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Healthcare Resource Use, Cost, and Sick Leave Following Kidney Transplantation in Sweden: A Population-Based, 5-Year, Retrospective Study of Outcomes: COIN

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Data Interpretation D
Manuscript Preparation E
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Background: Improved understanding of the impact of kidney transplantation on healthcare resource use/costs and loss of productivity could aid decision making about funding allocation and resources needed for the treatment of chronic kidney disease in stage 5.

Material/Methods: This was a retrospective study utilizing data from Swedish national health registers of patients undergoing kidney transplantation. Primary outcomes were renal disease-related healthcare resource utilization and costs during the 5 years after transplantation. Secondary outcomes included total costs and loss of productivity. Regression analysis identified factors that influenced resource use, costs, and loss of productivity.

Results: During the first year after transplantation, patients (N=3120) spent a mean of 25.7 days in hospital and made 21.6 outpatient visits; mean renal disease-related total cost was €66,014. During the next 4 years, resource use was approximately 70% (outpatient) to 80% (inpatient) lower, and costs were 75% lower. Before transplantation, 62.8% were on long-term sick leave, compared with 47.4% 2 years later. Higher resource use and costs were associated with age <10 years, female sex, graft from a deceased donor, prior hemodialysis, receipt of a previous transplant, and presence of comorbidities. Higher levels of sick leave were associated with female sex, history of hemodialysis, and type 1 diabetes. Overall 5-year graft survival was 86.7% (95% CI 85.3–88.2%).

Conclusions: After the first year following transplantation, resource use and related costs decreased, remaining stable for the next 4 years. Demographic and clinical factors, including age <10 years, female sex, and type 1 diabetes were associated with higher costs and resource use.

MeSH Keywords: **Cost of Illness • Dialysis • Graft Survival • Registries • Regression Analysis • Renal Insufficiency, Chronic**

Abbreviations: **CI** – confidence interval; **DRG** – Diagnosis-Related Group; **GLM** – generalized linear model; **HD** – hemodialysis; **ICD-10** – International Classification of Diseases 10th version; **IQR** – interquartile range; **LISA** – longitudinal integration database for health insurance and employment status; **NCDR** – National Cause of Death Register; **NDR** – National Prescribed Drug Register; **NPR** – National Patient Register; **PD** – peritoneal dialysis; **SD** – standard deviation

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Background

For patients with end-stage renal disease, kidney transplantation is associated with reduced risk of death, improved quality of life, and reduced healthcare cost compared with chronic dialysis treatment [1–3]. At 43.5 per million population, the annual rate of deceased and live donor kidney transplantation in Sweden lies between that of other European countries and those in North America (e.g., Germany at 27.2, Italy 31.5, Canada 40.0, United Kingdom 49.0, United States 57.8, and Spain 63.0) [4]. However, graft survival rates (including annual rates) vary considerably between countries; for example, the 5-year graft survival rate following a first deceased-donor kidney transplantation was 77.0% in Europe, and between 62.5% and 72.9% in the United States between 2005–2008 [5]. By comparison, 5-year graft survival rates are considerably higher in Sweden (more than 90%) [6].

The geographical differences in long-term graft survival may be partly driven by disparity in donor type, recipient comorbidities, or other patient characteristics among the countries being compared. Importantly, different healthcare funding systems may also influence follow-up routines and therapeutic choices, such as immunosuppressive regimen, which could influence graft survival. Therefore, better understanding of the long-term healthcare utilization for kidney transplanted patients in a country with high graft survival, such as Sweden, can support healthcare decision makers to prioritize between treatment options, and to provide information for cost-effectiveness and cost-benefit analyses.

Previous studies have investigated resource use and costs associated with kidney transplantation [7–12]. The applicability of findings from some of these studies has, however, been limited by a number of factors, such as the use of restricted patient groups. Other factors include the use of single centers in some studies [8–10], the use of data collection methods, such as interviews, which limit the types of data that can be collected and the interpretation of results [10], follow-up periods of 3 years or shorter [7–11], and failure to capture the costs of prescribed drugs [12]. In Sweden, healthcare data can be collected through a series of health registers with national coverage, such as the National Patient Register (NPR), the National Prescribed Drug Register (NDR), the National Cause of Death Register (NCDR), and the longitudinal integration database for health insurance and employment status (LISA). These registers provide longitudinal data, with close to complete coverage of patients, that can be utilized in healthcare and real-world evidence research [13].

A better understanding of the long-term healthcare utilization for kidney transplant recipients might improve transplant outcomes, and the efficient allocation of healthcare funding. We conducted a retrospective study to estimate healthcare resource utilization and related costs during the 5 years following renal transplant, for patients in Sweden. These post-transplantation cost data can feed into cost-effectiveness evaluations, and provide information to help decision makers prioritize between treatment options. To our knowledge, this is the first national study of its kind on this topic based on a large, population-based cohort with long-term follow-up that includes a comprehensive list of resource use categories collected from compulsory administrative registers.

Material and Methods

Design and setting

This was a non-interventional, retrospective population-based cohort study. The study utilized anonymized patient data from the health registers with national coverage in Sweden, including the NPR, NDR, NCDR, and LISA.

Patients

All patients who underwent at least one kidney transplantation in Sweden between 1 July, 2005, and 31 December, 2013, were identified in the NPR (Figure 1). The date of admission for their first kidney transplantation was defined as the index date for each patient. Individual patient data for demographics and baseline characteristics (i.e., pre-transplantation) were derived from the period 2 years before transplantation. Patients were followed to the end of study period, or date of emigration from Sweden or death, if earlier. All patient-level data were de-identified.

Study outcomes

The primary outcome was renal disease-related healthcare resource utilization and costs in kidney transplant patients at annual intervals for the first 5 years following their transplant. The secondary outcomes were the total healthcare costs for these patients, at annual intervals over 5 years, and loss of productivity for patients (the proportion taking early retirement from work and the total number of long-term sick leave days during the 3 years before and after transplantation).

A post-hoc regression analysis was also performed to explore the relationships between patient-related factors, such as patient demographics and comorbidities, and healthcare resource use and related costs. In the post-hoc analysis, loss of productivity following kidney transplantation and graft survival were also assessed.

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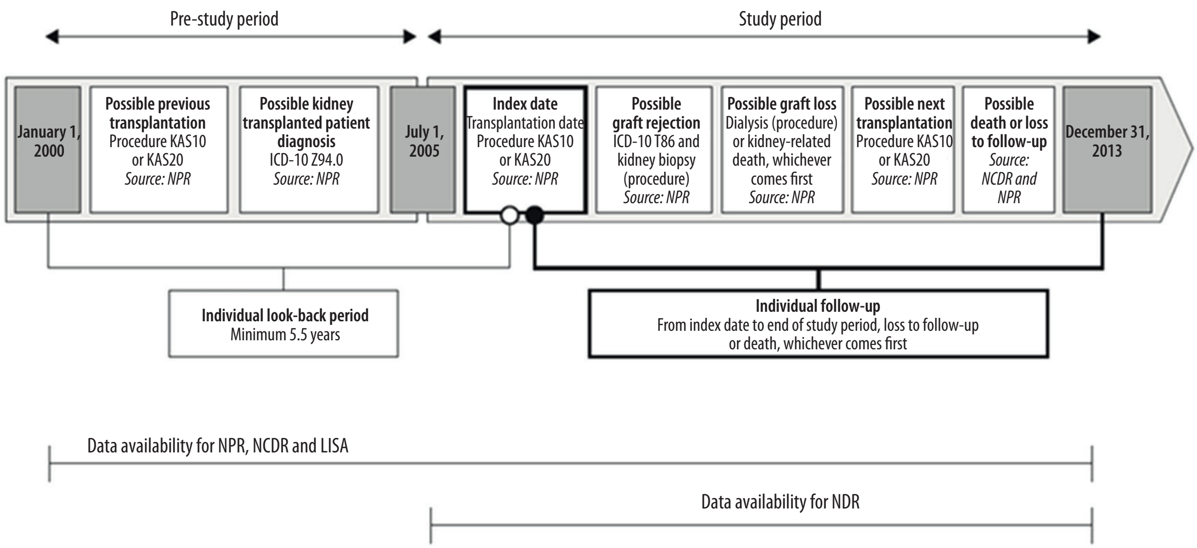

Figure 1. Study timeline and data sources. ICD-10 – International Classification of Diseases 10th version; LISA – longitudinal integration database for health insurance and employment status; NCDR – National Cause of Death Register; NDR – National Prescribed Drug Register; NPR – National Patient Register

Analysis of resource use and costs

Data on both outpatient and inpatient visits (including data on procedures and diagnoses) were derived from the NPR. Primary care visits were not included in the study, as transplantation-related healthcare is mainly provided in secondary care in Sweden. The NDR includes data of all dispensations of prescribed medication and was used to derive total cost per patient during follow-up. Non-prescription medication was out of scope for the study, due to lack of a national registry. The NCDR was used to derive dates of deaths, which were used to establish length of follow-up. Productivity loss was derived from the LISA register by calendar year, with long-term sick leave defined as episodes >14 days. Healthcare resource use was analyzed for inpatient visits, inpatient days, outpatient visits, dialysis outpatient visits, and any other outpatient visits. Healthcare costs included the cost of these resources plus the cost of prescribed medications. The analysis distinguishes between healthcare resource use and costs related to renal disease, and those unrelated to renal disease.

Healthcare visits were considered renal disease-related if the department was a nephrology clinic, transplantation clinic, or an internal medicine clinic; the primary diagnosis was kidney transplant status or an encounter for care involving renal dialysis; or a kidney transplant procedure was performed during the visit (Supplementary Table 1, SDC). The following drug categories were considered renal disease-related: antibacterials, antimycotics, antivirals, glucocorticoids, immunoglobulins, monoclonal antibodies, calcineurin inhibitors, selective immunosuppressants, interleukin inhibitors, and any other immunosuppressant agents (see Supplementary Methods 1, SDC).

Resource use and costs were estimated based on the dates of hospital admission or outpatient healthcare contact and the dispensing dates of drugs with respect to the index date. Costs associated with healthcare resource use were derived according to the Diagnosis-Related Groups (DRG) for each visit (see Supplementary Methods 2, SDC). Costs of prescribed medication included both the subsidy and the out of pocket payment, with costs for medication used at hospitals included in the DRG. Costs associated with the occurrence of acute rejection were included within the costs of medication use and hospitalizations. All costs were presented in Euros as at year 2015 (exchange rate: 1 SEK=0.1070 EUR).

General statistical analysis

No statistical power or sample size calculations were performed. Continuous outcome variables were presented with means, medians and other descriptive statistics. Results were presented for the population as a whole without accounting for any post-transplantation events. Categorical variables were presented as numbers with percentages.

Graft survival (defined as time to the first occurrence of chronic dialysis, re-transplantation, or death) was evaluated using Kaplan-Meier survival analysis. The proportion of patients with functioning grafts (with or without censoring at death) was presented at each year of follow-up.

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Table 1. Patient characteristics.

	Main cohort (N=3210)	Previously received a graft (n=496)	Transplant naïve (n=2714)
Age at index date			
Mean (SD)	48.8 (15.4)	48.1 (13.3)	48.9 (15.8)
Median	51.0	49.0	52.0
IQR	40.0, 61.0	40.0, 59.0	40.0, 61.0
Range	1.0–79.0	9.0–75.0	1.0–79.0
Female, n (%)	1161 (36.2)	180 (36.3)	981 (36.1)
Charlson comorbidity index			
Mean (SD)	3.0 (1.5)	3.0 (1.4)	3.1 (1.5)
Median	2.0	2.0	2.0
IQR	2.0, 4.0	2.0, 3.0	2.0, 4.0
Range	0.0–12.0	2.0–12.0	0.0–12.0
Number of hospitalization days during 2 years before index date			
Mean (SD)	31.8 (30.9)	34.0 (27.0)	31.4 (31.5)
Median	23.0	26.0	22.0
IQR	15.0, 38.0	16.0, 43.0	14.0, 38.0
Range	2.0–472.0	4.0–237.0	2.0–472.0
Number of outpatient visits during 2 years before index date			
Mean (SD)	69.6 (102.6)	89.4 (121.5)	66.0 (98.3)
Median	20.0	25.5	19.0
IQR	11.0, 74.0	12.0, 120.5	11.0, 67.0
Range	0.0–598.0	0.0–596.0	0.0–598.0

IQR – interquartile range; SD – standard deviation.

Data analyses were performed using SAS version 9.3 (SAS institute, Cary, NC, USA). P<0.05 was considered statistically significant.

Regression analysis

Regression analysis was applied to identify patient-related factors that could be associated with the resource use and cost following transplantation. Generalized linear models (GLM) with log link were fitted for each outcome given the skewed distribution of costs and resource use. Three analyses were performed for these outcome variables, a base case outcome after 3 years' follow-up, plus 2 sensitivity analyses for outcomes after 1 and 5 years. Covariates for analyses were selected based on clinical opinion about key drivers of resource use and costs in newly-transplanted patients. These were as follows: age stratified into 10-year bands (i.e., 0–9, 10–19, 20–29 years, etc.), male or female sex, transplant center (transplants are conducted at 4 centers in Sweden), transplant-naïve or previously received at least one other graft, deceased or living donor, type of dialysis (i.e., hemodialysis [HD], peritoneal dialysis [PD], HD+PD, or none), time in dialysis (in months), underlying kidney disease, comorbidities (glomerulonephritis, polycystic kidney adult type, hypertension, chronic tubule-interstitial nephritis, type 1 and 2 diabetes, other congenital malformations of the kidney, malignancy, and heart failure), and index year. The same set of covariates were used for all models.

All covariates were defined at index or during the 2 years before the index date; therefore, only patients with at least 2 years' pre-index data available were included in the analyses. Similar regression analyses were performed to estimate predictors of long-term sick leave. This was measured as the total number of days of long-term sick leave during the 2 calendar

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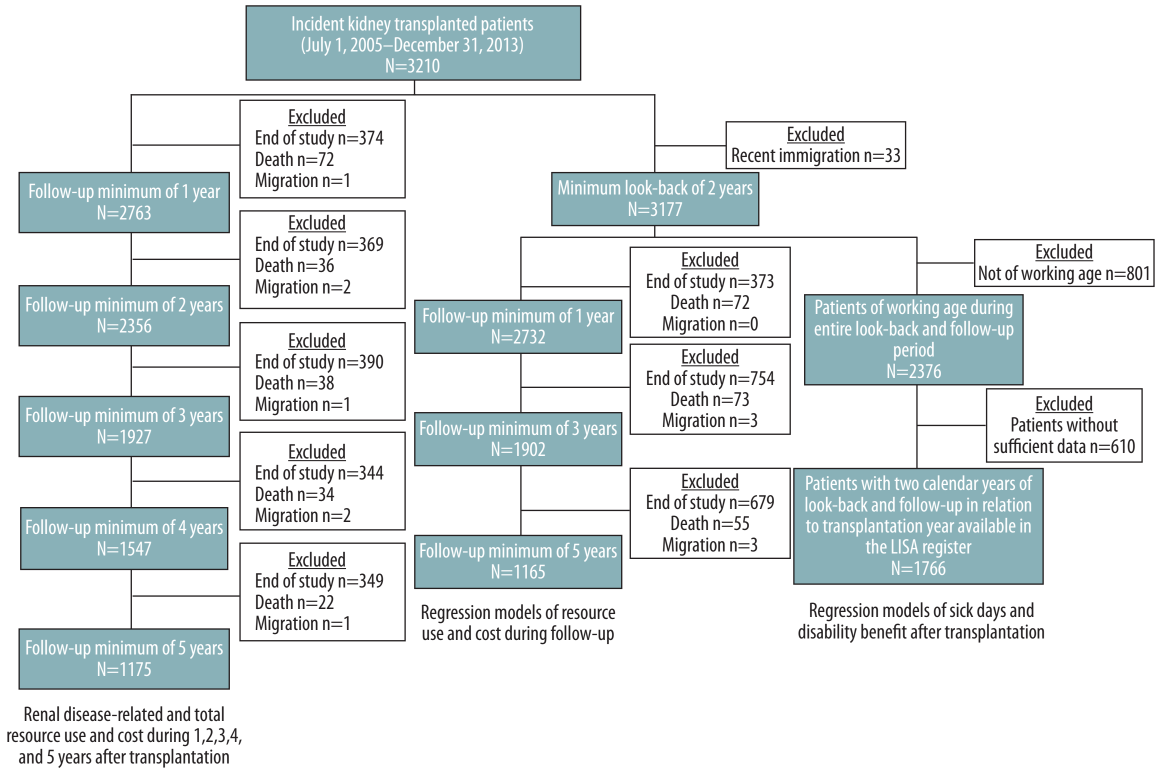

Figure 2. Patient flow overview. LISA – longitudinal integration database for health insurance and employment status.

years following the calendar year of transplantation. In addition to the covariates above, baseline productivity status (number of sick leave days during the 2 calendar years before transplantation), the quarter when the transplantation was performed (as sick leave days are measured by calendar year), and the receipt of disability benefit during 2 calendar years before transplantation were included.

Results

Patient population

Overall, 3210 patients (mean age at index: 48.8 years; 36.2% women), constituting the total patient population, underwent at least one kidney transplant procedure during the study period. Most (84.5%; 2714) were renal transplantation-naïve, but 496 (15.5%) patients had previously received at least one other kidney graft (Table 1). Grafts from deceased donors were received by 1950 (60.7%) patients. The median duration of patient follow-up was 3.8 years (interquartile range [IQR] 1.9–5.9) with 3177 (99.0%) patients having at least 2 years of look-back (characteristics for these patients presented in Supplementary Table 2, SDC). An overview of the number of patients with data for each year of the follow-up period is shown in Figure 2.

Healthcare resource use and costs

During the first year after transplantation, patients spent a mean (standard deviation; SD) of 25.7 (25.5) days (median 18.0, range 3.0–321.0 days) as inpatients, with a mean (SD) of 3.2 (2.7) (median 2.0, range 1.0–44.0) hospitalizations (including that for transplantation) and had a mean (SD) of 21.6 (8.2) (median 21.0, range 0.0–64.0) outpatient visits (excluding visits for laboratory tests only). In the second year, there was a sharp decline in both inpatient days and outpatient visits (approximately 80% and 70% decreases, respectively), which remained at a lower level through to year 5 (mean 4.0–4.3 inpatient days and 4.5–6.5 outpatient visits annually during Years 2–5). The mean number of dialysis visits, however, increased over time as more patients experienced graft loss and required chronic dialysis (Figure 3).

Renal disease-related costs were highest during the first year after transplantation (mean €66,014 per patient; Figure 4), with hospitalization accounting for more than half of this (mean €45,165 per patient). Renal disease-related costs decreased somewhat after the first year, mainly because of fewer hospitalizations and outpatient visits (Figure 4). Drug-related costs, however, remained constant between Years 2 and 5 (€5661–6635 per patient/year), and were the largest renal disease-related cost from year 2 onwards (i.e., 43.0–46.4% per year).

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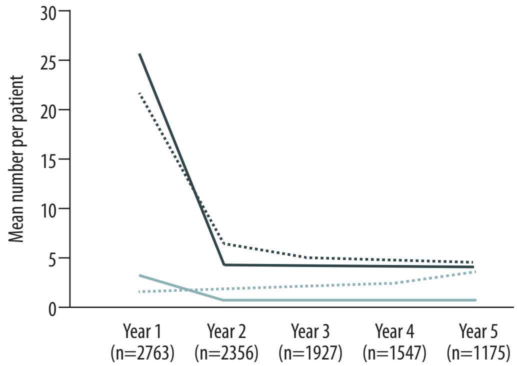
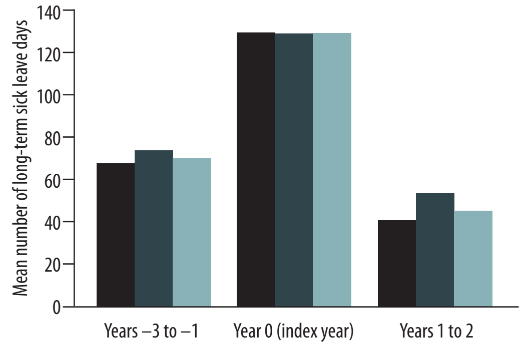


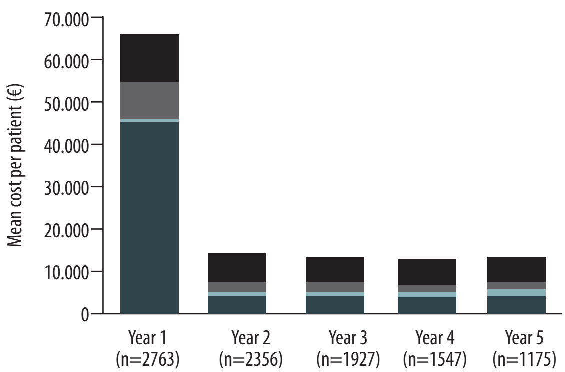
	Year 1 (n=2763)	Year 2 (n=2356)	Year 3 (n=1927)	Year 4 (n=1547)	Year 5 (n=1175)
Hospitalizations	3.2 (2.7)	0.8 (1.9)	0.8 (1.7)	0.8 (1.6)	0.8 (1.9)
Days in hospital	25.7 (25.5)	4.3 (13.3)	4.2 (14.1)	4.0 (12.2)	4.0 (11.9)
Dialysis visit	1.7 (12.4)	1.9 (15.4)	2.2 (17.7)	2.4 (17.9)	3.5 (22.1)
Outpatient visits	21.6 (8.2)	6.5 (4.0)	5.1 (3.4)	4.7 (3.3)	4.5 (3.2)

Figure 3. Number of renal disease-related healthcare visits and hospital days per patient and by year of follow-up. Data presented in the table are mean (standard deviation).



	Years –3 to –1	Year 0 (index year)	Years 1 to 2
Men (n=915)	67.0 (85.8)	129.0 (130.4)	40.2 (75.0)
Women (n=546)	73.3 (91.6)	128.8 (138.0)	53.1 (87.0)
Total (n=1461)	69.3 (88.0)	128.9 (133.3)	45.0 (79.9)

Figure 5. Number of long-term sick leave days per patient and year. Data presented in the table are mean (standard deviation).



	Year 1 (n=2763)	Year 2 (n=2356)	Year 3 (n=1927)	Year 4 (n=1547)	Year 5 (n=1175)
Cost of drug use	11,207 (4888)	6635 (3330)	6205 (3087)	6011 (3218)	5661 (3029)
Cost of other outpatient visits	8893 (3443)	2672 (1665)	2097 (1404)	1937 (1361)	1852 (1370)
Cost of outpatient dialysis visits	749 (5416)	828 (6712)	947 (7629)	1032 (7624)	1452 (9225)
Cost of hospitalizations	45,165 (17,905)	4184 (10,647)	4178 (11,490)	3969 (9389)	4208 (9838)

Figure 4. Renal disease-related costs per patient and by year of follow-up. Data presented in the table are mean (standard deviation).

A substantial proportion of the total prescribed drug costs during the follow-up period was due to renal disease-related drugs. These accounted for 81.9% of total drug costs during the first year (€11,207 of €13,681 per patient), decreasing to 75.5% (€5661 of €7497 per patient) after 5 years. Similarly, renal disease-related costs accounted for 94.1% of the total healthcare cost during the first year, but decreased to 79.5–80.0% during Years 2–5 (data not shown).

Loss of productivity

During the 3 years preceding the index year, 647 (44.3%) working-age patients were in early retirement. The number of early retirees increased to 688 (47.1%) by the end of the index year, and was 696 (47.6%) at the end of the 2 years following the index year. In the 3 years before transplantation, the proportion of patients on long-term sick leave (mean number of annual sick leave days) was 62.8% (69 days), and then 61.4% (129 days) during the index year. This decreased to 47.4% (45 days) in the 2 years following the index year (Figure 5).

Regression analysis: Factors affecting healthcare resource use

The number of inpatient days during the first 3 years after transplantation was significantly higher for women than for men (by 18.3%; p<0.0001) (Table 2). Patients older than 10 years had fewer inpatient days compared with those younger than 10 years (all age bands p<0.0001), with the differences

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ranging from 56.5% to 75.0% fewer days in those aged 70 to 79 and 30 to 39 years, respectively. Patients who had previously received at least one other graft spent 21.6% more days in hospital than transplant-naïve patients (p<0.0001). Patients who had been on HD prior to transplantation spent more days in hospital than patients who were not in dialysis (preemptive patients) before their transplantation (14.5%; p=0.0427). Each additional month in dialysis was also associated with 0.9% more inpatient days (p=0.0021). Transplant clinics B, C, and D were associated with significantly fewer inpatient days compared with site A (all p<0.0001). Significantly higher numbers of inpatient days were observed in patients with 'other congenital malformations of kidney' (by 58.2%; p=0.0420), heart failure (57.3%; p<0.0001), type 1 diabetes (24.9%; p<0.0001), type 2 diabetes (15.1%; p<0.0162), and malignancies (12.9%; p<0.0161). Significantly lower numbers of inpatient days were observed in patients with chronic tubulointerstitial nephritis (by 20.1%; p=0.0137) and glomerulonephritis (14.9%; p=0.0002) (Table 2).

Women made 10.7% more outpatient visits than men (p<0.0001), and patients younger than 10 years made more than those older than 10 years; for example, patients younger than 10 years had 47.4% more outpatient visits than those aged 40 to 49 years (p<0.0001), and 30.0% more than those aged 10 to 19 years (p=0.001) (Table 2). Patients who had been on HD prior to transplantation made 22.3% more outpatient visits than those who had not received preemptive dialysis (p<0.0001); the effects of other types of dialysis were not significant. Donor status and previous receipt of a graft were not associated with the number of outpatient visits. Similar to inpatient days, transplant clinics C and D were associated with significantly fewer outpatient visits compared with site A (both p<0.0001). Compared with index year 2005, all later index years, except 2009, were associated with significantly fewer outpatient visits. Significantly higher numbers of outpatient days were observed in patients with malignancies (by 17.7%; p<0.0001), type 1 (but not type 2) diabetes (13.7%; p=0.0003), and hypertension (10.1%; p=0.0001) (Table 2).

Sensitivity analyses of 1 and 5 years of follow-up data for the regression analysis showed that the results from the main analysis were generally robust, with no unexpected differences in parameters during follow-up (Supplementary Table 3, SDC).

Regression analysis: Factors affecting healthcare costs

Total healthcare costs during the first 3 years after transplantation were 8.1% higher (p<0.0001) for women than for men, and for patients younger than 10 years compared with all the older 10-year age groups, ranging from 63.0% higher than for those aged 60 to 69 years, to 70.9% higher than for those aged 10 to 19 years (all p<0.0001) (Table 2). Patients with 'other congenital malformations of kidney', type 1 diabetes, heart failure, malignancies, and hypertension also had significantly higher healthcare costs, by 30.5% (p=0.0048), 13.9% (p<0.0001), 12.6% (p=0.0008), 6.1% (p=0.0051), and 3.7% (p=0.0232), respectively.

Sensitivity analyses of 1 and 5 years of follow-up data showed that the results from the main analysis were generally robust (Supplementary Table 3, SDC).

Regression analysis: Predictors of loss of productivity

Long-term sick leave during the first 2 years after transplantation was significantly higher among women compared with men (by 29.4%; p=0.0005). Higher levels of long-term sick leave were also associated with presence of type 1 diabetes (higher by 53.2%; p<0.0001) (Supplementary Table 3, SDC).

Graft survival

Graft survival was 95.6% (95% confidence interval [CI] 94.9–96.3%) and 86.7% (85.3–88.2%) after 1 and 5 years, respectively. Graft survival with censoring at death was 97.9% (95% CI 97.4–98.4%) and 94.2% (93.2–95.2%), respectively.

Discussion

This real-world, retrospective study used data from Swedish national health registers to examine healthcare resource use and costs associated with kidney transplantation, and loss of productivity, for up to 5 years following transplantation. The patient population was comparable with those included in other publications regarding, for example, the proportion of women, patient age, comorbidities, and donor types [7,8,10].

In this study, healthcare resource use and costs (including the cost of transplantation) declined after the first year following renal transplantation, and then was stable and sustained. The decline in costs was expected, given that dialysis is known to be more costly (outpatient HD costs €75,800 per patient annually in Sweden [12]) than a successful transplantation and that the 5-year death-censored graft survival rate following kidney transplantation is high in Sweden (91.2% and 95.0% for first graft from deceased and living donors, respectively, between 2006 and 2015 [6]). Lower healthcare costs after the first year post kidney transplantation have been reported previously, for example, up to 3 years and 10 years after kidney transplantation in Spain and Sweden, respectively [7,12].

Hospitalization cost was the highest out of all costs during the first year after transplantation, which was expected since the cost of transplantation was included, and the number of

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Table 2. Analysis of predictors for 9 covariates on inpatient days, outpatient visits, and total cost (euros) during the 3 years following transplantation based on multivariate generalized linear regression analyses.

Coefficient	Inpatient days (N=1902)		Outpatient visits (N=1902)		Total cost (N=1902)	
	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value
Intercept	127.203	<0.0001	79.169	<0.0001	158124.21	<0.0001
Age group (ref. 0–9), years						
10–19	0.308	<0.0001	0.700	0.0010	0.709	<0.0001
20–29	0.285	<0.0001	0.541	<0.0001	0.658	<0.0001
30–39	0.250	<0.0001	0.550	<0.0001	0.647	<0.0001
40–49	0.279	<0.0001	0.526	<0.0001	0.631	<0.0001
50–59	0.268	<0.0001	0.556	<0.0001	0.618	<0.0001
60–69	0.314	<0.0001	0.587	<0.0001	0.630	<0.0001
70–79	0.434	<0.0001	0.677	0.0009	0.674	<0.0001
Female	1.183	<0.0001	1.107	<0.0001	1.081	<0.0001
Transplant clinic (ref. A)						
B	0.698	<0.0001	1.056	0.1317	0.946	0.0159
C	0.704	<0.0001	0.815	<0.0001	0.947	0.0048
D	0.535	<0.0001	0.766	<0.0001	0.881	<0.0001
Received previous transplant	1.216	<0.0001	1.012	0.7064	1.064	0.0018
Living donor	0.925	0.0436	1.011	0.6865	0.922	<0.0001
Dialysis type (ref. preemptive)						
HD	1.145	0.0427	1.223	<0.0001	1.065	0.0252
HD and PD	1.089	0.2664	1.046	0.3783	1.043	0.1947
PD	0.903	0.1285	0.938	0.1560	0.964	0.1892
Unspecified dialysis type	1.328	0.0675	1.165	0.1314	1.058	0.3743
Time in dialysis, months	1.009	0.0021	1.003	0.1108	1.002	0.1985
Index year (ref. 2005)						
2006	0.974	0.7103	0.875	0.0048	0.971	0.3206
2007	0.921	0.2464	0.897	0.0211	0.986	0.6302
2008	0.948	0.4439	0.876	0.0043	0.997	0.9233
2009	0.943	0.4011	0.913	0.0514	1.018	0.5367
2010	0.912	0.1935	0.859	0.0013	0.982	0.5381
Comorbidities						
Glomerulonephritis (N00–N03)	0.851	0.0002	0.988	0.6920	0.967	0.0667
Polycystic kidney adult type (Q612)	0.906	0.0714	1.023	0.5319	0.957	0.0540
Hypertension (I109, I129)	1.063	0.1124	1.101	0.0001	1.037	0.0232
Chronic tubulo-interstitial nephritis (N119)	0.799	0.0137	0.989	0.8550	0.932	0.0646

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Table 2 continued. Analysis of predictors for 9 covariates on inpatient days, outpatient visits, and total cost (euros) during the 3 years following transplantation based on multivariate generalized linear regression analyses.

Coefficient	Inpatient days (N=1902)		Outpatient visits (N=1902)		Total cost (N=1902)	
	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value
Type 1 diabetes (E10)	1.249	<0.0001	1.137	0.0003	1.139	<0.0001
Type 2 diabetes (E11)	1.151	0.0162	1.070	0.0885	1.041	0.1104
Other congenital malformations of kidney (Q63)	1.582	0.0420	1.027	0.8592	1.305	0.0048
Malignancies (C00–C99, D01–D48)	1.129	0.0161	1.177	<0.0001	1.061	0.0051
Heart failure (I50)	1.573	<0.0001	1.012	0.8296	1.126	0.0008
Scale	6.455	–	65.898	–	37678.266	–

* Exponentiated coefficient estimates are presented ($e^{coefficient}$). HD – hemodialysis; PD – peritoneal dialysis.

hospitalizations and immunosuppression use is higher early post transplantation. Prescribed medications for renal disease accounted for the greatest proportion (almost half) of healthcare costs associated with renal disease during subsequent years. This is consistent with a European study in which immunosuppression induction and maintenance therapy accounted for approximately 45% of the total post-transplantation costs over a 3-year period [7]. Furthermore, in our study, prescribed medications for renal disease accounted for most of the overall cost of all prescribed drugs. However, it should be noted that our study did not include data after 2013, when generic tacrolimus was launched in Sweden; data after 2013 would likely show decreased cost for immunosuppressive medication.

In our study, the proportion of patients on long-term sick leave decreased from 63% in the 3 years before transplantation, to 47% in the 2 years following the index year. The reduction in the proportion of patients on long-term sick leave after transplantation are consistent with findings from a study in Finland, in which a higher proportion of patients who had received a kidney transplant were employed compared with patients who underwent dialysis in outpatient centers (but not compared with home dialysis) [14]. The study also showed that employment rate increased with time since transplantation [14]. However, unlike the Finnish study, we compared pre- and post-transplantation status in the same patient cohort. Another study from Finland showed that health-related quality of life (including a dimension for discomfort and symptoms) increased following transplantation for a considerable proportion of patients who had previously been receiving dialysis [15]. Although our study did not evaluate quality of life, it could be argued that improved health status might be associated with improved productivity.

In this study, the female sex was associated with higher resource use and cost, and women had more sick leave than men. However, the present study did not explore why this might be the case, and similar results have not been previously published. By contrast, a Swedish study of register data by Jarl et al. found that female sex had no significant impact on cost savings in the immediate post-transplant year compared with the year before transplantation [12]. Furthermore, another Swedish study showed that men experienced more days of sick leave than women for most diagnoses, although the frequency of sick leave was significantly higher in women than in men [16]. The disparity between studies may be due to differences in comorbidity levels, or to socioeconomic factors. Additionally, compared with the Swedish register study by Jarl et al. [12], our study may be more robust, as it included the total Swedish population, and may have included a greater number of costing types. Collectively, the data suggest that further investigation into the effect of sex on productivity after kidney transplantation may be warranted.

Various studies have shown that outcomes are better for patients who receive their kidney from a living rather than from a deceased donor [10,17–19]. In line with these findings, we observed that patients who received a graft from a deceased donor had higher levels of long-term sick leave after transplantation.

Previous kidney transplantation was associated with increased resource use compared with being transplant-naïve prior to the index date. Furthermore, a history of HD was associated with more outpatient visits compared with patients who were not in dialysis (preemptive patients). This is consistent with observations that prior kidney transplantation and a history of HD are important predictors of post-transplantation outcomes [17,19]. It is possible that patients with a history of transplantation and HD were in worse health prior to transplantation and, therefore, more prone to post-transplantation complications than those who were transplantation-naïve and

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pre-emptive transplant patients. By contrast, previous PD was not associated with the number of inpatient and outpatient visits versus patients who were not in dialysis (preemptive patients). It is unclear why some comorbidities, such as glomerulonephritis, were associated with fewer inpatient days.

Type 1 diabetes was an important predictor for post-transplantation resource use and costs. It was also associated with higher levels of sick leave than being without type 1 diabetes. Similar findings have been previously reported, for example, a large-scale study looking at Medicare payments identified type 1 diabetes as one of the important factors driving post-transplantation costs [11]. Furthermore, diabetes has been associated with increased hospital charges, renal dysfunction, and mortality [20]. Unlike in our study, however, no difference in the length of stay during hospitalization was found between diabetic and non-diabetic patients. This difference may be attributed to many factors, including the geographic spread of data, and a smaller patient population.

The overall high cost of kidney transplantation in this study suggests that resources should be invested to prevent kidney disease, this could include more frequent screening for high blood pressure, proteinuria and diabetes in the primary care setting. However, the high cost of dialysis, and the increased resource use seen in this study for patients on HD pre-transplantation emphasizes the overall cost-effectiveness of transplantation for those patients already requiring HD. Organ donation must also be considered as, in order to keep waiting times short for transplantation, it is necessary to maintain well-functioning organ donation activities. It is also important to allocate healthcare funding to resources that can have a positive impact on increasing the longevity of the transplant, such as optimizing post-transplant care, including medical and psycho-socio-economic factors.

This study had some limitations, given its retrospective nature. Some costs were not included, such as those associated with primary care, outpatient visits without physician involvement, and non-prescription drugs. Furthermore, the potential association between uncollected variables (e.g., laboratory results, and additional donor and patient characteristics) and outcomes could not be evaluated. Additionally, the sick leave outcome data were available according to calendar year, as opposed to running from the index date, and only episodes longer than 14 days were included. As such, data for sick leave between transplantation and the end of the year in which the procedure was carried out, and for short sick leave periods, were not available, and sick leave days may have been underestimated. It would also have been useful to compare healthcare costs for matched patients undergoing dialysis versus kidney transplantation.

The key strengths of this study were the population-based approach and the inclusion of all transplanted patients in Sweden. The national coverage in the registers facilitated long-term retrospective follow-up, low attrition, and a large sample size. Furthermore, use of administrative, compulsory registers facilitated inclusion of a comprehensive list of outcomes and covariates, including national data on productivity, and differentiation between renal disease-related and total cost.

Conclusions

This real-world, retrospective cohort study demonstrated that healthcare resource use and cost decreased dramatically after the first year after kidney transplantation in Sweden, and remained stable for the next 4 years. Furthermore, female patients had longer hospitalizations, more outpatient visits, higher total cost, and more long-term sick days than males. Other important predictors for higher resource use and cost were age less than 10 years, use of HD prior to transplantation, and certain comorbidities, particularly type 1 diabetes. These findings can be used to support healthcare decision makers when allocating funding and resources for the treatment of chronic kidney diseases.

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Supplementary Digital Content

Supplementary Methods 1. Renal disease-related drugs.

Renal disease-related drugs were defined as the following:

Glucocorticoids (H02AB): All
Antibacterials for systemic use (J01): All
Antimycotics for systemic use (J02): All
Antivirals for systemic use (J05): All
Immunoglobulins, normal human (J06BA)
Immunoglobulins, normal human, for intravascular administration (J06BA02)
Monoclonal antibodies (L01XC)
Rituximab (L01XC02)
Calcineurin inhibitors (L04AD)
Ciclosporin (L04AD01)
Tacrolimus (L04AD02)
Voclosporin (L04AD03)
Selective immunosuppressants (L04AA)
Mycophenolic acid (L04AA06)
Sirolimus (L04AA10)
Everolimus (L04AA18)
Anti-thymocyte-immunoglobulin (rabbit) (L04AA04)
Eculizumab (L04AA25)
Belatacept (L04AA28)
Interleukin inhibitors (L04AC)
Basiliximab (L04AC02)
Other immunosuppressants (L04AX)
Azathioprine (L04AX01)

Supplementary Methods 2. Cost of healthcare contacts.

The cost of healthcare contacts was estimated based on the Diagnosis-Related Groups (DRG) of the visits, which are included in the National Patient Register. Each visit (both inpatient and outpatient) has an assigned DRG, which is a measure of the resource that is generally demanded by a visit of a certain type based on diagnoses, procedures performed, patient characteristics, etc.

National mean DRG weights were assigned to each DRG and national mean cost per DRG weight was applied. The data were extracted from publications made by the National Board of Health and Welfare. Since the retrospective data spans from 2005, we used both DRG weight from the new system (2015 weights) and DRG weights from the old system (2012 weights). For all visits the mean cost per DRG weight from 2015 was used. For some visits the DRG code was not available in the patient register and for other visits the DRG code was available, but the corresponding DRG weight was not available in data from the National Board of Health and Welfare. For these visits, the DRG weight was imputed based on the following hierarchy:
- Mean weight for visits with same main diagnosis among all patients,
- Mean weight for all other visits for the specific patient,
- Mean weight for all visits among all patients.

Supplementary Table 1. Criteria for renal disease-related classification of care contacts.

All care contacts that met <u>at least one</u> of the following criteria were defined as renal disease-related contacts:	
Primary or secondary diagnosis was one of the following:	ICD-10 Z94.0 (kidney transplant status) ICD-10 Z49 (encounter for care involving renal dialysis)
Department (MVO code) of the visit was one of the following:	Nephrology clinic (151) Transplantation clinic (371) Internal medicine clinic (101) (at hospitals without the clinics above, 151 and 371, follow-up visits after transplantation to a kidney specialist occur at the internal medicine clinic)
Procedure code was the following:	Kidney transplantation (KAS10; KAS20)

ICD-10 – International Classification of Diseases 10th version.

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Supplementary Table 2. Patient characteristics for patients with minimum look-back of 2 years.

	Patients with minimum look-back of 2 years (N=3177)	
Age group, n (%)		
0–9	61	(1.9)
10–19	100	(3.1)
20–29	215	(6.8)
30–39	389	(12.2)
40–49	682	(21.5)
50–59	806	(25.4)
60–69	807	(25.4)
70–79	117	(3.7)
Female, n (%)	1152	(36.3)
Transplantation clinic, n (%)		
A	779	(24.5)
B	650	(20.5)
C	1190	(37.5)
D	558	(17.6)
Transplantation experienced, n (%)	495	(15.6)
Living donor, n (%)	1246	(39.2)
Dialysis type, n (%)		
HD	1148	(36.1)
PD	800	(25.2)
HD and PD	606	(19.1)
Unspecified dialysis type	55	(1.7)
No dialysis	568	(17.9)

HD – hemodialysis; IQR – interquartile range; PD – peritoneal dialysis; SD – standard deviation.

	Patients with minimum look-back of 2 years (N=3177)	
Months in dialysis during 2 years prior to transplantation		
Mean (SD)	13.7	(9.2)
Median	15.2	
IQR	4.7, 23.3	
Range	(0.0–24.3)	
Index year, n (%)		
2005	174	(5.5)
2006	355	(11.2)
2007	361	(11.4)
2008	409	(12.9)
2009	373	(11.7)
2010	349	(11.0)
2011	406	(12.8)
2012	372	(11.7)
2013	378	(11.9)
Comorbidities, n (%)		
Glomerulonephritis (N00–N03)	725	(22.8)
Polycystic kidney adult type (Q612)	395	(12.4)
Hypertension (I109, I129)	1190	(37.5)
Chronic tubulo-interstitial nephritis (N119)	107	(3.4)
Type 1 diabetes (E10)	557	(17.5)
Type 2 diabetes (E11)	429	(13.5)
Other congenital malformations of kidney (Q63)	15	(0.5)
Malignancies (C00–C99, D01–D48)	468	(14.7)
Heart failure (I50)	153	(4.8)

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Supplementary Table 3. Sensitivity analysis of predictors for 9 covariates on inpatient days, outpatient visits, total cost (euros), and long-term sick leave after transplantation based on multivariate generalized linear regression analyses.

Coefficient	Inpatient days				Outpatient visits				Total cost				Long-term sick leave (days)	
	1 year (N=2732)		5 years (N=1165)		1 year (N=2732)		5 years (N=1165)		1 year (N=2732)		5 years (N=1165)		2 years (N=1766)	
	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value
Intercept	82.135	<0.0001	176.057	<0.0001	39.093	<0.0001	111.814	<0.0001	90018.38	<0.0001	213358.6	<0.0001	89.861	<0.0001
Age group (ref. 0–9), years														
10–19	0.406	<0.0001	0.277	<0.0001	0.876	0.0727	0.658	0.0025	0.850	0.0004	0.684	<0.0001	NA (ref. 20–29)	
20–29	0.372	<0.0001	0.262	<0.0001	0.683	<0.0001	0.517	<0.0001	0.778	<0.0001	0.625	<0.0001	NA (ref. 20–29)	
30–39	0.351	<0.0001	0.209	<0.0001	0.666	<0.0001	0.508	<0.0001	0.767	<0.0001	0.588	<0.0001	0.894	0.4804
40–49	0.394	<0.0001	0.226	<0.0001	0.675	<0.0001	0.526	<0.0001	0.775	<0.0001	0.596	<0.0001	0.993	0.9621
50–59	0.389	<0.0001	0.237	<0.0001	0.672	<0.0001	0.581	<0.0001	0.757	<0.0001	0.594	<0.0001	1.031	0.8404
60–69	0.415	<0.0001	0.273	<0.0001	0.712	<0.0001	0.570	<0.0001	0.757	<0.0001	0.606	<0.0001	1.304	0.1331
70–79	0.543	<0.0001	0.456	0.0006	0.742	<0.0001	0.865	0.3517	0.792	<0.0001	0.722	0.0011	NA (only 20–69)	
Female	1.093	0.0010	1.158	0.0017	1.035	0.0360	1.168	<0.0001	1.037	0.0004	1.095	<0.0001	1.294	0.0005
Transplant clinic (ref. A)														
B	0.731	<0.0001	0.693	<0.0001	1.030	0.2252	1.051	0.3080	0.965	0.0198	0.967	0.2800	0.857	0.1674
C	0.647	<0.0001	0.702	<0.0001	0.861	<0.0001	0.796	<0.0001	0.962	0.0027	0.918	0.0010	0.955	0.6210
D	0.553	<0.0001	0.586	<0.0001	0.736	<0.0001	0.885	0.0134	0.878	<0.0001	0.917	0.0056	0.924	0.4820
Received previous transplant	1.118	0.0027	1.306	<0.0001	0.986	0.5208	1.140	0.0017	1.042	0.0033	1.114	<0.0001	1.069	0.5106
Living donor	0.920	0.0041	0.903	0.0520	0.992	0.6529	0.972	0.4288	0.908	<0.0001	0.917	0.0001	0.890	0.1245
Dialysis type (ref. preemptive)														
HD	1.098	0.0633	1.130	0.1751	1.158	<0.0001	1.341	<0.0001	1.036	0.0609	1.126	0.0022	1.459	0.0043
HD and PD	1.038	0.5259	1.042	0.6858	1.057	0.1241	1.132	0.0795	1.032	0.1530	1.040	0.3767	1.366	0.0474
PD	0.942	0.2436	0.874	0.1408	0.998	0.9375	0.963	0.5420	0.994	0.7407	0.974	0.5145	1.381	0.0195
Unspecified dialysis type	1.079	0.4784	1.299	0.1457	1.112	0.1025	1.152	0.2388	1.159	0.0002	1.049	0.5298	1.155	0.5488
Time in dialysis, months	1.006	0.0053	1.01	0.0081	1.001	0.5431	0.999	0.8283	0.999	0.3357	1	0.8435	0.997	0.6169
Index year (ref. 2005)														
2006	1.090	0.1726	0.945	0.4446	0.933	0.0730	0.812	<0.0001	1.055	0.0235	0.943	0.0635	0.899	0.4916
2007	0.949	0.4082	0.865	0.0497	0.971	0.4457	0.829	0.0002	1.042	0.0805	0.963	0.2432	0.929	0.6410
2008	0.908	0.1178	0.909	0.1866	0.943	0.1256	0.858	0.0020	1.034	0.1535	0.970	0.3376	0.933	0.6442
2009	0.968	0.6092	NA	NA	0.936	0.0868	NA	NA	1.049	0.0429	NA	NA	1.106	0.5257
2010	0.898	0.0880	NA	NA	0.860	0.0001	NA	NA	1.020	0.4073	NA	NA	0.978	0.8846
2011	0.854	0.0113	NA	NA	0.900	0.0055	NA	NA	1.028	0.2308	NA	NA	1.036	0.8138

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Coefficient	Inpatient days				Outpatient visits				Total cost				Long-term sick leave (days)	
	1 year (N=2732)		5 years (N=1165)		1 year (N=2732)		5 years (N=1165)		1 year (N=2732)		5 years (N=1165)		2 years (N=1766)	
	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value	Exp (est)*	P value
2012	0.845	0.0078	NA	NA	0.919	0.0284	NA	NA	0.986	0.5572	NA	NA	NA	NA
Comorbidities														
Glomerulo-nephritis (N00–N03)	0.880	0.0001	0.848	0.0039	1.005	0.8055	0.988	0.7640	0.980	0.1055	0.981	0.4299	0.921	0.3359
Polycystic kidney adult type (Q612)	0.981	0.6482	1.018	0.8017	1.061	0.0210	0.972	0.5522	1.000	0.9809	0.989	0.7124	1.003	0.9808
Hypertension (I109, I129)	1.006	0.8438	1.071	0.1828	1.006	0.7168	1.092	0.0114	1.008	0.4492	1.032	0.1532	1.015	0.8463
Chronic tubulo-interstitial nephritis (N119)	0.863	0.0365	0.908	0.3895	0.975	0.5651	1.106	0.1891	0.946	0.0351	1.015	0.7612	1.312	0.1496
Type 1 diabetes (E10)	1.132	0.0024	1.375	<0.0001	1.069	0.0076	1.146	0.0054	1.140	<0.0001	1.184	<0.0001	1.532	<0.0001
Type 2 diabetes (E11)	1.132	0.0044	1.066	0.4141	1.051	0.0658	1.097	0.0951	1.046	0.0060	1.028	0.4385	0.954	0.7180
Other congenital malformations of kidney (Q63)	1.391	0.0797	1.703	0.0507	1.095	0.4305	0.999	0.9960	1.143	0.0578	1.288	0.0308	1.164	0.7182
Malignancies (C00–C99, D01–D48)	1.065	0.0945	1.110	0.1163	1.071	0.0031	1.085	0.0703	1.044	0.0027	1.039	0.1781	0.927	0.4737
Heart failure (I50)	1.197	0.0040	1.415	0.0013	0.968	0.3885	1.073	0.3362	1.015	0.5268	1.117	0.0176	1.312	0.1608
Sick days 2 calendar years before index	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.001	<0.0001
Scale	9.451	–	6.052	–	393.168	–	48.262	–	7602196.6	–	13094.94	–	2.756	–

* Exponentiated coefficient estimates are presented ($e^{coefficient}$). HD – hemodialysis; PD – peritoneal dialysis; NA – not applicable.

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