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Original Research

Donor Age and Ischemia Time Are Independent Factors Affecting Graft Survival after En Bloc Kidney Transplantation from Donors Less than Three Years of Age

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Abstract

This study aimed to investigate the outcomes of transplantation from donors aged less than three years in a single-center consecutive series. A total of 52 en bloc kidney graft transplantations were performed. In 22 cases, organs were procured from donors aged less than one year (group 1). In 30 cases, the age of donors varied from one to three years (group 2). After transplantation, renal function and graft and patient survival were evaluated retrospectively. No significant difference was observed between the groups regarding

recipient age, time on dialysis, ischemia time, human leukocyte antigen matching, the time needed to reach serum creatinine levels of ≤2 mg/mL, and patient survival. Eight grafts were lost during the first six months after grafting in group 1, whereas only two grafts were lost in group 2. Immature glomeruli were observed in three preimplantation biopsy samples. Graft survival was significantly longer in group 2 (hazard ratio, 0.5 [95% CI, 0.28–0.91]; $p = 0.025$). In a multivariate analysis, donor age ($p = 0.01$) and ischemia time ($p = 0.02$) were independent factors affecting graft survival. En bloc kidney transplantation from donors aged less than one year was associated with high early graft loss and poor long-term survival rates. Further investigations are needed to confirm the possible relationship to the histological glomerular maturity.

Keywords
Pediatric donors; en bloc kidney transplantation; adult recipients

1. Introduction

The limited number of donors is a challenging problem to be faced to avoid long-term dialysis while awaiting kidney transplantation, which is the best treatment for end-stage renal disease and provides a higher quality of life and longer survival compared with long-term dialysis [1]. Several strategies have been developed over the past decades to reduce the difference between the number of patients on the waiting list and the available kidney donors and the mean waiting time.

The use of extended criteria donors, including donors of extreme ages, has proved to be beneficial [2]. En bloc kidney transplantation (EBKT) from extremely young donors to adult recipients is a reliable option [2-4] with higher long-term survival rates [5]. However, using it still presents a challenge with poor early outcomes associated with a high risk of graft loss [6, 7].

Pediatric kidneys, typically not affected by any underlying pathology, compensate for the initial mismatch between the nephron mass of the graft and the recipient body mass by a hypertrophic compensation phenomenon. They have the potential to grow rapidly once connected to the adult recipient vascular stream, doubling in size in two to three weeks to attain adult volume within 18 months [8]. This study aimed to investigate transplant outcomes with donors aged less than three years and verify whether age is a discriminating factor in the selection of organs for transplantation.

2. Patients and Methods

2.1 Study Population

Between May 1979 and December 2017, 3700 kidney transplants were performed at the Cliniques Universitaires Saint-Luc, Brussels, Belgium. Out of which, a cohort of consecutive 52 EBKT was identified. The donors were less than three years old, and kidneys were transplanted into adult recipients. To investigate the effect of donor's age on the transplantation outcomes, particularly extremely young donors, recipients were divided into two groups: less than or one-year-old donors in recipient group 1 (n = 22) and more than one-year-old donors in recipient

group 2 (n = 30). The medical records for both donors and recipients were reviewed retrospectively.

2.2 Surgical Procedure

Before transplantation, all the paired kidneys were procured from brain-dead donors using Euro-Collins (n = 9), University of Wisconsin (n = 32), or histidine-tryptophan-ketoglutarate (n = 11) solutions and placed in cold static storage. A pretransplant biopsy was performed in 10 cases. All kidneys were harvested and transplanted in the retroperitoneal space using an en bloc technique. The proximal donor aorta and inferior vena cava were oversewn with 7–0 polypropylene sutures. The distal donor aorta and inferior vena cava were anastomosed to the recipient's iliac vessels in an end-to-side manner. En bloc paired kidneys were positioned in the iliac fossa. The ureter-to-bladder anastomosis was performed separately or by conjoined implantation using the Lich-Gregoir method [9, 10].

2.3 Immunosuppression

Immunosuppression therapy has evolved considerably during the study period. Before 1986, the maintenance regimen included prednisolone and azathioprine. Calcineurin inhibitors such as cyclosporine and tacrolimus were included in the treatment in 1986 and 1999, respectively. For six patients, transplantations were performed before the advent of calcineurin inhibitor-based immunosuppression.

Pretransplant assessment and outcome evaluation:

The following pretransplant data were collected: age, gender, and weight of the donors and recipients; cause of donor death; cause of primary nephropathy; time on dialysis; human leukocyte antigen (HLA) mismatches; and ischemia time.

After transplantation, renal function was evaluated using the serum creatinine levels obtained at one, five, and ten years and during the last follow-up. Delayed graft function (DGF), the time needed to reach serum creatinine levels of $\leqslant$2 mg/mL, graft loss, and graft and patient survivals were also evaluated. DGF is defined as the need for dialysis within the first week posttransplant.

2.4 Statistical Analysis

Continuous variables (body weight, creatinine levels, age, etc.) were described using median and ranges. Categorical variables were described using frequencies and percentages. Nonparametric statistics were used to compare variables in different groups: the Wilcoxon test was performed for continuous variables and the Chi-square test for categorical variables.

Survival analyses were performed without censoring graft survival, patient survival, and time to reach serum creatinine levels of $\leqslant$2 mg/dL, and related Kaplan-Meier plots were generated.

A multivariate linear regression analysis was performed for graft survival. Following uncorrelated covariates were tested: ischemia time, donor age, recipient age, and HLA mismatch. A stepwise approach was used for covariate analysis with a *p*-value of 0.05 for inclusion in the model.

Overall, a *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed using JMP software (version 10, SAS group, Cary, NC).

3. Results

3.1 Patients

Table 1 summarizes the demographic characteristics of the donors and recipients. Both groups had similar age, weight, body mass index, total ischemia time, HLA mismatches, and pretransplant time on dialysis. The main causes of donor death in group 1 were trauma (n = 7), cerebral infection (n = 5), cerebral anoxia (n = 9), and cerebral tumor (n = 1), whereas donor death was associated with trauma (n = 18), cerebral infection (n = 2), cerebral anoxia (n = 8), cerebral tumor (n = 1), and cerebral embolism (n = 1) in group 2. Two (9.5%) and six (26.08%) recipients in groups 1 and 2, respectively, had previous transplantation. The median follow-up was 79 (ranges, 0–288) months. A histogram of the graft number is provided in Figure 1.

Table 1 Demographic characteristics of the population.

	Group 1 (n = 22)	*Group 2 (n = 30)*	*P-value**
Donors age (months)	6.28 (0.26–11.06)	20.2 (13–26)	-
Donors weight (Kg)	8 (4–13)	12 (6.5–25)	-
Total ischemia time (hours)	19.43 (9.5–48)	19.90 (7.3–63)	0.78
HLA matches	2.5 (1–4)	2 (0–5)	0.76
Donor sex (male/female)	14 / 8	17 / 13	-
Recipient sex (male/female)	9 / 13	16 / 14	-
Recipients age (years)	39 (17–62)	39 (15–76)	0.41
Recipients weight (Kg)	56 (40–92)	59 (27–81)	0.68
Pre-transplant dialysis (months)	24 (0–144)	66 (0–229)	0.12

Results are expressed as median and range. *, Wilcoxon test. +, Chi-square test.

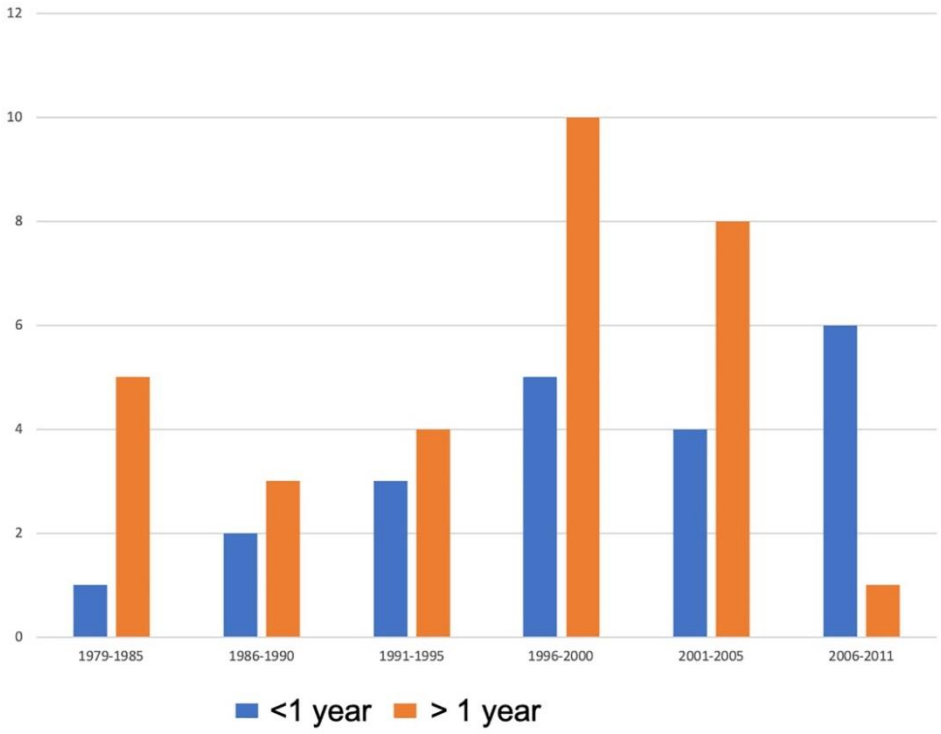

Figure 1 Transplantation histogram from 1979 to 2011.

3.2 Graft and Patient Survivals

After transplantation, eight grafts (36.36%) were lost during the first six months in group 1 because of arterial thrombosis (n = 3), poor function or primary nonfunction (n = 3), and patient's death (n = 2), whereas in the same period, only two grafts were lost in group 2 because of early rejection. In addition, in group 1, three other grafts were, respectively lost at 16.5, 26, and 182 months because of delayed humoral rejection (n = 1), graft hydronephrosis (n = 1), and nonadherence-related rejection (n = 1). Whereas in group 2, four grafts were lost because of patient's death (n = 2) and chronic allograft nephropathy (n = 2) at 26 and 36 months postgrafting, respectively (Table 2).

Table 2 Delayed graft function and graft loss.

	Group 1 n = 22	Group 2 n = 30	P-value
Delayed graft function (n,%)	6/21 (28.57%)	3/30 (10%)	<0.01*
Early graft loss (⩽6 months)	8/22 (36.36%)	2/30 (6.66%)	<0.01*
- Thrombosis	3	-	
- Poor function	3	-	
- Patient death	2	-	
- Rejection	-	2	

Results are expressed as the number of observation and percentage. * Chi square test. , in one case grafts thrombosis occurred at the end of surgery.

Graft survival over time after transplantation is shown in Figure 2. A multivariable analysis was performed to identify factors affecting long-term graft survival. Independent covariates included donor age, recipient age, time on dialysis, ischemia time, and HLA mismatches. Donor age (p = 0.01) and ischemia time (p = 0.02) are independent factors affecting the long-term graft survival. Recipient survival did not differ between groups (Figure 3).

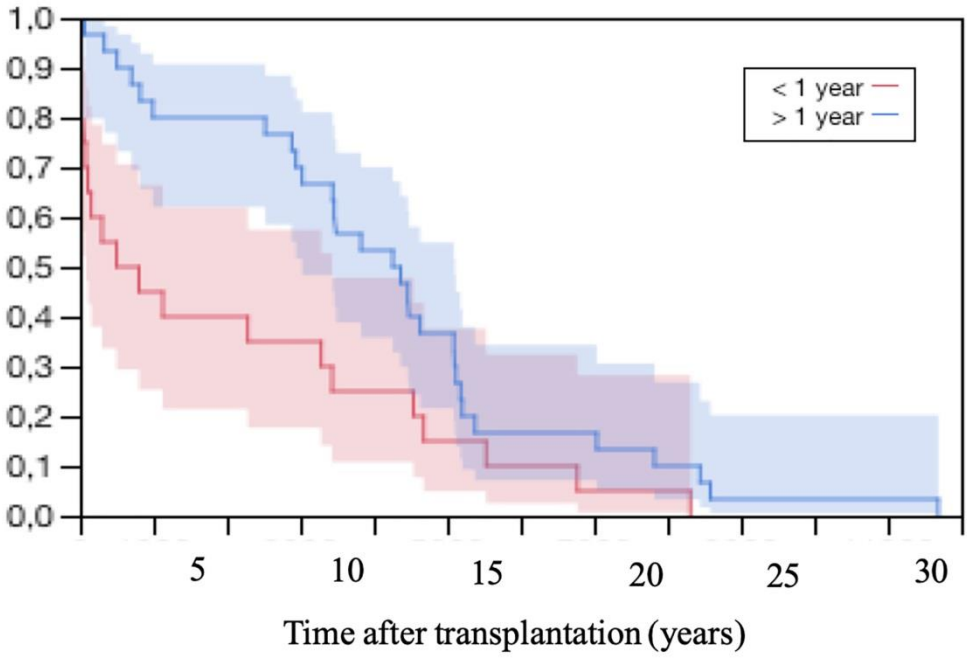

Figure 2 Kaplan-Meier graft survival estimates (death not censored).

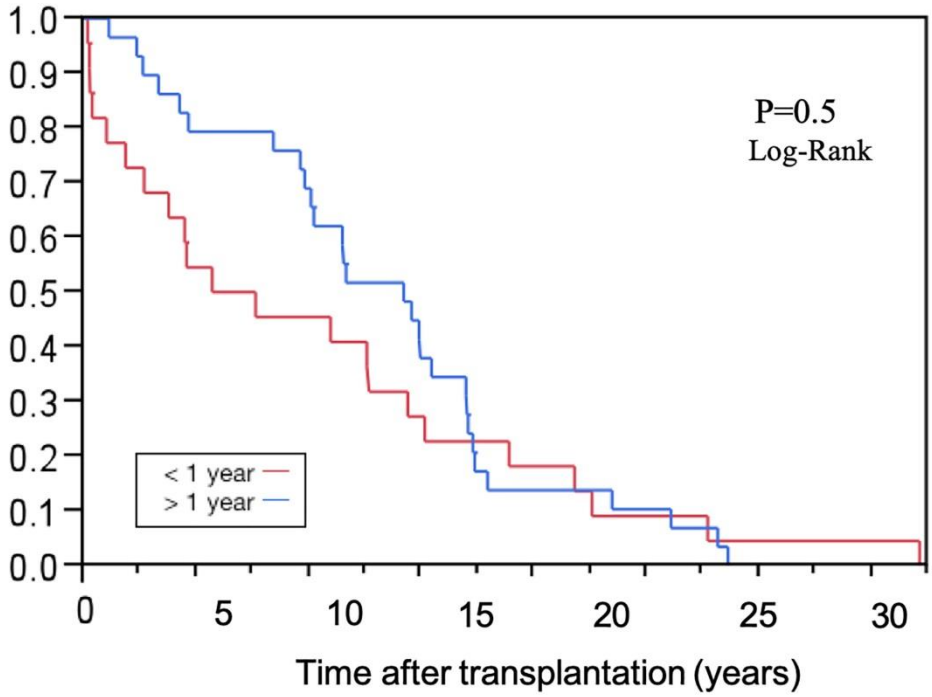

Figure 3 Kaplan-Meier patient survival estimate.

3.3 Renal Function

DGF occurred in six (28.57%) and three (10%) patients in groups 1 and 2, respectively ($p < 0.01$). The time needed to reach serum creatinine levels of ⩽2 mg/mL was similar between groups (Figure 4). The median serum creatinine levels (and range) at one, five, and ten years in groups 1 and 2 are summarized in Table 3.

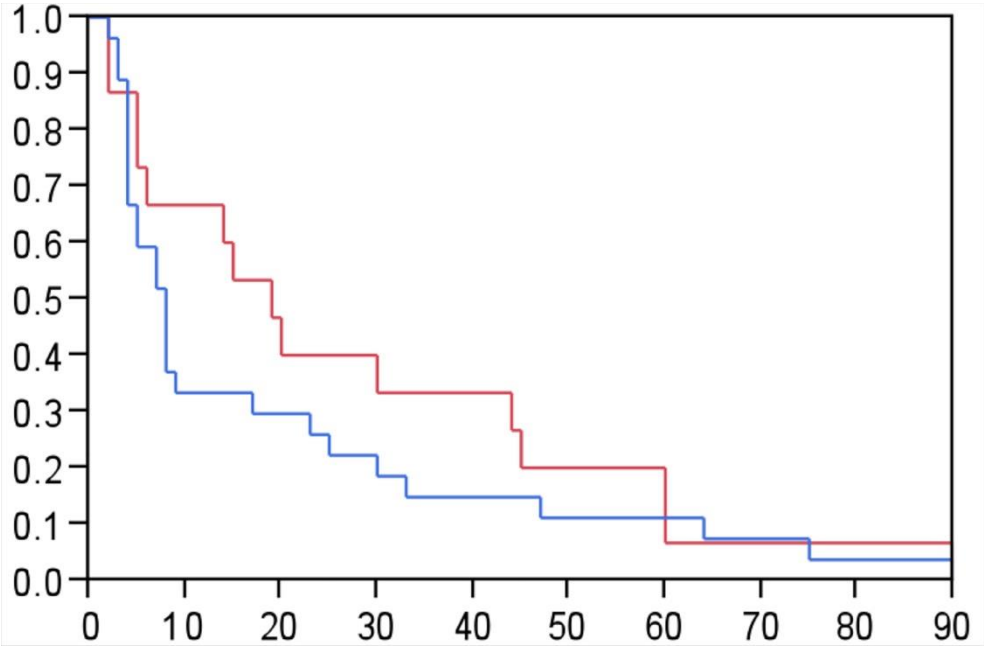

Figure 4 Kaplan-Meier estimates for the time needed to reach creatinine ⩽ 2 mg/dL.

Table 3 Renal function at follow up.

	Group 1 n = 22	Group 2 n = 30	p*
sCr one year (mg/dL)	1 (0.6–12.55) *n = 19*	1.1 (0.6–3.75) *n = 28*	0.87
sCr five year (mg/dL)	0.7 (0.6–1) *n = 9*	1 (0.35–2) *n = 25*	0.11
sCr ten year (mg/dL)	0.71 (0.46–1.03) *n = 7*	0.91 (0.49–2.38) *n = 20*	0.28

Results are expressed as median and range. *, Wilcoxon test. sCr = serum creatinine

3.4 Histological Assessment

A total of 10 pretransplant biopsy samples were obtained and analyzed. All three biopsy samples obtained from group 1 showed 100% immature glomeruli, which are defined by an indistinct capillary formation and a high prevalence of epithelial cells. The seven histological samples obtained from group 2 showed mature glomeruli (Figure 5).

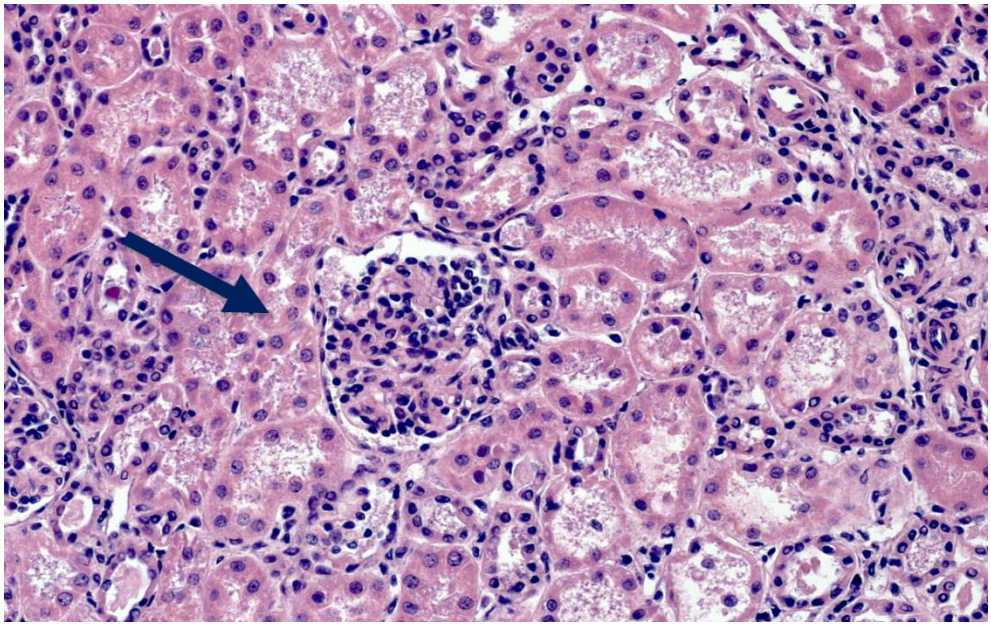

Figure 5 Histological appearance of immature glomerulus where the capillary formation is indistinct and epithelial cells are prominent.

4. Discussion

Given the low incidence of extremely young pediatric donors, EBKTs are relatively uncommon, and the optimal use of these organs remains to be determined. Therefore, the published series tend to be center specific, with a small number of patients lacking standardized selection criteria capable of obtaining satisfactory outcomes. According to the results from our single-center experience of more than three decades, this study confirmed the strong correlation between donor age and outcomes after transplantation.

Age is used as a discriminating factor because of its greater reliability to determine the degree of organ maturation [11].

Patients receiving EBKT from donors aged less than one year showed significantly higher DGF and graft loss occurring up to the first six months after transplantation. In addition, once the critical period of the first six months post-transplant was exceeded, the recipient survival and graft function were comparable in the long term with those obtained when transplants are procured from donors aged more than one year. These results are in line with several published studies demonstrating that despite a higher graft loss during the first six months posttransplant, the EBKT procedures assure a higher long-term graft survival when compared with living donor kidney transplantation [5]. Notably, in contrast to our study, few studies focused on extremely young donors, younger than 12 months, and a critical donor age has not been well established. However, graft survival was shorter when donors aged one year [11].

In addition to age, other variables such as donor weight, recipient body mass index, donor-recipient size match, and kidney length were previously evaluated [12]. A weight of 15 kg is typically recommended to guide the surgeon in selecting the operative technique between EBKT and single kidney transplantation [13, 14]. In this study, no correlation was observed between weight and transplant outcomes. We focused more on the degree of kidney maturation than on morphometric characteristics. In three preimplantation biopsy samples taken before EBKT,

histologic analysis showed a surprisingly immature glomeruli rate of 100% in lost grafts. Moreover, the degree of parenchymal maturation can be a major factor affecting the outcomes. In fact, embryological investigations in recent years [15] have clearly shown that nephrogenesis and renal maturation start approximately from the ninth week of gestation. This event follows a centrifugal trend from the inside to the outside of the renal parenchyma through essentially three "nephron waves." Considering this phenomenon, the kidney surface contains glomeruli that are less mature than deeper ones. Therefore, this observation, albeit cautiously, supports that renal biopsy may be a valuable parameter to be considered before accepting a kidney from donors aged less than one year.

However, Halldorson et al. reported that pediatric en bloc transplanted kidneys adapt to the workload of acquired adult recipient's body without hyperfiltration injury, and kidney graft size increases shortly after transplantation [16].

They suggested that hyperfiltration syndrome occurs because of weight gain only in recipients with fully matured kidney grafts, which are unable to adapt to an increasing workload.

Therefore, although an excess of immature glomeruli is unlikely to be compatible with satisfactory results in adult transplanted patients, glomerular immaturity may allow the kidney to adapt to the needs of an adult recipient's body.

In consistence with recent data [17], our results confirmed that cold ischemia time was also associated with poor outcome and graft loss. The effect of ischemic injury on renal transplant outcome is associated with several intracellular changes during ischemia, including reactive oxygen species production, acidosis, a decrease in Na/K ATPase pump function, and cell swelling. During reperfusion, inflammation lesions triggering endothelial and tubular cells lead to apoptosis and necrosis. Consequently, this study results demonstrated that cold ischemia might increase the susceptibility of young kidneys (from donors less than one year of age) with a certain degree of immaturity to graft loss.

In our series, the ischemia time was particularly longer than other transplant categories. This is probably because of the longer time needed to allocate organs, as several centers do not accept en bloc kidneys.

Notably, kidneys from donors aged younger than 12 months should be carefully handled because of an increased risk of technical complications, including vascular thrombosis [18-20] that is often associated with the graft twist, bleeding, and ureterovesical anastomosis leakage or stenosis [6, 21]. Several recommendations may be proposed to lower the postoperative complication rates, including the fixing of the capsule of the two kidneys to the surrounding muscles and systematic anticoagulation prophylaxis. With respect to the ureterovesical anastomosis, some studies have used a "bladder trigone patch technique" provided that there is an adequate blood supply of donor bladder patch. We suggested using an extravesical approach described by Lich-Gregoir [9, 10] either by a single conjoined ureteral implantation or by two separate anastomoses with or without the use of a stent.

To optimize patients' outcomes after EBKT from young donors, a uniform prospective strategy was set in our center: 1) EBKT was performed by an experienced surgical team capable of performing complex microsurgery proceedings; 2) considering the morphometric characteristics and ages of donors and recipients, obese or overweight recipients were excluded, and the degree of glomerular maturation was assessed using a preimplantation biopsy (less than 20% of immature

glomeruli); 3) cold ischemia time was reduced (less than 10 h) to avoid DGF; and 4) to minimize the risk of early acute rejection, highly sensitized recipients need to be avoided.

Our study has several limitations, primarily in relation to its retrospective nature. The study period was long, with an inhomogeneous population in terms of immunosuppressive treatment and surgical team. However, the diversity of patients was balanced in both groups. The absence of systematic implementation of a preoperative biopsy does not allow comparing between the various categories of donors and defining a critical proportion of immature glomeruli as an acceptable threshold.

In conclusion, despite these limitations, the study gives a particular insight into the relevance of renal maturation combined with ischemia time as major factors affecting outcomes after transplantation of kidneys from extremely young donors.

Author Contributions

Antoine Buemi: Conception, statistical analysis and writing; Jerome Duisit: Data collection and writing; Flora Musuamba: Statistical analysis; Tom Darius: Review; Martine De Meyer: Review; Selda Aydin: Anatomopathological analysis; Nada Kanaan: Review; Arnaud Devresse: Review; Eric Goffin: Review; Michel Mourad: Conception and writing.

Competing Interests

The authors have declared that no competing interests exist.

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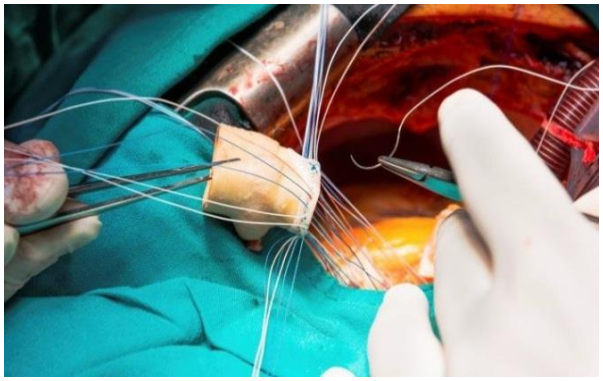

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