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# SURVIVORSHIP ANALYSIS OF TRANSPLANTED RENAL DISEASE PATIENTS

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Summary

As a part of the development of a model for different scenarios which reflect the prevailing and alternative policies concerning kidney replacement, survival times of transplanted renal disease patients have been analyzed. A proportional hazards model is assumed with two explanatory variables : year of transplantation and recipient age at transplantation. Other variables which, according to the literature, influence survival, e.g., HLA-matching, are not taken into account. Using different informal tests it is concluded that the unobserved heterogeneity has not biased the estimates. It may be assumed, rather speculatively, that the year of transplantation, a variable which in fact reflects the development of other variables, captures the unobserved heterogeneity.

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## 1. Introduction

Before 1960 End Stage Renal Disease (ESRD) resulted invariably in death. In the last two decades several therapeutic methods have become available which more or less replace renal function and which postpone death. The most commonly used methods are (Colombi 1983 ) :

(a) Heamodialysis
(b) Continuous ambulatory peritoneal dialysis
(c) Renal transplantation

Since the early sixties dialysis has provided a practical means of long term replacement of renal function. Despite many improvements in technique, however, it remains an arduous form of treatment. Three four times a week a patient has to be dialyzed, each treatment lasting several hours. A relatively new therapy, which encompasses some of the problems of heamodialysis, is C.A.P.D. This therapy relies on the presence of a permanent indwelling catheter giving access to the patient´s peritoneal cavity. The major advantage is that the patient can go about normal activities without any need to be attached to a machine. The main disadvantage, also the reason why it is still in an experimental stage, is the risk of peritonitis.
Transplantation, when successful, is the preferred form of treatment, both in terms of rehabilitation and well-being of the patient and from the point of view of costs to the health services.

In economic terms the kidney replacement program costs are considerable, often demanding between 1%-2% of the health budget. Facing budgetary restraints and a growing number of patients suffering from ESRD, health care planning authorities in industrialized countries attempt to control costs and attempt to optimize the use of resources for their kidney replacement programs.

In this paper an analysis is presented of survival of transplanted renal disease patients. This analysis was part of the development of a model, using Dutch data, which facilitates the calculation of both costs and the quality adjusted life years for different scenarios which in turn reflect the prevailing and alternative policies concerning kidney replacement. For the development of this model, data were kindly made available by Eurotransplant, the European organization which coordinates all kidney transplantations in Germany, Holland, Belgium, Luxembourg, and France.
Section 2 presents the empirical data. Attention is drawn to the limited number of explanatory variables : year of transplantation (ytr) and age of the recipient (age). Other variables which, according to the literature, influence

survival, e.g., HLA-matching and the number of blood transfusions are not taken into account. After a short introduction of the proportional hazards model of Cox, the third section presents estimates of the parameters of this model. Some informal tests do not reject the the estimated model.
From the econometric literature on duration data ( see for example Heckman and Singer 1984a), it is known that uncontrolled, unobserved variables bias estimated hazards towards negative duration dependence. The null hypothesis that there is no unobserved heterogeneity, therefore should be tested. In Cox´s proportional hazards model no formal test is available to do this. An informal test suggested by Ridder and Verbakel (1984) is used in section 4. If, in contrast with Cox´s model, a parametric model is assumed for the base line hazard function, the presence of unobserved heterogeneity can be tested. The method used in section 5 was proposed by Lancaster and Nickell (1980). The central assumption of this method is that the omitted variables can be captured by a single random variable which follows a Gamma distribution with unit mean and unknown variance. For the base line hazard function several well known distributions were assumed and estimated. The variance of the unobserved heterogeneity converges to zero in the models which lead to the highest likelihood. This indicates that no unobserved heterogeneity has biased the regression coefficients. In section 6 some remarks are made on the informal graphical techniques which are developed in the literature to check the appropriateness of the model assumptions. A more formal test is proposed, but application of this test did not lead to a rejection of the estimated models. Division of the sample into sub-samples according to the values of the exogeneous variables and analysis of the parameter estimates show that the year of transplantation should only be implemented as an explanatory variable after 1976. This leads to a revision of the models, which indicates that one should not rely on the informal graphical tests to accept the estimated model. This paper concludes with a brief summary.

## 2. The data on renal transplantation

In the analysis data was used from all 2179 cadaver-donor transplants performed in the Netherlands from 1967 to 1983. Data were censored if the patient was still alive at the date of the last follow up or if an irreversible rejection (graft failure) occurred. After graft failure the patient has to return to dialysis as treatment modality. In this case, the time between transplantation and graft failure is defined as the censored survival time. If the patient was still alive with a functioning graft at the time of last follow up the time between transplantation and last follow up is defined as the censored survival time. These data are generally defined as type I censored data.
Of the 2179 transplanted patients 272 died before censoring. For each

transplant data was available on a number of donor and recipient variables. Eurotransplant is conducting a research program in which emphasis is placed on the effect of primary and constructed variables which reflect how well matched donor and recipient are with respect to tissue antigens ( due to the involved procedure, this is called the HLA-match). In 1100 cases at least, one, but usually all scores on these variables were not known. This can largely be explained by the fact that it was only since 1980 that the effects of mismatching in the D locus was known to be relevant. Also because of the short follow up of the complete cases these variables have not been taken into account. Apart from some of the matching variables only 5 variables showed differences at a 5% significance level, according to the generalized Wilcoxon statistic (Gehan 1965). These were :

(A) year of transplantation
(B) recipient age at transplantation
(C) number of pre-operative blood transfusions
(D) follow up center
(E) high urgency

After the operation a patient is treated in his/her follow up center. Each patient on the waiting list has an urgency-code. The High Urgency variable (E) expresses the patient´s urgency-code at the time of transplantation. Because interaction is expected between the variables C and E, and between C-E and the probability to survive, these variables also have also not been taken into further account.

## 3. Analyzing the data using Cox´s proportional hazards model

Only a concise introduction is given here on Cox´s model as some excellent expositions exist in the textbooks of Kalbfleisch and Prentice (1980), Lawless (1982), and Cox and Oakes (1984). In all methods developed to analyze survival times, it is assumed that survival time can be represented by a non negative random variable T with an absolutely continuous distribution function $F(t)$ and density $f(t)$. T can be uniquely characterized by its hazard function $h(t)$. This hazard function is the conditional density of T, given $T \geqslant t$ :

$$h(t) = \lim_{\Delta t \to 0} \frac{P\,(t \leqslant T < t + \Delta t \mid T \geqslant t).}{\Delta t}$$

Conversely, knowledge of $F(t)$ determines $h(t)$.
The proportional hazards model assumes :

$$h(t;x) = h_0(t).\exp(x'\beta).$$

Two different approaches can be followed. A parametric model can be assumed for $h_0(t)$, so, estimates can be obtained by maximization of the likelihood function. Cox proposed in 1972 the utilization of a conditional likelihood, based on the ranks of the observations, so it would be possible to estimate the $\beta$-coefficients without making any assumptions about the shape of $h_0(t)$. Kalbfleisch and Prentice showed that Cox's conditional likelihood should not be interpreted as a conditional likelihood but as a marginal likelihood. Cox returned to this subject in 1975 by showing that his conditional likelihood can be interpreted as a partial likelihood. With this he showed that the method used to construct this likelihood gives maximum 'partial' likelihood estimates that are consistent and asymptotically normally distributed with asymptotic covariance matrix estimated consistently by the inverse of the matrix of second partial derivates of the log likelihood function.

Applying Cox's model, we used $x_{age}$ (the recipient age at transplantation in years) and $x_{ytr}$ ( the year of transplantation, i.e., 67 - 83) as explanatory variables.

$$h(t;x) = h_0(t).\exp\ (\ x_{age}.\beta_{age} + x_{ytr}.\beta_{ytr}\ )$$

The parameters $\beta_{age}$ and $\beta_{ytr}$ are estimated by maximum partial likelihood, without making assumptions on the shape of $h_0(t)$. Our parameter estimates, using Eurotransplant data, are (t-values between parentheses) :

$$\hat{\beta}_{age} = 0.049\ (8.39) \qquad \hat{\beta}_{ytr} = -\ 0.089\ (-5.0)$$

The survivor function can be written as :

$$S(t;x) = S_0(t)^{\exp(x'\beta)}$$

After the parameters have been estimated by maximum partial likelihood, the base-line survivor function $S_0(t)$ can be estimated as a stepfunction by maximizing the full likelihood.
Plots of the estimated survivor function for three different values of the exogeneous variables are presented in section 5 together with those resulting from a model in which a log-normal model has been assumed for the base-line hazard function.
The appropriateness of the proportional hazards model can be tested by graphical inspection as explained by Lawless (Lawless 1982 § 6.2). This graphical inspection however gives no formal rule on which rejection or acceptation can be based. Graphical inspection of the same model, etimated on data which were

simulated in such a way that it was known that the model was perfect, led to similar graphs. This permitted the conclusion that the model-assumptions could not be rejected. In section 6 we will return to this subject.

## 4. The effects of unobserved heterogeneity

Ridder and Verbakel (1984) showed that, if neglected heterogeneity is present, the estimated regression coefficients in Cox´s proportional hazards model are biased towards zero. Also the estimate of the base line hazard function is less increasing or more decreasing than the true base line hazard function. In section 2 it is indicated that such bias can be expected, since we used only a small number of explanatory variables. Ridder and Verbakel have suggested an informal test for omitted heterogeneity. They propose to order the observed durations (which may be censored) in order of increasing length. Next, the sample is censored, e.g., at the median. If there is unobserved heterogeneity, the resulting estimates on the artificially censored sample should be larger (in absolute value) than the estimates from the original sample. With regard to their suggestion, the data were divided in quarters, censoring at the 545th, 1090th and 1635th observation. The estimates of Cox´s model on these data are presented in TABLE 4.1.
The estimate of $\beta_{age}$ is only larger if the sample is censored from the 545th observation. The estimate of $\beta_{ytr}$ is larger if the sample is censored from the 1635th and the 545th observation. Because the same kind of results can be found on simulated data without unobserved heterogeneity, these values give no reason to accept the null hypothesis that unobserved heterogeneity influenced the estimates.

Table 4.1. Ridder and Verbakel test on Cox´s proportional hazards model, Eurotransplant data, 1967-1983

| $n_1$ | $n_2$ | $\hat{\beta}_{age}$ | $\hat{\beta}_{ytr}$ |
|---|---|---|---|
| 2179 | 272 | 0.0489 | -0.0894 |
| 1635 | 224 | 0.0455 | -0.0908 |
| 1090 | 176 | 0.0422 | -0.0842 |
| 545 | 66 | 0.0503 | -0.0930 |

$n_1$ = number of observations not artificially censored
$n_2$ = number of remaining observed deaths

## 5. Testing for unobserved heterogeneity if a parametric model is assumed.

In Cox´s proportional hazards model, no assumption has to be made on the exact distribution of the base line hazard function. Assuming a parametric specification, if it is the correct one, leads to more efficient estimates. Because the potential improvement of the efficiency is only small and because it introduces the possibility of misspecification, Cox´s model is generally preferred.
Following Lancaster and Nickell (1980), it may be assumed that the unobserved heterogeneity can be captured by a random variable V with unit mean and unknown variance $\sigma^2$ which can be implemented in the model by the following relation :

$$h(t;x,v) = h_0(t).\exp(x'\beta).v$$

Analogous to the error term in the linear model it is assumed that V is independently distributed.
If the censoring time is assumed to be independent of the survival time and the censoring time is assumed to be functionally independent of the survival time the full likelihood can be written as :

$$L(t;x,v) = \prod_{i=1}^{2179} \int_v h(t_i;x,v)^{d_i}.S(t_i;x,v)\, dG(v)$$

In which G(v) is the distribution of v and $d_i = 0$, if survival time $t_i$ is censored, and $d_i = 1$, if the complete survival time has been observed.
In the medical and econometric literature, different assumptions are made with respect to the distribution G(v). Lancaster and Nickell (1980) and, more specifically, Hougaard (1984) describe a method using different well-known parametric distributions. Heckman and Singer, calling the model overparameterized, describe a method to estimate G(v) non-parametrically.
In contradiction with Cox´s proportional hazards model, in all these methods h(t;x) has to be specified.
The most tractable method was adopted in which a Gamma distribution with unit mean and unknown variance is assumed for G(V). The parameters are estimated by maximization of the full likelihood, i.e., the $\beta$´s, the parameters of the assumed distribution of $h_0(t)$ and the unknown variance $\sigma^2$ of the Gamma distribution.
Different models have been assumed for $h_0(t)$. Most illustrative are the exponential, the Weibull, and the log-normal model. In the estimation an intercept $\beta_0$ is added to the $\beta$-vector so that :

$$\exp(x'\beta) = \exp(\beta_0 + x_{age}.\beta_{age} + x_{ytr}.\beta_{ytr}),$$

then the concomitant hazard functions can be written as :

- the exponential model

$$h(t;x,v) = \exp(x'\beta).v$$

- the Weibull model :

$$h(t;x,v) = p.t^{p-1}.\exp(x'\beta).v$$

- the log normal model

$$h(t;x,v) = (f(t)/S(t)).\exp(x'\beta).v \qquad \text{in which :}$$

$$f(t) = (t.\lambda)^{-1}.\exp[-\tfrac{1}{2}\{(\log t-p)/\lambda\}^2] \quad \text{and} \quad S(t) = \int_t^{\infty} f(g)\,dg \ .$$

The subsequent estimation results are presented in TABLE 5.1 ( t-values between parentheses). In the estimates of the Weibull and the log-normal distribution, the estimated variance of the neglected heterogeneity converges to zero. Estimating all parameters with $\sigma$ fixed on different values, led to the conclusion that this is a global optimum in both cases. The likelihood which results from $\sigma = 0$ is the same as would have resulted if no error term, representing the neglected variables, had been added. As a result, it may be assumed that the estimates have not been biased because of unobserved heterogeneity.

Table 5.1 Parameter estimates in three parametric proportional hazards models, Eurotransplant data, 1967-1983

| Base line hazardfunction | Log(L) | $\hat{\sigma}^2$ | $\hat{\beta}_0$ | $\hat{\beta}_{age}$ | $\hat{\beta}_{ytr}$ | $\hat{p}$ | $\hat{\lambda}$ |
|---|---|---|---|---|---|---|---|
| Exponential | -1039 | 3.285 | -7.071 | 0.080 | 0.154 | | |
| | | (1.14) | (-2.30) | (4.15) | (2.06) | | |
| Weibull | -1017 | 0 | 2.640 | 0.049 | -0.092 | 0.531 | |
| | | | (2.04) | (8.4) | (-5.4) | (18.7) | |
| Log normal | -1008 | 0 | 3.38 | 0.049 | -0.011 | -1.301 | 1.88 |
| | | | (3.8) | (8.4) | (-8.0) | (-2.3) | (9.1) |

For three different values of the exogeneous variables, using the log normal model for the base line hazard function, figure 5.1 presents plots of the

Figure 5.1 Estimated survivor functions : log-normal base line hazard function

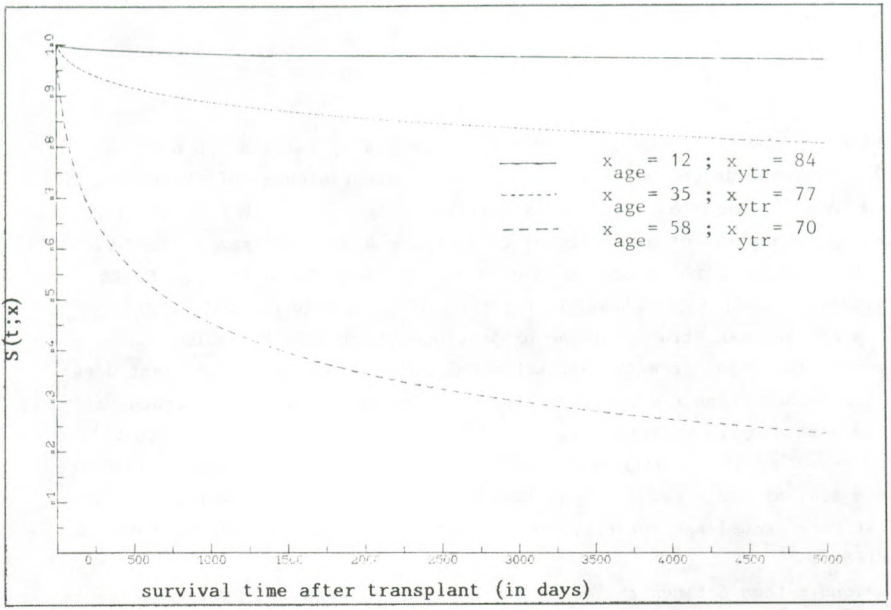
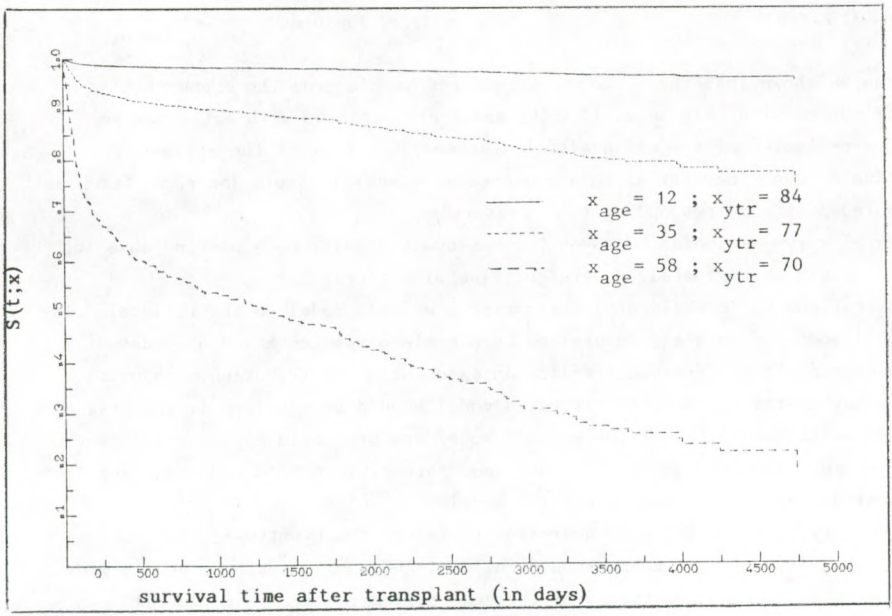



Figure 5.2 Estimated survivor functions estimated from Cox´s proportional hazards model ( non parametric base line hazard function )



estimated survivor functions. Plots of the concomitant survivor functions from Cox´s model are presented in figure 5.2.

## 6. Testing the model assumptions

According to the text-book literature (Lawless § 6.2, Kalbfleisch and Prentice § 4.5), two methods can be used to check the appropriateness of the model. Both methods are graphical and relatively informal. The first method is developed to check the assumption of proportionality in Cox´s model. The sample is divided in strata according to values of an explanatory variable, e.g., $x_{ytr}$. Plots of $\log(-\log(S(t;x_{age})))$ in which $x_{age}$ is the mean of $x_{age}$ should exhibit constant differences between strata, if the proportionality assumption holds.
The graphs resulting from the estimated Cox model on the Eurotransplant data didn´t show any notable departures from the expected behavior if strata were defined according to values of $x_{age}$. If strata were defined according to values of $x_{ytr}$, plots result of different length so interpretation was more difficult. Because similar plots resulted on simulated data, of which it was known that the estimated model was perfect, the proportionality assumption could not be rejected.
The second method defines residuals and carries out residual plots such as in ordinary linear regression. Let $t_i$ be the survival time of the i´th individual and define :

$$e_i = H_0(t_i).\exp(x'\beta) \qquad \text{where } H_0(t) = \int_0^t h_0(u)\,du.$$

It can be shown that the $e_i$´s are a censored sample from the exponential distribution with unit mean. If $H_0(t)$ and $\beta$ are replaced with estimates we obtain estimates of the residuals. If the model is correct the estimated residuals should be similar to a censored exponential sample (an $e_i$ is taken as censored if the corresponding $t_i$ is censored).
Survival curve estimates based on the residuals should, when plotted on a log scale, yield approximately a straight line with slope -1.
This test can be formalized by estimating a Weibull model on the residuals. The Weibull model is uniquely determined by a scale-parameter k and an index-parameter p. If the residuals follow an exponential distribution with unit mean, both parameters of the estimated model should be equal to 1. In table 6.1 the parameter estimates of the Weibull model are presented applying this method for the residuals resulting from Cox´s non-parametric method and resulting from the Weibull and log-normal parametric models.
The results in table 6.1 give no reason to reject the hypothesis that the residuals follow a unit mean exponential distribution. Because no use is made of any detailed sampling theory of the generalized residuals, no formal

Table 6.1 A Weibull model estimated on the residuals of different models.
( t-values between parentheses)

| hazard | Cox´s model | Weibull | log-normal |
|---|---|---|---|
| log(L) | 272.88 | 272.00 | 271.37 |
| $\hat{p}$ | 1.03 (35.10) | 1.00 (43.84) | 1.02 (44.76) |
| $\hat{k}$ | 1.02 (17.63) | 1.00 (21.29) | 1.04 (23.18) |

decision rule is present to accept the model as well. At this stage, following Lancaster and Chesher (1985), a score test, in fact an Information Matrix procedure as developed by White (1982), could be used to test more formally.

Dividing the data into sub-samples, according to the values of the explanatory variables, showed serious variation in the estimates of $_{ytr}$. An extensive analysis using dummies showed significant parameter estimates for all years after 1976. As a part of this analysis the following model was estimated :

$$h(t;x) = h_0(t).\exp\left\{x_{age}.\beta_{age} + \sum_{i=76}^{82} D_i\beta_i\right\}$$

in which $d_i = 1$ if $i = x_{ytr}$
$d_i = 0$ if $i \neq x_{ytr}$.

The following estimates resulted :

Log L( ) = -1834.9
$\hat{\beta}_{age}$ = 0.0484 ( 8.3)
$\hat{\beta}_{77}$ = -0.2708 ( -1.3)
$\hat{\beta}_{78}$ = -0.4532 ( -2.0)
$\hat{\beta}_{79}$ = -0.8428 ( -3.0)
$\hat{\beta}_{80}$ = -0.8671 ( -3.0)
$\hat{\beta}_{81}$ = -1.0408 ( -3.3)
$\hat{\beta}_{82}$ = -1.2399 ( -2.9)
(only one dummy for 1982 and 1983).

This result suggests a linear effect of $x_{ytr}$ from 1977. A model with dummies for different periods, therefore was estimated using a stepwise regression method in which covariates are entered or removed on the basis of the likelihood ratio test:

$$h(t;x) = h_0(t).\exp\left\{x_{age}.\beta_{age} + x_{ytr}.\beta_{ytr} + \sum_{i=72}^{82} D_i.x_{ytr}.\beta_i\right\}$$

In which $D_i = 0$ if $i < x_{ytr}$

$D_i = 1$ if $i \geq x_{ytr}$

Having set the limit for significance to enter a term at 0.10 and the limit to remove a term at 0.15, the following model results :

$$h(t;x) = h_0(t).\exp\ \{\ x_{age}.\beta_{age} + D_{77}.x_{ytr}.\beta_{77} + D_{78}.x_{ytr}.\beta_{78}\ \}.$$

Log likelihood = -1836.

$\hat{\beta}_{age} = 0.0479\ (\ 8.3212)$

$\hat{\beta}_{77} = 0.0052\ (-1.8446)$

$\hat{\beta}_{78} = 0.0062\ (-1.9132)$.

From this model it can be concluded that the year of tranplantation should only be used as an explanatory variable after 1976. By the former methods in this section the model in which $x_{ytr}$ is an explanatory variable for all years could not be rejected. It is implicitly rejected in the stepwise procedure. This fact indicates that if a model cannot be rejected by the informal text-book methods (which have even been implemented in standard computer packages as B.M.D.P. ), it should not mean that the estimated model is correct.

## 7. Conclusion

Survival times of transplanted renal disease patients have been analyzed in a model with two explanatory variables: year of transplantation and recipient age at transplantation. Two types of proportional hazards models have been used. In the first type, due to Cox, the form of the base line hazard function has been left arbitrarily. In the second type, the hazard function of some well known parametric distributions have been inserted, the log normal yielding the highest value of the likelihood. In the last type, it is possible to correct for the bias due to unobserved heterogeneity using a time invariant random variable which represents the unobserved variables. The results suggest that no unobserved heterogeneity can be found in the used data. It may be assumed, rather speculatively, that the year of transplantation, a variable which in fact reflects other underlying variables, captures the unobserved heterogeneity. In the last section some remarks are made about the graphical tests which are developed in the literature to test the appropriateness of the model-assumptions. These tests did not lead to a rejection of the estimated models. A stepwise procedure using dummies for different periods to test for breaks shows that the year of transplantation should only be used as an explanatory variable after 1976. This leads to the conclusion that one should not rely on the graphical tests to accept the estimated models.

References

Colombi A., (1983) A Review of the clinical evaluation of dialysis, in : A.J. Cuyler and B. Horisberger, eds., Economic and Medical Evaluation of Health Care Technologies (Springer, Berlin Heidelberg).

Cox D.R. (1972) Regression models and life tables (with discussion). J.R. Stat. Soc. B, 30, 248-275.

Cox D.R. (1975) Partial likelihood. Biometrika, 62, 269-276.

Cox D.R. & D. Oakes (1984) Analysis of survival data. Chapman and Hall: London.

Gehan E.A. (1965) A generalized Wilcoxon test for comparing arbitrarily single-censored samples. Biometrika, 52, 203-223.

Heckman J.J. & B. Singer (1982) The identification problem in econometric models for duration data. In: W. Hildenbrand (ed.), Advances in Econometrics. Cambridge: Cambridge University Press, 39-77.

Heckman J.J. & B. singer (1984a) Econometric duration analysis. Journal of Econometrics, 24, 63-132.

Heckman J.J. & B. Singer (1984b) A Method for minimizing the impact of distributional assumptions in econometric models for duration data. Econometrica, 52, 271-320.

Hougaard P. (1984) Life table method for heterogeneous populations: distributions describing the heterogeneity. Biometrika, 71, 75-83.

Kalbfleish J.D. & R.L. Prentice (1973) Marginal likelihoods based on Cox´s regression and life model. Biometrika, 60, 267-278.

Kalbfleish J.D. & R.L. Prentice (1980) The Statistical Analysis of Failure Time Data. New York: Wiley.

Lancaster T. & J.S. Nickell (1980) The analysis of reëmployment probabilities for the unemployed. J.R. Stat. Soc. A., 143, 141-165.

Lancaster T. & A. Chesher (1985) Residuals, Tests and Plots with a Job Matching Illustration. Annales de l´insee. No 59/60, 47-69.

Lawless J.F. (1982) Statistical Models and Methods for Lifetime Data. New York: Wiley.

Ridder G. & W. Verbakel (1984) On the estimation of the proportional hazards model in the presence of unobserved heterogeneity (University of Amsterdam, A & E Report AE 17/84).