Estimation of renal allograft half-life: fact or fiction?

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Abstract

Introduction. Renal allograft half-life time (t½) is the most straightforward representation of long-term graft survival. Since some statistical models overestimate this parameter, we compare different approaches to evaluate t½.

Patients and methods. Patients with a 1-year functioning graft transplanted in Spain during 1990, 1994, 1998 and 2002 were included. Exponential, Weibull, gamma, lognormal and log-logistic models censoring the last year of follow-up were evaluated. The goodness of fit of these models was evaluated according to the Cox–Snell residuals and the Akaike's information criterion (AIC) was employed to compare these models.

Results. We included 4842 patients. Real t½ in 1990 was 14.2 years. Median t½ (95% confidence interval) in 1990 and 2002 was 15.8 (14.2–17.5) versus 52.6 (35.6–69.5) according to the exponential model (P < 0.001). No differences between 1990 and 2002 were observed when t½ was estimated with the other models. In 1990 and 2002, t½ was 14.0 (13.1–15.0) versus 18.0 (13.7–22.4) according to Weibull, 15.5 (13.9–17.1) versus 19.1 (15.6–22.6) according to gamma, 14.4 (13.3–15.6) versus 18.3 (14.2–22.3) according to the log-logistic and 15.2 (13.8–16.6) versus 18.8 (15.3–22.3) according to the lognormal models. The AIC confirmed that the exponential model had the lowest goodness of fit, while the other models yielded a similar result.

Conclusions: The exponential model overestimates t½, especially in cohorts of patients with a short follow-up, while any of the other studied models allow a better estimation even in cohorts with short follow-up.

Keywords: death-censored allograft survival; kidney transplantation; median half-life

Introduction

Death-censored graft survival is the gold standard used to evaluate long-term graft outcome [1]. While 1-year graft survival has improved after the introduction of cyclosporine [2], studies aimed to demonstrate an improvement of graft survival after the first year have yielded contradictory results [3–6].

Donor and recipient characteristics, type of immunosuppression, incidence of acute rejection and other major determinants of outcome are rapidly changing. In countries like Spain, in which nearly all transplants are obtained from deceased donors, the proportion of kidneys harvested from expanded criteria donors has continuously increased and there is concern that this decrease in the quality of transplanted organs may finally be associated with a significant decrease in graft survival [7]. Hence, it is necessary to permanently monitor graft survival in order to evaluate the overall effect of different transplant policies on graft outcome.

A straightforward representation of late allograft survival is to calculate the renal allograft half-life time [8], that is, the time elapsed until 50% of grafts have failed. To evaluate graft attrition rate after the first year, death-censored allograft half-life only considering patients with a functioning graft at the end of the first year has been employed [9]. However, calculation of this parameter implies a rather long follow-up depending on the characteristics of the studied transplant population. In order to estimate projected half-life in cohorts of patients followed for short periods of time, different assumption-based statistical models have been proposed. In many studies, it has been assumed that survival times are exponentially distributed. For example, in a large epidemiological study aimed to compare graft survival between 1988 and 1996, it was concluded that projected half-life time steadily increased during the study period [3]. However, some years later, reanalysis of this cohort of patients with longer follow-up, once graft survival was <50%, showed that real half-life time has remained rather stable during the study period [4]. These data suggest that the exponential method overestimates half-life time in cohorts with a short time of follow-up. Alternative approaches to estimate projected half-life consider different models, such as Weibull, gamma, log-logistic and lognormal functions.

Thus, we evaluate different statistical approaches to estimate death-censored renal allograft half-life in patients with a 1-year functioning graft and different times of follow-up.

Patients and methods

Study design

To describe modifications in allograft half-life time between 1990 and 2002, patients receiving a renal allograft in Spain in 1990, 1994, 1998 and 2002 were considered for the study. Only adult transplant centres were

invited to participate and only adult patients (≥18 years) receiving a single kidney that was functioning at the end of the first year of follow-up were considered. Patients receiving multi-organ or dual transplants were excluded. Last follow-up was 30 December 2005.

Clinical variables

The following variables were evaluated in each patient at the time of surgery: source of the organ (living or deceased donor), donation before or after cardiac death, cause of donor death, age and gender of the donor and the recipient, height and weight of the recipient, presence of hepatitis B surface antigen and hepatitis C virus (HCV) antibodies in the donor and the recipient, aetiology of end-stage renal disease, time on dialysis, last panel reactive antibodies, number of human leucocyte antigen (HLA) mismatches and cold ischaemia and reanastomosis times.

After transplant, surgical complications, the presence of delayed graft function and acute rejection were recorded. Immunosuppressive treatment employed at the time of transplantation was classified in five major groups: (i) cyclosporine-based not associated with mycophenolate mofetil, (ii) cyclosporine-based associated with mycophenolate mofetil, (iii) tacrolimus based (iv) sirolimus based and (v) other. At 3 months and 1 year, serum creatinine, 24-h proteinuria, serum fasting glucose and serum cholesterol and triglycerides were recorded.

Definition of variables

Total number of HLA mismatches was calculated as the addition of the number of mismatches in the A, B and DR loci. A surgical complication was defined as reintervention for any cause. Delayed graft function was defined as haemodialysis requirements during the first week after surgery once accelerated or hyperacute rejection, vascular complications and urinary tract obstruction were ruled out. The diagnosis of acute rejection was defined at each centre based on clinical and/or histological data.

This study was approved by the Ethical Committee of the Hospital Universitari de Bellvitge. Medical records review was performed according to Spanish law with reference to clinical data confidentiality protection. A blinded code was assigned to each participating hospital in order to take into consideration the centre effect.

Statistics

Descriptive results are expressed as the mean ± SD for continuous variables. Frequency and contingency tables were employed to describe categorical and ordinal variables. Comparison between years of transplant was done by means of chi-square test for categorical data, Kruskal–Wallis test for ordinal or not normally distributed continuous data and analysis of variance for continuous normally distributed data. Kaplan–Meier analysis was used to estimate overall graft survival after censoring for death. Real half-life time was only calculated in the cohort of patients transplanted in 1990 since this was the only group with a death-censored graft survival <50% at the end of follow-up. Projected half-life time for death-censored allograft survival was estimated according to the exponential, Weibull, gamma, log-logistic and lognormal models using the SAS procedure PROC LIFEREG. The adequacy of the fitted models was assessed by the analysis of the Cox–Snell residuals [10]. To compare goodness of fit among different models, the Akaike's information criterion (AIC) was calculated [11]. The AIC provides a method to compare competing models penalizing the log likelihood achieved by a given model for its complexity to obtain a more unbiased assessment of the model's worth. After ranking several models according to their AIC, lower AIC represents the better fitted model. Statistical analysis was performed with SPSS 15.0 and SAS 9.0.

Results

Patients

During 1990, 1994, 1998 and 2002, 6657 renal transplants were performed in Spain in 38 adult centres. One centre declined to participate ($n = 127$) and five additional centres did not include patients transplanted in 2002 ($n = 174$). Thus, 6356 patients were considered and a total of 1514 were excluded for the following reasons: age <18 years ($n = 114$), dual transplant ($n = 52$), multi-organ transplant

($n = 153$), graft loss during the first year ($n = 855$) and loss to follow-up ($n = 340$). Finally, 4842 patients accomplishing the inclusion criteria were considered. The end of follow-up was up-dated at December 2005 except in five centres only providing information from patients transplanted in 1990, 1994 and 1998 cohorts. In these patients, last follow-up was December 2001.

Characteristics of patients grouped by transplant year are summarized in Table 1. During the study period, donor age and the proportion of donors deceased due to stroke steadily increased. The proportion of donors after cardiac death increased from 1990 to 1994 and remained stable thereafter, while the number of living donors remained low during the study period. Recipient age and weight increased as well as the proportion of recipients with diabetes as the cause of end-stage renal disease and the number of HLA mismatches. Mean time on dialysis before transplant, reanastomosis time and cold ischaemia time decreased in a time-dependent manner, while there was a reduction in the proportion of HCV-positive recipients (Table 1).

The proportion of patients suffering from delayed graft function remained stable. A substantial reduction of the incidence of acute rejection was noticed after 1994. However, modifications of serum creatinine and proteinuria between years were rather small despite the differences reached statistical significance (Table 1).

While cyclosporine and azathioprine were the most frequent treatment in 1990, tacrolimus associated with mycophenolate mofetil was the most frequent immunosuppressive regimen in 2002 (Figure 1).

Graft survival

Maximum follow-up was 16 years in patients transplanted in January 1990 and minimum follow-up was 3 years in patients transplanted in December 2002. Kaplan–Meier estimates of graft survival are shown in Figure 2.

Renal allograft half-life time

Renal allograft half-life time in the 1990 cohort was 14.2 years. Additionally, projected renal allograft half-life time was estimated by the exponential, Weibull, gamma, log-logistic and lognormal models in each cohort (Table 2). Projected graft survival significantly increased from 1990 to 2002 when it was estimated with the exponential method, while it did not show a significant difference using the other models.

To evaluate the goodness of fit, Cox–Snell residuals were calculated and plotted against the Kaplan–Meier estimates of the cumulative hazard function (Figure 3). To order the studied models according to their goodness of fit, we employed the AIC parameter that was 5371 for the exponential, 5193 for the Weibull, 5145 for the gamma, 5178 for the log-logistic and 5144 for the lognormal models.

In order to estimate the observation time needed for a rather stable calculation of death-censored graft survival, we compared real 10-year death-censored graft survival in the 1990 and 1994 cohorts with the 10-year estimated graft survival censoring patients at 3 and 6 years using the different models. As shown in Table 3, the estimation of 10-year graft survival censoring patients at 3 years yields

Table 1. Demographic and clinical characteristics of donors and recipients in1990, 1994, 1998 and 2002 at the time of transplantation; ESRD, end-stage renal disease; PRA, panel reactive antibodies; HbsAg, hepatitis B antigen; SCr, serum creatinine; ns, non significant

Year of transplantation	1990	1994	1998	2002	P
Number of patients	851	1124	1512	1355	
Donor characteristics					
Age (years)	32 ± 15	40 ± 16	44 ± 17	47 ± 16	0.0001
Donors ≥ 50 years (%)	17.6	33.2	43.7	49.9	0.0001
Gender (% male)	72	63	64	61	0.0001
Cause of death (% stroke)	23	44	49	53	0.0001
Donors after cardiac death (%)	5.7	8.4	8.9	8.2	ns
Living donors (%)	1.6	0.7	1.1	1.8	ns
Recipient characteristics					
Age (year)	43 ± 12	45 ± 13	47 ± 13	49 ± 13	0.0001
Gender (% male)	63	63	63	63	ns
Weight (kg)	63 ± 11	65 ± 12	67 ± 12	69 ± 13	0.0001
Time on dialysis (year)	3.8 ± 3.4	3.5 ± 3.6	3.2 ± 3.8	3.1 ± 3.7	0.0001
Prior transplantation (%)	8.9	11.7	13.7	12.2	0.0078
Diabetes as cause for ESRD (%)	2.5	4.2	6.1	7.2	0.0001
Last PRA (%)	4.3 ± 13	3.5 ± 12	5.0 ± 15	4.0 ± 14	0.0034
Transplant variables					
HLA mismatches (A + B + DR)	2.9 ± 1.2	3.0 ± 1.1	3.2 ± 1.2	3.4 ± 1.3	0.0001
Cold ischaemia time (h)	21 ± 7	20 ± 6	19 ± 6	18 ± 6	0.0001
Reanastomosis time (min)	47 ± 16	48 ± 17	46 ± 19	39 ± 23	0.0001
Anti-HCV antibodies (% positive)	29	19	10	6	0.0001
HbsAg (% positive)	2.9	1.8	1.8	2.7	0.0085
Surgical complication (%)	11.4	10.2	12.3	12.8	ns
Delayed graft function (%)	30.4	30.8	29.3	32.3	ns
Acute rejection (%)	37.8	39.2	25.1	15.7	0.0001
SCr 3 months (mg/dL)	1.61 ± 0.69	1.72 ± 0.73	1.65 ± 0.65	1.59 ± 0.59	0.0001
Proteinuria 3 months (g/day)	0.27 ± 0.60	0.33 ± 0.88	0.30 ± 0.65	0.31 ± 0.71	0.0001

inconsistent estimates, while censoring patients at 6 years of follow-up showed that the estimation between models was more consistent.

Discussion

Factors associated with death-censored graft survival during the first year of follow-up are different from factors associated with graft failure occurring after the first year [12–14]. Main causes for early graft failure are surgical complications and acute rejection [15]. After the first year, progressive renal scarring due to the interaction of multiple and sometimes ill-defined risk factors constitutes the main reason for death-censored graft failure [16]. Among these factors, the best characterized from the epidemiological point of view are donor and recipient characteristics [17], primary disease, time on dialysis, percentage of panel re-active antibodies, number of HLA mismatches, delayed graft function and acute rejection [6, 15, 17, 18]. However, as shown in the present study, all these risk factors are changing year by year. In countries like Spain, mainly relying on deceased transplants, the number of expanded criteria donors has steadily increased [7]. This modification on donor characteristics should be theoretically associated with a time-dependent worsening of late graft survival. On the contrary, the incidence of acute rejection has significantly decreased in the modern transplant era and this modification should theoretically be associated with an improvement of late graft survival. Since nearly all factors associated with late outcome are changing in a time-dependent manner, it is important to permanently monitor

the effect of such modifications on allograft survival in order to properly adapt transplant policies to the changing characteristics of renal transplants.

The gold standard variable to monitor the overall results of renal transplantation is survival and it is often represented by means of the Kaplan–Meier survival function [19]. In a typical survival curve, three different domains can be distinguished. During the first year, graft attrition is maximal and from the first year on, the yearly graft attrition rate varies approximately between 3 and 6%. At the end of follow-up, graft attrition rate apparently decreases, and this phenomenon represents the delay in reporting events at the end of follow-up [3]. For most clinicians, the most straightforward representation of graft survival is renal half-life time. This parameter represents the time elapsed until 50% of grafts have been lost. In the present study, death-censored real half-life only considering patients with a functioning graft at 1 year was calculated in the cohort transplanted in 1990, and it was 14.2 years. This represents a rather long period of time to detect the consequences of transplant policies on survival. Thus, it is desirable to accurately estimate this parameter before 50% of grafts have been lost. For this purpose, different assumption-based statistical models have been applied in large observational studies. The most common approach has been to assume that the survival curve follows an exponential function. In other words, this implies that the hazard of graft failure during follow-up is constant. However, it has been recently shown that the exponential function overestimates renal allograft half-life as time of follow-up shortens [3, 4]. This was the case in the present set of data in which projected half-life progressively increased in more recent cohorts to reach 52.5

years in 2002, which represent a fictitious estimation of graft survival. In the other statistical models despite there was a trend for estimating longer half-life time in the 2002 cohort, this difference is not statistically significant. Thus, the interpretation of the evolution of median survival is completely different depending on the method employed.
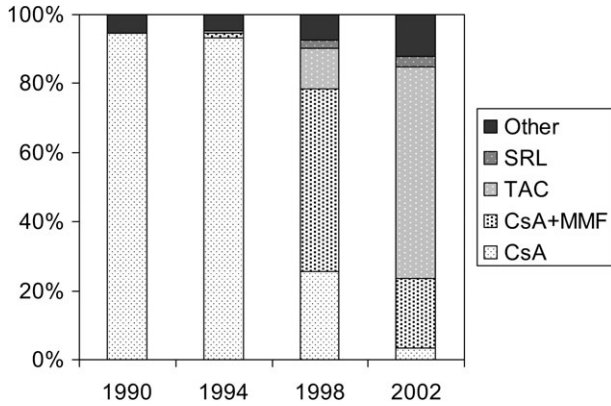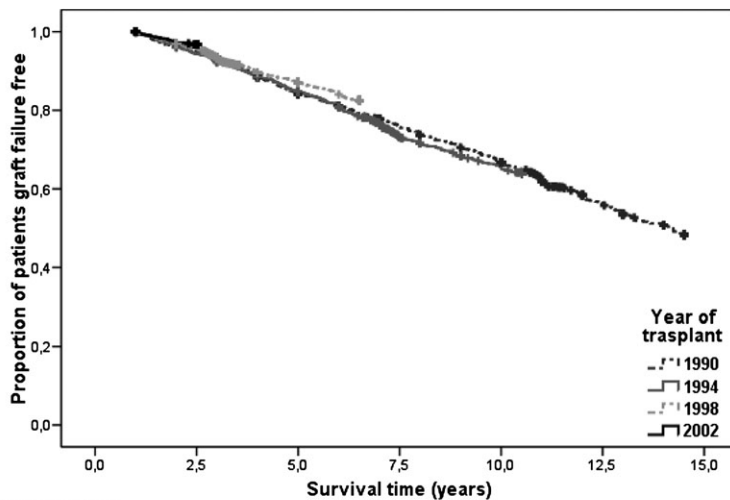

Fig. 1. Immunosuppressive regimens employed in patients transplanted in 1990, 1994, 1998 and 2002. CsA, cyclosporine; MMF, mycophenolate mofetil; TAC, tacrolimus; SRL, sirolimus.

The Weibull, gamma, log-logistic and lognormal methods yielded similar estimations of median half-life. According to the AIC parameter, the best-fitted model was the lognormal function; however, it should be taken into consideration that the differences in the goodness of fit for any of these four models were marginal. Despite the fact that the goodness of fit looks better in the case of Weibull model (Figure 3), it should be taken into consideration that there are different numbers of patients in each domain of the function. Since there are more patients with low risk than patients with high risk, small deviations from the reference line in the first domain of the function contributes to the goodness of fit as much as higher deviations in the last domain.

In order to calculate the observation time needed to obtain a consistent estimate of death-censored graft survival, we compared real 10-year death-censored graft survival and estimated survival with different methods censoring patients at 3 and 6 years. Our results suggest that 3 years is a too short follow-up to consistently estimate allograft survival, while 6 years yielded a consistent result especially when lognormal model was employed. Our data point out that death-censored graft survival only considering kidney transplants functioning at 1 year has not significantly improved between 1990 and 2002. We interpret that the beneficial effect of the progressive reduction of acute rejection

Fig. 2. Kaplan–Meier estimate of death-censored graft survival in the 1990, 1994, 1998 and 2002 cohorts.

Table 2. Estimated death-censored median half-life time and 95% confidence interval with different statistical models; ns, non significant

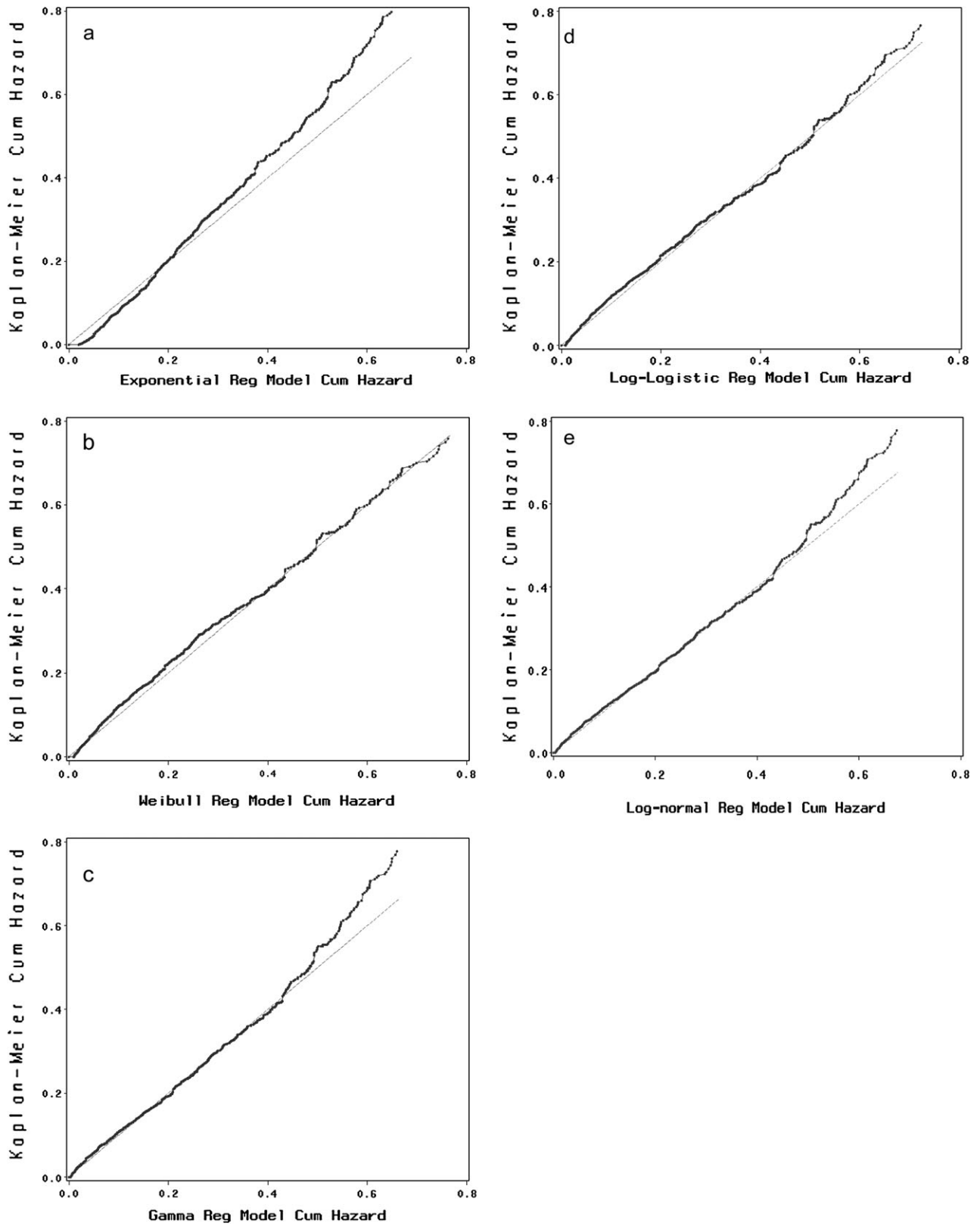|	Exponential	Weibull	Gamma	Log-logistic	Lognormal
1990	15.8 (14.2–17.5)	14.0 (13.1–15.0)	15.5 (13.9–17.1)	14.4 (13.3–15.6)	15.2 (13.8–16.6)
1994	17.3 (15.4–19.1)	13.6 (12.6–14.6)	15.8 (14.2–17.4)	14.3 (13.1–15.4)	15.4 (14.0–16.8)
1998	24.6 (21.4–27.9)	14.9 (13.4–16.4)	17.9 (15.8–20.0)	15.9 (14.3–17.5)	17.5 (15.6–19.4)
2002	52.6 (35.6–69.5)	18.0 (13.7–22.3)	19.1 (15.6–22.6)	18.3 (14.2–22.3)	18.8 (15.3–22.3)
P	<0.001	ns	ns	ns	ns

Fig. 3. Cox–Snell residual analysis for the (**a**) exponential, (**b**) Weibull, (**c**) gamma, (**d**) log-logistic and (**e**) lognormal models.

Table 3. Comparison between real 10-year death-censored graft survival estimated with the Kaplan–Meier method in the 1990 and 1994 cohorts and 10-year estimated graft survival censoring patients at 3 and 6 years using the different models

	Kaplan–Meier survival	Exponential	Weibull	Gamma	Log-logistic	Lognormal
Censoring at 3 years						
1990	65.7	80.3	34.6	84.0	40.3	60.1
1994	63.9	77.0	28.1	84.3	41.8	58.3
Censoring at 6 years						
1990	65.7	71.0	60.2	71.0	62.8	66.3
1994	63.9	70.9	59.9	72.3	62.6	66.2

rate during the study period may have been counterbalanced by increasing donor and recipient age. In this regard, we observed in a case–control study conducted with this population that renal allograft survival has improved between 1990 and 2002 when donors and recipients of similar characteristics are compared [20].

In summary, we conclude that the exponential method overestimates allograft half-life time and consequently, it is not fair to employ this model. The other evaluated models, Weibull, gamma, log-logistic and lognormal, yielded similar estimations of half-life time. Despite the fact that the AIC parameter and estimation of 10-year death-censored graft survival showed that the lognormal model is the best fitted, the difference between these four models was rather small to show a clear superiority of any of them. Thus, larger studies will be necessary to further characterize the utility of the Weibull, gamma, log-logistic and lognormal functions for the estimation of half-life time in renal transplantation.

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