ORIGINAL ARTICLE

Effects of expanded allocation programmes and organ and recipient quality metrics on transplant-related costs in kidney transplantation – an institutional analysis

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SUMMARY

Expansions of donor pools have a controversial impact on healthcare expenditures. The aim of this study was to investigate the emerging costs of expanded criteria donor (ECD) kidney transplantations (KT) and to identify independent risk factors for increased transplant-related costs. We present a retrospective explorative analysis of hospital costs and reimbursements of KTs performed between 2012 and 2016 in a German university hospital. A total of 174 KTs were examined, including 92 (52.9%) ECD organ transplantations. The ECD group comprised 43 (24.7%) 'old-for-old' transplantations. Median healthcare costs were 19 570€ (IQR 18 735–27 405€) in the standard criteria donor (SCD) group versus 25 478€ (IQR 19 957–29 634€) in the ECD group (+30%; $P = 0.076$). 'Old-for-old' transplantations showed the highest healthcare expenditures [26 702€ (19 570–33 940€)]. Irrespective of the allocation group, transplant-related costs increased significantly in obese (+6221€; $P = 0.009$) and elderly recipients (+6717€; $P = 0.019$), in warm ischaemia time exceeding 30 min (+3212€; $P = 0.009$) and in kidneys with DGF or surgical complications (+8976€ and +10 624€; both $P < 0.001$). Transplantation of ECD organs is associated with incremental costs, especially in elderly and obese recipients. A critical patient selection, treatment of obesity before KT and keeping warm ischaemia times short seem to be crucial, in order to achieve a cost-effective KT regardless of the allocation group.

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Introduction

The incidence of end-stage renal disease (ESRD) is increasing worldwide [1]. The healthcare expenditures and resource utilization caused by ESRD are considerable challenges to national healthcare systems [2]. In 2015, Medicare payments for the treatment of ESRD equaled $34 billion USD in the United States [3]. A similar burden on European health systems can be assumed [4,5]. Demographic changes in terms of ageing

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of the general population and the increase in chronic diseases and associated conditions (e.g. obesity) are additional factors that will further exacerbate the situation [6]. Therefore, the identification of risk factors for increased costs and the awareness for cost-effective therapies are becoming major issues in medicine and as well as in the transplant community. Without a doubt, kidney transplantation (KT) is the most cost-effective treatment of ESRD and has been shown to be superior to dialysis in terms of survival of patients, quality of life and utilization of resources [3,7,8]. Considering utilization of resources, the yearly costs per patient have been reported to be three times lower after KT compared to dialysis [9].

However, organ shortage and growing waiting lists limit access to KT. Living donor KT represents a possible solution, but this approach can only partially fill the organ deficiency [10]. Hence, international and national programmes have been initiated to increase organ supply by expanding deceased donor pools with organs that would have previously been considered unsuitable for transplantation [11–15]. Despite quality concerns and higher rates of inferior transplant outcome, the utilization of such expanded criteria donor (ECD) kidneys is associated with a survival benefit, compared to patients who remain on dialysis or a waiting list [11]. Similar results were reported for the 'old-for-old' Eurotransplant Senior Program (ESP), which addresses donor shortage by assigning organs from ageing donors to older recipients [16–18].

The clinical evidence of these programmes is well documented, however, the effects on additional healthcare costs are controversial [15–19]. Furthermore, the role of donor and recipient metrics on transplant-related costs in KT has not yet been clearly defined.

In this paper, we report results of a comprehensive single-centre study evaluating both, the effects of donor pool expansion programmes and individual donor and recipient characteristics on transplant-related costs and reimbursement in deceased KT.

Patients and methods

Patients and study design

The study was conducted as a retrospective analysis at the Department of Surgery of the Charité University Hospital, Berlin, Germany. All adult deceased organ recipients, who underwent KT between January 1, 2012, and January 1, 2016, were included. Donation after circulatory death is not permitted in Germany and therefore no such grafts were included in this study. The date of the last follow-up was July 31, 2018. The study has been evaluated and approved by the institutional ethics committee (Charité – Universitätsmedizin Berlin; ID: EA4/060/17).

Definitions

Expanded criteria donor kidneys were defined by the United Network for Organ Sharing (UNOS) criteria as organs from donors aged 60 years or older, or between 50 and 59 years with at least two of the following three conditions: [1] death from cerebrovascular accident, [2] history of hypertension or [3] terminal serum creatinine >1.5 mg/dl [19]. 'Old-for-old' transplantations were defined by the ESP criteria as a subgroup of ECD KTs, consisting of donors and recipients both older than 65 years [20]. Warm ischaemia time (WIT) was defined as the anastomosis period during transplantation. Delayed graft function (DGF), which represents the clinical manifestation of acute kidney injury was defined by UNOS criteria as the need for dialysis within 7 days after transplantation [21]. Primary nonfunction (PNF) was defined as a permanent lack of graft function, with the need for chronic dialysis from the time of transplantation. Graft survival was defined by UNOS criteria, as a composite overall graft survival from the date of transplantation to the date of irreversible graft failure, the date of the last follow-up or to the date of patient death [22,23].

Data collection and cost analysis

Electronic records of recipient clinical data were collected from the hospital information system (SAP® SE, Walldorf, Germany). Anonymous donor data were acquired from the Eurotransplant Network Information System (ENIS). Department accounting information was provided by the institutional financial bureau and was used to calculate costs and reimbursements.

Basic charges were defined as all departmental expenditures for surgical procedures, immunosuppressive and medical therapies, and ward and personnel costs. Basic remuneration was calculated based on the German diagnosis-related groups (DRGs) case rate payment system. The reimbursement of a DRG category can be modified according to performed procedures, patient morbidity and secondary diagnoses. The last two are expressed in the Patient Clinical Complexity Level (PCCL) [24]. In our analysis two DRG reimbursement categories were distinguished: Uncomplicated clinical courses with no

need for dialysis were remunerated in group A17B, whereas the occurrence of DGF or an increased patient clinical complexity (defined as PCCL > 4) triggered the case fee into the higher remuneration group A17A. Donor criteria were not considered for DRG-grouping. Additionally, dialysis and rejection therapy costs were refunded separately. Gross profits were defined as departmental earnings after deduction of all additional costs. The outcome variable of the main research question were costs and remunerations analysed with respect to the allocation groups as defined above. In a second research question we calculated the effects of the donor, recipient and perioperative characteristics on transplant-related costs in the total study population without stratification for allocation group and compared them with the basic remunerations of a reference patient (classified as DRG-category A17B).

Statistical analyses

All statistical analyses were carried out using IBM SPSS STATISTICS, version 25 (IBM Corporation, Armonk, NY, USA). Categorical data are presented as frequencies and percentages and compared by the Pearson chi-squared test or Fisher's exact test. Continuous data are presented either as the mean and standard deviation and compared with the two-sample t-test or as median and interquartile range (IQR) and compared with the non-parametric Mann–Whitney *U* test for two samples or Kruskal–Wallis test for three samples.

Organ survival was analysed with the Kaplan–Meier method and the log-rank test to compare groups. To identify risk factors for increased transplant-related costs, the effects of clinical parameters on relative costs were compared with the basic remunerations of the 'reference patient' DRG-category by Mann–Whitney *U* test, and further analysed with univariate linear regression analyses and a multiple linear regression analysis (regression coefficients and *P*-values given). Only clinically relevant variables were selected for the regression analyses. Univariate regression analyses were calculated for all independent variables. The univariate regression analyses show unadjusted associations (standardized beta coefficients). Consequently, the multiple regression analyses provide multivariable adjustments for the effects of confounding. A first aim for the multiple linear regression analyses was to find a model with a small set of relevant independent variables, so a stepwise multiple linear regression model with backward variable selection based on partial correlation coefficients was estimated. Another aim for the model building process was to estimate and compare univariable and multivariable effects of the associations between potential predictor variables and the outcome. Thus, a multiple regression analysis with a larger set of potential predictor variables was estimated with the enter method. The variable selection process for the 2nd multiple regression model consisted of two steps: In a first step, variables with a *P*-value ≤ 0.05 in the univariate linear regression analyses were selected for the multiple regression model. In a second step, intercorrelations of all remaining predictor variables were checked to avoid multicollinearity effects. For the variables with high intercorrelations, the selection was based on clinical relevance and two variables were excluded (checked with the parameters tolerance and variance inflation factor). For the final model, the linearity assumption was tested with an analysis of residuals (normal distribution, Durbin–Watson Test).

A number of group comparisons and regression analyses and tests for normal distribution in the case of continuous variables were applied in this exploratory study. Hence, *P*-values are given as an orientation and described as significant for two-sided *P*-values ≤ 0.05, but are not to be interpreted as confirmatory.

Results

Study population

Clinical and accounting data were available for all 174 KTs. A total of 92 (52.9%) ECD organs were transplanted including 43 (24.7%) 'old-for-old' transplantations and 49 (28.2%) non 'old-for-old' transplantations (41 'young-for-young', 6 'old-for-young' and 2 'young-for-old transplantations). Of the 174 patients, three patients died during the observation time of 1 year, and in eight patients irreversible graft failure was observed. The overall DGF rate was 47.1%. A total of 51 (29.3%) surgical complications were observed in the postoperative follow-up, among them seven Dindo I–II (seven superficial wound complications) and 44 Dindo ≥III complications (11 cases of vascular or ureteral kinking; seven bleedings; seven lymphoceles; five ureteral leakages and 14 deep wound complications). The median hospital stay was 20 (IQR 14–30) days.

No difference in cold ischaemia time (CIT) and warm ischaemia time (WIT) was observed between the SCD and ECD transplantations (687 ± 287 min vs. 623 ± 261 min; $P = 0.123$ and 30 ± 7.3 vs. 30 ± 7.7 min; $P = 0.959$ respectively). The ECD organ recipients showed significantly higher rates of DGF (55% vs. 38%; $P = 0.020$), surgical complications (37% vs. 21%; $P = 0.019$) and longer

hospital stays [22 (IQR 15–34) vs. 17 (IQR 13–26) days; $P = 0.008$], compared to the SCD organ recipients. No difference in intensive care unit (ICU) stay was observed between the groups [0 (IQR 0–2) both; $P = 0.963$]. Graft survival at 1 year was significantly lower after ECD transplantations (98% vs. 90%; $P = 0.050$). A detailed overview of the SCD and ECD organ recipient characteristics is provided in Table 1.

Within the ECD group, the median recipient body mass index (BMI) was significantly higher in the 'old-for-old' organ recipients [28.2 (IQR 24.6–31.6) vs. 25.4 (IQR 22.5–27.0) kg/m^2; $P = 0.021$] No differences were observed in the WIT and general postoperative markers, whereas the CIT was significantly lower in the 'old-for-old' ECD organ recipients (558 ± 246 vs. 679 ± 263; $P = 0.026$). The median hospital stay was longest [27 (IQR 17–41) vs. 21 (14–28) days, $P = 0.047$]. The one-year graft survival rate was lowest in 'old-for-old' organ recipients (86% vs. 94%; $P = 0.221$; Table 2).

Costs and reimbursement

The median basic charges estimated 18 576 € (IQR 13 874–28 585 €) per SCD and 21 881 (IQR 15 939–30 712 €) € per ECD organ transplantation (+3305 €; $P = 0.101$). 'Old-for-old' transplantations showed the highest basic charges within the allocation groups with 24 222 € (IQR 16 011–33 484 €); +5646 €; $P = 0.073$; compared to SCD). Refunds differed significantly between the allocation groups, with the highest basic remunerations for the 'old-for-old' transplantations [26 404 € (IQR 19 343–26 619 €)]. Total reimbursement was also highest in the 'old-for-old' transplantations with 26 702 € (IQR 19 570–33 940 €), whereas

Table 1. Epidemiological and clinical patient characteristics of all patients ($n = 174$), who underwent kidney transplantation from deceased donors between January 2012 and January 2016 sorted by SCD versus ECD transplantations.

Variables	Total ($n = 174$)	SCD ($n = 82$)	ECD ($n = 92$)	P-value†
General				
Recipient gender, male: *n* (%)	117 (67.2%)	47 (57.3%)	70 (76.1%)	**0.008**
Donor age (years)	56.0 (48–67)	48.0 (38–53)	66.5 (59–74)	
Recipient age (years)	57.0 (48–66)	52.0 (45–59)	65.0 (50–70)	**<0.001**
Donor BMI (kg/m^2)	26.0 (23.6–29.4)	24.8 (23.4–27.8)	27.3 (24.2–29.4)	0.052
Recipient BMI (kg/m^2)	25.7 (22.4–29.1)	24.4 (21.7–28.9)	26.0 (22.1–29.4)	0.119
Perioperative characteristics				
Induction therapy: basiliximab, *n* (%)	154 (88.5%)	70 (85.4%)	84 (91.3%)	0.220
Induction therapy: thymoglobulin, *n* (%)	20 (11.5%)	12 (14.6%)	8 (8.7%)	0.220
Cold ischaemia time (min), mean ± SD	653 ± 274	687 ± 287	623 ± 261	0.123
Warm ischaemia time (min), mean ± SD	30 ± 7.5	30 ± 7.3	30 ± 7.7	0.959
Delayed graft function, *n* (%)	82 (47.1%)	31 (38.0%)	51 (55.4%)	**0.020**
Primary nonfunction, *n* (%)	6 (3.4%)	1 (1.2%)	5 (5.4%)	0.128
Intraoperative graft function, *n* (%)	55 (31.6%)	32 (39.0%)	23 (25.0%)	**0.047**
Biopsy, *n* (%)	62 (35.6%)	23 (28.0%)	39 (42.4%)	0.058
Rejection therapy, *n* (%)	39 (22.4%)	15 (18.3%)	24 (26.1%)	0.221
Biopsy-proven rejection, *n* (%)	22 (12.6%)	10 (12.2%)	12 (13.0%)	0.867
Surgical complications, yes *n* (%)	51 (29.3%)	17 (20.7%)	34 (37.0%)	**0.019**
No complications, *n* (%)	123 (70.7%)	65 (79.3%)	58 (63.0%)	0.058*
Clavien–Dindo Grade I–II, *n* (%)	7 (4.0%)	2 (2.4%)	5 (5.4%)	
Clavien–Dindo Grade ≥III, *n* (%)	44 (25.3%)	15 (18.3%)	29 (31.5%)	
Amount of dialysis, *n* (%)	0 (0–2)	0 (0–2)	1 (0–3)	0.066
Hospital stay (days)	20 (14–30)	17 (13–26)	22 (15–34)	**0.008**
ICU stay (days)	0 (0–2)	0 (0–2)	0 (0–2)	0.963
Graft survival rate at 1 year, (%)	163 (93.7%)	80 (97.6%)	83 (90.0%)	**0.050**

BMI, body mass index; ECD, expanded criteria donor; ICU, intensive care unit; *n*, number; SCD, standard criteria donor; SD, standard deviation.

Annotations: data presented as median and interquartile range (Q1–Q3), if not stated otherwise.

†Group comparisons: (i) categorial data: Pearson chi-square test or Fisher's exact test*. (ii) Continuous variables: parametric *t*-test and nonparametric Mann–Whitney *U* test where appropriate. (iii) Log-rank test was used to compare survival times.

Two-sided *P*-values ≤ 0.05 were considered as significant (bold values).

Table 2. Subgroup analysis of patient and treatment characteristics in ECD organs separated into non 'old-for-old' and 'old-for-old' transplantations.

Variables	Non 'old-for-old' KTs (*n* = 49)	'old-for-old' KTs (*n* = 43)	*P*-value†
General			
Recipient gender, male: *n* (%)	39 (80.0%)	31 (72.0%)	0.406
Donor age (years)	51.0 (44.0–60.5)	70.0 (67.0–74.0)	
Recipient age (years)	59.0 (56.0–63.0)	72.0 (68.0–76.3)	
Donor BMI (kg/m^2)	29.2 (24.2–30.6)	25.7 (24.0–27.8)	**0.003**
Recipient BMI (kg/m^2)	25.4 (22.5–27.0)	28.2 (24.6–31.6)	**0.021**
Perioperative characteristics			
Induction therapy: basiliximab, *n* (%)	43 (87.8%)	41 (95.3%)	0.797
Induction therapy: thymoglobulin, *n* (%)	6 (12.2%)	2 (4.7%)	0.797
Cold ischaemia time (min), mean ± SD	679 ± 263	558 ± 246	**0.026**
Warm ischaemia time (min), mean ± SD	30.2 ± 6.7	29.7 ± 8.8	0.787
Delayed graft function, *n* (%)	25 (51.0%)	26 (60.0%)	0.369
Primary nonfunction, *n* (%)	3 (6.0%)	2 (5.0%)	0.759
Intraoperative graft function, *n* (%)	11.0 (22.0%)	12 (28.0%)	0.551
Biopsy, *n* (%)	20.0 (41.0%)	19 (44.0%)	0.747
Rejection therapy, *n* (%)	9 (18.0%)	15 (35.0%)	0.073
Biopsy-proven rejection, *n* (%)	5 (10.0%)	7 (16.0%)	0.394
Surgical complications, yes, *n* (%)	19 (38.8%)	15 (34.9%)	0.978
No complications, *n* (%)	30 (61.2%)	28 (65.1%)	0.681*
Clavien–Dindo Grade I–II, *n* (%)	2 (4.1%)	3 (6.1%)	
Clavien–Dindo Grade ≥III, *n* (%)	17 (34.6%)	12 (27.9%)	
Amount of dialysis, *n* (%)	1 (0–2)	1 (0–3)	0.320
Hospital stay (days)	21 (14–28)	27 (17–41)	**0.047**
ICU stay (days)	0 (0–2)	0 (0–2)	0.925
Graft survival rate at 1 year, (%)	46 (94.0%)	37 (86.0%)	0.221

BMI, body mass index; ECD, expanded criteria donor; ICU, intensive care unit; *n*, number; SCD, standard criteria donor; SD, standard deviation.

Annotations: Data presented as median and interquartile range (Q1–Q3), if not stated otherwise.

†Group comparisons: (i) categorical data: Pearson chi-square test or Fisher's exact test*. (ii) Continuous variables: parametric *t*-test if and nonparametric Mann–Whitney *U* test where appropriate. (iii) Log-rank test was used to compare survival times.

Two-sided *P*-values ≤ 0.05 were considered as significant (bold values).

the SCD reimbursement was the lowest with 19 570 € (IQR 18 735–27 405 €; $P = 0.024$). Gross profits were the lowest in the 'old-for-old' transplantations and the highest in the SCD organ recipients (2142 vs. 3334 €; $P = 0.841$; Fig. 1).

Relative transplant-related costs

The descriptive analyses in Table 3 show the comparisons of the remuneration in relation to the 'reference patient' for all independent variables examined in this study. Several independent variables were identified as potential predictors for increased transplant-related costs. First, a recipient age over 65 years and a BMI ≥30 kg/m^2 showed significant differences compared to the 'reference patient' (+35.7%, $P = 0.019$ and +33.1%, $P = 0.009$). Induction therapy with basiliximab was cost neutral (0.0%, $P = 0.114$), whereas the use of thymoglobulin was associated with significant cost occurrence (+61.6%, $P = 0.001$). Prolonged CIT for ≥12 h showed a nonsignificant association with increased costs (+11.8%; $P = 0.206$), and in cases with a WIT exceeding 30 min, the transplant-related costs increased significantly (+17.1%; $P = 0.009$). A detailed overview of the effects of the WIT and BMI on transplant-related cost development is shown in Fig. 2. Organs with intraoperative diuresis as a sign of graft function, showed significantly lower costs (−16.1%; $P < 0.001$), whereas the occurrence of DGF was associated with significant expenses (+47.7%; $P < 0.001$). Dialysis therapy costs were remunerated separately from basic remunerations. However, more than one postoperative dialysis increased the expenditures disproportionately, regardless of refunds for dialysis treatment (+61.4%; $P < 0.001$). In patients, who needed solely one dialysis within the first 24 h after KT a non-significant

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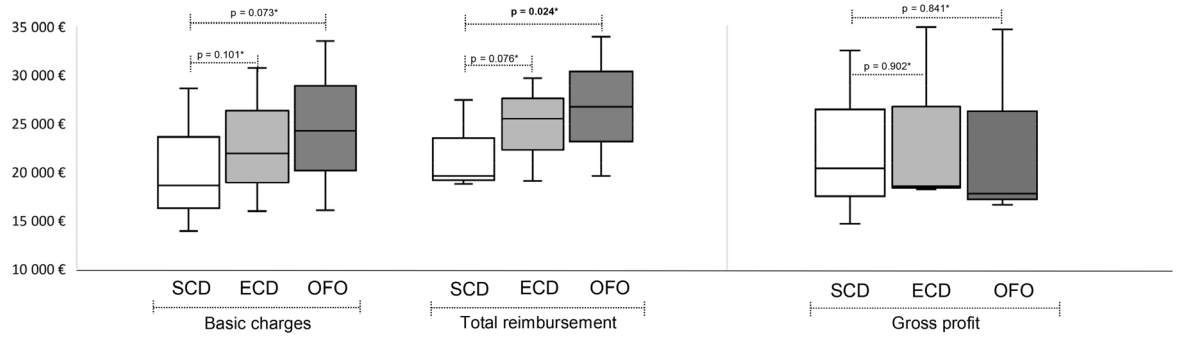
Variable	SCD (*n* = 82)	ECD (*n* = 92)	ESP (*n* = 43**)
Basic charges	18,576 € (13,874–28,585 €)	21,881 € (15,939–30,712 €)	24,222 € (16,011–33,484 €)
Basic remuneration	19,343 € (18,611–24,843 €)	24,806 € (18,735–26,842 €)	26,404 € (19,343–26,619 €)
Additional remuneration	228 € (0–1622 €)	442 € (221–1,743 €)	455 € (221–2,309 €)
Total reimbursement	19,570 € (18,735–27,405 €)	25,478 € (19,057–29,634 €)	26,702 € (19,570–33,940 €)
Gross profit	3,334 € (–1,524–7,179 €)	2,646 € (–2,751–7,948 €)	2,142 € (–2,513–7,874 €)



Annotations:
Data presented as median and interquartile range (Q1-Q3)
* Group comparisons: Mann-Whitney U test.
** Subgroup of ECD.
Abbreviations: significance (p); standard criteria donor (SCD); expanded criteria donor (ECD); Eurotransplant Senior Program "old-for-old" transplantations (ESP)

Figure 1 Comparison of basic charges, remunerations and gross profits between the transplantation groups shown as median interquartile range costs in € (ECD, expanded criteria donor; ESP, Eurotransplant Senior Programme 'old-for-old' transplantations; SCD, standard criteria donor).

cost-reducing effect was observed (−141 €, $P = 0.788$). Furthermore, the necessity of a biopsy [I] or acute rejection therapies [II] and the presence of surgical complications [III] were associated with additional costs (I: +53.3%; II: +72.2%; III: +56.6%; all $P < 0.001$).

The results of the univariate and multiple linear regression analyses are shown in Table 4. The stepwise multiple regression analysis found a small set of relevant predictor variables. In a second approach variables with significant results in the univariate regression analyses were subsequently included into a multiple linear regression model (adjusted $R^2 = 0.542$). Among the independent variables representing characteristics of the recipients, obesity was the only predictor variable associated with significantly increased costs ($P = 0.004$). Within the postoperative parameters, induction therapy with thymoglobulin ($P < 0.001$), necessity of more than one dialysis ($P = 0.016$), biopsy-proven acute rejection ($P = 0.003$) and complications classified as Clavien–Dindo grade ≥III ($P < 0.001$) showed significant associations with increased transplant-related costs.

Discussion

Kidney transplantation is the first line treatment for ESRD and was reported to have cost savings of up to 200 000 USD after 5 years and of up to 380 000 € after 10 years in United States and European cohorts, respectively, compared to chronic dialysis treatment [2,25]. Given the current situation of organ shortage and ageing of the population new strategies were developed to reduce the time on waiting lists and to address the increase in elderly donors and recipients of KT. Despite the clinical value of several donor pool expansion programmes, the effects on transplant-related costs remain less clear.

Several publications have attempted to correlate costs with ECD organs. In 1998, Whiting *et al.* [26] first reported a series of 78 patients showing significant expenses after ECD transplantations, compared to SCD organs. In our study, we evaluated the effects of ECD and 'old-for-old' transplantations on hospital charges and reimbursement and compared the results to SCD KTs. We observed a nonsignificant increase of 18% in basic charges after ECD transplantations, compared to SCD procedures (+3305 € per patient). A further cost increase was observed after 'old-for-old' transplantations. Here, the basic charges were 30% higher than in the SCD group and totalled 5646 € difference per patient.

Despite the higher basic charges in ECD organs, basic remunerations were cost-covering in all groups. This result can be explained by higher DGF rates for ECD organs, which triggered refunds into higher remuneration groups and compensated increased basic costs.

Table 3. Effects of donor, recipient and perioperative characteristics on relative transplant-related cost in relation to the average of the basic remuneration of a reference patient† shown as difference in Euro (€) and percent (%).

Variables	*n*	€, median (IQR)	%	*P*-value‡
Recipient age ≥ 65 years	46	**+**6717 € (−2320 to 15 424 €)	**+**35.7	**0.019**
Donor age ≥ 65 years	56	**+**4584 € (−3572 to 13 166 €)	**+**24.4	0.187
ECD organ transplantation	92	**+**3187 € (−2980 to 12 049 €)	**+**16.9	0.099
Old-for-old transplantation	43	**+**5742 € (−2601 to 15 003 €)	**+**30.5	0.075
Donor diagnosis: stroke	116	**+**2564 € (−3572 to 14 679 €)	**+**13.6	**0.032**
Donor diagnosis: ICB (atraumatic)	102	**+**2425 € (−3807 to 13 615 €)	**+**12.9	0.168
Donor BMI ≥ 30 kg/m^2	35	**+**602 € (−5126 to 12 215 €)	**+**3.2	0.873
Recipient BMI ≥ 30 kg/m^2	38	**+**6221 € (−1254 to 18 319 €)	**+**33.1	**0.009**
Perioperative markers				
Induction therapy: basiliximab	154	−5 € (−4720 to 9486 €)	**+**0.0	0.114
Induction therapy: thymoglobulin	20	**+**11 580 € (2607–17 174 €)	**+**61.6	**0.001**
Cold ischaemia time ≥ 12 h	56	**+**2219 € (−3016 to 16 394 €)	**+**11.8	0.206
Warm ischaemia time ≥ 30 min	93	**+**3212 € (−2583 to 14 354 €)	**+**17.1	**0.009**
Postoperative markers				
Intraoperative graft function	55	−3029 € (−7524 to 2512 €)	−16.1	**<0.001**
Delayed graft function	82	**+**8976 € (−157 to 18 290 €)	**+**47.7	**<0.001**
Only one dialysis within 24 h after transplantation	11	−141 € (−5201 to 11 025 €)	−0.7	0.788
Dialysis, *n* > 1	55	**+**11 552 € (2623–19 491 €)	**+**61.4	**<0.001**
Biopsy	62	**+**10 028 € (2421–19 580 €)	**+**53.3	**<0.001**
Biopsy-proven rejection	22	**+**19 073 € (10 267–31 694 €)	**+**101.4	**0.001**
Rejection therapy	39	**+**13 585 € (4794–25 009 €)	**+**72.2	**<0.001**
Surgical complications, yes	51	**+**10 624 € (3323–20 371 €)	**+**56.6	**<0.001**
No complications	123	−1760 € (−6552 to 4269 €)	−3.4%	
Clavien–Dindo Grade I–II	7	**+**10 590 € (1606–15 003 €)	**+**56.3	**<0.001***
Clavien–Dindo Grade ≥III	44	**+**11 420 € (3620–25 799 €)	**+**60.7	

BMI, body mass index; ECD, expanded criteria donor; ICB, intracranial bleeding; *n*, number.

Annotations: Data presented as median and interquartile range (Q1–Q3).

†Defined by an uncomplicated patient course, with no need for dialysis therapy.

‡Group comparisons: Mann–Whitney *U* test or Kruskal–Wallis test*.

Two-sided *P*-values ≤ 0.05 were considered as significant (bold values).

Furthermore, the utilization of ECD organs resulted in a 30% increase in compensation payments compared to SCD organs. Similar results were reported in a single-centre analysis by Saidi *et al.* [27], where charges were 47% higher after ECD KTs than in SCD KTs.

Within the ECD group, 'old-for-old' transplantations showed significantly higher remunerations and resulted in a 36% increase in healthcare costs compared to SCD organs. Despite a significantly higher reimbursement in ECD KTs, effective gross margins were 21% lower compared to SCD organ recipients. This effect was even more pronounced in 'old-for-old' KTs, causing a gross margin reduction of 36%. In 2008, Engelsbe and colleagues reported similar negative effects on medical centre incremental margins in transplantations utilizing ECD organs (−5887 USD per patient) [28].

However, more recent data published by Stahl *et al.* [29] questioned the association of ECD transplantations with increased costs. The authors evaluated 19 527 KTs in the United States and observed slightly lower costs in ECD patients compared to SCD organs with an OR of 0.97 (−2986 USD). Additionally, the authors calculated the more sensitive kidney donor profile index (KDPI) and compared the results of high KDPI kidneys (KDPI 85+) to SCD organs. Here again, the costs after KDPI 85+ KTs were significantly lower compared to SCD organs. These results are in contrast to most previous publications. Despite the impressive cohort size and good data quality of this publication, it appears to be necessary to draw a more precise picture of transplant-related cost reality in Europe. First, kidney discard rates because of quality concerns in the United States seem considerably higher than in Europe [30,31]. Thus, US transplant data may be of limited value to characterize the transplant situation in Europe. Since ECD recipients are well-known to be prone to DGF and the cause-and-

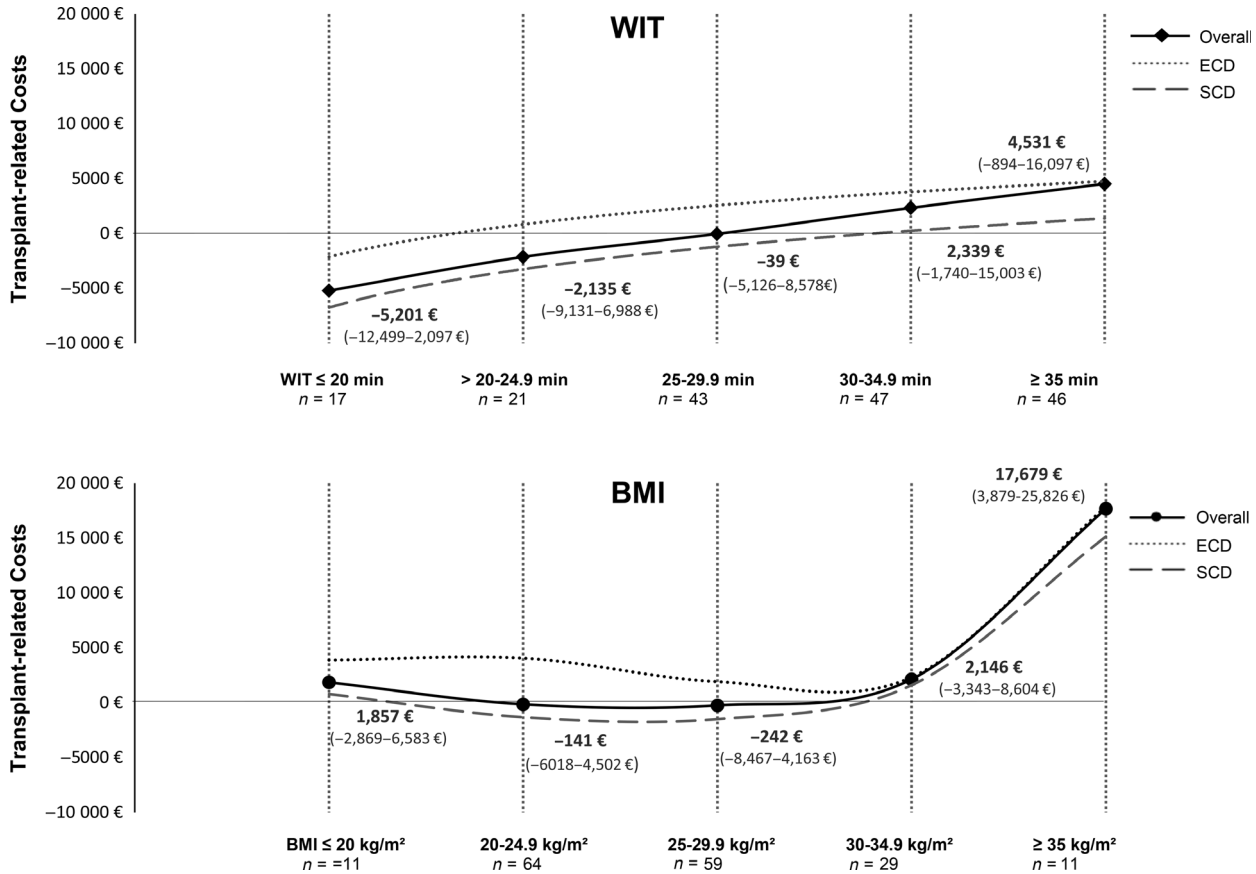


Figure 2 Effects of body mass index and warm ischaemia time on transplant-related cost development in the overall cohort, standard criteria donor organ recipients and expanded criteria donor organ recipients shown as categorial variables with estimaded curves. The data is presented as median and interquartile range (Q1–Q3).

effect relationship between DGF and increased costs has already been confirmed by several publications, the higher costs in ECD organs in our cohort seem to emphasize the broader utilization of organs from sicker donors in Europe than in the United States [32–34].

As the donor criteria are mostly nonmodifiable cost factors, we further investigated the cost effects of recipient- and perioperative characteristics. Prior studies have reported increased rates of surgical site infections in elderly and obese KT recipients [35,36]. In our observation, both factors resulted in inferior patient outcome and were further significantly associated with increased costs. Even more importantly, obesity rate was highest among 'old-for-old' organ recipients. This finding is of particular interest since our data show that costs escalated exponentially throughout all allocation groups when BMI exceeded 30 kg/m^2. Thus, obesity represents a potentially modifiable independent recipient risk factor for the incurrence of costs.

Regarding the perioperative characteristics, prolonged ischaemia time is linked to inferior transplant outcome [37]. Hence, it is reasonable to assume its impact on transplant-related costs. While prolonged CIT showed only minor effects on cost accrual, we observed a significant association between WIT and costs. In particular, a WIT of 30 min or more was identified to be related to increased costs in our overall cohort. With respect to ECD organs, a WIT of less than 25 min appeared to be crucial in order to prevent additional costs. In contrast, in SCD organs a WIT up to 35 min remained cost-neutral. Beyond its well-documented impact on transplant success, we could demonstrate the effect of WIT on financial aspects in ECD kidneys. Therefore, vascular anastomosis, especially in ECD organ transplantations, should be carried out with a special focus on short anastomosis time. In our experience, this includes optimum vessel exposure in obese patients, ideal choice of arterial implantation site, utilization of reverse cutting polypropylene sutures and eventually vascular modifications (i.e. jump graft prior to implantation) in patients with severe arteriosclerosis. These procedures should be accompanied by experienced surgeons.

Table 4. Univariate and multiple linear regression analyses of donor, recipient and perioperative characteristics on transplant-related cost alterations in relation to the basic remuneration of a reference patient* (shown as *P*-values and standardized beta coefficients).

		Univariate regression model		Multiple regression model†			Stepwise multiple regression model‡	
Variables	*n*	β	*P*-value	Inclusion	β	*P*-value	β	*P*-value
Recipient age ≥ 65 years	46	−0.152	**0.045**	Yes	−0.029	0.594	–	–
Recipient BMI ≥ 30 kg/m^2	38	−0.221	**0.003**	Yes	−0.161	**0.004**	−0.180	**0.001**
Induction therapy: thymoglobulin	20	−0.184	**0.015**	Yes	−0.202	**<0.001**	−0.208	**<0.001**
Warm ischaemia time ≥ 30 min	93	−0.117	**0.048**	Yes	−0.020	0.713	–	–
Intraoperative graft function	55	0.230	**0.020**	Yes	0.014	0.807	–	–
Delayed graft function	82	−0.431	**<0.001**	Yes	−0.085	0.254	–	–
Dialysis, *n* > 1	55	−0.433	**<0.001**	Yes	−0.176	**0.016**	−0.232	**<0.001**
Biopsy	62	−0.469	**<0.001**	**No**	–	–	–	–
Biopsy-proven rejection	22	−0.445	**<0.001**	Yes	−0.225	**0.003**	−0.211	**0.005**
Rejection therapy	39	−0.461	**<0.001**	Yes	−0.144	0.061	−0.171	**0.021**
Surgical complications, of these:	51	−0.521	**<0.001**	**No**	–	–	–	–
Clavien–Dindo Grade ≥III	44	−0.511	**<0.001**	Yes	−0.405	**<0.001**	−0.415	**<0.001**

n, number.

Annotations: Univariate linear regression models were calculated for all independent variables. Shown in this table are only potential predictor variables for the multiple linear regression analysis (with significant cost alterations in the univariate analyses, step 1 of the variable selection process). In the 2nd step of the selection process for the multiple regression model, intercorrelations of all predictor variables were checked. Of the variables with high intercorrelation, the selection was based on clinical relevance and two variables were excluded.

*Defined by an uncomplicated patient course, with no need for dialysis therapy.

†Enter method. Adjusted $R^2 = 0.542$.

‡Backward selection method. Adjusted $R^2 = 0.548$.

Two-sided *P*-values ≤ 0.05 were considered as significant (bold values).

Beside the recipient characteristics, postoperative markers played a crucial role in transplant-related costs. Charges increased distinctly with every dialysis. Despite separate remunerations for dialysis, refunds did not fully cover the expenditures of DGF and we observed a decline in profit margins. In particular, DGF and the need for more than one dialysis were associated with additional costs. We suggest that these results may be because of the elusive snowball effect of DGF on costs of additional diagnostics and treatment. Furthermore, induction therapy with thymoglobulin, as well as acute rejection diagnostics and therapies were associated with significant increases in transplant-related costs. Biopsies were more often performed, and far more rejection therapies were administered in ECD organ recipients compared to SCD organ recipients. Interestingly, the percentage of biopsy-proven rejections was similar in both groups. Therefore, we believe additional costs emerged from increased empiric treatments for possible rejection in patients with dysfunctional kidneys and borderline biopsy findings. Finally, surgical complications were independent predictors for higher costs. Severe complications, requiring interventions or surgical revisions were especially associated with tremendous cost. Again, recipients of ECD organs were significantly more affected.

Considering all our previous results, the question arises, whether the effort and the expenses of pool expansion programmes do pay off financially. Our research complements this debate with relevant departmental data and identifies cost-related parameters, which should be considered in the discussion. It is important to sensitize the transplant community about the costs that individual donor and recipient characteristics can cause, especially in a sensitive cohort, such as ECD organ recipients. We believe these results can help to predict cost-critical patient courses and develop strategies to prevent costly courses in advance. Recipient's obesity is a crucial example and some centres tend to exclude obese ESRD patients from KT evaluation [38,39]. In regard to the effects of obesity on increased costs and inferior transplant outcome enhanced patient management, lifestyle modifications and weight-reduction programmes prior to KT

seem to be reasonable strategies to address this ethical and financial dilemma, particularly in elderly KT recipients. The additional healthcare costs of such programmes may be justified with an improvement in transplant outcome and cost reduction after KT. Additionally, compared to dialysis therapy ECD transplantations have been reported to be cost saving on the long-term, although the time to breakeven costs does exceed the reported time in deceased donor transplantations [2,35]. Furthermore, the ESP 'old-for-old' programme often remains the only possibility to ensure access to KT for elderly ESRD patients. Taking into account the survival advantage and the amelioration of ESRD accompanying diseases, the reported increased costs in elderly patients may be outweighed by the benefits, especially compared to highly resource-intensive alternatives, such as chronic dialysis [40]. Hence, we do believe the benefits of the abovementioned donor pool expansion strategies need to be considered from a broader social-economic perspective.

To our knowledge, we are the first to perform a holistic cost analysis considering clinically relevant donor and recipient characteristics in the context of expanded criteria organs. However, some limitations need to be addressed. First, all the restrictions of a single-centre analysis apply. Second, donation after circulatory death is not permitted in Germany. Therefore, effects of such organ grafts on transplant-related costs could not be considered. Last, the study was conducted in Germany, where the allocation system and donor pools differ from those in other countries [31,41]. Furthermore, healthcare charges are calculated via the DRG case rate payment system in Germany and therefore calculations and cost estimations may not be entirely comparable to other healthcare refund systems. However, our findings were mostly in agreement with previous findings and may be seen as a further piece of the puzzle to gain a deeper understanding into cost incurrence in KT. An ageing society, restrictions in recipient selection, limitations in resources and growing financial pressure are already present and need to be addressed in the future. In light of this fact, cost analyses are thought to become more relevant for decision-making for such patients and will form an important part of future research focus.

Conclusion

In times of limited healthcare resources, an accurate understanding of the potential risk factors affecting the costs of KT is essential to properly demonstrate the benefits of different allocation programmes compared with competing therapies.

Expanded criteria organs are associated with inferior outcome and incremental costs, especially when transplanted into elderly and obese recipients. Regardless of the allocation group, a critical patient selection, treatment of modifiable factors, such as obesity, before KT and keeping warm ischaemia times short seem to be crucial to achieve a cost-effective KT.

Authorship

TD: research design, data analysis, statistics, writing and supervision of the paper. Approval of the article. MJ: data analysis, statistics, writing and supervision of the paper. Approval of the article. JH: statistical consulting and analysis. Review for statistics and methods contents. Writing and supervision of the paper. Approval of article. SW: data analysis, writing and supervision of the paper. Approval of the article. PVR: data analysis, writing and supervision of the paper. Approval of the article. CD: writing and supervision of the paper. Approval of the article. MB: writing and supervision of the paper. Approval of the article. UG: writing and supervision of the paper. Approval of article. PR: writing and supervision of the paper. Approval of the article. JP: Supervision of the paper. Approval of the article. RÖ: research design, data analysis, writing and supervision of the paper. Approval of article.

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