Survival Data Analysis
Parametric Models

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Agenda

- Basic Parametric Models
  - Review: hazard & cumulative hazard functions; likelihood function
  - Proportional hazards versus accelerated failure
  - Exponential model
  - Weibull model
  - Log-Normal model
  - Log-Logistic model
  - Checking assumptions
  - Gamma model
  - Goodness of fit and residuals
- Other Models
  - Changepoint model (piecewise exponential model)
    - Reference: Matthews & Farewell 1982
  - Gamel-Boag (cure fraction) model
    - Reference: Frankel & Longmate 2002
  - Bayesian analysis

Probability density function

$$Random\ survival\ time\ T > 0$$

$$f(t) = h(t)S(t)$$

Hazard function

- Specifies the instantaneous rate of failure at T=t

$$h(t) = \lim_{\Delta t \to 0^+} \frac{P(t \le T < t + \Delta t \mid T \ge t)}{\Delta t}$$

$$h(t) = \frac{f(t)}{S(t)}$$

See K&M Section 2.3

Cumulative hazard function

$$S(t) = P[T > t] = e^{-H(t)},$$

$$where\ H(t) = \int_{u=0}^{t} h(u)du\,.$$

$$Note\ H(t) = -\log S(t)$$

Likelihood

- Full likelihood for parametric models
- Assuming censoring is independent of failure and non-informative:

$$L \propto \prod_{i \in D}^{n} f(x_i) \prod_{i \in R} S(C_r)$$

K&M 3.5.1

$$L = \prod_{i=1}^{n} \Pr(t_i, \delta_i)$$

$$where\ T = \min(X, C_r)$$

$$and\ \Pr(t, \delta) = [f(t)]^{\delta} [S(t)]^{1-\delta}$$

Likelihood

$$\mathrm{L} = \prod_{i=1}^{n} f(t_i)^{\delta_i} S(t_i)^{1-\delta_i}$$

K&M 3.5.3

$$= \prod_{i=1}^{n} \Big[h(t_i) \exp[-\int_0^{t_i} h(s) ds \Big]^{\delta_i} \Big[\exp[-\int_0^{t_i} h(s) ds \Big]^{1-\delta_i}$$

$$= \prod_{i=1}^{n} [h(t_i)]^{\delta_i} \exp\Big[-\int_0^{t_i} h(s) ds\Big]$$

$$= \prod_{i=1}^{n} [h(t_i)]^{\delta_i} \exp\big[-H(t_i)\big]$$

Parametric Survival models

- Fully specified model with hazard rate a function of covariates (including intercept)
- Proportional Hazards (PH)
  - constant **hazard ratios** across time
  - Exponential, Weibull
- Accelerated Failure Models (AFT)
  - constant **time ratios** across survival percentiles
  - Exponential, Weibull, Log Normal, Log Logistic

PH versus AFT

$$e.g. \quad X \text{ is binary}$$

PH

$$HR = \frac{h_1(x=1,t)}{h_0(x=0,t)} = e^{-\beta}$$

AFT

$$TR = \frac{t_{50}(x=1,\beta)}{t_{50}(x=0,\beta)} = e^{\beta}$$

Exponential Model

PH versus AFT

PH

$$h(t \mid X) = h_0(t)e^{-\beta' X}$$

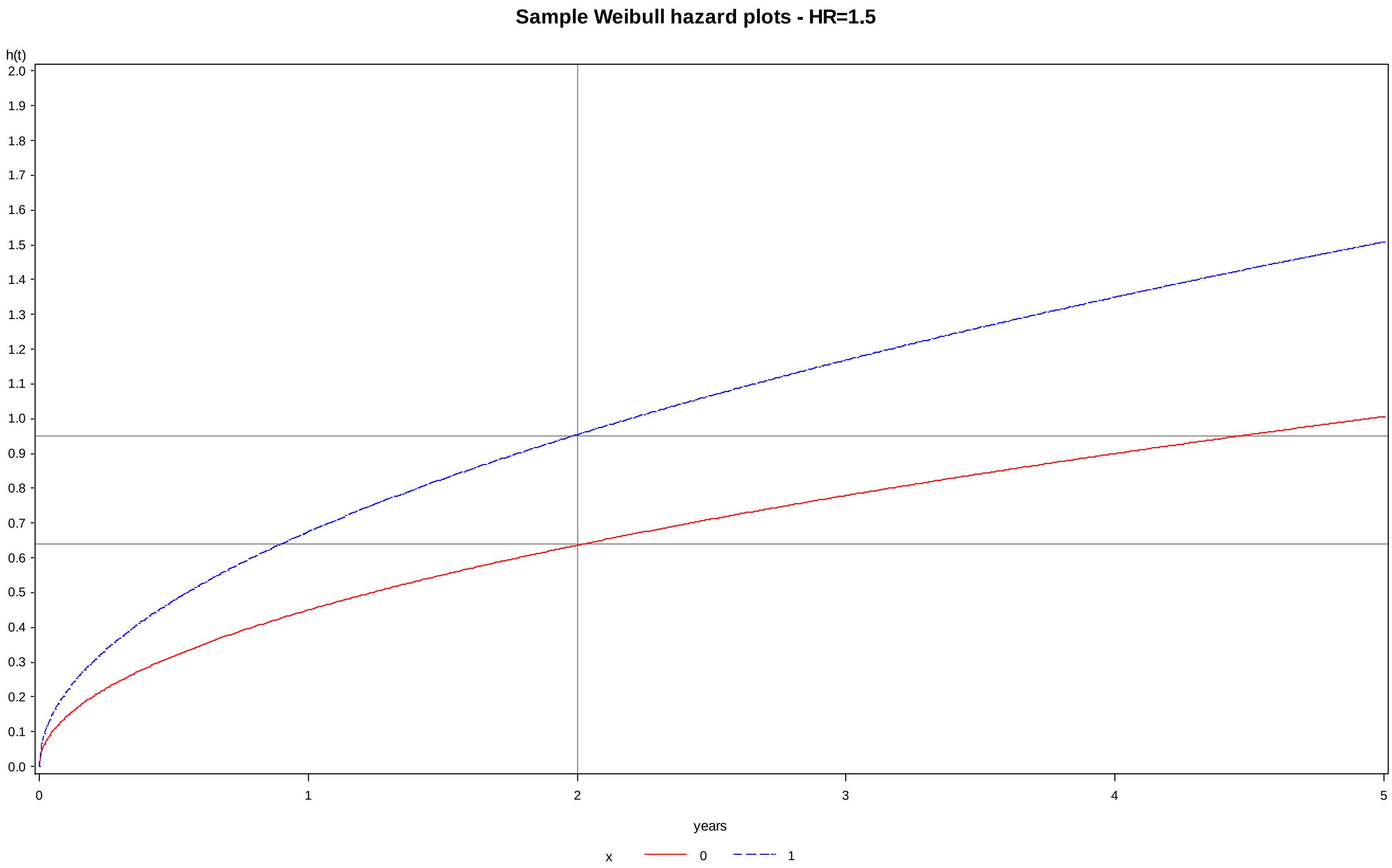
$$S(t \mid X) = S_0(t)^{e^{-\beta' X}}$$

AFT

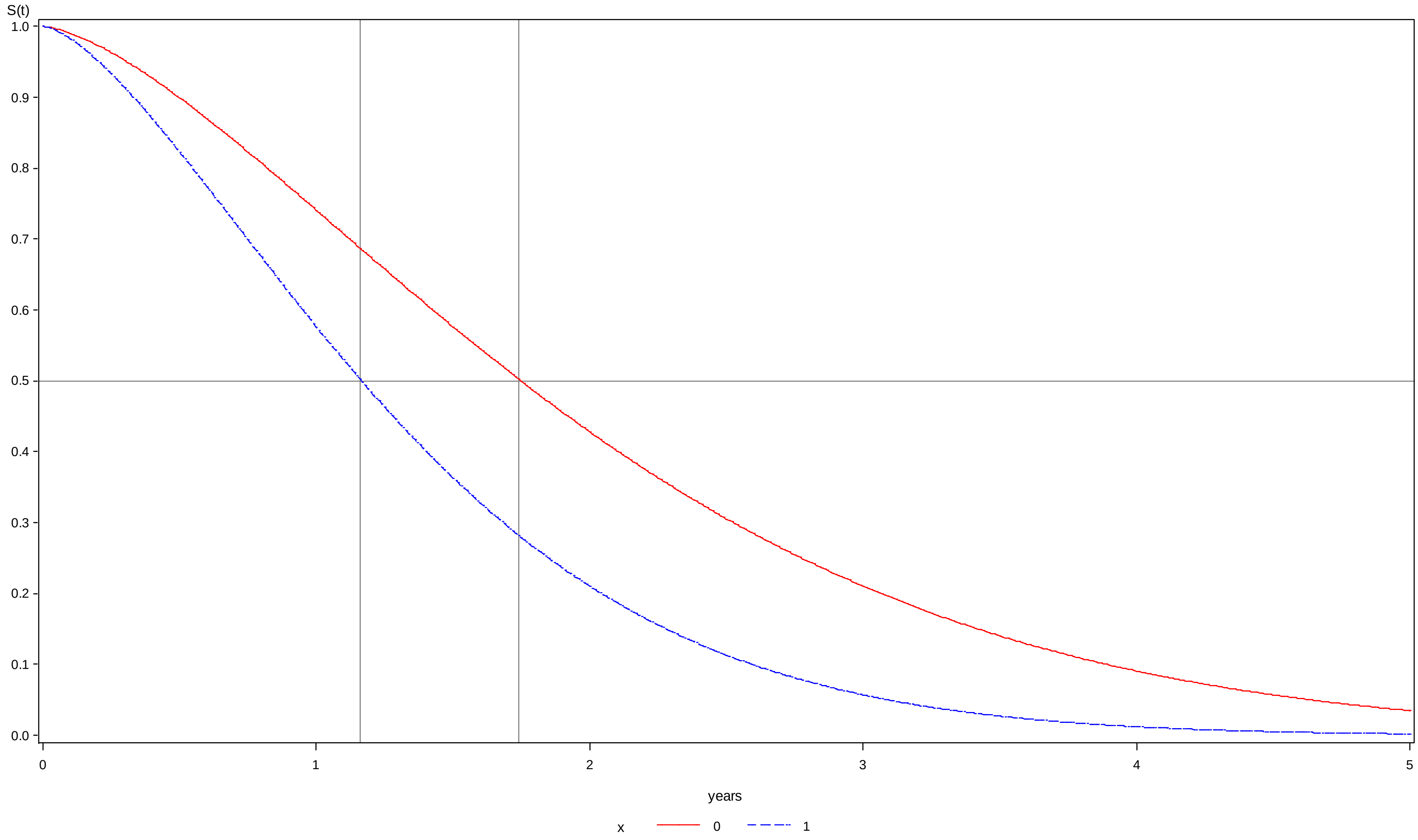
$$h(t \mid X) = h_0(e^{-\beta' X} t)e^{-\beta' X}$$

$$S(t \mid X) = S_0(e^{-\beta' X} t)$$

Be careful of parameterization of models in texts and software.


Sample Weibull hazard plots - HR=1.5
h(t)
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
years
x
0
1

Sample Weibull survival plots - TR=.67 (or AF=1.5)



Error distributions

$$f(\varepsilon) = \exp(\varepsilon - \exp(\varepsilon))$$

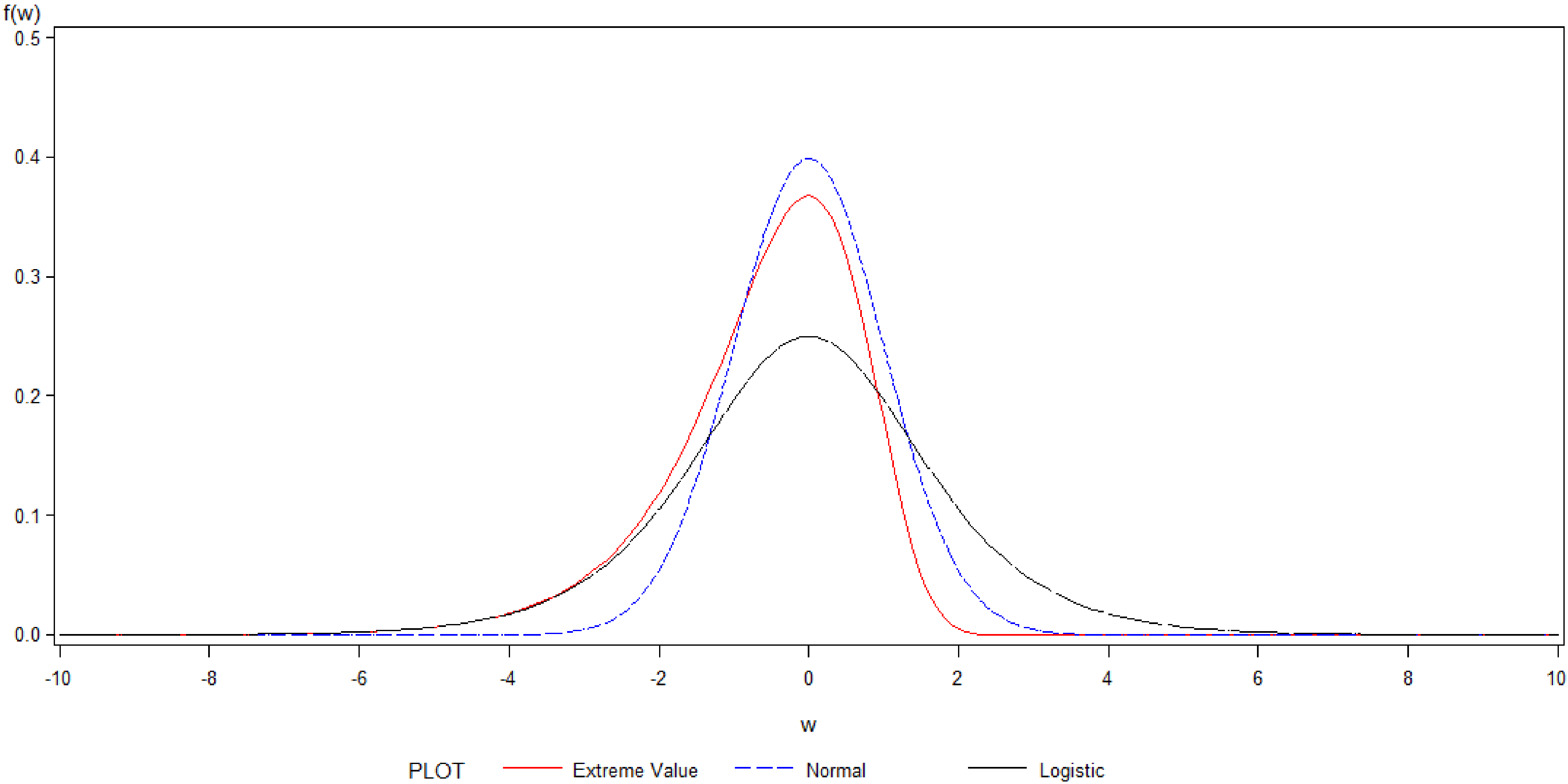
$$f(\varepsilon) = \frac{\exp(-\frac{\varepsilon^2}{2})}{\sqrt{2\pi}}$$

$$Y = \log T = X\beta + \sigma\varepsilon$$

$$f(\varepsilon) = \frac{e^{\varepsilon}}{\left(1 + e^{\varepsilon}\right)^2}$$

Be careful of parameterization of models in texts and software.

Error distributions



Exponential Model

- constant hazard functions
- both PH and AFT model
- underlying error function has an extreme value function with σ=1

$$S(t) = e^{-\lambda t}$$

$$h(t) = \lambda$$

$$Median = \frac{-\ln(.5)}{\lambda} = \frac{.69}{\lambda}$$

$$Mean = \frac{1}{\lambda}$$

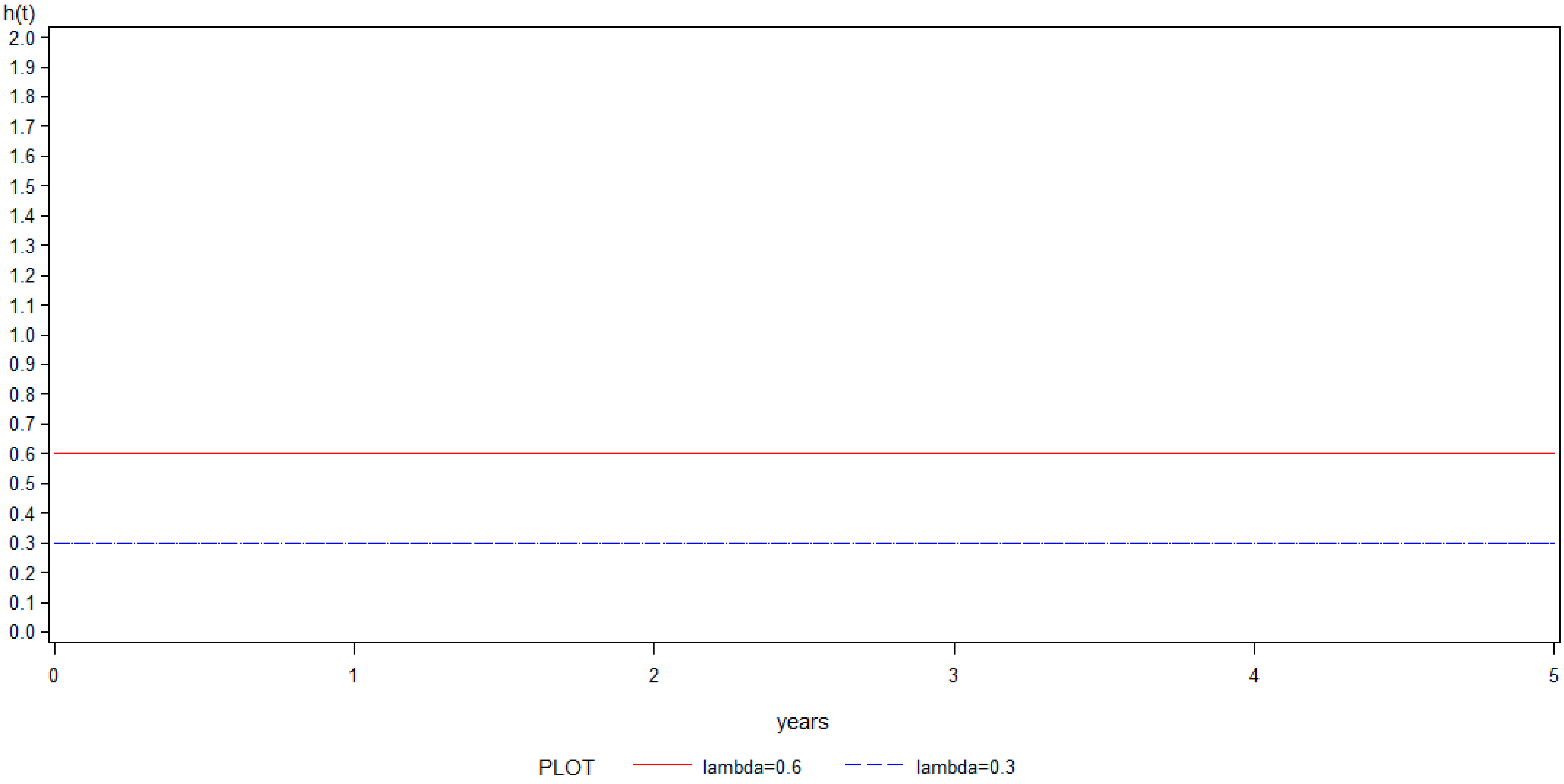
Exponential Model

$$L(\lambda) = \prod_{i=1}^{n} [\lambda]^{\delta_i} \exp\left[-\lambda t_i\right]$$

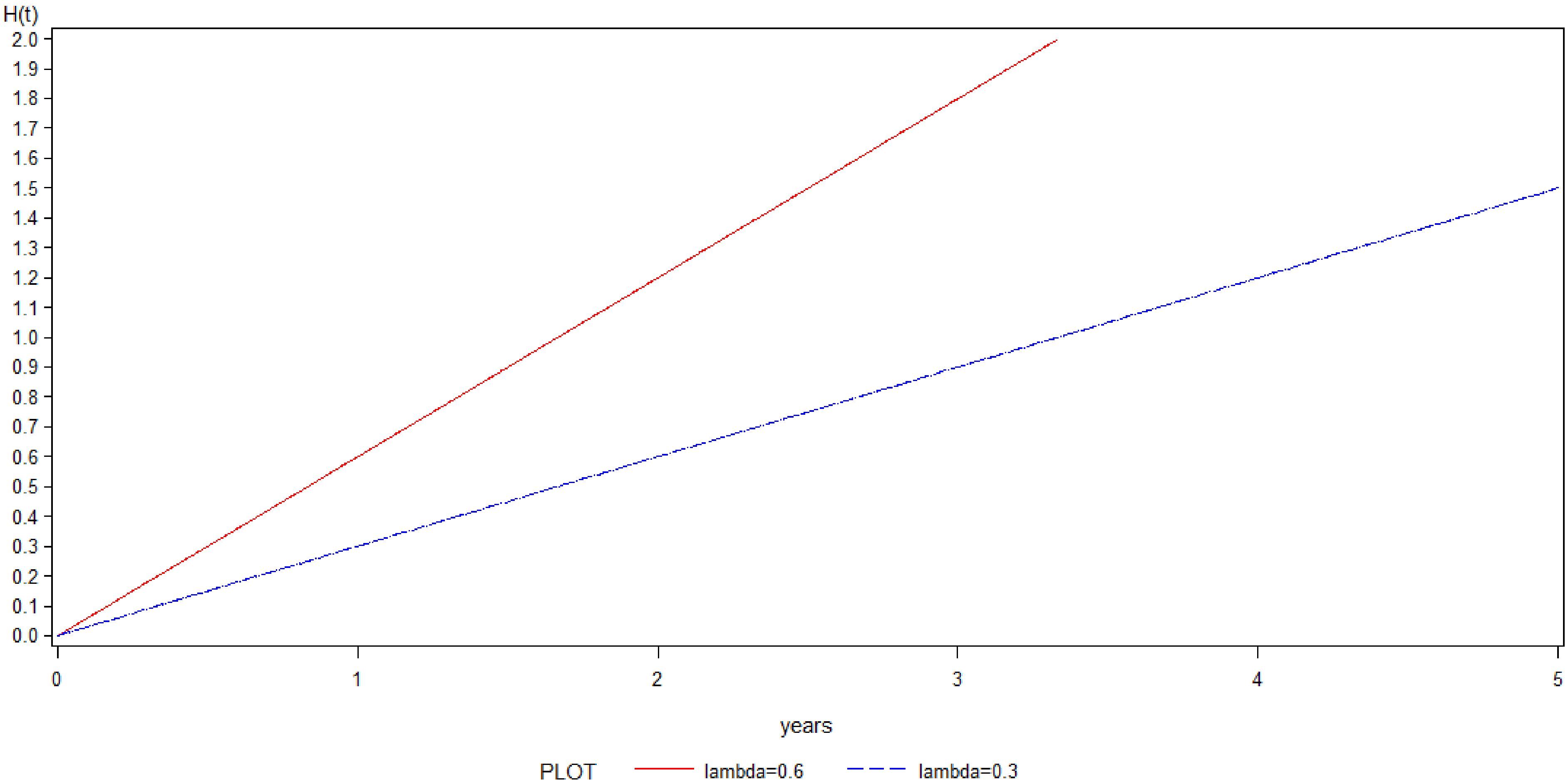
$$l(\lambda) = \sum_{i=1}^{n} (\delta_i \log[\lambda] - \lambda t_i)$$

$$mle \quad \hat{\lambda} = \frac{\sum_{i=1}^{n} \delta_i}{\sum_{i=1}^{n} t_i}$$

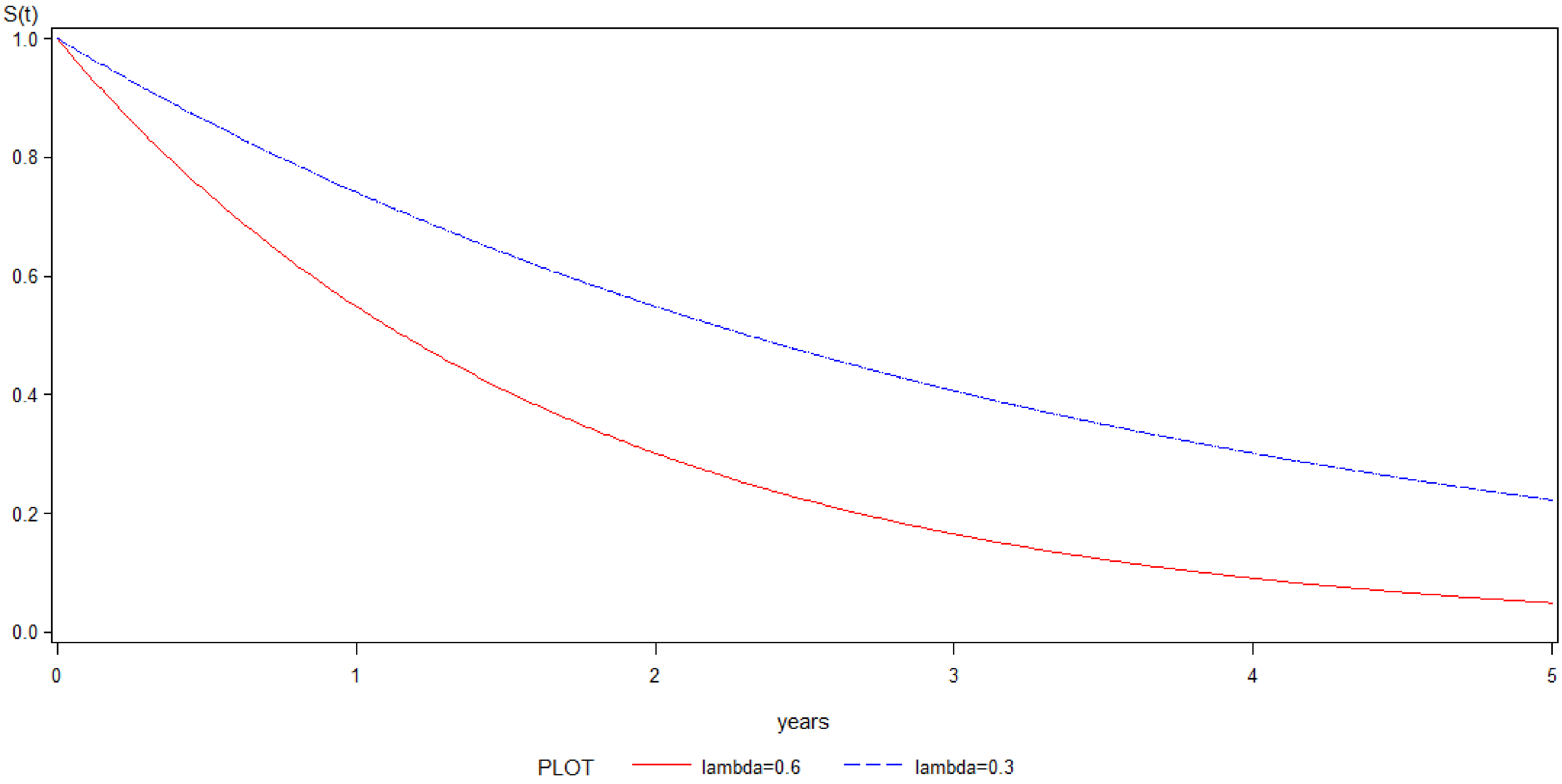
Exponential hazard plots



Exponential cumulative hazard plots



Exponential survival plots



Weibull

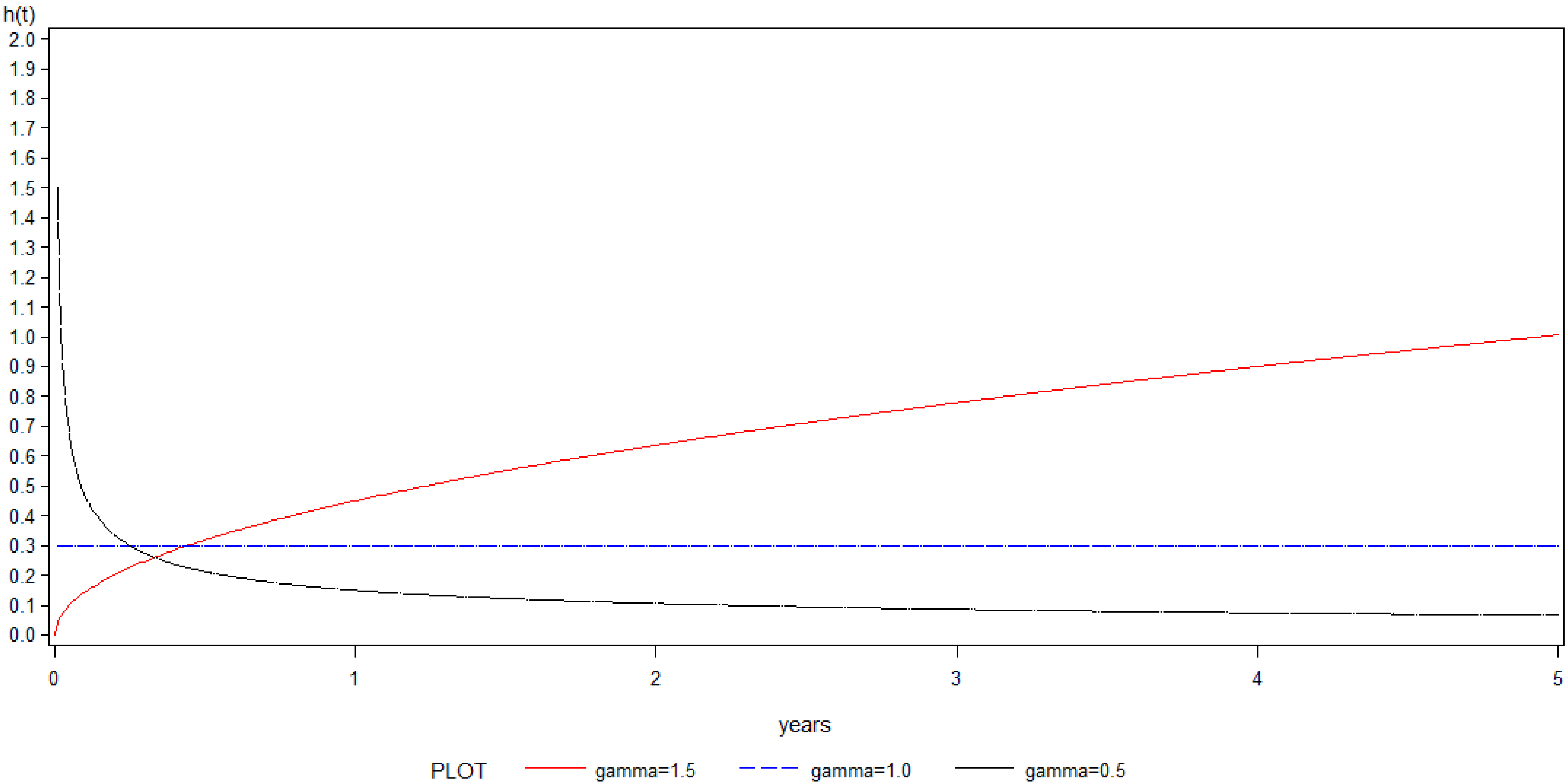
- monotone increasing or decreasing hazard functions
- both PH and AFT model
- Exponential model is special case (γ=1)

$$S(t) = e^{-\lambda t^{\gamma}}$$

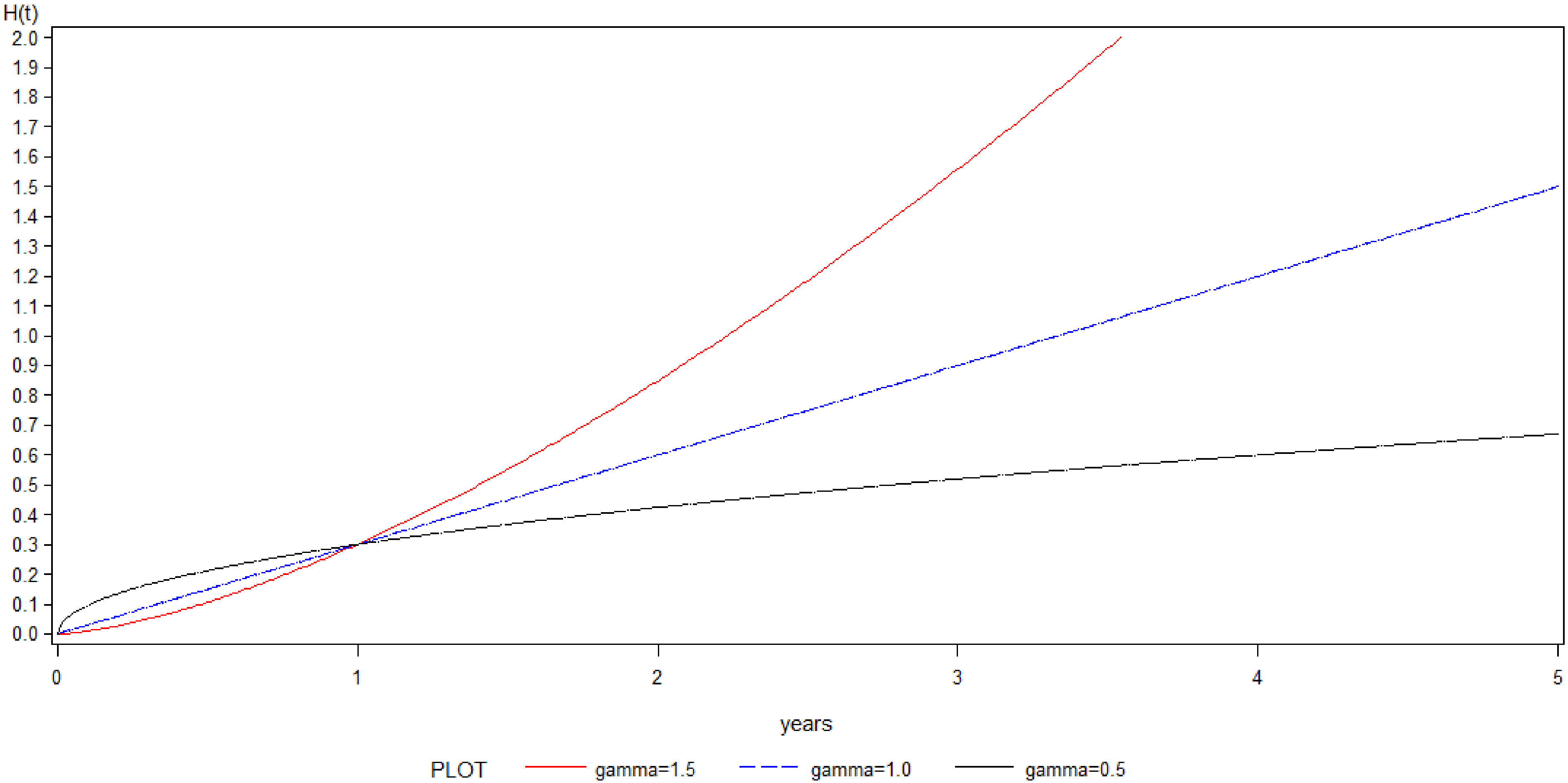
$$h(t) = \gamma \lambda t^{\gamma - 1}$$

$$Median = \left(\frac{-\ln(.5)}{\lambda} \right)^{\frac{1}{\gamma}}$$

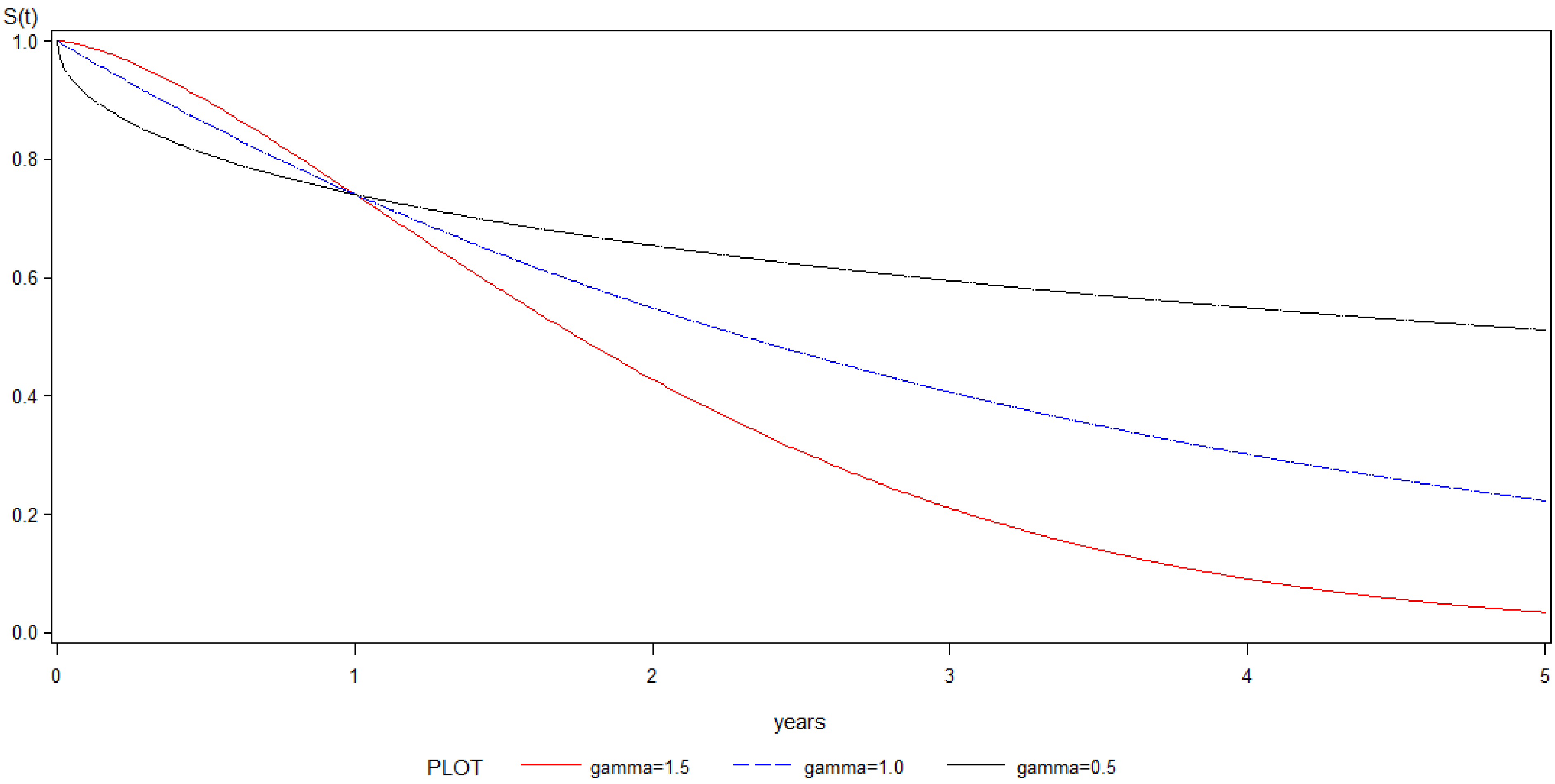
Weibull hazard plots - lambda=.3



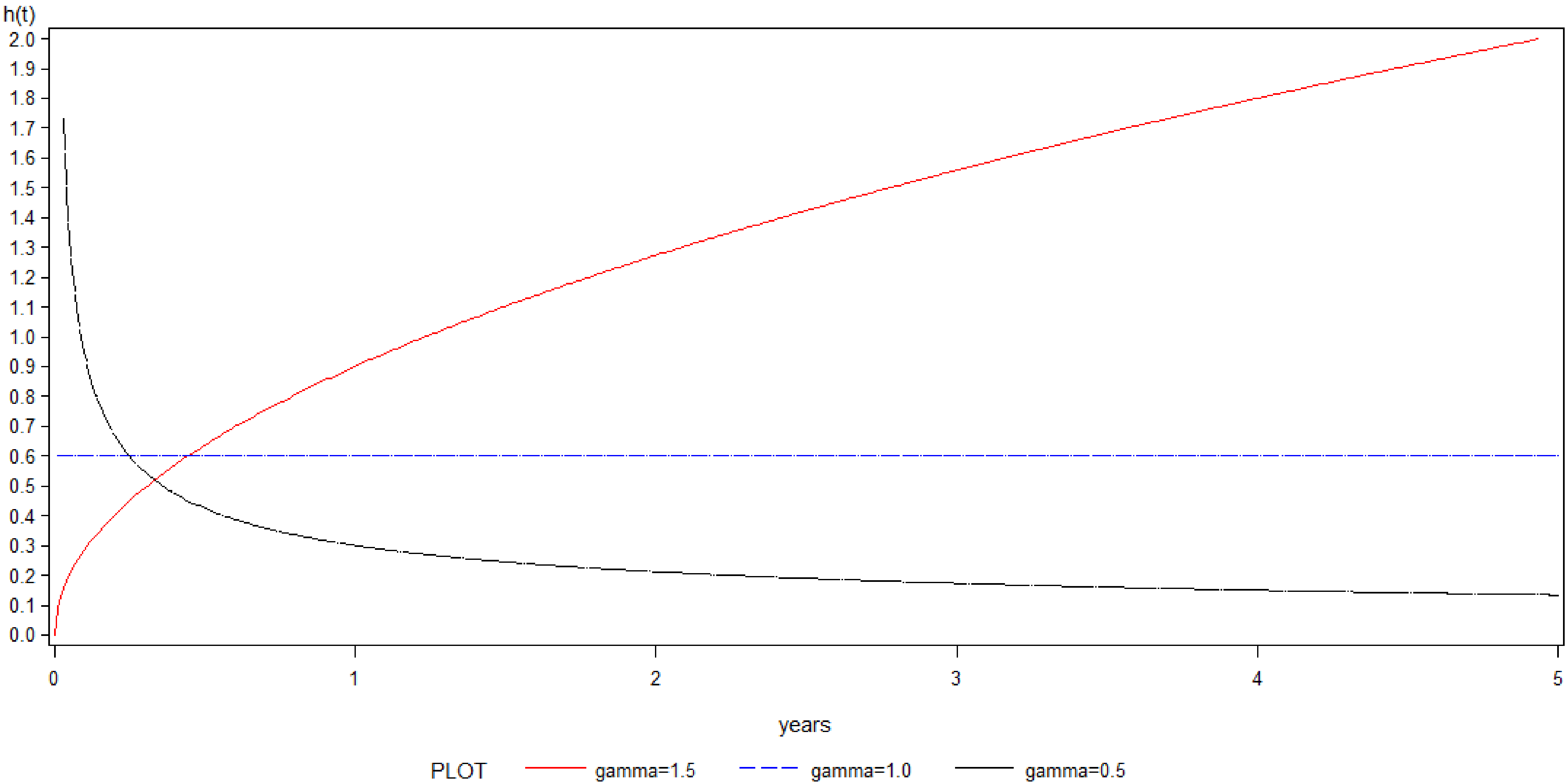
Weibull cumulative hazard plots - lambda=.3



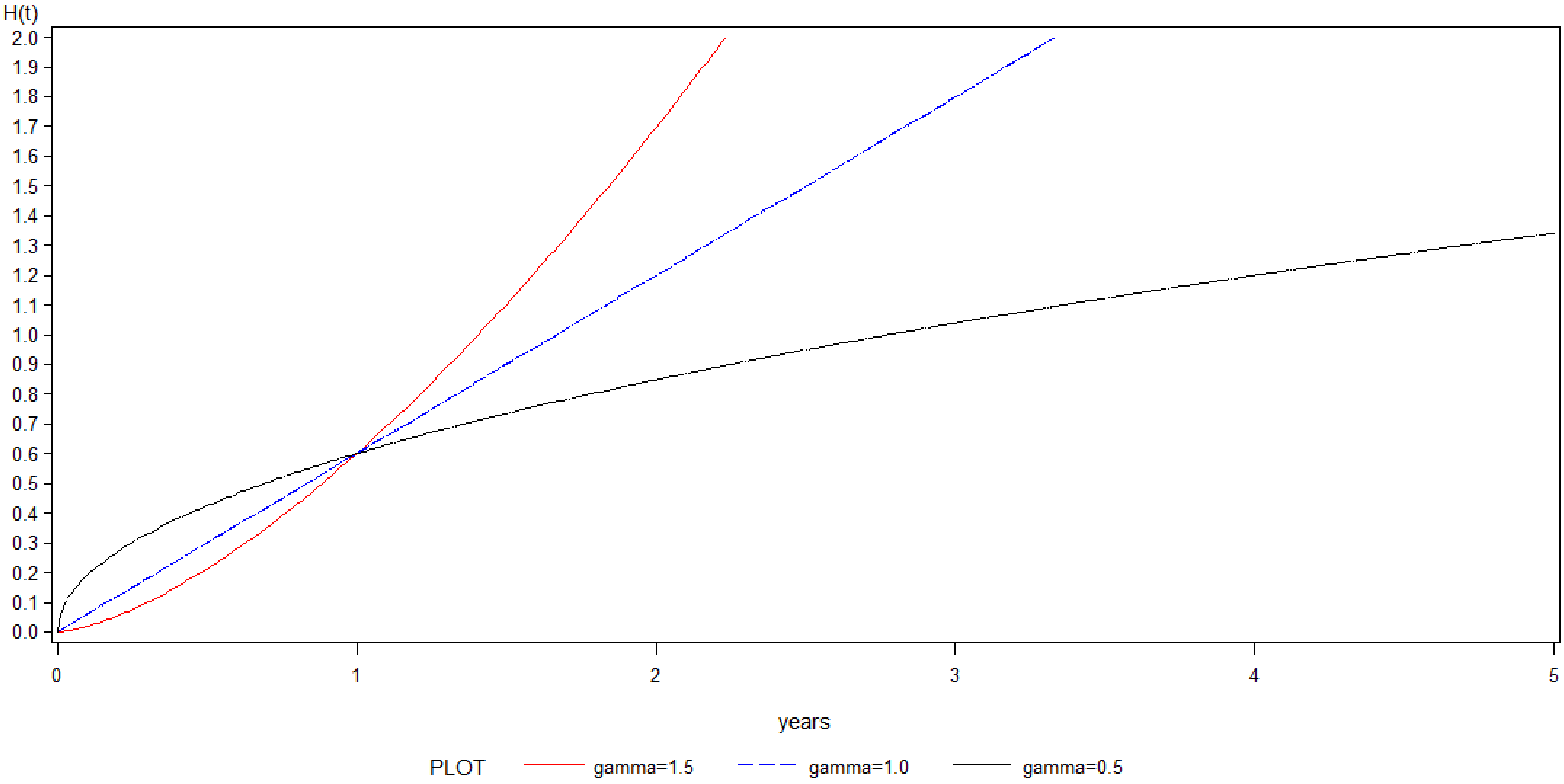
Weibull survival plots - lambda=.3



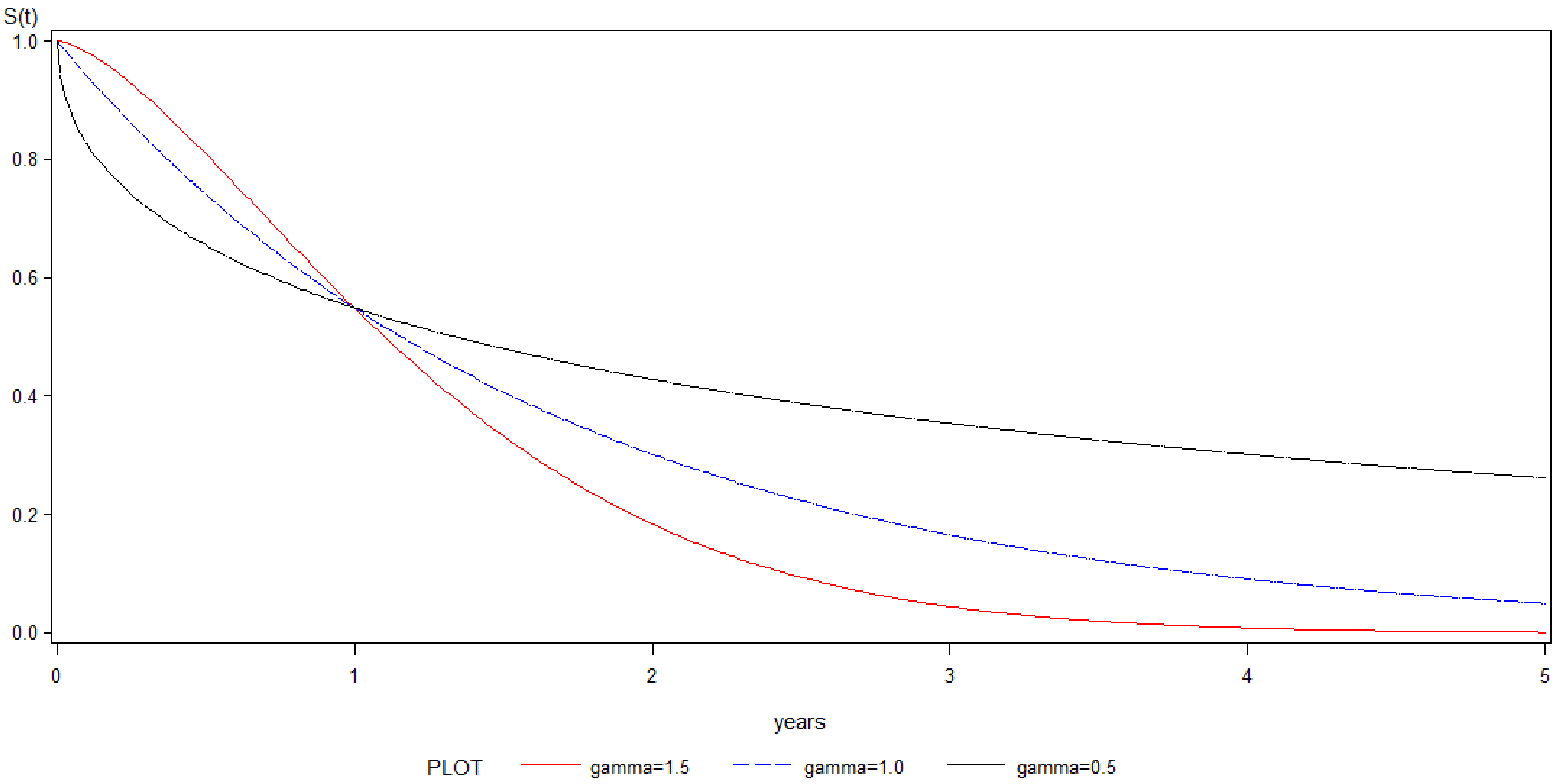
Weibull hazard plots - lambda=.6



Weibull cumulative hazard plots - lambda=.6



Weibull survival plots - lambda=.6



Log Normal

- hazard functions rise to a maximum then slowly decline, AFT model only

$$S(t) = 1 - \Phi\left(\frac{\ln(t) - \mu}{\sigma}\right)$$

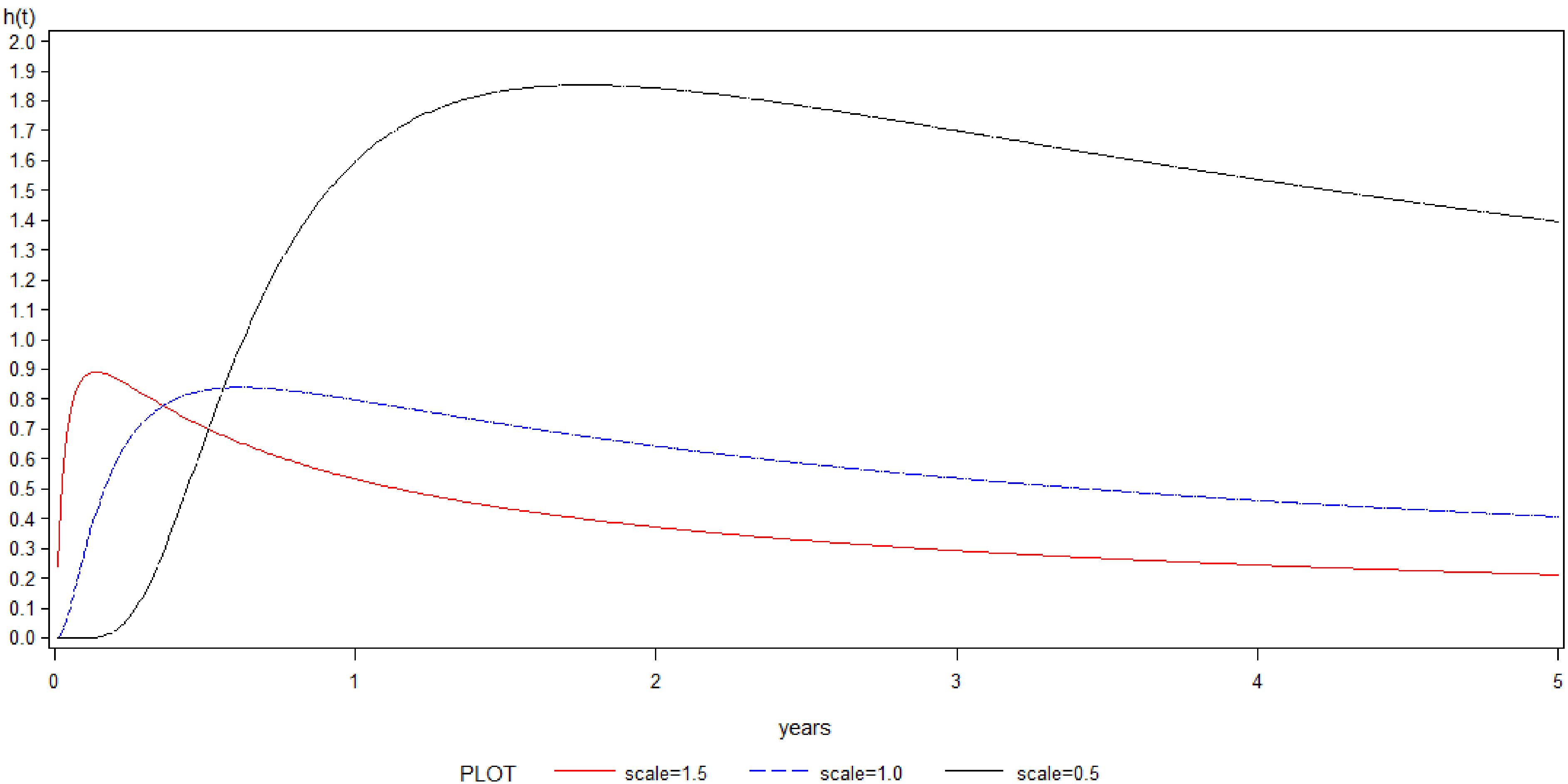
$$f(t) = \frac{1}{t\sigma\sqrt{2\pi}} e^{\left(-\frac{1}{2}\left(\frac{\ln(t)-\mu}{\sigma}\right)^2\right)}$$

$$h(t) = \frac{f(t)}{S(t)}$$

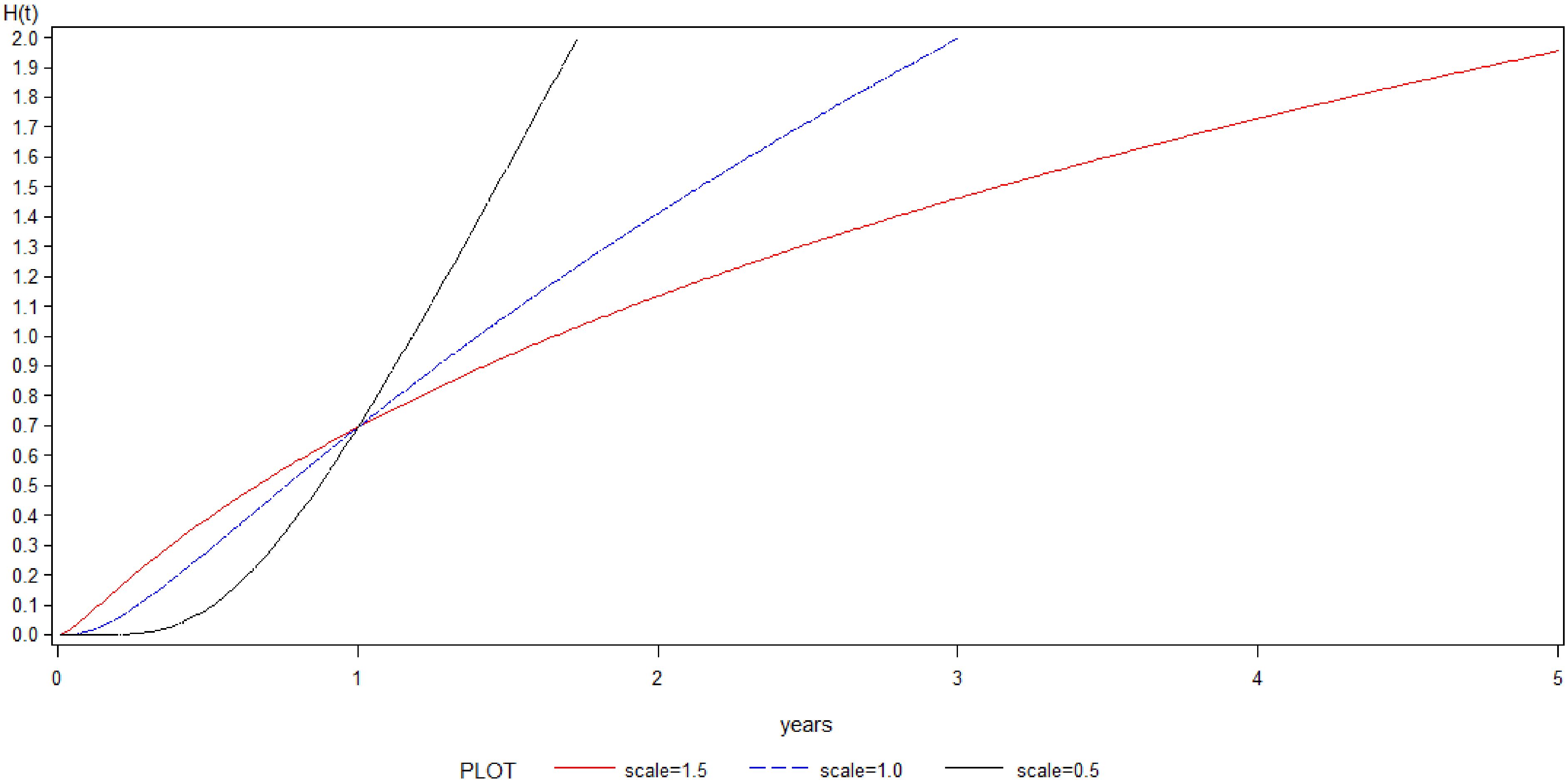
$$Median = e^{\left(\sigma\Phi^{-1}(.5)+\mu\right)} = e^{\mu}$$

$$Mean = e^{\left(\mu+0.5\sigma^2\right)}$$

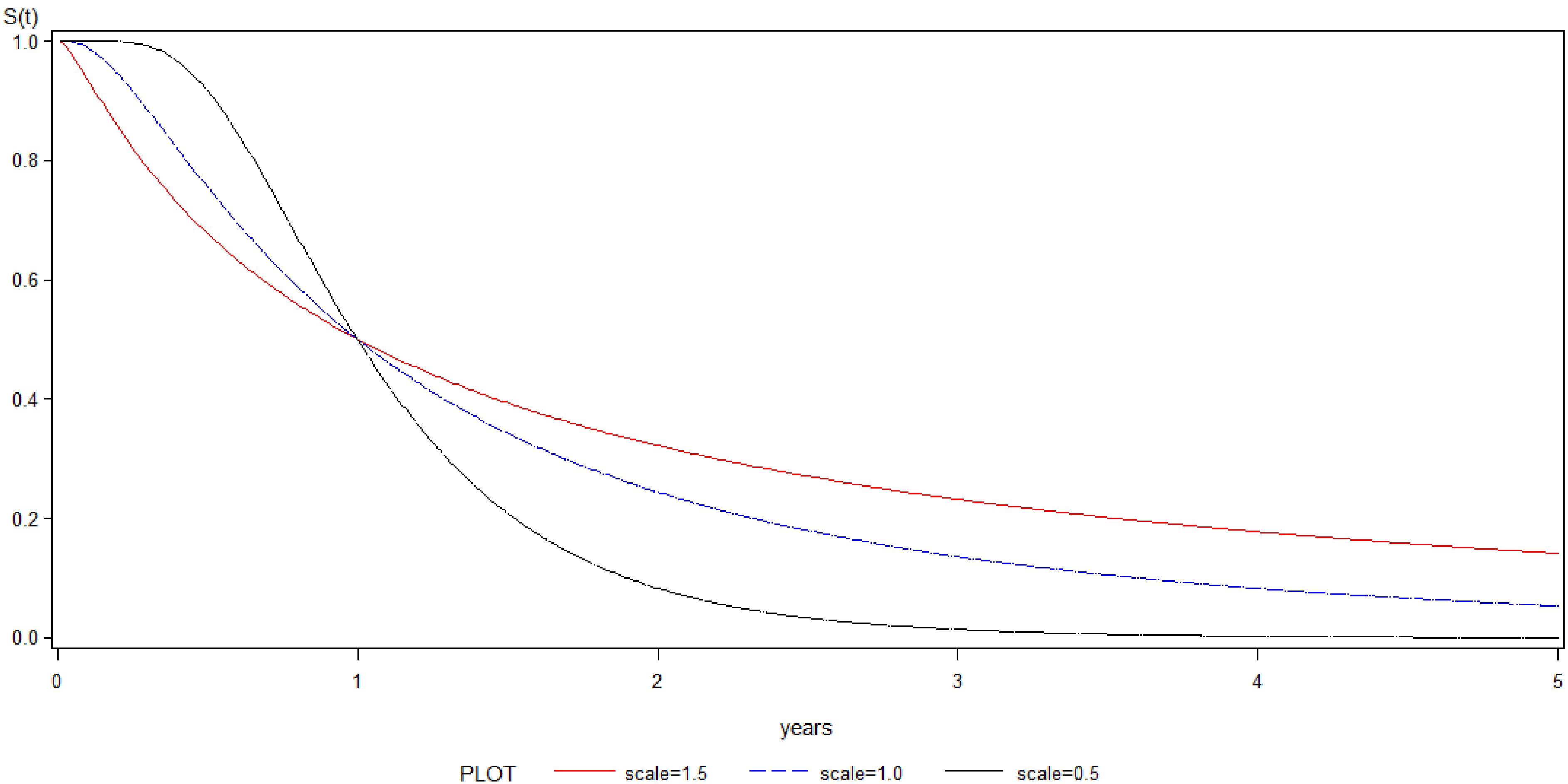
Log normal hazard plots - u=0



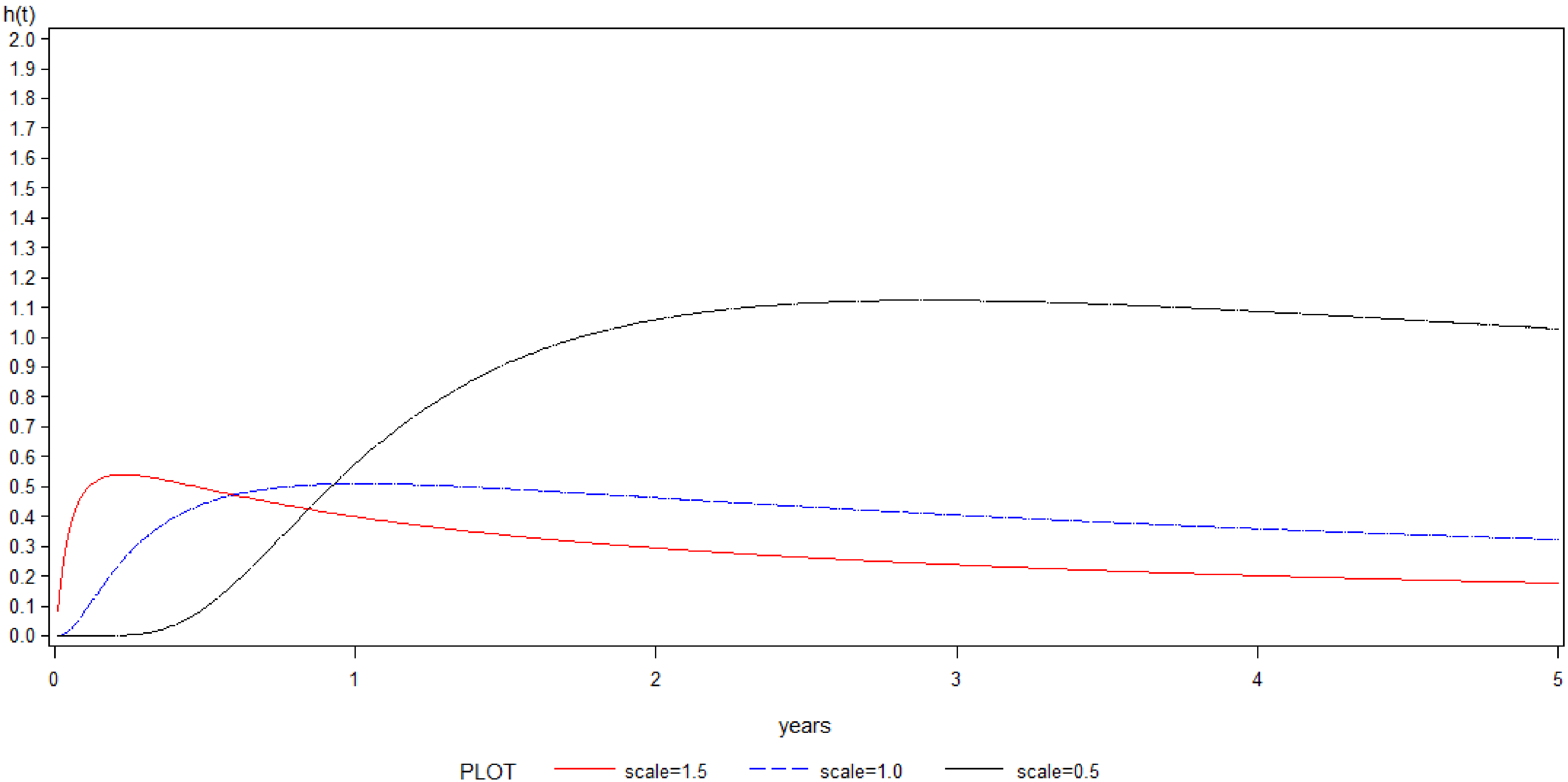
Log normal cumulative hazard plots - u=0



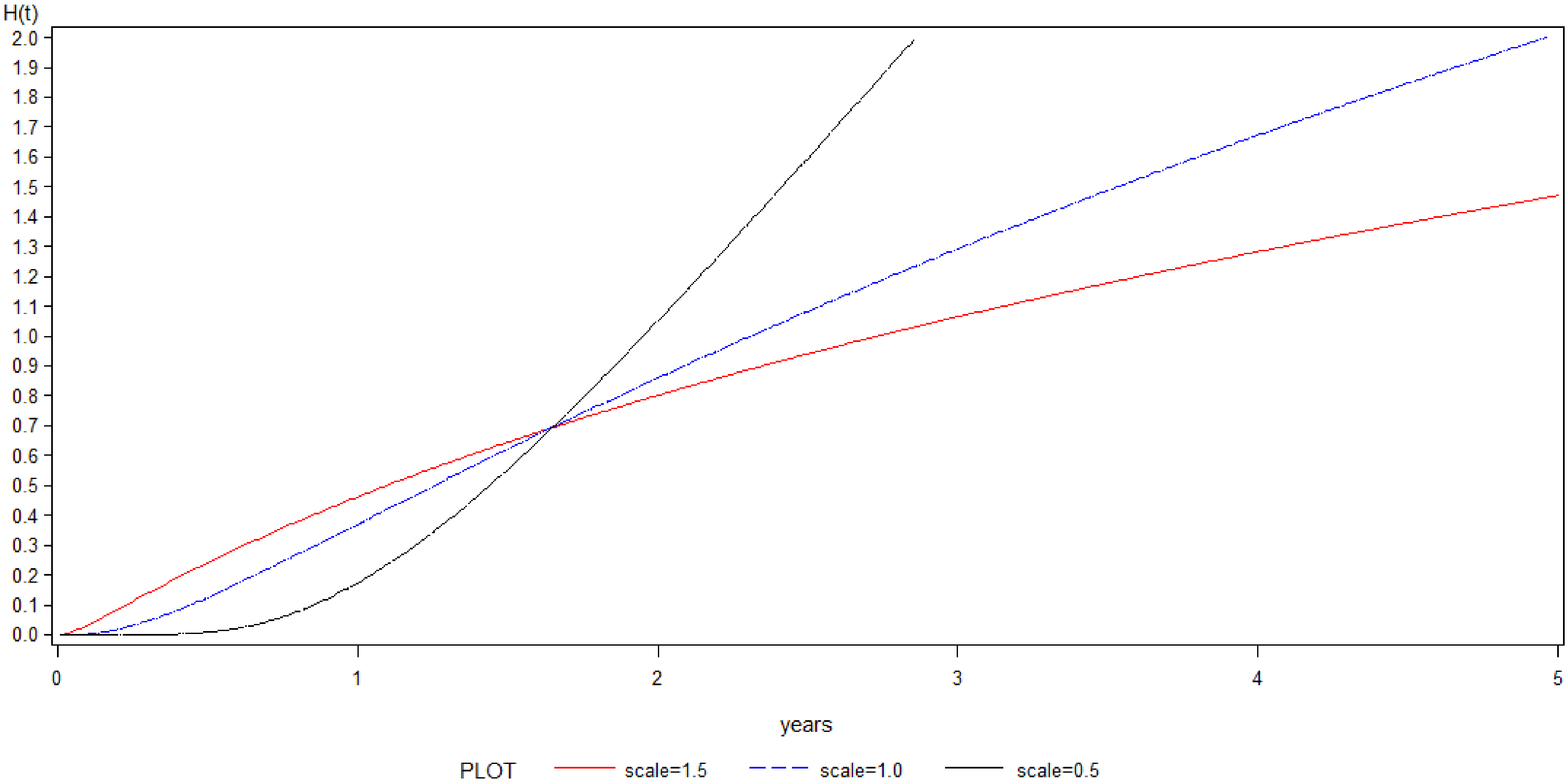
Log normal survival plots - u=0



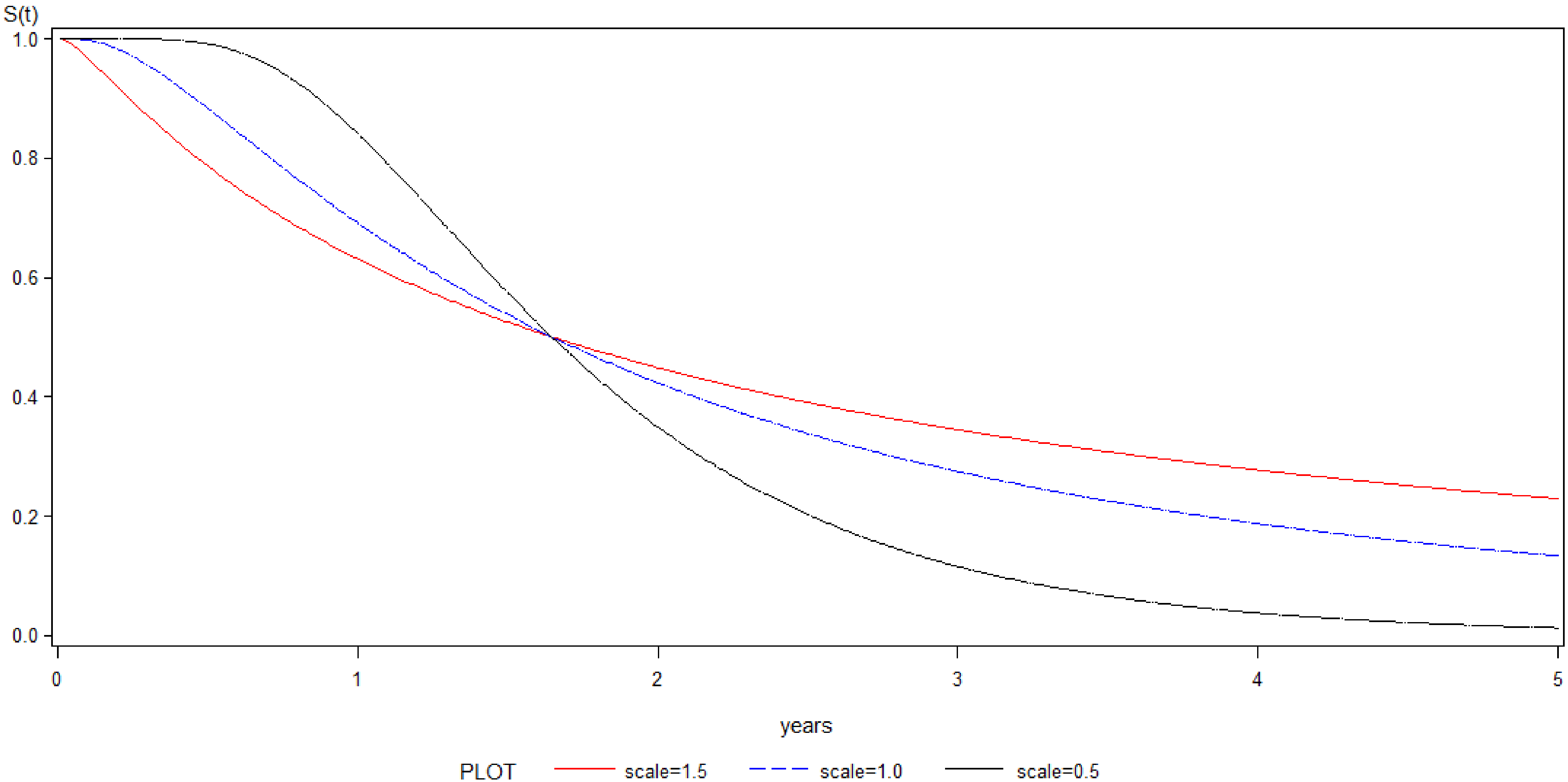
Log normal hazard plots - u=.5



Log normal cumulative hazard plots - u=.5



Log normal survival plots - u=.5



Log Logistic

- hazard functions rise to a maximum then slowly decline or are monotone decreasing , AFT model only

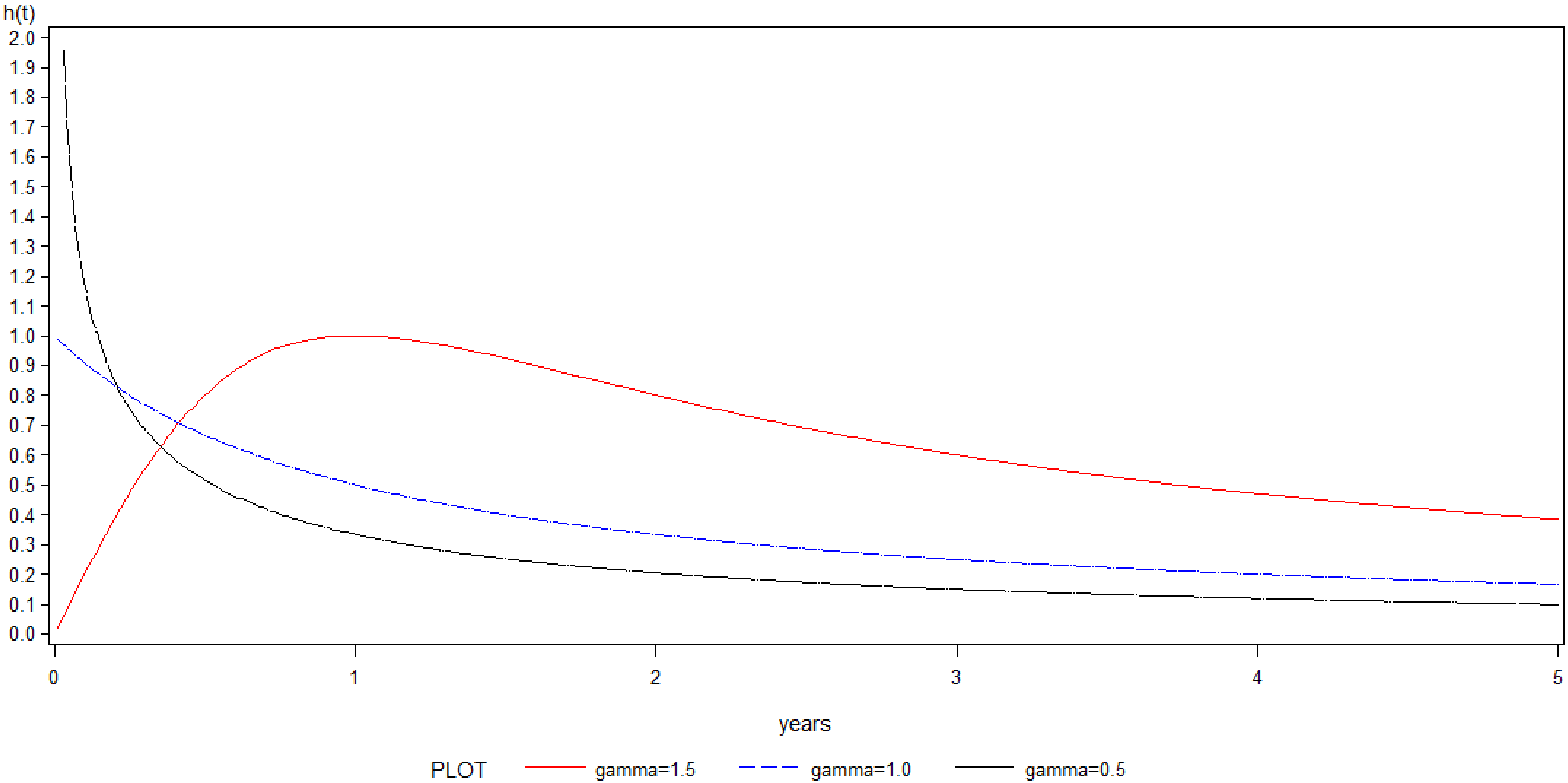
$$S(t) = \frac{1}{1+\alpha t^{\gamma}}$$

$$f(t) = \frac{\alpha \gamma t^{(\gamma-1)}}{(1+\alpha t^{\gamma})^{2}}$$

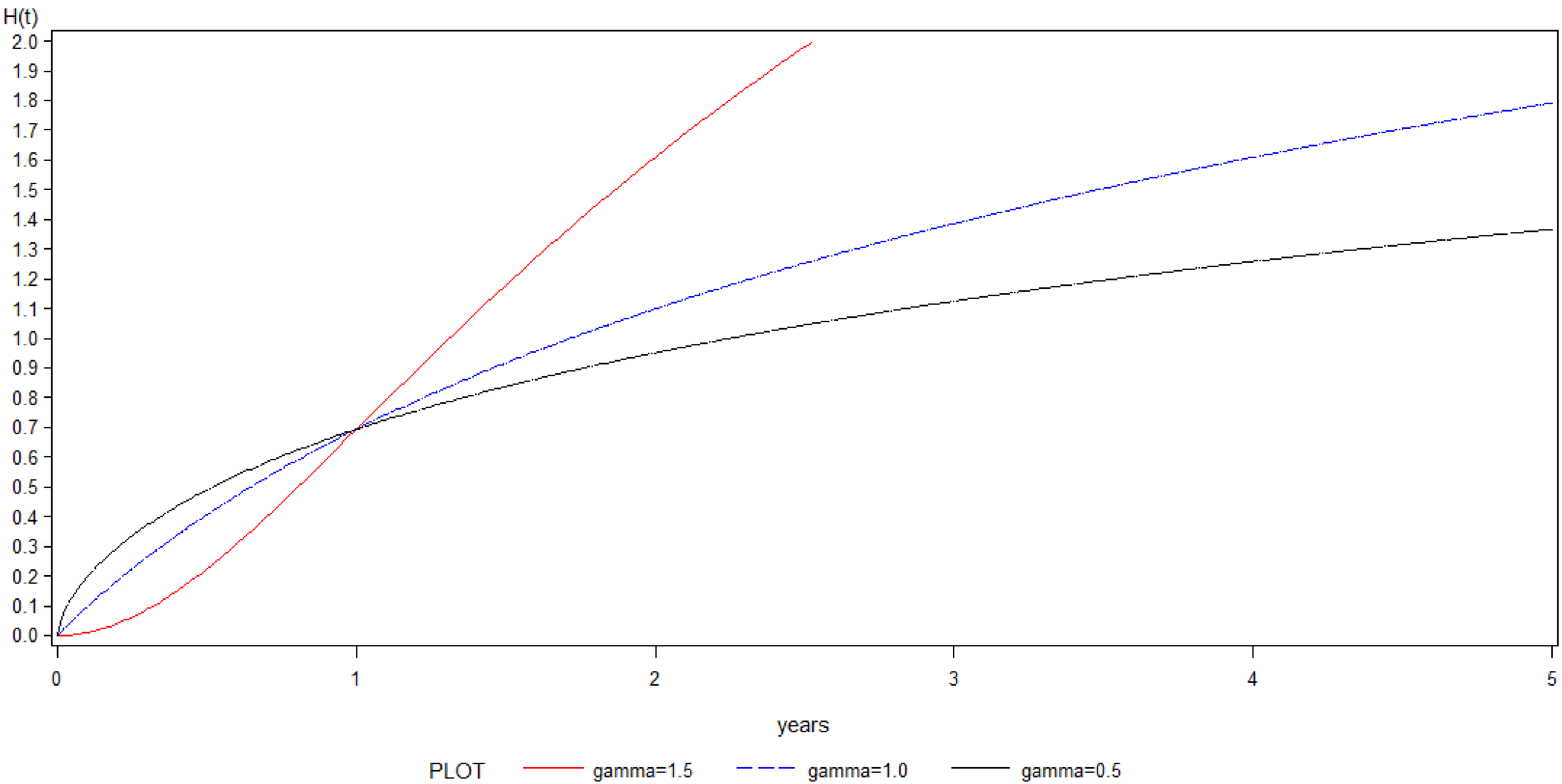
$$h(t) = \frac{f(t)}{S(t)} = \frac{\alpha \gamma t^{(\gamma-1)}}{1+\alpha t^{\gamma}}$$

$$Median = \left(\frac{1}{\alpha}\right)^{\frac{1}{\gamma}}$$

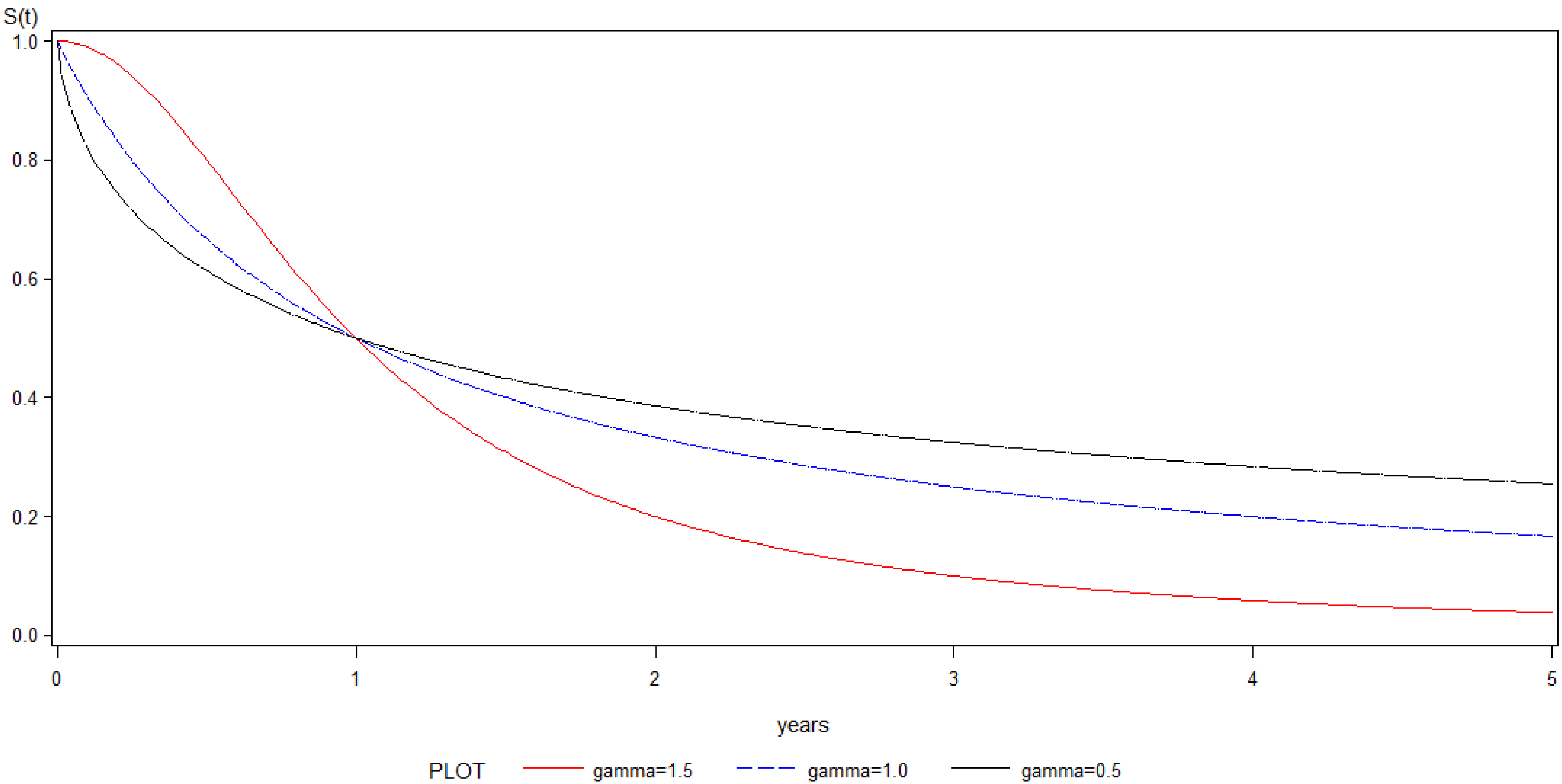
Log logistic hazard plots - alpha=1



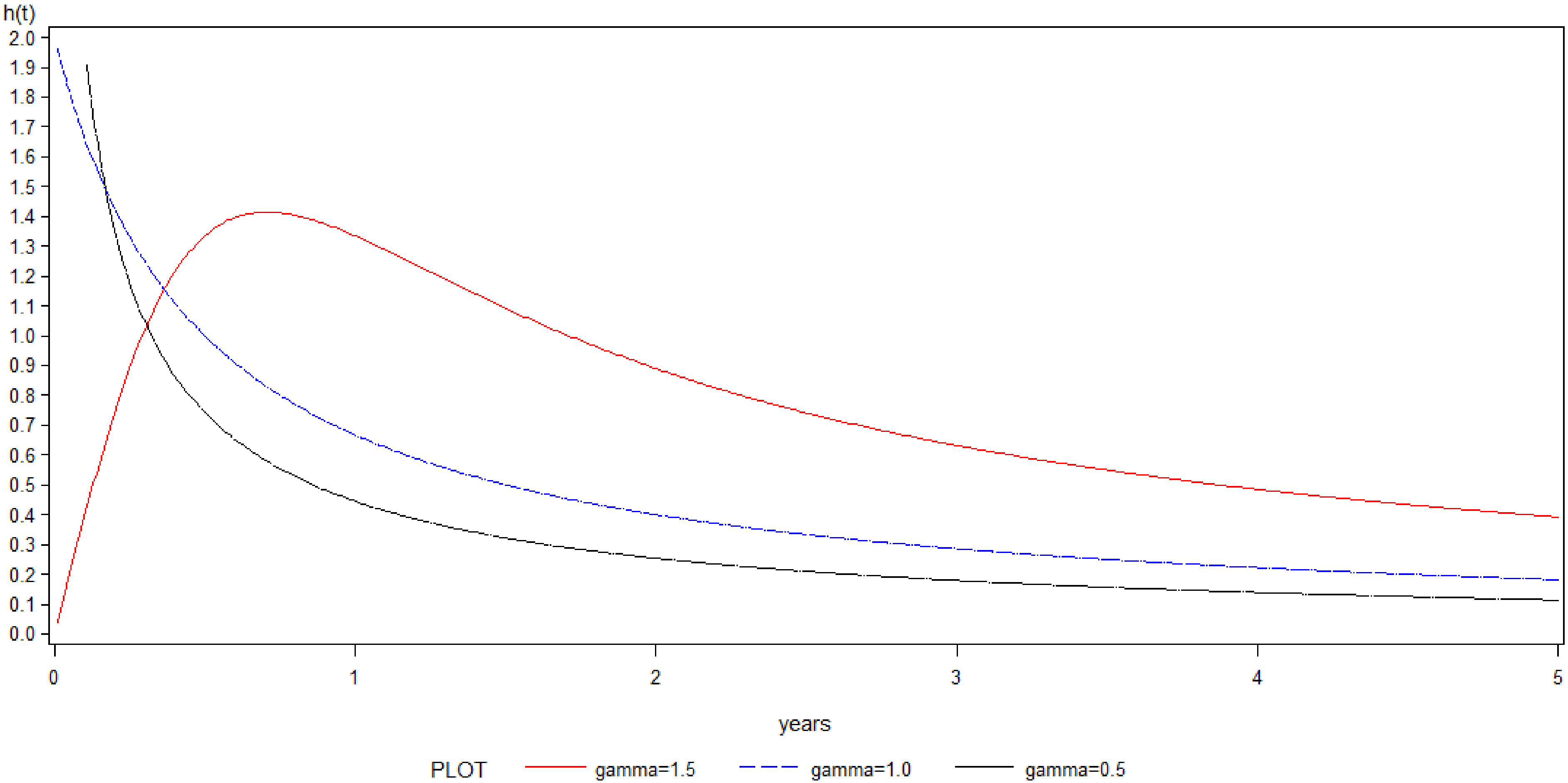
Log logistic cumulative hazard plots - alpha=1



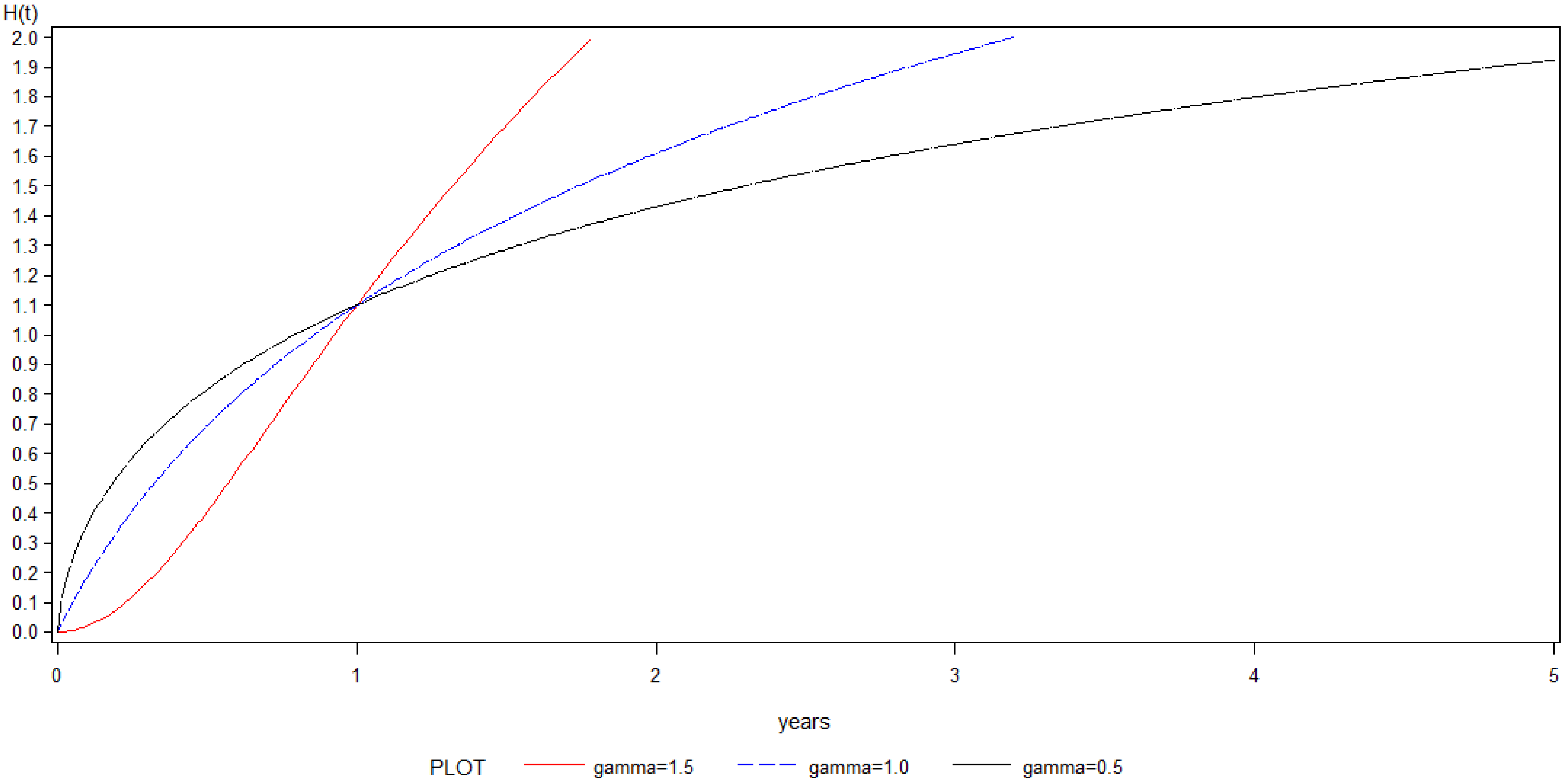
Log logistic survival plots - alpha=1



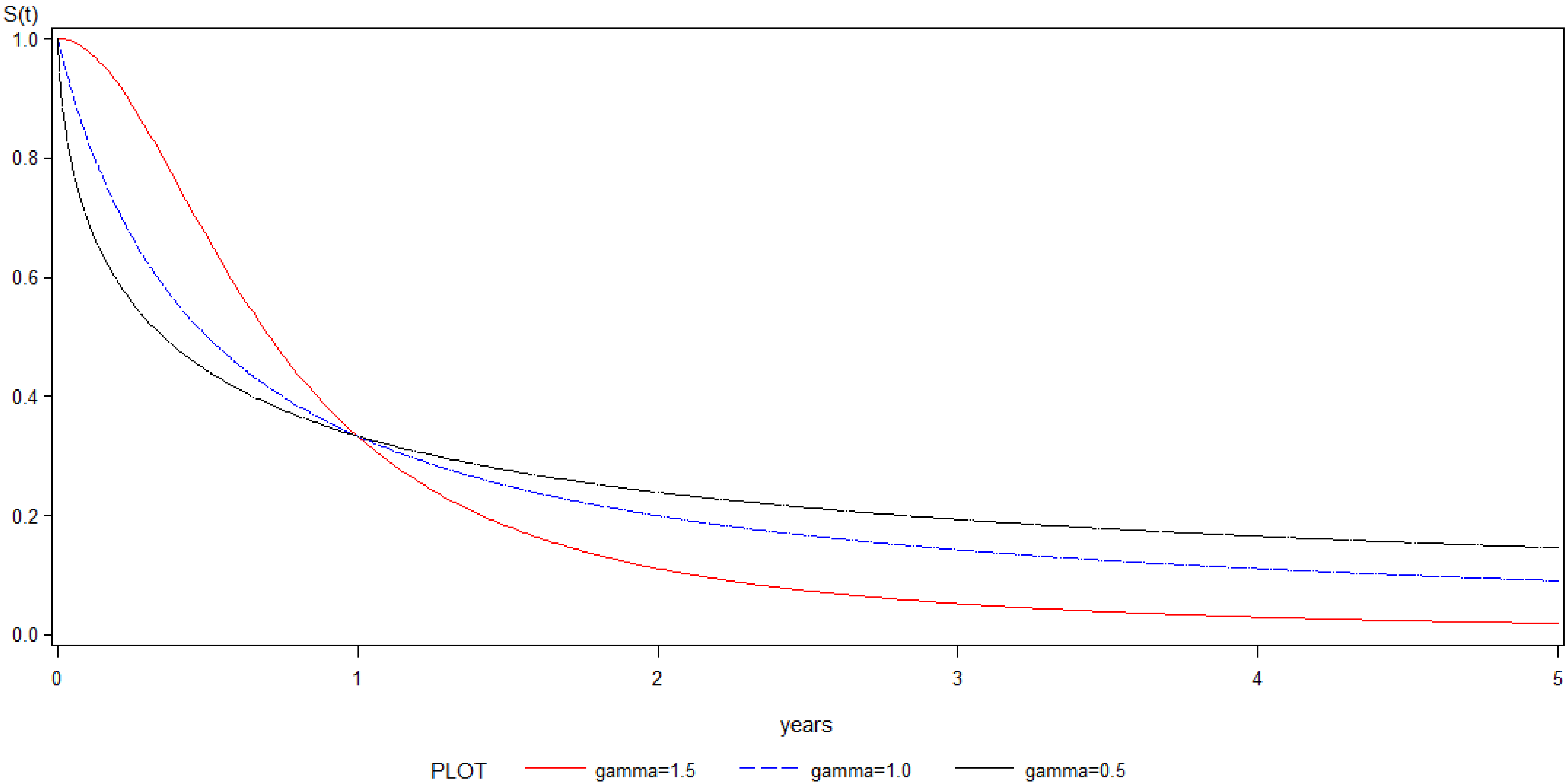
Log logistic hazard plots - alpha=2



Log logistic cumulative hazard plots - alpha=2



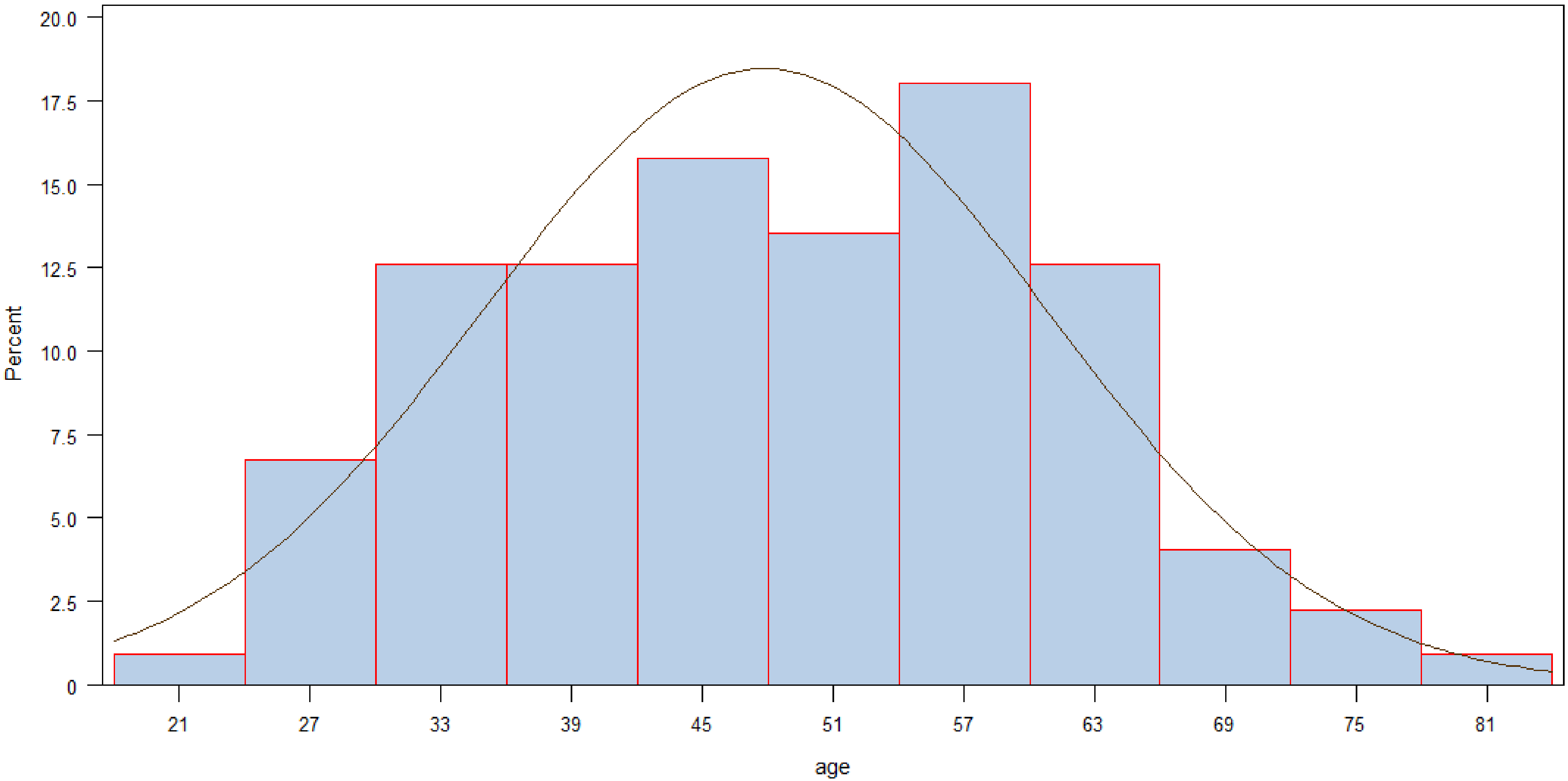
Log logistic survival plots - alpha=2



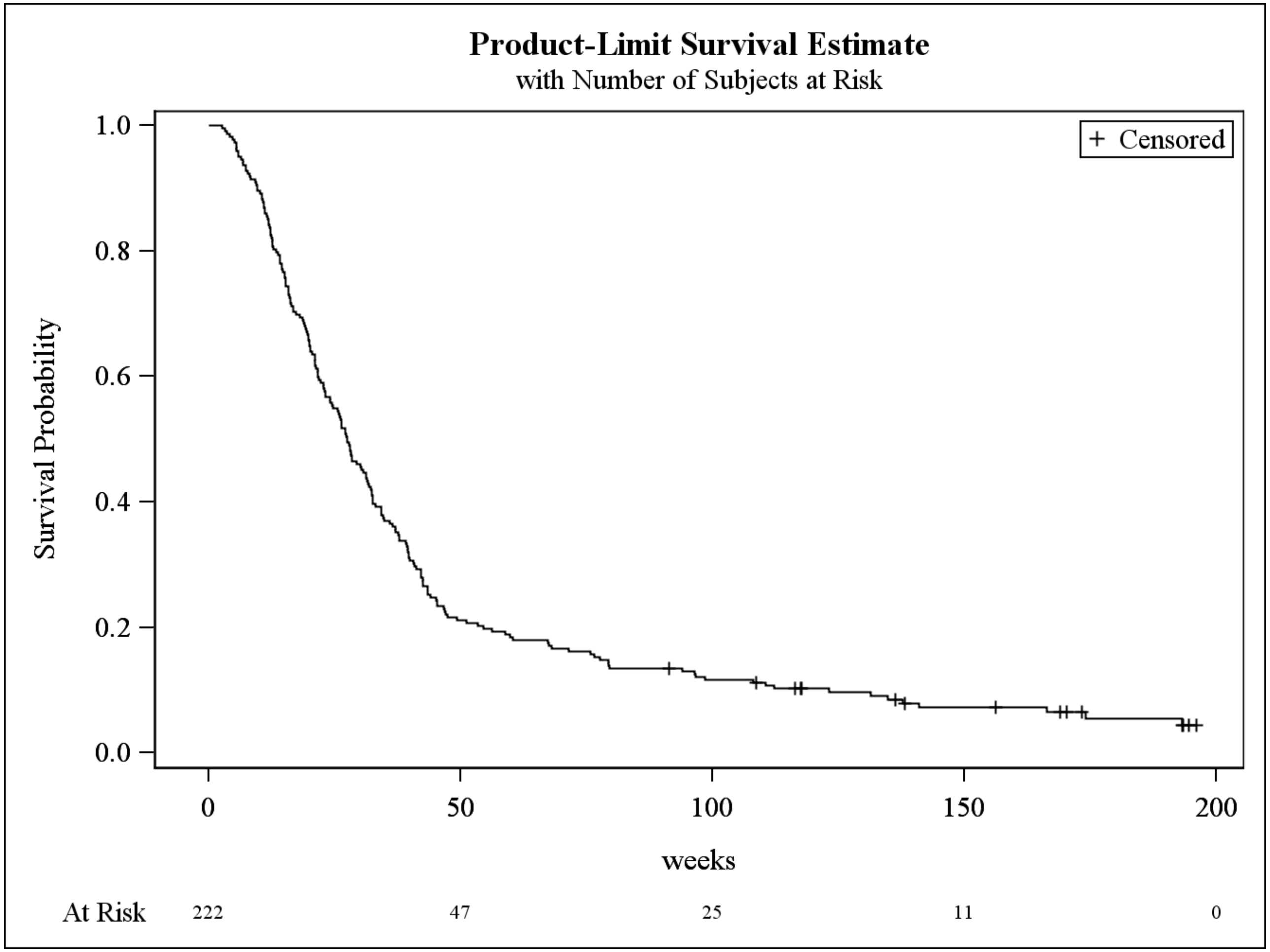
Example Data Set

- Patients diagnosed with brain cancer are randomized to a treatment group versus placebo.
- N=222, with only 15 censored cases
- Mean age around 48 years and 64% male.
- Other covariates are available in data set.

Distribution age



Overall Survival

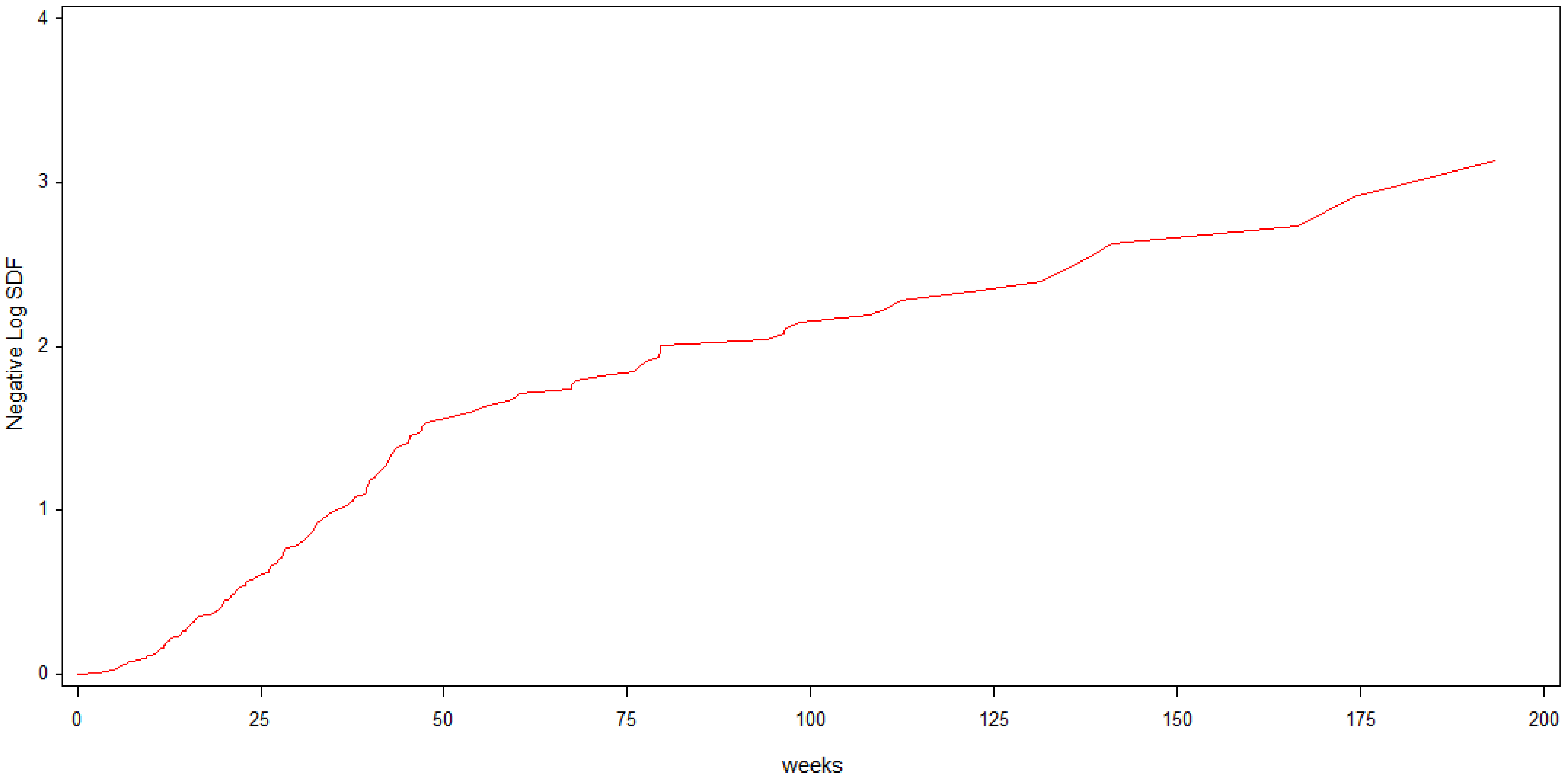


Estimated median=27.4 and mean=44.5

-logS(t) Plot

- Plot versus t
- If a straight line then exponential model ($H(t)=\lambda t$)

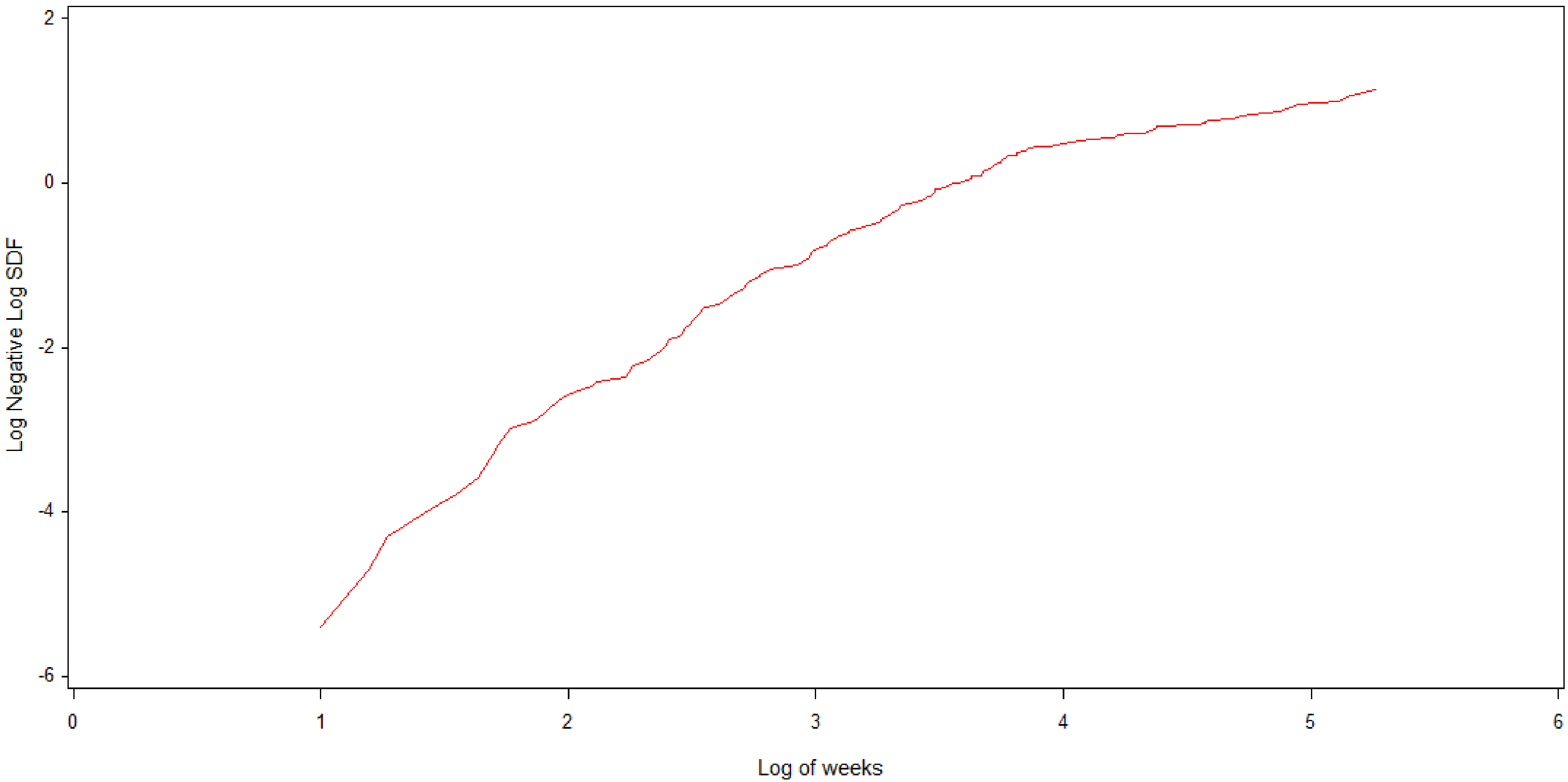
LifeTest: Overall Survival



log-logS(t) Plot

- Plot versus log(t)
- If a straight line then Weibull model
  - $H(t)=\lambda t^{\gamma}$
  - $\log H(t)=\log(\lambda)+\gamma\log(t)$

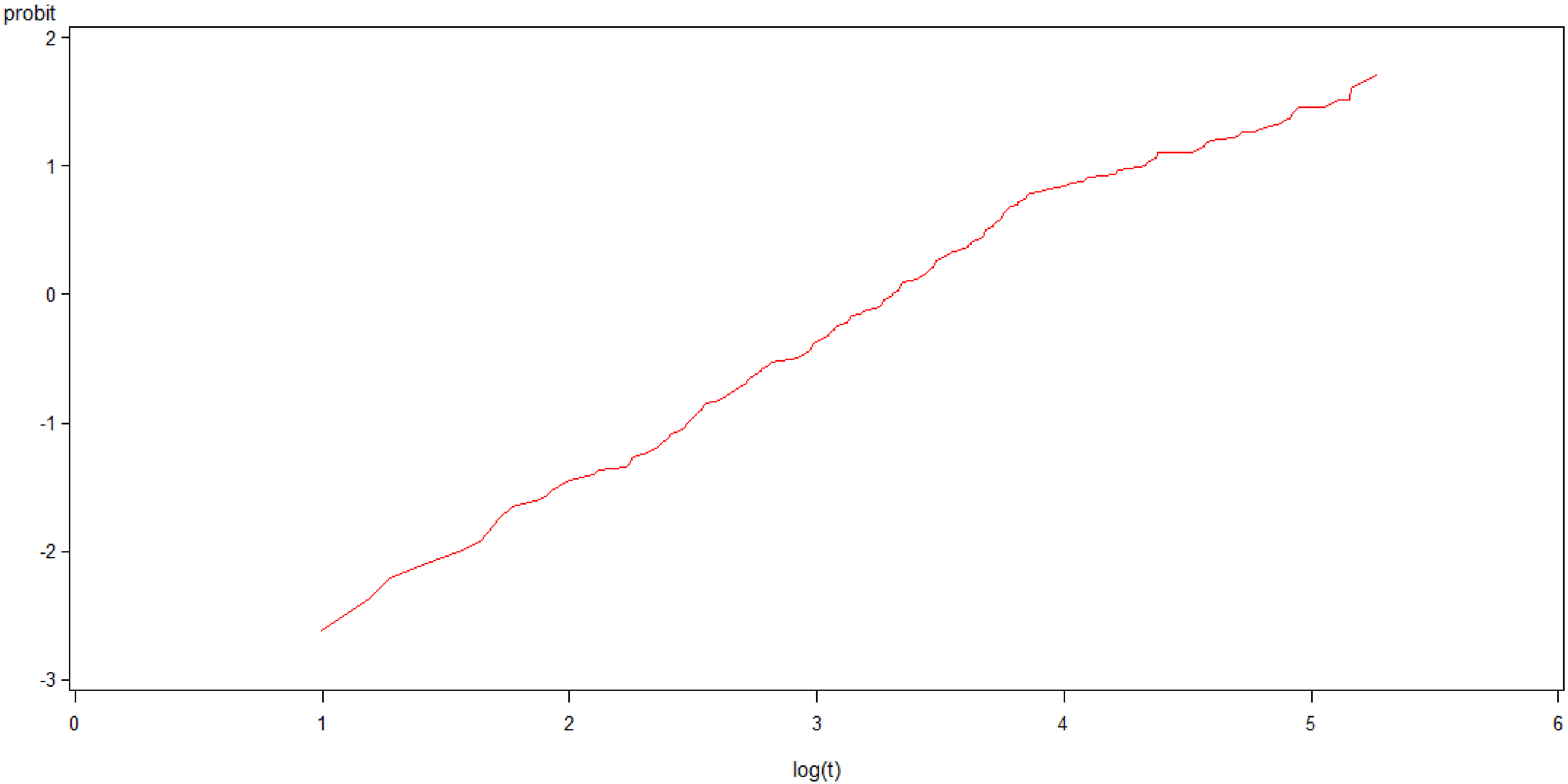
LifeTest: Overall Survival



Probit Plot

- Plot $\Phi^{-1}(1-S(t))$ versus $\log(t)$
- If a straight line then Log Normal model
  - $S(t)=1-\Phi((\log(t)-u)/\sigma)$

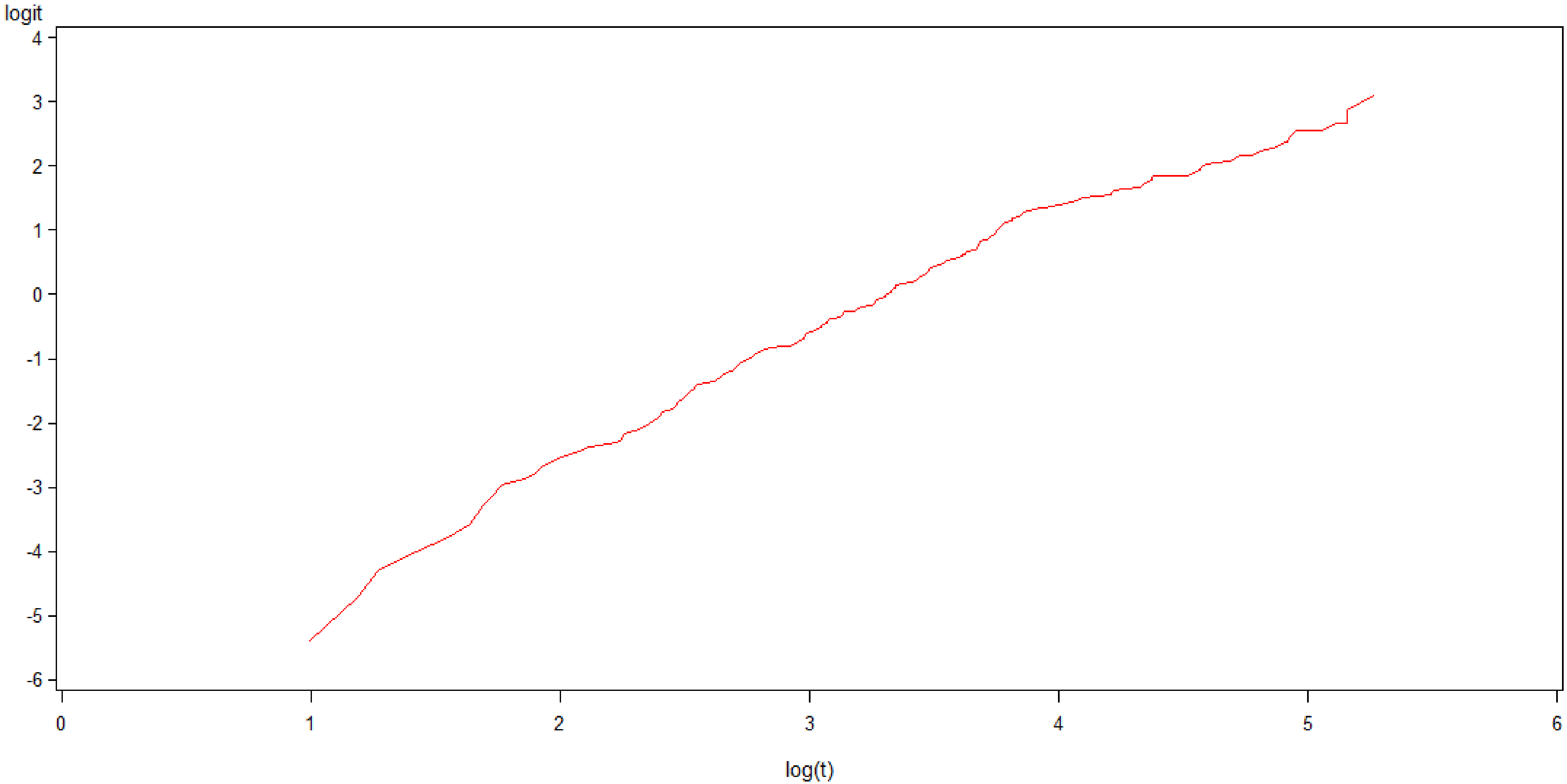
Probit(CDF) Plot



Logit Plot

- Plot $\log((1-S(t))/S(t))$ versus $\log(t)$
- Plot of odds of having the event by time t
- If a straight line then Log Logistic model
  - $S(t)=1/(1+\alpha t^{\gamma})$

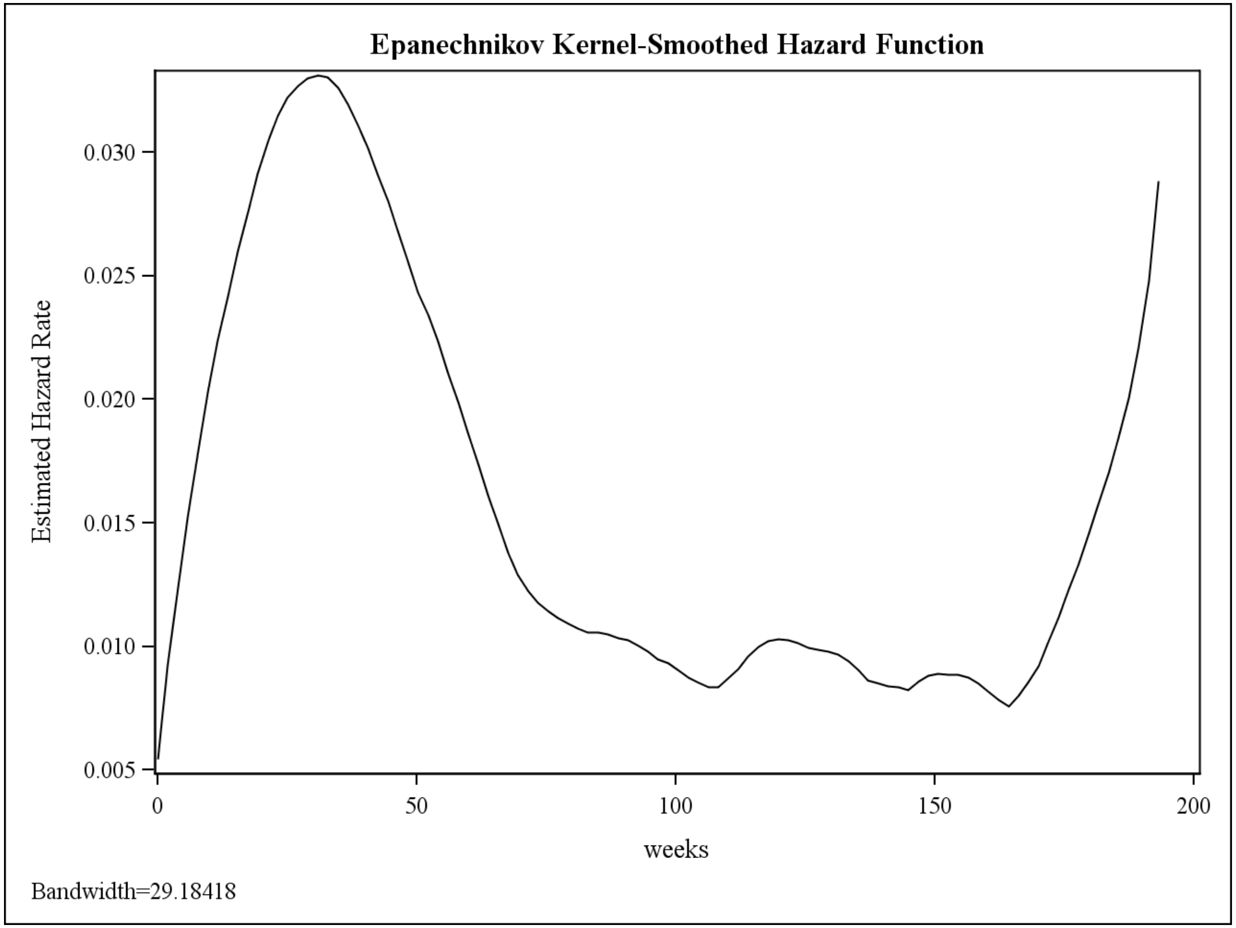
Logit(CDF) Plot



Other options

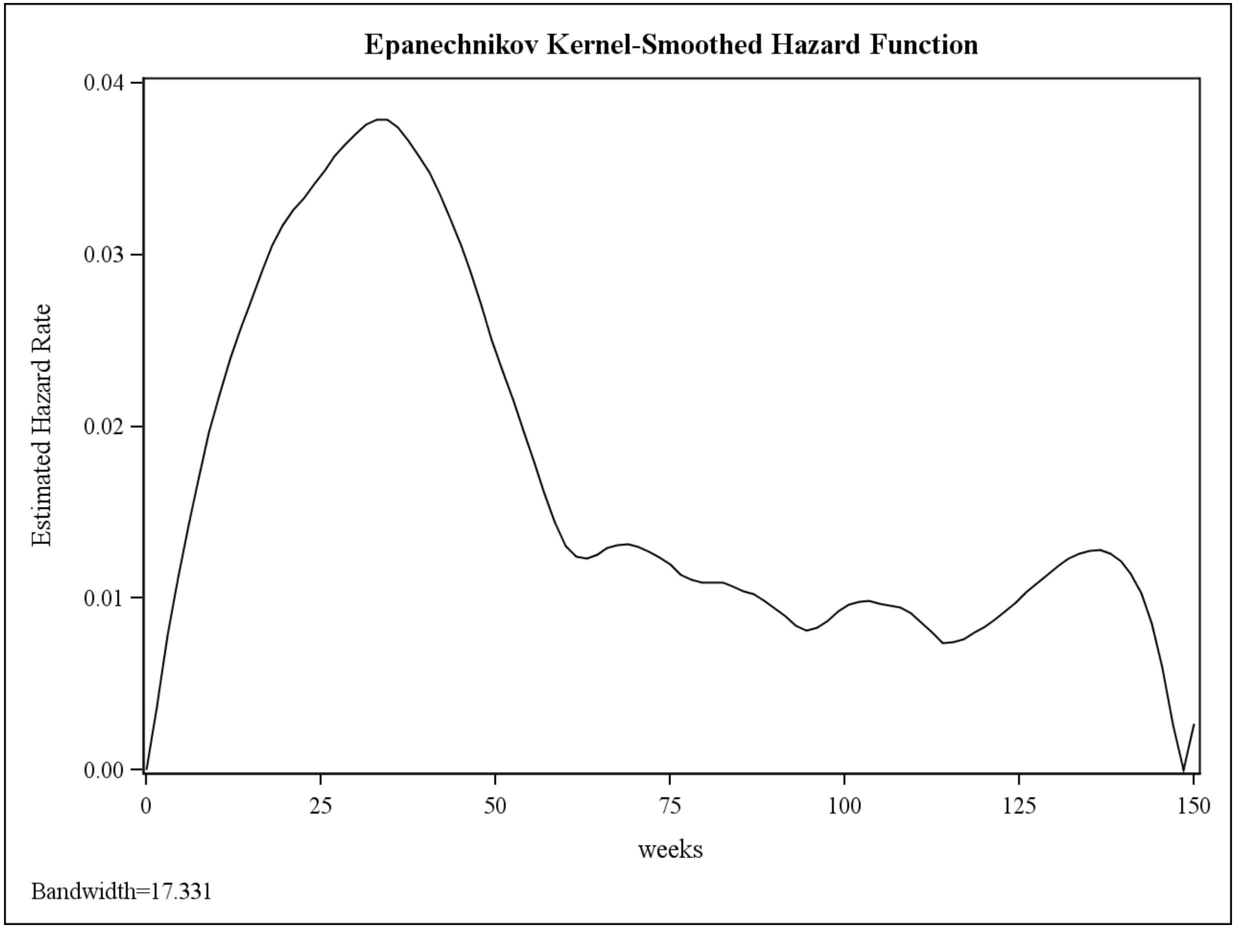
- Non-parametric smoothing of hazard function
- Probability plots
- Likelihood ratio tests of nested models (Gamma)
- Check distribution of t or log(t) for the non-censored cases

Smoothed Hazard Function



Smoothed Hazard Function

(reduced range)

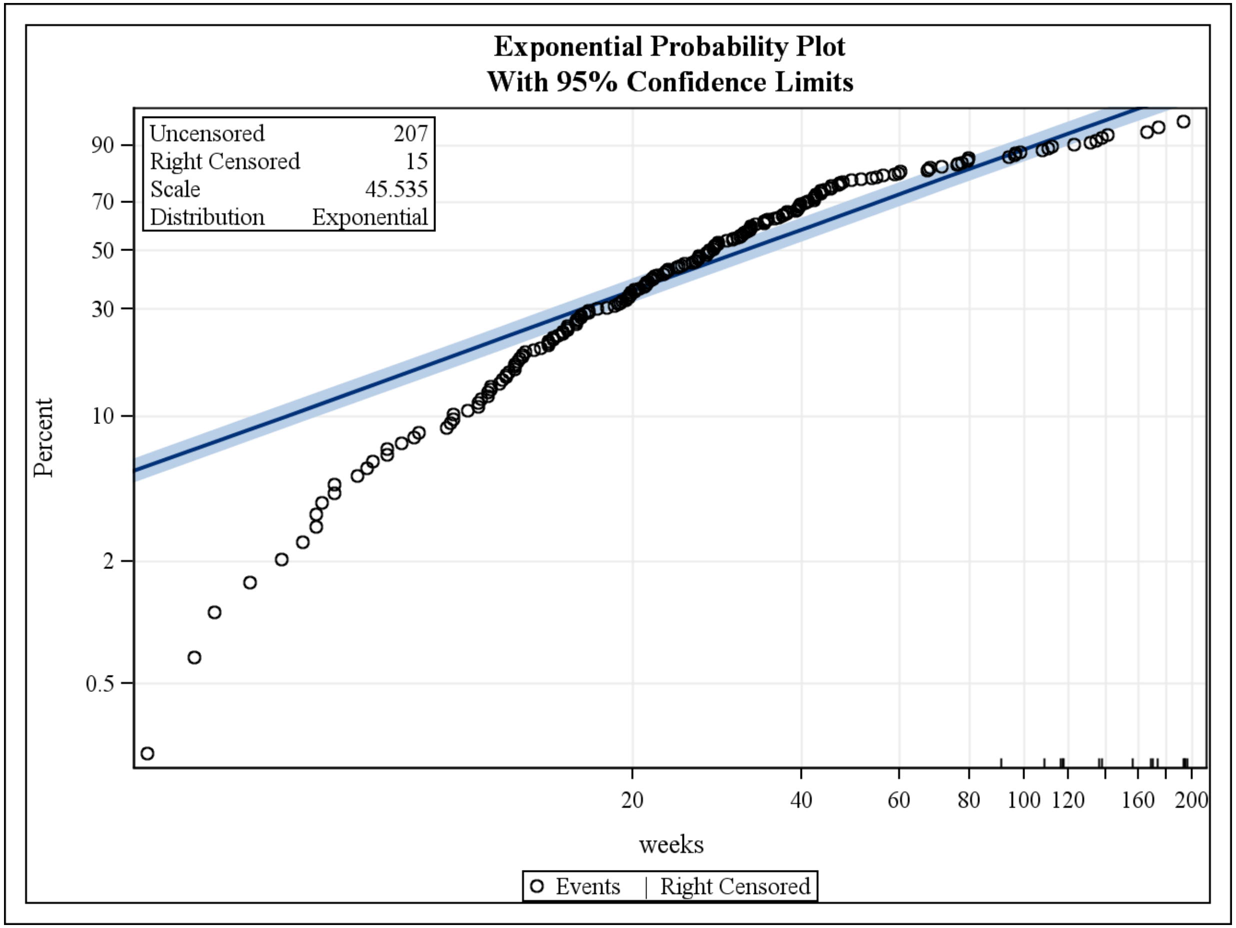


SAS Code (SAS 9.4 using ODS graphics)

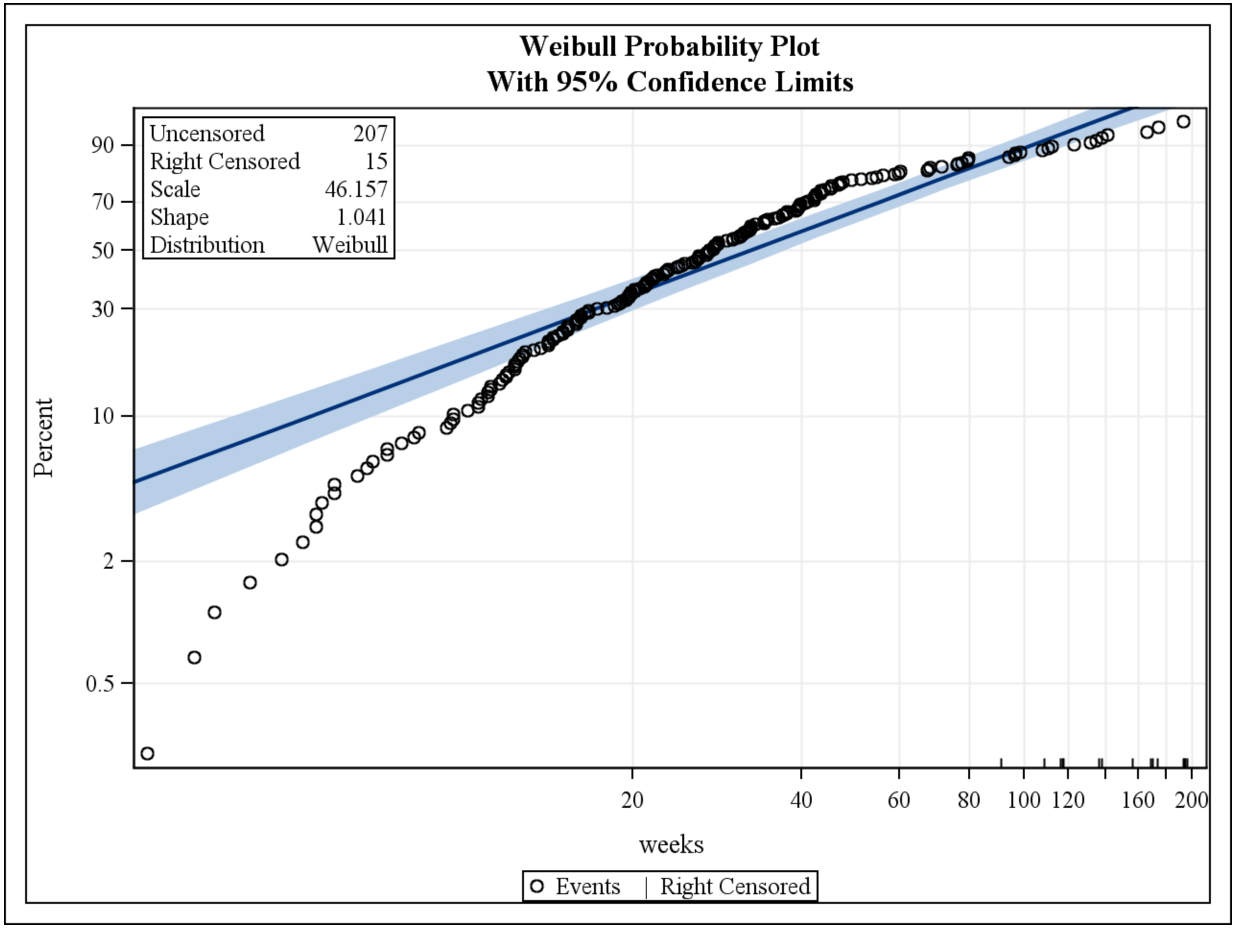
```
proc lifereg data=sda.brain;
  model weeks*event(0)=/d=exponential;
  probplot;
  inset;
  title 'LifeReg: Overall Survival - Probability Plot (Exponential)';
run;
```

```
proc lifetest data=sda.brain
              plot=(survival(atrisk outside) hazard logsurv loglogs)
              notable;
  time weeks*event(0);
  title 'LifeTest: Overall Survival: hazard';
run;
```

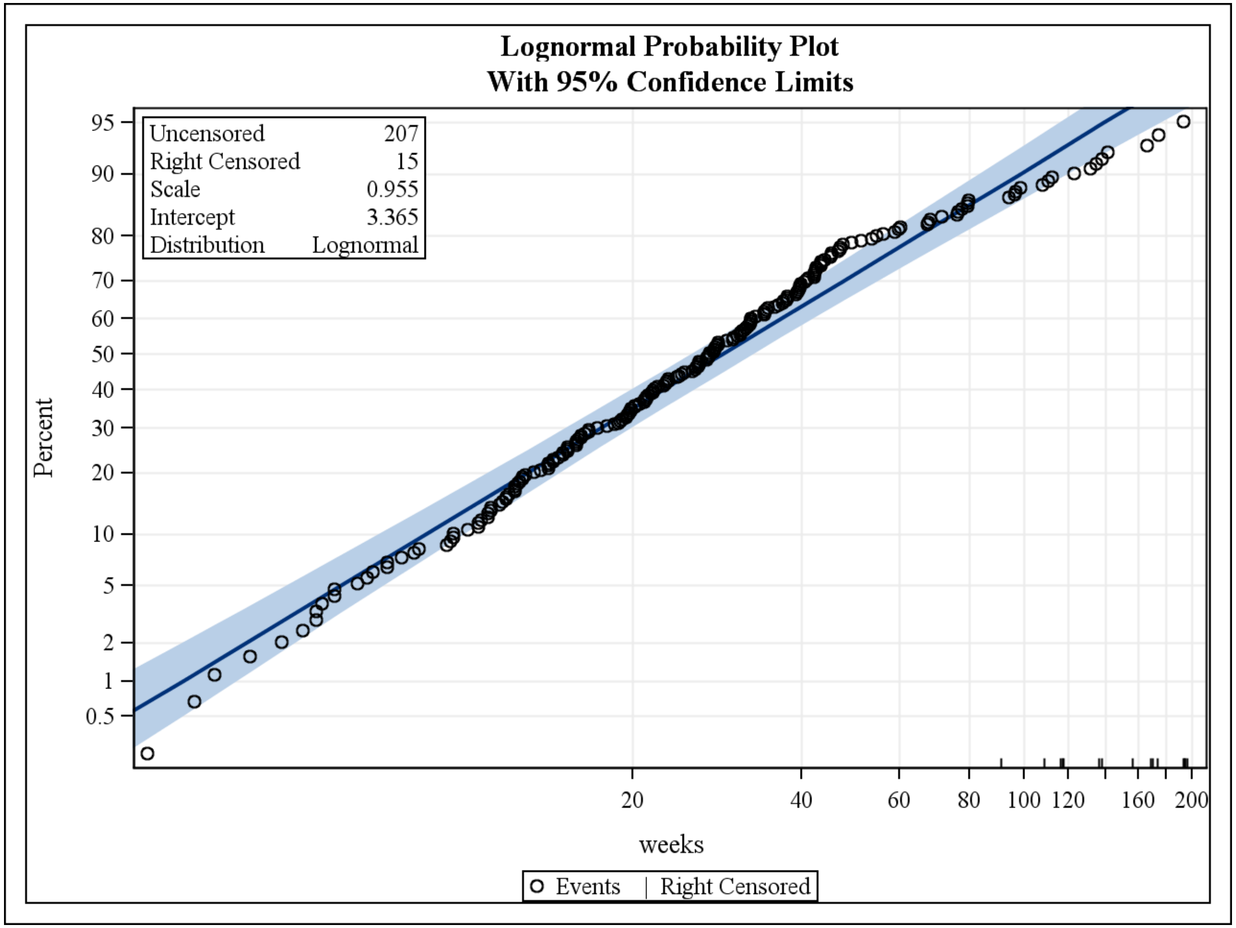
Exponential Probability Plot



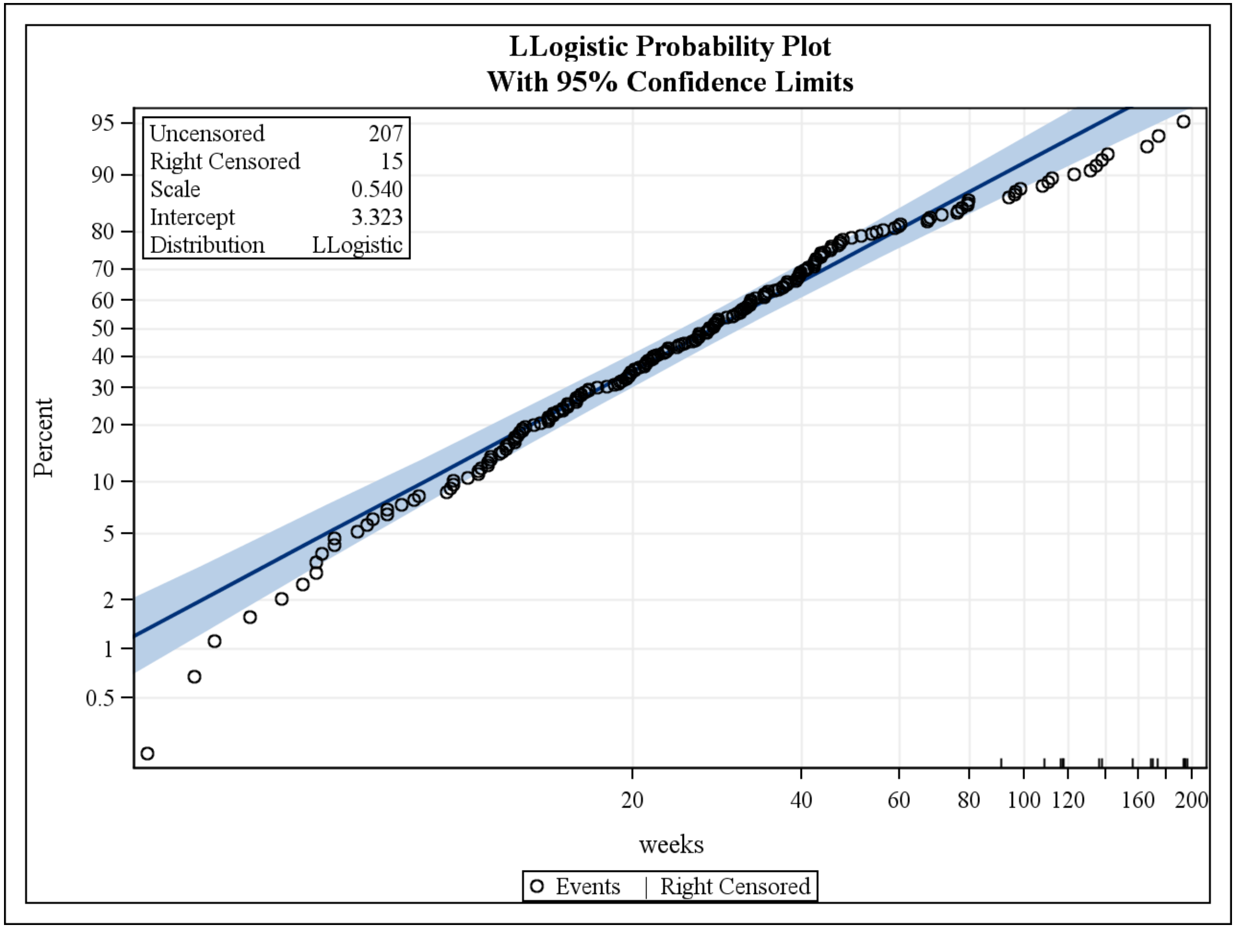
Weibull Probability Plot



Log Normal Probability Plot

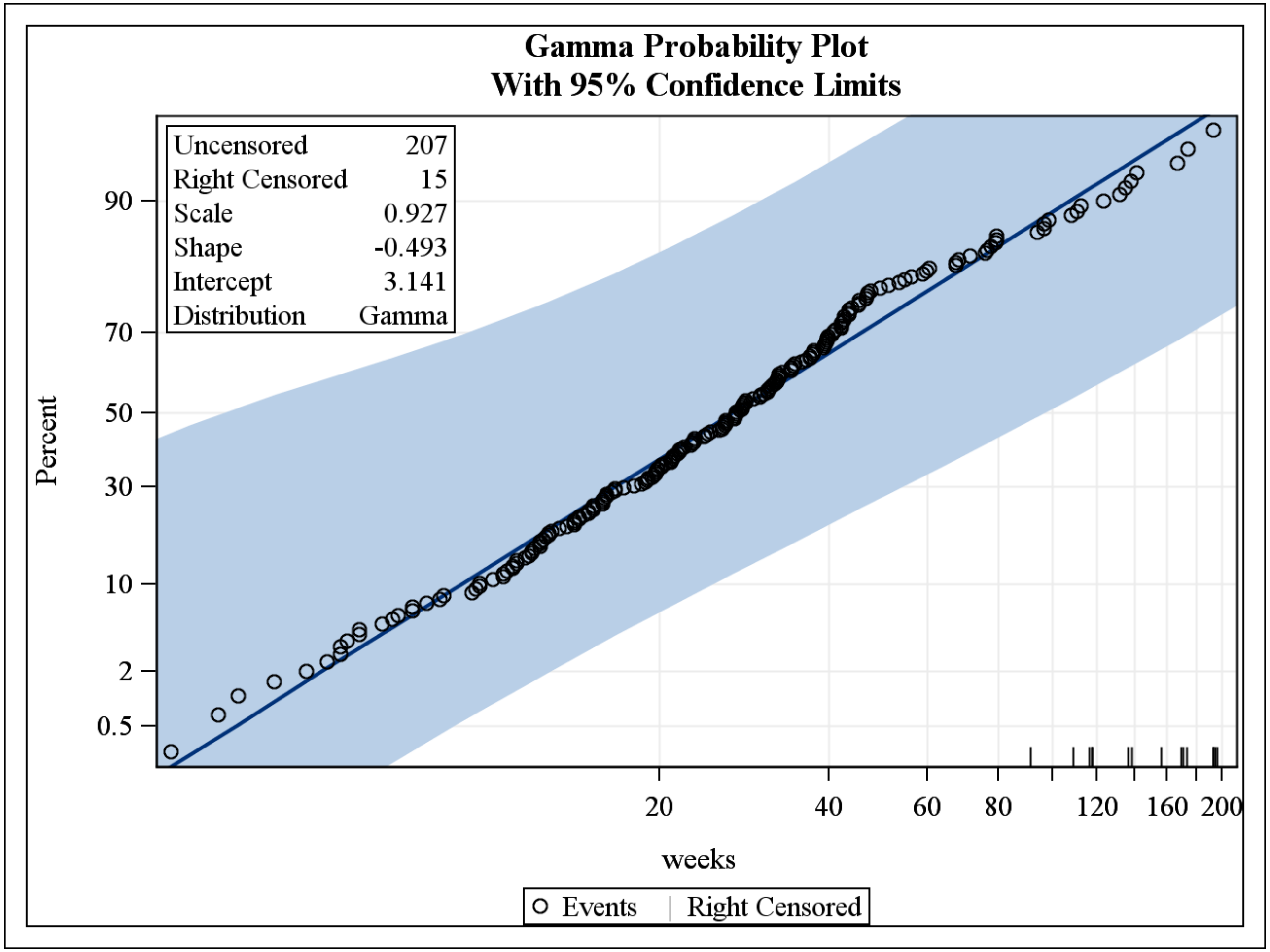


Log Logistic Probability Plot

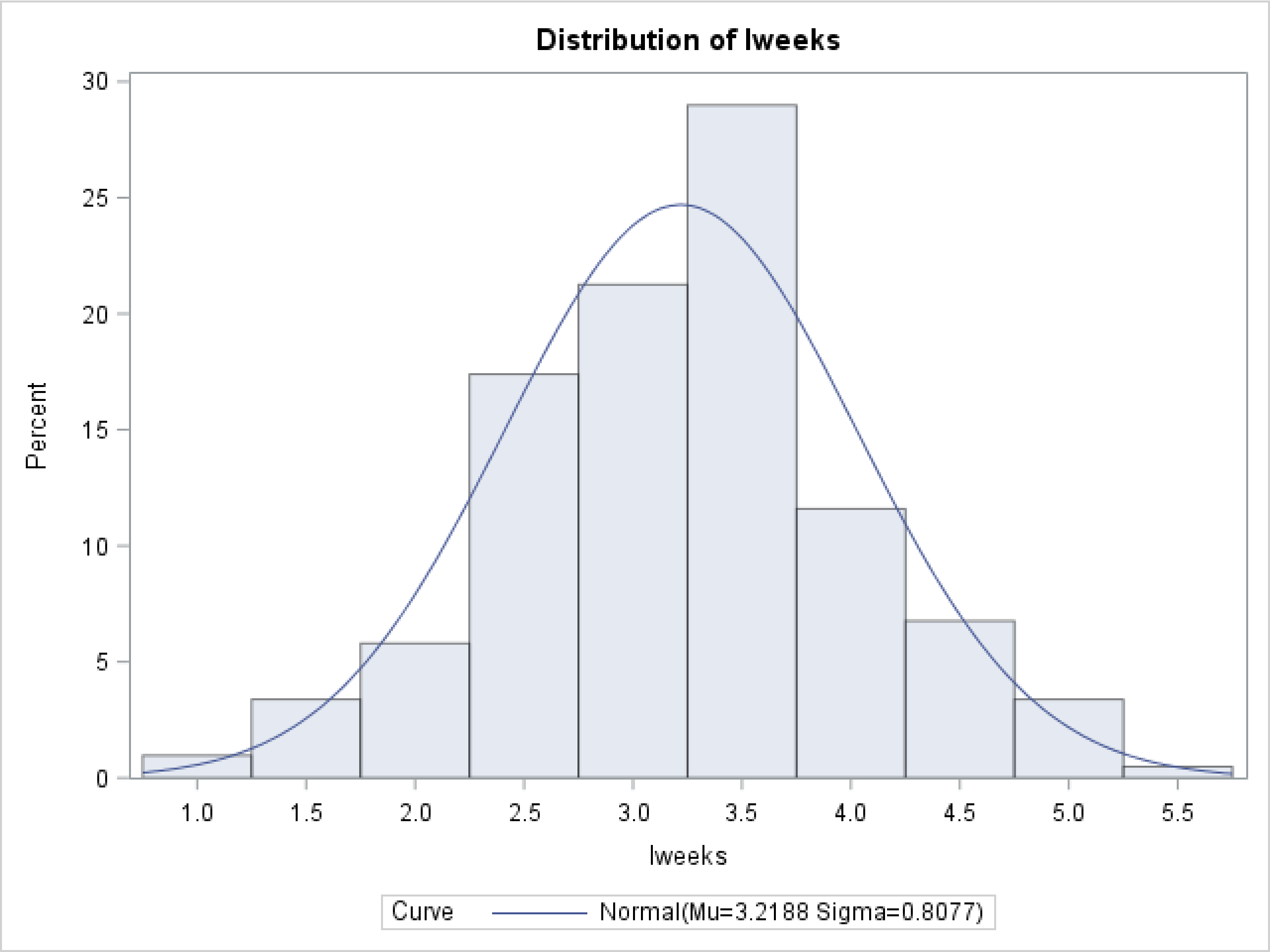


Gamma Model

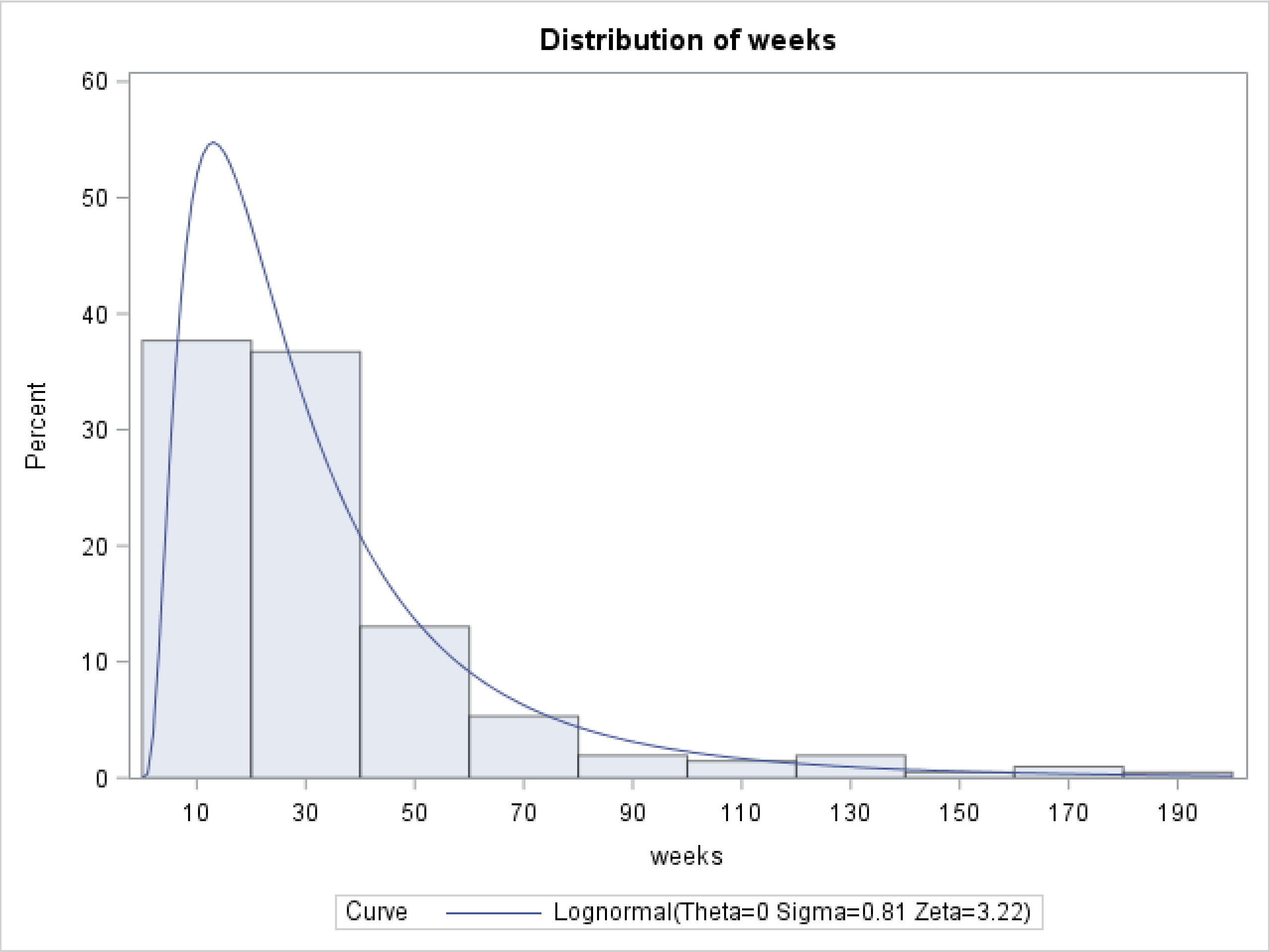
- SAS fits the generalized 3-parameter model
- it can fit a Weibull (exponential) and log-normal model (test using likelihood ratio test)
- it can also fit a model with a U-shaped hazard function
- Survivor and hazard functions involve incomplete gamma functions


Gamma Probability Plot
With 95% Confidence Limits
Uncensored 207
Right Censored 15
Scale 0.927
Shape -0.493
Intercept 3.141
Distribution Gamma
Percent
90
70
50
30
10
2
0.5
20
40
60
80
120
160
200
weeks
Events
Right Censored

Events only (Proc Univariate):

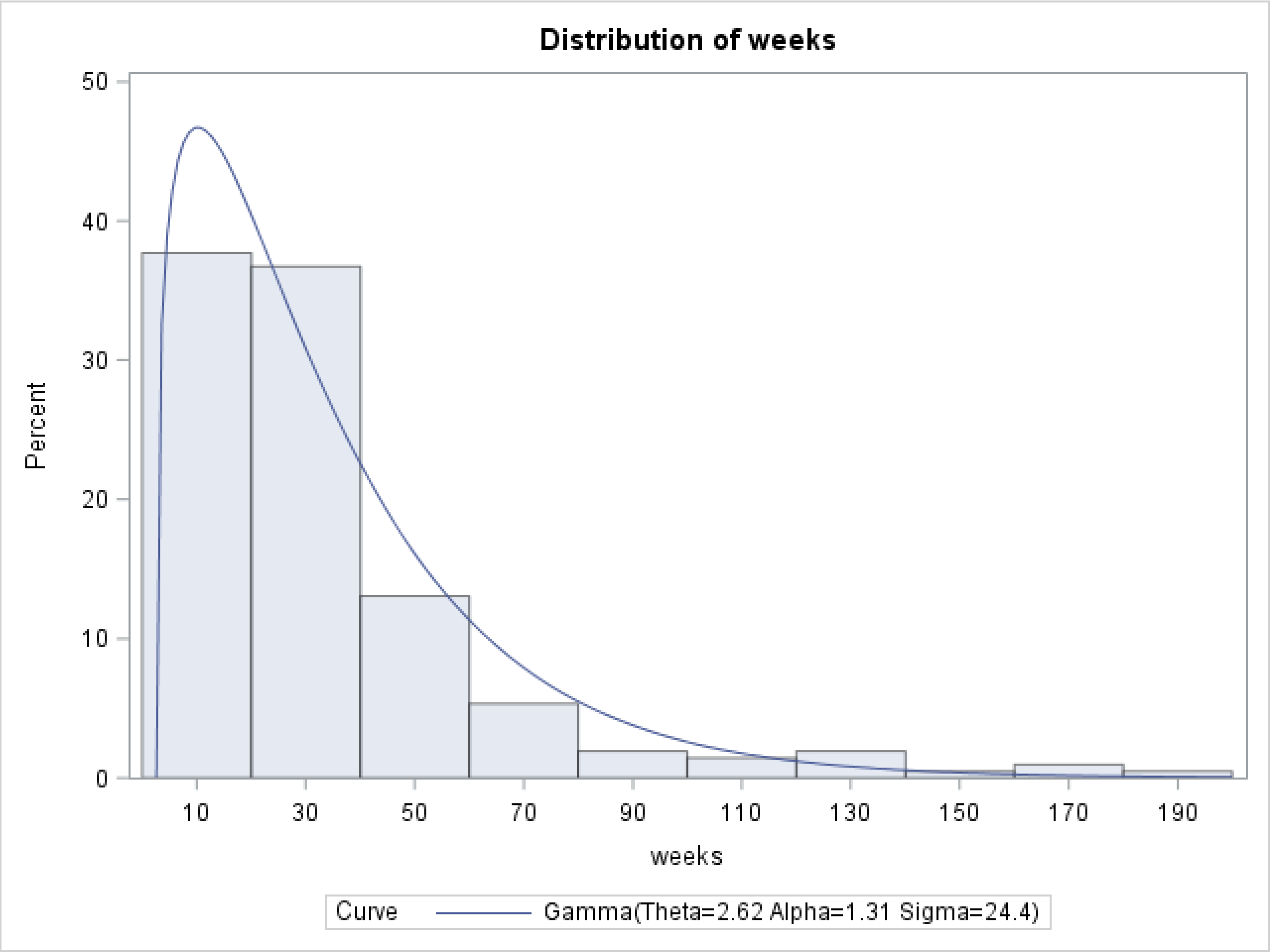


Events only (Proc Univariate):



Note: CDF plots also available in Proc Univariate

Events only (Proc Univariate):



Note: different parameterization than Proc Lifetest.

Unadjusted model

Basic data summary

Variable	Sum
event	207
weeks	9426

Estimated rate: 207/9426=0.02196
ln(0.02196)=-3.8185

overall median	27.430	95% CI (23.14, 31.43)
mean	44.528	SE= 3.285

Exponential (Intercept only)

```
-2 Log Likelihood=662.275, AIC=664.275
```

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.8185	0.0695	3.6823	3.9547	3018.22	<.0001
Scale	0	1.0000	0.0000	1.0000	1.0000		
Weibull Scale	1	45.5348	3.1649	39.7357	52.1803		
Weibull Shape	0	1.0000	0.0000	1.0000	1.0000		

Lagrange Multiplier Statistics

Parameter	Chi-Square	Pr > ChiSq
Scale	0.6216	0.4304

$\lambda = \exp(-3.8185) = 0.02196$

$S(t) = \exp(-\lambda^* t)$

$h(t) = \lambda$

$\text{Median} = -\ln(.5)/\lambda = 31.4$

$\text{Mean} = 1/\lambda = 45.5$

Weibull(Intercept only)

```
-2 Log Likelihood=661.693 AIC=665.693

                                         Standard    95% Confidence       Chi-
Parameter      DF Estimate     Error        Limits         Square Pr > ChiSq

Intercept       1   3.8321   0.0692   3.6965   3.9676 3069.48     <.0001
Scale           1   0.9608   0.0498   0.8679   1.0636   * 1/shape
Weibull Scale   1  46.1571   3.1925  40.3054  52.8583
Weibull Shape   1   1.0408   0.0540   0.9402   1.1522   * gamma

  λ = exp(- 1.0408 * 3.8321) = 0.0185
  γ = 1.0408
  S(t) = exp(-λ*t**γ)
  h(t) = γ*λ*(t**(γ-1))
  Median = (-ln(.5)/λ)**(1/γ) = 32.3

  Using extreme value distribution:
  μ=3.8321
  σ=0.9608
  S(t) = exp(-exp((log(t)-3.8321) / 0.9608))
```

Log Normal(Intercept only)

```
-2 Log Likelihood=608.002, AIC=612.002

                             Standard   95% Confidence      Chi-
Parameter      DF Estimate     Error        Limits        Square Pr > ChiSq

Intercept       1    3.3653    0.0644   3.2389   3.4916 2726.77      <.0001
Scale           1    0.9553    0.0479   0.8659   1.0540
```

```
u = 3.3653
σ = 0.9553
S(t) = 1-Φ((ln(t)-u)/σ)
f(t) = 1/(sqrt(2*π)*t*σ)*exp(-1/2*((ln(t)-u)/σ)**2)
h(t) = f(t)/S(t)
Median = exp(u) = 28.9
Mean = exp(u+0.5σ**2) = 45.7
```

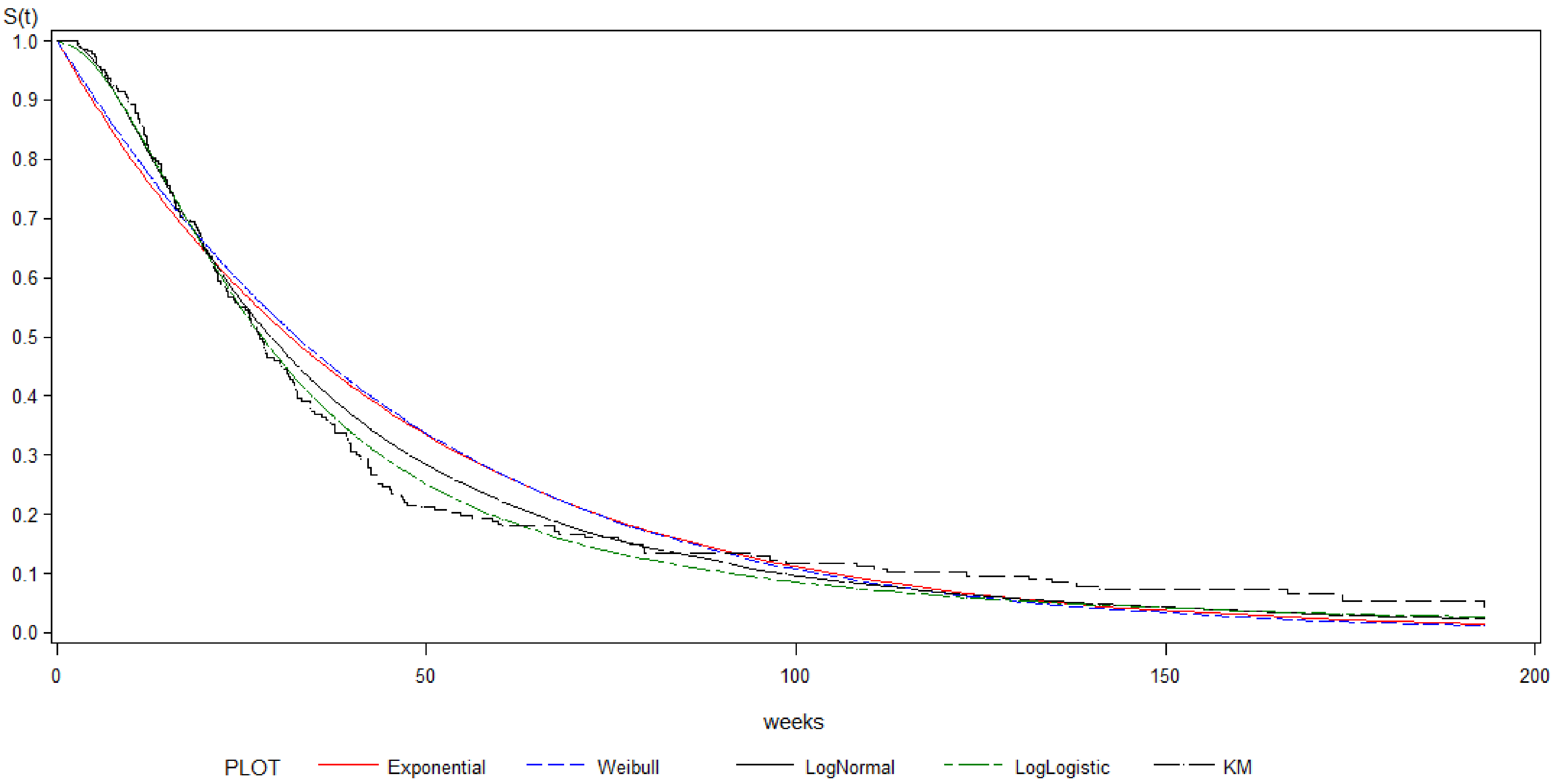
Log Logistic (Intercept only)

```
-2 Log Likelihood=604.338, AIC=608.338
```

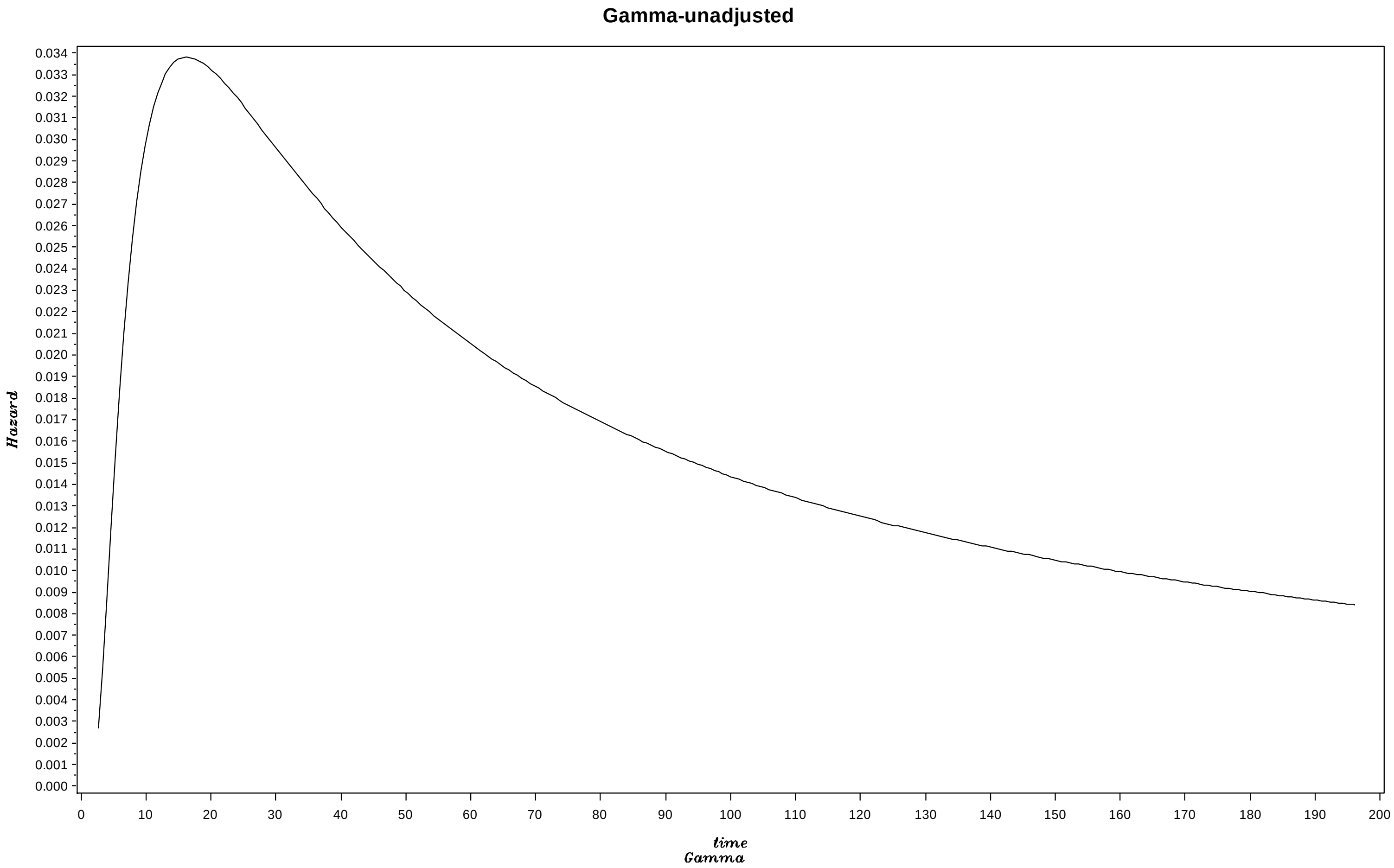
Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.3233	0.0625	3.2008	3.4458	2828.98	<.0001
Scale	1	0.5398	0.0315	0.4815	0.6052		

```
α = exp(- 3.3233 / 0.5398) = 0.0021
γ = 1/ 0.5398 = 1.8525
S(t) = 1/(1+α*t**γ)
f(t) = (α*γ*t**(γ-1))/(1+α*t**γ)**2
h(t) = f(t)/S(t)
Median = (1/α)**(1/γ) = 27.8
```

Comparison of Survival Models



Gamma hazard (Allison LIFEHAZ macro)



Gamma model (Intercept only)

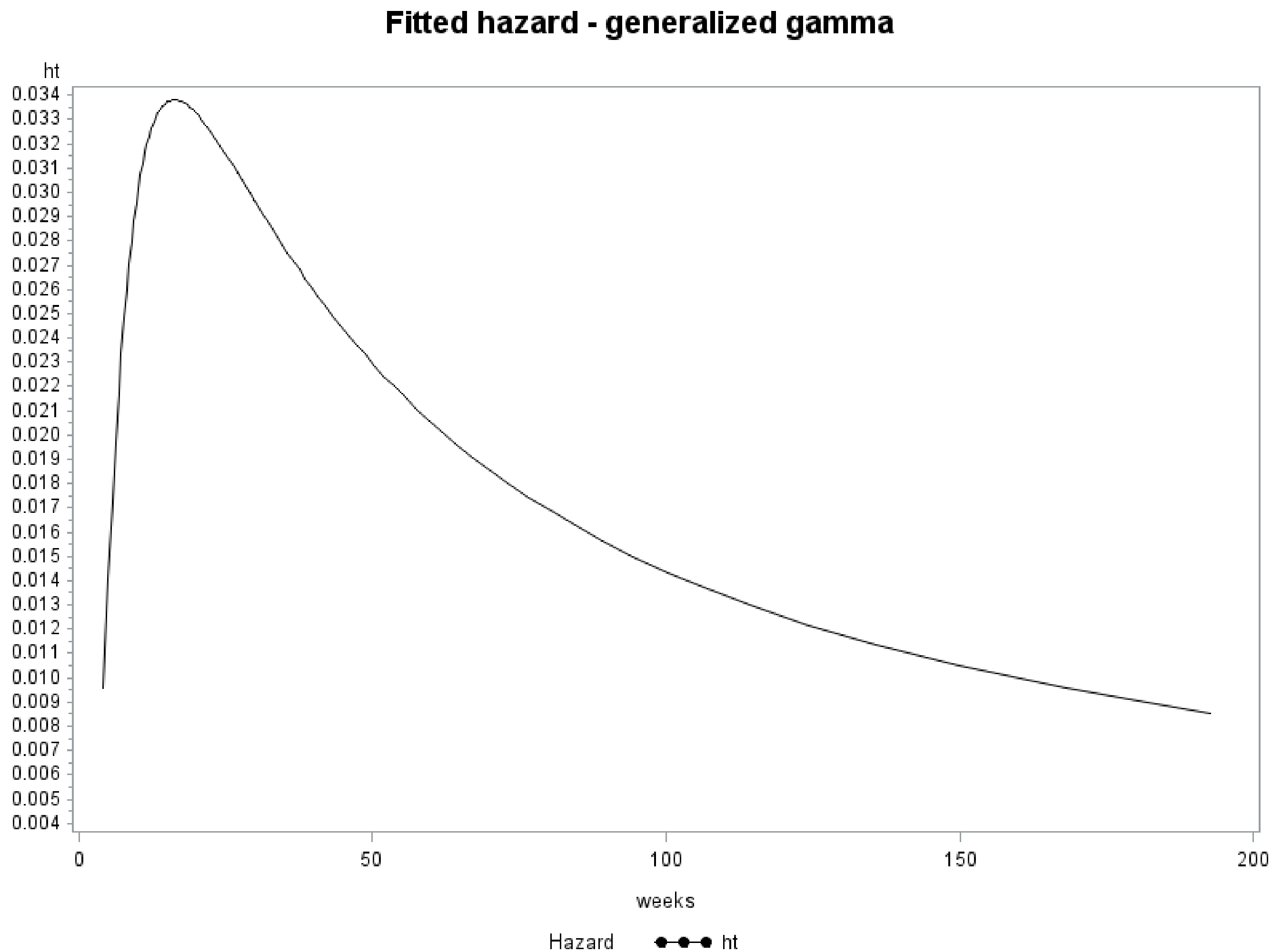
-2 Log Likelihood=600.334, AIC=606.334

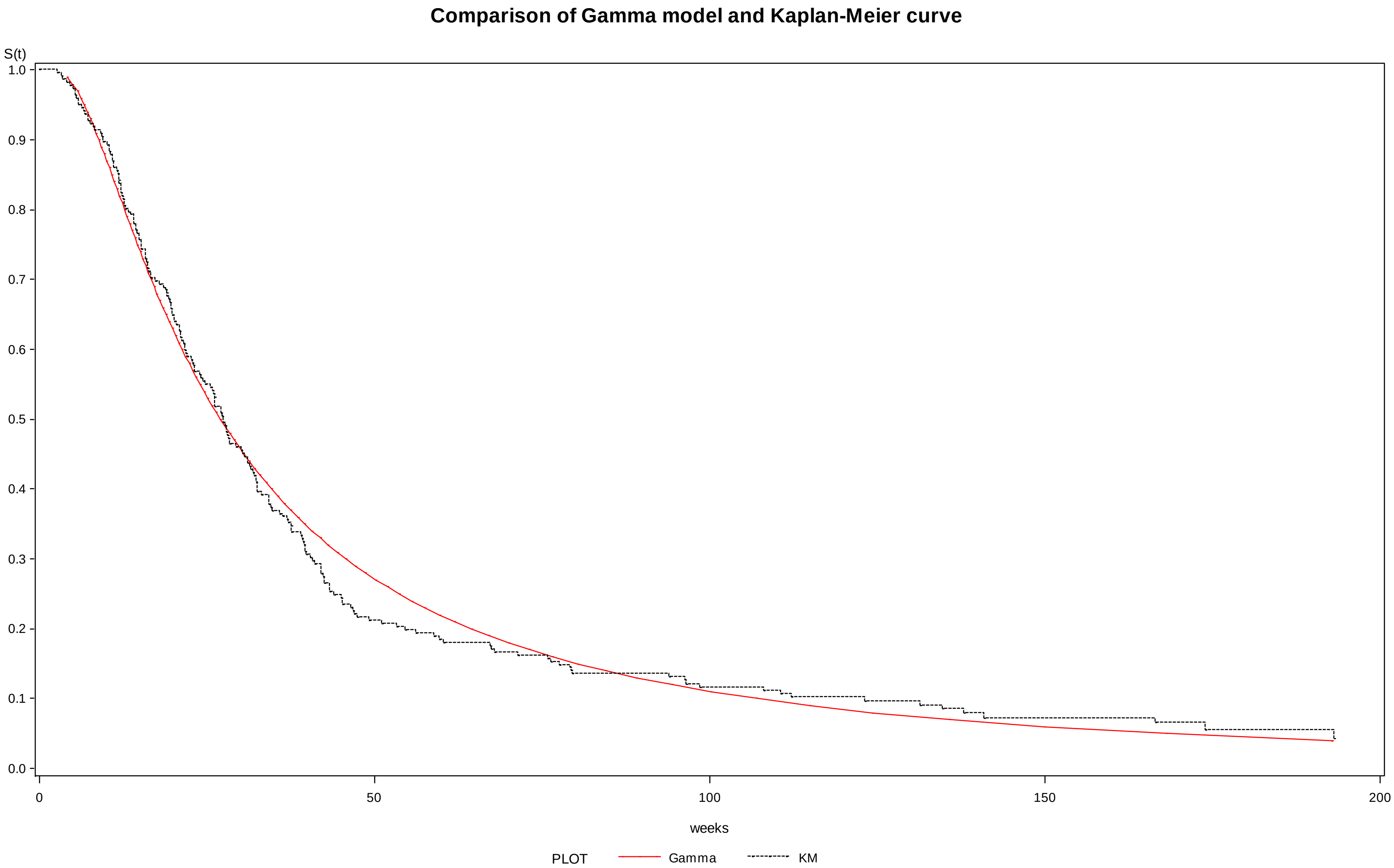
Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.1407	0.1006	2.9434	3.3380	973.70	<.0001
Scale	1	0.9272	0.0479	0.8379	1.0259		
Shape	1	-0.4929	0.1733	-0.8326	-0.1533		

If shape parameter is 0 then log-normal model
If shape parameter is 1 then Weibull model
If shape =1 and scale=1 then exponential model
If shape and scale are equal, then standard gamma distribution

Likelihood ratio test: Gamma vs log normal
chi-square = 608.001-600.334 = 7.667 , p=0.006

Unadjusted model fit




Comparison of Gamma model and Kaplan-Meier curve
S(t)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
weeks
PLOT
Gamma
KM

Model Comparison

Model	-2logL	AIC	AICC	BIC
Exponential	662.3	664.3	664.3	667.7
Weibull	661.7	665.7	665.7	672.5
LogNormal	608.0	612.0	612.1	618.8
LogLogistic	604.3	608.3	608.4	615.1
Gamma	600.3	606.3	606.4	616.5

Akaike Information Criteria

- AIC=-2log(Likelihood)+2(p+k)

K&M 12.4.3

- k=1 (exponential)
- k=2 for Weibull, log logistic and log normal
- k=3 for generalized gamma
- In our example, AIC for gamma (606.3) is close to AIC for log-logistic (608.3).

$$AICC = AIC + \frac{2p(p+1)}{n-p-1} \qquad BIC = -2\log L + p\log(n)$$

Adjusted model

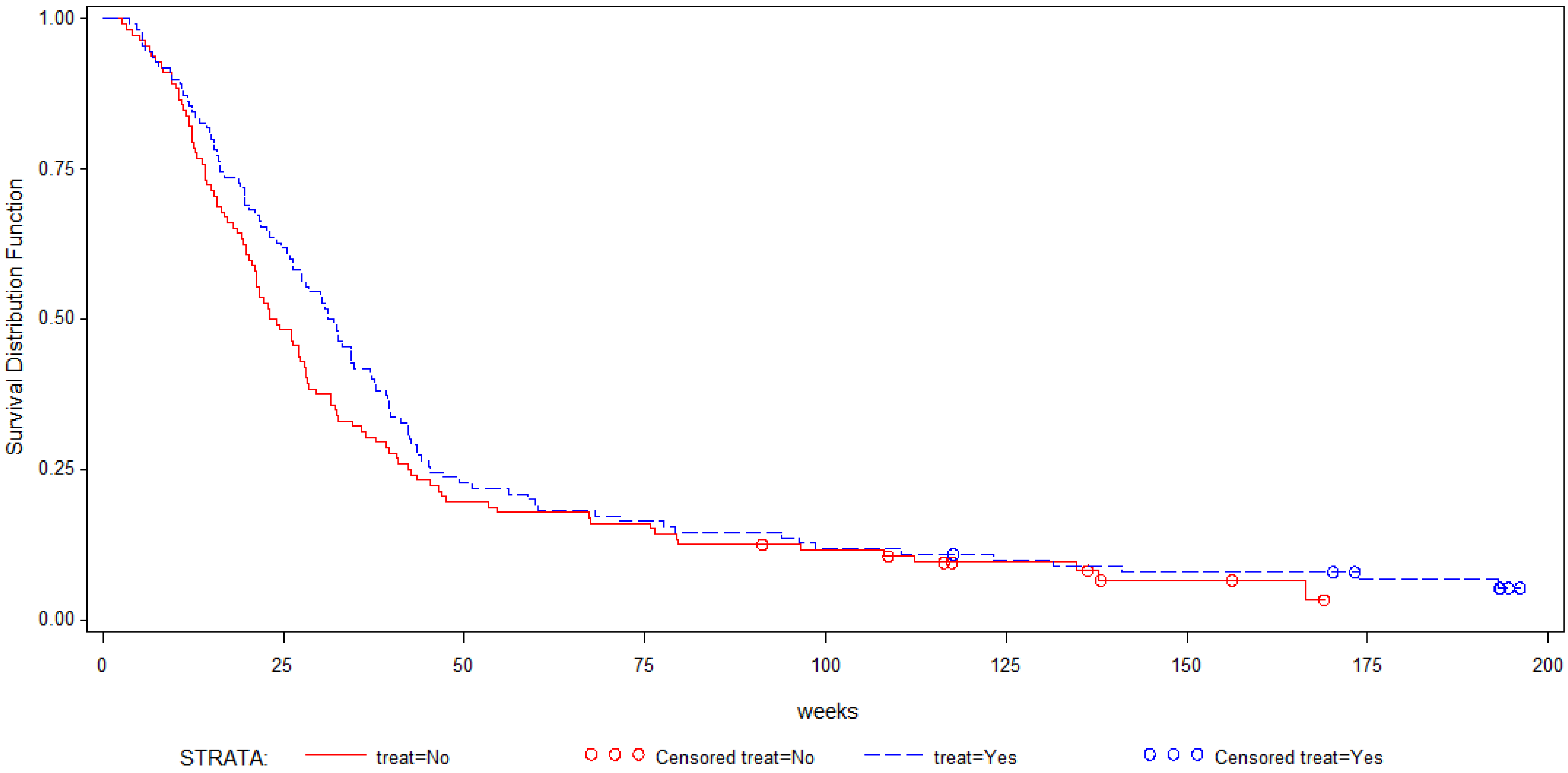
- Use preferred model building strategy to add covariates into the model (to be discussed further next month)
- Choosing two binary covariates for illustration
  - Treated (treat=1); not treated (treat=0)
  - Age <50 (age50=0) and age≥50 (age50=1)

Covariates: median survival

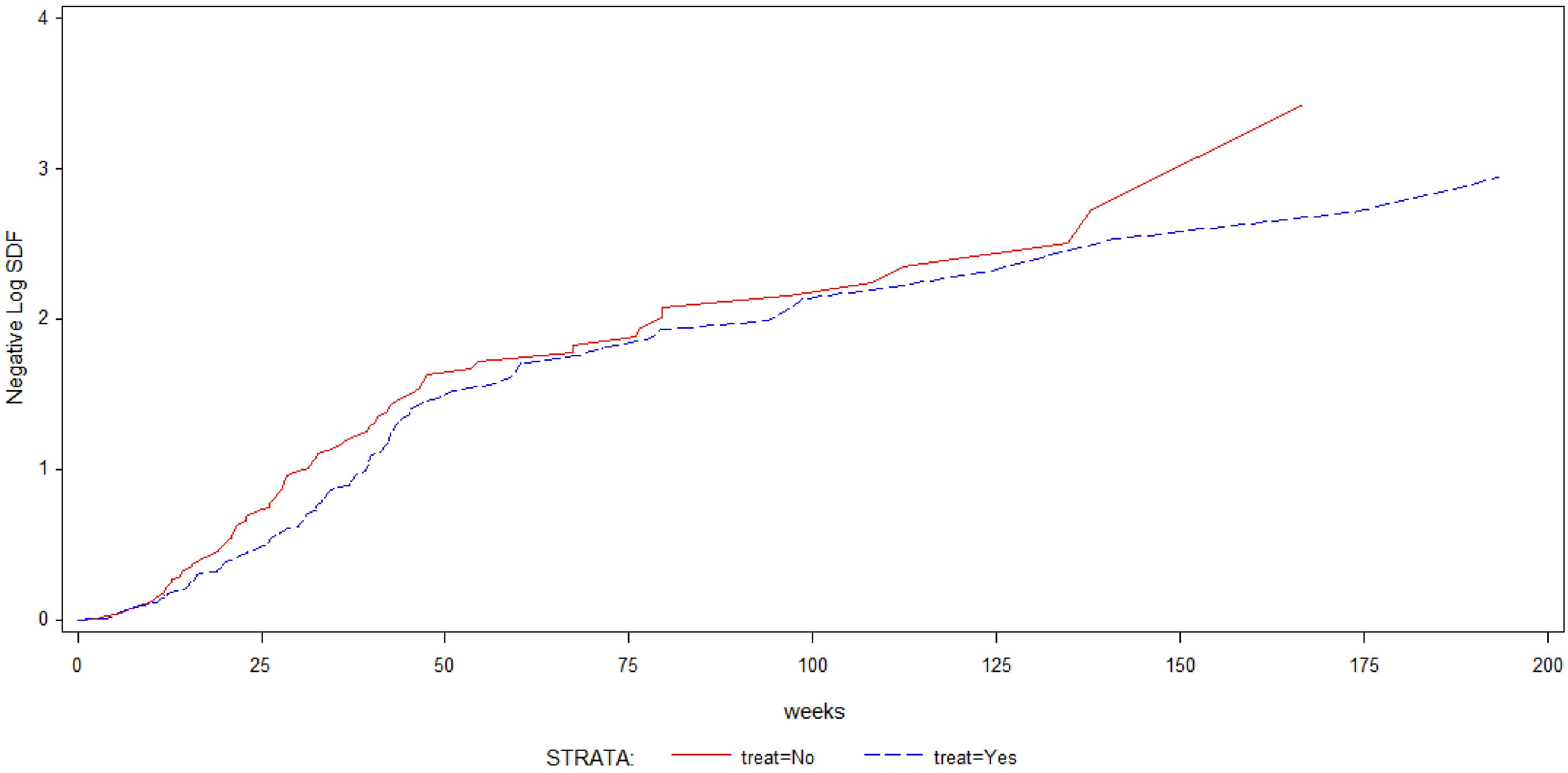
```
median treat=No :   23.57  (20.57, 28.00)

median treat=Yes :  31.50  (26.29, 37.00)
```

```
median age<50 :   32.43  (27.14, 39.71)

median age>=50 :  21.50  (19.00, 27.29)
```

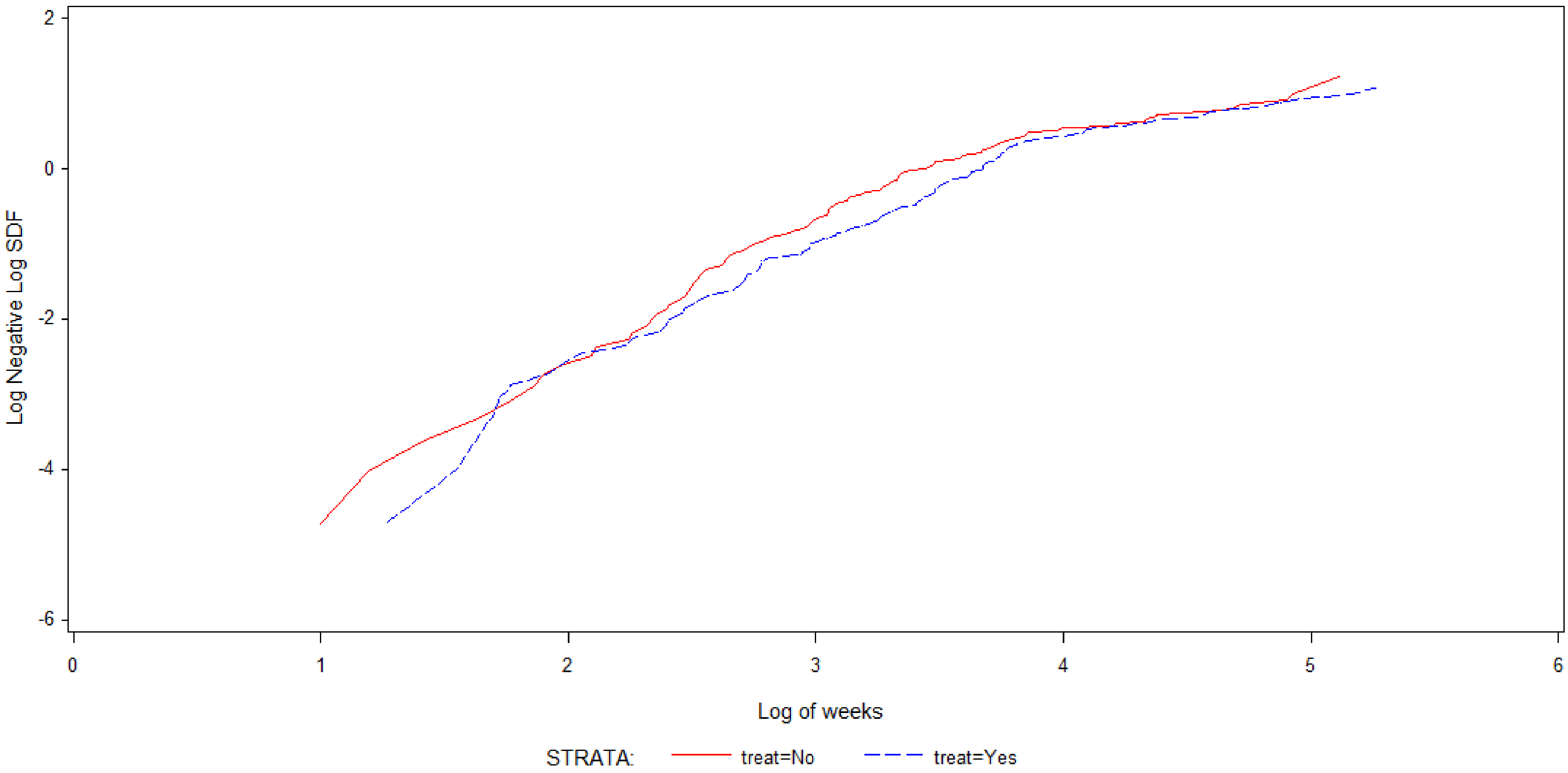
LifeTest: Treatment group



LifeTest: Treatment group



LifeTest: Treatment group



Exponential (treatment)

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.7220	0.0981	3.5298	3.9142	1440.73	<.0001
treat	1	0.1853	0.1390	-0.0871	0.4578	1.78	0.1825
Scale	0	1.0000	0.0000	1.0000	1.0000		
Weibull Shape	0	1.0000	0.0000	1.0000	1.0000		

HR=exp(-beta)=exp(-0.1853)=0.83

TR=exp(beta)=exp(0.1853)=1.20

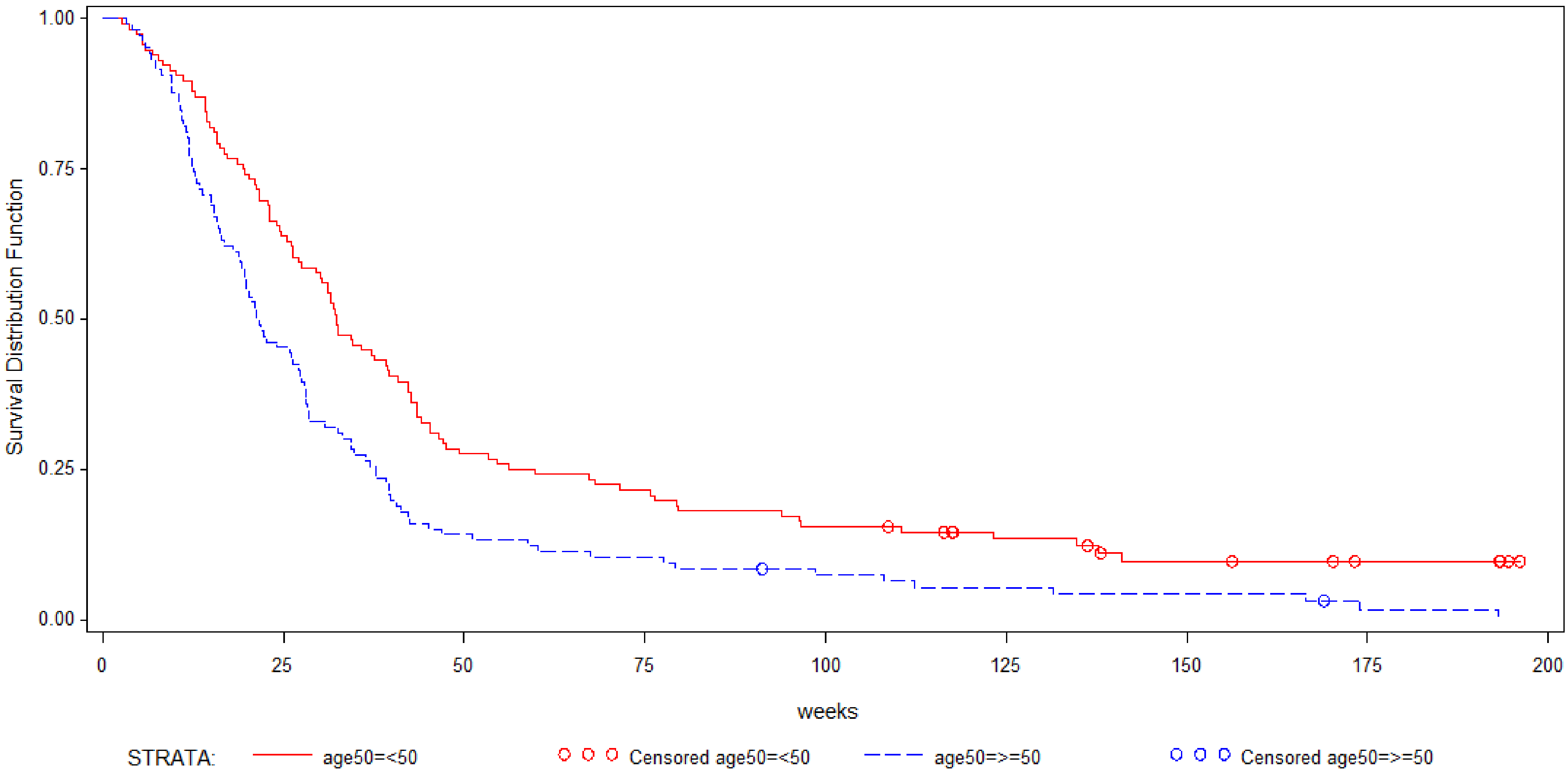
Exponential (Hazard Ratio)

```
Note closed form solution for hazard ratio can be calculated
from the summary data below (unadjusted for other covariates):

No treatment: 104/4300=0.0242 (note log(0.0242)=-3.722) and
Yes, treated: 103/5126=0.0201

HR:  0.0201/0.0242 = 0.8306
Log(HR): log(0.0201/0.0242)=-0.1856
TR: exp(0.1856)=1.204
```

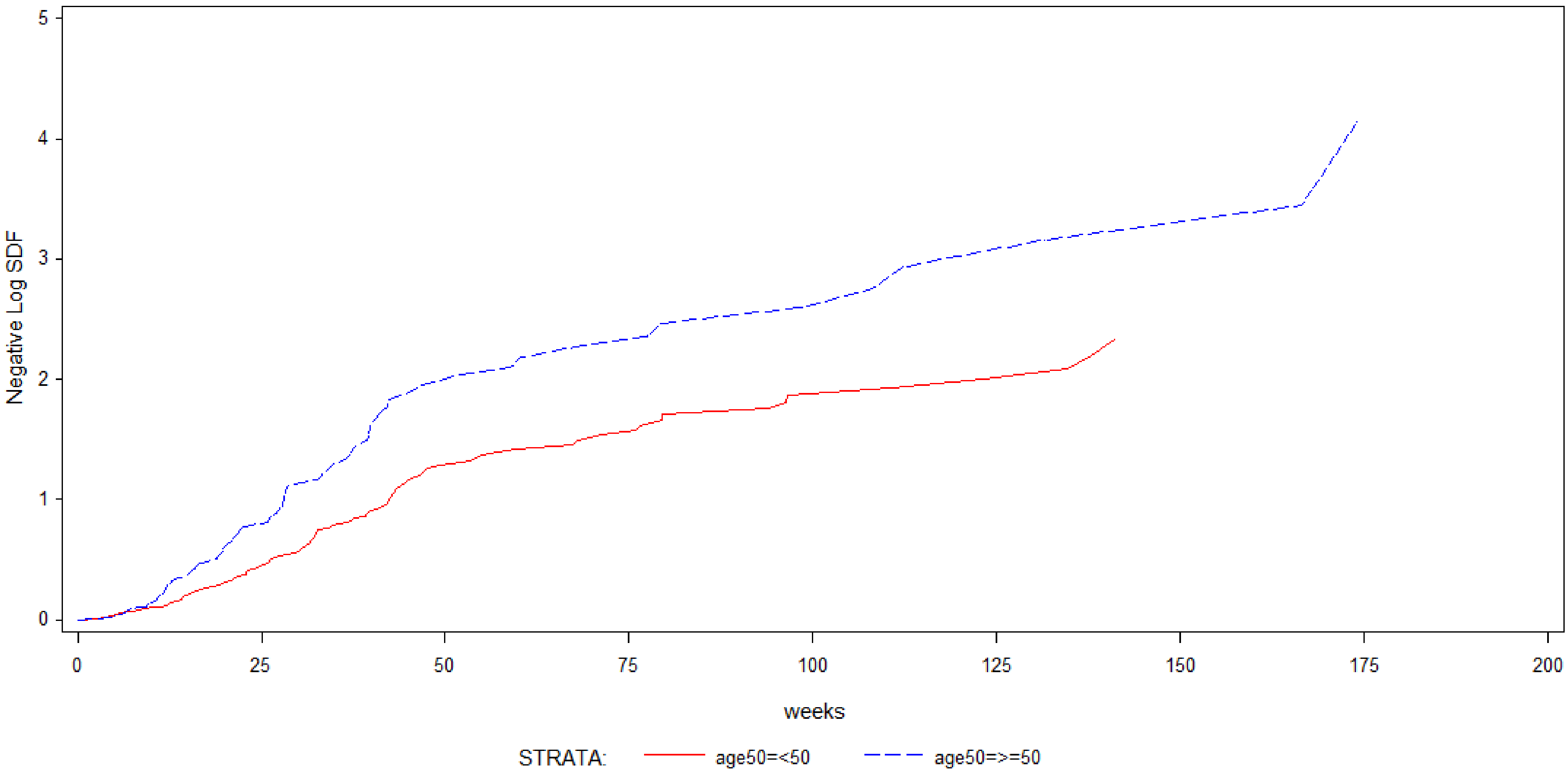
(output from proc means)

treat	Obs	Variable	Sum
No	112	event	104
		weeks	4300
Yes	110	event	103
		weeks	5126

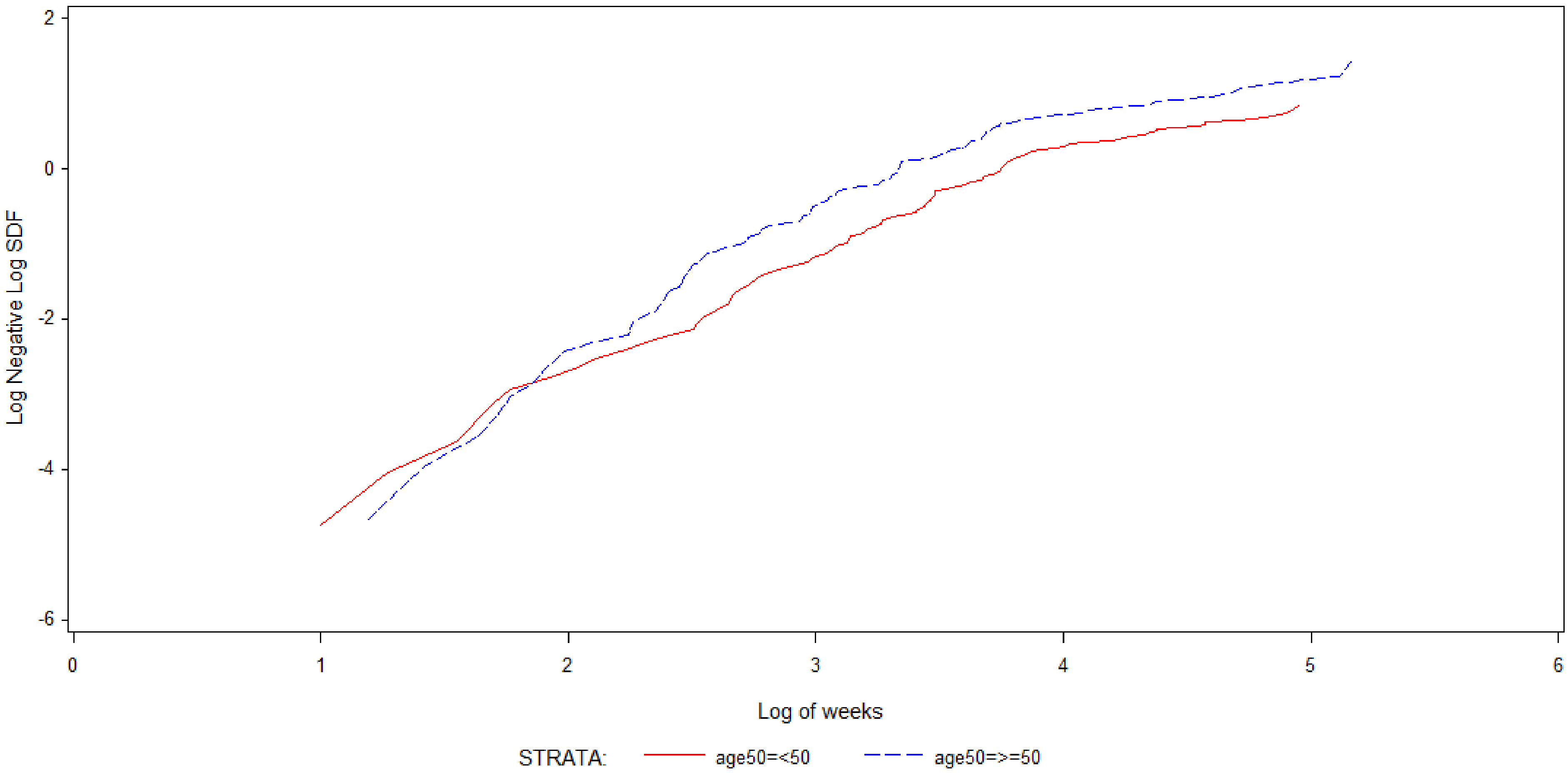
LifeTest: Age group



LifeTest: Age group



LifeTest: Age group



Exponential/Weibull (age grouped)

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	4.0394	0.0985	3.8463	4.2325	1680.64	<.0001
age50	1	-0.5018	0.1390	-0.7743	-0.2293	13.03	0.0003

λ = exp(-(4.0394 - 0.5018*age50))

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	4.0569	0.0933	3.8740	4.2397	1891.78	<.0001
age50	1	-0.4927	0.1303	-0.7480	-0.2374	14.31	0.0002
Scale	1	0.9356	0.0481	0.8459	1.0349		
Weibull Shape	1	1.0688	0.0550	0.9663	1.1822		

λ = exp(- 1.0688 *(4.0569 - 0.4927*age50))
HR = exp(-beta*1.0688) = 1.69
TR = exp(beta) = 0.61 AF = 1.64

Goodness of fit

- Sample plots
  - How well does model match Kaplan-Meier curves?
- Cox-Snell residuals
  - Log-log(SDF) or cumulative hazard of residuals is a straight line?

$$r_j = \hat{H}(T_j \mid Z_j)$$

$$\textit{where } \hat{H} \textit{ is estimated from data}$$

$$\textit{and } r_j \textit{ distributed } \exp(1)$$

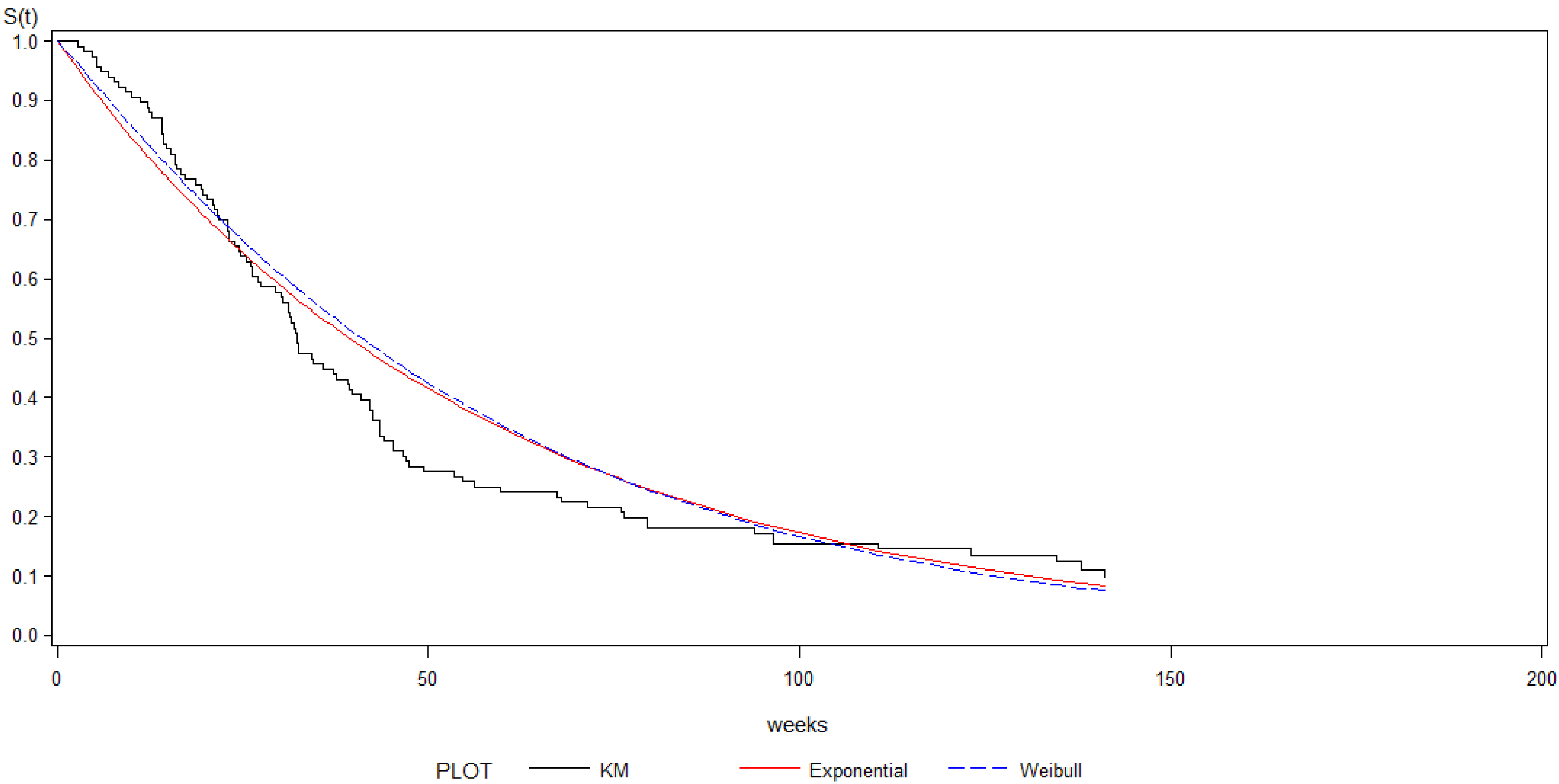
$$\textit{SAS output}: -\log(S(\frac{\log t_i - x_i^{'} b}{\sigma}))$$

Other residuals: e.g. normal deviate residuals, see Nardi & Schemper

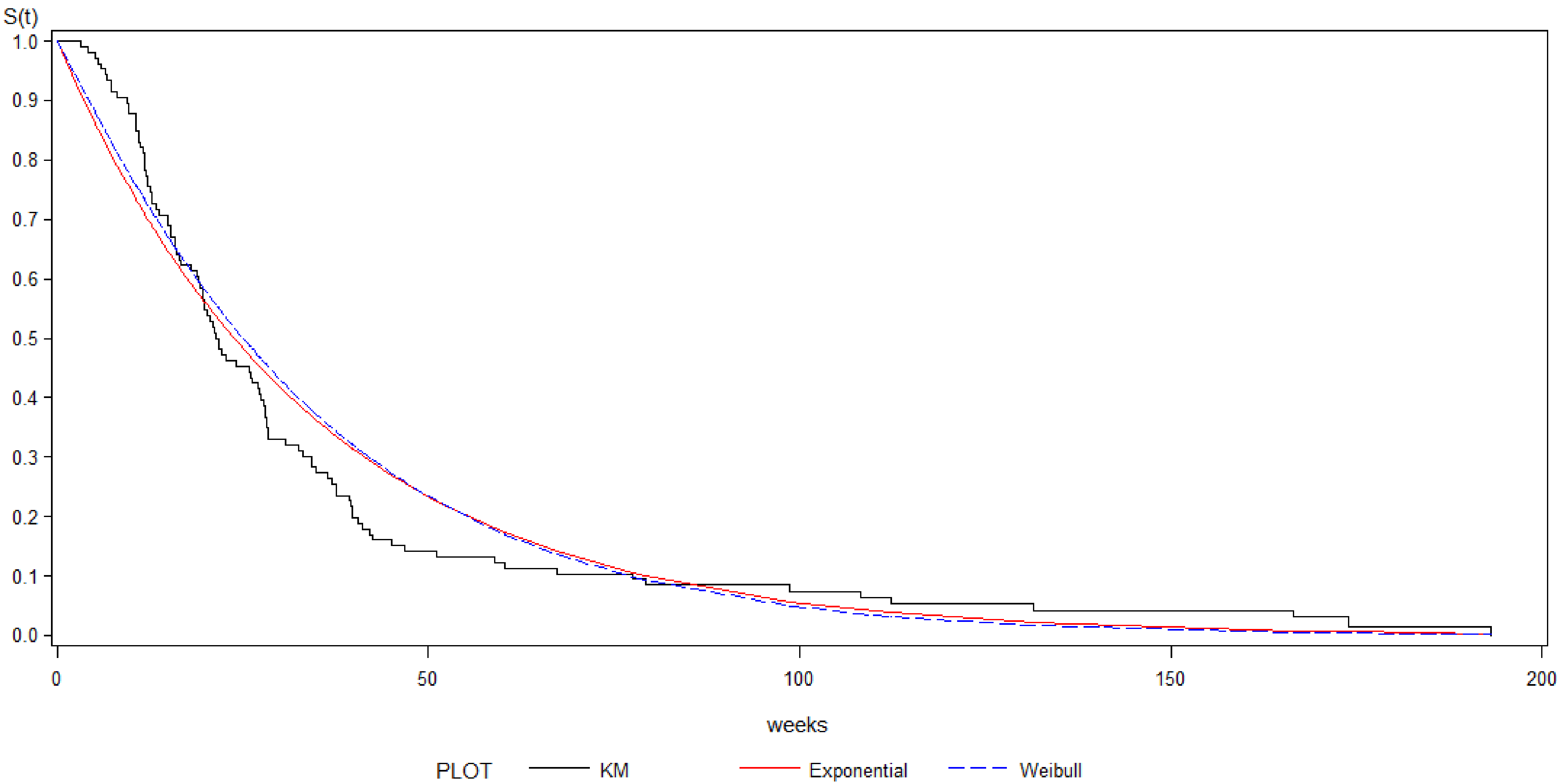
Goodness of fit

- Martingale residuals
  - Klein & Moeschberger: “estimate of the excess number of deaths seen in the data, but not predicted by model”
  - $\delta_j - H(T_j|Z_j)$ i.e. $\delta_j - r_j$
- Deviance residuals
  - Klein & Moeschberger: “more symmetric about 0”
  - Transformed martingale residuals

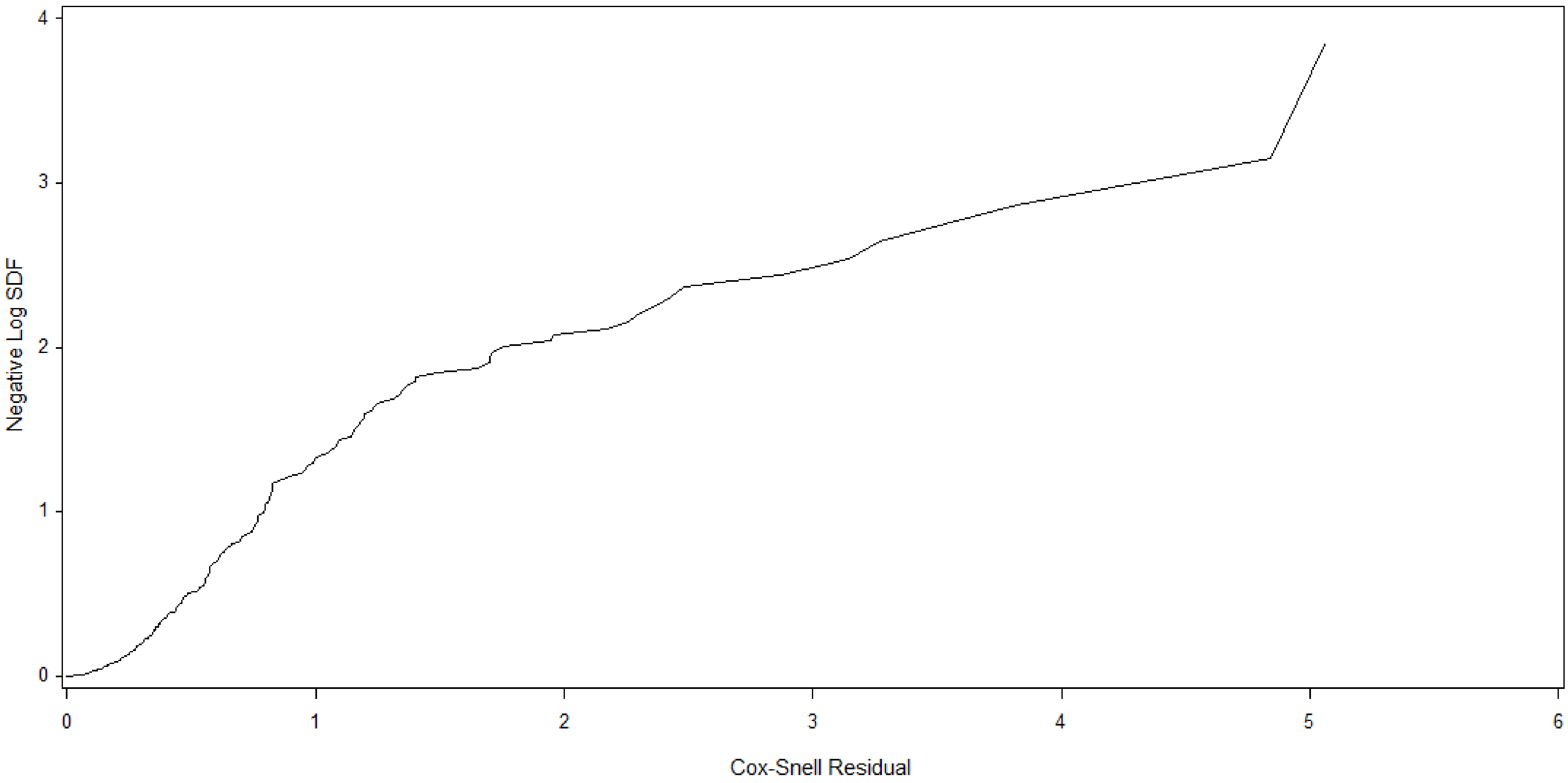
Comparison of Exponential and Weibull Models-Age<50



Comparison of Exponential and Weibull Models-Age>=50



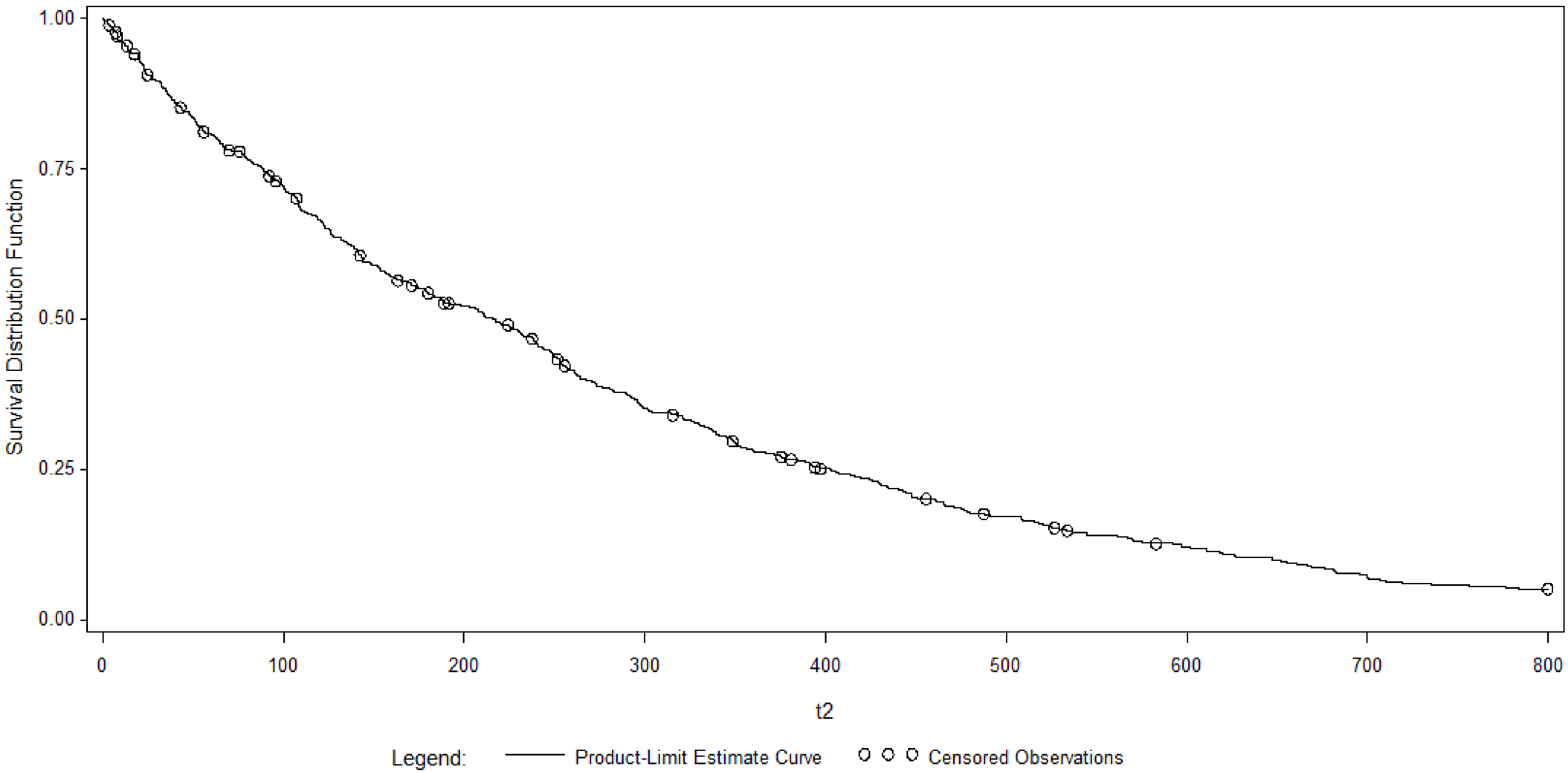
Cox-Snell Residuals-Exponential



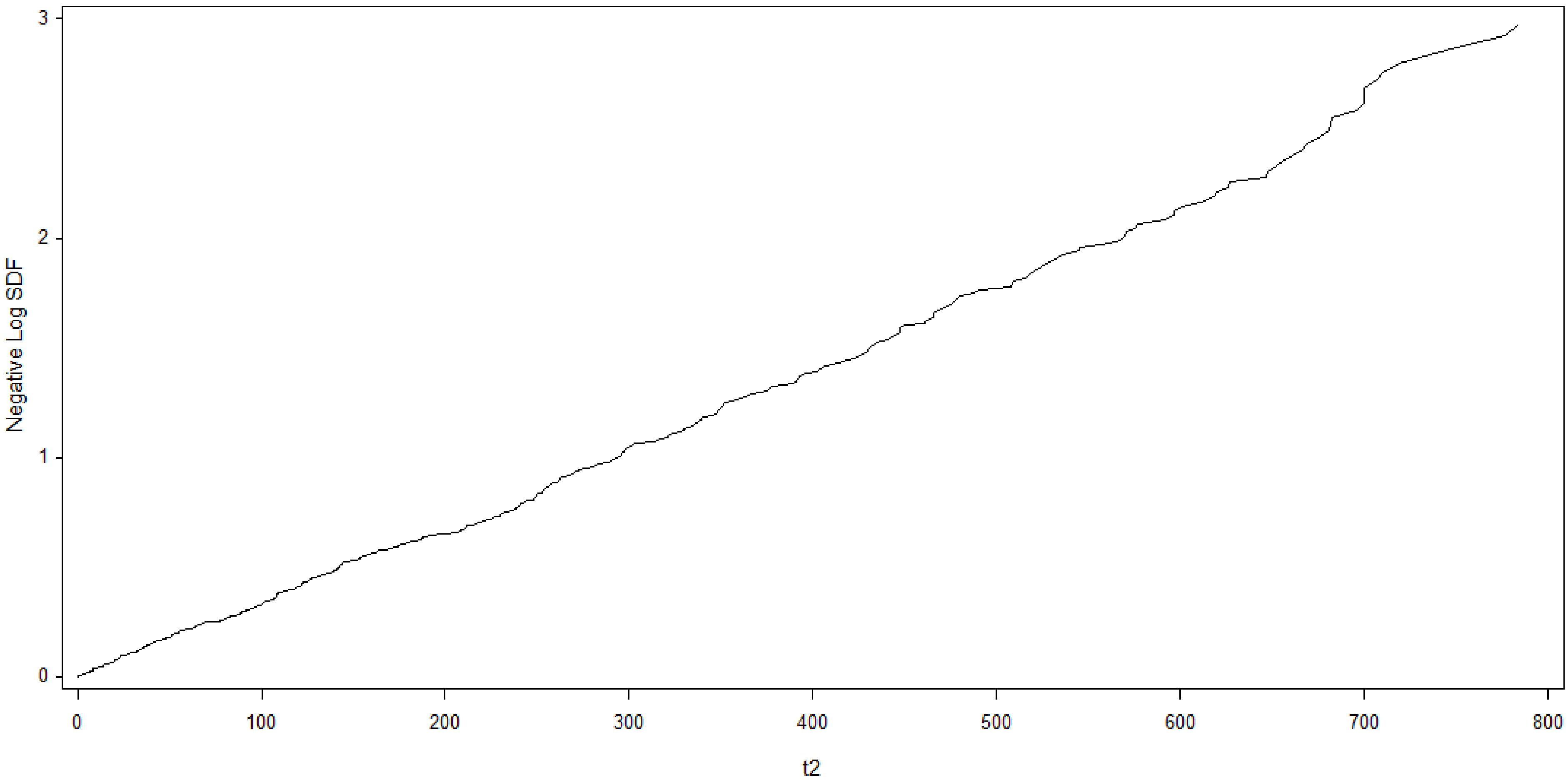
Simulated Exponential Data

- To show what plots look like using randomly generated data from an exponential distribution

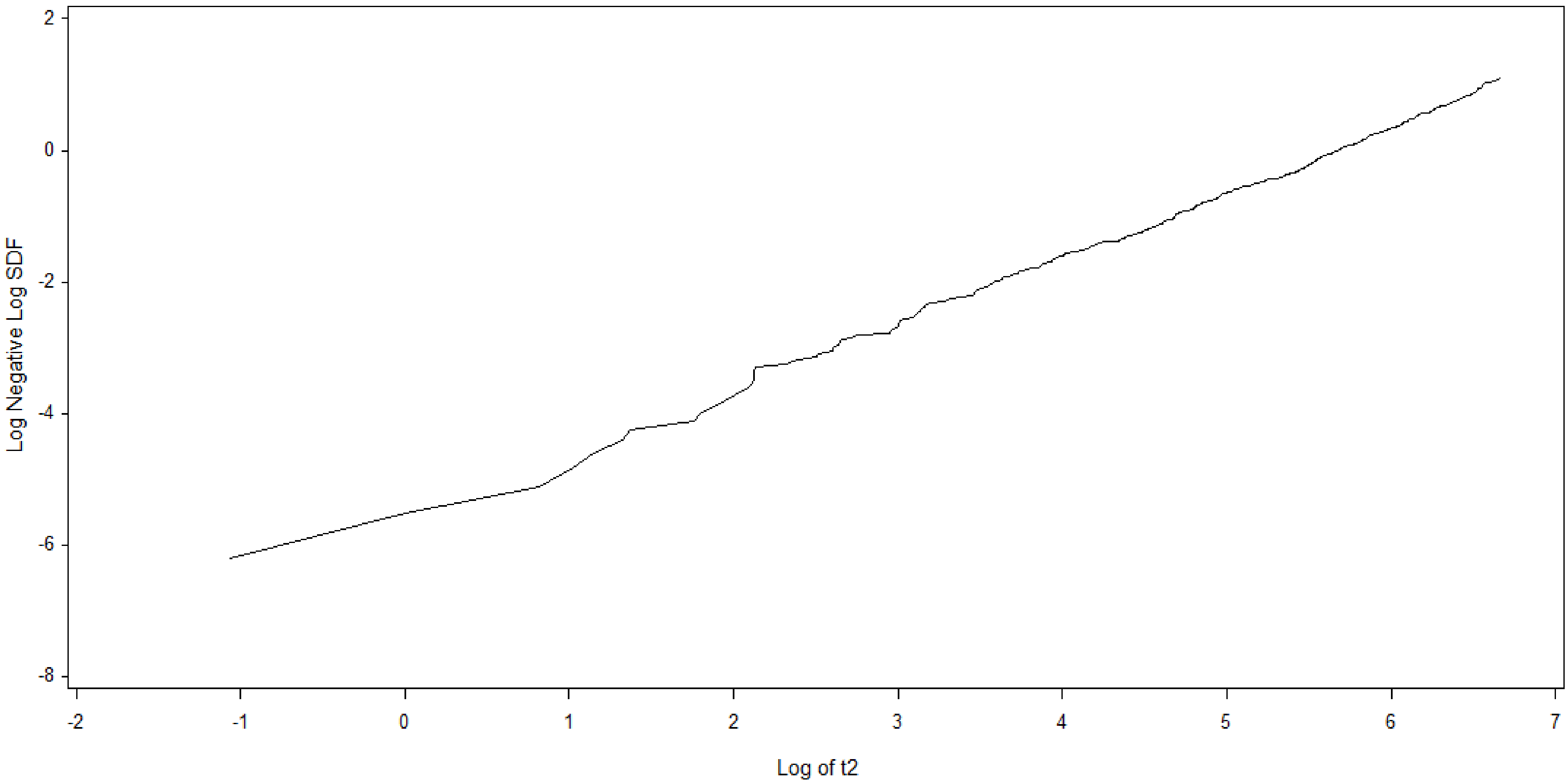
Simulated Exponential Data



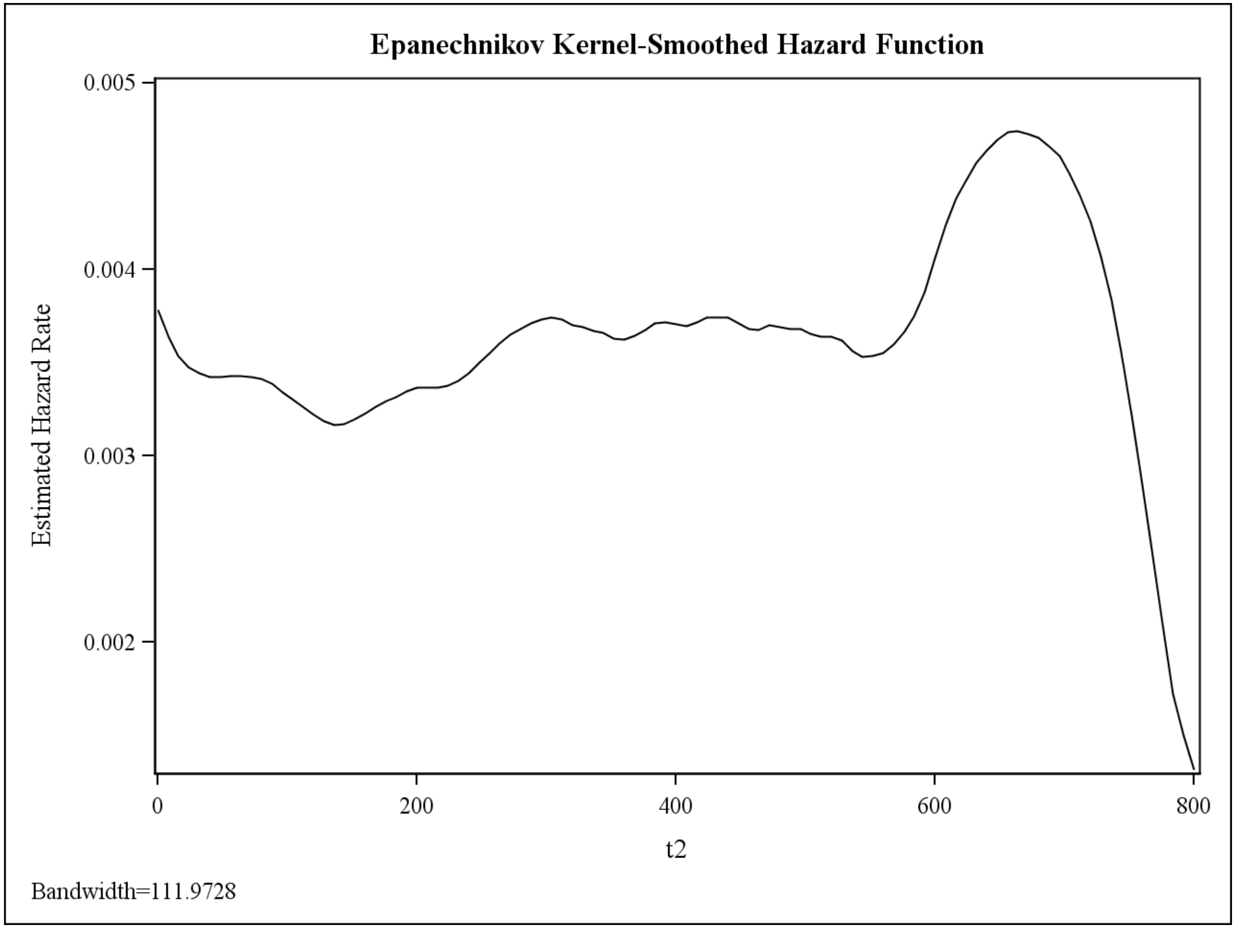
Simulated Exponential Data



Simulated Exponential Data



Simulated Exponential Data

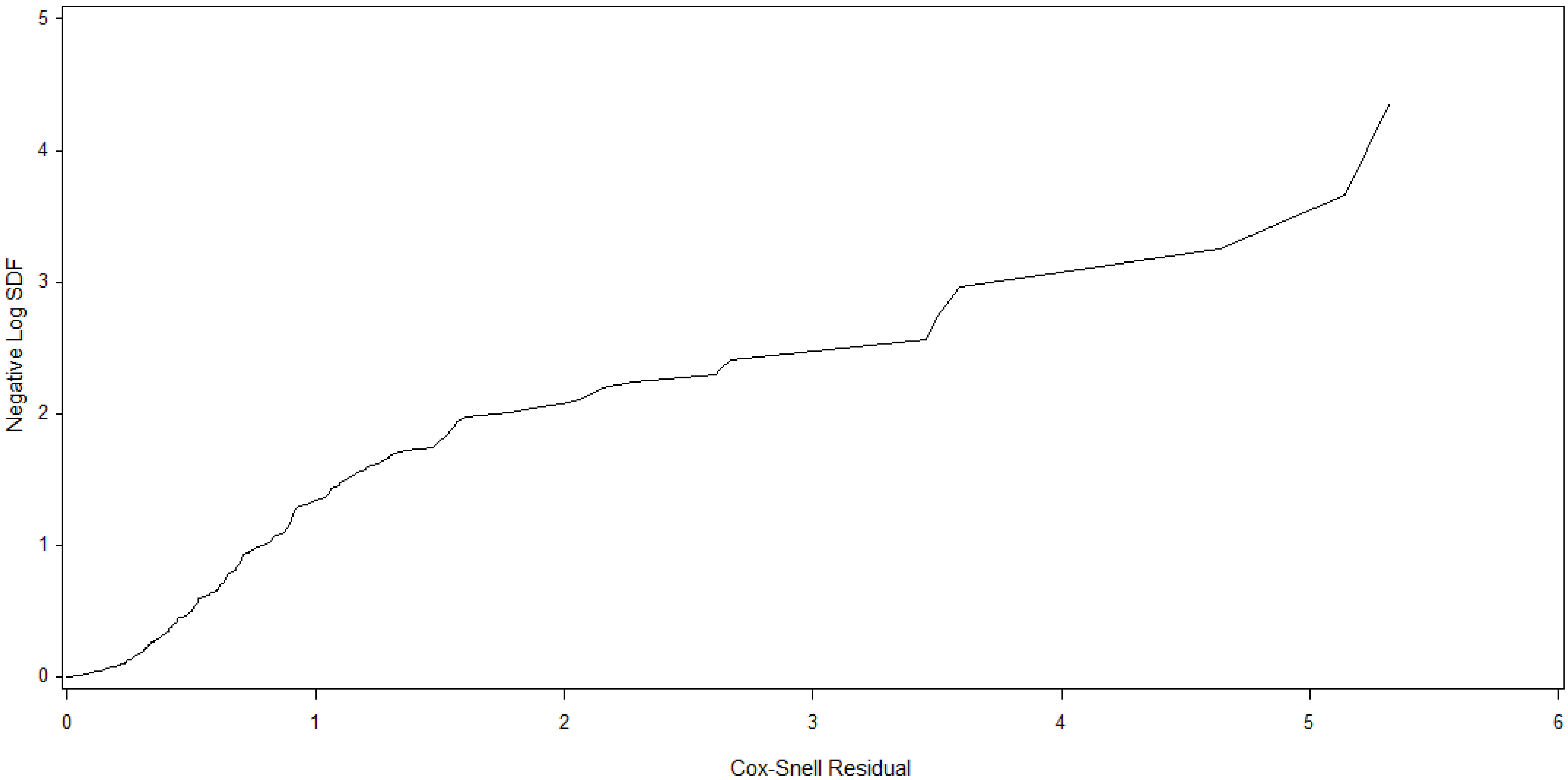


Exponential (treatment and age)

-2 Log Likelihood = 647.648

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.9439	0.1206	3.7075	4.1804	1069.08	<.0001
treat	1	0.1825	0.1390	-0.0900	0.4549	1.72	0.1893
age50	1	-0.5007	0.1390	-0.7732	-0.2283	12.98	0.0003
Scale	0	1.0000	0.0000	1.0000	1.0000		
Weibull Shape	0	1.0000	0.0000	1.0000	1.0000		

Cox-Snell Residuals - Exponential

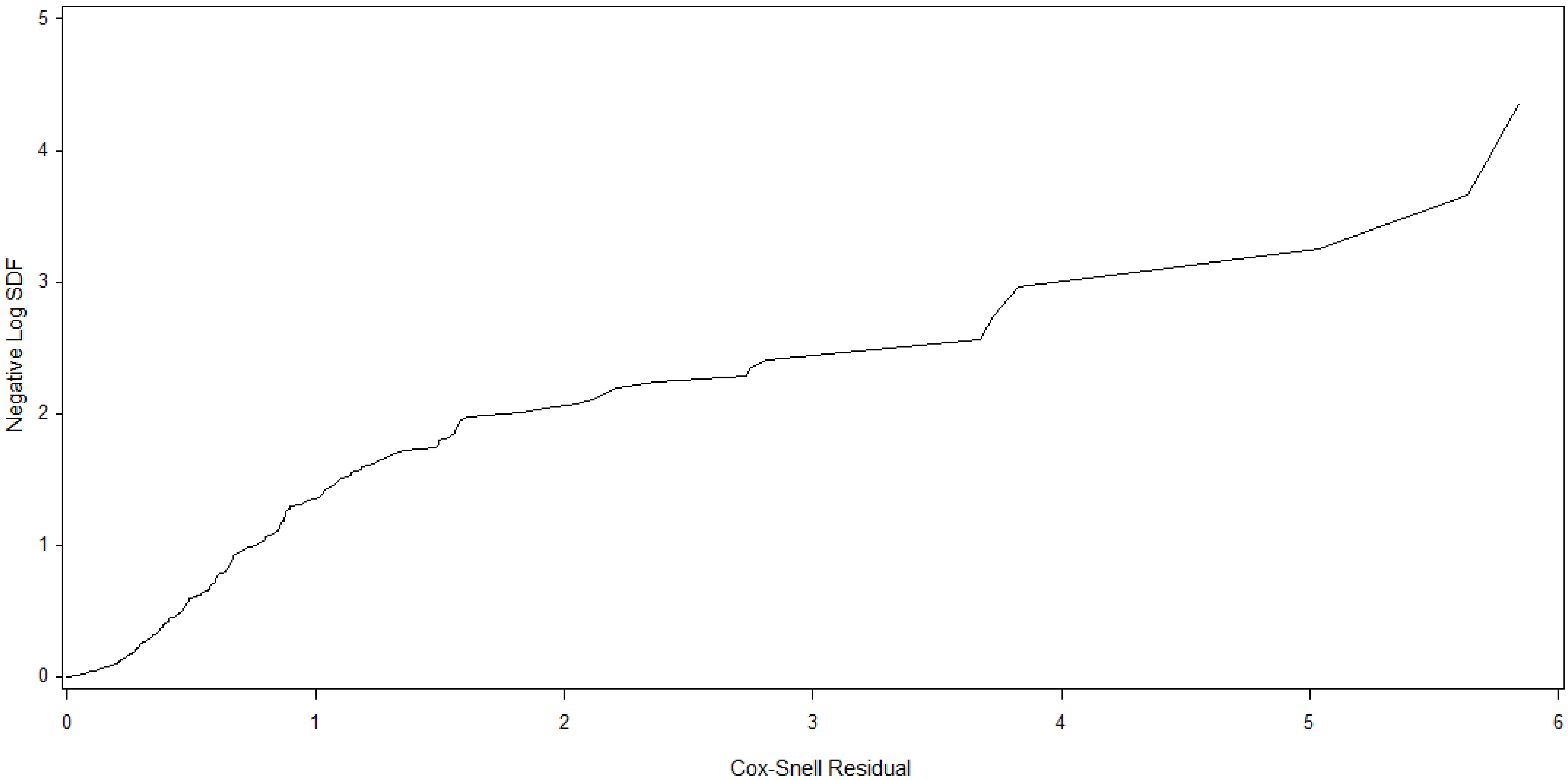


Weibull(treatment and age)

-2 Log Likelihood = 645.784

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.9622	0.1132	3.7403	4.1842	1224.33	<.0001
treat	1	0.1825	0.1294	-0.0711	0.4361	1.99	0.1585
age50	1	-0.4904	0.1296	-0.7444	-0.2363	14.31	0.0002
Scale	1	0.9308	0.0479	0.8415	1.0296		
Weibull Shape	1	1.0744	0.0553	0.9713	1.1884		

Cox-Snell Residuals - Weibull

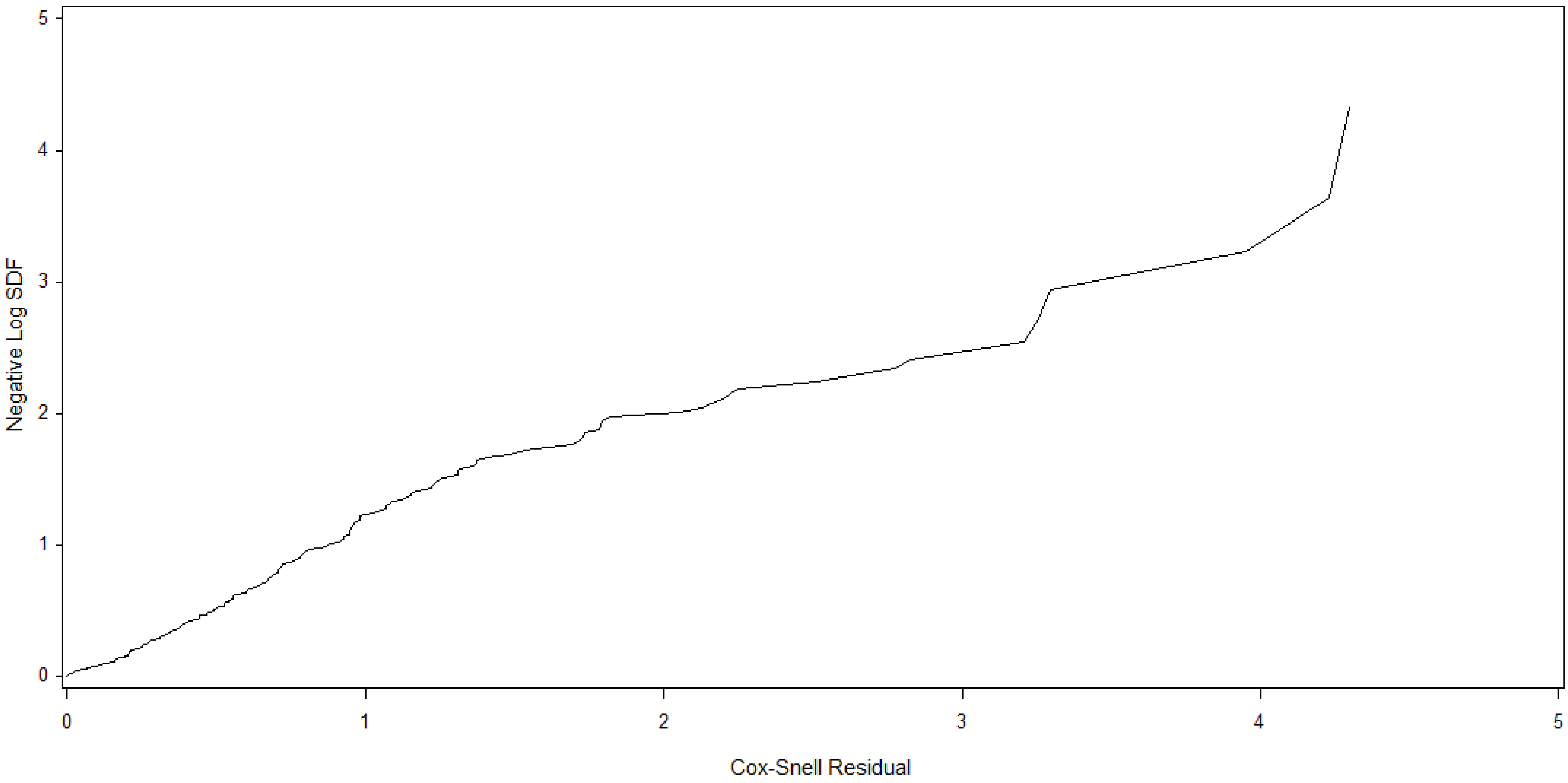


Log Normal(treatment and age)

-2 Log Likelihood = 595.383

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.4768	0.1072	3.2667	3.6869	1051.87	<.0001
treat	1	0.1744	0.1253	-0.0711	0.4200	1.94	0.1639
age50	1	-0.4144	0.1254	-0.6602	-0.1686	10.92	0.0010
Scale	1	0.9288	0.0466	0.8418	1.0247		

Cox-Snell Residuals - LogNormal

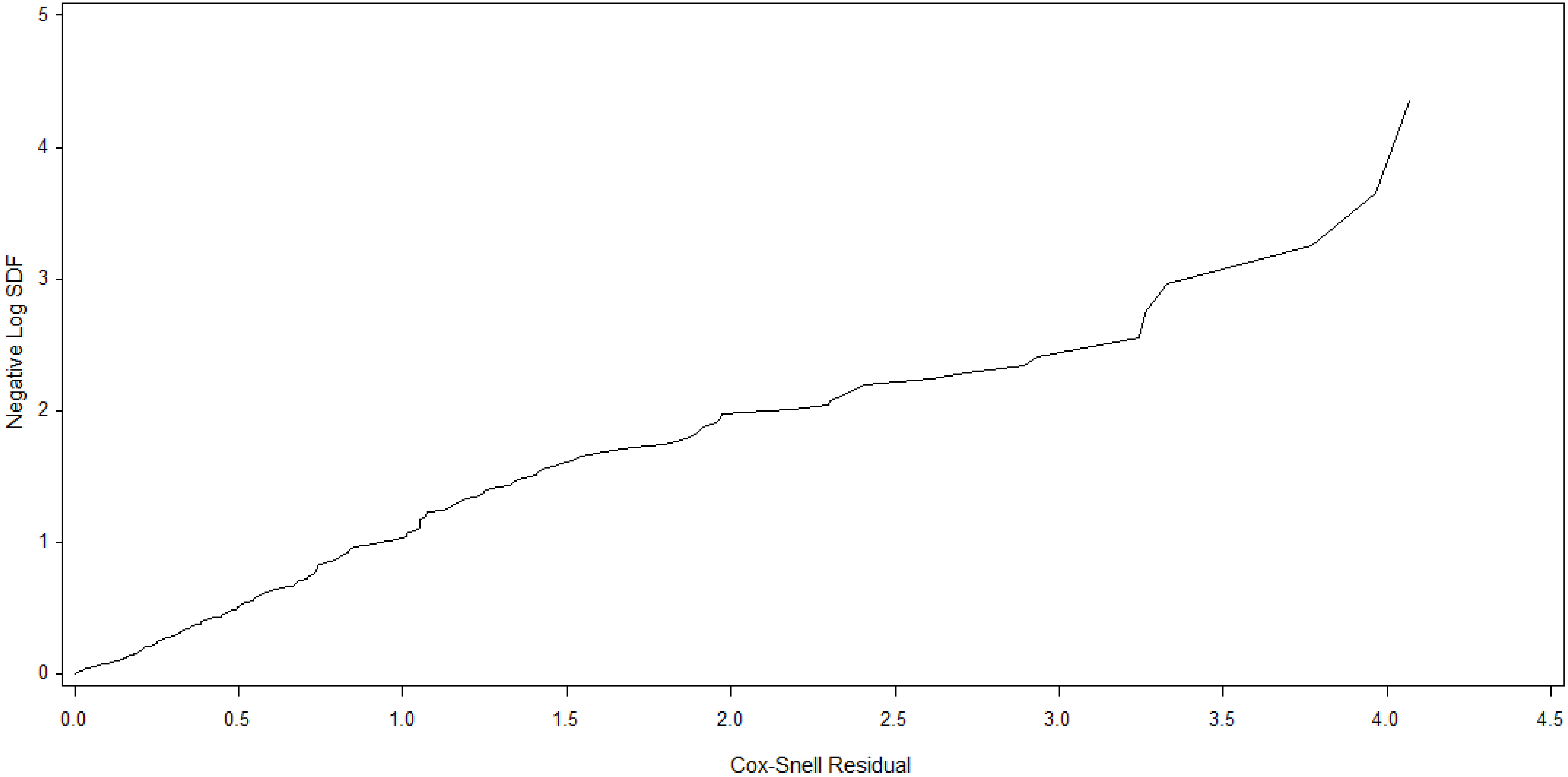


Log Logistic(treatment and age)

-2 Log Likelihood = 589.891

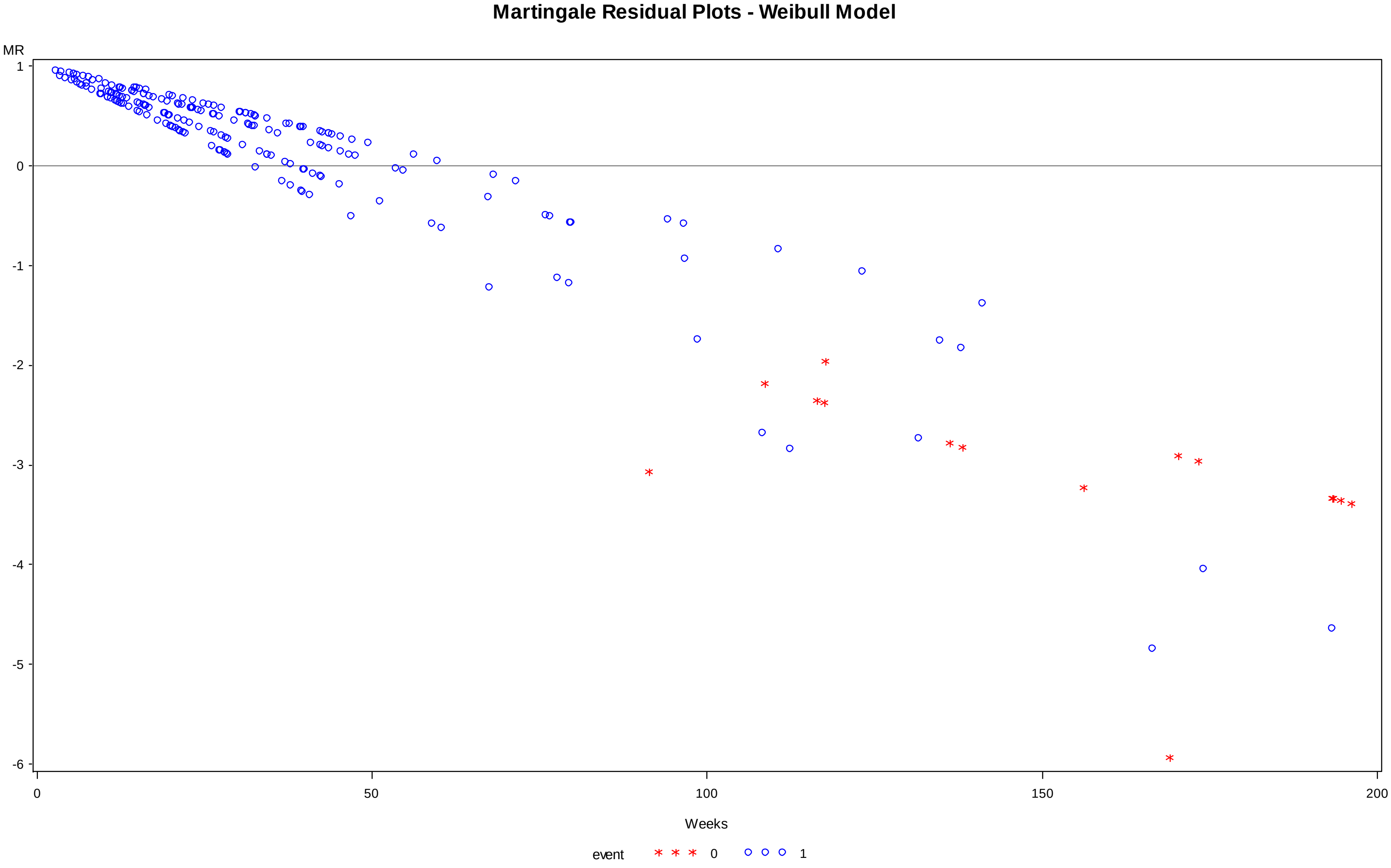
Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.4289	0.1031	3.2268	3.6309	1105.96	<.0001
treat	1	0.2029	0.1200	-0.0323	0.4380	2.86	0.0909
age50	1	-0.4204	0.1200	-0.6555	-0.1852	12.28	0.0005
Scale	1	0.5198	0.0304	0.4635	0.5830		

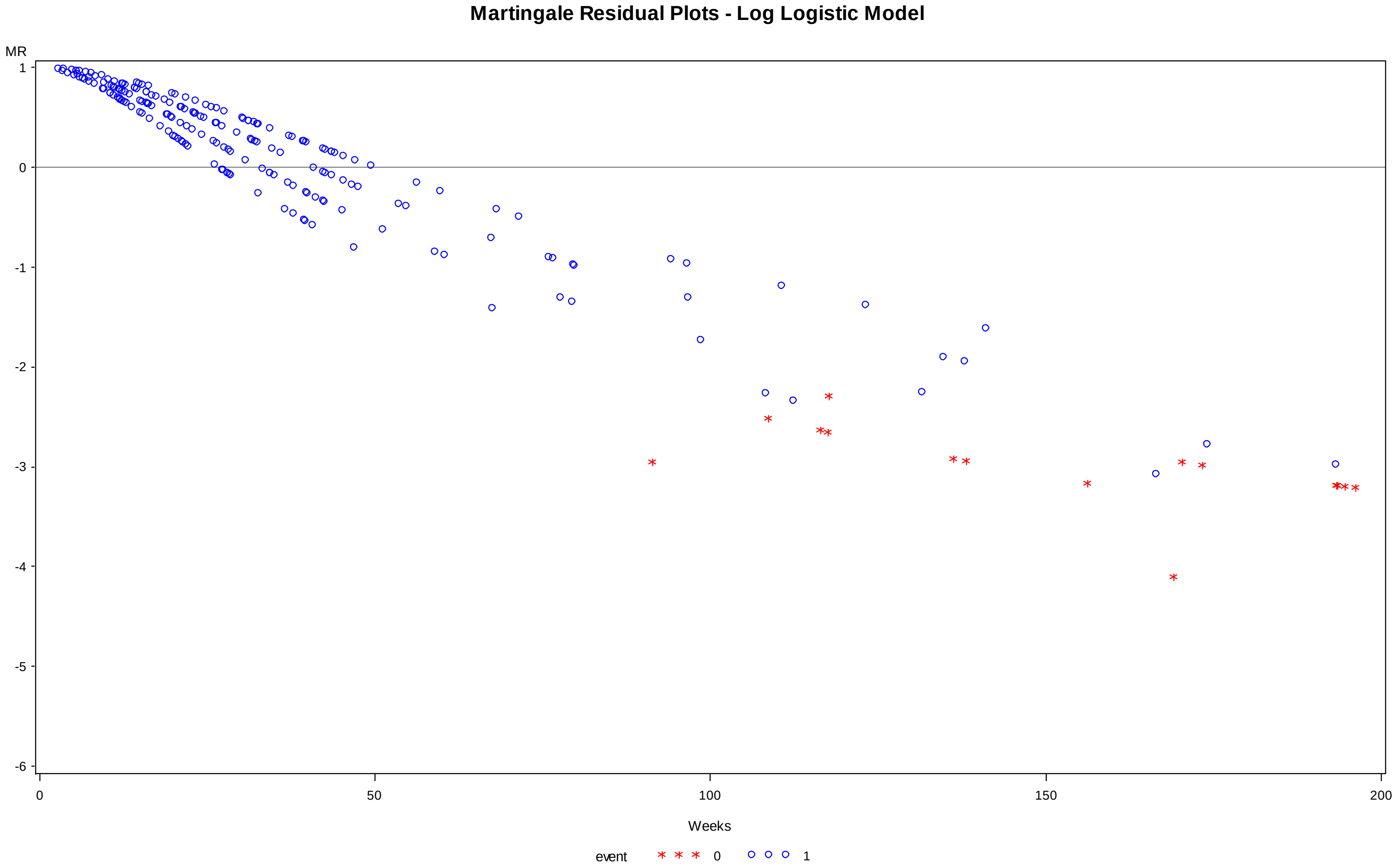
Cox-Snell Residuals - LogLogistic



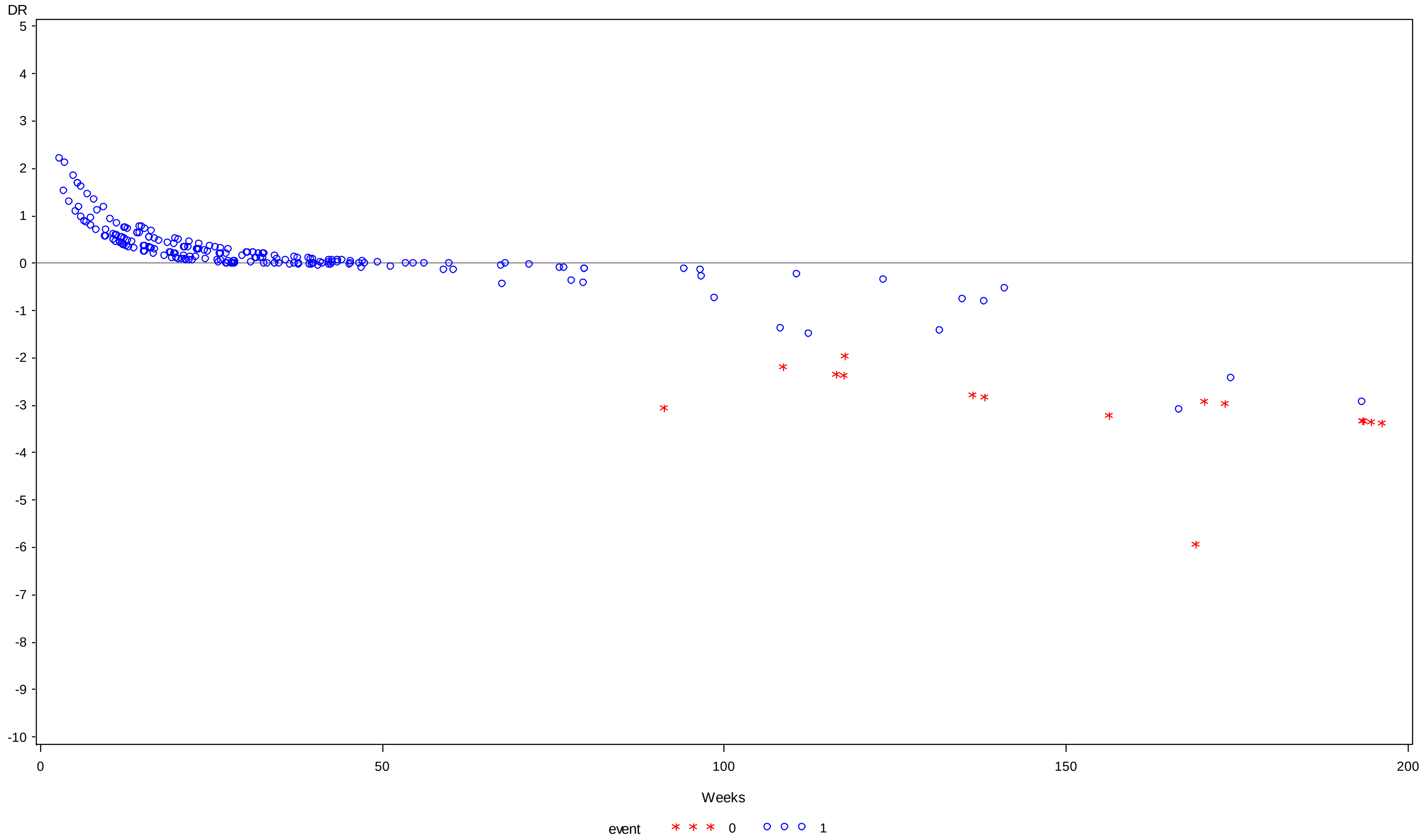
Residuals (SAS Code)

```
/* Cox-Snell */
proc lifereg data=sda.brain;
  model weeks*event(0)=treat age50/d=weibull;
  output out=wout cres=cres sres=sres p=predm  std=stdm;
  title 'LifeReg: Treatment & Age groups - Weibull';
run;

proc lifetest data=wout plots=(ls) notable;
  * looking for evidence that cres is exponential using the -log(S(t)) plot;
  * note that censoring value is maintained from original data set;
  time cres*event(0);
  title1 'Cox-Snell Residuals - Weibull';
run;

 /* martingale and deviance*/
  lambda=exp(-(3.9439+0.1825*treat-0.5007*age50));
  sexp=exp(-lambda*weeks);
  xbexp=3.9439+0.1825*treat-0.5007*age50;
  chexp=-log(sexp);
  martexp=event-chexp;
  devexp=sign(martexp)*(-2*(martexp+event*log(event-martexp)))**1/2;
```

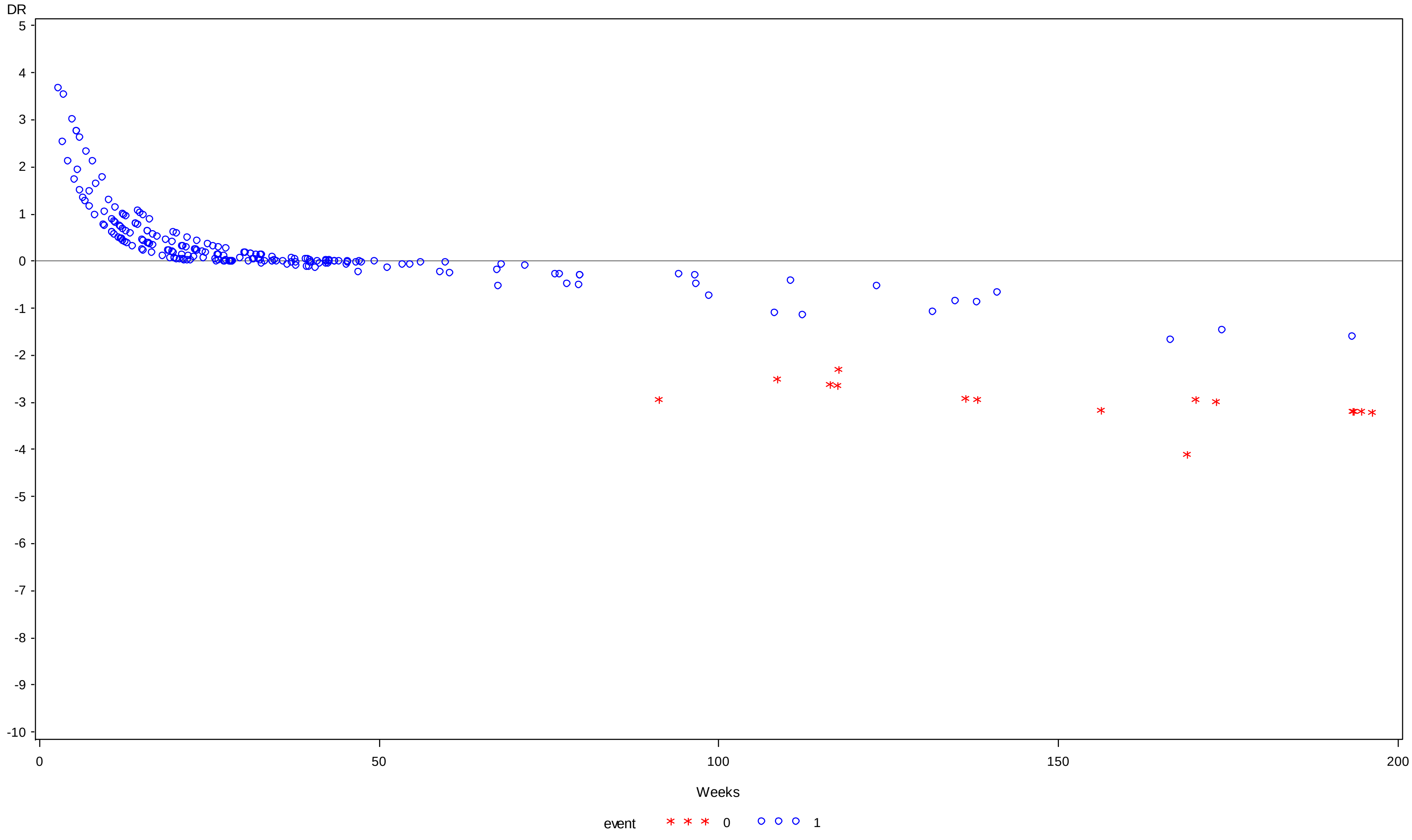

Martingale Residual Plots - Weibull Model
MR
1
0
-1
-2
-3
-4
-5
-6
0
50
100
150
200
Weeks
event
0
1


Martingale Residual Plots - Log Logistic Model
MR
1
0
-1
-2
-3
-4
-5
-6
0
50
100
150
200
Weeks
event
0
1

Deviance Residual Plots - Weibull Model

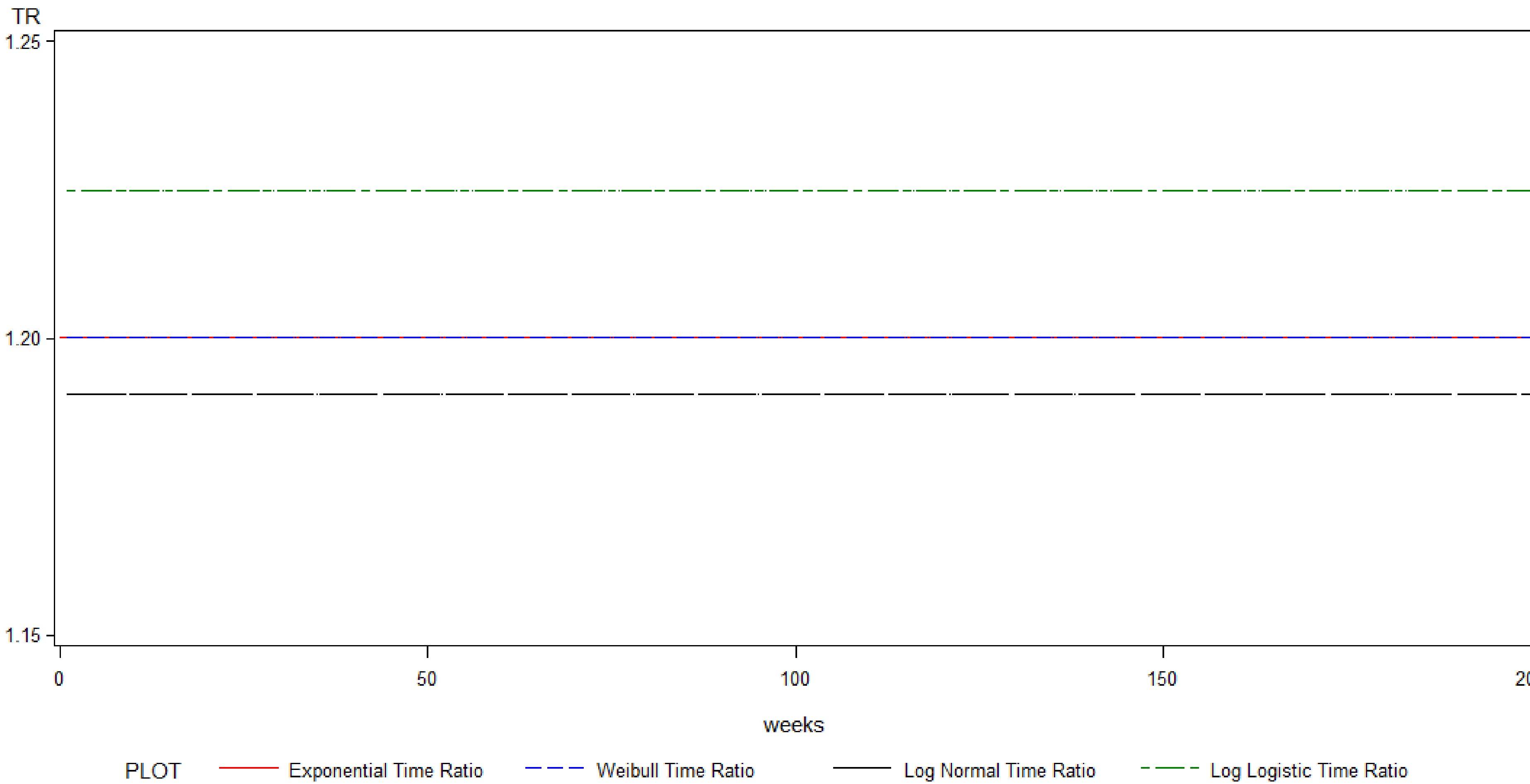


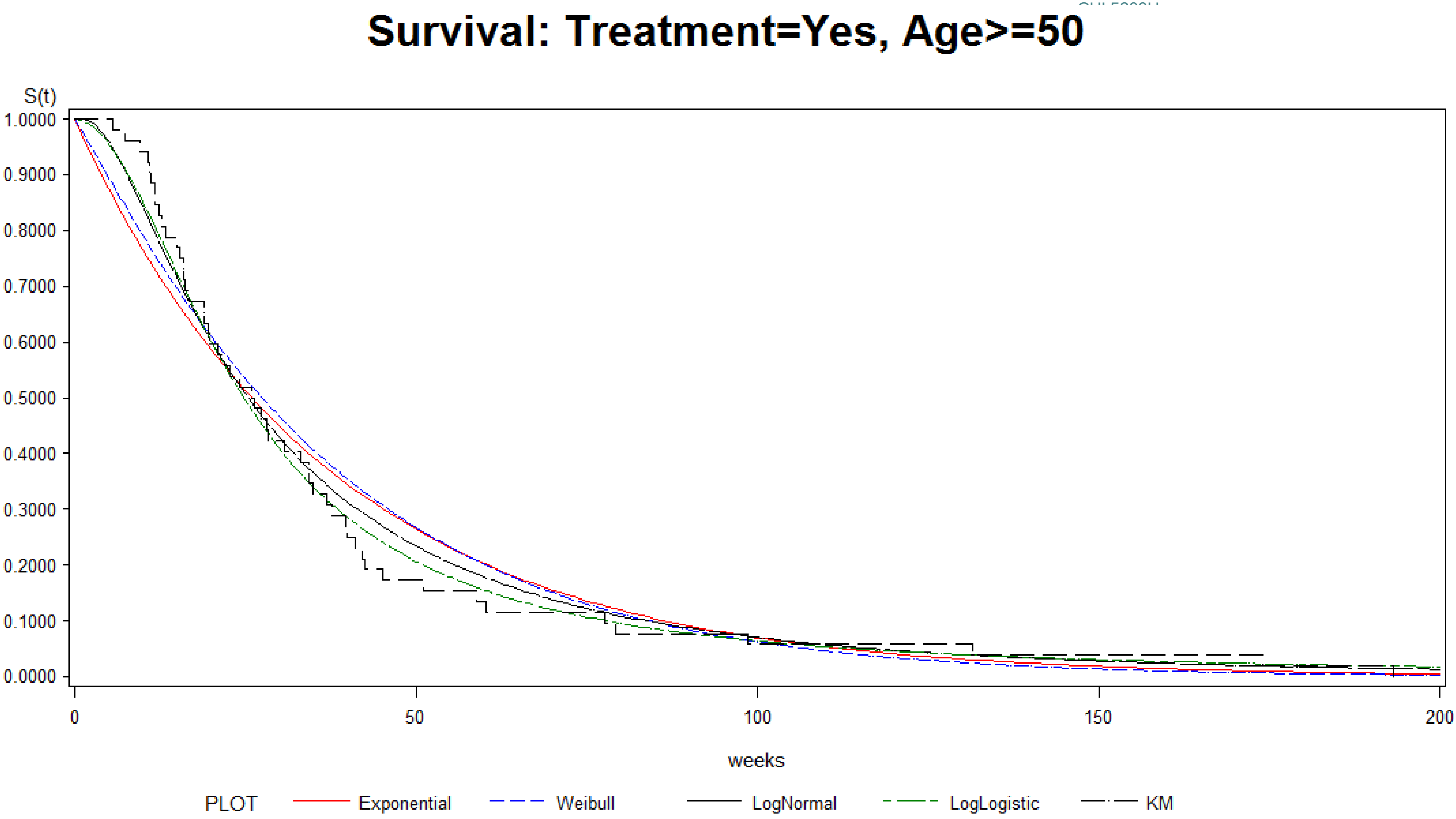
Deviance Residual Plots - Log Logistic Model



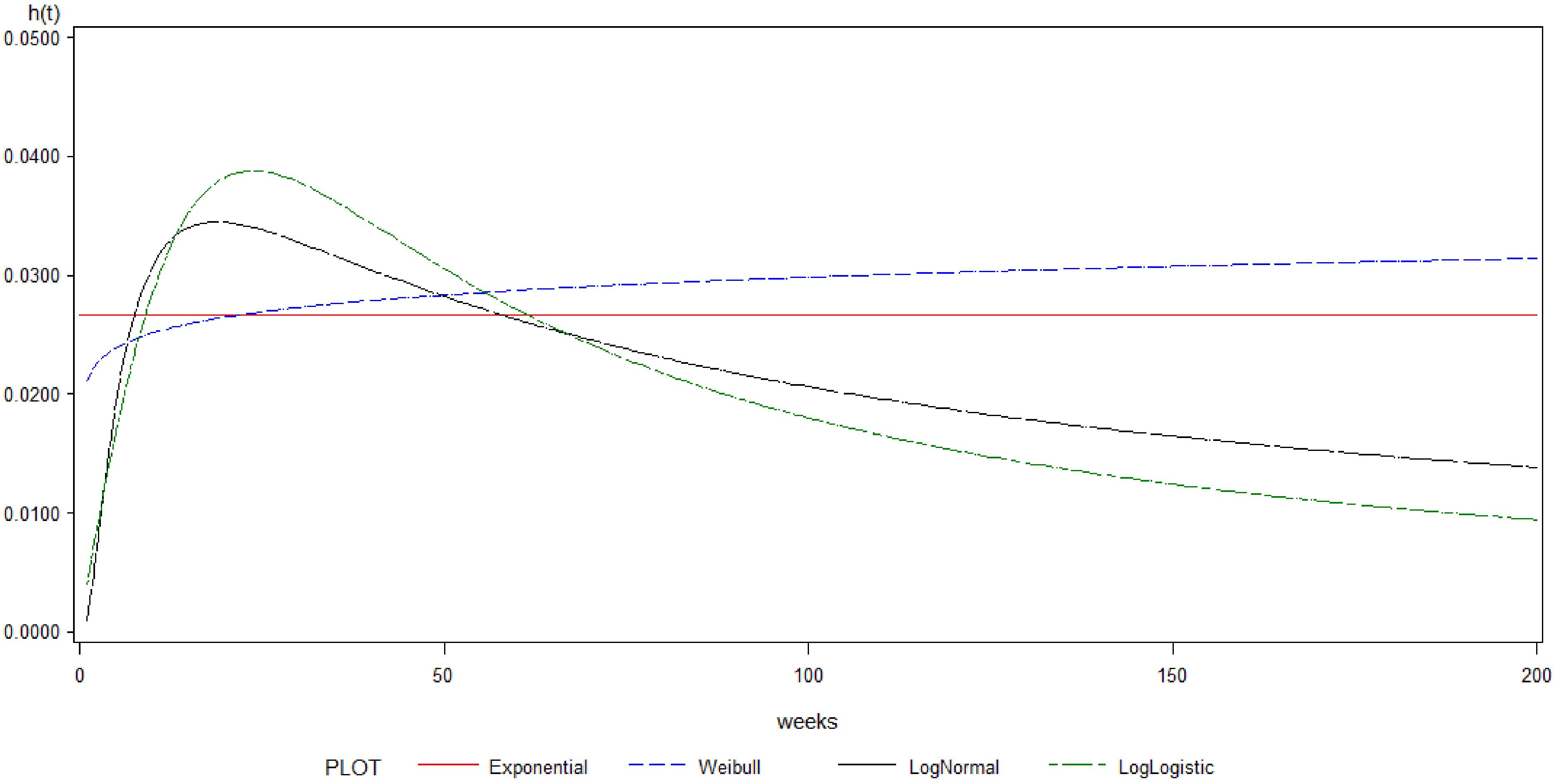
Model summaries

Time Ratios for Treatment - All Models

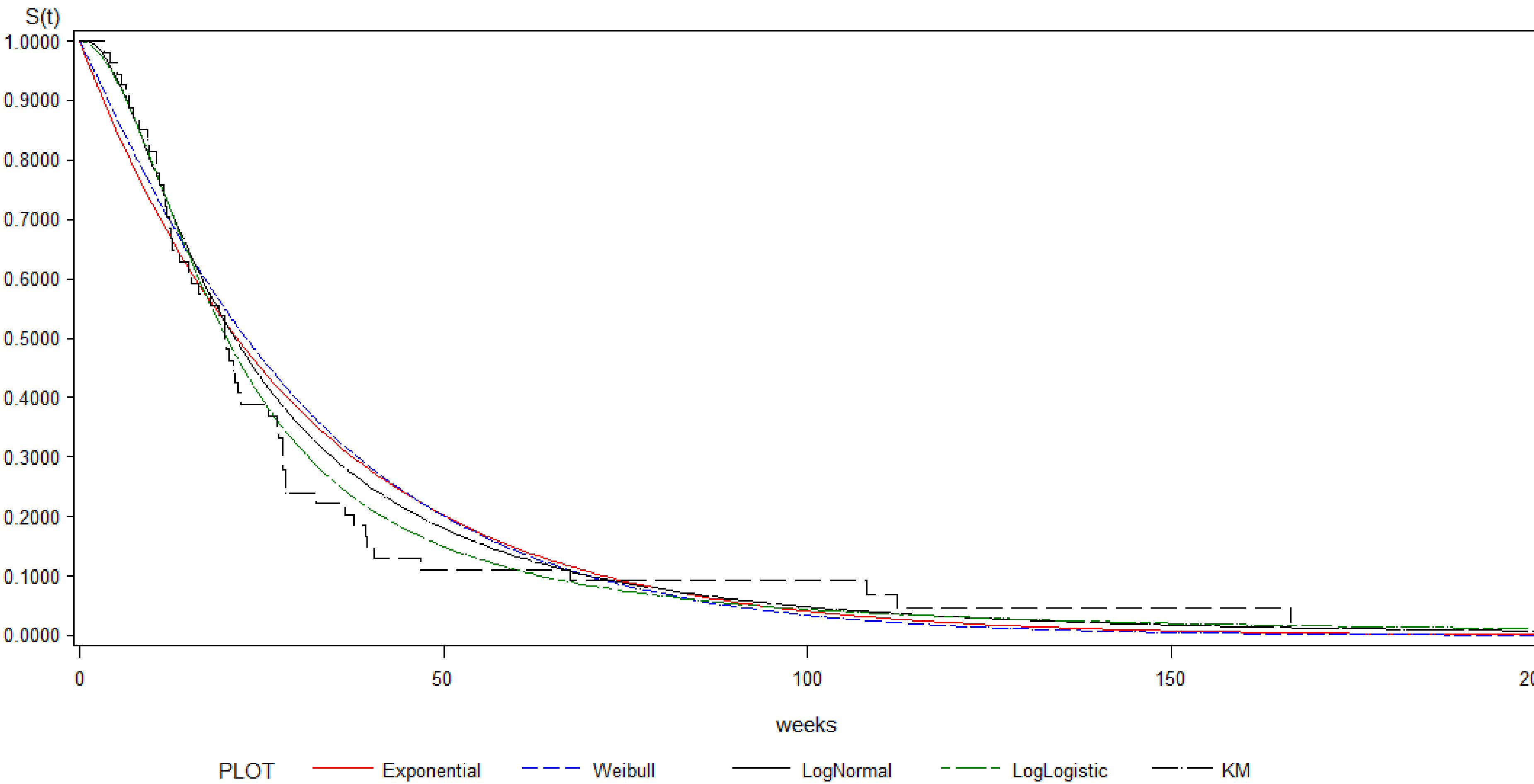



Survival: Treatment=Yes, Age>=50
S(t)
1.0000
0.9000
0.8000
0.7000
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
0
50
100
150
200
weeks
PLOT
Exponential
Weibull
LogNormal
LogLogistic
KM

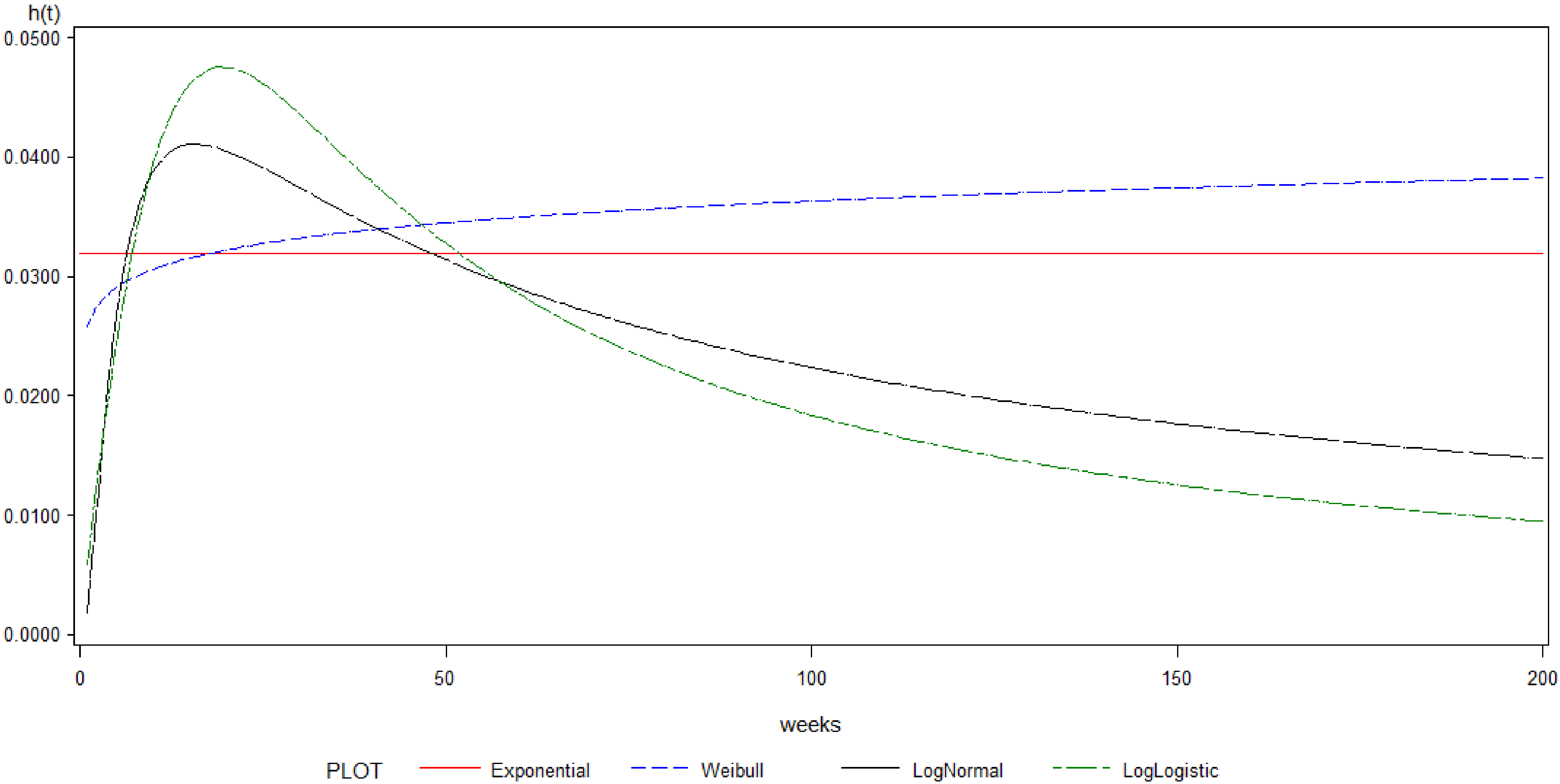
Hazard: Treatment=Yes, Age>=50



Survival: Treatment=No, Age>=50



Hazard: Treatment=No, Age>=50



Exponential Summary

t (weeks)	Age>=50	Exponential S(t), Treatment=1	Exponential h(t), Treatment=1	Exponential Median, Treatment=1	Exponential S(t), Treatment=0	Exponential h(t), Treatment=0
26	Yes	0.5004	0.0266	26.0284	0.4356	0.0320
52	Yes	0.2504	0.0266	26.0284	0.1898	0.0320
104	Yes	0.0627	0.0266	26.0284	0.0360	0.0320

t (weeks)	Exponential Median, Treatment=0	Exponential Hazard Ratio(t)	Exponential beta(Treatment);	Exponential Time Ratio	Exponential Median Ratio
26	21.6864	0.8332	0.1825	1.2002	1.2002
52	21.6864	0.8332	0.1825	1.2002	1.2002
104	21.6864	0.8332	0.1825	1.2002	1.2002

Weibull Summary

t (weeks)	Age>=50	Weibull S(t), Treatment=1	Weibull h(t), Treatment=1	Weibull Median, Treatment=1	Weibull S(t), Treatment=0	Weibull h(t), Treatment=0
26	Yes	0.5203	0.0270	27.4720	0.4516	0.0328
52	Yes	0.2526	0.0284	27.4720	0.1875	0.0346
104	Yes	0.0552	0.0299	27.4720	0.0295	0.0364

t (weeks)	Weibull Median, Treatment=0	Weibull Hazard Ratio(t)	Weibull beta(Treatment);	Weibull Time Ratio	Weibull Median Ratio
26	22.8892	0.8219	0.1825	1.2002	1.2002
52	22.8892	0.8219	0.1825	1.2002	1.2002
104	22.8892	0.8219	0.1825	1.2002	1.2002

Log Normal Summary

t (weeks)	Age>=50	Log Normal S(t), Treatment=1	Log Normal h(t), Treatment=1	Log Normal Median, Treatment=1	Log Normal S(t), Treatment=0	Log Normal h(t), Treatment=0
26	Yes	0.4909	0.0336	25.4521	0.4166	0.0388
52	Yes	0.2209	0.0278	25.4521	0.1693	0.0309
104	Yes	0.0648	0.0202	25.4521	0.0443	0.0219

t (weeks)	Log Normal Median, Treatment=0	Log Normal Hazard Ratio(t)	Log Normal beta(Treatment);	Log Normal Time Ratio	Log Normal Median Ratio
26	21.3788	0.8675	0.1744	1.1905	1.1905
52	21.3788	0.9013	0.1744	1.1905	1.1905
104	21.3788	0.9237	0.1744	1.1905	1.1905

```
beta=σ*(probit(1-slnorm0) - probit(1-slnorm1));
   /* log normal scale and S(t) for each group */
TR=exp(beta)
```

Log Logistic Summary

t (weeks)	Age>=50	Log Logistic S(t), Treatment=1	Log Logistic h(t), Treatment=1	Log Logistic Median, Treatment=1	Log Logistic S(t), Treatment=0	Log Logistic h(t), Treatment=0
26	Yes	0.4776	0.0387	24.8138	0.3822	0.0457
52	Yes	0.1941	0.0298	24.8138	0.1402	0.0318
104	Yes	0.0597	0.0174	24.8138	0.0412	0.0177

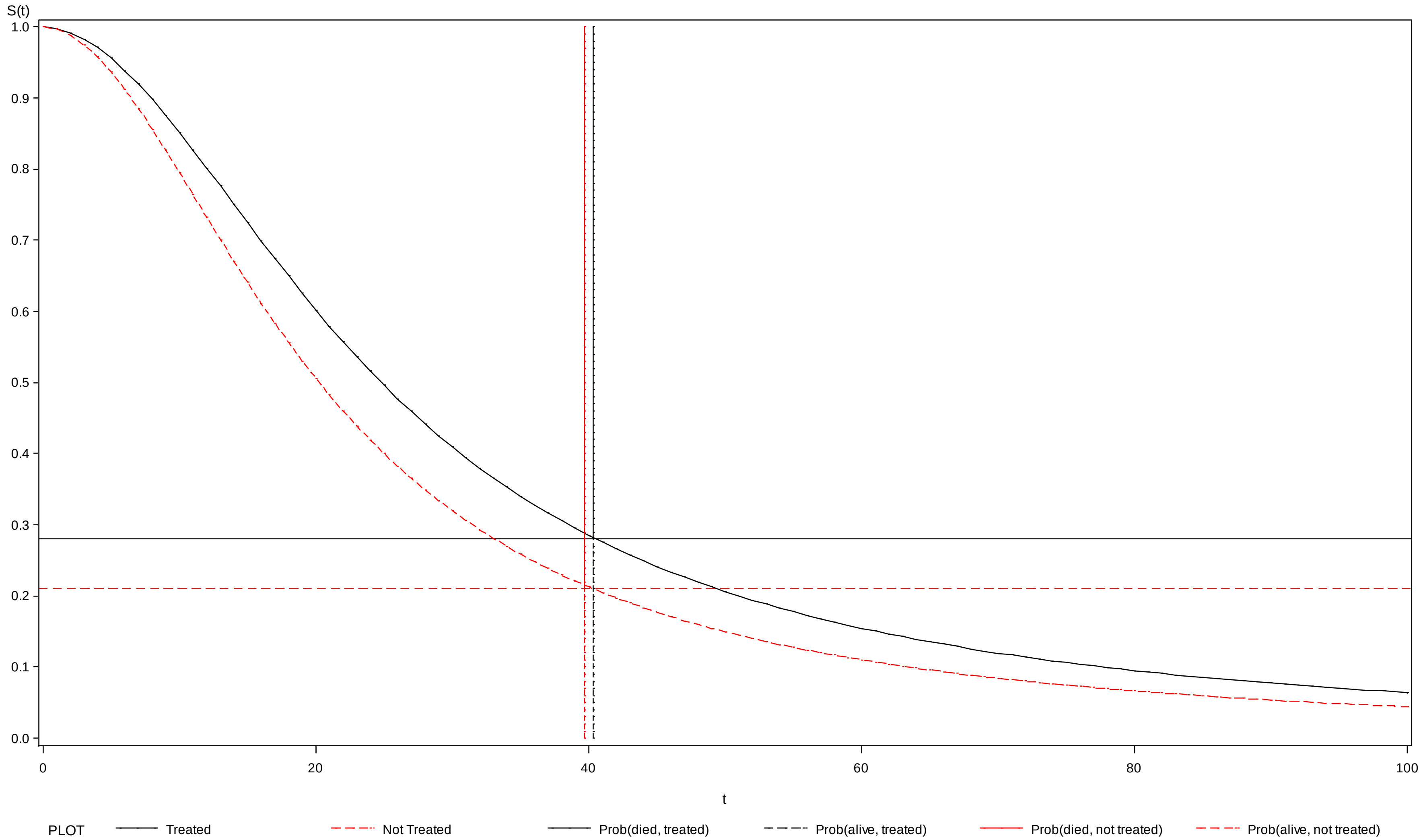
t (weeks)	Log Logistic Median, Treatment=0	Log Logistic Hazard Ratio(t)	Log Logistic beta(Treatment);	Log Logistic Time Ratio	Log Logistic Median Ratio	Log Logistic Odds S(t)/(1-S(t) , Treatment=1
26	20.2570	0.8457	0.2029	1.2249	1.2249	0.9141
52	20.2570	0.9373	0.2029	1.2249	1.2249	0.2409
104	20.2570	0.9807	0.2029	1.2249	1.2249	0.0635

t (weeks)	Log Logistic Odds S(t)/(1-S(t) , Treatment=0	Log Logisitic Odds Ratio	Log Logistic Alpha, Treatment=1	Log Logistic Alpha, Treatment=0	Log Logisitic Alpha Ratio
26	0.6187	1.4775	0.0021	0.0031	1.4775
52	0.1631	1.4775	0.0021	0.0031	1.4775
104	0.0430	1.4775	0.0021	0.0031	1.4775

Log logistic Odds Ratio (SAS Code)

```
hrllog=hllog1/hllog0;
if sllog1^=1 then odds1=sllog1/(1-sllog1);
if sllog0^=1 then odds0=sllog0/(1-sllog0);
oddsratio=odds1/odds0;
alpharatio=alpha0/alpha1;
beta_llog=log(oddsratio)*σ;
  /* log logistic scale; oddsratio=exp(beta_llog/σ) */
trllog=exp(beta_llog);
mrllog=mllog1/mllog0;
```

Odds of survival=Prob(alive)/Prob(died)   Odds ratio (treated to not treated)= 1.47



Discussion

- Not limited to parametric models discussed today. For example:
  - Changepoint model (piecewise exponential model)
  - Gamel-Boag model (allows for a proportion of subjects to be long term survivors)
- Bayesian analysis

Changepoint model

- When the hazard rate is constant within in time periods and changes at known timepoint
- For example, brain cancer hazard rate is constant for the first year of follow up but hazard rate is reduced if patient survives at least one year.

$$
\begin{aligned}
S(t) &= e^{-\lambda_1 t} && t \le \tau \\
&= e^{-\lambda_1 \tau} e^{-\lambda_2 (t-\tau)} && t > \tau
\end{aligned}
$$

SAS code to restructure data

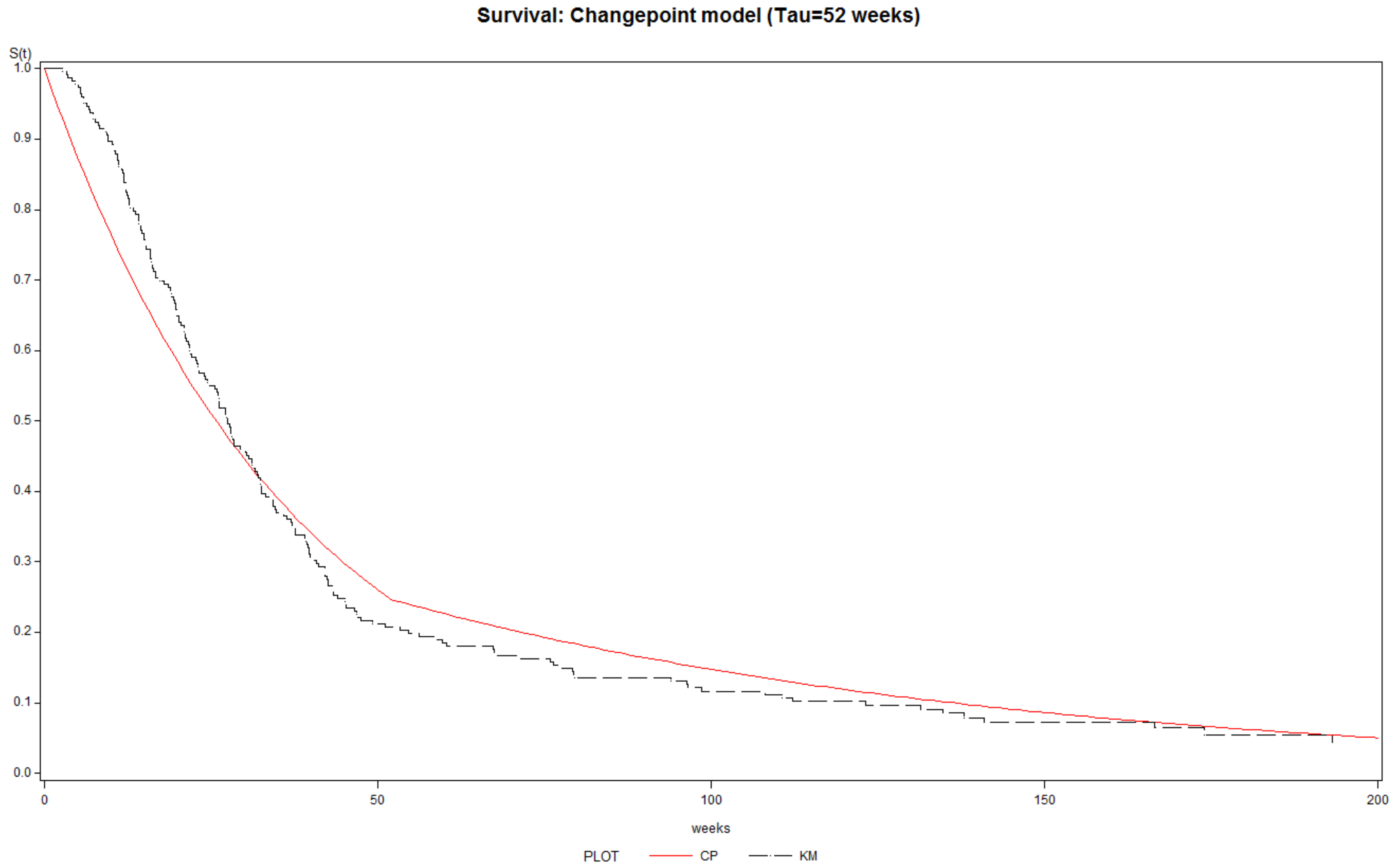
```
data brain2(keep=id weeks event weeks2 event2 year1);
  set sda.brain;
  id=_n_;
  if weeks<=52
     then do;
              event2=event;
               weeks2=weeks;
               year1=1;
               output;
         end;
     else do;
             event2=0;
               weeks2=52;
              year1=1;
               output;
               event2=event;
               weeks2=weeks-52;
              year1=0;
               output;
         end;
run;
```

SAS code to fit the model

```
proc lifereg data=brain2;
  model weeks2*event2(0)=year1/d=exponential;
  title 'Piecewise Exponential';
run;

data brain3;
  do weeks=0 to 200 by 1;  /* time frame */
  lambda1=exp(-(4.533-.9175));  * = 0.0269;
  lambda2=exp(-(4.533));        * = 0.0107;
  if weeks<=52
     then sexp=exp(-lambda1*weeks);
     else sexp=exp(-lambda1*52)*exp(-lambda2*(weeks-52));
  output;
  end;
run;
```

Changepoint model

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	4.5330	0.1796	4.1809	4.8850	636.98	<.0001
year1	1	-0.9175	0.1948	-1.2993	-0.5357	22.19	<.0001
Scale	0	1.0000	0.0000	1.0000	1.0000		
Weibull Shape	0	1.0000	0.0000	1.0000	1.0000		


Survival: Changepoint model (Tau=52 weeks)
S(t)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
weeks
PLOT
CP
KM

Gamel-Boag Model

- Allows for a proportion of subjects to be long term survivors.
- Events are modeled using log-normal model.

$$S(t \mid x) = p(x) + (1 - p(x))S_f(t \mid x)$$

$$p(x) = \frac{e^{x'\beta}}{1 + e^{x'\beta}}$$

$$\ln(t_i) = x_i'\gamma + e_i \qquad e_i \sim N(0, \sigma)$$

SAS code to fit log-normal model

```
/* log normal model using proc lifereg */
proc lifereg data=sda.brain;
  model weeks*event(0)=age50/d=lnormal;
  title 'LifeReg: Survival by age group (Log normal)';
run;

/* log normal model using proc nlp (SAS/OR) - maximize loglikelihood */
proc nlp data=sda.brain tech=tr cov=2 stderr;
   parms int gamma sig;
   pi=3.14159;
   u=int+gamma*age50;
   if event=1 then logl=log(1/(sqrt(2*pi)*weeks*sig)*
                       exp(-1/2*((lweeks-u)/sig)**2));
   if event=0 then logl=log(1-probnorm((lweeks-u)/sig));
   max logl;
run;
```

SAS code to fit Gamel-Boag model

```
/* Gamel-Boag cure model using proc nlp (SAS/OR), maximize modified
loglikelihood, reference Frankel & Longmate */

proc nlp data=sda.brain tech=tr cov=2 stderr;
   parms intg gamma intb beta sig;
   pi=3.14159;
   p=exp(intb+beta*age50)/(1+exp(intb+beta*age50)); /* model proportion
                                                      cured by age group */
   u=intg+gamma*age50;
   if event=1 then logl=log((1-p)*(1/(sqrt(2*pi)*weeks*sig)*
                        exp(-1/2*((lweeks-u)/sig)**2)));
   if event=0 then logl=log(p+(1-p)*(1-probnorm((lweeks-u)/sig)));
   max logl;
run;
```

SAS output from Proc Lifereg

Analysis of Maximum Likelihood Parameter Estimates							
Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	3.5643	0.0875	3.3929	3.7357	1660.94	<.0001
age50	1	-0.4161	0.1260	-0.6631	-0.1691	10.90	0.0010
Scale	1	0.9335	0.0468	0.8461	1.0298		

SAS output from Proc NLP (1)

Optimization Results							
Parameter Estimates							
N	Parameter	Estimate	Approx Std Err	t Value	Approx Pr > |t|	Gradient Objective Function
1	int	3.564322	0.088055	40.478316	1.22822E-103	0.000000118
2	Gamma (age 50)	-0.416088	0.126899	-3.278898	0.001212	-0.000000176
3	sig	0.933454	0.047114	19.812805	9.793712E-51	0.000002754

Value of Objective Function = -964.9427317

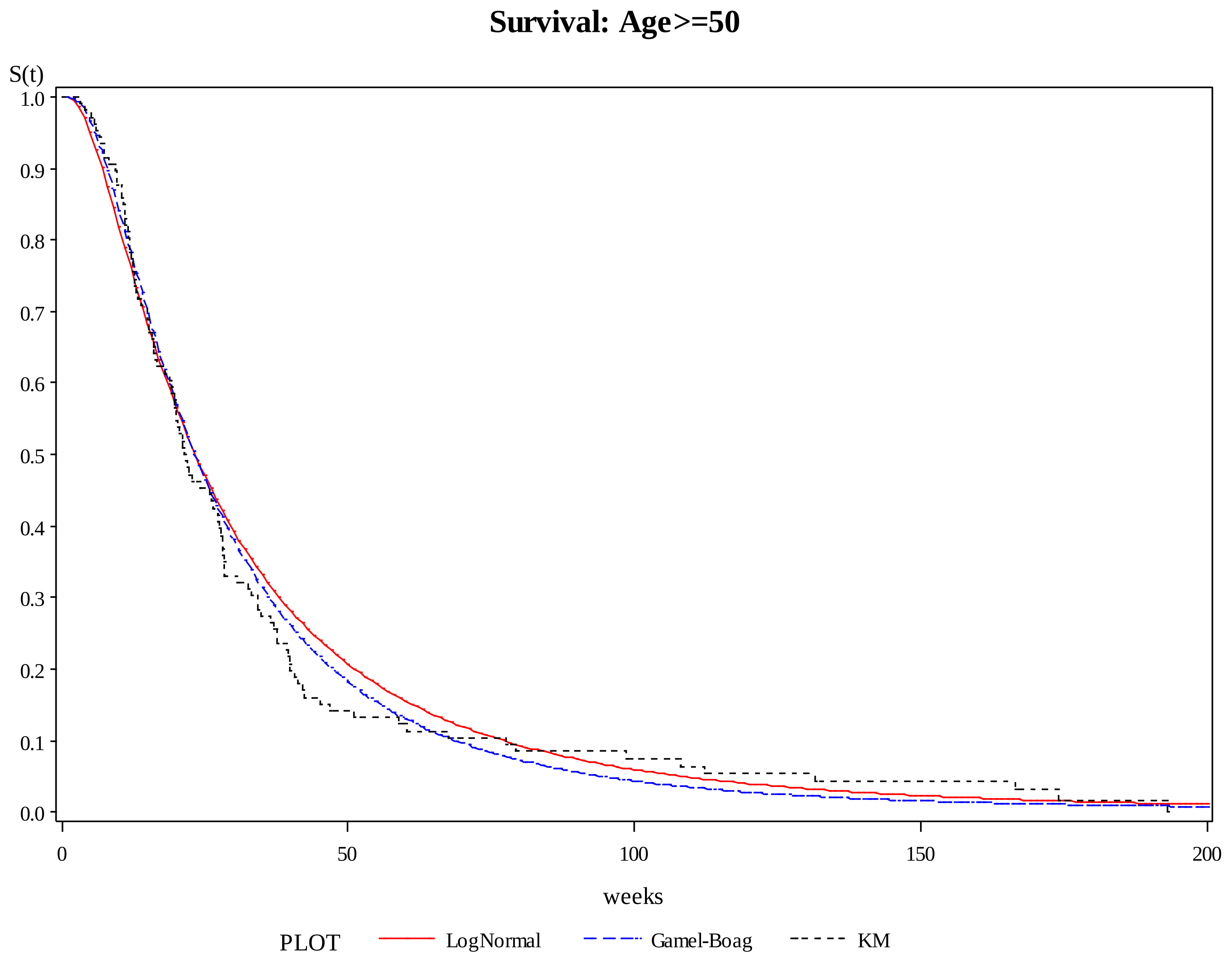
SAS output from Proc NLP (2)

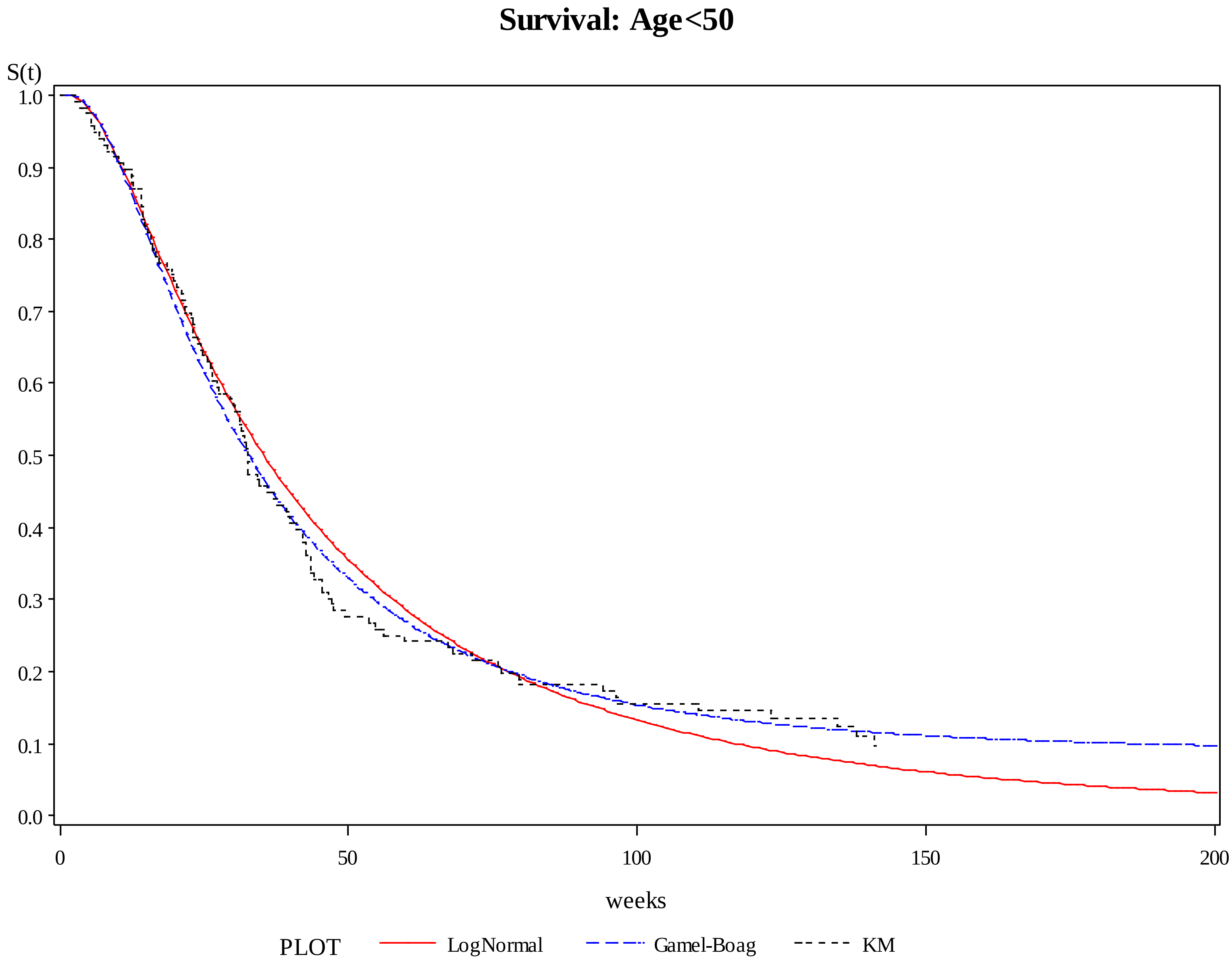
Optimization Results						
Parameter Estimates						
N	**Parameter**	**Estimate**	**Approx Std Err**	**t Value**	**Approx Pr > |t|**	**Gradient Objective Function**
1	**intg**	3.383333	0.090495	37.387072	1.546812E-96	-0.000003440
2	**gamma (Age50)**	-0.241294	0.124095	-1.944430	0.053136	-0.000003444
3	**intb**	-2.354737	0.397974	-5.916817	1.2664557E-8	-0.000000870
4	**beta (Age50)**	-3.695206	5.265763	-0.701742	0.483592	-0.000000867
5	**sig**	0.841890	0.048823	17.243571	1.534361E-42	-0.000007602

Value of Objective Function = -959.5044921

Proportion cured each age group and OR:

p1	p0	or	lor
0.002	0.087	0.025	-3.695


Survival: Age>=50
S(t)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
weeks
PLOT
LogNormal
Gamel-Boag
KM


Survival: Age<50
S(t)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
weeks
PLOT
LogNormal
Gamel-Boag
KM

Bayesian analysis

- Gibbs sampling used for the location-scale models
- Can add priors for model parameters
- Can output posterior samples

```
proc lifereg data=sda.brain;
  model weeks*event(0)=age50/d=weibull;
  bayes WeibullShapePrior=gamma seed=1254 outpost=postweibull;
run;
```

Analysis of Maximum Likelihood Parameter Estimates

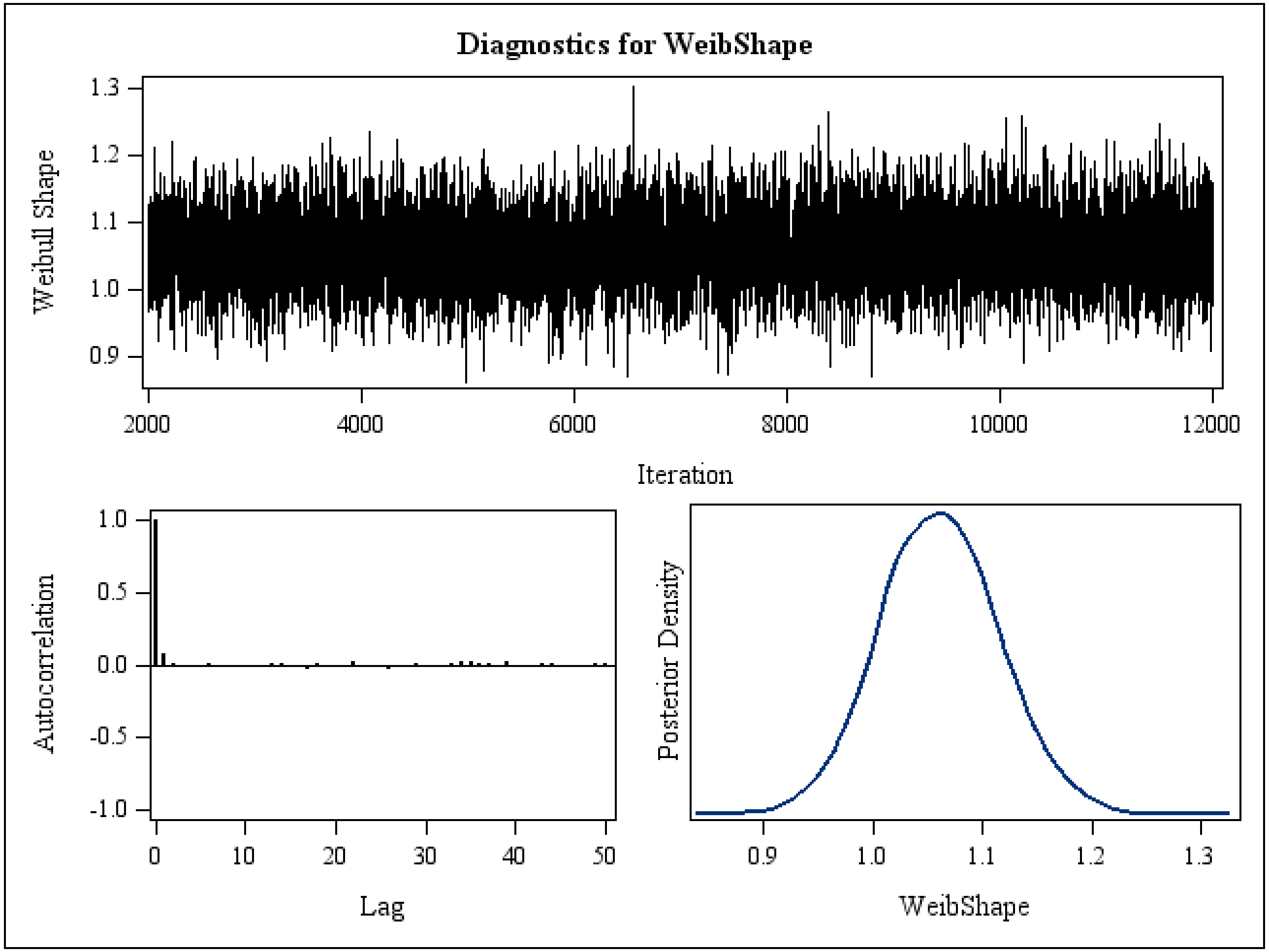
Parameter	DF	Estimate	Standard Error	95% Confidence Limits	
Intercept	1	4.0569	0.0933	3.8740	4.2397
age50	1	-0.4927	0.1303	-0.7480	-0.2374
Scale	1	0.9356	0.0481	0.8459	1.0349
Weibull Shape	1	1.0688	0.0550	0.9663	1.1822

Posterior Summaries

Parameter	N	Mean	Standard Deviation	Percentiles 25%	50%	75%
Intercept	10000	4.0594	0.0942	3.9950	4.0584	4.1222
age50	10000	-0.4922	0.1325	-0.5815	-0.4922	-0.4039
WeibShape	10000	1.0613	0.0545	1.0241	1.0605	1.0977

Posterior Intervals

Parameter	Alpha	Equal-Tail Interval		HPD Interval	
Intercept	0.050	3.8787	4.2463	3.8755	4.2407
age50	0.050	-0.7532	-0.2307	-0.7571	-0.2368
WeibShape	0.050	0.9555	1.1703	0.9551	1.1695


Diagnostics for WeibShape
Weibull Shape
1.3
1.2
1.1
1.0
0.9
2000
4000
6000
8000
10000
12000
Iteration
Autocorrelation
1.0
0.5
0.0
-0.5
-1.0
0
10
20
30
40
50
Lag
Posterior Density
0.9
1.0
1.1
1.2
1.3
WeibShape

Discussion: Why fit parametric models?

- Able to describe the hazard rate
- AF model alternative when hazard rates are non-proportional
- Easier and more convenient to predict outcome for a particular outcome (see Reid (1994) conversation with D.R. Cox)
- If underlying hazard function is correctly specified, then parametric models 'give more precise estimates' (K & M, p.373).
- Applications where parametric models are compared to Cox proportional hazard models:
  - Chapman et al (2006). Application of log-normal model which authors conclude has a 'major advantage over the Cox model'
  - Nardi and Schemper (2003). Authors 'compare Cox and parametric models in clinical settings'.
  - Carroll (2003). Author 'illustrates the practical benefits of a Weibull-based analysis'.

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