ORIGINAL ARTICLE

High resource utilization in liver transplantation—how strongly differ costs between the care sectors and what are the main cost drivers?: a retrospective study

Lena Harries[1,2], Harald Schrem[2,3], Jona T. Stahmeyer[1], Christian Krauth[1,2] & Volker E. Amelung[1,2]

1 Institute for Epidemiology, Social Medicine and Health Systems Research, Hannover Medical School, Hannover, Germany
2 Core Facility Quality Management & Health Technology Assessment in Transplantation, Integrated Research and Treatment Center Transplantation, Hannover Medical School, Hannover, Germany
3 Department of General, Visceral and Transplantation Surgery, Hannover Medical School, Hannover, Germany

Correspondence
Lena Harries, Department of Health Economics and Health Policy, Institute of Epidemiology, Social Medicine, and Health System Research (OE 5410); Core Facility Quality Management & Health Technology Assessment in Transplantation, Integrated Research and Treatment Center Transplantation (IFB-Tx), Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany.
Tel.: +49-511-532-6826;
fax: +49-511-532-5347;
e-mail: harries.lena@mh-hannover.de

SUMMARY

To control treatment pathways of transplant patients across healthcare sectors, a profound knowledge of the underlying cost structure is necessary. The aim of this study was to analyze the resource utilization of patients undergoing liver transplantation. Data on resource utilization for 182 liver-transplanted patients was investigated retrospectively. The observational period started with the entry on the waiting list and ended up to 3 years after transplantation. Median treatment cost was 144 424€. During waiting time, median costs amounted to 9466€; 72% of costs were attributed to inpatient care, 3% to outpatient care, and 26% to pharmaceuticals. During the first year after transplantation, median costs of 105 566€ were calculated; 83% were allocated for inpatient and 1% outpatient care, 14% for drugs, and 1% for rehabilitative care. During follow-up after the first year of transplantation, median costs amounted to 20 115€; 75% of these were caused by pharmaceuticals, 21% by inpatient, 4% by outpatient, and <1% by rehabilitative services. Subgroup analyses (e.g., for labMELD scores) were done. Costs incurred by inpatient care and pharmaceuticals are the dominating cost factors. These findings encourage a debate on challenges and improvements for cost-efficient clinical management between different healthcare sectors.

Transplant International 2017; 30: 621–637

Key words
cost analysis, cross-sectoral costs, German healthcare costs, liver transplantation economics, sectors of health care

Received: 10 August 2016; Revision requested: 5 September 2016; Accepted: 7 March 2017

Introduction

Liver transplantation (LTx) is known to be a very resource-intensive therapy. Patients need comprehensive diagnostic evaluation by a multidisciplinary team. Medical care necessitates the availability of highly qualified staff at every daytime. After transplantation (Tx), patients need intensive care treatment while lifelong immunosuppression is mandatory [1–3]. Due to the MELD-based allocation system, most of the patients are transplanted with a MELD score higher than 30, which underlines the necessary medical care while patients are on the waiting list (Figs 1 and 2) [4].

Various stakeholders and institutions across different healthcare sectors are involved in the treatment process (Figs 3 and 4). Within this process, different

doi:10.1111/tri.12950

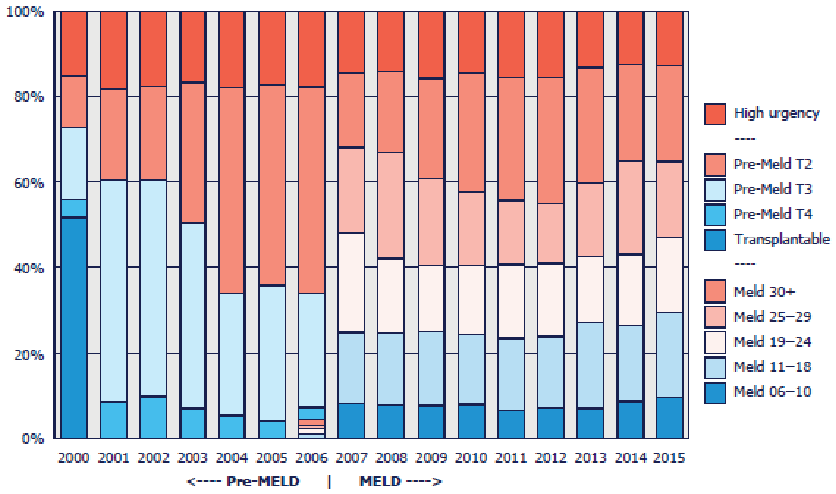

Figure 1 Percentage of deceased donor liver transplants, by recipient urgency at transplant [4]. Due to the MELD-based allocation system, most of the patients are transplanted with a MELD score higher than 30, which underlines the necessary medical care while patients are on the waiting list.

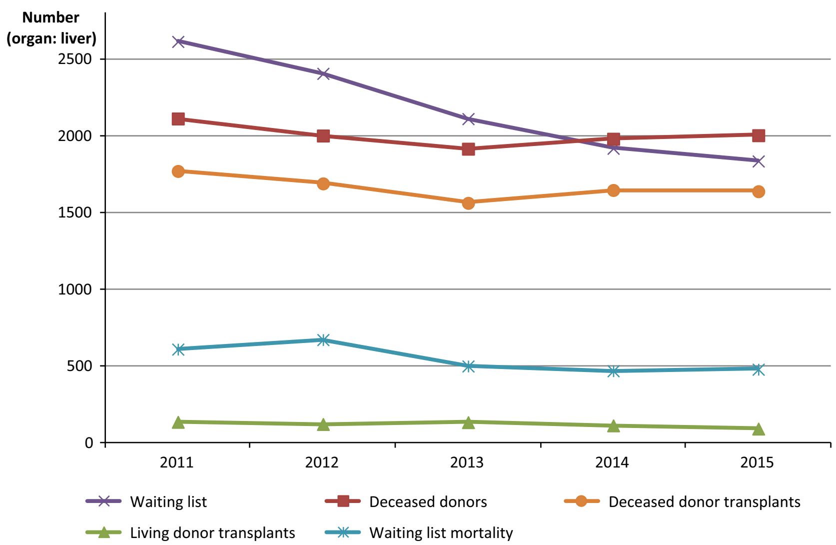

Figure 2 Development in the number of donors and patients on the waiting list for a liver transplant. The number of deceased donor transplants is still lower than the number of patients on the waiting list, even though the number of deceased donors raises slightly [4].

forms of compensation exist though (Fig. 3) [5]. General practitioners (GP) and specialists are reimbursed within the Statutory Health Insurance (SHI) scheme (Einheitlicher Bewertungsmaßstab, EBM) [6]. However, the inpatient pre- to postoperative activities are compensated by the German diagnosis-related groups system (G-DRG) [7]. By contrast to that, the outpatient transplant clinic remunerates on the EBM scheme wherefore a certain authorization of the physicians' association (Kassenärztliche Vereinigung, KV) is required [8].

So far, there is only scarce information available on total treatment costs of liver transplantation. Existing German studies give only an insight into inpatient costs, without providing information on medical services prior to and after the inpatient treatment [1,3,9–12]. In relation to the overall costs, these are of particular interest to understand the complete picture of the healthcare cost structure in liver transplantation.

The aim of this study is to determine inpatient and outpatient costs for LTx including costs for rehabilitation and drugs with a focus on identifying the main cost drivers. The underlying hypothesis of this study is that a more detailed insight into cross-sectoral cost structures of LTx in Germany is necessary to manage, control and improve treatment pathways across healthcare sector interfaces. A profound knowledge of the underlying cost structure is necessary to understand possible incentives as well as the potential for conflict and process optimization to ensure cost-efficient clinical management. We believe that the findings of this study are of general relevance as they indicate quantitative costs that are incurred in different healthcare sectors and treatment phases of liver transplant patients.

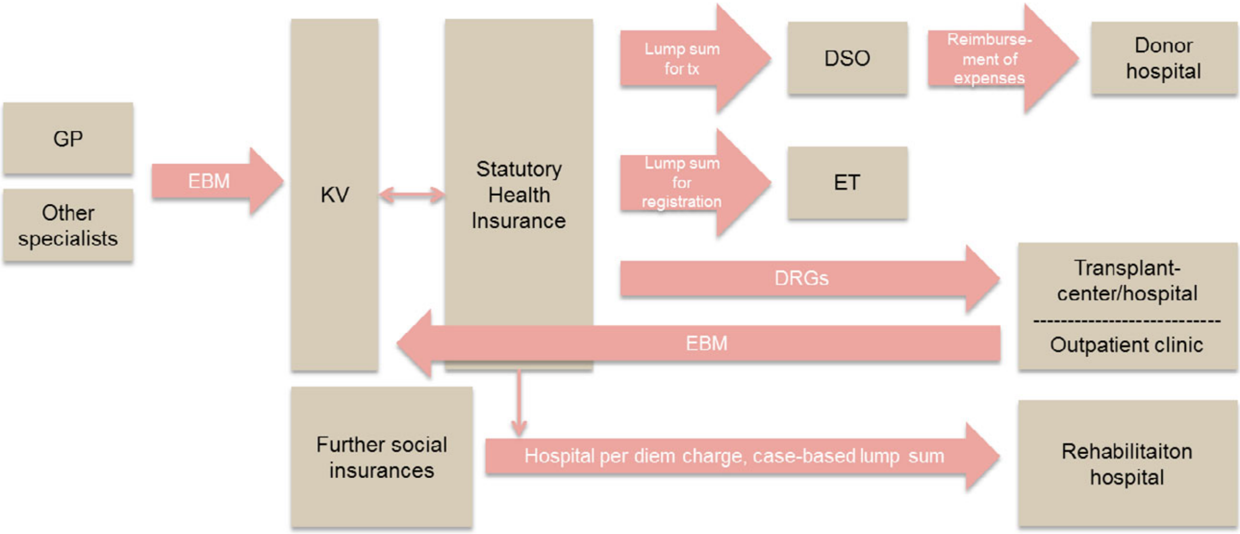

Figure 3 Pattern of finance of organ transplantation and donation for transplantation in Germany. (Source: Own presentation supplemented and based on [7]).

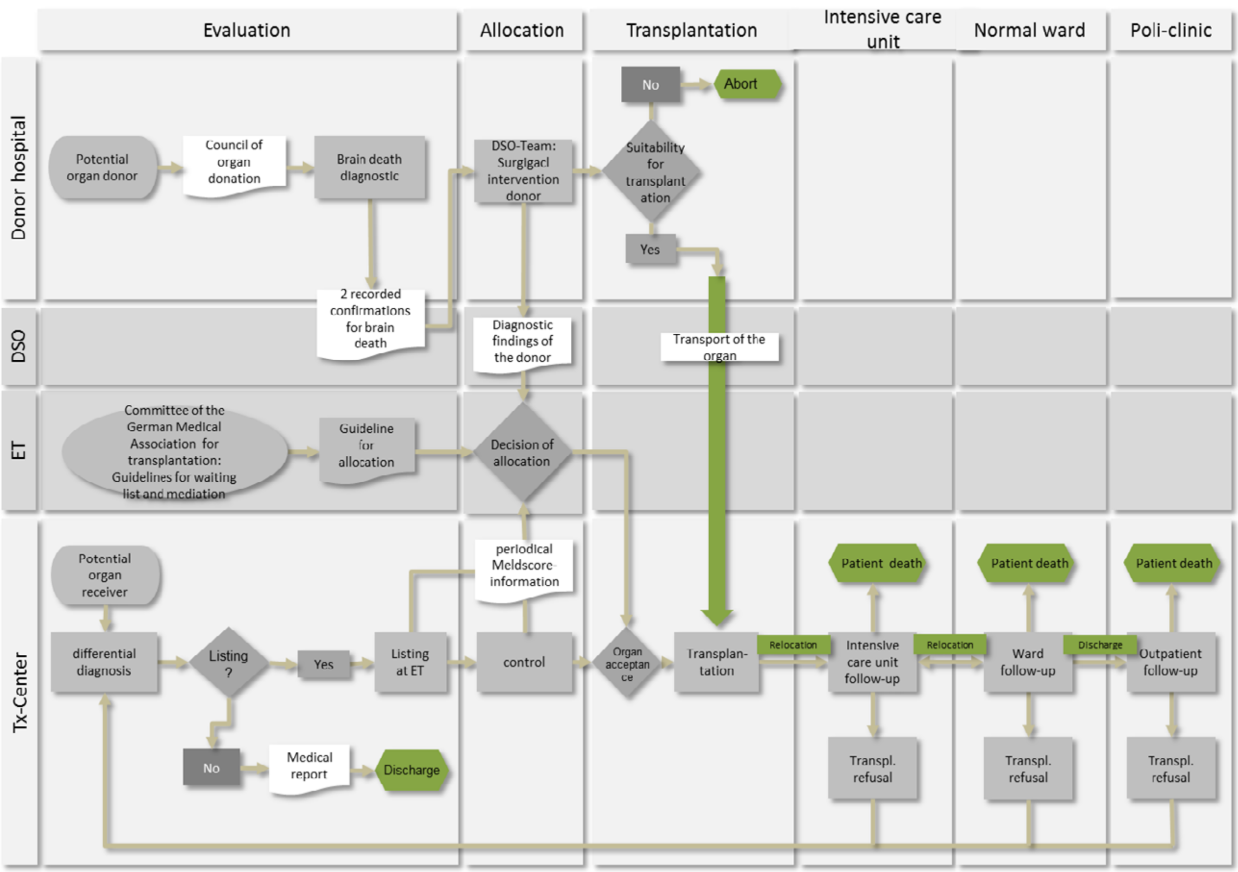

Figure 4 Process map liver transplantation after postmortal donation. ET, eurotransplant; DSO, German foundation for organ transplantation (Deutsche Stiftung für Organtransplantation); Poli-clinic, outpatient clinic. (Source: Own presentation based on the process map of the Core Facility Quality Management and HTA Transplantation of the IFB-Tx (Authors: Carola Stumpp, Torsten Kirsch, Harald Schrem).

Patients and methods

This is a single-center retrospective cohort study from a transplant center in Germany. The Ethics Committee at Hannover Medical School has approved this study and stated that an observational retrospective study with ongoing data collection, according to the Professional Code of the German Medical Association (article B.III. § 15.1), neither informed consent nor approval of the ethics committee was needed.

Inclusion and exclusion criteria

Included were liver recipients (≥18 years) who were transplanted between 01.01.2010 and 31.12.2013 ($n = 212$). Patients with combined transplants were excluded ($n = 11$), while patients who were transplanted with another organ earlier or later were included into analysis. As this study was conducted from the perspective of the SHI System, 18 patients who were not covered by this system were excluded from analysis due to a lack of available data for analysis. One additional patient had to be excluded due to loss to follow-up. Data of 182 patients were finally available for analysis.

Observational period

The observational period starts with the entry on the waiting list and ends 3 years after transplantation, with the date of death or on the 31.12.2015. In Germany, it is obligatory to report survival rates up to 3 years after transplantation for quality assurance purposes, so we used this to justify the end of our observational period [13,14].

The observational period was segregated into three time frames

1. T1 starts with the entry on the waiting list until transplantation;
2. T2 comprises the first year after transplantation;
3. T3 starts after the first after transplantation year until the end of follow-up.

If a patient had a subsequent liver retransplant, we used the date of the first transplant as the reference for analyzed time frames. For each time frame, we collected the services a patient received at the following healthcare sectors (Table 1):

1. Outpatient clinical care;
2. Inpatient hospital care;
3. Inpatient rehabilitation.

Table 1. Database.

Sector	Data
Outpatient care	Clinic: • Date of visit • Scheduled fee position • The price associated with the fee • Department in which the service was performed Drugs: • Date of outpatient visit and prescription of immunosuppressants • Pharmaceuticals prescribed from a local physician • Dose
Inpatient care	• Date of admission and discharge • The G-DRG-code and associated price of the stay • Discount and surcharges depending on the length of hospitalization • Any other surcharges besides the G-DRG-flat rate Drugs: • Are included within the G-DRG-flat rate
Rehabilitation care	• Number of days spent in a rehabilitation clinic Drugs: • Prescriptions are considered when documented at outpatient care

Database and cost calculation

The clinical and demographic data were retrieved from patient records. Besides the sociodemographic data, we extracted the allocation MELD scores, the type of transplanted graft (split liver, partial, reduced size, or full size graft), living-related versus postmortem donation after brain death, the indication for transplantation, and whether the patient received one or more transplants during follow-up.

Data on prescribed drugs, hospitalizations, services in the outpatient transplant clinics and days of rehabilitation were systematically extracted using several clinical information systems and files. Prescribed drugs were classified into immunosuppressants and other pharmaceuticals.

Outpatient clinical care included the services a patient received at a doctor visit in terms of a scheduled fee position which was derived from the German Doctors' Fee Scale [15].

Costs of any drug prescribed at the outpatient service were taken from the German Medical Prescriptions Record [16] or if not applicable, from the database of the Lauer-Taxe (German reference work for prices of pharmaceuticals) [17]. These were derived in relation to the prescribed dose and number of days until the next date of visit. If no further date of visit was available, we used the calculated average days between visits.

Hospitalization costs were calculated using the G-DRG system [18]. The G-DRG-codes A01A, A01B, A01C, A18Z (see Table 2 for definitions) are relevant for reimbursement for LTx and were available for all analyzed cases. Discount and surcharges depending on the length of hospitalization were applied.

The prices for the days of rehabilitation were taken from the report of the Federation of German Pension Insurance Institutions. In 2013, the costs for medical rehabilitation for the direct treatment of a physical illness were amounted to 2685€ for a single patient [19]. The average duration of a stay in a rehabilitation clinic was 23.5 days. So 1 day of rehabilitation amounted to 114.26€. All costs which were provided through the data (Table 1) refer to the year in which they were accounted. All other costs refer to the price year 2013, as this was the year of the data cut.

Statistical analyses

Statistical analyses were carried out with JMP® PRO 11.2.0 (SAS Institute Inc., Cary, NC, USA). The two-sided Student's *t*-test was used for nominal dependent and analysis of variance (ANOVA) for continuous-dependent outcome parameters. Univariable linear regression was used where appropriate. The level of significance was defined as $P < 0.05$.

Results

Patient characteristics

Among 182 analyzed patients, the median pre-transplant labMELD score was 16.5. The most frequent diagnosis leading to transplantation was a hepatocellular carcinoma (HCC) (23.6%), followed by alcoholic cirrhosis of liver (13.2%). Sixteen patients were retransplanted once, while one patient was retransplanted twice. The mean age was 49.3 years, and 54.4% of patients were male; 94.5% of patients were transplanted with a full size organ and there were no living donations (Table 3).

Table 2. Definitions of most frequent G-DRG-codes.

DRG-code	Definition
A01A	Liver transplantation with mechanical ventilation >179 h
A01B	Liver transplantation with mechanical ventilation >59 and <180 h or acute graft rejection or combined kidney transplantation
A01C	Liver transplantation with mechanical ventilation >59 h without graft rejection, without combined kidney transplantation
A18Z	Mechanical ventilation >999 h and transplantation of the liver, lung, heart, and bone marrow or stem cell transfusion
A60C	Failure and rejection of a transplanted organ, more than 1 day of an inpatient stay, without removal of a transplanted organ, without complex operation room procedure, without very severe CC, age >15 years
A60D	Failure and rejection of a transplanted organ, 1 day of an inpatient stay
A64Z	Inpatient evaluation for liver or kidney—pancreas transplantation
H41A	Complex therapeutic ERCP with very severe CC or photodynamic therapy
H41B	Complex therapeutic ERCP with severe CC, without photodynamic therapy or age <16 years or complex intervention
H41C	Complex therapeutic ERCP without very severe or severe CC, without photodynamic therapy, age >15 years, without complex intervention, or other ERCP
H60Z	Cirrhosis of the liver and certain non-infectious hepatitis with very severe CC
H61B	Malignant neoplasm of the hepatobiliary system and pancreas, 1 day of an inpatient stay or without complex diagnosis or without very severe CC, without portal vein thrombosis
H63A	Liver disease other than malignant neoplasm, cirrhosis of the liver, and certain non-infectious hepatitis, more than 1 day of an inpatient stay, complex diagnosis and very severe or severe CC, or complex diagnosis or very severe or severe CC, age <1 year
H64Z	Disorders of gallbladder and biliary tract
Z64B	Other factors influencing health status and treatment after an completed treatment without radioiodine diagnostic, with a certain occasion for contact
Z64C	Other factors influencing health status and treatment after an completed treatment without radioiodine diagnostic, without a certain occasion for contact

Table 3. Shown are the patient characteristics. Binary data given in frequency (*n*) and percent (%), and continuous data described with mean, standard deviation (SD), median and range.

Variables	*n* (%)	Mean	SD	Median	Range
Age ≥18		49.3	11.4		
Sex					
F	83 (45.6)				
M	99 (54.4)				
Re-transplantation					
0	165 (90.6)				
1	16 (8.8)				
2	1 (0.5)				
labMELD	182 (100)	21.8	12.6	16.5	6–40
excMELD	91 (50)	31.1	4.87	31	20–40
matchMELD	182 (100)	30.8	8.43	32	6–40
Type of graft					
Split	5 (2.7)				
Reduced	2 (1.1)				
Partial	3 (1.6)				
Full size	172 (94.5)				
Type of donor					
Deceased	182 (100)				
Most frequent diagnoses for Tx					
Hepatocellular carcinoma	43 (23.6)				
Alcoholic cirrhosis of liver	25 (13.7)				
Primary sclerosing cholangitis	19 (10.4)				
Acute and subacute liver failure	18 (9.9)				
Viral cirrhosis	17 (9.3)				
Cryptogenic cirrhosis	15 (8.2)				
Polycystic disease	13 (7.1)				
Other	12 (6.6)				
Re-Tx	8 (4.4)				
Budd–Chiari syndrome	6 (3.3)				
Inherited metabolic disorder	6 (3.3)				

The median length of the observational period was 1183 days (range: 6–4347 days). The median waiting time (T1) for transplantation was 227 days (range: 2–3251 days). In T2, 50% of the patients spend up to 365 days (range: 1–365 days) and in T3 up to 731 days (range: 0–731 days). Thirty-five patients died after transplantation (19.2%). Of these deceased patients, 29 died during T2 (82.9%) and six during T3 (17.1%). After the observational period, four more patients died without their death influencing the results of the cost calculations in this study.

Costs per time frame

Complete observational period

The total amount of costs for all patients was 36 118 547€, with median costs that amounted to 144 424€ (Table 4, Fig. 5). The duration of the observational period did not have a significant influence on overall costs ($P = 0.20$, ANOVA).

Females incurred lower median treatment costs (135 010€) as compared to males (154 923€) without reaching statistical significance ($P = 0.61$, two-sided *t*-test).

The labMELD score at the time of allocation had no significant influence on overall treatment costs ($P = 0.11$, ANOVA).

The age of the recipient at the time of transplantation had a significant influence on overall costs ($P = 0.02$, ANOVA) (Fig. 6). The increase in median overall costs was calculated to increase by 2155€ for every year the organ recipients were 1 year older at the time of transplant (Fig. 6).

Patients with subsequent retransplants incurred significantly higher overall costs: 241 283€ (range: 128 795–507 586€) compared to 139 434€ (range: 16 162–887 418€) for patients without subsequent retransplants ($P = 0.02$, two-sided *t*-test).

Table 4. Overall costs per time frame and sector of care.

Sector	T1 (waiting time) Median € (range) Median US$* (range)	T1 Mean € (95% CI) Median US$* (range)	T1 % Of total	T2 (transplant year) Median € (range) Median US$* (range)	T2 Mean € (95% CI) Median US$* (range)	T2 % Of total	T3 (2 years post T2) Median € (range) Median US$* (range)	T3 Mean € (95% CI) Median US$* (range)	T3 % Of total	Total Median € (range) Median US$* (range)	Total Mean € (95% CI) Median US$* (range)	Total % Of total
Outpatient	130 (0–3930) 143 (0–4317)	338 (253–423) 371 (278–465)	3	1484 (0–4819) 1630 (0–5293)	1465 (1303–1626) 1609 (1431–1786)	1	1570 (0–5697) 1724 (0–6257)	1682 (1487–1877) 1847 (1633–2062)	4	3511 (0–8791) 3856 (0–9656)	3485 (3130–3839) 3828 (3438–4217)	2
Inpatient	6294 (0–73 759) 6680 (0–78 284)	9483 (7720–11 246) 10 065 (8194–11 936)	72	75 531 (9051–75 531) 80 165 (9606–80 165)	122 156 (105 529–138 784) 129 650 (112 003–147 298)	83	732 (0–285 017) 777 (0–302 502)	8318 (4349–12 287) 8828 (4616–13 041)	21	94 902 (12 486–616 857) 100 724 (13 252–654 699)	139 958 (122 479–157 437) 148 544 (129 993–167 096)	71
Immuno-suppressive drugs	– –	– –	–	6576 (0–27 260) 6979 (0–28 932)	7964 (7116–8812) 8453 (7553–9353)	5	10 602 (0–46 616) 11 253 (0–49 476)	11 130 (9805–12 455) 11 813 (10 407–13 219)	29	16 838 (0–66 704) 17 871 (0–70 796)	19 095 (17 138–21 051) 20 266 (18 189–22 342)	10
Other drugs	175 (0–50 538) 185 (0–53 404)	3377 (2296–4458) 3580 (2434–4726)	26	5356 (0–193 110) 5678 (0–204 722)	13 868 (9328–18 408) 17 702 (9889–19 515)	9	2590 (0–379 036 2746 (0–401 827)	17 728 (9272–26 183) 18 794 (9830–27 757)	46	11 397 (0–555 236) 12 082 (0–588 622)	34 973 (22 808–47 139) 37 076 (24 179–49 974)	18
Rehabilitation	– –	– –	–	0 (0–6856) 0 (0–7268)	930 (726–1133) 985 921 (770–1201)	1	0 (0–2399) 0 (0–2543)	13 (–13 to 39) 14 (–14 to 41)	0.03	0 (0–6856)	943 (739–1147)	0.004
Total	9466 (0–76 374) 10 035 (0–80 966)	13 199 (10 914–15 483) 13 993 (11 570–16 414)	100	105 566 (10 054–612 605) 111 914 (10 659–649 441)	146 383 (129 427–163 340) 155 185 (137 209–173 162)	100	20 115 (0–402 181) 21 325 (0–426 364)	38 871 (29 337–48 406) 41 208 (31 101–51 317)	100	144 424 (16 162–887 418) 153 108 (17 133–940 778)	198 454 (176 904–220 003) 210 387 (187 541–233 232)	100
Additional information												
Patients (*n*)	182			182			153			182		
Mortality (*n* (%))	–			29 (15.9)			6 (3.3)			35 (19.2)		
Median/mean days of observation	227/470			365/320			731/573			1183/1364		

*Currency translation done on 24.11.2016 on https://www.oanda.com/lang/de/currency/converter/, 1 EUR = 1.06013 USD.

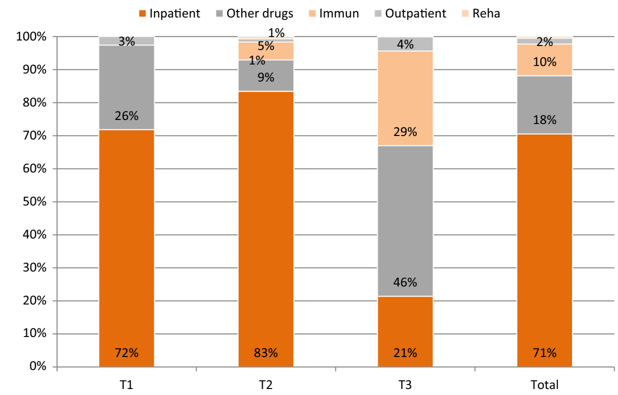

Figure 5 Overall costs per time frame.

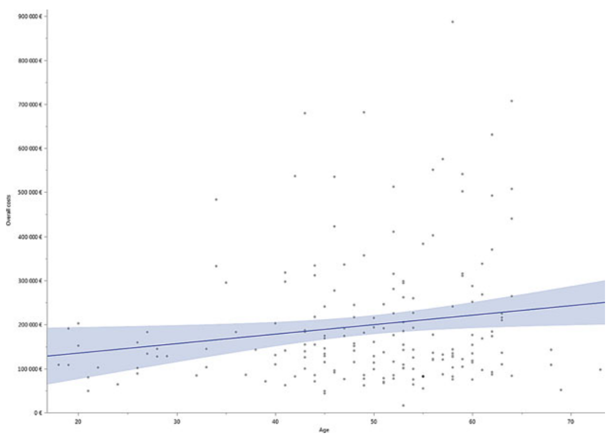

Figure 6 Overall costs and age. The graphs show the results of linear regression analysis with a 95% CI (shadowed areas). The graph pictures clearly the influence of the age of the overall costs ($P = 0.02$) during the whole observational period.

Waiting time (T1)

With a longer time on the waiting list, treatment costs rose significantly ($P < 0.01$, ANOVA). Total costs for all patients amounted to 2 402 164€, with a median of 9466€. The most cost-intensive part was caused by inpatient stays with a total sum for all patients of 1 725 939€ (72%) with the median of costs at 6294€. The outpatient service costs summed up for all patients to 61 538€ (3%) with median costs at 130€. All patients received medications amounting to 614 686€ (26%) with a median of costs at 175€ (Table 4).

The labMELD score at the time of donor organ allocation had a significant influence on overall treatment costs in T1. Patients with a lower labMELD score incurred higher costs as compared to patients with a higher labMELD score ($P = 0.01$, ANOVA). Patients with a higher labMELD score had significantly shorter waiting times ($P < 0.001$, ANOVA) and therefore caused lower costs.

Primary sclerosing cholangitis (PSC) leading to transplantation was accountable for the highest median costs in T1 (22 771€), followed by patients with a subsequent transplantation (21 461€) and the indication of HCC (13 521€) (Table 5).

Post-transplant year (T2)

During the second time frame, overall costs of 26 641 777€ were accrued (median costs: 105 566€). For inpatient care, the total amount was 22 232 459€ (83%) with median costs at 75 531€. The outpatient service did amount to 266 560€ in total (1%) (median: 1484€). Above that, for all patients together 1 449 496€ (5%) were spent on immunosuppressants and 2 524 043€ (9%) on other medications (median: 6576€ and 5356€, respectively); 36.8% of the patients had an inpatient rehabilitation after transplantation. In total, this service amounted to 169 219€, with an average value of 930€ (median: 0€; most of the patients did not receive a rehabilitation program and were thus taken into account with 0€) (Table 4).

In contrast to T1, patients with higher labMELD scores incurred higher costs as compared to patients with lower labMELD scores during T2 ($P = 0.01$, ANOVA) (Fig. 7). Patients who died during follow-up (19.2%) incurred significantly higher costs (median: 159 321€, range: 10 054–495 351€) as compared to surviving patients (80.8%) (median: 91 057€, range: 29 103–612 605€) ($P = 0.01$, two-sided t-test) (Fig. 8). This is due to the fact that deceased patients typically required intensive medical care before they die. The majority (82.9%) died after a median of 88 days after transplantation (mean: 132 days).

The indication which led to the highest median costs during T2 was cryptogenic cirrhosis (159 298€). Patients with viral cirrhosis were accountable for the second highest costs (137 800€), while HCC led to median costs of 28 464€ (Table 5).

Follow-up after the transplantation year (T3)

A longer duration of T3 was associated with significantly higher treatment costs ($P = 0.01$, ANOVA). A total amount of 7 074 607€ was accrued, with a median of 20 115€; 46% of this sum was caused by costs for prescribed drugs (3 226 439€), and 29% of total costs for all patients was caused by expenses for immunosuppressive drugs (2 025 726€). For inpatient treatments, a

Table 5. Costs of indications groups per time frame (T1–T3) and sectors of care.

Indication group	Time frame and sector							
					Outpatient care			
	T1	T2	T3	Inpatient Care	Clinic	Immunosuppression	Other drugs	Rehabilitation
	Median € (IQR)							
	Median US$ (IQR)*							
Acute and subacute liver failure	0 (0)	127 339 (109 004)	21 228 (28 676)	114 689 (108 731)	3426 (3556)	21 009 (25 638)	10 474 (10 527)	1885 (3199)
	0 (0)	134 996 (115 558)	22 504 (30 400)	121 585 (115 269)	3632 (3770)	22 272 (27 180)	11 104 (11 160)	1998 (3391)
Alcoholic cirrhosis	6108 (13 895)	131 913 (152 891)	0 (19 164)	131 913 (169 129)	514 (3523)	11 542 (20 569)	3740 (9222)	0 (0)
	6475 (14 731)	139 845 (162 084)	0 (20 316)	139 845 (179 299)	545 (3735)	12 236 (21 806)	396 (9777)	0 (0)
Budd–Chiari syndrome	9568 (23 019)	67 379 (74 257)	31 655 (16 925)	64 900 (80 179)	5729 (2327)	35 686 (6504)	6865 (7257)	0 (3114)
	10 143 (24 403)	71 431 (78 722)	33 558 (17 943)	68 802 (85 000)	6073 (2467)	37 832 (6895)	7278 (7693)	0 (3301)
Cryptogenic cirrhosis	0 (15 074)	159 298 (196 291)	18 604 (14 306)	157 380 (191 812)	4173 (5294)	10 656 (11 435)	8295 (11 523)	0 (2400)
	0 (15 980)	168 877 (208 094)	19 723 (15 166)	166 843 (203 346)	4424 (5612)	11 297 (12 123)	8794 (12 216)	0 (2544)
Inherited metabolic disorder	180 (9904)	79 014 (105 571)	23 094 (44 729)	59 313 (105 560)	2547 (4274)	16 060 (38 446)	6717 (14 558)	286 (3399)
	191 (10 500)	83 765 (111 919)	24 483 (47 419)	62 880 (111 907)	2 700 (4 531)	1703 (40 758)	7121 (15 433)	303 (3603)
Hepatocellular carcinoma	13 521 (10 520)	103 994 (143 624)	28 464 (39 693)	93 156 (100 774)	3317 (4260)	15 941 (12 672)	17 819 (34 170)	0 (2400)
	14 334 (1115)	110 247 (152 260)	30 176 (42 080)	98 757 (106 834)	3516 (452)	16 900 (13 434)	18 890 (3622)	0 (2544)
Other	0 (4951)	117 805 (141 999)	21 523 (16 000)	102 099 (178 467)	3030 (3577)	20 707 (17 725)	11 171 (14 486)	0 (2057)
	0 (5249)	124 889 (150 537)	22 817 (17)	108 238 (189 198)	321 (3792)	21 952 (18 791)	11 843 (15 357)	0 (2181)
Polycystic disease	7735 (7937)	57 554 (15 867)	19 558 (11 056)	42 907 (19 468)	3788 (3090)	21 480 (13 317)	13 251 (14 553)	0 (2400)
	8200 (8414)	61 015 (16 821)	20 734 (11 721)	45 487 (20 639)	4016 (328)	2277 (14 118)	14 048 (15 428)	0 (2544)
Primary sclerosing cholangitis	22 771 (23 601)	76 571 (86 007)	23 510 (32 398)	78 184 (81 929)	4447 (2926)	17 000 (17 345)	19 512 (26 629)	0 (2400)
	24 140 (25 020)	81 175 (91 179)	2492 (34 346)	82 885 (86 855)	4714 (3102)	18 (18 388)	20 685 (28 230)	0 (2544)
Re-Tx	21 461 (39 581)	125 480 (119 938)	16 247 (24 940)	143 597 (143 420)	3150 (3458)	22 045 (29 072)	3103 (4952)	0 (2400)
	22 751 (41 961)	13 303 (127 150)	17 224 (2644)	152 231 (15 204)	334 (3666)	23 371 (30 820)	3290 (5250)	0 (2544)
Viral cirrhosis	12 130 (35 044)	137 800 (176 817)	29 222 (83 952)	131 190 (116 408)	3750 (3748)	14 949 (13 809)	42 805 (136 710)	0 (1086)
	1286 (37 151)	1461 (187 449)	30 979 (89 000)	13 908 (123 408)	398 (3973)	15 848 (14 639)	45 379 (144 930)	0 (1151)

*Currency translation done on 24.11.2016 on https://www.oanda.com/lang/de/currency/converter/, 1 EUR = 1.06013 USD.

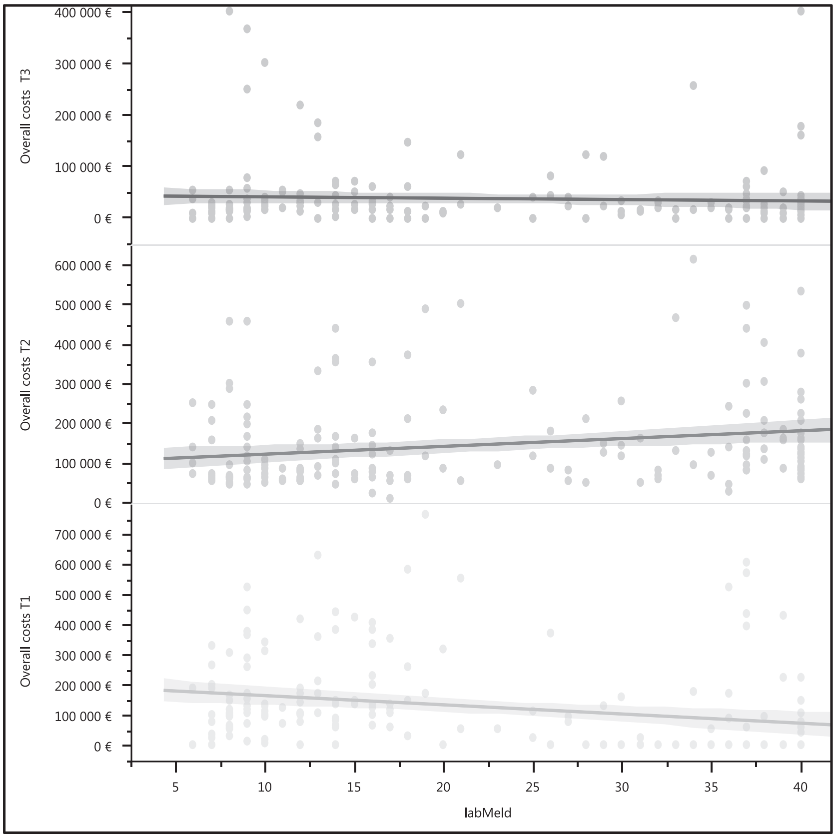

Figure 7 Overall costs per time frames T1–T3 and labMELD. The graphs show the results of linear regression with a 95% CI (shadowed areas). The analysis illustrates the influence of the labMELD score of the overall costs during the waiting time (T1) ($P = 0.01$), the transplant year (T2) ($P = 0.01$), and 2 years after T2 (T3) ($P = 0.49$).

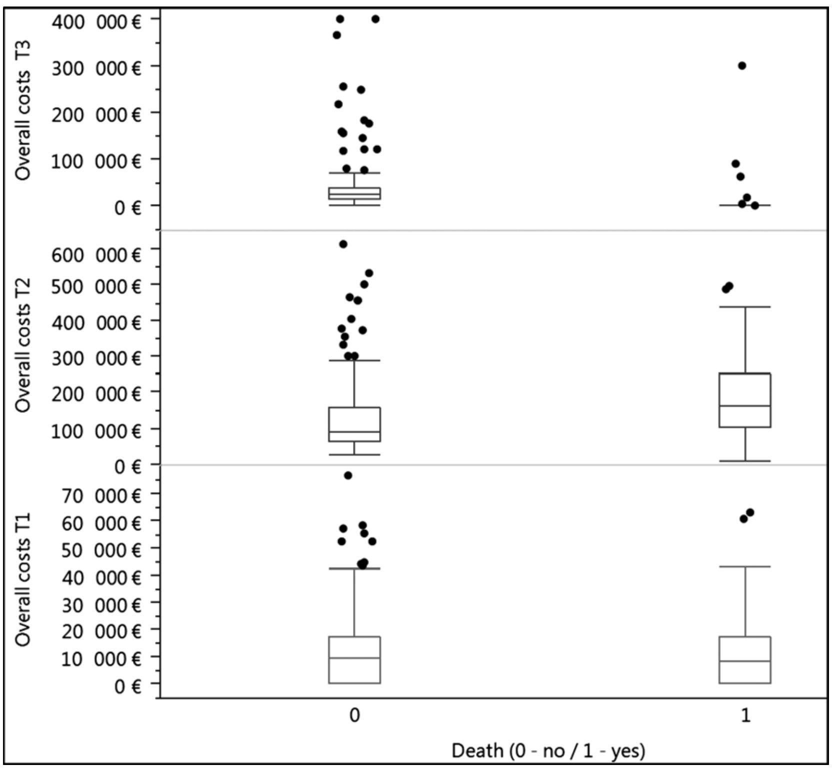

Figure 8 Overall costs and death during waiting time (T1), the transplant year (T2), and 2 years after T2 (T3). The overall costs are presented as boxplots. The difference of costs incurred by deceased versus surviving patients was significantly higher for deceased patients in T2 ($P = 0.01$) while costs were significantly lower for deceased patients in T3 ($P = 0.01$). This difference was not significant in T1 ($P = 0.97$). As a consequence of the inclusion criteria for this study, no deaths were reported during T1 (time on the waiting list for transplantation).

total of 1 513 955€ (21%) was incurred. The costs for the outpatient service in this period amounted to 306 087€ (4%) (Table 4).

During T3, the pre-transplant labMELD score had no significant influence on the overall costs ($P = 0.49$, two-sided *t*-test) (Fig. 7). Patients who died during follow-up incurred significantly lower treatment costs compared to surviving patients ($P = 0.01$, two-sided *t*-test) going along with a shorter follow-up time in T3 for deceased patients (median: 0 days, range: 0–554; mean: 32 days) (Fig. 8).

Patients with Budd–Chiari syndrome as underlying disease incurred the highest median costs during T3 (31 655€), while viral cirrhosis led to median costs of 29 222€ and HCC to 28 464€ (Table 5).

Costs per sector

Inpatient care

The most frequent (≥5%) G-DRG-codes reflecting hospitalization treatment costs during each time frame T1–T3 are represented in Table 6.

The labMELD score at the time of donor organ allocation had a significant influence on inpatient overall costs. Higher labMELD scores incurred significantly higher costs ($P = 0.01$, ANOVA) (Fig. 9).

Patients with cryptogenic cirrhosis as underlying disease incurred the highest median costs at 157 380€ during inpatient care, followed by those patients with a subsequent liver retransplantation (143 597€) and an alcoholic cirrhosis (131 913€) (Table 5).

Waiting time (T1). During T1, clinical evaluation for transplantation (G-DRG: A64Z) accounted for the highest costs, with a total amount of 544 610€. A further cost-intensive factor during inpatient stay was complex endoscopic retrograde cholangiopancreatography (ERCP) amounting to 274 916€. Hereby, PSC was the most frequent indication (45%) leading to ERCP. The indications viral cirrhosis (41%), HCC (23%) and PSC, cryptogenic cirrhosis, and alcoholic cirrhosis accounted together for the third biggest amount of costs (90 036€ in total) and are presented through the G-DRG-code H63A (Table 6).

Lower allocation labMELD scores were associated with significantly higher inpatient costs in T1 ($P = 0.03$, ANOVA), which is due to usually longer treatment durations.

Post-transplant year (T2). The G-DRG-codes which account for the biggest cost part with a total sum of 20 594 702€ are shown in Figure 10. The main indications for the most expensive G-DRG-code (A18Z) were HCC (27%) and alcoholic cirrhosis (27%). For the second most cost-intensive code A01A, HCC (20%) and an acute and subacute liver failure (20%) were the main indications. HCC (24%) and viral cirrhosis led to the third most cost-intensive code A01B, while HCC (25%) and a PSC (15%) were most accountable for the G-DRG-code A01C.

After the costs for the transplant procedure, the most cost-intensive codes were for different ERCP interventions, representing a total amount of 299 787€. Hereby, liver malignancy was the main diagnosis group (45%) leading to ERCP. Graft failure or rejection led to the third most cost-intensive code (in total 129 483€) (Table 6).

During T2 higher allocation, labMELD scores incurred significantly higher inpatient costs ($P < 0.01$, ANOVA).

Follow-up after the first post-transplant year (T3). The majority of costs for hospital treatments were incurred through ERCP interventions, which were mainly (41%) associated with liver malignancy (total costs: 267 140€). Treatment for graft failure and rejection accounted for the second most cost-intensive treatments in T3 (89 053€), while other factors represented the rest (44 970€) (Table 6).

The allocation labMELD scores had no significant influence ($P = 0.73$, ANOVA) on inpatient costs during the third time frame (T3).

Outpatient care

In contrast to inpatient care, lower allocation labMELD scores had a significant influence on higher outpatient costs ($P = 0.05$, ANOVA) (Fig. 9). Split by different investigated time frames T1, T2, and T3, this relationship was statistical significant during waiting time (T1) ($P < 0.01$, ANOVA) but not during T2 and T3 ($P = 0.14$; $P = 0.39$, ANOVA).

Patients with Budd–Chiari syndrome as underlying disease were accountable for the highest median costs during outpatient care (5729€), followed by patients with PSC (4447€) and cryptogenic cirrhosis (4173€) (Table 5).

During outpatient care, the total costs for immunosuppression after transplantation in T2 and T3 were 3 475 222€, with a median of 16 838€ (range: 0–66 704€). Table 7 summarizes the costs for the most commonly used immunosuppressive drugs.

About 1500 different medications other than immunosuppression were analyzed. Some patients received very expensive medications for a long duration due to the nature of their underlying chronic disease, such as a viral hepatitis B or C (Table 5). The ten most cost-intensive pharmaceuticals before and after transplantation administered during outpatient treatment are

Table 6. Most frequent (≥5%) G-DRG-Codes and hospital treatment costs* during each time frame.

T1 (waiting time)					T2 (transplant year)					T3 (Two years post T2)				
G-DRG-code		% Of all G-DRG-codes	Median € (range) Median US$ (range)*	Mean € (95% CI) Median US$ (range)*	G-DRG-code		% Of all G-DRG-codes	Median € (range) Median US$ (range)*	Mean € (95% CI) Median US$ (range)*	G-DRG-code		% Of all G-DRG-codes	Median € (range) Median US$ (range)*	Mean € (95% CI) Median US$ (range)*
Evaluation	A64Z	18.29	5789 (778–60 685) 6137 (825–64 334)	6894 (6184–7603) 7309 (6556–8060)	Liver transplantation	A01A	8.44	124 510 (97 766–303 504) 131 997 (103 645–321 754)	140 564 (130 747–150 382) 149 016 (138 609–159 424)	ERCP	H41A	9.38	5839 (2283–7544) 6190 (2420–7998)	5093 (4041–6146) 5399 (4284–6516)
ERCP	H41A	7.64	5135 (3045–8934) 5444 (3228–9471)	4878 (3781–5976) 5171 (4008–6335)		A01B	11.32	53 367 (20 919–157 380) 56 576 (22 177–166 843)	61 144 (52 668–69 620) 64 821 (55 835–73 806)		H41B	4.86	3930 (1731–5231) 4166 (1835–5546)	4065 (2603–5527) 4309 (2760–5859)
	H41C	12.04	2284 (738–3812) 2421 (782–4041)	2191 (1317–3065) 2323 (1396–3249)		A01C	12.76	36 373 (10 054–106 719) 38 560 (10 659–113 136)	41 846 (33 862–49 830) 44 362 (35 898–52 826)		H41C	10.07	2516 (1008–4429) 2667 (1069–4695)	2418 (1402–3434) 2563 (1486–3640)
Liver disease	H63A	5.09	4309 (2333–4494) 4568 (2473–4764)	4093 (2748–5437) 4339 (2913–5764)		A18Z	5.35	323 655 (197 352–598 949) 343 116 (209 219–634 964)	341 314 (328 986–353 642) 361 837 (348 768–374 906)	Graft failure	A60C	5.90	3426 (2347–15 614) 3632 (2488–16 553)	3969 (2642–5295) 4208 (2801–5613)
Liver cirrhosis	H60Z	7.87	3969 (1164–4298) 4208 (1234–4556)	3053 (1972–4135) 3237 (2091–4384)	ERCP	H41A	8.23	5857 (2144–11 543) 6209 (2273–12 237)	5527 (−4412 to 15 466) 5859 (−4677 to 16 396)		A60D	6.60	1180 (1008–1205 1251 (1069–1277)	1136 (−118 to 2391) 1204 (−125 to 2535)
Gallbladder disorder	H64Z	5.09	1600 (403–3555) 1696 (427–3769)	1266 (−78 to 2610) 1342 (−83 to 2767)		H41C	7.20	2284 (867–2742) 2421 (919–2907)	2249 (−8377 to 12 874) 2384 (−8881 to 13 648)	Other factors	Z64B	5.90	1199 (732–1753) 1271 (776–1858)	1155 (−172 to 2481) 1224 (−182 to 2630)
Malignant neoplasm	H61B	4.86	794 (671–2814) 842 (711–2983)	1326 (−50 to 2702) 1406 (−53 to 2864)	Graft failure	A60C	8.03	3426 (2347–4577) 3632 (2488–4852)	3320 (−6746 to 13 386) 352 (−7152 to 14 191)		Z64C	7.29	1157 (1153–2061) 1227 (1222–2185)	1754 (−24 to 3483) 1859 (−25 to 3692)

*Currency translation done on 24.11.2016 on https://www.oanda.com/lang/de/currency/converter/, 1 EUR = 1.06013 USD.

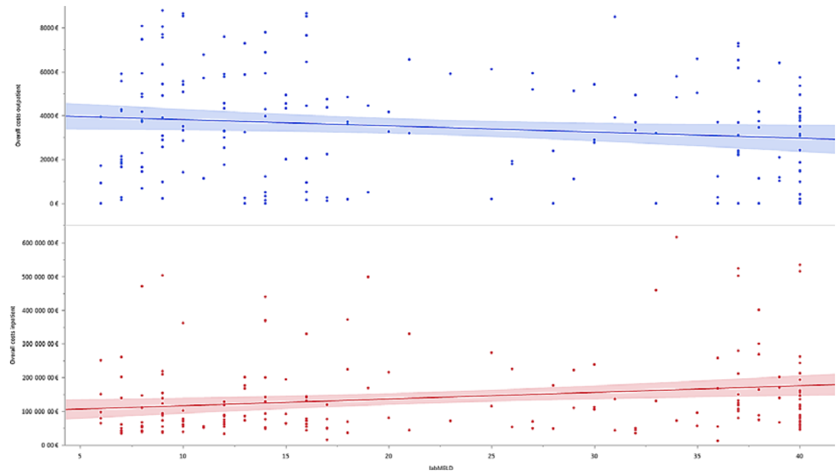

Figure 9 Inpatient and outpatient overall costs. The graphs show the results of linear regression analysis with a 95% CI (shadowed areas). The analysis illustrates the influence of the labMELD score of the overall costs for the inpatient stay (P = 0.01) and the outpatient services (P = 0.05) during the whole observational period.

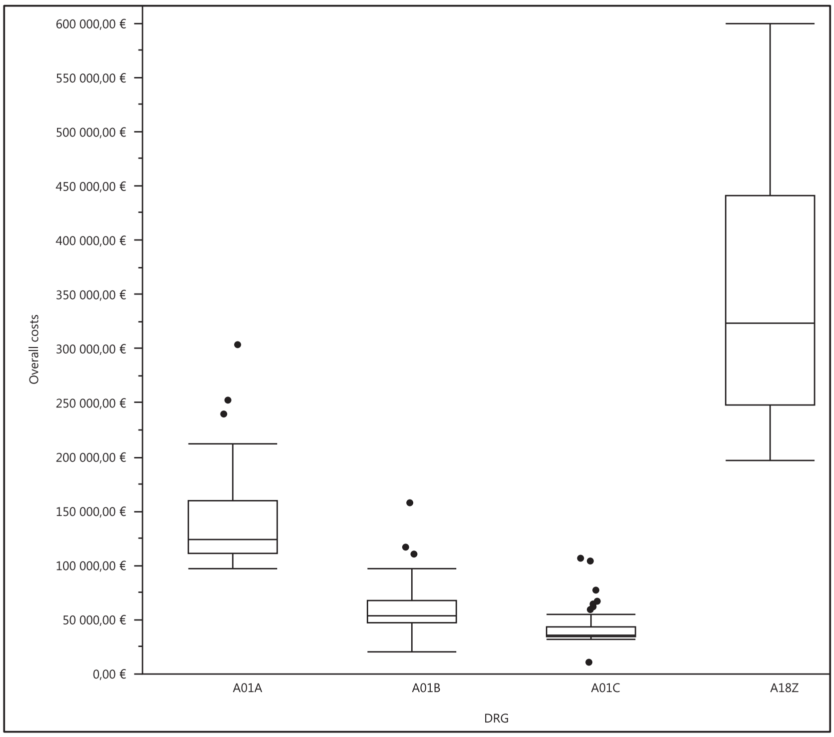

Figure 10 Costs for G-DRG-codes for liver transplantation. The overall costs are presented as boxplots. The boxplots illustrate the great variety among each of the different LTx codes, as each code comprises different stages of mechanical ventilation or graft rejection.

listed in Table 8. Costs for these drugs ranged between 2000€ and 16 000€ before transplantation and from 12 000€ to 125 000€ after transplantation in total per patient (rounded for thousands of €).

Rehabilitation

After transplantation, 67 patients (36.8%) had an inpatient stay in a rehabilitation clinic. Almost all of these hospitalizations were within T2; only one patient had inpatient rehabilitation in T3. The mean number of days spent in a rehabilitation clinic was 24, whereby the shortest stay was 5 days and the longest 60. The total cost for rehabilitation was 171 619€ with an average cost of 943€ (95% CI: 739–1147€).

Discussion

The results of this study clearly highlight the dominating role of costs incurred by inpatient care for the treatment

Table 7. Overall costs of immunosuppressive drugs.

	Time frame					
	T2 (transplant year)			T3 (Two years post T2)		
Immuno suppressants	Number of patients	Total cost € Total cost US$	Median € (range) Total cost US$	Number of patients	Total cost € Total cost US$	Median € (range) Total cost US$
Azathioprine	–	–	–	1	167	167 (167–167)
					177	177 (177–177)
Mycophenolate mofetil (CellCept®)	150	338 397	2178 (22–7627)	136	623 411	4669 (116–12 484)
		358 745	2309 (23–8086)		660 897	4950 (123–13 235)
Mycophenolat-mofetil (Myfortic®)	5	5799	1247 (230–2042)	5	10 381	824 (576–4116)
		6148	1322 (244–2165)		11 005	874 (611–4363)
Prednisolone	128	16 479	112 (12–727)	119	20 520	178 (5–567)
		17 470	119 (13–771)		2175	189 (5–601)
Cyclosporine	77	213 468	2696 (41–14 088)	62	258 034	4415 (282–9184)
		226 304	2858 (43–14 935)		273 550	4680 (299–9736)
Tacrolimus	94	832 219	8045 (246–23 809)	87	1 018 236	10 185 (777–39 477)
		882 260	8529 (261–25 241)		1 079 463	10 797 (824–41 851)
Sirolimus	1	2385	2385 (2385–2385)	1	676	676 (676–676)
		2528	2528 (2528–2528)		717	717 (717–717)
Everolimus	3	40 749	11 368 (7348–22 033)	8	94 303	8631 (1505–34 244)
		43 199	12 052 (7790–23 358)		99 973	9150 (1595–36 303)

of liver transplant candidates and recipients. These services constantly dominate each time frame (T1–T3) and are responsible for 71% of total costs. It is striking that pre- and post-transplant outpatient medical services (2%) and post-transplant rehabilitation costs (<1%) incur a comparatively small part of the total costs. Hence, process improvement of inpatient treatment is most likely enabling optimization treatment costs.

This study further highlights the meaningful proportion of total costs for necessary lifelong medication, especially during T2 (14%) and T3 (28%) (Table 4). In this context, some underlying chronic diseases leading to LTx such as viral cirrhosis require highly expensive drugs over prolonged periods of time (Table 5). Cost optimization for pharmaceuticals provides additional pressure to use cheaper generic drugs.

It is interesting to note that during T1 lower allocation labMELD scores incurred higher overall costs due to significantly longer waiting times. This may be surprising as patients with higher labMELD scores would be expected to require more intensive medical inpatient treatment during their waiting time as a consequence of a more progressed liver disease. This study shows that this is obviously more than offset by their shorter waiting times.

As expected, patients with higher pre-transplant labMELD scores incurred significantly higher treatment costs in T2 probably as a result of their associated higher morbidity prior to transplantation. Moreover, higher labMELD scores led to higher inpatient costs and to lower outpatient costs. This illustrates that patients with higher labMELD scores incurred less outpatient costs, as these patients spend more time in hospital. This is in congruence to the finding that patients with higher labMELD scores obviously spend most of their treatment time in hospital, especially during T2.

All of these results need to take the national donor liver allocation policy into account, especially when comparing treatment costs between countries without a MELD-based donor organ allocation policies. In this context, it is remarkable that the allocation labMELD scores had no statistically significant influence on costs during follow-up (T3). This is understandable as the labMELD score indicates the severity of liver disease, which has been removed during transplantation. However, patients with HCC or PSC had significantly lower labMELD scores due to the fact that liver allocation for these patients is guided by standard exception MELD points instead of labMELD score points [20].

Our findings may suggest transplanting patients earlier in the course of their end-stage liver disease with lower labMELD scores as this would probably lower the dominating cost factor caused by inpatient treatments after transplantation. However, such an approach has been shown recently to be associated with lower transplant survival benefits for patients within the first 90 days after transplantation [21].

Table 8. Most cost-intensive pharmaceuticals.

Pharmaceutical	Field of application in the context of liver transplantation
Waiting time (T1)	
Nexavar®	Used for neo adjuvant treatment of hepatocellular carcinoma
TOBI®	Used to suppress chronic lung infection caused by bacteria called pseudomonas aeruginosa in patients who have cystic fibrosis
Pulmozyme®	Indicated for the management of cystic fibrosis (CF)
Hepsera®	Used to treat adults with chronic (long-term) hepatitis B
	Patients with compensated or decompensated liver disease
Inspra®	Used to reduce the risk of cardiovascular mortality and morbidity, as well as clinical signs for a heart failure after recent myocardial infarction onset
	To reduce the risk of cardiovascular mortality and morbidity in adult patients with (chronic) heart failure
PegIntron®	Used to treat long-term hepatitis C
	Can be given to adults with a compensated liver disease
	In other adults with hepatitis C virus
Pantozol®	Used for the short-term treatment of the symptoms of acid reflux in adults
	Eradication of *Helicobacter pylori* in combination therapy with appropriate antibiotics in patients with duodenal ulcers caused by *H. pylori*
	Gastric ulcer and duodenal ulcer
	Zollinger–Ellison syndrome and other diseases associated with pathological hypersecretion of gastric acid
Humatin®	Treatment and prevention of portosystemic encephalopathy, preoperative reduction of intestinal flora, treatment of noninvasive amoebic infection of the intestinal lumen
Zeffix®	Used to treat adults who have chronic (long term) hepatitis B
	Patients with compensated or decompensated liver disease
Baraclude®	Used to treat chronic (long term) hepatitis B
	Used in adults with compensated or decompensated liver disease
After transplantation (T2–T3)	
Hepatect®	Used to prevent re-infection with the hepatitis B virus
Sovaldi®, Olysio®, Daklinza®, Harvoni®	Used to treat chronic (long term) hepatitis C in adults
Durogesic®	Used to relieve severe, chronic pain for a longer, continuous treatment
Zutectra®	Used in adults who have had a liver transplant because of liver failure that was caused by hepatitis B infection
	Used to prevent re-infection with the hepatitis B virus
Nexavar®	Used for adjuvant treatment of hepatocellular carcinoma
Vfend®	Used for the treatment of invasive aspergillosis, candidaemia, serious invasive candida infections when the fungus is resistant to fluconazole, serious fungal infections caused by Scedosporium or Fusarium
Valcyte®	Used for the prophylaxis of the Cytomegalovirus (CMV) disease in CMV-negative adults and children who have received an organ transplant from a CMV-positive donor

It comes as no surprise that patients who died early during the first year after transplantation (T2) incurred higher costs compared to surviving patients. This is caused by more frequent prolonged intensive care treatments due to severe complications after transplantation.

During inpatient stays, multiple ERCP interventions were responsible for high costs during each analyzed time frame. During waiting time (T1), the total costs for ERCP interventions are the second most cost-intensive part. In T2, these were one of the most frequent G-DRG-codes and in T3 the ERCP codes were responsible for the biggest part of the costs. These findings point out the severity and intensity of ERCP usage in LTx patients which may point to a need for clinical outcome improvement of biliary reconstruction during transplantation.

During T2, the four G-DRG-codes for transplantation (A01A, A01B, A01C, A18Z) reflect the medical and economic complexity of the intervention per se, as associated costs vary enormously (range: 36 373–323 655€).

In a Finnish cost-effectiveness study, the overall cost per quality-adjusted life year (QALY) in LTx patients was analyzed, with up to 5 years of follow-up [1]. The results showed median annual costs of 141 768€ for the period between listing for transplantation and 1 year after transplantation. As the waiting time was only 41 days in average, this time frame may be comparable with our time period T2 (median costs 105 566€). The difference in costs between this study and the Finish study might be due to various reasons. For example, the inpatient hospital stay for transplantation is remunerated on the basis of fees (DRGs) in Germany, whereas the inpatient stay and the transplantation procedure are reimbursed separately in the Finnish setting. Furthermore, our Finish colleagues considered costs for organ procurement as well, which was not accounted for in this study. The total cost during the observational period added up to a median of 177 618€ in the Finnish setting, and to a median of 144 424€ within this study. It is interesting to note that the main cost-intensive part in both studies was incurred by the inpatient sector (71–75%).

A meta-analysis of an international systematic review found an average cost of $163 438 for LTx in the United States and of $103 438 for other countries that are members of the Organization for Economic Co-Operation and Development [3]. Within this meta-analysis, one German study was included which calculated average inpatient treatment costs of 49 000€ (range: 18 000–189 000€) on the basis of G-DRGs [9]. Another German study analyzed the influence of organ failure and severe complications, which determined average inpatient cost for the liver transplant procedure at 52 570€ (range: 18 330–397 450€) [10] while in the current study these costs were significantly higher (average costs 111 928€). This may be due to relevant clinical differences in patient populations between treatment centers and the frequency of post-transplant complications compounded by generally increasing costs over time.

A recent study of organ and tissue transplant costs in the United States analyzed billed charges during a time period of 30 days pre-transplant to 180 days post-transplant. For LTx, the total amount of costs was $739 100 [12]. These data provide a valuable orientation to the great variation of the dimension of costs for LTx in different countries. However, these results are difficult to compare to our findings due to substantial differences between the healthcare systems [22–24].

This analysis serves as a substructure for a subsequent analysis. We are planning to perform a multivariate analysis of determined cost-driving factors to identify independent factors that drive costs significantly. Such an analysis might provide insight into how these cost drivers may be avoided or reduced.

Some limitations affect the results of this study. No data on medical services at other institutions were analyzed. Our observational period represents only a small part of therapeutic care as patients who receive a transplanted organ require lifelong treatment. The overall lifelong costs of transplantation are therefore probably substantially higher as estimated in this study with limited follow-up times for analysis. Due to the lack of a national transplant registry, we unfortunately cannot state with confidence whether or not the analyzed sample is representative for Germany. It is, however, unlikely that the sample is representative for the Eurotransplant region because of different organ allocation rules in different Eurotransplant member countries.

Conclusion

As interfaces between healthcare sectors contain the hazard of breaks within treatment paths, it is important to support a holistic course of treatment. High requirements for optimized coordination and communication between all involved actors of care implicate a formidable management challenge. Here, the role of the transplant center implies a leading role as our study points out [25,26]. An integrated and guided exchange of information between decentralized actors is essential to avoid ambiguity and to prevent information loss. Prerequisite for this is the large-scale use of structured information and communication tools, as, for example, an electronic health card or medical record [27]; especially during aftercare, these points gain in importance as potential interactions of different drugs have to be considered in typically complex medication schemes [28].

Authorship

LH, JTS, CK and VEA: designed research/study. LH, HS, CK and VEA: performed research/study. LH and HS: collected data. LH, HS and JTS: analyzed data. LH and HS: wrote the paper.

Funding

This work was supported by a grant from the German Federal Ministry of Education and Research (reference number: 01EO1302).

Conflicts of interest

The authors declare that there are no conflicts of interest.

REFERENCES

1. Aberg F, Maklin S, Rasanen P, *et al.* Cost of a quality-adjusted life year in liver transplantation: the influence of the indication and the model for end-stage liver disease score. *Liver Transpl* 2011; **17**: 1333.
2. Schrem H, Barg-Hock H, Strassburg CP, Schwarz A, Klempnauer J. Aftercare for patients with transplanted organs. *Dtsch Arztebl Int* 2009; **106**: 148.
3. van der Hilst CS, Ijtsma AJ, Slooff MJ, Tenvergert EM. Cost of liver transplantation: a systematic review and meta-analysis comparing the United States with other OECD countries. *Med Care Res Rev* 2009; **66**: 3.
4. Branger P, Samuel U. Annual Report 2015. Eurotransplant International Foundation, 2015.
5. Harries L, Schrem H, Krauth C, Amelung VE. Behandlungswege in der Transplantationsmedizin – Herausford erungen bei der Bewältigung von ambu lanten und stationären Schnittstellen. In: Klauber J, Geraedts M, Friedrich J, Wasem J, eds. *Krankenhaus-Report 2016*. Schwerpunkt: Ambulant im Kranken haus. Schattauer GmbH, Stuttgart, 2016: 181–193.
6. KBV. Kassenärztliche Bundesvereinigung. Einheitlicher Bewertungsmaßstab (EBM) Stand: 2. Quartal 2015, 2015. Available at: http://www.kbv.de/media/sp/EBM_Gesamt___Stand_2._Quartal_2015.pdf. Accessed 10/06, 2015.
7. GKV-Spitzenverband. Transplantation – Finanzierung, 2012. Available at: http://www.gkv-spitzenverband.de/krankenversicherung/krankenhaeuser/transplantation/transplantation_finanzierung/finanzierung.jsp. Accessed 10/06, 2015.
8. Münzel H, Nicola Z. Ambulante Leistungen in und an Krankenhäusern, 2008.
9. Kraus TW, Mieth M, Schneider T, *et al.* Cost distribution of orthotopic liver transplantation: single-center analysis under DRG-based reimbursement. *Transplantation* 2005; **80**(1 Suppl.): S97.
10. Lock J, Reinhold T, Bloch A, *et al.* The cost of graft failure and other severe complications after liver transplantation – experience from a German Transplant Center. *Ann Transplant* 2010; **15**: 11.
11. Longworth L, Young T, Buxton MJ, *et al.* Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups. *Liver Transpl* 2003; **9**: 1295.
12. Bentley TS, Hansons SG. 2014 U.S. organ and tissue transplant cost estimates and discussion. Milliman Research Report, 2014. http://www.milliman.com/uploadedFiles/insight/Research/health-rr/1938HDP_20141230.pdf.
13. Petzhold T, Hannemann F, Eberlein-Gonska M. Externe Qualitätssicherung. Follow-up in die weite Welt. *Deutsches Ärzteblatt* 2014; **111**: A588.
14. Gemeinsamer Bundesausschuss. Rich tlinie des Gemeinsamen Bundesauss chusses gemäß § 137 Abs. 1 SGB V i.V.m. § 135a SGB V über Maßnahmen der Qualitätssicherung für nach § 108 SGB V zugelassene Krankenhäuser, 2015.
15. Kassenärztliche Bundesvereinigung. Einh eitlicher Bewertungsmaßstab (EBM). Stand 4. Quartal 2013. Available at: http://www.kbv.de/html/ebm.php. Acces sed 02/16, 2016.
16. Schwabe U, Paffrath D, eds. *Arzneive rordnungs-Report 2013*. Berlin, Heidelb erg: Springer, 2013.
17. Lauer Fischer. Lauer-Taxe. Available at: http://www2.lauer-fischer.de/produkte/lauer-taxe/lauer-taxe/. Accessed 02/16, 2016.
18. InEK – Institut für das Entgeltsystem im Krankenhaus. Fallpauschalen-Katalog, 2013; Available at: http://www.g-drg.de/cms/Archiv/DRG_Systemjahr_2013_Datenjahr_2011. Accessed 02/16, 2016.
19. Deutsche Rentenversicherung. Reha-Berichte. Update 2014. Die medizinische und berufliche Rehabilitation der Rentenversicherung im Licht der Statistik, 2014.
20. Bundesärztekammer. Richtlinien zur Organtransplantation gem. § 16TPG. Richtlinie gemäß § 16 Abs. 1 S. 1 Nrn. 2 u. 5 TPG für die Wartelistenführung und Organvermittlung zur Lebertransplanta tion, 2015.
21. Schrem H, Focken M, Gunson B, *et al.* The new liver allocation score (LivAS) for transplantation is validated in Germany but not in the UK due to different selection and survival benefits. *Liver Transplant* 2016; **22**: 743 accepted for publication.
22. Schöffski O, Graf von der Schulenburg J.-M, eds. *Gesundheitsökonomische Eval uation*, 4th edn. Berlin, Heidelberg: Springer Verlag; 2012.
23. Drummond M, Barbieri M, Cook J, *et al.* Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. *Value Health* 2009; **12**: 409.
24. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. *Pharmacoec onomics* 2004; **22**: 857.
25. Den Hertog F, Groen M, Weehuizen R. *Mapping Health Care Innovation: Tracing Walls and Ceilings*. Maastricht: Maastricht Economic Research Institute on Innovation and Technology (MERIT); International Institute of Infonomics; 2005.
26. Schmitz C, Berchthold P. Managing professionals – Führung im Krankenhaus. In: Amelung VE, Sydow J, Windeler A, eds. *Vernetzung im Gesundheitswesen Wettbew erb und Kooperation*. Stuttgart: W. Kohlhammer Druckerei GmbH + Co. KG; 2009: 167–180.
27. Amelung VE, Wolf S. Integrierte Versorgung – Vom Hoffnungsträger zum Ladenhüter der deutschen Gesundheitspolitik? *G+S* 2012; **1**: 13.
28. Harries L, Schrem H, Krauth C, Amelung VE. Pathways in transplantation medicine – Challenges in overcoming interfaces between cross-sectoral care structures. In: Amelung VE, Stein V, Goodwin N, Balicer R, Nolte E, Suter E, eds. *Handbook Integrated Care* 2017. Springer, Berlin, Heidelberg, 2017: Chapter 26