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ORIGINAL ARTICLE

Prevalence and Risk Factors for Death with Graft Function among Egyptian Kidney Transplant Recipients in Mansoura.

Mostafa Gamal Abu Gharbia[1*], Yasser Abdelmonem Hendy[2], Ayman Fathy Refaie, Ahmed Mohamed salah[2]

1 Urology and Nephrology center, Mansoura University, Mansoura, Egypt
2 Internal Medicine and Nephrology Department, Faculty of Medicine Zagazig University, Zagazig, Egypt

Corresponding author
Mostafa Gamal Abu Gharbia

E-mail:
dr.mostafa2050@gmail.com

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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 2019.

Methods: From March 2002 to December 2018, 1,499 living donor renal transplants were done in Mansoura. Their data were retrospectively analyzed. Out of 285 reported deaths, 193 patients died with good graft function without the need for dialysis.

Results:
Death with graft function occurred in about 27% of kidney transplant recipients at a mean age of 36 +10.7 years. Males were 140 (72.5%). They reached end-stage renal disease (ESRD) secondary to GN in 14, PN in 35, PCK in 7, and nephrosclerosis in 12 patients. 125 patients had acute rejections (64.8%). Post-transplant hypertension occurred in 115 patients (59.5%), DM in 44 patients (22.9%), infections in 99 (51.5%), hepatic complications in 44 (22.9%), and malignancy in 25 patients (13%). Fatal infections in 60 patients (31.3%) were the main causes of death followed by cardiovascular causes in 29 patients (15.2%), liver cell failure in 20 patients (10.7%), and malignancy in 9 patients (4.6%). The mean serum creatinine at the last follow-up was 2 ± 0.6 mg/dl.

Conclusions: In our study, DWGF constitutes of 27% of total graft loss. The most typical causes were fatal infections and CVS disease, respectively. DWGF develops due to co-morbid medical illness, pre-transplant dialysis, and other transplantation-related factors. Understanding different causes of death are mandatory to improve long-term outcomes.

Keywords: Death; Transplantation; Risk factors.

INTRODUCTION

Although kidney transplantation is the best alternative to dialysis regarding patient survival, A higher mortality among kidney transplant recipients is still being documented and needs much improvement [1]. The main risk factors for mortality with good graft function were medical co-morbidities, pre-transplant dialysis, and immune-suppressive side effects [2, 3]. Some studies identified anemia and hypoalbuminemia as risk factors for DWGF [4]. In 9-43% of kidney transplant recipients, death with graft function (DWGF) was recorded [5–11]. DWGF develops throughout the early five years after transplantation and consistently increases by reaching ten years, despite graft failure having decreased steadily over time [12, 13]. Previous reports found that DWGF caused 42% of all graft failures within the first five year after transplantation, and 54% within the first ten years [13]. Therefore, reducing DWGF is crucial for improving kidney transplant outcomes. Our aim of this work was to investigate the main predisposing risk factors and causes that led to DWGF in our kidney transplant population.

METHODS

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

Ethical consideration: Our study is a retrospective study. The data was retrieved from our patient information system at the urology and nephrology center after taking an agreement from the head of the department and the director of the center. We confirm that we do not use patients' names, initials, or hospital numbers. The 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. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University

***Subjects*:** The data of all kidney transplant recipients who underwent renal transplantation in the Urology & Nephrology Center, Mansoura University, Egypt, from March 2002 to December 2018, were retrospectively analyzed. A total of 1,499 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 at a dose of 12 mg/kg/day or triple therapy protocol with prednisolone and azathioprine at a dose of 10 mg/kg/day. We targeted cyclosporine (CsA) trough level between 200 and 400 ng/ml in the first 2 months then we aimed for a level between 125 and 175 ng/ml thereafter. Tacrolimus therapy was introduced to the patients at 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 for CsA in case of inevitable side effects. A 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 [22]. We have grouped patients into DWGF and AWGF groups to be compared with each other to investigate the clinical characteristics and causes that led to death with functioning grafts. 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, the occurrence of malignancies were analyzed and considered as risk factors affecting patient survival. Risk factors also were analyzed by uni and multi-variate studies.

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 the Mann-Whitney test was used for non-parametric data. Categorical data were compared using the chi-square test. Multivariate analysis was carried out using Cox logistic regression. P-value < 0.05 was considered statistically significant.

RESULTS

A total number of 1,499 live donor renal allografts transplantation were done Between March 2002 and December 2019. A total number of 285 (19%) patients died during the follow-up period after renal transplantation. Among these patients, 193 died with a good graft function (67.7%). About 18.2% (35 patients) died within the first year after transplantation, 18.9% (36 patients) died by 1-5 years, 25.8% (50 patients) died by 5-10 years and 37.1% (72 patients) died after 10 years of kidney transplantation **(figure 1)**. The median duration between transplantation and death with a functioning graft was 37 months. Baseline creatinine was defined as the lowest value within 6 months before the last visit. The mean baseline serum creatinine was 2.0 ± 0.6 mg/dl. The baseline characteristics of DWGF patients were shown in **table 1**. Higher mortality was found in older recipients at the time of transplantation. No statistical significance was found regarding the recipient's sex, original kidney disease, and pre-transplant dialysis.

Table 2 shows that DWGF patients experienced more rejections and post-transplant co-morbidities. **Table 3** summarizes the causes of DWGF. Infection and sepsis were the main causes leading to death with graft function.

Our data show that Infection was the main cause of DWGF. Cardiovascular disease was the second cause of DWGF. Malignancies 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 a medical infection, by multivariate analysis (p = 0.001)

Table (1): Pre-transplant characteristics.

	Death with graft function (DWGF) (N = 193)	Alive with graft function (AWGF) (N = 1306)	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 (GN)	7.6%	11%	0.2
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): Post-transplantation course

	Death with graft function (DWGF) (N = 193)	Alive with graft function (AWGF) (N = 1306)	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%	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): causes of DWGF.

causes	Death with graft function (DWGF) (N = 193)
cardiovascular	15.2%

causes	Death with graft function (DWGF) (N = 193)
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

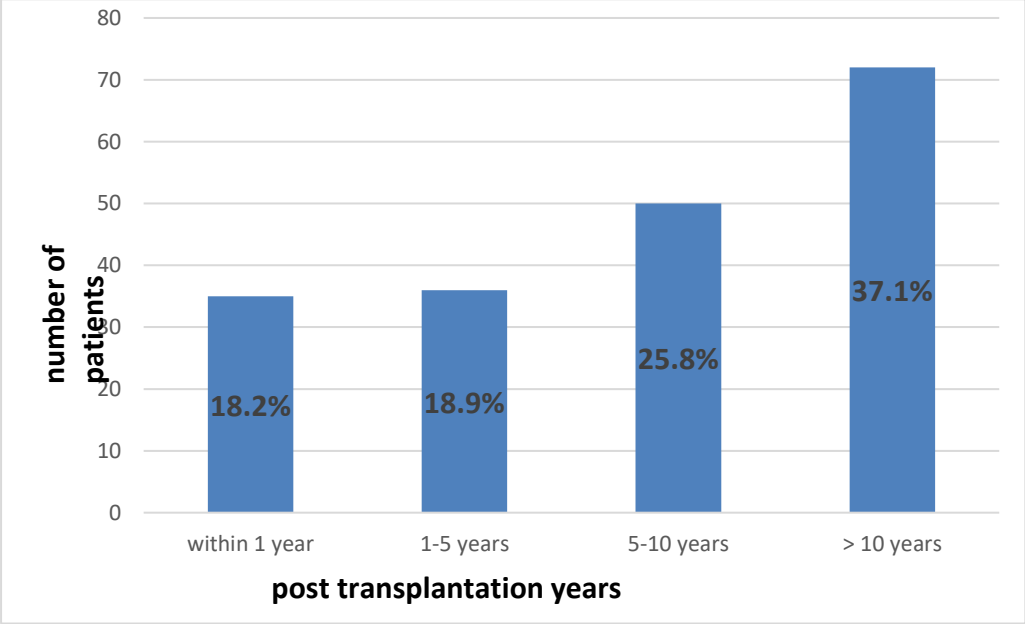

Figure (1): Numbers and percentages of died recipients with functioning graft within different post transplantation years.

DISCUSSION

About 27% of graft losses in our center from March 2002 to December 2018 were due to DWGF. This finding comes in agreement with other studies [7, 8]. As time passed, graft loss etiologies have changed with an increased period post-transplantation [7]. DWGF is considered an important cause of graft loss in several studies [5, 9, 10]. 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 death frequency increases recently. A higher risk of infection in our population may be attributed to the use of intense immunosuppression for example the use of ATG for treatment of acute rejections and also the use of higher doses of steroids early post-transplantation. Many other

studies have reported serious medical infections as the leading cause of death [8, 18, 21]. In contrast to many other studies which reported cardiovascular deaths as the most frequent causes of kidney transplant recipient death [5, 6]. The increased cardiovascular deaths may be attributed to the 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 the 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 [18]. 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 a higher first-year mortality ratio for older recipients [19]. The mean recipient age was significantly higher in the DWGF group. In line with a Korean study [22]. The number of older kidney transplant recipients increases in most kidney transplant programs in Europe and the United States. It is found that younger age at the time of transplantation is associated with long-term graft and patient outcomes [23]. A study from the Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients (OPTN and SRTR) in the United States showed that when the recipient age is ≥65 years, 5-year patient survival is 67.2%, while it is 80.1% when the recipient is younger [24]. With expanding criteria of recipients' selection in transplantation programs, recipients' median age at the time of transplantation increased from 40 to 60 years in the most recent era of transplantation. It was reported that drugs have a different effect on older recipients due to immune senescence [25]. Because of their pharmacokinetic and pharmacodynamics 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 the recipient's ability to survive [26, 27]. This immune senescence exposes older patients to the risk of serious infections [28].

Using uni- and multivariate analysis, we found that the 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, 6, 9], 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 the time of transplantation had higher mortality [19]. The primary cause of the 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 [5, 6, 8], 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 CKD associated with the patient survival [29]. Others noted that recipient survival after kidney transplantation is related to the degree of glycemic control [30, 31, 32]. Cosio and associates found that in comparison to non-diabetic patients, diabetic recipients had an increased risk of post-transplant cardiovascular 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 [14–17]. HCV infection was highly prevalent among hemodialysis patients, reaching 60% [10, 14]. The development of fulminant hepatitis in our kidney transplant patients is a 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. [20].

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

***Study Limitations*:** Our study had some limitations as it was a retrospective study, and a 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 to similar renal recipients from our geographic area, but not other recipients with different ethnic compositions.

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

CONCLUSION

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

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