

Time dependent ROC curve with Cox regression (ggplot2)

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Time dependent ROC curve with Cox regression

Loading packages

```
library(survival)
library(timeROC)
```

```
## Warning: 'timeROC' R 4.1.3
```

```
library(timereg)
```

```
## Warning: 'timereg' R 4.1.3
```

pbc data

```
data(pbc)
pbc<-pbc[,-1] # delete ID
pbc$status<-as.numeric(pbc$status==2) # create event indicator: 1 for death, 0 for censored
head(pbc)
```

```
## time status trt age sex ascites hepato spiders edema bili chol albumin
## 1 400 1 1 58.76523 f 1 1 1 1.0 14.5 261 2.60
## 2 4500 0 1 56.44627 f 0 1 1 0.0 1.1 302 4.14
## 3 1012 1 1 70.07255 m 0 0 0 0.5 1.4 176 3.48
## 4 1925 1 1 54.74059 f 0 1 1 0.5 1.8 244 2.54
## 5 1504 0 2 38.10541 f 0 1 1 0.0 3.4 279 3.53
## 6 2503 1 2 66.25873 f 0 1 0 0.0 0.8 248 3.98
## copper alk.phos ast trig platelet protime stage
## 1 156 1718.0 137.95 172 190 12.2 4
## 2 54 7394.8 113.52 88 221 10.6 3
## 3 210 516.0 96.10 55 151 12.0 4
## 4 64 6121.8 60.63 92 183 10.3 4
## 5 143 671.0 113.15 72 136 10.9 3
## 6 50 944.0 93.00 63 NA 11.0 3
```

Calculate risk score with Cox proportional hazard model

```
cox.pbc <- coxph(Surv(time,status) ~ ., data=pbc)
summary(cox.pbc)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ ., data = pbc)
##
## n= 276, number of events= 111
## ( 142 .)
##
##      coef exp(coef) se(coef) z Pr(>|z|)
## trt    -1.242e-01  8.832e-01 2.147e-01 -0.579 0.56290
## age     2.890e-02  1.029e+00 1.164e-02  2.482 0.01305 *
## sexf    -3.656e-01  6.938e-01 3.113e-01 -1.174 0.24022
## ascites  8.833e-02  1.092e+00 3.872e-01  0.228 0.81955
## hepato   2.552e-02  1.026e+00 2.510e-01  0.102 0.91900
## spiders  1.012e-01  1.107e+00 2.435e-01  0.416 0.67760
## edema    1.011e+00  2.749e+00 3.941e-01  2.566 0.01029 *
## bili     8.001e-02  1.083e+00 2.550e-02  3.138 0.00170 **
## chol     4.918e-04  1.000e+00 4.442e-04  1.107 0.26829
## albumin  -7.408e-01  4.767e-01 3.078e-01 -2.407 0.01608 *
## copper    2.490e-03  1.002e+00 1.170e-03  2.128 0.03337 *
## alk.phos  1.048e-06  1.000e+00 3.969e-05  0.026 0.97893
## ast       4.070e-03  1.004e+00 1.958e-03  2.078 0.03767 *
## trig     -9.758e-04  9.990e-01 1.333e-03 -0.732 0.46414
## platelet  9.019e-04  1.001e+00 1.184e-03  0.762 0.44629
## protime   2.324e-01  1.262e+00 1.061e-01  2.190 0.02850 *
## stage     4.545e-01  1.575e+00 1.754e-01  2.591 0.00958 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## trt      0.8832    1.1323    0.5798    1.3453
## age      1.0293    0.9715    1.0061    1.0531
## sexf      0.6938    1.4414    0.3769    1.2771
## ascites   1.0924    0.9155    0.5114    2.3332
## hepato    1.0259    0.9748    0.6273    1.6777
## spiders   1.1066    0.9037    0.6865    1.7835
## edema     2.7487    0.3638    1.2697    5.9505
## bili      1.0833    0.9231    1.0305    1.1388
## chol      1.0005    0.9995    0.9996    1.0014
## albumin   0.4767    2.0977    0.2608    0.8714
## copper     1.0025    0.9975    1.0002    1.0048
## alk.phos  1.0000    1.0000    0.9999    1.0001
## ast       1.0041    0.9959    1.0002    1.0079
## trig      0.9990    1.0010    0.9964    1.0016
## platelet  1.0009    0.9991    0.9986    1.0032
## protime   1.2617    0.7926    1.0247    1.5534
## stage     1.5754    0.6348    1.1170    2.2219
##
## Concordance= 0.849 (se = 0.018 )
## Likelihood ratio test= 167.7 on 17 df, p=<2e-16
## Wald test          = 174.1 on 17 df, p=<2e-16
## Score (logrank) test = 283.7 on 17 df, p=<2e-16
```

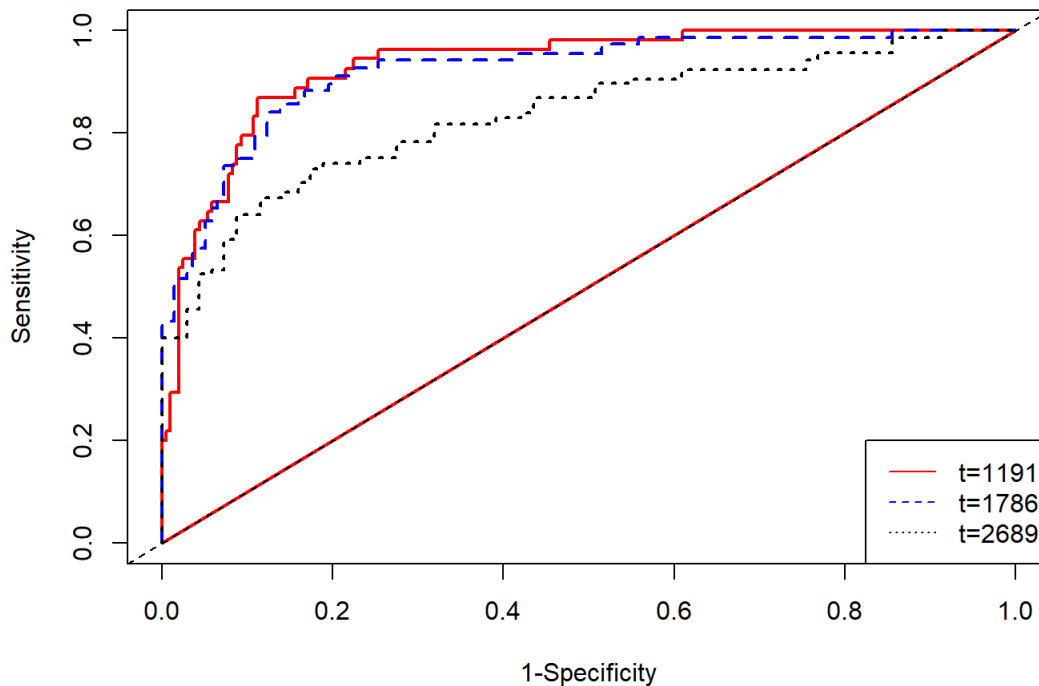
```
risk.pbc <- predict(object=cox.pbc, newdata=pbc, type="risk") # risk score
pbc$risk <- risk.pbc
pbc <- pbc[!is.na(pbc$risk),]
```

Time dependent AUC with risk score

```
ROC.risk.marginal <- timeROC(T=pbc$time,
                             delta=pbc$status,marker=pbc$risk,
                             cause=1,weighting="marginal",
                             times=pbc$time)
ROC.risk.marginal
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    275    1    NA
## t=1191  54    205    17   93.15
## t=1786  73    138    65   92.21
## t=2689  91    69    116  83.47
## t=4556 111    0    165   NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.09 secs.
```

```
# plot all ROC curves
par(mar=c(4,4,3,1))
plot(ROC.risk.marginal,time=1191,lwd=2,title=FALSE)
plot(ROC.risk.marginal,time=1786,col="blue",add=TRUE,lwd=2,lty=2)
plot(ROC.risk.marginal,time=2689,col="black",add=TRUE,lwd=2,lty=3)
# add legend
legend("bottomright",c("t=1191","t=1786","t=2689"),
      col=c("red","blue","black"),lty=1:3)
```



time VS AUC

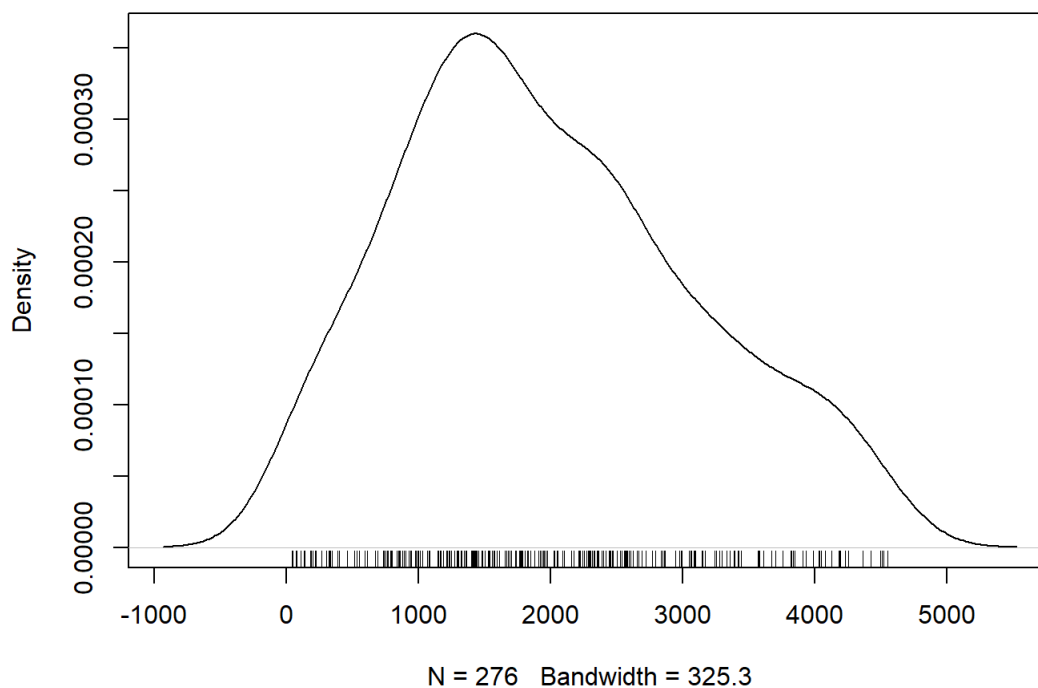
Make density of time

```
time.density <- density(ROC.risk.marginal[["times"]])
data1 <- data.frame(time=time.density[["x"]], density=time.density[["y"]])
data1$density.normal1 <- 0.9*(time.density[["y"]]-min(time.density[["y"]]))/(max(time.density[["y"]])-min(time.density[["y"]]))
data1$density.normal2 <- 0.9*(max(na.omit(ROC.risk.marginal[["AUC"]]))-min(na.omit(ROC.risk.marginal[["AUC"]]]))*(time.density[["y"]]-min(time.density[["y"]]))/(max(time.density[["y"]])-min(time.density[["y"]]))+min(na.omit(ROC.risk.marginal[["AUC"]]))
```

Plot of density of time

```
par(mar=c(4,4,3,1))
plot(time.density)
rug(jitter(ROC.risk.marginal[["times"]]))
```

density.default(x = ROC.risk.marginal[["times"]])



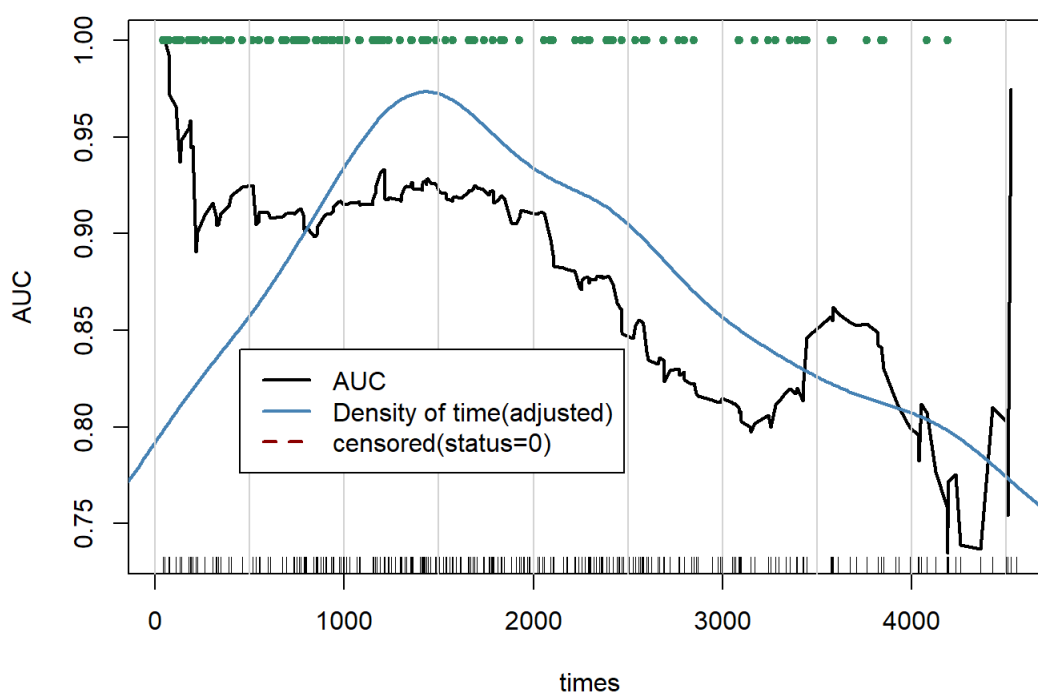
Coloring status

```
pbc$status.color <- ifelse(pbc$status==1,"seagreen","darkred")
pbc$status1 <- ifelse(pbc$status==1,1,0.7)
```

Plot of Time dependent AUC with Adjusted Density of time and Status of censoring

```
par(mar=c(4,4,3,1))
plot(x=ROC.risk.marginal[["times"]],y=ROC.risk.marginal[["AUC"]],
     type="l",xlab="times",ylab="AUC",lwd=2,
     main="Time dependent AUC with risk score (pbc data)")
lines(x=data1$time,y=data1$density.normal2,col="steelblue",type="l",lwd=2)
points(x=pbc$time,y=pbc$status1,col=pbc$status.color,pch=20)
abline(v=seq(0,5000,500),col="lightgray",lty=1)
rug(jitter(ROC.risk.marginal[["times"]]))
legend(450,0.84,c("AUC","Density of time(adjusted)","censored(status=0)",
  col=c("black","steelblue","darkred"),lwd=c(2,2,2),lty=c(1,1,2))
```

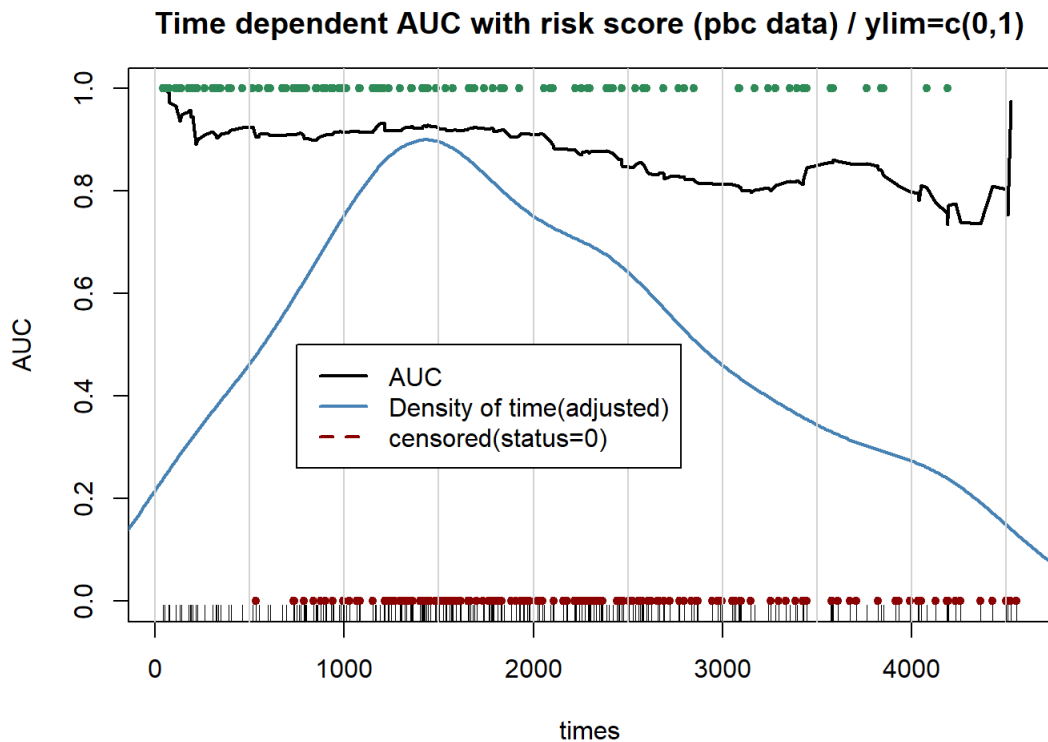
Time dependent AUC with risk score (pbc data)



```

par(mar=c(4,4,3,1))
plot(x=ROC.risk.marginal[["times"]],y=ROC.risk.marginal[["AUC"]],
     type="l",xlab="times",ylab="AUC",ylim=c(0,1),lwd=2,
     main="Time dependent AUC with risk score (pbc data) / ylim=c(0,1)")
lines(x=data1$time,y=data1$density.normal1,col="steelblue",type="l",lwd=2)
points(x=pbc$time,y=pbc$status,col=pbc$status.color,pch=20)
abline(v=seq(0,5000,500),col="lightgray",lty=1)
rug(jitter(ROC.risk.marginal[["times"]]))
legend(750,0.5,c("AUC", "Density of time(adjusted)", "censored(status=0)"),
     col=c("black", "steelblue", "darkred"),lwd=c(2,2,2),lty=c(1,1,2))

```



Using ggplot2

```

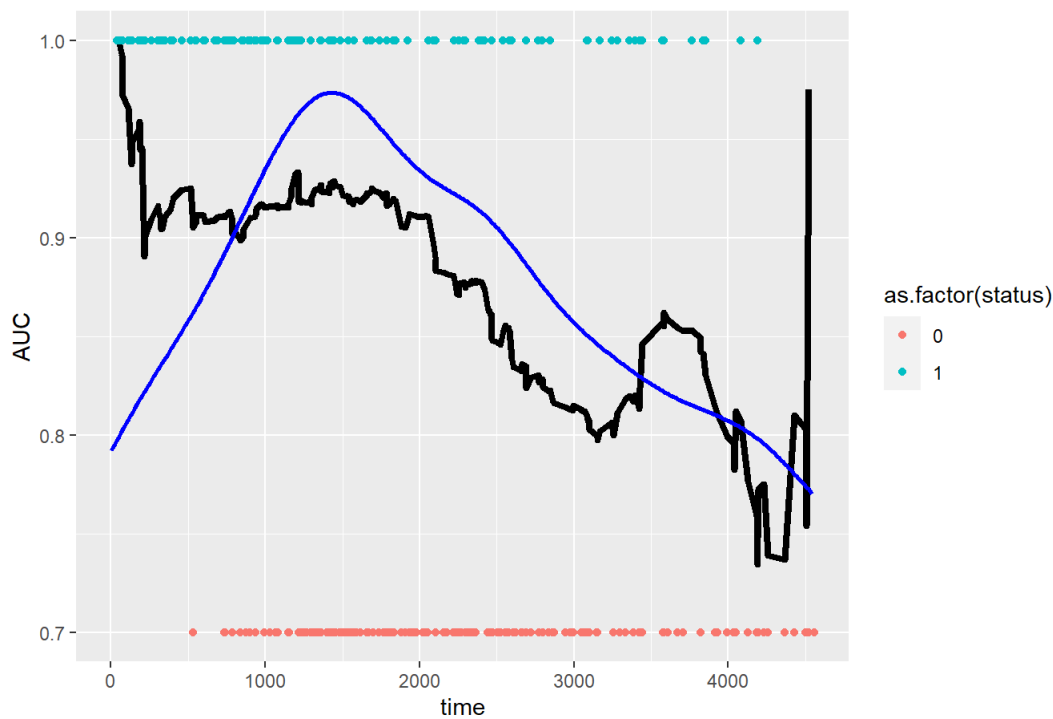
library(ggplot2)
data2 <- data.frame(time=ROC.risk.marginal[["times"]],
                    AUC=ROC.risk.marginal[["AUC"]])
ggplot() +
  geom_line(data=data2, aes(x=time, y=AUC), size=1.5, colour='black') +
  geom_point(data=pbc, aes(x=time, y=status1, color=as.factor(status))) +
  geom_line(data=data1, aes(x=time, y=density.normal2), size=1, colour='blue') +
  scale_x_continuous(limits = c(0, max(pbc$time))) +
  labs(title="Time dependent AUC with risk score (pbc data)") +
  theme(plot.title = element_text(hjust = 0.5))

```

Warning: Removed 2 row(s) containing missing values (geom_path).

Warning: Removed 152 row(s) containing missing values (geom_path).

Time dependent AUC with risk score (pbc data)



Counting censored data

```
library(tidyverse)
```

```
## Warning: 'tidyverse' R 4.1.3
```

```
## -- Attaching packages ----- tidyverse 1.3.1 --
```

```
## v tibble 3.1.5 v dplyr 1.0.7
## v tidyr 1.1.4 v stringr 1.4.0
## v readr 2.1.2 v forcats 0.5.1
## v purrr 0.3.4
```

```
## Warning: 'tidyr' R 4.1.2
```

```
## Warning: 'readr' R 4.1.3
```

```
## Warning: 'purrr' R 4.1.2
```

```
## Warning: 'forcats' R 4.1.3
```

```
## -- Conflicts ----- tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
## x dplyr::lag() masks stats::lag()
```

```
pbc.censor <- pbc[pbc$status==0,]
pbc.censor <- pbc.censor %>%
  mutate(n.cen=cut(pbc.censor$time,
    breaks=seq(from=0,to=5000,by=500)))
table(pbc.censor$n.cen)
```

```
##
## (0,500] (500,1e+03] (1e+03,1.5e+03] (1.5e+03,2e+03] (2e+03,2.5e+03]
## 0 10 33 34 28
## (2.5e+03,3e+03] (3e+03,3.5e+03] (3.5e+03,4e+03] (4e+03,4.5e+03] (4.5e+03,5e+03]
## 21 14 10 12 3
```

Variable selection (backward)

All explanatory variables

```
data(pbc)
pbc<-pbc[,-1] # delete ID
pbc$status<-as.numeric(pbc$status==2) # create event indicator: 1 for death, 0 for censored
cox.pbc0 <- coxph(Surv(time,status) ~ trt+age+sex+ascites+hepato+spiders+edema
  +bili+chol+albumin+copper+alk.phos+ast+trig
  +platelet+protime+stage, data=pbc)
summary(cox.pbc0)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ trt + age + sex + ascites +
##   hepato + spiders + edema + bili + chol + albumin + copper +
##   alk.phos + ast + trig + platelet + protime + stage, data = pbc)
##
## n= 276, number of events= 111
## (      142      .)
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## trt   -1.242e-01  8.832e-01  2.147e-01 -0.579  0.56290
## age    2.890e-02  1.029e+00  1.164e-02  2.482  0.01305 *
## sexf   -3.656e-01  6.938e-01  3.113e-01 -1.174  0.24022
## ascites 8.833e-02  1.092e+00  3.872e-01  0.228  0.81955
## hepato  2.552e-02  1.026e+00  2.510e-01  0.102  0.91900
## spiders 1.012e-01  1.107e+00  2.435e-01  0.416  0.67760
## edema   1.011e+00  2.749e+00  3.941e-01  2.566  0.01029 *
## bili    8.001e-02  1.083e+00  2.550e-02  3.138  0.00170 **
## chol    4.918e-04  1.000e+00  4.442e-04  1.107  0.26829
## albumin -7.408e-01  4.767e-01  3.078e-01 -2.407  0.01608 *
## copper   2.490e-03  1.002e+00  1.170e-03  2.128  0.03337 *
## alk.phos 1.048e-06  1.000e+00  3.969e-05  0.026  0.97893
## ast     4.070e-03  1.004e+00  1.958e-03  2.078  0.03767 *
## trig    -9.758e-04  9.990e-01  1.333e-03 -0.732  0.46414
## platelet 9.019e-04  1.001e+00  1.184e-03  0.762  0.44629
## protime 2.324e-01  1.262e+00  1.061e-01  2.190  0.02850 *
## stage   4.545e-01  1.575e+00  1.754e-01  2.591  0.00958 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## trt    0.8832    1.1323    0.5798    1.3453
## age     1.0293    0.9715    1.0061    1.0531
## sexf    0.6938    1.4414    0.3769    1.2771
## ascites  1.0924    0.9155    0.5114    2.3332
## hepato   1.0259    0.9748    0.6273    1.6777
## spiders  1.1066    0.9037    0.6865    1.7835
## edema    2.7487    0.3638    1.2697    5.9505
## bili     1.0833    0.9231    1.0305    1.1388
## chol     1.0005    0.9995    0.9996    1.0014
## albumin  0.4767    2.0977    0.2608    0.8714
## copper    1.0025    0.9975    1.0002    1.0048
## alk.phos 1.0000    1.0000    0.9999    1.0001
## ast      1.0041    0.9959    1.0002    1.0079
## trig     0.9990    1.0010    0.9964    1.0016
## platelet 1.0009    0.9991    0.9986    1.0032
## protime  1.2617    0.7926    1.0247    1.5534
## stage    1.5754    0.6348    1.1170    2.2219
##
## Concordance= 0.849 (se = 0.018 )
## Likelihood ratio test= 167.7 on 17 df,  p=<2e-16
## Wald test            = 174.1 on 17 df,  p=<2e-16
## Score (logrank) test = 283.7 on 17 df,  p=<2e-16
```

```
risk.pbc0 <- predict(object=cox.pbc0, newdata=pbc, type="risk") # risk score
pbc$risk0 <- risk.pbc0
pbc <- pbc[!is.na(pbc$risk0),]
```

Except explanatory variables with (p-value > 0.5)

```
cox.pbc1 <- coxph(Surv(time,status) ~ age+sex+edema
  +bili+chol+albumin+copper+ast+trig
  +platelet+protime+stage, data=pbc)
summary(cox.pbc1)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + sex + edema + bili +
##   chol + albumin + copper + ast + trig + platelet + protime +
##   stage, data = pbc)
##
## n= 276, number of events= 111
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## age      0.0304884  1.0309579  0.0112140  2.719  0.00655 **
## sexf     -0.3487456  0.7055726  0.3066725 -1.137  0.25546
## edema     1.0590785  2.8837125  0.3859859  2.744  0.00607 **
## bili      0.0786517  1.0818275  0.0244999  3.210  0.00133 **
## chol      0.0005349  1.0005350  0.0004383  1.221  0.22226
## albumin  -0.7696731  0.4631644  0.2828569 -2.721  0.00651 **
## copper     0.0026736  1.0026772  0.0010652  2.510  0.01207 *
## ast       0.0038284  1.0038358  0.0019238  1.990  0.04659 *
## trig     -0.0006270  0.9993732  0.0012029 -0.521  0.60217
## platelet  0.0007189  1.0007192  0.0011416  0.630  0.52886
## protime   0.2326228  1.2619053  0.1028002  2.263  0.02364 *
## stage     0.4688869  1.5982142  0.1498588  3.129  0.00175 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##           exp(coef) exp(-coef) lower .95 upper .95
## age           1.0310    0.9700    1.0085    1.0539
## sexf           0.7056    1.4173    0.3868    1.2870
## edema          2.8837    0.3468    1.3533    6.1447
## bili           1.0818    0.9244    1.0311    1.1350
## chol           1.0005    0.9995    0.9997    1.0014
## albumin        0.4632    2.1591    0.2661    0.8063
## copper          1.0027    0.9973    1.0006    1.0048
## ast            1.0038    0.9962    1.0001    1.0076
## trig           0.9994    1.0006    0.9970    1.0017
## platelet       1.0007    0.9993    0.9985    1.0030
## protime        1.2619    0.7925    1.0316    1.5436
## stage          1.5982    0.6257    1.1914    2.1439
##
## Concordance= 0.848 (se = 0.018 )
## Likelihood ratio test= 167.1 on 12 df,  p=<2e-16
## Wald test            = 172.4 on 12 df,  p=<2e-16
## Score (logrank) test = 259.6 on 12 df,  p=<2e-16
```

```
risk.pbc1 <- predict(object=cox.pbc1, newdata=pbc, type="risk") # risk score
pbc$risk1 <- risk.pbc1
```

Except explanatory variables with (p-value > 0.5)

```
cox.pbc2 <- coxph(Surv(time,status) ~ age+sex+edema
+bili+chol+albumin+copper+ast+protime+stage, data=pbc)
summary(cox.pbc2)
```



```
## Call:
## coxph(formula = Surv(time, status) ~ age + sex + edema + bili +
##   chol + albumin + copper + ast + protime + stage, data = pbc)
##
## n= 276, number of events= 111
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## age    0.0306155 1.0310889 0.0110093 2.781 0.005421 **
## sexf   -0.2969957 0.7430472 0.2980594 -0.996 0.319041
## edema   1.0242170 2.7849139 0.3650750 2.805 0.005024 **
## bili    0.0747229 1.0775856 0.0223787 3.339 0.000841 ***
## chol    0.0005966 1.0005967 0.0004310 1.384 0.166272
## albumin -0.7330353 0.4804485 0.2784487 -2.633 0.008474 **
## copper   0.0026904 1.0026940 0.0010660 2.524 0.011610 *
## ast     0.0036099 1.0036164 0.0018321 1.970 0.048794 *
## protime  0.2327870 1.2621126 0.1027797 2.265 0.023518 *
## stage    0.4530538 1.5731088 0.1486060 3.049 0.002298 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.0311   0.9698   1.0091   1.0536
## sexf     0.7430   1.3458   0.4143   1.3327
## edema    2.7849   0.3591   1.3616   5.6959
## bili     1.0776   0.9280   1.0313   1.1259
## chol     1.0006   0.9994   0.9998   1.0014
## albumin  0.4804   2.0814   0.2784   0.8292
## copper    1.0027   0.9973   1.0006   1.0048
## ast      1.0036   0.9964   1.0000   1.0072
## protime  1.2621   0.7923   1.0318   1.5438
## stage    1.5731   0.6357   1.1756   2.1050
##
## Concordance= 0.849 (se = 0.019 )
## Likelihood ratio test= 166.5 on 10 df,  p=<2e-16
## Wald test          = 174 on 10 df,  p=<2e-16
## Score (logrank) test = 259.2 on 10 df,  p=<2e-16
```

```
risk.pbc2 <- predict(object=cox.pbc2, newdata=pbc, type="risk") # risk score
pbc$risk2 <- risk.pbc2
```

Except explanatory variables with (p-value > 0.3)

```
cox.pbc3 <- coxph(Surv(time,status) ~ age+edema
+bili+chol+albumin+copper+ast+protime+stage, data=pbc)
summary(cox.pbc3)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + edema + bili + chol +
##   albumin + copper + ast + protime + stage, data = pbc)
##
##   n= 276, number of events= 111
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## age      0.0341784 1.0347692 0.0104057 3.285 0.00102 **
## edema     0.9687143 2.6345550 0.3607037 2.686 0.00724 **
## bili      0.0722101 1.0748812 0.0221400 3.262 0.00111 **
## chol       0.0005929 1.0005930 0.0004282 1.384 0.16622
## albumin -0.6834089 0.5048929 0.2732708 -2.501 0.01239 *
## copper     0.0030566 1.0030613 0.0009893 3.090 0.00200 **
## ast        0.0037882 1.0037954 0.0017963 2.109 0.03496 *
## protime    0.2309035 1.2597377 0.1015657 2.273 0.02300 *
## stage      0.4518254 1.5711775 0.1487946 3.037 0.00239 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##           exp(coef) exp(-coef) lower .95 upper .95
## age           1.0348   0.9664   1.0139   1.0561
## edema          2.6346   0.3796   1.2992   5.3424
## bili           1.0749   0.9303   1.0292   1.1226
## chol           1.0006   0.9994   0.9998   1.0014
## albumin        0.5049   1.9806   0.2955   0.8626
## copper          1.0031   0.9969   1.0011   1.0050
## ast            1.0038   0.9962   1.0003   1.0073
## protime        1.2597   0.7938   1.0324   1.5372
## stage          1.5712   0.6365   1.1737   2.1032
##
## Concordance= 0.848 (se = 0.018 )
## Likelihood ratio test= 165.6 on 9 df,  p=<2e-16
## Wald test           = 173.5 on 9 df,  p=<2e-16
## Score (logrank) test = 258.9 on 9 df,  p=<2e-16
```

```
risk.pbc3 <- predict(object=cox.pbc3, newdata=pbc, type="risk") # risk score
pbc$risk3 <- risk.pbc3
```

Except explanatory variables with (p-value > 0.1)

```
cox.pbc4 <- coxph(Surv(time,status) ~ age+edema+bili+albumin+copper+ast+protime+stage, data=pbc)
summary(cox.pbc4)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + edema + bili + albumin +
##   copper + ast + protime + stage, data = pbc)
##
##   n= 276, number of events= 111
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## age      0.0313836 1.0318812 0.0102036 3.076 0.00210 **
## edema     0.8217952 2.2745795 0.3471465 2.367 0.01792 *
## bili      0.0851214 1.0888492 0.0193352 4.402 1.07e-05 ***
## albumin -0.7185954 0.4874364 0.2724486 -2.638 0.00835 **
## copper     0.0028535 1.0028576 0.0009832 2.902 0.00370 **
## ast        0.0043769 1.0043865 0.0018067 2.423 0.01541 *
## protime    0.2275175 1.2554794 0.1013729 2.244 0.02481 *
## stage      0.4327939 1.5415584 0.1456307 2.972 0.00296 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##           exp(coef) exp(-coef) lower .95 upper .95
## age           1.0319   0.9691   1.0114   1.0527
## edema          2.2746   0.4396   1.1519   4.4915
## bili           1.0888   0.9184   1.0484   1.1309
## albumin        0.4874   2.0515   0.2858   0.8314
## copper          1.0029   0.9972   1.0009   1.0048
## ast            1.0044   0.9956   1.0008   1.0079
## protime        1.2555   0.7965   1.0292   1.5314
## stage          1.5416   0.6487   1.1588   2.0508
##
## Concordance= 0.845 (se = 0.019 )
## Likelihood ratio test= 163.8 on 8 df,  p=<2e-16
## Wald test           = 176.1 on 8 df,  p=<2e-16
## Score (logrank) test = 257.5 on 8 df,  p=<2e-16
```

```
risk.pbc4 <- predict(object=cox.pbc4, newdata=pbcc, type="risk") # risk score
pbcc$risk4 <- risk.pbc4
```

Time dependent AUC with Backward elimination

```
ROC.risk.marginal0 <- timeROC(T=pbct$time,  
                             delta=pbct$status,marker=pbct$risk0,  
                             cause=1,weighting="marginal",  
                             times=pbct$time)  
ROC.risk.marginal0
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      275      1      NA
## t=1191    54      205     17    93.15
## t=1786    73      138     65    92.21
## t=2689    91       69    116    83.47
## t=4556   111       0     165     NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.06 secs.
```

```
ROC.risk.marginal1 <- timeROC(T=pbct$time,  
                             delta=pbct$status,marker=pbct$risk1,  
                             cause=1,weighting="marginal",  
                             times=pbct$time)  
ROC.risk.marginal1
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      275      1      NA
## t=1191    54      205     17    93.26
## t=1786    73      138     65    92.14
## t=2689    91      69     116    82.85
## t=4556   111       0     165     NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.14 secs.
```

[illegible]

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      275      1      NA
## t=1191    54      205     17    93.09
## t=1786    73      138     65    92.23
## t=2689    91      69     116    82.71
## t=4556   111       0     165     NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.04 secs.
```

[illegible]

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      275      1      NA
## t=1191    54      205      17    92.90
## t=1786    73      138      65    91.90
## t=2689    91       69     116    82.58
## t=4556   111       0     165     NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.05 secs.
```

```
ROC.risk.marginal4 <- timeROC(T=pbcs$time,
                             delta=pbcs$status,marker=pbcs$risk4,
                             cause=1,weighting="marginal",
                             times=pbcs$time)
ROC.risk.marginal4
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      275      1      NA
## t=1191    54      205      17    92.89
## t=1786    73      138      65    91.40
## t=2689    91       69     116    82.23
## t=4556   111       0     165     NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.06 secs.
```

```
data3 <- data.frame(time=ROC.risk.marginal0[["times"]],
                    cox.pbc0=ROC.risk.marginal0[["AUC"]],
                    cox.pbc1=ROC.risk.marginal1[["AUC"]],
                    cox.pbc2=ROC.risk.marginal2[["AUC"]],
                    cox.pbc3=ROC.risk.marginal3[["AUC"]],
                    cox.pbc4=ROC.risk.marginal4[["AUC"]])
library(reshape)
```

```
## Warning: 'reshape' R 4.1.3
```

```
##
##      : 'reshape'
```

```
## The following object is masked from 'package:dplyr':
##
##      rename
```

```
## The following objects are masked from 'package:tidyr':
##
##      expand, smiths
```

```
library(plyr)
```

```
## Warning: 'plyr' R 4.1.3
```

```
## -----
```

```
## You have loaded plyr after dplyr - this is likely to cause problems.
## If you need functions from both plyr and dplyr, please load plyr first, then dplyr:
## library(plyr); library(dplyr)
```

```
## -----
```

```
##
##      : 'plyr'
```

```
## The following objects are masked from 'package:reshape':  
##  
##   rename, round_any
```

```
## The following objects are masked from 'package:dplyr':  
##  
##   arrange, count, desc, failwith, id, mutate, rename, summarise,  
##   summarize
```

```
## The following object is masked from 'package:purrr':  
##  
##   compact
```

```
data3.melt <- melt(data = data3,  
  id.vars = "time",  
  measure.vars = c("cox.pbc0", "cox.pbc1", "cox.pbc2",  
    "cox.pbc3", "cox.pbc4"))  
data3.melt <- rename(data3.melt,  
  replace=c("variable"="model",  
    "value"="AUC"))
```

Except each explanatory variables in model cox.pbc4

```
#Except age  
cox.pbc4_1 <- coxph(Surv(time,status) ~ edema+bili+albumin+copper+ast+protime+stage, data=pbcc)  
summary(cox.pbc4_1)
```

```
## Call:  
## coxph(formula = Surv(time, status) ~ edema + bili + albumin +  
##   copper + ast + protime + stage, data = pbcc)  
##  
##   n= 276, number of events= 111  
##  
##           coef exp(coef) se(coef)      z Pr(>|z|)  
## edema   0.6740120  1.9620935  0.3391553  1.987 0.046886 *  
## bili    0.0845497  1.0882269  0.0197460  4.282 1.85e-05 ***  
## albumin -0.8231909  0.4390285  0.2675223 -3.077 0.002090 **  
## copper   0.0034140  1.0034199  0.0009622  3.548 0.000388 ***  
## ast      0.0032110  1.0032161  0.0018031  1.781 0.074945 .  
## protime  0.2679380  1.3072661  0.1020519  2.626 0.008652 **  
## stage    0.4847947  1.6238417  0.1451184  3.341 0.000836 ***  
## ---  
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1  
##  
##           exp(coef) exp(-coef) lower .95 upper .95  
## edema      1.962    0.5097    1.0093   3.8143  
## bili       1.088    0.9189    1.0469   1.1312  
## albumin    0.439    2.2778    0.2599   0.7417  
## copper      1.003    0.9966    1.0015   1.0053  
## ast         1.003    0.9968    0.9997   1.0068  
## protime    1.307    0.7650    1.0703   1.5967  
## stage      1.624    0.6158    1.2219   2.1581  
##  
## Concordance= 0.833 (se = 0.02 )  
## Likelihood ratio test= 154.4 on 7 df,  p=<2e-16  
## Wald test            = 169.5 on 7 df,  p=<2e-16  
## Score (logrank) test = 247.6 on 7 df,  p=<2e-16
```

```
risk.pbc4_1 <- predict(object=cox.pbc4_1, newdata=pbcc, type="risk") # risk score  
pbcc$risk4_1 <- risk.pbc4_1  
ROC.risk.marginal4_1 <- timeROC(T=pbcc$time,  
  delta=pbcc$status,marker=pbcc$risk4_1,  
  cause=1,weighting="marginal",  
  times=pbcc$time)  
ROC.risk.marginal4_1
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    275    1    NA
## t=1191  54    205    17  91.89
## t=1786  73    138    65  89.83
## t=2689  91    69    116  81.86
## t=4556 111    0    165    NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.07 secs.
```

```
#Except edema
```

```
cox.pbc4_2 <- coxph(Surv(time,status) ~ age+bili+albumin+copper+ast+protime+stage, data=pbcb)
summary(cox.pbc4_2)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + bili + albumin + copper +
##      ast + protime + stage, data = pbcb)
##
## n= 276, number of events= 111
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## age    0.0280100 1.0284060 0.0099951  2.802 0.005073 **
## bili   0.0961186 1.1008896 0.0182860  5.256 1.47e-07 ***
## albumin -0.8693842 0.4192096 0.2563560 -3.391 0.000696 ***
## copper   0.0030260 1.0030306 0.0009944  3.043 0.002342 **
## ast     0.0042683 1.0042774 0.0017845  2.392 0.016762 *
## protime 0.2764212 1.3184030 0.0943866  2.929 0.003405 **
## stage   0.4463564 1.5626083 0.1426094  3.130 0.001749 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.0284   0.9724   1.0085   1.0488
## bili     1.1009   0.9084   1.0621   1.1411
## albumin   0.4192   2.3854   0.2536   0.6929
## copper     1.0030   0.9970   1.0011   1.0050
## ast       1.0043   0.9957   1.0008   1.0078
## protime   1.3184   0.7585   1.0957   1.5863
## stage     1.5626   0.6400   1.1816   2.0665
##
## Concordance= 0.839 (se = 0.02 )
## Likelihood ratio test= 158.4 on 7 df,  p=<2e-16
## Wald test            = 169.9 on 7 df,  p=<2e-16
## Score (logrank) test = 236.2 on 7 df,  p=<2e-16
```

```
risk.pbc4_2 <- predict(object=cox.pbc4_2, newdata=pbcb, type="risk") # risk score
pbcb$risk4_2 <- risk.pbc4_2
ROC.risk.marginal4_2 <- timeROC(T=pbcb$time,
                                delta=pbcb$status,marker=pbcb$risk4_2,
                                cause=1,weighting="marginal",
                                times=pbcb$time)
ROC.risk.marginal4_2
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    275    1    NA
## t=1191  54    205    17  92.15
## t=1786  73    138    65  90.84
## t=2689  91    69    116  82.57
## t=4556 111    0    165    NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.06 secs.
```

```
#Except bili
```

```
cox.pbc4_3 <- coxph(Surv(time,status) ~ age+edema+albumin+copper+ast+protime+stage, data=pbcb)
summary(cox.pbc4_3)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + edema + albumin +
##   copper + ast + protime + stage, data = pbc)
##
## n= 276, number of events= 111
##
##      coef exp(coef) se(coef) z Pr(>|z|)
## age  0.0304623 1.0309310 0.0101276 3.008 0.002631 **
## edema  1.1754792 3.2396950 0.3339186 3.520 0.000431 ***
## albumin -0.7920128 0.4529322 0.2689595 -2.945 0.003232 **
## copper  0.0035399 1.0035462 0.0009361 3.782 0.000156 ***
## ast    0.0064508 1.0064717 0.0015872 4.064 4.82e-05 ***
## protime 0.2807281 1.3240935 0.1014109 2.768 0.005636 **
## stage  0.4252640 1.5299944 0.1440847 2.951 0.003162 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age  1.0309  0.9700  1.0107  1.0516
## edema  3.2397  0.3087  1.6837  6.2336
## albumin  0.4529  2.2078  0.2674  0.7673
## copper  1.0035  0.9965  1.0017  1.0054
## ast  1.0065  0.9936  1.0033  1.0096
## protime  1.3241  0.7552  1.0854  1.6153
## stage  1.5300  0.6536  1.1536  2.0292
##
## Concordance= 0.835 (se = 0.019 )
## Likelihood ratio test= 147.8 on 7 df, p=<2e-16
## Wald test = 161 on 7 df, p=<2e-16
## Score (logrank) test = 206.6 on 7 df, p=<2e-16
```

```
risk.pbc4_3 <- predict(object=cox.pbc4_3, newdata=pbc, type="risk") # risk score
pbc$risk4_3 <- risk.pbc4_3
ROC.risk.marginal4_3 <- timeROC(T=pbc$time,
                                delta=pbc$status,marker=pbc$risk4_3,
                                cause=1,weighting="marginal",
                                times=pbc$time)
ROC.risk.marginal4_3
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    275    1    NA
## t=1191  54    205    17  91.91
## t=1786  73    138    65  89.74
## t=2689  91    69    116 78.92
## t=4556 111    0    165  NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.07 secs.
```

```
#Except albumin
cox.pbc4_4 <- coxph(Surv(time,status) ~ age+edema+bili+copper+ast+protime+stage, data=pbc)
summary(cox.pbc4_4)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + edema + bili + copper +
##   ast + protime + stage, data = pbc)
##
## n= 276, number of events= 111
##
##      coef exp(coef) se(coef)  z Pr(>|z|)
## age   0.0348150 1.0354282 0.0101185 3.441 0.000580 ***
## edema  1.0742595 2.9278239 0.3325514 3.230 0.001236 **
## bili   0.0876174 1.0915704 0.0189254 4.630 3.66e-06 ***
## copper  0.0029773 1.0029817 0.0009721 3.063 0.002194 **
## ast    0.0048983 1.0049104 0.0018136 2.701 0.006916 **
## protime 0.2185562 1.2442789 0.1020663 2.141 0.032249 *
## stage  0.5233615 1.6876913 0.1431375 3.656 0.000256 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.035   0.9658    1.015   1.056
## edema     2.928   0.3416    1.526   5.618
## bili     1.092   0.9161    1.052   1.133
## copper     1.003   0.9970    1.001   1.005
## ast       1.005   0.9951    1.001   1.008
## protime   1.244   0.8037    1.019   1.520
## stage     1.688   0.5925    1.275   2.234
##
## Concordance= 0.844 (se = 0.017 )
## Likelihood ratio test= 157.1 on 7 df,  p=<2e-16
## Wald test          = 168.7 on 7 df,  p=<2e-16
## Score (logrank) test = 246.7 on 7 df,  p=<2e-16
```

```
risk.pbc4_4 <- predict(object=cox.pbc4_4, newdata=pbc, type="risk") # risk score
pbc$risk4_4 <- risk.pbc4_4
ROC.risk.marginal4_4 <- timeROC(T=pbc$time,
                                delta=pbc$status,marker=pbc$risk4_4,
                                cause=1,weighting="marginal",
                                times=pbc$time)
ROC.risk.marginal4_4
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      275      1      NA
## t=1191    54      205      17  93.36
## t=1786    73      138      65  91.27
## t=2689    91       69     116  80.19
## t=4556   111       0     165    NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.07 secs.
```

```
#Except copper
cox.pbc4_5 <- coxph(Surv(time,status) ~ age+edema+bili+albumin+ast+protime+stage, data=pbc)
summary(cox.pbc4_5)
```



```
## Call:
## coxph(formula = Surv(time, status) ~ age + edema + bili + albumin +
##   ast + protime + stage, data = pbc)
##
## n= 276, number of events= 111
##
##      coef exp(coef) se(coef)   z Pr(>|z|)
## age    0.037606  1.038322  0.010429  3.606 0.000311 ***
## edema   0.872403  2.392653  0.347234  2.512 0.011990 *
## bili    0.092980  1.097439  0.018365  5.063 4.13e-07 ***
## albumin -0.752793  0.471049  0.267842 -2.811 0.004945 **
## ast     0.005551  1.005566  0.001663  3.337 0.000845 ***
## protime 0.234741  1.264581  0.098231  2.390 0.016863 *
## stage   0.486440  1.626516  0.142379  3.417 0.000634 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.038   0.9631   1.0173   1.0598
## edema     2.393   0.4179   1.2115   4.7255
## bili     1.097   0.9112   1.0586   1.1377
## albumin   0.471   2.1229   0.2787   0.7963
## ast       1.006   0.9945   1.0023   1.0088
## protime   1.265   0.7908   1.0431   1.5331
## stage     1.627   0.6148   1.2305   2.1501
##
## Concordance= 0.833 (se = 0.02 )
## Likelihood ratio test= 156.2 on 7 df,  p=<2e-16
## Wald test            = 161.3 on 7 df,  p=<2e-16
## Score (logrank) test = 246.1 on 7 df,  p=<2e-16
```

```
risk.pbc4_5 <- predict(object=cox.pbc4_5, newdata=pbc, type="risk") # risk score
pbc$risk4_5 <- risk.pbc4_5
ROC.risk.marginal4_5 <- timeROC(T=pbc$time,
                                delta=pbc$status,marker=pbc$risk4_5,
                                cause=1,weighting="marginal",
                                times=pbc$time)
ROC.risk.marginal4_5
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    275    1    NA
## t=1191  54    205    17  91.59
## t=1786  73    138    65  89.82
## t=2689  91    69    116 81.02
## t=4556 111    0    165  NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.23 secs.
```

```
#Except ast
cox.pbc4_6 <- coxph(Surv(time,status) ~ age+edema+bili+albumin+copper+protime+stage, data=pbc)
summary(cox.pbc4_6)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + edema + bili + albumin +
##   copper + protime + stage, data = pbc)
##
## n= 276, number of events= 111
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## age    0.0263257 1.0266752 0.0098001 2.686 0.007226 **
## edema   0.8032302 2.2327415 0.3421422 2.348 0.018892 *
## bili    0.0995662 1.1046917 0.0177483 5.610 2.02e-08 ***
## albumin -0.7767104 0.4599165 0.2711922 -2.864 0.004183 **
## copper   0.0034773 1.0034834 0.0009342 3.722 0.000197 ***
## protime 0.1949481 1.2152479 0.0987626 1.974 0.048392 *
## stage   0.3922052 1.4802415 0.1422135 2.758 0.005818 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.0267   0.9740   1.0071   1.0466
## edema     2.2327   0.4479   1.1418   4.3659
## bili      1.1047   0.9052   1.0669   1.1438
## albumin   0.4599   2.1743   0.2703   0.7826
## copper     1.0035   0.9965   1.0016   1.0053
## protime   1.2152   0.8229   1.0014   1.4748
## stage     1.4802   0.6756   1.1202   1.9561
##
## Concordance= 0.841 (se = 0.02 )
## Likelihood ratio test= 158.6 on 7 df,  p=<2e-16
## Wald test            = 174.9 on 7 df,  p=<2e-16
## Score (logrank) test = 256.2 on 7 df,  p=<2e-16
```

```
risk.pbc4_6 <- predict(object=cox.pbc4_6, newdata=pbc, type="risk") # risk score
pbc$risk4_6 <- risk.pbc4_6
ROC.risk.marginal4_6 <- timeROC(T=pbc$time,
                                delta=pbc$status,marker=pbc$risk4_6,
                                cause=1,weighting="marginal",
                                times=pbc$time)
ROC.risk.marginal4_6
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      275      1      NA
## t=1191    54      205      17  92.21
## t=1786    73      138      65  90.38
## t=2689    91       69     116  83.01
## t=4556   111       0     165   NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.05 secs.
```

```
#Except protime
cox.pbc4_7 <- coxph(Surv(time,status) ~ age+edema+bili+albumin+copper+ast+stage, data=pbc)
summary(cox.pbc4_7)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + edema + bili + albumin +
##   copper + ast + stage, data = pbc)
##
## n= 276, number of events= 111
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## age    0.0333572 1.0339198 0.0100291 3.326 0.000881 ***
## edema   1.0340804 2.8125187 0.3422521 3.021 0.002516 **
## bili    0.0905335 1.0947582 0.0191242 4.734 2.2e-06 ***
## albumin -0.7019566 0.4956146 0.2748171 -2.554 0.010641 *
## copper   0.0029094 1.0029136 0.0009664 3.011 0.002607 **
## ast     0.0038824 1.0038900 0.0017802 2.181 0.029191 *
## stage   0.4884641 1.6298111 0.1485562 3.288 0.001009 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.0339   0.9672   1.0138   1.0544
## edema     2.8125   0.3556   1.4380   5.5007
## bili     1.0948   0.9134   1.0545   1.1366
## albumin   0.4956   2.0177   0.2892   0.8493
## copper     1.0029   0.9971   1.0010   1.0048
## ast       1.0039   0.9961   1.0004   1.0074
## stage     1.6298   0.6136   1.2181   2.1807
##
## Concordance= 0.844 (se = 0.019 )
## Likelihood ratio test= 159.3 on 7 df,  p=<2e-16
## Wald test            = 174.2 on 7 df,  p=<2e-16
## Score (logrank) test = 253.1 on 7 df,  p=<2e-16
```

```
risk.pbc4_7 <- predict(object=cox.pbc4_7, newdata=pbc, type="risk") # risk score
pbc$risk4_7 <- risk.pbc4_7
ROC.risk.marginal4_7 <- timeROC(T=pbc$time,
                                delta=pbc$status,marker=pbc$risk4_7,
                                cause=1,weighting="marginal",
                                times=pbc$time)
ROC.risk.marginal4_7
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0    275      1    NA
## t=1191    54    205     17  92.94
## t=1786    73    138     65  91.64
## t=2689    91     69    116  83.35
## t=4556   111     0    165   NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.05 secs.
```

```
#Except stage
cox.pbc4_8 <- coxph(Surv(time,status) ~ age+edema+bili+albumin+copper+ast+protime, data=pbc)
summary(cox.pbc4_8)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + edema + bili + albumin +
##   copper + ast + protime, data = pbc)
##
## n= 276, number of events= 111
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## age    0.0350160 1.0356363 0.0100369 3.489 0.000485 ***
## edema   0.9012469 2.4626718 0.3452466 2.610 0.009042 **
## bili    0.0831482 1.0867028 0.0190267 4.370 1.24e-05 ***
## albumin -0.9498499 0.3867991 0.2660793 -3.570 0.000357 ***
## copper   0.0034059 1.0034117 0.0009654 3.528 0.000419 ***
## ast     0.0036433 1.0036500 0.0017587 2.072 0.038299 *
## protime 0.2452319 1.2779176 0.0884607 2.772 0.005568 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.0356   0.9656   1.0155   1.0562
## edema     2.4627   0.4061   1.2518   4.8449
## bili      1.0867   0.9202   1.0469   1.1280
## albumin   0.3868   2.5853   0.2296   0.6516
## copper     1.0034   0.9966   1.0015   1.0053
## ast       1.0036   0.9964   1.0002   1.0071
## protime   1.2779   0.7825   1.0745   1.5198
##
## Concordance= 0.839 (se = 0.021 )
## Likelihood ratio test= 154.3 on 7 df,  p=<2e-16
## Wald test          = 174.7 on 7 df,  p=<2e-16
## Score (logrank) test = 254.5 on 7 df,  p=<2e-16
```

```
risk.pbc4_8 <- predict(object=cox.pbc4_8, newdata= pbc, type="risk") # risk score
pbc$risk4_8 <- risk.pbc4_8
ROC.risk.marginal4_8 <- timeROC(T=pbc$time,
                                delta=pbc$status,marker=pbc$risk4_8,
                                cause=1,weighting="marginal",
                                times=pbc$time)
ROC.risk.marginal4_8
```

```
## Time-dependent-Roc curve estimated using IPCW (n=276, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      275      1      NA
## t=1191    54      205      17    91.86
## t=1786    73      138      65    90.57
## t=2689    91       69     116    81.01
## t=4556   111       0     165     NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.05 secs.
```

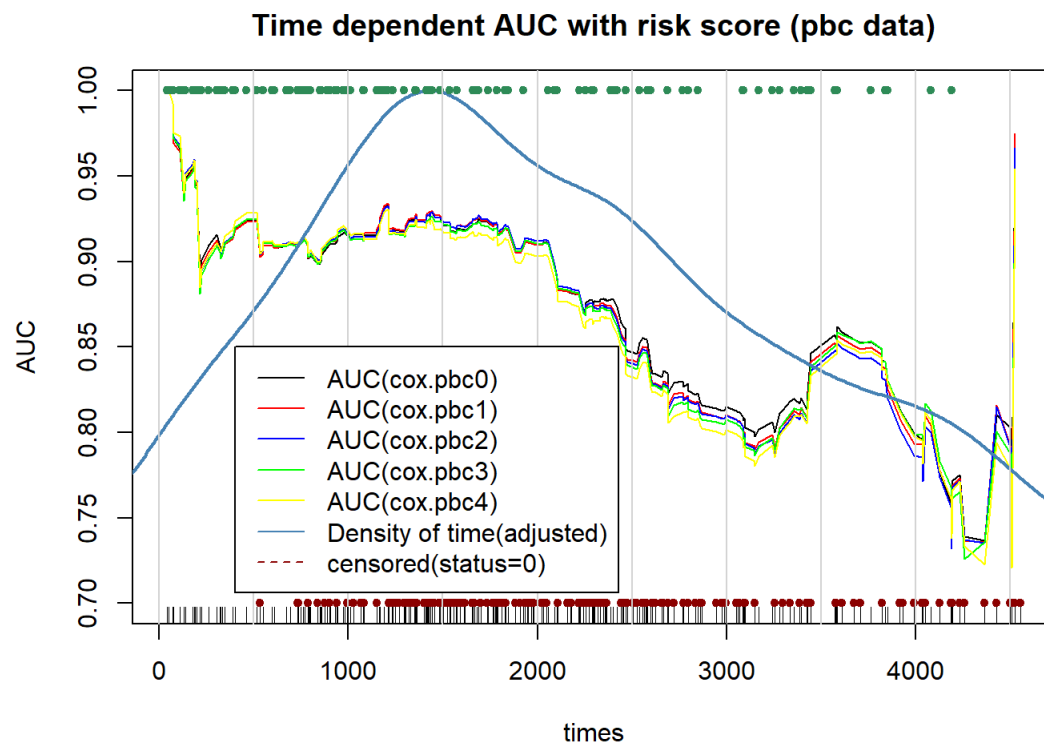
```
data4 <- data.frame(time=ROC.risk.marginal4[["times"]],
                    cox.pbc4=ROC.risk.marginal4[["AUC"]],
                    cox.pbc4_1=ROC.risk.marginal4_1[["AUC"]],
                    cox.pbc4_2=ROC.risk.marginal4_2[["AUC"]],
                    cox.pbc4_3=ROC.risk.marginal4_3[["AUC"]],
                    cox.pbc4_4=ROC.risk.marginal4_4[["AUC"]],
                    cox.pbc4_5=ROC.risk.marginal4_5[["AUC"]],
                    cox.pbc4_6=ROC.risk.marginal4_6[["AUC"]],
                    cox.pbc4_7=ROC.risk.marginal4_7[["AUC"]],
                    cox.pbc4_8=ROC.risk.marginal4_8[["AUC"]])
data4.melt <- melt(data = data4,
                  id.vars = "time",
                  measure.vars = c("cox.pbc4","cox.pbc4_1","cox.pbc4_2",
                                   "cox.pbc4_3","cox.pbc4_4","cox.pbc4_5",
                                   "cox.pbc4_6","cox.pbc4_7","cox.pbc4_8"))
data4.melt <- rename(data4.melt,
                    replace=c("variable"="model",
                               "value"="AUC"))
```

```
time.density <- density(ROC.risk.marginal[["times"]])
data1 <- data.frame(time=time.density[["x"]], density=time.density[["y"]])
data1$density.normal1 <- (time.density[["y"]]-min(time.density[["y"]]))/(max(time.density[["y"]])-min(time.density[["y"]]))
data1$density.normal2 <- (max(na.omit(ROC.risk.marginal0[["AUC"]]))-min(na.omit(ROC.risk.marginal0[["AUC"]]))*(time.density[["y"]]-min(time.density[["y"]])))/(max(time.density[["y"]])-min(time.density[["y"]])+min(na.omit(ROC.risk.marginal0[["AUC"]])))
```

```
pbcc$status.color <- ifelse(pbcc$status==1,"seagreen","darkred")
pbcc$status1 <- ifelse(pbcc$status==1,1,0.7)
```

Plot of Time dependent AUC with Adjusted Density of time and Status of censoring (cox.pbc0~4)

```
par(mar=c(4,4,3,1))
plot(x=ROC.risk.marginal0[["times"]],y=ROC.risk.marginal0[["AUC"]],
     type="l",xlab="times",ylab="AUC",lwd=1,lty=1,col="black",ylim=c(0.7,1),
     main="Time dependent AUC with risk score (pbc data)")
lines(x=ROC.risk.marginal1[["times"]],y=ROC.risk.marginal1[["AUC"]],
      type="l",lwd=1,lty=1,col="red")
lines(x=ROC.risk.marginal2[["times"]],y=ROC.risk.marginal2[["AUC"]],
      type="l",lwd=1,lty=1,col="blue")
lines(x=ROC.risk.marginal3[["times"]],y=ROC.risk.marginal3[["AUC"]],
      type="l",lwd=1,lty=1,col="green")
lines(x=ROC.risk.marginal4[["times"]],y=ROC.risk.marginal4[["AUC"]],
      type="l",lwd=1,lty=1,col="yellow")
lines(x=data1$time,y=data1$density.normal2,col="steelblue",type="l",lwd=2)
points(x=pbcc$time,y=pbcc$status1,col=pbcc$status.color,pch=20)
abline(v=seq(0,5000,500),col="lightgray",lty=1)
rug(jitter(ROC.risk.marginal[["times"]]))
legend(400,0.85,c("AUC(cox.pbc0)","AUC(cox.pbc1)","AUC(cox.pbc2)","AUC(cox.pbc3)","AUC(cox.pbc4)","Density of time(adjusted)","censored(status=0)",
),col=c("black","red","blue","green","yellow","steelblue","darkred"),lwd=c(1,1,1,1,1,1,1),lty=c(1,1,1,1,1,1,2))
```



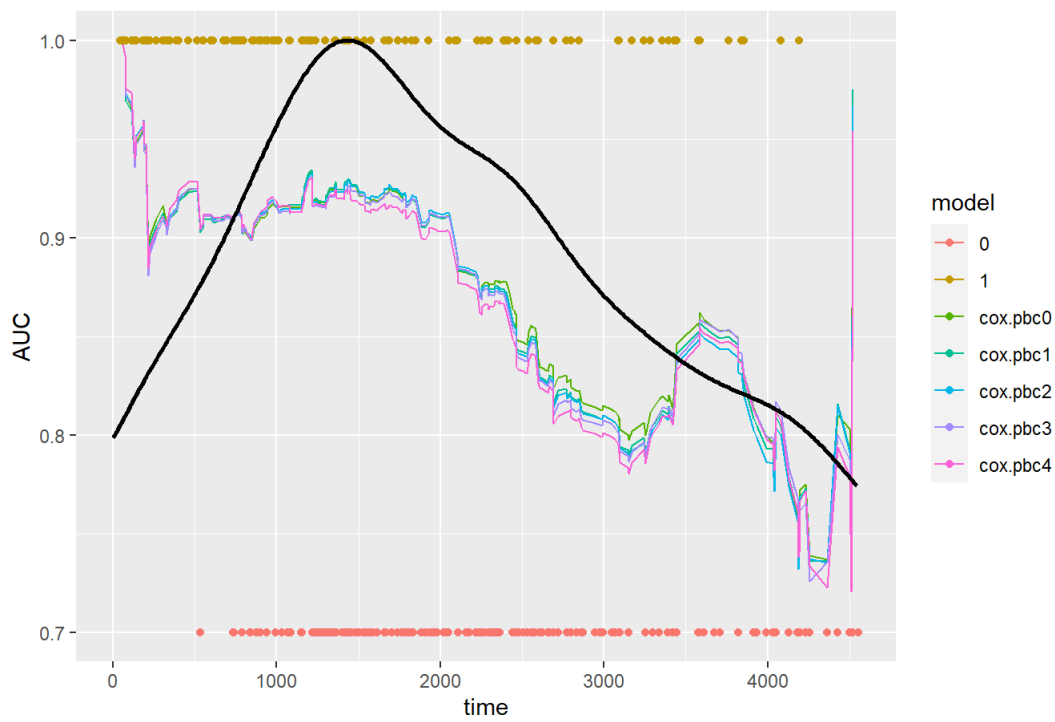
Using ggplot2 (cox.pbc0~4)

```
pbcc$status1 <- ifelse(pbcc$status==1,1,0.7)
ggplot() +
  geom_line(data=data3.melt, aes(x=time, y=AUC,
                                group=model, color=model)) +
  geom_point(data=pbcc, aes(x=time, y=status1, color=as.factor(status))) +
  geom_line(data=data1, aes(x=time, y=density.normal2), size=1, colour='black') +
  scale_x_continuous(limits = c(0, max(pbcc$time))) +
  labs(title="Time dependent AUC with risk score (cox.pbc0~4)",
       xlab="time", ylab="AUC") +
  theme(plot.title = element_text(hjust = 0.5))
```

```
## Warning: Removed 10 row(s) containing missing values (geom_path).
```

```
## Warning: Removed 152 row(s) containing missing values (geom_path).
```

Time dependent AUC with risk score (cox.pbc0~4)



Mean value of Time dependent AUC (cox.pbc0~4)

```
mean(ROC.risk.marginal0[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.8839434
```

```
mean(ROC.risk.marginal1[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.8823727
```

```
mean(ROC.risk.marginal2[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.8816435
```

```
mean(ROC.risk.marginal3[["AUC"]],na.rm=TRUE)
```

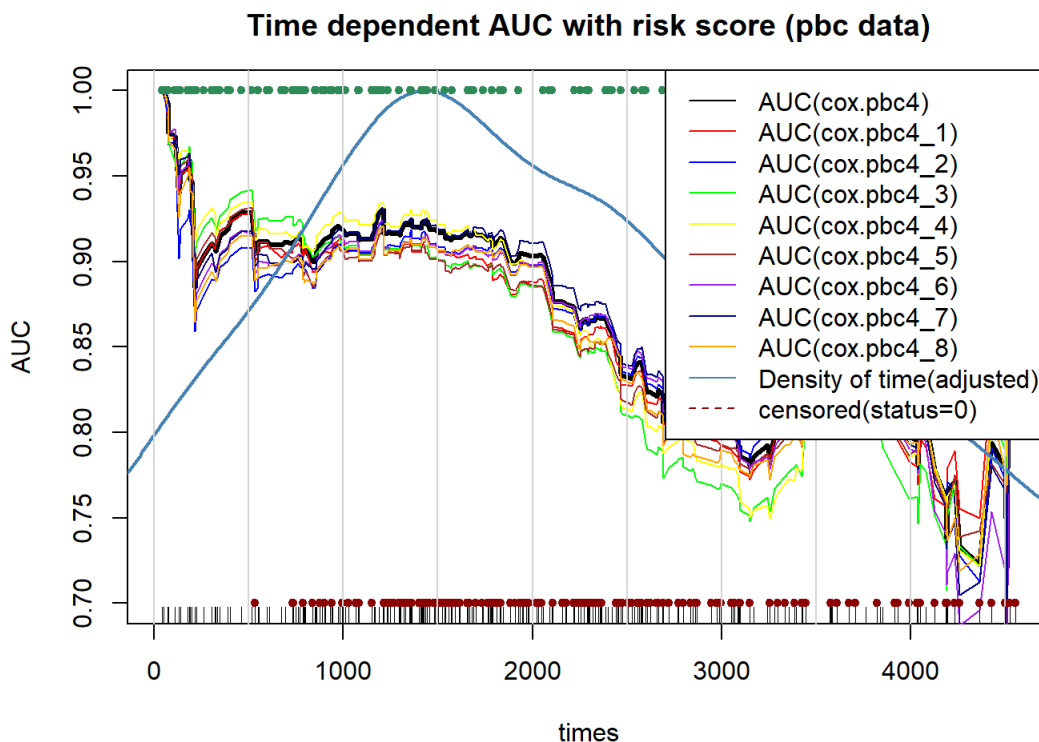
```
## [1] 0.8806345
```

```
mean(ROC.risk.marginal4[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.877869
```

Plot of Time dependent AUC with Adjusted Density of time and Status of censoring (cox.pbc4~4_8)

```
par(mar=c(4,4,3,1))
plot(x=ROC.risk.marginal4[["times"]],y=ROC.risk.marginal4[["AUC"]],
     type="l",xlab="times",ylab="AUC",lwd=3,lty=1,col="black",ylim=c(0.7,1),
     main="Time dependent AUC with risk score (pbc data)")
lines(x=ROC.risk.marginal4_1[["times"]],y=ROC.risk.marginal4_1[["AUC"]],
      type="l",lwd=1,lty=1,col="red") #Except age
lines(x=ROC.risk.marginal4_2[["times"]],y=ROC.risk.marginal4_2[["AUC"]],
      type="l",lwd=1,lty=1,col="blue") #Except edema
lines(x=ROC.risk.marginal4_3[["times"]],y=ROC.risk.marginal4_3[["AUC"]],
      type="l",lwd=1,lty=1,col="green") #Except bili
lines(x=ROC.risk.marginal4_4[["times"]],y=ROC.risk.marginal4_4[["AUC"]],
      type="l",lwd=1,lty=1,col="yellow") #Except albumin
lines(x=ROC.risk.marginal4_5[["times"]],y=ROC.risk.marginal4_5[["AUC"]],
      type="l",lwd=1,lty=1,col="brown") #Except copper
lines(x=ROC.risk.marginal4_6[["times"]],y=ROC.risk.marginal4_6[["AUC"]],
      type="l",lwd=1,lty=1,col="purple") #Except ast
lines(x=ROC.risk.marginal4_7[["times"]],y=ROC.risk.marginal4_7[["AUC"]],
      type="l",lwd=1,lty=1,col="navy") #Except protime
lines(x=ROC.risk.marginal4_8[["times"]],y=ROC.risk.marginal4_8[["AUC"]],
      type="l",lwd=1,lty=1,col="orange") #Except stage
lines(x=data1$time,y=data1$density.normal2,col="steelblue",type="l",lwd=2)
points(x=pbcs$time,y=pbcs$status1,col=pbcs$status.color,pch=20)
abline(v=seq(0,5000,500),col="lightgray",lty=1)
rug(jitter(ROC.risk.marginal[["times"]]))
legend("topright",c("AUC(cox.pbc4)","AUC(cox.pbc4_1)","AUC(cox.pbc4_2)","AUC(cox.pbc4_3)","AUC(cox.pbc4_4)","AUC(cox.pbc4_5)","AUC(cox.pbc4_6)","AUC(cox.pbc4_7)","AUC(cox.pbc4_8)","Density of time(adjusted)","censored(status=0)"),col=c("black","red","blue","green","yellow","brown","purple","navy","orange","steelblue","darkred"),lwd=c(1,1,1,1,1,1,1,1,1,1),lty=c(1,1,1,1,1,1,1,1,1,2))
```



Using ggplot2 (cox.pbc4~4_8)

```

pbc$status1 <- ifelse(pbc$status==1,1,0.65)
ggplot() +
  geom_line(data=data4.melt, aes(x=time, y=AUC,
                                group=model, color=model)) +
  geom_point(data=pbc, aes(x=time, y=status1, color=as.factor(status))) +
  geom_line(data=data1, aes(x=time, y=density.normal2, size=1, colour='black') +
  scale_x_continuous(limits = c(0, max(pbc$time)))) +
  labs(title="Time dependent AUC with risk score (cox.pbc4~4_8)",
        xlab="time", ylab="AUC") +
  theme(plot.title = element_text(hjust = 0.5))

```

```
## Warning: Removed 18 row(s) containing missing values (geom path).
```

```
## Warning: Removed 152 row(s) containing missing values (geom path).
```

Time dependent AUC with risk score (cox.pbc4~4_8)



Mean value of Time dependent AUC (cox.pbc4~4_8)

```
mean(ROC.risk.marginal4[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.877869
```

```
mean(ROC.risk.marginal4_1[["AUC"]],na.rm=TRUE) #Except age
```

```
## [1] 0.8699606
```

```
mean(ROC.risk.marginal4_2[["AUC"]],na.rm=TRUE) #Except edema
```

```
## [1] 0.8720034
```

```
mean(ROC.risk.marginal4_3[["AUC"]],na.rm=TRUE) #Except bili
```

```
## [1] 0.8632788
```

```
mean(ROC.risk.marginal4_4[["AUC"]],na.rm=TRUE) #Except albumin
```

```
## [1] 0.8748845
```

```
mean(ROC.risk.marginal4_5[["AUC"]],na.rm=TRUE) #Except copper
```

```
## [1] 0.8668689
```

```
mean(ROC.risk.marginal4_6[["AUC"]],na.rm=TRUE) #Except ast
```

```
## [1] 0.8713267
```

```
mean(ROC.risk.marginal4_7[["AUC"]],na.rm=TRUE) #Except protime
```

```
## [1] 0.880141
```

```
mean(ROC.risk.marginal4_8[["AUC"]],na.rm=TRUE) #Except stage
```

```
## [1] 0.8673557
```


Train vs Test

```
data(pbc)
pbc<-pbc[,-1] # delete ID
pbc$status<-as.numeric(pbc$status==2) # create event indicator: 1 for death, 0 for censored
pbc <- na.omit(pbc)
```

train:test = 7:3

```
set.seed(55364)
idx_train <- sample(1:nrow(pbc), round(0.7*nrow(pbc)))
pbc.train <- pbc[idx_train,]
pbc.test <- pbc[setdiff(x = 1:nrow(pbc), y = idx_train), ]
```

Cox PH model with train data

Null model

```
cox.train0 <- coxph(Surv(time,status) ~ trt+age+sex+ascites+hepato+spiders+edema
  +bili+chol+albumin+copper+alk.phos+ast+trig
  +platelet+protime+stage, data=pbc.train)
summary(cox.train0)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ trt + age + sex + ascites +
##   hepato + spiders + edema + bili + chol + albumin + copper +
##   alk.phos + ast + trig + platelet + protime + stage, data = pbc.train)
##
## n= 193, number of events= 71
##
##      coef exp(coef) se(coef)  z Pr(>|z|)
## trt    -1.006e-01  9.043e-01  2.844e-01 -0.354  0.7237
## age     2.463e-02  1.025e+00  1.474e-02  1.671  0.0948 .
## sexf     3.678e-01  1.445e+00  4.344e-01  0.847  0.3972
## ascites  1.522e-01  1.164e+00  5.068e-01  0.300  0.7639
## hepato   2.027e-01  1.225e+00  3.384e-01  0.599  0.5492
## spiders  9.796e-02  1.103e+00  3.149e-01  0.311  0.7557
## edema    6.967e-01  2.007e+00  5.017e-01  1.389  0.1649
## bili     6.694e-02  1.069e+00  3.241e-02  2.065  0.0389 *
## chol     5.443e-04  1.001e+00  4.972e-04  1.095  0.2736
## albumin  -5.479e-01  5.782e-01  4.661e-01 -1.175  0.2398
## copper    3.447e-03  1.003e+00  1.446e-03  2.385  0.0171 *
## alk.phos  3.146e-05  1.000e+00  5.514e-05  0.571  0.5683
## ast       3.161e-03  1.003e+00  2.564e-03  1.233  0.2177
## trig      1.390e-03  1.001e+00  2.332e-03  0.596  0.5511
## platelet  1.744e-04  1.000e+00  1.447e-03  0.121  0.9041
## protime   2.146e-01  1.239e+00  1.362e-01  1.576  0.1150
## stage     4.813e-01  1.618e+00  2.260e-01  2.130  0.0332 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## trt           0.9043    1.1058  0.5179  1.579
## age           1.0249    0.9757  0.9957  1.055
## sexf          1.4446    0.6922  0.6165  3.385
## ascites       1.1644    0.8588  0.4312  3.144
## hepato        1.2247    0.8166  0.6309  2.377
## spiders       1.1029    0.9067  0.5950  2.045
## edema         2.0071    0.4982  0.7508  5.366
## bili          1.0692    0.9353  1.0034  1.139
## chol          1.0005    0.9995  0.9996  1.002
## albumin       0.5782    1.7296  0.2319  1.442
## copper        1.0035    0.9966  1.0006  1.006
## alk.phos      1.0000    1.0000  0.9999  1.000
## ast           1.0032    0.9968  0.9981  1.008
## trig          1.0014    0.9986  0.9968  1.006
## platelet      1.0002    0.9998  0.9973  1.003
## protime       1.2394    0.8068  0.9491  1.618
## stage         1.6181    0.6180  1.0391  2.520
##
## Concordance= 0.859 (se = 0.022 )
## Likelihood ratio test= 110.2 on 17 df,  p=1e-15
## Wald test           = 113 on 17 df,  p=3e-16
## Score (logrank) test = 196.6 on 17 df,  p=<2e-16
```

```
risk.train0 <- predict(object=cox.train0, newdata=pbc.test, type="risk") # risk score
pbc.test$risk0 <- risk.train0
ROC.risk.train0 <- timeROC(T=pbc.test$time,
                           delta=pbc.test$status,marker=pbc.test$risk0,
                           cause=1,weighting="marginal",
                           times=pbc.test$time)
ROC.risk.train0
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      82      1    NA
## t=1271    18      61      4  90.51
## t=1932    26      41     16  90.60
## t=2847    33      21     29  76.75
## t=4523    40       0     43    NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.01 secs.
```

Except explanatory variables with p-value > 0.5

```
cox.train1 <- coxph(Surv(time,status) ~ age+sex+edema
+bili+chol+albumin+copper+ast
+protime+stage, data=pbcc.train)
summary(cox.train1)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + sex + edema + bili +
## chol + albumin + copper + ast + protime + stage, data = pbcc.train)
##
## n= 193, number of events= 71
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## age    0.0240664  1.0243584  0.0135153  1.781  0.07497 .
## sexf    0.3575226  1.4297829  0.4113394  0.869  0.38476
## edema    0.5561899  1.7440149  0.4552818  1.222  0.22184
## bili    0.0805407  1.0838730  0.0267098  3.015  0.00257 **
## chol    0.0005167  1.0005168  0.0004809  1.074  0.28270
## albumin -0.6789684  0.5071399  0.4399692 -1.543  0.12278
## copper   0.0038808  1.0038883  0.0012875  3.014  0.00258 **
## ast     0.0028882  1.0028923  0.0024129  1.197  0.23133
## protime  0.2465435  1.2795949  0.1291942  1.908  0.05635 .
## stage    0.5305820  1.6999214  0.1889291  2.808  0.00498 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.0244   0.9762   0.9976   1.052
## sexf     1.4298   0.6994   0.6385   3.202
## edema     1.7440   0.5734   0.7145   4.257
## bili     1.0839   0.9226   1.0286   1.142
## chol     1.0005   0.9995   0.9996   1.001
## albumin   0.5071   1.9718   0.2141   1.201
## copper     1.0039   0.9961   1.0014   1.006
## ast       1.0029   0.9971   0.9982   1.008
## protime   1.2796   0.7815   0.9933   1.648
## stage     1.6999   0.5883   1.1738   2.462
##
## Concordance= 0.856 (se = 0.022 )
## Likelihood ratio test= 108.5 on 10 df,  p=<2e-16
## Wald test          = 112.5 on 10 df,  p=<2e-16
## Score (logrank) test = 172.4 on 10 df,  p=<2e-16
```

```
risk.train1 <- predict(object=cox.train1, newdata=pbcc.test, type="risk") # risk score
pbcc.test$risk1 <- risk.train1
ROC.risk.train1 <- timeROC(T=pbcc.test$time,
delta=pbcc.test$status,marker=pbcc.test$risk1,
cause=1,weighting="marginal",
times=pbcc.test$time)
ROC.risk.train1
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    82    1    NA
## t=1271  18    61    4  90.95
## t=1932  26    41    16  88.95
## t=2847  33    21    29  75.90
## t=4523  40    0    43    NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.01 secs.
```

Except explanatory variables with p-value > 0.2

```
cox.train2 <- coxph(Surv(time,status) ~ age+bili+albumin+copper
+protime+stage, data=pbcc.train)
summary(cox.train2)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ age + bili + albumin + copper +
##   protime + stage, data = pbc.train)
##
## n= 193, number of events= 71
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## age    0.010224  1.010277  0.011540  0.886 0.375618
## bili   0.110360  1.116680  0.020760  5.316 1.06e-07 ***
## albumin -1.015544  0.362205  0.399391 -2.543 0.010999 *
## copper   0.003878  1.003885  0.001112  3.489 0.000486 ***
## protime  0.268004  1.307352  0.116959  2.291 0.021938 *
## stage   0.492891  1.637043  0.178026  2.769 0.005629 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## age      1.0103   0.9898   0.9877   1.0334
## bili     1.1167   0.8955   1.0722   1.1631
## albumin   0.3622   2.7609   0.1656   0.7924
## copper     1.0039   0.9961   1.0017   1.0061
## protime   1.3074   0.7649   1.0395   1.6442
## stage     1.6370   0.6109   1.1548   2.3206
##
## Concordance= 0.845 (se = 0.027 )
## Likelihood ratio test= 103.6 on 6 df,  p=<2e-16
## Wald test          = 111.5 on 6 df,  p=<2e-16
## Score (logrank) test = 159.2 on 6 df,  p=<2e-16
```

```
risk.train2 <- predict(object=cox.train2, newdata=pbctest, type="risk") # risk score
pbctest$risk2 <- risk.train2
ROC.risk.train2 <- timeROC(T=pbctest$time,
                           delta=pbctest$status,marker=pbctest$risk2,
                           cause=1,weighting="marginal",
                           times=pbctest$time)
ROC.risk.train2
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41      0      82      1      NA
## t=1271    18      61      4    90.56
## t=1932    26      41     16    88.17
## t=2847    33      21     29    75.87
## t=4523    40       0     43     NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.01 secs.
```

Except explanatory variables with p-value > 0.2

```
cox.train3 <- coxph(Surv(time,status) ~ bili+albumin+copper
+protime+stage, data=pbctest)
summary(cox.train3)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ bili + albumin + copper +
##   protime + stage, data = pbc.train)
##
##   n= 193, number of events= 71
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## bili    0.109343  1.115545  0.020959  5.217 1.82e-07 ***
## albumin -1.069026  0.343343  0.393912 -2.714 0.006650 **
## copper   0.004073  1.004082  0.001088  3.744 0.000181 ***
## protime  0.278172  1.320713  0.118224  2.353 0.018627 *
## stage   0.524138  1.689002  0.176235  2.974 0.002939 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##           exp(coef) exp(-coef) lower .95 upper .95
## bili    1.1155    0.8964    1.0706    1.1623
## albumin  0.3433    2.9125    0.1586    0.7431
## copper   1.0041    0.9959    1.0019    1.0062
## protime  1.3207    0.7572    1.0476    1.6651
## stage   1.6890    0.5921    1.1957    2.3858
##
## Concordance= 0.839 (se = 0.027 )
## Likelihood ratio test= 102.8 on 5 df,  p=<2e-16
## Wald test          = 107.9 on 5 df,  p=<2e-16
## Score (logrank) test = 154.5 on 5 df,  p=<2e-16
```

```
risk.train3 <- predict(object=cox.train3, newdata=pbctest, type="risk") # risk score
pbctest$risk3 <- risk.train3
ROC.risk.train3 <- timeROC(T=pbctest$time,
                           delta=pbctest$status,marker=pbctest$risk3,
                           cause=1,weighting="marginal",
                           times=pbctest$time)
ROC.risk.train3
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0      82      1    NA
## t=1271  18      61      4  90.12
## t=1932  26      41      16  87.85
## t=2847  33      21      29  75.61
## t=4523  40       0      43    NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.02 secs.
```

Time dependent AUC plot with ggplot2 (cox.train0~3)

```
time.density <- density(ROC.risk.train0[["times"]])
data1 <- data.frame(time=time.density[["x"]], density=time.density[["y"]])
data1$density.adjusted <- (max(na.omit(ROC.risk.train0[["AUC"]]))-min(na.omit(ROC.risk.train0[["AUC"]]))*(time.density[["y"]]-min(time.density[["y"]]))/(max(time.density[["y"]]-min(time.density[["y"]]))+min(na.omit(ROC.risk.train0[["AUC"]]))))
dt1 <- data.frame(time=ROC.risk.train0[["times"]],
                  cox.train0=ROC.risk.train0[["AUC"]],
                  cox.train1=ROC.risk.train1[["AUC"]],
                  cox.train2=ROC.risk.train2[["AUC"]],
                  cox.train3=ROC.risk.train3[["AUC"]])
dt1.melt <- melt(data = dt1,
                id.vars = "time",
                measure.vars = c("cox.train0", "cox.train1", "cox.train2",
                                "cox.train3"))
dt1.melt <- rename(dt1.melt,
                  replace=c("variable"="model",
                              "value"="AUC"))
```

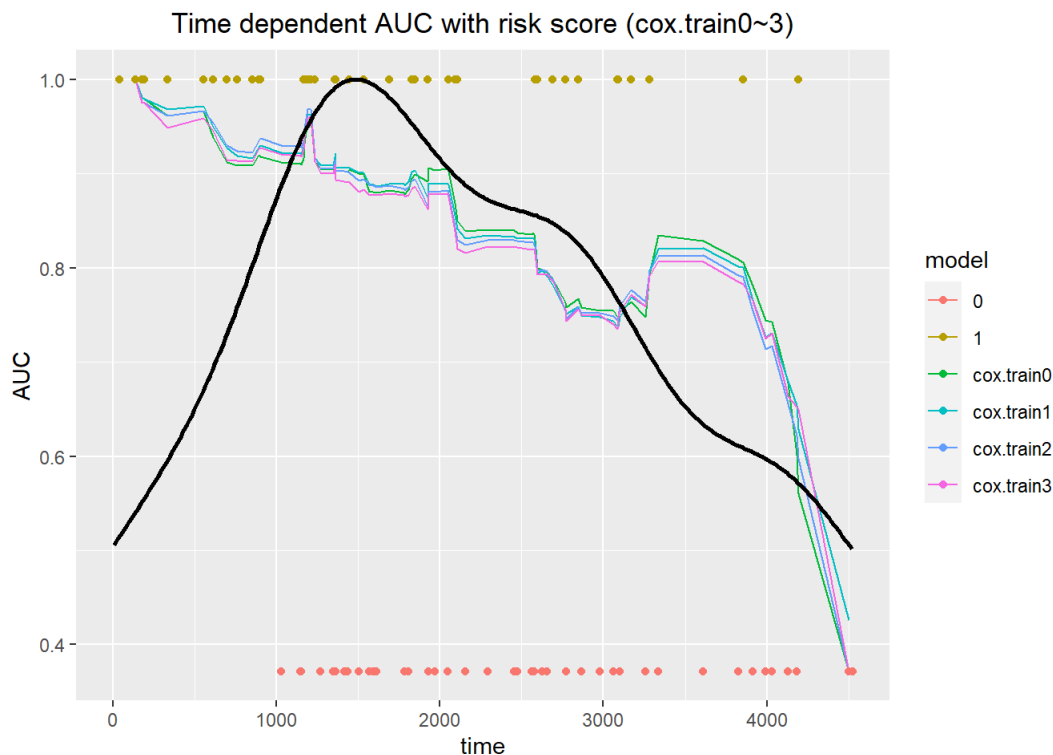
```

pbc.test$status1 <- ifelse(pbc.test$status==1,1,min(na.omit(ROC.risk.train0[["AUC"]]))))
ggplot() +
  geom_line(data=dt1.melt, aes(x=time, y=AUC,
                             group=model, color=model)) +
  geom_point(data=pbc.test, aes(x=time, y=status1, color=as.factor(status))) +
  geom_line(data=data1, aes(x=time, y=density.adjusted), size=1, colour='black') +
  scale_x_continuous(limits = c(0, max(pbc.test$time))) +
  labs(title="Time dependent AUC with risk score (cox.train0~3)",
       xlab="time", ylab="AUC") +
  theme(plot.title = element_text(hjust = 0.5))

```

```
## Warning: Removed 8 row(s) containing missing values (geom_path).
```

```
## Warning: Removed 181 row(s) containing missing values (geom_path).
```



Mean value of Time dependent AUC (cox.train0~3)

```
mean(ROC.risk.train0[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.8485442
```

```
mean(ROC.risk.train1[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.8501646
```

```
mean(ROC.risk.train2[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.8466657
```

```
mean(ROC.risk.train3[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.8420762
```

Counting censored data

```

pbc.test.censor <- pbc.test[pbc.test$status==0,]
pbc.test.censor <- pbc.test.censor %>%
  mutate(n.cen=cut(pbc.test.censor$time,
                   breaks=seq(from=0,to=5000,by=500)))
table(pbc.test.censor$n.cen)

```

```
##
##      (0,500]   (500,1e+03] (1e+03,1.5e+03] (1.5e+03,2e+03] (2e+03,2.5e+03]
##      0         0         8         9         5
## (2.5e+03,3e+03] (3e+03,3.5e+03] (3.5e+03,4e+03] (4e+03,4.5e+03] (4.5e+03,5e+03]
##      8         4         4         4         1
```

Except each explanatory variables in model cox.train3

```
# Except bili
cox.train3_1 <- coxph(Surv(time,status) ~ albumin+copper
  +protime+stage, data=pbcc.train)
summary(cox.train3_1)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ albumin + copper + protime +
##   stage, data = pbcc.train)
##
## n= 193, number of events= 71
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## albumin -1.35109  0.25896  0.38019 -3.554  0.00038 ***
## copper   0.00524  1.00525  0.00102  5.138 2.78e-07 ***
## protime  0.39236  1.48047  0.11041  3.554  0.00038 ***
## stage    0.51811  1.67886  0.16511  3.138  0.00170 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## albumin   0.259   3.8617   0.1229  0.5456
## copper     1.005   0.9948   1.0032  1.0073
## protime    1.480   0.6755   1.1924  1.8382
## stage      1.679   0.5956   1.2147  2.3203
##
## Concordance= 0.822 (se = 0.029 )
## Likelihood ratio test= 82.57 on 4 df,  p=<2e-16
## Wald test            = 89.29 on 4 df,  p=<2e-16
## Score (logrank) test = 105.3 on 4 df,  p=<2e-16
```

```
risk.train3_1 <- predict(object=cox.train3_1, newdata=pbcc.test, type="risk") # risk score
pbcc.test$risk3_1 <- risk.train3_1
ROC.risk.train3_1 <- timeROC(T=pbcc.test$time,
  delta=pbcc.test$status,marker=pbcc.test$risk3_1,
  cause=1,weighting="marginal",
  times=pbcc.test$time)
ROC.risk.train3_1
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0      82      1    NA
## t=1271  18      61      4  87.48
## t=1932  26      41      16  85.08
## t=2847  33      21      29  72.72
## t=4523  40      0      43    NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.02 secs.
```

```
# Except albumin
cox.train3_2 <- coxph(Surv(time,status) ~ bili+copper
  +protime+stage, data=pbcc.train)
summary(cox.train3_2)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ bili + copper + protime +
##   stage, data = pbc.train)
##
## n= 193, number of events= 71
##
##      coef exp(coef) se(coef)    z Pr(>|z|)
## bili   0.119416  1.126839 0.020217 5.907 3.49e-09 ***
## copper   0.004607  1.004618 0.001042 4.422 9.76e-06 ***
## protime  0.264790  1.303158 0.117665 2.250 0.024425 *
## stage   0.620198  1.859296 0.176777 3.508 0.000451 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## bili      1.127   0.8874   1.083   1.172
## copper      1.005   0.9954   1.003   1.007
## protime    1.303   0.7674   1.035   1.641
## stage      1.859   0.5378   1.315   2.629
##
## Concordance= 0.834 (se = 0.023 )
## Likelihood ratio test= 95.36 on 4 df,  p=<2e-16
## Wald test          = 100.6 on 4 df,  p=<2e-16
## Score (logrank) test = 145 on 4 df,  p=<2e-16
```

```
risk.train3_2 <- predict(object=cox.train3_2, newdata=pbctest, type="risk") # risk score
pbctest$risk3_2 <- risk.train3_2
ROC.risk.train3_2 <- timeROC(T=pbctest$time,
                             delta=pbctest$status, marker=pbctest$risk3_2,
                             cause=1, weighting="marginal",
                             times=pbctest$time)
ROC.risk.train3_2
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
## Cases Survivors Censored AUC (%)
## t=41  0  82  1  NA
## t=1271 18  61  4 88.94
## t=1932 26  41 16 88.19
## t=2847 33  21 29 78.09
## t=4523 40  0 43  NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.01 secs.
```

```
# Except copper
cox.train3_3 <- coxph(Surv(time,status) ~ bili+albumin
+protime+stage, data=pbctest)
summary(cox.train3_3)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ bili + albumin + protime +
##   stage, data = pbc.train)
##
## n= 193, number of events= 71
##
##      coef exp(coef) se(coef)    z Pr(>|z|)
## bili   0.12113  1.12877 0.01908 6.348 2.17e-10 ***
## albumin -1.32516  0.26576 0.39037 -3.395 0.000687 ***
## protime  0.27641  1.31839 0.11376 2.430 0.015107 *
## stage   0.57076  1.76961 0.17006 3.356 0.000790 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## bili      1.1288   0.8859   1.0873   1.1718
## albumin   0.2658   3.7628   0.1237   0.5712
## protime   1.3184   0.7585   1.0549   1.6477
## stage     1.7696   0.5651   1.2680   2.4696
##
## Concordance= 0.817 (se = 0.03 )
## Likelihood ratio test= 91.02 on 4 df,  p=<2e-16
## Wald test          = 98.19 on 4 df,  p=<2e-16
## Score (logrank) test = 142.2 on 4 df,  p=<2e-16
```



```
risk.train3_3 <- predict(object=cox.train3_3, newdata=pbctest, type="risk") # risk score
pbctest$risk3_3 <- risk.train3_3
ROC.risk.train3_3 <- timeROC(T=pbctest$time,
                             delta=pbctest$status,marker=pbctest$risk3_3,
                             cause=1,weighting="marginal",
                             times=pbctest$time)
ROC.risk.train3_3
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    82    1   NA
## t=1271  18    61    4  90.12
## t=1932  26    41   16  86.09
## t=2847  33    21   29  74.47
## t=4523  40     0   43   NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.01 secs.
```

```
# Except protime
cox.train3_4 <- coxph(Surv(time,status) ~ bili+albumin+copper
                     +stage, data=pbctrain)
summary(cox.train3_4)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ bili + albumin + copper +
##       stage, data = pbctrain)
##
## n = 193, number of events = 71
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## bili   0.118617  1.125938  0.019800  5.991 2.09e-09 ***
## albumin -1.058714  0.346902  0.400931 -2.641 0.008275 **
## copper   0.004066  1.004074  0.001072  3.792 0.000150 ***
## stage   0.644258  1.904574  0.177707  3.625 0.000289 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## bili   1.1259   0.8881   1.0831   1.1705
## albumin  0.3469   2.8827   0.1581   0.7612
## copper   1.0041   0.9959   1.0020   1.0062
## stage   1.9046   0.5251   1.3444   2.6981
##
## Concordance= 0.827 (se = 0.026 )
## Likelihood ratio test= 98.02 on 4 df,  p=<2e-16
## Wald test            = 103.7 on 4 df,  p=<2e-16
## Score (logrank) test = 145.1 on 4 df,  p=<2e-16
```

```
risk.train3_4 <- predict(object=cox.train3_4, newdata=pbctest, type="risk") # risk score
pbctest$risk3_4 <- risk.train3_4
ROC.risk.train3_4 <- timeROC(T=pbctest$time,
                             delta=pbctest$status,marker=pbctest$risk3_4,
                             cause=1,weighting="marginal",
                             times=pbctest$time)
ROC.risk.train3_4
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    82    1   NA
## t=1271  18    61    4  89.75
## t=1932  26    41   16  88.75
## t=2847  33    21   29  78.35
## t=4523  40     0   43   NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0.01 secs.
```

```
# Except stage
cox.train3_5 <- coxph(Surv(time,status) ~ bili+albumin+copper
+protime, data=pbcc.train)
summary(cox.train3_5)
```

```
## Call:
## coxph(formula = Surv(time, status) ~ bili + albumin + copper +
##   protime, data = pbcc.train)
##
## n= 193, number of events= 71
##
##      coef exp(coef) se(coef)      z Pr(>|z|)
## bili   0.109181  1.115364  0.020300  5.378 7.51e-08 ***
## albumin -1.282944  0.277220  0.376698 -3.406 0.000660 ***
## copper   0.004608  1.004618  0.001079  4.272 1.94e-05 ***
## protime  0.326271  1.385791  0.095653  3.411 0.000647 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## bili    1.1154    0.8966    1.0719    1.1606
## albumin  0.2772    3.6072    0.1325    0.5801
## copper    1.0046    0.9954    1.0025    1.0067
## protime  1.3858    0.7216    1.1489    1.6715
##
## Concordance= 0.827 (se = 0.029 )
## Likelihood ratio test= 92.84 on 4 df,  p=<2e-16
## Wald test            = 105 on 4 df,  p=<2e-16
## Score (logrank) test = 149.2 on 4 df,  p=<2e-16
```

```
risk.train3_5 <- predict(object=cox.train3_5, newdata=pbcc.test, type="risk") # risk score
pbcc.test$risk3_5 <- risk.train3_5
ROC.risk.train3_5 <- timeROC(T=pbcc.test$time,
delta=pbcc.test$status,marker=pbcc.test$risk3_5,
cause=1,weighting="marginal",
times=pbcc.test$time)
ROC.risk.train3_5
```

```
## Time-dependent-Roc curve estimated using IPCW (n=83, without competing risks).
##      Cases Survivors Censored AUC (%)
## t=41    0    82    1    NA
## t=1271  18    61    4  89.40
## t=1932  26    41    16 88.12
## t=2847  33    21    29 69.96
## t=4523  40    0    43  NA
##
## Method used for estimating IPCW:marginal
##
## Total computation time : 0 secs.
```

Time dependent AUC plot with ggplot2 (cox.train3~3_5)

```
time.density <- density(ROC.risk.train3[["times"]])
data1 <- data.frame(time=time.density[["x"]], density=time.density[["y"]])
data1$density.adjusted <- (max(na.omit(ROC.risk.train3[["AUC"]]))-min(na.omit(ROC.risk.train3[["AUC"]]))*(time.density[["y"]]-min(time.density[["y"]]))/(max(time.density[["y"]]-min(time.density[["y"]]))+min(na.omit(ROC.risk.train3[["AUC"]]))))
dt2 <- data.frame(time=ROC.risk.train3[["times"]],
cox.train3=ROC.risk.train3[["AUC"]],
cox.train3_1=ROC.risk.train3_1[["AUC"]],
cox.train3_2=ROC.risk.train3_2[["AUC"]],
cox.train3_3=ROC.risk.train3_3[["AUC"]],
cox.train3_4=ROC.risk.train3_4[["AUC"]],
cox.train3_5=ROC.risk.train3_5[["AUC"]])
dt2.melt <- melt(data = dt2,
id.vars = "time",
measure.vars = c("cox.train3","cox.train3_1","cox.train3_2",
"cox.train3_3","cox.train3_4","cox.train3_5"))
dt2.melt <- rename(dt2.melt,
replace=c("variable"="model",
"value"="AUC"))
```

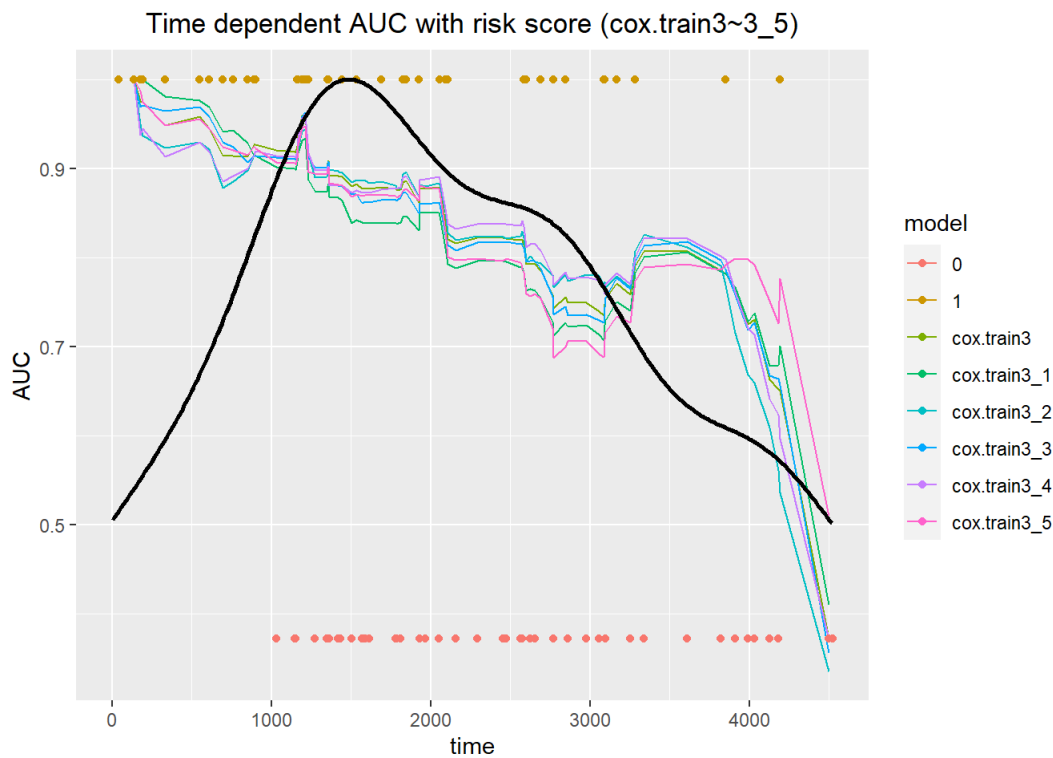
```

pbc.test$status1 <- ifelse(pbc.test$status==1,1,min(na.omit(ROC.risk.train3[["AUC"]]])))
ggplot() +
  geom_line(data=dt2.melt, aes(x=time, y=AUC,
                              group=model, color=model)) +
  geom_point(data=pbc.test, aes(x=time, y=status1, color=as.factor(status))) +
  geom_line(data=data1, aes(x=time, y=density.adjusted), size=1, colour='black') +
  scale_x_continuous(limits = c(0, max(pbc.test$time))) +
  labs(title="Time dependent AUC with risk score (cox.train3~3_5)",
        xlab="time", ylab="AUC") +
  theme(plot.title = element_text(hjust = 0.5))

```

```
## Warning: Removed 12 row(s) containing missing values (geom_path).
```

```
## Warning: Removed 181 row(s) containing missing values (geom_path).
```



Mean value of Time dependent AUC (cox.train3~3_5)

```
mean(ROC.risk.train3[["AUC"]],na.rm=TRUE)
```

```
## [1] 0.8420762
```

```
mean(ROC.risk.train3_1[["AUC"]],na.rm=TRUE) # Except bili
```

```
## [1] 0.8250884
```

```
mean(ROC.risk.train3_2[["AUC"]],na.rm=TRUE) # Except albumin
```

```
## [1] 0.8376043
```

```
mean(ROC.risk.train3_3[["AUC"]],na.rm=TRUE) # Except copper
```

```
## [1] 0.8376651
```

```
mean(ROC.risk.train3_4[["AUC"]],na.rm=TRUE) # Except protime
```

```
## [1] 0.8440317
```

```
mean(ROC.risk.train3_5[["AUC"]],na.rm=TRUE) # Except stage
```

```
## [1] 0.8352137
```