
Median cold ischemia time (min)	400
Survival	
Alive	*n* = 39 (63.9%)
Dead	*n* = 22 (36.1%)
Follow-up (months)	
Median	45.93
Range	1–157
Interquartile range	14.44–84.10
Indications	
HCC not specified	*n* = 3 (4.9%)
HCC induced by hepatitis-B liver cirrhosis	*n* = 10 (16.4%)
HCC induced by hepatitis-C liver cirrhosis	*n* = 19 (31.1%)
HCC induced by alcoholic liver cirrhosis	*n* = 11 (18%)
HCC induced by hereditary hemochromatosis liver cirrhosis	*n* = 1 (1.6%)
HCC induced by autoimmune hepatitis liver cirrhosis	*n* = 1 (1.6%)
HCC induced by alpha-1 antitrypsin deficiency liver cirrhosis	*n* = 1 (1.6%)
Epithelioid hemangioendothelioma	*n* = 3 (4.9%)
Hepatitis-C liver cirrhosis	*n* = 2 (3.3%)
Alcoholic cirrhosis	*n* = 2 (3.3%)
Alpha-1 antitrypsin deficiency liver cirrhosis	*n* = 1 (1.6%)
Hereditary hemochromatosis liver cirrhosis	*n* = 1 (1.6%)
Cryptogenic cirrhosis	*n* = 1 (1.6%)
Other	*n* = 5 (8.2%)
Comorbidities	
Smoking	*n* = 6 (9.8%)
History of alcohol consumption	*n* = 20 (32.8%)
Diabetes	
Pre-DLT	*n* = 20 (32.8%)
Post-DLT	*n* = 30 (49.2%)
Arterial Hypertension	
Pre-DLT	*n* = 18 (29.5%)
Post-DLT	*n* = 30 (49.2%)
Graft rejection episodes	*n* = 23
Retransplantations	*n* = 3 (4.9%)
De novo amyloidosis	*n* = 2 (3.3%)

SD, Standard deviation; DLT, Domino liver transplantation; HCC, Hepatocellular carcinoma.

The immunosuppressive therapy applied by the transplant centers was heterogenous. Follow-up was available for 38 of 61 (62.2%) domino recipients; 22 patients died and one was lost to follow-up. The immunosuppression being either a monotherapy with a calcineurin inhibitor or a combination of different agents was composed of a glucocorticoid ($n = 7$), a calcineurin inhibitor ($n = 30$), and a

purine inhibitor ($n = 26$). A total of 8 patients received a therapy with a mTOR-inhibitor especially those with HCC as underlying condition. In the whole recipient group, there were 23 rejection episodes in 20 patients. There were 9 rejection episodes in hepatitis C and 3 rejection episodes in hepatitis B positive recipients (39.1% and 13.0%, respectively). All liver transplants were blood group identical.

A remarkable proportion of domino recipients presented with diabetes ($n = 30$, 49.2%) after liver transplantation: 17 (17/30, 56.7%) with insulin-dependent diabetes mellitus and 13 (13/30, 43.3%) with non-insulin-dependent diabetes mellitus. In 20 (66.7%) cases, the diagnosis was established pre- and in 10 (33.3%) cases post-transplantation. Thus, post-transplant diabetes mellitus (PTDM) occurred in 16.4% of the domino recipients. A significant difference in PTDM between the ciclosporin (13/30, 43.3%) and tacrolimus (17/30, 56.7%) subgroup could not be shown because of the limited number of patients ($P = 0.962$). In total, 18 (29.5%) domino recipients had a diagnosis of hypertension pre- and 30 (49.2%) post-transplantation. Moreover, a total of 20 (32.8%) domino recipients had a history of alcohol consumption.

The overall 1-, 3-, and 5-year actuarial survival was 81.6% (11 deaths, 48 patients at risk, and 2 censored), 70.8% (17 deaths, 36 patients at risk, and 8 censored) and 68.8% (18 deaths, 34 patients at risk, and 9 censored). Median follow-up after DLT was 46 (interquartile range 14.44–84.10) months. The Kaplan–Meier curve is depicted in Fig. 1. A significant difference in survival between recipients of grafts with p.Val30Met mutation and Non-p.Val30-Met mutation was not observed ($P = 0.253$). Altogether, 22 of 61 (36.1%) domino recipients died. Causes of death were sepsis ($n = 6$), tumor recurrence ($n = 5$), multiorgan failure ($n = 4$), cardiovascular complications ($n = 2$), pulmonary embolism ($n = 2$), cachexia ($n = 1$), kidney ($n = 1$), and liver failure ($n = 1$). In total, there were three deaths from tumor recurrence in patients with HCC exceeding Milan criteria.

Two cases of *de novo* amyloidosis occurred after DLT. Barreiros *et al.* reported the first case of a 75-year-old-woman who developed *de novo* amyloidosis 9 years after DLT. The underlying disease was hepatitis C liver cirrhosis complicated by HCC. The patient exhibited dysesthesia, burning pain, and progressive sensory loss in the lower limbs. Finally, the patient died of cachexia because of malnutrition and persistent diarrhea 12 years after liver transplantation [23]. The second case is a 73-year-old-man who underwent DLT in 1997 because of hepatitis B liver cirrhosis complicated by HCC. He presented with post-transplant diabetes and started to develop a progressive length-dependent polyneuropathy 3 years after transplantation. In spite of an extensive work-up in several hospitals with Nerve Conduction Studies (NCS) showing a mixture of axonal degeneration and demyelination, sural nerve biopsy was not performed until October 2010. At this point in time, amyloid deposits were detected by sural nerve biopsy and rectal tissue biopsies, but it was difficult to determine the onset of *de novo* amyloidosis accurately.

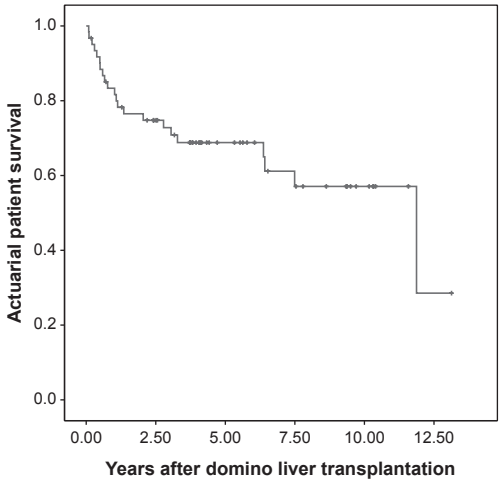

Figure 1 The overall 1-, 3-, and 5-year actuarial survival of DLT recipients was 81.6%, 70.8% and 68.8%.

Discussion

In our evaluation of DLTs in Germany, we revealed that only two of seven transplant centers had a specific follow-up of domino recipients concerning the risk of transmitting FAP by DLT. However, two cases of *de novo* amyloidosis could be identified and classified as probable (first case) and possible (second case) *de novo* amyloidosis. There are more reports in literature describing *de novo* amyloidosis after DLT. In 2005, Stangou *et al.* reported the first domino liver recipient, a 55-year-old man who developed symptoms of amyloidosis 8 years after DLT. The indication was hepatitis C liver cirrhosis complicated by HCC. The patient showed symptoms of dysesthesia in the lower limbs and developed progressive peripheral neuropathy. Sural nerve biopsy revealed TTR amyloid deposits [24]. A second patient was described by Goto *et al.* in 2006. A 57-year-old woman who received part of a domino liver started to develop sensory neuropathy 7 years after transplantation [25]. In their domino liver transplant program, Castaing *et al.* reported one out of 106 patients who developed peripheral neuropathy with histologically proven amyloid deposits 8 years after transplantation [26]. The French reference centers for FAP reported a series of 114 DLTs between 1997 and 2008. A total of seven domino recipients developed peripheral neuropathy during follow-up. Endoneurial amyloid deposits were detected by nerve biopsy in three patients [27]. Lladó *et al.* evaluated the transmission

incidence of familial amyloidosis in 17 patients. In total, four patients were diagnosed with *de novo* amyloidosis at an average of 7.5 years after transplantation [28]. Conceicao *et al.* described a patient who developed peripheral neuropathy in the lower limbs 9 years after DLT. Sural nerve biopsy confirmed the presence of amyloid deposits [29]. Obayashi *et al.* reported the case of a 35-year-old man with primary sclerosing cholangitis who underwent DLT and developed peripheral neuropathy 10 years later [30].

This and previous studies indicate that symptoms and signs of familial amyloidosis could occur within a period of 10 years after DLT. Thus, the onset of neuropathy is significantly earlier than observed in patients with inherited FAP [15,23]. In addition, it is noteworthy that half of the domino recipients in our study were less than 60 years old. This may be because of the fact that consistent selection criteria for domino recipients have not been established yet. Furthermore, the transplant centers varied in tumor stage policy. HCC was the most common indication for DLT encountered in 46 (75.40%) patients. In total, 14 (30.4%) domino recipients exceeded Milan criteria retrospectively. However, in our study the overall 5-year survival of 68.8% was reasonable and in accordance with Wilczek *et al.* who reported an overall 5-year survival in domino recipients of 65.3% [31]. The outcomes are similar to those after conventional liver transplantation [32,33]. Bispo *et al.* even concluded that younger donors and shorter ischemic time associated with DLT may be protective with regard to graft dysfunction and perioperative bleeding, two important determinants of early morbidity after liver transplantation [34].

The advantages of DLT such as an increased supply of liver grafts and excellent liver function may outweigh the risk in well-selected patients. It is important that domino recipients are elucidated on the nature of FAP, the characteristics of the liver and possible complications after DLT. An essential condition is that the recipients sign a written informed consent before undergoing the procedure.

Follow-up

In addition to general care after liver transplantation focusing on common problems such as organ rejection, infections, arterial hypertension, diabetes, dyslipidemia, osteoporosis, renal disease, and malignancy domino recipients require a neurologic follow-up. After establishing a baseline, we favor neurologic evaluations 1, 5, and 7 years after DLT. Hereafter and in the case of neuropathy, neurologic evaluation should be carried out annually.

The baseline evaluations prior to DLT should include the following: demographics, medical history including comorbidities such as diabetes and arterial hypertension, concomitant medication, blood sample collection for hematology, serum chemistry, coagulation panel and virology (testing for HBV, HCV and HIV), symptom score of the United Kingdom screening test, Neuropathy Impairment Score Lower Limbs (NIS-LL), if available quantitative sensory testing (QST) including vibration and temperature thresholds, NCS (peroneal, tibial and sural nerves), electrocardiogram, 24-hour blood pressure monitoring, echocardiography, gastro- and colonoscopy.

The neurologic follow-up for domino recipients is illustrated in Table 3. The assessment of peripheral neuropathy regarding underlying cause and severity is complex. However, diabetic peripheral neuropathy (DPN) has been studied thoroughly [35,36]. In line with DPN, a main feature of familial amyloidosis is length-dependent peripheral neuropathy [2,3]. Therefore, we propose to use the symptom score of the United Kingdom screening test [37,38] and the NIS-LL [39] validated in DPN to evaluate and quantify symptoms and signs of peripheral neuropathy in domino transplant recipients. The symptom score of the United Kingdom screening test is based on five questions as illustrated in Table 3 [37,38]. A modification of the Neurologic Disability Score (NDS) described by Dyck [35] is the NIS-LL [39]. The NIS-LL evaluates changes in motor, sensory, and reflex activity in the lower extremities [39]. Dyck *et al.* have suggested that in controlled clinical trials, a mean change of 2 points on the NDS is clinically detectable and meaningful [40]. Thus, a change from baseline of at least 2 points on the NIS-LL scale is expected to occur in domino recipients with progressive neuropathy. Furthermore, Dyk *et al.* showed that their Computer-Assisted Sensory Examination (CASE IV) system provides reproducible estimates of sensory thresholds [41]. If CASE IV equipment is available, we suggest it to determine vibration and temperature thresholds in domino recipients. Thereby, subtle abnormalities at baseline and progression of neuropathy after DLT could be identified. Nerve conduction studies should include a standard assessment of sural nerves as afferent fibers and peroneal and tibial nerves as motor fibers. The advantage is that they are sensitive and reproducible [39]. Finally, sural nerve biopsy should be performed in domino recipients with two or more abnormalities in neurologic evaluation including neuropathic symptoms, NIS-LL, QST, and NCS.

When evaluating patients with neuropathy, it is crucial to acknowledge other causes of neuropathy than familial amyloidosis [42]. In our study, we revealed a total of 20 (32.8%) patients with a history of alcohol consumption and 30 (49.2%) patients with diabetes after transplantation. Among the studied domino recipients, new onset of diabetes mellitus occurred in 16.4%. Furthermore, neurotoxicity of calcineurin inhibitors is a well-known side effect [43,44]. Therefore, laboratory tests including glucose, glycated hemoglobin, viral serologies (HAV, HBV, HCV and HIV),

Table 3. Neurologic follow-up for domino recipients.

<table>
<tr><td>Baseline
prior to DLT</td><td>One year
after DLT</td><td>Five years
after DLT</td><td>Seven years
after DLT</td><td>Hereafter and in case of neuropathy annually</td></tr>
<tr><td colspan="5">1. Signs of peripheral neuropathy</td></tr>
<tr><td colspan="2">Neuropathic symptom score
Symptom score of the United Kingdom screening test [37,38]</td><td colspan="3">Neurologic examination
Neuropathy impairment score lower limbs [39]</td></tr>
<tr><td colspan="2">• What is the sensation felt?
Burning, numbness, tingling (2 points); fatigue, cramping or aching (1 point).
Maximum is 2 points.
• What is the location of symptoms?
Feet (2 points); calves (1 point); elsewhere (0 point). Maximum is 2 points.
• Have the symptoms ever awakened you at night? Yes (1 point); no (0 point)
• What is the timing of the symptoms?
Worse at night (2 points); present day and night (1 point); present only during the day (0 point).
Maximum is 2 points.
• How are symptoms relieved?
Walking around (2 points); standing (1 point); sitting, lying or no relief (0 point).
Maximum is 2 points.</td><td colspan="3">Muscle groups tested
• Hip flexion and extension
• Knee flexion and extension
• Ankle dorsiflexion
• Ankle plantar flexion
• Toe flexion and extension
Reflexes tested
• Quadriceps femoris
• Triceps surae
Sensory modalities tested
• Touch pressure
• Pinprick
• Vibration
• Joint position</td></tr>
<tr><td colspan="5">2. Quantitative sensory testing including vibration and temperature threshold if available</td></tr>
<tr><td colspan="5">3. Nerve conduction studies (peroneal, tibial and sural nerves)</td></tr>
<tr><td colspan="5">4. Sural nerve biopsy in domino recipients with two or more abnormalities</td></tr>
<tr><td>Symptom score of the United Kingdom Screening test change from baseline ≥ 2 points</td><td>NIS-LL score change from baseline ≥ 2 points</td><td>Significant change in quantitative sensory testing</td><td colspan="2">Nerve conduction studies abnormalities</td></tr>
</table>

DLT, Domino liver transplantation.

Table 4. Scheme to estimate the likelihood of de novo amyloidosis.

Unlikely	Possible	Probable	Confirmed
Less than two abnormalities identified in neurologic evaluation or other conditions, including concurrent illnesses or immunosuppression best explain symptoms and signs of neuropathy	Two or more abnormalities identified in neurologic evaluation and other etiologies of neuropathy could not be ruled out	Two or more abnormalities identified in neurologic evaluation and other etiologies could be ruled out	Two or more abnormalities identified in neurologic evaluation, other etiologies could be ruled out and biopsy proven amyloid

liver and renal function tests, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), vitamin B_1, B_6, B_{12}, vitamin E, folic acid, and serum protein electrophoresis as well as serum levels of immunosuppression are worthwhile [28]. In spite of an extensive work-up, the etiology of neuropathy could not always be identified. Consequently, we developed a scheme to estimate the likelihood of *de novo* amyloidosis for research purposes and physicians, providing diagnostic criteria. Our proposal is presented in Table 4. Thus, the highest likelihood of *de novo* amyloidosis occurred when a combination of neuropathic symptoms (symptom score of the United Kingdom screening test) and signs (NIS-LL, QST, NCS) are accompanied by biopsy proven amyloid and other causes of neuropathy are excluded. In agreement with Lldao *et al.* we recommend sural nerve biopsy to confirm *de novo* amyloidosis [28].

The gastrointestinal evaluation focuses on indigestion, malabsorption, diarrhea, and obstipation. A symptomatic gastrointestinal amyloidosis should be suspected if there are other findings related to FAP. The diagnosis should be confirmed by rectal tissue biopsies. The first study by Bittencourt *et al.* observed no evidence of gastrointestinal amyloid deposition in seven domino recipients after a mean follow-up of 24 months [45]. Takei *et al.* screened and identified gastric mucosal amyloid deposits in two patients 2 years after transplantation, though none of them developed neuropathic symptoms [46].

The cardiologic evaluation focuses on syncopes, orthostatic hypotension and arrhythmia. Electrocardiographic abnormalities are common even in asymptomatic patients. Since none of these findings alone is pathognomonic, a symptomatic amyloid cardiomyopathy should be suspected if there are other findings related to FAP. The earliest echocardiographic abnormality is left ventricular wall thickening with evidence of diastolic dysfunction and a rising brain natriuretic peptide (BNP) [47,48]. In addition, the cardiac involvement could be underlined by gadolinium enhanced cardiovascular magnetic resonance imaging [49].

Selection of domino recipients

The selection of a particular domino recipient depends on a number of factors. Matching for size and blood group are important as well as time on the waiting list, medical urgency and the condition of the donor liver. However, DLT is a highly specialized procedure with the risk of transmitting familial amyloidosis. We suppose a variety of factors to be implicated in the genesis and course of *de novo* amyloidosis, including age, gender, specific mutation within the TTR gene and immunosuppression. Further prospective studies are necessary to evaluate the implication of these factors. After evaluating DLTs in Germany and reviewing the literature, our proposal is to offer domino grafts to recipients older than 60 years. Since the assessment of post-transplant neuropathy is a challenging task, patients diagnosed with diabetes prior to transplantation and risk factors of post-transplant diabetes such as hepatitis C [50,51] and obesity [52] seem to be less favorable. In our opinion, these factors should be taken into account in prioritizing patients for DLT.

Conclusions

In conclusion, DLT is an appropriate alternative for patients who are in need of a liver transplant, but bear the risk of not receiving a deceased donor graft by standard or nonstandard allocation in time. Furthermore, livers from younger donors with FAP may be suitable for splitting, enabling transplantation into two recipients. Although complications of *de novo* amyloidosis can result in significant morbidity, they seemed not to be the leading cause of death after DLT. In domino recipients with confirmed amyloidosis risks and advantages of retransplantation and experimental pharmacologic treatment, i.e., Tafamidis [53], have to be balanced.

This study is limited by a meticulous analysis of data from transplant centers. However, the results of our study, the proposal of an advanced follow-up program with a scheme to estimate the likelihood of *de novo* amyloidosis provide the basis for prospective studies addressing the

accurate onset and incidence of *de novo* amyloidosis. It will be an issue to establish more strict selection criteria defining who qualifies for DLT.

Authorship

FJB: designed research, collected data, analyzed data, and wrote the manuscript. HS: designed research, contributed important data for research, and wrote the manuscript. TB: contributed important data for research. FeB: contributed important data for research. AP: contributed important data for research. JK: contributed important data for research. JS: contributed important data for research. SN: contributed important data for research. GO: contributed important data for research. APB: designed research, contributed important data for research, and wrote the manuscript.

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References

1. Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE. Tabulation of human transthyretin (TTR) variants, 2003. *Amyloid* 2003; **10**: 160.
2. Benson M, Kincaid J. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve* 2007; **36**: 411.
3. Ando Y, Nakamura M, Araki S. Transthyretin-related familial amyloidotic polyneuropathy. *Arch Neurol* 2005; **62**: 1057.
4. Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. *Brain* 1952; **75**: 408.
5. Sousa A, Andersson R, Drugge U, Holmgren G, Sandgren O. Familial amyloidotic polyneuropathy in Sweden: geographical distribution, age of onset, and prevalence. *Hum Hered* 1993; **43**: 288.
6. Herlenius G, Wilczek HE, Larsson M, Ericzon BG. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. *Transplantation* 2004; **77**: 64.
7. Holmgren G, Ericzon BG, Groth CG, *et al.* Clinical improvement and amyloid regression after liver transplantation in hereditary transthyretin amyloidosis. *Lancet* 1993; **341**: 1113.
8. Parrilla P, Ramirez P, Bueno FS, *et al.* Clinical improvement after liver transplantation for type I familial amyloid polyneuropathy. *Br J Surg* 1995; **82**: 825.
9. Pomfret EA, Lewis WD, Jenkins RL, *et al.* Effect of orthotopic liver transplantation on the progression of familial amyloidotic polyneuropathy. *Transplantation* 1998; **65**: 918.
10. Suhr OB, Herlenius G, Friman S, Ericzon BG. Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transpl* 2000; **6**: 263.
11. Adams D, Slama M, Samuel D. Liver transplantation for familial amyloid polyneuropathy. *Presse Med* 2010; **39**: 17.
12. Holmgren G, Steen L, Ekstedt J, *et al.* Biochemical effect of liver transplantation in two Swedish patients with familial amyloidotic polyneuropathy (FAP-met30). *Clin Genet* 1991; **40**: 242.
13. Ericzon BG, Larsson M, Wilczek HE. Domino liver transplantation: risks and benefits. *Transplant Proc* 2008; **40**: 1130.
14. Ericzon BG, Larsson M, Herlenius G, Wilczek HE. Report from the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) and the Domino Liver Transplant Registry (DLTR). *Amyloid* 2003; **10**: 67.
15. Samuel D, Adams D. Domino liver transplantation from familial amyloidotic polyneuropathy donors: how close is the damocles sword to the recipient? *Transpl Int* 2007; **20**: 921.
16. Tojo K, Sekijima Y, Machida K, Tsuchiya A, Yazaki M, Ikeda S. Amyloidogenic transthyretin Val30Met homozygote showing unusually early-onset familial amyloid polyneuropathy. *Muscle Nerve* 2008; **37**: 796.
17. Furtado A, Tome L, Oliveira FJ, Furtado E, Viana J, Perdigoto R. Sequential liver transplantation. *Transplant Proc* 1997; **29**: 467.
18. Furtado A. Domino liver transplantation using FAP grafts. HUC experience – hopes and realities. *Amyloid* 2003; **10**: 84.
19. Schmidt HH, Nashan B, Propsting MJ, *et al.* Familial Amyloidotic Polyneuropathy: domino liver transplantation. *J Hepatol* 1999; **30**: 293.
20. Dept of Transplantation Surgery, Karolinska University Hospital Huddinge. Familial Amyloidotic Polyneuropathy World Transplant Registry and Domino Liver Transplant Registry. 2011. Available at: http://www.fapwtr.org/ram_domino.htm (accessed 02 March 2013).
21. Information about how the Model for End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD), numerical scales that are currently used for liver allocation. MELD/PELD Calculator Q & A. 2009. Available at: http://www.unos.org/ docs/MELD_PELD_Calculator_Documentation.pdf (accessed 17 July 2011).
22. Mazzaferro V, Regalia E, Doci R, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693.

23. Barreiros AP, Geber C, Birklein F, Galle PR, Otto G. Clinical symptomatic de novo systemic transthyretin amyloidosis 9 years after domino liver transplantation. *Liver Transpl* 2010; **16**: 109.
24. Stangou AJ, Heaton ND, Hawkins PN. Transmission of systemic transthyretin amyloidosis by means of domino liver transplantation. *N Engl J Med* 2005; **352**: 2356.
25. Goto T, Yamashita T, Ueda M, *et al.* Iatrogenic amyloid neuropathy in a Japanese patient after sequential liver transplantation. *Am J Transplant* 2006; **6**: 2512.
26. Castaing D, Salloum C, Azoulay D, *et al.* Adult liver transplantation: the Paul Brousse experience. *Clin Transpl* 2007; 145.
27. Adams D, Lacroix C, Antonini T, *et al.* Short Communications. Risk of developing de novo amyloid deposits and induced polyneuropathy in FAP domino liver recipients. *Eur J Neurol* 2009; **16**: 16.
28. Llado L, Baliellas C, Casasnovas C, *et al.* Risk of transmission of systemic transthyretin amyloidosis after domino liver transplantation. *Liver Transpl* 2010; **16**: 1386.
29. Conceicao I, Evangelista T, Castro J, *et al.* Acquired amyloid neuropathy in a Portuguese patient after domino liver transplantation. *Muscle Nerve* 2010; **42**: 836.
30. Obayashi K, Yamashita T, Tasaki M, *et al.* Amyloid neuropathy in a younger domino liver transplanted recipient. *Muscle Nerve* 2011; **43**: 449.
31. Wilczek HE, Larsson M, Yamamoto S, Ericzon B. Domino liver transplantation. *J Hepatobiliary Pancreat Surg* 2008; **15**: 139.
32. Wolff M, Kalff JC, Schwarz NT, *et al.* Liver transplantation in Germany. *Zentralbl Chir* 2003; **128**: 831.
33. Mazzaferro V, Llovet JM, Miceli R, *et al.* Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35.
34. Bispo M, Marcelino P, Marques HP, *et al.* Domino versus deceased donor liver transplantation: Association with early graft function and perioperative bleeding. *Liver Transpl* 2011; **17**: 270.
35. Dyck PJ. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. *Muscle Nerve* 1988; **11**: 21.
36. Dyck PJ, Kratz KM, Lehman KA, *et al.* The Rochester Diabetic Neuropathy Study: design, criteria for types of neuropathy, selection bias, and reproducibility of neuropathic tests. *Neurology* 1991; **41**: 799.
37. Feldman EL, Shefner JM, Dashe JF. Clinical manifestations and diagnosis of diabetic polyneuropathy. 2010. Available at: http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-diabetic-polyneuropathy?source=search_result&selected Title=1%7E102 (accessed 17 July 2011).
38. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993; **36**: 150.
39. Bril V. NIS-LL: the primary measurement scale for clinical trial endpoints in diabetic peripheral neuropathy. *Eur Neurol* 1999; **41**(Suppl. 1): 8.
40. Dyck P. Quantitating severity of neuropathy. In: Dyck P, Thomas P, Griffin J, Low P, Poduslo J, eds. *Peripheral Neuropathy*. Philadelphia: Saunders, 1993: 685.
41. Dyck PJ, O'Brien PC, Kosanke JL, Gillen DA, Karnes JL. A 4, 2, and 1 stepping algorithm for quick and accurate estimation of cutaneous sensation threshold. *Neurology* 1993; **43**: 1508.
42. Yamamoto S, Wilczek HE, Iwata T, *et al.* Long-term consequences of domino liver transplantation using familial amyloidotic polyneuropathy grafts. *Transpl Int* 2007; **20**: 926.
43. Ayres RC, Dousset B, Wixon S, Buckels JA, McMaster P, Mayer AD. Peripheral neurotoxicity with tacrolimus. *Lancet* 1994; **343**: 862.
44. The U.S Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994; **331**: 1110.
45. Bittencourt PL, Couto CA, Leitao RM, *et al.* No evidence of de novo amyloidosis in recipients of domino liver transplantation: 12 to 40 (mean 24) month follow-up. *Amyloid* 2002; **9**: 194.
46. Takei Y, Gono T, Yazaki M, *et al.* Transthyretin-derived amyloid deposition on the gastric mucosa in domino recipients of familial amyloid polyneuropathy liver. *Liver Transpl* 2007; **13**: 215.
47. Klein AL, Hatle LK, Burstow DJ, *et al.* Comprehensive Doppler assessment of right ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol* 1990; **15**: 99.
48. Barreiros AP, Post F, Hoppe-Lotichius M, *et al.* Liver transplantation and combined liver-heart transplantation in patients with familial amyloid polyneuropathy: a single-center experience. *Liver Transpl* 2010; **16**: 314.
49. Di Bella G, Minutoli F, Mazzeo A, *et al.* MRI of cardiac involvement in transthyretin familial amyloid polyneuropathy. *AJR Am J Roentgenol* 2010; **195**: W394.
50. Bigam DL, Pennington JJ, Carpentier A, *et al.* Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. *Hepatology* 2000; **32**: 87.
51. Delgado-Borrego A, Liu YS, Jordan SH, *et al.* Prospective study of liver transplant recipients with HCV infection: evidence for a causal relationship between HCV and insulin resistance. *Liver Transpl* 2008; **14**: 193.
52. Laish I, Braun M, Mor E, Sulkes J, Harif Y, Ben Ari Z. Metabolic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. *Liver Transpl* 2011; **17**: 15.
53. Coelho T, Maia LF, Martins da Silva A, *et al.* Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology* 2012; **79**: 785.

