International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 10, 2020
ISSN: 1475-7192

Death with graft functionamong Egyptian kidney transplant recipients: A single center experience.

Mostafa Gamal Abu Gharbia[1], Ahmed Salah Ibrahim[2], Yasser El Hendy[3], Ayman FathiRefaie[4]

Abstract

Background: *Death with graft function (DWGF) is an important cause of long-term loss of grafts and patients. In this study, we investigated clinical characteristics and causes of DWGF among kidney transplant recipients in Mansoura from 2002 to 2010.*

Methods: *From January 2002 to December 2010, a total of 800 living donor renal transplants were done in Mansoura. Their data was retrospectively analyzed. Out of 159 reported deaths, 81 patients died with good kidney graft function without need of dialysis.*

Results:

About 27% of graft losses caused by DWGF at mean age of 36 ± 10.7. Males were 59 (72.5%). They reached end stage renal disease (ESKD) secondary to glomerulonephritis in 6, pyelonephritis in 15, polycystic kidney disease in 3 and nephrosclerosis in 5 patients. 52 patients had acute rejections (64.8%). Post-transplant hypertension occurred in 48 patients (59.5%), diabetes mellitus in 18 patients (22.9%), infections in 42 (51.5%), hepatic complications in 19 (22.9%) and malignancy in 11 patients (13.6%). Fatal infections in 25 patients (31.3%) were the main causes of death followed by cardiovascular causes in 12 patients (15.2%), liver cell failure in 9 patients (10.7%) and malignancy in 4 patients (4.6%). Mean serum creatinine at last follow up was 2 ± 0.6 mg/dl.

Conclusions: *DWGF constitutes of 27% of total graft loss. The commonest cause is fatal infections followed by cardio-vascular illness. DWGF develops due to co-morbid medical illness, pre-transplant dialysis and other factors related to transplantation. Understanding different causes of death is mandatory in order to improve the long-term outcomes.*

Key words: *Death; Transplantation; Risk factors.*

[1] *Nephrology and transplantation unit, Urology and Nephrology Center, Mansoura University, Egypt*
[2] *Department of Nephrology, Faculty of Medicine, Zagazig University,*
[3] *Department of Nephrology, Faculty of Medicine, Zagazig University,*
[4] *Nephrology and transplantation unit, Urology and Nephrology Center, Mansoura University, Egypt*

I. INTRODUCTION

Although kidney transplantation is the best alternative to dialysis regarding patient survival, A higher mortality between kidney transplant recipients is still being documented and need much improvement [1]. Main risk factors for mortality with good graft function were medical co-morbidities, pre-transplant dialysis, immune-suppressive side effects [2, 3]. Death with graft function (DWGF) was documented in 9–43% of kidney transplant recipients [4–9]. The causes and risk factors of mortality may have improved with time with advances in immunosuppressive therapies. Our aim from thiswork was to investigate the main predisposing risk factors and causes that led to DWGF in our kidney transplant population.

II. SUBJECTS AND METHODS

A case-control(retrospective) study was conducted at urology and nephrology center, Mansoura University.

Ethical consideration: Our study is a retrospective study. The data was retrieved from our patient information system at urology and nephrology center after taking an agreement from the head of the department and director of the center. We confirm that we do not use patients' names, initials or hospital numbers.Medical research and ethics committee of Zagazig University approved the study. The work was carried out in accordance with The Code of Ethics of the World Medical Association.

Subjects: The data of all kidney transplant recipients who underwent renal transplantation in the Urology & Nephrology Center, Mansoura University, Egypt, from January 2000 to December 2010, were retrospectively analyzed. A total of 800 patients underwent renal allograft transplantation from live-donors during this period.

Immunosuppression Protocols:all patients received calcineurin inhibitors (CNI)-based immunosuppressive therapy which consists mainly of cyclosporine (CsA) or tacrolimus. Cyclosporine was introduced either in dual therapy with prednisolone by a dose of 12 mg/kg/day or triple therapy protocol with prednisolone and azathioprine by a dose of 10 mg/kg/day. We targeted cyclosporine (CsA) trough level between 200 and 400 ng/mlin the first 2 months then we aimed the level between 125 and 175 ng/ml thereafter. Tacrolimus therapy was introduced to the patients by a dose of 0.15 mg/kg in two divided doses. Tacrolimus was also used as a rescue therapy in some patients or as a substitution of CsA in case of inevitable side effects. Trough level between 5 and 10 ng/ml was targeted for tacrolimus. All acute rejections were biopsy proven and managed by pulses of methylprednisolone 500 mg/day for 5 days. Antithymocyte globulin (ATG) or orthoclone (OKT3) were used in cases of steroid-resistant rejections.

Follow-Up Data: Death with graft function was considered if death occurred without needing dialysis or graft nephrectomy. The demographic data of the recipients and donors, HLA matching, pre-transplant co-morbidities, original kidney disease (OKD), immunosuppression regimens, number of biopsy-proven acute rejection episodes, post-transplant hypertension, diabetes mellitus, infections, hepatic problems, occurrence of malignancies were analyzed and considered as risk factors affecting patient survival. Risk factors also were analyzed by uni and

multi-variate studies. All kidney transplant recipients who died with a good kidney graft function were compared with patients who are alive with functioning grafts.

III. Statistical analysis

The findings were recorded, tabulated and analyzed using SPSS for windows (SPSS inc. Chicago). Student-t test was used to compare normally distributed continuous data between the four groups. While Mann-Whitney test was used for non-parametric data. Categorical data were compared using chi square test. Multivariate analysis was carried out using Cox logistic regression. P-value < 0.05 was considered statistically significant.

IV. RESULTS

A total number of 800 live donor renal allografts transplantation were done Between January 2000 and December 2010. A total number of 152 (19%) patients died during the follow-up period after renal transplantation. Among these patients, 81 died with a good graft function (53.3%). The median duration between transplantation and death with functioning graft was 37 months. Mean pre-mortality serum creatinine was 2.0 ± 0.6 mg/dl. Base line characteristics of DWGF patients were shown in **table 1**. Higher mortality was found in older recipients at time of transplantation. No statistical significance was found regarding recipient's sex, original kidney disease and pre-transplant dialysis.

Table (1): Pre-transplant characteristics:

	Death with graft function (DWGF) (N = 81)	**Alive with graft function (AWGF) (N = 548)**	***p*-value**
Recipient factors			
Age,years	36 ± 10.7	30 ± 10.3	0.00
Male gender	72.5%	74.6	0.5
Original kidney disease (OKD)			
Glomerulonephritis	7.6%	11%	0.2

(GN)			
Pyelonephritis	18.3%	18.4%	
Nephrosclerosis	6.1%	2.4%	
Amyloidosis	3.8%	1.8%	
Polycystic kidney (PCK)	3.8%	1.8%	
Unknown	60.4%	64%	
Prior renal transplant	4.6%	4.07%	0.9
Pre-transplant dialysis (yes)	92.4%	93.1%	0.7
Donor factors			
Age, Years	33.2 ± 9.8	34.5 ± 9.9	0.3
Gender (male: female)	51.2:48.8	48.3:51.7	0.2

Table 2 shows that DWGF patients experienced more rejections and post transplant co-morbidities.

Table (2): Post-transplantation course:

	Death with graft function (DWGF) (N = 81)	**Alive with graft function (AWGF) (N = 584)**	**p-value**
Acute tubular necrosis (ATN)	8.6%	3.5%	0.03

Acute rejection episodes (yes)	64.8%	45.2%	0.00
Total dose of steroid (g) after 3 months	7.9 ± 3.1	5.3 ± 2.7	0.002
Post-transplant complications			
Hypertension (HTN)	59.5%	74.8%	0.00
Diabetes mellitus (DM)	22.9%	11.4%	0.00
infection	51.5%	19.3%	0.00
hepatic	22.9%	5.6%	0.00
malignancy	13.6%	1.5%	0.00
Mean serum creatinine, mg/dl			
At last follow-up	2.2 ± 0.7	1.7 ± 0.9	0.1

Table 3 summarizes the causes of DWGF. Infection and sepsis were the main causes leading to death with graft function.

Table (3): causes of DWGF:

causes	**Death with graft function (DWGF) (N = 81)**
cardiovascular	15.2%
infection	31.3%
hepatic	10.7%

cerebrovascular	9.9%
malignancy	4.6%
others	10.7%
unknown	17.6%

Table (4): Risk factors associated to death with graft function (DWGF) in our series of kidney transplantation:

	***p*-value**
Univariate analysis	
Recipient age at transplantation	0.115
Recipient gender	0.380
Donor age	0.315
Pre-transplant hypertension	0.712
Pre-transplant schistosomal infection	0.549
High HLA mismatch	0.571
Total dose of steroid at 3 months	0.997
Post-transplant hypertension	0.979
Post-transplant diabetes mellitus	0.098
Post-transplant infection	0.000
Post-transplant malignancy	0.005
Multi-variate analysis	
Post-transplant infection	0.001

Our data show that Infection was the main cause of DWGF. Cardiovascular disease was the second cause of DWGF. Tumors accounted for about 4.6% of DWGF with 87.5% of them after 5 years post-transplantation, 10.7% of deaths from liver cell failure and 9.9% of deaths due to cerebrovascular causes were documented, nearly all of these cases were after the first 30 days after transplantation. Only 3 reported deaths due to accidents were reported.

Using Uni- and multivariate Cox logistic regression analysis was done to identify risk factors leading to DWGF **(table 4)**. The only significant risk factor leading to DWGF was medical infection, by multivariate analysis ($p = 0.001$).

V. DISCUSSION

About 27% of graft losses in our center from January 2002 to December 2010 was due to DWGF. This finding come in agreement with other studies [6, 7].As time passed, graft loss etiologies have changed with increased time period post-transplantation [6]. DWGF is considered an important cause of graft loss in several studies [4, 8, 9]. In our series, graft survival has improved over years. The risk of death from infection was most prevalent in our series and was nearly double the risk of cardiovascular disease, however cardiovascular deaths frequency increases recently. Many other studies have reported serious medical infections as the leading cause of death [7, 14, 17]. In contrast to many other studies which reported cardiovascular deaths as the most frequent causes of kidney transplant recipient death [4, 5]. The increased cardiovascular deaths may be attributed to acceptance of older and sicker recipients in most recent transplantation programs. The infection rate in our study (51.5%) exceeded the rate found in other published studies. Our results show that infection was more prevalent in patients who are lost as early as first year post-transplantation and most of them were secondary to chest infections and closely related to more intensive immunosuppression as using ATG or OKT3. In 2000, it was reported that mortality risk was markedly increased due to post transplant serious infections which occur during admission for transplantation [14]. The 64-year-old recipients at the time of transplantation had a higher relative risk of death with a functioning graft. This comes in agreement with other studies which reported higher first year mortality ratio for older recipients [15]. Mean recipient age was significantly higher in DWGF group. In line with a Korean study [18]. The number of older kidney transplant recipients increases in most kidney transplant programs in Europe and United States. It is found that younger age at time of transplantation is associated with long term graft and patient outcomes [19]. A study from the OPTN and SRTR in the United States showed that when recipient age is ≥65 years, 5-year patient survival is 67.2%, while it is 80.1% when recipient is younger [20]. With expanding criteria of recipients' selection in transplantation programs, recipients' median age at time of transplantation increased from 40 to 60 years in the most recent era of transplantation. It was reported that drugs have different effect in older recipients due to immune senescence [21]. Because of their pharmacokinetic and pharmaco-dynamic changes, doses of immunosuppressive drugs may be too high for older recipients. As age advances, the immune system is reconstituted and also becomes old, affecting recipient ability to survive [22, 23]. This immune senescence exposes older patients to risk of serious infections [24].

Using uni- and multi-variate analysis, we found that highest age category has no increased risk for death with graft function, and this finding comes in contrast with other previously published studies in the literature where age has been linked significantly with patient survival [3, 5, 8], and this is explained by rejecting 60 years old patients for kidney transplantation. However, it was reported in other studies that recipients aged 60 years at time of transplantation had higher mortality [15]. The primary cause of end stage renal disease (ESRD) has no effect on mortality risk with functioning graft, by multivariate analysis, in our study. Many studies found that ESRD caused by DM was the most prevalent risk factor for DWGF [4, 5, 7], and the risk of death in these recipients can be attributed to both cardiovascular disease and stroke. Menon et al confirmed that levels of HbA1c are linked significantly with the patient survival with CKD [25]. Others noted that recipient survival after kidney transplantation is related to the degree of glycemic control [26, 27, 28]. Cosio and associates found that in comparison to non-diabetic patients, diabetic recipients had increased risk of post transplant cardio-vascular morbidities, all-cause mortality and CV mortality.

Hepatic complications are considered a major problem after kidney transplantation in our center. high schistosomal infection among our transplant population and HCV infection may be the contributing factor [10–13]. HCV infection was highly prevalent among hemodialysis patients, reaching 60% [9, 10]. The development of fulminant hepatitis in our kidney transplant patients is clear predictor of death. The issue of consideration of DWGF patients or whether their death was secondary to impaired kidney graft function was reported by West et al. [16].

Our study pointsof strength: our study has strengths as it included high risk kidney transplant recipients while most of other studies reported only patients at low risk.

Study Limitations: Our study had some limitations as it was retrospective study, Lack of randomization. Our study was a single-center study. All patients in our center received their kidney grafts from living donors; therefore, our results might differ and could not be applied to the general transplant societies where cadaveric donors represent the main source of kidney grafts. Our study results could be applied on similar renal recipients from our geographic area, but not other recipients with different ethnic composition.

Recommendations: We recommend giving attention to pretransplant medical disorders as pretransplant DM, hypertension. Pretransplant dialysis duration to be as short as possible. Preemptive transplantation has the best graft and patient survival outcomes. Proper HLA matching is also highly recommended in order to decrease rejection episodes and the burden of immunosuppression.

VI. CONCLUSION

Kidney transplant recipients' survival has markedly improved recently. Causes of DWGF varies in different eras. Infection precedes cardiovascular causes at all times during follow-up of our transplant recipients. Our study demonstrates that kidney transplant recipients who died with a functioning graft had good kidney function, but on expense of their lives unfortunately. Lastly, kidney transplant recipient survival still needs more efforts to be improved on the long term.

Conflict of Interest: Nothing to declare.

Financial Disclosures: Nothing to declare**.**

REFERENCES

1. **Arend SM, Mallat MJ, Westendorp R, van der Woude FJ, van Es LA**. Patient survival after renal transplantation: More than 25 years' follow-up. Nephrol Dial Transplant 1997;12: 1672–1679.
2. **Arrazola L, Sozen H, Humar A, Ukins M, Papalois, AJ, Matas AJ**. Death with function: The next major hurdle. Transplant Proc 2000; 32:1832.
3. **Briggs ID**. Causes of death after renal transplantation. Nephrol Dial Transplant 2001;16: 1545–1549.
4. **Denny RR, Sumrani N, Miles AMV, Dibenedetto A, Distant DA, Hong JH et al**. Survival on hemodialysis versus renal transplantation following primary renal allograft failure. Transplant Proc 1997;29:3602–3604.
5. **Ekstrand A**. Kidney transplantation with and without prior dialysis therapy in diabetic patients with end-stage renal failure. Scand J Urol Nephrol 1993;27:83–87.
6. **Hariharan S, Johnson CP, Breshnahan BA**. improved graft survival after renal transplantation in the United States 1988–1996. N Engl J Med 2000;342:605–612.
7. **Hill MN, Grossman RA, Feldman HI, Hwravitz S, Dafooe DC**. Changes in the causes of death after renal transplantation, 1966–1987. Am J Kidney Dis 1991;27:512–518.
8. **Hirata M, Cho YW, Cecka JM, Terasaki PI**. Patient death after renal transplantation. An analysis of its role in graft outcome. Transplantation 1996;61:1479–1483.
9. **Howard RJ, Reed AI, Hemming AW, Van der Werf WJ, Patton, PR, Ptaff et al**. Graft loss and death: Changing causes after kidney transplantation. Transplant Proc 2001;33:3416.
10. **Mahmoud IM, Sobh MA, Amer GM, El-Chenawy FA, Gazarren SH, El-Sherif A et al**. A prospective study of hepatitis C viremea in renal allograft recipients. Am J Nephrol 1999;19:576–585.
11. **Mahmoud KM, Sobh MA, EL-Agroudy AE, Mostafa FE, EL-Baz M, Shokeir AA et al**. Impact of schistosomiasis on patient and graft outcome after renal transplantation: 10 years follow-up. Nephrol Dial Transplant 2001;16:2214–2221.
12. **Matas AJ, Gillingham KJ, Sutherland, DER. Half-life and risk factors for kidney transplant outcome**. Importance of death with function. Transplantation 1993;55:757–761.
13. **Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK**. Long-term survival in renal transplant recipients with graft function. Kidney Int 2000;57:307–313.

14. **Pelletier SJ, Crabtree TD, Gleason TG, Raymound DP, Oh Ck, Pruett TL et al**. Characteristics of infectious complications associated with mortality after solid organ transplantation. Clin Transplant 2000;14:401–408.

15. **Schauelle P, Lorenz D, Trede M, Von der Woude FJ**. Impact of cadaveric transplantation on survival in end-stage renal failure: Evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol 1998;9:2135- 2141.

16. **West M, Sutherland DER, Matas AJ**. Kidney transplant recipients who die with functioning grafts: Serum creatinine level and cause of death. Transplantation 1996;62:1029–1030.

17. **Lee SH, Oh CK, Shin GT, Kim H, Kim SJ, Kim SI**. Age matching improves graft survival after living donor kidney transplantation. Transplant Proc. 2014;46(2):449-53.

18. **Yu MY, Kim YC, Lee JP, Lee H, Kim YS**. Death with graft function after kidney transplantation: a single-center experience. Clin Exp Nephrol. 2018 Jun;22(3):710-718.

19. **Gondos A, Döhler B, Brenner H, Opelz G**. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. Transplantation. 2013 Jan 27;95(2):267-74.

20. **Knoll GA**. Kidney transplantation in the older adult. Am J Kidney Dis. 2013 May 1;61(5):790-7.

21. **Turnheim K**. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol. 2003 Aug;38(8):843-53. [21]

22. **Weiskopf D, Weinberger B, Grubeck-Loebenstein B**. The aging of the immune system. Transpl Int. 2009 Nov;22(11):1041-50.

23. **Jiang N, He J, Weinstein JA, Penland L, Sasaki S, He XS, Dekker CL et al**. Lineage structure of the human antibody repertoire in response to influenza vaccination. Sci Transl Med. 2013 Feb 6;5(171):171ra19.

24. **Yoshikawa TT**. Epidemiology and unique aspects of aging and infectious diseases. Clin Infect Dis. 2000 Jun;30(6):931-3.

25. **Menon V, Greene T, Pereira AA, Wang X, Beck GJ, Kusek JW et al**. Glycosylated hemoglobin and mortality in patients with nondiabetic chronic kidney disease. J Am Soc Nephrol. 2005 Nov;16(11):3411-7.

26. **Kasiske BL, Chakkera HA, Roel J**. Explained and unexplained ischemic heart disease risk after renal transplantation. J Am Soc Nephrol. 2000 Sep;11(9):1735-43.

27. **Stadler M, Auinger M, Anderwald C, Kastenbauer T, Kramar R, Feinbock C et al**. Long-term mortality and incidence of renal dialysis and transplantation in type 1 diabetes mellitus. J Clin Endocrinol Metab. 2006 Oct;91(10):3814-20.

28. **Cosio FG, Hickson LJ, Griffin MD, Stegall MD, Kudva Y**. Patient survival and cardiovascular risk after kidney transplantation: the challenge of diabetes. Am J Transplant. 2008 Mar;8(3):593-9.