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Factors Affecting Survival in Kidney Recipients at Kermanshah

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ABSTRACT

Purpose: To evaluate patient and graft survivals in kidney recipients and factors impacting on survival rates at Kermanshah.

Materials and Methods: This study was done on 712 kidney transplants from 1989 through 2001 in Kermanshah. One of the most important applications of survival analysis is assessing the role of explanatory factors in the studied event. In this study Kaplan-Meier method was used to calculate patient and graft survivals and in order to determine the factors affecting survival, Cox proportional hazard model was used. The iterations in Cox model was four times and the inclusion and exclusion criteria, calculated by forward conditional method were less than 5% and 10%, respectively.

Results: Of the recipients, 47.6% were female and most of them (94.4%) had received kidneys from living unrelated donors. One-year patient survivals in recipients from living unrelated donors (LURD) and living related donors (LRD) were 89.4% and 100%, 3-year survivals were 82% and 97.4%, and 10-year survivals were 61.4% and 72%, respectively. In addition, graft survival rates in one year were 85.6% and 97.4%, in three years were 77.2% and 92.3%, and in 10 years were 33.3% and 60.6% in LURD and LRD, respectively. In Cox model, four factors, including the presence of surgical or other complications, known primary disease, and donor-recipient relationship had significant association with patient survival and seven factors, including the presence of surgical complications, known primary disease, donor-recipient relationship, gender, weight, same side transplanted kidney, and donor's age had significant relationship with graft survival.

Conclusion: In summary, it can be concluded that patient and donor demographic characteristics and transplantation conditions may affect patient and graft survival. With the use of multivariate regression analysis methods, the characteristics that have high probability for survival can be determined. Controlling these situations, where they have high survival probability, effectively help better treatment and high survival rate.

KEY WORDS: kidney transplantation, survival rate, Cox regression, affecting factor, Log Rank test

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Introduction

The 1980s has been named organ transplantation decade. Significant advances which has occurred in immunosuppressive therapy has lead to performance of more transplantations and increase in patients and graft survival.[1]

The prevalence and incidence of end stage renal disease (ESRD) was 15000 and 3175 cases in 60 million Iranian people per year, respectively.[2] The first kidney transplantation in Iran was done in 1967, in Shiraz. From 1967 through 1985 about 100 transplantations were performed. There is no national center for recording short-term and long term results of renal transplants in Iran. In 2000, the rule of officially recognizing brain death and cadaveric transplantation was established in the parliament.[2,3] Kidney transplantation has two periods in Iran: first period (1967-1988), which was living related donor (LRD) transplant era and transplantation was less than the expected demand, and second period (1367-1379), in which living unrelated donor transplant (LURD) was established. In the past 12 years more than ten thousand kidney transplantations have been done and the waiting list was eliminated in 1999. Diabetes mellitus and hypertension were the two main causes of ESRD. Few cadaveric transplantations have been performed in Iran (less than 1%) and most donors are unrelated and males (64.7%).[4]

Little information is available about kidney transplantation activity in developing countries.[5] The initial organ transplant was from living related donors in 1954. In 1997, the correction of transplant rules for unrelated donors in Germany got approved.[4] Besides 81% of recipients from living unrelated donors had living related donors, but they didn't do so. Living unrelated donor program can prevent the development of uncontrolled commercial and illegal transplantation which in the absence of cadaver is the single choice.[2,3]

Demand for resources and social management of patients who require renal replacement therapy is one of the health care service problems in all nations. Performance of transplantation and dialysis programmes are related not only to art and medical knowledge but to the socio-economic status of the nations as well. Due to above-mentioned reasons the inclusion criteria to these programmes differs from one country to the other. The prevalence of patients who undergo renal replacement therapy in Iran is identical to Eastern European countries, such as Poland and is more when compared to the previous Soviet Union and less than high prevalence reported in the United States, Japan, and Western Europe.[4]

The comparison of survival between dialysis and transplanted patients is not correct because of their differences. Even if we consider those patients who are in waiting list (as they have similar conditions to be in waiting list), the conditions that lead to transplantation in some and dialysis in the others are not identical. Due to these reasons, the differences in patient survival may correspond to patient differences. In these situations, the consideration of the factors affecting survival such as immunity, gender, age, race, and socioeconomic status and controlling these factors can enable us to make the survival of the two above-mentioned groups comparable. The differentiation between two groups according to the presence or absence of only one risk factor might not be possible with simple statistical analysis.[6]

The majority of studies, which have been done in our country were based mainly on the clinical aspects of transplantation and no study was found about determination of the factors affecting survival in kidney recipient patients, so this study might be the first assessment regarding this subject. In Kermanshah, kidney transplantation was initiated in 1989. The determination of patient survival after transplantation and clarifying the role of affecting factors on survival is of specific importance. The purpose of this study was clarifying the role of the factors that affect patient and graft survival from 1989 through 2001 at the Forth-Shaheed-e-Mehrab hospital in Kermanshah.

Materials and Methods

Seven hundred and twelve patients who had undergone kidney transplantation since 1368 (the time of initiation of transplantation in Kermanshah), until 1380, were enrolled in this study. Patients had been usually hospitalized for two weeks after operation and visited daily. Afterwards, they asked to refer to the transplant center, weekly in the first month, twice a month up to 3 months, and then every other month for physical examination and performing laboratory tests.

With the usage of patients' hospital records, forms for collecting data about the past history of recipients and donors were filled. Laboratory tests and patients' follow-up, which had been

recorded in their clinic files, were also considered. The transplantation ward staff cooperated in these procedures.

In this study, Kaplan-Meier method was used to calculate patient and graft survivals, Cox proportional hazard model with forward conditional method to determine the factors affecting survival, and Pearson's correlation coefficient to evaluate correlation between continuous variables and survival time.[6,7,8] SPSS 9.0 and SPSS 10.0 under windows program were the software packages used for analysis. Patient survival was defined as the interval between transplantation and death or the last follow-up. Graft survival was considered from transplantation until irreversible graft failure (defined as returning to long-term dialysis or second transplant), or the last follow-up with a graft still functioning, or death time. Thus, in this study, death while functioning graft was considered as graft failure.[7]

The patients had received one of the three immunosuppressive regimens listed below:

Two-drug regimen (cyclosporine+prednisolone)

Three-drug regimen (cyclosporine+prednisolone+azathioperine)

Three-drug regimen (cyclosporine+prednisolone+cellcept)

Total transplantations from the beginning of transplantation to the time of the study were 800 cases and all the transplanted patients since 1989 up to the present time who has been transplanted in the Forth Shahid-e-Mehrab in Kermanshah were enrolled in this study. Only 88 patients who were followed for less than one year were excluded from the study.

For determination of the relationship between potential affecting factors and patient and graft survival time in Cox model, a series of variables were considered, including: height (cm), weight (kg), body mass index (BMI) (kg/m^2), donor and recipient age (year), difference between donor and recipient age (year), donors and recipient gender, donor-recipient sex matching, blood group matching, PH matching, donor's and recipient's Rh, Rh matching, Rh and blood group matching, familial relationship, the side of donor's and recipient's kidney, same sided kidney transplantation, primary renal disease, presence of concomitant diseases, dialysis duration (month), date of transplantation, date of birth, residence region (defined as Kermanshah, far way cities, and nearby cities), surgical complications, other complications, and number of previous transplants.

Cox model converged after four iterations and variables were entered to removed from the model using forward conditional method by 5% and 10 % probability, respectively.

Results

Most of the recipients were 217 cases (30.5%) from Kermanshah, 135 (19%) from other cities of Kermanshah province, 135 (19%) from Kordestan province, 68 (9.6%) from Eilam province, 59 (8.3%) from Lorestan province, and 46 (6.5%) from Hamedan province. Three hundred and thirty-nine cases out of total number of recipients were female (47.6%), while only 191 cases (26.8%) were females in the donors. Log Rank test did not show any significant difference in survivals between the two genders (p=0.621).

Regarding the familial relationship between donors and recipients, most of the donors were unrelated (94.4%) and only 40 cases where related, from which 16 cases (2.2%) were sibling, 11 cases were offspring (1.5%), 8 cases (1.1%) were parent, and 5 cases (0.7%) were spouse. A total of 153 deaths (21.5%) occurred in this study, from which 21.9% were recipients from living-unrelated donors (LURD) and 15% from living-related donors (LRD). Log Rank test showed a significant difference between the two related and unrelated groups' survival and it was more in LRD group (p=0.0056).

The most common known primary diseases among kidney recipients, in descending order, were glomerulonephritis in 277 cases (38.9%), hypertension in 136 (19.1%), nephrolithiasis in 46 (6.5%), polycystic kidney disease in 24 (3.4%), pyelonephritis in 20 (2.8%), post partum hemorrhage in 18 (2.5%), and diabetes mellitus in 11 (1.5%).

As a whole, 61 cases (8.6%) of the recipients had a concomitant disease that their frequency was as follows: hypertension in 19 (2.7%), diabetes mellitus in 12 (2.2%), congestive heart failure (CHF) in 6 (0.8%), and tuberculosis (TB) in 4 (0.6%).

Fifty-four cases (7.6%) out of the total number of transplantations, performed in Kermanshah, had surgical complications and 131 cases (18.4%) had other complications. Surgical complications were mostly ureter fistula in 17 cases (2.4%), hemorrhage in 13 (1.8%), and venous thrombosis in 6 (0.8%). Among other complications, the most commons were as follow: liver

TABLE 1. *Mean graft and patient survival time (months) according to recipient and donor characteristics and transplant condition*

Variables		Number	%	Graft survival		Patient survival	
				Mean	SD	Mean	SD
Primary disease	Pregnancy hemorrhage	18	2.5	39.5	30.5	40.6	29.3
	Hypertension	136	19.1	47.6	32.0	48.0	29.3
	Glomerulonephritis	277	38.9	45.2	37.1	46.2	36.6
	Nephrolithiasis	46	6.5	39.6	29.9	39.6	29.9
	Pyelonephritis	20	2.8	45.5	25.6	45.5	25.6
	Polycystic kidney	24	3.4	44.4	32.3	46.8	31.0
	Unknown	140	19.7	40.1	35.0	40.7	34.6
	Total	712	100	44.0	34.6	44.8	34.2
Accompanying disease	Diabetes	16	2.2	43.6	31.6	43.6	31.6
	Hypertension	19	2.7	75.7	22.3	75.7	22.3
	Overall diseases	61	8.6	60.2	38.4	60.4	38.3
Surgical complications	Hemorrhage	13	1.8	22.1	38.2	22.4	38.0
	Ureteral fistula	17	2.4	50.6	42.7	53.6	40.1
	Overall complications	54	7.6	39.2	45.9	41.1	44.7
Other complications	Psychological disorders	11	1.5	74.7	40.1	74.7	40.1
	pneumonia	13	1.8	32.1	39.0	32.1	39.0
	Liver cancer	14	2.0	58.4	36.9	58.4	36.9
	Overall complications	131	18.4	46.4	38.3	46.7	38.1
Recipient's gender	Female	339	47.6	45.1	34.6	45.7	34.1
	Male	373	52.4	43.2	34.6	44.0	34.3
Donor's gender	Female	191	26.8	40.1	31.6	40.6	31.1
	Male	518	72.8	45.6	35.4	46.4	35.0
Transplanted side	Left	18	2.5	32.2	21.3	32.2	21.3
	Right	692	97.2	44.5	34.9	45.2	34.4
Donor nephrectomy side	Left	566	79.5	46.7	34.5	47.4	34.1
	Right	126	18.0	33.5	29.9	34.6	29.6
Citizen	Kermanshah	217	30.5	46.4	35.9	47.0	35.5
	Neighboring cities	153	21.5	43.8	32.6	44.5	32.1
	Faraway cities	342	48.0	42.8	34.7	43.6	34.3
Donor-recipient relationship	LURD	672	94.4	42.2	33.7	42.9	33.2
	LRD	40	5.6	75.9	35.3	76.2	34.9
Rh compatibility	Different	53	7.4	52.0	38.1	52.5	37.6
	Identical	652	91.6	43.3	33.9	44.1	33.5
Blood group matching	Different	40	5.6	46.1	35.4	46.3	35.1
	Identical	669	94.0	44.0	34.4	44.7	34.0
Gender matching	Different	336	47.2	46.9	35.6	47.5	35.2
	Identical	373	52.4	41.6	33.3	42.4	32.8
Kidney side matching	Different	553	77.7	47.0	34.7	47.6	34.3
	Identical	138	19.4	33.7	29.4	34.8	29.1
Concomitant Rh and blood group matching	Different	86	12.1	49.6	37.8	50.0	37.4
	Identical	623	87.5	43.4	34.0	44.1	33.5
Total		712	100	44.0	34.6	44.8	34.2

cancer in 17 cases (2%), pneumonia in 13 (1.8%), psychological disorders in 11 (1.5%), myocardial infarction in 9 (1.3%), cirrhosis of the liver in 8 (1.1%), Kaposi sarcoma in 8 (1.1%), cytomegalovirus infection in 7 (10%), CHF in 6 (0.8%), and TB in 5 (0.7%).

Out of the total number of patients only 5 cases (0.7%) had received two-drug regimen (cyclosporine+prednisolone) and the majority (664 cases or 93.3%) had received triple therapy (cyclosporine+prednisolone+azathioperine), and 43 cases (6%) had been treated with cyclosporine+prednisolone+cellcept.

The differences in mean survival rate ($p<0.001$), graft survival rate ($p<0.001$), donors' age ($p=0.008$), and duration of dialysis ($p=0.026$) were significant between LRD and LURD groups.

One-year patient survivals in LURD and LRD were 89.4% and 100%, 3-year survivals were 82% and 97.4%, and 10-year survivals were 61.4% and 72%, respectively. In addition, graft survival rates in one year were 85.6% and 97.4%, in three years were 77.2% and 92.3%, and in 10 years were 33.3% and 60.6% in LURD and LRD, respectively.

Considering the similarities in recipients and donors characteristics, the least patient and graft survivals were associated with the same sided kidney transplantation and the most were related to LURD and Rh mismatched groups.

According to donor and patient age, the least survival rate was associated with female donor and the most with male donor. Left-sided kidney transplantation in recipient was associated with lower survival rate; whereas, left-sided donor nephrectomy was associated with higher survival rate (table 1).

According to primary disease, post partum hemorrhage and nephrolithiasis were associated with the lowest and hypertension with the highest survival rates. Patients having concomitant hypertension had the highest patient and graft survivals and hemorrhage was associated with the lowest and psychological disorders with highest survival time among complications.

Transplantation date showed the highest inverse correlation with patient survival ($r=-0.477$) and graft survival ($r=-0.47$) using Pearson's correlation coefficient (table 2).

Due to insignificant association of height, donor age, blood group matching, Rh matching, blood group and Rh compatibility, donor and recipient Rh, duration of dialysis, and number of previous transplantations with survival rates after primary analysis, these variables were deleted from the list of explanatory variables for Cox regression model. Of 712 transplant cases, 43 cases of transplant survival data and 17 cases of patient survival data had been missed and consequently, were omitted. Thus, 669 and 695 transplant cases were studied in the two regression analyses, respectively. In these cases, 226 (33.8%) graft rejection and 150 (21.6%) patient deaths have occurred.

TABLE 2. *Correlation between numerical variables and survival rates (Pearson's correlation coefficient)*

Numerical variables	Number	Graft survival		Patient survival	
		Correlation coefficient	P value	Correlation coefficient	P value
Donor's age (year)	695	0.01	0.791	0.013	0.726
Recipient's age (year)	711	-0.138	0.000	-0.14	0.000
Birth date	711	0.000	0.995	-0.001	0.975
Age difference	695	-0.13	0.001	-0.133	0.000
Transplant date	712	-0.47	0.000	-0.477	0.000
Height (cm)	712	0.018	0.624	0.024	0.516
Weight (kg)	699	0.068	0.07	0.075	0.048
BMI (kg/m^2)	699	0.086	0.023	0.091	0.016
Dialysis duration (months)	712	0.131	0.000	0.129	0.001

The remaining 17 variables were enrolled in Cox model to describe patient and graft survivals. Of 17 variables, seven, including weight, donor's age, recipient gender, donor-recipient familial relationship, same sided kidney transplantation, known primary renal disease, and presence of surgical complications had significant relationship with graft survival and other ten variables had no significant relationship. Furthermore, of the 17 above-mentioned variables, familial relationship, known primary renal disease, and presence of surgical and other complications had shown significant relationship with the patient survival and the other 13 variables didn't show any significant relationship (table 3).

Cox regression equations are as follows:

For grafts:

-0.89 (if LRD) +0.60 (if surgical complications occurred) -0.45 (if female recipient) +0.41 (if same sided kidney transplanted) -0.40 (if primary disease was known) +0.02 (donors age) -0.01(patients weight)

For patients:

+0.94 (if surgical complications occurred) +1.30 (if other complications occurred) -0.89 (if LRD) -0.54 (if primary disease was known)

TABLE 3. *Factors affecting survivals in Cox regression model*

	Factors affecting survival	Inclusion conditions				Exclusion conditions	
		B	P	R	Relative Risk	X2 regression	P value
Graft survival	Donor's age	0.022	0.0311	0.0321	1.022	4.5237	0.0334
	Weight	-.0.141	0.0155	-0.0387	0.986	5.9166	0.0150
	Recipient's gender	-0.4516	0.0016	-0.055	0.636	10.0607	0.0015
	Primary disease	-0.4039	0.0121	-0.0409	0.669	5.8556	0.0155
	Donor-recipient relationship	-0.889	0.0063	-0.0461	0.441	9.4203	0.0021
	Kidney side matching	0.4123	0.0139	0.0397	1.510	5.6103	0.0179
	Surgical complications	0.5951	0.0058	0.0467	1.813	6.5984	0.0102
Patient survival	Primary disease	-0.5393	0.0043	-0.0586	0.583	7.471	0.0063
	Donor-recipient relationship	-0.8876	0.0363	-0.0365	0.411	5.71	0.0169
	Surgical complications	0.9446	0.0001	0.0872	2.571	12.7459	0.0004
	Other complications	1.2971	0.0000	0.1834	3.658	56.4939	0.0000

Discussion

This study was done on 712 renal transplant patients. After calculating patient and graft survival rates, the association of 27 variables with survival was evaluated. In our country, limited number of investigations has been performed on renal transplant patients' survival. Of course, more investigations have been done on other fields, but all have considered the clinical aspects of transplant in the absence of survival analysis.

In this study, patient survival rate had significant relation with donor-recipient relationship, known primary kidney disease, and presence of surgical and other complications. Other 13 variables hadn't significant relation with patient survival. Graft survival had also significant association with weight, donor's age, recipient gender, same sided kidney transplantation, known primary kidney disease, and presence of surgical complications.

The factors including presence of surgical complications, known primary kidney disease, and donor-recipient relationship were enrolled in Cox models for graft and patient survivals, but other complications was only related to patient survival and the four factors of recipient gender, weight, same sided kidney transplantation, and donor's age were only related to graft survival.

There is a wide variety of suggestions about factors affecting kidney transplanted patients' survival. In Shaheed Hasheminejad Hospital, Tehran, 1020 renal transplantations were done, from which 571 cases were from LRD and 449 cases from LURD and 65.9% were male donors between ages 8 and 86 years. Graft survival was significantly higher in LRD group when compared to LURD ones ($p<0.005$). But there was no significant difference in patient survival between the two groups. Log Rank test showed a significant correlation between patient survival and age group ($p<0.002$) and donor-recipient relationship ($p<0.02$); however, no correlation between patient survival and recipient's or donor's age was observed.[9] The result of this study in some cases such as the correlation of donor-recipient relationship with graft survival was similar to the results of Kermanshah study, but not in other aspects. The reason might be that Tehran study hasn't used regression method, as survival can related to patients differences. In these situations considering the factors affecting survival in a multivariate analysis can measure each variable effect in the presence of the other factors. These effects can not be differentiated with simple statistical analysis according to the presence or absence of only one risk factor.

In the United States, one-, five-, and ten-year survival for patients above 60 years oldwas 98%, 78%, and 44%, and for patients less than 60 years old was 97% ,93%, and 81%, respectively ($p<0.0001$), but graft survival was not different between the two age groups and no significant correlation with the donor's age was present.[10] Besides, another study was designed in the United Kingdom from 1992 through 1994 to signify the factual rate of renal damage in organ harvesting and to measure its effect on graft survival. Patients' age was an important factor in one-year and three-year survivals ($p<0.001$).[11] Nonetheless, in Kermanshah study, they were related to donors' age.

Also, in the United Kingdom, 6363 cadaveric transplants were followed up to 1 and 5 years after transplantation and were analysed with multivariate and Cox proportional hazard model. Date of transplantation, donor's age, recipient's age, and recipient diabetes mellitus had significant correlation in multivariate analysis, but gender, blood groups, primary disease of kidney,

waiting period until transplantation, and side of kidney were not significantly associated.[12] With increasing age of recipient and donor, the risk of transplant failure increased, that agrees with our study in Kermanshah and few differences may be due to differences in donors (cadaver and live) in the two studies.

Patient survival determinants after transplantation has been incompletely understood and different reports have been published. These differences might be due to differences in the time of patient selection, post transplant management, and immunosuppressive therapy. Leiden Renal Transplant Database (LRTD) is the analysis of data from the first renal transplant done in Leiden, Holland, between 1966 and 1994. On 86 living donors and 916 cadaveric donors, the effect of time passed from transplantation, gender, age at the time of transplantation, cause of graft failure, immunosuppressive regimen, type and duration of dialysis before transplantation, hypertension, diabetes mellitus, smoking, and cause of death has been studied. After adjusting for age and gender, relative risk of mortality rate for living donor transplants versus cadaveric donors was 0.5 ($p<0.06$). Mortality risk in the first year for those who received their first graft from cadaver had improved significantly, which was associated with the introduction of cyclosporine. Mortality rate after the first year was higher in older patients (age>40), males, smokers, and patients with diabetes or hypertension, but individual characteristic factors had little effect. Type and duration dialysis was not associated with patient's mortality rate. Also, in this study, time dependent variations in patient management were responsible for improvement of one-year survival.[13] The little effect of individual characteristic factors and ineffectiveness of type and duration of dialysis, was similar to the finding of our study and differences might be due to more cadaveric transplantations in Leiden analysis.

A study was done on 608 patients in Sweden between 1991 and 1997. Five-year survival in recipients from living donors and cadaveric donors were 94% and 81%, respectively, and for all diabetics was 78%. Date of birth, date of initial dialysis, diagnosis of primary disease, date of transplantation, and date of death or missing were the studied variables,[14] but the number of variables were more in our study.

Non-diabetic patients (287 cases), who were in waiting list for cadaveric donor were enrolled in a study from 1998 through 1999. The health status (according to nephrological evaluation) was divided into four groups (1: high risk, 2: normal, 3: good, 4: excellent). The relative significance of clinical score, age, and age at dialysis initiation in patient survival were overviewed by univariate and multivariate Cox regression model. Survival had significant difference in the four above-mentioned clinical groups (Mantel Cox, $p<0.0001$). Ten-year survival declined from 100% in group 4 to almost 40% in group 1. According to Cox model, the best model for predicting patient survival included age and clinical score ($p<0.0001$). Age at dialysis initiation had negative relation, but was diluted in the presence of age and clinical score.[6] Unfortunately, clinical evaluation hasn't been done in our study, but if supposed to be equivalent to primary disease and concomitant diseases, the results of our study agree with these findings.

In a study, factors correlated with higher survival in recipients from their spouse were evaluated using Kaplan-Meier analysis for calculating survival rates. Three-year survival in spouses who didn't have blood transfusion before operation was 81% and for those who had 1 to 10 transfusion before operation was 40% ($p=0.008$). Higher survival rate was not associated with better HLA matching, white race, younger donor's age, or shorter time of ischemia, except for damage during the shock before harvesting the kidney from cadaver.[15] In our study, HLA matching was not measured because HLA matching is rarely done, due to rarity of cadaveric or LRD transplantation in Iran.

In Geneva university hospital, 310 renal transplantation was done in 283 patients, between 1983 and 1999, from which 49 transplants were done in 48 patients >60 years old. As a whole, multivariate logistic regression analysis showed that patients' and donors' age were not predictors of graft survival.[10] The result of above-mentioned study was similar to ours; however, in our study, recipients age did not show any relation with survival rates.

Conclusion

In summary, it can be concluded that patient and donor characteristics and transplantation conditions may affect patient and graft survival. With the use of multivariate regression analysis methods, the characteristics that have high probability for survival can be determined.

Controlling these situations, where they have high survival probability, effectively help better treatment and higher survival rate.

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