FINAL EXAMINATION
Analysis of survival data (7.5hp) 2019-01-18

INFORMATION:

A. Allowed means of assistance:
Book, handouts from lectures, handwritten notes, ethical guidelines by ISI, RSS, ASA, and Svenska statistikfrämjandet. Calculator, ruler, dictionary.

B. Writing time: 8.00-13.00 (5 hours).

C. The examination consists of 3 tasks, for a total of 80 points. Including any attendance and home assignment bonus points, at least 48 points are needed to pass the course (G), and 72 points to pass with distinction (VG).

D. For every task the maximum score is shown (for every part of the task). Sometimes the parts cannot be judged independent of each other, which means that points might not be able to be set for a later part if the previous part has not been solved in a correct way (in principle). Negative points will never be set.

E. You can write your answers in English or Swedish.

F. If you desire clarification regarding the test, especially the wording of a problem, then please contact an examination proctor. The examination proctors can contact the responsible teacher.

G. After turning in your test, you will keep the test pages with the question statements (not to be handed in!). Preliminary solutions will be posted at Studentportalen.

INSTRUCTIONS:

A. Follow the instructions on the front page to be stapled to your solutions. E.g., the solutions for each task should be started on a new sheet.

B. Present all your solutions in a way that makes it easy to follow your way of thinking! What is unclearly presented is assumed to be unclearly thought. Motivate all important steps of your solution, including any assumptions that need to be fulfilled (and check if they are).

C. When constructing confidence intervals you must (besides what is presented in B above) state what the interval is intended to cover, and present the formula for the interval before you present the calculation (if needed), and interpret the calculated interval.

D. When performing hypothesis testing you must (besides what is presented in B above) present null and alternative hypotheses, choice of significance level, choice of test, *P*-value, result, and conclusion.

Good luck!

Task 1

(21)

Centralization of surgery in cancer has been discussed in Europe. In a paper in the British Journal of Surgery (Dikken et al. 2013), the relation between hospital volume (the number of surgeries of a certain type per year in a given hospital) and overall survival for oesophageal[1] cancer was studied, in four countries in Europe. The table on the next page, taken from that paper, shows the results of a Cox proportional hazards regression analyzing the relation between survival and hospital volume, sex, age, histology[2], and TNM stage[3]. The article also includes an analysis of postoperative mortality within 30 days after surgery (results not shown here).

Patients diagnosed with oesophageal cancer between 2004 and 2009 were included in the study (n=19 864).

Survival time was defined as survival after surgery until death from any cause (event) or alive at last follow-up (censored). The patients were followed for two years.

[1] The *esophagus* is the muscular tube that conveys food from the back of the mouth to the stomach.
[2] A description of the type of tumor.
[3] A system to describe the amount and spread of cancer in a patient's body. T describes the size of the tumor and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body). A higher stage means a worse amount and spread.

(4) **A** Describe the type(s) of censoring and/or truncation that is/are represented in this study. Motivate your answer.

(1) **B** The primary interest is in hospital volume. Why did the researchers include the other covariates as well?

(2) **C** Are there any competing risk(s) present in this study? If so, how does that affect the results of the analysis?

(4) **D** What is your conclusion with respect to the research question:
"How does hospital volume influence overall survival in oesophageal cancer"?
Please discuss also the direction of the effect of hospital volume on overall survival.

(2) **E** Calculate and interpret the relative risk of death for individuals older than 75 years compared to 60-75 year-olds.

(4) **F** The authors also fitted a Cox model like that of the table below, but now with hospital volume as a continuous covariate (unit: 10 surgeries/year). For simplicity, you can view the largest volume category as an interval of 41-50 surgeries/year.

i. Looking at the results of the table below, is it reasonable to assume that the effect of hospital volume as a continuous covariate is linear? Motivate your answer.

ii. How large would the hazard ratio of hospital volume, as a continuous covariate, be approximately? Choose between 0.85, 0.90 and 0.95, and motivate your choice.

(4) **G** Which ethical aspects (if any) are important to consider in this type of study, from a statistical point of view?

Analysis of relationship between annual hospital volume and survival

	Oesophagectomy
	2-year survival (%)†
	Hazard ratio
Annual hospital volume	
1–10	1·00 (reference)
11–20	0·92 (0·78, 1·08)
21–30	0·84 (0·63, 1·11)
31–40	0·77 (0·63, 0·94)
≥ 41	0·79 (0·66, 0·96)
P for trend#	0·004
Sex	
M	1·00 (reference)
F	0·78 (0·69, 0·90)
Age (years)	
< 60	1·00 (reference)
60–75	1·40 (1·27, 1·55)
> 75	1·87 (1·58, 2·23)
Histology	
Adenocarcinoma	1·00 (reference)
SCC	1·29 (1·15, 1·44)
Other carcinoma	1·45 (1·03, 2·05)
TNM stage	
0	0·57 (0·29, 1·14)
I	1·00 (reference)
II	1·96 (1·46, 2·62)
III	3·71 (2·74, 5·04)
IV	8·13 (4·39, 15·08)
Unknown	1·77 (1·01, 3·11)

Values in parentheses are 95% confidence intervals.
† Analyzed by Cox regression.
# Cox regression test for trend.
Histology: describes three different types of tumors. Adenocarcinoma tend to occur closer to the stomach. SCC, squamous cell carcinoma, tend to occur closer to the mouth.

Task 2

(23)

In a study of depression, remission times for a number of patients are recorded, and all subjects who did not have a depression episode at the end of the study period are censored.

Variable specification:
time: Time to remission (time until depression returns) in months
age: years of age at the start of the study

Among other things, it is of interest to investigate the relationship between age and risk of depression. Previous studies have indicated that the risk of depression decreases after 30 years of age.

Use the SAS output on the following pages, and answer the questions below.

NOTE: In each of the questions, translate "survival" to what is referred to in this case.

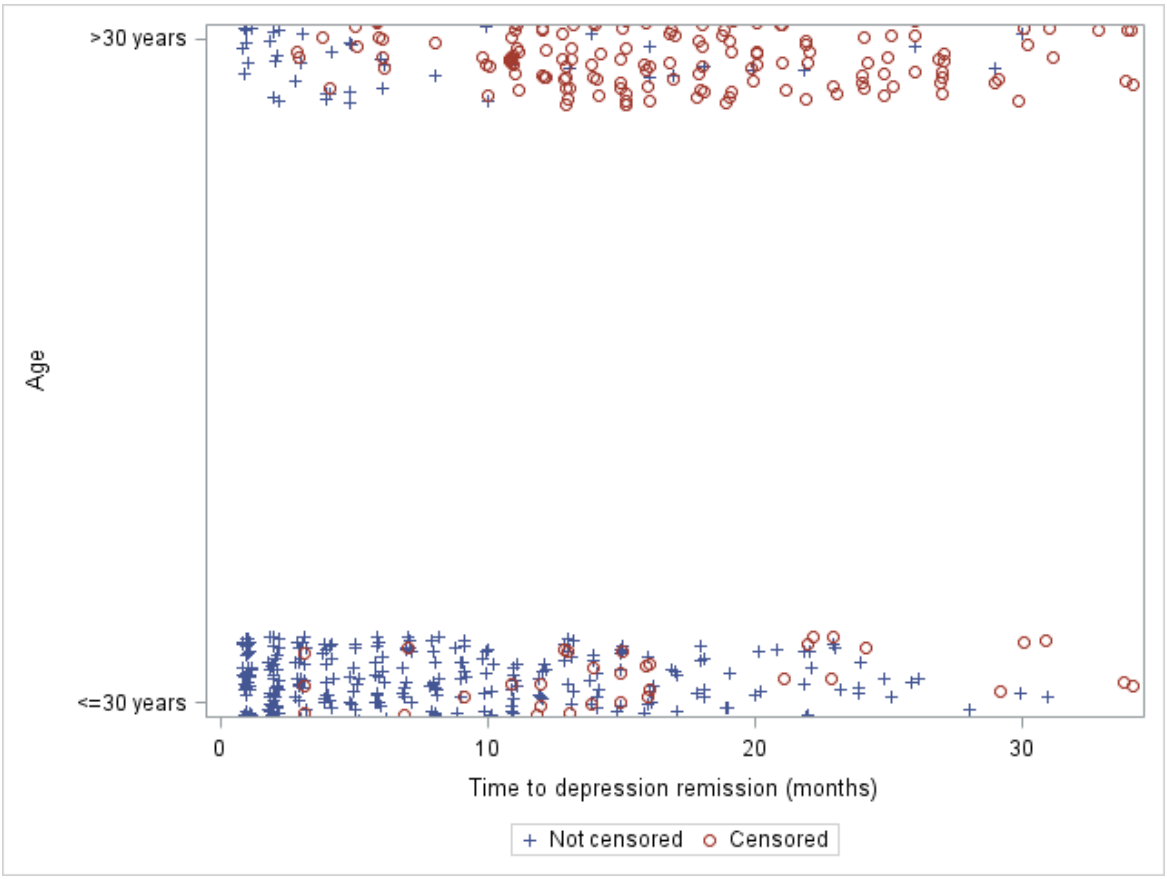
(8) **A** Present, interpret, and compare for the two age groups:
The 25 percentile, 75 percentile and median (50 percentile) of survival times. If the measures cannot be estimated, explain why and present the minimum time of the measures.

(3) **B** Present and compare the probability of surviving at least 1 year for each of the two age groups.

(12) **C** Is there a significant difference in survival between the two age groups? Perform an appropriate hypothesis test to find out. Remember to follow the instructions on the front page

Summary of the Number of Censored and Uncensored Values					
Stratum	**Age group**	**Total**	**Failed**	**Censored**	**Percent Censored**
1	**<=30 years**	407	356	51	12.53
2	**>30 years**	203	54	149	73.40
Total		610	410	200	32.79

Censoring pattern



Stratum 1: age group ≤ 30 years

Product-Limit Survival Estimates

time		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.0000		1.0000	0	0	0	407
1.0000		.	.	.	1	406
	…	*(only parts of the table shown)*				
1.0000		0.8845	0.1155	0.0158	47	360
2.0000		.	.	.	48	359
	…					
2.0000		0.7617	0.2383	0.0211	97	310
3.0000		.	.	.	98	309
	…					
3.0000		0.6880	0.3120	0.0230	127	280
3.0000	*	.	.	.	127	281
	…					
4.0000		0.6433	0.3567	0.0238	145	259
4.0000	*	.	.	.	145	258
	…					
6.0000		0.5607	0.4393	0.0247	178	224
	…					
7.0000		0.5131	0.4869	0.0249	197	205
7.0000	*	.	.	.	197	204
	…					
8.0000		0.4595	0.5405	0.0249	218	180
9.0000		.	.	.	219	179
	…					
11.0000		0.3360	0.6640	0.0237	266	130
11.0000	*	.	.	.	266	129
	…					
12.0000		0.3097	0.6903	0.0233	276	118
	…					

Product-Limit Survival Estimates

time		Survival	Failure	Survival Standard Error	Number Failed	Number Left
12.0000	*	.	.	.	276	112
13.0000		.	.	.	277	111
	…					
13.0000		0.2765	0.7235	0.0227	288	100
13.0000	*	.	.	.	288	99
	…					
14.0000		.	.	.	295	88
14.0000		0.2533	0.7467	0.0222	296	87
14.0000	*	.	.	.	296	86
14.0000	*	.	.	.	296	85
15.0000		.	.	.	297	84
	…					
15.0000		0.2324	0.7676	0.0217	303	78
	…					
23.0000		0.0843	0.9157	0.0159	346	22
23.0000	*	.	.	.	346	21
	…					
28.0000		0.0348	0.9652	0.0127	356	5
29.0000	*	.	.	.	356	4
	…					
34.0000	*	0.0348	0.9652	.	356	0

Note: The marked survival times are censored observations.

Stratum 2: age group > 30 years

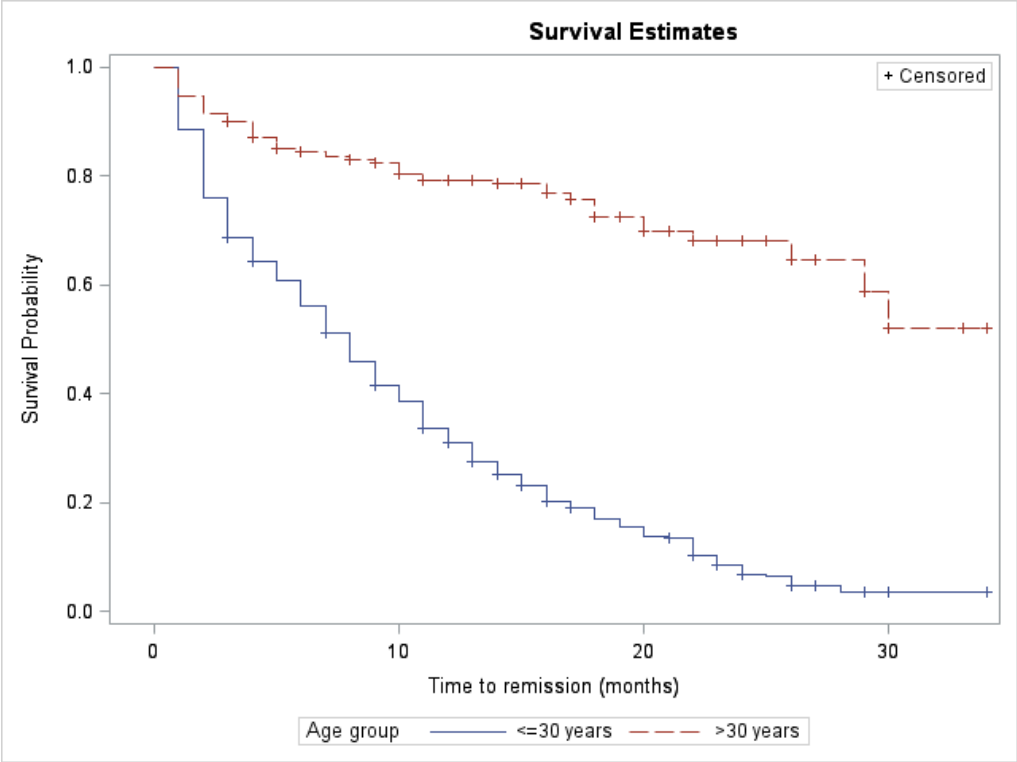
Product-Limit Survival Estimates

time		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.0000		1.0000	0	0	0	203
1.0000		.	.	.	1	202
	…	*(only parts of the table shown)*				
1.0000		0.9458	0.0542	0.0159	11	192
2.0000		.	.	.	12	191
	…					
4.0000		0.8716	0.1284	0.0235	26	175
4.0000	*	.	.	.	26	174
	…					
11.0000		0.7928	0.2072	0.0289	41	145
	…					
11.0000	*	.	.	.	41	131
12.0000	*	.	.	.	41	130
	…					
12.0000	*	.	.	.	41	126
13.0000	*	.	.	.	41	125
	…					
13.0000	*	.	.	.	41	109
14.0000		0.7855	0.2145	0.0295	42	108
14.0000	*	.	.	.	42	107
	…					
16.0000		0.7676	0.2324	0.0314	44	86
16.0000	*	.	.	.	44	85
	…					
16.0000	*	.	.	.	44	80
17.0000		0.7580	0.2420	0.0325	45	79
17.0000	*	.	.	.	45	78
	…					

Product-Limit Survival Estimates

time		Survival	Failure	Survival Standard Error	Number Failed	Number Left
18.0000		.	.	.	47	68
18.0000		0.7256	0.2744	0.0361	48	67
18.0000	*	.	.	.	48	66
	...					
20.0000		.	.	.	49	52
20.0000		0.6982	0.3018	0.0396	50	51
	...					
26.0000		0.6453	0.3547	0.0530	52	18
26.0000	*	.	.	.	52	17
	...					
29.0000		0.5866	0.4134	0.0738	53	10
29.0000	*	.	.	.	53	9
30.0000		0.5215	0.4785	0.0899	54	8
30.0000	*	.	.	.	54	7
	...					
34.0000	*	0.5215	0.4785	.	54	0

Note: The marked survival times are censored observations.



Test of Equality over Strata			
Test	**Chi-Square**	**DF**	**Pr > Chi-Square**
Log-Rank	166.0967	1	<.0001
Wilcoxon	110.8521	1	<.0001
-2Log(LR)	188.2766	1	<.0001

Task 3

(36)

Following up on the study described in Task 2, the effectiveness of a new treatment for depression is to be investigated. 754 patients are followed for up to 34 months.

The following variables are included in the data:

time: Time to remission (time until depression returns) in months
trt: 1 = new treatment, 0 = standard care
gender: 1 = woman, 2 = man, 3 = other
civil status: 1 = married or equivalent partnership, 2 = single, 3 = divorced, separated, or widowed
age: years of age at the start of the study

(2) **A** Would you choose parametric regression or Cox regression to analyze the relationship between the variables above? Motivate your choice.
NOTE: The questions below are not a guidance to the correct answer here.

Use the output on the following pages, generated from SAS PROC PHREG, and answer the following questions:

(4) **B** Do any of the covariates above need to be handled in any special way (e.g. by recoding or transforming them), or can they be used as they are in the regression analysis? Motivate your answer.

(18) **C** Which of the five models below would you choose to analyze the data? Motivate your choice carefully.

(10) **D** Explain/interpret the relationships between the covariates in the model you chose above and time to remission.

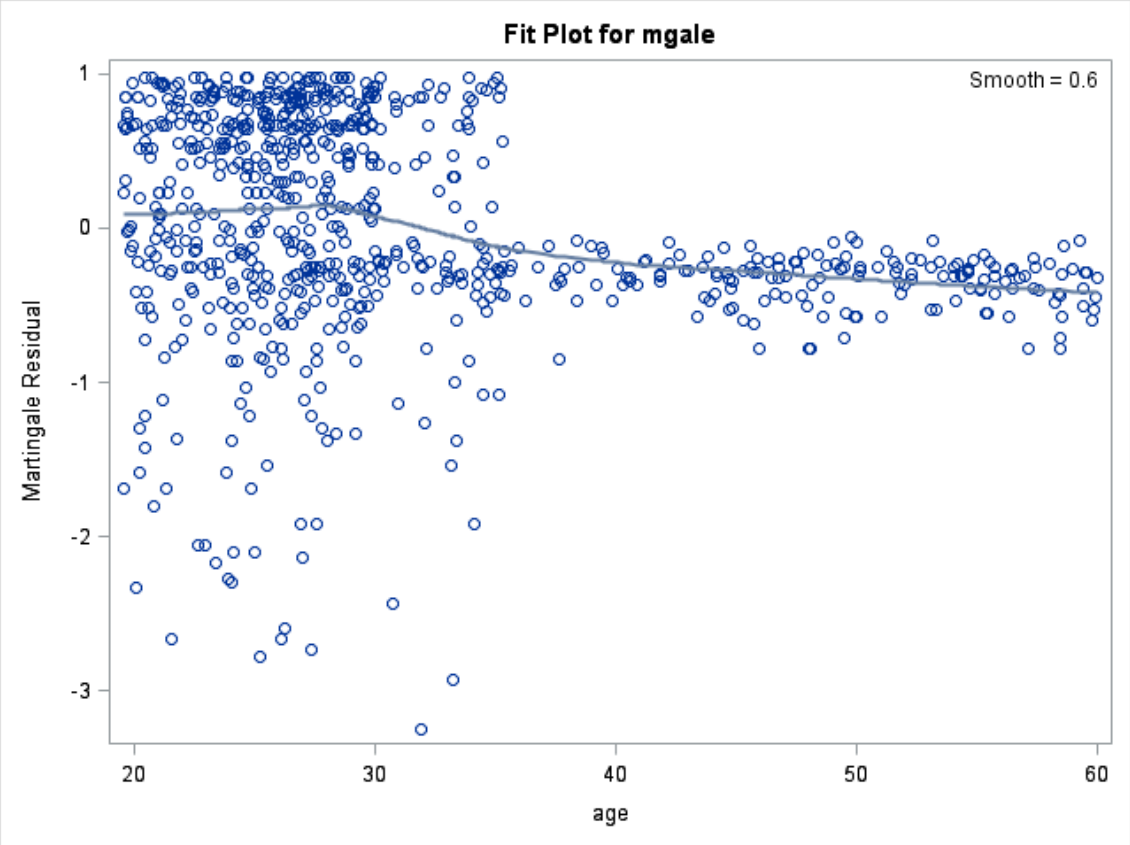
If you've chosen a stratified model, remember to also interpret the stratifying variable.

If you've chosen a model with a time-dependent coefficient, calculate the hazard ratio at 3, 12, and 25 months, respectively (no confidence intervals needed).

(2) **E** Calculate and interpret the generalized R^2 for the selected model.

Summary of the Number of Event and Censored Values			
Total	**Event**	**Censored**	**Percent Censored**
754	486	268	35.54

gender	Frequency	Percent	Cumulative Frequency
1	406	53.85	406
2	347	46.02	753
3	1	0.13	754

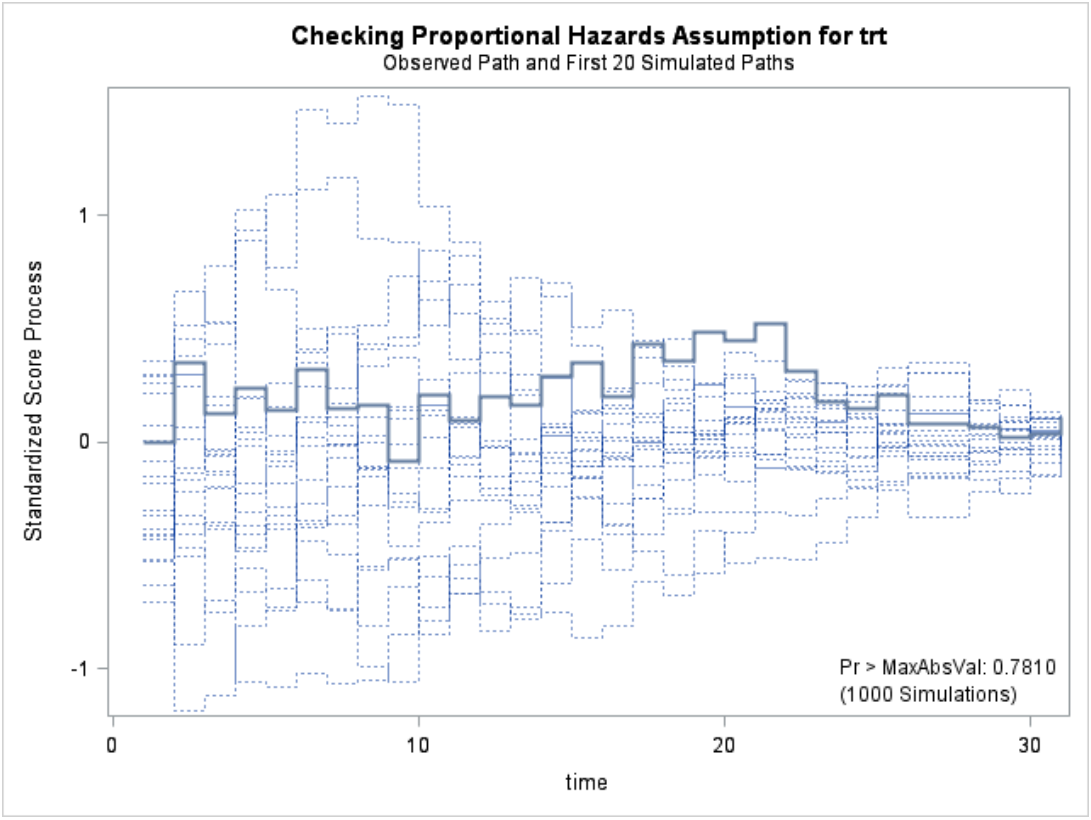


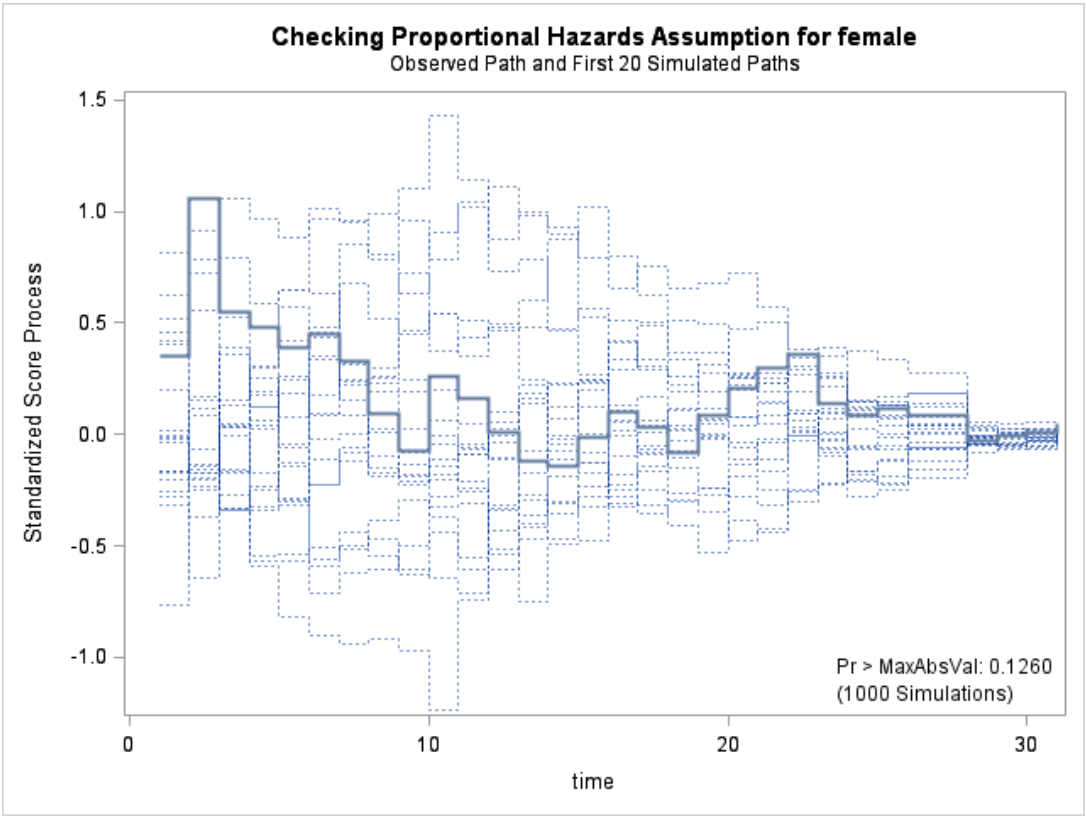
Analysis of Maximum Likelihood Estimates						
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**
trt	1	-0.37587	0.25145	2.2344	0.1350	0.687
lnt_trt	1	-0.03448	0.12443	0.0768	0.7817	0.966
age	1	-0.07302	0.01473	24.5773	<.0001	0.930
lnt_age	1	-0.02105	0.00778	7.3177	0.0068	0.979
civil status	2			108.4598	<.0001	4.047
lnt_civil_status	1	0.22189	0.06809	10.6191	0.0011	1.248
gender	2			0.8044	0.6688	0.861
lnt_gender	1	0.18222	0.09096	4.0133	0.0451	1.200
female (vs male and other)	1	0.13505	0.17836	0.5733	0.4489	1.145
lnt_female	1	-0.17478	0.09133	3.6624	0.0557	0.840
female (vs male, excl. other*)	1	0.13057	0.17835	0.5360	0.4641	1.139
ln_female	1	-0.17115	0.09137	3.5088	0.0610	0.843

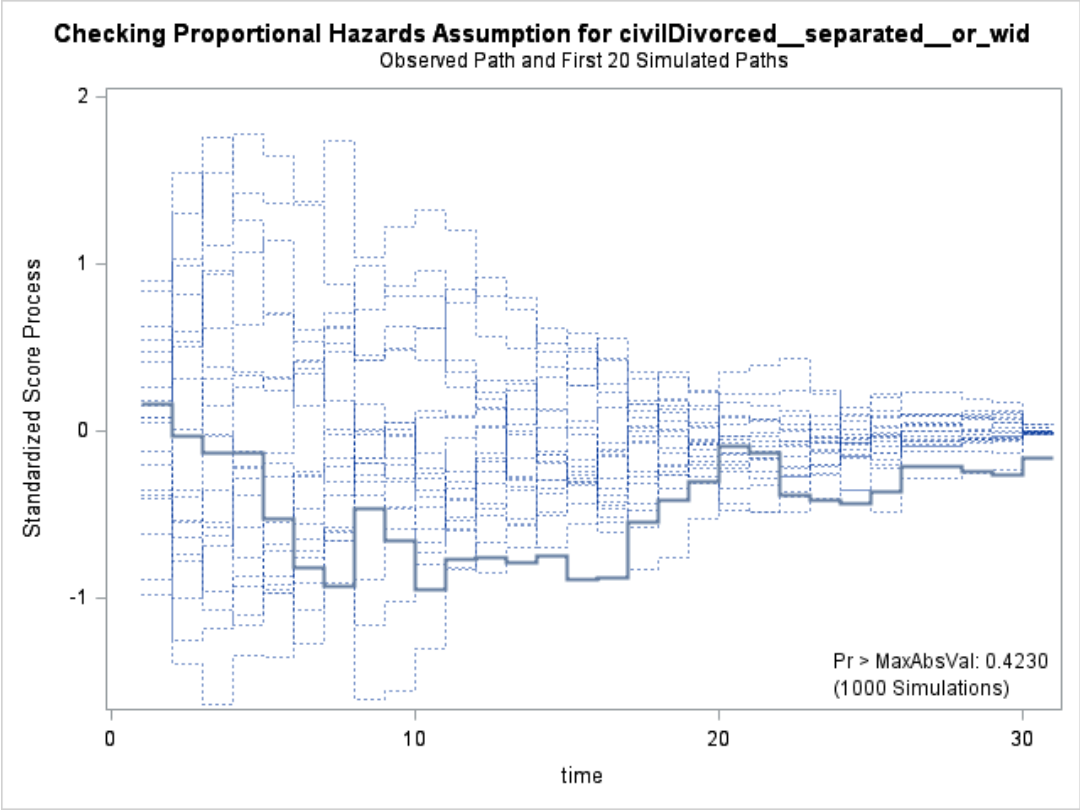
"lnt_x" denotes a time-dependent coefficient, calculated as x*ln(time).

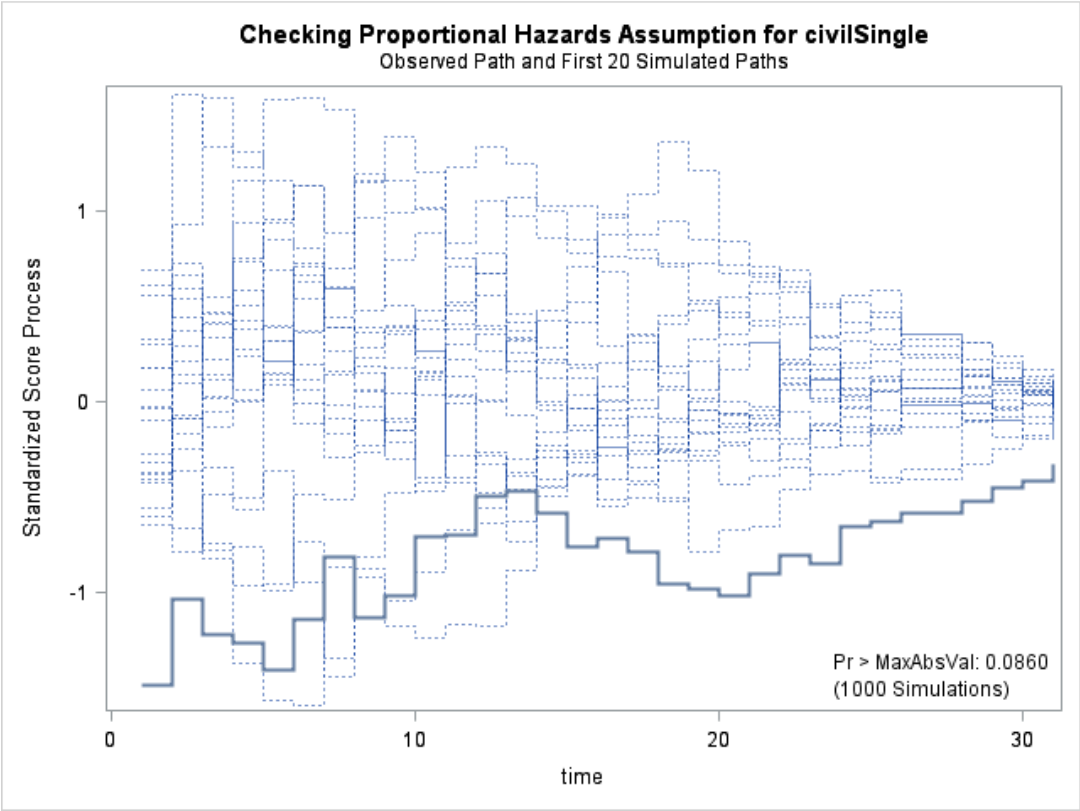
female = 1 if gender = 1, 0 otherwise.

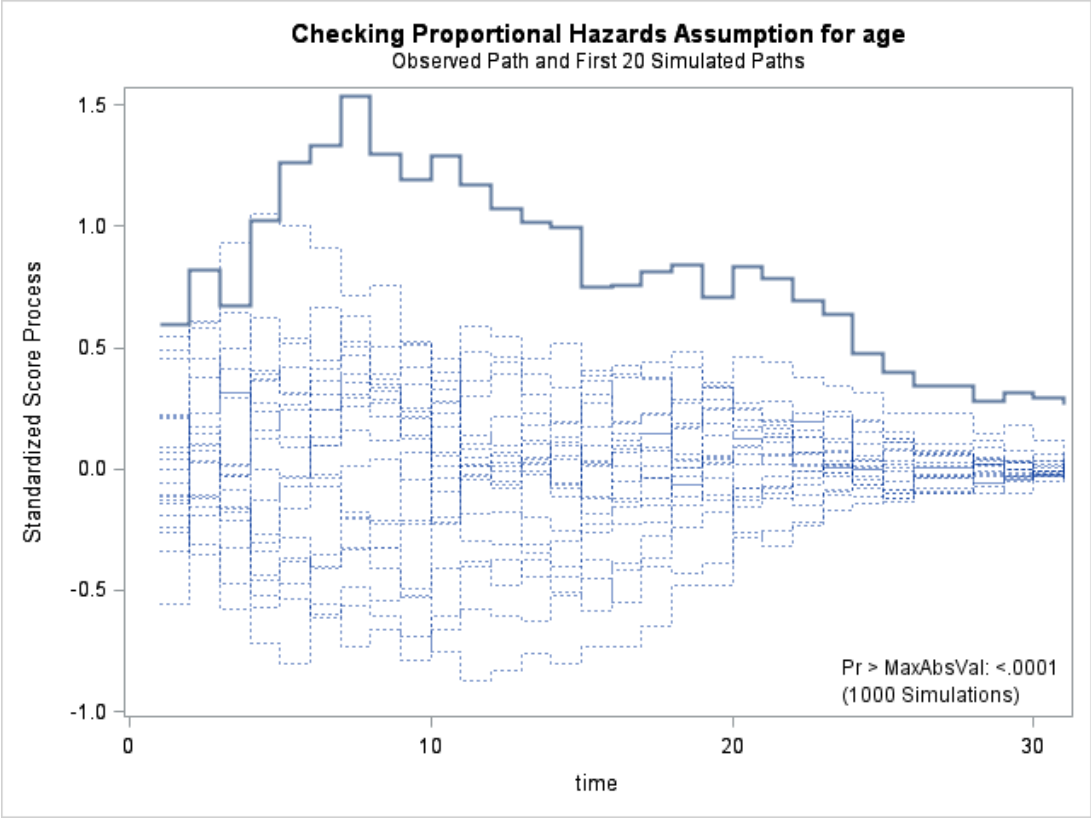
* The "other" individual (gender=3) is excluded, reducing the sample size by one.

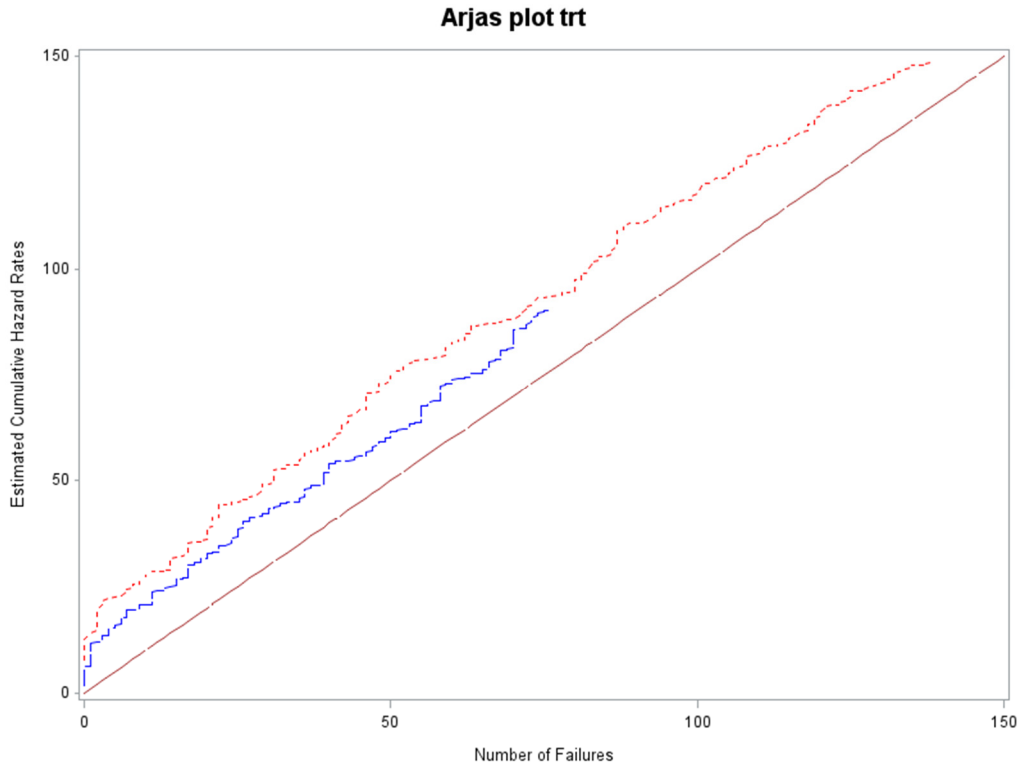

Checking Proportional Hazards Assumption for trt
Observed Path and First 20 Simulated Paths
Standardized Score Process
1
0
-1
0
10
20
30
time
Pr > MaxAbsVal: 0.7810
(1000 Simulations)

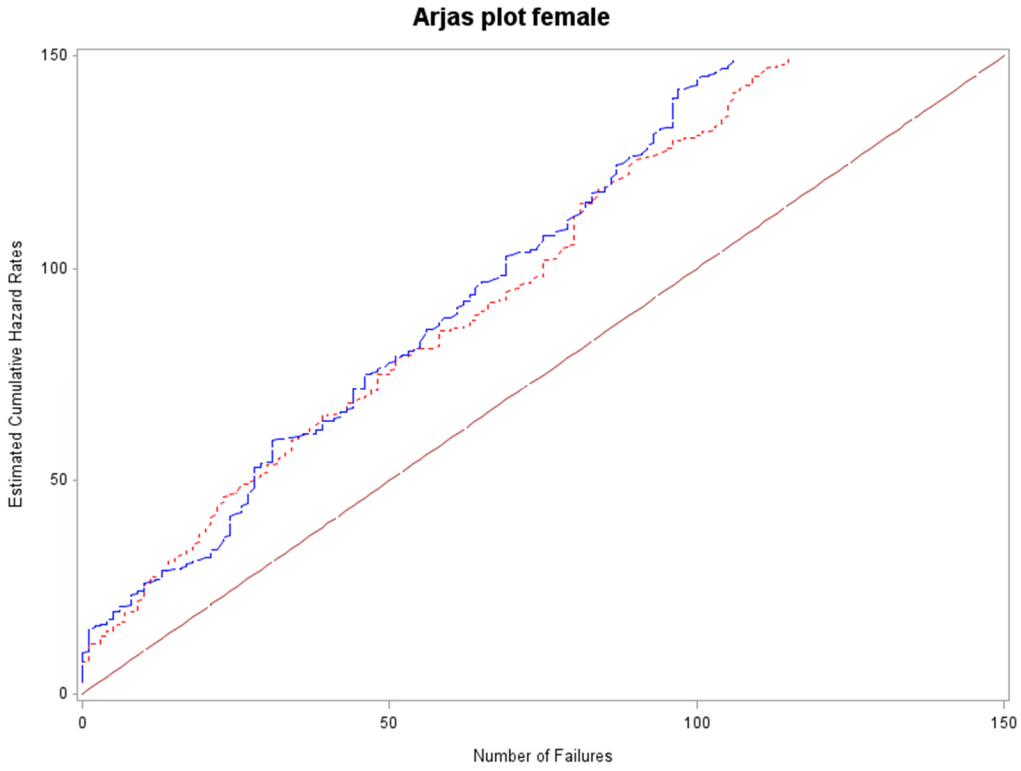

Checking Proportional Hazards Assumption for female
Observed Path and First 20 Simulated Paths
Standardized Score Process
1.5
1.0
0.5
0.0
-0.5
-1.0
0
10
20
30
time
Pr > MaxAbsVal: 0.1260
(1000 Simulations)

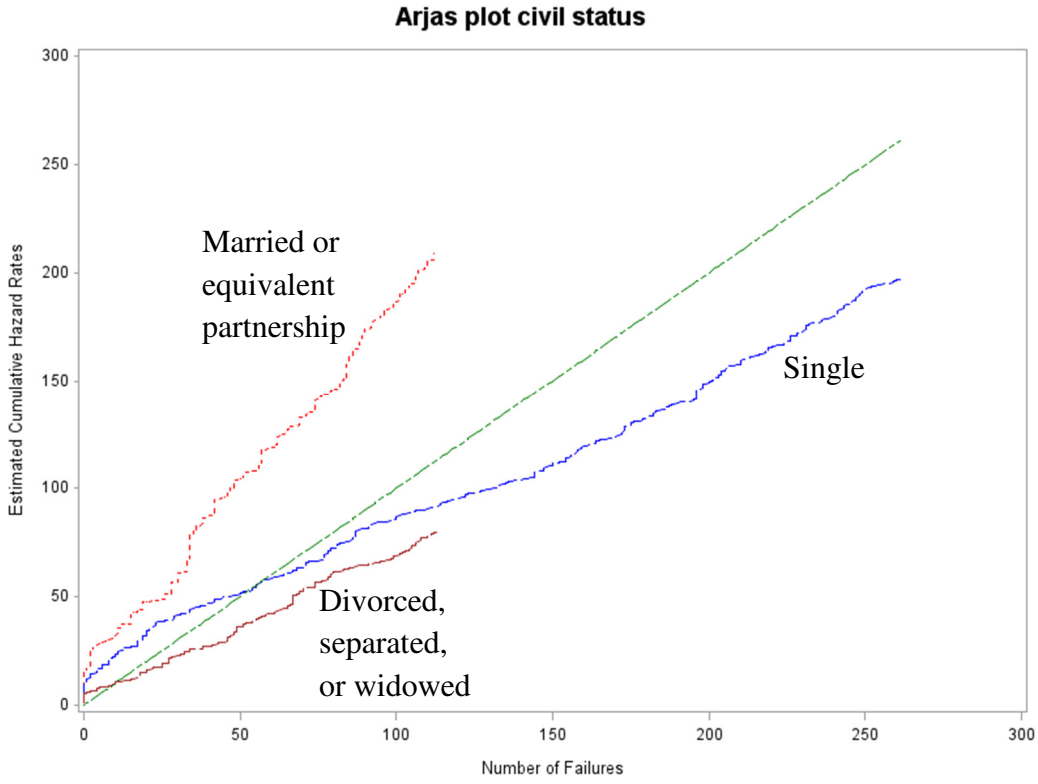

Checking Proportional Hazards Assumption for civilDivorced__separated__or_wid
Observed Path and First 20 Simulated Paths
Standardized Score Process
2
1
0
-1
0
10
20
30
time
Pr > MaxAbsVal: 0.4230
(1000 Simulations)


Checking Proportional Hazards Assumption for civilSingle
Observed Path and First 20 Simulated Paths
Standardized Score Process
1
0
-1
0
10
20
30
time
Pr > MaxAbsVal: 0.0860
(1000 Simulations)


Checking Proportional Hazards Assumption for age
Observed Path and First 20 Simulated Paths
Standardized Score Process
1.5
1.0
0.5
0.0
-0.5
-1.0
0
10
20
30
time
Pr > MaxAbsVal: <.0001
(1000 Simulations)

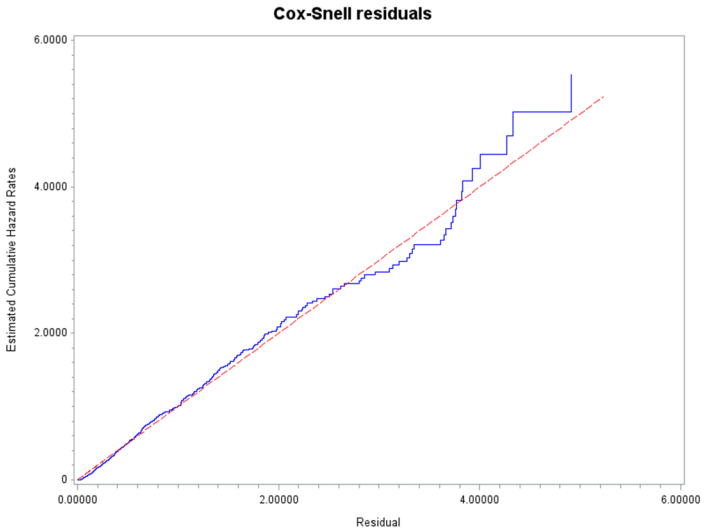

Arjas plot trt
Estimated Cumulative Hazard Rates
150
100
50
0
0
50
100
150
Number of Failures


Arjas plot female
Estimated Cumulative Hazard Rates
Number of Failures
0
50
100
150


Arjas plot civil status
Estimated Cumulative Hazard Rates
Number of Failures
Married or equivalent partnership
Single
Divorced, separated, or widowed
0
50
100
150
200
250
300

Model 1: trt, gender, civil status, age

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	3538.501	3087.586
AIC	3538.501	3099.586
SBC	3538.501	3124.703



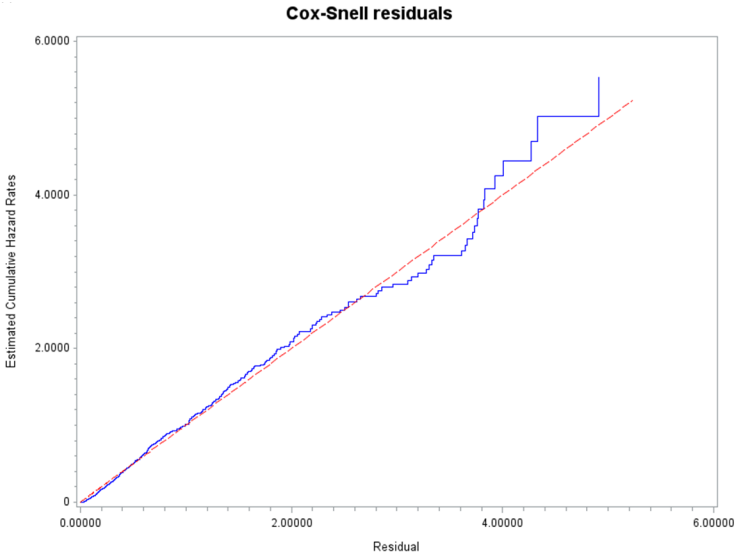
Type 3 Tests			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
trt	1	3.1863	0.0743
gender	2	0.2712	0.8732
age	1	85.7232	<.0001
civil	2	90.5281	<.0001

Analysis of Maximum Likelihood Estimates									
Parameter		**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Profile Likelihood Confidence Limits**	
trt		1	-0.22516	0.12614	3.1863	0.0743	0.798	0.619	1.016
gender	**Man**	1	0.04766	0.09179	0.2697	0.6036	1.049	0.876	1.255
gender	**Other**	1	0.06109	1.00454	0.0037	0.9515	1.063	0.060	4.753
age		1	-0.07945	0.00858	85.7232	<.0001	0.924	0.908	0.939
civil	**Divorced, separated, or widowed**	1	1.14781	0.14027	66.9611	<.0001	3.151	2.394	4.152
civil	**Single**	1	1.09570	0.12254	79.9457	<.0001	2.991	2.361	3.818

Model 2: trt, female*, civil status, age

* To be used for both options of *female*

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	3538.501	3087.586
AIC	3538.501	3097.586
SBC	3538.501	3118.517



Type 3 Tests			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
trt	1	3.1886	0.0742
female	1	0.2710	0.6027
age	1	85.7899	<.0001
civil	2	90.5983	<.0001

Analysis of Maximum Likelihood Estimates									
Parameter		**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Profile Likelihood Confidence Limits**	
trt		1	-0.22519	0.12611	3.1886	0.0742	0.798	0.619	1.016
female		1	-0.04772	0.09168	0.2710	0.6027	0.953	0.797	1.141
age		1	-0.07944	0.00858	85.7899	<.0001	0.924	0.908	0.939
civil	**Divorced, separated, or widowed**	1	1.14782	0.14027	66.9614	<.0001	3.151	2.394	4.152
civil	**Single**	1	1.09576	0.12245	80.0779	<.0001	2.991	2.361	3.818

Model 3: trt, female*, age, stratified by civil status

* To be used for both options of *female*.

Summary of the Number of Event and Censored Values

Stratum	civil	Total	Event	Censored	Percent Censored
1	Divorced, separated, or widowed	113	113	0	0.00
2	Married or equivalent partnership	380	112	268	70.53
3	Single	261	261	0	0.00
Total		754	486	268	35.54

Model Fit Statistics

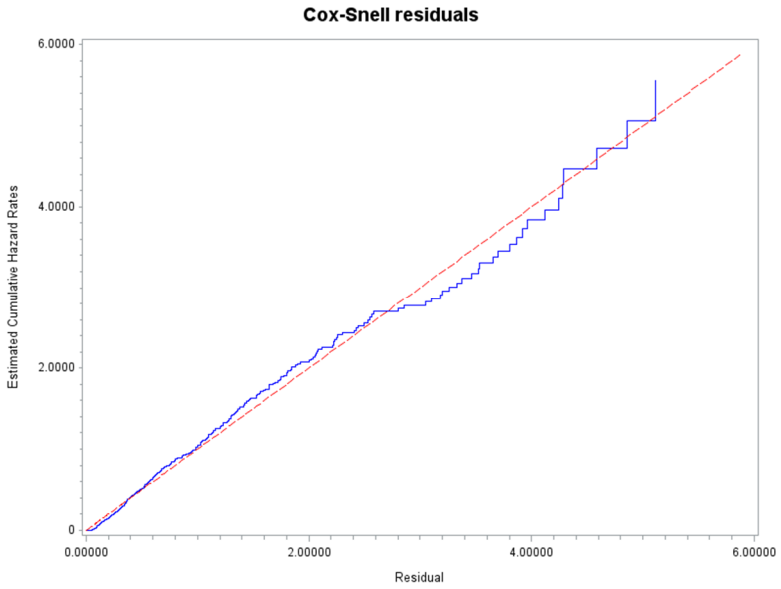
Criterion	Without Covariates	With Covariates
-2 LOG L	2999.934	2891.285
AIC	2999.934	2897.285
SBC	2999.934	2909.844

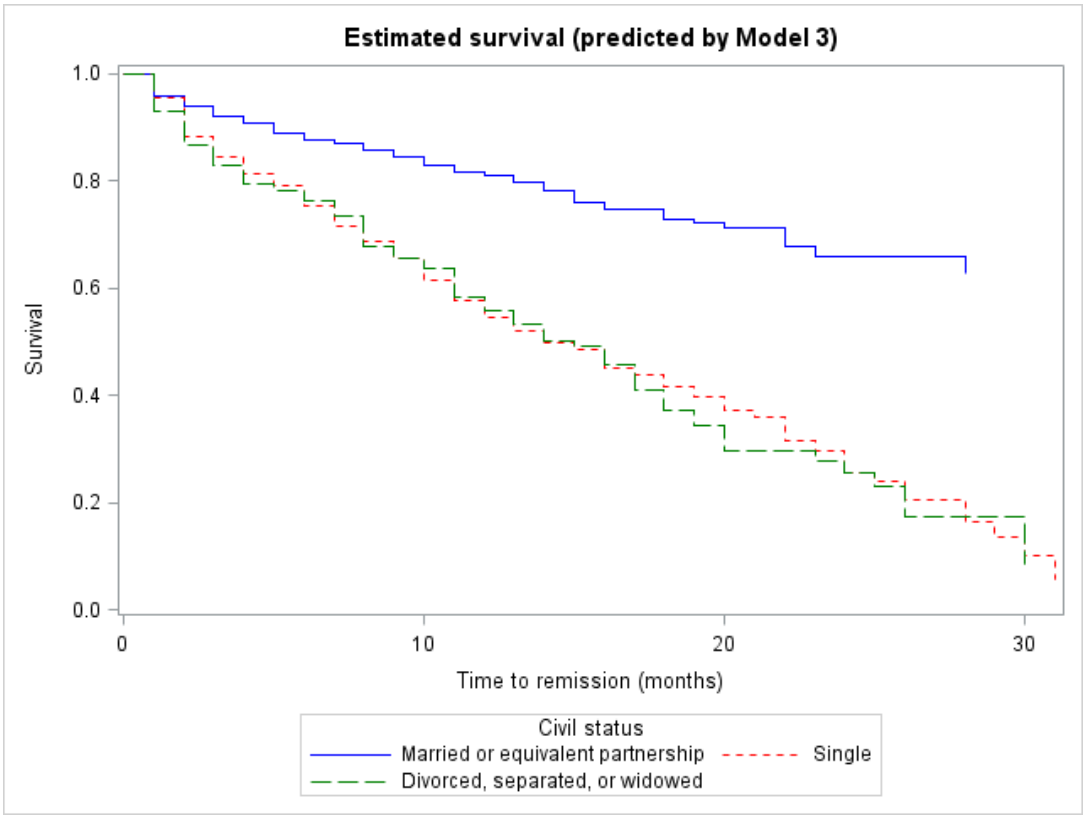
Model Fit Statistics

Criterion	With Covariates, Stratum 1	With Covariates, Stratum 2	With Covariates, Stratum 3
-2 LOG L	799.819	1444.486	578.732
AIC	805.819	1450.486	584.732
SBC	813.975	1461.180	592.914

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Profile Likelihood Confidence Limits	
trt	1	-0.25753	0.12847	4.0183	0.0450	0.773	0.596	0.988
female	1	-0.05742	0.09224	0.3875	0.5336	0.944	0.788	1.132
age	1	-0.07820	0.00866	81.5828	<.0001	0.925	0.909	0.940



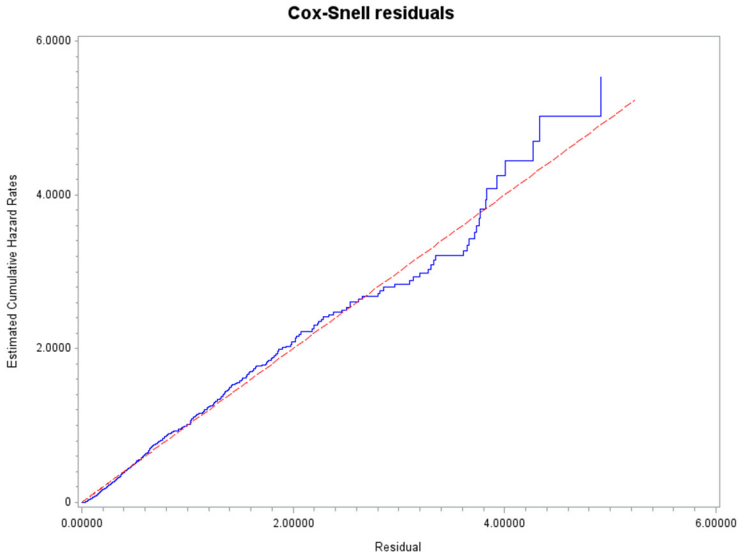


Predicted survival for reference value(s) of categorical variable(s), and mean value(s) of continuous variable(s). Time-dependent variable(s) excluded.

Model 4: trt, female*, civil status, age, lnt_age

* To be used for both options of *female*.

Model Fit Statistics		
Criterion	**Without Covariates**	**With Covariates**
-2 LOG L	3538.501	3081.284
AIC	3538.501	3093.284
SBC	3538.501	3118.401



Type 3 Tests			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
trt	1	3.1779	0.0746
female	1	0.2877	0.5917
age	1	8.1261	0.0044
lnt_age	1	6.4614	0.0110
civil	2	90.1736	<.0001

Analysis of Maximum Likelihood Estimates									
Parameter		**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Profile Likelihood Confidence Limits**	
trt		1	-0.22490	0.12616	3.1779	0.0746	0.799	0.619	1.016
female		1	-0.04918	0.09170	0.2877	0.5917	0.952	0.795	1.140
age		1	-0.04412	0.01548	8.1261	0.0044	0.957	0.927	0.985
lnt_age		1	-0.01999	0.00786	6.4614	0.0110	0.980	0.965	0.996
civil	**Divorced, separated, or widowed**	1	1.14004	0.13995	66.3580	<.0001	3.127	2.377	4.118
civil	**Single**	1	1.08980	0.12204	79.7468	<.0001	2.974	2.349	3.792

Model 5: trt, female*, age, lnt_age, stratified by civil status

* To be used for both options of *female*.

Summary of the Number of Event and Censored Values

Stratum	civil	Total	Event	Censored	Percent Censored
1	Divorced, separated, or widowed	113	113	0	0.00
2	Married or equivalent partnership	380	112	268	70.53
3	Single	261	261	0	0.00
Total		754	486	268	35.54

Model Fit Statistics

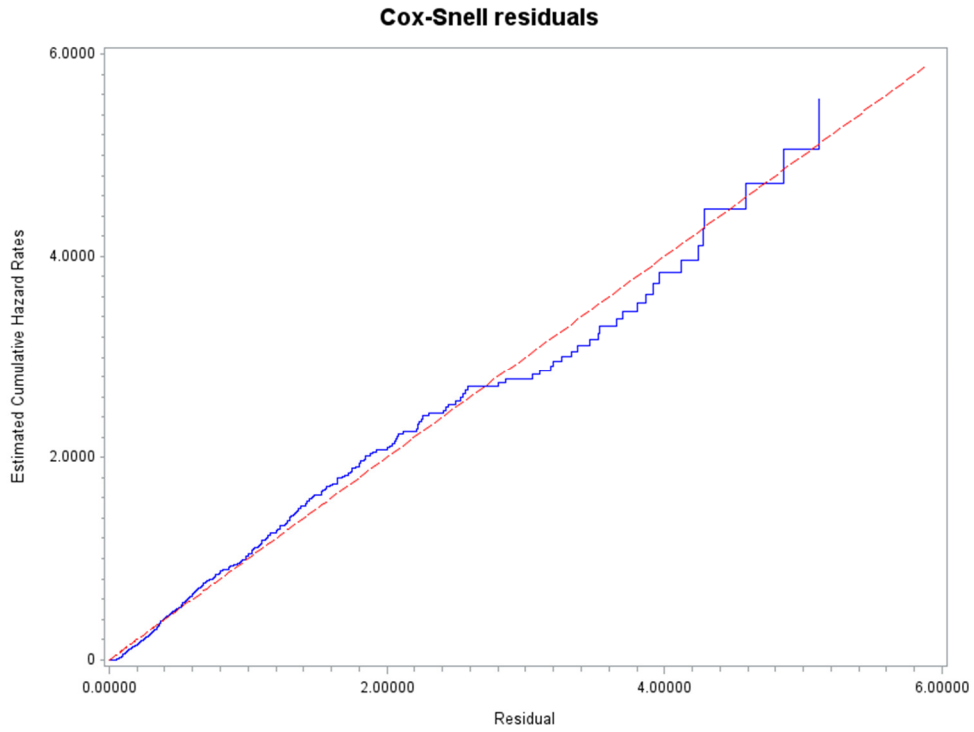
Criterion	Without Covariates	With Covariates
-2 LOG L	2999.934	2889.152
AIC	2999.934	2897.152
SBC	2999.934	2913.896

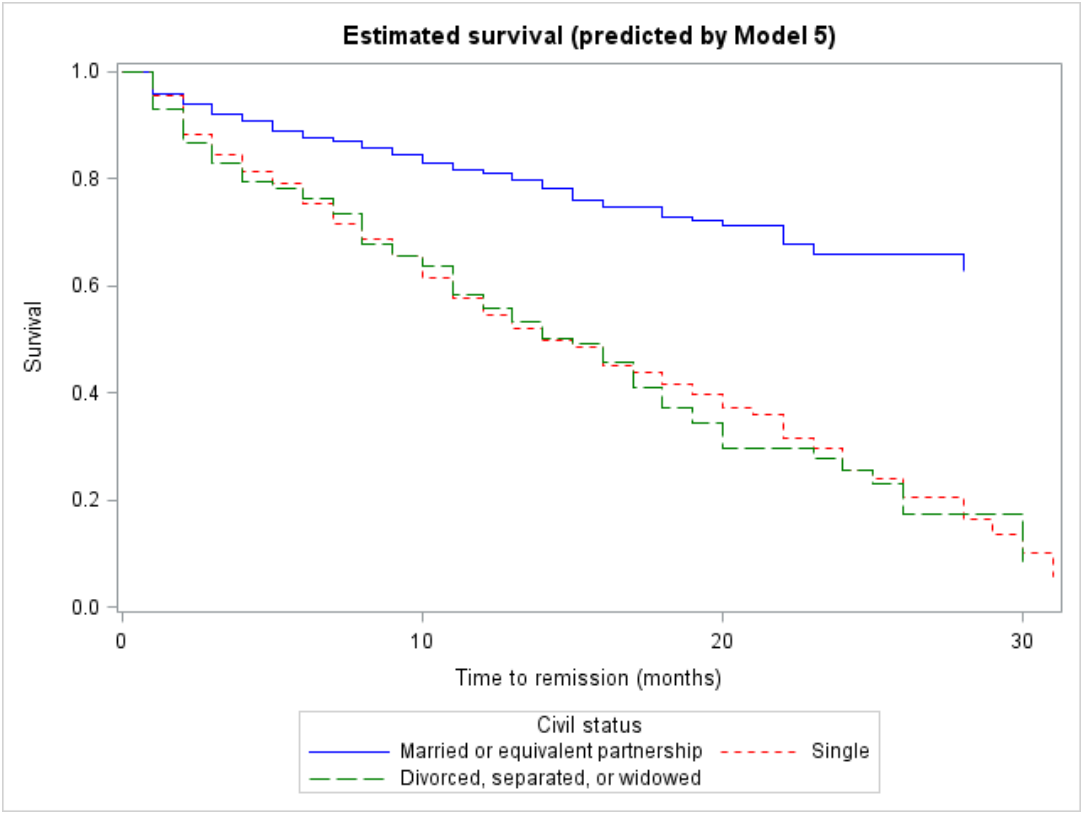
Model Fit Statistics

Criterion	With Covariates, Stratum 1	With Covariates, Stratum 2	With Covariates, Stratum 3
-2 LOG L	822.234	1459.118	593.481
AIC	830.234	1467.118	601.481
SBC	841.108	1481.376	612.390

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Profile Likelihood Confidence Limits	
trt	1	-0.25822	0.12857	4.0334	0.0446	0.772	0.596	0.987
female	1	-0.05662	0.09227	0.3765	0.5395	0.945	0.789	1.133
age	1	-0.05773	0.01595	13.0953	0.0003	0.944	0.914	0.973
lnt_age	1	-0.01236	0.00841	6.4614	0.0120	0.988	0.972	1.004





Predicted survival for reference value(s) of categorical variable(s), and mean value(s) of continuous variable(s). Time-dependent variable(s) excluded.

TABLE C.2
Upper Percentiles of a Chi-Square Distribution

Degrees of Freedom	*Upper Percentile* 0.1	0.05	0.01	0.005	0.001
1	2.70554	3.84146	6.63489	7.87940	10.82736
2	4.60518	5.99148	9.21035	10.59653	13.81500
3	6.25139	7.81472	11.34488	12.83807	16.26596
4	7.77943	9.48773	13.27670	14.86017	18.46623
5	9.23635	11.07048	15.08632	16.74965	20.51465
6	10.64464	12.59158	16.81187	18.54751	22.45748
7	12.01703	14.06713	18.47532	20.27774	24.32130
8	13.36156	15.50731	20.09016	21.95486	26.12393
9	14.68366	16.91896	21.66605	23.58927	27.87673
10	15.98717	18.30703	23.20929	25.18805	29.58789

END OF TASK 3