An Assessment of the Transplant's Survival Level for Recipients after Kidney Transplantations using Cox Proportional-Hazards Model

Yaroslav Tolstyak[a,b], Myroslav Havryliuk[c]

[a] *Department of Clinical Immunology and Allergology, Danylo Halytsky Lviv National Medical University, Pekarska str., 69, Lviv, 79010, Ukraine*
[b] *Lviv Regional Clinical Hospital, Chernihivska str., 7, Lviv, 79010, Ukraine*
[c] *Department of Artificial Intelligence, Lviv Polytechnic National University, S. Bandera str., 12, Lviv, 79013, Ukraine*

Abstract

On the basis of the preliminary analysis, a simulation of graft survival in recipients is carried out 3 years after kidney transplantation to find the most significant factors that non-randomly affect the probability of graft survival after kidney transplantation. A semiparametric Cox proportional hazards regression model was constructed to estimate the survival of a functioning graft. It was shown that the risk of rejection in the group of recipients with changes in key hematological and immunological indicators is more aggressive and prognostically unfavorable. It has been proven that the most significant signs ($p<0.001$) include four signs: the number of HLA-antigen mixmatches before kidney transplantation, the concentration of creatinine and leukocytes in the blood, as well as the level of proteins in the urine after kidney transplantation. The possibility of further use of the obtained model for predicting the survival of recipients 3 years after transplantation is indicated.

Keywords 1

Cox regression, HLA-antigens, creatinine, blood leukocytes, proteins in urine, transplant survival analysis

1. Introduction

In recent years, there has been an increase in the frequency of kidney transplants in Ukraine. Sometimes two or more transplants of organs originating from the same cadaver donor are performed. Thus, in Ukraine, the interval between the first and second kidney transplantation is, on average, 11 to 20 years [1]. Modeling the nature of the recipients' survival required a preliminary assessment of their survival, taking into account the presence of hematological and immunological risk factors in the recipients.

There are different methods of assessing graft survival and functioning, as there is no single universal method of graft prediction. Currently, four different methods of survival prediction are used in statistics, each of which has its own tasks. The most common method that allows us to empirically estimate the probability of surviving a separate time survival function is the Kaplan-Meier method [2]. With the help of this method, the results of which are presented in our previous work [3], in the group of recipients 30 days after transplantation, it was determined that in the perioperative period, survival after kidney transplantation is influenced by 6 indicators, first of all, the absence of the previous hemodialysis, high leukocytosis, urea and creatinine in the blood, proteinuria, and erythrocyturia in the urine. Another method that allows you to estimate the cumulative risk function is the Nelson-Aalen

IDDM-2022: 5th International Conference on Informatics & Data-Driven Medicine, November 18–20, 2022, Lyon, France
EMAIL: tolstyakyaroslav@gmail.com (A. 1); myroslav.a.havryliuk@lpnu.ua (A. 2)
ORCID: tolstyakyaroslav@gmail.com (A. 1); myroslav.a.havryliuk@lpnu.ua (A. 2)
ORCID: 0000-0002-5990-5977 (A. 1); 0000-0001 -5259-7564 (A. 2)

method [4]. These two methods do not require additional information in the form of a survival function, but the errors allow us to estimate the effect on graft survival. Only one category of predictors not being able to correct for covariates and based on the assumption of non-informativeness. The use of these methods in conditions of competing risks gives a premature estimate of survival [5]. The most common method of survival analysis in the presence of competing risks is the cause-specific Cox proportional hazards model [6].

This method is used when the purpose of the research is to study the cause-and-effect relationships of various factors and determined consequences. However, it is necessary to correctly analyze the results of such forecasting. The Cox method allows for estimating the risk of a specific event among patients who lived to the corresponding moment and were not exposed to any of the competing events. Since competing events are censored, it is impossible to directly assess the influence of covariates on their frequency of occurrence [7]. An alternative model for the Cox index can be the model of competing risks of Fine and Gray – a study of the probability of a certain outcome [8]. This method models the influence of covariates on the cumulative incidence function and can be applied when the goal of the study is not to study etiological associations but to evaluate each probability from possible competing events. Therefore, the question arose regarding the possibility of modeling the survival of recipients, in the time period from 0 to 3 years after transplantation, by the Cox proportional hazards model, based on the search for the most significant factors that non-randomly affect the probability of survival of recipients with multiple risk factors with the aim of further use of this model, and possibly an alternative model of Fine and Gray, for predicting survival in a certain feature space. The main objective of this study is to use the Cox proportional hazards regression model to independently confirm the key risk factors associated with early transplant rejection (during the period from 0 to 5 years after transplantation) according to changes in the blood concentration of the main hematological and immunological indicators before and after transplantation.

2. State-of-the-arts

Cox's risk prediction model for predicting mortality was used in 2021 by a group of Latvian scientists from Riga, who included 68 patients with immunoglobulin A nephropathy in the regression analysis. A moderate degree of correlation between the predicted and observed five-year risk was found ($p=0.001$) due to such factors as gender, tubular atrophy/interstitial fibrosis, and diastolic blood pressure, which affect the survival of the kidney in this pathology [9]. In the Republic of Poland, it was determined that a poor 5-year mortality risk was observed in patients with high levels of interleukin 6 and coronary artery calcification in patients with chronic renal insufficiency [10]. PRA Other scientists from 6 transplantation centers from different cities of the Republic of Poland analyzed the data, which included age, sex, PRA, HLA, number and time of hemodialysis after transplantation, time of cold ischemia and etiology of end-stage renal failure.

The impact of the data that was considered in this study was evaluated at a specific point in time 5, 10, 15 years after transplantation. In this study, statistical methods included Kaplan-Meier univariate and multivariate survival analysis and the Cox proportional hazards model to predict mortality. The authors concluded that elevated PRA in kidney recipients is a risk factor that increases mortality after transplantation [11]. In the U.S.A, in the modern donor kidney distribution system, the regression equation used to calculate the estimated post-transplant survival was analyzed, and it was determined that several terms are represented by the interaction of factors [12]. In contrast to the Kaplan-Meier method, Cox regression models the hazard function rather than survival but can provide an adjusted survival estimate. It is also necessary to take into account that some events may occur earlier and thus mask those events that mainly occur later if the patient drops out of the study after the occurrence of any of the events [13]. In order to avoid losing information about subsequent events, which may also be of some importance, different hierarchical models can be used, which in turn complicates the study [14].

In addition, it should not be forgotten that, in addition to this, that such an approach does not require compliance with the assumption of independence of competing events. It assumes that competing events have a similar nature or genesis and are equivalent in direction and strength of effect [15]. This assumption is sometimes not followed. For example, as a result of a multivariate analysis (Cox

proportional hazards method), which evaluates the relationship between the panel-reactive antibody (PRA) indicator and the composite end point of exit from the waiting list - transplantation or death on the waiting list, it is possible to reach a paradoxical conclusion that high values PRAs are associated with a lower dropout risk [16].it was caused by combining two opposite mutually exclusive events into one composite endpoint. In risk analysis adjusted for competing events, an increase in PRA was associated with an increased risk of death and a decreased risk of being removed from the transplant waiting list. At the same time, the size of the effect on the risk of the second event was significantly larger than on the risk of the first. Perfentseva N.O., Golubova G.V. When modeling the survival of cancer patients, four methods of implementing Cox regression in statistical data processing packages, their advantages and disadvantages are substantiated. Statistical criteria characterizing the suitability of the model are described. The issue of data censoring and the concept of a "critical" event, which is usually understood as the death of a patient, are considered. The existence of a trend is proved, provided that more than 25% of the observations are censored in the studied sample population.

It is noted that deviation residuals, Martingale residuals, and Schoenfeld residuals are not residuals in the classical sense, as in linear regression. Abnormal observations (outliers) are detected by residual deviations [19].

3. Materials and Methods

These recipients received HLA-compatible kidney allografts from donors who were their first- and second-line relatives in Ukraine and unrelated cadaveric organs abroad (Poland, Belarus, and others). Among the 152 recipients, there were 64 (42.1%) female recipients and 88 (57.9%) male recipients with a mean age of 32.6 ± 8.7 years (the minimum-maximum age range was 18–60 years) at the time of kidney transplantation. From this group of patients, within 3 years, 107 (70.4%) patients remained with a functioning transplant. To model the prediction of the loss of kidney transplant function in recipients from 0 to 3 years after kidney transplantation, we used the semi-parametric Cox regression model [6], in which "hazard" is considered as a risk calculation as a time-dependent function.

The main advantage of this model is that it allows working with categorical and censored data. In general, the model can be presented in the following form: where $h(t)$ is the risk function determined by a set of k factors $x_1, x_2, ..., x_k$; t – survival time; $b_1, b_2, ..., b_k$ – coefficients determining the influence of $x_1, x_2, \ldots, x_k$ respectively; h_0 is the basic risk. For the general characteristics of survival, 152 recipients who received special treatment in the department of nephrology and dialysis of the ENT hospital "Lviv Regional Clinical Hospital" from 1992 to December 2020 within the framework of a retrospective controlled open study on the selection criteria of acute rejection were included in the sample base.

The collected data included information on basic clinical and laboratory parameters and methods of immunosuppressive therapy in these recipients 30 days after kidney transplantation. The clinical and laboratory data evaluation results are described in our previous work [2]. For modeling, after an in-depth analysis, it was decided to build Cox regression using the forward method. Its essence is that the inclusion of factors in the model starts with a smaller number of effects and step by step goes to a larger number with the possibility of only adding effects to the model at each iteration, in contrast to the stepwise method, which involves adding and removing effects from the model at each iteration.

As for the backward method, the first step is to process all the effects, and then it starts removing the effects from the model step by step. If an effect is removed at any step, it is no longer added to the model at any other step. Cox regression is designed to work with censored data. The standard data model was built in Excel, and the analytical data model was built in the SAS 9.4 software environment. All calculations were also done in the SAS 9.4 software environment.

4. Results and Discussion

According to Cox's proportional hazards regression analysis results, only four factors associated with loss of graft function in recipients after kidney transplantation were found out of 66 research indicators. When building a forecasting model of a semi-parametric Cox proportional hazards

regression model. The result was considered positive if the patient lived with a satisfactorily functioning kidney transplant for more than 3 years (Fig. 1)

The result was considered negative in case of loss of function of the transplant and return of the patient to hemodialysis treatment or in case of death of the patient (Fig. 2). In order to identify the factors associated with the reliable cessation of graft functioning, a mathematical selection of the most significant signs was carried out [20-22]. It was found that the most significant signs ($p<0.001$) include four signs: the number of HLA-antigen mixmatches before kidney transplantation, the concentration of creatinine and leukocytes in the blood, as well as the level of proteins in the urine after kidney transplantation. A Cox proportional hazards regression model was built on the selected set of features.

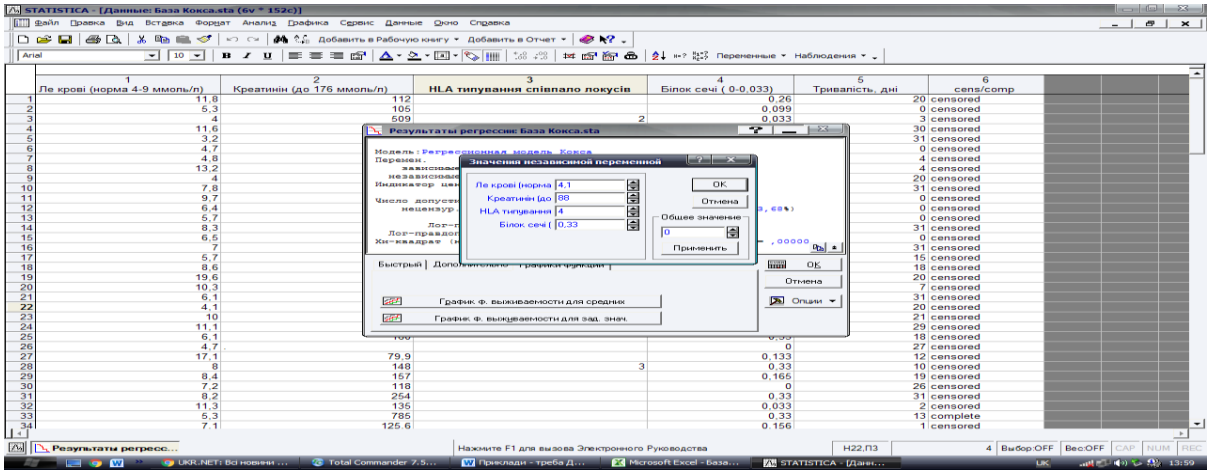

Figure 1: Patient R., based on these indicators, the line does not go down (not shown in the picture), which indicates a good prognosis for the transplant.

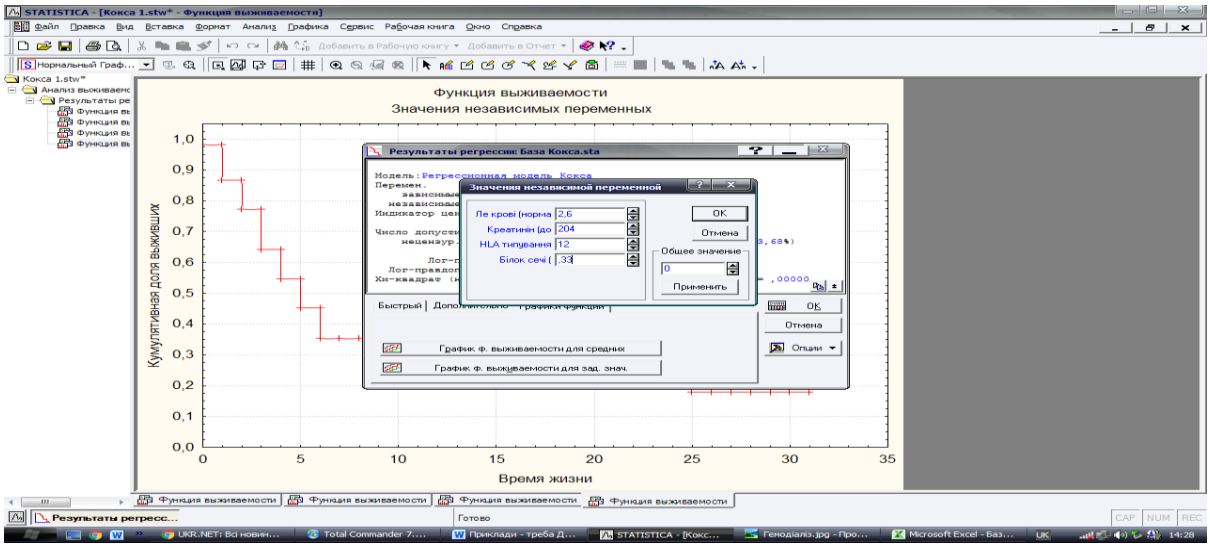

Figure 2: Patient R., the line descends, which indicates the danger of acute transplant rejection.

As a result, it has been proven that the developed Cox regression model for the general sample makes sense and can be used to predict transplant survival in recipients after kidney transplantation based on the presence of immunological or biochemical changes in indicators. A semi-parametric Cox proportional hazards regression model considers "hazard" as a risk calculation as a time-dependent function. It models the impact of predictors on the hazard level, taking into account the observation period, and allows for incomplete (censored) observations. The risk function describes the instantaneous probability of an event for subjects who are still prone to risk [23]. Similar results were obtained by other authors from Ukraine who studied patients with CKD of the 5th stage who are treated

with hemodialysis. According to the results of univariate Cox regression analysis, they found that high prognostic values of the Hazard Ratio are an independent predictor of the occurrence of new cardiovascular events, being older than 35 years, current/previous asymptomatic nasal carriage of methicillin-resistant Staphylococcus aureus (MRSA) and initial vascular access type of anastomosis [24, 25].

5. Conclusions

In this article, it is determined that this mathematical model for predicting the loss of kidney transplant function was obtained as a result of an examination of 152 patients who were in the perioperative period (30 days after kidney transplantation). When building a prediction model, the result was considered positive if the patient lived with a satisfactorily functioning kidney transplant for more than 3 years. The result was considered negative in case of loss of function of the graft and return of the patient to hemodialysis treatment or in case of death of the patient. In order to identify the factors associated with the reliable cessation of graft functioning, a mathematical selection of the most significant signs was carried out. It was found that the most significant signs ($p<0.001$) include four signs: the number of HLA-antigen mixmatches before kidney transplantation, the concentration of creatinine and leukocytes in the blood, as well as the level of proteins in the urine after kidney transplantation. A Cox proportional hazards regression model was built on the selected set of features.

Thus, on the basis of these data in the blood, it is possible to predict the first signs of possible transplant rejection by performing these tests. Our study shows a strong correlation between groups of recipients who are at risk of rejection versus those who are not. Therefore, to improve the quality of the prediction model, it is necessary to use different versions of the Cox model or an alternative model of Fein and Gray. Also, the future research will be based on the using machine learning model for solving the stated task [26, 27].

6. References

[1] Chopyak V.V., et. al. Modern transplantology: immunodiagnostics and immunotherapy. - Lviv: "NeoDruk" Publishing House — 2020. -122 p.

[2] Kaplan E.L., Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53(282):457-481

[3] Y Tolstyak ej. al. “The Ensembles of Machine Learning Methods for Survival Predicting after Kidney Transplantation”, Applied Sciences. 2021; 11(21): 10380. https:doi.org/10.3390/ app112110380

[4] Hobbs B.P. On nonparametric hazard estimation. J Biom Biostat. 2015;6. pii: 232. DOI: 10.4172/2155-6180.1000232

[5] Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks.Circulation. 2016; 133(6):601-9. DOI: 10.1161/CIRCULATIONAHA.115.017719

[6] Cox D.R. Regression Models and Life-Tables. Journal of the Royal Statistical Society, Series B. 1972; 34(2): 187-220

[7] Sedgwick P., Joekes K. Interpreting hazard ratios. BMJ. 2015;351:h4631 DOI: 10.1136/bmj.h4631

[8] Andersen P.K., et al. Competingrisks in epidemiology: possibilities and pitfalls. Int J Epidemiol. 2012 Jun;41(3):861-70. DOI: 10.1093/ije/dyr213

[9] Saulite J.A., et al. Renal Survival and validation of Novel international Imunoglobulin A nephropaty prediction tool in Latvian population: pleminary data. Proceceding of the Latvian Academy of Sciences. Section B. 2021; Vol 75. №734. pp. 379-386.

[10] Kaminska J., et al. IL6 but not TNF is linked to coronary artery calcification in patients with chronic kidney disease. Cytokine. 2019. Aug 120. p 9-14. doi; 10.1016 /j.cyto.2019.04.002.

[11] Kaczmarchyk M., et al. Effect of recipient sensitization (peak panel reactive antibodies) on 15-year survival after kindey transplantation. Transplant Proc. 2014: 46(8) 2699-702. doi: 10.1016/j.transprocced.2014.08.021

[12] OPTN.transplant.hrsa.gov [Internet]. OPTN policies (lastupdated 10/01/2019). 2019. Available at: https://optn.transplant. hrsa.gov/media/1200/optn_policies.pdf
[13] Srinivas T.R., et al. Post hoc analyses: after the facts. Transplantation. 2015;99(1):17-20. DOI: 10.1097/TP.0000000000000581
[14] Dong G., et al. A generalized analyticsolution to the win ratio to analyze a composite endpoint considering the clinical importance order among components. Pharm Stat. 2016;15(5):430-7. DOI: 10.1002/pst.1763
[15] Rauch G., et al. Opportunities andchallenges of clinical trials in cardiology using composite primary endpoints. World J Cardiol. 2015; 7(1):1-5. DOI: 10.4330/wjc. v7.i1.1
[16] Sapir-Pichhadze R., et al. Survival Analysis in the Presence of Competing Risks: The Example of Waitlisted Kidney Transplant Candidates. Am J Transplant. 2016 Jul;16(7):1958-66. DOI: 10.1111/ajt.13717
[17] Chopra B., Sureshkumar K.K. Changing organ allocation policy for kidney transplantation in the United States. World J Transplant. 2015; 5(2):38-43. DOI: 10.5500/wjt.v5.i2.38
[18] Hahn A.B., et al. The newkidney allocation system does not equally advantage all very high cPRA candidates – A single center analysis. Hum Immunol. 2017; 78(1):37-40. DOI: 10.1016/j.humimm.2016.10.010
[19] Parfentseva, N. and Holubova, H., "Survival modeling of cancer patients based on cox regression: applied aspects", Ekonomika ta derzhava, 2022, vol. 3, pp. 15–21. DOI: 10.32702/2306-6806.2022.3.15
[20] Berezsky, O., Datsko, T. & Verbovyy, S. “The intelligent system for diagnosing breast cancers based on image analysis”. Proceedings of Information Technologies in Innovation Business (ITIB). Kharkiv: Ukraine. 7-9 October, 2015. p. 27–30. DOI: https://doi.org/10.1109/ITIB.2015.7355067.
[21] O. Berezsky, et. al., "Segmentation of cytological and histological images of breast cancer cells," *2015 IEEE 8th International Conference on IDAACS*, 2015, pp. 287-292, doi: 10.1109/IDAACS.2015.7340745.
[22] Berezsky O. M., e. al., “Design of computer systems for biomedical image analysis”. *Proceedings of the Xth International Conference CADSM 2009, 24-28 February 2009, Lviv-Polyana, Ukraine.* Lviv: Publishing House Vezha&CoC., pp. 186-191.
[23] Zulkarnaev A.B. Features of survival analysis on patients on the waiting list for kidney transplantation. Bullettin of Siberian Medicine. 2019; 18(2) 215-222. http: doi.org.10.20538/1682-0363-2019-2-215-222
[24] Shifris I.M., at. al., “Predictors of cardiovascular disease in patients with chronic kidney disease VD stage treated with hemodialysis”, Medicni perspektivi. 2021;26(2):59-66 https://doi.org/10.26641/2307-0404.2021.2.234513
[25] Babichev, S., Škvor, J. Technique of Gene Expression Profiles Extraction Based on the Complex Use of Clustering and Classification Methods (2020) Diagnostics, 10 (8), art. no. 584
[26] Dmytro Peleshko, Taras Rak, Ivan Izonin, "Image superresolution via divergence matrix and automatic detection of crossover", IJISA, Vol.8, No.12, pp. 1-8, 2016. DOI: 10.5815/ijisa.2016.12.01
[27] Ivan Izonin, et. al., "The Combined Use of the Wiener Polynomial and SVM for Material Classification Task in Medical Implants Production", IJISA, Vol.10, No.9, pp.40-47, 2018. DOI: 10.5815/ijisa.2018.09.05