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Survival analysis of renal patients underwent transplantation in Kyrgyz Republic and various countries by 10 years follow-up

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Abstract

In our study we conducted survival analysis of 204 patients visited Scientific-Research Institute of Heart Surgery and Organs transplantation and who underwent renal transplantation in Kyrgyzstan and other Eurasian countries between 2005 and 2016 years (age range: 9-71 years, mean: 38.21 (12.74) years, median: 34.0 (0.89) years; gender: 142 male (69.6%)).

During follow-up period, mortality event was observed in 16 (7.84%) patients. Survival function probabilities of patients and rational risk factors of survival functions were evaluated by Kaplan-Meier and Cox regression analyses, respectively. According to Kaplan-Meier results survival probabilities calculated for 1st year: 0.96 (0.014), for 3rd year: 0.94 (0.018), for 5th year: 0.86 (0.04), for 7th year: 0.75 (0.10). Among age groups 28-39 age ranges prevailed by 11 patients. Nevertheless, that difference did not show statistical significance: p=0.322. The intensity of transplantation also analyzed according to years, which revealed increasing in numbers of operations by time. For instance, when in 2006 only two cases were registered in our center, but numbers of transplanted patients reached up to 48 in 2015. The association of mortality states and years of transplantation found significantly by Kaplan-Meier test (Breslow p<0.001). The survival analysis was compared according to countries and revealed significant results (Breslow p<0.05). From other factors influencing mortality, sex did not show strong impact on survival by Kaplan-Meier analysis, but significant association was found by Cox regression analysis.

Key words: renal transplantation, survival function, cumulative survival, mortality, follow-up, Kaplan-Meier analysis, Cox regression analysis, event, censored value

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Introduction

The graft transplantation has been used in kidney failure as reliable and effective treatment option since 1936 (1). Studies show the increase in survival rate by transplantation in comparison to hemodialysis (2-4). On the background of technological modernizations, surgical achievements, survival improvements the transplantation was further motivated by healthcare institutions. Intensive demands, appropriate donor challenges and other factors led to the development of high-income economic sector in transplantational management (5). This situation is expressed with the concept of transplantation tourism. The approximate cost of kidney transplantation is $18,000 in India, $32,000 in Nigeria (the most active center), $78,000 in the UK and $117,000 in the US (6). If the transplantation was achieved by several countries in 1960s, now it is performed by vast majority of centers. It is stated that this number is around 80 (7, 8). The Transplant Society and the International Society of Nephrology state, that despite the Istanbul Declaration, which was approved by more than 110 professional and governmental organizations in 2008 for the prevention of crime in transplantation and the prevention of illegal programs, is still not known to what extent the situation is controlled (9).

Nevertheless, nowadays, despite the well-developed surgical techniques, preoperational and postoperational workup, donor-recipient relationships significantly affect the survival (7, 8). From that standpoint, posttransplantational survival performance differs by countries and medical centers (2). Shortly, countries and transplantation centers demonstrates variation of survival estimations and risk ratios (2, 7, 8).

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In this study, we investigated posttransplantational survival analysis of patients who underwent renal transplantation in Kyrgyzstan and other Eurasian, predominantly neighboring countries. Besides the general analysis of survival after renal transplantation, analysis by transplantation years and differences among countries was also included in our study.

Methods

A total of 204 patients operated in various 8 countries were included to our study: 142 (69.6%) males, 62 (30.4%) females. Mean age was 38.0 (0.89) years, median 34.0 (12.7) years. Conservative treatment at 1st year after transplantation was started in corresponding country where the patient was operated. After the 1st year of procedure, treatment and follow-up was continued by our clinic. We excluded from analysis rejections and complications, mortality cases during the 1st year of follow-up. Differences of survival by operated countries, by transplantation years, by age and gender groups are investigated in this study.

Statistical analysis: Demographic properties of study population were depicted by descriptive techniques of SPSS version 22 program (IBM SPSS 22, New York, USA). Distribution and homogeneity of variations were calculated by Kolmogorov-Smirnov and Shapiro-Wilk tests, which identified nonparametric distribution ($p<0.001$). Survival estimates according to years were analyzed by Kaplan-Meier analysis. Factors such as, age, gender, transplantation years, operating countries, affecting survival parameters were investigated by log-rank test, Breslow and Tarone-Ware techniques. Differences between countries were calculated by post hoc test. Cox regression analysis was applied for rational risk factors of age, gender, country and transplantation years. Mortality probabilities under these factors were calculated by logistic regression analysis.

Results

As seen from Table 1, out of 204 patients 16 (7.8%) died, whereas other 188 are surviving and by statistical description, they belong to censored state.

Table 1. Descriptive parameters of study population

Variables	Numbers and statistical expressions	
Status	Dead -16 (7.8%)	
	Alive -188 (91.7%)	
	Valid percent – 92.2%	
Age	Range -9-71years	Std error-0.892
	Mean-38.9 years	SD-12.739
	Median-34.00	Variance-165.819
Gender	Male – 142 (69.6%)	
	Female – 62 (30.4%)	

Kaplan-Meier calculations depicted general survival as followings: for 1st year 0.961 (0.014), for 3rd: 0.94 (0.018), for 5th: 0.861 (0.042), for 7th: 0.753 (0.107) (Fig. 1).Mortality rate was 7.8%. Age and gender factors on survival functions were distinctly calculated by Kaplan-Meier analysis and both of them did not show statistical significance.

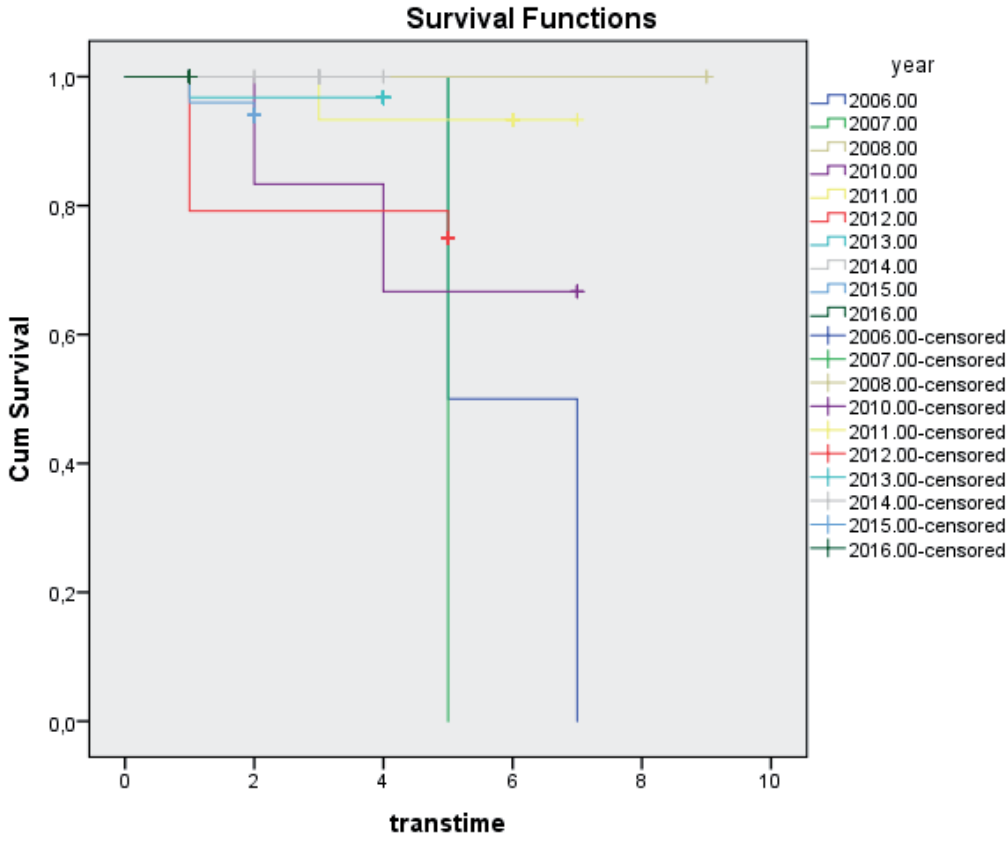

Figure 1. Survival functions

Table 2. Patient numbers undergone transplantation according to years

Years	2006	2007	2008	2010	2011	2012	2013	2014	2015	2016
Patients, %	2.1	1.05	2.1	6.29	15.7	24.11	31.15	36.17	50.24	37.18
Mortality	2	1	0	2	1	6	1	0	3	0

As seen from Table 2, beginning with 2006 the number of transplanted patients was increasing. Mortality number rationally to patient number was also increasing. Especially in 2012, mortality extremely increased in contrast to other years. Patient survival affected by transplantation year indicated statistical significance (Log-rank $p<0.001$, Breslow $p<0.05$, Tarone-Ware $p<0.05$).Hazard function analysis revealed increase of mortality risk from 5th year to 6th and 7th years in contrast to 4th year (Fig. 2).

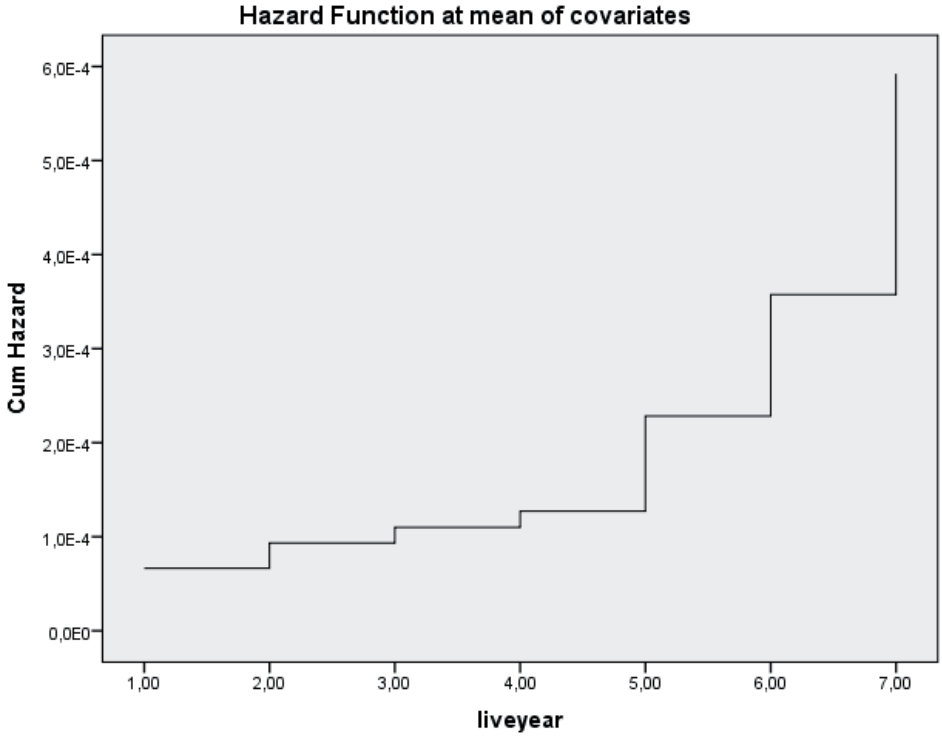

Figure 2. Hazard function analysis

Table 3. Distribution of patients by transplanted countries

	Countries	Frequency of transplantation	Percent	Mortality events	Event- free (alive)	Mortality percent
1	China	6	2.94	2	4	33
2	India	7	3.43	-	7	0
3	Kazakhstan	13	6.37	-	13	0
4	Kyrgyzstan	24	11.76	5	19	21
5	Pakistan	26	12.7	5	21	19
6	Russia	11	5.39	1	10	9
7	Tajikistan	8	3.92	1	7	12
8	Turkey	109	53.43	2	107	2

As seen from Table 3, transplanted patient numbers varied by countries. Mortality conditions of countries are analyzed by Kaplan-Meier and Breslow test revealed significant difference ($p<0.05$) whereas Log rank and Tarone-Ware tests did not give strong results. Post hoc test was used for defining of difference between countries and proved significant difference among China, Pakistan, Kyrgyzstan and Tajikistan.

Table 4. Estimates of cumulative survival according to transplanted countries

Country	Loss year	Cumulative pro Est	Std error
China	5 6 10	0.83 0.66 0.66	0.15 0.19 0.19
India	3	0.1	0.1
Kazakhstan	3	0.1	0.1
Kyrgyzstan	1 5 6	0.87 0.65 0.65	0.06 0.19 0.19
Tajikistan	1 5	0.87 0.87	0.11 0.11
Pakistan	1 2 3 5	0.96 0.88 0.84 0.78	0.03 0.06 0.07 0.87
Russia	5 7	0.85 0.85	0.13 0.13
Turkey	1 4 7	0.99 0.96 0.96	0.009 0.032 0.032

The Table 4 reflects admission of patients to different countries in different years for renal transplantation. According to that point, survival estimates of patients were presented in different countries by different time periods.

Relationships of considered independent factors of mortality were analyzed by Cox regression test.

In summary, age was found as a significant factor affecting mortality (B: 0.080; SE: 0.040; Exp B: 0.923; CI 0.853-100, $p<0.05$) Thus, age by 1.08 decreases mortality. Sex had a strong relation to mortality (B:-2.738; SE: 0.876; Exp: 0.065; CI: 0.012-0.360, $p<0.05$) Male sex was found as a factor by 15 times decreasing the mortality. From other factors affecting the mortality in our model, transplant years did not show strong relations statistically. By our model, four countries (China, Pakistan, Kyrgyzstan, Tajikistan) were found with significant risk results by time periods in mortality. Mortality risk was increased by 84 times in Pakistan (B:4.430; SE:1.274; ExpB:83.953 ; CI:6.909-1020.064 $p<0.01$;); by 15 times in Kyrgyzstan (B: 2.767, SE:1.123; ExpB:15.905; CI:1.759-143.791, $p<0.05$;); 128 times in Tajikistan (B4.854;SE:1.798; ExpB:128.246; CI:3.782-4348.269, $p<0.01$;).

Mortality rates under the circumstances of considered predictor variables (odds ratios) were evaluated by logistic regression analysis. According to obtained results, age decreased mortality rate by 1.16 times (B:-0.149; SE: 0.060; ExpB: 0.862; CI: 0.767-0.969, $p<0.001$), whereas, male gender decreased mortality by 47.6 times significantly ($p<0.001$; B-3.849; SE: 1.337; ExpB: 0.021; CI: 0.002-0.293). Years of transplantation were not found as strong factors. Oppositely, when countries compared, Pakistan ($p<0.01$); Kyrgyzstan ($p<0.01$) and Tajikistan ($p<0.01$), presented with 670; 175 and 1494-fold increase in mortality.

Discussion

Currently, renal transplantation is preferred over hemodialysis as a treatment option for renal failure due to high positive outcomes in terms of survival (3, 4). Hence, intensive studies are continuing on renal transplantation practices and factors affecting survival after transplantation.

Not only preoperative and postoperative medical predictors, but donors, operating centers and countries, age, gender, ethnical and other factors also included in these studies (2, 11-16).

If we mention about impact of sex and age on survival, despite the insignificant results of Kaplan-Meier analysis, both Cox regression and logistic regression analyses identified them as statistically strong factors in our research. Compared to Neri's study, where mortality increased by over 60 years old (15), mortality in our study was not observed in 17 patients elder the 60 years. The high mortality frequency was registered as 11 patients (68.75%) in 28-39 age group. This result is similar to the study on survival after transplantation in Canada and United States (2). Both Cox and logistic regression tests revealed strong association of decreased of mortality rate

and male gender. Nevertheless, according to Nyberg and associates, gender did not implied effective role on mortality (14). Contrarily, Chen et al. stated the significant difference of survival in gender comparison (13). This point can be explained by some social grounds rather than medical reasons and it also requires further evidence-based investigations.

In the initial years, if renal transplantation was performed by certain countries, in time, procedure spread to much more countries and medical centers on the background of improved surgeries and positive outcomes. According to some thoughts, expansion of financial aspects of transplantational management is alarming (6).

One of other factors of current problem is the increasing the number of candidates for transplantation regarding to propagation of procedure on the level of countries. Number of patients visiting our clinic is steadily increasing as seen from Table 3. The main purpose of our study directed to analyze the presence of difference in patient loss by transplantation years and operating countries. Where the Kaplan-Meier analysis showed transplantation years as significant factors (Breslow $p<0.05$), both regression tests did not give meaningful results. When the analysis of operating country conducted, both Kaplan-Meier and regression tests demonstrated significant mortality factors in case of three countries (Pakistan, Kyrgyzstan and Tajikistan). The result can be associated with various factors. Thus, it can be explained by versatility of factors on survival of transplanted patients both in preoperative and postoperative periods. Several studies devoted to post-transplant survival comparisons in numerous countries around the world. In a study, survival conditions between the USA and Canada, significant differences were found between the two countries after the first year of transplantation (2). Factors influencing the frequency of mortality in this age group may also be subject for debates. In a study of survival differences of 622 patients at different transplantation centers in different countries in Europe, multivariate analysis between countries and centers showed that the risk of mortality increased four-fold for low to moderate risk patients and 1.6-fold for the medium to high risk group (12). Including the pre-transplantation workup and management, detailed studies are required in order to investigate the patient loss in these countries.

On the other hand, the cumulative survival rate of patients receiving post-transplantation treatment in our center is high at 1 and 5 years, considering survival in other countries (16).

Conclusion

To sum up, despite the high frequency of mortality, which is considered due to preoperative and intraoperative issues, Kyrgyzstan is presented by high survival rate for 10 years by 92.8% in posttransplanted patients. In this case, it may be effective management for the patients to return our center after the transplantation where they underwent, as well as the dynamic follow-up in well-being natural conditions. This point must be approved by evidence. Notwithstanding, mortality challenges in aforementioned countries necessitates further investigations of procedural facilities and methods to find out exact factors.

Conflict of interest: None to declare

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