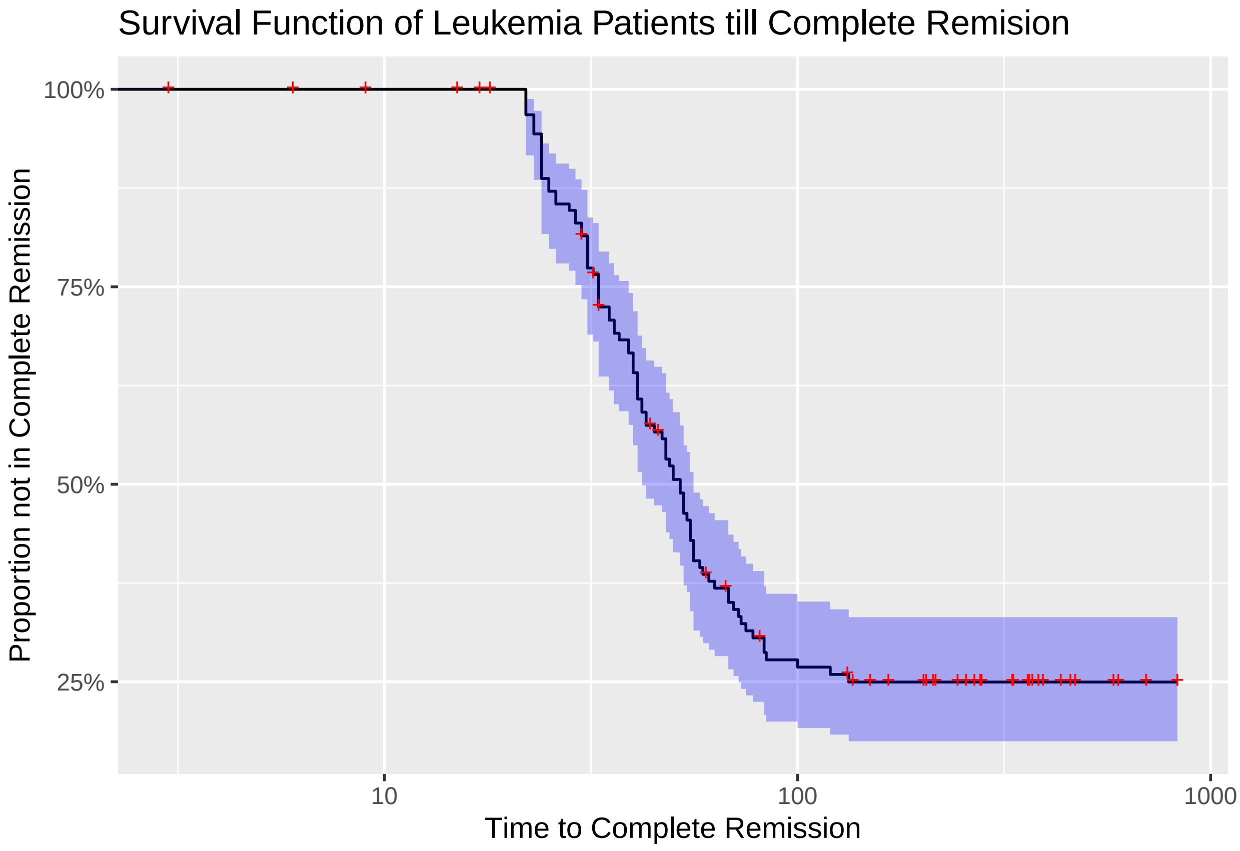
Statistical Analysis of Reliability and Survival Data Final Report

Kendall Brown r0773111

KU Leuven: 2019-2020

Question 1.1

Shown here is a plot of the survival function of patients diagnosed with leukemia. We are tracking their time till complete remission and have imposed the 95% "log-log" confidence interval around the expected probabilities. For added interpretability, the X-axis of the plot is scalled logarithmically.



From this function we can calculate that after about 75 days, 70% of patients are expected to be in complete remission remission.

We may also calculate the probability a person takes longer than 3 months (90 days) to enter complete remission. We calculate the mean probability for this to be true at 27.78% with a 95% confidence band of 19.96% and 36.12%.

Question 1.2

We now wish to determine the effect of treatment type on a patients time to enter complete remission. We are examining two treatment types, Daunorubicin and Idarubicin, and we wish to determine if there is a significant difference in the time till complete remission. Here we plot the survival function respective of both treatment types. Visual analysis shows a stark difference in performance in favor of Idarubicin.

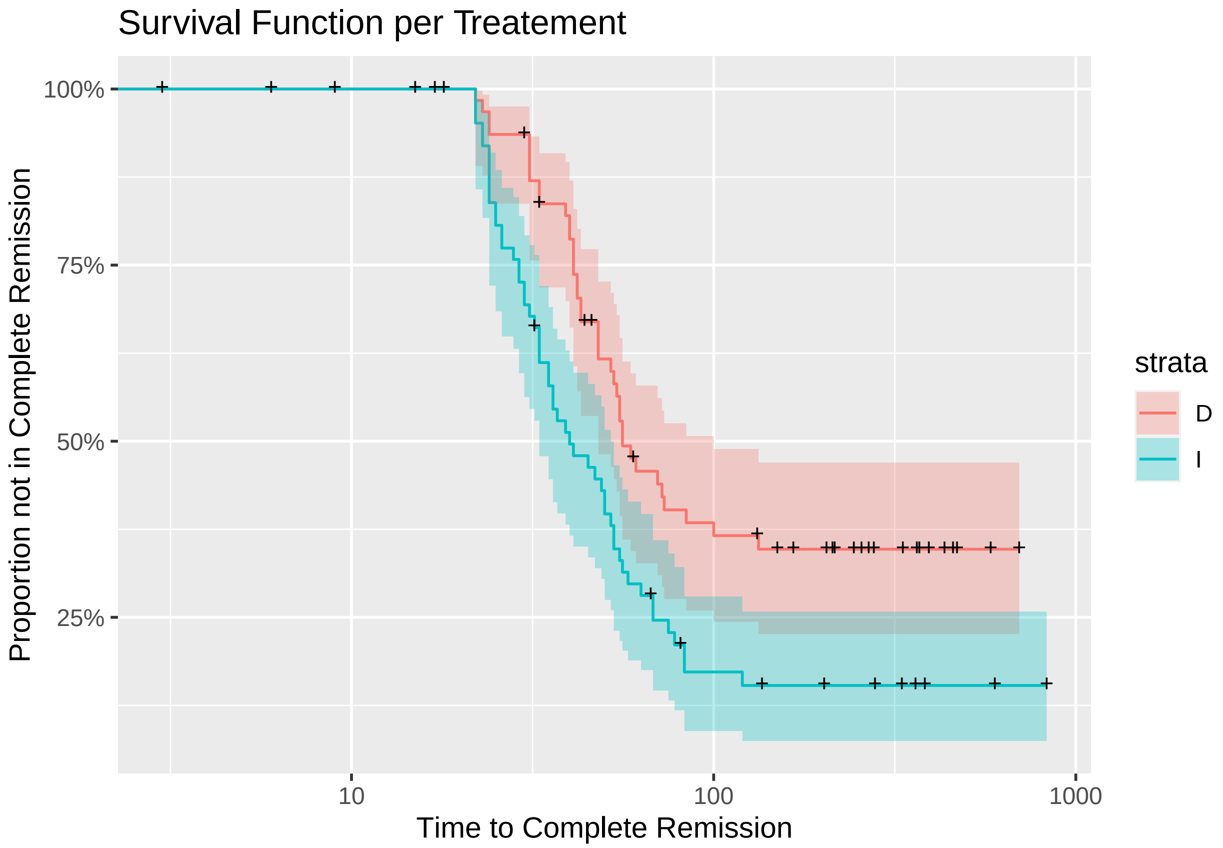
Numerically we can examine the effect further. We do this by examing the median time to complete remission for both drugs. Upon doing this we find that 50% of patients treated with Idarubicin are expected to enter complete remission within 40 days. This is compared to expectation of 56 days for patients treated with Daunorubicin.

Utilizingthe formal Gehan-Wilcoxon wilcoxon test, we observes a chi-squared value of 10.4 on a single degree of freedom with a corresponding p-value of .001.

We consider the following hypothesises:

H0: There does not exist a significant difference between the treatments of Daunorubicin and Idarubicin.
Ha: There does exist a significant difference between the treatments of Daunorubicin and Idarubicin.

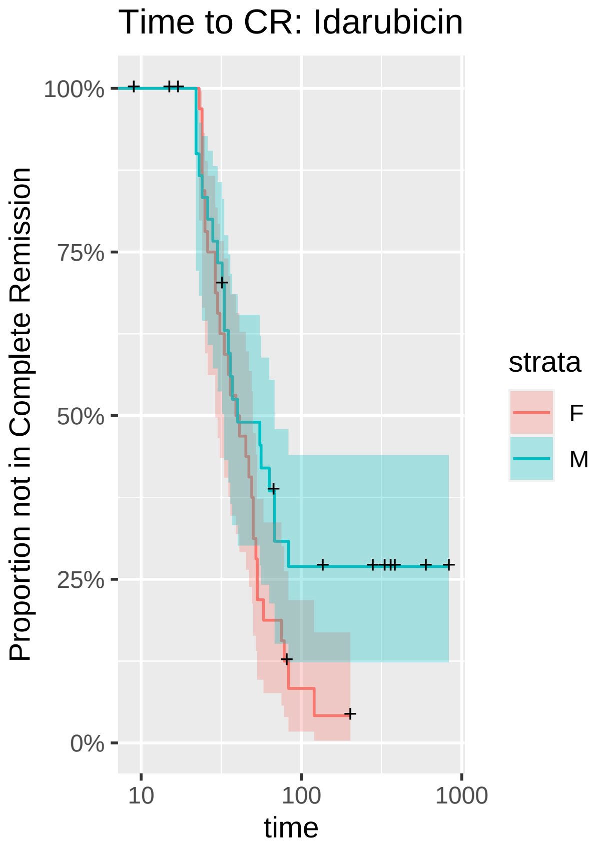
At the alpha level of .01, we reject the null hypothesis and claim that there does exist a significant difference between the treatments of Daunorubicin and Idarubicin.

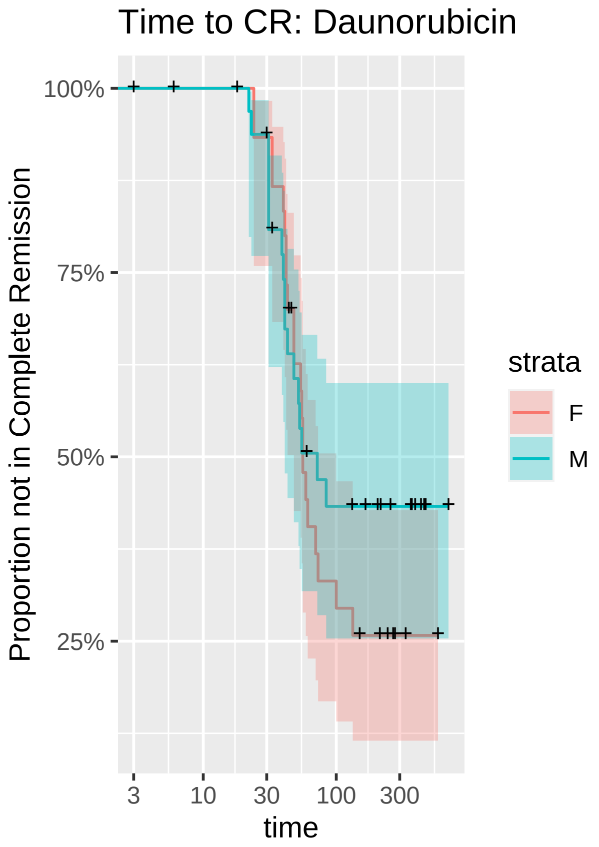


Now we wish to determine which drug performs best within a two month time limit. Using similar methods from the previous analysis we can determine that a patient undergoing treatment with Idarubicin will have a probability to enter complete remission within two months of approximately 70.24% with a 95% confidence bound of 58.57% and 71.12%. We can also claim that a patient undergoing treatment with Daunorubicin will have a probability of 52% to enter complete remission within two months. This prediction carries a 95% confidence boundry of 40.35% and 65.62%.

Question 1.3

Now we wish to determine the effect of treatment respective to the sex of the patient. Firstly, we must determine the survival function for each sex seperately. Plots of both sex's response to the treaments can be seen here. Initial Visual analysis does indicate patient sex influenceing the performance of the drug.





Further visual examination of each sex group and treatment type does not show signs of devation from the expectation gathered from the original plot detailing treatment type vs remission time. We can numerically examine this relation further. We use the respective survival functions for each sex to compute the median time to complete remission. Doing so shows that 50% of men and women undergoing treatment with Daunorubicin are expected to enter complete remission before 72 and 56 days respecitively. Whereas, 50% of men and women undergoing treatment with Idarubicin are expected to enter complete remission before 40 days.When we examine the confidence intervals of each groups median probabilities we arrive at a similar conclusion as the bounds for each treatment are quite large and generally encapsulate each other.

We will now use formal tests to determine if there is a difference between males and females in regard to treatment.

To begin we will consider the male/female responce to the drug Idarubicin.

We shall consider the following null and alternative hypothesis.

H0: There is not a significant difference between men and women taking Idarubicin. Ha: There is a significant difference between men and women taking Idarubicin.

Utilizing the Gehan-Wilcoxon test, we calculate a chisq test statistic of 1.1 on 1 degree of freedom. This test statistic carries a p-value of .3.

Given the result of the formal test we fail to reject the null hypothesis and claim that there is not a significant difference between men and women taking Idarubicin.

Now we will be considering the drug Daunorubicin.

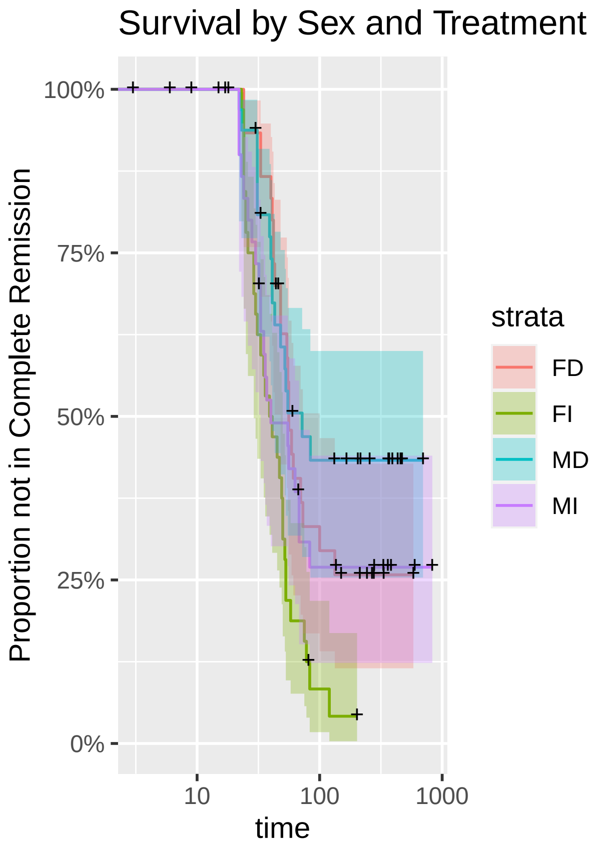
We shall consider the following null and alternative hypothesis.

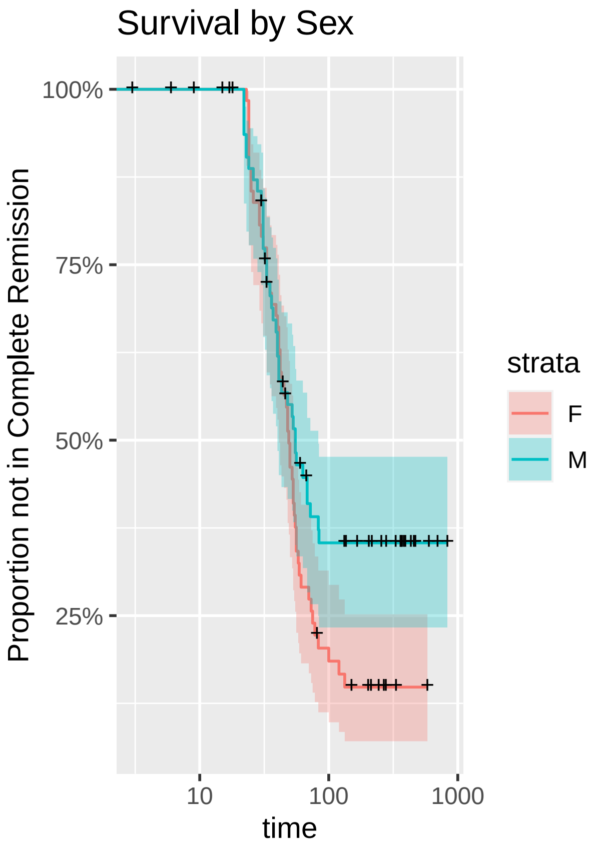
H0: There is not a significant difference between men and women taking Daunorubicin. Ha: There is a significant difference between men and women taking Daunorubicin.

From theformal Gehan-Wilcoxon test, we calculate a chisq test statistic of 0 on 1 degree of freedom. The corresponding p-value here is .9.

Given this result we fail to reject the null hypothesis and claim that sex does not influence reaction to Daunorubicin.

To further exemplify this point, comparrison plots of the survival function per sex and sex+treatment type comparing each distribution can be found here.





Based on the results from the seperate models it is difficult to claim sex to be a confounding variable. To formally test if sex has a confounding effect on treatment, we shall construct a cox proportional hazard model which considers the interaction effect of sex and treatment.

From this model we determine that (given sex and the sex:treatment interaction) treatment, carrying a z score of 2.661 with a corresponding p-value of .00779, is a statistically significant variable at the 1% level. The variable sex, carrying a z score of -.797 with a corresponding p-value of .42522, is statistically insignificant. The Interaction effect, with a z score of -.604 and p-value of .54602, is statistically significant as well. When undergoing three different significance tests (Likelihood Ratio, Wald, Score), the model proved to be significant in each test. The p-values for these tests are as follows LRT:0.005, Wald:0.004, and Score:0.003.

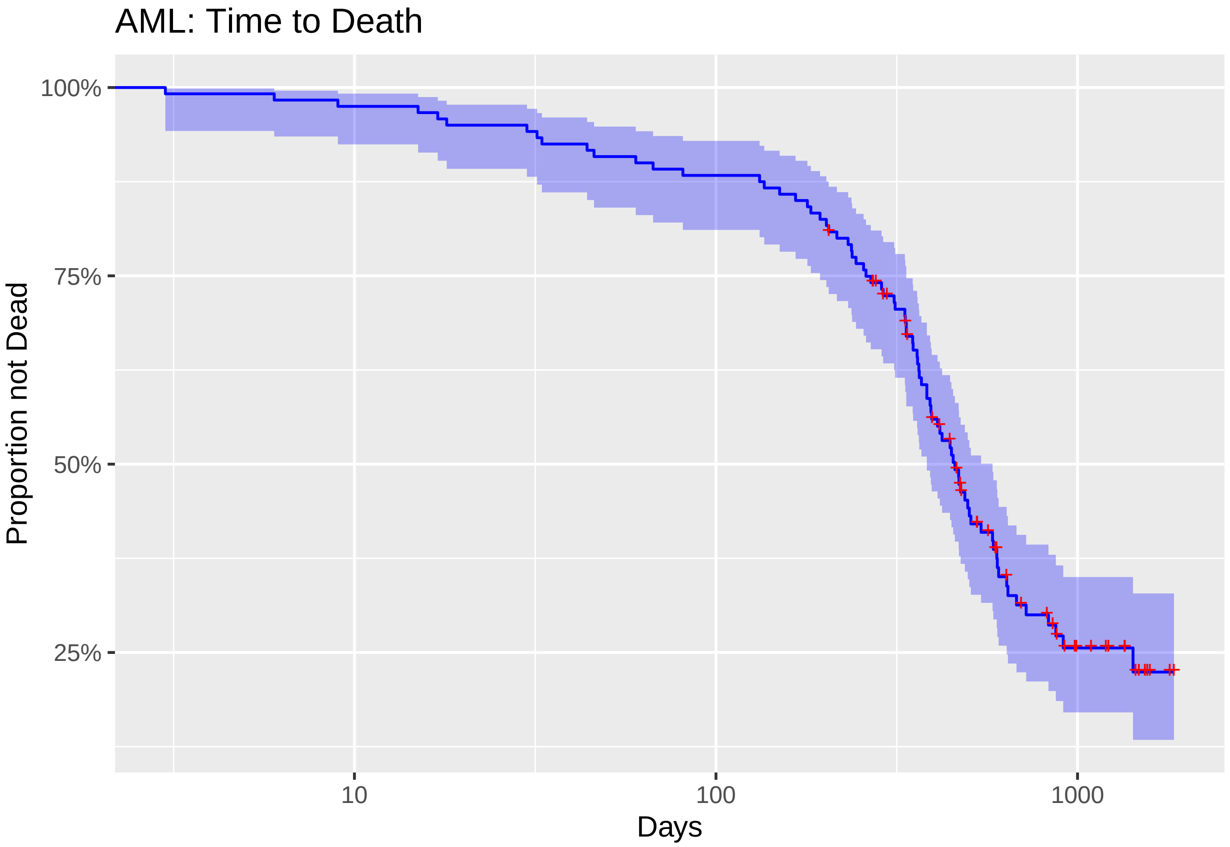
We evaluate the following hypotheses.

H0:Sex is not confounding on treatment. Ha:Sex is confounding on treatment.

Based on the formal results, we fail to reject the null hypothesis and claim that sex does not carry a confounding effect on treatment.

Question 2.1

Now we wish to determine a patients survival time. We will be focusing only on patients diagnosed with acute myelogenous leukemia (AML). To begin, we will calculate and plot the survival function detailing the time until death. From this survival function we can calculate the median survival time to be 458 days, with 25% of patients passing before 260 days and 75% of patients passing before 1424 days.



Question 2.2

Now we wish to use a cox proprtional hazard model to determine the effect of the patients age and their treatment (Daunorubicin and Idarubicin).

As we are constructing this model we observe to parameter Age to achieve a z-score of 2.109 with a corresponding p-value of 0.035. The Treatment effect carries a z-score of -2.002 with a corresponding p-value of 0.0453. The three global tests achieve the following p-values as follows LRT:0.01, Wald:0.01, and Score:0.009.

From these results we claim the model to be significant. Additionally we can claim that a patients age and their treatment are statistically significant factors.

The Age parameter carries a coefficient of .018499 with a standard error of .008772. From this we claim that per unitary increase in age, the probability of death increases by 1.83% with a 95% confidence bound of 0.13% and 3.51%.

The Treatment parameter, when considering Idarubicin as the reference level, carries a regression coefficient of -.461316 with a standard error of .230394. From this we claim that should a patient opt for Daunorubicin, we can expect their hazard ratio to be 58.62% higher than those that opt for Idarubicin. This esimate carries a 95% confidence bound of .9795% and 149.1281%

Question 2.3

Now we wish to determine the effect of going into complete remssion or undergoing a bone marrow transfusion has on the hazard function.

Fitting these parameters to the model assigns Age a z-score of 2.711 with a corresponding p-value of .0067. The treatment factor is assigned a z-score of -.954 with a corresponsing p-value of .3403. Taking "Yes" as the reference group, the complete remission tracker achieves a z-score of -6.398 with a corresponing p-value of approximately 0. Taking "Yes" as the reference group, the status of a bone marrow transfussion achieves a z-score of -.612 with a p-value of.5408. The model proves significant under the LRT, Wald test, and Score test, achieving near zero p-values in each of these tests with corresponding test statistics of 50.7, 53.32, and 64.27 each on 4 degreesof freedom.

From these results we conclude that Age and status of complete remission are statistcally significant. Given these variables are in the model, the treatment type and status of bone marrow transfusion are statistically insignificant.

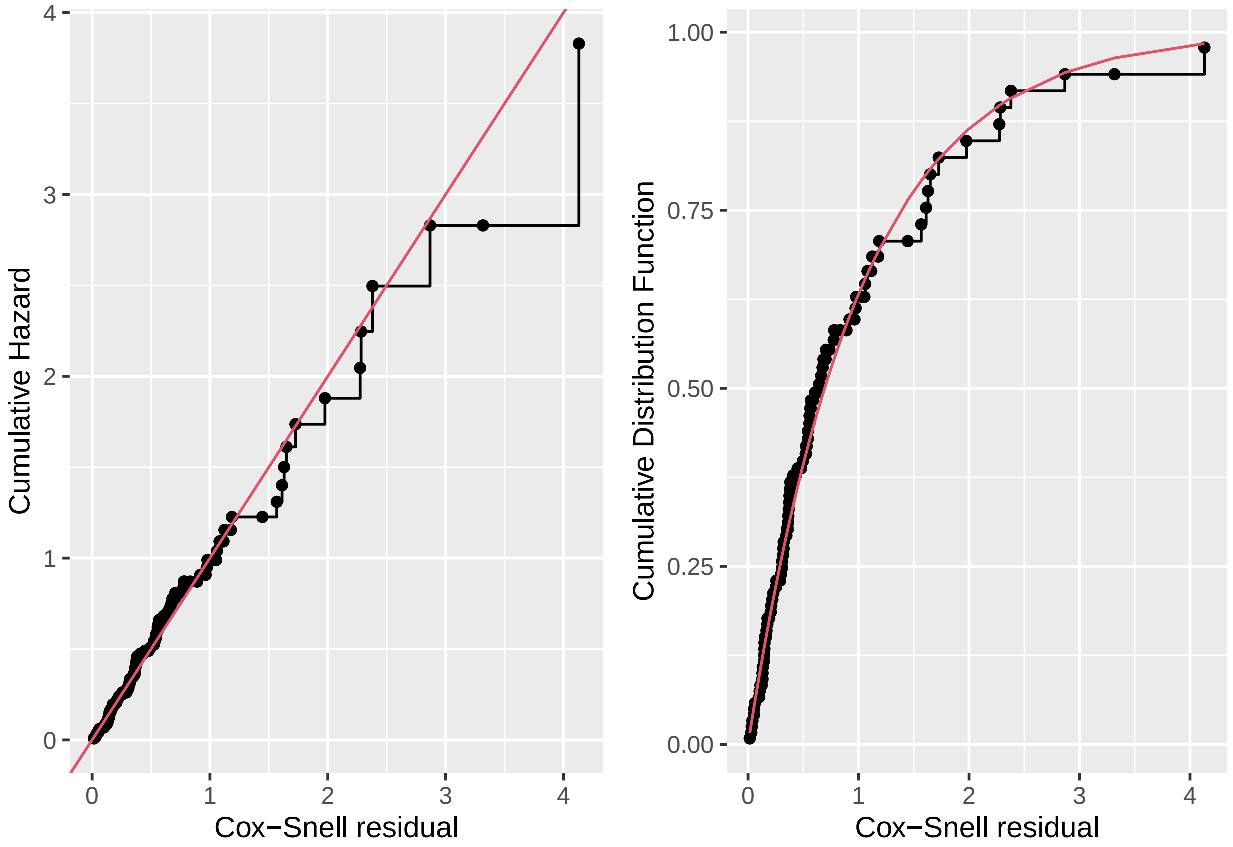
Question 2.4

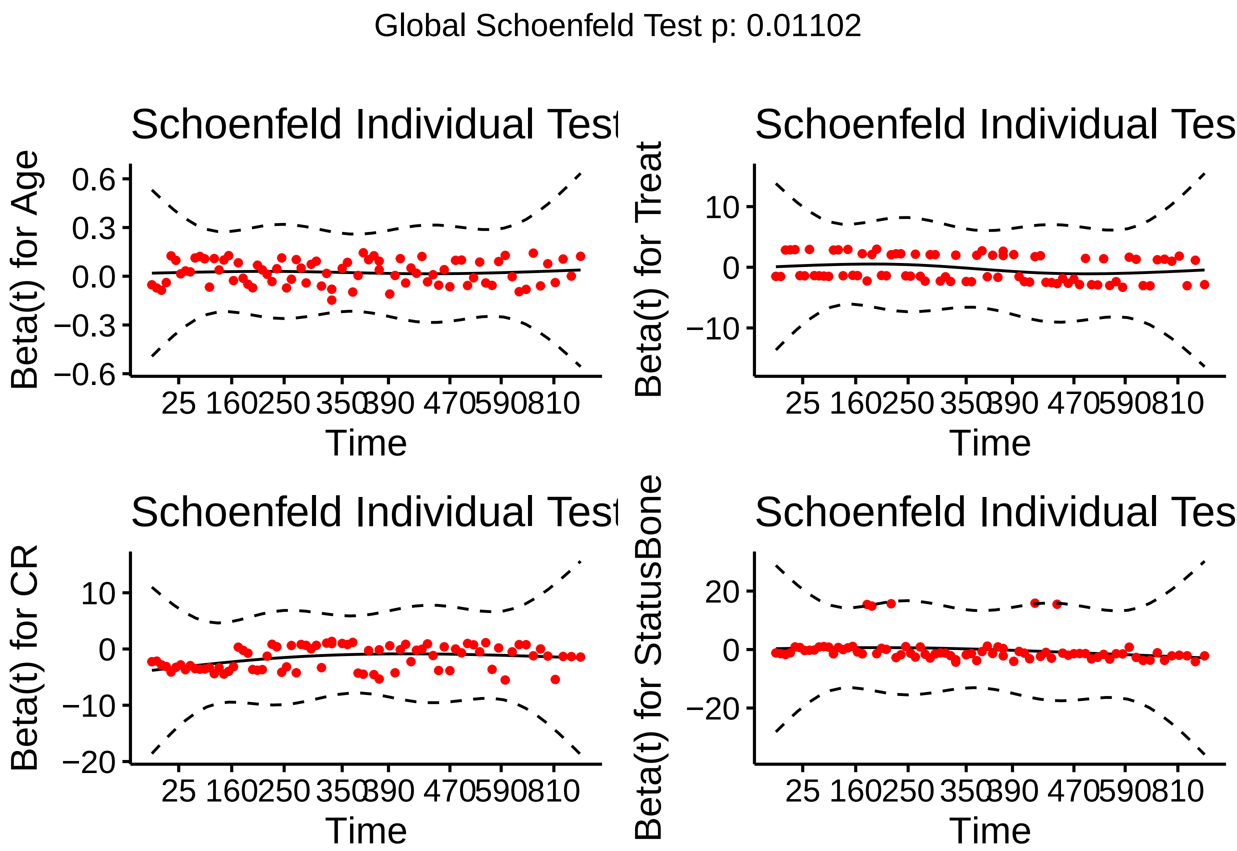
Now we wish to determine which covariates satisfy the assumptions of a cox proportional hazard model. To begin we can test the Schoenfeld residuals against time.

From this test we determine the parameter Age to have a chisq value of .496 on a single degreeof freedom yielding a p-value of .481. Treatment achieves a chisq test statistic of 3.642 on a single degreeof freedom with a p-value of .056. The complete remission check achieves a chisq of 4.335 with a p-value of .037. The Bone marrow transplant check achieves a chisq statistic of 2.628 on 1 degree of freedom with a p-value of .105.

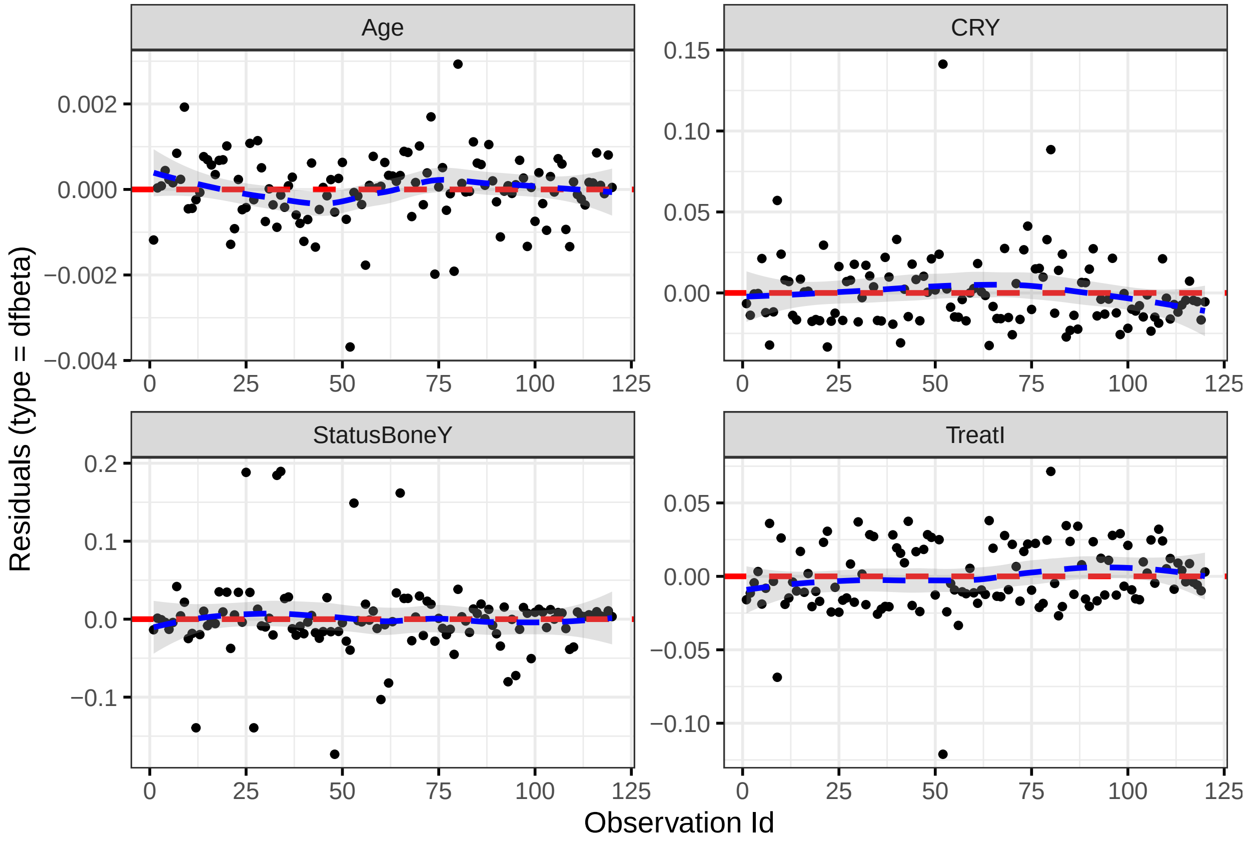
We see that all covariates aside from age are significant or very close to significance at the 10% level. Age is largely insigniifcant. Visual diagnostics will be used to assess these formal tests.

The cox-snell residuals show that the model does fit the data well. Residual plots reconfirm this claim, with the schoenfeld, martingale, dfbeta, and dfbetas (dfbeta/standardized residuals) showing no signs of stark deviance from the model assumptions aside from a few outliers.

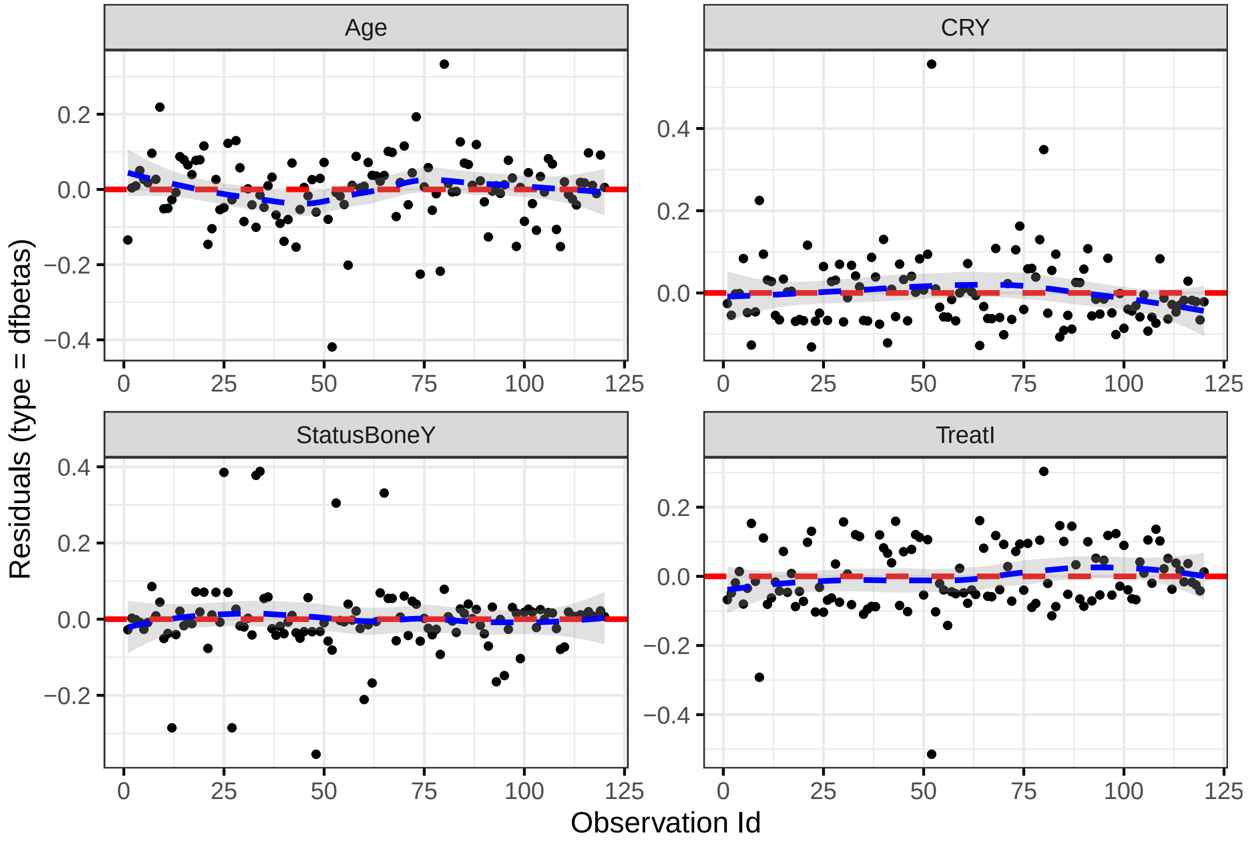

Cumulative Hazard
4
3
2
1
0
0
1
2
3
4
Cox−Snell residual
Cumulative Distribution Function
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
Cox−Snell residual



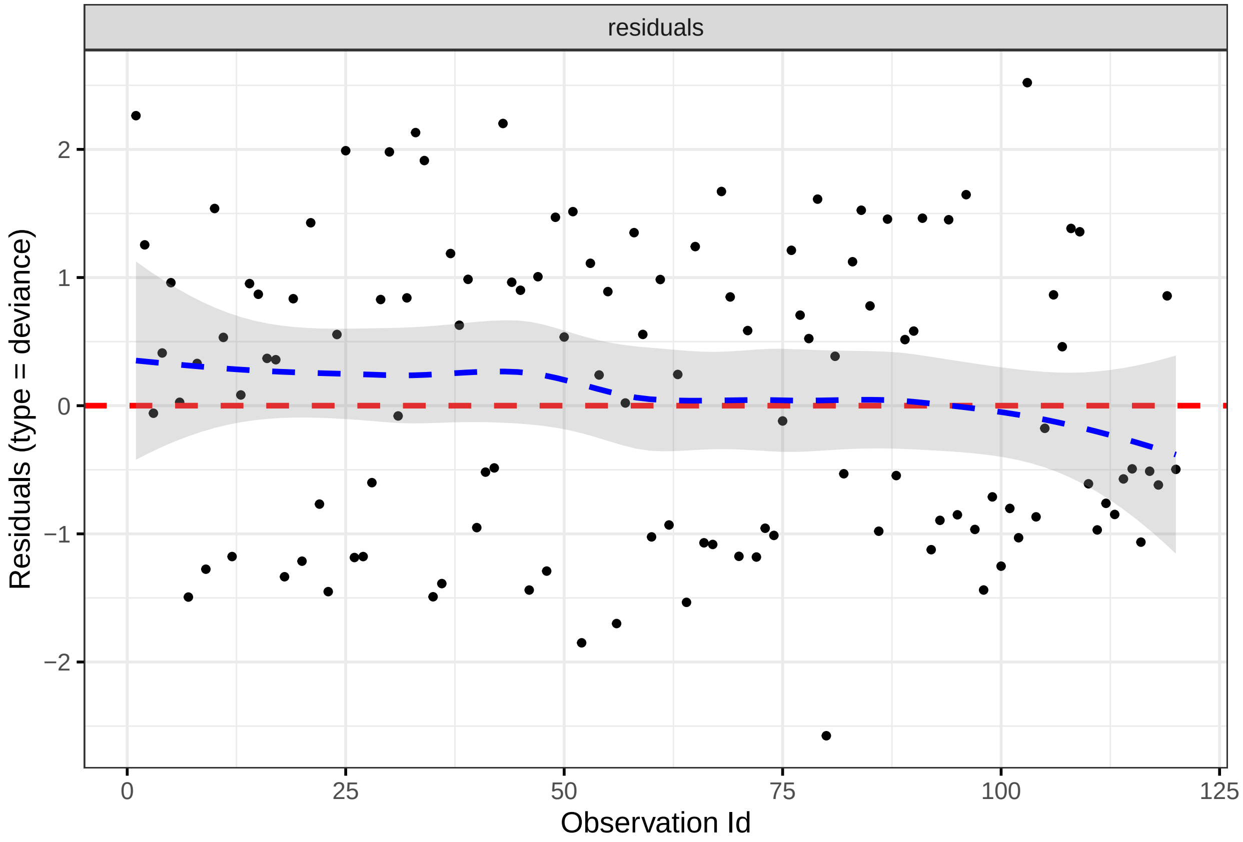
```
## ‘geom_smooth()‘ using formula ’y ~ x’
```



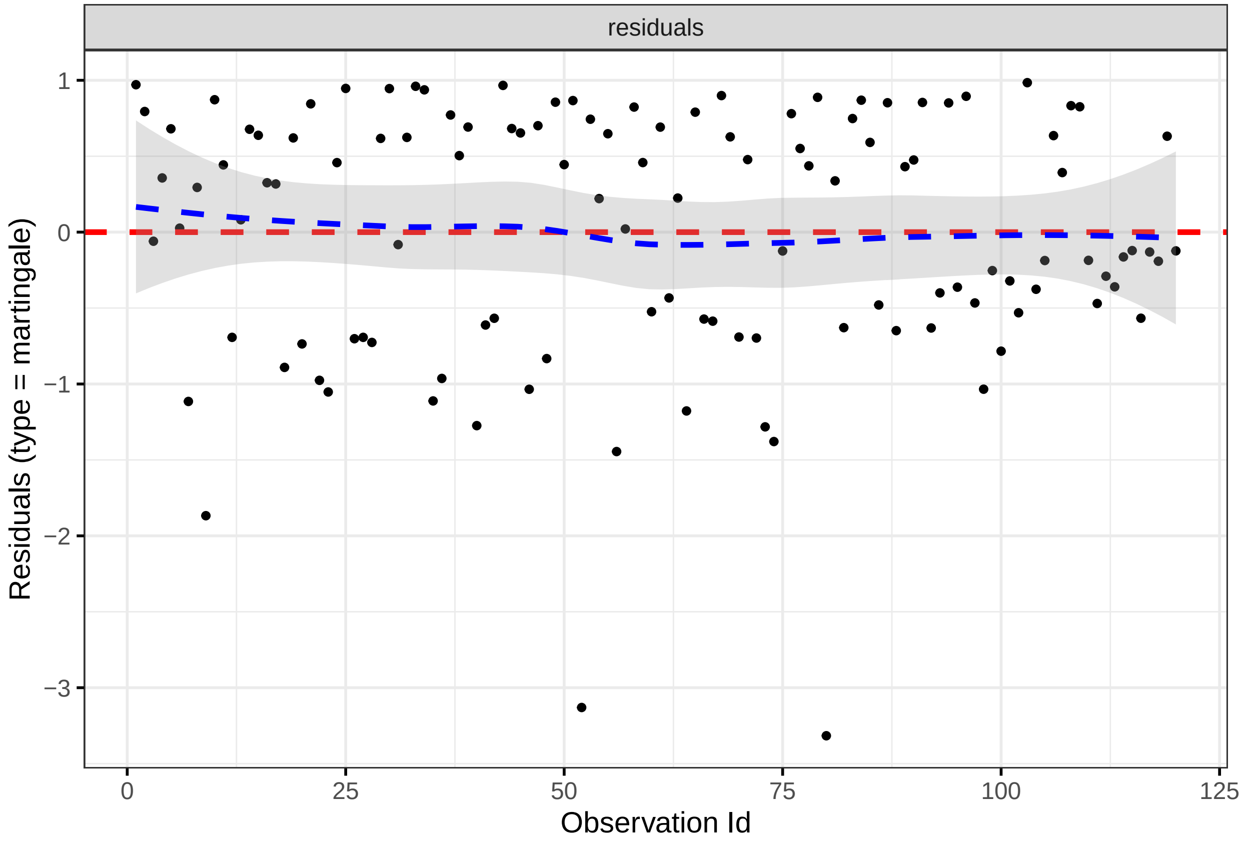
```
## `geom_smooth()` using formula 'y ~ x'
```



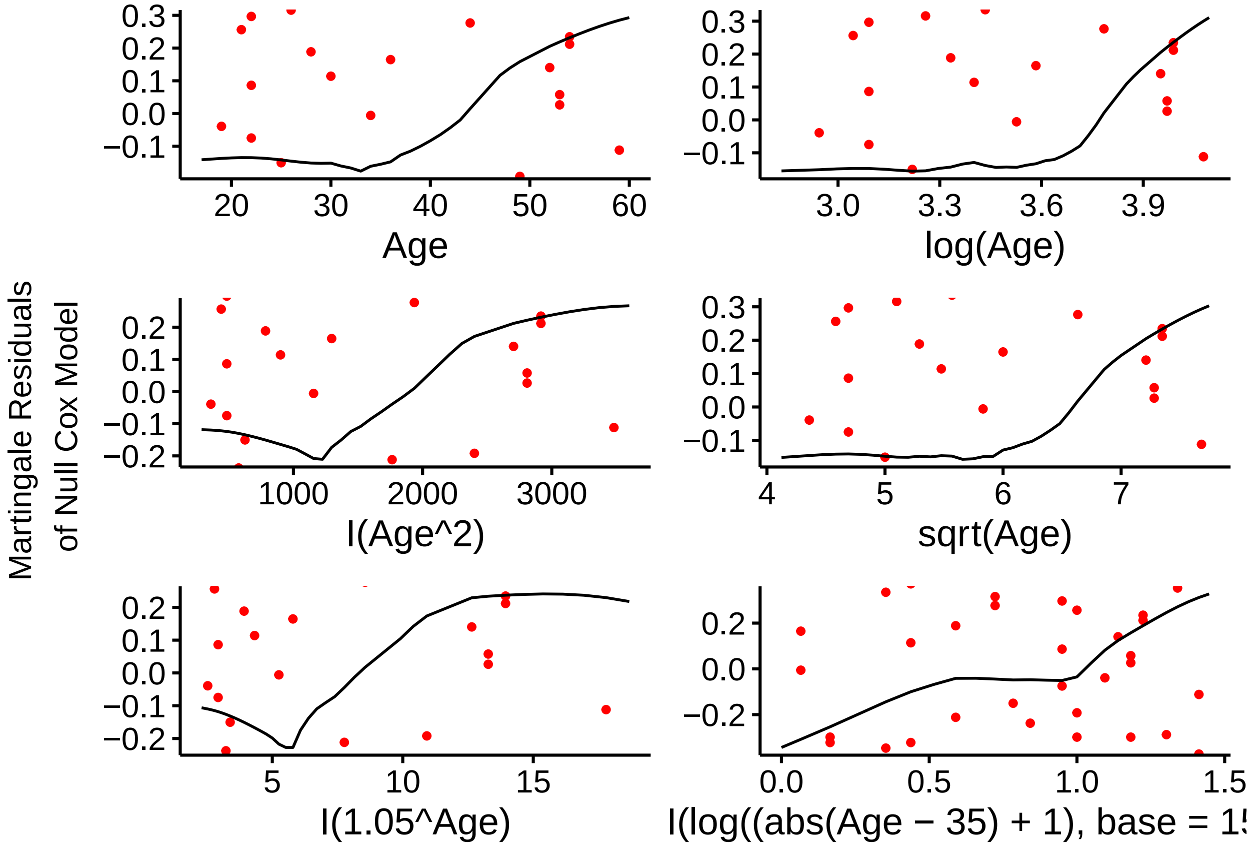
```
## `geom_smooth()` using formula 'y ~ x'
```



```
## `geom_smooth()` using formula 'y ~ x'
```



To enssure that our continuous variable, Age, is in its correct form we will examine the martingale residuals of various transforms (logarithmic, exponential, power, and root, and a combination transform). From these plots we clearly see evidence of non-linearity for the Age parameter. Our combination transform does appear to somewhat resolve this issue, albeit it is quite messy and may be practically uninterpretable. The transformation function used is as follows log((abs(Age-35)+1),base=15)ˆ2.



Question 3.1-3.2

Now we wish to model the relationship between survival, age, and treatment as an accelerated failure time model with a Weibull baseline. Within the model, the Intercept parameter carries a z-score of 17.2 with a corresponding p-value of approximately 0, the Age parameter carries a z-score of -2.01 with a correspondinig p-value of 0.045, the treatment factor carries a z-score of value 2.2 with a p-value of 0.028, and the log of the weibull scale parameter carries a z-score of 0.17 with a p-value of 0.868. The model achieves a chisqtest statistic of 9.92 on 2 degrees of freedom with a p-value of 0.007. With this information we claim that the AFT model

We can interperet the coefficients as such. A patient of age 0 undergoing treatment with Daunorubicin will be expected to have a survial time of 1212.26 days exp(7.10024). A per unitary increase in age will decelerate survival time by approximately 1.81% (exp(-.01831)-1). A patient using Idarubicin will accelerate their survival time by about 66.9% (exp(.51223)-1). The scale parameter generated for the weibull baseline distribution is 1.015905 (exp(.01578)).

Question 3.3

Now we wish to interpret the AFT model ans a proportional hazards model with a weibull baseline distribution. We can do this by applying a transform amongst the coefficients.

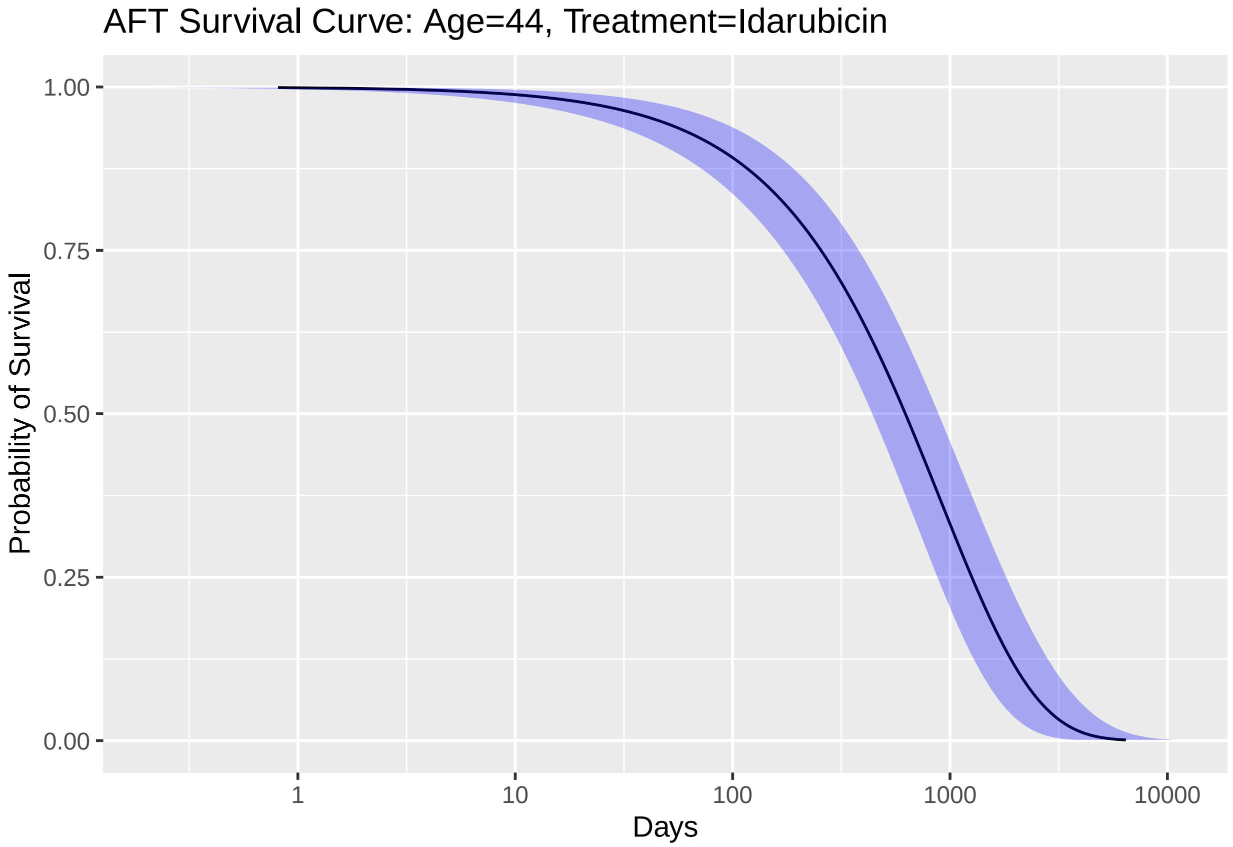
Applying the necessary transforms we are able to asses the influence of the age parameter.

We estimate the log proportional hazard coefficient for age to be .018 with a standard error of .0089. These values generate a chisq test statistic of 4.043 on a single degree of freedom with a corresponding p-value of 0.0444. With this in consideration we consider the age parameter to be significant at the 5% level.

We claim that a unitary increase in age will result in the proprotional hazard increasing by a factor of exp(0.0180225253)=1.018186. This estimate carries a confidence 95% interval of (1.000455, 1.036231). From this we say that per unitary increase in age we are 95% confident the hazard function will increase by a factor of 1.0005 and 1.0362%.

Question 3.4

Now we wish to perform a prediciton on the AFT model we drafted earlier. We will be estimating the survival function of a patient of age 44 and undergoing treatment with Idarubicin. From this estimate of the survival curve, we calculate that the estimated median survival time to be 622.98 days with a 95% confidence bound of 438.5 days and 885.08 days. A plot detailing the patient's estimated survival function bounded by a 95% confidence interval is seen here.



Now we wish to compare the survival function generated by our AFT model to the one generated by the cox proportional hazard model. As we discovered earlier the age parameter should undergo a transform to resolve its non-linearity issue. Unfortunately, we cannot view the right tail of this function as we did with the AFT model. This is because we can only view the survival rate as a proportional probability relative to the patients in the training data. With the AFT model we can regress through time in perpetuity.This allows us to calculate survival rates well past those observed in the training data. Fortunately, we are still able to extract usefull information regarding the distribution of the patient's cox proportional hazard estimated survival function.

From this distribution we can say that, under the assumption of the cox model, the patient's median survival time can be calculated to be 582 days with a 95% confidence bound of 422 and 871 days. Furthermore, the maximum survival time we are able to calculate now is 1424 days. This value represents the 69th quantile of the patients survival distribution and because of the nature of cox proportional hazard models we are unable to calculate a precise two-tail confidence interval for this estimation. For perspective the 69th quantile for the AFT model was 1061.4483 days with a 95% confidence bound of 742.996 and 1516.391 days. With the estimation of the cox model being well within the confidence boundry of the AFT model, we can say that the two models are indead consistent with each other.

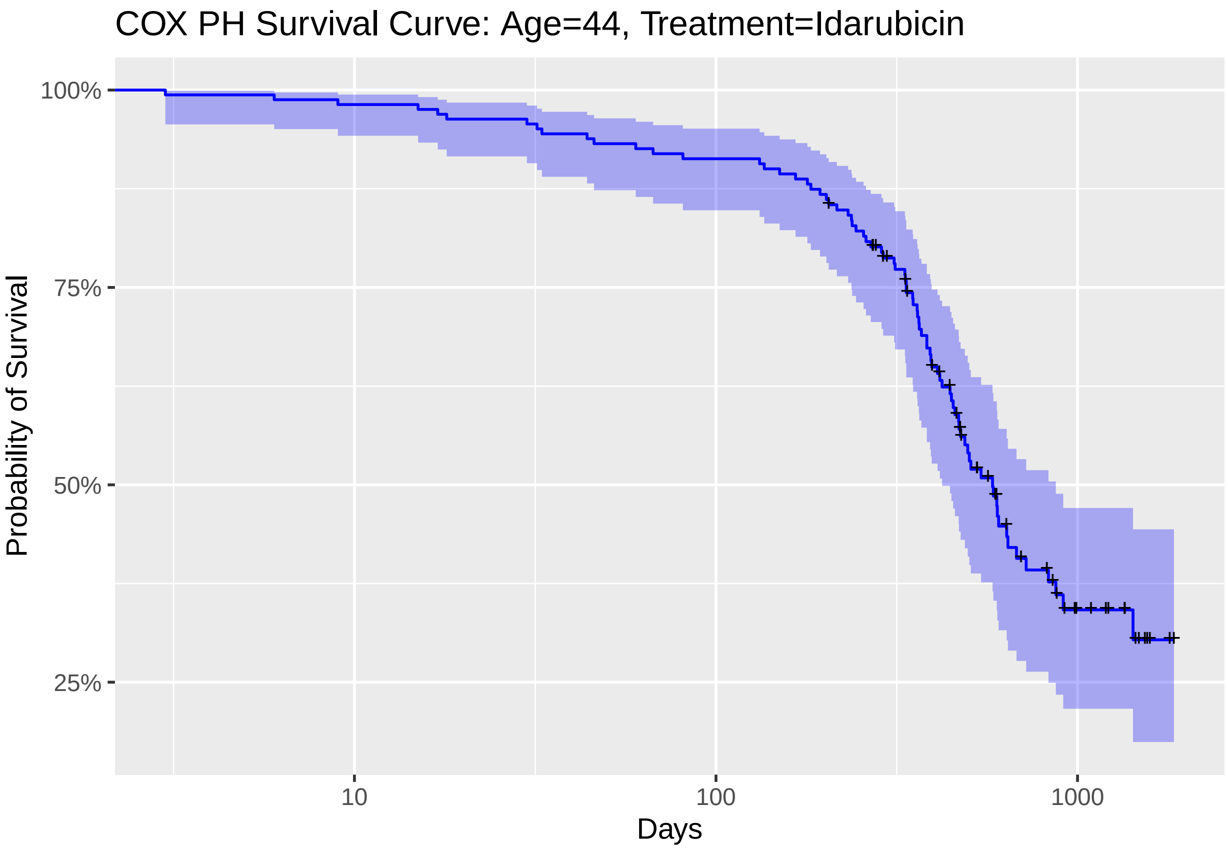
To formally test the similarity between the survival functions we shall use the Kolmogorov-Smirnov test between the 0 and 73rd quantiles of the survival time.

From this test we calculate a test statistic D=.10526. This carries a p-value of .2246.

In consideration of the following hypotheses

H0: The AFT and CoxPH estimated survival functions are equivalent. Ha: The AFT and CoxPH estimated survival functions are not equivalent.

Based on the result from the Kolmogorov-Smirnov distribution comparrison test, we fail to reject the null hypothesis and claim that there is not enough evidence to reject the AFT and CoxPH estimated survival functions are equivalent.



Code and Output Appendix

```
rm(list=ls())
#======================
# Loading the dataset
#======================
leukem<-read.table(
  file="C:/Users/kebro/OneDrive/KU_Leuven/Survivial & Reliability/Leuk.dat",
  na.strings=".",colClasses=c(NA,"character",
                              NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,
                              "character","character",NA,NA,"character",NA),
  col.names=c("ID","DateStudy","Treat","Sex",
              "Age","FAB","Karnof","WhiteCells","Platelets",
              "Hemoglobin","Eval","CR","NumbCR","DateCR",
              "DateFollow","StatusFollow","StatusBone",
              "DateBone","Incl"))
head(leukem)
```

```
##   ID DateStudy Treat Sex Age FAB Karnof WhiteCells Platelets Hemoglobin Eval CR
## 1  1    072384     D   M  27   5     80      179.0        51        8.8    Y  N
## 2  2    071984     D   M  43   3     90        0.9        14       13.1    Y  N
## 3  3    082984     I   M  36   1     90        1.8        71        6.9    Y  N
## 4  4    090184     I   M  54   1     70       31.9        46       10.8    Y  Y
## 5  5    112984     D   F  49   4     60       24.4        23       10.2    Y  Y
## 6  6    120584     I   M  49   4     90       46.2        21        9.5    Y  Y
##   NumbCR DateCR DateFollow StatusFollow StatusBone DateBone Incl
## 1     NA   <NA>     072984            D          N     <NA>    Y
## 2     NA   <NA>     082184            D          N     <NA>    Y
## 3     NA   <NA>     082585            D          N     <NA>    Y
## 4      1 100884     010286            D          N     <NA>    Y
## 5      1 011185     111485            D          N     <NA>    Y
## 6      1 122884     112686            D          N     <NA>    Y
```

```
attach(leukem)

#===================================
# Creating time to event variables
#===================================
DatumStudy<-as.Date(DateStudy,"%m%d%y")
DatumCR<-as.Date(DateCR,"%m%d%y")
DatumFollow<-as.Date(DateFollow,"%m%d%y")
DatumBone<-as.Date(DateBone,"%m%d%y")

TimeCR<-difftime(DatumCR,DatumStudy)
TimeSurv<-difftime(DatumFollow,DatumStudy)
TimeBone<-difftime(DatumBone,DatumStudy)
TimeEvent<-data.frame(DatumStudy,DatumCR,
                      DatumFollow,DatumBone,
                      TimeCR,TimeBone)
head(TimeEvent)
```

```
##   DatumStudy    DatumCR DatumFollow DatumBone  TimeCR TimeBone
## 1 1984-07-23       <NA>  1984-07-29      <NA> NA days  NA days
## 2 1984-07-19       <NA>  1984-08-21      <NA> NA days  NA days
## 3 1984-08-29       <NA>  1985-08-25      <NA> NA days  NA days
## 4 1984-09-01 1984-10-08  1986-01-02      <NA> 37 days  NA days
## 5 1984-11-29 1985-01-11  1985-11-14      <NA> 43 days  NA days
## 6 1984-12-05 1984-12-28  1986-11-26      <NA> 23 days  NA days
```

```
#================================================
# Creating the observed time to event variables
#================================================
IndCR<-1*I(CR=="Y")
TimetoCR<-TimeCR
TimetoCR[IndCR==0]<-TimeSurv[IndCR==0]
IndSurv<-1*I(StatusFollow=="D")
IndBone<-1*I(StatusBone=="Y")
TimetoBone<-TimeBone
TimetoBone[IndBone==0]<-TimeSurv[IndBone==0]
TimeObs<-data.frame(TimetoCR,IndCR,
                    TimetoBone,IndBone,
                    TimeSurv,IndSurv)
head(TimeObs)
```

```
##   TimetoCR IndCR TimetoBone IndBone TimeSurv IndSurv
## 1   6 days     0     6 days       0   6 days       1
## 2  33 days     0    33 days       0  33 days       1
## 3 361 days     0   361 days       0 361 days       1
## 4  37 days     1   488 days       0 488 days       1
## 5  43 days     1   350 days       0 350 days       1
## 6  23 days     1   721 days       0 721 days       1
```

```
Leukefinal<-data.frame(leukem,TimeEvent,TimeObs)
head(Leukefinal)
```

```
##   ID DateStudy Treat Sex Age FAB Karnof WhiteCells Platelets Hemoglobin Eval CR
## 1  1    072384     D   M  27   5     80      179.0        51        8.8    Y  N
## 2  2    071984     D   M  43   3     90        0.9        14       13.1    Y  N
## 3  3    082984     I   M  36   1     90        1.8        71        6.9    Y  N
## 4  4    090184     I   M  54   1     70       31.9        46       10.8    Y  Y
## 5  5    112984     D   F  49   4     60       24.4        23       10.2    Y  Y
## 6  6    120584     I   M  49   4     90       46.2        21        9.5    Y  Y
##   NumbCR DateCR DateFollow StatusFollow StatusBone DateBone Incl DatumStudy
## 1     NA   <NA>     072984            D          N     <NA>    Y 1984-07-23
## 2     NA   <NA>     082184            D          N     <NA>    Y 1984-07-19
## 3     NA   <NA>     082585            D          N     <NA>    Y 1984-08-29
## 4      1 100884     010286            D          N     <NA>    Y 1984-09-01
## 5      1 011185     111485            D          N     <NA>    Y 1984-11-29
## 6      1 122884     112686            D          N     <NA>    Y 1984-12-05
##      DatumCR DatumFollow DatumBone  TimeCR TimeBone TimetoCR IndCR TimetoBone
## 1       <NA>  1984-07-29      <NA> NA days  NA days   6 days     0     6 days
## 2       <NA>  1984-08-21      <NA> NA days  NA days  33 days     0    33 days
## 3       <NA>  1985-08-25      <NA> NA days  NA days 361 days     0   361 days
## 4 1984-10-08  1986-01-02      <NA> 37 days  NA days  37 days     1   488 days
## 5 1985-01-11  1985-11-14      <NA> 43 days  NA days  43 days     1   350 days
## 6 1984-12-28  1986-11-26      <NA> 23 days  NA days  23 days     1   721 days
##   IndBone TimeSurv IndSurv
## 1       0   6 days       1
## 2       0  33 days       1
## 3       0 361 days       1
## 4       0 488 days       1
## 5       0 350 days       1
## 6       0 721 days       1
```

```r
#Required Packages
library(ggplot2)
library(survival)
library(survminer)
```

```
## Loading required package: ggpubr
```

```r
library(ggfortify)
library(dplyr)
```

```
##
## Attaching package: 'dplyr'

## The following objects are masked from 'package:stats':
##
##     filter, lag

## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
```

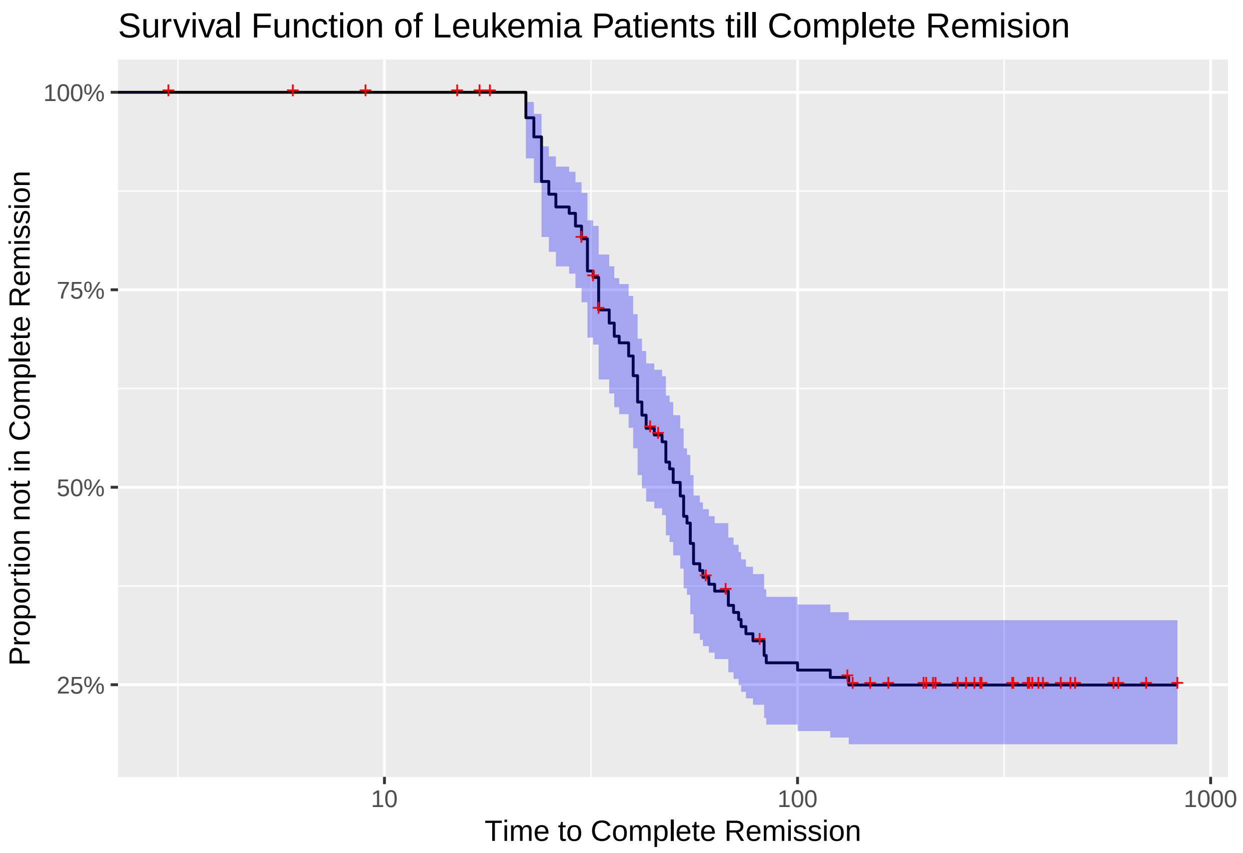
```r
library(ciTools)
```

```
## Registered S3 methods overwritten by 'lme4':
##   method                          from
##   cooks.distance.influence.merMod car
##   influence.merMod                car
##   dfbeta.influence.merMod         car
##   dfbetas.influence.merMod        car

## ciTools version 0.5.1 (C) Institute for Defense Analyses
```

```r
library(ldatools)
```

```
# Question 1.1



#Adding censored values to data set.
Leukefinal$CRkm=Surv(as.numeric(Leukefinal$TimetoCR),Leukefinal$IndCR)



#Fitting and plotting km estimate
fit1.1 = survfit(CRkm~1,
                 data = Leukefinal,conf.type="log-log")
autoplot(fit1.1,surv.colour = ’black’,
         censor.colour = "red",
         conf.int.fill = ’blue’)+
  scale_x_log10()+
  ggtitle("Survival Function of Leukemia Patients till Complete Remision")+
  xlab("Time to Complete Remission")+
  ylab("Proportion not in Complete Remission")
```

```
## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis
```



```
sumfit1.1=summary(fit1.1)
.3*124
```

```
## [1] 37.2
```

```
sumfit1.1
```

```
## Call: survfit(formula = CRkm ~ 1, data = Leukefinal, conf.type = "log-log")
##
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    22    124       4    0.968  0.0159        0.916        0.988
##    23    120       3    0.944  0.0207        0.885        0.973
##    24    117       7    0.887  0.0284        0.817        0.932
##    25    110       2    0.871  0.0301        0.798        0.919
##    26    108       2    0.855  0.0316        0.780        0.906
##    28    106       1    0.847  0.0323        0.770        0.899
##    29    105       2    0.831  0.0337        0.752        0.886
##    30    103       2    0.815  0.0349        0.734        0.873
##    31    100       5    0.774  0.0376        0.689        0.838
##    32     95       1    0.766  0.0381        0.681        0.831
##    33     93       5    0.724  0.0402        0.636        0.795
##    35     87       2    0.708  0.0410        0.619        0.780
##    36     85       2    0.691  0.0417        0.601        0.765
##    37     83       1    0.683  0.0420        0.593        0.757
##    39     82       2    0.666  0.0426        0.575        0.742
##    40     80       3    0.641  0.0434        0.549        0.719
##    41     77       4    0.608  0.0442        0.515        0.688
##    42     73       2    0.591  0.0445        0.499        0.672
##    43     71       2    0.575  0.0448        0.482        0.657
##    45     68       1    0.566  0.0449        0.473        0.649
##    47     66       1    0.558  0.0451        0.465        0.641
##    48     65       3    0.532  0.0454        0.439        0.616
##    49     62       1    0.523  0.0455        0.431        0.608
##    50     61       2    0.506  0.0456        0.414        0.591
##    52     59       2    0.489  0.0456        0.397        0.575
##    53     57       3    0.463  0.0456        0.372        0.549
##    54     54       1    0.455  0.0455        0.364        0.541
##    55     53       3    0.429  0.0453        0.339        0.515
##    56     50       3    0.403  0.0449        0.315        0.490
##    58     47       1    0.395  0.0448        0.307        0.481
##    59     46       1    0.386  0.0446        0.299        0.472
##    61     44       1    0.377  0.0445        0.291        0.463
##    63     43       1    0.368  0.0443        0.282        0.455
##    68     41       2    0.350  0.0439        0.266        0.436
##    70     39       1    0.341  0.0437        0.257        0.427
##    72     38       1    0.333  0.0435        0.249        0.418
##    73     37       1    0.324  0.0432        0.241        0.409
##    75     36       1    0.315  0.0429        0.233        0.399
##    78     35       1    0.306  0.0426        0.225        0.390
##    83     33       2    0.287  0.0420        0.208        0.371
##    84     31       1    0.278  0.0417        0.200        0.361
##   100     30       1    0.269  0.0413        0.191        0.352
##   120     29       1    0.259  0.0409        0.183        0.342
##    133     27       1    0.250  0.0405        0.175        0.332
```

```
#calculating day 90 probabilities
fit1.1$surv[fit1.1$time==84]
```

```
## [1] 0.2777733
```

```
fit1.1$lower[fit1.1$time==84]
```

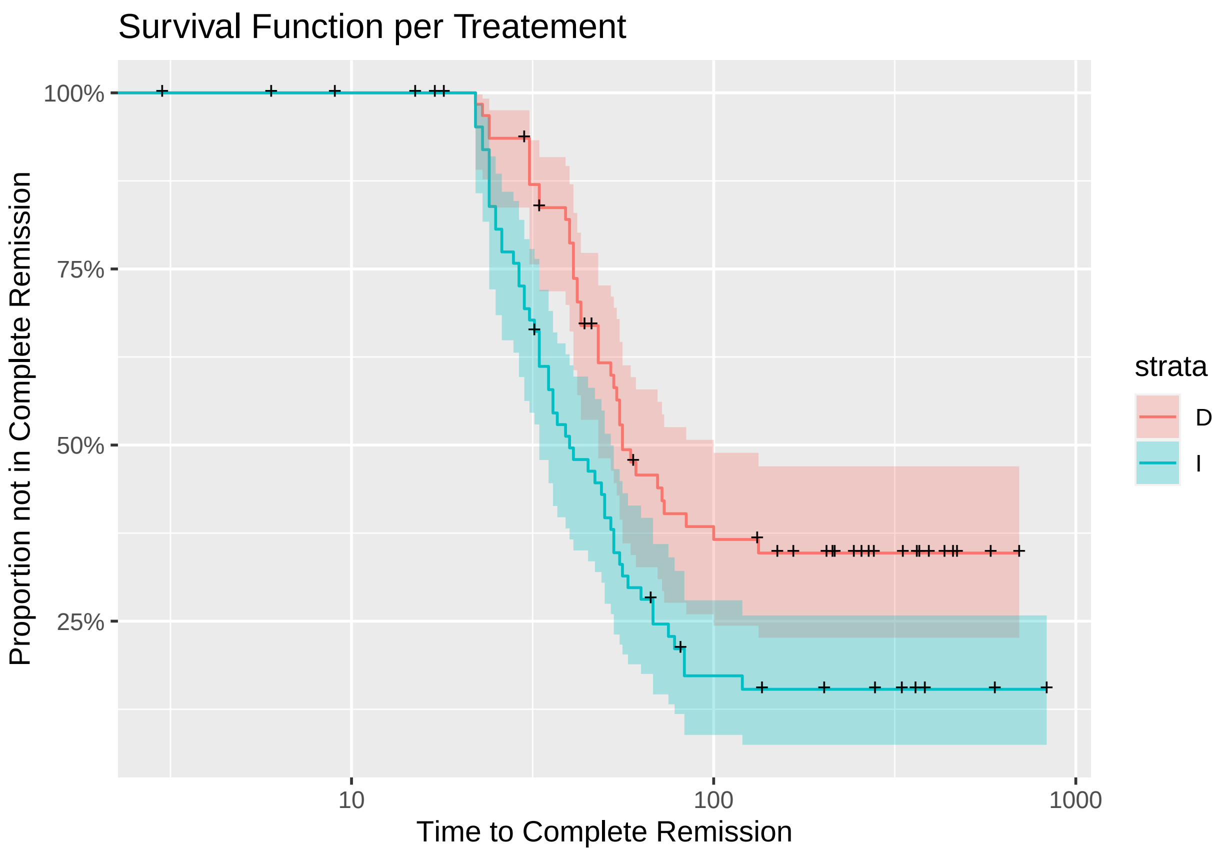
```
## [1] 0.1995904
```

```
fit1.1$upper[fit1.1$time==84]
```

```
## [1] 0.3612412
```

```
#Question 1.2



#fitting and plotting survival function respective of treatment
fit1.2=survfit(CRkm~Treat,
               data = Leukefinal,
               conf.type="log-log")
treat.plot=autoplot(fit1.2)+
  scale_x_log10()+
  ggtitle("Survival Function per Treatement")+
  xlab("Time to Complete Remission")+
  ylab("Proportion not in Complete Remission")
treat.plot
```

```
## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis
```



```
#summarizing and evaluate strata differences of survival function
fit1.2
```

```
## Call: survfit(formula = CRkm ~ Treat, data = Leukefinal, conf.type = "log-log")
##
##           n events median 0.95LCL 0.95UCL
## Treat=D 65     38     56      48     100
## Treat=I 65     51     40      33      52
```

```
sumfit1.2=summary(fit1.2)
sumfit1.2
```

```
## Call: survfit(formula = CRkm ~ Treat, data = Leukefinal, conf.type = "log-log")
##
##                 Treat=D
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    22     62       1    0.984  0.0160        0.891        0.998
##    23     61       1    0.968  0.0224        0.877        0.992
##    24     60       2    0.935  0.0312        0.837        0.975
##    31     57       4    0.870  0.0429        0.756        0.933
##    33     53       2    0.837  0.0472        0.718        0.909
##    39     50       1    0.820  0.0491        0.699        0.896
##    40     49       2    0.787  0.0525        0.661        0.870
##    41     47       3    0.737  0.0566        0.606        0.830
##    42     44       2    0.703  0.0588        0.571        0.802
##    43     42       2    0.670  0.0605        0.536        0.773
##    48     38       3    0.617  0.0630        0.481        0.727
##    52     35       1    0.599  0.0636        0.463        0.711
##    53     34       1    0.582  0.0641        0.446        0.695
##    54     33       1    0.564  0.0646        0.428        0.679
##    55     32       2    0.529  0.0652        0.394        0.646
##    56     30       2    0.493  0.0654        0.360        0.613
##    59     28       1    0.476  0.0654        0.344        0.596
##    61     26       1    0.457  0.0654        0.327        0.579
##    70     25       1    0.439  0.0653        0.310        0.561
##    72     24       1    0.421  0.0651        0.293        0.544
##    73     23       1    0.403  0.0648        0.276        0.526
##    84     22       1    0.384  0.0644        0.260        0.507
##   100     21       1    0.366  0.0638        0.244        0.489
##   133     19       1    0.347  0.0633        0.226        0.470
## 
##                 Treat=I 
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##    22     62       3    0.952  0.0273       0.8574        0.984
##    23     59       2    0.919  0.0346       0.8170        0.966
##    24     57       5    0.839  0.0467       0.7210        0.910
##    25     52       2    0.806  0.0502       0.6844        0.885
##    26     50       2    0.774  0.0531       0.6487        0.860
##    28     48       1    0.758  0.0544       0.6312        0.846
##    29     47       2    0.726  0.0567       0.5966        0.820
##    30     45       2    0.694  0.0585       0.5626        0.792
##    31     43       1    0.677  0.0594       0.5459        0.778
##    32     42       1    0.661  0.0601       0.5293        0.764
##    33     40       3    0.612  0.0620       0.4788        0.720
##    35     37       2    0.579  0.0629       0.4458        0.690
##    36     35       2    0.546  0.0635       0.4135        0.660
##    37     33       1    0.529  0.0637       0.3975        0.644
##    39     32       1    0.513  0.0638       0.3817        0.629
##    40     31       1    0.496  0.0639       0.3660        0.613
##    41     30       1    0.479  0.0639       0.3504        0.597
##    45     29       1    0.463  0.0638       0.3350        0.581
##    47     28       1    0.446  0.0636       0.3197        0.565
##    49     27       1    0.430  0.0634       0.3046        0.549
##    50     26       2    0.397  0.0626       0.2747        0.516
##    52     24       1    0.380  0.0622       0.2600        0.499
##    53     23       2    0.347  0.0610       0.2311        0.466
##    55     21       1    0.331  0.0603       0.2168        0.449
##    56     20       1    0.314  0.0595       0.2028        0.432
##    58     19       1    0.298  0.0586       0.1888        0.414
##    63     18       1    0.281  0.0577       0.1751        0.397
##    68     16       2    0.246  0.0555       0.1461        0.359
##    75     14       1    0.228  0.0543       0.1320        0.341
##    78     13       1    0.211  0.0529       0.1182        0.321
##    83     11       2    0.172  0.0497       0.0886        0.280
##   120      9       1    0.153  0.0477       0.0745        0.258
```

```
survdiff(CRkm~Treat,data = Leukefinal,rho=1)
```

```
## Call:
```

```
## survdiff(formula = CRkm ~ Treat, data = Leukefinal, rho = 1)
##
##           N Observed Expected (O-E)^2/E (O-E)^2/V
## Treat=D 65     22.5     32.6      3.14      10.4
## Treat=I 65     34.9     24.8      4.12      10.4
##
##  Chisq= 10.4  on 1 degrees of freedom, p= 0.001
```

```
#Two month survival probabiliites
D2month=c(sumfit1.2$surv[sumfit1.2$time==59],
          sumfit1.2$lower[sumfit1.2$time==59],
          sumfit1.2$upper[sumfit1.2$time==59])

I2month=c(sumfit1.2$surv[sumfit1.2$time==58],
          sumfit1.2$lower[sumfit1.2$time==58],
          sumfit1.2$upper[sumfit1.2$time==58])

1-D2month
```

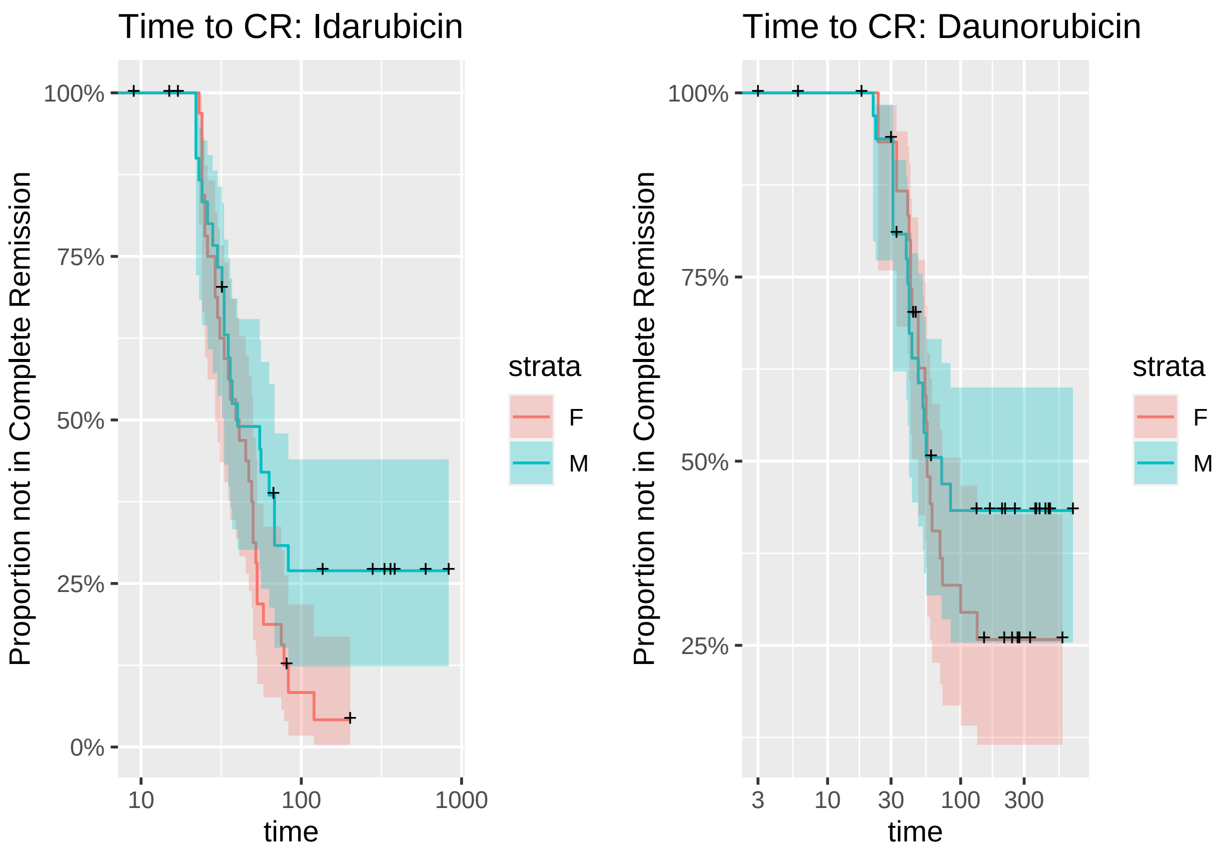
```
## [1] 0.5242248 0.6561648 0.4035932
```

```
1-I2month
```

```
## [1] 0.7024194 0.8111535 0.5857919
```

```
#Question 1.3



#fitting survival function respective of tratment and sex
fit1.3.I=survfit(CRkm~Sex,
                 data = Leukefinal[Leukefinal$Treat=="I",],
                 conf.type="log-log")
fit1.3.D=survfit(CRkm~Sex,
                 data = Leukefinal[Leukefinal$Treat=="D",],
                 conf.type="log-log")
I.plot=autoplot(fit1.3.I)+ggtitle("Time to CR: Idarubicin")+
  scale_x_log10()+
  ylab("Proportion not in Complete Remission")
D.plot=autoplot(fit1.3.D)+ggtitle("Time to CR: Daunorubicin")+
  scale_x_log10()+
  ylab("Proportion not in Complete Remission")

gridExtra::grid.arrange(I.plot,D.plot,ncol=2)
```

```
## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis
```



```r
#evaluating survival functions of treatment and sex
survdiff(CRkm~Sex,data = Leukefinal[Leukefinal$Treat=="I",],rho=1)
```

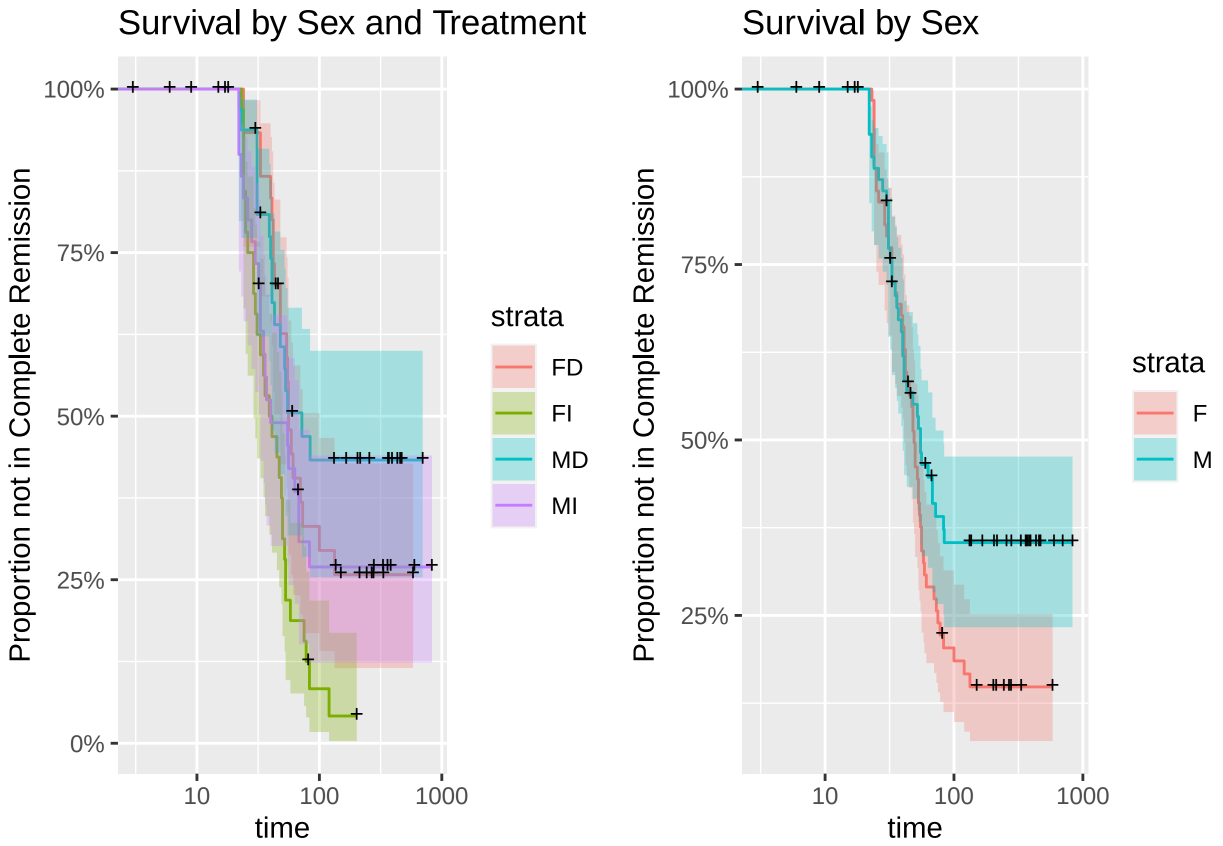
```
## Call:
## survdiff(formula = CRkm ~ Sex, data = Leukefinal[Leukefinal$Treat ==
##     "I", ], rho = 1)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## Sex=F 35     17.5     15.2     0.364      1.06
## Sex=M 30     13.2     15.5     0.355      1.06
##
##  Chisq= 1.1  on 1 degrees of freedom, p= 0.3
```

```r
survdiff(CRkm~Sex,data = Leukefinal[Leukefinal$Treat=="D",],rho=1)
```

```
## Call:
## survdiff(formula = CRkm ~ Sex, data = Leukefinal[Leukefinal$Treat ==
##     "D", ], rho = 1)
##
##         N Observed Expected (O-E)^2/E (O-E)^2/V
## Sex=F 30     13.6     13.3   0.00719    0.0197
## Sex=M 35     13.0     13.3   0.00720    0.0197
##
##  Chisq= 0  on 1 degrees of freedom, p= 0.9
```

```
#survival plot of each sex and each sex treatment combination.

md=rep(0,130)
md=md+1*(Leukefinal$Sex=="M"&Leukefinal$Treat=="D")

mi=rep(0,130)
mi=mi+1*(Leukefinal$Sex=="M"&Leukefinal$Treat=="I")

fd=rep(0,130)
fd=fd+1*(Leukefinal$Sex=="F"&Leukefinal$Treat=="D")

fi=rep(0,130)
fi=fi+1*(Leukefinal$Sex=="F"&Leukefinal$Treat=="I")
cr.treat.sex=tibble(CRkm=Leukefinal$CRkm)%>%
  mutate(MD=md)%>%
  mutate(MI=mi)%>%
  mutate(FD=fd)%>%
  mutate(FI=fi)
cr.treat.sex$SexTreat=rep("",130)
for(i in 1:130){
  if(md[i]==1){
    cr.treat.sex$SexTreat[i]="MD"
  }
  if(mi[i]==1){
    cr.treat.sex$SexTreat[i]="MI"
  }
  if(fd[i]==1){
    cr.treat.sex$SexTreat[i]="FD"
  }
  if(fi[i]==1){
    cr.treat.sex$SexTreat[i]="FI"
  }
}



fit1.3.sex=survfit(CRkm~Sex,
                   data = Leukefinal,conf.type="log-log")
sex.plot=autoplot(fit1.3.sex)+
  ggtitle("Survival by Sex")+scale_x_log10()+
  ylab("Proportion not in Complete Remission")
fit1.3.full=survfit(CRkm~SexTreat,
                    data = cr.treat.sex,conf.type="log-log")
full.plot=autoplot(fit1.3.full)+
  ggtitle("Survival by Sex and Treatment")+scale_x_log10()+
  ylab("Proportion not in Complete Remission")

gridExtra::grid.arrange(full.plot,sex.plot,ncol=2)
```

```
## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis
## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis
```



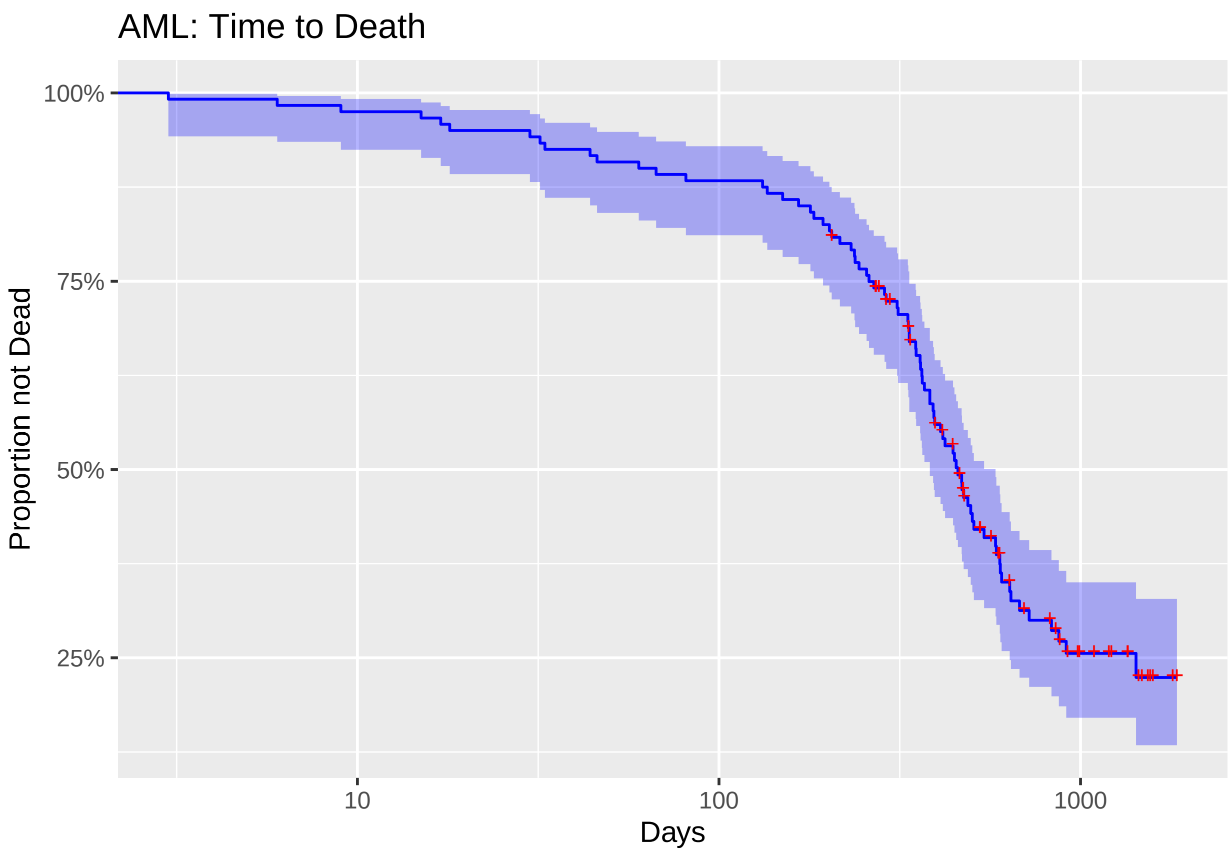
```
#making coxph to test if sex is confounding on treatment
coxsextreat=coxph(CRkm~Treat*Sex,data = Leukefinal)
summary(coxsextreat)
```

```
## Call:
## coxph(formula = CRkm ~ Treat * Sex, data = Leukefinal)
##
##   n= 130, number of events= 89
##
##                 coef exp(coef) se(coef)      z Pr(>|z|)
## TreatI        0.7623    2.1433   0.2865  2.661  0.00779 **
## SexM         -0.2605    0.7706   0.3267 -0.797  0.42522
## TreatI:SexM -0.2619    0.7696   0.4338 -0.604  0.54602
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##             exp(coef) exp(-coef) lower .95 upper .95
## TreatI         2.1433     0.4666    1.2224     3.758
## SexM           0.7706     1.2976    0.4062     1.462
## TreatI:SexM    0.7696     1.2994    0.3288     1.801
##
```

```
## Concordance= 0.604  (se = 0.03 )
## Likelihood ratio test= 12.82  on 3 df,   p=0.005
## Wald test            = 13.26  on 3 df,   p=0.004
## Score (logrank) test = 14.02  on 3 df,   p=0.003
```

```
#Question 2.1


#subsetting data setto only include patients with AML
leukem.aml=Leukefinal[Leukefinal$Eval=="Y",]
leukem.aml$statusnum=rep(0,120)
for(i in 1:120){
  if(leukem.aml$StatusFollow[i]=="D"){
    leukem.aml$statusnum[i]=1
  }
}
leukem.aml.surv=with(leukem.aml,
                     Surv(TimeSurv,statusnum))
leukem.aml$km=leukem.aml.surv

#survival function of aml patients
fit2.1=survfit(km~1,leukem.aml,conf.type="log-log")
autoplot(fit2.1, surv.colour = ’blue’,
         censor.colour = ’red’)+
  ggtitle("AML: Time to Death")+
  xlab("Days")+
  ylab("Proportion not Dead")+
  scale_x_log10()
```

```
## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis
```



```
#quantiles of aml patient survival time
fit2.1
```

```
## Call: survfit(formula = km ~ 1, data = leukem.aml, conf.type = "log-log")
##
##        n  events  median 0.95LCL 0.95UCL
##      120      79     458     383     582
```

```
quantile(fit2.1,c(.25,.5,.75))
```

```
## $quantile
##   25   50   75
##  260  458 1424
##
## $lower
##  25  50  75
## 194 383 637
##
## $upper
##  25  50  75
## 336 582  NA
```

```
#Question 2.2
```

```r
#coxph model of age and treatment on survival time
cox2.2=coxph(km~Age+Treat,
             data=leukem.aml)
summary(cox2.2)
```

```
## Call:
## coxph(formula = km ~ Age + Treat, data = leukem.aml)
## 
##   n= 120, number of events= 79 
## 
##            coef exp(coef)  se(coef)      z Pr(>|z|)  
## Age    0.018499  1.018671  0.008772  2.109   0.0350 *
## TreatI -0.461316  0.630453  0.230394 -2.002   0.0453 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## 
##        exp(coef) exp(-coef) lower .95 upper .95
## Age       1.0187     0.9817    1.0013    1.0363
## TreatI    0.6305     1.5862    0.4014    0.9903
## 
## Concordance= 0.587  (se = 0.036 )
## Likelihood ratio test= 9.15  on 2 df,   p=0.01
## Wald test            = 9.26  on 2 df,   p=0.01
## Score (logrank) test = 9.43  on 2 df,   p=0.009
```

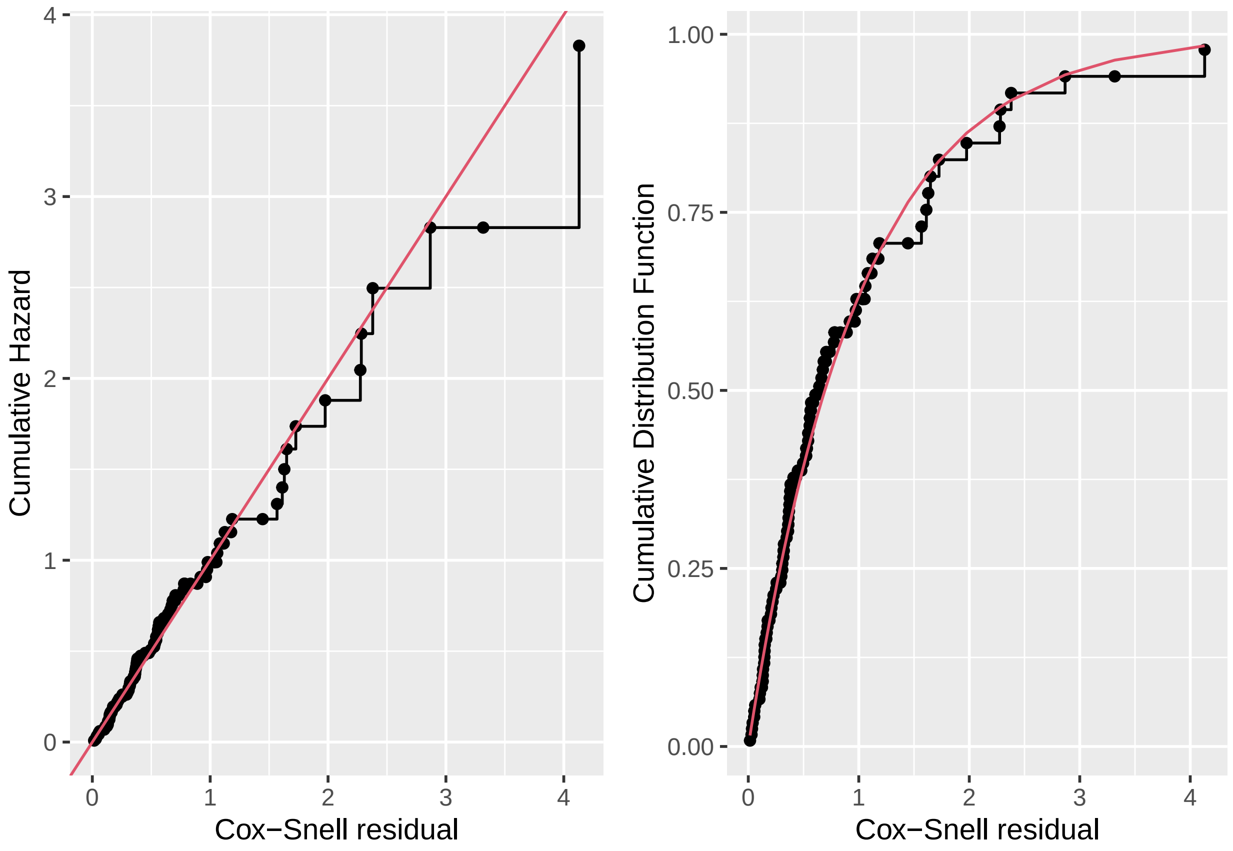
```r
#Question 2.3

cox2.3=coxph(km~Age+Treat+CR+StatusBone,
             data=leukem.aml)
summary(cox2.3)
```

```
## Call:
## coxph(formula = km ~ Age + Treat + CR + StatusBone, data = leukem.aml)
## 
##   n= 120, number of events= 79 
## 
##                 coef exp(coef)  se(coef)      z Pr(>|z|)    
## Age          0.023842  1.024128  0.008794  2.711   0.0067 ** 
## TreatI      -0.224481  0.798931  0.235414 -0.954   0.3403    
## CRY         -1.623896  0.197129  0.253821 -6.398 1.58e-10 ***
## StatusBoneY -0.298732  0.741758  0.488430 -0.612   0.5408    
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## 
##             exp(coef) exp(-coef) lower .95 upper .95
## Age             1.0241     0.9764    1.0066    1.0419
## TreatI          0.7989     1.2517    0.5036    1.2673
## CRY             0.1971     5.0728    0.1199    0.3242
## StatusBoneY     0.7418     1.3481    0.2848    1.9320
## 
## Concordance= 0.716  (se = 0.031 )
## Likelihood ratio test= 50.7  on 4 df,   p=3e-10
## Wald test            = 53.32  on 4 df,   p=7e-11
## Score (logrank) test = 64.27  on 4 df,   p=4e-13
```

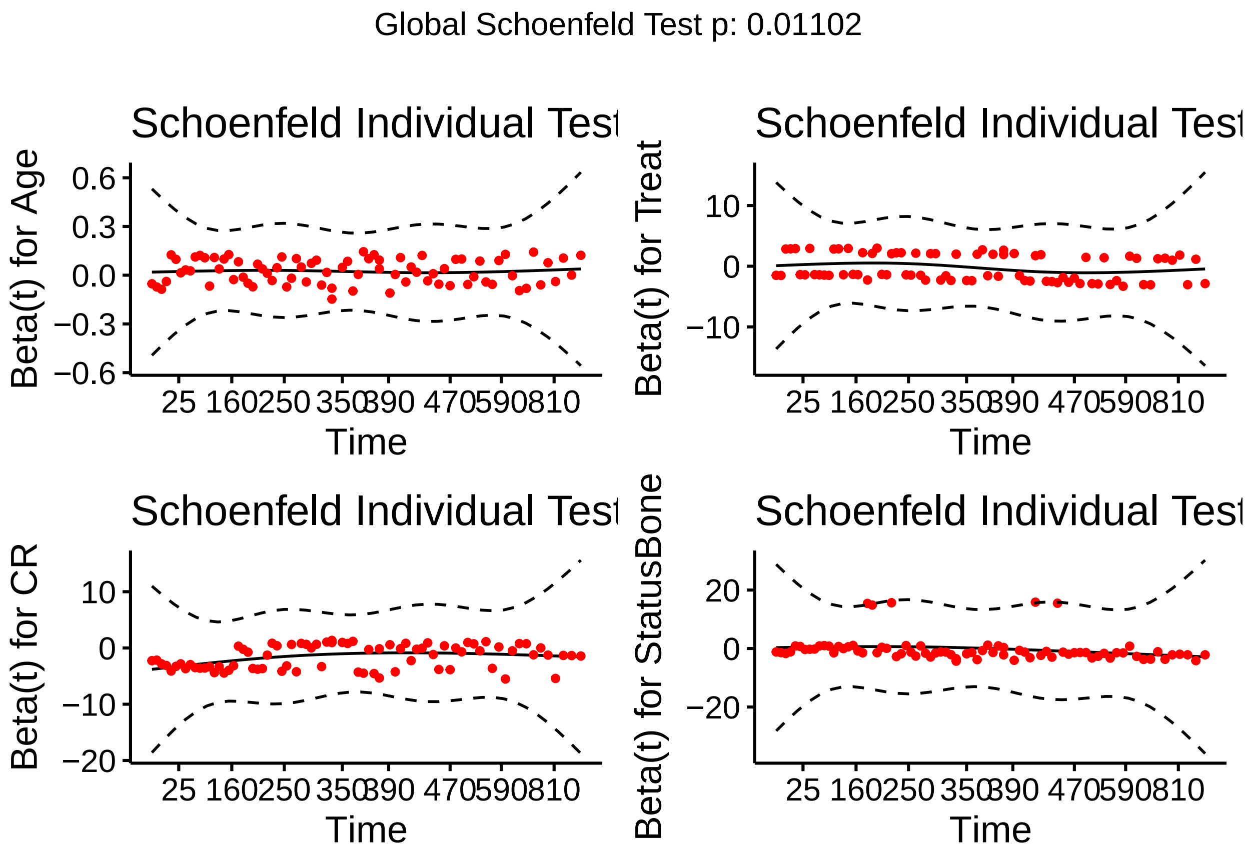
```
#Question 2.4

#testig cox assumptions
test2.4=cox.zph(cox2.3,transform = "km")
test2.4
```

```
##              chisq df     p
## Age          0.496  1 0.481
## Treat        3.642  1 0.056
## CR           4.335  1 0.037
## StatusBone   2.628  1 0.105
## GLOBAL      13.054  4 0.011
```

```
#cox diagnostic plots: coxsnell
coxsnellplot=gg_coxsnell(cox2.3)+
  geom_abline(intercept=0, slope=1, col=2)

coxsnellplot.cdf=gg_coxsnell(cox2.3,type="cdf")+
  geom_line(aes(y=F), col=2)

gridExtra::grid.arrange(coxsnellplot,
                        coxsnellplot.cdf,ncol=2)
```

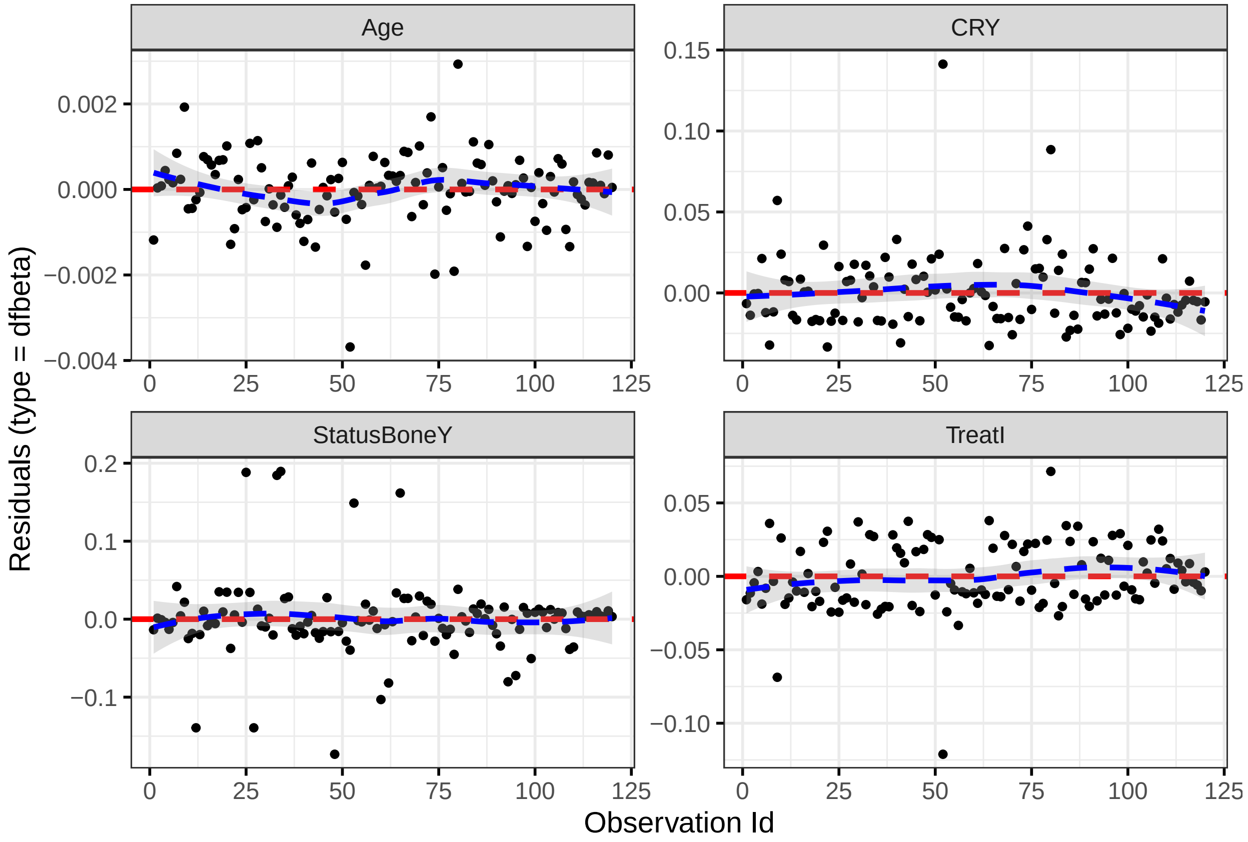


```
#cox diagnostic plots: residuals
ggcoxzph(test2.4)
```



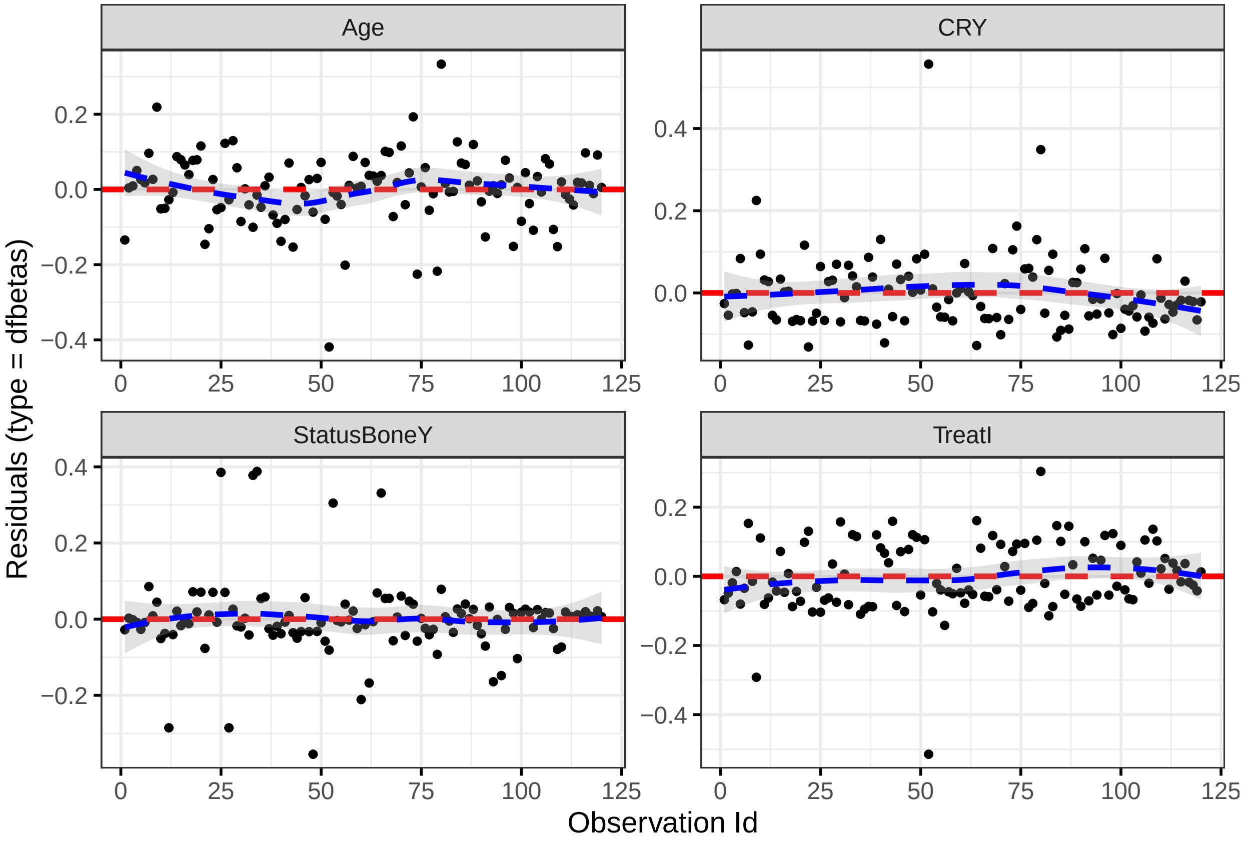
```
ggcoxdiagnostics(cox2.3, type = "dfbeta",
                 linear.predictions = F,
                 ggtheme = theme_bw())
```

```
## `geom_smooth()` using formula 'y ~ x'
```



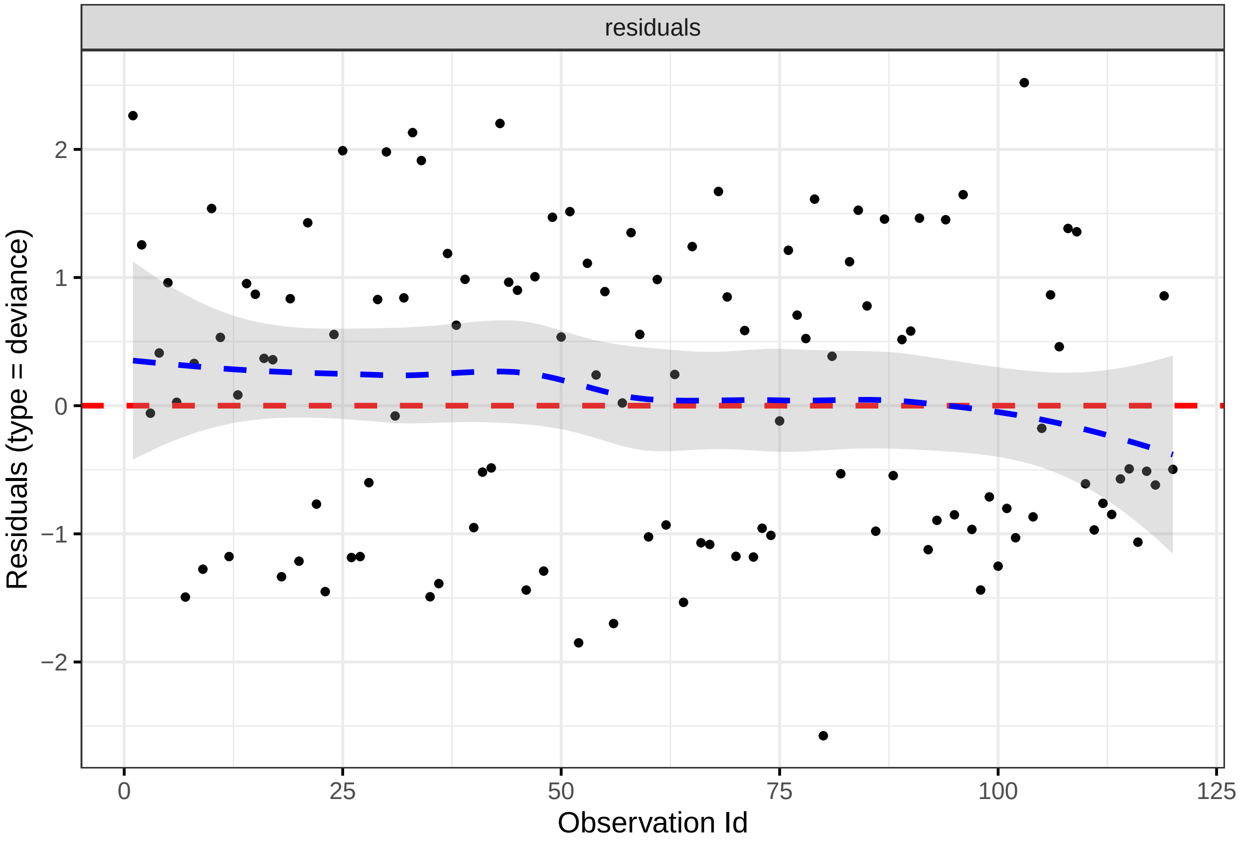
```r
ggcoxdiagnostics(cox2.3, type = "dfbetas",
                 linear.predictions = F,
                 ggtheme = theme_bw())
```

```
## ‘geom_smooth()‘ using formula ’y ~ x’
```



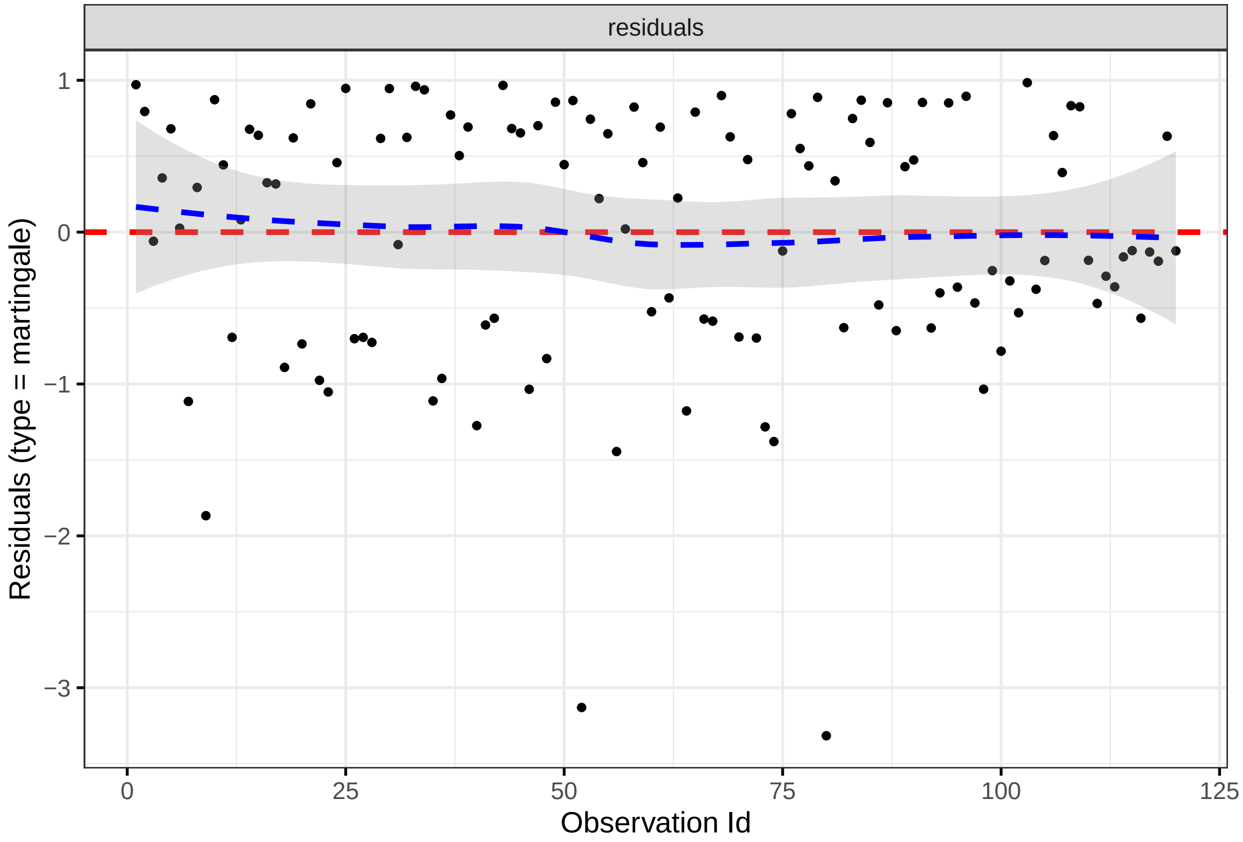
```r
ggcoxdiagnostics(cox2.3, type = "deviance",
                 linear.predictions = F,
                 ggtheme = theme_bw())
```

```
## ‘geom_smooth()‘ using formula ’y ~ x’
```

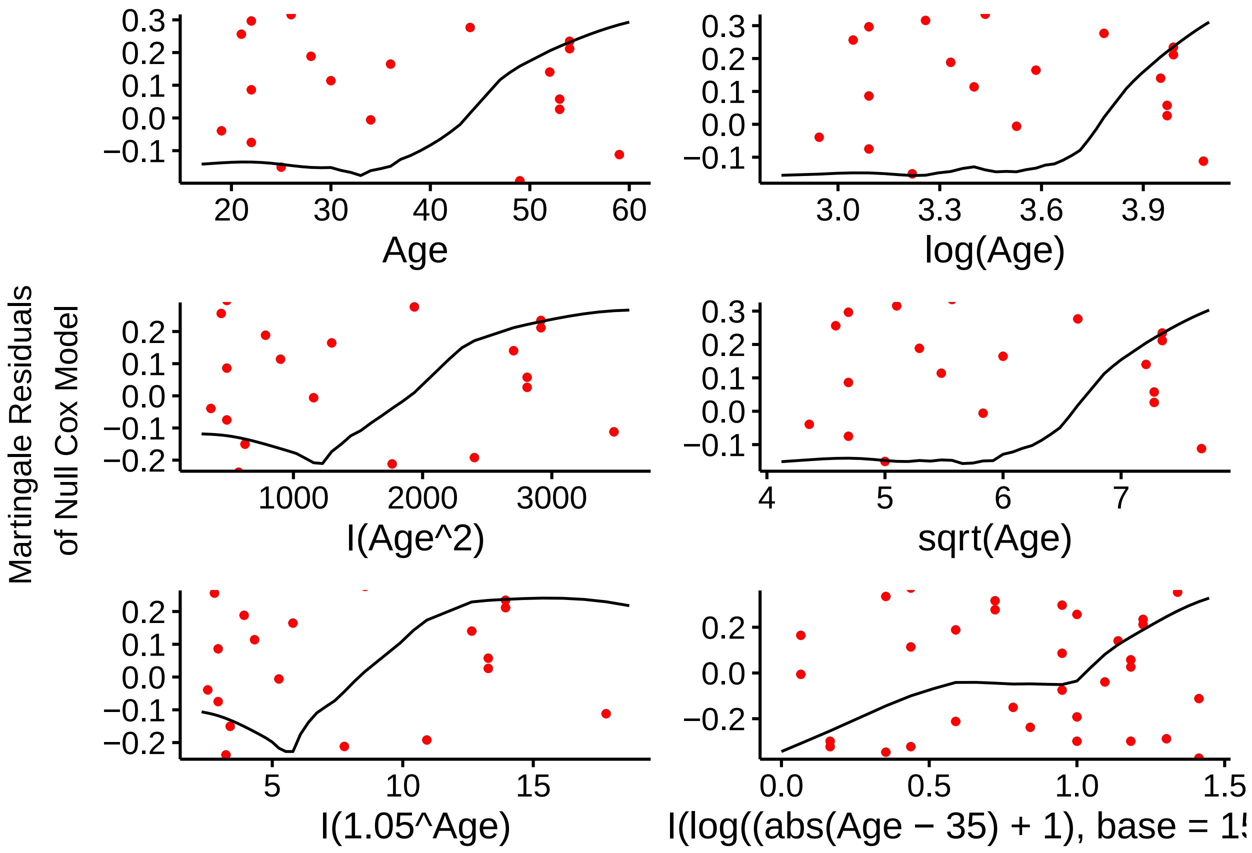


```
ggcoxdiagnostics(cox2.3, type = "martingale",
                 linear.predictions = F,
                 ggtheme = theme_bw())
```

```
## ‘geom_smooth()‘ using formula ’y ~ x’
```



```
#determine functional form of age
set.seed(12345)
cox.age=coxph(km~Age+log(Age)+I(Age^2)+sqrt(Age)+I(1.05^Age)+I(log((abs(Age-35)+1),base=15)^2),data=leuk
lin2.4=ggcoxfunctional(cox.age,data=leukem.aml)
lin2.4
```



```
#Question 3.1-3.2


#AFT model
fit3.1=survreg(km~Age+Treat,data=leukem.aml)
summary(fit3.1)
```

```
##
## Call:
## survreg(formula = km ~ Age + Treat, data = leukem.aml)
##                Value Std. Error     z       p
## (Intercept)  7.10024    0.41283 17.20 <2e-16
## Age         -0.01831    0.00913 -2.01  0.045
## TreatI       0.51223    0.23285  2.20  0.028
## Log(scale)   0.01578    0.09461  0.17  0.868
##
## Scale= 1.02
##
## Weibull distribution
## Loglik(model)= -599.1   Loglik(intercept only)= -604.1
##  Chisq= 9.92 on 2 degrees of freedom, p= 0.007
## Number of Newton-Raphson Iterations: 5
## n= 120
```

```
fit3.1.surv=survfit(km~Age+Treat,data=leukem.aml)

#Question 3.3


#transform aft model to ph model
para=fit3.1$coefficients
lscale=log(fit3.1$scale)
V=fit3.1$var
# para
# lscale
# V
lambda<-exp(-para[1]*exp(-lscale))
alpha<-exp(-lscale)
beta<--para[-1]*exp(-lscale)
x<-c(lambda,alpha,beta)
names(x)[1]<-"Intercept"
names(x)[2]<-"lambda"
m<-length(para[-1])
G<-matrix(0,nrow=m+2,ncol=m+2)
G[1,1]<--exp(-para[1]*exp(-lscale))*exp(-lscale)
G[2:(m+1),3:(m+2)]<-diag(m)*(-exp(-lscale))
G[m+2,1]<-exp(-para[1]*exp(-lscale))*para[1]*exp(-lscale)
G[m+2,2]<--exp(-lscale)
G[m+2,3:(m+2)]<-para[-1]*exp(-lscale)
# G
PrVar<-t(G)%*%V%*%G
# PrVar
PrStd<-sqrt(diag(PrVar))
# PrStd
PrChisq<-c(" "," ",(x[3:(m+2)]/PrStd[3:(m+2)])^2)
PrPvalue<-c(" "," ",pchisq((x[3:(m+2)]/PrStd[3:(m+2)])^2,1,lower.tail=F))
out<-data.frame(x,PrStd,PrChisq,PrPvalue)
names(out)<-c("Estimate","StdError","Chisq","P-value")
out
```

```
##                Estimate     StdError            Chisq            P-value
## Intercept  0.0009219183 0.0006803664
## lambda     0.9843411517 0.0931305471
## Age        0.0180225253 0.0089632209 4.04299391246284  0.044355066728441
## TreatI    -0.5042111027 0.2303038312 4.79316615145063 0.0285728583696877
```

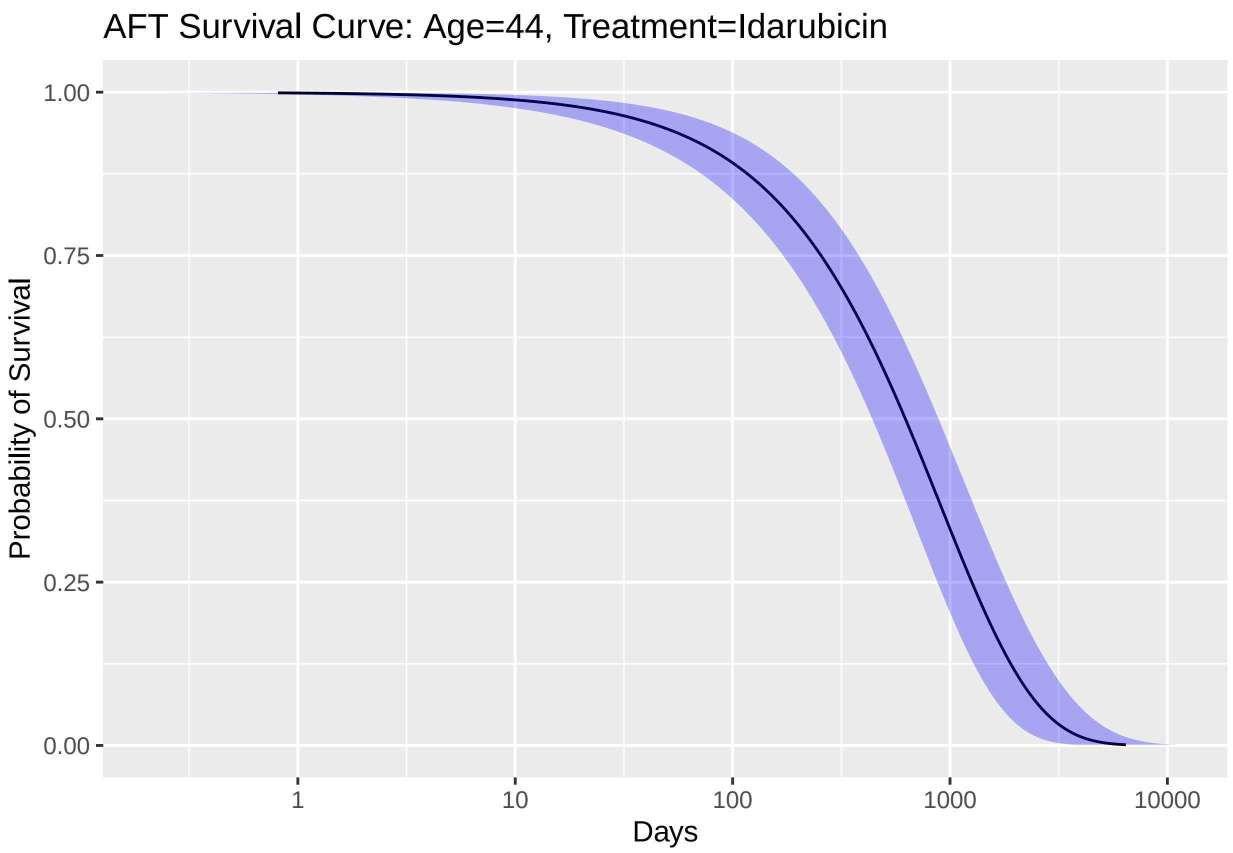
```
#Question 3.4

#Getting aft estimated survival function for patient age=44 treat=I

pred.data=tibble(Age=44,
                 Treat=as.factor("I"))

#median response
predict(fit3.1,pred.data,
        type = "quantile",p=.5)
```

```
##        1
## 622.9823
```

```
seq_0_1_1000=seq(0.001,.999,by=.001)

days.aft=predict(fit3.1,pred.data,
                 type = "quantile",p=seq_0_1_1000)


upperbound=rep(0,length(seq_0_1_1000))
lowerbound=rep(0,length(seq_0_1_1000))

#the add_quantile() function cannot compute quantiles at 0 and 1.
#To get around this I set the range to be (.001, .999).
#Exact quantile estimates will be slightly off by a bit,
#but this should not be a problem.

for(i in 1:length(seq_0_1_1000)){
  cis=add_quantile(pred.data,
                   fit3.1,
                   p=seq_0_1_1000[i],
                   alpha=.05)[1,5:6]
  lowerbound[i]=cis[[1]]
  upperbound[i]=cis[[2]]

}
```

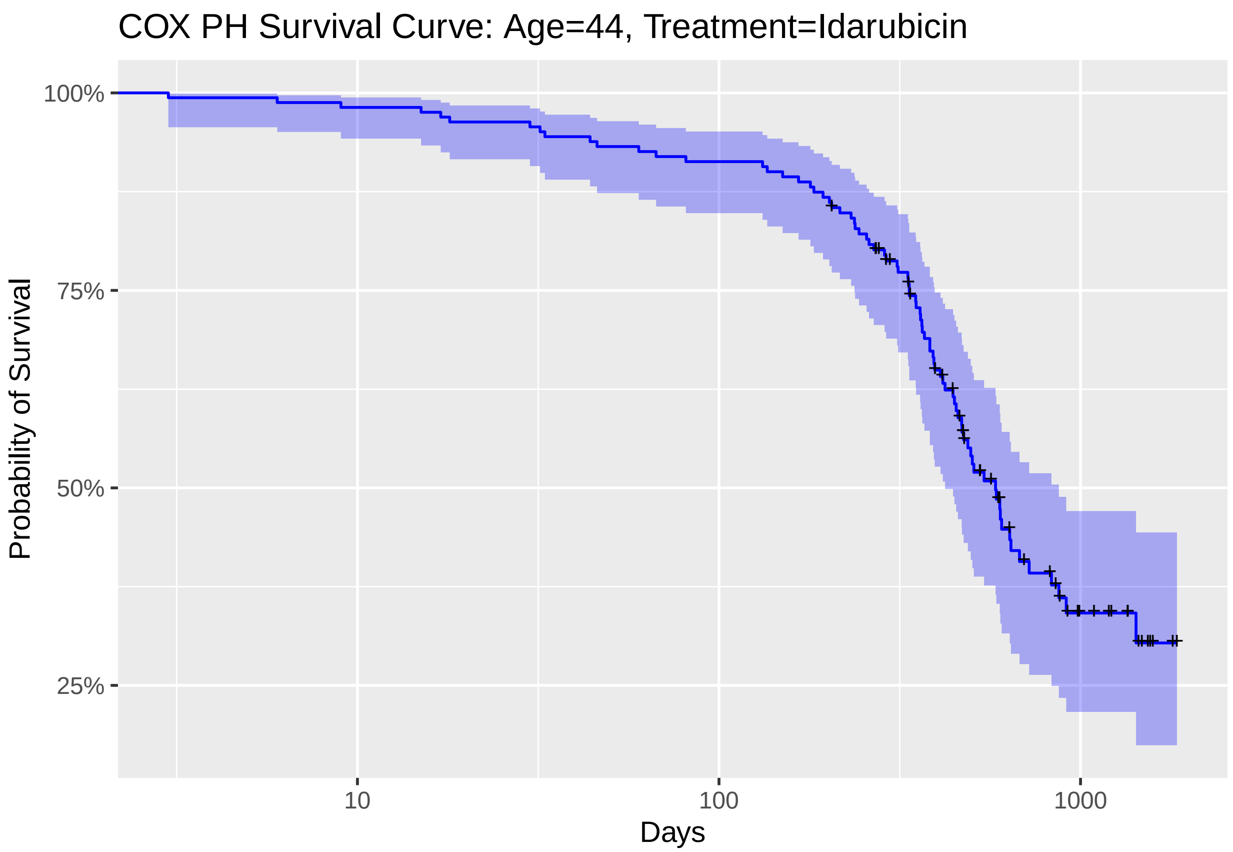
```
## Warning: ‘as_data_frame()‘ is deprecated as of tibble 2.0.0.
## Please use ‘as_tibble()‘ instead.
## The signature and semantics have changed, see ‘?as_tibble‘.
## This warning is displayed once every 8 hours.
## Call ‘lifecycle::last_warnings()‘ to see where this warning was generated.
```

```
aft.preds=tibble(days=days.aft)%>%
  mutate(prob=rev(seq_0_1_1000))%>%
  mutate(ul=upperbound)%>%
  mutate(ll=lowerbound)

#plotting aft survival function based on prediciton
ggplot(aft.preds,aes(x=days,y=prob))+
  geom_line()+
  ggtitle("AFT Survival Curve: Age=44, Treatment=Idarubicin")+
  xlab("Days")+
  ylab("Probability of Survival")+
  geom_ribbon(aes(xmin=ll,xmax=ul),
            alpha=0.3,fill="blue")+
  scale_x_log10()
```



```r
#ploting coxph estimated survival function based on predicition
cox2.2=coxph(km~I(log((abs(Age-35)+1),base=15)^2)+Treat,data=leukem.aml)
cox.pred=survfit(cox2.2,newdata=pred.data, conf.type = "log-log")
autoplot(cox.pred,surv.colour = "blue")+
  ggtitle("COX PH Survival Curve: Age=44, Treatment=Idarubicin")+
  xlab("Days")+
  ylab("Probability of Survival")+
  scale_x_log10()
```

```
## Warning: Transformation introduced infinite values in continuous x-axis

## Warning: Transformation introduced infinite values in continuous x-axis
```



```
#calculating necessary quantiles and performing ks test on coxph and aft survival functions.
aft.preds[c(500,690),1:4]
```

```
## # A tibble: 2 x 4
##    days  prob    ul    ll
##   <dbl> <dbl> <dbl> <dbl>
## 1  623.  0.5   885.  438.
## 2 1061.  0.31 1516.  743.
```

```
quantile(cox.pred,p=c(.5,.69))
```

```
## $quantile
##   50   69
##  582 1424
##
## $lower
##  50  69
## 422 637
##
## $upper
##  50  69
## 871  NA
```

```
ks.test(aft.preds$days[0:730],cox.pred$time)
```

```
##
##  Two-sample Kolmogorov-Smirnov test
##
## data:  aft.preds$days[0:730] and cox.pred$time
## D = 0.10526, p-value = 0.2246
## alternative hypothesis: two-sided
```