OPEN

The Last Year Before Graft Failure Negatively Impacts Economic Outcomes and is Associated With Greater Healthcare Resource Utilization Compared With Previous Years in the United Kingdom: Results of a Retrospective Observational Study

Gorden Muduma, PhD,[1] Varuna Aluvihare, MBBS, PhD, MRCP,[2]
Marc Clancy, M.A, BM ChB, Ph.D, F.R.C.S (Eng.), F.R.C.S. (Gen. Surg.),[3,4] Enrico de Nigris, MSc,[1]
Carolyn Whitlock, BSc Pharm, MRPharm S,[1] Margarita Landeira, MSc,[1] and Jameel Nazir, PhD.[1]

Background. Kidney and liver transplantation is the standard of care for end-stage renal or liver disease. However, long-term survival of kidney and liver grafts remain suboptimal. Our study aimed to understand the healthcare resources utilized and their associated costs in the years before graft failure. **Methods.** Two noninterventional, retrospective, observational studies were conducted in cohorts of kidney or liver transplant patients. Once identified, patients were followed using the UK Clinical Practice Research Datalink linked to the Hospital Episode Statistics databases from the date of transplantation to the date of the first graft failure. Total healthcare costs in the year before graft failure (primary endpoint) and during years 2–5 before graft failure (secondary endpoint) were collected. **Results.** A total of 269 kidney and 81 liver transplant patients were analyzed. The mean total costs were highest for all resource components in the last year before graft failure, except for mean costs of immunosuppressive therapy per patient, which decreased slightly by index date (ie, graft failure). The mean total healthcare costs in the last year before graft failure were £8115 for kidney and £9988 for liver transplant patients and were significantly ($P < 0.05$) higher than years 2–5 before graft failure. Mean healthcare costs for years 2, 3, 4, and 5 before graft failure were £5925, £5575, £5469, and £5468, respectively, for kidney, and £6763, £7042, £6020, and £5651, respectively, for liver transplant patients. **Conclusions.** Total healthcare costs in the last year before graft failure are substantial and statistically significantly higher than years 2–5 before graft failure, in both kidney and liver transplant patients. Our findings show the economic burden placed on healthcare services in the years before graft failure.

(*Transplantation Direct* 2019;5:e443; doi: 10.1097/TXD.0000000000000884. Published online 15 April, 2019.)

INTRODUCTION

Renal transplantation is considered the gold standard treatment choice among the available renal replacement therapy options for patients with end-stage renal disease.[1] Compared with dialysis, renal transplantation is associated with reductions in cardiac events, improved quality

Received 2 October 2018. Revision received 16 January 2019.
Accepted 3 February 2019.
[1] Medical Affairs, Astellas Pharma Europe Ltd., Chertsey, Surrey, United Kingdom.
[2] Institute of Liver Studies, King's College Hospital, London, United Kingdom.
[3] Department of Transplantation, NHS Lothian, Edinburgh, United Kingdom.
[4] Transplant Unit, Queen Elizabeth University Hospital, Glasgow, United Kingdom.
G.M., E.D.N., C.W., and J.N. affiliated at the time of the study conduct.
C.W., G.M., J.N., and M.C. contributed to study design. C.W., E.D.N., G.M., M.L., and V.A. contributed to data analysis and interpretation. M.C. contributed to the writing of the manuscript. All authors contributed to the critical review of the manuscript and read and approved the final manuscript.
C.W., E.D.N., G.M., J.N., and M.L. were employees of Astellas Pharma Europe Ltd. at the time of the study conduct. M.C. reports speaker fees from Astellas Pharma and Sandoz and sponsorship for attending meetings from Sanofi Genzyme. V.A. has consulted for/received honoraria from Astellas Pharma, Novartis, Chiesi, Gilead Sciences and reports grant support from Roche Pharmaceuticals.
Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).
Correspondence: Jameel Nazir, Astellas Pharma Europe Ltd., 2000 Hillswood Dr, Chertsey, Surrey KT16 0RS, United Kingdom. (jamx7773@outlook.com).

ISSN: 2373-8731
DOI: 10.1097/TXD.0000000000000884

of life, and increased survival.[2] For patients with end-stage liver disease, liver transplantation provides the only effective treatment option.[3,4]

Both kidney and liver transplantation are cost-effective interventions compared with dialysis and other treatments.[5-7] However, the number of kidney transplant patients with a failed allograft from 1988 to 2010 in the United States has substantially increased[8] and complications following liver transplantation are common, with approximately 22% of patients in the United States developing biliary complications post-liver transplantation.[9] In addition, 20-year graft survival rates for both kidney and liver transplant patients in Europe are poor (<22%).[10,11] Due to the increasing size of transplant waiting lists (United Kingdom patients awaiting a liver transplant have tripled from 1999 to 2009) and shortage of grafts available,[12,13] maximizing the long-term survival and function of each transplant by minimizing or controlling the foremost causes of graft loss is a clinical priority.

In many areas of medicine, costs rise substantially in the year before significant clinical events,[14-17] indicating the need for specific strategies to be determined before these events occur. Although the average costs for transplantation, specifically the surgical procedure and preoperative care, are well established in the United Kingdom,[18] knowledge of healthcare resource utilization and the associated costs during the last year before kidney and liver graft failure is limited.

In this analysis, we present the results of two similarly designed studies. The primary aim was to describe the distribution of healthcare costs during the last year before kidney or liver graft failure in the United Kingdom. Secondary aims were to describe the distribution of these healthcare costs between years 2 and 5 before graft failure and compare these costs with the last year before graft failure. We hypothesized that the total healthcare costs in the last year before graft failure would be significantly higher than the costs during years 2–5.

MATERIALS AND METHODS

Study Overview/Design

Two noninterventional, retrospective, observational studies examined cohorts of either kidney or liver transplant patients in the United Kingdom. Data were collected from the National Health Service (NHS), Clinical Practice Research Datalink (CPRD), and Hospital Episode Statistics (HES) databases, allowing for a longitudinal analysis of resource and drug utilization. For both studies, the index date was defined as the date of the first graft failure. Details of graft failure and how it was identified are described further in the methods below.

Data Sources

Patients were selected from the CPRD and cross-referenced with HES databases[19,20] based on evidence (medcodes) for kidney or liver transplantation between 2004 and 2013 and subsequent graft failure between 2005 and 2014. Patient data were collected on demographic information, prescription details, clinical events (symptoms, diagnoses), preventive care provided, diagnostic/pathological tests, immunizations, specialist referrals, hospital admissions and their major outcomes, and details relating to death.

Patient Populations

Kidney and liver transplant patients were identified using transplant medcodes from CPRD and ICD-10 code Z94.4 from HES (**Supplementary Tables 1 and 2, SDC,** http://links.lww.com/TXD/A203). Kidney transplant patients receiving dialysis treatment were identified using dialysis medcodes from CPRD and ICD-10 codes T86.1, Z49.1, and Z99.2 from HES. Kidney transplant patient deaths were identified from the CPRD and HES and combined with the dialysis dataset to determine the index date (Figure 1A). Patients who received additional liver transplants were identified using the same codes from CPRD and HES as before. Liver transplant patient deaths were identified, and these data were combined with datasets for additional liver transplants to determine the index date (Figure 1B). Duplicate patients receiving kidney or liver transplants and those receiving additional liver transplants or dialysis were removed from both cohorts. Patients were matched to kidney and liver transplant patients who were receiving dialysis, a secondary liver transplant, or who had died using the common patient identifier. The time differences between liver transplant and a second transplant or death, and kidney transplant and dialysis or death, were calculated for each patient (Figure 1).

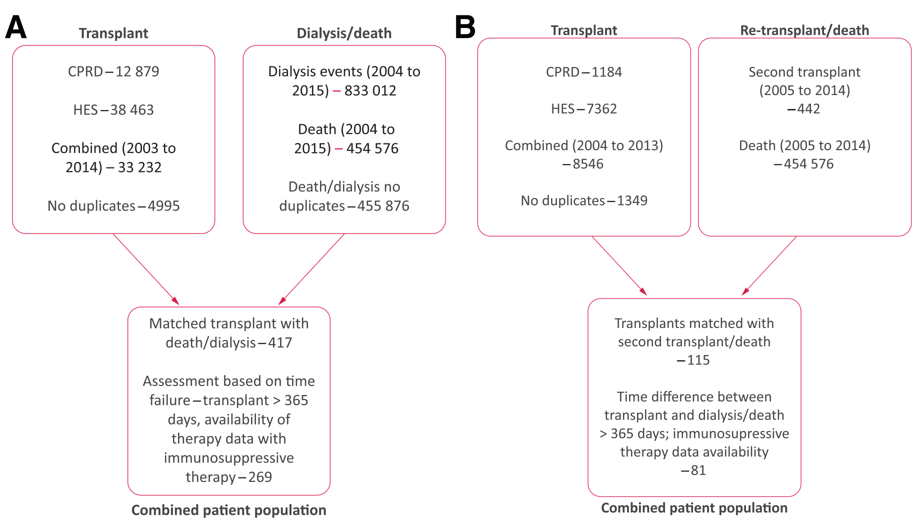

FIGURE 1. Summary of search strategy and number of patients included. A, Kidney transplant cohort. B, Liver transplant cohort. CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics.

The studies included all kidney or liver transplant patients identified between 2004 and 2013 and those with graft failure between 2005 and 2014, for whom the time between receiving a transplant and subsequent graft failure was >365 days. To prevent the costs of initial posttransplantation resource use (not related to graft failure) affecting total healthcare costs, the studies excluded patients with <1 year between kidney or liver transplant and graft failure, and those patients who died within <1 year of receiving a transplant.

Outcomes and Endpoints

The primary endpoint for both studies was the total healthcare costs collected in the year before graft failure. A secondary endpoint was the total healthcare costs in years 2–5 before graft failure. For the primary objective, there was no comparison group or control. For the secondary objective, a repeated measures analysis was used.

Resource Utilization

Healthcare resource utilization was calculated for the following elements (each costed by their appropriate, respective 2015/2016 tariff): healthcare visits, hospital length of stay, procedures and operations performed, transplant-related resources, and drugs dispensed. The covariates examined included sex, age at kidney or liver failure (children <18 y vs adults), and type of donor (deceased vs live).

Costs

Cost data for resource components were obtained from the same sources for both kidney and liver transplant patients. The costs for services provided in the community were obtained from the Unit Costs of Health and Social Care[21] and the cost of immunosuppressive agents from the British National Formulary.[22] Diagnostic and pathology test costs were obtained from the NHS Reference Cost Schedule 2014–2015,[23] and the cost of services provided in secondary care were obtained from the NHS Reference Schedule 2015–2016.[18] A summary of all inpatient events captured by the Healthcare Resource Group in the last year before graft failure and from years 2–5 before graft failure are shown in **Supplementary Tables 3, 4, 5, and 6, SDC,** http://links.lww.com/TXD/A203.

The unit costs for the resources utilized leading up to graft failure are summarized in Table 1. Total healthcare costs were calculated by combining the following individual resource components: general practitioner (GP) consultations, diagnostic tests, immunosuppressive drugs, outpatient visits, day cases, and inpatient stays with associated interventions.

Statistical Analyses

Continuous and nominal variables were described using standard statistical measures. Repeated measures mixed model analysis (Stata 12.1)[24] was conducted to estimate the impact of time to graft failure on resource utilization while adjusting for covariates (sex, age, and type of donor). Covariates were added to model the outcome, starting with a random intercept model. Generalized linear models (log-link with a gamma error) were used to model healthcare costs in the last year before graft failure. Specifically, total healthcare costs for the period 5 years to >1 year before graft failure were compared with total healthcare costs in the last year before graft failure. Because they avoid the restrictions of repeated-measures

TABLE 1

Summary of unit costs for resources utilized by kidney and liver transplant patients

Type of resource	Unit cost (£)
GP consultations	
Per min of patient contact[a]	3.80
Per patient contact lasting 11.7 min[a]	44 (3.80/min)
Per patient contact lasting 17.2 min[a]	65 (3.80/min)
GP telephone conversation lasting 7.1 min	27 (3.80/min)
GP-led telephone triage	14 (3.50/min)
Nurse-led telephone triage	8 (1.20/min)
Home visit[b]	89 (3.80/min)
Diagnostic and pathology tests	
Cytology	6.99
Histopathology and histology	28.82
Integrated blood services	1.74
Clinical biochemistry	1.19
Hematology	3.01
Immunology	5.49
Microbiology	6.89
Phlebotomy	3.46
Other	7.13
Outpatient visits	
First attendance—single professional	181
First attendance—multiprofessional	256
Follow up attendance—single professional	107
Follow up attendance—multiprofessional	138
Immunosuppressive drugs	
Adoport 1 mg capsules (Sandoz Ltd)	1 mg, 50-cap pack = £55.69
Adoport 5 mg capsules (Sandoz Ltd)	5 mg, 50-cap pack = £205.74
Advagraf 1 mg modified-release capsules (Astellas Pharma Ltd)	1 mg, 50-cap pack = £71.59
Advagraf 3 mg modified-release capsules (Astellas Pharma Ltd)	3 mg, 50-cap pack = £214.76
Advagraf 5 mg modified-release capsules (Astellas Pharma Ltd)	5 mg, 50-cap pack = £266.92
Azathioprine 25 mg tablets	25 mg, 28-tab pack = £3.24
Azathioprine 50 mg tablets	50 mg, 56-tab pack = £3.13
Capsorin 50 mg capsules (Morningside Healthcare Ltd)	50 mg, 30-cap pack = £25.59
CellCept 250 mg capsules (Roche Products Ltd)	250 mg, 100-cap pack = £82.26
CellCept 500 mg tablets (Roche Products Ltd)	500 mg, 50-tab pack = £82.26
Ciclosporin 100 mg capsules	100 mg, 30-cap pack = £48.89
Ciclosporin 25 mg capsules	25 mg, 30-cap pack = £13.05
Ciclosporin 50 mg capsules	50 mg, 30-cap pack = £25.59
Imuran 25 mg tablets (Aspen Pharma Trading Ltd)	25 mg, 100-tab pack = £10.99
Imuran 50 mg tablet (Wellcome Medical Division)	50 mg, 100-tab pack = £7.99
Imuran 50 mg tablets (Aspen Pharma Trading Ltd)	50 mg, 100-tab pack = £7.99
Mycophenolate mofetil 1 g/5 mL oral suspension sugar free	1 g/5 mL, 175 mL bottle = £115.16
Mycophenolate mofetil 250 mg capsules	250 mg, 100-cap pack = £82.26
Mycophenolate mofetil 500 mg powder for solution for infusion vials	500 mg, 50-tab pack = £6.64
Mycophenolate mofetil 500 mg tablets	500 mg, 50-tab pack = £6.64
Mycophenolic acid 180 mg gastroresistant tablets	180 mg, 120-tab pack = £96.72
Mycophenolic acid 360 mg gastroresistant tablets	360 mg, 120-tab pack = £193.43

(Continued next page)

TABLE 1 (Continued)

Type of resource	Unit cost (£)
Myfortic 360 mg gastroresistant tablets (Novartis Pharmaceuticals UK Ltd)	360 mg, 120-tab pack = £193.43
Neoral 100 mg capsules (Novartis Pharmaceuticals UK Ltd)	100 mg, 30-cap pack = £68.28
Neoral 100 mg/mL oral solution (Novartis Pharmaceuticals UK Ltd)	100 mg/mL, 50 mL = £102.30
Neoral 10 mg capsules (Novartis Pharmaceuticals UK Ltd)	10 mg, 60-cap pack = £18.25
Neoral 25 mg capsules (Novartis Pharmaceuticals UK Ltd)	25 mg, 30-cap pack = £18.37
Neoral 50 mg capsules (Novartis Pharmaceuticals UK Ltd)	50 mg, 30-cap pack = £35.97
Prednisolone 1 mg tablets	1 mg, 28-tab pack = £1.07
Prednisolone 2.5 mg gastroresistant tablets	2.5 mg, 28-tab pack = £1.52
Prednisolone 25 mg tablets	25 mg, 56-tab pack = £75.00
Prednisolone 5 mg gastroresistant tablets	5 mg, 28-tab pack = £1.24
Prednisolone 5 mg soluble tablets	5 mg, 30-tab pack = £53.48
Prednisolone 5 mg tablets	5 mg, 28-tab pack = £1.24
Prograf 1 mg capsules (Astellas Pharma Ltd)	1 mg, 50-cap pack = £80.28
Prograf 500 µg capsules (Astellas Pharma Ltd)	500 µg, 50-cap pack = £61.88
Prograf 5 mg capsules (Astellas Pharma Ltd)	5 mg, 50-cap pack = £296.58
Rapamune 1 mg tablets (Pfizer Ltd)	1 mg, 30-tab pack = £86.49
Rapamune 2 mg tablets (Pfizer Ltd)	2 mg, 30-tab pack = £172.98
Sandimmun 100 mg capsules (Novartis Pharmaceuticals UK Ltd)	100 mg, 30-cap pack = £68.28
Sandimmun 100 mg/mL oral solution (Novartis Pharmaceuticals UK Ltd)	100 mg/mL, 50 mL = £102.30
Sandimmun 25 mg capsules (Novartis Pharmaceuticals UK Ltd)	25 mg, 30-cap pack = £18.37
Sandimmun 50 mg capsules (Novartis Pharmaceuticals UK Ltd)	50 mg, 30-cap pack = £35.97
Sirolimus 1 mg tablets	1 mg, 30-tab pack = £86.49
Sirolimus 2 mg tablets	2 mg, 30-tab pack = £172.98
Sirolimus 500 µg tablets	500 µg, 30-tab pack = £69.00
Tacrolimus 1 mg capsules	1 mg, 50-cap pack = £55.69
Tacrolimus 1 mg modified-release capsules	1 mg, 50-cap pack = £71.59
Tacrolimus 2.5 mg/5 mL oral suspension	1 mg, 50-sachet pack = £356.65
Tacrolimus 500 µg capsules	500 µg, 50-cap pack = £42.92
Tacrolimus 500 µg modified-release capsules	500 µg, 50-cap pack = £61.88
Tacrolimus 5 mg capsules	5 mg, 50-cap pack = £205.74
Vivadex 1 mg capsules (Dexcel Pharma Ltd)	1 mg, 50-cap pack = £60.21

[a]Excludes travel.
[b]Assumes an average of 12 min of travel time per visit and a visit duration of 11.4 min.
Cap, capsule; GP, general practitioner; tab, tablet.

analysis of variance, linear mixed models (containing both fixed and random effects) were used to ensure that total costs in the last year before graft failure were different to the total costs in years 2–5 before graft failure.[25]

RESULTS

Patients

The final number of patients included in the analysis was 269 kidney and 81 liver transplant patients. The number of patients available for analysis varied according to the time lapse between transplant and graft failure or death (Table 2). In the kidney cohort, the mean (standard deviation [SD]) age of patients was 57.4 (15.4) years (males: 56.8 [15.4] y; females: 58.4 [15.5] y). In the liver cohort, the mean (SD) age of patients was 57.8 (16.4) years (males: 60.0 [13.6] y; females: 54.9 [19.3] y).

TABLE 2

Number of patients available for analysis based on the time before graft failure

Time before graft failure or death after transplantation[a]	No. of kidney transplant patients	No. of liver transplant patients
Last y	269	81
From 1 to 2 y	208	62
From 2 to 3 y	159	42
From 3 to 4 y	108	31
From 4 to 5 y	82	24

[a]Refers to the number of y before graft failure or death, not the number of y posttransplantation.

In the kidney transplant cohort, the graft failure categories at the index date were as follows: death (41%; n = 111), dependence on renal dialysis (23%; n = 61), complications of kidney transplant (18%; n = 49), extracorporeal dialysis (7%; n = 18), and other categories (11%; n = 30). In the liver transplant cohort, graft failure categories at the index date were as follows: death (89%; n = 72) and additional liver transplant (11%; n = 9).

GP Consultations

The mean number of GP consultations in the year before graft failure were 30.0 in the kidney transplant cohort and 34.1 in the liver transplant cohort with mean total durations of 7.3 and 9.3 minutes, respectively (Table 3). The mean duration and number of GP consultations for both studies, in years 2–5 before graft failure increased in the time periods closest to graft failure. Compared with years 2–5, the last year before graft failure demonstrated the highest mean duration and number of GP consultations for both studies (Table 3).

Drug Utilization and Costs

The mean number of prescriptions per patient was 110.9 and 97.5 in the kidney and liver transplant cohorts, respectively (Table 3). The total cost of immunosuppressive therapies in the year before graft failure were £673 709 and £179 618 in the kidney and liver transplant cohorts, respectively (Table 4). Mean (SD) per patient costs were £2504 (£2298) and £2218 (£2849), respectively (Table 4). In the 5 years before graft failure, mean immunosuppressant costs per patient were lowest between years 1 and 2 for the kidney cohort and in the year before graft failure for the liver cohort. In the kidney transplant cohort, the other most frequently used drug therapies in the last year before graft failure were as follows: statins (59.9%; n = 161); calcium-channel blockers (55.4%; n = 149); proton pump inhibitors (54.3%; n = 146); antiplatelet drugs (52.4%; n = 141); and loop diuretics (52.0%; n = 140; Table 5). In the liver transplant cohort, these included proton pump inhibitors (63.0%; n = 51); broad-spectrum penicillin antibiotics (46.9%; n = 38); opioid analgesics (43.2%; n = 35); and antiplatelet drugs (40.7%; n = 33; Table 5). In years 2–5 before graft failure, other frequently used drug therapies for the kidney and liver cohorts included statins

TABLE 3.

Mean healthcare resource use for kidney and liver transplants in the year before and years 2–5 before graft failure

Time before graft failure/death after transplantation[a]	GP consultations per patient	Duration of GP consultations	Prescriptions dispensed per patient	Diagnostic tests per patient	Referrals from GPs per patient	Inpatient procedures per patient	Day case procedures per patient	Outpatient visits per patient
Kidney transplant cohort								
Last y	30.0	7.3	110.9	61.7	0.9	1.4	1.1	7.5
From 1 to 2 y	26.0	6.3	104.3	50.0	0.8	0.7	0.5	6.0
From 2 to 3 y	22.7	7.0	95.4	45.4	0.7	0.6	0.5	5.1
From 3 to 4 y	22.3	6.6	92.7	47.4	0.8	0.4	0.6	4.8
From 4 to 5 y	24.1	6.4	92.9	39.0	0.7	0.4	0.3	4.7
Liver transplant cohort								
Last y	34.1	9.3	97.5	65.4	1.1	2.2	4.4	2.9
From 1 to 2 y	26.5	7.0	91.9	51.6	0.8	1.1	3.4	2.8
From 2 to 3 y	24.0	7.9	85.7	58.3	0.7	1.2	4.3	2.5
From 3 to 4 y	19.9	11.1	63.7	64.2	0.9	0.7	4.9	1.5
From 4 to 5 y	21.6	6.7	62.8	46.2	0.5	0.6	1.0	2.4

[a]Refers to the number of y before graft failure, not the number of y posttransplantation.
GP, general practitioner.

TABLE 4.

Mean annual costs of immunosuppressive therapies

Time before graft failure after transplantation[a]	Total cost (£)	Mean cost (SD) per patient (£)	Median (IQR) cost per patient (£)
Kidney transplant cohort			
Last y	673 709	2504 (2298)	2175 (2194)
From 1 to 2 y	519 346	2497 (1804)	2375 (2015)
From 2 to 3 y	421 258	2649 (2005)	2379 (2069)
From 3 to 4 y	302 121	2797 (2079)	2638 (1839)
From 4 to 5 y	233 338	2846 (1599)	2603 (1376)
Liver transplant cohort			
Last y	179 618	2218 (2849)	1613 (1788)
From 1 to 2 y	138 434	2233 (1882)	2015 (1344)
From 2 to 3 y	98 277	2340 (1932)	2111 (1160)
From 3 to 4 y	74 490	2403 (1320)	2403 (809)
From 4 to 5 y	66 620	2776 (1894)	2776 (912)

[a]Refers to the number of y before graft failure, not the number of y posttransplantation.
IQR, interquartile range; SD, standard deviation.

and proton pump inhibitors and broad-spectrum penicillin antibiotics, calcium-channel blockers, and antiplatelet drugs, respectively (**Supplementary Tables 7 and 8, SDC,** http://links.lww.com/TXD/A203).

Diagnostic Tests

In both cohorts, the mean number of diagnostic tests in the year before graft failure (61.7 and 65.4 per patient in the kidney and liver transplant cohorts, respectively) was higher compared with years 2–5 (Table 3). The most frequently used tests in the year before graft failure included serum creatinine (kidney: 5.1%; n = 839; liver: 3.9%; n = 208), potassium (kidney: 3.8%; n = 636; liver: 3.6%; n = 189), and sodium (kidney: 3.4%; n = 563; liver: 3.5%; n = 185; Table 6).

Referrals from GPs

Compared with years 2–5, the mean number of referrals from GPs to other providers differed were higher in the year before graft failure for both cohorts (0.9 and 1.1 per patient for kidney and liver transplant cohorts, respectively; Table 3).

Inpatient Stays

The mean number of inpatient procedures in both cohorts was higher in the last year before graft failure (1.4 and 2.2 per patient for kidney and liver transplant cohorts, respectively) compared with years 2–5 (Table 3).

Day Cases

The mean number of day cases in the last year before graft failure was 1.1 and 4.4 per patient in the kidney and liver cohorts, respectively (Table 3). Day care procedures were highest in the last year before graft failure for the kidney transplant cohort and from years 3 to 4 (4.9 per patient) for the liver transplant cohort.

Outpatient Visits

In both cohorts, the mean number of outpatient visits in the last year before graft failure (7.5 and 2.9 per patient in kidney and liver transplant cohorts, respectively) was higher compared with years 2–5 (Table 3).

Total Costs by Year

The mean totals per patient healthcare costs in the last year before graft failure were £8115 (SD: £4539; 95% confidence interval [CI], £7570–£8659) for the kidney transplant cohort and £9988 (SD: £6703; 95% CI, £8506–£11 470) for the liver transplant cohort (Figure 2). For years 2, 3, 4, and 5, mean (SD) total healthcare costs for kidney transplant patients were £5925 (£3155), £5575 (£3253), £5469 (£2976), and £5468 (£3242) and for liver transplant patients were £6763 (£4940), £7042 (£5812), £6020 (£5518), and £5651 (£3074), respectively (Figure 2). Results of mixed-level modeling demonstrated total healthcare costs as a function of time to graft failure (last year compared with years 2–5) were statistically significant ($P < 0.05$; Figure 3).

For the kidney transplant cohort, the main cost components were immunosuppressive drugs, inpatient stays (both displayed similar costs), and outpatient visits. For the liver

TABLE 5.

Use of other drug therapies for kidney and liver transplants in the last year before graft failure

Kidney transplant cohort		Liver transplant cohort	
BNF chapter[a]	No. of patients (%)	BNF chapter[a]	No. of patients (%)
Statins	161 (59.9)	Proton pump inhibitors	51 (63.0)
Calcium-channel blockers	149 (55.4)	Broad-spectrum penicillins	38 (46.9)
Proton pump inhibitors	146 (54.3)	Opioid analgesics	35 (43.2)
Antiplatelet drugs	141 (52.4)	Antiplatelet drugs	33 (40.7)
Loop diuretics	140 (52.0)	Nonopioid and compound analgesics	33 (40.7)
Broad-spectrum penicillins	121 (45.0)	Statins	32 (39.5)
Vitamin D	117 (43.5)	Vitamin D	31 (38.3)
Alpha-adrenoceptor-blocking drugs/alpha-blockers (in urinary retention)	112 (41.6)	Calcium-channel blockers	27 (33.3)
Angiotensin-converting enzyme inhibitors	99 (36.8)	Drugs affecting biliary composition and flow	21 (25.9)
Beta-adrenoceptor-blocking drugs	87 (32.3)	Nonopioid and compound analgesics/opioid analgesics	20 (24.7)
Nonopioid and compound analgesics	80 (29.7)	Angiotensin-converting enzyme inhibitors	19 (23.5)
Oral bicarbonate	79 (29.4)	Detection strips, blood for glucose—biosensor strips	19 (23.5)
Angiotensin II receptor antagonists	77 (28.6)	Loop diuretics	19 (23.5)
Nonopioid and compound analgesics/opioid analgesics	62 (23.0)	Osmotic laxatives	18 (22.2)
Cephalosporins	58 (21.6)	Selective beta 2 agonists	17 (21.0)
Oral iron	58 (21.6)	Bisphosphonates and other drugs affecting bone metabolism	16 (19.8)
Long-term control of gout	55 (20.4)	Emollients	16 (19.8)
Opioid analgesics	53 (19.7)	Drug used in nausea and vertigo—domperidone and metoclopramide	15 (18.5)
H^2-receptor antagonists	51 (19.0)	Intermediate- and long-acting insulins	15 (18.5)
Osmotic laxatives	46 (17.1)	Lancet sterile single use	15 (18.5)

[a]Drug therapies are defined by BNF chapter.
BNF, British National Formulary.

transplant cohort, the main cost components were inpatient stays (approximately twice the cost of immunosuppressive drugs), immunosuppressive drugs, and day cases. Total healthcare costs were higher in the last year before graft failure in all components compared with previous years, apart from immunosuppression (Figure 2). The mean (SD) inpatient cost per patient in the year before graft failure was £2521 (£3001) for kidney and £4494 (£4761) for liver transplant cohorts and was higher in the last year before graft failure compared with previous years (Figure 4). Median (interquartile range) inpatient costs per patient in the year before graft failure were £1510 (£3674) and £3221 (£5573) for kidney and liver transplant cohorts, respectively.

Total Costs by Sex, Age, and Type of Donor

For patients receiving a kidney transplant, the mean total costs during the last year before graft failure for males and females were £8413 (SD: £4726; 95% CI, £7685–£9142) per patient and £7648 (SD: £4210; 95% CI, £6833–£8462) per patient, respectively (Table 7). For patients receiving liver transplant, mean annual costs for males and females during the last year were £8421 (SD: £5651; 95% CI, £6743–£10 099) and £12 048 (SD: £7468; 95% CI, £9483–£14 613), respectively. Total costs by sex were statistically significantly different ($P < 0.05$) for liver transplant patients only, with higher total costs for females compared with males (Figure 5).

Kidney grafts from live donors were less expensive than those from deceased donors (mean costs: £5511 vs £9054), although not reaching statistical significance (due to small numbers of clearly identifiable grafts from live or deceased donors). For liver transplant patients, there were no sufficient data to analyze costs by donor type.

DISCUSSION

To our knowledge, this is the first study to accurately describe the distribution of healthcare costs and resource utilization in the years leading up to kidney and liver graft failure. The results of this study, based on real-world data, confirm the underlying hypothesis of the study that total healthcare costs in the last year before graft failure are significantly higher ($P < 0.05$) than years 2–5. Therefore, these studies show the later stages of a graft's lifetime, specifically the last year before graft failure, to be associated with greater consumption of healthcare resources, with inpatient stays being the main cost driver.

Traditionally, economic evaluations in the field of transplantation (eg, a German study by Jüurgensen et al[26]) have taken into consideration potential changes in posttransplantation costs. However, few studies adequately reflect the actual patient pathway of graft failure. Kidney transplant patients typically present with slow functional decreases over time, eventually culminating in graft failure.[27] Comparably, liver transplant patients also follow a similar course with 10-year graft failure estimated at approximately 35%.[28] Moreover, studies have generally not accounted for cost variations in transplant patients using graft failure as the index date. Therefore, our analysis provides a novel insight into the additional costs incurred in the later years of a kidney and liver transplant patient's clinical course.

In the present study, the mean total costs (median; interquartile range) during the last year before graft failure

TABLE 6.

Diagnostic tests used for kidney and liver transplants in the last year before graft failure

Kidney transplant cohort		Liver transplant cohort	
Diagnostic test[a]	**Frequency (%)**	**Diagnostic test[b]**	**Frequency (%)**
Serum creatinine	839 (5.1)	Serum creatinine	208 (3.9)
Serum potassium	636 (3.8)	Serum potassium	189 (3.6)
Serum sodium	563 (3.4)	Serum sodium	185 (3.5)
Hemoglobin estimation	540 (3.3)	Platelet count	169 (3.2)
Platelet count	481 (2.9)	Serum albumin	165 (3.1)
Serum urea level	462 (2.8)	Hemoglobin estimation	160 (3.0)
Total white cell count	455 (2.7)	Total white cell count	158 (3.0)
Mean corpuscular volume	443 (2.7)	Serum alkaline phosphatase	150 (2.8)
Serum albumin	443 (2.7)	Mean corpuscular volume	144 (2.7)
Red blood cell count	395 (2.4)	Neutrophil count	143 (2.7)
Serum alkaline phosphatase	393 (2.4)	Serum urea level	141 (2.7)
Neutrophil count	383 (2.3)	Lymphocyte count	136 (2.6)
Lymphocyte count	380 (2.3)	Monocyte count	136 (2.6)
Monocyte count	379 (2.3)	Red blood cell count	136 (2.6)
Eosinophil count	375 (2.3)	Eosinophil count	135 (2.6)
Mean corpuscular hemoglobin	368 (2.2)	Mean corpuscular hemoglobin	132 (2.5)
Basophil count	357 (2.1)	Basophil count	123 (2.3)
International normalized ratio	345 (2.1)	Hematocrit	119 (2.2)
Hematocrit	324 (2.0)	Serum total bilirubin level	98 (1.9)
Mean corpuscular hemoglobin concentration	291 (1.8)	GFR calculated abbreviated MDRD	97 (1.8)
Serum calcium	256 (1.5)	Mean corpuscular hemoglobin concentration	95 (1.8)
Serum inorganic phosphate	242 (1.5)	ALT/SGPT serum level	93 (1.8)
Corrected serum calcium level	238 (1.4)	Red blood cell distribution width	93 (1.8)
Full blood count	216 (1.3)	Serum total protein	90 (1.7)
Serum total bilirubin level	201 (1.2)	International normalized ratio	83 (1.6)
ALT/SGPT serum level	194 (1.2)	Serum bilirubin level	59 (1.1)
GFR calculated abbreviated MDRD	194 (1.2)	Serum globulin	59 (1.1)
Serum cholesterol	188 (1.1)	Liver function test	57 (1.1)
Serum total protein	184 (1.1)	Serum gamma-glutamyl transferase level	54 (1.0)
Serum bicarbonate	181 (1.1)	Serum TSH level	50 (0.9)

[a]The 30 most frequent diagnostic tests represent 65.9% of all 16 610 tests.
[b]The 30 most frequent diagnostic tests represent 69.1% of all 5293 tests.
ALT, alanine aminotransferase; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease study equation; SGPT, serum glutamic pyruvic transaminase; TSH, thyroid stimulating hormone.

were £8115 (£7450.26; £5840.11) and £9988 (£8237.24; £8187.15) for kidney and liver transplants, respectively. Total costs substantially increased during the last year before graft failure, compared with the relatively stable costs reported during years 2–5. For liver transplant patients, costs were statistically significantly ($P < 0.05$) higher for female patients compared with male patients. Although the exact explanation for the higher reported cost in female liver transplant patients is unclear, it is possible that this may reflect, in part, the disparities in posttransplantation outcomes between male and female patients. For example, compared with male transplant patients, females have a slightly greater incidence of retransplantation.[29] This is possibly related to the recurrence of diseases, such as primary biliary cirrhosis and autoimmune hepatitis, which were responsible for the primary liver transplant.[29] Likewise, the recurrence of hepatitis C is also possibly related.[30] However, the development of effective antiviral treatments[31] questions whether sex differences will exist in future hepatitis C populations.

Inpatient visits were the biggest cost driver in the year before graft failure, confirming findings from other studies which analyzed the costs associated with kidney and liver transplant patients.[32,33] In the last year before graft failure, the reasons for hospitalization in our study were widespread and either related or unrelated to transplantation. Therefore, if strategies to avoid or defer inpatient interventions, such as those recommended by the Consensus on Managing Modifiable Risk in Transplantation group,[34] can be implemented, this will most likely impact the total healthcare costs in the last year before graft failure. In addition, the assessment of hospitalizations that could potentially be managed in a less costly outpatient setting may also help to reduce overall costs.

The Consensus on Managing Modifiable Risk in Transplantation group reports the importance of using comprehensive methods to identify and manage potentially reversible risk factors for graft failure in kidney and liver transplant recipients.[34] These modifiable risk factors over the longer term include issues related to immunosuppression, such as nonadherence and side effects. It is possible that closer clinical management of these risk factors in transplanted patients could plateau the costs in all the years before failure rather than significantly increasing costs in the last year.

Strategies that might accurately diagnose early graft failure would be beneficial. A study being conducted by Dorling et al[35] is evaluating the use of a combined antibody/treatment program in patients receiving a kidney transplant. The study

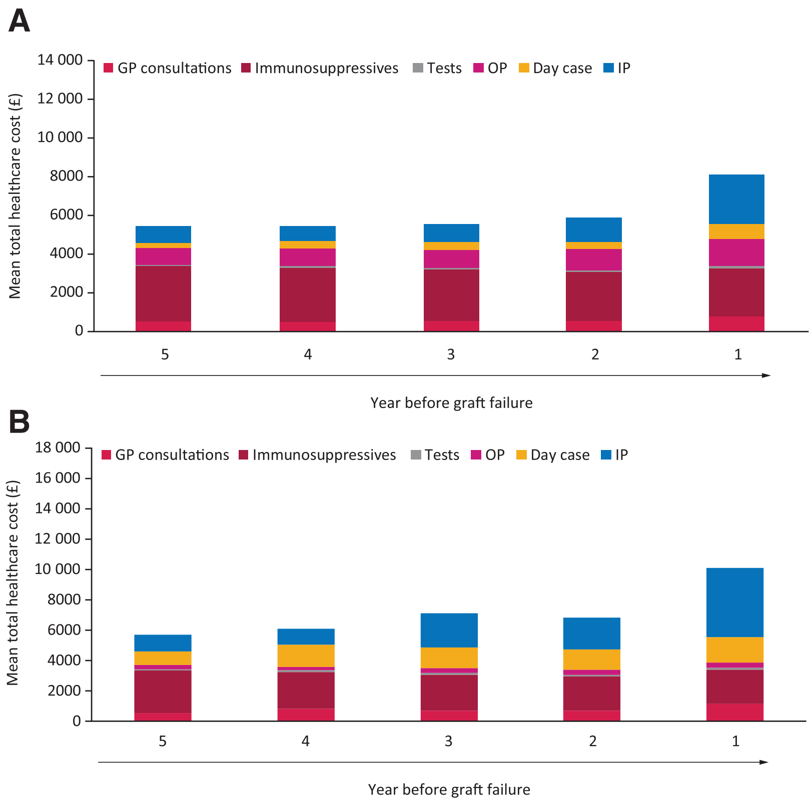

FIGURE 2. Mean total healthcare costs by year and component. A, Kidney. B, Liver. GP, general practitioner; IP, inpatient visits; OP, outpatient visits.

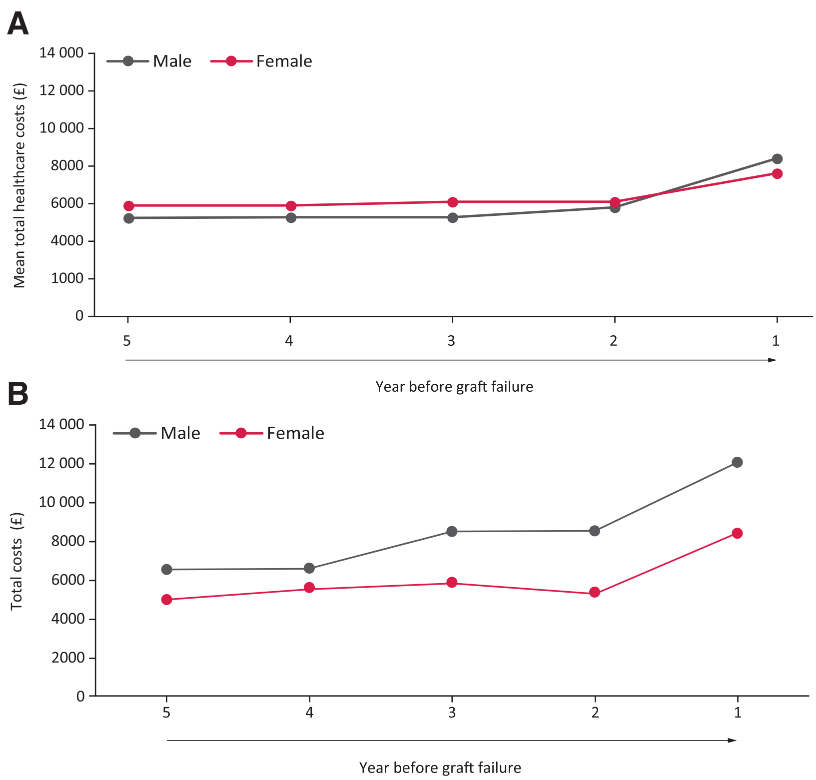

FIGURE 3. Total costs as a function of time to graft failure and sex. A, Kidney transplant cohort. B, Liver transplant cohort.

aims to enhance graft function and delay graft failure through screening patients for antibodies against human leukocyte antigens to ensure that these patients, who are at a high risk of premature graft failure, are identified and treated accordingly. If a biomarker-led care regimen proved clinically beneficial and delayed the onset of graft failure, this may also reduce

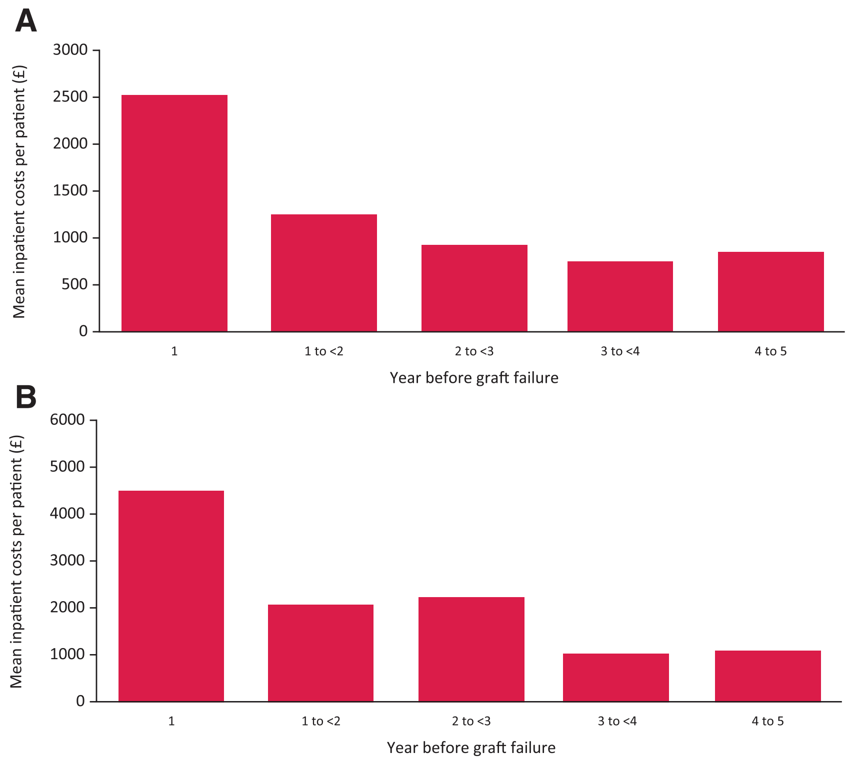

FIGURE 4. Mean inpatient costs per patient in the year before graft failure and years 2–5 before graft failure. A, Kidney transplant cohort. B, Liver transplant cohort.

TABLE 7.

Mean total healthcare costs by year

Time before graft failure/death after transplantation[a]	Mean cost (SD) per patient (£)	Median cost (IQR) per patient (£)
Kidney transplant cohort		
Last y	8115 (4539)	7450 (5840)
Males	8413 (4726)	7705 (5722)
Females	7648 (4210)	6897 (5677)
From 1 to 2 y	5925 (3155)	5697 (4276)
From 2 to 3 y	5575 (3253)	4812 (4181)
From 3 to 4 y	5469 (2976)	4723 (3203)
From 4 to 5 y	5468 (3242)	4818 (3319)
Liver transplant cohort		
Last y	9988 (6703)	8237 (8187)
Males	8421 (5651)	6927 (5627)
Females	12 048 (7468)	10 027 (10 264)
From 1 to 2 y	6763 (4940)	5451 (6107)
From 2 to 3 y	7042 (5812)	5433 (5870)
From 3 to 4 y	6020 (5518)	4089 (3272)
From 4 to 5 y	5651 (3074)	5797 (3406)

[a]Refers to the number of y before graft failure, not the number of y posttransplantation.
IQR, interquartile range; SD, standard deviation.

treatment costs per year, as graft failure has been shown to be a cost-driving event.[36] Measurement of serum creatinine is a common approach for the assessment of graft function or risk for graft loss, and ≥3.0 mg/dL appears to be associated with the lowest projected kidney graft half-life.[37] In our study, 839 creatinine tests were performed in 269 kidney patients in the year before graft failure.

Compared with randomized controlled trials, this study was able to measure healthcare resource utilization and costs over a longer time period through the use of real-world data.[38-40] As such, our results were based on data taken from a representative transplant patient population in the CPRD and associated HES databases in the United Kingdom. While unit costs would vary, it is likely that our key findings (significantly higher costs in the last year before graft failure, compared with years 2–5) would also pertain to other countries.

Our analysis also provides an accurate source of data to estimate healthcare resource use and costs associated with graft failure in the time leading up to the event. Higher resource use and costs in the last year before graft failure compared with

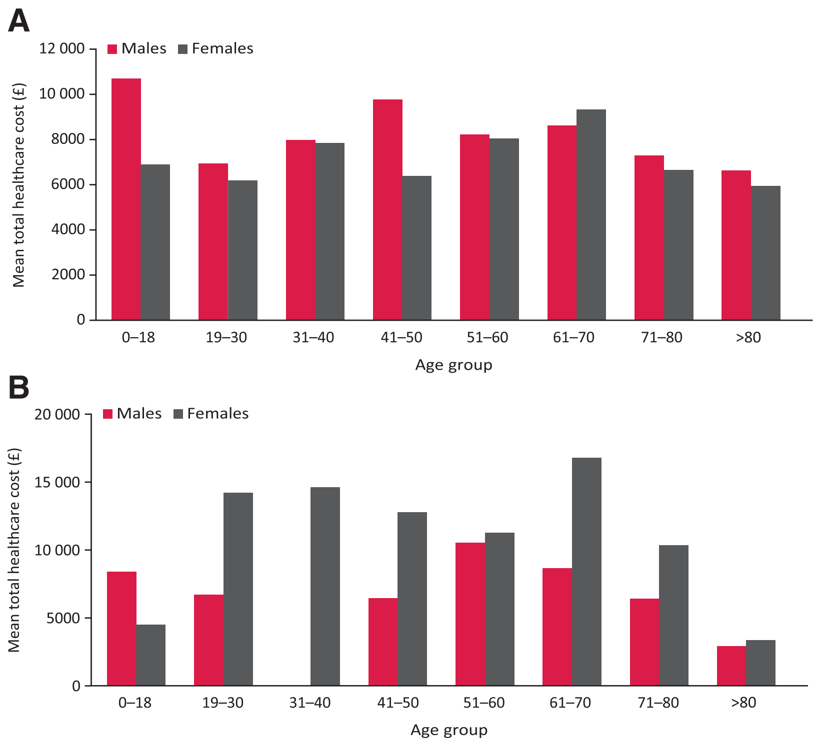

FIGURE 5. Mean total healthcare costs by age and sex. A, Kidney transplant cohort. B, Liver transplant cohort.

years 2–5 is probably not unexpected. However, this study represents the first time that resources and costs have been estimated in the year before graft failure in renal and liver transplantation. These data could be used as inputs in future health economic assessments (eg, cost-effectiveness analyses of immunosuppressant therapies) and support payers in their decision-making. In addition, there may be justification to update cost-effectiveness analyses to account for intermediate states of disease progression, where the costs substantially increase before failure. Implications from our study may suggest that the cost of treating transplanted patients with immunosuppressants has been previously underestimated.

Important limitations of our studies should be noted. For instance, these studies have the established limitations of any retrospective analysis. However, given the lengthy period of this analysis, such studies would be difficult to undertake prospectively. The possibility of misclassification bias, and the fact that temporal relationships are often difficult to assess, are also limitations. Critically, this study is a conservative analysis and potentially underestimates the actual costs incurred leading up to kidney or liver graft failure. For example, as kidney graft failure is not an acute event and happens over time, dialysis is often implemented as a part of a care package before allograft failure; however, our analysis does not account for these costs. Additional renal costs, such as management of episodes of antibody-mediated rejection and re-establishing vascular access for patients whose grafts fail and need to be returned to dialysis, have not been fully captured in the total healthcare costs. Likewise, other secondary care costs, such as those associated with radiology (inpatient/outpatient) and bed stays (by type of bed: general ward, high dependency unit, intensive care unit) are not included in our analysis.

Nevertheless, a longitudinal analysis has been possible due to the size of the original database. To this end, our novel findings highlight the substantial burden placed on healthcare services in the years leading up to graft failure. On the basis of our results, future studies are recommended to compare healthcare resource utilization and costs in patients with and without graft failure. For example, it may be of value to evaluate resource use in patients whose creatinine rises above a certain threshold (eg, 3.0 mg/dL).

CONCLUSION

In conclusion, total healthcare costs in the year before graft failure in both kidney and liver transplant patients are substantial and significantly greater ($P < 0.05$) than the earlier years posttransplantation.

ACKNOWLEDGMENTS

The research presented in this manuscript was funded by Astellas Pharma Inc. Medical writing support was provided by Joseph Norvill of Bioscript Medical and funded by Astellas Pharma Inc.

REFERENCES

1. Boissier R, Hevia V, Bruins HM, et al. The risk of tumour recurrence in patients undergoing renal transplantation for end-stage renal disease after previous treatment for a urological cancer: a systematic review. *Eur Urol*. 2018;73:94–108.
2. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant*. 2011;11:2093–2109.
3. Yang LS, Shan LL, Saxena A, et al. Liver transplantation: a systematic review of long-term quality of life. *Liver Int*. 2014;34:1298–1313.
4. Hou X, Sui W, Che W, et al. Current status and recent advances in liver transplant using organs donated after cardiac death. *Exp Clin Transplant*. 2015;13:6–18.

5. Garcia GG, Harden P, Chapman J, et al. The global role of kidney transplantation. *J Nephropathology*. 2012;1:69–76.
6. NHS Blood and Transplant Factsheet 7. *Cost-effectiveness of transplantation 2009*. Available at https://nhsbtmediaservices.blob.core.windows.net/organ-donation-assets/pdfs/Organ_Donation_Registry_Fact_Sheet_7_21337.pdf. Accessed February, 2018.
7. Sagmeister M, Mullhaupt B, Kadry Z, et al. Cost-effectiveness of cadaveric and living-donor liver transplantation. *Transplantation*. 2002;73:616–622.
8. Pham P-T, Everly M, Faravardeh A, et al. Management of patients with a failed kidney transplant: dialysis reinitiation, immunosuppression weaning, and transplantectomy. *World J Nephrol*. 2015;4:148–159.
9. Ostroff JW. Management of biliary complications in the liver transplant patient. *Gastroenterol Hepatol (N Y)*. 2010;6:264–272.
10. Traynor C, Jenkinson A, Williams Y, et al. Twenty-year survivors of kidney transplantation. *Am J Transplant*. 2012;12:3289–3295.
11. Dopazo C, Bilbao I, Castells LL, et al. Analysis of adult 20-year survivors after liver transplantation. *Hepatol Int*. 2015;9:461–470.
12. Arulraj R, Neuberger J. Liver transplantation: filling the gap between supply and demand. *Clin Med*. 2011;11:194–198.
13. Courtney AE, Maxwell AP. The challenge of doing what is right in renal transplantation: balancing equity and utility. *Nephron Clin Pract*. 2009;111:c62–c67.
14. Hwang I, Shin DW, Kang KH, et al. Medical costs and healthcare utilization among cancer decedents in the last year of life in 2009. *Cancer Res Treat*. 2016;48:365–375.
15. Tanuseputro P, Wodchis WP, Fowler R, et al. The health care cost of dying: a population-based retrospective cohort study of the last year of life in Ontario, Canada. *PLoS One*. 2015;26:10:e0121759.
16. Geue C, Briggs A, Lewsey J, et al. Population ageing and healthcare expenditure projections: new evidence from a time to death approach. *Eur J Health Economics*. 2014;15:885–896.
17. Ferraz M, Miranda IC, Padovan J, et al. Health care costs in the last four years of life for private health care plan beneficiaries in Brazil. *Rev Panam Salud Publica*. 2008;24:7120–7126.
18. Department of Health. *NHS reference costs 2015 to 2016*. 2016. Available at https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016. Accessed February, 2018.
19. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44:827–836.
20. NHS Digital. *Hospital Episode Statistics 2017*. Available at https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics#about-the-hes-database. Accessed February, 2018.
21. Curtis L, Burns A. Unit Costs of Health and Social Care 2015. Canterbury: Personal Social Services Research Unit, University of Kent; 2015.
22. British National Formulary (BNF). Available at https://bnf.nice.org.uk/drug. Accessed February, 2018.
23. Department of Health. *NHS reference costs 2014 to 2015*. Available at https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Accessed February, 2018.
24. Diggle P, Heagarty, P, Liang K-Y, et al. Analysis of Longitudinal Data. Oxford Statistical Science Series No 25. 2nd ed. Oxford: Oxford University Press; 2002.
25. Fitzmaurice GM, Ravichandran C. A primer in longitudinal data analysis. *Circulation*. 2008;118:2005–2010.
26. Jüurgensen JS, Arns W, Hass B, et al. Cost-effectiveness of immunosuppressive regimens in renal transplant recipients in Germany: a model approach. *Eur J Health Economics*. 2010;11:15–25.
27. Marcén R, Morales JM, Fernández-Rodriguez A, et al. Long-term graft function changes in kidney transplant recipients. *NDT Plus*. 2010;3(Suppl_2):ii2–ii8.
28. Schoening W, Buescher N, Rademacher S, et al. Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. *Am J Transplant*. 2013;13:2384–2394.
29. Oloruntoba OO, Moylan CA. Gender-based disparities in access to and outcomes of liver transplantation. *World J Hepatol*. 2015;7:460–467.
30. Sarkar M, Watt KD, Terrault N, et al. Outcomes in liver transplantation: does sex matter? *J Hepatol*. 2015;62:946–955.
31. Doyle JS, Thompson AJ, Higgs P, et al. New hepatitis C antiviral treatments eliminate the virus. *Lancet*. 2017;390:358–359.
32. Oostenbrink JB, Kok ET, Verheul RM, et al. A comparative study of resource use and costs of renal, liver and heart transplantation. *Transplant Int*. 2005;18:437–443.
33. 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;15:11–18.
34. Neuberger JM, Bechstein WO, Kuypers DR, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus On Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation*. 2017;101(4S Suppl 2):S1–S56.
35. Dorling A, Rebollo-Mesa I, Hilton R, et al. Can a combined screening/treatment programme prevent premature failure of renal transplants due to chronic rejection in patients with HLA antibodies: study protocol for the multicentre randomised controlled OuTSMART trial. *Trials*. 2014;15:30.
36. Hagenmeyer EG, Häussler B, Hempel E, et al. Resource use and treatment costs after kidney transplantation: impact of demographic factors, comorbidities, and complications. *Transplantation*. 2004;77:1545–1550.
37. Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int*. 2002;62:311–318.
38. Garrison L Jr, Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: The ISPOR Real-World Data Task Force report. *Value Health*. 2007;10:326–335.
39. Sawinski D, Trofe-Clark J, Leas B, et al. Calcineurin inhibitor minimization, conversion, withdrawal, and avoidance strategies in renal transplantation: a systematic review and meta-analysis. *Am J Transplant*. 2016;16:2117–2138.
40. Goring SM, Levy AR, Ghement I, et al. A network meta-analysis of the efficacy of belatacept, cyclosporine and tacrolimus for immunosuppression therapy in adult renal transplant recipients. *Curr Med Res Opin*. 2014;30:1473–1487.