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Original Article

Cadaveric renal transplantation: Our experience at a tertiary care centre in India

Debabrata Mukherjee^a, Ranjith K. Nair^a, Sourabh Sharma^{b,*},
Bhaskar Datt^c, Ananth Rao^b, Sudeep Prakash^b

^a Senior Advisor (Nephrology), Army Hospital (Research & Referral), Delhi, India

^b Senior Resident (Nephrology), Army Hospital (Research & Referral), Delhi, India

^c Classified Specialist, (Nephrology), Army Hospital (Research & Referral), Delhi, India

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ABSTRACT

Background: Renal transplantation in developing countries like India is largely live donor transplantation. Cadaveric transplantation comprises <2% of all transplants in India.

Methods: Ninety-two cadaveric renal transplantations were included. Various donor and recipient characteristics were analysed along with graft and patient survival, using Kaplan–Meier method.

Results: The mean age of the recipients was 35.5 ± 10.9 years while that of cadaver was 43.9 ± 17.0 years. Proportion of females among recipients was 47.8% while that of donors was 34.8%. The most common underlying pathology was chronic glomerulonephritis (44.6%). Antithymocyte globulin was used as induction in 84.8% of cases. Tacrolimus-based triple-drug regimen was most commonly used as maintenance (80.4%). The mean follow-up time was 39.02 ± 28.24 months. The most common cause of death was sepsis (47%). More than 50% deaths (9/17) occurred within first 3 years, while 61.5% of graft loss occurred 5 years after transplantation. The mean graft survival time was 81.6 months (95% confidence interval [CI]: 72.8–90.4). Cumulative proportion of graft survival was 91.6% at 3 years and 77.1% at 5 years. Although females have better mean graft survival time (91.6 vs 73.5 months), it was not a significant difference as shown by log-rank test (p value = 0.062). Pretransplant haemodialysis has no significant effect on graft loss, but patients on peritoneal dialysis have significantly higher odds of graft loss (odds: 4.86, p value < 0.05 [0.018]). The mean patient survival time was 99.5 months (95% CI: 84.0–114.9). Cumulative proportion of patient survival was 83.3% at 3 years and 70.8% at 5 years.

Conclusion: Graft and patient survival rate of cadaveric transplant at our centre was satisfactory. There is need to sensitise and augment the rate of cadaveric transplantation to increase the donor pool.

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* Corresponding author.

E-mail address: drsourabh05@gmail.com (S. Sharma).

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Introduction

In south Asian countries including India, end-stage renal disease (ESRD) is associated with high morbidity and mortality. In India, the crude incidence rate of ESRD is 151 per million population per year¹ and age-adjusted incidence rates is 232 per million population per year.¹ In south Asian countries including India, majority of ESRD patients die within months of diagnosis because of unaffordability or poor availability of renal replacement therapy such as haemodialysis, peritoneal dialysis or renal transplantation.² Renal transplantation has most favourable outcomes in ESRD and stays the treatment of choice for ESRD.³ In India, 15,000 new patients begin maintenance haemodialysis, 3000 patients are started on continuous ambulatory peritoneal dialysis, and 3500 patients undergo renal transplantation in a year.⁴ Renal transplantation rates are around 3.20 per million populations per year.¹ Cadaveric transplantation comprises around 2% of all transplants in India.⁵ Over 90% of patients awaiting renal transplantation die without getting the organ.⁶ Cadaveric transplantation can bridge this gap efficiently. However, progress of cadaveric programs has been halted by lack of awareness, religious stigmas and infrastructural deficiencies.⁷ In this study, we have analysed the outcome of cadaveric transplantation at our centre since its inception.

Materials & methods

This is a retrospective analysis of a cadaveric renal transplantation program at a tertiary care centre in New Delhi, India. Ninety-two cadaveric renal transplantations, performed from August 1998 to June 2017, have been included in this study. All transplants were blood group compatible. Human leucocyte antigen (HLA) matching could not be carried out because of temporal and logistic reasons. Crossmatch test was performed by complement-dependent micro-lymphocytotoxicity method. The induction agent used was interleukin-2 receptor antagonist till 2005, and from 2007 onwards, antithymocyte globulin (ATG) was used as an induction agent in all patients. For maintenance immunosuppression, cyclosporine, mycophenolate mofetil (MMF) and prednisolone were given till 2005, and from 2007 onwards, it was tacrolimus, MMF and prednisolone in weight-based dosage. Primary cytomegalovirus and pneumocystis carinii prophylaxis was given to all patients. Data analysis included age, sex and comorbidities of the donor; and age, sex, basic disease, immunosuppression and follow-up period of the recipient. The data so collected were entered in MS Excel. Results are expressed as mean $\pm$ standard deviation and median. SPSS® (Statistical Package for the Social Sciences), version 22, Statistics for windows (IBM® Corp, Armonk, NY) was used for data analysis. Univariate analysis was performed by using logistic regression to compare odds of graft loss in diverse groups to find significant factors in graft survival. Graft survival was compared by using log-rank test among male and females. Kaplan–Meier analysis was performed to evaluate survival rates of the patient and graft.

Results

First cadaver transplantation was held at our centre on 7th August 1998. Since then, 92 cadaveric transplantations have been performed till July 2017. The total number of renal transplants performed during this period was around 1100. Cadaveric transplantation comprised less than 1% of total transplants at our centre. Demographic and survival analysis of these 92 renal transplant recipients has been performed (Table 1). The mean age of the recipients was 35.5 ± 10.9 years while that of cadaver was 43.9 ± 17.0 years. The proportion of females among recipients was 47.8% (N = 44) and among donors, 34.8%. It was in stark contrast with our live renal transplant program in which females contributed 62% as donors while 23% as recipients. Prevalence of chronic glomerulonephritis (CGN; 44.6%) and chronic interstitial nephritis (40.2%) was highest, other prevalent causes include diabetic

Table 1 – Demographic and clinical profile of patients undergoing renal transplantation.

Variable	Values
Number (recipients)	92
Age (recipients)	35.5 ± 10.9
Female (%) (recipients)	44 (47.8%)
BMI	22 ± 4.1
Basic disease (%)	
CGN	44.6
CIN	40.2
Others	15.2
Blood transfusion (%)	39.1
Age (cadaver)	43.9 ± 17.0
Female (%) (cadaver)	34.8%
Induction	
No induction	2.2
IL-2 Rab	13
ATG	84.8
Immunosuppression	
TMP	80.4
CMP	15.2
Others	4.3
Last creatinine	1.59 ± 1.06
Total events	
Number of graft loss (%)	13 (14.1%)
Number of deaths (%)	17 (18.5%)
Reported cause of death	
Sepsis	8
CMV	2
CAD	1
Pneumonia	1
CVA	1
Not known	4
Timing of deaths	
First year	1
Second year	3
Third year	5
After third year	8

ATG, antithymocyte globulin; BMI, body mass index; CIN, chronic interstitial nephritis; CGN, chronic glomerulonephritis; IL-2, interleukin-2. TMP-Tacrolimus/ MMF/ Prednisolone; CMP- Cyclosporine/ MMF/ Prednisolone; CAD- Coronary artery disease; CVA- Cerebro-vascular accident.

nephropathy and Autosomal Dominant Polycystic Kidney Disease (ADPKD). Recipients (39.1%) had received at least single blood transfusion before transplantation. The mean number of dialysis sessions per recipient before transplantation was 159.76 ± 65.05 . The induction agent was given to most of the patients (84.8% received ATG as an induction agent). Triple-drug immunosuppression with tacrolimus, MMF and prednisolone was the most commonly used maintenance regimen (80.4%). The mean follow-up time was 39.02 ± 28.24 months. The follow-up time distribution of patients undergoing cadaveric transplantation has been depicted in Table 2.

There were total 13 graft losses and 17 deaths. Sepsis was the most common cause of death (47%). Cytomegalovirus infection, pneumonia and cerebrovascular accident were other causes, while in case of four deaths, cause was unknown (Table 1). More than 50% of deaths (nine of 17) happened in first 3 years of transplantation, while 61.5% of graft loss occurred after 5 years of renal transplantation. Thirteen of 17 patients expired with functioning graft, while four deaths were associated with graft loss.

As depicted in Table 3, the mean graft survival time was 81.6 months (95% confidence interval [CI]: 72.8–90.4), while the median graft survival time was 89 months (95% CI: 84.0–93.9). Cumulative proportion of graft survival was 98.9% at 1 year, 98.2% at 2 years, 91.6% at 3 years, 88.6% at 4 years and 77.1% at 5 years. Kaplan–Meier curve depicting graft survival in patients undergoing cadaveric renal transplantation is shown in Fig. 1(A). Although females have better mean graft survival time (91.6 vs 73.5 months), it was not a significant difference as shown by log-rank test (p value = 0.062). Logistic regression shows the age of the recipient, and the donor has no significant effect on graft survival (p value: 0.6 and 0.6), although all the recipients were young and none had crossed 50 years of age. Body mass index (BMI) also was found to be insignificant. Basic disease category and the type of induction have no significantly different odds of graft loss as shown by logistic regression. Pretransplant haemodialysis has no significant effect on graft loss, but patient with peritoneal dialysis have significantly higher odds of graft loss (odds: 4.86, p value < 0.05 [0.018]). As depicted in Table 3, the mean patient survival time was 99.5 months (95% CI: 84.0–114.9). Cumulative proportion of patient survival was 98.9% at 1 year, 94.4% at 2 years, 83.3% at 3 years, 80.9% at 4 years and 70.8% at 5 years. Kaplan–Meier curve depicting patient survival in patients undergoing cadaveric renal transplantation is shown in Fig. 1(B). Univariate analysis comparing odds of graft loss in

Table 3 – Means for graft and patient survival time of patients undergoing cadaveric renal transplantation.

Estimated mean	Standard error	95% confidence interval	
		Lower bound	Upper bound
Graft survival 81.603 months	4.467	72.848	90.359
Patient survival 99.463 months	7.871	84.037	114.889

diverse groups to find significant factors in graft survival is depicted in Table 4.

Discussion

In south Asian countries including India, renal transplant program relies on live donor transplantation. Recently, some Indian states have established a strong, effective, and efficient cadaveric transplantation program, a best example of which is Tamil Nadu.⁸ India has huge potential of organ donation following brain death. In India, the number of deaths because of road traffic accidents exceeds 110,000 per year. According to an estimate, 67% of these deaths occur because of brain death.⁹ Four southern states (Tamil Nadu, Andhra Pradesh, Gujarat and Maharashtra) are leading in cadaveric organ donation in India, with a donation rate of 0.3 per million population per year (national average 0.08 per million population per year).¹⁰ If we are able to augment the cadaver donation rate from current 0.08 to one per million population per year, it would provide all livers, hearts and lungs required in the country and significantly increase our kidney donor pool. According to an estimate, the aforementioned four southern states will soon reach a cadaveric donation rate of one per million population per year.¹⁰

Cadaveric transplantation program commenced at our centre on 7th August 1998, when first cadaveric renal transplantation was performed. Till June 2017, 92 cadaveric renal transplantations have been performed among which less than 1% were total renal transplants. According to the Indian Transplant Registry (data from 48 hospitals), a total of 783 cadaveric renal transplantations have been performed in India from 1971 to 2017.

The mean age of recipients was 35.5 ± 10.9 years which was comparable to that reported by Kute et al¹¹ and Ghafari et al¹². However, more females (1:1) benefitted in our study as compared with that reported by Kute et al¹¹ (1:2). There was no sex preponderance because an equal number of male and female cases of ESRD are on follow-up at our centre. The mean age of cadaveric donors was 43.9 ± 17.0 years and male:female ratio was 2:1 which was comparable to studies carried out by Kute et al¹¹ and Feroz et al⁷. Gopalakrishnan et al¹³ reported comparable mean age of cadaveric donors but much higher male:female ratio of 6:1. These trends are in contrast to live donor renal transplantation in India as well as our institute, where majority of recipients are males and majority of donors are females.

In our study, the most common cause of ESRD was chronic glomerulonephritis (44.6%), closely followed by chronic

Table 2 – Follow-up time distribution of patients undergoing cadaveric renal transplantation.

Follow-up duration	Number of recipients	Event (graft loss)	Event (death)
≤1 year	8	1	1
1–2 years	29	0	3
2–3 years	19	3	5
3–4 years	8	1	1
4–5 years	7	1	3
>5 years	21	8	4

Fig. 1 – (A) Kaplan–Meier curve depicting graft survival in patients undergoing cadaveric renal transplantation; (B) Kaplan–Meier curve depicting patient survival in cadaveric renal transplantation.

Table 4 – Univariate analysis comparing odds of graft loss in diverse groups to find significant factors in graft survival.

Statistics	Variable	Results	Interpretation
Log-rank test	Gender	Mean graft survival male: 73.5 months, female: 91.6, p value > 0.05	Difference in survival among males and females is not statistically significant.
Binominal logistic regression	Age (recipient)	Exp (B): 1.011, p value > 0.05	Odds of graft loss increases by 1.1% per year but results were not statistically significant
Binominal logistic regression	Age (donor)	Exp (B): 0.993, p value > 0.05	With increasing age lesser odds but not significant
Binominal logistic regression	BMI	Exp (B): 1.091, p value > 0.05	9% increase per unit increase in BMI but not statistically significant.
Binominal logistic regression	Basic disease	Category 1 Exp (B): 0.833 and category 2 Exp(B): 1.161, p value > 0.05	Both categories CIN and CGN have different odds but not significant.
Binominal logistic regression	Induction	Exp (B): 0.985, p value > 0.05	Not statistically significant difference in odds between ATG or IL-2 receptor antagonists.
Binominal logistic regression	Pretransplant haemodialysis	Exp (B): 1.00, p value > 0.05	Odds do not vary significantly; duration of dialysis not significantly associated.
Binominal logistic regression	Pretransplant peritoneal dialysis	Exp (B): 4.86, p value < 0.05 ^a	Higher odds of graft loss (86%) with every increase in PD. Results are statistically significant.

PD- Peritoneal dialysis ATG, antithymocyte globulin; BMI, body mass index; CIN, chronic interstitial nephritis; CGN, chronic glomerulonephritis; IL-2, interleukin-2.

^a Results were statistically significant.

interstitial nephritis (40.2%). Recently, Kute et al¹¹ have also reported CGN to be the most common cause of ESRD in their study involving 294 cadaveric transplantations.

The mean follow-up time in our study was 39.02 ± 28.24 months which is similar to that reported by Kute et al¹¹ but much higher than that reported by Feroz et al⁷ (190 ± 98 days). Our centre is a publicly funded facility, and all authorised patients

are treated free of cost including medicines. That is the reason we were able to follow-up all recipients for a long duration.

A majority of mortality happened in the first 3 years of transplantation, and the most common cause of death was sepsis. Gopalakrishnan et al,¹³ Ghafari et al¹² and Patel et al¹⁴ reported higher incidence of mortality in the first year after transplantation. Sepsis was reported to be the most common

Table 5 – Comparison of mean graft and patient survival among different Asian studies.

Studies	N	Cumulative proportion of graft survival at			Cumulative proportion of patient survival at		
		1 year	3 years	5 years	1 year	3 years	5 years
Shroff et al ¹⁸	100	82%			86%		
Mani ¹⁵	88	72%					
Gopalakrishnan et al ¹³	173	82.6%	81.5%	80%	80.34%	78%	76%
Kute et al ¹¹	294	92.6%		88.3%	81.7%		77.5%
Ghafari et al ¹²	39				89.7%		
Feroz et al ⁷	38	85% (6 months)			90% (6 months)		
Prabakar et al ¹⁹	68			58.8%			61.7%
Present study	92	98.9%	91.6%	77.1%	98.9%	83.3%	70.8%

cause of death by Kute et al¹¹ and Feroz et al⁷. In our study, three-fourth of patients who expired had functioning graft at the time of death. The cause of high rate of infection could be the triple-drug immunosuppression with ATG induction, socioeconomic factors such as unhygienic living conditions or delayed presentation and diagnosis as experience by other studies.^{15–17}

The mean graft survival time in this study was 81.6 months, while the mean patient survival time was 99.5 months which was higher as compared with other Asian studies, as depicted in Table 5. There was better graft survival in our study because of better drug compliance as all medicines are available free of cost to authorised patients. We also found that age of the recipient and donor, BMI, basic disease or type of induction had no significant effect on graft survival. However, patients who were on peritoneal dialysis before transplantation had a higher risk of graft loss which was statistically significant. Gopalakrishnan et al¹³ had reported age of recipient, cold ischaemia time and rejection episodes as independent predictors of graft survival. Most studies have reported that pretransplant dialysis modality has no effect on graft survival.^{20,21} However, Snyder et al²² had reported more frequent early graft failure in the peritoneal dialysis arm for which they attributed early graft thrombosis to be the causative factor. We could not determine any cause for higher rate of graft failure in patients who were on peritoneal dialysis before transplantation.

Our study has limitations inherent for a retrospective study. HLA matching could not be carried out in all patients because of temporal and logistic reasons.

Conclusion

The graft and patient survival rate of cadaveric transplant at our centre was satisfactory. There is a need to sensitise and augment the rate of cadaveric transplantation to increase the donor pool. A deeply committed cadaveric transplant program is needed to improve the cadaveric donation rate. Cadaveric organs are nation's invaluable resources, and an organ wasted is a life wasted.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

The authors have none to declare.

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