

Influence of clinical parameters on five year patient and graft survival after first renal transplantation

Vergoulas G, Miserlis Gr, Leontsini M, Papanikolaou V, Gakis D, Atmatzidis E, Karasavvidou F, Antoniadi G, Pantzaki A

Hippokratia, General Hospital of Thessaloniki, Greece

Background: Survival after renal transplantation is the most important outcome measure when transplantation results are analysed. The determinators of patient and graft survival after renal transplantation are incompletely known and conflicting results have been reported. The purpose of this study was to evaluate the effect of common clinical parameters on patient and graft survival.

Material and Methods: Three hundred sixty three patients (pts), 235 men and 128 women, 39 years old (range 16-69), who received a first renal transplantation (Rt) from 1.1.1987 to 31.12.96, were studied. The influence of graft origin (LR or CD donor), method of dialysis (HD, PD), donor and recipient hypertension (DH, RH) before transplantation, delayed graft function (DGF), acute rejection (AR), recipient and donor sex on patient and graft survival was investigated. The methods Kaplan Meier, Log Rank, Breslow and Tarone Ware were used for statistical analysis.

Results: One and 5 year patient survival of the whole sample was 96.14% and 90.63% respectively. Pts with LRD or CD presented 1 and 5 survival 97.84%-95.24% and 93.13%-82.44% respectively (p:0.00005). Pts on HD

or PD before Rt had 97.31%-92.59% and 90.74%-85.19% 1 and 5 year survival respectively (p:0.03). Pts with RH or not before Rt had 96.26%-90.37% and 98.39%-96.77% 1 and 5 year survival respectively (p:0.02). Pts with DH or not had 95.29%-83.33% and 98.92%-96.77% 1 and 5 year survival respectively (p:0.0015). One and 5 year graft survival (gs) of the whole sample was 87.33% and 68.60% respectively. Grafts from LRD or CD had 1 and 5 year survival 91.34%-72.73% and 80.94%-61.83% respectively (p:0.03). Grafts from DH or not had 1 and 5 year survival 88.10%- 64.29% and 96.77%-84.41% respectively (p:0.001). Grafts with DGF or not had 1 and 5 year survival 73.02%-55.56% and 91.67%-73.26% respectively (p:0.0001). Grafts with AR or not had 1 and 5 year survival 82.98%-48.94% and 89.52%-76.61% respectively (p:0.00005).

Conclusions: In conclusion better 5-year survival had pts with a LRD, previously on HD, without hypertension before Rt or a normotensive donor. Better survival presented grafts coming from a normotensive donor, a LRD, without DGF or AR.

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Renal transplantation is the treatment of choice for most of patients with end stage renal failure. Unfortunately, until now, there are two major obstacles in renal transplantation: a) the limited number of kidneys available¹ and b) the unsolved problem of chronic allograft nephropathy². The effort to augment the kidney supply, allowed the use of marginal donors while the research for the reasons of kidney rejection resulted in new immunosuppressive protocols that prolonged the rate of graft survival³. Cadaveric graft survival rates now approximate 90% at 1 year and 70% at 5 years^{4,5}.

Survival after renal transplantation is the most important outcome measure when transplantation results are analysed. The determinators of patient and graft survival after renal transplantation are incompletely known and conflicting results have been reported. Also it is universally accepted that there are various factors that may influence graft and patient survival. There are differences between centers that can result in 10% higher or lower graft survival. This may have been influenced

by time related changes in patient selection, post – transplantation management and immunosuppressive regimens.

This study was performed in order to examine retrospectively the impact of various clinical parameters on patient and graft survival after first renal transplantation.

Material and Methods

From January 1, 1987 through December 31, 1996 four hundred forty two renal transplantations took place in Hippokratia General Hospital of Thessaloniki. The study cohort consisted of three hundred sixty three patients (363) that had their first kidney transplantation. There were 235 men and 128 women. Patients under the age of 16 considered to be pediatric cases.

Thirty four pediatric renal transplants (7.63%), thirty three second or more transplants (7.48%), and twelve transplants lost to follow up (2.71%) were excluded from the study.

The mode of dialysis before RT was hemodialysis in

297 and CAPD in 54 patients. Of the 363 evaluable transplantations, 232 patients received a transplant from living related donor (63.91 %) and 131 from a cadaveric one (36.09 %). As a whole they were 38.83 ± 11.86 years old (range 16.38 to 68.86 years). Cadaveric kidney transplant recipients' mean (SD) age was 46.43 (11.16) and LRD recipients' was 34.49 (9.93). The donors were 163 male and 200 female. The mean (SD) age of cadaveric donors was 37.70 (17.84) compared with 58.02 (12.39) of living related donors. Acute rejections according to Banff criteria were recorded in 94 patients and delayed graft function in 63 cases.

We considered that there was hypertension when systolic blood pressure was more than 140 mmHg or diastolic blood pressure more than 90 mmHg in two or more different readings or the patient was taking anti-hypertensive treatment. Hypertension was recorded in 187 recipients (RHT) before RT. Forty two donors had past history of hypertension (DHT)

The influence of graft origin (LRD or CD), recipient and donor sex, mode of dialysis (HD or CAPD), delayed graft function, donor and recipient hypertension before Rt and acute rejection was studied.

Descriptive statistics were used for the demographic data, independent T test was used to compare the means. The cumulative survival was estimated with the product

Table 1. Study period, number of transplants and patients excluded.

Study period	1987-1996
Sum of transplants	442
Excluded from the study	
pediatric transplants	34 (7.63%)
2 nd or > transplants	33 (7.48%)
lost to follow up	12 (2.71%)

Table 2. Number of transplants studied and demographic data

Cohort studied (1 st Rt)	363
age (years)	38.83 ± 11.86
range	16.38 - 68.86 years
men	235 (age: 39.16 ± 11.71 years)
women	128 (age: 38.24 ± 12.59 years)
Recipients with LRD	235 (age: 34.49 ± 9.93 years)
Recipients with CD	131 (age: 46.43 ± 11.16 years)
Previous mode of treatment hemodialysis	297
CAPD	54
Recipients with hypertension before Rt	187
Recipients with acute rejection episode/s	94
Recipients with DGF	63
Recipients' deaths	56

Table 3. Donor demographic data

men	163 (age: 47.06 ± 20.13)
women	200 (age: 53.70 ± 14.62)
LRD	232 (63.91 %)
age	58.02 ± 12.39 (mean \pm SD)
CD	131 (36.09 %)
age	37.70 ± 17.84 (mean \pm SD)
Hypertensive donors:	42

limit method (Kaplan Meier) and the differences between group survival were estimated by the methods Log rank, Breslow and Tarone - Ware. Statistical analysis was performed using the SPSS for windows (v 10.1) software package.

Results

One and 5 year patient survival of the whole sample was 96.14% and 90.63% respectively (Table 4, Figure 1). Pts with LRD or CD presented 1 and 5 survival 97.84%-95.24% and 93.13%-82.44% respectively, p: 0.00005, (Table 4, Figure 1). Pts on HD or CAPD before Rt had 97.31%-92.59% and 90.74%-85.19% 1 and 5 year survival respectively, p: 0.03 (Table 5, Figure 2). Pts with RH or not before Rt had 96.26%-90.37% and 98.39%-96.77% 1 and 5 year survival respectively, p: 0.02 (Table 6, Figure3). Pts with DH or not had 95.29%-83.33% and 98.92%-96.77% 1 and 5 year survival respectively, p: 0.0015 (Table 7, Figure 4). One and 5 year graft survival (gs) of the whole sample was 87.33% and 68.60% respectively (Table 8, Figure 5). Grafts from LRD or CD had 1 and 5 year survival 91.34%-72.73% and 80.94%-61.83% respectively, p: 0.03 (Table 8, Figure 5). Grafts from DH or not had 1 and 5 year survival 88.10%- 64.29% and 96.77%-84.41% respectively, p: 0.001 (Table 9, Figure 6). Grafts with DGF or not had 1 and 5 year survival 73.02%-55.56% and 91.67%-73.26% respectively, p:0.0001 (Table 10, Figure 7). Grafts with AR or not had 1 and 5 year survival 82.98%-48.94% and 89.52%-76.61% respectively, p:0.00005, (Table 11, Figure 8).

Graft survival was not influenced by recipient or donor sex, recipient hypertension and mode of dialysis. Patient survival was not influenced by recipient or donor sex, delayed graft function and acute rejection episodes.

Discussion

Although long term patient survival following renal transplantation remains considerably below that of the general population, it is much superior to that experienced by dialysis patients. Recently it was reported that the mortality risk of dialysis patients placed on a transplantation waiting list was 68% lower among those receiving a transplant when compared with patients remaining on the waiting list⁶. However life expectancy beyond 10 years is still considerably less than in the general population and this is mainly for three reasons: comorbid illness affecting the cardiovascular system, ma-

Table 4. Recipient survival according to graft origin (LRD or CD) (period 1987-1996)

	all patients no 363	pts with LRD no 231	pts with CD no 132
1 st year	96.14%	97.84%	93.13%
2 nd year	94.21%	96.54%	90.08%
3 rd year	93.11%	96.10%	87.79%
4 th year	91.74%	95.24%	85.50%
5 th year	90.63%	95.24%	82.44%

Log Rank : p=0.00005, Breslow : p=0.00005, Tarone - Ware : p=0.00005

Figure 1. Recipient survival according to graft origin (LRD or CD) (period 1987-1996)

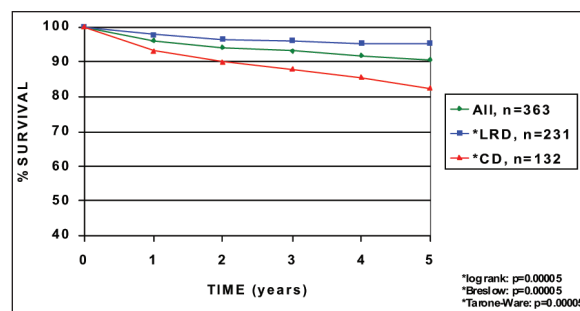


Table 5. Recipient survival according method of dialysis (HD or CAPD)

	method : HD no 297	method : CAPD no : 54
1 st year	97.31%	90.74%
2 nd year	95.96%	87.04%
3 rd year	94.95%	87.04%
4 th year	93.94%	85.19%
5 th year	92.59%	85.19%

Log Rank : p= 0.032, Breslow: p= 0.015, Tarone - Ware: p= 0.020

Figure 2. Recipient survival according to method of dialysis (HD or CAPD)

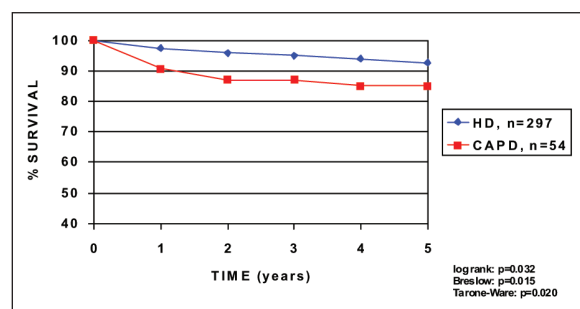


Table 6. Recipient survival in the presence of hypertension or not before RT

	pts with hypertension before transplantation no 187	pts without hypertension before transplantation no 124
1 st year	96.26%	98.39%
2 nd year	94.12%	98.39%
3 rd year	93.05%	96.77%
4 th year	91.44%	96.77%
5 th year	90.37%	94.15%

Log Rank : p= 0.014, Breslow : p= 0.021, Tarone - Ware : p= 0.017

Figure 3. Recipient survival in the presence of hypertension or not before RT

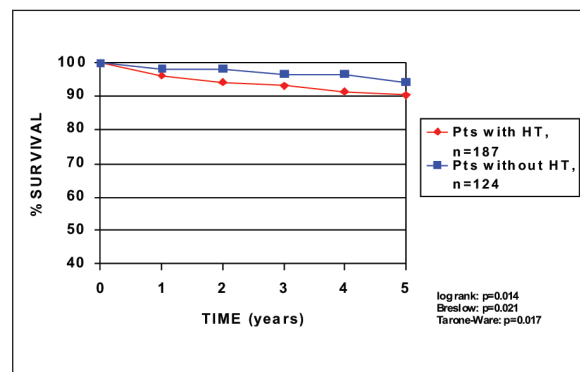


Table 7. Recipient survival in the presence of a hypertensive donor or not

	pts with hypertensive donor no 42	pts with normotensive donor no 221
1 st year	95.24%	98.92%
2 nd year	88.10%	98.39%
3 rd year	88.10%	97.85%
4 th year	83.33%	97.85%
5 th year	83.33%	96.77%

Log Rank : p= 0.001, Breslow : p=0.001, Tarone - Ware : p= 0.001

Figure 4. Recipient survival in the presence of hypertensive donor or not

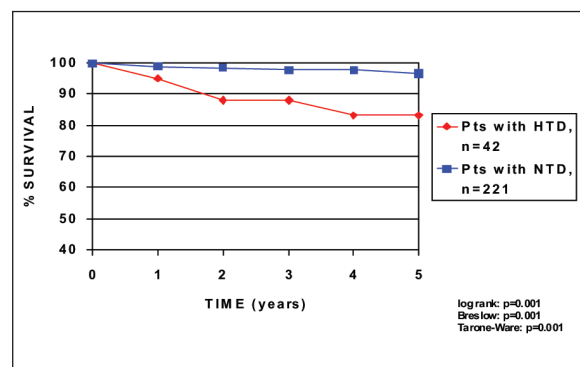


Figure 5. Graft survival according to its origin (LRD or CD) (period 1987 - 1996)

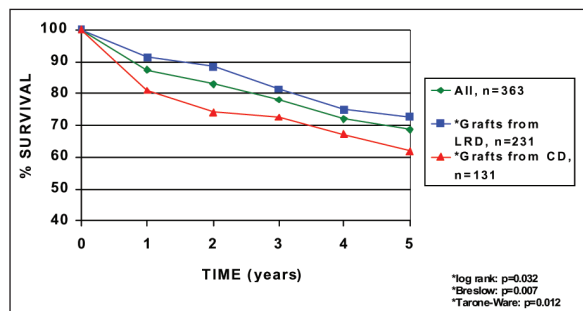


Table 8. Graft survival according to its origin (LRD or CD)

	all grafts no: 363	grafts from LRD* no : 231	grafts from CD* no : 131
1 st year	87.33%	91.34%	80.92%
2 nd year	82.92%	88.31%	74.05%
3 rd year	77.97%	81.39%	72.52%
4 th year	71.90%	74.89%	67.18%
5 th year	68.60%	72.73%	61.83%

Log Rank: p= 0.032, Breslow: p= 0.007, Tarone - Ware: p= 0.012

Figure 6. Graft survival and donor hypertension

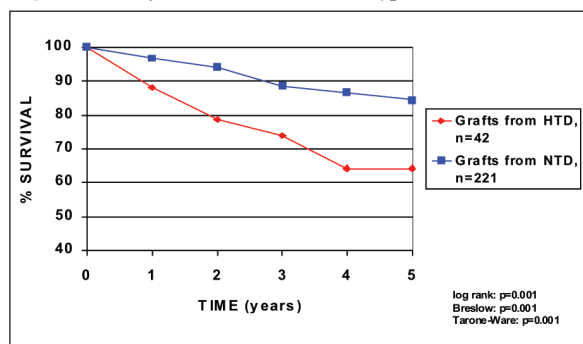


Table 9. Graft survival and donor hypertension before Rt

	grafts with hypertensive donor no 42	grafts with normotensive donor no 221
1 st year	88.10%	96.77%
2 nd year	78.57%	94.09%
3 rd year	73.81%	88.71%
4 th year	64.29%	86.56%
5 th year	64.29%	84.41%

Log Rank : p= 0.001, Breslow : p= 0.001, Tarone - Ware : p= 0.001

Figure 7. Graft survival and DGF

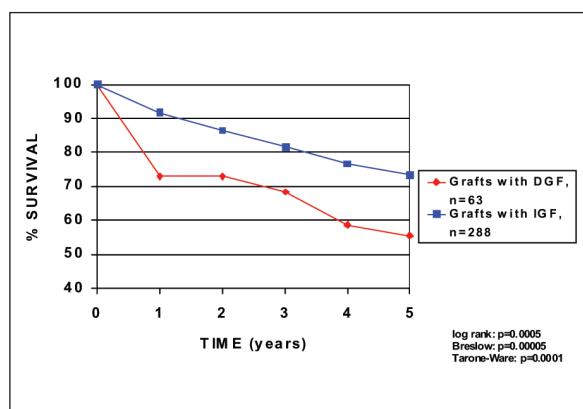


Table 10. Graft survival and DGF

	grafts with delayed function no 63	grafts with immediate function no 288
1 st year	73.02%	91.67%
2 nd year	73.02%	86.46%
3 rd year	68.25%	81.60%
4 th year	58.73%	76.74%
5 th year	55.56%	73.26%

Log Rank : p= 0.0005, Breslow : p= 0.00005, Tarone - Ware : p= 0.0001

Figure 8. Graft survival and acute rejection

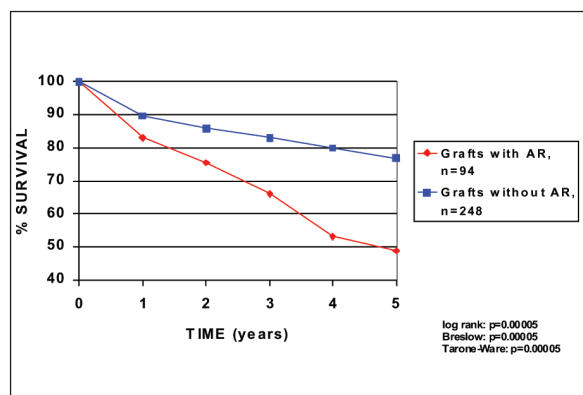


Table 11. Graft survival and acute rejection

	grafts with acute rejection no 94	grafts without acute rejection no 248
1 st year	82.98%	89.52%
2 nd year	75.53%	85.98%
3 rd year	65.96%	83.06%
4 th year	53.19%	79.84%
5 th year	48.94%	76.76%

Log Rank : p= 0.00005, Breslow : p= 0.00005, Tarone -Ware : p= 0.00005

lignant disease and infective illness. Co-morbid disease and conditions such as hypertension, coronary artery disease or peripheral vascular disease in the patient may have a significant effect on mortality risk⁷. The incidence of deaths per year per 1000 transplant recipients, as reported to the UNOS Scientific Registry, revealed 25 among pediatric recipients, 10 among adults under the age 75 years and 80 among adults at or above age 75 years⁸.

The overall, LRD and CD patient and graft survival of our material (table 4, 8), is in agreement with the results published recently in the Guidelines for Renal Transplantation by the EDTA⁹. The survival of patients who undergo renal transplantation has improved over the past three decades. In the mid 1970s 1-year patient survival in those over 35 years of age was only around 60% while in the younger adult it was around 85%. Most recent data indicate a 1-year mortality rate of 6%, a 5-year patient survival rate of 81% for cadaveric and 90% for living renal transplant recipients with patient half lives of 21 and 30 years respectively¹⁰. A multivariate analysis suggested that reduced survival of cadaveric renal transplant recipients correlated with older age, longer duration of pretransplant dialysis treatments, diabetes, and /or smoking, but not with any specific posttransplant variables¹¹. Our findings suggest that graft origin (LRD v CD) has a statistically significant impact on patient survival (in favor of LRD) and this is in agreement with the above mentioned and other reports^{10,12}. Although recipients of living related donor kidneys are at a lower risk of death than cadaveric kidney recipients, the risks among living-unrelated and cadaveric kidney recipients are similar. However, the mortality rates do not differ substantially between HLA – matched and – mismatched recipients, nor between African – American and non – African – American recipients^{7,8}.

Until now the results as far as the influence of dialysis modality on patient survival are conflicting. It has been reported that there is no effect of the dialysis modality on patient survival after 10 years of follow up^{13,14}, that the relative risk of mortality is lower in PD patients without the effect being significant¹² and that survival is better in HD patients without the difference being significant after three year follow up¹⁵. In our study (Table 5, Figure 2) we found that patients previously on HD had ss better survival compared to patients previously on CAPD. The fact that this study was a retrospective and the two groups contained transplants from living related and cadaveric donors does not allow to discuss about causative reasons for the difference. The relation of dialysis modality with graft outcome has been connected with conflicting results. It was supported that PD patients may have altered T-cell subset ratios that could adversely affect graft outcome¹⁶. Others have shown no difference in outcome either the patients were o CAPD or HD^{12,15}. We did not find difference in graft survival between patients on HD or CAPD.

About 50% of our patients were known hypertensives before transplantation. These patients had signifi-

cantly worse survival after transplantation compared to that of normotensives (Table 6, Figure 3) while graft survival did not present difference. On the contrary, Ojo et al found that recipient hypertension before transplantation affected significantly graft survival but not patient survival¹⁷. In this work only recipients with primary renal disease hypertensive nephrosclerosis were compared with the normotensives¹⁷ while we included all the hypertensive recipients irrelevant of primary renal disease and duration of hypertension.

Donor factors are strong determinants of renal transplant outcomes¹⁸. Cadaveric organs are considered suitable for allotransplantation only after a satisfactory assessment of organ viability. Adequacy of renal function is a major factor used to determine the viability of cadaver kidneys. However, beyond a requirement for primary brain death, there are no standardized criteria for the acceptance of cadaver organ donors¹⁹. Faced with a perennial shortage of transplantable organs, donor acceptability criteria are being relaxed cautiously to include marginal donors as a means of expanding the potential donor pool²⁰. The marginal donor pool includes non-heart beating donors, donors at the extremes of age, systemic illness leading to renal parenchymal damage, preexisting renal disease and hypertension.

Successful renal transplantations have been reported from donors with clinically detectable hypertension²¹. It is well known that hypertension predisposes to systemic atherosclerosis with renal involvement. Primary hypertension affects 25% of US adult population²² and is leading cause of end stage renal failure. Renal disease from HTN does not manifest with diminished renal function for one or more decades after the onset. Thus advanced hypertensive nephrosclerosis may be undetected by the routine methods used to assess renal function in potential donors. Recently it was reported that cadaveric renal transplants from donors with HTN accounted for 15% in USA, that the duration of hypertension was an independent risk factor for graft survival²³ and that programs transplanting fewer affected donor kidneys had better than average survival. Our results, in agreement with others, showed that hypertensive donors are connected with significantly lower patient and graft survival (Table 7, 9 Figure 4, 6). Donor hypertension was found by others to significantly affect graft survival¹⁷, while patient survival was not affected. Ojo et al in the group of hypertensive marginal donors included only patients with >10 year history of hypertension and compared them with donors with less than 10 year hypertension¹⁷.

Clinical studies have confirmed an association between posttransplant hypertension and poorer graft outcome²⁴. In these studies graft dysfunction considered to be causative factor of hypertension and not vice versa.

Recipient's sex has very little or not at all influence on the survival of renal transplants. There is a small but statistically significant advantage for females, which becomes obvious about 3 years after transplantation. Women who receive male donor kidneys have some-

what better outcomes than those who receive female donor kidneys or than men who are transplanted with female donor kidneys⁷. In our material, sex was, in agreement with others²⁵, not found to have significant impact on patient survival.

Delayed graft function (DGF) after renal transplantation remains a vexing problem. For the clinician, post-operative care becomes more complex: assessment of graft function and detection of early rejection require increased vigilance and result in more frequent use of both noninvasive and invasive testing methods. DGF entails reinstitution of dialysis and re-exposure to the associated morbidity, prolongation of hospital stay and postponed social and professional rehabilitation. For society and the already overburdened Health Care System, DGF considerably increases hospital costs²⁶. In addition to these well recognized immediate detrimental consequences, substantial controversy persists as to the long term impact of DGF on kidney graft survival. Studies analyzing the effects of DGF on cadaver renal transplantation outcome are inconsistent. In line with others²⁷ our findings show that there is no significant impact of DGF on patient survival. On the other hand there are reports supporting that DGF has significant impact on patient survival²⁸. On the contrary we found a significant effect of DGF on graft function over the five year follow up in agreement with others^{10,25,29,30}.

While there is no doubt about the adverse effect of acute rejection episodes on long term graft survival^{27,30}, there is still controversy about acute rejection and patient survival. We found that acute rejection has no impact on graft but not on patient survival. It has been reported that when DGF and acute rejection are present simultaneously there is lower patient survival²⁷.

Περίληψη

Γ. Βέργουλας, Γρ. Μυσερλής, Μ. Λεονταΐνη, Β. Παπανικολάου, Δ. Γάκης, Ε. Ατματζίδης, Φ. Καρασαββίδου, Γ. Αντωνιάδη, Α. Παντζάκη. Η επίδραση κλινικών παραμέτρων στην πενταετή επιβίωση ασθενών και μοσχευμάτων μετά από πρώτη νεφρική μεταμόσχευση. *Ιπποκράτεια* 2004, 8 (2): 62-68

Σκοπός: Σκοπός αυτής μελέτης ήταν η εκτίμηση της επίδρασης κοινών κλινικών παραμέτρων στην επιβίωση ασθενών και μοσχευμάτων. Τριακόσιοι εξήντα τρεις ασθενείς (pts), 235 άνδρες και 128 γυναίκες, με μέση ηλικία 39 έτη, (διακύμανση 16-69 έτη), υπεβλήθησαν σε πρώτη νεφρική μεταμόσχευση (Rt) από 1.1.1987 μ.ε.χρ. 31.12.96.

Υλικό και μέθοδοι: Μελετήθηκαν η επίδραση της προέλευσης του μοσχεύματος (συγγενής ζωντανός δότης: LRD, πτωματικός δότης: CD), το φύλο δότη και λήπτη, η μέθοδος εξωνεφρικής κάθαρσης (αιμοκάθαρση: HD, περιτοναϊκή κάθαρση: PD), η καθυστερημένη έναρξη νεφρικής λειτουργίας (DGF), η υπέρταση δότη (DH) και λήπτη (RH) πριν από την Rt και τα επεισόδια οξείας απόρριψης (AR). Οι μέθοδοι Kaplan Meier, Log Rank, Breslow and Tarone Ware

χρησιμοποιήθηκαν για στατιστική ανάλυση.

Αποτελέσματα: Η επιβίωση ενός και 5 ετών ασθενών και μοσχευμάτων όλου του δείγματος ήταν 96.14% και 90.63% αντίστοιχα. Pts με LRD ή CD παρουσίασαν επιβίωση 1 και 5 ετών 97.84%-95.24% και 93.13%-82.44% αντίστοιχα (p:0.00005). Pts σε HD ή PD πριν από τη Rt είχαν επιβίωση 1 και 5 ετών 97.31%-92.59% και 90.74%-85.19% αντίστοιχα (p:0.03). Pts με RH ή όχι πριν από τη Rt επιβίωση 1 και 5 ετών 96.26%-90.37% και 98.39%-96.77% αντίστοιχα (p:0.02). Pts με DH ή όχι είχαν 1 και 5 ετών επιβίωση 95.29%-83.33% και 98.92%-96.77% αντίστοιχα (p:0.0015). Η επιβίωση ενός και 5 ετών των μοσχευμάτων όλου του δείγματος (gs) ήταν 87.33% και 68.60% αντίστοιχα. Μοσχεύματα από LRD ή CD είχαν επιβίωση 1 και 5 ετών 91.34%-72.73% και 80.94%-61.83% αντίστοιχα (p:0.03). Μοσχεύματα από DH ή όχι είχαν 1 και 5 ετών επιβίωση 88.10%- 64.29% και 96.77%-84.41% αντίστοιχα (p:0.001). Μοσχεύματα με DGF ή όχι είχαν 1 και 5 ετών επιβίωση 73.02%-55.56% και 91.67%-73.26% αντίστοιχα (p:0.0001). Μοσχεύματα με AR ή όχι είχαν 1 και 5 ετών επιβίωση 82.98%-48.94% και 89.52%-76.61% αντίστοιχα (p:0.00005).

Συμπεράσματα: Καλύτερη πενταετή επιβίωση παρουσίασαν οι pts με LRD, που πριν ήταν στην HD, χωρίς υπέρταση πριν από τη μεταμόσχευση με νορμοτασικό δότη. Μεγαλύτερη επιβίωση παρουσίασαν τα μοσχεύματα που προέρχονταν από νορμοτασικό δότη που ήταν LRD, χωρίς DGF ή AR.

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Corresponding author: Vergoulas G - 53, Alkminis str
542 49 Thessaloniki, Greece, Tel.: 0030 2310 302311
e-mail geover@otenet.gr

Υπεύθυνος αλληλογραφίας: Γ. Βέργουλας, Αλκμίνης 53
Θεσσαλονίκη 542 49, Τηλ 0030 2310 302311, Fax 0030 2310 302311
e-mail: geover@otenet.gr