



SURVIVAL ON PHARMACOTHERAPY ANALYSIS FOR PATIENTS AFTER KIDNEY TRANSPLANTATION

Svetla St. Georgieva^{1*}, Konstantin V. Mitov², Maria N. Dimitrova², Guenkal. Petrova²

¹Medical University of Sofia, University Hospital "Alexandrovska", Sofia, Bulgaria.

²Medical University of Sofia, Faculty of Pharmacy, Sofia, Bulgaria.

*Corresponding author's E-mail: svetla.georgieva@gmail.com

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ABSTRACT

The aim of the study is to explore the survival time on pharmacotherapy after kidney transplantation. It is a prospective analysis of the time on pharmacotherapy of kidney transplant patients receiving its immunosuppressive medicines from the University hospital during the period 2006 – 2011. The point of view is that of the hospital pharmacy. On total 411 patients were included in the study which took their medicines at least for one year. By using the Kaplan Myers survival analytic technic was calculated the survival probability and number of patients on risk. Logrank regression and Chi-square analyses were also used to explore the relation among the survival and patients' age group, place of transplantation, and development of cytomegalovirus (CMV) infections. The maximal survival time is 6 years corresponding to the length of the observed period. No statistical significance was found among different age groups. There is a statistically significant difference among the survival on pharmacotherapy for patients transplanted in Europe and Asia ($p=0.0233$). There is a statistically significant difference among the survival in groups with and without CMV infection ($p = 0,0004$). The hazard ratio is 2,0354 (CI 1,3779 -3,0066) which means that the risk for drop out from the sample is twice higher in the group with CMV infection than without. For the general population the risk will be among 1,3779 and 3,0066 higher in the group with CMV infection. Measurement of the survival on pharmacotherapy provides evidences about the risks for regular medicines uptake for kidney transplant patients.

Keywords: Kidney transplantation, pharmacotherapy, survival analysis, hospital pharmacy.

INTRODUCTION

Survival is a long term health care result and main health care goal. For transplanted patients the survival is crucial for the graft and their own life. Kidney transplantation is considered to be the optimal treatment option for chronic kidney disease¹. The major health results of the transplantation are the increase in survival, improvement in the quality of life when compared to dialysis^{2,3}. These benefits have been demonstrated for all patients suffering from chronic kidney diseases, regardless of their age⁴.

The standard therapeutic approach after kidney transplantation is the intensive immunosuppressive pharmacotherapy⁵. Immunosuppressive therapy includes calcineur inihibitor (CI), or cyclosporin, or tacrolimus (sirolimus), combined with at least one more medicine and it is aimed at increasing the graft survival time by suppressing the rejection of the organ^{6,7}. Therefore the pharmacotherapy plays crucial role in the survival process. Variety of other factor affecting the graft and patients survival has been explored in different settings, but the pharmacotherapy and its relation to survival remains relatively unexplored⁸⁻¹³.

The aim of the study is to explore the survival time on pharmacotherapy after kidney transplantation.

Basic study questions posed in the study are:

1. What is the survival time on pharmacotherapy?
2. Which factors influence the survival time on pharmacotherapy?

MATERIALS AND METHODS

This study is a prospective analysis of the time on pharmacotherapy of kidney transplant patients receiving its immunosuppressive medicines from the University hospital "Alexandrovska" in Sofia during the period 2006 – 2011. The point of view is that of the hospital pharmacy. On total 411 patients were included in the study which took their medicines at least for one year.

Patients' medication records were reviewed and information about the medicines intake was collected, as well as for other patients' characteristics.

For the purposes of this study as "survival time on pharmacotherapy" was considered the time when the patients regularly receive their medicines from the hospital pharmacy during the observed period. The system of medicines supply and reimbursement for transplant patients in the country is organized on a regional basis and patients could take their medicines only from their specific hospital pharmacy. Thus if the patients do not take their medicines for more than 1 years period it means that they do not need them, either because of the graft rejection or death of the patient.

By using the Kaplan Myers survival analytic technic was calculated the survival probability and number of patients on risk. Logrank regression and Chi-square analyses were also used to explore the relation among the survival and patients' age group, place of transplantation, and development of cytomegalovirus (CMV) infections.



All calculations were done through statistical package STATMAT.

RESULTS AND DISCUSSION

Survival time on pharmacotherapy differs for different patients' age groups - Table 1.

Table 1: Difference in the survival time among patients' age groups

Indicator	Comparison of age group to 30 vs 30-60 years			
Sample size	to 30 years n = 44		30-60 years n = 270	
Survival time	Survival proportion	Standard error	Survival Proportion	Standard error
2	0.955	0.0314	0.952	0.0130
3	0.886	0.0478	0.907	0.0176
4	0.841	0.0551	0.856	0.0214
5	-	-	0.819	0.0235
6	0.773	0.0632	0.737	0.0268
Comparison of the survival curves (Logrank test)				
Endpoint (n)	10		71	
Expected number	11,4		69,6	
Chi-square	0.2050			
Degree of freedom (DF)	1			
Significance (p)	p = 0,6507			
Hazard ratio (95% CI)	0,8612 (CI 0,4510 - 1,6445)			
Comparison of age group 30-60 years vs up to 60 years				
Sample size	30-60 years n = 270		Up to 60 years n = 97	
Survival time	Survival Proportion	Standard error	Survival Proportion	Standard error
2	0.952	0.0130	0.918	0.0279
3	0.907	0.0176	0.856	0.0357
4	0.856	0.0214	0.814	0.0395
5	0.819	0.0235	0.773	0.0425
6	0.737	0.0268	0.648	0.0484
Comparison of the survival curves (Logrank test)				
Endpoint (n)	71		34	
Expected number	78,1		26,9	
Chi-square	2.6944			
Degree of freedom (DF)	1			
Significance (p)	p = 0,1007			
Hazard ratio (95% CI)	0,6835 (CI 0,4340 - 1,0766)			
Comparison of age group to 30 years vs up to 60 years				
Sample size	to 30 years n = 44		Up to 60 years n = 97	
Survival time	Survival proportion	Standard error	Survival proportion	Standard error
2	0.955	0.0314	0.918	0.0279
3	0.886	0.0478	0.856	0.0357
4	0.841	0.0551	0.814	0.0395
5	-	-	0.773	0.0425
6	0.773	0.0632	0.648	0.0484
Comparison of the survival curves (Logrank test)				
Endpoint (n)	10		34	
Expected number	14,2		29,8	
Chi-square	1.9520			
Degree of freedom (DF)	1			
Significance (p)	p =0,1624			
Hazard ratio (95% CI)	0,6251 (CI 0,3234 - 1,2083)			

The maximal survival time is 6 years corresponding to the length of the observed period. Survival proportion on table 1 provides information about the probability to survive on pharmacotherapy and is similar among compared age groups of patients. The lack of statistical significance is also proved with the chi square method where $p > 0.05$.

Figure 1, 2, and 3 provide graphical view of Kaplan Myer curves comparing age subgroups of patients from Table 1.

It also gives information about the number of patients at risk of discontinuation of therapy in every paired groups for the observed period.

Out of all 411 patients, for 333 was available information about the place of transplantation. 178 patients were transplanted in Bulgaria, 64 in other European Countries, and 91 in Asian countries. Based on this, the relation among the survival on pharmacotherapy and continent of transplantation was explored (Table 2, 3; Figure 4).



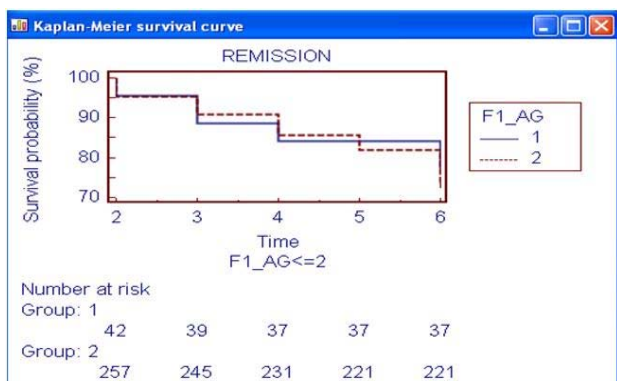


Figure 1: Survival curve for age group to 30 (1) vs 30-60 (2) years

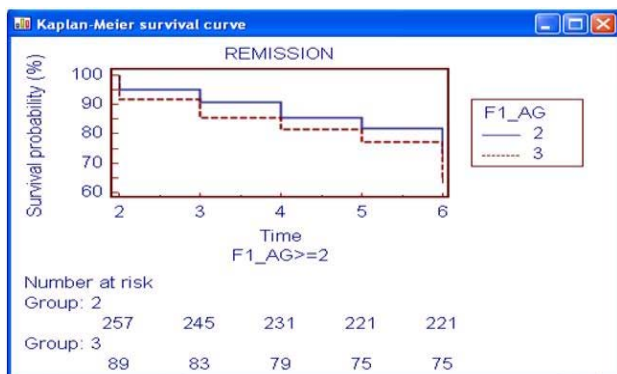


Figure 2: Survival curve for age group 30-60 (2) years vs up to 60 years (3)

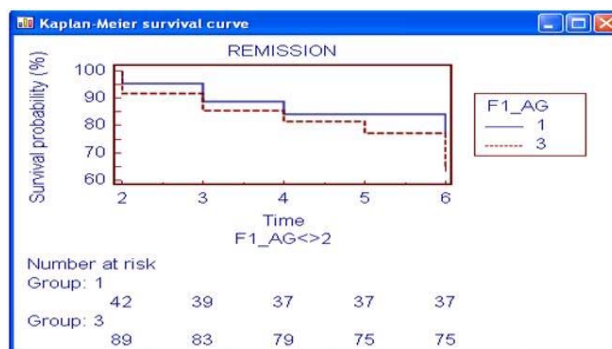


Figure 3: Survival curve for age to 30 (1) years vs up 30-60 years (3)

Graphical view of the survival probability for patients transplanted in Bulgaria vs those of Asia is shown on Figure 4. There is a statistically significant difference among the survival on pharmacotherapy for patients transplanted in Bulgaria and Asia ($p=0.0233$). For the patients transplanted in Asia the survival probability decrease permanently, while for Bulgaria remain quite stable – Figure 4.

In contrast there is no statistically significant differences among the survival of patients transplanted in Bulgaria vs those in other European countries ($p=0.1101$) - Table 3.

The survival among countries was also compared and it was found that only for patients transplanted in Pakistan the survival time is statistically significantly lower than for patients transplanted in Bulgaria. The risk for drop out the pharmacotherapy is 30% higher for transplanted in Pakistan than in Bulgaria.

Table 2: Difference in the survival time among patients transplanted in Bulgaria vs Asia

Sample size	Transplanted in Bulgaria vs Asia			
	Bulgarian = 178		Asian = 91	
Survival time	Survival proportion	Standard error	Survival proportion	Standard error
2	-	-	0.989	0.0109
3	0.994	0.0056	0.978	0.0154
4	-	-	0.967	0.0187
6	0.916	0.0208	0.824	0.0399
Comparison of the survival curves (Logrank test)				
Endpoint (n)	15		16	
Expected number	20,7		10,3	
Chi-square	5.1464			
DF	1			
Significance	$p = 0,0233$			
Hazard ratio (95% CI)	0,4047 (CI 0,1852 - 0,8842)			

Table 3: Difference in the survival time among patients transplanted in Bulgaria vs other European countries

Sample size	Transplanted in Bulgaria vs other European countries			
	Bulgarian = 178		Other European countries n = 64	
Survival time	Survival proportion	Standard error	Survival proportion	Standard error
3	0.994	0.0056	-	-
6	0.916	0.0208	0.844	0.0454
Comparison of the survival curves (Logrank test)				
Endpoint (n)	15		10	
Expected number	18,4		6,6	
Chi-square	2.5534			
DF	1			
Significance	$p = 0,1101$			
Hazard ratio (95% CI)	0,4679 (CI 0,1843 - 1,1878)			



Table 4: Comparison among survival for patients with and without CMV infections

Sample size	Survival time for patients with and without CMV infection			
	Without infection n = 267		With infection n = 144	
Survival time	Survival proportion	Standard error	Survival proportion	Standard error
2	0.918	0.0166	0.993	0.00692
3	0.839	0.0225	0.993	0.00692
4	0.783	0.0252	0.958	0.0167
5	0.749	0.0265	0.924	0.0221
6	0.667	0.0288	0.819	0.0321
Comparison of the survival curves (Logrank test)				
Endpoint (n)		89		26.0
Expected number		71,1		43,9
Chi-square		12.7469		
DF		1		
Significance		p = 0,0004		
Hazard ratio (95% CI)				2,0354 (CI 1,3779 - 3,0066)

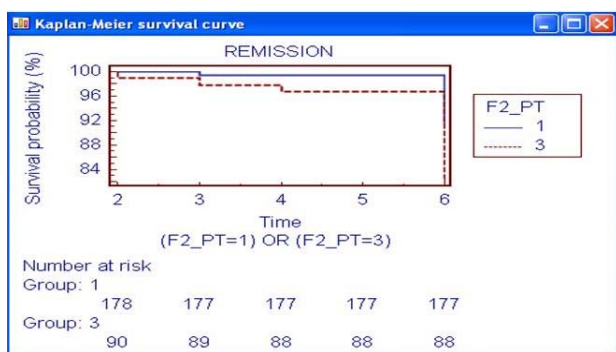


Figure 4: Graphical view of the survival on pharmacotherapy for patients transplanted in Bulgaria (1) vs Asia (3)

The last explored factor was the appearance of cytomegalovirus (CMV) infection and its influence on the survival. For those patients that develop CMV infection is included gancyclovir in addition to the standard pharmacotherapy. During the studied period 144 patients develop CMV infections and were treated with antiretroviral products - Table 4.

There is a statistically significant difference among the survival in both groups ($p = 0,0004$). The hazard ratio is 2,0354 (CI 1,3779 -3,0066) which means that the risk for drop out from the sample is twice higher in the group with CMV infection than without (Table 4, Figure 5). For the general population the risk will be among 1,3779 and 3,0066 higher in the group with CMV infection.

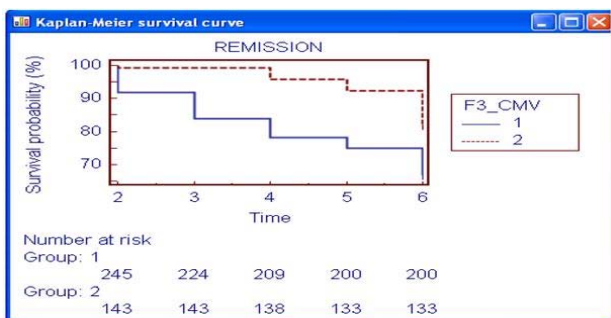


Figure 5: Differences in the survival on pharmacotherapy for patients with (2) and without (1) CMV infection

To our knowledge this is the first survival analysis based on information about the regular medicines uptake. It provides important evidences for the hospital pharmacy for patients that are at risk to drop out from pharmacotherapy, as well as for factors influencing the process.

Survival of graft is critical during the first 3 years after transplantation a fact that was also proved by our study⁴.

We also confirm other studies for the importance of CMV infection and pharmacotherapy, as well as survival time^{9, 13}. In addition we found that this factor appears connected with the geographic region and even with the country where transplantation was made. Such a difference could be explained with approved medical standards and transplantation procedures in the regions.

In spite of the fact that the observed period was of only 6 years, the data received is reliable and could be used from the hospital for budget allocation of medicines. It could also be used for patients' safety evaluation as a new and very important role of the hospital pharmacist¹⁴.

CONCLUSION

Measurement of the survival on pharmacotherapy provides evidences about the risks for regular medicines uptake and patient safety for kidney transplant individuals.

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