432 Class 21 Slides

github.com/THOMASELOVE/2020-432

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Preliminaries

```
library(here); library(janitor); library(magrittr)
library(broom); library(knitr); library(rms)
library(survival); library(survminer)
library(tidyverse)

theme_set(theme_bw())
```

```
brca <- read_csv(here("data", "brca.csv")) %>%
    type.convert()
```

Working with Time-to-Event Data

- The `brca` trial of three treatments for Breast Cancer
- Cox Proportional Hazards Regression with `coxph`
- Diagnostics for Cox Proportional Hazards Regression
- Using `cph` from the `rms` package to fit a Cox model

The `brca` trial

The `brca` trial

The `brca` data describes a parallel randomized trial of three treatments, adjuvant to surgery in the treatment of patients with stage-2 carcinoma of the breast. The three treatment groups are:

- `S_CT` = Surgery plus one year of chemotherapy
- `S_IT` = Surgery plus one year of immunotherapy
- `S_Both` = Surgery plus one year of chemotherapy and immunotherapy

The measure of efficacy were "time to death" in weeks. In addition to `treat`, our variables are:

- `trial_weeks`: time in the study, in weeks, to death or censoring
- `last_alive`: 1 if alive at last follow-up (and thus censored), 0 if dead
- `age`: age in years at the start of the trial

`brca` tibble (note big problem: n = 31!)

Source: Chen and Peace (2011) *Clinical Trial Data Analysis Using R*, CRC Press, section 5.1

```
# A tibble: 31 x 5
   subject treat  trial_weeks last_alive   age
   <fct>   <fct>        <int>      <int> <int>
 1 A01     S_CT           102          0    55
 2 A02     S_IT           192          0    62
 3 A03     S_Both          73          0    72
 4 A04     S_CT            58          1    48
 5 A05     S_CT            48          1    26
 6 A06     S_IT           182          1    52
 7 A07     S_IT           196          1    50
 8 A08     S_CT           177          1    49
 9 A09     S_IT           191          1    62
10 A10     S_Both          36          0    60
# ... with 21 more rows
```

Analytic Objectives

This is a typical right-censored survival data set with interest in the comparative analysis of the three treatments.

1. Does immunotherapy added to surgery plus chemotherapy improve survival? (Comparing S_Both to S_CT)
2. Does chemotherapy add efficacy to surgery plus immunotherapy? (S_Both vs. S_IT)
3. What is the effect of age on survival?

Create survival object

- `trial_weeks`: time in the study, in weeks, to death or censoring
- `last_alive`: 1 if alive at last follow-up (and thus censored), 0 if dead

So `last_alive` = 0 if the event (death) occurs.

What's next?

Create survival object

- `trial_weeks`: time in the study, in weeks, to death or censoring
- `last_alive`: 1 if alive at last follow-up (and thus censored), 0 if dead

So `last_alive` = 0 if the event (death) occurs.

```
brca$S <- with(brca, Surv(trial_weeks, last_alive == 0))

head(brca$S)
```

```
[1] 102  192   73   58+  48+ 182+
```

Build Kaplan-Meier Estimator

```
kmfit <- survfit(S ~ treat, dat = brca)

print(kmfit, print.rmean = TRUE)
```

```
Call: survfit(formula = S ~ treat, data = brca)

               n events *rmean *se(rmean) median 0.95LCL
treat=S_Both 10      4    188        23.7     NA     139
treat=S_CT   11      6    153        21.1    144     102
treat=S_IT   10      5    188        17.9    192     144
             0.95UCL
treat=S_Both      NA
treat=S_CT        NA
treat=S_IT        NA
    * restricted mean with upper limit =  242
```

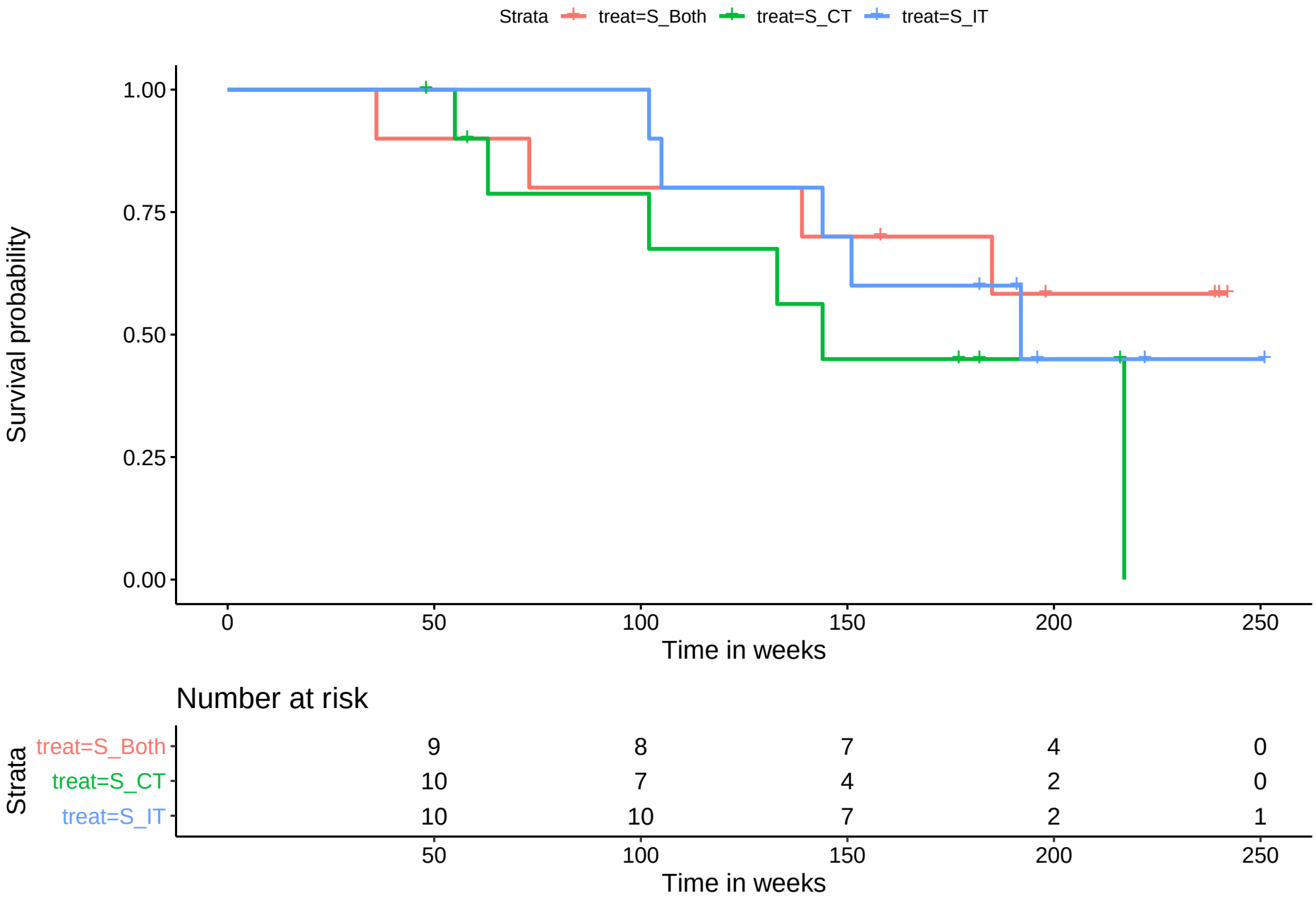
```
> summary(kmfit)
Call: survfit(formula = S ~ treat, data = brca)

                treat=S_Both
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
   36     10       1    0.900  0.0949        0.732            1
   73      9       1    0.800  0.1265        0.587            1
  139      8       1    0.700  0.1449        0.467            1
  185      6       1    0.583  0.1610        0.340            1

                treat=S_CT
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
   55     10       1    0.900  0.0949        0.732        1.000
   63      8       1    0.787  0.1340        0.564        1.000
  102      7       1    0.675  0.1551        0.430        1.000
  133      6       1    0.562  0.1651        0.316        1.000
  144      5       1    0.450  0.1660        0.218        0.927
  217      1       1    0.000     NaN           NA           NA

                treat=S_IT
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  102     10       1     0.90  0.0949        0.732        1.000
  105      9       1     0.80  0.1265        0.587        1.000
  144      8       1     0.70  0.1449        0.467        1.000
  151      7       1     0.60  0.1549        0.362        0.995
  192      4       1     0.45  0.1743        0.211        0.961
```

K-M Plot via `survminer`



K-M Plot via survminer (code)

```
ggsurvplot(kmfit, data = brca,
           risk.table = TRUE,
           risk.table.height = 0.25,
           xlab = "Time in weeks")
```

Testing the difference between curves

```
survdiff(S ~ treat, dat = brca)
```

```
Call:
survdiff(formula = S ~ treat, data = brca)

                N Observed Expected (O-E)^2/E (O-E)^2/V
treat=S_Both 10        4     5.62    0.4676    0.7725
treat=S_CT   11        6     3.80    1.2772    1.7647
treat=S_IT   10        5     5.58    0.0605    0.0981

 Chisq= 1.9  on 2 degrees of freedom, p= 0.4
```

What do we conclude?

A Cox Model for Treatment

Fit Cox Model mod_T: Treatment alone

```
mod_T <- coxph(S ~ treat, data = brca)
mod_T
```

```
Call:
coxph(formula = S ~ treat, data = brca)

             coef exp(coef) se(coef)     z     p
treatS_CT 0.8313    2.2963   0.6547 1.270 0.204
treatS_IT 0.2481    1.2816   0.6740 0.368 0.713

Likelihood ratio test=1.75  on 2 df, p=0.4164
n= 31, number of events= 15
```

```
> summary(mod_T)
Call:
coxph(formula = S ~ treat, data = brca)

  n= 31, number of events= 15

              coef exp(coef) se(coef)     z Pr(>|z|)
treatS_CT 0.8313    2.2963   0.6547 1.270    0.204
treatS_IT 0.2481    1.2816   0.6740 0.368    0.713

           exp(coef) exp(-coef) lower .95 upper .95
treatS_CT      2.296     0.4355    0.6364     8.286
treatS_IT      1.282     0.7803    0.3420     4.803

Concordance= 0.577  (se = 0.083 )
Likelihood ratio test= 1.75  on 2 df,   p=0.4
Wald test            = 1.82  on 2 df,   p=0.4
Score (logrank) test = 1.89  on 2 df,   p=0.4
```

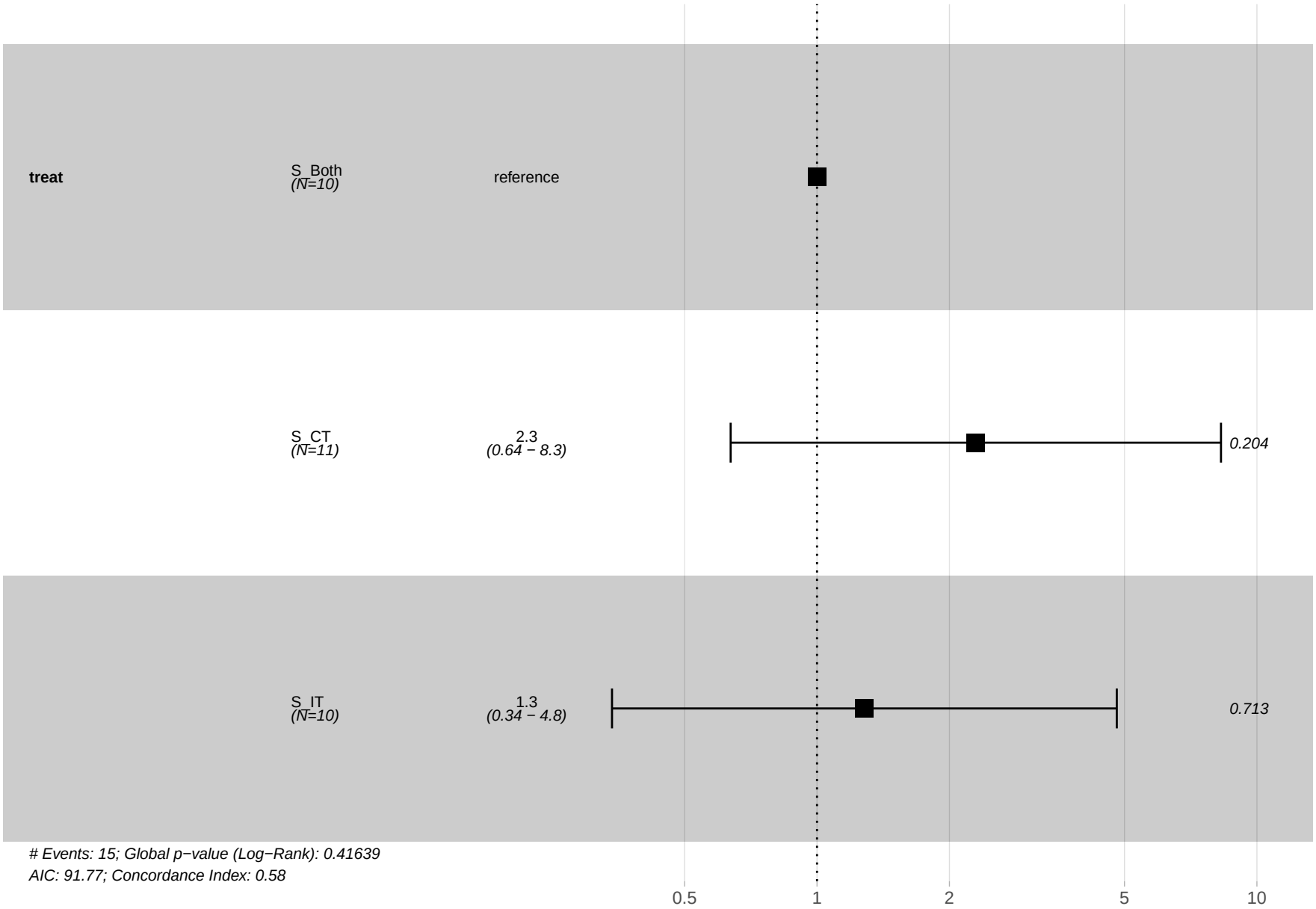
Interpreting the Summaries

```
tidy(mod_T, exponentiate = TRUE) %>%
    select(term, estimate, std.error, conf.low, conf.high) %>%
    kable(digits = 3)
```

term	estimate	std.error	conf.low	conf.high
treatS_CT	2.296	0.655	0.636	8.286
treatS_IT	1.282	0.674	0.342	4.803

- A subject treated with `S_CT` is estimated to have 2.296 times the hazard (95% CI: 0.636, 8.286) of a subject treated with `S_Both` (the baseline).
- A subject treated with `S_IT` is estimated to have 1.282 times the hazard (95% CI 0.342, 4.803) of a subject treated with `S_Both`.

ggforest(mod_T, data = brca)



Summarizing `mod_T`

All of this comes from `glance(mod_T)`

- `n` = 31 cases, with `nevent` = 15 events (so 16 censored)
- log rank test statistic = 1.752, $p = 0.416$
- Score test statistic = 1.895, $p = 0.388$
- Wald test statistic = 1.820, $p = 0.403$
  - Each tests H_0: Treatment adds no value
- (Cox-Snell) R-Squared = 0.055, Maximum Pseudo R-Square = 0.944
  - Cox and Snell's pseudo-R^2 reflects the improvement of this model over the model with the intercept alone, with higher values indicating more substantial improvement over an intercept-only model.
  - Not really a percentage of anything: often the maximum value here is less than 1.

Summarizing `mod_T`

Again, all of this comes from `glance(mod_T)` - see next slide

- Concordance = 0.577 (standard error = 0.083)
  - Really only appropriate when we have at least one quantitative predictor in the Cox model
  - Assesses probability of agreement between survival time and the risk score generated by the predictors
  - 1 indicates perfect agreement, 0.5 indicates no better than chance
- log Likelihood = -43.886, AIC = 91.773, BIC = 93.189
  - Usual summaries, used to compare models, mostly

`glance(mod_T)` Fit Quality Summaries (edited)

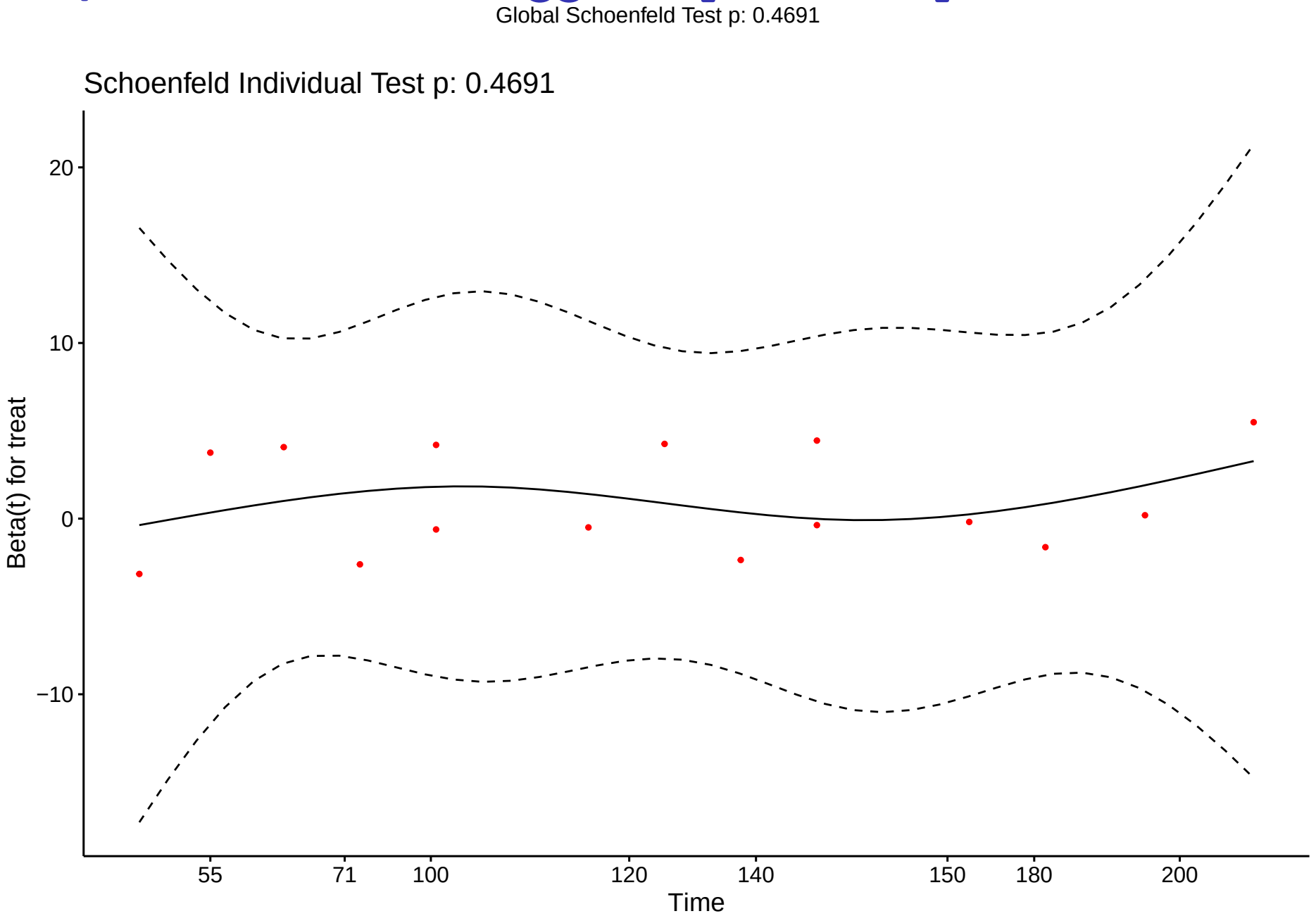
n	31.000
nevent	15.000
statistic.log	1.752
p.value.log	0.416
statistic.sc	1.895
p.value.sc	0.388
statistic.wald	1.820
p.value.wald	0.403
r.squared	0.055
r.squared.max	0.944
concordance	0.577
std.error.concordance	0.083
logLik	-43.886
AIC	91.773
BIC	93.189

Checking the Proportional Hazards Assumption

- If the proportional hazards assumption is appropriate, we should see a slope of essentially zero in the residuals that are plotted against time on the next slide.
- If we see a slope that seriously different from zero, that will suggest a violation of the proportional hazards assumption.
- A hypothesis test is also performed, where a significant result also indicates a potential problem with the assumption.

If we did see a violation of assumptions, we could either add a non-linear predictor term or use a different kind of survival model.

Graphical PH Check `ggcoxzph(cox.zph(mod_T))`



A Two-Predictor Cox Model (Age + Treatment)

Fit Cox Model mod_AT: Age + Treatment

```
mod_AT <- coxph(S ~ age + treat, data = brca)
mod_AT
```

```
Call:
coxph(formula = S ~ age + treat, data = brca)

              coef exp(coef) se(coef)     z      p
age        0.07807   1.08119  0.03672 2.126 0.0335
treatS_CT 0.59960   1.82139  0.65741 0.912 0.3617
treatS_IT 0.28799   1.33375  0.68566 0.420 0.6745

Likelihood ratio test=6.99  on 3 df, p=0.07224
n= 31, number of events= 15
```

```
> summary(mod_AT)
Call:
coxph(formula = S ~ age + treat, data = brca)

  n= 31, number of events= 15

              coef exp(coef) se(coef)     z Pr(>|z|)
age        0.07807   1.08119  0.03672 2.126   0.0335 *
treatS_CT  0.59960   1.82139  0.65741 0.912   0.3617
treatS_IT  0.28799   1.33375  0.68566 0.420   0.6745
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

           exp(coef) exp(-coef) lower .95 upper .95
age            1.081     0.9249    1.0061     1.162
treatS_CT      1.821     0.5490    0.5021     6.607
treatS_IT      1.334     0.7498    0.3479     5.113

Concordance= 0.701  (se = 0.065 )
Likelihood ratio test= 6.99  on 3 df,   p=0.07
Wald test            = 5.85  on 3 df,   p=0.1
Score (logrank) test = 6.15  on 3 df,   p=0.1
```

Interpreting the Coefficients of mod_AT

```
tidy(mod_AT, exponentiate = TRUE) %>%
  select(term, estimate, std.error, conf.low, conf.high) %>%
  kable(digits = 2)
```

term	estimate	std.error	conf.low	conf.high
age	1.08	0.04	1.01	1.16
treatS_CT	1.82	0.66	0.50	6.61
treatS_IT	1.33	0.69	0.35	5.11

- If Harry and Sally receive the same `treat` but Harry is one year older, the model estimates Harry will have 1.08 times the hazard of Sally (95% CI 1.01, 1.16).

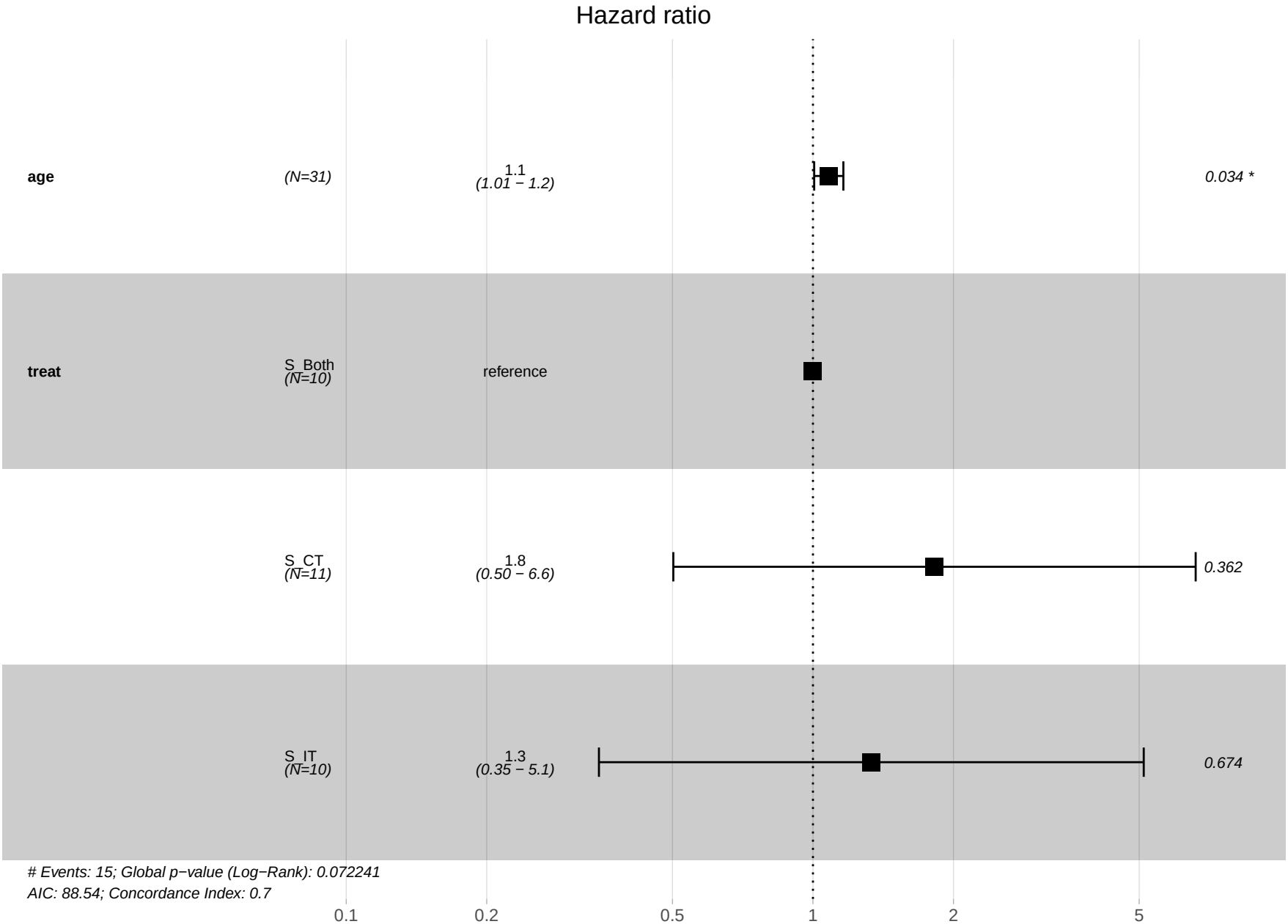
Interpreting the Coefficients of mod_AT

```
tidy(mod_AT, exponentiate = TRUE) %>%
  select(term, estimate, std.error, conf.low, conf.high) %>%
  kable(digits = 2)
```

term	estimate	std.error	conf.low	conf.high
age	1.08	0.04	1.01	1.16
treatS_CT	1.82	0.66	0.50	6.61
treatS_IT	1.33	0.69	0.35	5.11

- If Harry receives S_CT and Sally receives S_Both, and they are the same age, the model estimates Harry will have 1.82 times the hazard of Sally (95% CI 0.50, 6.61).
- If Cyrus receives S_IT and Sally receives S_Both, and they are the same age, the model estimates Cyrus will have 1.33 times the hazard of Sally (95% CI 0.33, 5.11).

ggforest(mod_AT, data = brca)



Comparing the Two Models

n = 31, nevent = 15 for each model.

```
bind_rows(glance(mod_T), glance(mod_AT)) %>%
    mutate(model = c("mod_T", "mod_AT")) %>%
    select(model, p.value.log, concordance, r.squared,
           max_r2 = r.squared.max, AIC, BIC) %>%
  kable(digits = c(0,3,3,3,3,1,1))
```

model	p.value.log	concordance	r.squared	max_r2	AIC	BIC
mod_T	0.416	0.577	0.055	0.944	91.8	93.2
mod_AT	0.072	0.701	0.202	0.944	88.5	90.7

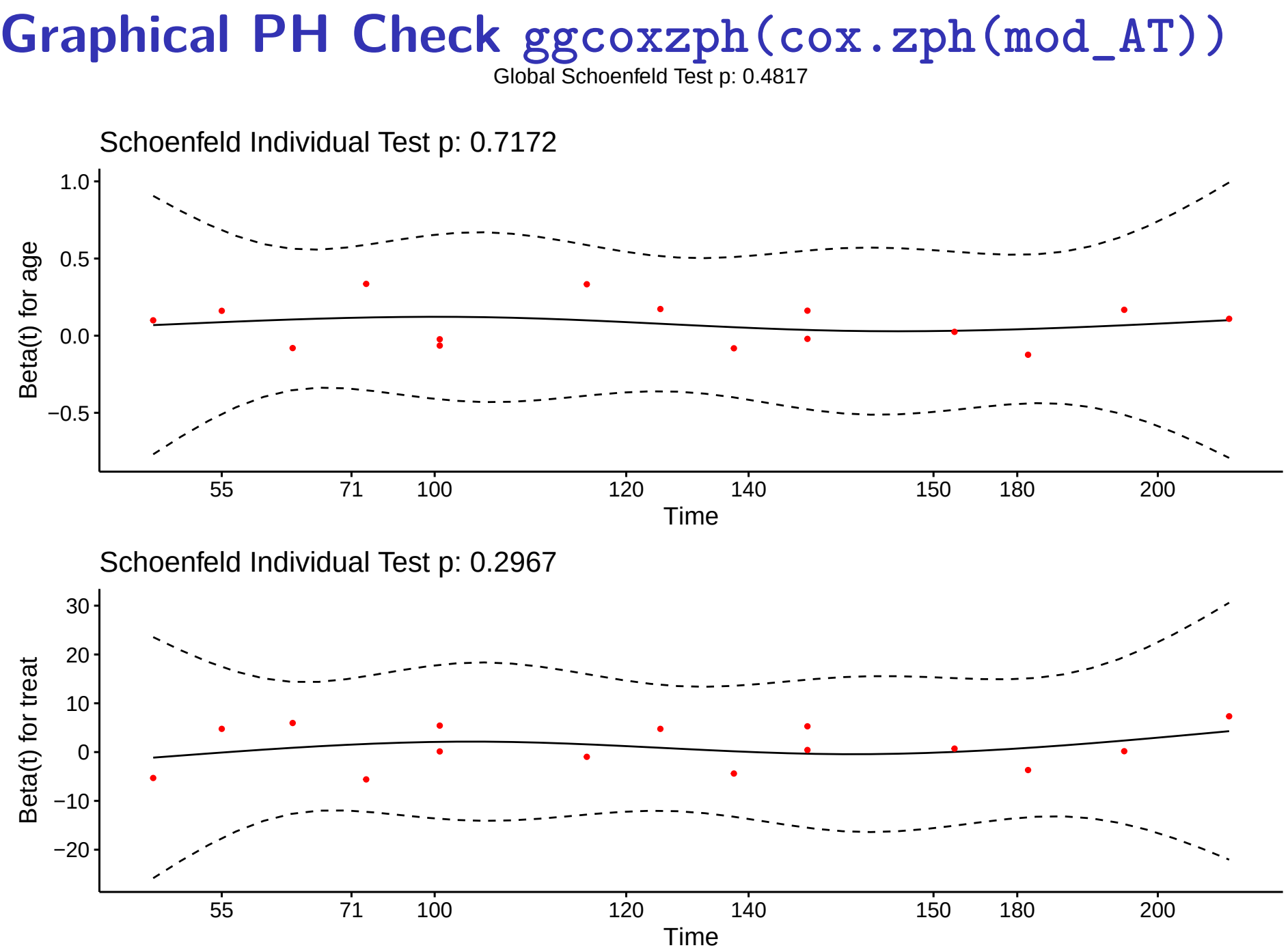
What do the glance results indicate?

Significance Test via Likelihood Ratio ANOVA

```
anova(mod_AT, mod_T)
```

```
Analysis of Deviance Table
 Cox model: response is  S
 Model 1: ~ age + treat
 Model 2: ~ treat
   loglik Chisq Df P(>|Chi|)
1 -41.268
2 -43.886 5.237  1   0.02211 *
---
Signif. codes:
0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Graphical PH Check `ggcoxzph(cox.zph(mod_AT))`



Back to the Analytic Objectives

1. Does immunotherapy added to surgery plus chemotherapy improve survival? (Comparing S_Both to S_CT)
2. Does chemotherapy add efficacy to surgery plus immunotherapy? (S_Both vs. S_IT)
3. What is the effect of age on survival?

So . . . what do you think?

Building a Cox Model with `cph` from the `rms` package

Using rms::cph to fit a fancier AxT

```
brca <- read_csv(here("data/brca.csv")) %>% type.convert()

d <- datadist(brca)
options(datadist="d")

brca$S <- with(brca, Surv(trial_weeks, last_alive == 0))

cph_AxT <- cph(S ~ rcs(age, 4) + treat + age %ia% treat,
               data = brca,
               x = TRUE, y = TRUE, surv = TRUE)
```

cph_AxT (and see next slide)

```
Cox Proportional Hazards Model

 cph(formula = S ~ rcs(age, 4) + treat + age %ia% treat, data
     x = TRUE, y = TRUE, surv = TRUE)

                        Model Tests       Discrimination
                                              Indexes
 Obs            31    LR chi2     11.66    R2        0.332
 Events         15    d.f.            7    Dxy       0.488
 Center 14.2906       Pr(> chi2) 0.1123    g         1.980
                      Score chi2  11.89    gr        7.245
                      Pr(> chi2) 0.1042

                     Coef    S.E.   Wald Z Pr(>|Z|)
 age                  0.3011 0.2330  1.29  0.1963
 age'                -1.2521 0.7528 -1.66  0.0963
 age''                2.7316 1.5490  1.76  0.0778
 treat=S.CT          -4.9327 6.6650 -0.74  0.4592
```

```
> cph_AxT
Cox Proportional Hazards Model

 cph(formula = S ~ rcs(age, 4) + treat + age %ia% treat, data = brca,
     x = TRUE, y = TRUE, surv = TRUE)

                      Model Tests       Discrimination
                                           Indexes
 Obs           31    LR chi2     11.66    R2        0.332
 Events        15    d.f.            7    Dxy       0.488
 Center 14.2906    Pr(> chi2) 0.1123    g         1.980
                   Score chi2  11.89    gr        7.245
                   Pr(> chi2) 0.1042

                    Coef    S.E.   Wald Z Pr(>|Z|)
 age                 0.3011 0.2330  1.29  0.1963
 age'               -1.2521 0.7528 -1.66  0.0963
 age''               2.7316 1.5490  1.76  0.0778
 treat=S_CT         -4.9327 6.6650 -0.74  0.4592
 treat=S_IT          0.1210 4.8180  0.03  0.9800
 age * treat=S_CT    0.1006 0.1157  0.87  0.3846
 age * treat=S_IT   -0.0005 0.0835 -0.01  0.9949
```

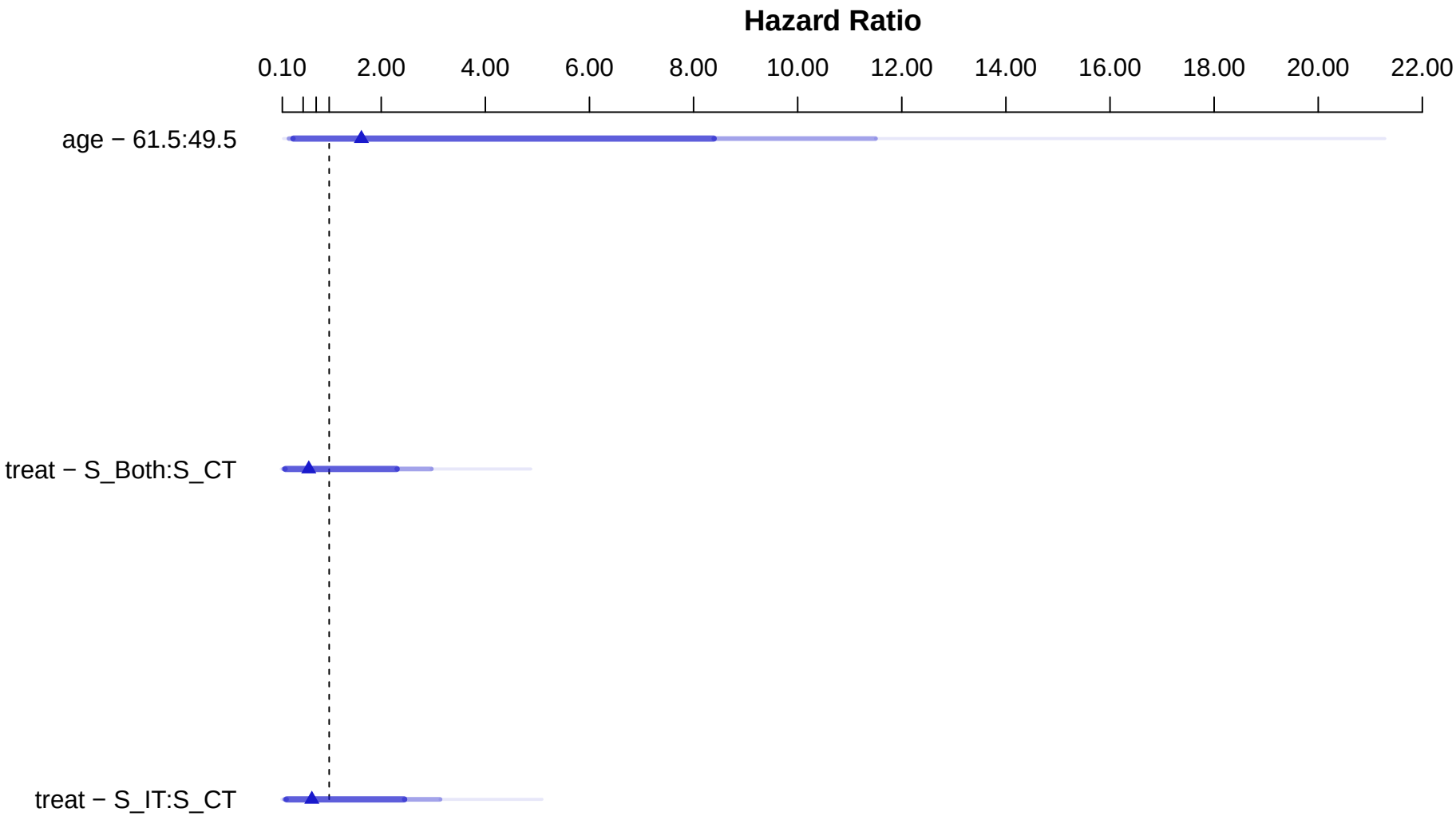
summary(cph_AxT)

```
                Effects                    Response : S

 Factor                  Low  High Diff. Effect   S.E.
 age                     49.5 61.5 12     0.48200 0.99998
  Hazard Ratio           49.5 61.5 12     1.61930      NA
 treat - S_Both:S_CT      2.0  1.0 NA    -0.49745 0.80805
  Hazard Ratio            2.0  1.0 NA     0.60808      NA
 treat - S_IT:S_CT        2.0  3.0 NA    -0.40504 0.78888
  Hazard Ratio            2.0  3.0 NA     0.66695      NA
 Lower 0.95 Upper 0.95
 -1.47790    2.4419
  0.22811   11.4950
 -2.08120    1.0863
  0.12478    2.9633
 -1.95120    1.1411
  0.14210    3.1303

Adjusted to: age=54 treat=S_CT
```

plot(summary(cph_AxT))



Adjusted to:age=54 treat=S_CT

```
set.seed(432)
validate(cph_AxT)
```

```
Warning in fitter(..., strata = strata, rownames = rownames,
offset = offset, : Ran out of iterations and did not
converge


Divergence or singularity in 1 samples

      index.orig training    test optimism index.corrected
Dxy       0.4883   0.5965  0.3693   0.2273           0.2610
R2        0.3320   0.4741  0.2061   0.2680           0.0640
Slope     1.0000   1.0000  0.3819   0.6181           0.3819
D         0.1191   0.2078  0.0650   0.1428          -0.0237
U        -0.0223  -0.0226  1.0971  -1.1196           1.0973
Q         0.1414   0.2303 -1.0321   1.2624          -1.1210
g         1.9803   4.2315  1.2169   3.0145          -1.0342
       n
Dxy   39
R2    39
```

ANOVA for `cph_AxT` model

```
> anova(cph_AxT)
                Wald Statistics          Response: S

 Factor                                     Chi-Square d.f. P
 age  (Factor+Higher Order Factors)         7.71       5    0.1727
  All Interactions                          0.96       2    0.6175
  Nonlinear                                 3.73       2    0.1548
 treat  (Factor+Higher Order Factors)       2.58       4    0.6297
  All Interactions                          0.96       2    0.6175
 age * treat  (Factor+Higher Order Factors) 0.96       2    0.6175
 TOTAL NONLINEAR + INTERACTION              3.74       4    0.4423
 TOTAL                                      8.55       7    0.2868
```

survplot in rms (code)

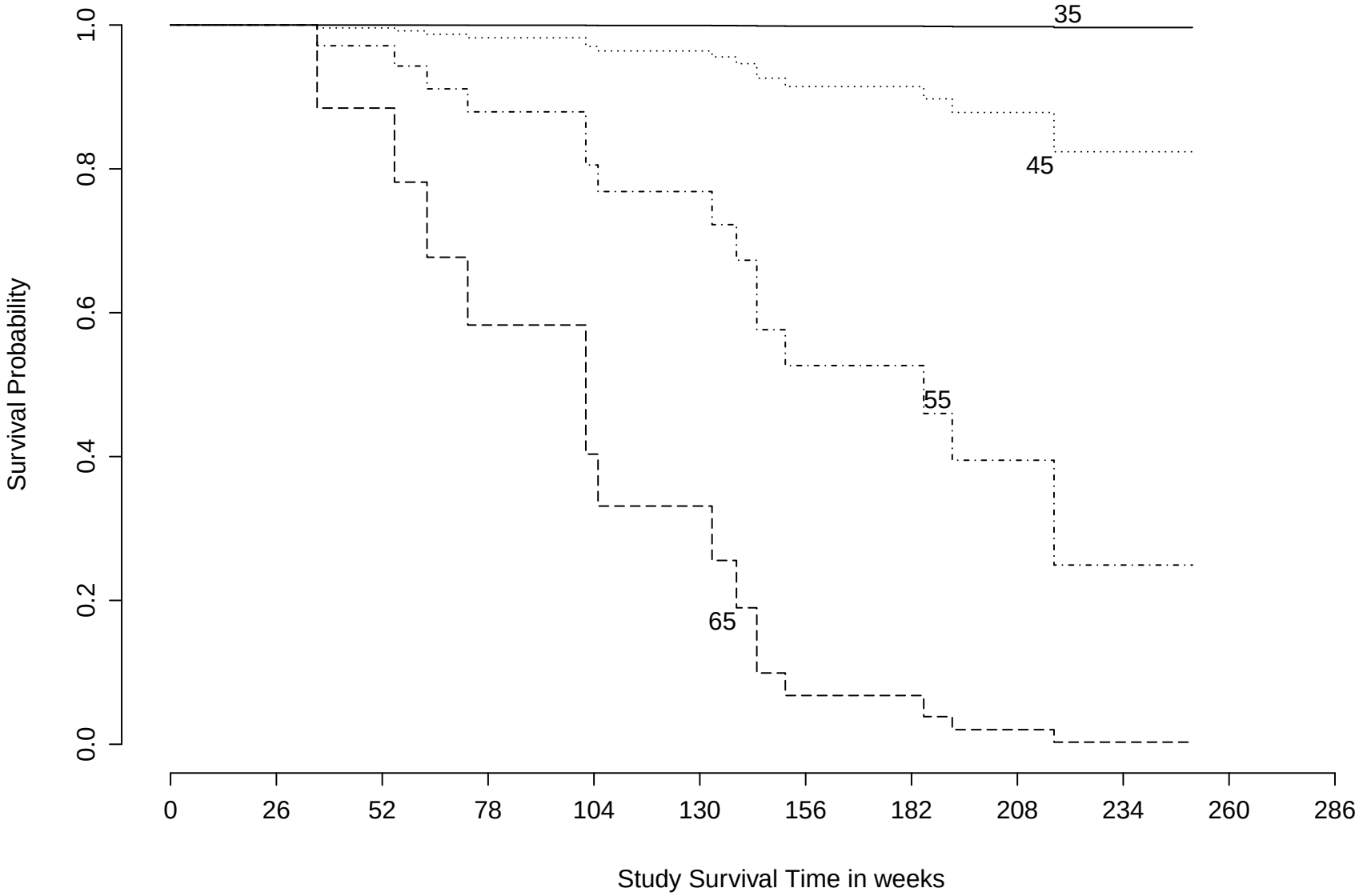
For age comparison:

```
survplot(cph_AxT,
         age = c(35, 45, 55, 65),
         time.inc = 26,
         type = "kaplan-meier",
         xlab = "Study Survival Time in weeks")
```

For treat comparison:

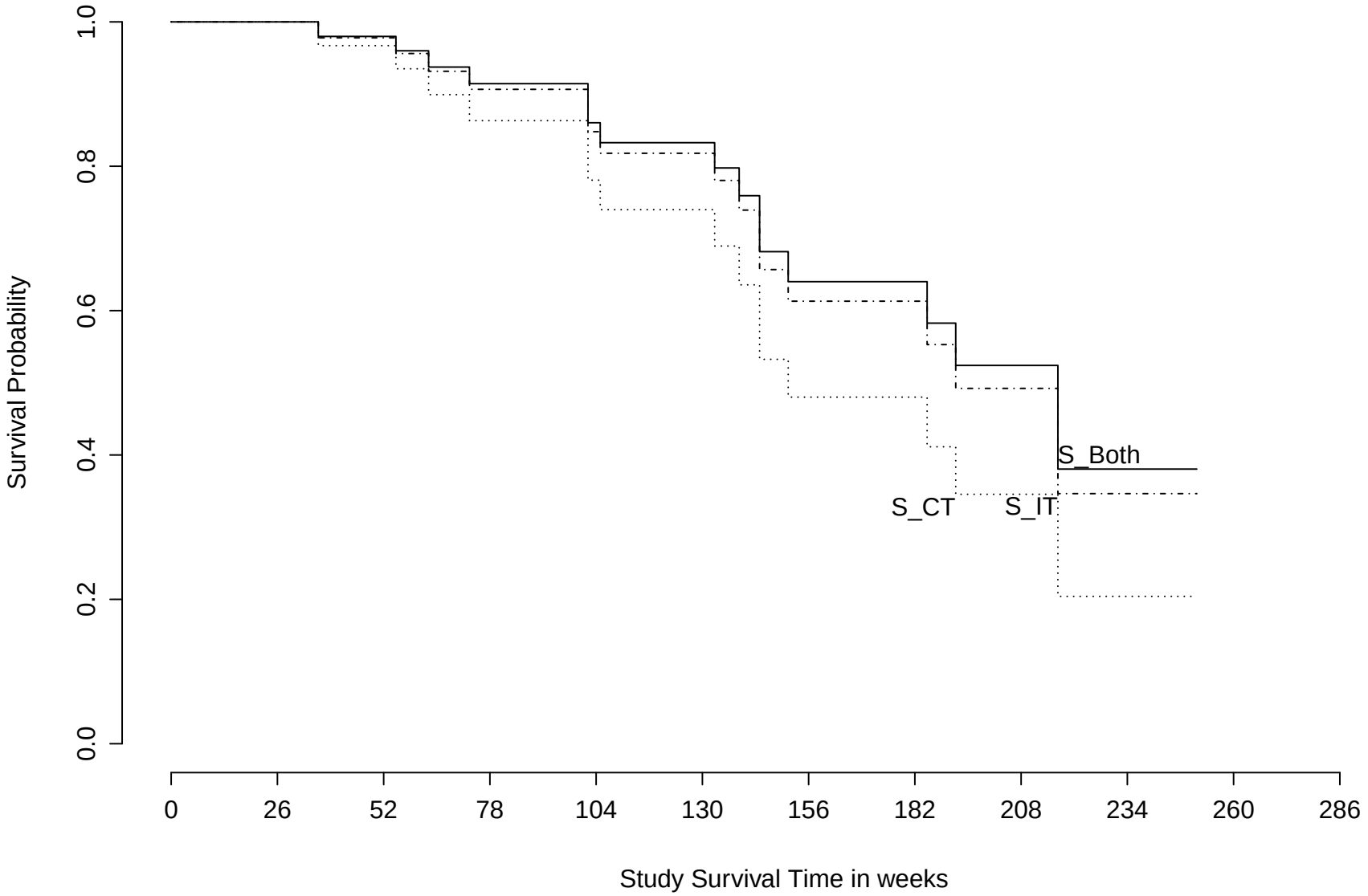
```
survplot(cph_AxT,
         treat,
         time.inc = 26,
         type = "kaplan-meier",
         xlab = "Study Survival Time in weeks")
```

survplot in rms (Result)



Adjusted to: treat=S_CT

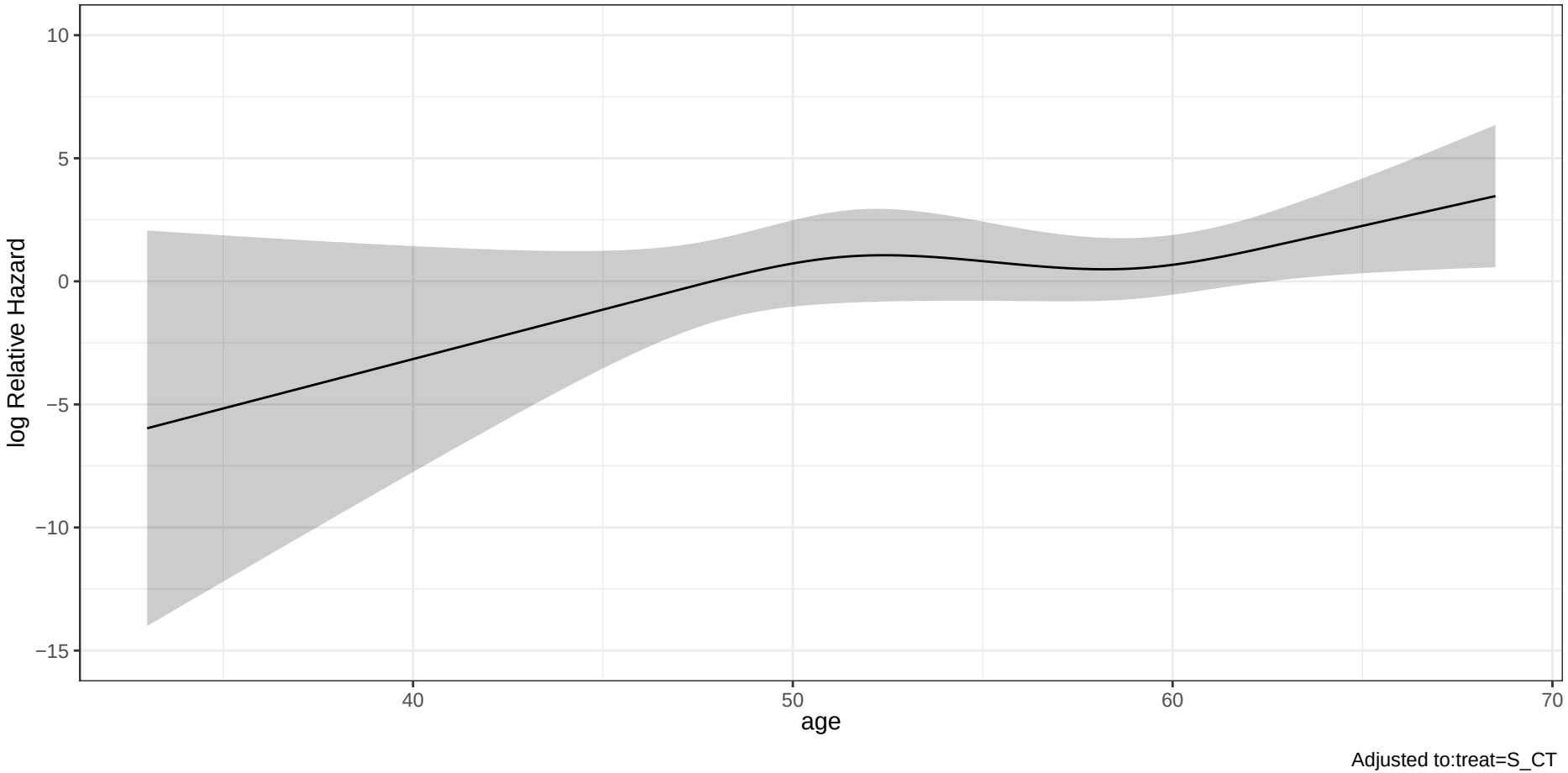
survplot for treat in rms (Result)



Adjusted to: age=54

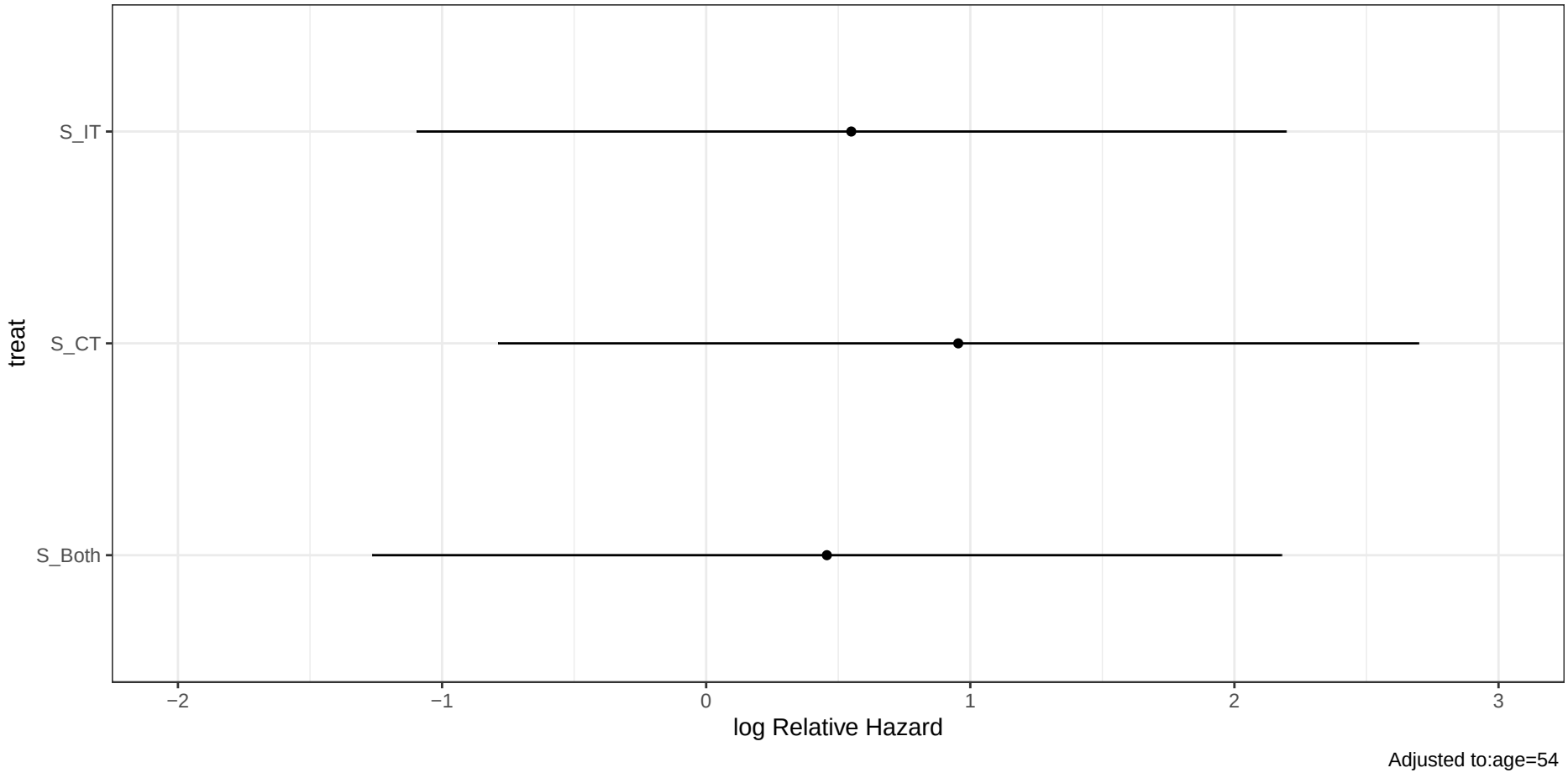
Plotting age effect implied by cph_AxT model

```
ggplot(Predict(cph_AxT, age))
```



Plotting `treat` effect implied by `cph_AxT` model

```
ggplot(Predict(cph_AxT, treat))
```

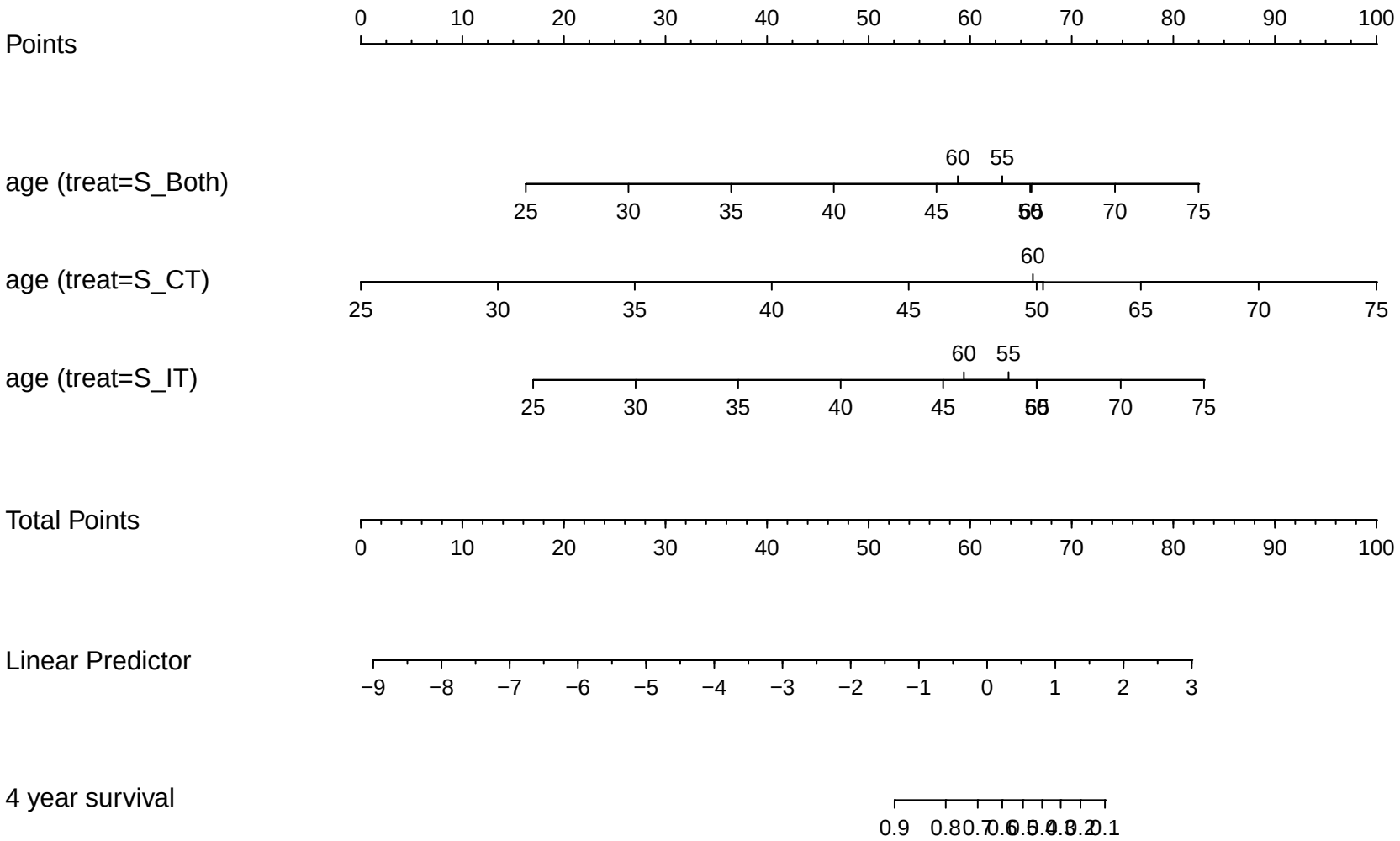


cph_AxT nomogram (code)

```
sv <- Survival(cph_AxT)
surv4 <- function(x) sv(208, lp = x)

plot(nomogram(cph_AxT,
              fun = surv3,
              funlabel = c("4 year survival")))
```

cph_AxT nomogram (Results)

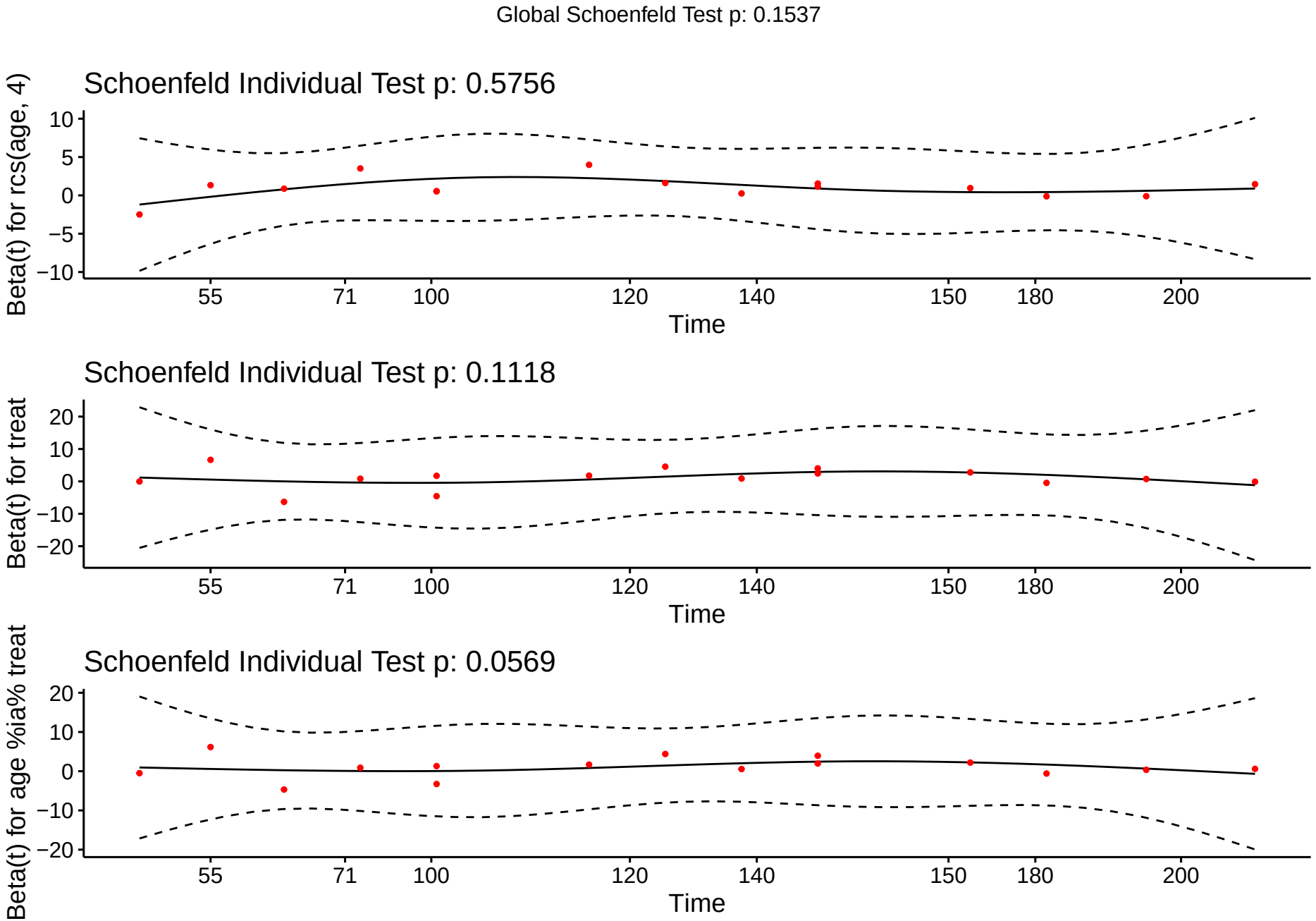


Checking the Proportional Hazards Assumption

```
cox.zph(cph_AxT, transform = "km", global = TRUE)
```

```
                chisq df     p
rcs(age, 4)      1.98  3 0.576
treat            4.38  2 0.112
age %ia% treat   5.73  2 0.057
GLOBAL          10.67  7 0.154
```

```
ggcoxzph(cox.zph(cph_AxT))
```



Additional Diagnostic Plots for your Cox model?

- `survminer` has a function called `ggcoxdiagnostics()` which plots different types of residuals as a function of time, linear predictor or observation id.
- The type of residual can be "martingale", "deviance", "score", "schoenfeld", "dfbeta"', "dfbetas", or "scaledsch".

What to do if the PH assumption is violated

- If the PH assumption fails on a categorical predictor, fit a Cox model stratified by that predictor (use `strata(var)` rather than `var` in the specification of the `coxph` model.)
- If the PH assumption is violated, this means the hazard isn't constant over time, so we could fit separate Cox models for a series of time intervals.
- Use an extension of the Cox model that permits covariates to vary over time.

Visit https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf for details on building the relevant data sets and models, with examples.