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Primary Biliary Cholangitis Study

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What is PBC!

Primary Biliary Cholangitis is an autoimmune disease leading to destruction of the small bile ducts in the liver. The progression is slow but unavoidable, eventually leading to cirrhosis and liver decompensation.

THE DATA

- The data is from the Mayo Clinic trial in PBC conducted between 1974 and 1984.
- A total of 424 PBC patients were referred to Mayo Clinic during the ten-year interval.
- The first 312 cases in the data set participated in the randomized trial of the drug D-penicillamine.
- The additional 112 cases did not participate in the clinical trial, but consented to have basic measurements recorded and to be followed for survival.
- The data used for the survival analysis was the complete cases of the randomized trial of D-penicillamine (DPCA), which were 276 cases.

Data Dictionary

Variable	Label	Codings
TIME	Time to death, years	Range: 0.11 - 12.48
STATUS	Event / Censoring Indicator	1 = Died, 0 = Censored
TRT	Treatment	1 = DPCA, 0 = Control
STAGE	Histologic stage of the disease, severity of liver damage	1 = "lowest" 4 = "highest"
BILI	Serum Bilirubin (mg/dl)	Range: 0.3 - 28

BASIC DESCRIPTIVES

Statistic	N	Mean	St. Dev.	Min	Median	Max
id	276	158.616	91.663	1	157.5	312
time	276	1,979.167	1,112.380	41	1,788	4,556
status	276	0.402	0.491	0	0	1
trt	276	1.507	0.501	1	2	2
age	276	49.800	10.523	26.278	49.710	78.439
ascites	276	0.069	0.254	0	0	1
hepato	276	0.514	0.501	0	1	1
spiders	276	0.290	0.455	0	0	1
edema	276	0.107	0.270	0.000	0.000	1.000
bili	276	3.334	4.601	0.300	1.400	28.000
chol	276	371.261	234.788	120	310	1,775
albumin	276	3.517	0.405	1.960	3.545	4.400
copper	276	100.768	88.269	4	74	588
alk.phos	276	1,996.612	2,115.478	289.000	1,277.500	13,862.400
ast	276	124.119	56.720	28.380	116.625	457.250
trig	276	124.978	65.281	33	108	598
platelet	276	261.772	93.129	62	257	563
protime	276	10.736	1.008	9.000	10.600	17.100
stage	276	3.040	0.854	1	3	4
survtime	276	5.422	3.048	0.112	4.899	12.482



CROSS TAB

Cell Contents

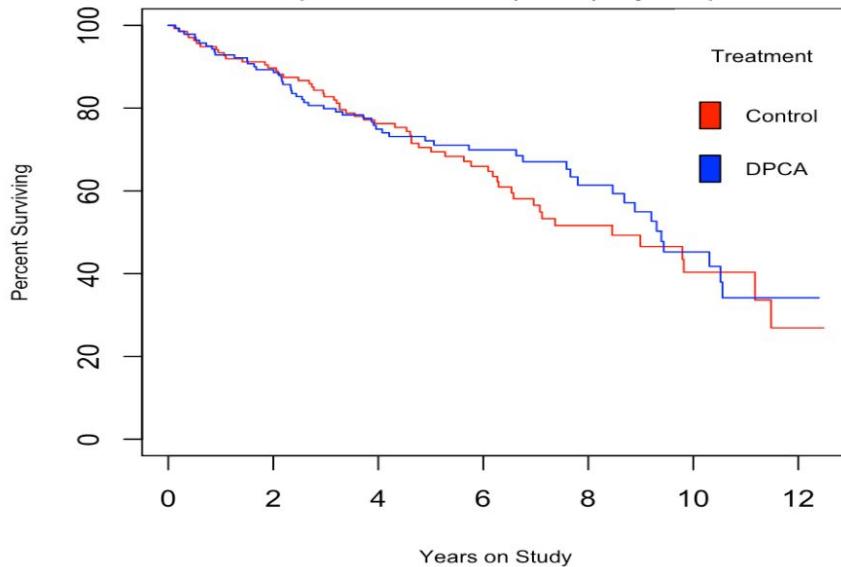
	N	
	N / Row Total	

Total Observations in Table: 276

Randomization/Treatment	Event		Row Total
	0	1	
1	79	57	136
	0.58	0.42	0.49
2	86	54	140
	0.61	0.39	0.51
Column Total	165	111	276

KAPLAN-MEIER BY GROUP

II. DPCA Study of Primary Biliary Cirrhosis
Kaplan-Meier Survival (95% CI) - By Group



```
Call: survfit(formula = Surv(time, status) ~ trt,
conf.type = "log-log", conf.int = 0.95)
n events median 0.95LCL 0.95UCL
trt=1 136      57    8.45    6.54    11.2
trt=2 140      54    9.39    8.47    10.6
```

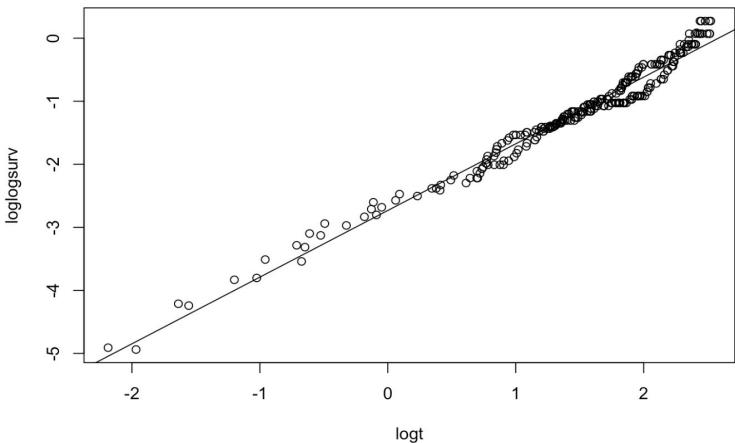
LOG-RANK TEST

```
Call:  
survdiff(formula = Surv(pbc.df$survtime, pbc.df$status)  
~ trt, data = pbc.df)  
  
      N Observed Expected (O-E)^2/E (O-E)^2/V  
trt=1 136      57     53.7     0.209     0.405  
trt=2 140      54     57.3     0.195     0.405  
  
Chisq= 0.4  on 1 degrees of freedom, p= 0.5
```

Null hypothesis: Both groups have identical distribution curves.

Alternative hypothesis: Both groups have different distribution curves.

WEIBULL MODEL



Call:

```
survreg(formula = Surv(survtime, status) ~ trt, data = pbc.df,
        dist = "weibull")
            Value Std. Error      z          p
(Intercept) 2.3611     0.2608  9.05 <0.0000000000000002
trt         0.0947     0.1642  0.58      0.564
Log(scale) -0.1462     0.0831 -1.76      0.078
```

Scale= 0.864

Weibull distribution

Loglik(model)= -398.1 Loglik(intercept only)= -398.3
Chisq= 0.33 on 1 degrees of freedom, p= 0.56

Number of Newton-Raphson Iterations: 5

n= 276

O COX MODEL - SINGLE PREDICTORS

Single Predictor Logistic Regression Models

Dependent variable: y=status (1=died)		
	rx (1)	histol (2)
trt	-0.121 (0.885)	
factor(stage) 2		1.337 (3.808)
factor(stage) 3		1.928* (6.873)
factor(stage) 4		2.811*** (16.632)
bili		0.145*** (1.156)
Observations	276	276
R2	0.001	0.145
Max. Possible R2	0.981	0.981
Log Likelihood	-549.987	-528.609
Wald Test	0.410 (df = 1)	37.460*** (df = 3)
LR Test	0.406 (df = 1)	43.163*** (df = 3)
Score (Logrank) Test	0.406 (df = 1)	44.662*** (df = 3)
		-513.723

Note:

*p<0.1; **p<0.05; ***p<0.01

RESULTING AIC MODEL

Call:

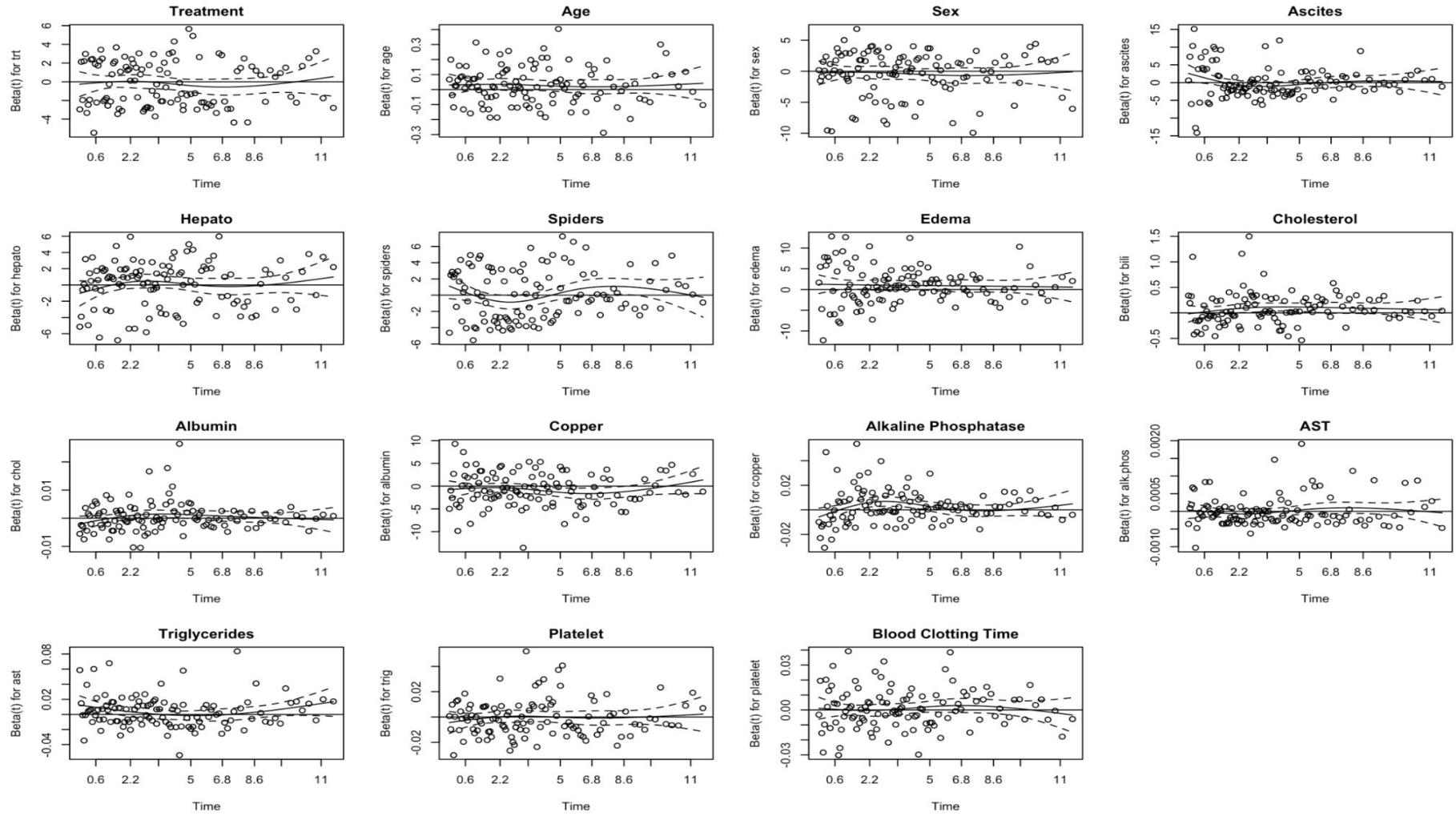
```
coxph(formula = Surv(survtime, status) ~ trt + age + edema +
      bili + albumin + copper + ast + protime + stage, data =
      pbc.df)
```

	coef	exp(coef)	se(coef)	z	p
trt	-0.1820688	0.8335440	0.2113377	-0.862	0.38896
age	0.0295924	1.0300346	0.0104121	2.842	0.00448
edema0.5	0.0816619	1.0850889	0.3196175	0.255	0.79834
edemal	0.9277714	2.5288671	0.3565479	2.602	0.00927
bili	0.0884402	1.0924689	0.0200074	4.420	0.00000985
albumin	-0.7230927	0.4852492	0.2803764	-2.579	0.00991
copper	0.0027060	1.0027096	0.0009907	2.731	0.00631
ast	0.0041103	1.0041188	0.0018606	2.209	0.02717
protime	0.2743950	1.3157345	0.1138259	2.411	0.01592
stage2	1.3768311	3.9623257	1.0768103	1.279	0.20103
stage3	1.7068158	5.5113844	1.0443789	1.634	0.10220
stage4	2.0979495	8.1494424	1.0412326	2.015	0.04392

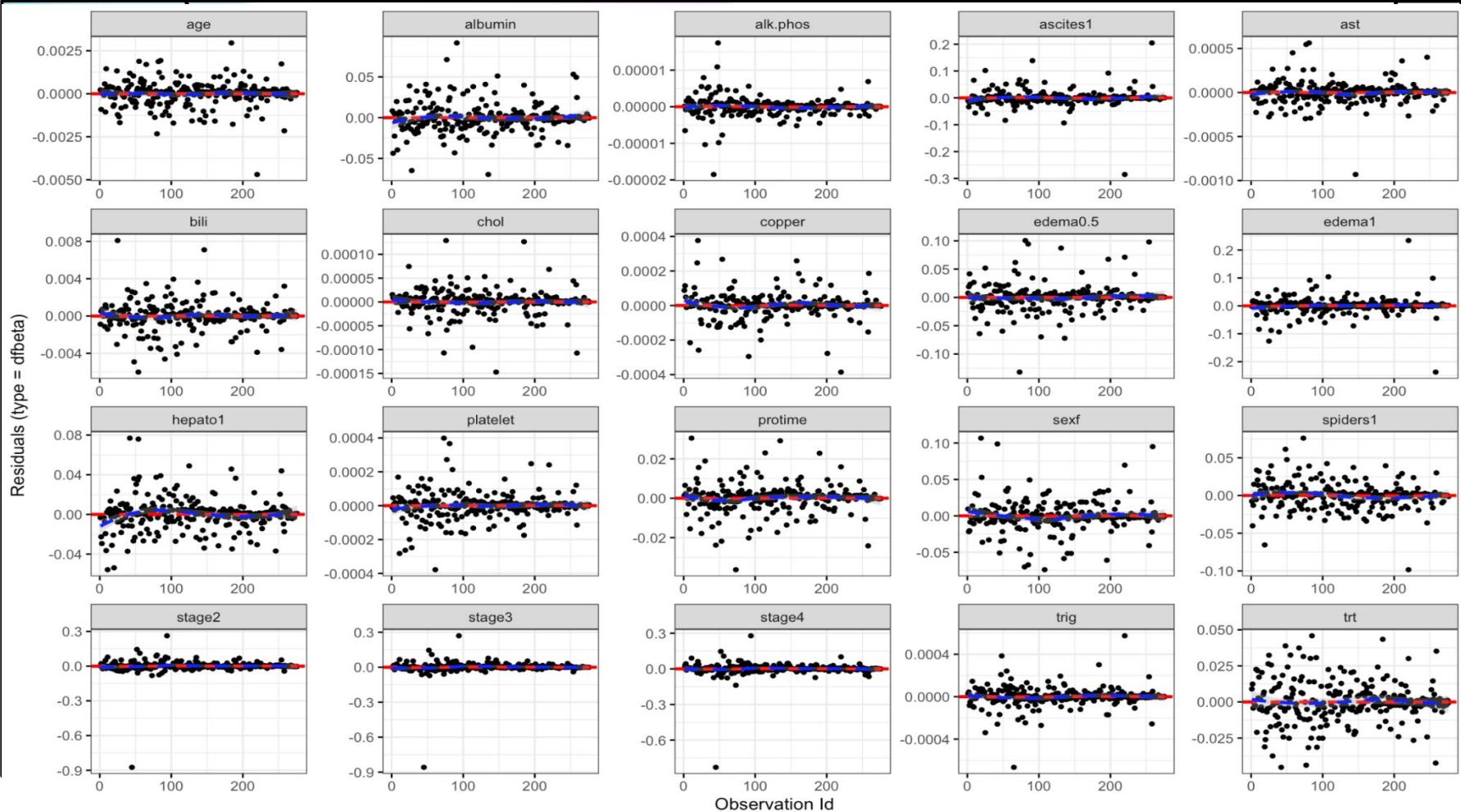
Likelihood ratio test=166.4 on 12 df, p=< 0.0000000000000022
n= 276, number of events= 111

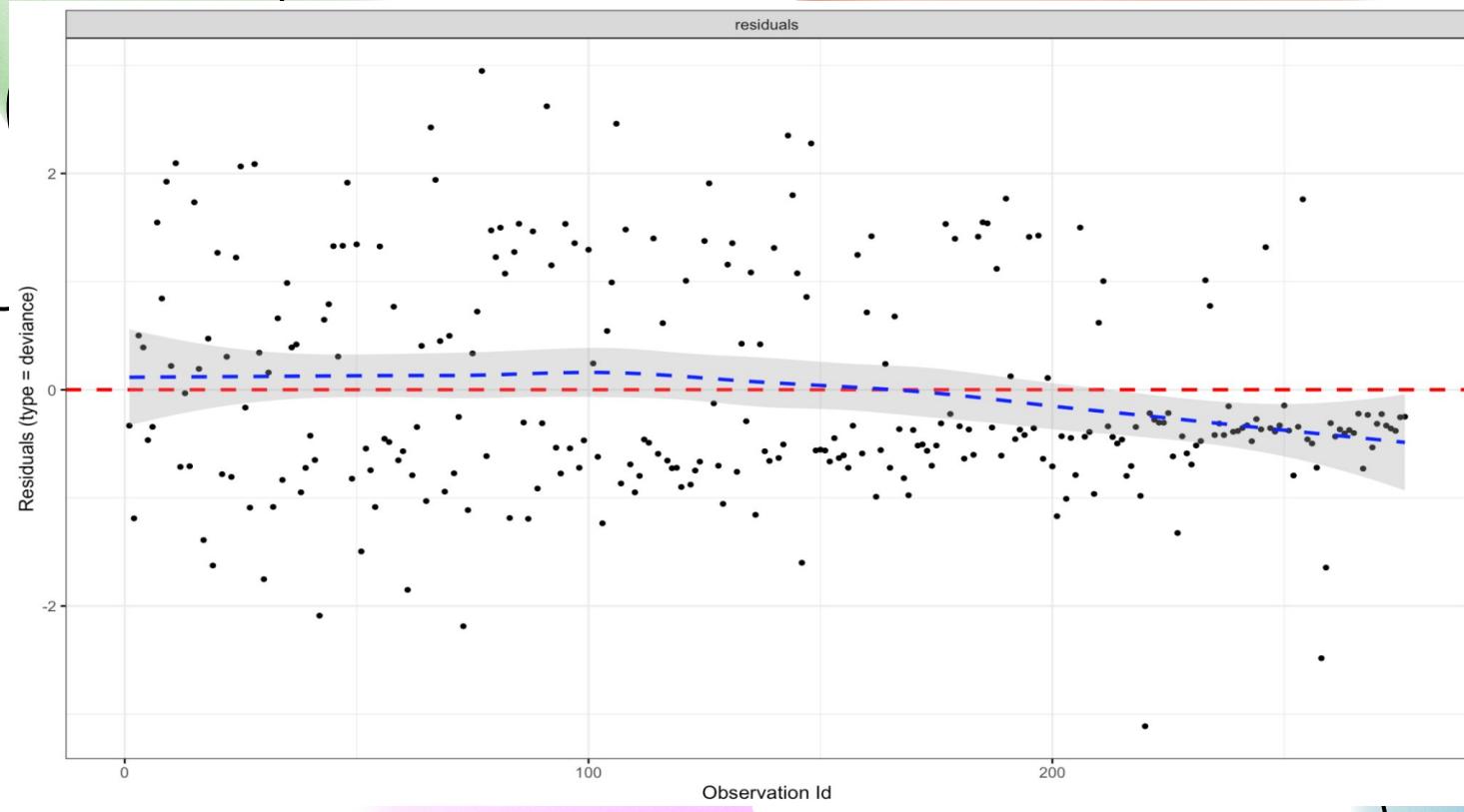
TEST OF PROPORTIONAL HAZARDS

	chisq	df	p
trt	0.23988	1	0.6243
age	1.91620	1	0.1663
sex	0.00231	1	0.9617
ascites	1.80196	1	0.1795
hepato	0.10709	1	0.7435
spiders	0.59045	1	0.4422
edema	5.40191	2	0.0671
bili	7.68884	1	0.0056
chol	10.53819	1	0.0012
albumin	0.11941	1	0.7297
copper	0.14099	1	0.7073
alk.phos	1.45071	1	0.2284
ast	1.28065	1	0.2578
trig	3.99531	1	0.0456
platelet	1.73195	1	0.1882
protime	3.96932	1	0.0463
stage	3.69074	3	0.2969
GLOBAL	28.89383	20	0.0899



INFLUENTIAL OBSERVATIONS





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Multivariable Logistic Regression Models: 95% CI

	Dependent variable: y=status (1=died)			
	(1)	(2)	(3)	(4)
trt	-0.121 (-0.494, 0.252)	-0.235 (-0.611, 0.140)	-0.269 (-0.651, 0.113)	-0.251 (-0.628, 0.126)
stage2		1.361 (-0.669, 3.391)		
stage3		1.962* (-0.024, 3.948)		
stage4		2.859*** (0.877, 4.842)		
factor(stage) 2				1.275 (-0.756, 3.306)
factor(stage) 3				1.725* (-0.266, 3.715)
factor(stage) 4				2.589** (0.604, 4.574)
bili			0.149*** (0.121, 0.176)	0.146*** (0.117, 0.175)
Observations	276	276	276	276
R2	0.001	0.149	0.238	0.329
Max. Possible R2	0.981	0.981	0.981	0.981
Log Likelihood	-549.987	-527.852	-512.770	-495.097
Wald Test	0.410 (df = 1)	38.850*** (df = 4)	112.520*** (df = 2)	130.320*** (df = 5)
LR Test	0.406 (df = 1)	44.677*** (df = 4)	74.841*** (df = 2)	110.187*** (df = 5)
Score (Logrank) Test	0.406 (df = 1)	46.104*** (df = 4)	162.347*** (df = 2)	185.823*** (df = 5)

Note:

*p<0.1; **p<0.05; ***p<0.01

Likelihood Ratio Tests

Analysis of Deviance Table

```
Cox model: response is Surv(survtime, status)
Model 1: ~ factor(stage)
Model 2: ~ trt + stage
loglik  Chisq Df Pr(>|Chi|)
1 -528.61
2 -527.85 1.514 1      0.2185
```

Analysis of Deviance Table

```
Cox model: response is Surv(survtime, status)
Model 1: ~ bili
Model 2: ~ trt + bili
loglik  Chisq Df Pr(>|Chi|)
1 -513.72
2 -512.77 1.9067 1      0.1673
```

Analysis of Deviance Table

```
Cox model: response is Surv(survtime, status)
Model 1: ~ stage + bili
Model 2: ~ trt + factor(stage) + bili
loglik  Chisq Df Pr(>|Chi|)
1 -495.95
2 -495.10 1.7052 1      0.1916
```

Conclusions

- D-Penicillmine did not appear to reduce the risk of mortality
- DPCA is actually not recommended for people diagnosed in stages 1 or 2 and even for stages 3 and 4 it only shows a very marginal influence.