THE COST DISTRIBUTION OF THE TRANSPLANT HOSPITALIZATION AND THE RISK FACTORS FOR HIGHER COSTS ASSOCIATED WITH KIDNEY TRANSPLANTATION OF GRAFTS FROM DONATION AFTER CITIZEN'S DEATH IN CHINA: MONOCENTRIC EXPERIENCE

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ABSTRACT

Objective*: Although transplantation is a more cost-effective renal replacement therapy alternative to dialysis, it is still a resource-intensive service. The purpose of this retrospective study were to 1) investigate cost constitution and 2) determine the potential modifiable risk factors for higher costs of the kidney transplant hospitalization.*

Methods: *Sixty adult patients underwent consecutive donation after citizen's death (DCD) kidney transplantation in our transplant center during the first half of 2019. The economic and other data were analyzed and the risk factors related to higher costs of the transplant hospitalization were evaluated.*

Results: *Of these 60 kidney recipients with mean age 43, 34 (57%) were male and 40 (67%) underwent hemodialysis prior to transplantation. Approximately 33% of all recipients had chronic glomerulonephritis as underlying kidney diseases. Twenty-three percent of all recipients undergoing Hepatitis B or C as a comorbidity. Fifty (83%) of them were administrated induction therapy using antithymocyte globulin. Delayed graft function developed in 15 recipients. A sum of 7,864,444 yuan was spent by all recipients with cost of medications as a major cost driver. Twenty nine (48.3%) patients were in higher-cost group (>125,000 yuan) with higher proportion of costs of medications in comparison with its counterparts. Hepatitis B or C prior to transplantation (odds ratio [OR]=5.39, 95% confidence interval [CI]=1.27-22.95, P=0.023) and delayed graft function (OR=3.87, 95% CI=1.01-14.92, P=0.049) were independent predictors of higher costs of the transplant hospitalization.*

Conclusions: *Costs of medications were the major expenditure. Hepatitis B or C prior to transplantation and delayed graft function were two risk factors for higher costs of the transplant hospitalization. Reducing drug use, screening for hepatitis patients and improving early kidney function can greatly release the economic burden on kidney recipients.*

Keywords: *Kidney transplantation, cost, distribution, risk factors.*

DOI: 10.19193/0393-6384_2021_1_92

Received *March 15, 2020;* ***Accepted*** *October 20, 2020*

Background

Kidney transplant is the best option of treatment for patients with end-stage kidney failure due to offering a cost-saving treatment modality and the highest quality of life, lowering hospitalization index, improving survival, reducing direct and indirect costs with their comorbidities, and encouraging occupational rehabilitation[1, 2]. It is estimated that around one-half of the dialysis patients are waiting in the kidney transplant queue. Nevertheless, only 4.5% of them had the chance of transplantation because of the severe organ shortage[1].

Despite its cost-effectiveness, kidney transplant is a resource-intensive service[3, 4]. A recent study from Finland revealed that total annual costs were

median 59,583 EUR and the value ranging from R$ 40,743 to R$ 48,388 for the first post-transplantation year in another study from Brazil[1, 5].

There is no doubt that the cost of the first post-transplantation year is mainly incurred during the primary hospitalization for transplantation. Though the costs are substantial during that period of time, little information is available.

To the best of our knowledge, no study has investigated the cost distribution in China, nor has it confirmed the risk factors associated with higher costs of the transplant hospitalization in kidney transplant population worldwide.

Thus, the objective of this study was to:

• Investigate cost constitution;

• Compare the lower-cost group and higher-cost group and determine the potential risk factors for higher costs of the transplant hospitalization associated with donation after citizen's death (DCD) kidney transplantation to try to reduce the impact of these risk factors on economic aspects.

Methods

Study population

Based on medical records data of patients who underwent an adult kidney transplant, a retrospective cohort study was conducted in the transplantation center at the Third Xiangya Hospital of Central South University, Changsha, China, from the 1st of January 2019 to the 30th of June, 2019.

Elective adult recipients of grafts from DCD donors were identified sequentially excluding the following patient types: living-related kidney transplantation and age less than 18 years. All patients received third-generation cephalosporins or semi-synthetic penicillins/beta-lactamase inhibitors or a carbapenem perioperatively, usually for three to five days.

This study protocol has the approval of the Medical Ethical Committee of the Third Xiangya hospital.

Study design and data collection

After exclusions, remaining patients were assigned to either lower- or higher-cost group.

This retrospective cohort study analyzed the cost distribution of the transplant hospitalization and adopted logistic regression to evaluate the potential risk factors for higher costs associated with DCD kidney transplantation. Immunosuppression maintenance therapy after transplantation was a triple-drug scheme, with glucocorticosteroids and mycophenolate mofetil and the third drug varying between tacrolimus or cyclosporine, or an additional agent of monoclonal (basiliximab) and/or antithymocyte globulin in most recipients.

We collected and then compared demographics, clinical and laboratory data between patients with lower and higher costs of the primary hospitalization for transplantation.

These included donor's and recipients' age and sex, cold ischemia time, recipients' underlying kidney diseases and comorbidities, modalities of renal replacement therapy, duration of months of dialysis, protein and hemoglobin level prior to transplantation, human leukocyte antigen class I or II antibody positive status, duration of days between admission and transplantation, type of immunosuppressive used, reoperation, infection prior to and following transplantation, incidence of delayed graft function (DGF), days of intensive care unit and hospital stay, and costs of the transplant hospitalization.

The higher-cost group comprised all recipients who spent more than 125,000 yuan during the period of the transplant hospitalization. DGF was defined as the need for dialysis in the first week following kidney transplantation[6].

Cost data

All individual-level cost items for the primary hospitalization for transplantation were taken from the hospital billing database.

Costs were divided in the following categories:

• Medical service costs;

• Diagnostic costs, which include the costs of laboratory workup, radiology and pathology;

• Treatment costs, which include operations;

• Costs of medications;

• Blood transfusion costs;

• Material costs;

• The other costs.

Statistical analysis

Results are listed as mean (±standard deviation) for normally distributed continuous variables and median (1^{st}-3^{rd} quartile) for skewed continuous ones. Univariate comparisons of differences between 2 groups were made in continuous variables using the Student's t-test or Mann-Whitney U test and in categorical variables using Pearson's chi-squared test or Fisher's exact test when appropriate.

Variables that were significant or close to sig-

nificant risk factors in univariable analyses (P<0.1) were introduced into the subsequent multivariable model based on forward stepwise logistic regression. Associations were given as odds ratios (ORs) and 95% confidence intervals (CI) in the multivariable model. Calculations were performed using the statistical package SPSS for Windows, version 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, United States). Two-sided P-values <0.05 were considered to be statistically significant.

Results

A total of 60 adult recipients (34 males and 26 females, mean age 43.1±11.0 years, range 21-63 years) undergoing consecutive DCD kidney transplantation during the study period were included. Twenty patients (33.3%) and 14 (23.4%) were diagnosed with chronic glomerulonephritis and hepatitis (B or C), respectively. Forty patients were on maintenance hemodialysis before transplantation.

Nine (15%) and 4 (6.7%) of them were human leukocyte antigen class I or II antibody positive and infectious, respectively, prior to transplantation. Antithymocyte globulin were prescribed as induction therapy in 50 (83.3%) recipients. The all-cause in-hospital mortality was zero. Delayed graft function occurred in 15 (25%) recipients. Characterization of these 60 transplant patients included in the study were characterized in Table 1.

A sum of 7,864,444 yuan was spent by these 60 kidney recipients during the transplant hospitalization (mean costs 131,074±32,025 yuan, range 86,339-245,562 yuan). Costs related to medication (3,843,274 yuan) were the largest cost component in all patients (48.9%). A total of 29 (48.3%) patients were in higher-cost group where the gross costs were 4,453,328 yuan. Mean costs of each patient, in lower- and higher-cost groups, were 110,036 and 153,563 yuan, respectively.

The most costly component was medications in both groups, followed by diagnostic costs and material costs in higher-cost group and material and treatment costs in lower-cost group.

Values with medications totaled around 1.5 (45%) and 2.3 (52%) million yuan in lower- and higher-cost groups, respectively.

The proportion of costs of blood transfusion was also higher in higher-cost group (0.7%) in comparison with its counterpart (0.3%). Table 2 described the comparison of cost distribution of lower-cost versus higher-cost group.

Characteristics	Value
Donor age, mean yrs±SD	40.3±18.2
Donor sex, number of male (%)	51 (85%)
Cold ischemia time, mean hrs±SD	4.9±1.1
Recipients' age, mean yrs±SD	43.1±11.0
Recipients' sex, number of male (%)	34 (56.7)
Underlying kidney diseases, no. of cases (%)	
Chronic glomerulonephritis	20 (33.3)
Polycystic kidney disease	4 (6.7)
Previous transplanted kidney failure	4 (6.7)
Ig A nephropathy	11 (18.3)
Diabetic nephropathy	1 (1.7)
Other/unknown	20 (33.3)
Modalities of renal replacement therapy, no. of cases (%)	
Hematodialysis	40 (66.7)
Peritoneal dialysis	17 (28.3)
Without dialysis	3 (5)
Median duration of months of dialysis (IQR)	14.5 (10-24)
Comorbidities, no. of cases (%)	
Hepatitis B	10 (16.7)
Hepatitis C	4 (6.7)
Median protein level (mg/dL) prior to transplantation (IQR)	
Total protein level	70.5 (64.3-74.5)
Albumin level	43.9 (39.2-47.4)
Median preoperative hemoglobin level (g/L) (IQR)	109.5 (98.5-125.8)
HLA class I or II antibody positive prior to transplantation, no. of cases (%)	9 (15)
Infection prior to transplantation, no. of cases (%)	4 (6.7)
Duration of days between admission and transplantation, mean days±SD	0.6±0.9
Intraoperative or postoperative blood transfusion, no. of cases (%)	20 (33.3)
Induction therapy, no. of cases (%)	
Use of antithymocyte globulin	50 (83.3)
Use of baliximab	30 (50)
Patient immunosuppressant treatment, no. of cases (%)	
Tacrolimus	59 (98.3)
Cyclosporine A	1 (1.7)
Reoperation, no. of cases (%)	3 (5)
Infection after transplantation, no. of cases (%)	12 (20)
Delayed graft function, no. of cases (%)	15 (25)
Median days of ICU stay (IQR)	5 (4-6)
Median days of hospital stay (IQR)	21 (19-24)
Cost of the transplant hospitalization, no. of cases (%)	
Lower-cost group(<125,000 yuan)	31 (51.7)
Higher-cost group(>125,000 yuan)	29 (48.3)
All-cause in-hospital mortality	0(0)

Table 1: Characterization of 60 DCD kidney transplant patients included in the study.
DCD, donation after citizen's death; HLA; human leukocyte antigen; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

	Lower-cost group (<125,000 yuan) (n=31)	Higher-cost group (>125,000 yuan) (n=29)
Medical service costs	272,024 (7.97%)	310,732 (6.98%)
Diagnostic costs	518,181 (15.19%)	625,445 (14.04%)
Treatment costs	521,168 (15.29%)	560,015 (12.58%)
Costs of medications	1,534,320 (44.98%)	2,308,954 (51.85%)
Blood transfusion costs	8,930 (0.26%)	31,530 (0.71%)
Material costs	545,193 (15.98%)	602,986 (13.54%)
The other costs	11,300 (0.33%)	13,666 (0.31%)
Total costs	3,411,116 (100%)	4,453,328 (100%)
Average costs of each patient	110,036	153,563

Table 2: Comparison of cost distribution of lower- versus higher-cost group.

As shown in Table 3, in univariate analysis, when compared with lower-cost group, the risk factors associated with higher costs were hepatitis B or C prior to transplantation (P=0.01) and DGF following transplantation (P=0.025). Length of intensive care unit stay ≥3 days and reoperation showed trends to significance (P= 0.089 and 0.066, respectively). All these 4 variables were selected to the multivariate analysis which showed that hepatitis B or C prior to transplantation (OR=5.39, 95% CI=1.27-22.95, P=0.023) and DGF following transplantation (OR=3.87, 95% CI=1.01-14.92, P=0.049) remained independent predictors of higher costs of the transplant hospitalization. Results of the multivariable logistic regression analysis of the risk factors were also shown in Table 3.

Characteristics	Lower cost group	Higher cost group	*P*	OR (95% CI)
Total, n(%)	31 (51.7)	29(48.3)		
Univariate analysis				
Donor age≥55 yrs	8 (25.8)	4 (13.8)	0.245	
Donor male sex	28 (90.3)	23 (79.3)	0.233	
Cold ischemia time>5hrs	7 (22.6)	10 (34.5)	0.397	
Age≥40 yrs	17 (54.8)	20 (69)	0.261	
Male sex	15 (48.4)	19 (65.5)	0.181	
Polycystic kidney disease	2 (6.5)	2 (6.9)	0.586	
Peritoneal dialysis	11 (35.5)	6 (20.7)	0.176	
Duration of dialysis≥24months	12 (38.7)	12 (41.4)	0.833	
Hepatitis B or C prior to transplantation	3 (9.7)	11 (37.9)	0.01	
Total protein level prior to transplantation< 65 mg/dL	8 (25.8)	6 (20.7)	0.64	
Albumin level prior to transplantation< 40 mg/dL	8 (25.8)	10 (34.5)	0.464	
Preoperative hemoglobin level< 100g/L	10 (32.3)	5 (17.2)	0.179	
HLA class I or II antibody positive prior to transplantation	3 (9.7)	6 (20.7)	0.233	
Infection prior to transplantation	2 (6.5)	2 (6.9)	0.945	
Intraoperative or postoperative blood transfusion	9 (29)	11 (37.9)	0.465	
Delayed graft function	4 (12.9)	11 (37.9)	0.025	
Reoperation	0 (0)	3 (10.3)	0.066	
Infection after transplantation	7 (22.6)	5 (17.2)	0.859	
Length of hospital stay≥20 days	20 (64.5)	23 (79.3)	0.204	
Length of ICU stay≥3 days	24 (77.4)	27 (93.1)	0.089	
Multivariate analysis				
Delayed graft function			0.049	3.87 (1.01-14.92)
Hepatitis B or C prior to transplantation			0.023	5.39 (1.27-22.95)

Table 3: Univariate and multivariate analysis of risk factors associated with a higher cost of the transplant hospitalization.

CI, confidence interval; HLA; human leukocyte antigen; ICU, intensive care unit; OR, odds ratio.

Discussion

Although kidney transplantation is standard of care and in the long run, the most cost-saving therapeutic option for patients with end-stage kidney disease compared with the alternative of dialysis, it is still a heavy economic burden of patients[1, 7-10].

Gouveia DSES, et al have shown that in 2014 in Brazil, the lowest cost of a kidney transplant in the first year was R$ 40,743 when tacrolimus was used. 1 We found the average cost of each patient was 131,074 (ranging from 86,339 to 245,562) yuan during transplant hospitalization, which concurs with the previous costing studies by Gouveia DSES et al and others[1, 5, 11]. Since transplanted patients have a high initial cost with the kidney transplant procedure, economic analysis for cost distribution of transplant hospitalization for further attempt of reducing the costs is of paramount importance. We found that the largest cost component in all recipients was costs related to medications (3,843,274 yuan; 48.9% of total cost) with a higher proportion in higher-cost group (51.9%) when compared with the lower-cost one (45%), in line with a study of kidney recipients where dispensed prescription drugs made up 44% of total cost[9]. It is reasonable that to maintain the different therapies for complex status, numerous medicines and blood were used, which increased the financial impact and led to higher costs and a higher proportion of costs of medications and blood transfusion in higher-cost group. It is pivotal to reduce the unnecessary prescription of medications since the majority of these costs were ascribed to medications in the higher-cost group.

We found patients with hepatitis B or C prior to transplantation were associated with a fivefold increased risk of higher costs of the transplant hospitalization. The finding in this study is compatible with that in the literature reporting that hepatitis C viral (HCV) is a significant threat to allograft and patient survival of kidney recipients and independently associated with increased costs[11-13]. HCV-positive recipients were easier to develop much more complications such as proteinuria, chronic rejection, infections, glomerulonephritis, and new-onset diabetes after transplant than HCV-negative patients[14]. Previous studies demonstrated that hepatitis B or C led to deranged liver function tests and worse patient and allograft survival in kidney recipients[15-17]. These findings indicated that kidney transplant candidates should be screened for hepatitis B and C virus infections to increase graft survival and improve

quality of life as well as save the costs of transplantation. Besides HCV, Nassir BA et al also confirmed several factors, such as female, the etiology of end-stage kidney failure, donor age, cold ischemia time and pretransplant dialysis duration ≥5 years as a cost driver, although these findings was not confirmed in our current analysis[11]. We also revealed that DGF was a cost-driving event, consistent with multiple studies reporting that patients with DGF had higher costs compared to patients with early graft function[5, 18, 19]. A previous Canadian study discovered that the cost of a failed graft was almost twofold higher than of a successful kidney transplant in the first year[20]. An economic study demonstrated that the length of hospital stay increased an average of 7 days in DGF patients compared with those with immediate graft function, resulting in a dramatic rise in costs[21]. Now that DGF has an important impact on early as well as long-term costs on basis of our present study and other studies mentioned above, management strategies promoting early graft function such as therapies of actively minimizing ischemia-reperfusion injury and immunotherapies targeted towards inhibition of complement activation, therefore, might prove promising towards mitigating DGF[5, 19, 22].

The strengths of this study include firstly investigating cost distribution of transplantation patients with individual-level actual cost data and determining the multiple clinical factors for higher costs of the transplant hospitalization associated with DCD kidney transplantation in China. Our study, however, has some limitations. First, this is a single-centre study. Results derived from multi-center studies may provide a more comprehensive view. Second, the relatively small sample size of our study could incur subsequently insufficient statistical power. Third, the retrospective nature of this study indicates that information may be not very accurate. Thus further investigations of larger sample size are needed to determine specific cost-effective practices to reduce the primary hospitalization during kidney transplantation procedure. Despite the retrospective characteristic and the design of relatively small sample size, we believe, the information generated herein is useful for cost impact analyses, serving as a reference for future studies in relation to a high-quality care and cost-saving strategies for kidney recipients.

Conclusions

Costs of medications were the major expenditure. Hepatitis B or C prior to transplantation and delayed graft function were two risk factors for higher costs of the transplant hospitalization. Reducing drug use, screening for hepatitis patients and improving early kidney function can greatly release the economic burden on kidney recipients.

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Financial Support:
This work was support by the Science and Technology Department of Hunan Province, China (grant 2020JJ4851).

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