NIK Recurence

Jose Tamez

2023-05-18

Contents

1 NIK and RRPlots

1.1 The libraries

```
library(survival)
library(FRESA.CAD)
```

```
## Loading required package: Rcpp

## Loading required package: stringr

## Loading required package: miscTools

## Loading required package: Hmisc

##
## Attaching package: 'Hmisc'

## The following objects are masked from 'package:base':
##
##      format.pval, units

## Loading required package: pROC

## Type 'citation("pROC")' for a citation.
```

```
## 
## Attaching package: 'pROC'

## The following objects are masked from 'package:stats':
## 
##     cov, smooth, var
```
```
library(Biobase)
```
```
## Loading required package: BiocGenerics

## 
## Attaching package: 'BiocGenerics'

## The following object is masked from 'package:pROC':
## 
##     var

## The following objects are masked from 'package:stats':
## 
##     IQR, mad, sd, var, xtabs

## The following objects are masked from 'package:base':
## 
##     anyDuplicated, append, as.data.frame, basename, cbind, colnames,
##     dirname, do.call, duplicated, eval, evalq, Filter, Find, get, grep,
##     grepl, intersect, is.unsorted, lapply, Map, mapply, match, mget,
##     order, paste, pmax, pmax.int, pmin, pmin.int, Position, rank,
##     rbind, Reduce, rownames, sapply, setdiff, sort, table, tapply,
##     union, unique, unsplit, which.max, which.min

## Welcome to Bioconductor
## 
##     Vignettes contain introductory material; view with
##     'browseVignettes()'. To cite Bioconductor, see
##     'citation("Biobase")', and for packages 'citation("pkgname")'.

## 
## Attaching package: 'Biobase'

## The following object is masked from 'package:Hmisc':
## 
##     contents

## The following object is masked from 'package:miscTools':
## 
##     rowMedians
```
```r
op <- par(no.readonly = TRUE)
pander::panderOptions('digits', 3)
pander::panderOptions('table.split.table', 400)
pander::panderOptions('keep.trailing.zeros',TRUE)
```
```r
if (!require("BiocManager", quietly = TRUE))
{
    install.packages("BiocManager")
    BiocManager::install("seventyGeneData")
}
```
```
## Bioconductor version '3.15' is out-of-date; the current release version '3.17'
```

```
##   is available with R version '4.3'; see https://bioconductor.org/install
```
```
library(seventyGeneData)
data(vanDeVijver)
class(vanDeVijver)
```

```
## [1] "ExpressionSet"
## attr(,"package")
## [1] "Biobase"
```

1.2   Getting the clinical data

```
pdata <- pData(vanDeVijver)
```

1.3   ROC Plots

```
table(pdata$Posnodes)
```

n y 151 144

```
pander::pander(table(pdata$TTMevent))
```

0	1
194	101

```
pmroc <- plotModels.ROC(cbind(pdata$TTMevent,-pdata$C1used),name="NIK",thr= -0.4) ## Using paper thresh
```
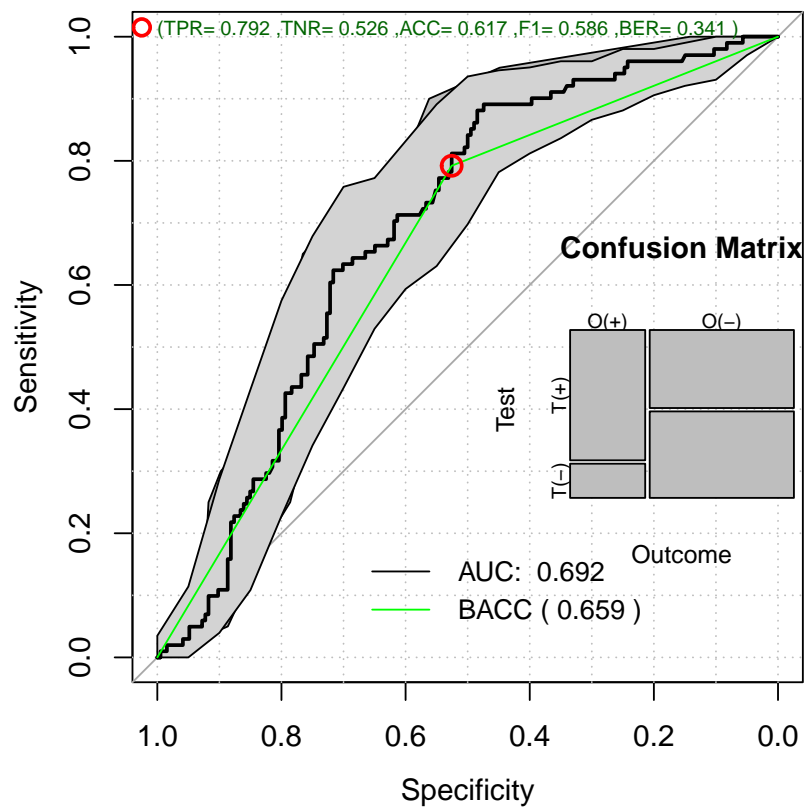
```
par(op)
```

1.4   RR Plot Signature correlation

```
rdata <- cbind(pdata$TTMevent,pdata$C1used)


RRAnalysisCI <- RRPlot(rdata,atRate=c(0.10,0.05),
                  timetoEvent=pdata$RFS,
                  title="Signature: Breast Cancer",
                  ysurvlim=c(0.00,1.0))
```

Relative Risk: Signature: Breast Cancer

ROC: Signature: Breast Cancer

(TPR= 0.891 ,TNR= 0.397 ,ACC= 0.566 ,F1= 0.584 ,BER= 0.356)

Sensitivity

Specificity

Confusion Matrix

Test

O(+) O(−)

T(+)

T(−)

Outcome

—— AUC: 0.692
—— BACC (0.644)

Kaplan–Meier: Signature: Breast Cancer
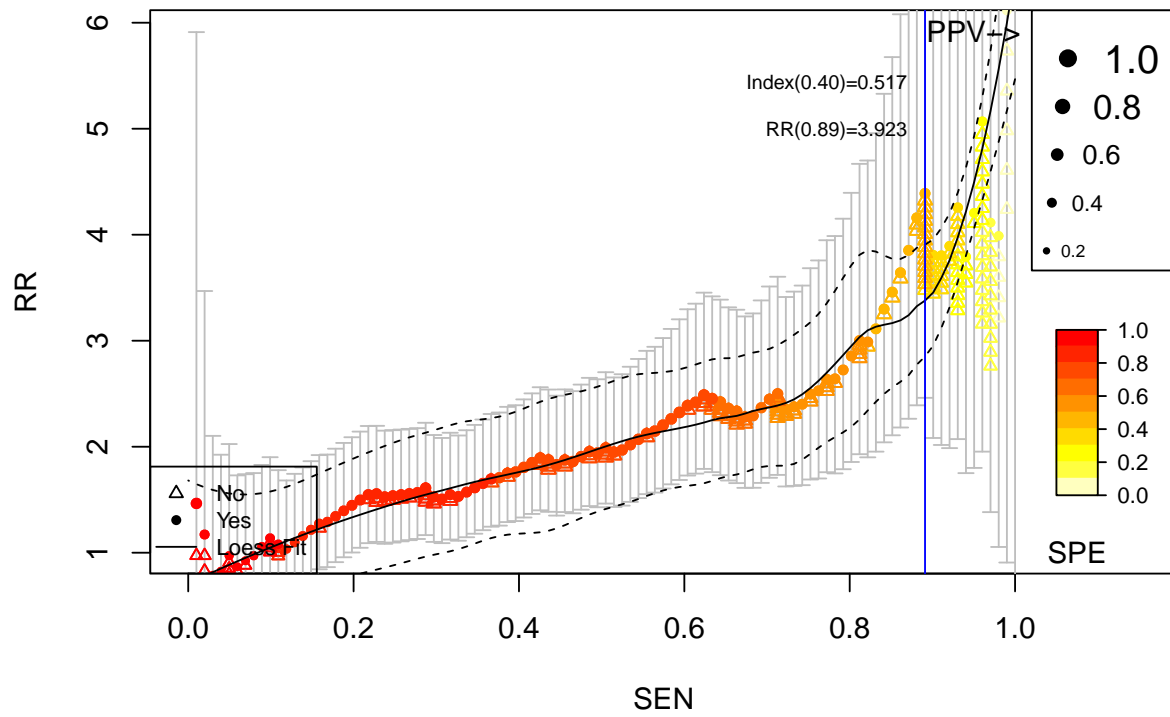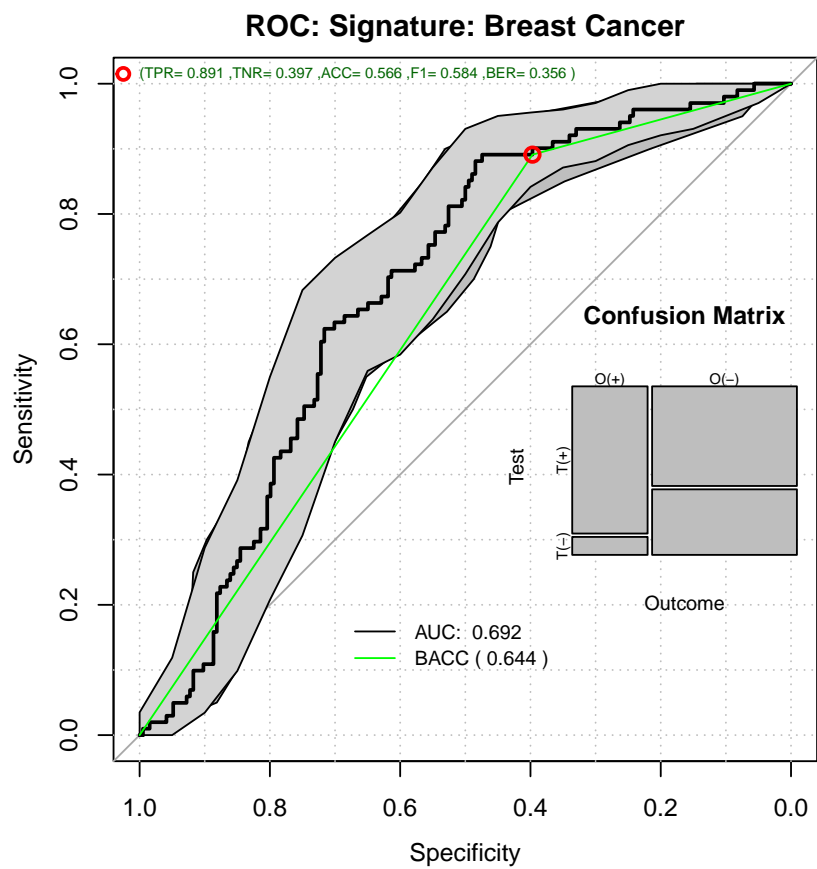
Strata ━╋━ Low Risk > 0.618　━╋━ 0.618 >= Risk > 0.517　━╋━ High Risk <= 0.517
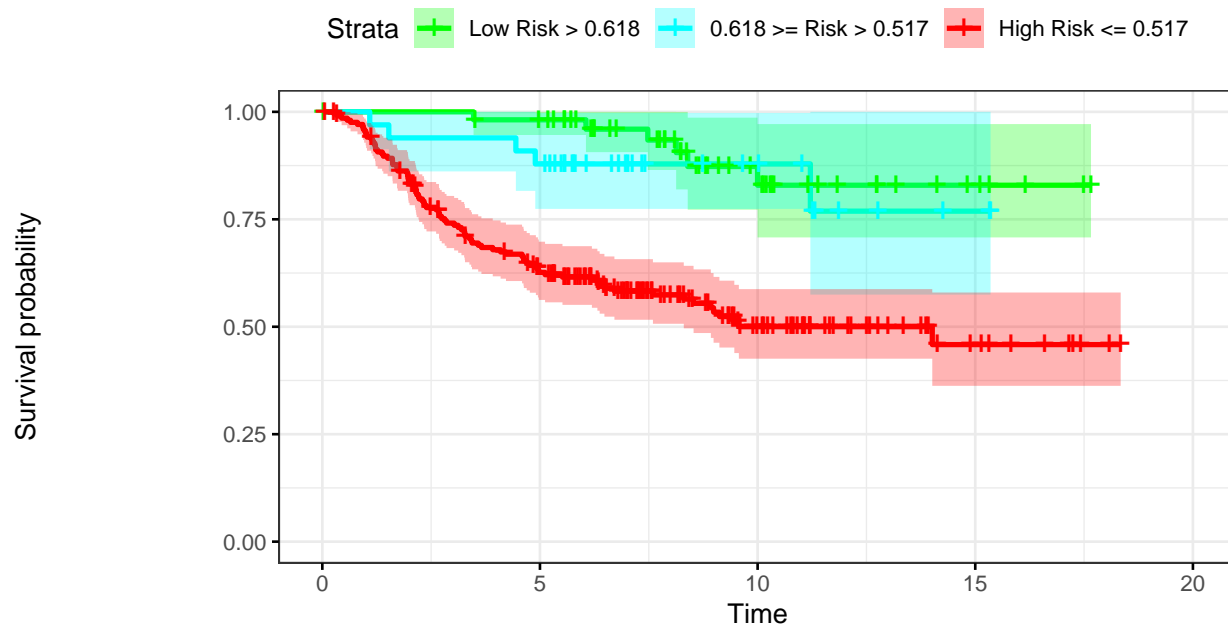
Number at risk

Low Risk > 0.618	55	51	19	5	0
0.618 >= Risk > 0.517	33	29	10	2	0
High Risk <= 0.517	207	116	39	9	0

```
par(op)
```

1.4.1 CI Performance all data

```
pander::pander(t(RRAnalysisCI$keyPoints),caption="Threshold values")
```

Table 2: Threshold values

	@:0.1	@:0.05	@MAX_BACC	@MAX_RR	@SPE100
Thr	0.519	0.619	0.465	0.623	7.56e-01
RR	3.806	3.548	4.160	5.069	3.91e+01
RR_LCI	2.082	1.642	2.391	1.954	8.17e-02
RR_UCI	6.957	7.666	7.237	13.150	1.87e+04
SEN	0.901	0.941	0.881	0.960	1.00e+00
SPE	0.397	0.247	0.485	0.242	5.67e-02
BACC	0.649	0.594	0.683	0.601	5.28e-01

```
pander::pander(RRAnalysisCI$c.index$cstatCI,caption="C. Index")
```

mean.C Index	median	lower	upper
0.698	0.698	0.649	0.747

```
pander::pander(t(RRAnalysisCI$ROCAnalysis$aucs),caption="ROC AUC")
```

Table 4: ROC AUC

est	lower	upper
0.692	0.631	0.752

```
pander::pander((RRAnalysisCI$ROCAnalysis$sensitivity),caption="Sensitivity")
```

Table 5: Sensitivity

est	lower	upper
0.891	0.813	0.944

```
pander::pander((RRAnalysisCI$ROCAnalysis$specificity),caption="Specificity")
```

Table 6: Specificity

est	lower	upper
0.397	0.328	0.469

```
pander::pander(t(RRAnalysisCI$thr_atP),caption="Probability Thresholds")
```

Table 7: Probability Thresholds

10%	5%
0.517	0.618

```
pander::pander(RRAnalysisCI$surdif,caption="Logrank test")
```

Table 8: Logrank test Chisq = 28.085735 on 2 degrees of freedom, p = 0.000001

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
class=0	55	6	23.5	13.01	17.1
class=1	33	5	12.9	4.87	5.6
class=2	207	90	64.6	10.00	27.9

1.5 Node positive data

1.6 RR Plot Signature correlation

```
NodePdata <- subset(pdata,Posnodes=="y")

rdata <- cbind(NodePdata$TTMevent,NodePdata$C1used)
```

```
RRAnalysisPos <- RRPlot(rdata,atRate=c(0.90,0.95),
                        timetoEvent=NodePdata$RFS,
                        title="Signature: Breast Cancer",
                        ysurvlim=c(0.00,1.0))
```


Relative Risk: Signature: Breast Cancer

ROC: Signature: Breast Cancer

(TPR= 0.894 ,TNR= 0.371 ,ACC= 0.542 ,F1= 0.560 ,BER= 0.368)

Sensitivity

Specificity

Confusion Matrix

Test

O(+) O(−)

T(+)

T(−)

Outcome

AUC: 0.669
BACC (0.632)
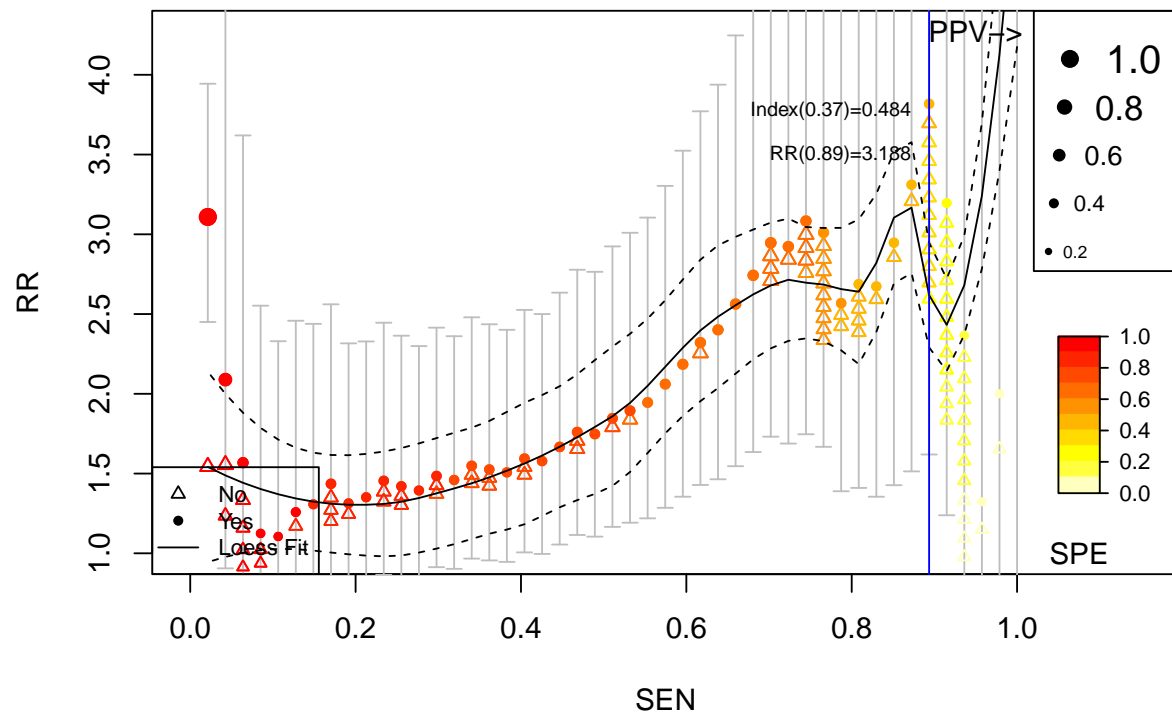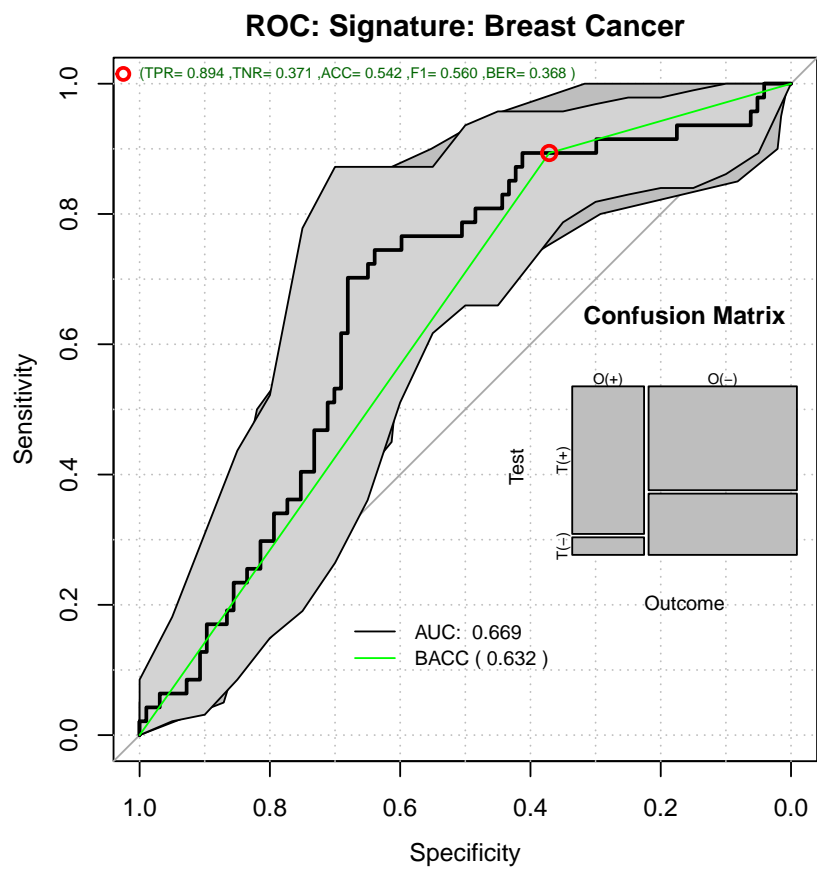
Kaplan–Meier: Signature: Breast Cancer
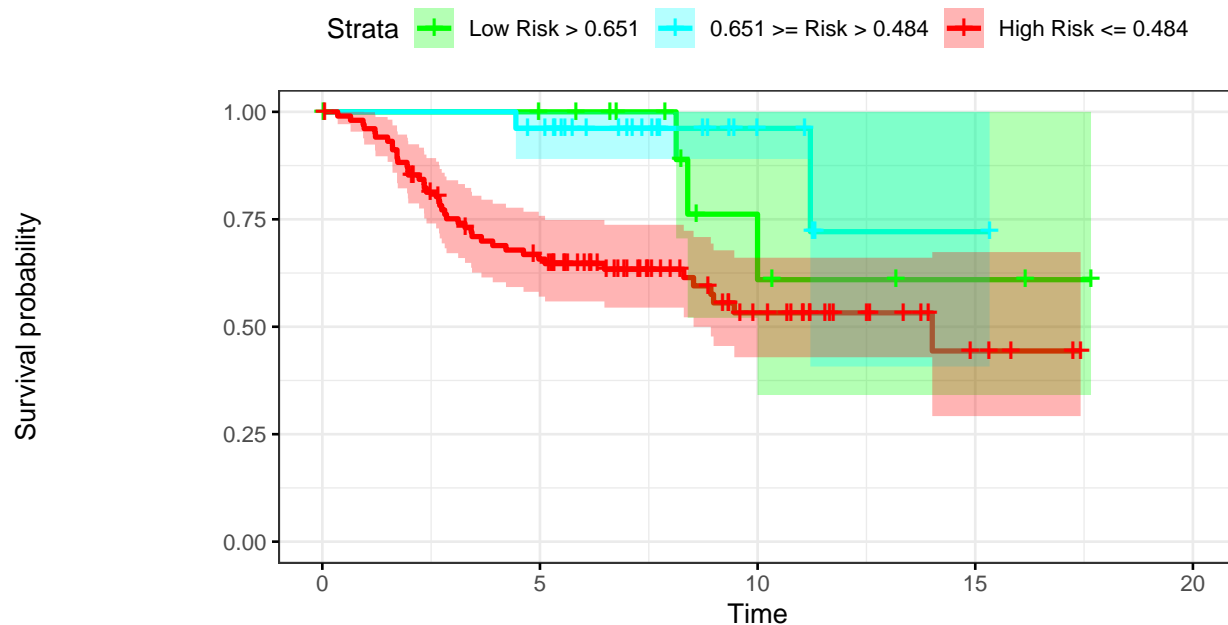
par(op)

1.6.1 CI Performance positive data

```
pander::pander(t(RRAnalysisPos$keyPoints),caption="Threshold values")
```

Table 9: Threshold values

	@:0.9	@:0.95	@MAX_BACC	@MAX_RR	@SPE100
Thr	0.486	0.655	0.267	0.486	7.17e-01
RR	3.231	1.579	3.083	3.231	1.34e+01
RR_LCI	1.377	0.563	1.746	1.377	2.94e-02
RR_UCI	7.578	4.431	5.444	7.578	6.14e+03
SEN	0.894	0.936	0.745	0.894	1.00e+00
SPE	0.361	0.113	0.639	0.361	4.12e-02
BACC	0.627	0.525	0.692	0.627	5.21e-01

```
pander::pander(RRAnalysisPos$c.index$cstatCI,caption="C. Index")
```

mean.C Index	median	lower	upper
0.7	0.7	0.629	0.768

```
pander::pander(t(RRAnalysisPos$ROCAnalysis$aucs),caption="ROC AUC")
```

Table 11: ROC AUC

est	lower	upper
0.669	0.576	0.761

```
pander::pander((RRAnalysisPos$ROCAnalysis$sensitivity),caption="Sensitivity")
```

Table 12: Sensitivity

est	lower	upper
0.894	0.769	0.965

```
pander::pander((RRAnalysisPos$ROCAnalysis$specificity),caption="Specificity")
```

Table 13: Specificity

est	lower	upper
0.371	0.275	0.475

```
pander::pander(t(RRAnalysisPos$thr_atP),caption="Probability Thresholds")
```

Table 14: Probability Thresholds

10%	5%
0.484	0.651

```
pander::pander(RRAnalysisPos$surdif,caption="Logrank test")
```

Table 15: Logrank test Chisq = 11.060876 on 2 degrees of freedom, p = 0.003964

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
class=0	15	3	5.80	1.35	1.55
class=1	26	2	9.73	6.14	7.77
class=2	103	42	31.47	3.52	10.71

1.7   Node Negative data

1.8   RR Plot Signature correlation

```
NodeNdata <- subset(pdata,Posnodes=="n")

rdata <- cbind(NodeNdata$TTMevent,NodeNdata$C1used)
```

```
RRAnalysisNeg <- RRPlot(rdata,atRate=c(0.90,0.95),
                        timetoEvent=NodeNdata$RFS,
                        title="Signature: Breast Cancer",
                        ysurvlim=c(0.00,1.0))
```

Relative Risk: Signature: Breast Cancer

ROC: Signature: Breast Cancer

(TPR= 0.889 ,TNR= 0.495 ,ACC= 0.636 ,F1= 0.636 ,BER= 0.308)

Sensitivity

Confusion Matrix

Test

O(+)   O(−)

T(+)

T(−)

Outcome

AUC: 0.708

BACC (0.692)

1.0   0.8   0.6   0.4   0.2   0.0

Specificity

14

Kaplan–Meier: Signature: Breast Cancer
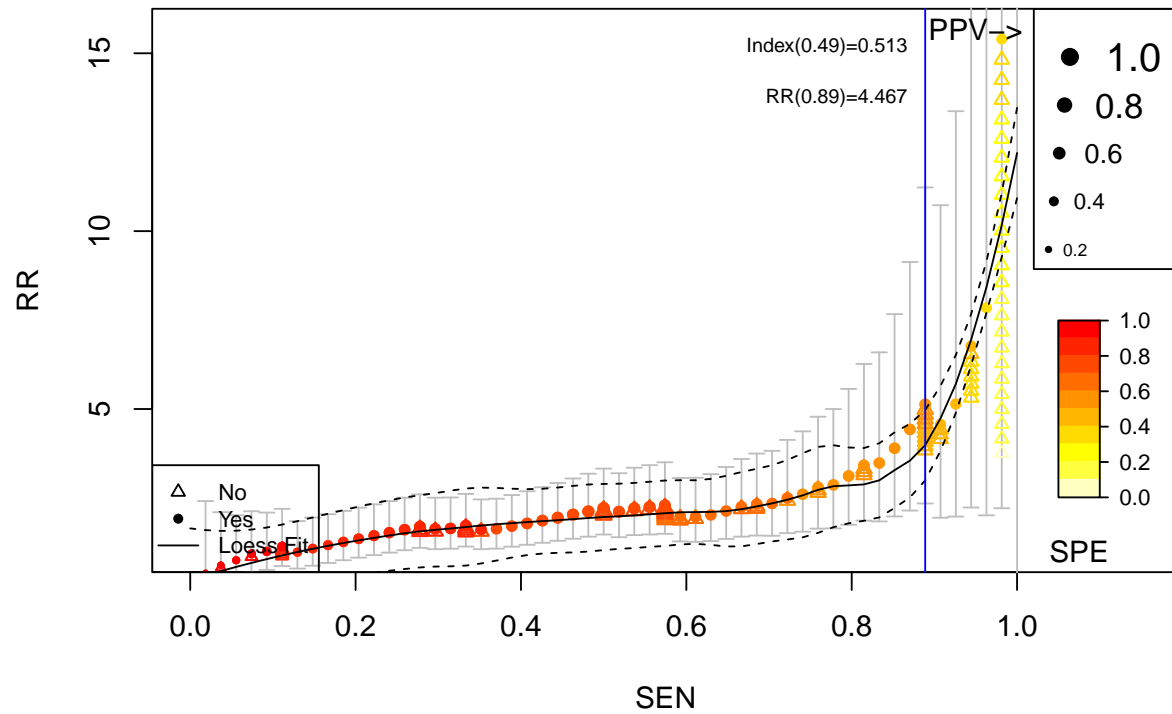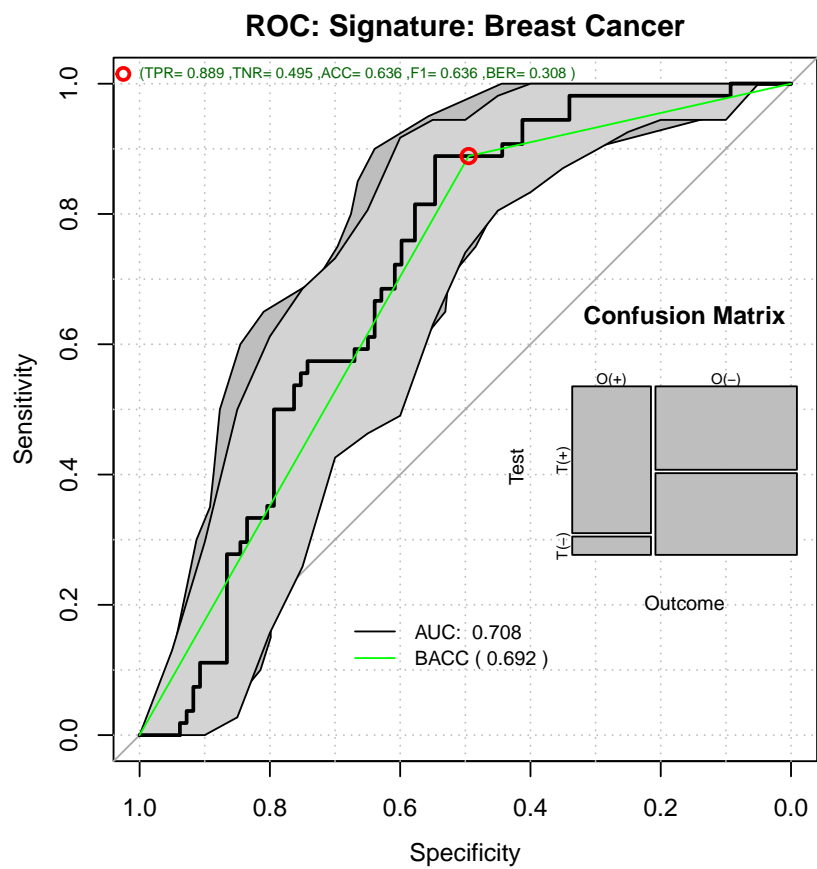
Strata —+— Low Risk > 0.583   —+— 0.583 >= Risk > 0.513   —+— High Risk <= 0.513
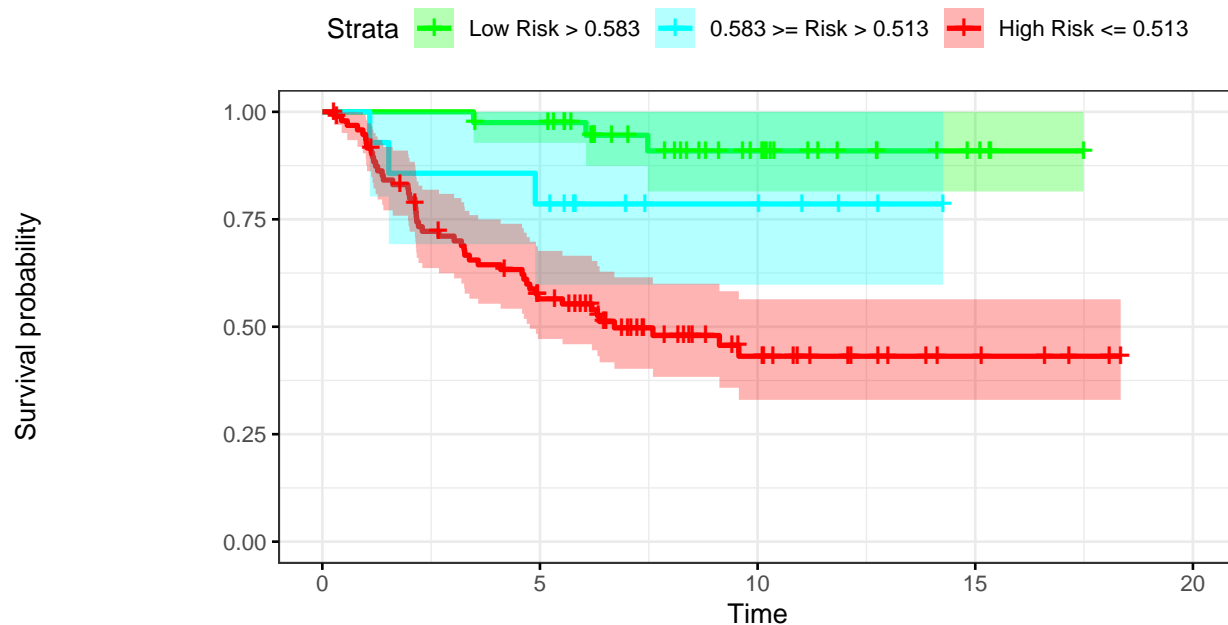
Number at risk

Low Risk > 0.583	40	38	16	4	0
0.583 >= Risk > 0.513	14	11	5	0	0
High Risk <= 0.513	97	48	17	5	0

```
par(op)
```

1.8.1 CI Performance negative data

```
pander::pander(t(RRAnalysisNeg$keyPoints),caption="Threshold values")
```

Table 16: Threshold values

	@:0.9	@:0.95	@MAX_BACC	@MAX_RR	@SPE100
Thr	0.507	0.585	0.465	0.623	7.56e-01
RR	4.454	5.920	5.130	15.402	3.42e+01
RR_LCI	2.040	1.959	2.344	2.211	7.18e-02
RR_UCI	9.723	17.889	11.228	107.305	1.63e+04
SEN	0.889	0.944	0.889	0.981	1.00e+00
SPE	0.495	0.371	0.546	0.340	9.28e-02
BACC	0.692	0.658	0.718	0.661	5.46e-01

```
pander::pander(RRAnalysisNeg$c.index$cstatCI,caption="C. Index")
```

mean.C Index	median	lower	upper
0.695	0.695	0.629	0.76

```r
pander::pander(t(RRAnalysisNeg$ROCAnalysis$aucs),caption="ROC AUC")
```

Table 18: ROC AUC

est	lower	upper
0.708	0.626	0.79

```r
pander::pander((RRAnalysisNeg$ROCAnalysis$sensitivity),caption="Sensitivity")
```

Table 19: Sensitivity

est	lower	upper
0.889	0.774	0.958

```r
pander::pander((RRAnalysisNeg$ROCAnalysis$specificity),caption="Specificity")
```

Table 20: Specificity

est	lower	upper
0.495	0.392	0.598

```r
pander::pander(t(RRAnalysisNeg$thr_atP),caption="Probability Thresholds")
```

Table 21: Probability Thresholds

10%	5%
0.513	0.583

```r
pander::pander(RRAnalysisNeg$surdif,caption="Logrank test")
```

Table 22: Logrank test Chisq = 24.223875 on 2 degrees of freedom, p = 0.000005

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
class=0	40	3	18.18	12.67	19.29
class=1	14	3	5.43	1.09	1.21
class=2	97	48	30.39	10.21	23.58

1.9 RRPlot Cox Model

```r
timeinterval <- 5 # Five years

h0 <- sum(pdata$TTMevent & pdata$RFS <= timeinterval)
h0 <- h0/sum((pdata$RFS > timeinterval) | (pdata$TTMevent==1))

mcox <- coxph(Surv(RFS,TTMevent)~C1used,pdata)
pander::pander(summary(mcox)$coefficients)
```
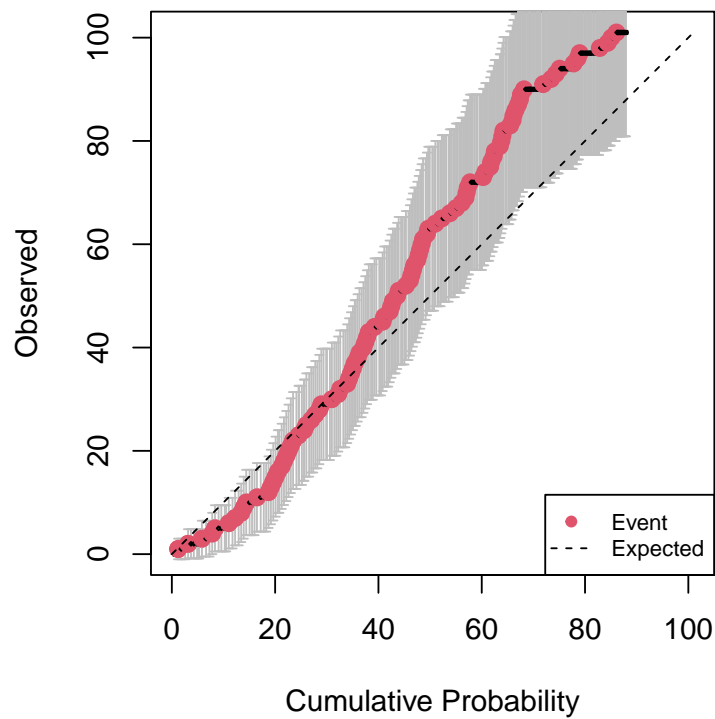
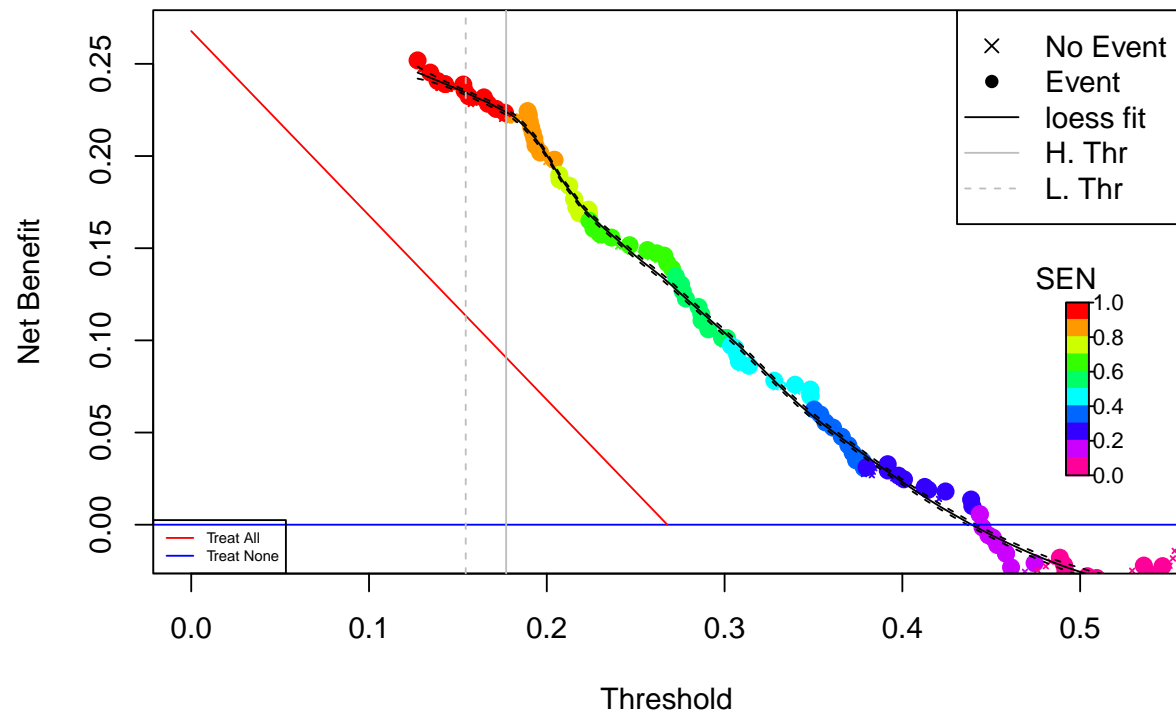|	coef	exp(coef)	se(coef)	z	Pr($>$|z|)
C1used	-1.5	0.224	0.263	-5.69	1.3e-08

```
index <- predict(mcox,pdata)
rdata <- cbind(pdata$TTMevent,ppoisGzero(index,h0))


RRAnalysisCox <- RRPlot(rdata,atRate=c(0.90,0.95),
                  timetoEvent=pdata$RFS,
                  title="NIK: Breast Cancer",
                  ysurvlim=c(0.00,1.0),
                  riskTimeInterval=timeinterval)
```
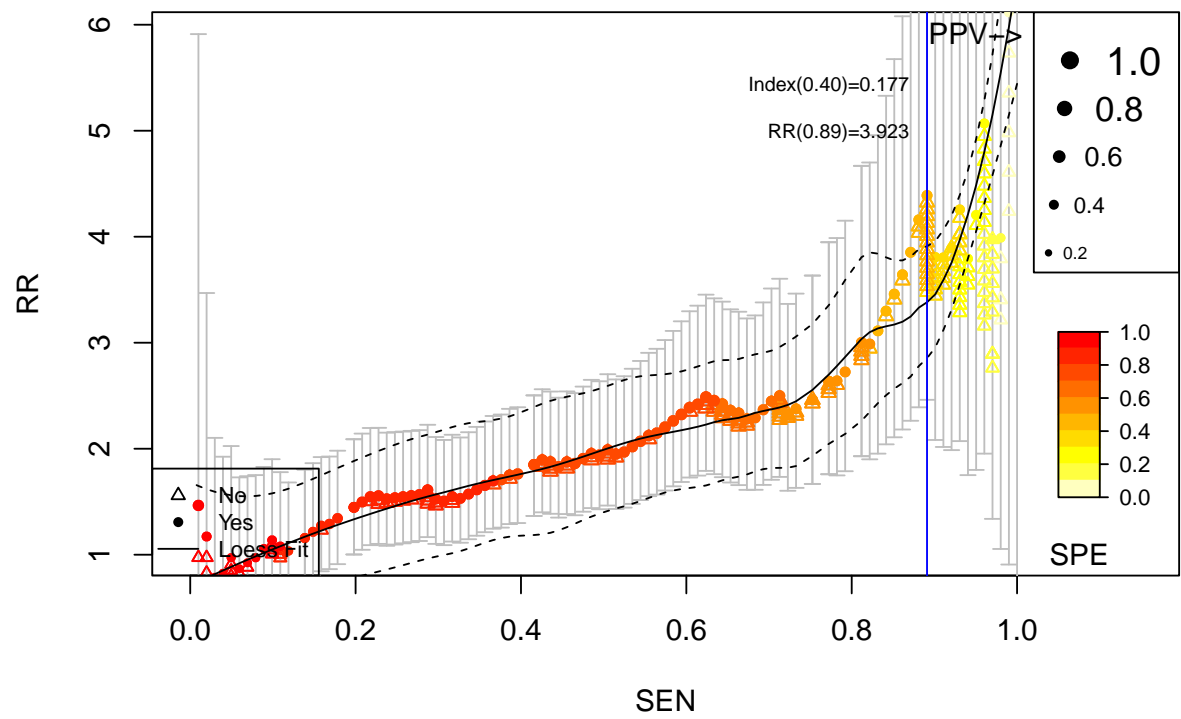

Cumulative vs. Observed: NIK: Breast Cancer

Decision Curve Analysis: NIK: Breast Cancer

Relative Risk: NIK: Breast Cancer
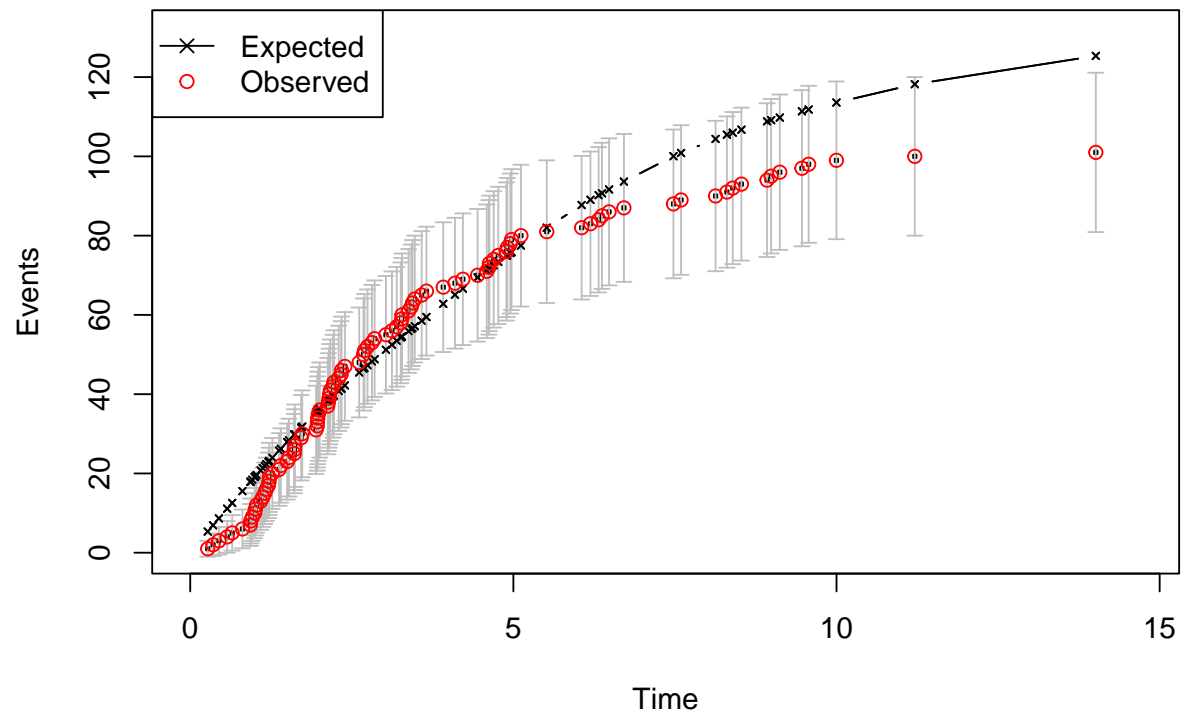
ROC: NIK: Breast Cancer
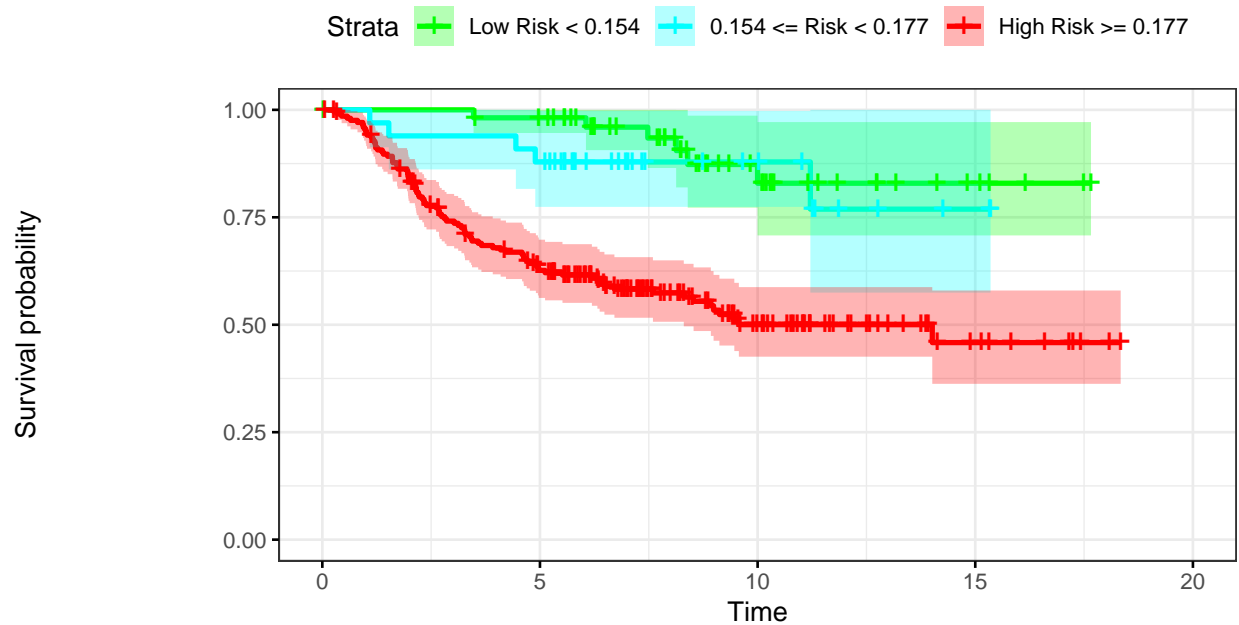
(TPR= 0.891 ,TNR= 0.397 ,ACC= 0.566 ,F1= 0.584 ,BER= 0.356)

AUC: 0.692

BACC (0.644)

Confusion Matrix

Test

O(+)   O(−)

T(+)

T(−)

Outcome

Sensitivity

Specificity
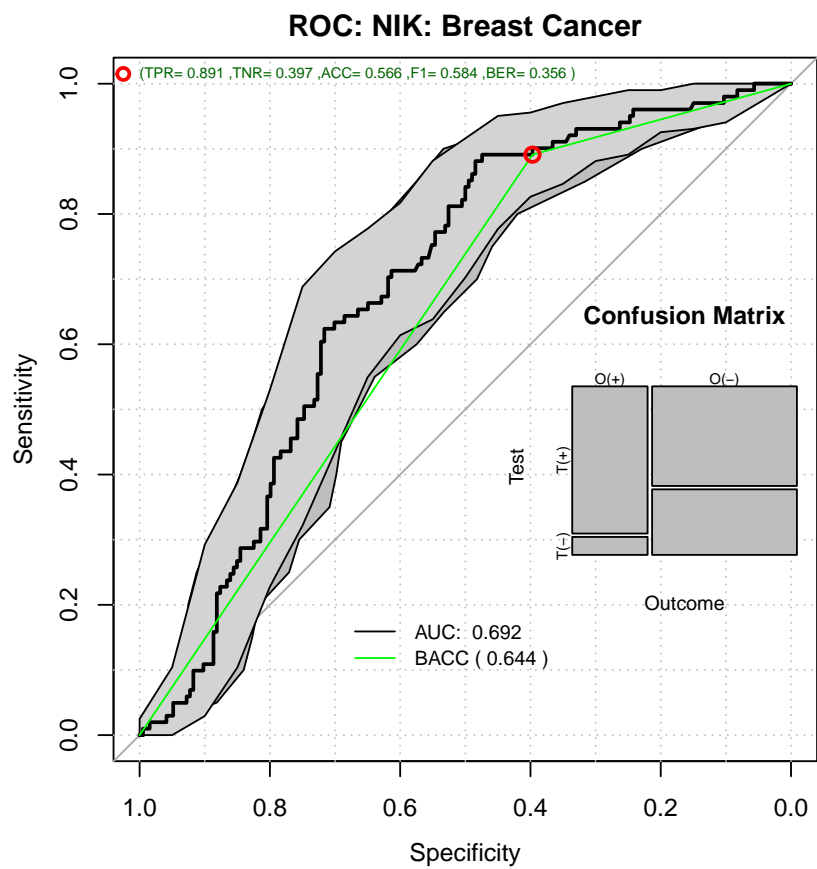
Time vs. Events: NIK: Breast Cancer

Kaplan–Meier: NIK: Breast Cancer

Number at risk

Low Risk < 0.154	55	51	19	5	0
0.154 <= Risk < 0.177	33	29	10	2	0
High Risk >= 0.177	207	116	39	9	0

```
par(op)
```

1.10 Expected time to event

```
toinclude <- rdata[,1]==1
obstiemToEvent <- pdata[,"RFS"]
tmin<-min(obstiemToEvent)
sum(toinclude)
```
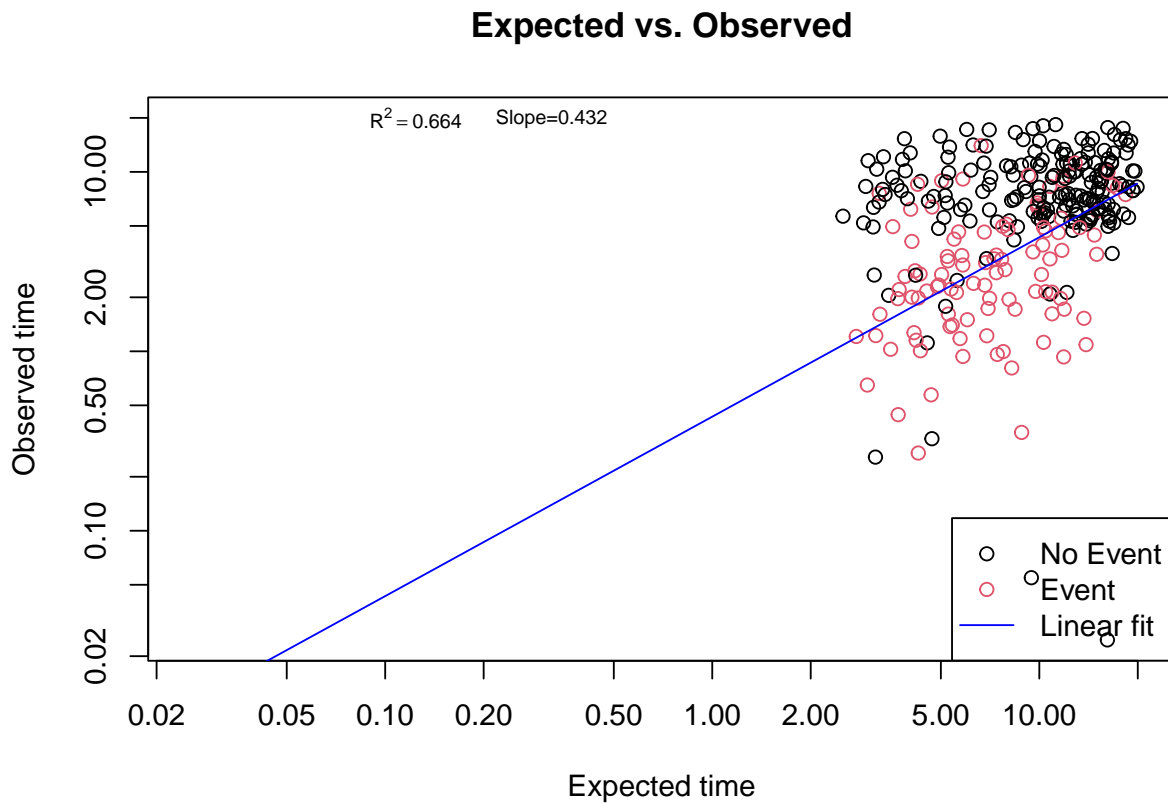
[1] 101

```
timetoEvent <- meanTimeToEvent(rdata[,2],timeinterval)
tmax<-max(c(obstiemToEvent,timetoEvent))
lmfit <- lm(obstiemToEvent[toinclude]~0+timetoEvent[toinclude])
sm <- summary(lmfit)
pander::pander(sm)
```

	Estimate	Std. Error	t value	Pr(>|t|)
timetoEvent[toinclude]	0.432	0.0308	14	2.1e-25

Table 25: Fitting linear model: obstiemToEvent[toinclude] ~ 0 + timetoEvent[toinclude]

Observations	Residual Std. Error	R^2	Adjusted R^2
101	2.67	0.664	0.66

```
plot(timetoEvent,obstiemToEvent,
     col=1+rdata[,1],
     xlab="Expected time",
     ylab="Observed time",
     main="Expected vs. Observed",
     xlim=c(tmin,tmax),
     ylim=c(tmin,tmax),
     log="xy")
lines(x=c(tmin,tmax),y=lmfit$coefficients*c(tmin,tmax),lty=1,col="blue")
txt <- bquote(paste(R^2 == .(round(sm$r.squared,3))))
text(tmin+0.005*(tmax-tmin),tmax,txt,cex=0.7)
text(tmin+0.015*(tmax-tmin),tmax,sprintf("Slope=%4.3f",sm$coefficients[1]),cex=0.7)
legend("bottomright",legend=c("No Event","Event","Linear fit"),
           pch=c(1,1,-1),
           col=c(1,2,"blue"),
           lty=c(-1,-1,1)
           )
```


Expected vs. Observed

23

```
MADerror2 <- mean(abs(timetoEvent[toinclude]-obstiemToEvent[toinclude]))
pander::pander(MADerror2)
```

4.75

1.10.1 Unadjusted Cox Performance

```
pander::pander(t(RRAnalysisCox$keyPoints),caption="Threshold values")
```

Table 26: Threshold values

	@:0.9	@:0.95	@MAX_BACC	@MAX_RR	@SPE100	p(0.5)
Thr	0.176	0.154	0.190	0.153	1.27e-01	0.5041
RR	3.806	3.548	4.160	5.069	3.91e+01	0.9241
RR_LCI	2.082	1.642	2.391	1.954	8.17e-02	0.4906
RR_UCI	6.957	7.666	7.237	13.150	1.87e+04	1.7407
SEN	0.901	0.941	0.881	0.960	1.00e+00	0.0693
SPE	0.397	0.247	0.485	0.242	5.67e-02	0.9227
BACC	0.649	0.594	0.683	0.601	5.28e-01	0.4960
NetBenefit	0.223	0.232	0.222	0.239	2.52e-01	-0.0279

```
pander::pander(t(RRAnalysisCox$OERatio$estimate),caption="O/E Ratio")
```

Table 27: O/E Ratio

O/E	Low	Upper	p.value
0.806	0.656	0.979	0.0285

```
pander::pander(t(RRAnalysisCox$OE95ci),caption="O/E Mean")
```

Table 28: O/E Mean

mean	50%	2.5%	97.5%
0.952	0.952	0.926	0.977

```
pander::pander(t(RRAnalysisCox$OAcum95ci),caption="O/Acum Mean")
```

Table 29: O/Acum Mean

mean	50%	2.5%	97.5%
1.15	1.15	1.14	1.17

```
pander::pander(RRAnalysisCox$c.index$cstatCI,caption="C. Index")
```

mean.C Index	median	lower	upper
0.698	0.7	0.65	0.746

```
pander::pander(t(RRAnalysisCox$ROCAnalysis$aucs),caption="ROC AUC")
```

Table 31: ROC AUC

est	lower	upper
0.692	0.631	0.752

```
pander::pander((RRAnalysisCox$ROCAnalysis$sensitivity),caption="Sensitivity")
```

Table 32: Sensitivity

est	lower	upper
0.891	0.813	0.944

```
pander::pander((RRAnalysisCox$ROCAnalysis$specificity),caption="Specificity")
```

Table 33: Specificity

est	lower	upper
0.397	0.328	0.469

```
pander::pander(t(RRAnalysisCox$thr_atP),caption="Probability Thresholds")
```

Table 34: Probability Thresholds

10%	5%
0.177	0.154

```
pander::pander(RRAnalysisCox$surdif,caption="Logrank test")
```

Table 35: Logrank test Chisq = 28.085735 on 2 degrees of freedom,
p = 0.000001

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
class=0	55	6	23.5	13.01	17.1
class=1	33	5	12.9	4.87	5.6
class=2	207	90	64.6	10.00	27.9

1.11 RRPlot Cox Adjusted Model

This time we will include Lymph node status from pathology report and Estrogen receptor alpha expression measurement from microarray

```
mcox <- coxph(Surv(RFS,TTMevent)~C1used*(ESR1 + Posnodes),pdata)
pander::pander(summary(mcox)$coefficients)
```

25

	coef	exp(coef)	se(coef)	z	Pr(>|z|)
C1used	-0.403	0.668	0.629	-0.640	0.52186
ESR1	0.123	1.131	0.255	0.481	0.63079
Posnodesy	-0.305	0.737	0.217	-1.401	0.16112
C1used:ESR1	-1.913	0.148	0.739	-2.588	0.00966
C1used:Posnodesy	0.378	1.460	0.583	0.649	0.51661

```
index <- predict(mcox,pdata)
rdata <- cbind(pdata$TTMevent,ppoisGzero(index,h0))


RRAnalysisAdCox <- RRPlot(rdata,atRate=c(0.90,0.95),
                 timetoEvent=pdata$RFS,
                 title="Adjusted: Breast Cancer",
                 ysurvlim=c(0.00,1.0),
                 riskTimeInterval=timeinterval)
```
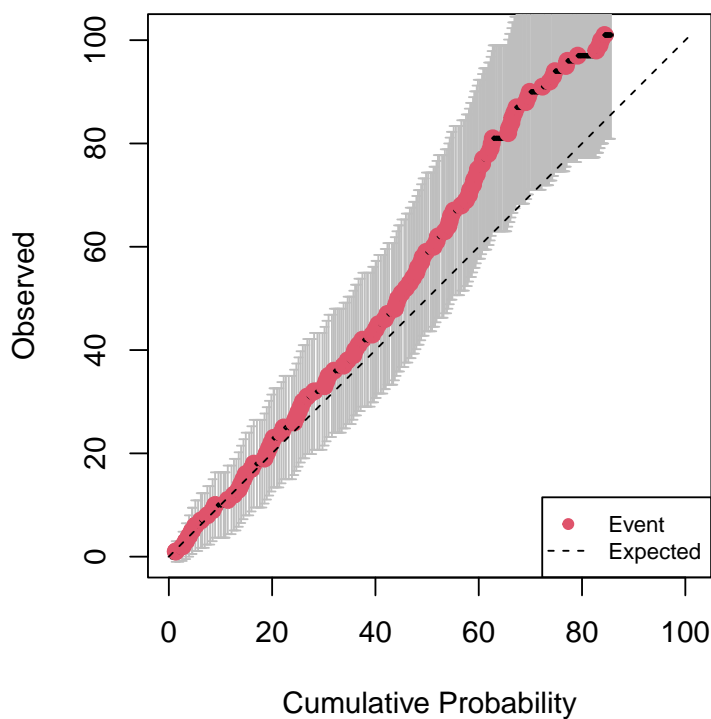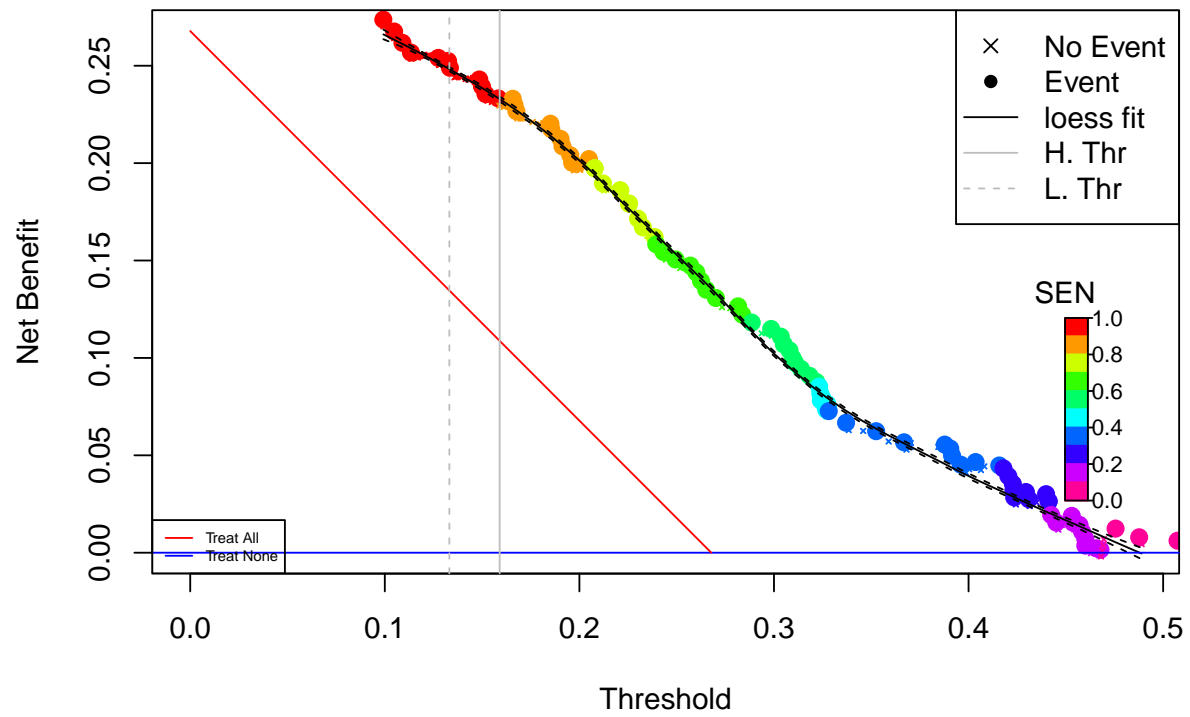
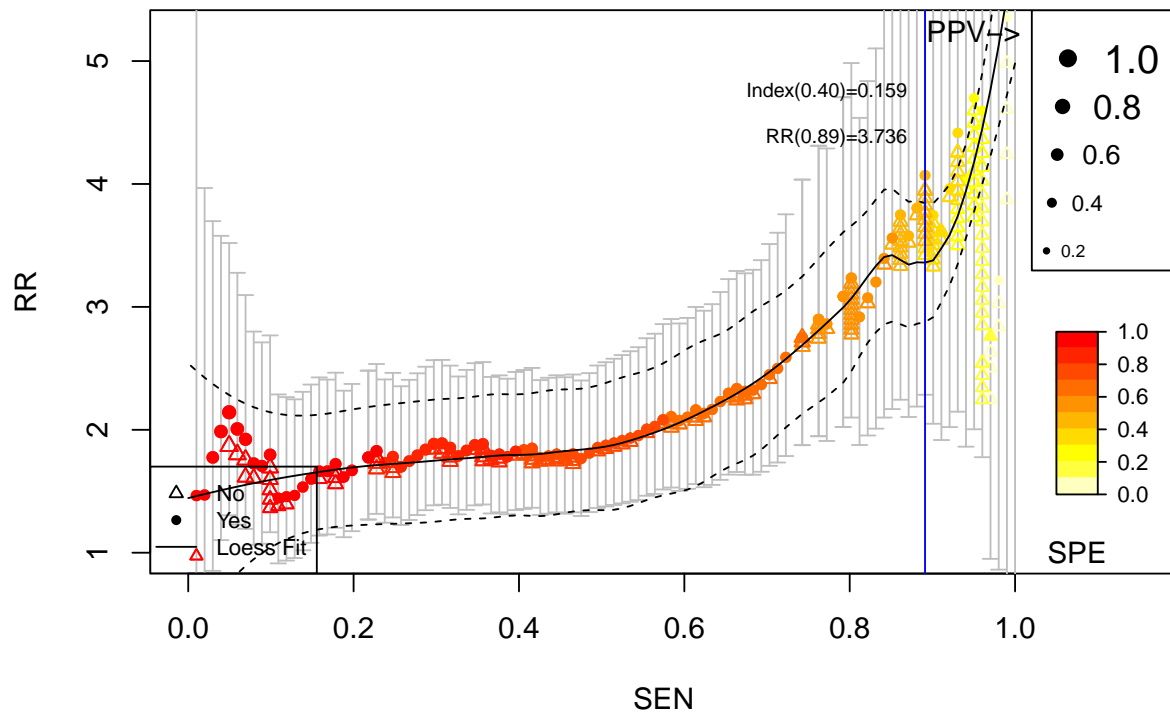## Cumulative vs. Observed: Adjusted: Breast Cancer
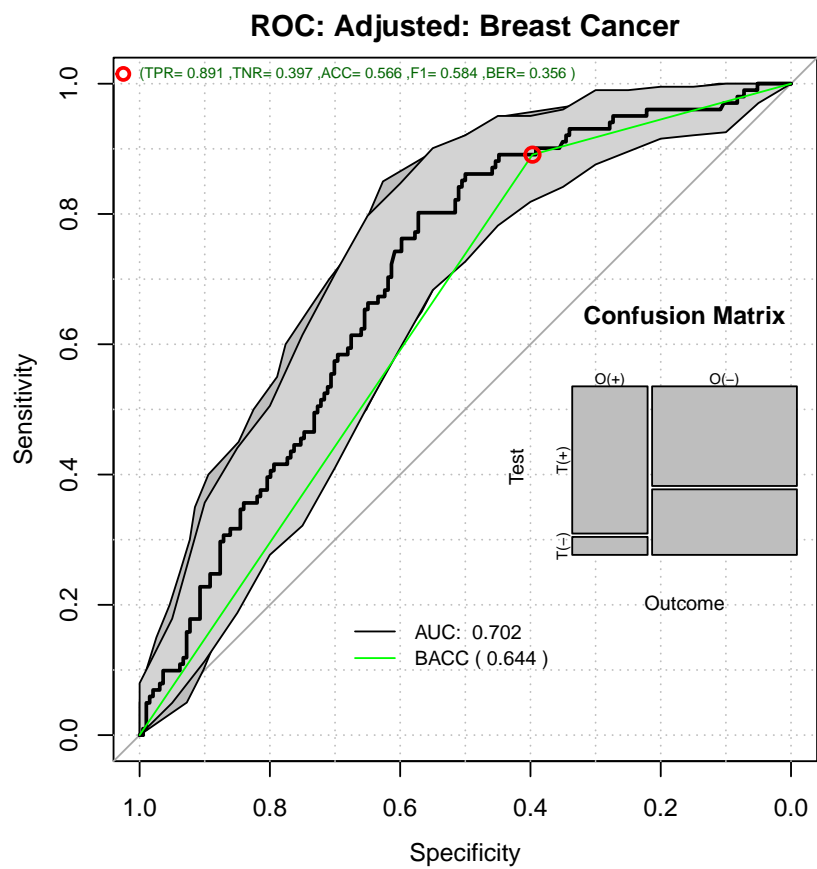
Decision Curve Analysis: Adjusted: Breast Cancer

Relative Risk: Adjusted: Breast Cancer

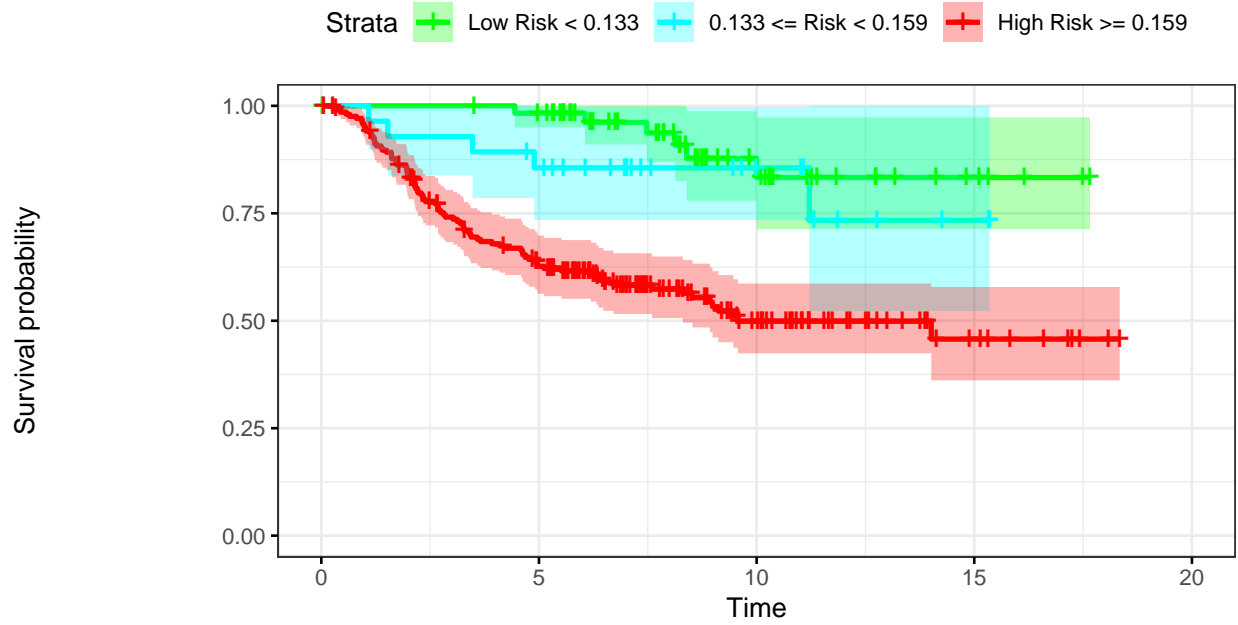# ROC: Adjusted: Breast Cancer

(TPR= 0.891 ,TNR= 0.397 ,ACC= 0.566 ,F1= 0.584 ,BER= 0.356)

Sensitivity

Specificity

Confusion Matrix

Test

T(+)

T(−)

O(+)   O(−)

Outcome

AUC: 0.702

BACC (0.644)

Time vs. Events: Adjusted: Breast Cancer
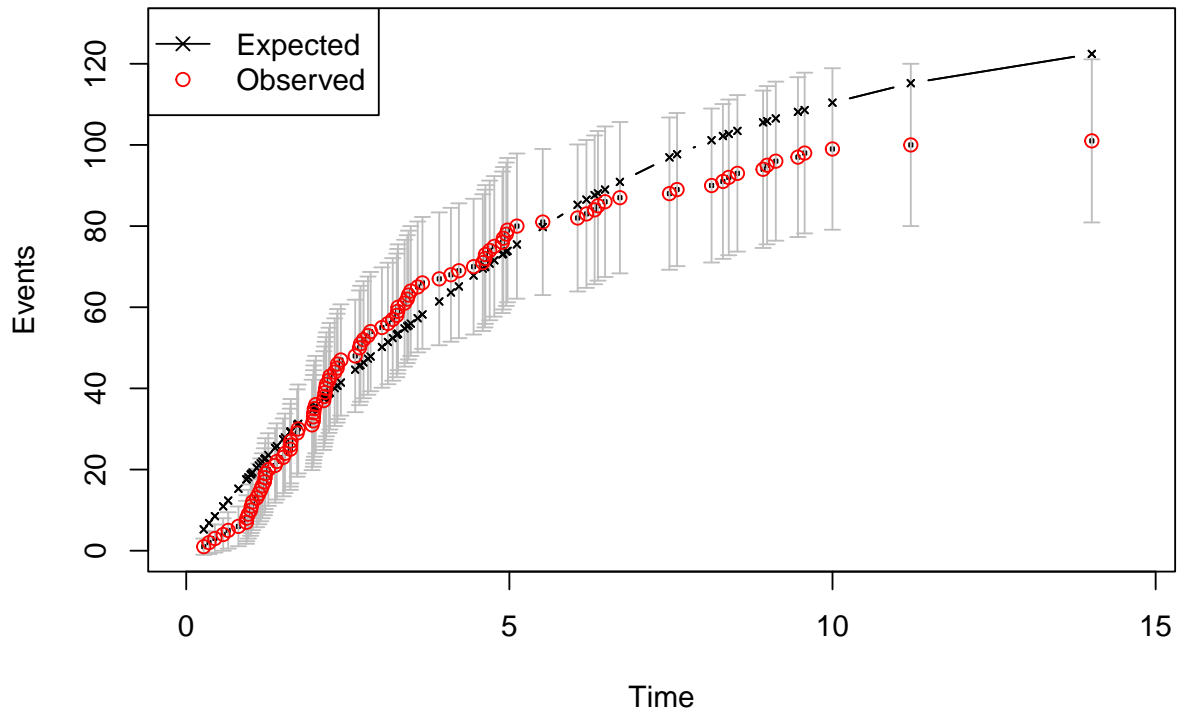
Kaplan–Meier: Adjusted: Breast Cancer

Number at risk

Strata					
Low Risk < 0.133	60	56	19	5	0
0.133 <= Risk < 0.159	28	23	9	2	0
High Risk >= 0.159	207	117	40	9	0

```
par(op)
```

1.12   Expected time to event

```
timetoEvent <- meanTimeToEvent(rdata[,2],timeinterval)
tmax<-max(c(obstiemToEvent,timetoEvent))
lmfit <- lm(obstiemToEvent[toinclude]~0+timetoEvent[toinclude])
sm <- summary(lmfit)
pander::pander(sm)
```

	Estimate	Std. Error	t value	Pr(>|t|)
timetoEvent[toinclude]	0.402	0.0289	13.9	4.17e-25

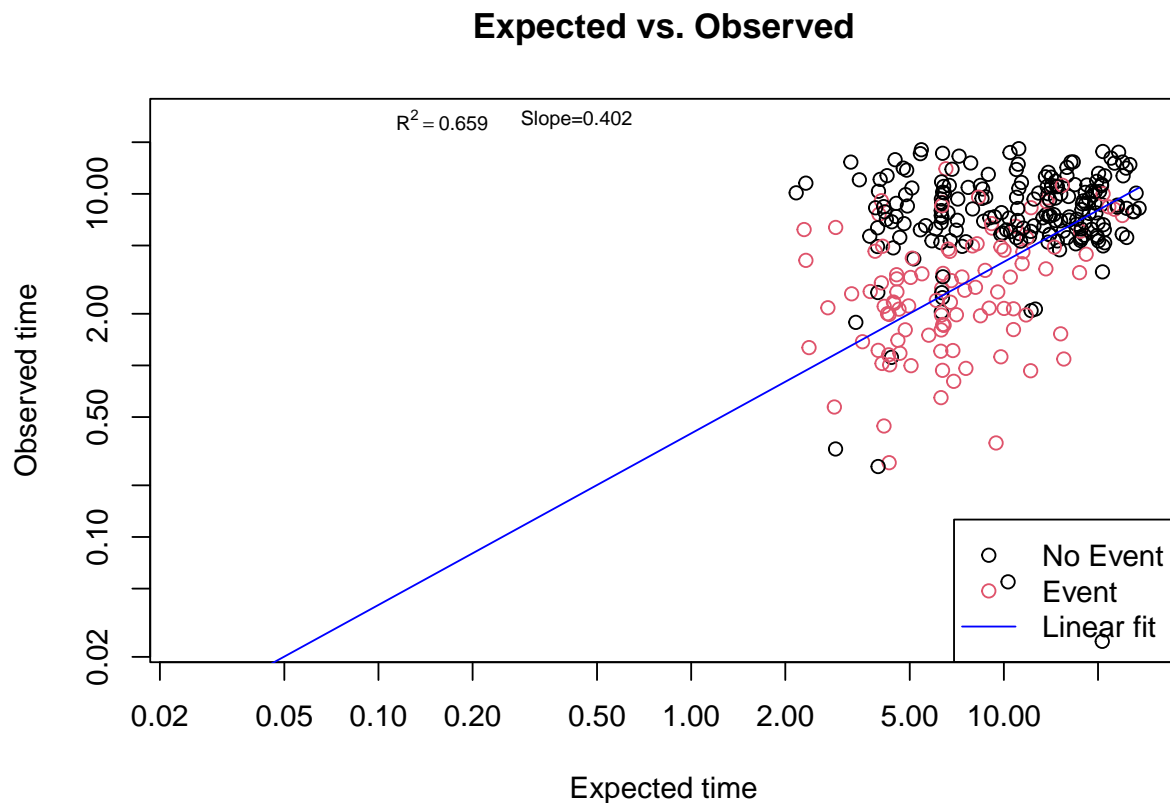Table 38: Fitting linear model: obstiemToEvent[toinclude] ~ 0 + timetoEvent[toinclude]

Observations	Residual Std. Error	R^2	Adjusted R^2
101	2.69	0.659	0.656

```
plot(timetoEvent,obstiemToEvent,
     col=1+rdata[,1],
```

```
    xlab="Expected time",
    ylab="Observed time",
    main="Expected vs. Observed",
    xlim=c(tmin,tmax),
    ylim=c(tmin,tmax),
    log="xy")
lines(x=c(tmin,tmax),y=lmfit$coefficients*c(tmin,tmax),lty=1,col="blue")
txt <- bquote(paste(R^2 == .(round(sm$r.squared,3))))
text(tmin+0.005*(tmax-tmin),tmax,txt,cex=0.7)
text(tmin+0.015*(tmax-tmin),tmax,sprintf("Slope=%4.3f",sm$coefficients[1]),cex=0.7)
legend("bottomright",legend=c("No Event","Event","Linear fit"),
        pch=c(1,1,-1),
        col=c(1,2,"blue"),
        lty=c(-1,-1,1)
        )
```


Expected vs. Observed

```
MADerror2 <-c(MADerror2,mean(abs(timetoEvent-obstiemToEvent)))
pander::pander(MADerror2)
```

4.75 and *6.09*

1.12.1 Adjusted Cox Performance

```
pander::pander(t(RRAnalysisAdCox$keyPoints),caption="Threshold values")
```

Table 39: Threshold values

	@:0.9	@:0.95	@MAX_BACC	@MAX_RR	@SPE100	p(0.5)
Thr	0.159	0.133	0.205	0.133	9.92e-02	0.50740
RR	3.422	4.043	3.235	4.699	3.54e+01	1.72657
RR_LCI	1.928	1.863	2.100	2.004	7.42e-02	1.06501
RR_UCI	6.075	8.773	4.984	11.015	1.69e+04	2.79908
SEN	0.891	0.941	0.802	0.950	1.00e+00	0.07921
SPE	0.392	0.278	0.572	0.273	5.15e-02	0.96907
BACC	0.641	0.609	0.687	0.612	5.26e-01	0.52414
NetBenefit	0.230	0.249	0.202	0.252	2.74e-01	0.00617

```
pander::pander(t(RRAnalysisAdCox$OERatio$estimate),caption="O/E Ratio")
```

Table 40: O/E Ratio

O/E	Low	Upper	p.value
0.825	0.672	1	0.0519

```
pander::pander(t(RRAnalysisAdCox$OE95ci),caption="O/E Mean")
```

Table 41: O/E Mean

mean	50%	2.5%	97.5%
0.973	0.974	0.945	0.999

```
pander::pander(t(RRAnalysisAdCox$OAcum95ci),caption="O/Acum Mean")
```

Table 42: O/Acum Mean

mean	50%	2.5%	97.5%
1.18	1.18	1.17	1.19

```
pander::pander(RRAnalysisAdCox$c.index$cstatCI,caption="C. Index")
```

mean.C Index	median	lower	upper
0.707	0.706	0.661	0.751

```
pander::pander(t(RRAnalysisAdCox$ROCAnalysis$aucs),caption="ROC AUC")
```

Table 44: ROC AUC

est	lower	upper
0.702	0.642	0.763

```
pander::pander((RRAnalysisAdCox$ROCAnalysis$sensitivity),caption="Sensitivity")
```

Table 45: Sensitivity

est	lower	upper
0.891	0.813	0.944

```
pander::pander((RRAnalysisAdCox$ROCAnalysis$specificity),caption="Specificity")
```

Table 46: Specificity

est	lower	upper
0.397	0.328	0.469

```
pander::pander(t(RRAnalysisAdCox$thr_atP),caption="Probability Thresholds")
```

Table 47: Probability Thresholds

10%	5%
0.159	0.133

```
pander::pander(RRAnalysisAdCox$surdif,caption="Logrank test")
```

Table 48: Logrank test Chisq = 28.504862 on 2 degrees of freedom, p = 0.000001

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
class=0	60	6	25.3	14.73	19.76
class=1	28	5	11.2	3.45	3.89
class=2	207	90	64.5	10.11	28.16

1.13 Calibrating the index

```
calprob <- CoxRiskCalibration(mcox,pdata,"TTMevent","RFS")
pander::pander(c(h0=calprob$h0,
                Gain=calprob$hazardGain,
                DeltaTime=calprob$timeInterval),
            caption="Cox Calibration Parameters")
```
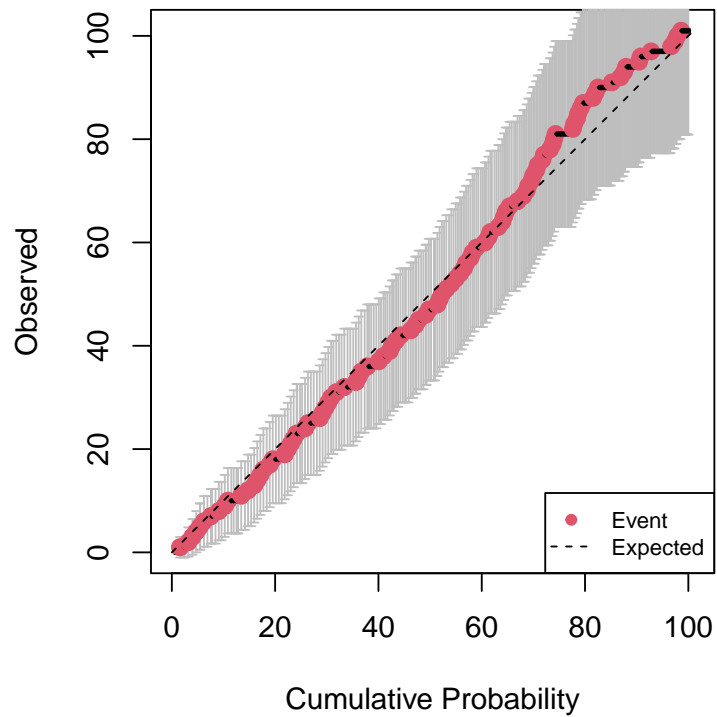
h0	Gain	DeltaTime
0.421	1.04	7.45

```
h0 <- calprob$h0
timeinterval <- calprob$timeInterval;

rdata <- cbind(pdata$TTMevent,calprob$prob)
```

```
RRAnalysisCalAdCox <- RRPlot(rdata,atRate=c(0.90,0.95),
                      timetoEvent=pdata$RFS,
                      title="Cal. NIK: Breast Cancer",
                      ysurvlim=c(0.00,1.0),
                      riskTimeInterval=timeinterval)
```

Cumulative vs. Observed: Cal. NIK: Breast Cancer

Decision Curve Analysis: Cal. NIK: Breast Cancer
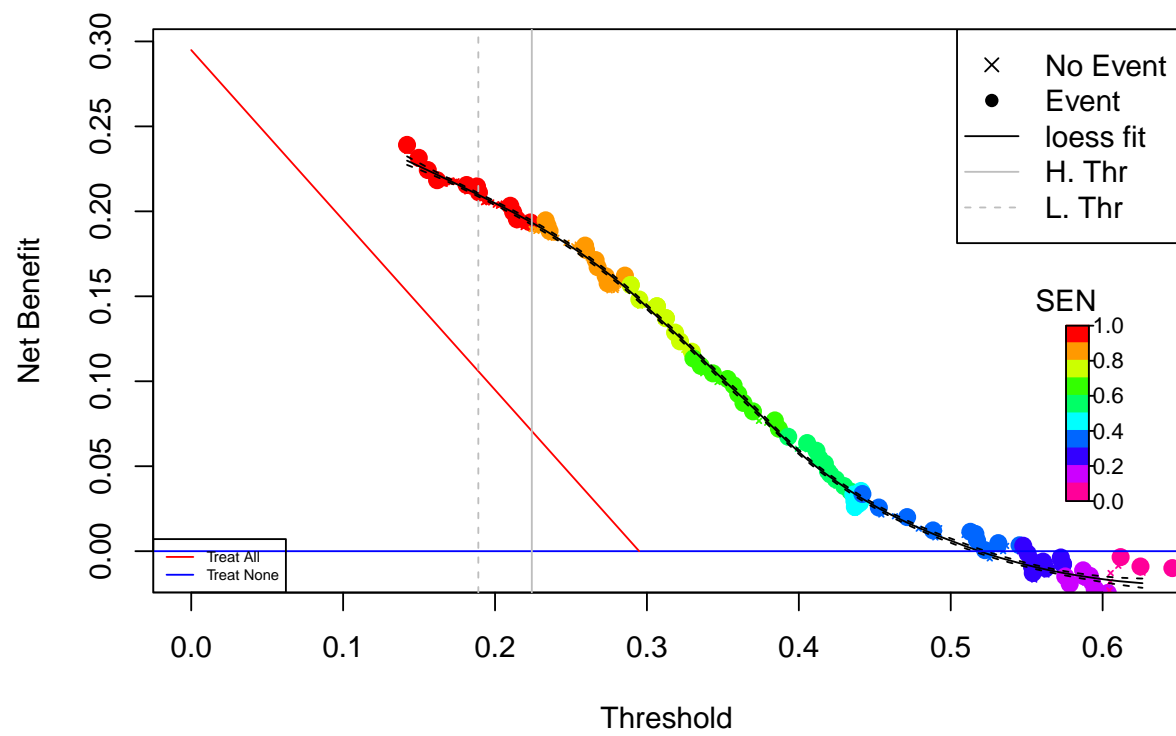
Relative Risk: Cal. NIK: Breast Cancer

Index(0.40)=0.224

RR(0.89)=3.736

PPV—>

SPE

△ No
● Yes
△ Loess Fit

1.0
0.8
0.6
0.4
0.2

1.0
0.8
0.6
0.4
0.2
0.0

RR

SEN

ROC: Cal. NIK: Breast Cancer

(TPR= 0.891 ,TNR= 0.397 ,ACC= 0.566 ,F1= 0.584 ,BER= 0.356)

Confusion Matrix

AUC: 0.702
BACC (0.644)

Sensitivity

Specificity

Test

Outcome

O(+)   O(−)

T(+)

T(−)
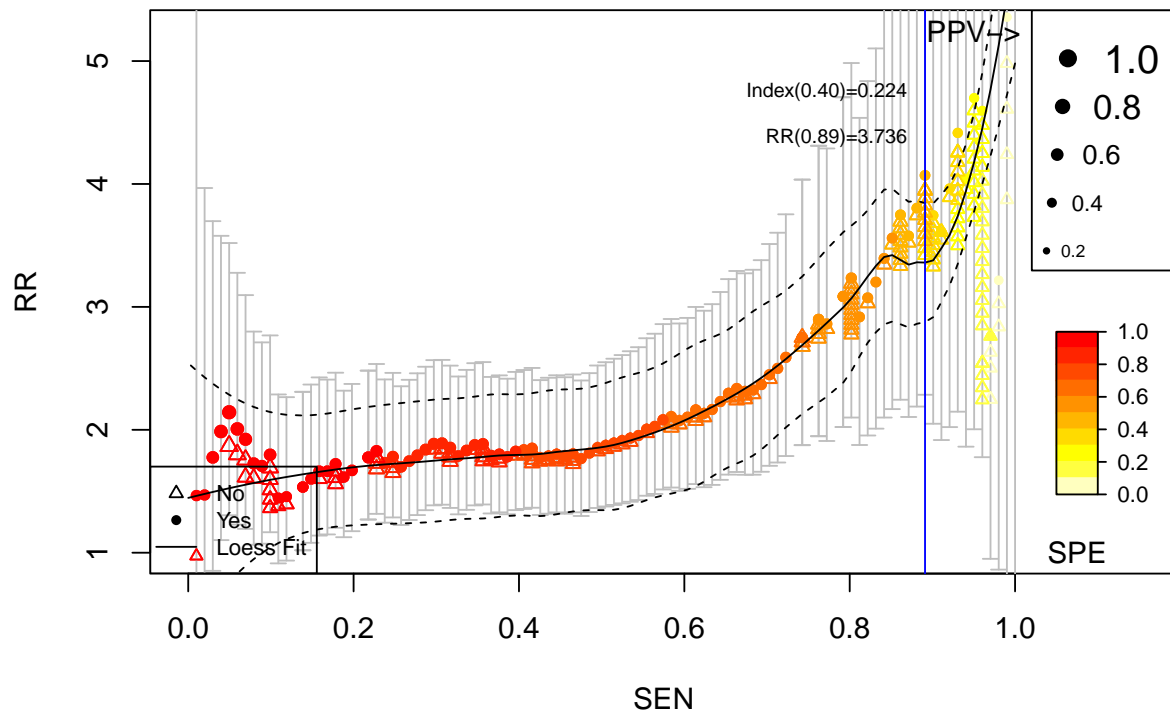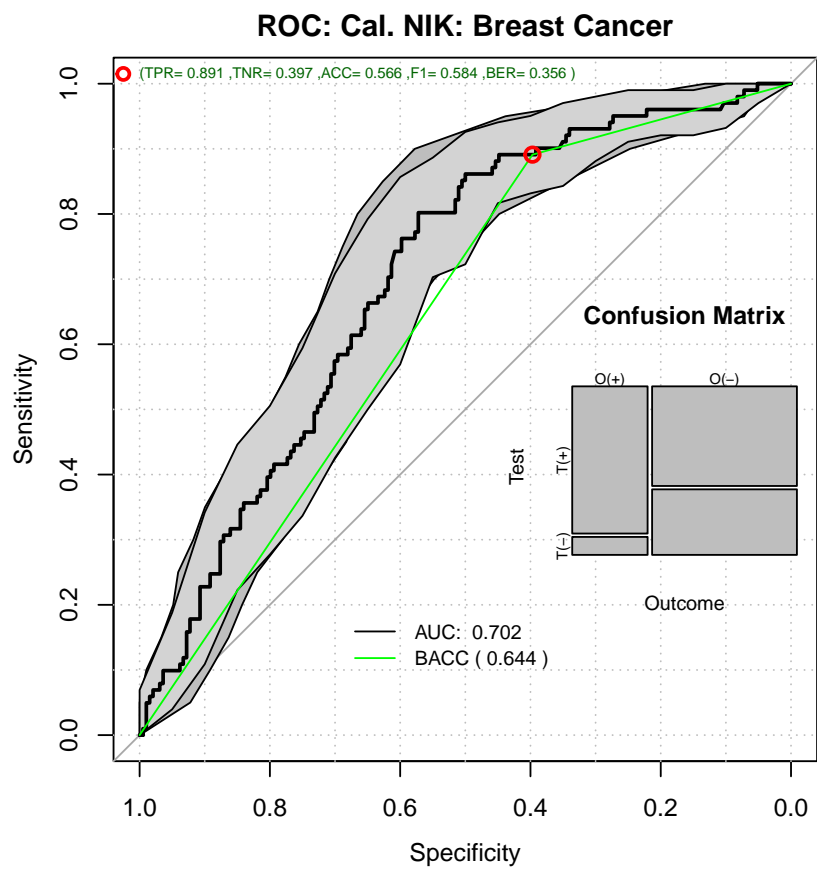
Time vs. Events: Cal. NIK: Breast Cancer
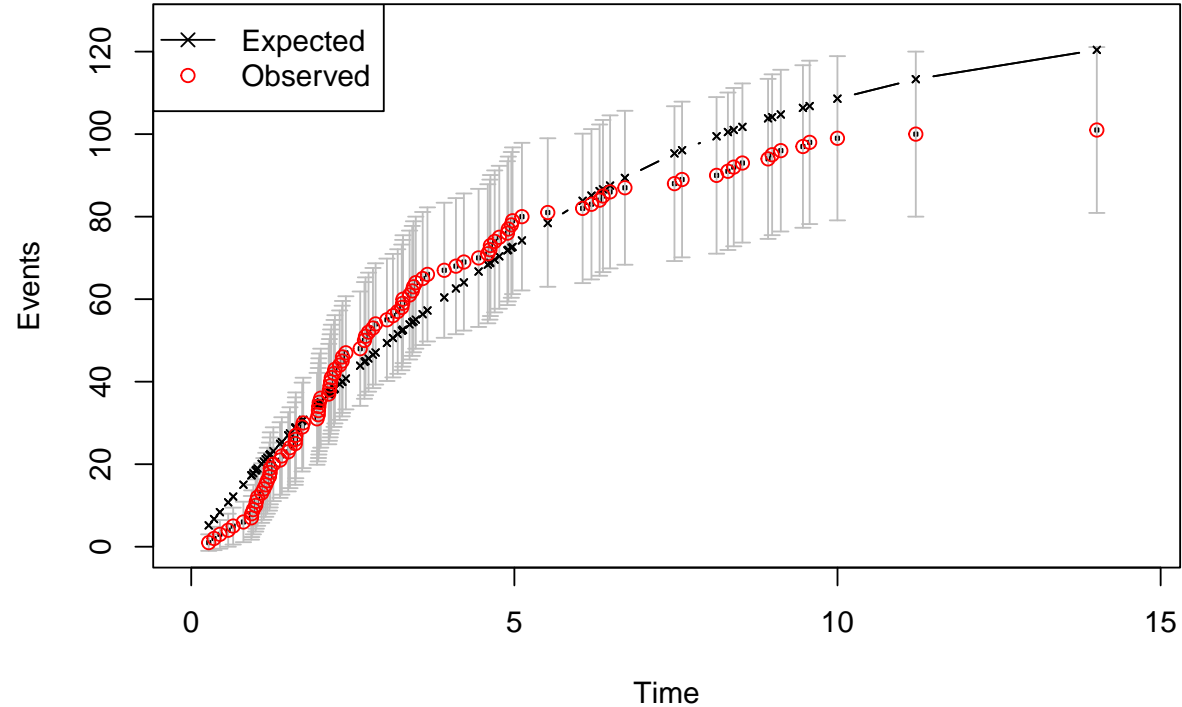
Kaplan–Meier: Cal. NIK: Breast Cancer
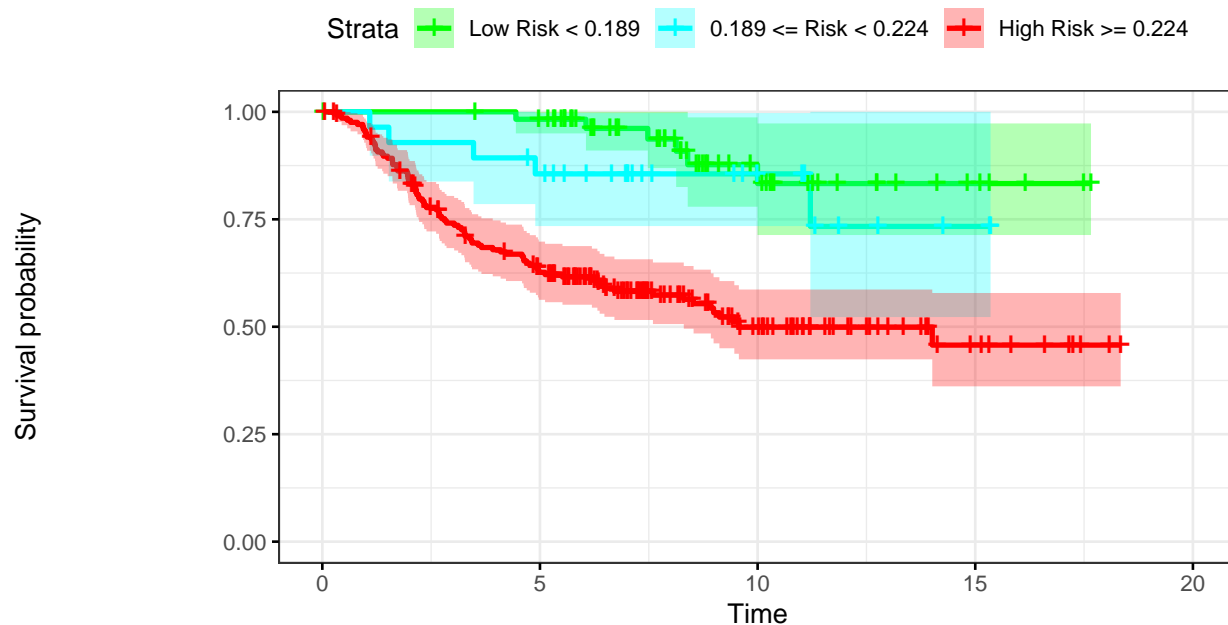
Number at risk

Low Risk < 0.189	60	56	19	5	0
0.189 <= Risk < 0.224	28	23	9	2	0
High Risk >= 0.224	207	117	40	9	0

```
par(op)
```

1.14 Expected time to event

```
timetoEvent <- meanTimeToEvent(rdata[,2],timeinterval)
tmax<-max(c(obstiemToEvent,timetoEvent))
lmfit <- lm(obstiemToEvent[toinclude]~0+timetoEvent[toinclude])
sm <- summary(lmfit)
pander::pander(sm)
```

	Estimate	Std. Error	t value	Pr(>|t|)
timetoEvent[toinclude]	0.395	0.0284	13.9	4.17e-25

Table 51: Fitting linear model: obstiemToEvent[toinclude] ~ 0 + timetoEvent[toinclude]

Observations	Residual Std. Error	R^2	Adjusted R^2
101	2.69	0.659	0.656

```
plot(timetoEvent,obstiemToEvent,
     col=1+rdata[,1],
```

```
    xlab="Expected time",
    ylab="Observed time",
    main="Expected vs. Observed",
    xlim=c(tmin,tmax),
    ylim=c(tmin,tmax),
    log="xy")
lines(x=c(tmin,tmax),y=lmfit$coefficients*c(tmin,tmax),lty=1,col="blue")
txt <- bquote(paste(R^2 == .(round(sm$r.squared,3))))
text(tmin+0.005*(tmax-tmin),tmax,txt,cex=0.7)
text(tmin+0.015*(tmax-tmin),tmax,sprintf("Slope=%4.3f",sm$coefficients[1]),cex=0.7)
legend("bottomright",legend=c("No Event","Event","Linear fit"),
        pch=c(1,1,-1),
        col=c(1,2,"blue"),
        lty=c(-1,-1,1)
        )
```

Expected vs. Observed


```
MADerror2 <-c(MADerror2,mean(abs(timetoEvent-obstiemToEvent)))
pander::pander(MADerror2)
```

4.75, *6.09* and *6.23*

1.14.1   Calibrated and Adjusted Cox Performance

```
pander::pander(t(RRAnalysisCalAdCox$keyPoints),caption="Threshold values")
```

Table 52: Threshold values

	@:0.9	@:0.95	@MAX_BACC	@MAX_RR	@SPE100	p(0.5)
Thr	0.224	0.189	0.285	0.188	1.42e-01	0.4924
RR	3.422	4.043	3.235	4.699	3.54e+01	1.8140
RR_LCI	1.928	1.863	2.100	2.004	7.42e-02	1.3369
RR_UCI	6.075	8.773	4.984	11.015	1.69e+04	2.4614
SEN	0.891	0.941	0.802	0.950	1.00e+00	0.3564
SPE	0.392	0.278	0.572	0.273	5.15e-02	0.8299
BACC	0.641	0.609	0.687	0.612	5.26e-01	0.5932
NetBenefit	0.190	0.211	0.162	0.215	2.39e-01	0.0135

```
pander::pander(t(RRAnalysisCalAdCox$OERatio$estimate),caption="O/E Ratio")
```

Table 53: O/E Ratio

O/E	Low	Upper	p.value
0.839	0.683	1.02	0.0831

```
pander::pander(t(RRAnalysisCalAdCox$OE95ci),caption="O/E Mean")
```

Table 54: O/E Mean

mean	50%	2.5%	97.5%
0.99	0.99	0.963	1.02

```
pander::pander(t(RRAnalysisCalAdCox$OAcum95ci),caption="O/Acum Mean")
```

Table 55: O/Acum Mean

mean	50%	2.5%	97.5%
1	1	0.994	1.01

```
pander::pander(RRAnalysisCalAdCox$c.index$cstatCI,caption="C. Index")
```

mean.C Index	median	lower	upper
0.707	0.708	0.661	0.75

```
pander::pander(t(RRAnalysisCalAdCox$ROCAnalysis$aucs),caption="ROC AUC")
```

Table 57: ROC AUC

est	lower	upper
0.702	0.642	0.763

```
pander::pander((RRAnalysisCalAdCox$ROCAnalysis$sensitivity),caption="Sensitivity")
```

Table 58: Sensitivity

est	lower	upper
0.891	0.813	0.944

```
pander::pander((RRAnalysisCalAdCox$ROCAnalysis$specificity),caption="Specificity")
```

Table 59: Specificity

est	lower	upper
0.397	0.328	0.469

```
pander::pander(t(RRAnalysisCalAdCox$thr_atP),caption="Probability Thresholds")
```

Table 60: Probability Thresholds

10%	5%
0.224	0.189

```
pander::pander(RRAnalysisCalAdCox$surdif,caption="Logrank test")
```

Table 61: Logrank test Chisq = 28.504862 on 2 degrees of freedom,
p = 0.000001

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
class=0	60	6	25.3	14.73	19.76
class=1	28	5	11.2	3.45	3.89
class=2	207	90	64.5	10.11	28.16

1.15 Comparing Risks

1.15.1 Comparing concordance Index

```
## Correlation Index
cindex <- RRAnalysisCI$c.index$cstatCI
## Cox Index
cindex <- rbind(cindex,RRAnalysisCox$c.index$cstatCI)
## Adjusted Cox Index
cindex <- rbind(cindex,RRAnalysisAdCox$c.index$cstatCI)
## Adjusted and Calibrated Cox Index
cindex <- rbind(cindex,RRAnalysisCalAdCox$c.index$cstatCI)
rownames(cindex) <- c("CI","Cox","Adj. Cox","Cal. Adj. Cox")


pander::pander(cindex)
```

	mean.C Index	median	lower	upper
CI	0.698	0.698	0.649	0.747
Cox	0.698	0.700	0.650	0.746
Adj. Cox	0.707	0.706	0.661	0.751
Cal. Adj. Cox	0.707	0.708	0.661	0.750

1.15.2 Comparing Risk Ratios Index

```
## Correlation Index
RRratio <- c(RR=RRAnalysisCI$keyPoints$RR[1],
             LCI=RRAnalysisCI$keyPoints$RR_LCI[1],
             UCI=RRAnalysisCI$keyPoints$RR_UCI[1])
## Cox Index
RRratio <- rbind(RRratio,c(RR=RRAnalysisCox$keyPoints$RR[1],
                           LCI=RRAnalysisCox$keyPoints$RR_LCI[1],
                           UCI=RRAnalysisCox$keyPoints$RR_UCI[1]))
## Adjusted Cox Index
RRratio <- rbind(RRratio,c(RR=RRAnalysisAdCox$keyPoints$RR[1],
                           LCI=RRAnalysisAdCox$keyPoints$RR_LCI[1],
                           UCI=RRAnalysisAdCox$keyPoints$RR_UCI[1]))
## Adjusted and Calibrated Cox Index
RRratio <- rbind(RRratio,c(RR=RRAnalysisCalAdCox$keyPoints$RR[1],
                           LCI=RRAnalysisCalAdCox$keyPoints$RR_LCI[1],
                           UCI=RRAnalysisCalAdCox$keyPoints$RR_UCI[1]))
rownames(RRratio) <- c("CI","Cox","Adj. Cox","Cal. Adj. Cox")
pander::pander(RRratio)
```

	RR	LCI	UCI
CI	3.81	2.08	6.96
Cox	3.81	2.08	6.96
Adj. Cox	3.42	1.93	6.07
Cal. Adj. Cox	3.42	1.93	6.07

1.15.3 Comparing logRank values

```
## Correlation Index
SurvDif <- c(chisq=RRAnalysisCI$surdif$chisq,pvalue=RRAnalysisCI$surdif$pvalue)
## Cox Index
SurvDif <- rbind(SurvDif,c(chisq=RRAnalysisCox$surdif$chisq,pvalue=RRAnalysisCox$surdif$pvalue))
## Adjusted Cox Index
SurvDif <- rbind(SurvDif,c(chisq=RRAnalysisAdCox$surdif$chisq,pvalue=RRAnalysisAdCox$surdif$pvalue))
## Adjusted and Calibrated Cox Index
SurvDif <- rbind(SurvDif,c(chisq=RRAnalysisCalAdCox$surdif$chisq,pvalue=RRAnalysisCalAdCox$surdif$pvalue
rownames(SurvDif) <- c("CI","Cox","Adj. Cox","Cal. Adj. Cox")

pander::pander(SurvDif)
```

	chisq	pvalue
CI	28.1	7.97e-07
Cox	28.1	7.97e-07

	chisq	pvalue
Adj. Cox	28.5	6.46e-07
Cal. Adj. Cox	28.5	6.46e-07

1.15.4 Comparing Sensitivity

```
## Correlation Index
sensi <- RRAnalysisCI$ROCAnalysis$sensitivity
## Cox Index
sensi <- rbind(sensi,RRAnalysisCox$ROCAnalysis$sensitivity)
## Adjusted Cox Index
sensi <- rbind(sensi,RRAnalysisAdCox$ROCAnalysis$sensitivity)
## Adjusted and Calibrated Cox Index
sensi <- rbind(sensi,RRAnalysisCalAdCox$ROCAnalysis$sensitivity)
rownames(sensi) <- c("CI","Cox","Adj. Cox","Cal. Adj. Cox")

pander::pander(sensi)
```

	est	lower	upper
CI	0.891	0.813	0.944
Cox	0.891	0.813	0.944
Adj. Cox	0.891	0.813	0.944
Cal. Adj. Cox	0.891	0.813	0.944

1.15.5 Comparing Specificity

```
## Correlation Index
speci <- RRAnalysisCI$ROCAnalysis$specificity
## Cox Index
speci <- rbind(speci,RRAnalysisCox$ROCAnalysis$specificity)
## Adjusted Cox Index
speci <- rbind(speci,RRAnalysisAdCox$ROCAnalysis$specificity)
## Adjusted and Calibrated Cox Index
speci <- rbind(speci,RRAnalysisCalAdCox$ROCAnalysis$specificity)
rownames(speci) <- c("CI","Cox","Adj. Cox","Cal. Adj. Cox")
pander::pander(speci)
```

	est	lower	upper
CI	0.397	0.328	0.469
Cox	0.397	0.328	0.469
Adj. Cox	0.397	0.328	0.469
Cal. Adj. Cox	0.397	0.328	0.469

1.15.6 Comparing O/E

```
OERatio <- NULL
## Cox Index
OERatio <- rbind(OERatio,RRAnalysisCox$OERatio$estimate)
## Adjusted Cox Index
```

```
OERatio <- rbind(OERatio,RRAnalysisAdCox$OERatio$estimate)
## Adjusted and Calibrated Cox Index
OERatio <- rbind(OERatio,RRAnalysisCalAdCox$OERatio$estimate)
rownames(OERatio) <- c("Cox","Adj. Cox","Cal. Adj. Cox")

pander::pander(OERatio)
```

	O/E	Low	Upper	p.value
Cox	0.806	0.656	0.979	0.0285
Adj. Cox	0.825	0.672	1.002	0.0519
Cal. Adj. Cox	0.839	0.683	1.019	0.0831

1.15.7 Comparing O/Acum

```
OARatio <- NULL
## Cox Index
OARatio <- rbind(OARatio,RRAnalysisCox$OARatio$estimate)
## Adjusted Cox Index
OARatio <- rbind(OARatio,RRAnalysisAdCox$OARatio$estimate)
## Adjusted and Calibrated Cox Index
OARatio <- rbind(OARatio,RRAnalysisCalAdCox$OARatio$estimate)
rownames(OARatio) <- c("Cox","Adj. Cox","Cal. Adj. Cox")
pander::pander(OARatio)
```

	O/A	Low	Upper	p.value
Cox	1.15	0.936	1.40	0.165
Adj. Cox	1.18	0.961	1.43	0.104
Cal. Adj. Cox	1.01	0.823	1.23	0.920

1.15.8 Comparing NetBenefit

```
NetBen <- NULL
## Cox Index
NetBen <- rbind(NetBen,RRAnalysisCox$keyPoints$NetBenefit)
## Adjusted Cox Index
NetBen <- rbind(NetBen,RRAnalysisAdCox$keyPoints$NetBenefit)
## Adjusted and Calibrated Cox Index
NetBen <- rbind(NetBen,RRAnalysisCalAdCox$keyPoints$NetBenefit)
colnames(NetBen) <- rownames(RRAnalysisCox$keyPoints)
rownames(NetBen) <- c("Cox","Adj. Cox","Cal. Adj. Cox")
pander::pander(NetBen)
```

	@:0.9	@:0.95	@MAX_BACC	@MAX_RR	@SPE100	p(0.5)
Cox	0.223	0.232	0.222	0.239	0.252	-0.02795
Adj. Cox	0.230	0.249	0.202	0.252	0.274	0.00617
Cal. Adj. Cox	0.190	0.211	0.162	0.215	0.239	0.01354

1.16 Compare the ROC AUC

```
pander::pander(pROC::roc.test(RRAnalysisCI$ROCAnalysis$ROC.analysis$roc.predictor,
                              RRAnalysisAdCox$ROCAnalysis$ROC.analysis$roc.predictor))
```

Table 70: DeLong's test for two correlated ROC curves: `RRAnalysisCI$ROCAnalysis$ROC.analysis$roc.predictor` and `RRAnalysisAdCox$ROCAnalysis$ROC.analysis$roc.predictor`

Test statistic	P value	Alternative hypothesis	AUC of roc1	AUC of roc2
-0.988	0.323	two.sided	0.692	0.702