A STUDY OF SURVIVAL MODELLING IN DIALYSIS PATIENTS APPLYING DIFFERENT STATISTICAL TOOLS[1]

Diana-Silvia ZILISTEANU
MD, PhD, Assistant Professor,
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

E-mail: diana@nefrolog.ro

Ion Radu ZILISTEANU
PhD, Bucharest University of Economic Studies, Romania

Mihai VOICULESCU
MD, PhD, Professor,
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Abstract:
The aim of this study is to develop a model for survival probabilities of incident dialysis patients based on demographic, clinical and biological characteristics. We used statistical methods, mainly Cox regression, and 2 statistical tools: SPSS version 21 and Excel. During the first stage, data were analysed using SPSS software, edition 21. We performed survival analysis using Cox proportional hazard regression test, to assess the relationship of explanatory variables with survival time. Second stage of analysis was performed using Excel computations based on the results provided by Cox analysis. Starting from the basal risk curve, and applying the coefficients derived from the Cox regression analysis, the hazard curve was calculated for any combination of values for the variables included in the equation. Based on these elements, we constructed an Excel model for survival simulation.

Key words: statistics, SPSS, survival analysis, Cox proportional hazard regression, mathematical model

1. Introduction

Utility of mathematical algorithms applied for assessing the risk of future negative health outcomes emerged from the Framingham Risk Score, which was first developed based on data obtained from the Framingham Heart Study in order to estimate the 10-year risk of developing coronary heart disease. Because risk scores give an indication of the likely benefits of prevention, they are useful for both the individual patient and for the clinician in

helping decide whether lifestyle modification and preventive medical treatment, and for patient education.

Morbidity and mortality in patients with chronic kidney disease included in the replacement of renal function program is influenced by a number of factors related both to the patient (age, sex, renal disease and comorbidities) and the "quantity and quality" of nephrological care in the predialysis period. O'Hare et all (2005) describe the impact of age on the mortality risk in chronic renal failure.

1.1. Working hypothesis

The aim of this study is to develop a model that can estimate the probability of survival of incident dialysis patients based on demographic, clinical and biological characteristics recorded at the time of dialysis initiation. Upon this model, we can make recommendations for optimization and planning care for a patient with chronic renal failure before and after inclusion in chronic dialysis.

The working hypothesis of the study is that late referral to the nephrologist adversely affect the survival of patients with chronic kidney disease included in the dialysis program. In this paper, we propose to assess the impact that can be attributed to nephrology referral on mortality in incident dialysis patients, analyzing the effect of this factor, controlling for other factors that may influence survival of these patients.

1.2. Material and method

Patients with chronic kidney disease, hospitalized in Nephrology Department, Fundeni Clinical Institute, aged over 18 years, incident in the dialysis program between January 1st, 2007 and July 1st, 2012, were included in this analysis. Follow-up period ended on September 1st, 2014. The main indicator of the evolution of patients was survival from the time of inclusion in the dialysis program.

For the study patients, we recorded the following data:

- Demographical data: date of birth, gender, age at initiation of dialysis;
- Etiology of renal disease: hypertensive nephropathy, diabetic nephropathy, tubulo-interstitial nephropathy, primitive or secondary glomerular disease, genetic diseases (including autosomal dominant polycystic disease, Alport syndrome), systemic vasculitis (systemic lupus erythematosus, ANCA vasculitis, Henoch Schonlein etc), multiple myeloma or amyloidosis; cases where etiology was unknown were also recorded;
- Type of dialysis (hemodialysis or peritoneal dialysis) and access method used for renal replacement (central venous or arteriovenous fistula for hemodialysis or peritoneal dialysis catheter);
- Nephrology monitoring interval in months from the time the patient was evaluated for the first time in a nephrology service until entry into dialysis;
- Clinical manifestations (hyperhydration status, presence of pericarditis, heart failure, arrhythmias, pleural effusion, pulmonary infections, neurological, digestive manifestations, bleeding syndrome);
- Biological parameters recorded at the time of dialysis initiation: glomerular filtration rate estimated using the CKD-EPI formula (ml/min/1.73m2), hemoglobin (g/dL), leucocytes (count/mmc), platelets (count/mmc), sideremia (mcg/dl), serum ferritin (ng/mL), serum sodium (mmol/ L), potassium levels (mmol/L) total serum calcium (mg/dL) serum phosphate

(mg/dL), an intact parathyroid hormone PTH (pg/mL), serum albumin (g/dL), blood pH and serum bicarbonate concentrations (mmol/L).

2. Statistical analysis

The study was performed on a total of 430 patients included in dialysis, hospitalized between January 2007 and July 2012. Survival data were collected until September 2014.

2.1. Identification of survival indicators

During the **first stage**, data were analyzed using SPSS software, edition 21. As shown by Kleinbaum and Klein (2005), we performed survival analysis using Cox proportional hazard regression test, to assess the relationship of explanatory variables to survival time. Cases were considered censored (value status = 0) if the patient was alive or lost to follow-up during the study period, while deceased patients were considered cases that met the study goal (value status = 1), as explained by Sedgwick (2011). We applied a Cox regression sequence using different control variables to identify indicators that significantly affect survival, gradually eliminating the variables for which we did not obtained significant values.

The final model for survival (Table 1) included the following variables that significantly influence survival: age ($p < 0.0001$), heart failure ($p = 0.001$), bleeding syndrome ($p = 0.003$), diagnosis of multiple myeloma / amyloidosis ($p < 0.0001$) serum albumin ($p < 0.0001$). Although we did not obtain statistically significant values for the variable coefficient logarithm-referral logR ($p = 0.252$), we included this variable in the final model in order to shape the effect of the nephrological monitoring on survival of incident dialysis patients.

Table 1. The final Cox regression analysis including the identified variables influencing significantly the survival: age, heart failure, hemorrhagic syndrome, serum albumin, etiology of multiple myeloma/amyloidosis, and length of referral period

Survival indicators	B	SE	Wald	df	Sig.	Exp(B)
Age	0,040	0,007	34,541	1	0,000	1,041
Heart failure	0,647	0,196	10,855	1	0,001	1,910
Hemorrhagic syndrome	0,694	0,230	9,089	1	0,003	2,001
Serum albumin	-0,676	0,158	18,267	1	0,000	0,508
Multiple myeloma/amyloidosis	1,845	0,290	40,569	1	0,000	6,328
logR	-0,061	0,053	1,314	1	0,252	0,941

By applying Cox regression analysis, we developed the basal risk curve, which expresses the probability of death at a certain time for patients who survived until that time. This probability is not constant over time, permanently changing depending on the time the analysis is done. Based on the risk curve, survival curve is calculated directly by the arithmetic operation, which does not require other parameters.

To model mathematically the chances of survival at a certain time, we used the above results obtained by determining statistically significant variables Cox analysis, to create a survival function.

The relationship between the survival curve S(t) and the cumulative hazard curve CumH is exponential, and is given by the ecuation:

$$S(t) = \exp(-CumH)$$

The hazard function h(t) for a given combination of characteristics (values of explanatory variables) is the product of:

- The basic hazard function (the baseline hazard), h0 (t),
- Exponential of linear sum of the products of the values of explanatory variables (x1, x2, ..., xn) and the corresponding coefficients (β_1, β_2, ..., β_n).

Thus, the hazard function becomes:

$$h(t) = h_0(t) \times \exp(\beta_1 x_1 + \beta_2 x_2 + ... + \beta_n x_n)$$

Using SPSS analysis, we determined:

- The basal cumulative hazard curve;
- Coefficients for each explanatory variable, β_1, β_2, ..., β_n.

Based on that information, one can calculate the cumulative curve hazard function and the survival curve for every combination of values of the explanatory variables.

Hazard or survival curves are well estimated by the following type of equations:

$$\hat{h}(t) = a \times t^b \Leftrightarrow \ln(\hat{h}(t)) = \ln(a) + b\ln(t)$$

This is visible when we exemplify the hazard or survival curve through a logarithmic scale chart. In such a graph, a linear relationship between the natural logarithm of the hazard curve, ln(h(t)), natural logarithm of the scale of the time, ln(t) shows the relationship expressed in the equation above.

The use of equations for computing the values on survival curve corresponding to a certain value on time axis and to a certain combination of explicative values, even if introduces some errors towards using the values obtained from data, has the advantage to highlight the main characteristics of survival curve and allows the focus on them, and the visual comparison between curves corresponding to different cathegories of patients are eased by eliminating non-essential variations.

2.2. Development of survival model

Second stage of analysis was performed using Excel computations based on the results provided by Cox analysis.

Using Cox analysis, we identified the following explanatory variables, which are statistically significant:

- X1 = patient age (in years);
- X2 = age of referral to the nephrologist (months x 10);
- X3 = presence of heart failure (categorical variable, which can take values of 0 or 1, signifying the absence or presence of disease);
- X4 = presence of bleeding syndrome (categorical variable, which can take values of 0 or 1, signifying the absence or presence of disease);
- X5 = serum albumin (10 x g / dl);
- X6 = multiple myeloma / amyloidosis (categorical variable, which can take values of 0 or 1, signifying the absence or presence of disease).

Also, the βi coefficients obtaind from Cox regression are:

β1 = 0.040;
β2 = -0.061;
β3 = 0.647;
β4 = 0.694;

β5 = -0.068;
β6 = 1.845.

Empirical survival curves can be described by mathematical functions that are more flexible, because they require knowledge of a small number of parameters; derived mathematical function well approximated survival curve which was empirically obtained (r^2 = 98%) (Figure 1). For this reason, we further applied the mathematical function for building survival curves.

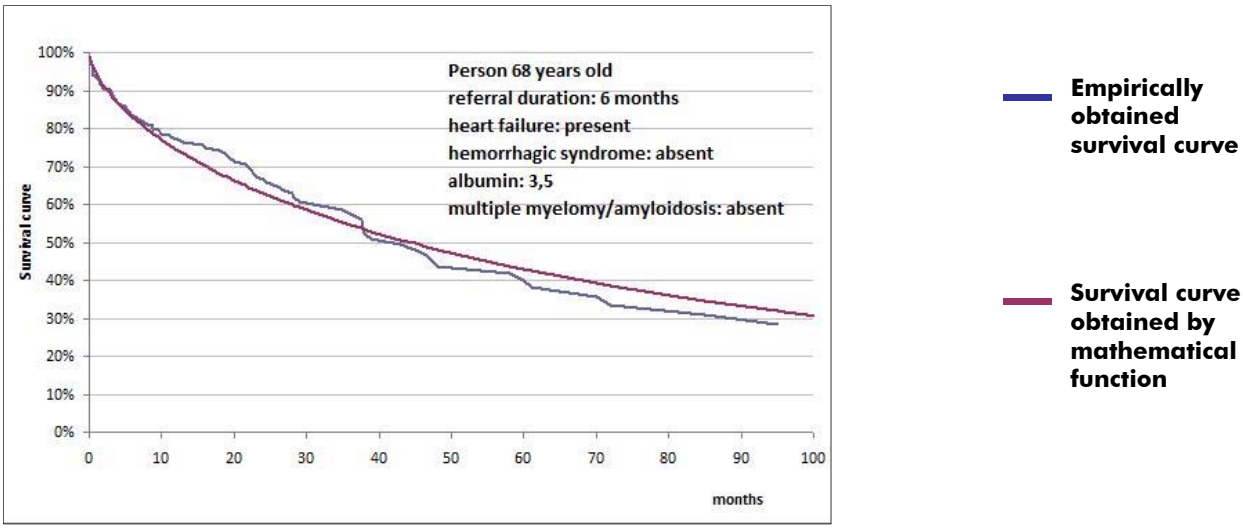

Figure 1. Correspondence between empirically obtained survival curve and curve obtained by the mathematical function

Starting from the basal risk curve, and applying the coefficients derived from the Cox regression analysis, the hazard curve can be calculated for any combination of values for the variables included in the equation.

Based on these elements, we constructed an Excel model for survival calculation (Figure 2), with the following advantages over SPSS output:

- Is more flexible than SPSS output, which can only express the curves for categorical variables, but not modeling for continuous variables;
- Allows a higher resolution analysis of the relationship between survival and variables of interest; thus, can analyze the impact of small changes in clinical and biological indicators on survival.

		coef
age	68	0,040
ln_referral	1,79	-0,061
referral duration (months x 10)	60	
heart failure	1	0,647
hemorrhagic syndrome	0	0,694
serum albumin (x 10)	35	-0,068
multiple myelomy/amyloidosis	0	1,845
survival treshold (months)	12	
survival odds for 12 months	74%	

Figure 2. Excel model for survival estimation

The Excel model for survival estimation allows different simulations based on combinations of values of included variables, even for hypothetical cases that have no counterpart in the database of patients in the study group. Thus, one can choose different values of continuous variables included (age, length of reference, serum albumin level), while selecting various combinations of categorical variables indicating the presence/absence of a diagnosis of multiple myeloma/amyloidosis and of the uremic complications (heart failure, bleeding syndrome).

Based on the selected combinations of values, Excel model estimates the survival chance calculated as a percentage, for a certain survival threshold.

We assessed whether increasing the length of nephrological care before dialysis, by earlier referral, can improve the survival handicap given by the presence of heart failure or bleeding syndrome after initiation of dialysis (Figure 3).

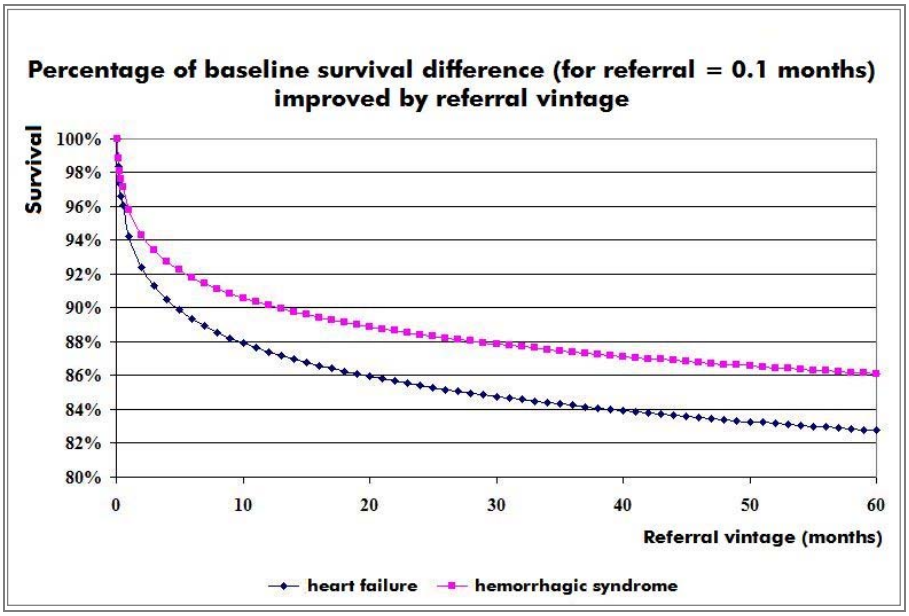

Figure 3. Percentage of initial survival difference between patients who have a certain status (heart failure or hemorrhagic syndrome) versus those without that clinical condition, which can be recovered by earlier referral to nephrologist. It is considered that at baseline (reference length = 0.1 months) there is a survival difference of 100% between the two categories

Considering that, for the referral length of 0.1 months, the difference in survival is 100%, we found the following:

- For patients with heart failure, the difference in survival drops to 94% if was referred at 1 month before dialysis, to 89% for the referral vintage of 6 months, at to 87% for referral of 12 months;
- For patients with bleeding syndrome, the difference in survival drops to 96% for 1 month referral, to 92% for the 6 months referral, and becomes 90% for 12 months referral vintage.

Therefore, we can say that for a patient with heart failure syndrome or bleeding syndrome at the time of initiation of dialysis, his chances of survival improve more so as he was referred earlier to the nephrologist.

3. Discussions and conclusions

The problem of late referral to nephrologist and initiation of renal replacement therapy in the emergency situation is extremely serious, considering that in Romania the number of dialysis patients incident has gradually increased in recent years, exceeding the number of 3000 in 2011 (from 1933 in 2007 to 3161 in 2011), as reported by Romanian Renal Registry. Medical care of these patients requires significant human and material costs, while being associated with a high mortality rate in short, medium and long term, as shown by Van Biesen (1999), Obialo (2005) and Black (2010). This justifies the need for coherent health policies related to chronic kidney disease, as shown by the report published by Levey and colleagues (2009). According to Vassalotti (2010) and McCullough (2011), a successful program has been promoted during the last years in United Stated, proving that a community-based screening approach can address disparities in chronic kidney disease.

This study emerged from the necessity of estimating the risk of future negative health outcomes for patients with chronic kidney disease included in the replacement of renal function program, based on influences by a number of factors related both to the patient (age, sex, renal disease and comorbidities) and the length of nephrological care in the predialysis period. Our results are similar with other of studies in the literature. Thus, Khan et all (2005) showed that consistent nephrology care may be more important than previously thought, especially because the frequency and severity of uremic complications increase as patients approach dialysis. This was supported also by Jones et al (2006), who showed the different decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease.

The mathematical model we developed is based on survival data in our group. Based on this model, we demonstrated that early referral can contribute to the partial recovery of handicap given by the unfavorable profile of a patient. This model we have developed, by estimating the chance of survival in patients enrolled in chronic renal dialysis program, could become a useful tool for scoring the severity of clinical and biological status in chronic renal patients. Future research will focus on expanding the patients' database in order to create a better approximation of survival chances based on cited parameters.

However, the utility of such mathematical model can be extended beyond the study in which was originally designed. This model can be considered a template for further survival analysis in different patients' categories, using diverse indicators and variables. Of great interest to the medical field would be the creation of modular software that can be used independently by each physician as a tool for tailored estimation of the risk score for an individual patient, by applying specific characteristics of each subject.

References

1. **Annual Report 2011 of Romanian Renal Registry**. Ministry of Health - Hospital Nephrology "Dr Carol Davila", Bucharest, Romania, 2012, available at http://www.srnefro.ro/media/RRR.Raport.2011.pdf
2. Black, C., Sharma, P., Scotland, G., McCullough, K., McGurn, D., Robertson, L., and Smith, C. **Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis,** NIHR Health Technology Assessment programme: Executive Summaries, Vol. 14, No. 21, 2010

3. Jones, C., Roderick, P., Harris, S. and Rogerson, M. **Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease,** Nephrology Dialysis Transplantation, Vol. 21, 2006, pp. 2133-2143
4. Khan, S., Xue, J., Kazmi, H., Gilbertson, D., Obrador, G., Pereira, B. and Collins, A. **Does predialysis nephrology care influence patient survival after initiation of dialysis?** Kidney International, Vol. 67, 2005, pp.1038–1046
5. Kleinbaum, D.G and Klein, M. **Survival Analysis. A Self-Learning Text**. 2nd ed. New York, Springer, 2005
6. Levey, A. S., Schoolwerth, A. C., Burrows, N. R., Williams, D. E., Stith, K. R. and McClellan, W. **Comprehensive public health strategies for preventing the development, progression, and complications of CKD: report of an expert panel convened by the Centers for Disease Control and Prevention,** American Journal of Kidney Diseases, Vol. 53, No. 3, 2009, pp. 522-535
7. McCullough, P. A., Vassalotti, J. A., Collins, A. J., Chen, S. C. and Bakris, G. L. **National Kidney Foundation's Kidney Early Evaluation Program (KEEP) annual data report 2009: executive summary,** American Journal of Kidney Diseases, Vol. 55, No. 3, 2010, S1-S3
8. Obialo, C. I., Ofili, E. O., Quarshie, A. and Martin, P. C. **Ultralate referral and presentation for renal replacement therapy: socioeconomic implications,** American journal of kidney diseases, Vol. 46, No. 5, 2005, pp. 881-886
9. O'Hare, A. M., Bertenthal, D., Covinsky, K. E., Landefeld, C. S., Sen, S., Mehta, K. and Walter, L. C. **Mortality risk stratification in chronic kidney disease: one size for all ages?,** Journal of the American Society of Nephrology, Vol. 17, No. 3, 2006, pp. 846-853
10. Sedgwick, P. **Survival (time to event) data: censored observations,** British Medical Journal; Vol. 343, 2011, d4816
11. Sedgwick, P. **Cox proportional hazards regression,** British Medical Journal, Vol. 347, 2013, f4919
12. Van Biesen, W., De Vecchi, A., Dombros, N., Dratwa, M., Gokal, R., LaGreca, G.,and Lameire, N. **The referral pattern of end-stage renal disease patients and the initiation of dialysis: a European perspective,** Peritoneal dialysis international, Vol. 19, Suppl. 2, 1999, pp. S273-S275
13. Vassalotti, J.A., Li, S., McCullough, P.A. and Bakris G.L. **Kidney early evaluation program: a community-based screening approach to address disparities in chronic kidney disease**. Seminars in Nephrology, Vol. 30, 2010, pp. 66–73
14. Zilisteanu, D.S. **Late nephrology referral and impact on morbidity and mortality of patients with chronic renal disease,** Ph.D. Thesis, Carol Davila University of Medicine and Pharmacy, Bucharest, 2013

[1] **Acknowledgment**
This paper was co-financed from the European Social Fund, through the Sectorial Operational Programme Human Resources Development 2007-2013, project number POSDRU/159/1.5/S/138907 "Excellence in scientific interdisciplinary research, doctoral and postdoctoral, in the economic, social and medical fields - EXCELIS", coordinator The Bucharest University of Economic Studies.