stepwise_cox_cx

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Data Preparation

Data Wrangling (wenjie, zhaokun)

```r
# Import data & data cleaning
cirrhosis <- read.csv("data/cirrhosis.csv") |> clean_names()

# Status convert to event indicator (1 = death, 0 = censored)
cirrhosis <- cirrhosis |>
  mutate(
    event = case_when(
      status == "D" ~ 1,
      status %in% c("C", "CL") ~ 0,
      TRUE ~ NA_real_
    ),
    sex = factor(sex),
    drug = factor(drug),
    ascites = factor(ascites),
    hepatomegaly = factor(hepatomegaly),
    spiders = factor(spiders),
    edema = factor(edema, levels = c("N", "S", "Y"), ordered = TRUE),
    stage = factor(stage) # Yixin: "Stage: histologic stage of disease (1, 2, 3, or 4)"
  )

cirrhosis <- cirrhosis |>
  mutate(age_years = age / 365.25)
```

```r
# drop variables not needed in the following modeling
cirrhosis_df = cirrhosis |>
  mutate(
    # log_transformed bilirubin
    log_bilirubin = log(bilirubin),

    # edema group "S" "Y" combined
    edema_bin = case_when(
      edema == "N" ~ 0L,
      edema %in% c("S", "Y") ~ 1L,
      TRUE ~ NA_integer_
    ),
  ) |>
  dplyr::select(-id, -status, -age, -tryglicerides, -cholesterol, -bilirubin, -edema) |>
  na.omit()
```

All rows with NA omitted for Stepwise and LASSO Cox model selection. Log-transformed `Bilirubin` is included in the Cox model. `Edama` derives a binary variable `Edema_bin` based on the presence or absence of Edema.

Stepwise Cox

```
sw_full = coxph(
  Surv(n_days, event) ~
    drug +
    sex + ascites + hepatomegaly +
    spiders + edema_bin + albumin +
    copper + alk_phos + sgot +
    platelets + prothrombin + stage +
    age_years + log_bilirubin,
  data = cirrhosis_df)

sw_null = coxph(
  Surv(n_days, event) ~
    1,
  data = cirrhosis_df)

step_cox = MASS::stepAIC(sw_full, direction = "both", na.rm = TRUE)
```

```
## Start:  AIC=1080.53
## Surv(n_days, event) ~ drug + sex + ascites + hepatomegaly + spiders +
##     edema_bin + albumin + copper + alk_phos + sgot + platelets +
##     prothrombin + stage + age_years + log_bilirubin
##
##                 Df    AIC
## - platelets      1 1078.5
## - spiders        1 1078.6
## - hepatomegaly   1 1078.6
## - ascites        1 1078.7
## - drug           1 1078.8
## - sex            1 1079.0
## - alk_phos       1 1079.2
## - stage          3 1079.5
## - sgot           1 1080.4
## <none>           1080.5
## - copper         1 1080.7
## - edema_bin      1 1082.5
## - age_years      1 1085.3
## - prothrombin    1 1086.1
## - albumin        1 1086.5
## - log_bilirubin  1 1107.1
##
## Step:  AIC=1078.53
## Surv(n_days, event) ~ drug + sex + ascites + hepatomegaly + spiders +
##     edema_bin + albumin + copper + alk_phos + sgot + prothrombin +
##     stage + age_years + log_bilirubin
##
##                 Df    AIC
## - spiders        1 1076.6
## - hepatomegaly   1 1076.6
## - ascites        1 1076.7
## - drug           1 1076.8
## - sex            1 1077.0
## - alk_phos       1 1077.2
## - stage          3 1077.6
## <none>             1078.5
## - sgot           1 1078.6
## - copper         1 1078.7
## + platelets      1 1080.5
## - edema_bin      1 1080.8
## - age_years      1 1083.3
## - prothrombin    1 1084.2
## - albumin        1 1084.5
## - log_bilirubin  1 1106.1
##
## Step:  AIC=1076.56
## Surv(n_days, event) ~ drug + sex + ascites + hepatomegaly + edema_bin +
##     albumin + copper + alk_phos + sgot + prothrombin + stage +
##     age_years + log_bilirubin
##
##                 Df    AIC
## - hepatomegaly   1 1074.6
## - ascites        1 1074.7
## - drug           1 1074.9
## - sex            1 1075.1
## - alk_phos       1 1075.2
## - stage          3 1075.6
## <none>             1076.6
## - copper         1 1076.7
## - sgot           1 1076.7
## + spiders        1 1078.5
## + platelets      1 1078.6
## - edema_bin      1 1078.8
## - age_years      1 1081.5
## - prothrombin    1 1082.2
## - albumin        1 1082.5
## - log_bilirubin  1 1104.9
##
## Step:  AIC=1074.6
## Surv(n_days, event) ~ drug + sex + ascites + edema_bin + albumin +
##     copper + alk_phos + sgot + prothrombin + stage + age_years +
##     log_bilirubin
##
##                 Df    AIC
## - ascites        1 1072.7
## - drug           1 1072.9
## - sex            1 1073.2
## - alk_phos       1 1073.3
## - stage          3 1074.5
## <none>             1074.6
## - copper         1 1074.7
## - sgot           1 1074.7
## + hepatomegaly   1 1076.6
## + spiders        1 1076.6
## + platelets      1 1076.6
## - edema_bin      1 1076.9
## - age_years      1 1079.5
## - prothrombin    1 1080.3
## - albumin        1 1080.7
## - log_bilirubin  1 1105.6
##
## Step:  AIC=1072.74
## Surv(n_days, event) ~ drug + sex + edema_bin + albumin + copper +
##     alk_phos + sgot + prothrombin + stage + age_years + log_bilirubin
##
##                 Df    AIC
## - drug           1 1071.0
## - sex            1 1071.4
## - alk_phos       1 1071.6
## - stage          3 1072.7
## <none>             1072.7
## - sgot           1 1072.8
## - copper         1 1073.4
## + ascites        1 1074.6
## + spiders        1 1074.7
## + hepatomegaly   1 1074.7
## + platelets      1 1074.7
## - edema_bin      1 1075.2
## - age_years      1 1077.8
## - prothrombin    1 1078.6
## - albumin        1 1080.9
## - log_bilirubin  1 1104.8
##
## Step:  AIC=1071.03
## Surv(n_days, event) ~ sex + edema_bin + albumin + copper + alk_phos +
##     sgot + prothrombin + stage + age_years + log_bilirubin
##
##                 Df    AIC
## - sex            1 1069.6
## - alk_phos       1 1069.9
## <none>             1071.0
## - stage          3 1071.1
## - sgot           1 1071.1
## - copper         1 1071.8
## + drug           1 1072.7
## + ascites        1 1072.9
## + spiders        1 1073.0
## + hepatomegaly   1 1073.0
## + platelets      1 1073.0
## - edema_bin      1 1073.3
## - age_years      1 1075.8
## - prothrombin    1 1077.1
## - albumin        1 1079.0
## - log_bilirubin  1 1102.8
##
## Step:  AIC=1069.63
## Surv(n_days, event) ~ edema_bin + albumin + copper + alk_phos +
##     sgot + prothrombin + stage + age_years + log_bilirubin
```

```
##
##                   Df    AIC
## - alk_phos       1 1068.6
## - stage          3 1069.5
## <none>             1069.6
## - sgot           1 1069.9
## + sex            1 1071.0
## + drug           1 1071.4
## - edema_bin      1 1071.5
## + ascites        1 1071.5
## + spiders        1 1071.5
## + hepatomegaly   1 1071.6
## + platelets      1 1071.6
## - copper         1 1072.1
## - prothrombin    1 1075.5
## - age_years      1 1076.6
## - albumin        1 1077.2
## - log_bilirubin  1 1101.0
##
## Step:  AIC=1068.62
## Surv(n_days, event) ~ edema_bin + albumin + copper + sgot + prothrombin +
##     stage + age_years + log_bilirubin
##
##                   Df    AIC
## <none>             1068.6
## - stage          3 1068.9
## - sgot           1 1069.2
## + alk_phos       1 1069.6
## + sex            1 1069.9
## + drug           1 1070.3
## + ascites        1 1070.3
## - copper         1 1070.3
## + platelets      1 1070.5
## + hepatomegaly   1 1070.6
## + spiders        1 1070.6
## - edema_bin      1 1070.7
## - prothrombin    1 1074.0
## - albumin        1 1075.3
## - age_years      1 1077.1
## - log_bilirubin  1 1100.0
```

```
summary(step_cox)
```

```
## Call:
## coxph(formula = Surv(n_days, event) ~ edema_bin + albumin + copper +
##     sgot + prothrombin + stage + age_years + log_bilirubin, data = cirrhosis_df)
##
##   n= 306, number of events= 123
##
##                     coef exp(coef)  se(coef)      z Pr(>|z|)
## edema_bin      0.475799  1.609300  0.231235  2.058  0.03962 *
## albumin       -0.763456  0.466053  0.255175 -2.992  0.00277 **
## copper         0.002001  1.002003  0.001003  1.995  0.04604 *
## sgot           0.002830  1.002834  0.001722  1.644  0.10020
## prothrombin    0.288718  1.334715  0.102905  2.806  0.00502 **
## stage2         1.346436  3.843701  1.060913  1.269  0.20440
## stage3         1.478849  4.387893  1.034096  1.430  0.15269
## stage4         1.762568  5.827381  1.032820  1.707  0.08790 .
## age_years      0.029909  1.030361  0.009256  3.231  0.00123 **
## log_bilirubin  0.715298  2.044795  0.121071  5.908 3.46e-09 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## edema_bin        1.6093     0.6214    1.0228    2.5320
## albumin          0.4661     2.1457    0.2826    0.7685
## copper           1.0020     0.9980    1.0000    1.0040
## sgot             1.0028     0.9972    0.9995    1.0062
## prothrombin      1.3347     0.7492    1.0909    1.6330
## stage2           3.8437     0.2602    0.4805   30.7468
## stage3           4.3879     0.2279    0.5781   33.3027
## stage4           5.8274     0.1716    0.7697   44.1176
## age_years        1.0304     0.9705    1.0118    1.0492
## log_bilirubin    2.0448     0.4890    1.6129    2.5924
##
## Concordance= 0.858  (se = 0.018 )
## Likelihood ratio test= 204.6  on 10 df,   p=<2e-16
## Wald test            = 195.2  on 10 df,   p=<2e-16
## Score (logrank) test = 254.9  on 10 df,   p=<2e-16
```

A Stepwise Cox Proportional Hazard regression was performed to identify the most parsimonious model that estimate subjects' hazard of Cirrhosis. The model selection was based on Akaike's Information Criterion (AIC). The final model achieved the lowest AIC of 1086.6, including the variables of Edema Presence, Albumin(mg/dl), Urine copper(ug/day), SGOT (U/ml), Prothrombin time (s), histologic stage of disease, age (years) and log-transformed serum Bilirubin (mg/dl) as predictors. Several variables showed significant associations ($p < 0.05$) with the hazard function, while disease stages (all p-value > 0.05) and SGOT (p-value > 0.01) are weaker contributors to the model. The overall model shows significant discriminatory ability over subjects' hazards with a concordance of 0.858. Global tests shows the model has a good fit (Wald test, p=<2e-16).

The final model from stepwise selection further supported the results from the above data Cox ph model that drug is an insignificant predictor. Urine copper and SGOT, in addition, was kept in the stepwise Cox model, but was removed in the final proposed model.

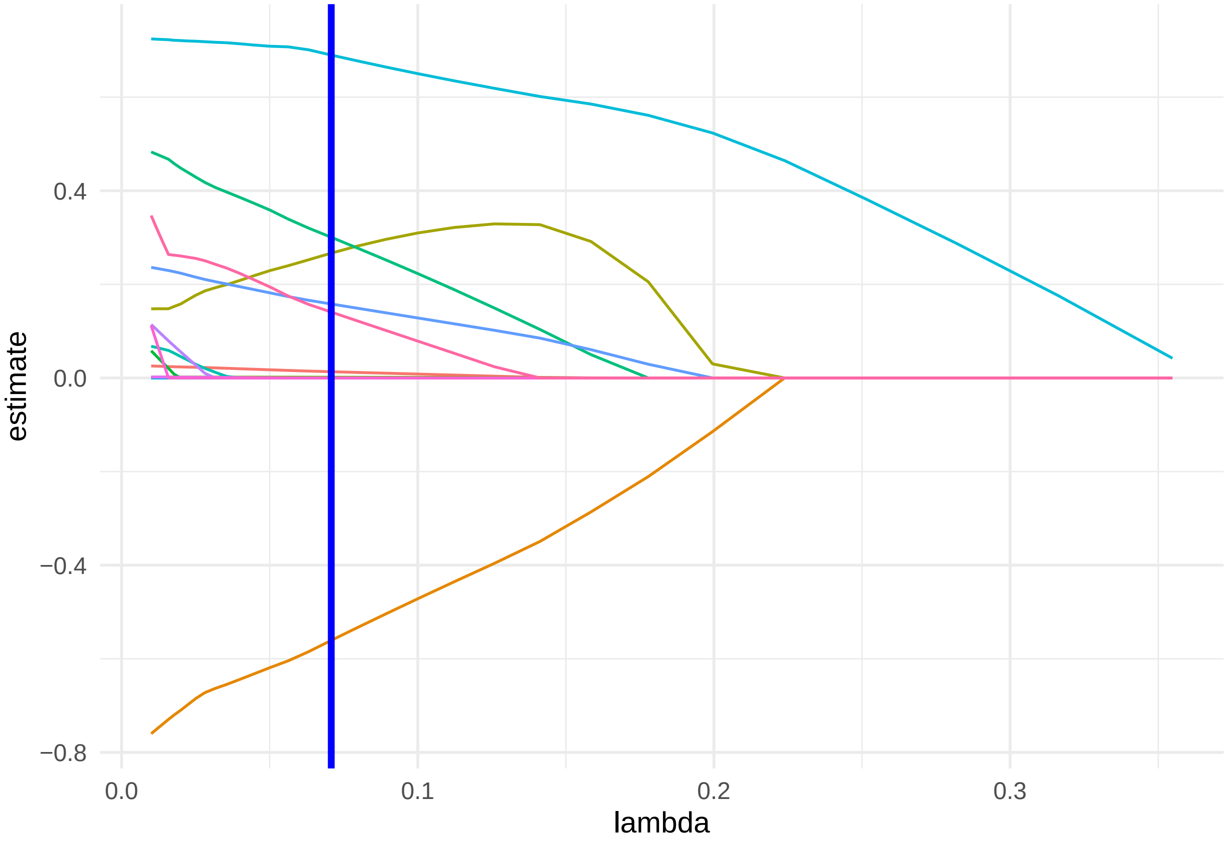
Lasso Cox

```r
set.seed(1234)
x = model.matrix(
    ~ drug +
      sex + ascites + hepatomegaly +
      spiders + edema_bin + albumin +
      copper + alk_phos + sgot +
      platelets + prothrombin + stage +
      age_years + log_bilirubin - n_days - event,
    data = cirrhosis_df)[, -1]

y = Surv(cirrhosis_df$n_days, cirrhosis_df$event)

lambda = 10^(seq(-2, 0, 0.05))
```

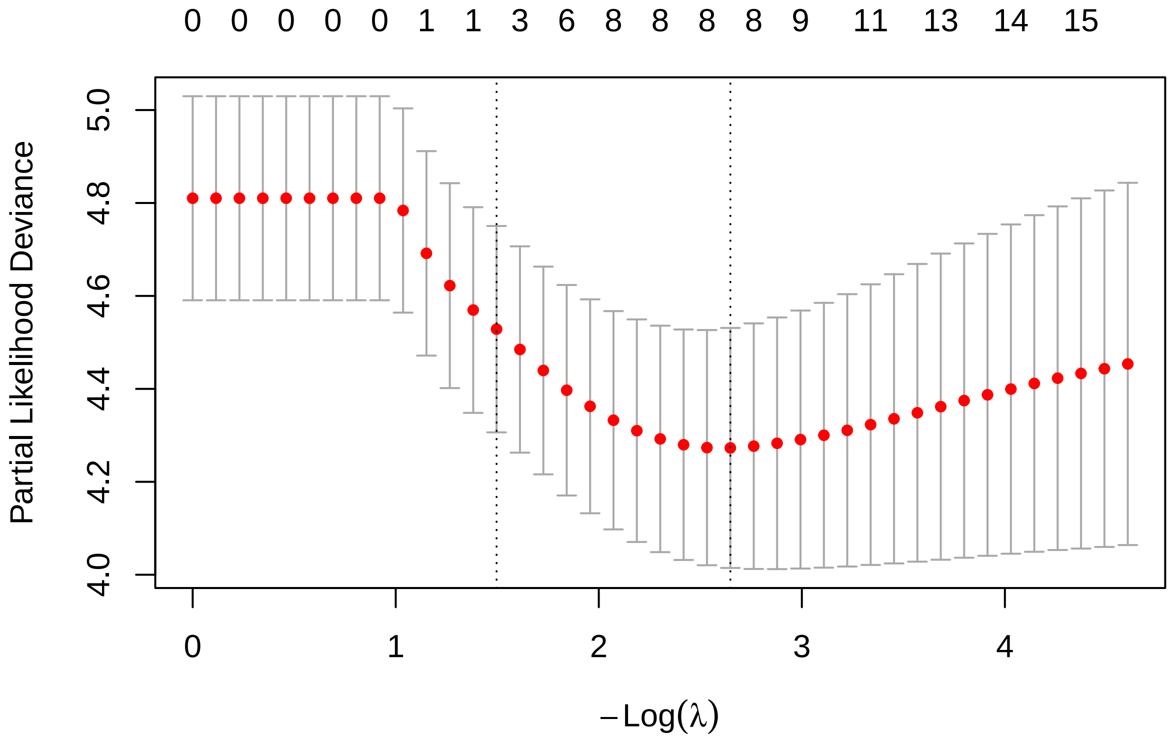
```
lasso_fit =
  glmnet(x, y, family = "cox", lambda = lambda)

lasso_cv =
  cv.glmnet(x, y, family = "cox", lambda = lambda, alpha = 1)

lambda_opt = lasso_cv[["lambda.min"]]
lambda_1se = lasso_cv[["lambda.1se"]]

lasso_plot1 = lasso_fit |>
  broom::tidy() |>
  select(term, lambda, estimate) |>
  complete(term, lambda, fill = list(estimate = 0) ) |>
  filter(term != "(Intercept)") |>
  ggplot(aes(x = lambda, y = estimate, group = term, color = term)) +
  geom_path() +
  geom_vline(xintercept = lambda_opt, color = "blue", size = 1.2) +
  theme_minimal() +
  theme(legend.position = "none")
```

```
## Warning: Using `size` aesthetic for lines was deprecated in ggplot2 3.4.0.
## i Please use `linewidth` instead.
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.
```

```
lasso_plot1
```



```r
plot(lasso_cv)
```



```r
coef(lasso_cv, s = "lambda.min")
```

```
## 17 x 1 sparse Matrix of class "dgCMatrix"
##                          1
## drugPlacebo     .
## sexM            .
## ascitesY        0.266748672
## hepatomegalyY   .
## spidersY        .
## edema_bin       0.300567715
## albumin        -0.560719880
## copper          0.001504712
## alk_phos        .
## sgot            .
## platelets       .
## prothrombin     0.158063509
## stage2          .
## stage3          .
## stage4          0.140786711
## age_years       0.013367584
## log_bilirubin   0.689920585
```

```r
coef(lasso_cv, s = "lambda.1se")
```

```
## 17 x 1 sparse Matrix of class "dgCMatrix"
##                       1
## drugPlacebo    .
## sexM           .
## ascitesY       .
## hepatomegalyY .
## spidersY      .
## edema_bin     .
## albumin       .
## copper        .
## alk_phos      .
## sgot          .
## platelets     .
## prothrombin   .
## stage2        .
## stage3        .
## stage4        .
## age_years     .
## log_bilirubin 0.4643493
```

Another Lasso Cox Proportional Hazard regression was performed to identify the most parsimonious model that estimate subjects' hazard of Cirrhosis. The model selection was based on Penalty Parameter, lambda, under a 10 fold cross-validation. The final model achieved the penalty parameter of 0.071, including the variables of Ascites Presence, Edema Presence, Albumin(mg/dl), Urine copper(ug/day), Prothrombin time (s), histologic stage 4 of disease, age (years) and log-transformed serum Bilirubin (mg/dl) as predictors. Another simpler model was provided with the log-transformed serum Bilirubin (mg/dl) as the only predictor, where allows the largest penalty parameter at which the MSE is within one standard error of the smallest MSE, which is 0.224. The model with the smallest penalty parameter was considered due to its better performance in estimation.

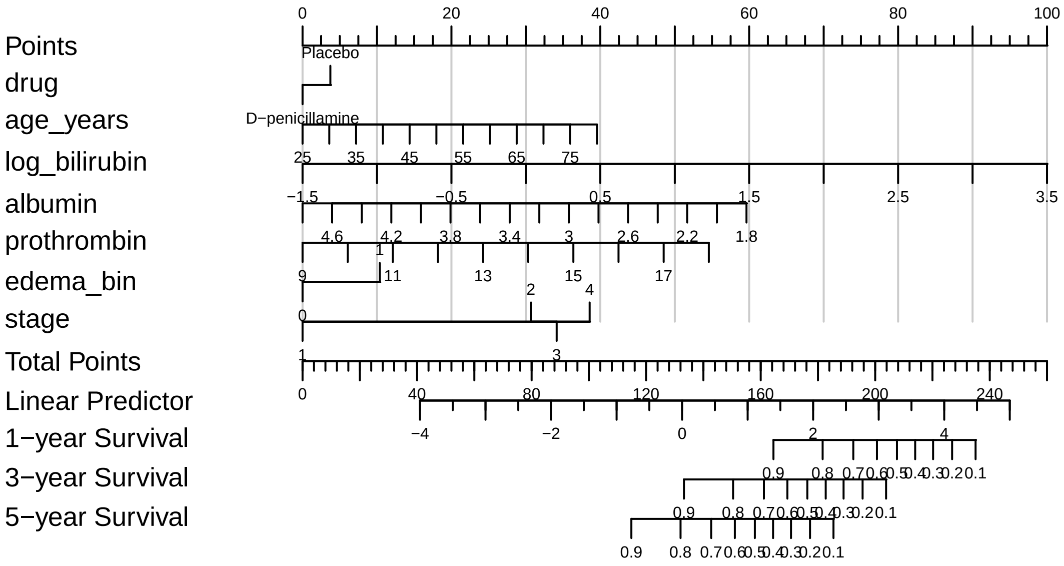
The final model from Lasso selection further supported the results from the above data Cox Proportional Hazard model that drug is an insignificant predictor. Ascites Presence and Urine copper, in addition, was kept in the Lasso Cox model, but was removed in the final proposed model.

Nomgram

```
# final model (Zhaokun)
dd <- datadist(cirrhosis_df)
options(datadist = "dd")

fit_nomo <- cph(
  Surv(n_days, event) ~
    drug +                # treatment: D-pen vs placebo
    age_years +           # age in years
    log_bilirubin +       # log-transformed bilirubin
    albumin +             # serum albumin
    prothrombin +         # prothrombin time
    edema_bin +           # edema: 0 = none, 1 = S/Y
    stage,                # histologic stage as stratification factor
  data = cirrhosis_df,
  x = TRUE, y = TRUE, surv = TRUE)

sf = Survival(fit_nomo)

# survival time for 1 year, 3 year and 5 year
surv_1y  <- function(lp) sf(365,  lp)
surv_3y  <- function(lp) sf(1095, lp)
surv_5y  <- function(lp) sf(1825, lp)

nomo <- nomogram(
```

```r
  fit_nomo,
  fun = list(
    "1-year Survival" = surv_1y,
    "3-year Survival" = surv_3y,
    "5-year Survival" = surv_5y
    ),
  funlabel = c("1-year Survival", "3-year Survival", "5-year Survival")
  )


plot(
  nomo,
  xfrac = 0.4,          # More room for labels
  lmgp = 0.5,           # left margin for variable names
  tcl = -0.5,           # Tick length
  cex.var = 0.8,        # variable label size
  cex.axis = 0.5,       # axis label size
  cex.points = 1.2,     # Points scale
  label.every = 2,      # Spread axis tick labels
  fun.spacing = 1.8,    # vertical spacing
  col.grid = "gray80",
)

title(
  main ="Nomogram for Cirrhosis Survival",
  sub = "1-, 3-, and 5-year survival predictions"
)
```

Nomogram for Cirrhosis Survival



1−, 3−, and 5−year survival predictions

The figure above is the nomogram generated to estimate the patients 1-, 3- and 5- year with predictors from the final Cox ph model. The nomogram produces similar results where treatment types are no strong predictors in the model.