

Original Article

An Estimation of the Chronic Rejection of Kidney Transplant Using an Eternal Weibull Regression: A Historical Cohort Study

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Background: We estimated the chronic rejection of kidney transplant using an eternal Weibull regression.

Methods: In this historical cohort study, we enrolled all patients with chronic renal failure who were admitted to Shahid Labbafinejad medical center (Tehran, Iran) from 1984 to 2003. Using Matlab 7.0, we considered the eternal proportion θ , as a logistic-type function of the covariates and modified the survival function. We estimated the survival function in unmodified and modified forms using Weibull distribution.

Results: The chance of chronic rejection was 1.95 times higher among those who received a kidney transplant before 1996. Considering all cases who received renal transplantation after 1984, males had a chance of rejection 20% less than females.

Next to the eternity, Weibull model was fitted to patients who received renal transplantation after 1996. Treatment protocol was changed after 1996 expecting fewer chronic rejections; thereafter, the eternal proportion was estimated to be 0.81. This seems quite considerable as a percentage of non-failure cases.

Conclusion: Providing a non-zero eternal proportion, the modified model would be superior over the unmodified model.

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Keywords: Cohort studies • graft rejection • kidney transplantation • regression analysis

Introduction

In the context of survival analysis, there are two broad approaches in estimating the survivor function: non-parametric and parametric. In the non-parametric approach, the hazard of failure has no specific form and one of the widely used procedures is the so-called Kaplan-Meier estimate. In the parametric approach, the probability distribution of survival

times and thereby the hazard of failure has a known functional form. The two most common parametric forms of hazard are the exponential and Weibull distribution.

In exponential distribution, the hazard function is taken to be constant over time; whereas in Weibull distribution, the hazard function is assumed to change monotonically over time. The latter distribution is in fact as central to the parametric analysis of survival data as the normal distribution is in the linear modeling. The same analogy exists in regression models, where the effect of explanatory variables on the hazard function is of interest.

In the above-mentioned procedures, the basic assumption regarding survival analysis is that by giving enough time, all cases will have the event of interest; however, there are situations, such as kidney transplantation, where this assumption is not necessarily true and a substantial percentage of patients will never experience allograft rejection

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and hence remain eternal according to this event. As a result, the survival function needs to be modified according to this eternal proportion.¹⁻⁴ This phenomenon exists in transplantation of other organs.⁵

The rationale for using Weibull distribution in the present study is that, not only the assumption of specific functional form of hazard is doable, but also the estimation of the eternal proportion is better possible. Previous studies on data collected from kidney transplantation centers were done using either Cox regression analysis, or in rare cases, parametric survival analysis. Moreover, to our knowledge, in none of those studies the eternal feature of the survivor function was taken into consideration. Therefore, in this study, we modified survival function considering eternal proportion by developing a new computerized statistical program. So, the modified and unmodified Weibull regression models were compared to obtain a survival estimate of kidney allografts in our medical center.

Patients and Methods

In this historical cohort study, all patients with chronic renal failure who received an allograft kidney from living donors were included. This study was done on patients admitted to Shaheed Labbafinejad Medical Center affiliated to Shaheed Beheshti University, M.C. from 1984 to 2003. In this medical center, recipients are generally in the age group of 18 to 65 years. Neither urologists nor nephrologists recommend renal transplantation to patients suffering from hemolytic uremic syndrome, focal segmental glomerulosclerosis, and oxalosis; therefore, our study did not include subjects suffering from underlying diseases mentioned above. All donors were evaluated in an outpatient visit 7 – 10 days after the operation. Laparoscopic or open nephrectomy was performed by 2 co-surgeons on the left kidney in all patients. Kidney transplantation was performed by the same urologist who did nephrectomies.

Urology and Nephrology Research Center (UNRC) has adopted codes of ethics to guide retrospective studies. All patients who received allograft kidney transplantation from 1984 up to 2003 were included for further analysis. All potential donors underwent extensive medical and psychological evaluations and routinely received a light mechanical bowel preparation 12 hours before the operation. Donors underwent

conventional angiography or digital subtraction angiography to evaluate the anatomy of the kidney vasculature. All donors with multiple renal arteries were excluded.

The surgical technique used in open donor nephrectomies was the standard retroperitoneal flank approach. In the laparoscopic donor nephrectomies, the conventional technique was utilized. All patients were visited in the clinic of transplantation affiliated to Shaheed Labbafinejad Medical Center at regular intervals of 2 weeks, 1 month, and 3 months after transplantation and every 6 months thereafter.

Chronic rejection was defined as an immunologic reaction to the transplanted organ resulting in a decrease in kidney function and developing a gradual rise in serum creatinine. Chronic rejection was diagnosed by findings in clinical assessments, radionuclide scan, renography, and other laboratory variables. For patients with biopsy-proven diagnosis, histological features included thickening of the intima of arterioles and arteries, sclerosis of glomeruli, and tubular atrophy.

The variables which were thoroughly recorded for donors and recipients were transplantation date, previous episodes of renal transplantation, donors' age, donors' sex, recipients' age, recipients' sex, degree of consanguinity between donors and recipients, blood group of donors and recipients, laparoscopy versus open donor nephrectomy, and results of HBsAg tests.

Parametric survival analysis was used to process data and right censoring was considered. The hazard function was assumed to change monotonically over time; hence, Weibull distribution was used. We calculated the estimation of the survival function using both unmodified and modified forms of the Weibull distribution. In the latter, the eternal proportion was taken into account. The survivor, density and hazard function with an eternal proportion θ is as follows (the index "m" refers to modified):

$$S_m(t) = 1 - (1 - \theta)F(t)$$

$$f_m(t) = (1 - \theta)f(t)$$

$$h_m(t) = \frac{(1 - \theta)f(t)}{1 - (1 - \theta)F(t)}$$

For the Weibull distribution, the above-mentioned functions are as follows:

$$f_m(t) = (1 - \theta) \lambda \gamma t^{\gamma-1} \exp(-\lambda t^\gamma)$$

$$S_m(t) = \theta + (1 - \theta) \exp(-\lambda t^\gamma)$$

$$h_m(t) = \frac{(1 - \theta) \lambda \gamma t^{\gamma-1} \exp(-\lambda t^\gamma)}{\theta + (1 - \theta) \exp(-\lambda t^\gamma)}$$

The parameter estimates of the Weibull distribution is obtained through maximizing the likelihood function, which should also be modified with respect to the eternal proportion.

In particular, the modified likelihood function would be:

$$L = \prod_{i=1}^n \{(1 - \theta) f(t)\}^{\delta_i} \prod_{i=1}^n \{\theta + (1 - \theta) S(t)\}^{1-\delta_i}$$

For the Weibull distribution, the modified likelihood would look like:

$$L = \prod_{i=1}^n \{(1 - \theta) \lambda \gamma t_i^{\gamma-1} e^{-\lambda t_i^\gamma}\}^{\delta_i} \prod_{i=1}^n \{\theta + (1 - \theta) e^{-\lambda t_i^\gamma}\}^{1-\delta_i}$$

Using Greenwood formula, the Kaplan-Meier estimate of the survival function with a 95% confidence interval was also obtained.

The required modification was also applied in the regression form. The eternal proportion θ was considered to be a logistic-type function of the covariates. We used the method of maximum likelihood to estimate the parameters of the new model, which is in some sense a mixed model having two parts: the basic part from a Weibull regression model, multiplied by the effect of the eternal proportion as the logistic-type function of covariates. The final system of non-linear equations of the log derivatives was solved using Newton-Raphson procedure⁸

With six covariates, there was a total of 15 parameters to be estimated: λ and γ , the scale and shape parameters of Weibull distribution respectively, β coefficients of the main part of the model, and β' coefficients of the logistic part. The standard errors of the coefficients were also calculated. The method of forward conditional likelihood ratio was used as the selection method in order to come up with the best final model.

Finally, the coefficients of the model were compared with and without the presence of the eternal proportion. Since treatment protocol was changed after 1996 and fewer chronic rejection cases were expected thereafter, we performed a separate analysis on those transplanted only after 1996.

Results

A total of 1236 patients were included. The mean (\pm standard deviation) age of the recipients and donors were 33.5 \pm 15.2 years and 28.33 \pm 5.33 years, respectively. Male to female ratio in recipients and donors was 1.68 and 5.43, respectively.

Approximately, 7.8% of the recipients received kidneys from their relatives. Thirty-seven (3%) recipients were HbsAg-positive. About 91.5% had a matched blood group. The frequency of blood groups A, B, AB, and O was 31.74%, 22.43%, 7.9%, and 37.93% in recipients and 30.0%, 21.4%, 6.6%, and 42.0% in donors, respectively.

The Kaplan-Meier estimate of the survivor function and its 95% confidence interval is shown in Figure 1, indicating an eternal proportion. Considering the eternity, Weibull model was fitted to data and the eternal proportion was estimated to be 0.81 (Figure 2).

Figure 3 shows the estimated survivor function using the modified and unmodified Weibull distribution together with the Kaplan-Meier estimate. The three estimated survivor functions also suggested an eternal proportion to exist, although those of Kaplan-Meier and modified Weibull distribution seemed to be more consistent on this issue.

The mean survival time for the unmodified model was about 7000 months confirming the eternal nature of the survivor function whereas the mean survival time for the modified model was 76.15 months.

Finally, the graph of the modified and unmodified hazard function is presented in Figure 4. The modified estimate of the hazard function suggests that the hazard will tend to zero over a long period of time. Considering the effect of covariates, we recalculated the modified Weibull regression model. The eternal proportion was taken as a logistic-type function of the covariates. The estimation of parameters was again obtained through the method of maximum likelihood using

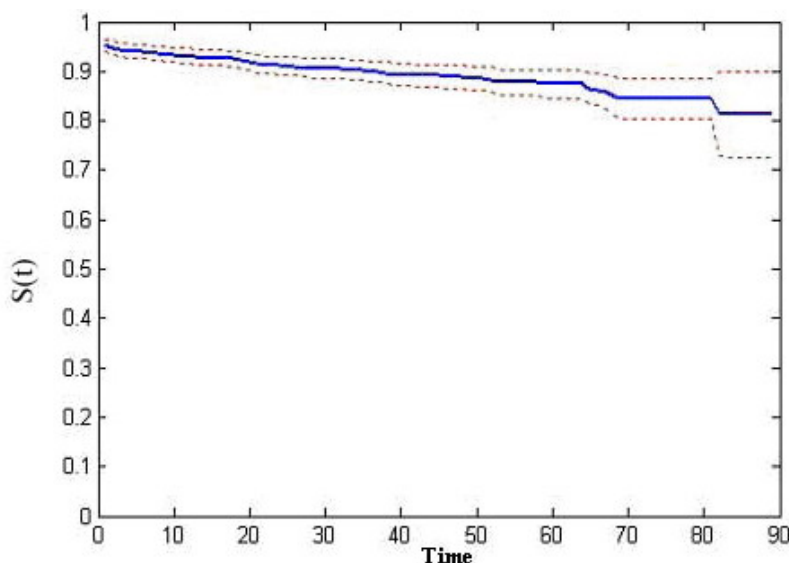


Figure 1. Kaplan-Meier estimate of the survivor function and its 95% confidence interval (Time=year).

forward conditional likelihood method.

The chance of chronic rejection was 1.95 times higher among those who received a kidney transplant before 1996 ($\exp(0.67)$). Considering all cases who received renal transplantation after 1984, males had a chance of rejection 20% less than females [$\exp(-0.23)=0.794$].

Considering patients who received allograft kidney transplantation after 1996 when treatment protocols had changed, the coefficient of the final model indicated that in comparison to women, the chance of chronic rejection was lower in men by 26%. Patients who had undergone kidney transplantation more than once were 4.8 times more at risk of chronic rejection. Our finding showed the younger the age of the recipient, the higher would be the chance of chronic rejection.

The coefficient of the eternal part confirmed our results demonstrating that men had a 1.6 time higher chance of being eternal [$\exp(.493)$] and those who were younger had better outcomes. Finally, those who had received kidney transplantation more than once had a higher chance of rejection by 33% (Table 1).

Discussion

In this study, we modified the basic functions $f(t)$, $S(t)$, $h(t)$ i.e. the density, survivor and hazard functions, respectively, considering the eternal proportion θ . Consequently, we applied the modification to the above-mentioned functions and considered the two-parameter Weibull distribution

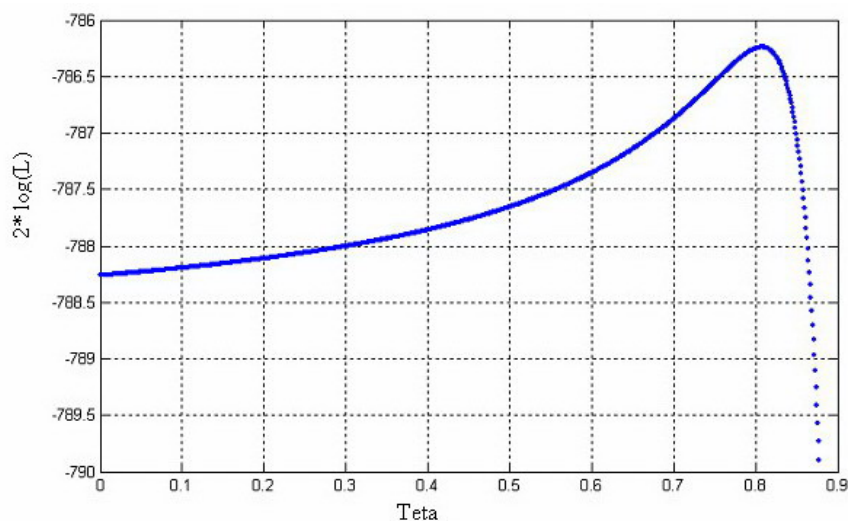


Figure 2. Plot of likelihood function versus θ values.

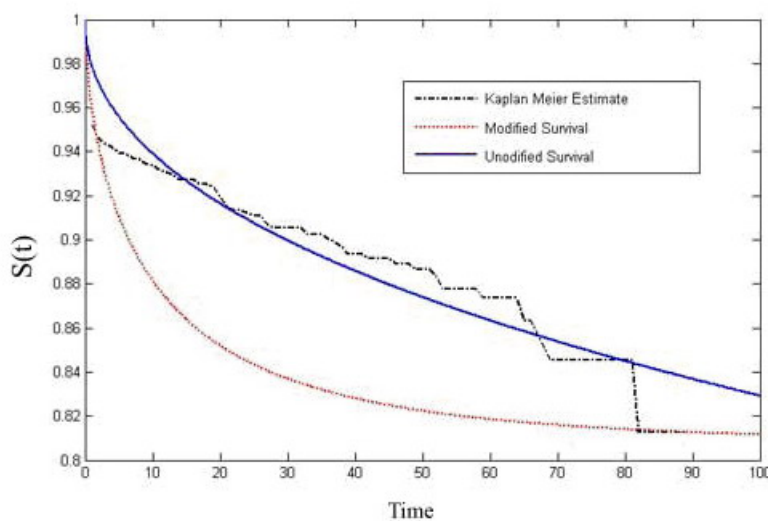


Figure 3. Estimated Kaplan-Meier, modified and unmodified Weibull distribution for patients with kidney transplantation (Time=year).

for survival times $[t \sim W(\lambda, \gamma)]$. To the best of our knowledge, this modification has not been made in previous studies and this proportion has not been taken into account in survival analysis of allografts and recipients.

Survival analysis is widely used in life-time studies and is often characterized by survival and hazard function. Parametric Weibull model has been used for survival analysis in many situations including organ transplantation. In comparison between parametric and non-parametric models, Collette⁶ noted that when the assumption of the specified probability distribution for the data was valid, parametric regression model was more

powerful and preferable in making inferences. However, in estimating the survival function, an important assumption is that the survivor function tends towards zero as time approaches to infinity, i.e. $S(t) \rightarrow 0$ as $t \rightarrow \infty$; in other words, the event of interest will eventually happen for all cases. On the other hand, to determine allograft survival in organ transplantation, we know that only a fraction of cases experience the event of interest; as a result, $S(t)$ will not tend to its final value which is zero, suggesting an eternal proportion θ to exist. Considering our results, the mean survival time reduced to reasonable values after the inclusion of eternal proportion for those the occurrence was

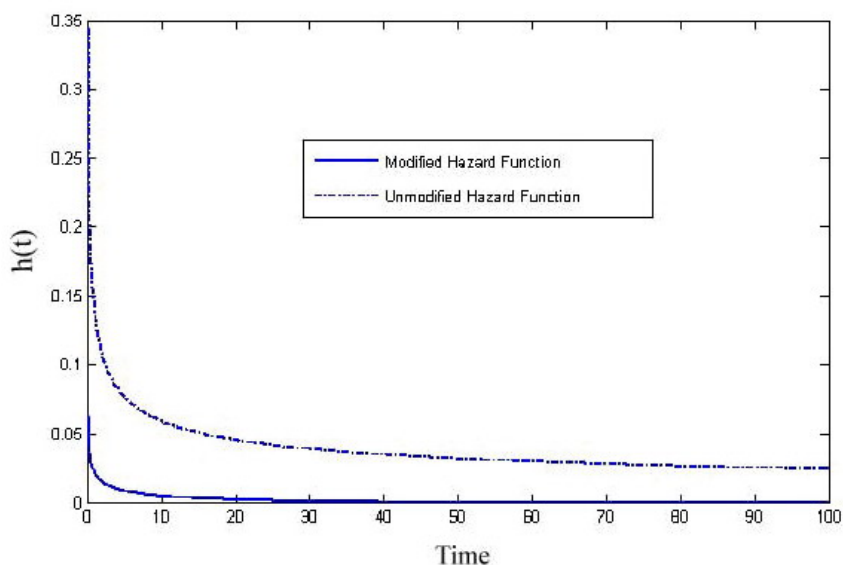


Figure 4. Estimated modified and unmodified hazard function for patients with kidney transplantation (Time=year).

Table 1. Results of the final modified regression Weibull model.

Variables	Scale parameter		Shape parameter		Regression coefficient		Regression coefficient of the eternal part			
	λ	SE(λ)	γ	SE(γ)	β	SE(β)	β'_0	SE(β'_0)	β'	SE(β')
Sex of recipients (male/female)	—	—	—	—	-0.300	0.170	—	—	0.493	0.145
Donors' age	—	—	—	—	-0.037	0.004	3.45	0.104	-0.074	0.003
No. of transplantation ($\pm 1/0$)	0.338	0.042	0.632	0.035	1.57	0.292	—	—	-0.393	0.282

SE=standard error

expected.

Mixture models have been utilized in previous studies. Ti et al.⁷ used a mixed model to evaluate the success rates of conjunctival autografts for primary and recurrent pterygium performed in a tertiary ophthalmologic medical center. However, their study estimated the survivor function without considering the effects of covariates in a mixed model or the eternal proportion.

The existence of the eternal proportion can be seen from the graph of the survival function. In Figure 3, the modified estimate of the survivor function is closer to Kaplan-Meier estimate, hence giving a better indication of the eternal proportion. The modified log likelihood ensures that there is a maximum value at $\theta=0.81$. The modified hazard function also confirms the tendency of the hazard to zero at an infinite time.

Our results show that when there are long-term survivors, considering an eternal proportion and using a modified model yields more realistic parameter estimations and consequently leads to more reliable prognostic factors. This is especially true when there is a considerable percentage of non-failure cases. However, when the eternal

proportion is negligible, there is not much gain in using modified models.

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