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Cutpoint determination in continous predictive variables in survival analysis

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Motivation

- Increasing interest in use of binary categorization for continous variables involving clinical or epidemiological data (gene expressions, biomarkers, biochemical parameters,etc.)
- Main objective to build prognostic scores for a follow-up event
    - Easy to compute
    - Classify in high and low risk
    - Allows to calculate impact measures (hazard ratios)

Examples

- Survival 60 days after leaving ICU depending on severity scores and biochemical index
- Time to death or AIDS in HIV infected subjects depending on age, CD4 counts , RNA viral load, etc.
- Cancer survival depending on gene expression or biomarkers

How to select a cutpoint

- Based on graphics of the relationship of the continous variable with the outcome
- Median or percentiles
- Based on previous literature
- Based on best fit or the most significant relation with outcome (minimun p-value of all possible cutpoints)

Minimum p-value

- All values of prognostic variable except a proportion of extrem are cutpoints candidates
- Value that best separates outcomes according to maximum test statistics or minimum p-value is choosen
- Max Log-rank test is chosen in R Maxstat package
- Likelihood profile is chosen in our aproximation in Stata

Caveats

- Inflation or type I error rates
- Overestimate measures of effect
- Loss of information when categorizing
- Replicate the cutpoint in similar data

Solutions

- Bonferroni correction $P_{bonf} = p_{min} * n$ values
- considering data out P_5 and P_{95}
  - $P_{alt=}$ $-3.13\ p_{min}\ (1+1.65\ \ln(p_{min}))$
- Benjamini-Hochberg q values (qqvalue in stata)
- Cross-validation

Stata Template

- Define local parameters (regression type, titles, variables)
- Delete missing values, select data between percentiles 5 & 95
- Store null model
- Loop among unique values of quantitative variable and dichotomize variable
- Fit a regression model and calculate likelihood ratio test
- Save likelihood, p value in a temporary file
- Calculate Bonferroni and Benjamini-Hochberg corrections

Stata Template

- Select the minimum p-value (first obs after gsorting)
- Plot likelihood profile and hr profile
- Top ten table of p-values
- Fit regression model with selected cutpoint
- Use html functions for output
- Saving results & graphs in html file

Example

- Data from GEMES Spanish HIV seroconverters study
  - 2257 HIV seroconventers
  - Interested in time to death
  - CD4 and age as covariates
  - Find cutpoint for CD4 and age

Descriptiu cohort GEMES

	N individus	N Events	Taxa de incidencia*100 pers. Temps (I.C.95%)	Temps a risc
Total	2257	599	2.83 (2.61; 3.07)	21133.35

```
******* TROBAR PUNT DE TALL PER A VARIABLES CONTINUAS (CUTPOINT FINDER) ********
 local titol = "Temps a mort"   // Titol del gràfic0
 local tit_time = "Anys de seguiment" // Unitat de temps . Eix X
 local y_ord = "% de supervivents  " // Unitat de temps. Eix Y

**** Selecciona el tipus de regressio ******************************

local tiporeg="stcox"

if "`tiporeg'"=="logit" local RR="OR"  // Regressió logística
if "`tiporeg'"=="stcox" local RR="HR"  // Regressió de Cox
if "`tiporeg'"=="regress" local RR="B" // Regressió Lineal
if "`tiporeg'"=="poisson" local RR="RR" // Regressió Poisson

if "`tiporeg'"=="logit" local tr="exp" // Regressió logística
if "`tiporeg'"=="stcox" local tr="exp" // Regressió de Cox
if "`tiporeg'"=="regress" local tr="" // Regressió Lineal
if "`tiporeg'"=="poisson" local tr="exp" // Regressió Poisson0

*** Selecciona la variable resposta ******************************

local var_resp=""  // Variable resposta . En blanc per a Regressió de Cox
tempvar constant
gen `constant'=1

 *** Selecciona les variables del model per trobar punts de tall  **************
************************************************ CAL CANVIAR OOOJOOOOOO   ******

foreach vartalli in  cd4 edad {   // Variables quantitatives a dicotomizar
```

Top ten table

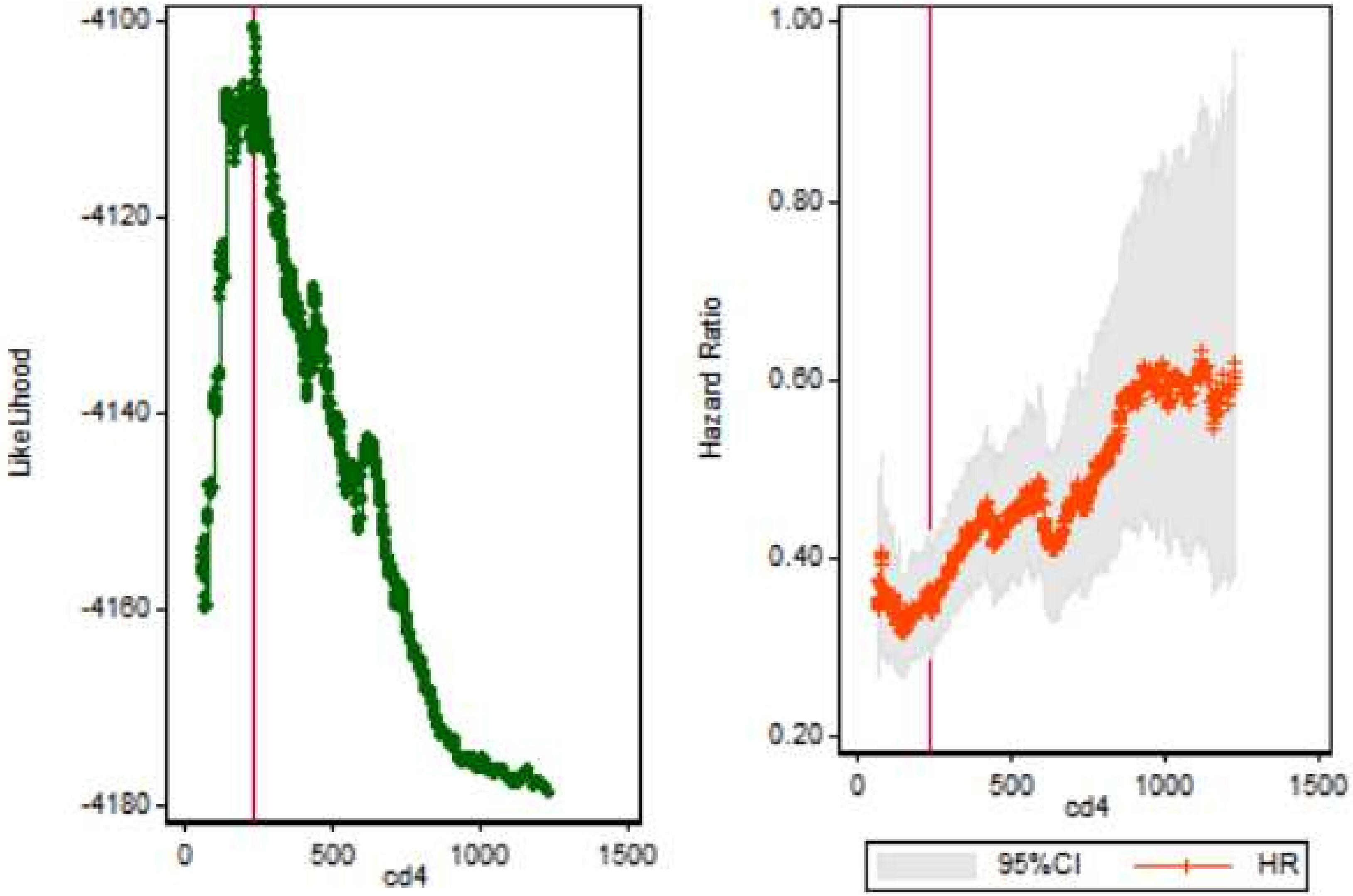
Anàlisi de supervivència Punts de tall de cd4

Top Ten Punts de tall de cd4

	P-value rank	Likelihood	Cutpoint	Hazard Ratio	Lower bound 95%CI	Upper bound 95%CI	p Value	p adjust Altman	Q value Benjamini-Hochberg	p adjust Bonferroni
1	1	-4100.598	240	0.34	0.29	0.40	5.89e-37	2.52e-34	3.338e-34	5.02e-34
2	2	-4100.882	241	0.34	0.29	0.40	7.84e-37	3.34e-34	3.338e-34	6.68e-34
3	3	-4101.718	242	0.34	0.29	0.40	1.82e-36	7.67e-34	3.439e-34	1.55e-33
4	4	-4101.774	243	0.34	0.29	0.40	1.92e-36	8.11e-34	3.439e-34	1.64e-33
5	5	-4101.822	244	0.34	0.29	0.40	2.02e-36	8.50e-34	3.439e-34	1.72e-33
6	6	-4102.542	245	0.34	0.29	0.40	4.16e-36	1.74e-33	5.909e-34	3.55e-33
7	7	-4104.054	246	0.35	0.30	0.41	1.91e-35	7.82e-33	2.188e-33	1.63e-32
8	8	-4104.128	246.5	0.35	0.30	0.41	2.05e-35	8.41e-33	2.188e-33	1.75e-32
9	9	-4105.076	247	0.35	0.30	0.41	5.33e-35	2.16e-32	5.048e-33	4.54e-32
10	10	-4105.958	248	0.35	0.30	0.41	1.30e-34	5.18e-32	1.104e-32	1.10e-31

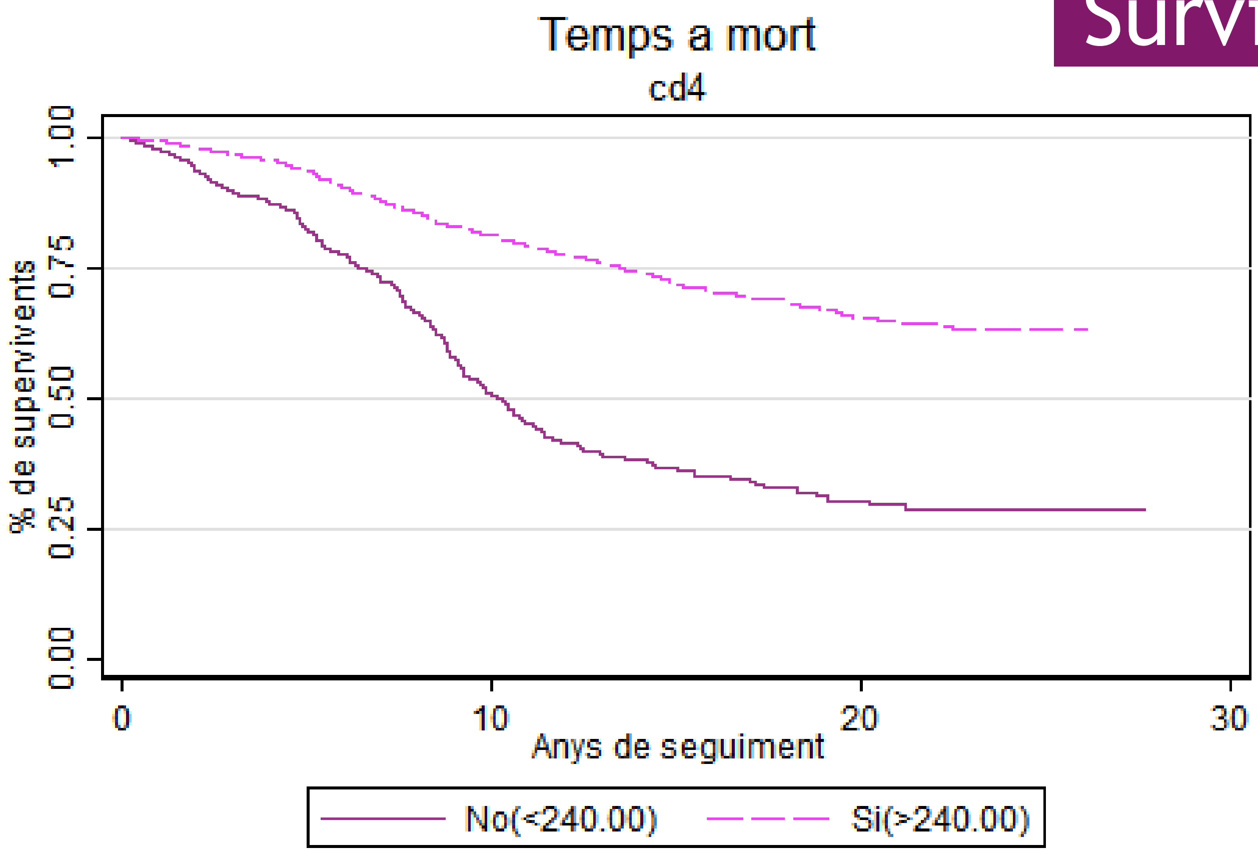
Profile plot

Punts de tall per cd4 en 240.00 (cd4 >240.00)



valor optimo 240.00, q value 0.0000

Survival after cutpoint



P valor = 0.0000 Bonferroni= 0.0000 Q valor =0.0000

cd4 >240.00	N individus	N Events	Taxa de incidencia*100 pers. Temps (I.C.95%)	Temps a risc	Temps Q_{25}	Temps Mediana (Temps)	Temps Q_{75}	P valor
No(<240.00)	491	274	5.84 (5.17; 6.57)	4693.86	6.45	10.16	.	
Si(>240.00)	1762	322	1.96 (1.76; 2.19)	16393.95	13.47	.	.	0.0000
Total	2253	596	2.83 (2.60; 3.06)	21087.81	9.32	.	.	

Cox after cutpoint

Regressio multivariant stcox

Number of obs = 2253

VARIABLE		HR	(95%CI)	p-value
cd4 >240.00	No(<240.00)	1		0.0000
	Si(>240.00)	0.34	(0.29; 0.40)	

LL model= -4100.60 ; AIC model= 8203.20 ; BIC model= 8208.92

p valor ajustado 0.0000

Regressio multivariant stcox. p valors ajustats

Number of obs = 2253

VARIABLE		HR	(95%CI)	p-value
cd4 >240.00	No(<240.00)	1		0.0000
	Si(>240.00)	0.34	(0.29; 0.40)	

valors p ajustats Bonferroni

Regressio multivariant stcox. p valors ajustats

Number of obs = 2253

VARIABLE		HR	(95%CI)	p-value
cd4 >240.00	No(<240.00)	1		0.0000
	Si(>240.00)	0.34	(0.29; 0.40)	

valors p ajustats Altman

Survival after cutpoint

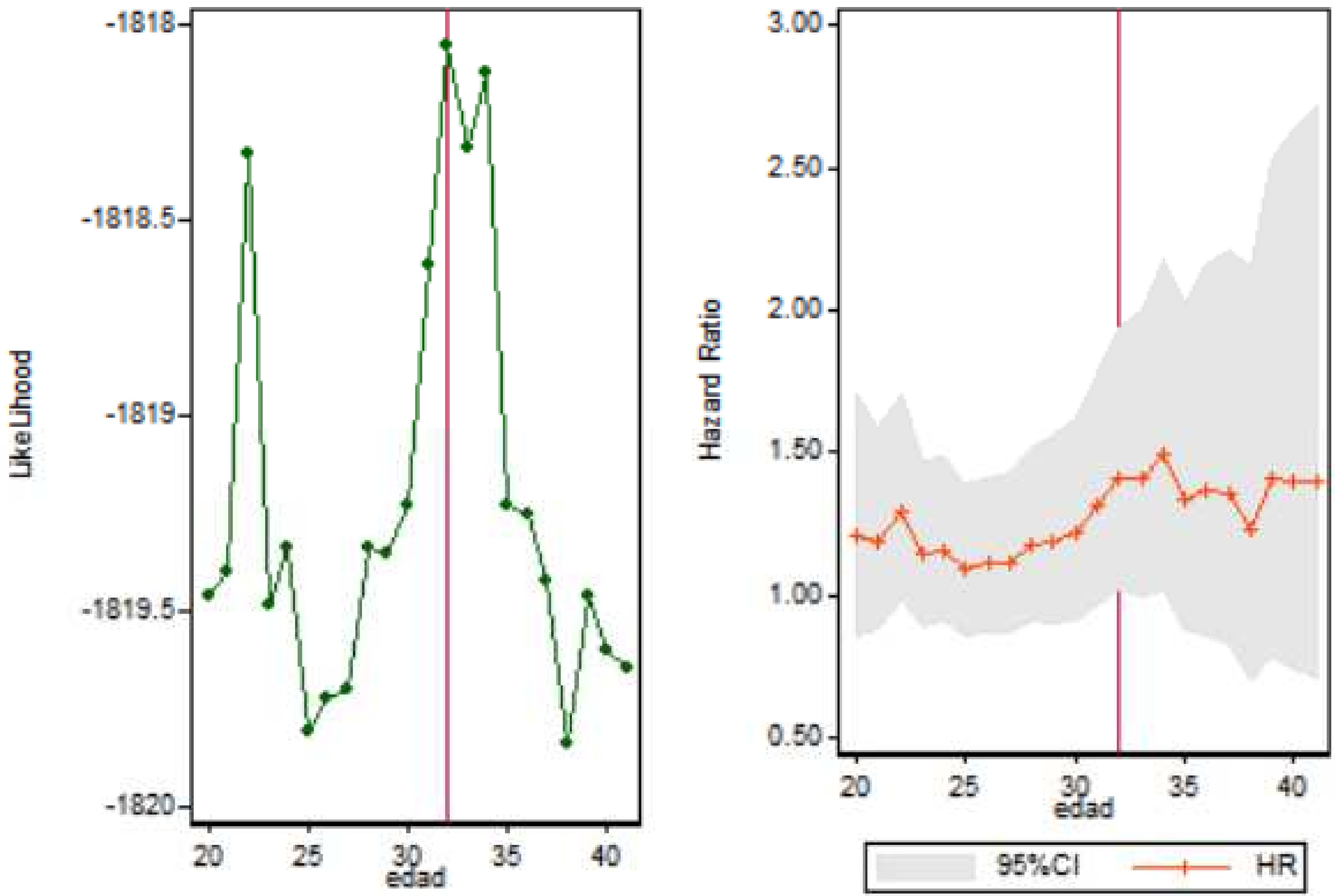
Anàlisi de supervivència Punts de tall de edad

Top Ten Punts de tall de edad

	P-value rank	Likelihood	Cutpoint	Hazard Ratio	Lower bound 95%CI	Upper bound 95%CI	p Value	p adjust Altman	Q value Benjamini-Hochberg	p adjust Bonferroni
1	1	-1818.052	32	1.41	1.02	1.94	.0440258	.572275	.33807288	.9685677
2	2	-1818.123	34	1.49	1.02	2.18	.0478806	.6016266	.33807288	1
3	3	-1818.315	33	1.41	1.00	2.00	.0602932	.685816	.33807288	1
4	4	-1818.331	22	1.29	0.98	1.70	.0614678	.6930518	.33807288	1
5	5	-1818.612	31	1.31	0.97	1.78	.0866564	.8233535	.37960526	1
6	6	-1819.226	35	1.33	0.88	2.02	.1912814	1.03524	.37960526	1
7	7	-1819.232	30	1.22	0.91	1.62	.1929407	1.035614	.37960526	1
8	8	-1819.252	36	1.37	0.87	2.16	.1983415	1.036324	.37960526	1
9	9	-1819.336	28	1.18	0.91	1.52	.2226326	1.030406	.37960526	1
10	10	-1819.338	24	1.16	0.91	1.48	.2232034	1.030096	.37960526	1

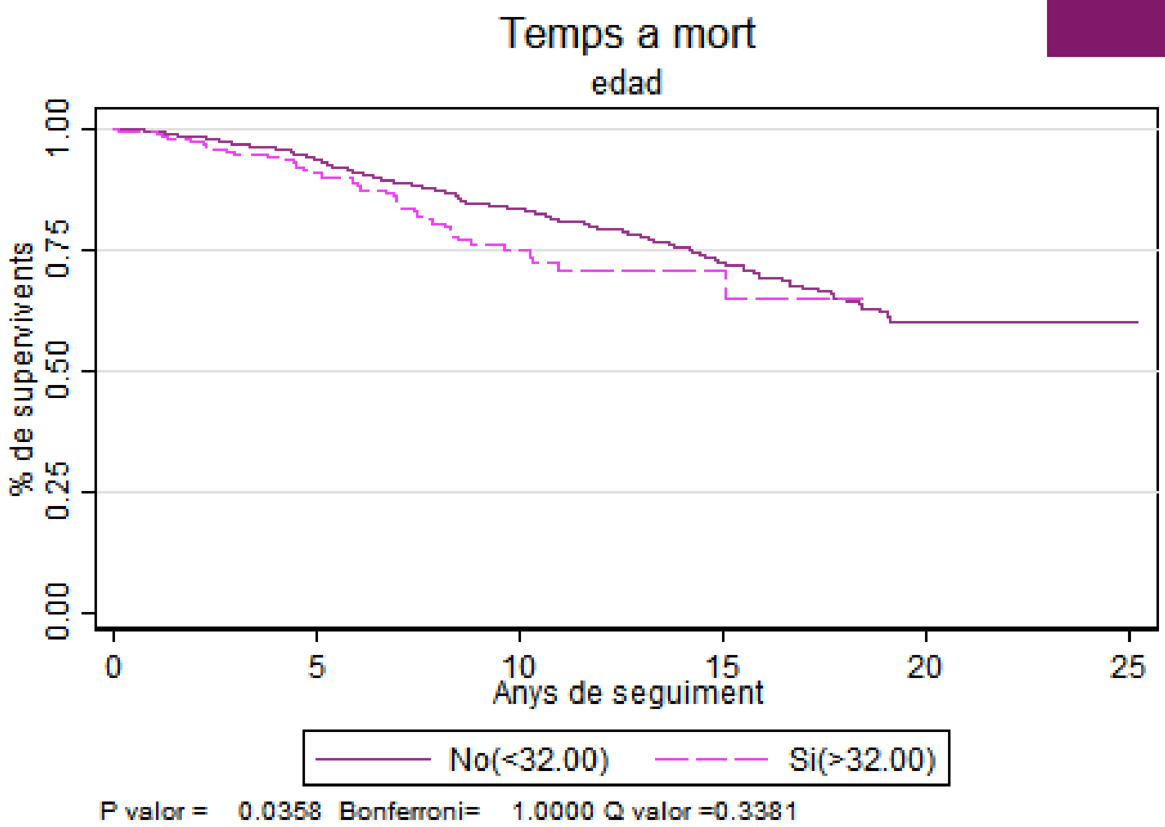
Profile plot

Punts de tall per edad en 32.00 (edad >32.00)



valor optimo 32.00, q value 0.3381

Profile plot



edad >32.00	N individus	N Events	Taxa de incidencia*100 pers. Temps (I.C.95%)	Temps a risc	Temps Q_{25}	Temps Mediana (Temps)	Temps Q_{75}	P valor
No(<32.00)	1332	230	1.96 (1.72; 2.23)	11717.50	14.20	.	.	0.0358
Si(>32.00)	363	46	2.39 (1.75; 3.19)	1924.95	9.58	.	.	
Total	1695	276	2.02 (1.79; 2.28)	13642.45	13.64	.	.	

Cox after cutpoint

Regressio multivariant stcox

Number of obs = 1695

VARIABLE		HR	(95%CI)	p-value
edad >32.00	No(<32.00)	1		0.0367
	Si(>32.00)	1.41	(1.02; 1.94)	

LL model= -1818.05 ; AIC model= 3638.10 ; BIC model= 3643.54

p valor ajustado 0.3381

Regressio multivariant stcox. p valors ajustats

Number of obs = 1695

VARIABLE		HR	(95%CI)	p-value
edad >32.00	No(<32.00)	1		0.8077
	Si(>32.00)	1.41	(1.02; 1.94)	

valors p ajustats Bonferroni

Regressio multivariant stcox. p valors ajustats

Number of obs = 1695

VARIABLE		HR	(95%CI)	p-value
edad >32.00	No(<32.00)	1		0.5117
	Si(>32.00)	1.41	(1.02; 1.94)	

valors p ajustats Altman

Further work

- Build an ado function in Stata
- Extent to more than one variable
- Extent to more than one cutpoint

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- William BA, Mandrekar JN, Mandrekar SJ, Cha SS, Furth AF. Finding optimal cutpoints for continous covariates with binary and time-to-event outcomes. Techical Report Series #79. Department of Health Scientes Research Mayo Clinic. 2006.
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Thanks

Gràcies

Gracias