

La supervivencia del injerto a largo plazo: Métodos estadísticos

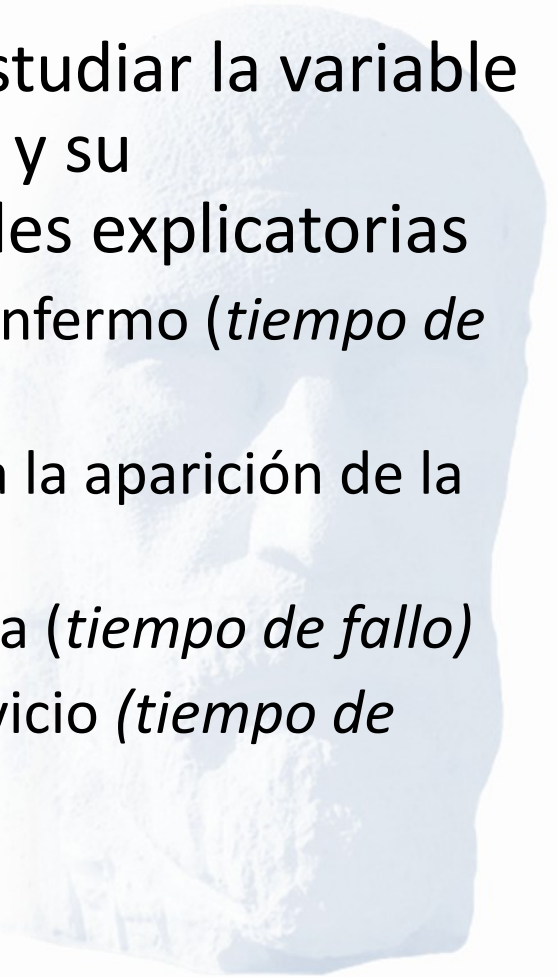
Víctor Abraira

Unidad de Bioestadística Clínica



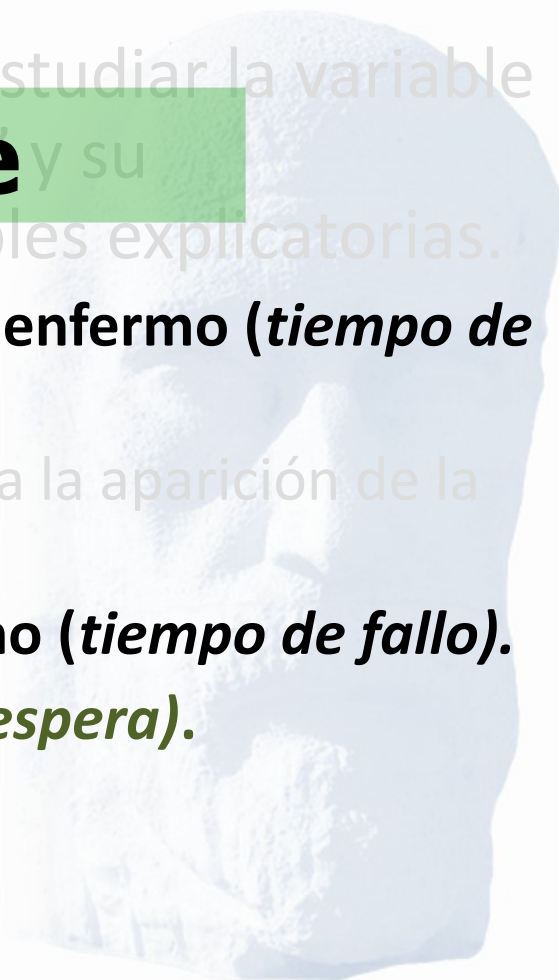
Análisis de supervivencia

- Conjunto de técnicas que permiten estudiar la variable “tiempo hasta que ocurre un evento” y su dependencia de otras posibles variables explicatorias
 - tiempo hasta que ocurre la muerte del enfermo (*tiempo de supervivencia*)
 - tiempo hasta la curación, o tiempo hasta la aparición de la enfermedad, o hasta la recaída
 - tiempo hasta que un cierto producto falla (*tiempo de fallo*)
 - el tiempo de espera hasta recibir un servicio (*tiempo de espera*), etc.



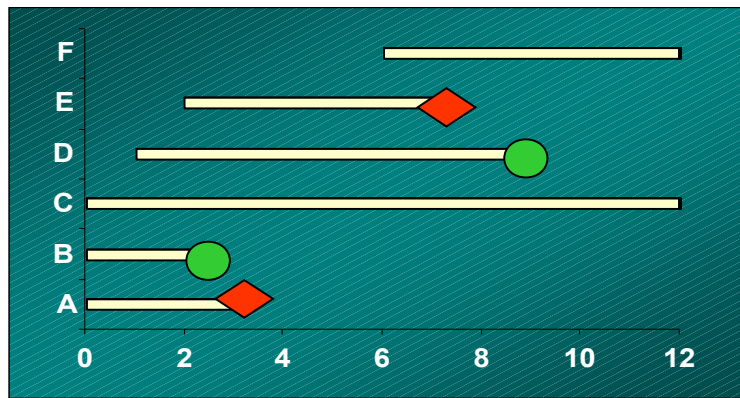
Análisis de supervivencia

- Conjunto de técnicas que permiten estudiar la variable “tiempo hasta que ocurre un evento” y su dependencia de otras posibles variables explicatorias.
 - **tiempo hasta que ocurre la muerte del enfermo (*tiempo de supervivencia*).**
 - tiempo hasta la curación, o tiempo hasta la aparición de la enfermedad, o hasta la recaída.
 - **tiempo hasta el rechazo/fallo del órgano (*tiempo de fallo*).**
 - **tiempo hasta el trasplante (*tiempo de espera*).**



¿Por qué?

- Problemas con la medición:



● Evento
◆ Pérdida

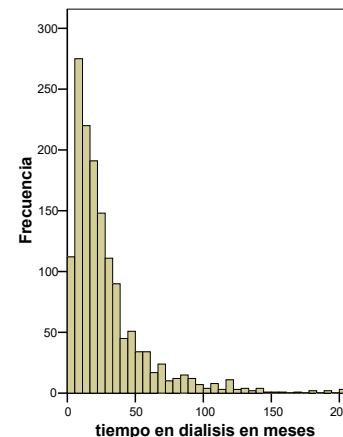
En general, no normal

Desconocido en

Pérdidas

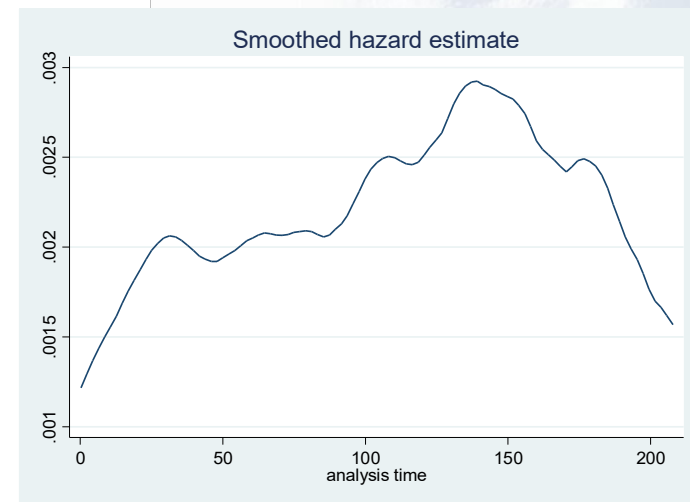
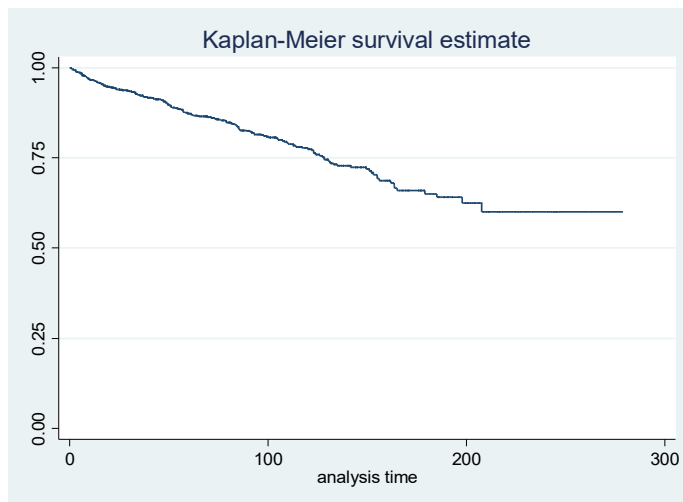
Fin de estudio
sin evento

Censuras



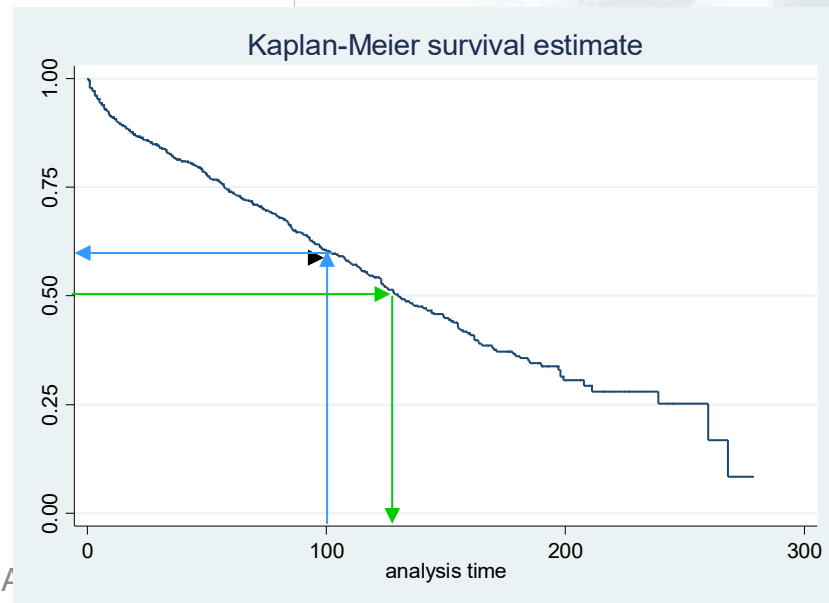
¿Cómo se describe?

- La variable tiempo de espera se describe con:
 - la función de supervivencia $S(t)$.
 - la función de riesgo $h(t)$.

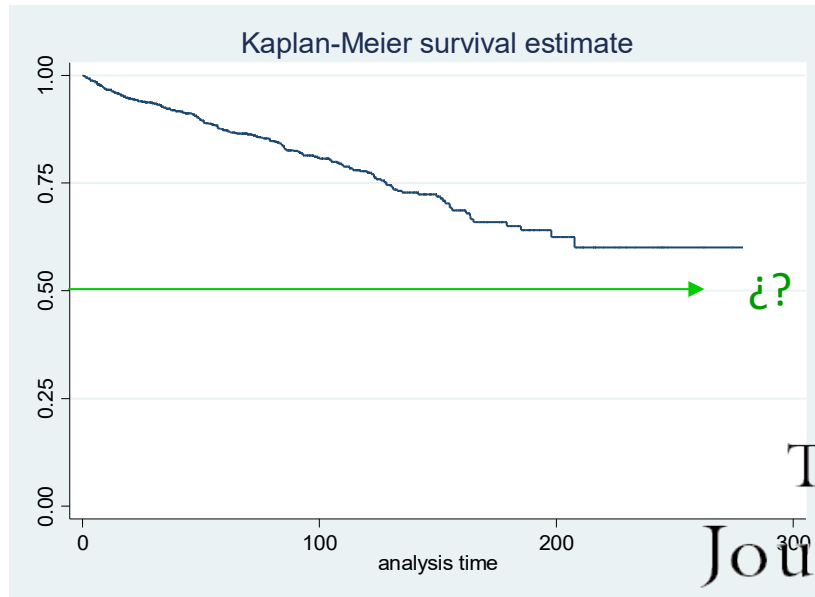


Resumiendo más

- La probabilidad de supervivencia en un tiempo predeterminado.
- El tiempo en el que la probabilidad de supervivencia es 0.5 (mediana de supervivencia o tiempo de “semi-vida”).



Problemas con la mediana



- **Extrapolaciones:**
 - siempre delicadas
 - exigen asumir modelo

The New England
Journal of Medicine

Nephrol Dial Transplant (2011)
doi: 10.1093/ndt/gfq788

Original Article

Conclusions: The exponential model overestimates $t^{1/2}$, 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.

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

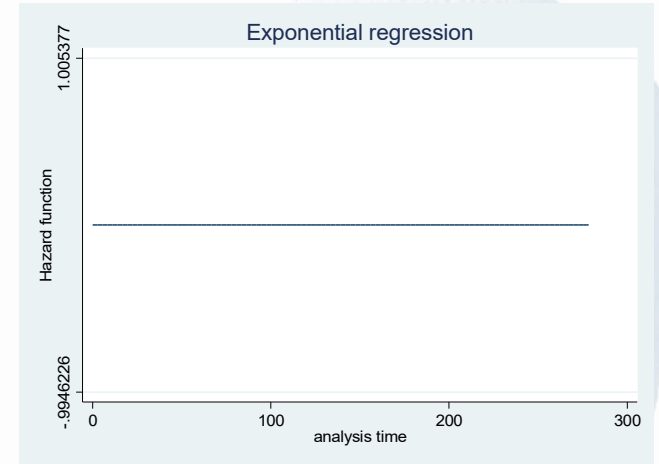
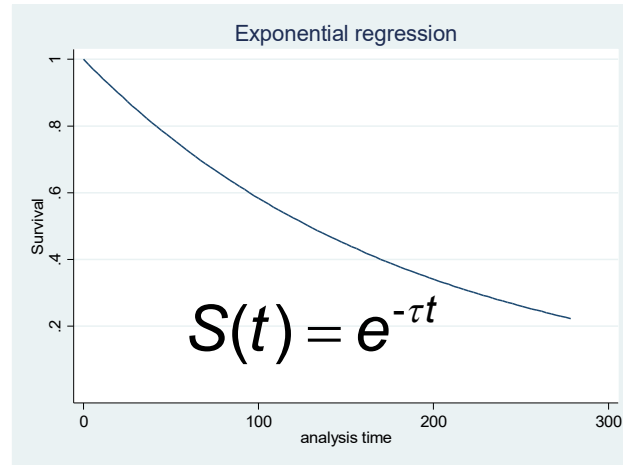
DANIEL SERÓN,^{2,3} MANUEL ARIAS
FOR THE SPA

Daniel Serón¹, Francesc Moreso¹, Manuel Arias², Josep M. Campistol³, Jordi Curto⁴, Domingo Hernandez⁵, José M. Morales⁶, Ana Sanchez-Fructuoso⁷ and Víctor Abraira⁸, for the Spanish Late Allograft Dysfunction Study Group⁹

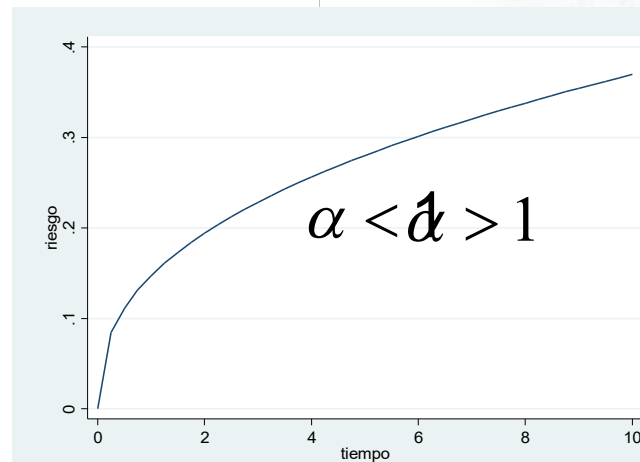
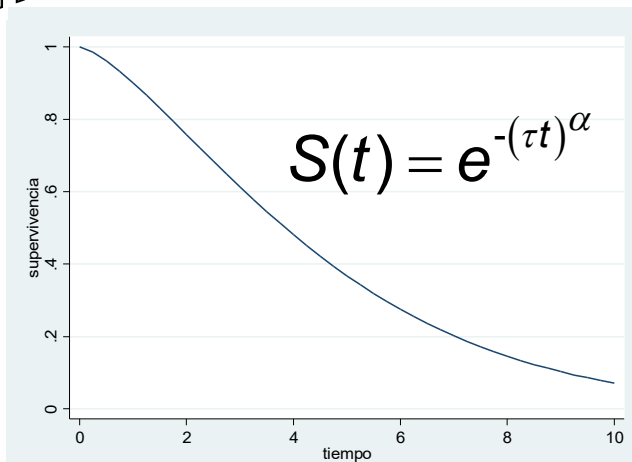
weibull

Modelos

Exponencial

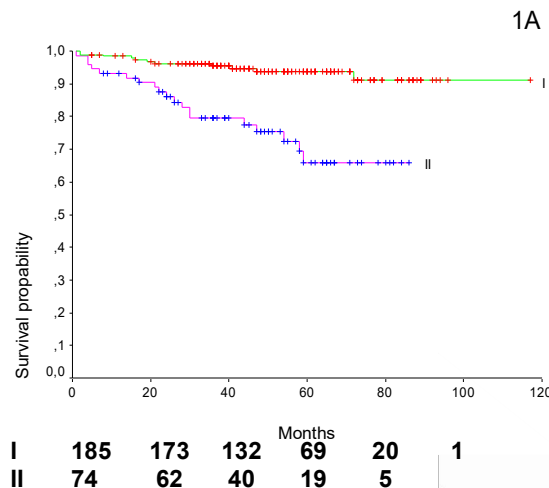
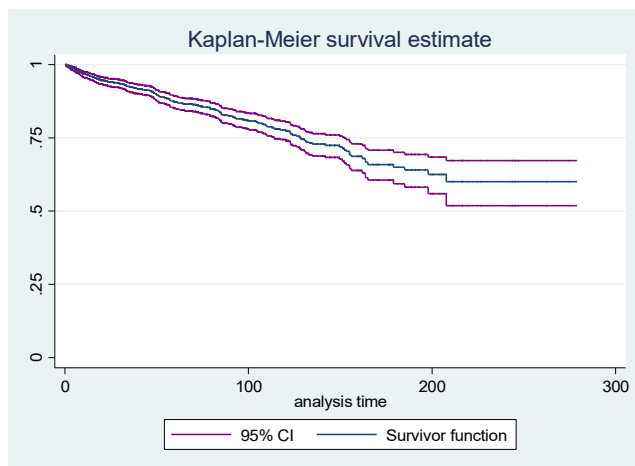


Weibull



Estabilidad de la gráfica

- La precisión de la estimación es variable: las gráficas deberían incluir algún índice de esa precisión.
 - Intervalos de confianza.
 - Tablas de individuos en riesgo.



Eje tiempo hasta el 10% de los individuos

Pocock, Clayton, Altman.
Lancet 2002; **359**:1686-89.

¿Cómo se publica?

- Revisión
- 3 de
- Nefr

Table 1. Number (percentage) of articles using survival analyses in the two analyzed periods, by medical journal specialty

Specialty	1991, N (%)	2007, N (%)	Rate ratio (95% confidence interval)
Internal medicine	26 (12.9)	47 (28.7)	2.2 (1.4, 3.4)
Cardiology	23 (9.4)	74 (31.1)	3.3 (2.1, 5.1)
Nephrology	1 (1.2)	13 (10.7)	8.6 (1.2, 64.7)
Oncology	54 (65.1)	106 (55.2)	0.8 (0.7, 1.0)
Total	104 (17.0)	240 (33.5)	2.0 (1.6, 2.4)

Tabl

Test of homogeneity (Mantel–Haenszel); $P = 0.0000$.

Key

Precision of estimates

Curves

30 (30.3)

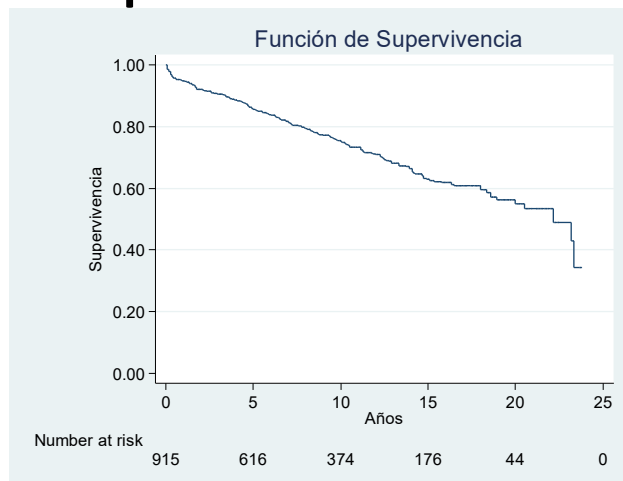
104 (50.5)

0.001

Abraira V, Muriel A, Emparanza JI, Pijoán JI, Royuela A, Plana MN et al. Reporting quality of survival analyses in medical journals still needs improvement. A minimal requirements proposal. *J Clin Epidemiol* 2013; **66**:1340-1346.

Otros puntos críticos

- El método asume que las censuras son al azar (no tienen información)
- Es decir, las censuras contribuyen a la estimación en la asunción de que se comportarían como los pacientes que siguen



Fallo del injerto. Muerte con injerto funcionando, ¿lo cumple?

Trasplantados en RyC entre 1979 y 2002

Otros puntos críticos (II)

- Tiempo de seguimiento “global”

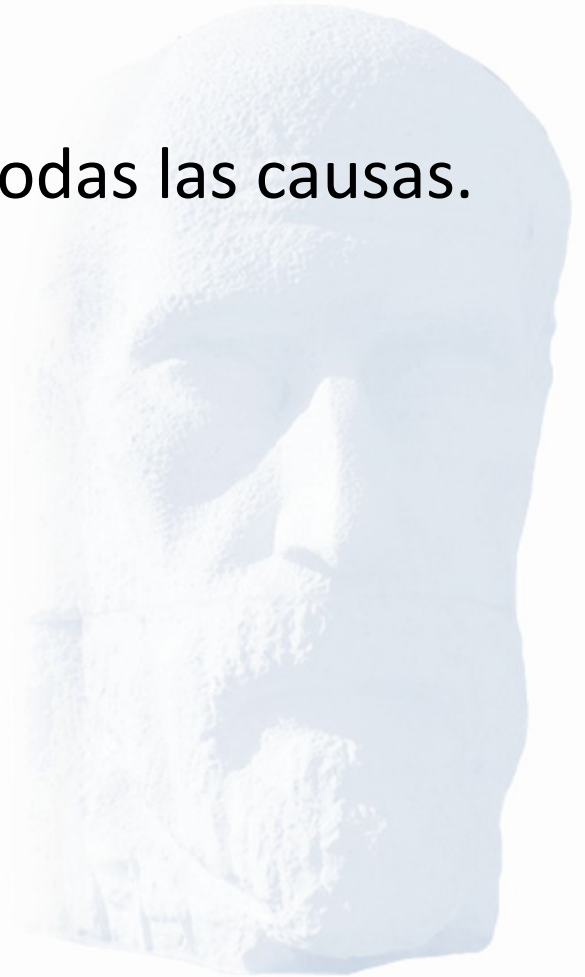
Table 4. Reporting of key elements in the two analyzed periods

Key element	1991, <i>N</i> (%) ^a	2007, <i>N</i> (%) ^a	<i>P</i> -value
Report of follow-up time			0.050
No	32 (30.8)	57 (23.8)	
No time unit	6 (5.8)	18 (7.5)	
Minimum, maximum, range	6 (5.8)	4 (1.7)	
Mean	21 (20.2)	49 (20.4)	
Median	27 (26.0)	98 (40.8)	
Median time to censoring	12 (11.5)	14 (5.8)	

- Efecto “cohorte”

Otros puntos críticos (III)

- Elección del evento
 - muerte por causa específica/por todas las causas.
 - muerte/fallo del injerto.
 - evento compuesto.

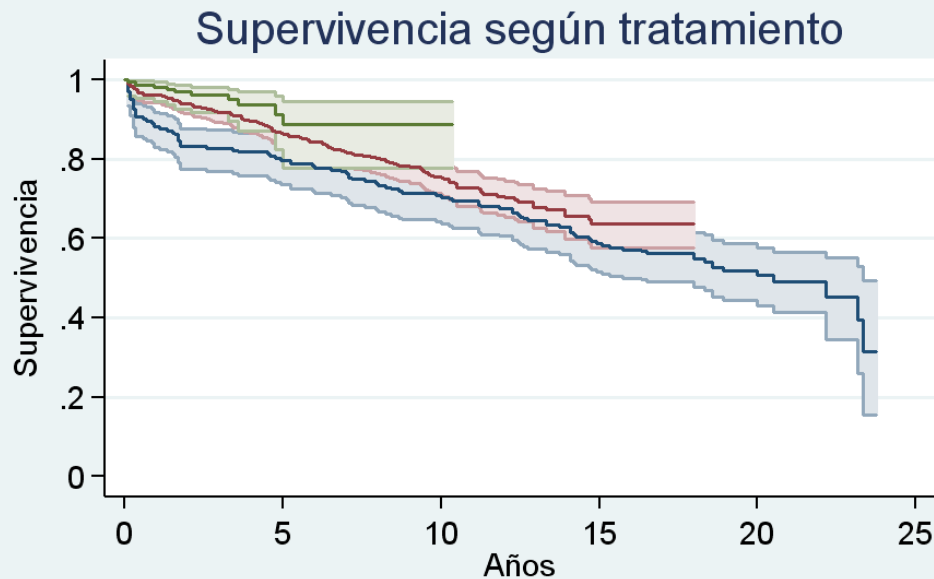


Objetivos del análisis de supervivencia

- Estimar e interpretar curvas de supervivencia y/o riesgo (*investigación fundamental en pronóstico*)
- Compararlas (*investigación sobre tratamiento y en factores pronósticos*)
- Modelos para predecir el riesgo individual de un futuro evento (*investigación en modelos pronósticos*)

Hemingway H, Croft P, Perel P, Hayden JA, Abrams K, Timmis A et al. Prognosis research strategy (PROGRESS) 1: A framework for researching clinical outcomes. *BMJ* 2013; 346:e5595.

Comparar curvas



Number at risk	0	5	10	15	20	25
tratacod = AZA 203	162	144	112	44	0	0
tratacod = CSA 539	419	229	64	0	0	0
tratacod = TACRO 170	35	1	0	0	0	0



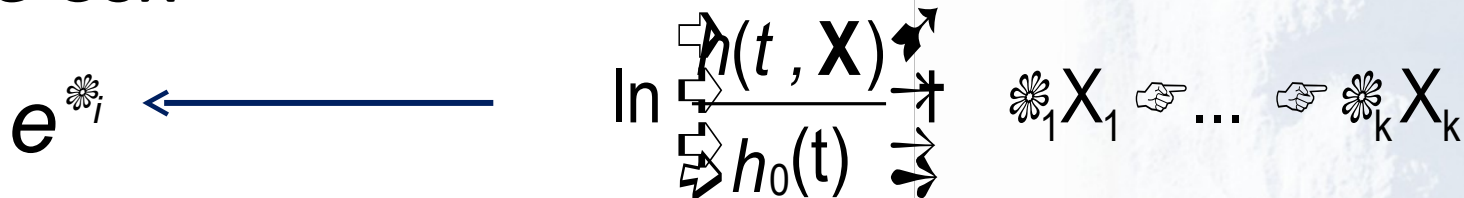
$$\text{chi}^2(2) = 8,41$$

$$\text{Pr} > \text{chi}^2 = 0,0149$$

Trasplantados en RyC entre 1979 y 2002

Otros análisis más avanzados

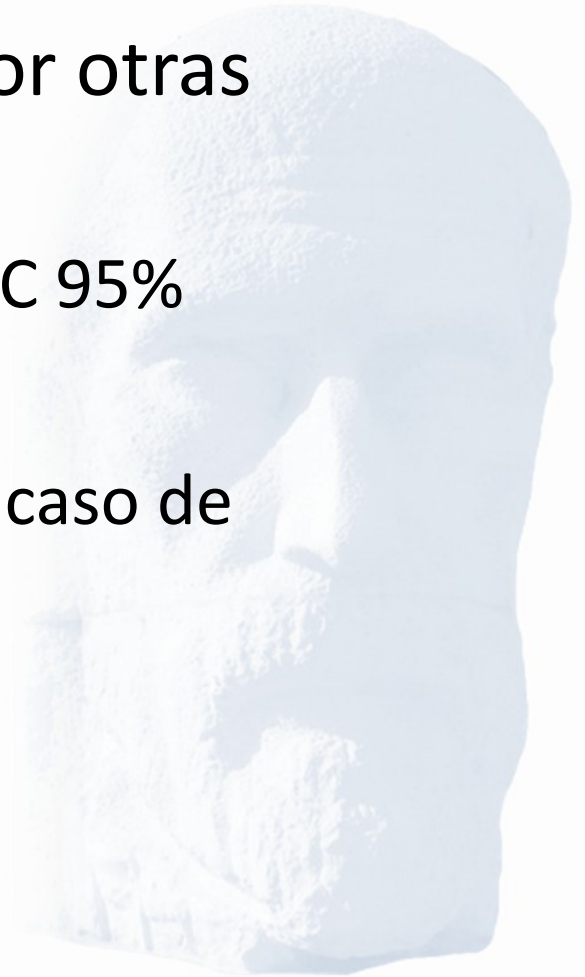
- Modelos de regresión, permiten:
 - Comparar curvas, controlando por otras variables
 - Cuantificar el “efecto”
 - Modelos predictivos
- En supervivencia se usa, sobre todo, el modelo de Cox

$$e^{\ast_i} \leftarrow \ln \frac{h(t, \mathbf{X})}{h_0(t)} \quad \ast_1 X_1 \dots \ast_k X_k$$
A diagram illustrating the Cox model equation. On the left, the term e^{\ast_i} is shown with a blue arrow pointing to the right towards the natural logarithm of the hazard ratio. The hazard ratio is represented as $\frac{h(t, \mathbf{X})}{h_0(t)}$. The numerator $h(t, \mathbf{X})$ has a blue arrow pointing to the right and a red arrow pointing up and to the right. The denominator $h_0(t)$ has a blue arrow pointing to the right and a red arrow pointing down and to the right. To the right of the fraction, the variables $\ast_1 X_1$ and $\ast_k X_k$ are shown, with blue arrows pointing to the right and red arrows pointing to the left, indicating their influence on the hazard function.

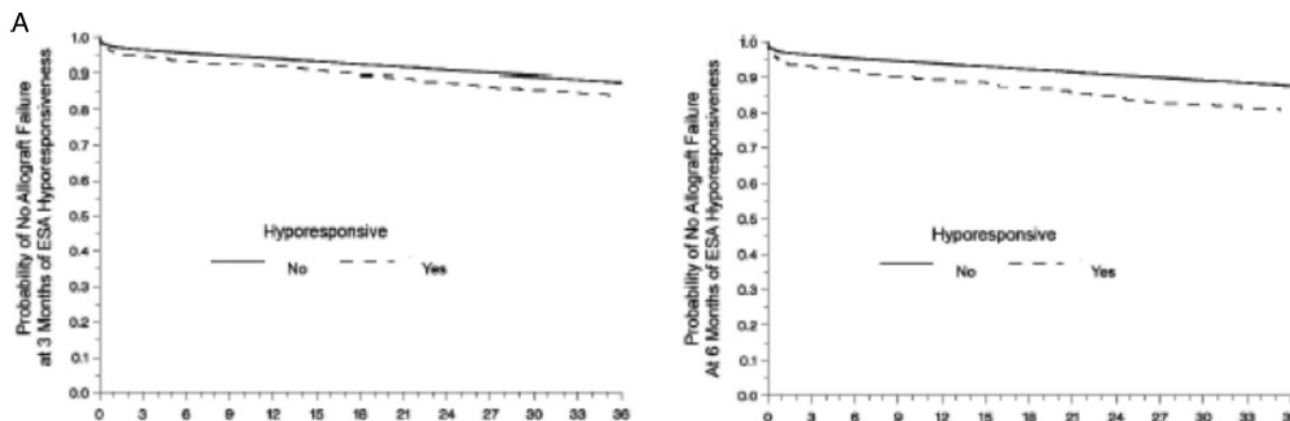
riesgo relativo (HR) cuando X_i aumenta una unidad, manteniéndose constantes las demás variables.

Resultados con modelos

- Comparar curvas controlando por otras variables:
 - Estimaciones del efecto (HR) con IC 95%
 - Ajustados (confusión)
 - Estimaciones por subgrupos en el caso de interacciones
- Modelos predictivos



Estimación del efecto



g Agent
reased
y

Alan Brookhart^{2,3}

TABLE 2. Crude and adjusted hazard ratios for posttransplantation outcomes according to the duration of ESA hyporesponsiveness

ESA hyporesponsiveness ^a	Allograft failure		Allograft loss		All-cause mortality	
	Crude HR ^b (95% CI)	Adjusted ^c HR ^b (95% CI)	Crude HR ^b (95% CI)	Adjusted ^c HR ^b (95% CI)	Crude HR ^b (95% CI)	Adjusted ^c HR ^b (95% CI)
3 months	1.39 (1.21–1.59)	1.23 (1.10–1.42)	1.44 (1.31–1.58)	1.39 (1.25–1.54)	1.52 (1.36–1.69)	1.61 (1.43–1.81)
6 months	1.65 (1.35–2.03)	1.43 (1.15–1.78)	1.60 (1.38–1.86)	1.59 (1.36–1.87)	1.61 (1.35–1.91)	1.85 (1.55–2.23)

^a ESA hyporesponsiveness defined as hematocrit $\leq 33\%$ and ESA dose $\geq 75,000$ units/month.

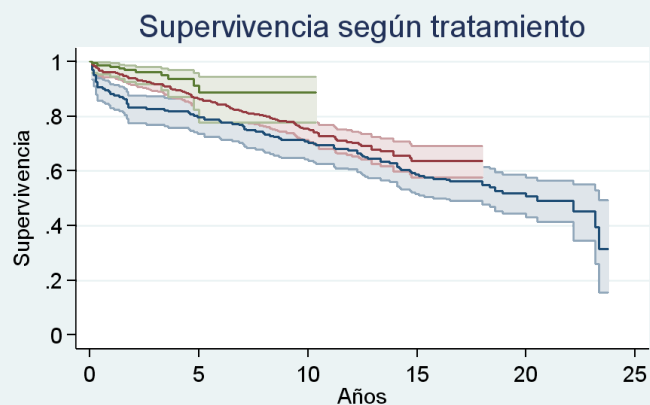
^b Hazard ratios derived from Cox proportional hazards models comparing ESA hyporesponsiveness to appropriate ESA response. All hazard ratios were statistically significant with $P < 0.01$.

^c Adjusted for age, gender, weight, race/ethnicity, hemodialysis vintage, hemodialysis catheter, diabetes status, and donor type.

Allograft failure, present if a second transplant, or return to dialysis. Allograft loss, present if a second transplant, or return to dialysis, or death with a functioning graft.

CI, confidence interval; HR, hazard ratio.

Más de dos grupos



Number at risk	0	5	10	15	20	25
tratacod = AZA 203	162	144	112	44	0	0
tratacod = CSA 539	419	229	64	0	0	0
tratacod = TACRO 170	35	1	0	0	0	0

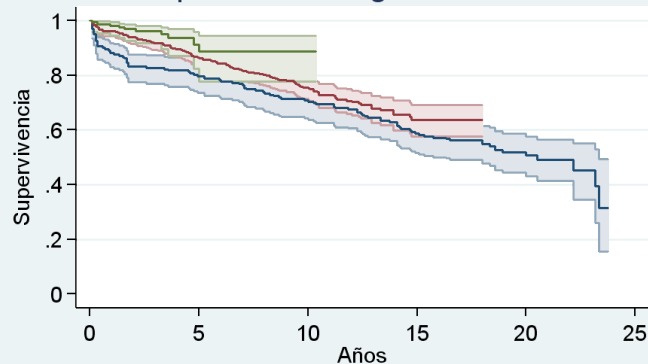


chi2(2) = 8,41
Pr>chi2 = 0,0149

Variable		α	HR (95% IC)	p
Sexo	O: ♂ 1: ♀	-0,29	0,74 (0,57 – 0,98)	0,031
Edad (años)		0,04	1,04 (1,03 – 1,05)	0,000
Tratamiento				0,010
	AZA	0,92	2,50 (1,27 – 4,91)	0,008
	CSA	0,68	1,97 (1,02 – 3,78)	0,043

Confusión

Supervivencia según tratamiento



Number at risk	0	5	10	15	20	25
tratacod = AZA 203	162	144	112	44	0	0
tratacod = CSA 539	419	229	64	0	0	0
tratacod = TACRO 170	35	1	0	0	0	0



Variable	α	HR (95% IC)	p
Sexo	-0,29	0,74 (0,57 – 0,98)	0,031
Edad (años)	0,04	1,04 (1,03 – 1,05)	0,000
Tratamiento			0,010
AZA	0,92	2,50 (1,27 – 4,91)	0,008
CSA	0,68	1,97 (1,02 – 3,78)	0,043

tratamiento
en 3 grupos

AZA	54
CSA	51
TACRO	49
Total	154

tratamiento
en 3
grupos

sexo
Varón Mujer

Variable	Análisis univariable			Análisis multivariable		
	α	HR (95% IC)	p	α	HR (95% IC)	p
Sexo	-0,29	0,74 (0,57 – 0,98)	0,031	-0,24	0,79 (0,60 – 1,03)	0,083
Edad (años)	0,04	1,04 (1,03 – 1,05)	0,000	0,04	1,04 (1,02 – 1,05)	0,000
Tratamiento			0,010			0,083
AZA	0,92	2,50 (1,27 – 4,91)	0,008	0,76	2,13 (1,08 – 4,19)	0,028
CSA	0,68	1,97 (1,02 – 3,78)	0,043	0,62	1,85 (0,96 – 3,56)	0,065

Total	203
	100.00
	540
	100.00
	171
	100.00

Interacción (análisis de subgrupos)

American Journal of Transplantation 2012; 13: 329–338
Wiley Periodicals Inc.

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doi: 10.1111/j.1600-6143.2012.04311.x

Does Expanded Criteria Donor Status Modify the Outcomes of Kidney Transplantation From Donors After Cardiac Death?

S. K. Singh^{a,d} and S. J. Kim^{a,b,c,d,*}

Received 31 May 2012, revised 19 September 2012 and
accepted for publication 20 September 2012

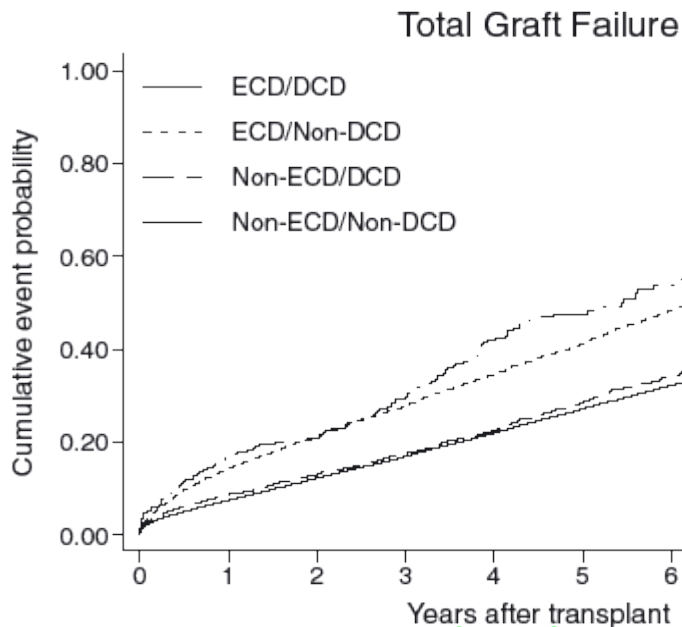


Table 3: Hazard ratios for DCD versus non-DCD kidney transplant recipients across ECD subgroups for total graft failure, death-censored graft failure and death with graft function

Outcome	ECD status	Hazard ratio for DCD vs. Non-DCD (95% CI)	p-Value for interaction
Total graft failure	Non-ECD	1.07 (1.01–1.15)	0.14
	ECD	1.21 (1.04–1.40)	
Death-censored graft failure	Non-ECD	1.12 (1.03–1.23)	0.34
	ECD	1.24 (1.04–1.54)	
Death with graft function	Non-ECD	1.01 (0.92–1.12)	0.26
	ECD	1.17 (0.93–1.45)	

95% CI = 95% confidence interval.

Interacción

A Primary Outcome

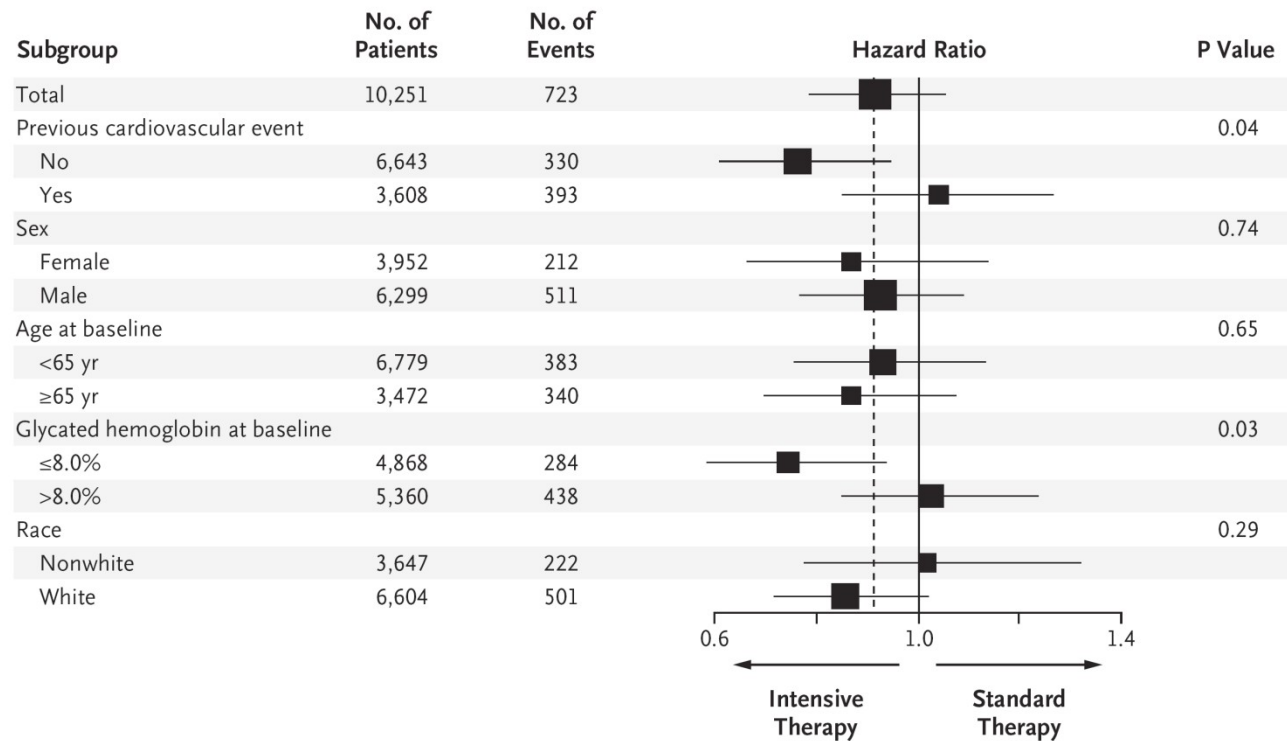


Figure 3. Hazard Ratios for the Primary Outcome and Death from Any Cause in Prespecified Subgroups. Data regarding glycated hemoglobin levels at baseline are presented for 10,288 patients; data were not available for 23 patients. Horizontal bars represent the 95% confidence interval. The size of each square indicates the overall hazard ratio. The size of each square is proportional to the number of patients in the subgroup.

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 12, 2008

VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

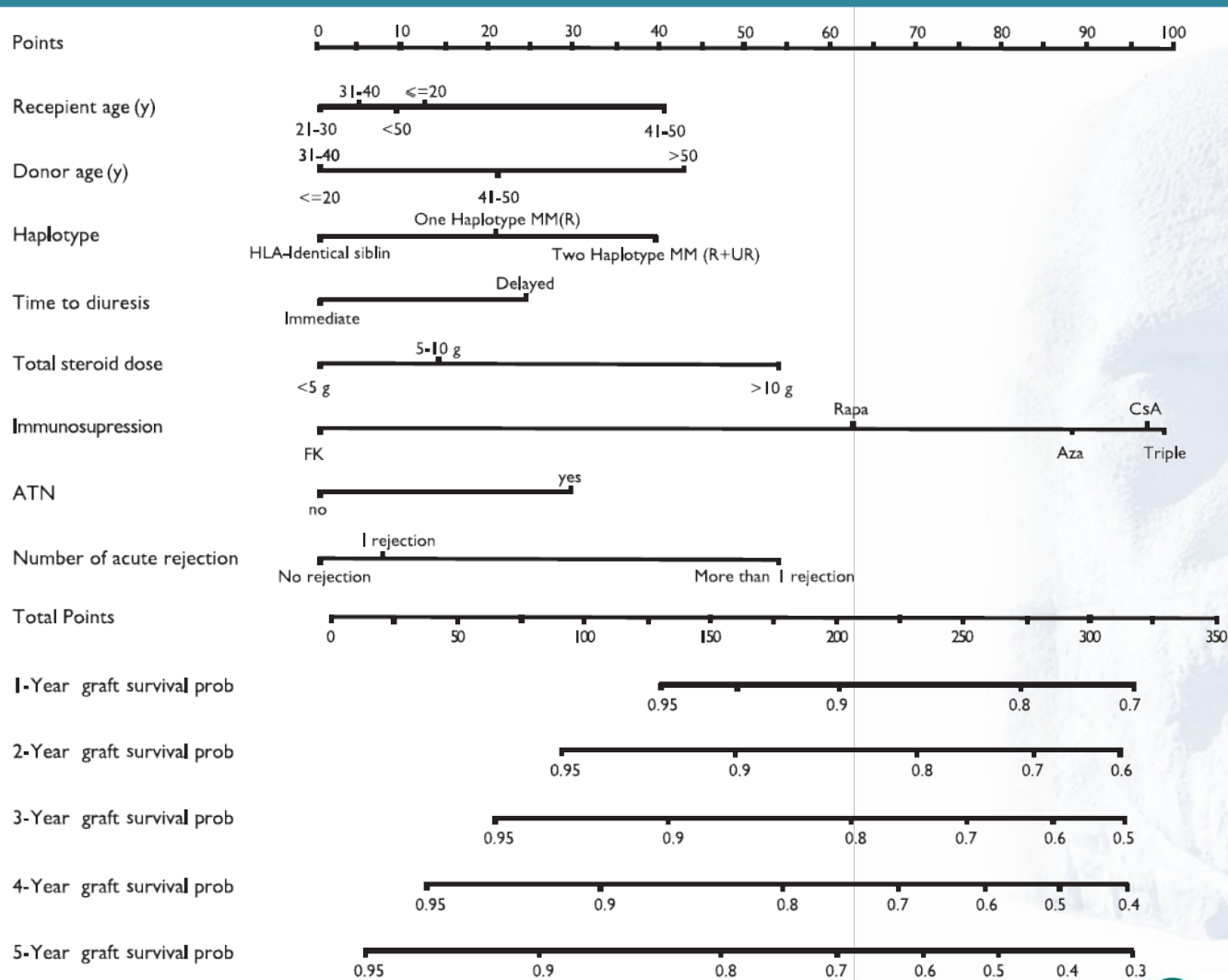
The Action to Control Cardiovascular Risk in Diabetes Study Group*

Table 4. Cox proportional hazard analysis.

	Regression estimate (B)	Relative risk Exp (B)	95.0% CI	P value
Recipient's age (years)				
< 20	---	1		
20 -	-0.111	0.895	0.7 - 1.	
30 -	-0.094	0.911	0.7 - 1.	
40 -	0.323	1.381	1.0 - 1.	
50+	0.069	1.072	0.6 - 2.	
Donor's age (years)				
< 30	---	1		
30 -	-0.002	0.998	0.8 - 1.	
40 -	0.201	1.223	1.0 - 1.	
50 +	0.414	1.513	1.1 - 2.	
Number of blood transfusions				
0	---	1		
1-2	-0.058	0.943	0.7 - 1.	
3-4	0.162	1.175	0.9 - 1.	
≥ 5	0.254	1.289	1.0 - 1.	
HLA-A, B, DR (class 1) MM				
0	---	1		
1	-0.533	0.587	0.3 - 1.	
2	-0.432	0.649	0.3 - 1.	
3	-0.581	0.559	0.2 - 1.	
4	-1.025	0.359	0.0 - 3.	
HLA-A, B, DR (class 2) MM				
0	---	1		
1	0.172	1.187	0.8 - 1.	
2	---	---	---	
Genetic consideration				
HLA-identical siblings	---	1		
1 haplotype MM (R)	0.363	1.437	0.6 - 3.4	.178
2 haplotype MM (R+UR)	0.581	1.788	0.7 - 4.3	.007
Time to diuresis				
Immediate (< 10 min)	---	1		
Delayed (> 10 min)	0.247	1.28	1.0 - 1.7	.045
Primary immunosuppression				
Azathioprine-based	---	1		
Cyclosporine-based	0.094	1.089	0.8 - 1.5	.521
Triple-based	0.105	1.124	0.8 - 1.5	.502
FK-based	-0.805	0.415	0.2 - 0.9	.010
Rapa-based	-0.314	0.707	0.4 - 1.2	.160
Total steroid dose (during first 3 months)				
< 5 g	---	1		
(5-10)	0.107	1.113	0.9 - 1.4	.228
> 10	0.484	1.622	1.3 - 2.1	< .001
ATN				
No	---	1		
Yes	0.278	1.321	1.0 - 1.8	.046
No. of acute rejection episodes (during first 3 months)				
No rejection	---	1		
1 rejection	0.112	1.118	0.9 - 1.4	.569
More than 1 rejection	0.648	1.912	1.3 - 2.7	.001

Abbreviations: FK, tacrolimus; MM, mismatch; R, related; Rapa, sirolimus; UR, unrelated.

Nomograma



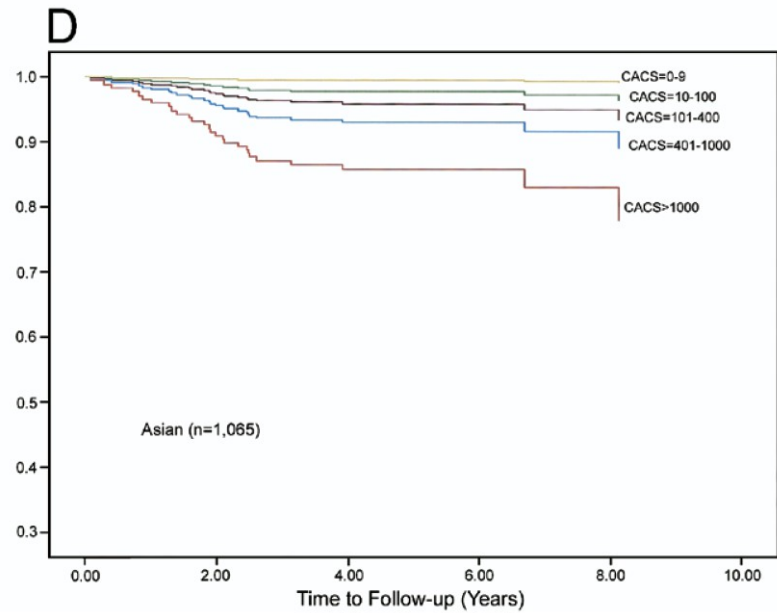
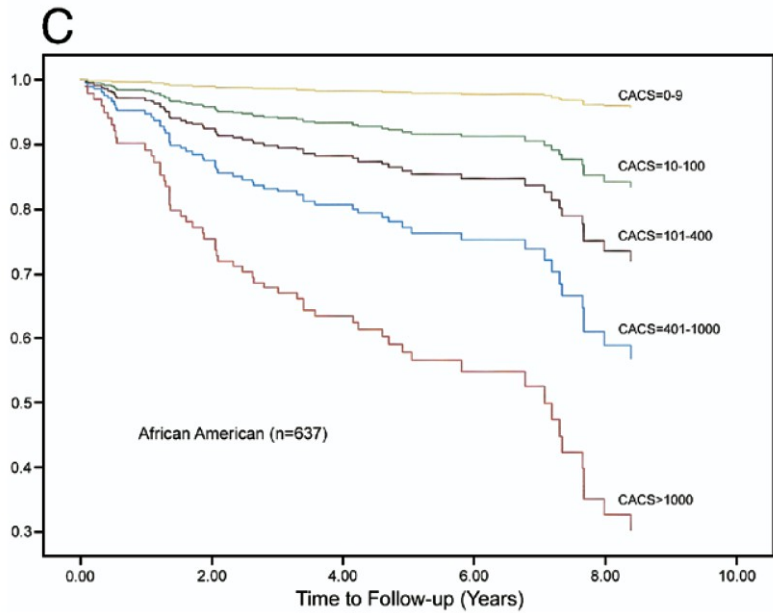
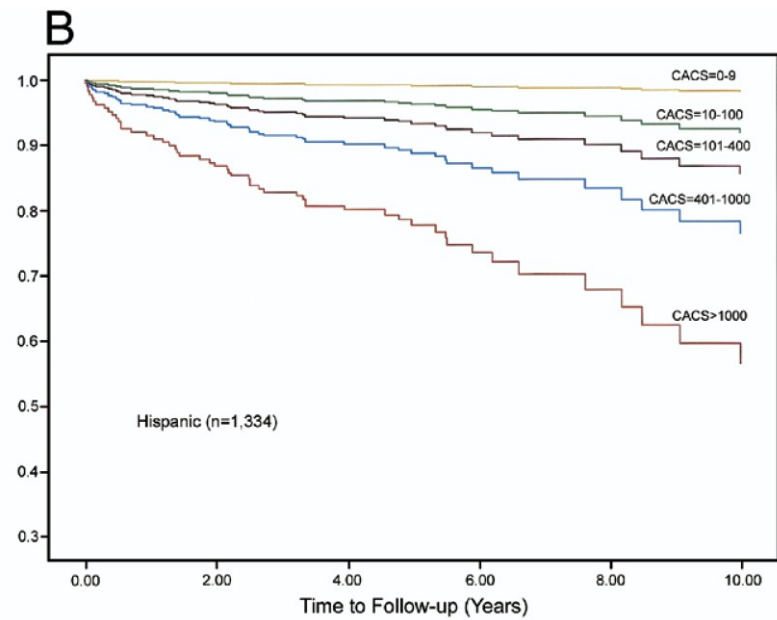
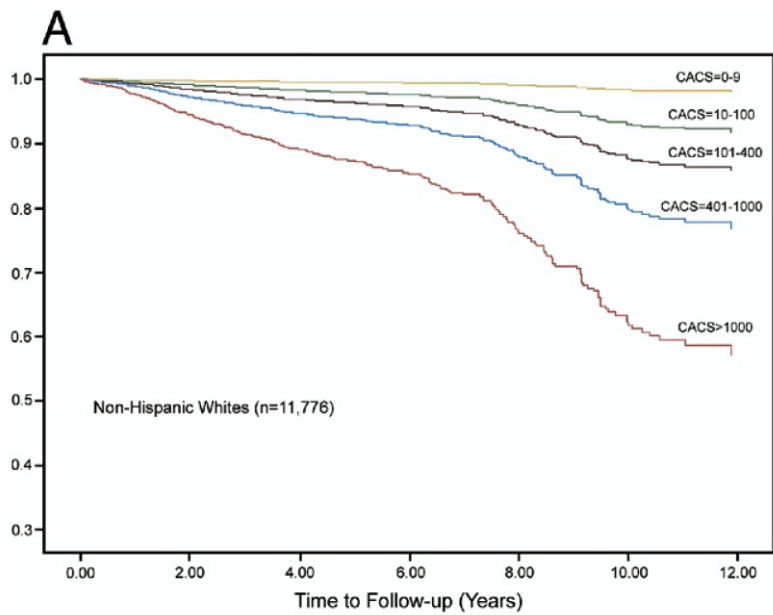
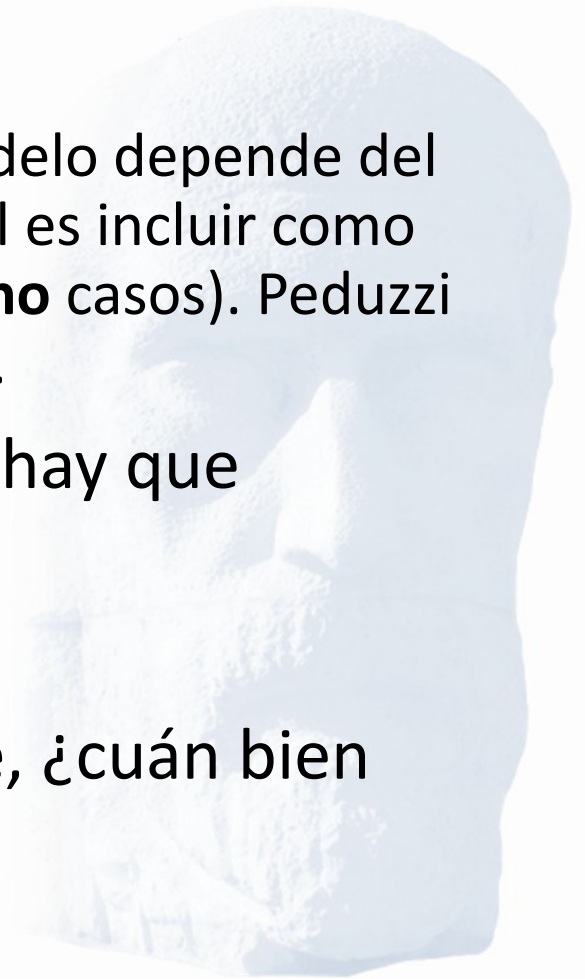


Figure 3 Cumulative Survival By CACS in Ethnic Subsets

(A to D) Using risk-stratified Cox proportional hazard survival analyses, the survival ranged from 98% to 57% in non-Hispanic whites, 97% to 30% in African Americans, 99% to 60% in Hispanics, and 100% to 80% in Asians for coronary artery calcium scores (CACS) of 0 to 10 to $\geq 1,000$.

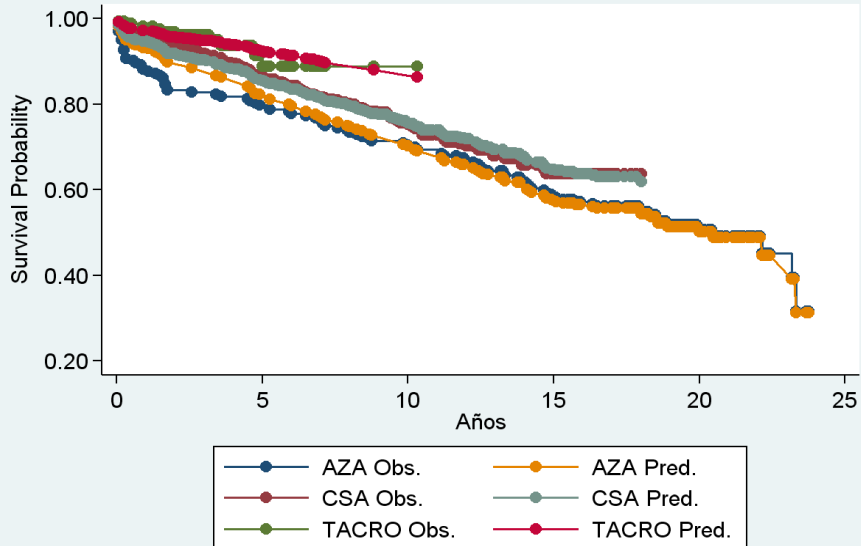
Puntos críticos con los modelos

- Número de variables:
 - el número máximo de variables del modelo depende del número de eventos (un criterio habitual es incluir como máximo una variable cada 10 eventos, **no** casos). Peduzzi et al. *J Clin Epidemiol* 1995; **48**:1503-10.
- Los modelos tienen asunciones, que hay que verificar:
 - Cox asume riesgo proporcional.
- Hay que evaluar la bondad del ajuste, ¿cuán bien ajustan los datos al modelo?
 - Prueba del LR

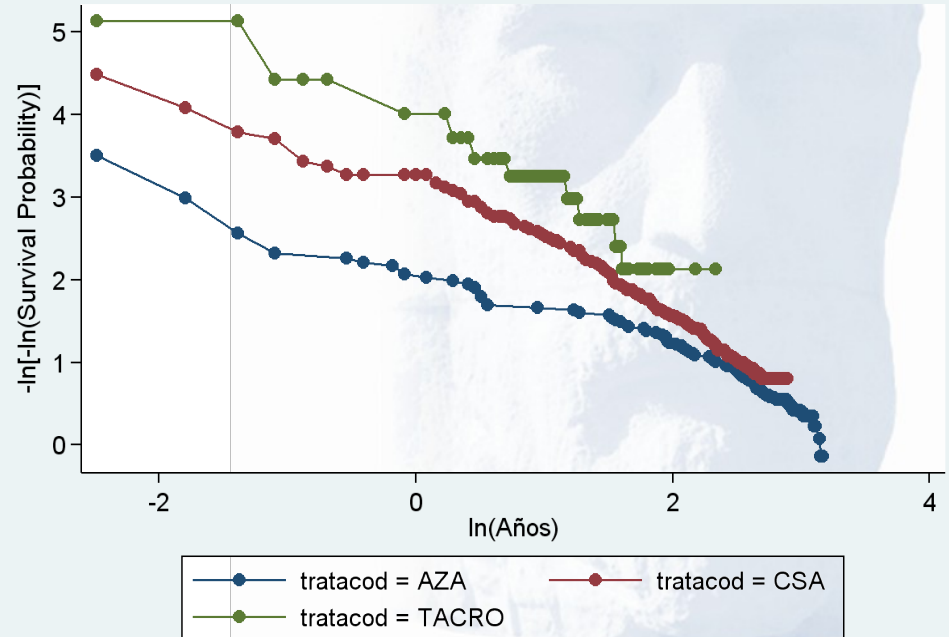


Verificación del riesgo proporcional

Comparación Cox vs. K-M



Log. del riesgo



Validez del modelo

- Las modelos deben validarse.

Wyatt JC, Altman DG. Prognosis models: clinically useful or quickly forgotten? *BMJ* 1995;**311**:1539-1541

- ¿se comporta igual en otras muestras extraídas de la misma población (*reproducibilidad*) y/o de otras similares (*transportabilidad*)?
 - En los modelos predictivos dos aspectos:
 - calibración : ¿probabilidades predichas coinciden con observadas?
 - discriminación: ¿separa pacientes de alto y bajo riesgo?
 - Otra muestra
 - Partir la muestra en dos (trabajo y validación)
 - Técnicas de re-muestreo (*jackknife* o *bootstrap*).

En la literatura

Table 4. Reporting of key elements in the two analyzed periods

Key element	1991, <i>N</i> (%) ^a	2007, <i>N</i> (%) ^a	<i>P</i> -value
Censoring description	31 (29.8)	94 (39.2)	0.097
Report of follow-up time			0.050
No	32 (30.8)	57 (23.8)	
No time unit	6 (5.8)	18 (7.5)	
Minimum, maximum, range	6 (5.8)	4 (1.7)	
Mean	21 (20.2)	49 (20.4)	
Median	27 (26.0)	98 (40.8)	
Median time to censoring	12 (11.5)	14 (5.8)	
Sample size	14 (13.7)	67 (28.0)	0.004
Precision of estimates			
Curves	30 (30.3)	104 (50.5)	0.001
Effects	26 (53.1)	177 (94.2)	<0.001
Regression models			
Proportional hazards check	5 (10.6)	47 (26.3)	0.024
Goodness-of-fit	3 (6.4)	11 (5.9)	0.904
Validity	0 (0)	14 (7.5)	0.052

^a *N* (%): number of articles (percentage) reporting the corresponding item.



Extensiones de Cox

- El modelo estándar asume variables constantes en el tiempo (sexo) o medidas al comienzo (edad)
- Hay una extensión para variables tiempo-dependen

– Ev

se

– Va

Predicting kidney graft failure using time-dependent renal function covariates

- Aun

Mattheus H.J. de Bruijne^a, Yvo W.J. Sijpkens^{b,*}, Leendert C. Paul^b, Rudi G.J. Westendorp^c, Hans C. van Houwelingen^a, Aeilko H. Zwinderman^a

American Journal of Transplantation 2003; 3: 178–185
Blackwell Munksgaard

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ISSN 1600-6135



Journal of Clinical Epidemiology 56 (2003) 448–455

Epidemiology

Extensiones (II)

- Eventos competitivos

[Transplantation](#). 2014 May 29. [Epub ahead of print]

Clinical Assessment of Mortality Risk in Renal Transplant Candidates in Spain.

[Hernández D¹](#), [de la Nuez PC](#), [Muriel A](#), [Ruiz-Esteban P](#), [González-Molina M](#), [Burgos D](#), [Cabello M](#), [Luengo S](#), [Palma E](#), [Ruda E](#), [Gutiérrez E](#), [Vozmediano C](#), [Torres A](#), [Alonso M](#).

⊕ Author information

Abstract

BACKGROUND: Prediction of mortality in wait-listed patients for kidney transplantation (KT) has not been well elucidated. We assessed whether application of the Charlson comorbidity index (CCI) and other uremia-related comorbidities, not included in the CCI, were associated with mortality in these patients.

METHODS: We included 3851 adult patients from the Andalusian Registry who were placed on the waiting list for KT during the study period (1984-2012). A total of 1975 patients received a successful KT and were censored at that point, whereas 1876 were on the waiting list at any time. Multivariate Cox proportional regression analysis and competing risk models, both of which included a propensity score for factors leading to KT, were constructed to examine death in wait-listed patients.

RESULTS: Overall mortality on the waiting list was 24%, and cardiovascular disease was the leading cause of death (25%), followed by infections (19%) and malignant disorders (7%). By competing risk models, age older than 50 years (subhazard ratio [SHR] 1.4; 95% CI, 1.1-1.9), CCI score higher than 3 (SHR 2.8; 95% CI, 2.1-3.7), a central venous catheter (SHR 1.8; 95% CI, 1.4-2.2) and unemployed status (SHR 1.7; 95% CI, 1.3-2.2) at dialysis entry were significantly associated with mortality. When these factors were incorporated in a composite risk model, mortality risk increased significantly with increasing risk levels.

CONCLUSION: A limited number of comorbidities, easily measurable at entry to dialysis, are associated with mortality in wait-listed patients. This simple clinical assessment may help prioritize high-risk wait-listed patients for receiving an age-matched deceased donor kidney.

PMID: 24879382 [PubMed - as supplied by publisher]

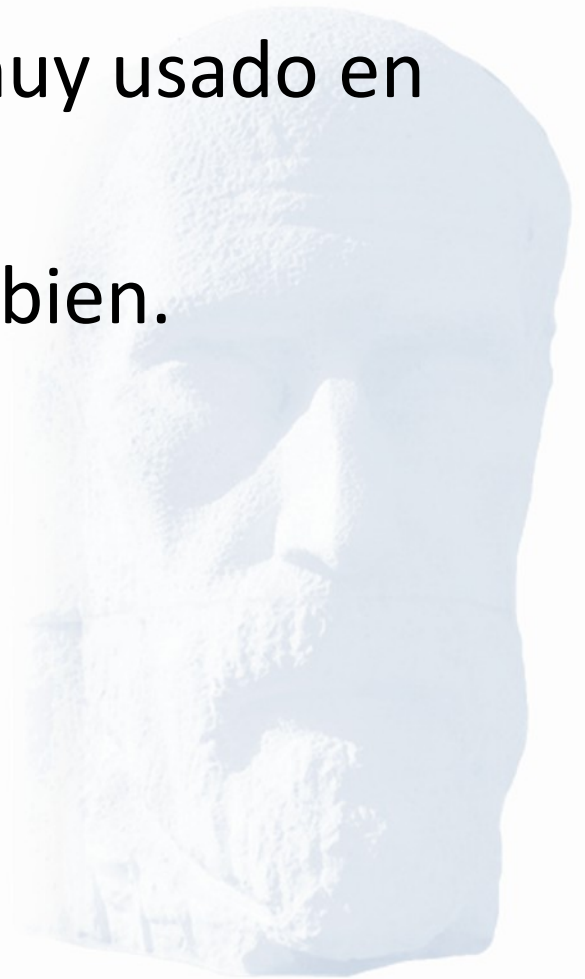


Extensiones (III)

- Aunque no se suele presentar, el proceso de estimación, también estima el riesgo basal ($h_0(t)$). Usualmente único.
 - Pero se pueden considerar estratos (p.e. hospitales o países), estimando un riesgo basal distinto para cada uno (modelo estratificado)
 - Modelo multinivel: se asume un único riesgo basal al que se añade una componente aleatoria (fragilidad), que se asume que tiene una distribución gamma.

Conclusiones

- El análisis de supervivencia es muy usado en trasplante renal (también).
- No se describe suficientemente bien.
- Hay espacio de mejora.



Nuestra propuesta

V. Abraira et al. / *Journal of Clinical Epidemiology* 66 (2013) 1340–1346

1346.e1

Appendix A

Suggestions for a set of “minimum requirements” for reporting survival analyses:

1. Describe assumptions and elements used in the sample size calculation and the estimation process.
2. Identify the type of event of interest under study (e.g., in mortality-related studies, specify whether the outcome variable represents all-cause mortality or cause-specific mortality) and describe the situations that make for censoring.
3. Report sample size and number of events. When examining different events or performing various analyses, report number of patients and events for each analysis.

4. Summarize follow-up time using the median time among the individuals with censored data.
5. Report the uncertainty of estimates with CIs or, at least, provide the number of patients at risk at different times in hazard or survival curves.
6. When using regression models, report the method used and results of model assumptions checking (e.g., the proportional hazards assumption in Cox models or distributional form in parametric models).
7. When using regression models, report the number of the full model variables included, variables selection criteria, and model building methods.
8. When using regression models with a predictive aim, report the goodness of fit of the model.

Bibliografía

- Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. *Br J Cancer* 2003; **89**:232-238.
- Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. *Br J Cancer* 2003; **89**:431-436.
- Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part III: multivariate data analysis -- choosing a model and assessing its adequacy and fit. *Br J Cancer* 2003; **89**:605-611.
- Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part IV: further concepts and methods in survival analysis. *Br J Cancer* 2003; **89**:781-786.
- Abraira V, Quereda C. Curvas de vida y supervivencia en el tratamiento sustitutivo de la insuficiencia renal: diálisis y trasplante renal. In: Arias M ed. *Métodos estadísticos en el trasplante renal*. Madrid: Drug Farma; 2004:67-133.