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First-year mortality in living donor kidney transplantation: twelve-year experience from a single center

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ABSTRACT

Objective: The mortality was seen in the early period after kidney transplantation is one of the most undesirable consequences of kidney transplant treatment. This study was aimed to evaluate the factors affecting the 1st-year mortality in patients who underwent living donor kidney transplantation (LDKT) in our center.

Material and Method: Adult patients who underwent LDKT developed mortality within the 1st-year in our center between 2008 and 2020. Mortality group and the control group are compared according to donor and recipient characteristics. The risk factors that have an adjusted effect on 1st-year mortality after kidney transplantation were evaluated by cox regression survival analysis.

Results: Total mortality incidence was 8.35% and the 1st-year mortality incidence was 1.67%. Median dialysis duration (13 months vs. 3 months) was longer in the mortality-group, p=0.022. Cardiovascular disease (CVD) was more common in the mortality-group (50% vs. 31.1%), p=0.037. Median HLA mismatch numbers was higher in the mortality-group (4 vs. 3), p=0.027. According to Model 1, in terms of 1st-year mortality, each 1 year increment in recipient's age increases the mortality by 1.034 times, and dialysis treatment increases the mortality 2.5 times. According to Model 2, in terms of 1st-year mortality, each 1 year increment in recipient's age increase the mortality by 1.039 times, dialysis treatment increases the mortality 2.8 times and each 1 mismatch increase in human leukocyte antigen (HLA) mismatch numbers increases the mortality by 1.3 times. Receiver operating characteristic analysis showed that the moderate predictive power for recipient age was area under the curve (AUC) 0.734 (95% CI 0.623-0.844, p<0.001) and the weak level predictive power AUC was for HLA mismatch 0.639 (95% CI 0.519-0.759, p=0.030) in terms of 1st-year mortality.

Conclusion: This study presented that the 1st-year mortality results of our organ transplant center are similar to the national and international literature. We determined recipient age, dialysis treatment and HLA mismatch numbers as independent risk factors affecting 1st-year mortality after LDKT.

Keywords: Living donor kidney transplantation, mortality, dialysis

INTRODUCTION

Cardiovascular diseases (CVD) are the most common cause of mortality in patients with chronic kidney disease (CKD), followed by infections (1). While the uremic environment causes defects in both cellular and humoral immune system in CKD patients, chronic inflammation also leads to accelerated atherosclerosis (1). In CKD patients, risk factors such as advanced age, diabetes mellitus (DM), hypertension (HT) and hyperlipidemia (HL), which are risk factors for CVD, are more common than in the general population. CVD clinical presentations in patients with CKD may be in the form of atherosclerosis, ischemic heart disease (IHD), heart failure (HF), myocardial infarction (MI), sudden cardiac death, and peripheral vascular disease (PVD) (2). Kidney transplantation is the most preferred treatment method in CKD patients which ends the uremic environment and causes improvement in the uremic environment's negative consequences. Since kidney transplant patients also have CVD risk factors such as DM, HT and HL, deaths due to cardiovascular reasons frequently cause deaths after transplantation (3,4). Immunosuppressive treatment causes more frequent infections in kidney transplanted patients than CKD and the general population, leading to infection-related mortality in these patients, which makes to ahead of CVD-related deaths (5).

The mortality was seen in the early period after kidney transplantation is one of the most undesirable consequences of kidney transplant treatment. Although

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improvement in kidney transplant treatment has led to a significant improvement in graft survival over the years, according to Turkish Society of Nephrology (TSN) registry reports, there has not been much change in the 1st-year mortality rates in the last ten years, and it has remained at a rate of 2-4% (6-9).

This study was aimed to evaluate the factors affecting the 1st-year mortality in patients who underwent living donor kidney transplantation (LDKT) in our center.

MATERIAL AND METHOD

Yeni Yüzyıl University Science, Social and Non-Invasive Health Sciences Research Ethics Committee approved this retrospective cohort study (Date: 05.04.2021, Decision No: 2021/04-649). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Adult patients who underwent LDKT developed mortality within the 1st-year were recruited in our center between 2008 and 2020. We had a similar number of adult patients with similar primary kidney disease as the control group. As donor and recipient characteristics, age, gender, BMI (kg/m²), relationship status (related/unrelated), duration of dialysis (months), primary disease that makes end stage renal disease (ESRD), recipient-DM, recipient-HT, recipient-CVD, Class I-II panel reactive antibody (PRA), human leukocyte antigen (HLA) mismatch number, induction therapy, total dose of rabbit anti-thymocyte globulin (rATG), and biopsy-proven acute rejection (BPAR) were recorded. The cause of death was recorded for the mortality-group.

Statistical Analysis

Numerical variables by descriptive statistical analysis were evaluated for whether they were distributed normal or not (Kolmogorov Smirnov/Shapiro-Wilk). Groups were compared in terms of donor and recipient characteristics. Groups were compared by Independent Sample t-test in terms of normally distributed numerical variables. In contrast, groups were compared by Man Whitney-U test for numerical variables that were not normally distributed. Groups were compared by Chi-Square analysis in terms of categorical variables. Fisher Exact and Pearson Chi-Square were used for categorical variables when they did not fit the Chi-Square goodness. The risk factors that have an adjusted effect on 1st-year mortality after kidney transplantation were evaluated by cox regression survival analysis. Numerical variables that were found to be significant by the Receiver Operating Characteristic (ROC) were evaluated to determine predictive accuracy in terms of 1st-year mortality. $p<0.05$ was considered statistically significant.

RESULTS

The number of patients who underwent LDKT between 2008 and 2020 in our center were 2143. While our center's total mortality incidence was 8.35% (n=179), the 1st-year mortality incidence was 1.67% (n=36). There was no difference in mean donor age among the groups (45 years vs. 47 years). In the mortality-group, female gender was found to be higher, 63.9% (p=0.003). In the mortality-group, donor median BMI was higher, 27.8 kg/m² (p=0.044). In the mortality-group, recipient mean age was higher than the group with no-mortality (53 vs. 43), p=0.002. There was no difference between the groups in terms of recipient BMI and gender. Preemptive kidney transplantation rate was lower in the mortality-group (16.7% vs. 44%), p=0.008. When evaluated in terms of dialysis duration, median-duration (13 months vs. 3 months) was longer in the mortality-group, p=0.022. CVD was more common in the mortality-group (50% vs. 31.1%), p=0.037. Median HLA mismatch numbers was higher in the mortality-group (4 vs. 3), p=0.027. There was no difference between the groups in terms of primary disease, Class I-I PRA, donor-specific antibody (DSA), induction therapy, rATG total dose and BPAR. The comparison of the groups in terms of donor and recipient characteristics are given in **Table 1**.

Table 1. The groups according to donor and recipient characteristics

	Mortality at 1 Year		p
	Yes (36)	No (50)	
Donor age, years	45±14	47±14	0.272
Donor sex, f/m (m%)	23/13 (36.1%)	16/34 (68.%)	0.003
Donor BMI, (kg/m²)	27.8 (21-42)	25.7 (18-36)	0.044
Recipient age, years	53±13	43±12	0.002
Recipient sex, f/m (m%)	15/21 (58.3%)	25/25 (50%)	0.445
Recipient BMI, (kg/m²)	26.3±6	25.78±5	0.730
Relative, yes%	20 (55.6%)	29 (58%)	0.821
Dialysis/Preemptive, Dialysis %	30/6 (83.3%)	22/28 (56%)	0.008
RRT duration, months	13 (0-228)	3 (0-156)	0.022
Primary disease			
• DM	13 (34.3%)	10 (20%)	0.331
• HT	6 (17.1%)	7 (14%)	
• Chr.Gn	5 (14.3%)	9 (18%)	
• Other	12 (34.3%)	24 (48%)	
CVD, yes%	18 (50%)	14 (31.3%)	0.037
HLA mismatch	4 (2-6)	3 (0-6)	0.027
Class I PRA, yes%	8 (22.2%)	11 (22.4%)	0.980
Clas II PRA, yes%	12 (33.3%)	12 (24.5%)	0.371
DSA, yes%	4 (11.7%)	7 (14.3%)	0.753
Induction			
• Bsx	0 (0%)	1 (2%)	0.606
• rATG	31 (86.1%)	44 (88%)	
• rATG+TPE	5 (13.9%)	5 (10%)	
rATG total dose, mg	950 (0-2200)	300 (0-1900)	0.263
BPAR			
• No	27 (75%)	34 (68%)	0.779
• ATCMR	5 (13.9%)	9 (18%)	
• AAMR	4 (11.1%)	7 (14%)	

BMI: Body mass index, RRT: renap replasman tedaivisi, DM: Diabetes mellitus, HT: Hypertension, Chr.Gn: Chronic glomerulonephritis, CVD: Cardiovascular disease, HLA: Human lokocyte antigen, PRA: Panel reactive antibody, DSA: Donor specific antibody, Bsx: Basiliximab, rATG: Rabbit antithmocyte globulin, TPE: Therapeutic plasma exchange, BPAR: biopsy proven acute rejection, ATCMR: Acute T-cell mediated rejection, AAMR: Acute antibody mediated rejection

Risk factors affecting 1st-year mortality after LDKT were evaluated by cox regression analysis. Results are given in **Table 2**. As a result of univariate analysis, donor gender, donor BMI, recipient age, dialysis, and HLA mismatch were determined as statistically significant factors. When these risk factors were evaluated together in model 1, recipient age and dialysis were independent risk factors. When statistically significant variables (p<0.25) in univariate analysis were analyzed in model 2, recipient age, dialysis and HLA mismatch number were independent risk factors in terms of 1st-year mortality. According to Model 1, in terms of 1st-year mortality, each 1 year increment in recipient's age increases the mortality by 1.034 times, and dialysis treatment increases the mortality 2.5 times. According to Model 2, in terms of 1st-year mortality, each 1 year increment in recipient's age increase the mortality by 1.039 times, dialysis treatment increases the mortality 2.8 times and each 1 mismatch increase in HLA mismatch numbers increases the mortality by 1.3 times.

Receiver operating characteristic analysis showed that the moderate predictive power for recipient age was AUC 0.734 (95% CI 0.623-0.844, p<0.001) and the weak level predictive power AUC was 0.639 (95% CI 0.519-0.759, p=0.030) for HLA mismatch. In **Figure 1**, the ROC curves of these variables are given. The recipient age cut off value was ≥50 years and the HLA mismatch number was ≥3. For the recipient age cut off value (≥50 years), sensitivity was 66.7%, specificity 72%, negative predictivite (NPV) 75%, positive predictivity (PPV) 63.2%, p <0.001. For the HLA mismatch cut off value (≥3), the sensitivity was 34%, specificity 88.9%, NPV 81%, PPV 49.2%, p <0.015.

In the mortality-group, we found cause of death rates 55.6% infection, 30.5% cardiovascular, 5.6% cerebrovascular event and 8.3% others.

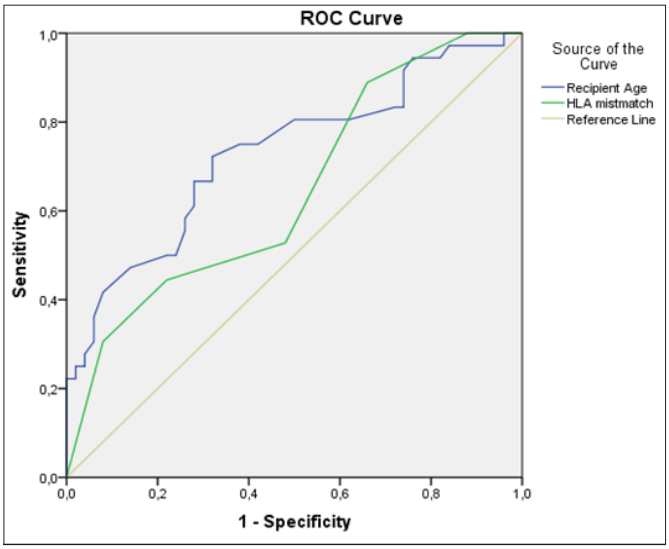

Figure 1. Receiver operating curve for recipient age and HLA mismatch

Table 2. Univariable and multivariable cox regression analysis for 1st-year mortality

1st-year mortality (Cox regression)	Univariable		Multivariable-Model 1 (p<0.001)		Multivariable-Model 2 (p<0.001)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Donor age	0.993 (0.970-1.017)	0.580				
Donor sex	2.545 (1.287-5.033)	0.007	1.887 (0.920-3.867)	0.083	1.772 (0.843-3.724)	0.131
Donor BMI	1.074 (1.010-1.143)	0.024	1.047 (0.980-1.118)	0.176	1.044 (0.976-1.116)	0.214
Recipient age	1.055 (1.024-1.086)	0.000	1.034 (1.005-1.064)	0.022	1.039 (1.003-1.076)	0.033
Recipient sex	0.748 (0.385-1.451)	0.390				
Recipient BMI	1.022 (0.957-1.091)	0.514				
Relative	0.951 (0.493-1.836)	0.881				
RRT/Preemptive	2.852 (1.185-6.863)	0.019	2.568 (1.059-6.225)	0.037	2.791 (1.082-7.201)	0.034
Diaylsis duration	1.005 (0.999-1.010)	0.097			0.998 (0.992-1.005)	0.583
DM	1.563 (0.792-3.086)	0.198			0.852 (0.392-1.852)	0.686
Hypertension	0.575 (0.239-1.381)	0.216			0.800 (0.315-2.031)	0.639
CVD	1.863 (0.968-3.586)	0.063			1.027 (0.481-2.190)	0.946
HLA mismatch	1.297 (1.040-1.617)	0.021	1.270 (0.994-1.623)	0.056	1.280 (1.002-1.635)	0.048
Class I PRA	0.915 (0.417-2.008)	0.824				
Clas II PRA	1.246 (0.622-2.496)	0.534				
Induction						
• rATG	Reference category	0.699				
• rATG+TPE	1.205 (0.468-3.102					
ATG total dose	1.000 (0.988-1.001)	0.675				
BPAR						
• No	Reference category					
• ATCMR	0.773 (0.298-2.008)	0.598				
• AAMR	0.738 (0.258-2.109)	0.570				

BMI: Body mass index, RRT: renap replasman tedaivisi, DM: Diabetes mellitus, HT: Hypertension, CVD: Cardiovascular disease, HLA: Human lokocyte antigen, PRA: Panel reactive antibody, DSA: Donor specific antibody, Bsx: Basiliximab, rATG: Rabbit antithmocyte globulin, TPE: Therapeutic plasma exchange, BPAR: biopsy proven acute rejection, ATCMR: Acute T cell mediated rejection, AAMR: Acute antibody mediated rejection

DISCUSSION

In this study, 1st-year mortality of the patients who underwent LKDT in our center was 1.67%. TSN 2019 registry reports revealed that 1st-year mortality 2.85% (9), US 2019 registry reports revealed that 1st-year mortality 2% (10), European Renal Association-European Dialysis, and Transplant Association (ERA-EDTA) 2017 reports showed that 1st-year mortality 1.2% (11), which was also very similar to our results. This study showed that recipient age, dialysis treatment and HLA mismatch numbers are independent risk factors for 1st-year mortality after LDKT. We found cause of death rates was infection (55.6%) and cardiovascular (30.5%), the second most common causes of mortality in the mortality-group at one year.

Although the mortality rate due to CVD has decreased in kidney transplant patients compared to dialysis patients, it is still higher than in the general population (3). In kidney transplant patients, CVD-related mortality is 2 times higher than the general population since non-classical risk factors such as proteinuria and decreased Glomerular filtration rate (GFR) is more common in addition to DM, HT, HL, which are the classical risk factors for CVD (3). Wu et al. (12) found a 2-year patient survival rate of 94.7%, and HF and DM were found as independent risk factors for transplant failure (considered as graft loss and/or patient death). Fuggle et al. (13) showed in their reports that come from the United Kingdom (UK), 1st-year survival after LKDT was found to be 99%. Donor age (especially >60 years) and recipient-DM as independent risk factors for 3th-year mortality after LKDT were determined. In contrast, recipient age and HLA mismatch numbers were not as independent risk factors for 3th-year mortality. In that study, in terms of recipient CVD, dialysis duration and preemptive transplantation were not evaluated. Although we found a difference in CVD between the mortality-group and the control group in our study, we found that the presence of CVD in the recipient did not affect the 1st-year mortality. However, independent risk factors for 1st-year mortality were recipient age, dialysis treatment and HLA mismatch numbers. We found the recipient age cut off value of ≥50 years to be moderately discriminating for 1st-year mortality. Also, we found ≥3 HLA mismatch numbers to be poorly discriminate in terms of 1st-year mortality. We think that the organ transplant team should consider patients of ≥50 years aged and with HLA mismatches ≥3 as risky in terms of development of 1st-year mortality and evaluate these patients from this perspective.

Studies show that preemptive kidney transplantation is associated with better graft and patient outcomes in both deceased-donor kidney transplantation (DDKT) and LDKT (14,15). In TSN 2019 registry reports (9), preemptive kidney transplantation rate in DDKT was limited to 3.6%, while it was 57.4% in patients with LDKT. In our country, we think that the rate of preemptive transplantation has increased, as the experience of LDKT has grown over the years in organ transplant centers. Our study shows that dialysis treatment increased 1st-year mortality by 2.7 times compared to preemptive kidney transplantation. As the time spent on dialysis increases, many defects in the immune system and chronic inflammation explain why CVDs are seen more frequently in dialysis patients and transplant patients. Moreover, it has been shown that chronic inflammation starts much earlier in predialysis CKD stage III-IV patients as a result of the decrease in the clearance of circulating proinflammatory cytokines and the prolongation of the half-lives of these cytokines. We think that preemptive kidney transplantation is an appropriate approach to protect CKD patients from the negative consequences of this uremic milieu and save them by preventing their exposure to dialysis.

In this study, we found the rates of 1st-year mortality causes (infection 55.6%, cardiovascular 30.5%, cerebrovascular event 5.6%) similar to the national data given in the TSN 2019 registry reports (9) (infection 46.6%, cardiovascular 26.1%, cerebrovascular event 4.85%).

This study has some limitations. Being a single-center study may not be sufficient to represent national results as the organ transplant team performs similar preferences in the kidney transplantation process. The control group may not represent the whole population since all LDKT patients' data couldn't be provided. Identifying specific subgroups of CVDs, which are the most common cause of mortality after kidney transplantation, would help analyze the causes of mortality better before and following transplantation.

CONCLUSSION

This study has shown that the 1st-year mortality results of our organ transplant center are similar to the national and international literature. We determined recipient age, dialysis treatment and HLA mismatch numbers as independent risk factors affecting 1st-year mortality after LDKT. We think that encouraging end stage renal disease (ESRD) patients to have preemptive transplantation without dialysis treatment and upgrading the conditions in this respect will reduce mortality in the early period after LDKT.

ETHICAL DECLARATIONS

Ethics Committee Approval: Yeni Yüzyıl University Science, Social and Non-Invasive Health Sciences Research Ethics Committee approved this retrospective cohort study (Date: 05.04.2021, Decision No: 2021/04-649).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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