# FINAL EXAMINATION
# Analysis of survival data (7.5hp) 2024-01-11

**INFORMATION:**

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

**B**. Writing time: 5 hours.

**C**. The examination consists of 4 tasks, for a total of 80 points. Including any 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 Studium.

**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!**

(16) **Task 1**

The lifetime of refrigerators was studied by a producer that began archival record keeping in year 2010. The dataset contains complete information from January 1, 2010, on production dates and date of failure for those that failed. There is also information on refrigerators that were produced before January 1, 2010 and failed after January 1, 2010. There is no information on refrigerators produced and failed before January 1, 2010. The time is noted in years.

(2) **A** What is the appropriate time scale for this study (i.e. when do we start measuring time, and time until which event)?

(2) **B** Describe the type(s) of truncation that is/are represented in this study. Motivate your answer.

(8) **C** For four selected refrigerators described below, what type(s) of censoring is/are represented in this study? Motivate your answer.

i) A refrigerator produced in 2010, failed in 2018.

ii) A refrigerator produced in 2018, still in service in 2023.

iii) A refrigerator produced in 2009, failed in 2021.

iv) A refrigerator produced in 2001, still in service in 2023.

(4) **D** Confining your attention to the four refrigerators described above, write down the likelihood for this portion of the study.

(26) **Task 2**

A new treatment for chronic migraine was studied and 754 participants were randomized into a double-blind randomized trial of the effectiveness of that treatment. Remission times for the patients were recorded, and all subjects who did not have a migraine episode at the end of the study period were censored.

Variable specification:

*time:* Time to remission (time until a new migraine episode) in months
*trt:* 1 = new treatment, 0 = standard care

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

(2) **A** Which method would you choose to estimate the survival function in this case, the Kaplan-Meier or the Nelson-Aalen estimator? Motivate your choice.

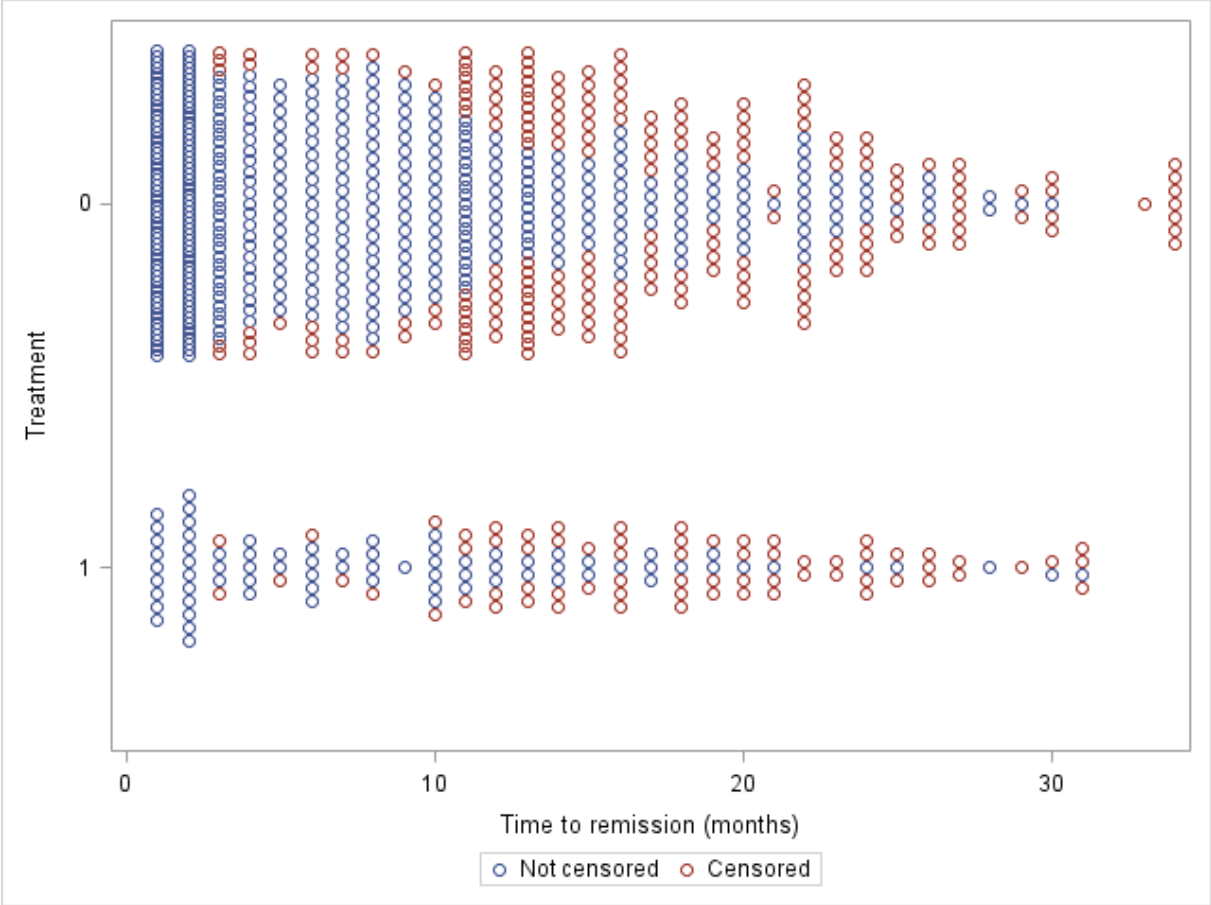
**B-D** Use the SAS output on the following pages, and answer the questions below.

(8) **B** Present, interpret, and compare for the two treatment 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) **C** Present and compare the probability of "surviving" at least 24 months for the two treatment groups.

(13) **D** Is there a significant difference in time to remission between the two treatment groups? Perform an appropriate hypothesis test to find out. Remember to follow the instructions on the front page.

## SAS OUTPUT Task 2




**Summary of the Number of Censored and Uncensored Values**

| Stratum | trt | Total | Failed | Censored | Percent Censored |
|---|---|---|---|---|---|
| **1** | **0** | 610 | 410 | 200 | 32.79 |
| **2** | **1** | 144 | 76 | 68 | 47.22 |
| **Total** | | 754 | 486 | 268 | 35.54 |

Stratum 1: trt = 0

| time | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
|---|---|---|---|---|---|---|
| **0.0000** | | 1.0000 | 0 | 0 | 0 | 610 |
| **1.0000** | | . | . | . | 1 | 609 |
| | | … | | | | |
| **1.0000** | | . | . | . | 57 | 553 |
| **1.0000** | | 0.9049 | 0.0951 | 0.0119 | 58 | 552 |
| | | … | | | | |
| **2.0000** | | . | . | . | 113 | 497 |
| **2.0000** | | 0.8131 | 0.1869 | 0.0158 | 114 | 496 |
| | | … | | | | |
| **3.0000** | | . | . | . | 146 | 464 |
| **3.0000** | | 0.7590 | 0.2410 | 0.0173 | 147 | 463 |
| | | … | | | | |
| **4.0000** | | . | . | . | 170 | 435 |
| **4.0000** | | 0.7192 | 0.2808 | 0.0182 | 171 | 434 |
| | | … | | | | |
| **10.0000** | | . | . | . | 285 | 300 |
| **10.0000** | | 0.5227 | 0.4773 | 0.0205 | 286 | 299 |
| | | … | | | | |
| **11.0000** | | . | . | . | 306 | 276 |
| **11.0000** | | 0.4856 | 0.5144 | 0.0206 | 307 | 275 |
| | | … | | | | |
| **15.0000** | | . | . | . | 344 | 178 |
| **15.0000** | | 0.4076 | 0.5924 | 0.0208 | 345 | 177 |
| | | … | | | | |
| **16.0000** | | . | . | . | 356 | 152 |
| **16.0000** | | 0.3776 | 0.6224 | 0.0210 | 357 | 151 |
| **16.0000** | * | . | . | . | 357 | 150 |
| | | … | | | | |
| **16.0000** | * | . | . | . | 357 | 139 |

| time | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
|---|---|---|---|---|---|---|
| | | … | | | | |
| **22.0000** | | . | . | . | 391 | 70 |
| **22.0000** | | 0.2627 | 0.7373 | 0.0221 | 392 | 69 |
| | | … | | | | |
| **23.0000** | | . | . | . | 396 | 56 |
| **23.0000** | | 0.2408 | 0.7592 | 0.0223 | 397 | 55 |
| | | … | | | | |
| **34.0000** | * | . | . | . | 410 | 1 |
| **34.0000** | * | 0.1449 | 0.8551 | . | 410 | 0 |

**Note: The marked survival times are censored observations.**

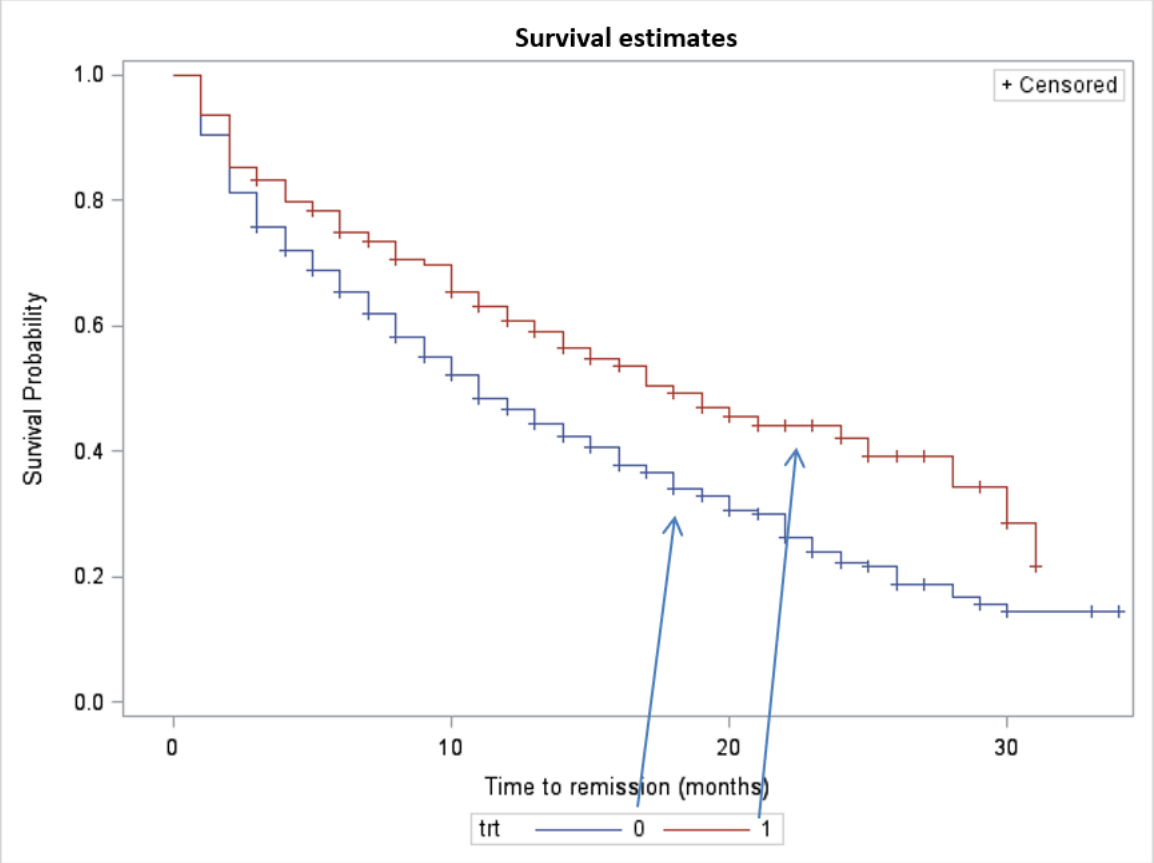
Stratum 2: trt = 1

| time | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
|---|---|---|---|---|---|---|
| **0.0000** | | 1.0000 | 0 | 0 | 0 | 144 |
| **1.0000** | | . | . | . | 1 | 143 |
| | | … | | | | |
| **1.0000** | | . | . | . | 8 | 136 |
| **1.0000** | | 0.9375 | 0.0625 | 0.0202 | 9 | 135 |
| | | … | | | | |
| **5.0000** | | . | . | . | 30 | 112 |
| **5.0000** | | 0.7839 | 0.2161 | 0.0344 | 31 | 111 |
| **5.0000** | * | . | . | . | 31 | 110 |
| **6.0000** | | . | . | . | 32 | 109 |
| | | … | | | | |

| time | | Survival | Failure | Survival Standard Error | Number Failed | Number Left |
|---|---|---|---|---|---|---|
| **6.0000** | | . | . | . | 35 | 106 |
| **6.0000** | | 0.7483 | 0.2517 | 0.0363 | 36 | 105 |
| **6.0000** | * | . | . | . | 36 | 104 |
| **7.0000** | | . | . | . | 37 | 103 |
| | | … | | | | |
| **15.0000** | | . | . | . | 61 | 60 |
| **15.0000** | | 0.5465 | 0.4535 | 0.0433 | 62 | 59 |
| **15.0000** | * | . | . | . | 62 | 58 |
| **15.0000** | * | . | . | . | 62 | 57 |
| **16.0000** | | 0.5369 | 0.4631 | 0.0436 | 63 | 56 |
| **16.0000** | * | . | . | . | 63 | 55 |
| | | … | | | | |
| **16.0000** | * | . | . | . | 63 | 50 |
| **17.0000** | | . | . | . | 64 | 49 |
| **17.0000** | | . | . | . | 65 | 48 |
| **17.0000** | | 0.5047 | 0.4953 | 0.0447 | 66 | 47 |
| **18.0000** | | 0.4940 | 0.5060 | 0.0451 | 67 | 46 |
| | | … | | | | |
| **29.0000** | * | . | . | . | 74 | 6 |
| **30.0000** | | 0.2869 | 0.7131 | 0.0756 | 75 | 5 |
| **30.0000** | * | . | . | . | 75 | 4 |
| **31.0000** | | 0.2152 | 0.7848 | 0.0841 | 76 | 3 |
| **31.0000** | * | . | . | . | 76 | 2 |
| **31.0000** | * | . | . | . | 76 | 1 |
| **31.0000** | * | 0.2152 | 0.7848 | . | 76 | 0 |

**Note: The marked survival times are censored observations.**

| Test of Equality over Strata | | | |
|---|---|---|---|
| **Test** | **Chi-Square** | **DF** | **Pr > Chi-Square** |
| **Log-Rank** | 12.4250 | 1 | 0.0004 |
| **Wilcoxon** | 9.6701 | 1 | 0.0019 |
| **-2Log(LR)** | 13.6907 | 1 | 0.0002 |



(38) **Task 3**

In the study of the effectiveness of a new treatment for migraine described in Task 2, three additional variables are investigated: gender, age, and employment status.

Variable specification:

*time:* Time to remission (time until a new migraine episode) in months
*trt:* 1 = new treatment, 0 = standard care
*gender*: 1 = woman, 2 = man
*age*: years of age
*employment status*: 1 = employed, 2 = unemployed

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

(2) **A** Fitting a Cox regression model to the data above, which method of handling ties would you choose and why?

(6) **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 Cox regression analysis? Motivate your answer.

(12) **C** Are the assumptions of Cox regression fulfilled? If not, suggest a possible way to deal with the violations.

Answer the questions below even if you conclude the assumptions to be violated.

(10) **D** Explain/interpret the relationships between all the covariates in the model and survival time.

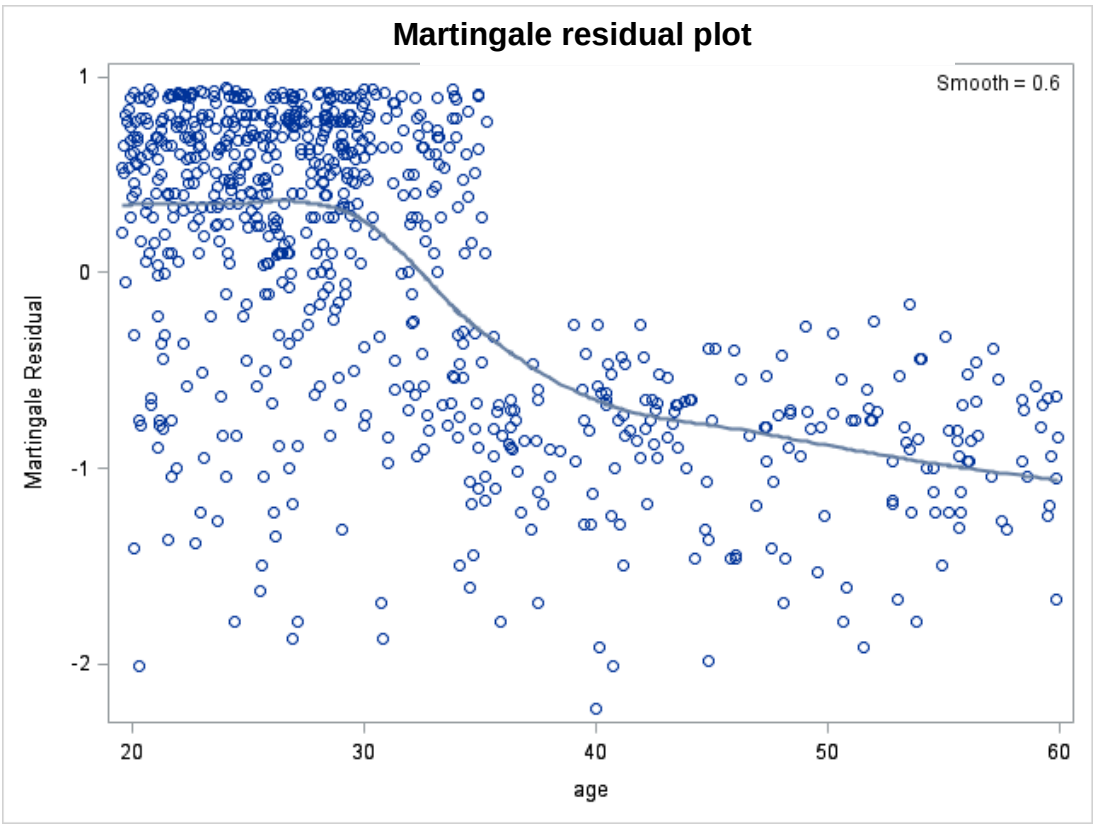
(4) **E** Does the estimated model fit the data well? Include an evaluation of the Cox-Snell residuals and generalized $R^2$ in your answer.

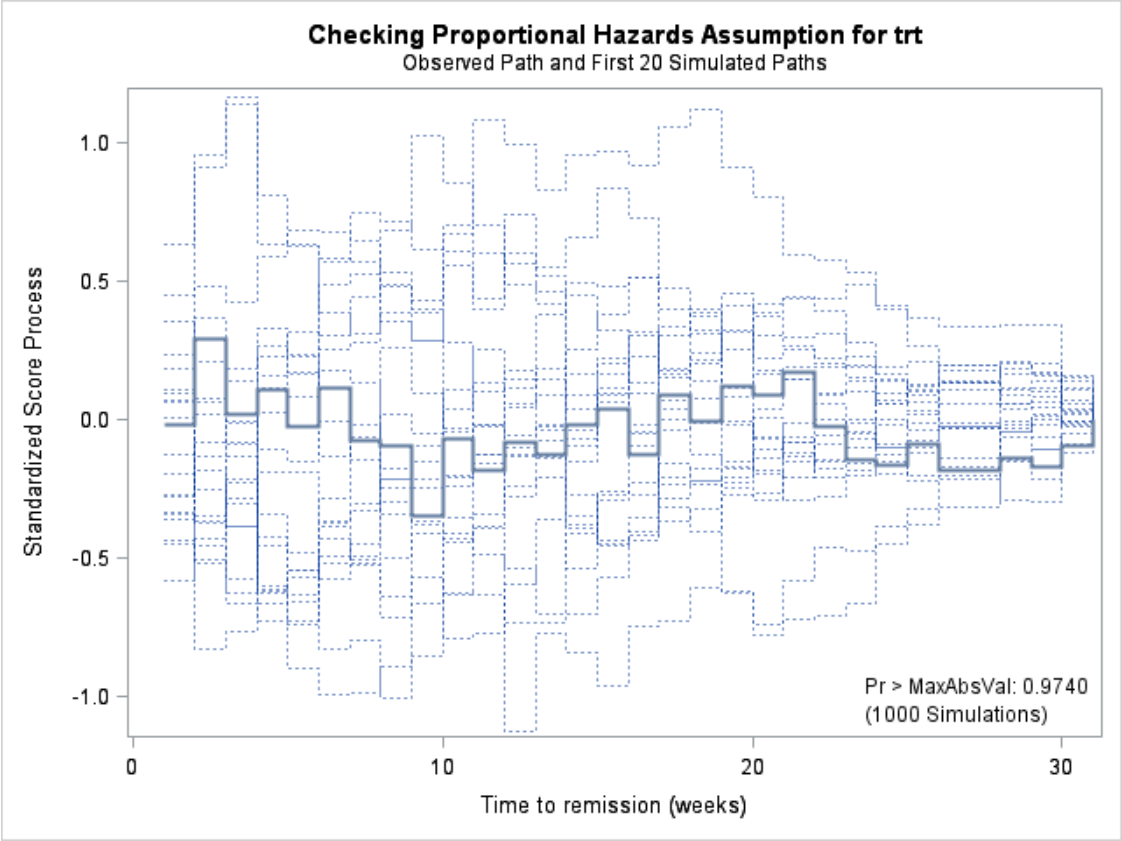
(4) **F** You are at your first job as a statistician, and you show these results to your employer to discuss the findings. You have some suggestions of how to improve the model in order to fulfill the assumption of proportional hazards, and to perhaps find a better functional form of one of the covariates based on your evaluation of residuals. Your employer (who is not a statistician) likes the first results, and asks you to keep them as they are. What do you do (what would be the ethically correct thing to do)?

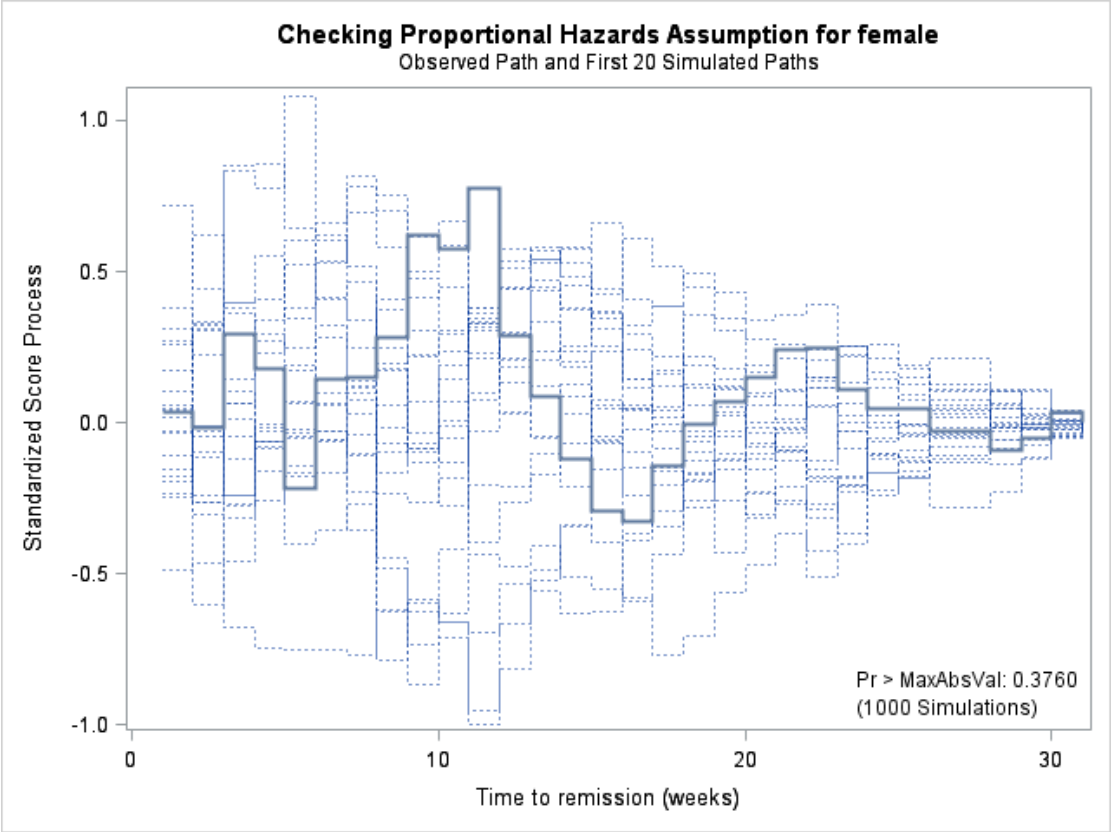
## SAS OUTPUT Task 3

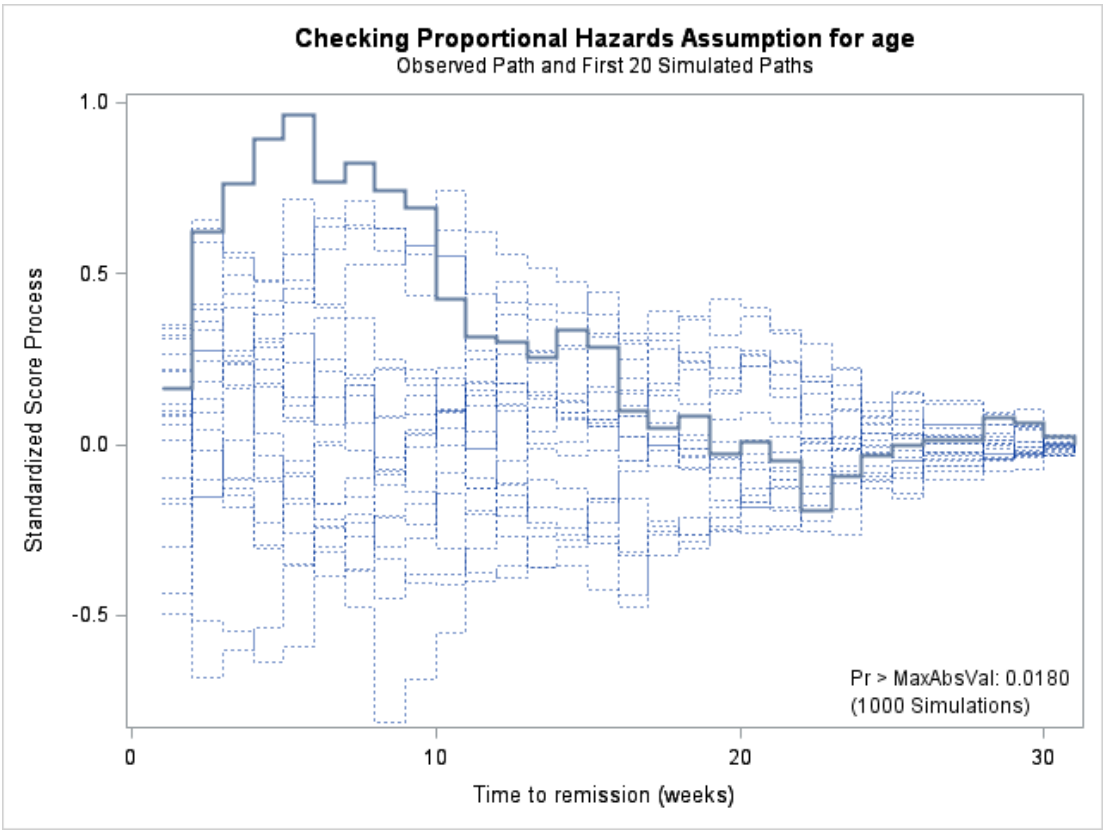
| Analysis of Maximum Likelihood Estimates | | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **DF** | **Parameter Estimate** | **Standard Error** | **Chi-Square** | **Pr > ChiSq** | **Hazard Ratio** |
| **trt** | 1 | -0.37587 | 0.25145 | 2.2344 | 0.1350 | 0.687 |
| **lnt_trt** | 1 | -0.03448 | 0.12443 | 0.0768 | 0.7817 | 0.966 |
| **female** | 1 | -0.25424 | 0.17818 | 2.0359 | 0.1536 | 0.776 |
| **lnt_female** | 1 | 0.05379 | 0.09119 | 0.3480 | 0.5553 | 1.055 |
| **age** | 1 | -0.08684 | 0.01474 | 34.7114 | <.0001 | 0.917 |
| **lnt_age** | 1 | -0.01146 | 0.00737 | 2.4225 | 0.0396 | 0.989 |
| **employed** | 1 | 0.18976 | 0.18339 | 1.0706 | 0.3008 | 1.209 |
| **lnt_employed** | 1 | -0.05698 | 0.09344 | 0.3719 | 0.5420 | 0.945 |

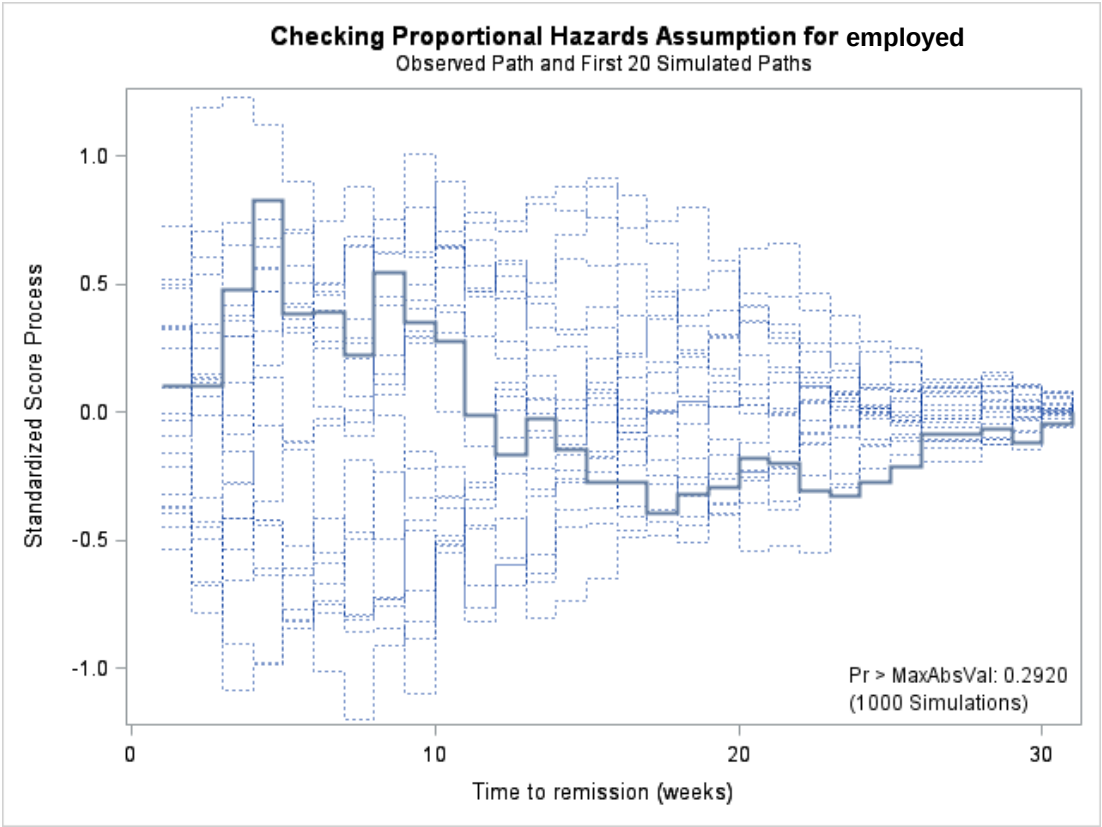
NOTE: "lnt_x" denotes a time-dependent covariate, calculated as x*log(time)

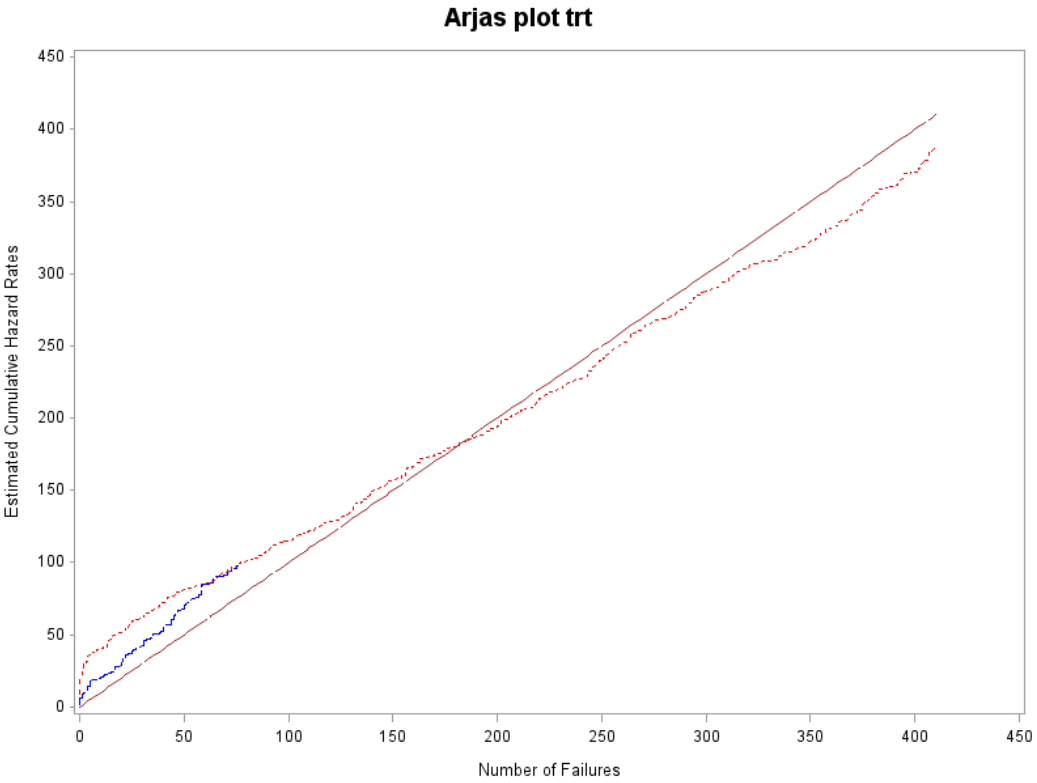


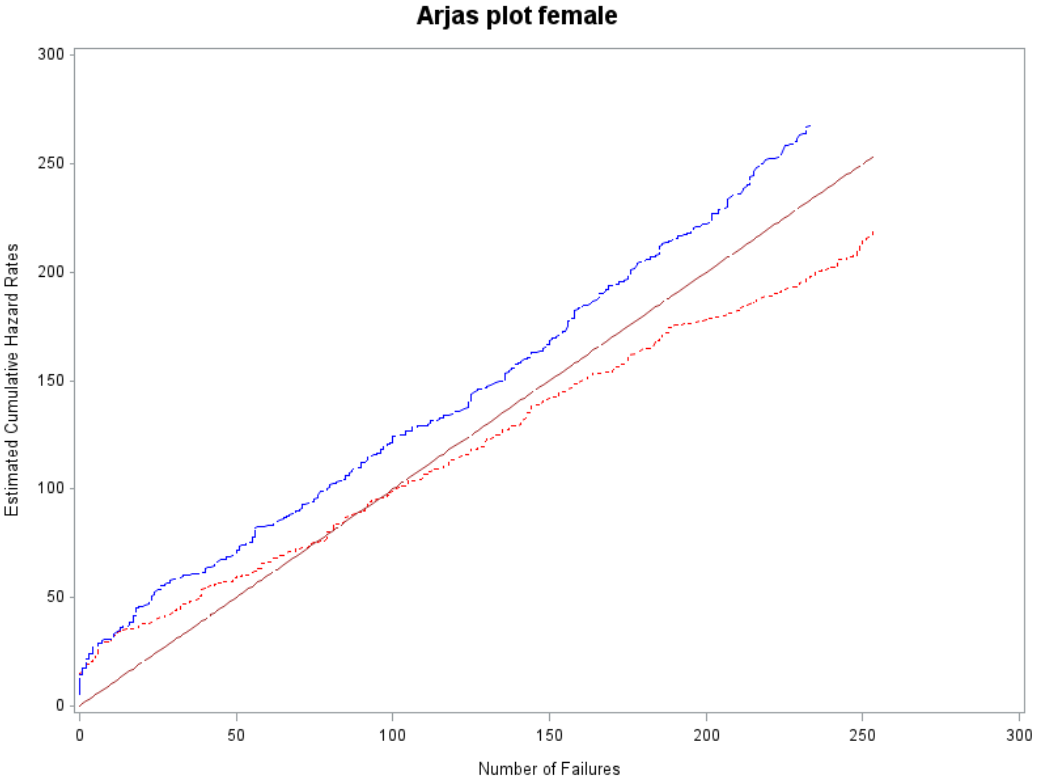

Checking Proportional Hazards Assumption for trt
Observed Path and First 20 Simulated Paths
Standardized Score Process
1.0
0.5
0.0
-0.5
-1.0
0
10
20
30
Time to remission (weeks)
Pr > MaxAbsVal: 0.9740
(1000 Simulations)

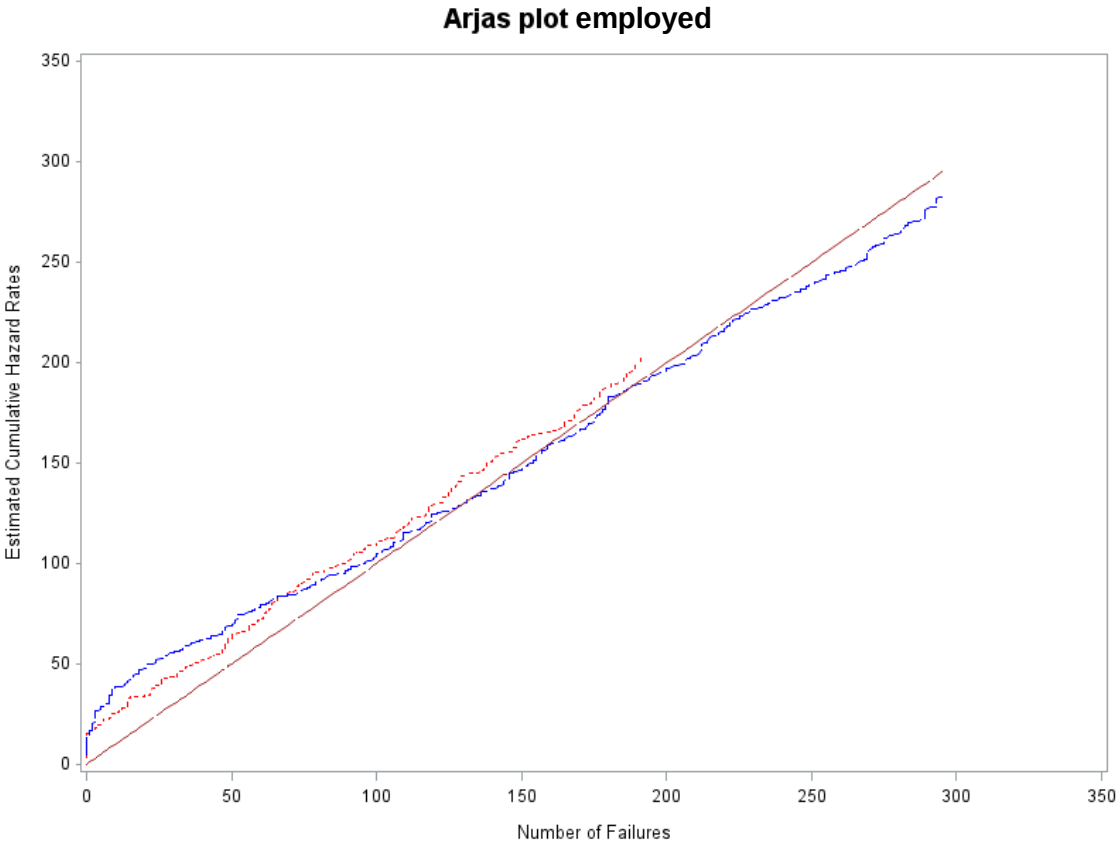

Checking Proportional Hazards Assumption for female
Observed Path and First 20 Simulated Paths
Standardized Score Process
1.0
0.5
0.0
-0.5
-1.0
0
10
20
30
Time to remission (weeks)
Pr > MaxAbsVal: 0.3760
(1000 Simulations)

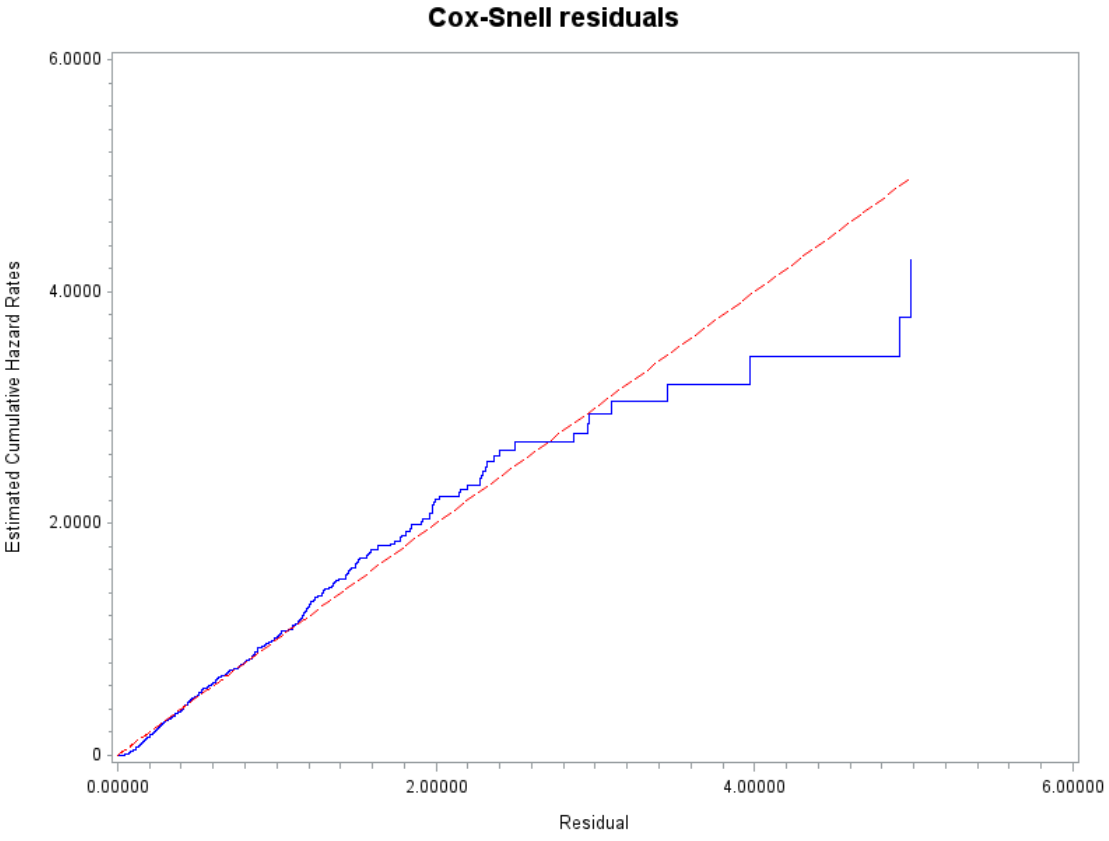

Checking Proportional Hazards Assumption for age
Observed Path and First 20 Simulated Paths
Standardized Score Process
1.0
0.5
0.0
-0.5
Pr > MaxAbsVal: 0.0180
(1000 Simulations)
0
10
20
30
Time to remission (weeks)


Checking Proportional Hazards Assumption for employed
Observed Path and First 20 Simulated Paths
Standardized Score Process
1.0
0.5
0.0
-0.5
-1.0
Pr > MaxAbsVal: 0.2920
(1000 Simulations)
0
10
20
30
Time to remission (weeks)


Arjas plot trt
Estimated Cumulative Hazard Rates
0
50
100
150
200
250
300
350
400
450
Number of Failures


Arjas plot female
Estimated Cumulative Hazard Rates
0
50
100
150
200
250
300
Number of Failures


Arjas plot employed
Estimated Cumulative Hazard Rates
0
50
100
150
200
250
300
350
Number of Failures


Cox-Snell residuals
Estimated Cumulative Hazard Rates
0
2.0000
4.0000
6.0000
0.00000
2.00000
4.00000
6.00000
Residual

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

| Model Fit Statistics | | |
|---|---|---|
| **Criterion** | **Without Covariates** | **With Covariates** |
| **-2 LOG L** | 3538.501 | 3189.377 |
| **AIC** | 3538.501 | 3197.377 |
| **SBC** | 3538.501 | 3214.122 |

| Analysis of Maximum Likelihood Estimates | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **DF** | **Parameter Estimate** | **Standard Error** | **Chi-Square** | **Pr > ChiSq** | **Hazard Ratio** | **95% Hazard Ratio Confidence Limits** | |
| **trt** | 1 | -0.32049 | 0.12563 | 6.5074 | 0.0107 | 0.726 | 0.563 | 0.922 |
| **female** | 1 | -0.29930 | 0.09179 | 10.6320 | 0.0011 | 0.741 | 0.619 | 0.887 |
| **age** | 1 | -0.10799 | 0.00743 | 211.5248 | <.0001 | 0.898 | 0.884 | 0.910 |
| **employed** | 1 | 0.11309 | 0.09325 | 1.4709 | 0.2252 | 1.120 | 0.934 | 1.346 |