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Analysis of Factors Influencing on Living Kidney Donors and Deceased Kidney Donors Transplantation Results

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Abstract

Introduction

Recognizing factors influencing kidney transplantation results may significantly affect therapeutic decisions made before, during and post transplantation.

Aim of the study

The aim of the study was to analyse factors influencing kidney graft function.

Material and methods

The group of 993 patients who received kidney graft from deceased and living donors, at Department of General and Transplantation Surgery, Baby Jesus Clinical Hospital in Warsaw, between January 1996 and August 2010 was analysed regarding factors that may have an influence on kidney transplantation results. Factors contingent from donor, recipient and time of kidney preservation were analysed.

Results

A multivariate analysis exhibited that time of dialyses prior transplantation is statistically significant factor influencing recipient's survival (p=0.017). We proved that donor age is a variable that affects both recipient and graft survival. The higher number of mismatches HLA, the lower graft survival (p=0,0028). Cold ischaemia time (CIT) (OR=1.182), HBV infection (OR=1.58) as well as number of mismatch HLA (OR=1.1496), are the factors that influenced on frequency of delayed graft function (DGF) episodes. Moreover, we evidenced that the cause of graft failure affects graft survival. Patients, who suffer from IgA nephropathy, as well as hypertensive nephropathy, have the worst survival ratio after kidney transplantation. Patients who had had received a kidney graft from cadaveric donor with intracranial bleeding had higher creatinine serum concentration up to 5 years post transplantation in comparison with recipients whose kidney had come from donor with cranial trauma (p<0.005).

Conclusions

Factors that significantly influence on kidney graft function are: time of dialyses prior transplantation, number of mismatch HLA, cause of renal failure, HBV infection and CIT.

Keywords: Kidney transplantation; Factors; Transplantation results

Introduction

There are a lot of factors that have an influence on the kidney transplantation results and their cumulative final effect decides about graft and kidney recipient survival, as well as the number of acute rejection episodes and complications. That factor can be divided into 3 groups: donor dependent, contingent on recipient and kidney preservation parameters. There are a lot of researches that assess the impact of the single factors on the kidney transplantation results, however among the papers that are multivariate analyses, still there are no concluding results and the conclusions are not alike. In the last decade there was no breakthrough in the field of immunosuppressive therapy, no new drugs have been discovered that might have a significant result on the improving the results of the kidney transplantation. Thus, factors that might have an influence on the kidney transplantation results should be reconsidered, therefore the aim of the study was to analyse factors influencing kidney graft function.

Material and Methods

Retrospective analysis of kidney transplantation results, harvested from cadaveric and living donors in the Department of General and Transplantation Surgery of Baby Jesus Clinical Hospital in Warsaw,

between January 1996 and August 2010, was conducted (917 patients received a kidney from deceased donors and 76 from living donors).

Kidney grafts from living donors were transplanted immediately after donation, proceeding by rinsing with Ringer solution.

Clinical characteristics of donors and recipients that have been taken to analysis are presented in Tables 1 to 10.

Graft function was expressed by creatinine concentration and GFR counted using Cockroft – Gault formula in 7 and 14 days post

Recipient									
		Deceased kidney donor A			Living kidney donor B			All		
		n	Med	Sn	n	Med	Sn	n	Med	Sn
Sex	Male	545	43	12	51	31	10.5	596	42	12
	Female	372	44	11	25	24	6	397	43	12
	All	917	43	12	76	27.5	10	993	42	12

Table 1: Recipients' age at the moment of transplantation, division to recipient' sex and a type of donor.

Donor type	Dialyses type	Number	%
Deceased	Peritoneal dialysis	54	6,05
	Haemodialysis	735	82,40
	Both	79	8,86
	Pre-emptive	49	2,69
Living	Peritoneal dialysis	5	6,67
	Haemodialysis	54	72,00
	Both	2	2,67
	Pre-emptive	15	18,66

Table 2: Type of dialyses with division to donor type.

Cause of renal failure	Deceased donor		Living donor		All	
Male	n	%	n	%	n	%
Glomerulonephritis	306	56,1	26	51	332	55,7
Other	48	8,8	4	7.8	52	8,7
Diabetes	45	8,3	2	3.9	47	7,9
Polycystic kidney disease	43	7,9	3	5.9	46	7,7
IgA nephropathy	32	5,9	2	3.9	34	5,7
Vesicoureteral reflux	19	3,5	6	11.8	25	4,2
Renal calculus	15	2,8	0	0	15	2,5
Unknown etiology	12	2,2	3	5.9	15	2,5
Pyelonephritis	11	2	2	3.9	13	2,2
Interstitial nephritis	10	1,8	2	3.9	12	2
Lack of renal disease	4	0,7	1	2	5	0,8
All	545	100	51	100	596	100

Table 3: Cause of renal failure.

Cadaveric donors		Male	Female	All
		n=376	n=187	N=563
Daily diuresis (Med.)		4000	4000	4000
Hourly diuresis (Med.)		200	200	200
Age (Med.)		40	46	42
Virus (n)		64	29	93
Concomitant disease (n)	Hypertension	47	35	82
	Other	41	33	74
	None	288	119	407
Cause of death (n)	Cardiac arrest	72	48	120
	Intracranial bleeding	131	112	243
	Cranial trauma	219	58	277
	Other	26	17	43
Hypotension (n)		174	98	272
Multi-organ donor (n)		157	70	227
Optimal donor (n)		173	94	267
Creatinine (Med.)		1.36	1.1	1.3
Drugs (n)	Levonor	66	45	111
	Dopamine	245	108	353
	Dobutamine	10	8	18
	Adrenaline	2	3	5
ICU (Med.)		3	3	3

Table 4: Descriptive statistic of cadaveric donors group.

Recipients		Deceased donor	Living donor	All
		n = 917	n =76	n = 993
No. of arteries	1	766	68	834
	2	121	6	127
	3	27	2	29
	4	3	0	3
No. of veins	1	893	75	968
	2	22	1	23
	3	2	0	2
No. of ureters	1	908	76	984
	2	9	0	9

Table 5: Number of vessels and ureters, depending on the type of donor.

Number of HLA ABC MM	0	1	2	3	4	5
Cadaveric donor	257	128	271	177	82	2
%	28	13,9	29,5	19,4	8,9	0,2
Living donor	32	8	27	6	2	1
%	42,1	10,5	35,5	7,8	2,6	0
All	289	136	298	183	84	3
%	29,1	13,6	30	18,4	8,4	0

Table 6: Number of HLA ABC MM, depending on the type of donor.

transplantation and 1, 3, 6, 9 months post operation et sequens for the next 10 years post procedure.

The follow – up period was 3 months – 10 years post transplantation.

Data was collected from patient's medical history, donor's charts and donation protocol, tissue typing, perfusion and follow – up charts post transplantation.

Patients were divided into 2 cohorts:

A – patients who received a kidney from cadaveric donors

B – patients whose kidneys came from living donors

The factors that affected the short – and long – term outcome were analysed.

Statistical analysis was conducted using SPSS for Windows release 18.0.

Kaplan–Meier curves were constructed for patient survival. The differences between survival curves were evaluated by the logrank test.

The comparison between graft survivals was made using Monte Carlo method.

Number of HLA DR MM	0	1	2
Cadaveric donor	435	394	88
%	47,4	42,9	9,5
Living donor	40	30	6
%	52,6	39,4	7,9
All	475	424	94
%	47,8	42,6	9,4

Table 7: Number of HLA DR MM, depending on type of donor.

				Lower limit	Upper limit
Recurrent urinary tract infection	4493	183,8		4133	4853
Unknown etiology	4671	629,6		3437	5905
IgA nephropathy	1992	356,8		1293	2692
Pyelonephritis	4092	328,9		3447	4736
Diabetes	4102	255,7		3601	4603
Renal calculus	3954	388,7		3192	4716
Glomerulonephritis	4780	122,5		4540	5020
Hypertensive nephropathy	2228	336,7		1568	2887
Vesicoureteral reflux	4191	509,2		3193	5189
Polycystic kidney disease	4883	129,0		4630	5136

Table 8: Graft survival in a relationship with cause of renal failure.

Comparisons between groups were made the chi-square test.

Rho – Spearman's rank correlation, Kruskal – Wallis test, U Mann – Whitney test, Cox regression were used to analyse the influence of particular factors.

Results

993 patients who received a renal graft were taken to analysis. 917 patients (92.35%) received a kidney from deceased donors and 76 (7.65%) from living kidney donors. A huge difference between in the strength of groups causes difficulties in interpreting the results.

What attracts attention is the difference between donor's age depending on the donor status. Living kidney donors are statistically 16 years younger than patients who received a graft from deceased donor. Regard for factors influencing transplantation results, it is not irrelevant.

Donors' age was comparable in both cohorts. The median deceased kidney donors' age was 40.4 years (SD=14.9) and living kidney donors' – 37.0 years (SD=18.3).

Time of dialyses before transplantations was different in both groups. Patients, whose kidneys came from a cadaveric donor, have been dialysed for 40.9 months (SD=34.6 days) before transplantation, whereas living kidney recipients for 30.3 months (SD=28.1 days).

Haemodialyses, as a renal replacement therapy, was more common in both cohorts, respectively 82% and 72% in deceased kidney recipient and living kidney recipients respectively (Table 2).

There was no difference in number of vessels between groups, however the number of HLA mismatches was significantly lower in living kidney recipients' group. Mean number of HLA mismatches in living kidney recipients group is 1.22 and is 27% lower than in the

Cause of renal failure	Time of measurment	% of graft survival
Recurrent urinary tract infection	1 yr	95,41%
	3 yrs	91,70%
	5 yrs	86,54%
	10 yrs	79,03%
Unknown etiology	1 yr	93,75%
	3 yrs	93,75%
	5 yrs	93,75%
	10 yrs	75,00%
IgA nephropathy	1 yr	75,76%
	3 yrs	75,76%
	5 yrs	75,76%
	10 yrs	75,76%
Pyelonephritis	1 yr	100,00%
	3 yrs	100,00%
	5 yrs	92,31%
	10 yrs	75,52%
Diabetes mellitus	1 yr	95,21%
	3 yrs	93,22%
	5 yrs	88,31%
	10 yrs	68,55%
Renal calculus	1 yr	100,00%
	3 yrs	100,00%
	5 yrs	83,33%
	10 yrs	83,33%
Glomerulonephritis	1 yr	95,79%
	3 yrs	92,15%
	5 yrs	88,63%
	10 yrs	79,94%
Hypertensive nephropathy	1 yr	82,89%
	3 yrs	82,89%
	5 yrs	56,99%
	10 yrs	37,99%
Vesicoureteral reflux	1 yr	94,74%
	3 yrs	94,74%
	5 yrs	94,74%
	10 yrs	54,81%
Polycystic kidney disease	1 yr	97,29%
	3 yrs	95,08%
	5 yrs	95,08%
	10 yrs	95,08%

Table 9: Graft survival, depending on cause of renal failure.

cadaveric kidney recipients' cohort (Tables 6 and 7).

The most common cause of kidney failure was glomerulonephritis (Table 3).

Among factors influencing the number of DGF episodes appertained to mention are CIT, donor's creatinine serum concentration and immunosuppressive therapy.

As long as BMI, recipient age, PRA max, donor's creatinine serum concentration, type of renal replacement therapy and CIT are concerned, they affected on the number of dialyses that patients with DGF required post transplantation.

There was a correlation between DGF episodes and number of HLA mismatches in both cohorts. An increase of 1 HLA mismatch is putting patients at 15% higher risk of DGF episode (OR=1.1496). CIT is also influencing on a DGF episodes. Extension of CIT for one hour increases the risk of DGF episode for 2% (OR=1.0182). HBV infection is affecting the risk of DGF episode, as well. HBV positive recipients

Cause of renal failure	Time of measurment	% of graft survival
Recurrent urinary tract infection	1 yr	95,41%
	3 yrs	91,70%
	5 yrs	86,54%
	10 yrs	79,03%
Unknown etiology	1 yr	93,75%
	3 yrs	93,75%
	5 yrs	93,75%
	10 yrs	75,00%
IgA nephropathy	1 yr	75,76%
	3 yrs	75,76%
	5 yrs	75,76%
	10 yrs	75,76%
Pyelonephritis	1 yr	100,00%
	3 yrs	100,00%
	5 yrs	92,31%
	10 yrs	75,52%
Diabetes mellitus	1 yr	95,21%
	3 yrs	93,22%
	5 yrs	88,31%
	10 yrs	68,55%
Renal calculus	1 yr	100,00%
	3 yrs	100,00%
	5 yrs	83,33%
	10 yrs	83,33%
Glomerulonephritis	1 yr	95,79%
	3 yrs	92,15%
	5 yrs	88,63%
	10 yrs	79,94%
Hypertensive nephropathy	1 yr	82,89%
	3 yrs	82,89%
	5 yrs	56,99%
	10 yrs	37,99%
Vesicoureteral reflux	1 yr	94,74%
	3 yrs	94,74%
	5 yrs	94,74%
	10 yrs	54,81%
Polycystic kidney disease	1 yr	97,29%
	3 yrs	95,08%
	5 yrs	95,08%
	10 yrs	95,08%

Table 10: Graft survival, depending on cause of renal failure.

have 1,5 higher risk of such episode (OR=1.58). The time of dialyses is also a statistically significant factor.

DGF episodes were statistically significant less frequent at patients who received graft from living kidney donor.

Time of dialyses (p=0.017), as well as the age of donors (p=0.044), affected patient survival post transplantation.

Both donors' age (p=0.038) and number of HLA mismatches (p=0.025), had statistically significant influence on graft survival.

The cause of renal failure affects graft survival. IgA nephropathy as well as hypertensive nephropathy has the worst survival ratio.

The relationship between donors' age, cadaveric donors' cause of death and recipients' serum creatinine concentration was revealed.

Patients who received a kidney from a cadaveric donor had higher BMI than living kidney recipients 23.1 (SD=3.6) vs. 22.1 (SD=3.8).

Average cadaveric donors age was 40.4 years, SD=14.9 years (from 3 to 75 years old), whereas living kidney donors with average age=37 years (SD=18.3 years, from 17 to 59 years old).

Number of arteries (p=0.11), veins (p=0.74) and ureters (p=0.37) are alike at both groups.

Numbers of HLA mismatches are not the same in the group of male kidney recipients. Coefficient in linear equation with Poisson's error distribution was β=-0.4183, which means that in the group of living kidney recipients average number of HLA mismatch was (1.14) was lower than average number of HLA mismatch at their deceased kidney counterparts (1.72) for 34%. That difference is accidental and statistically relevant (p=0.0028).

Mean amount of dialyses in patients who received induction immunosuppressive therapy was 4.23, whereas at group without induction - 6.27. This is not a coincidence (p= 0.0087). Among the patients with induction immunosuppressive therapy: 113 patients received anti-thymocyte globulin, 19 – basiliximab and 24 dacilizumab.

Time of hospitalization of cadaveric donor is not related neither with amount of dialyses, nor with delayed graft function (p=0.1014).

There was a relationship between DGF episodes and number of HLA mismatches at both cohorts. An increase of 1 HLA mismatch is putting patients at 15% higher risk of DGF episode (OR=1.1496). For instance, recipient whose number of HLA mismatches is 3, has 52% higher chance for acute rejection episode than a recipient with number of HLA mismatches=0.

Significant factor is also cold ischaemia time. A linear regression for that variable equals β=0.0181 which means that with every hour of ischaemia chance of acute rejection episode increases for 2% (OR=1.0182). For instance, patients whose CIT equals 40 hours have 43% more chances for acute rejection episode in comparison with patients, whose CIT is 20 hours. It concerns both living and deceased renal kidney graft recipients (p=0.6604).

Moreover, we proved that patients with immunosuppressive induction therapy have twofold chance of acute rejection episode (OR=1.87), as well as for living and deceased renal kidney graft recipients (p=0.6517).

The longer cold ischaemia time is, the higher probability of acute rejection episode. However it is always higher for patients with higher number of HLA mismatch.

U Mann-Whitney test revealed that patients with acute rejection episode post transplantation had higher period of dialyses prior procedure, time of dialyses (years) Z=2.56; p=0.010. Time of dialyses is statistically significant factor influencing frequency of acute rejection episodes.

On the basis of aggregated material, analysis was conducted to reveal factors that statistically significant affect kidney graft function. Donor age, BMI, addiction to nicotine, time of dialyses prior transplantation, PRA max and last PRA, number of vessels and ureters of transplanted kidney.

Cox regression analysis was conducted to check whether time of dialyses had had an influence of patients' survival. Death of a patient was a result variable. We proved that time of dialyses is statistically significant factor influencing patients' survival – Wald (1)=5.68; p=0.017.

Moreover Cox regression analysis was used to investigate if donor age had interplayed patients survival post transplantation. We showed

that time donor age is statistically significant factor influencing patients' survival - Wald (1)=4.32; p=0.038.

We made a use of Cox regression analysis also to verify the influence of HLA mismatch on graft survival. According to that analysis, number of HLA mismatch is statistically significant for graft survival. The higher number of HLA mismatch, the lower graft survival rate.

Log-rank test revealed statistically significant differences between groups: chi²(9)=19.99; p=0.018. The time of graft failure was different in groups (as long as time post transplantation and frequency are concerned). The shortest graft survival was noticed at patients with IgA and hypertensive nephropathy.

Rho-Spearman correlation analysis was conducted between recipient serum creatinine concentrations and particular donor depending factors.

The older donors were, the higher creatinine serum concentration at recipient, according to correlation analysis.

We also checked whether cause of donor death had an influence on recipient creatinine serum concentration during analysed period. Kruskal-Wallis test revealed that up to 1825 days the difference is statistically significant (p<0.05).

Multiple comparisons revealed, that patients who received a kidney from a donor with intracranial bleeding, had had higher creatinine serum concentration up to 5 years post transplantation in comparison with recipients who received a kidney from a donor with cranial injury.

Discussion

Few multicentre researches led to introducing indexes that should determine the probability of kidney transplantation success. One of the most popular is Kidney Donor Risk Index (KDRI), which was introduced by Rao that includes 14 different factors. In a comparison to KDRI in our study we proved that additionally time of dialyses prior transplantation as well as the cause of renal failure are statistically significant and may affect the kidney transplantation results. The attempts to use other models of predicting kidney transplantation results are unsuccessful. Index such as Deceased Donor Score (DDS), the Maryland Aggregate Pathology Index (MAPI) did not find the broad use. However, the aim of our study was not to create the new scale to predict the transplanted kidney function but discovering the biggest possible amount factors that have an impact on the kidney graft function, so that to use them to better match of the kidney to the recipient, that should effect in the better kidney results transplantation.

There are a lot of papers that confirm our results, however the majority of them are the analysis of the single factor.

Differences between results of kidney transplantation, as well as the significant increase of the kidney graft loss and recipient's death, appear at kidney recipients who received a kidney graft from a cadaveric donor who was over 70 years old [1]. Berger et al. analysed kidney transplantation results of kidney harvested from a living kidney donors older than 70 years old and they proved there is a correlation between donor's age and transplantation results. However, results are comparable with results of kidney transplantation that were harvested from cadaveric standard criteria donors [2]. In our research there was a correlation between donor's age and kidney function - the older donors were, the higher creatinine serum concentration at recipient.

Time between declaring brain death and the moment of harvesting, then transplantation may have an influence on the final kidney transplantation results. Changes that occur in all of the donor's organs, including kidneys, after brain death, are very similar to those that occur during cold ischaemia. Turning off central nervous system as a regulator of metabolic process leads to activating or slowing down of cellular death process or to an uncontrolled secreting of neuroendocrine substances, which disturb cellular metabolism. Thus, it is very important to optimise time of organs harvesting after declaring brain death. Brain death can also cause cardiovascular disturbances with rapid blood pressure decrease, which may cause organ damage. Organs can be also harvested from non-heart beating donors (NHBD). According to Summers et al. the results of kidney transplantation of that kind of organs can be compared to the results of brain death donors' organ transplantation results [3-6]. In our study we proved that patients, who received a kidney from a donor with intracranial bleeding, had had worse kidney graft function in comparison with recipients who received a kidney from a donor with cranial injury.

Deficiency of organs for transplantation and an increasing number of patients on the waiting lists caused that donor's with HbsAg antigen positive are accepted for recipients with the same antigen. According to the literature, results of kidney transplantation are alike in the group of patients who received a kidney graft from a HbsAg antigen positive donor and in the cohort of recipients of renal graft that was harvested from HbsAg antigen negative donor, with stipulation that the only recipients for HbsAg positive kidneys are patients with HbsAg antigen [7-10].

Major histocompatibility complex (MHC) coding human leukocyte antigens (HLA) has the major role in the immunological response, which has a huge influence on the results of transplantation. Despite better and better kidney transplantation results during the last decade it seems that HLA compatibility is still significant. Accurate immunosuppressive therapy may cause decreasing the difference of results of kidney transplantation between better and worse HLA compatibility, however it is still very important predictive factor [11]. A lot of authors claim that the number of HLA mismatches have significant influence on the kidney transplantation results that is in agreement with our results [12]. Moreover, HLA incompatibility may have an influence on the increase risk of recipient's death with functioning graft, which is connected with the necessity of using higher dosage of the immunosuppressive drugs and higher number of the acute rejection episodes.

The time of preservation and of transport, since the moment of organ harvesting is called cold ischaemia time (CIT), which is one of the most important factors influencing on the transplantation results. There are a lot of papers proving that extending CIT over 18 – 20 hours, as long as kidneys preserved in the hypothermia simple are concerned, is connected with more frequent delayed graft function, which leads to earlier graft loss [13]. That statement is unanimous with our results – CIT has a significant influence on the kidney graft function. Nevertheless, there are some researches that doubt that CIT alone is a factor that can affect kidney transplantation results, especially if CIT is no longer than 24 hours [14]. Keyler et al. are wondering if DGF induced by prolonged CIT is really affecting kidney transplantation results [15].

Patients with end-stage renal disease should be qualified to renal transplantation as soon as possible. Time of dialyses prior transplantation is one of the most important factors influencing early and late kidney transplantation results. Meier-Kriesche et al. just as Remport, analysed graft and patient survival after kidney transplantation regarding time of dialyses prior transplantation. They proved that time of dialyses affects negatively both graft and patient survival [16,17].

The feature that singles out our study is the multifactor analyses conducted on the one group of patients, thus it seems that the results are more reliable.

Conclusions

Factors that have a significant influence on the kidney graft function are: time of dialyses prior kidney transplantation, the number of HLA mismatch, cause of renal failure, donor age, cause of donor's death, HBV infection and cold ischaemia time.

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