

Cox_1

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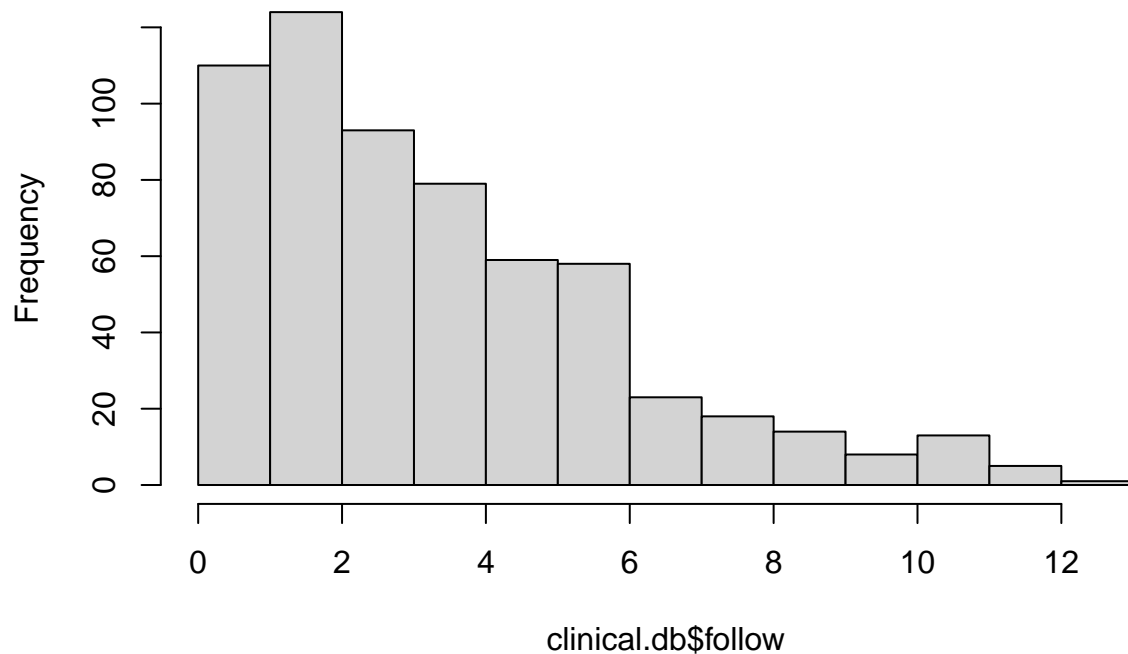
```
source("../R/linear_cox.R")
```

Clinical only

Statistiques descriptives

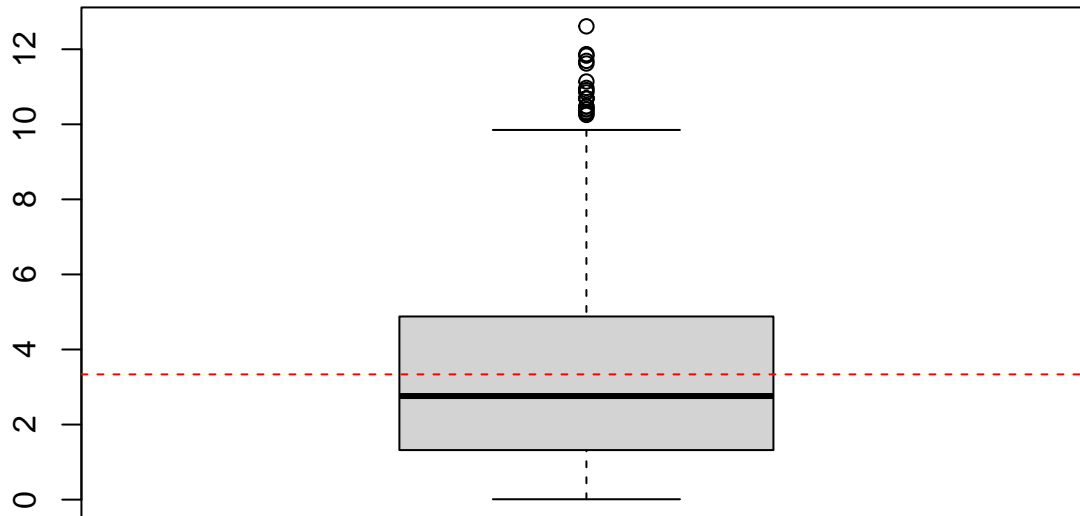
```
clinical.db$follow<-as.numeric(clinical.db$follow)
# histogramme
hist(clinical.db$follow,main='Histogramme de la durée de suivie')
```

Histogramme de la durée de suivie



```
#boxplot
boxplot(clinical.db$follow,main="distribution de follow")
abline(h=mean(clinical.db$follow,na.rm=T),col='red',lty=2)
```

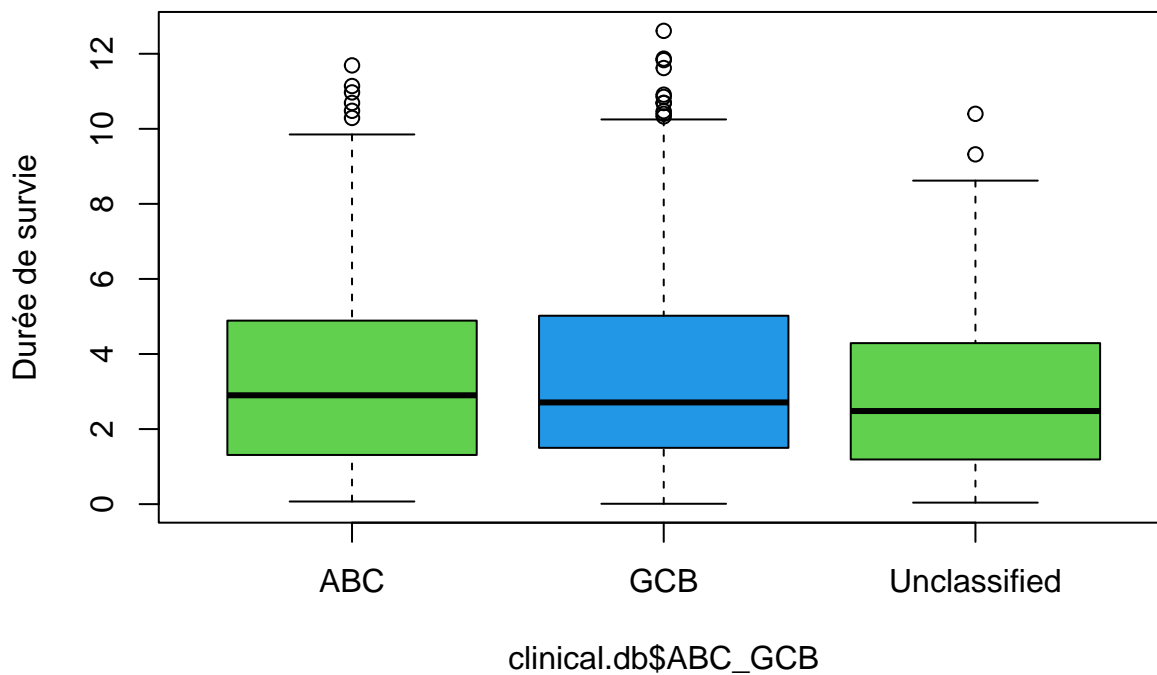
distribution de follow



#boxplot en fonction de classification

```
boxplot(clinical.db$follow~clinical.db$ABC_GCB,ylab="Durée de survie",col=c(3,4),main="boxplot de follow")
```

boxplot de follow en fonction de ABC_GCB



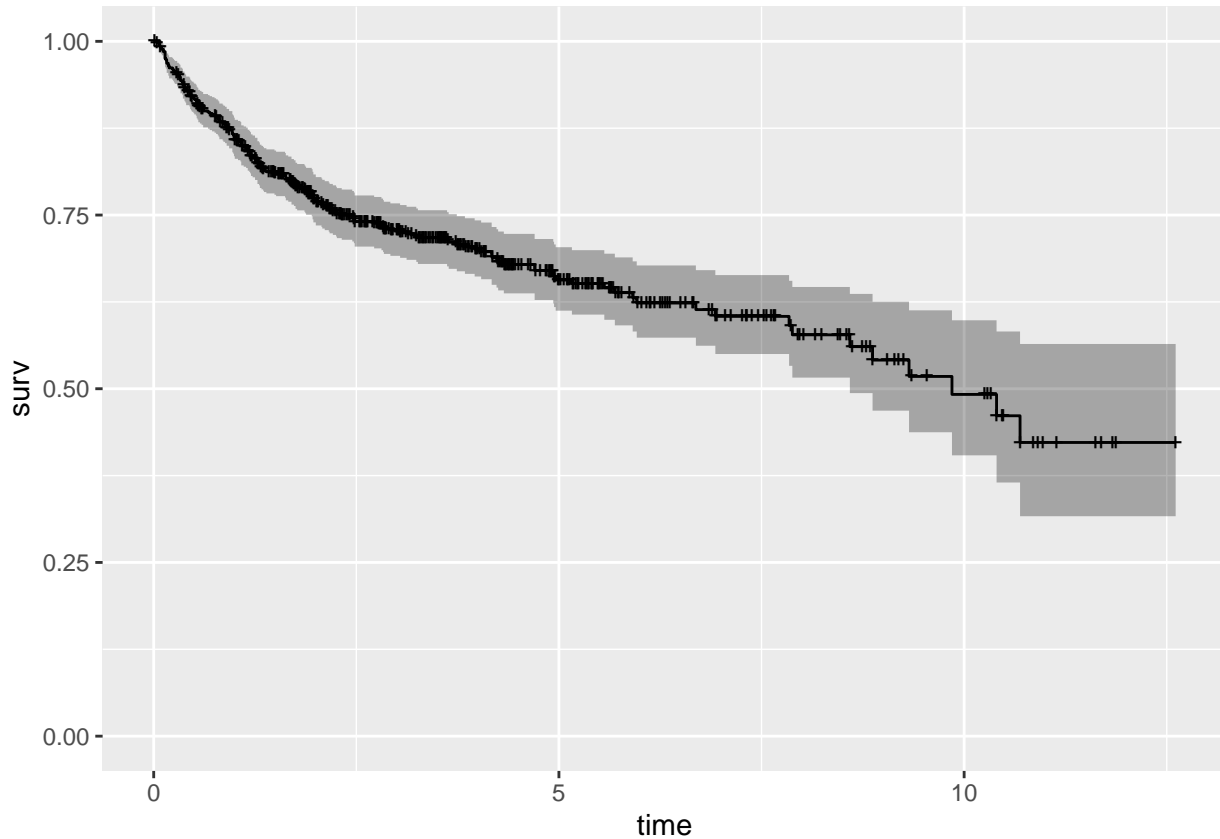
#taux de censure par grp

```
length(which(clinical.db$censor==0))/length(clinical.db$censor)#0=censored, 1=no-censored
```

```
## [1] 0.6942149
```

Cox général

```
survie<-Surv(clinical.db$follow,clinical.db$sensor)  
fit<-survfit(survie~1)  
autoplot(fit)+ylim(0,1)
```

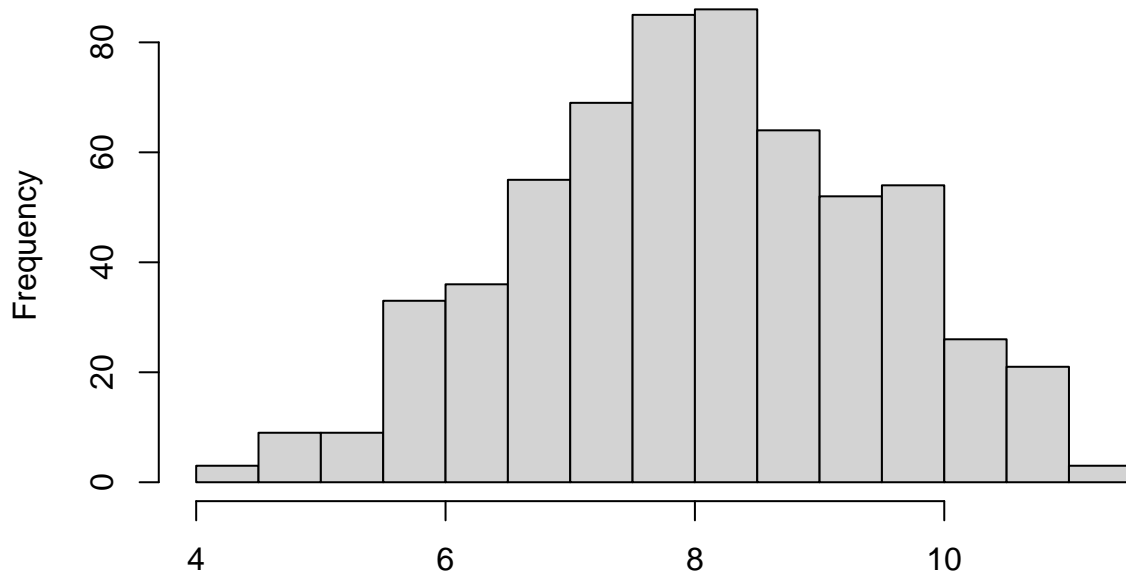


Clinical & RNA

Application de la procédure linéaire pour le gène BCL2

```
gene.code="BCL2"  
hist(as.numeric(rna.db[,which(colnames(rna.db)==gene.code)]),main=paste0("expression de ",gene.code," e
```

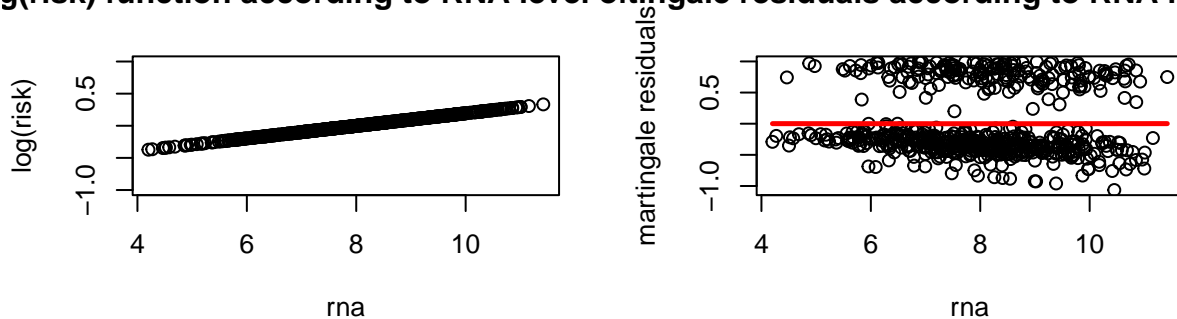
expression de BCL2 en log2



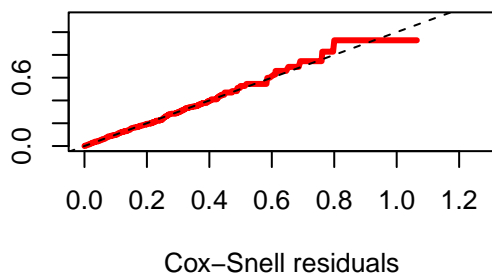
```
as.numeric(rna.db[, which(colnames(rna.db) == gene.code)])
```

```
par(mfrow=c(2,2))
linearCox.analyze(gene.code)
```

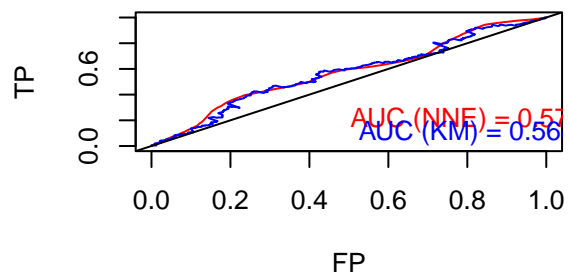
g(risk) function according to RNA level of **tingale residuals according to RNA level**



Cox-Snell residuals for BCL2



Courbe ROC à l'instant t = 10



```
## $model
## Call:
```

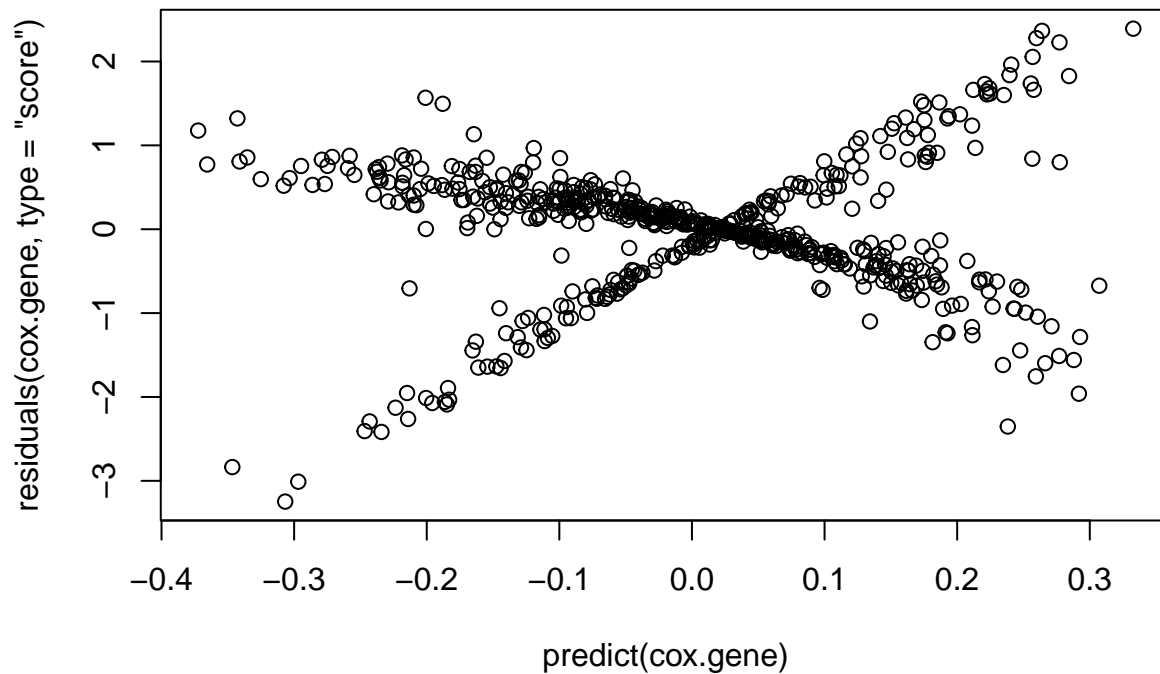
```
## coxph(formula = survie ~ rna)
##
##      coef exp(coef) se(coef)      z      p
## rna 0.09770   1.10263  0.05302  1.843 0.0654
##
## Likelihood ratio test=3.42 on 1 df, p=0.06439
## n= 605, number of events= 185
##
## $AIC
## [1] 2177.805
##
## $concordance
## $concordance$value
## [1] 0.5270652
##
## $concordance$concordance.IC.lower
## [1] 0.4825195
##
## $concordance$concordance.IC.upper
## [1] 0.571611
##
##
## $LRatio.pvalue
##      pvalue
## 0.06438906
##
## $LRank.pvalue
##      pvalue
## 0.06521076
##
## $R.squared
##      rsq
## 0.01831965

cox.gene<-linearCox.analyze(gene.code,graph=F)$m
rna<-as.numeric(rna.db[,which(colnames(rna.db)==gene.code)])
```

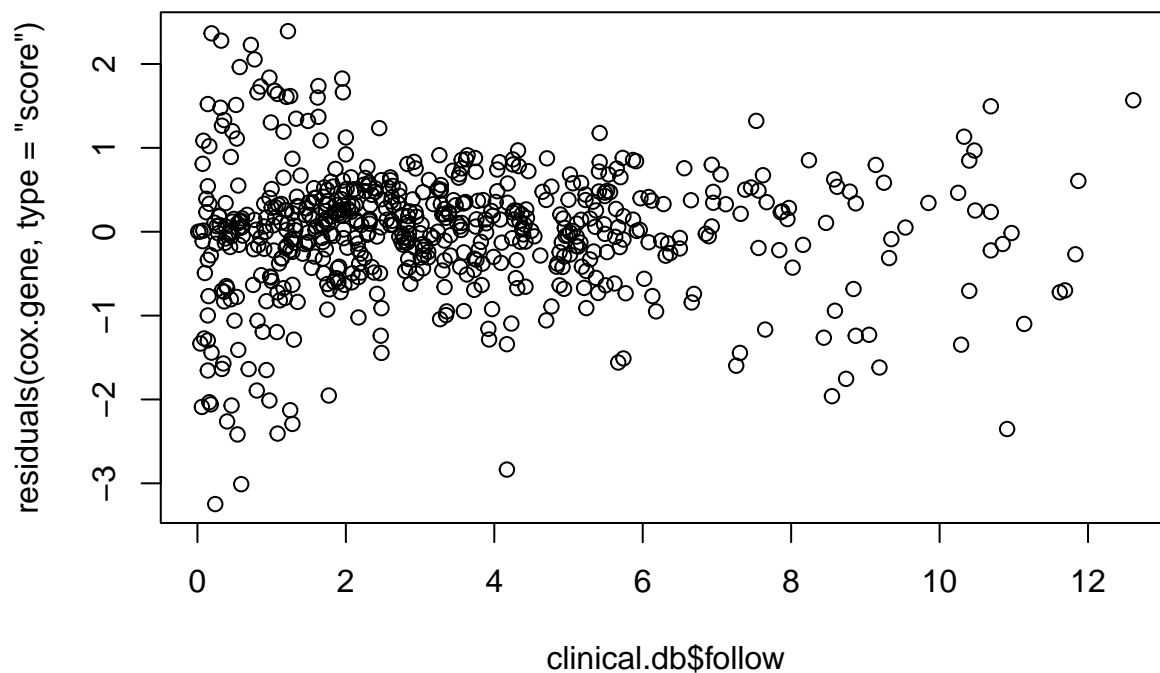
Productions graphiques (à intégrer)

Résidus score :

```
#residuals(cox.gene,type='score')
plot(predict(cox.gene),residuals(cox.gene,type='score'))
```



```
plot(clinical.db$follow, residuals(cox.gene, type='score'))
```



Courbes roc :

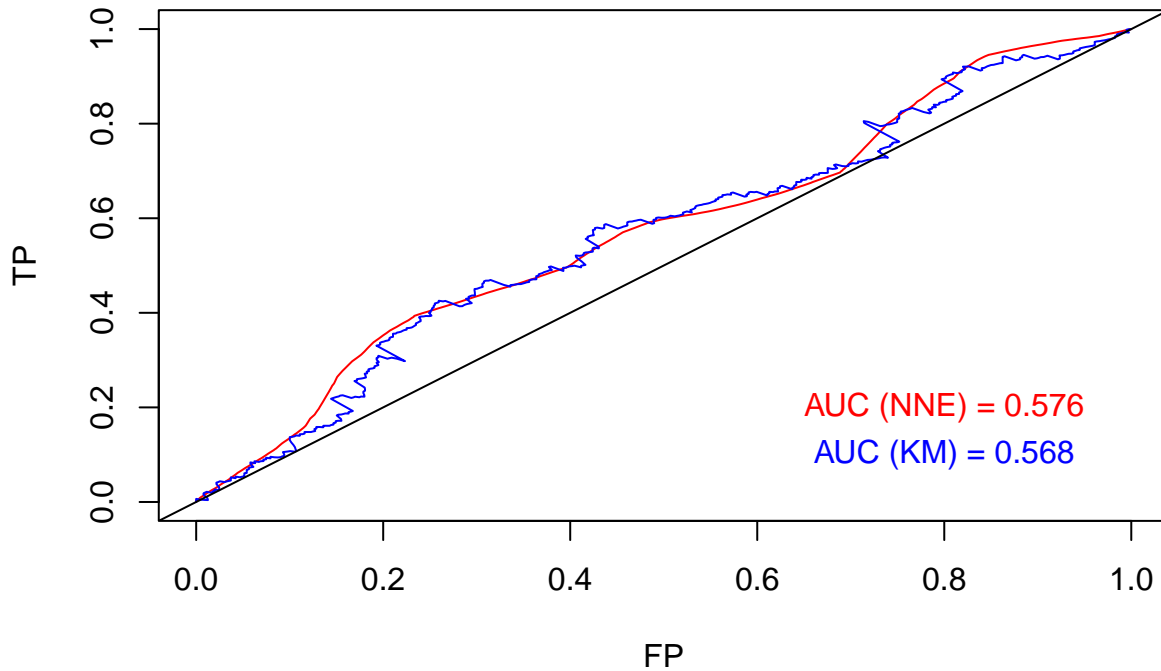
```
library(survivalROC)
scr<-predict(cox.gene, type='risk')

t<-10
roc.1<-survivalROC(Stime=clinical.db$follow, status=clinical.db$censor, marker=scr, predict.time=t, span=0.05)
roc.2<-survivalROC(Stime=clinical.db$follow, status=clinical.db$censor, marker=scr, predict.time=t, method="logrank")

plot(roc.1$FP, roc.1$TP, type='l', col='red', main=paste0("Courbe ROC à l'instant t = ", t), ylab="TP", xlab="FP")
```

```
points(roc.2$FP,roc.2$TP,type='l',col='blue')
text(c(0.8,0.8),c(0.2,0.1),labels=c(paste0("AUC (NNE) = ",round(roc.1$AUC,3)),paste0("AUC (KM) = ",round(roc.2$AUC,3))),col=c("red","blue"))
abline(a=0,b=1)
```

Courbe ROC à l'instant t = 10



#quel marker ?

R2 :

```
library(CoxR2)
coxr2(cox.gene)$rsq #R2, Difference in log partial likelihoods between the fitted model and the null model
```

```
##          rsq
## 0.01831965
```

#based on the partial likelihood ratio statistic

```
summary(cox.gene)$rsq[1] # R2, Difference in log partial likelihoods between the fitted model and the null model
```

```
##          rsq
## 0.00563787
```

Calibration :

```
rna<-as.numeric(rna.db[,which(colnames(rna.db)==gene.code)])
survie<-Surv(as.numeric(clinical.db$follow),clinical.db$censor)
library(rms)
```

```
## Le chargement a nécessité le package : Hmisc
```

```
##
```

```
## Attachement du package : 'Hmisc'
```

```
## Les objets suivants sont masqués depuis 'package:base':
```

```
##
```

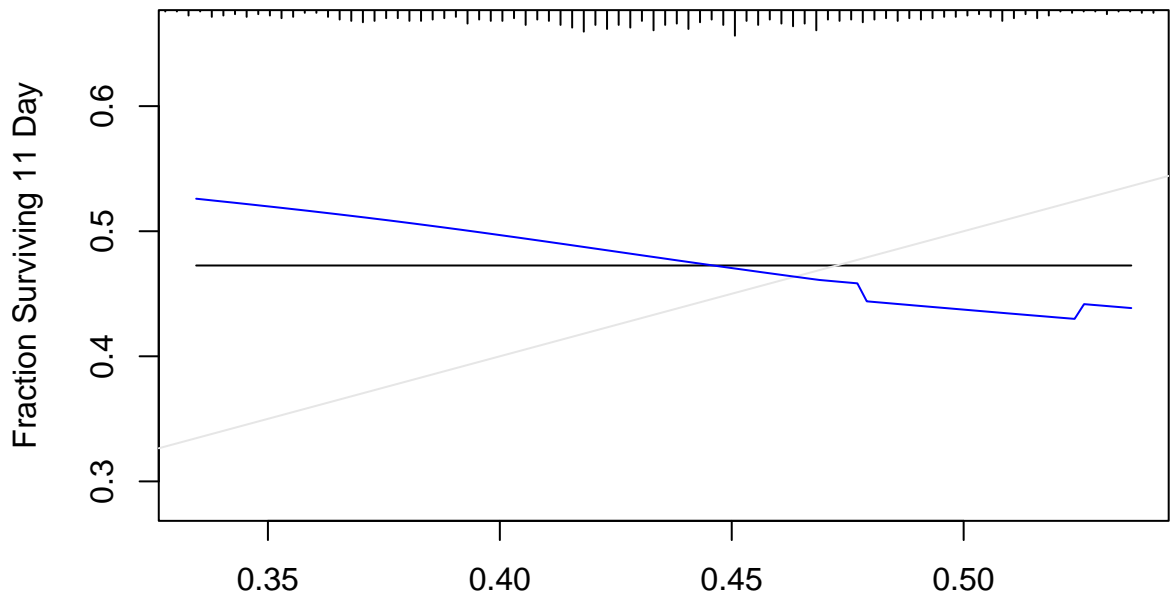
```
##      format.pval, units
## Le chargement a nécessité le package : lattice
## Le chargement a nécessité le package : SparseM
##
## Attachement du package : 'SparseM'
## L'objet suivant est masqué depuis 'package:base':
##
##      backsolve
```

```
nD=11
cox.gene<-cph(survie ~ rna,x=TRUE, y=TRUE,
              surv=TRUE, time.inc =nD, dxy = TRUE)

c1<-calibrate(cox.gene,u=nD)
```

```
## Using Cox survival estimates at 11 Days
```

```
plot(c1)
```



Black: observed Gray: ideal Blue : optimism corrected

B=40 based on observed-predicted
Mean |error|=0.073 0.9 Quantile=0.149

Comparaison des sorties pour les 4 premiers gènes BCL2, BCL6, MYC, TP53

```
#production graphiques
AIC<-c()
Concordance<-c()
LRatio.pvalue<-c()
LRank.pvalue<-c()
R2<-c()
for (gene.code in c('BCL2', 'BCL6', 'MYC', 'TP53')){
  par(mfrow=c(2,2))
  m<-linearCox.analyze(gene.code)
```

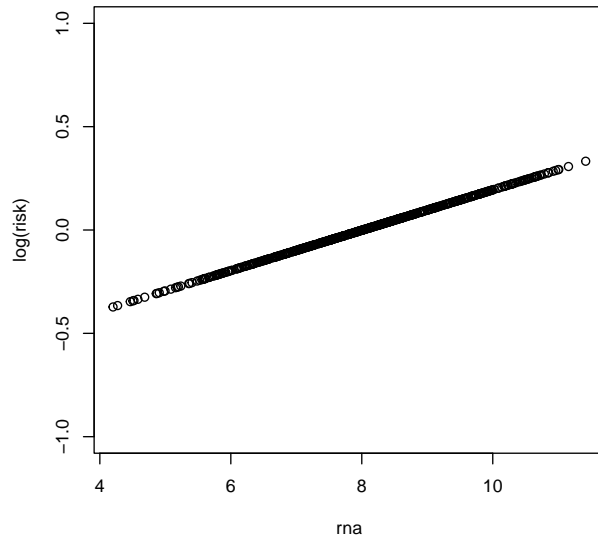


```

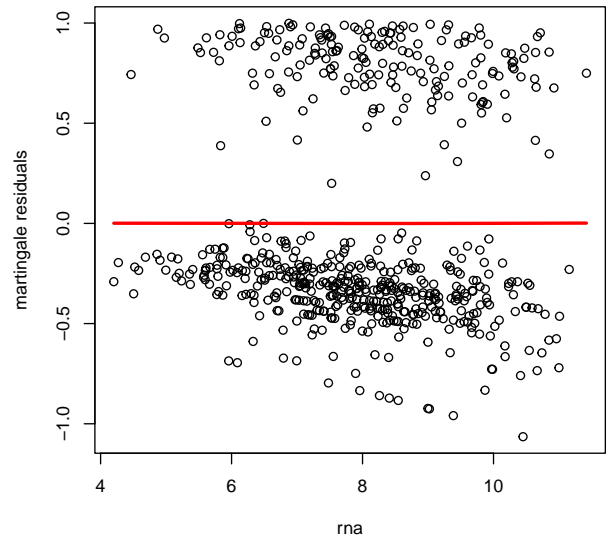
AIC<-c(AIC,m$AIC)
Concordance<-c(Concordance,m$concordance$value)
LRatio.pvalue<-c(LRatio.pvalue,m$LRatio.pvalue)
LRank.pvalue<-c(LRank.pvalue,m$LRank.pvalue)
R2<-c(R2,m$R.squared)
}

```

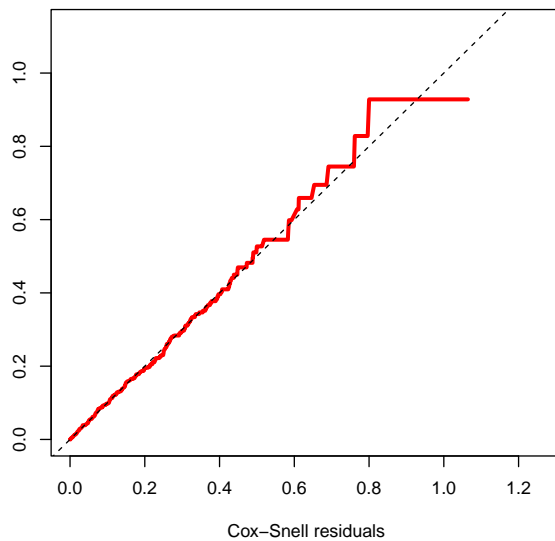
log(risk) function according to RNA level of BCL2



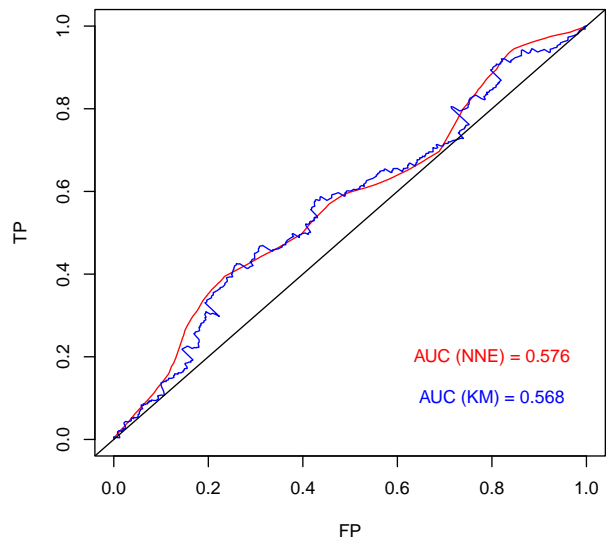
Martingale residuals according to RNA level of BCL2



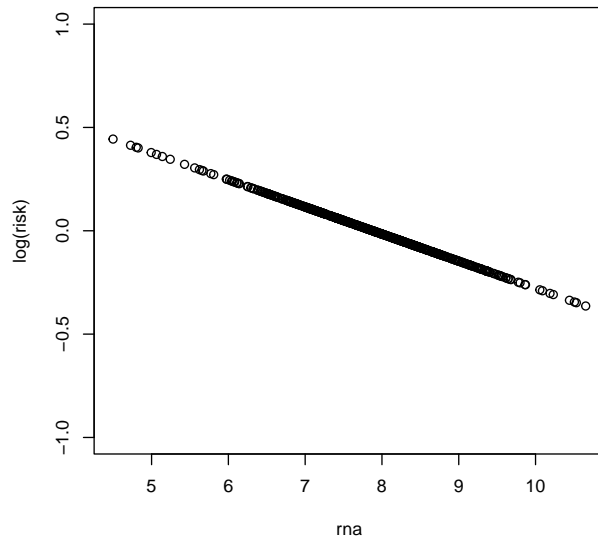
Cox-Snell residuals for BCL2



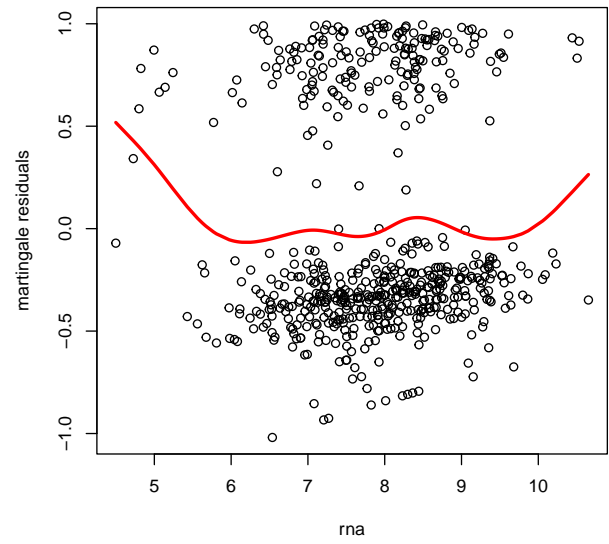
Courbe ROC à l'instant t = 10



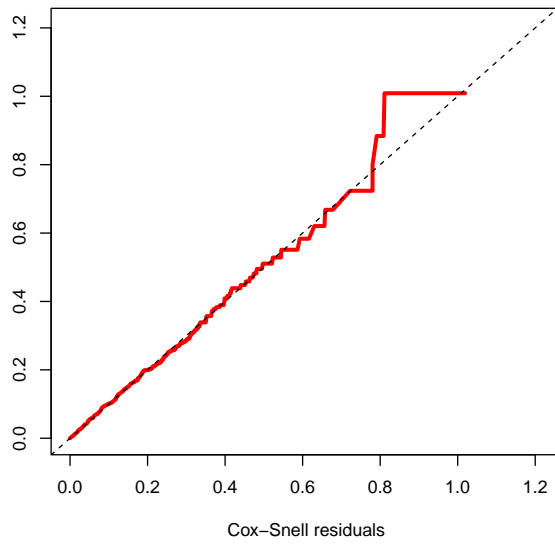
log(risk) function according to RNA level of BCL6



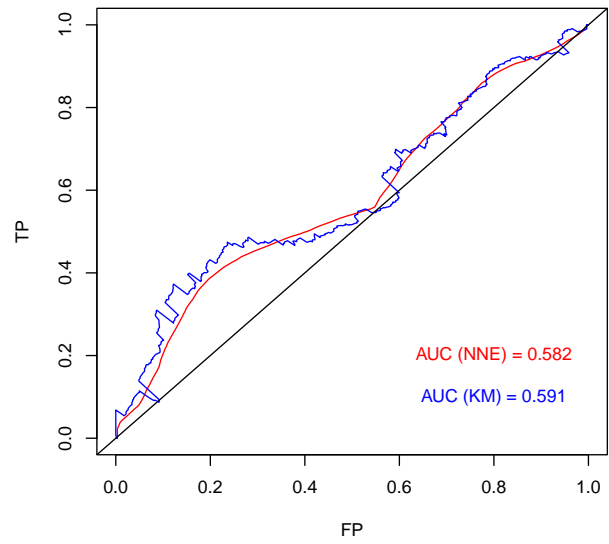
Martingale residuals according to RNA level of BCL6



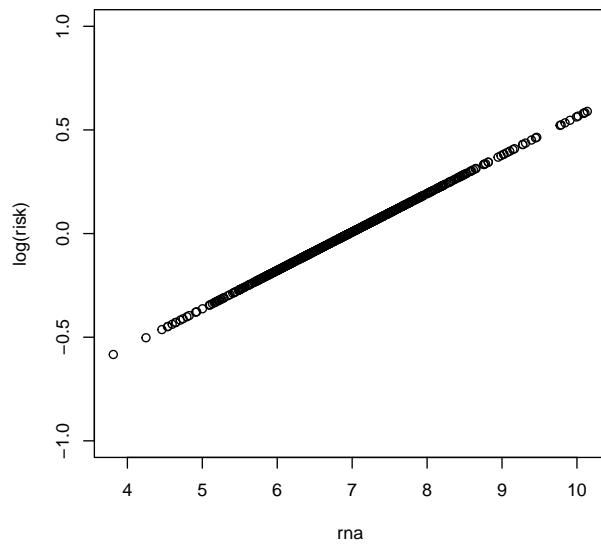
Cox-Snell residuals for BCL6



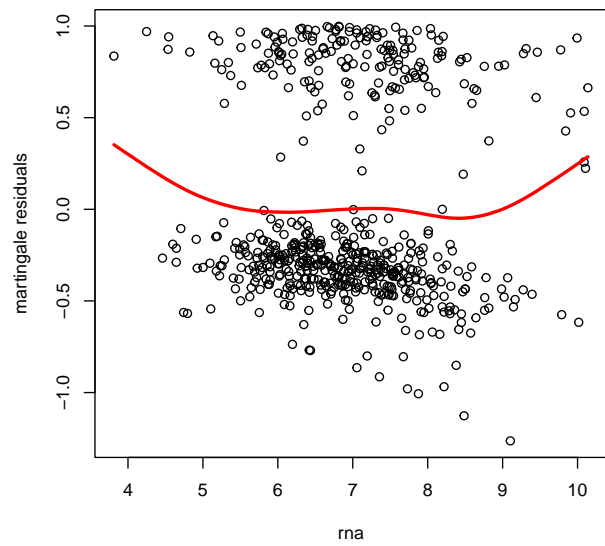
Courbe ROC à l'instant t = 10



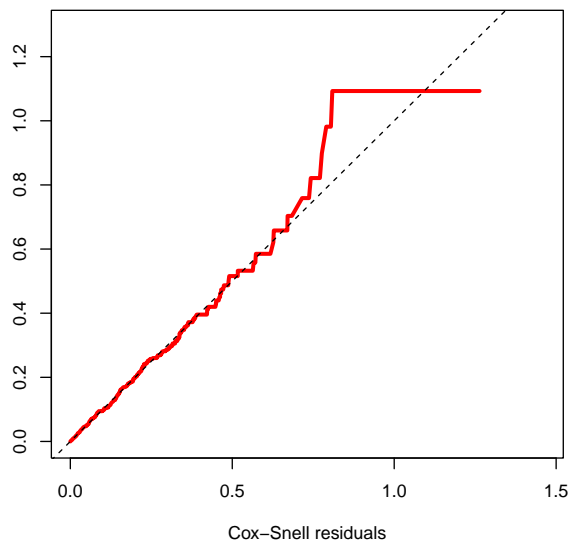
log(risk) function according to RNA level of MYC



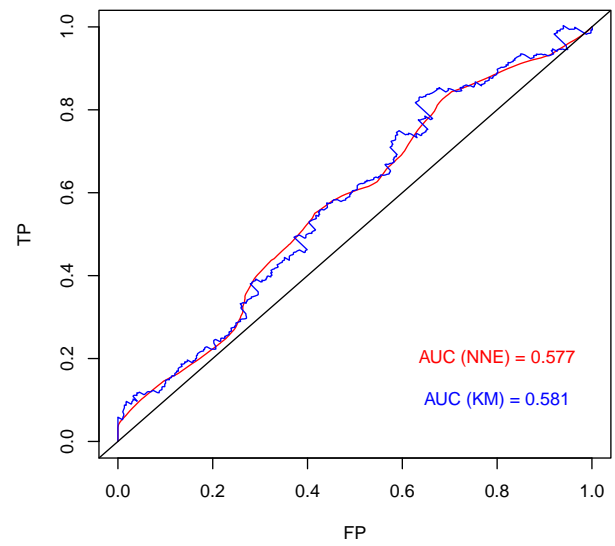
Martingale residuals according to RNA level of MYC

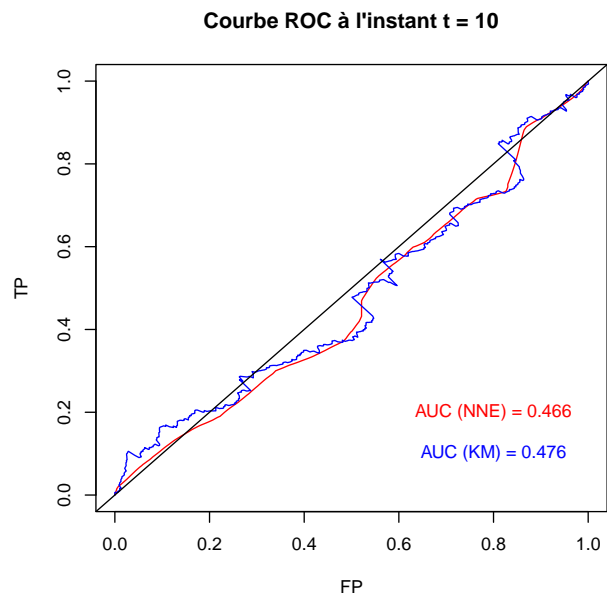
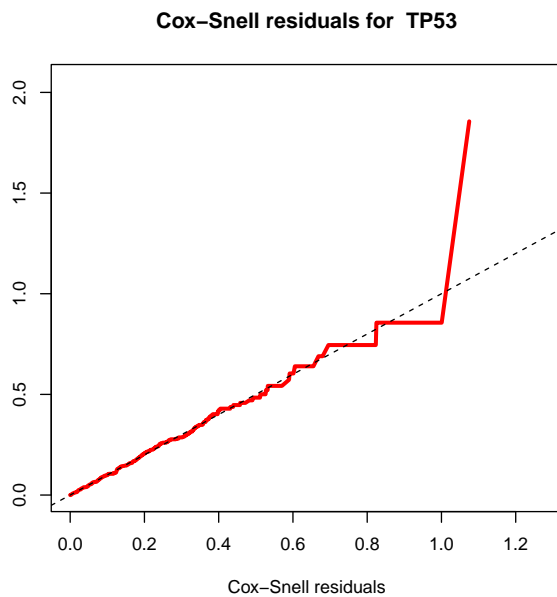
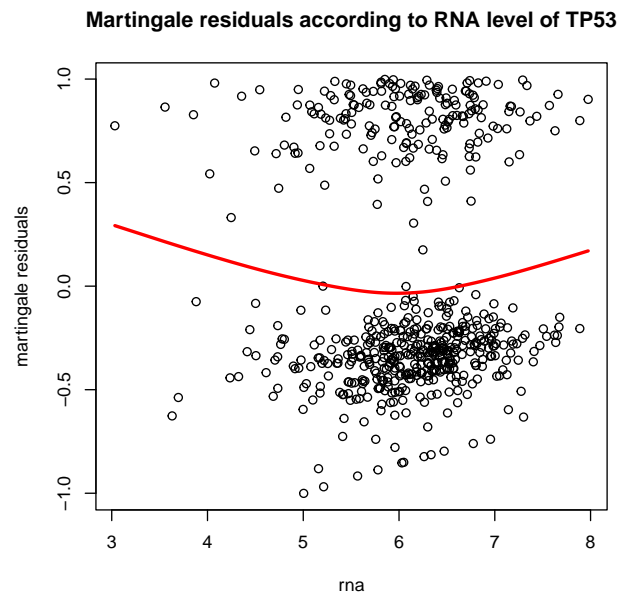
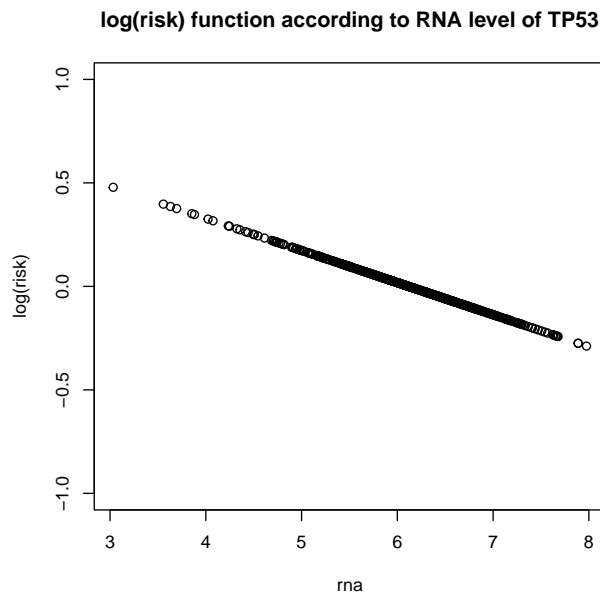


Cox-Snell residuals for MYC



Courbe ROC à l'instant t = 10





```
DF<-data.frame(cbind(AIC,Concordance,LRatio.pvalue,LRank.pvalue,R2))
rownames(DF)<-c('BCL2','BCL6','MYC','TP53')
DF
```

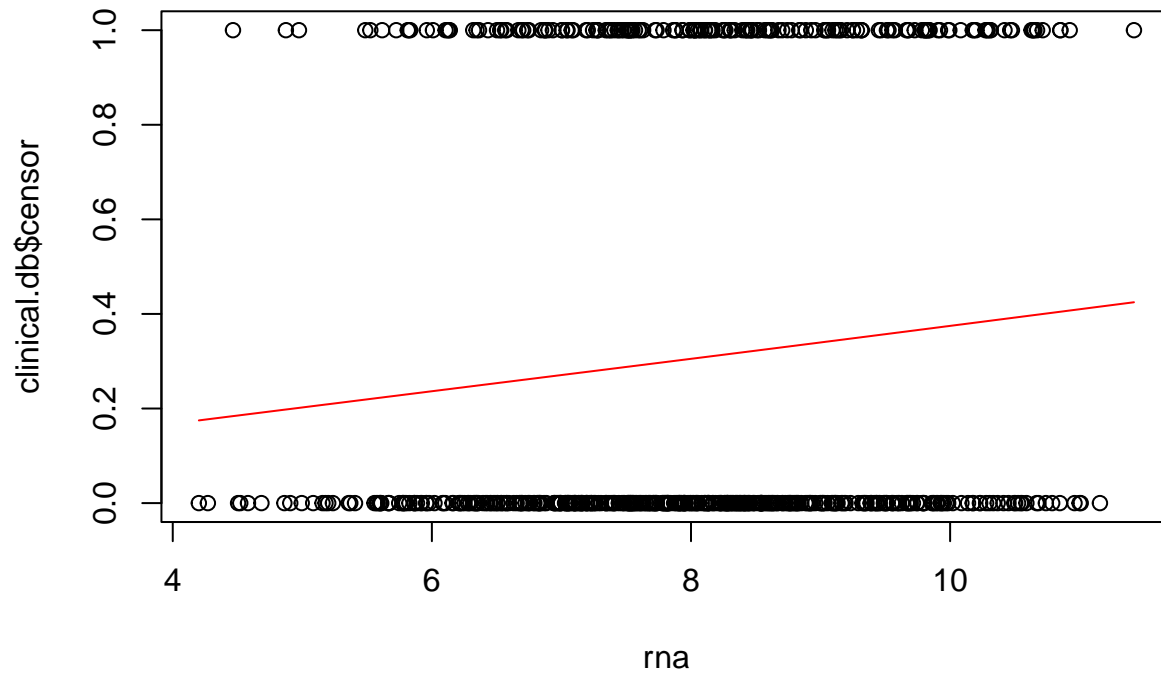
	AIC	Concordance	LRatio.pvalue	LRank.pvalue	R2
BCL2	2177.805	0.5270652	0.064389059	0.065210763	0.01831965
BCL6	2178.311	0.5199391	0.087805060	0.086807632	0.01562881
MYC	2173.979	0.5506186	0.007102277	0.006566685	0.03841521
TP53	2178.984	0.5285237	0.134374471	0.130242757	0.01204164

Productions graphiques à intégrer si linéaire pas adéquate

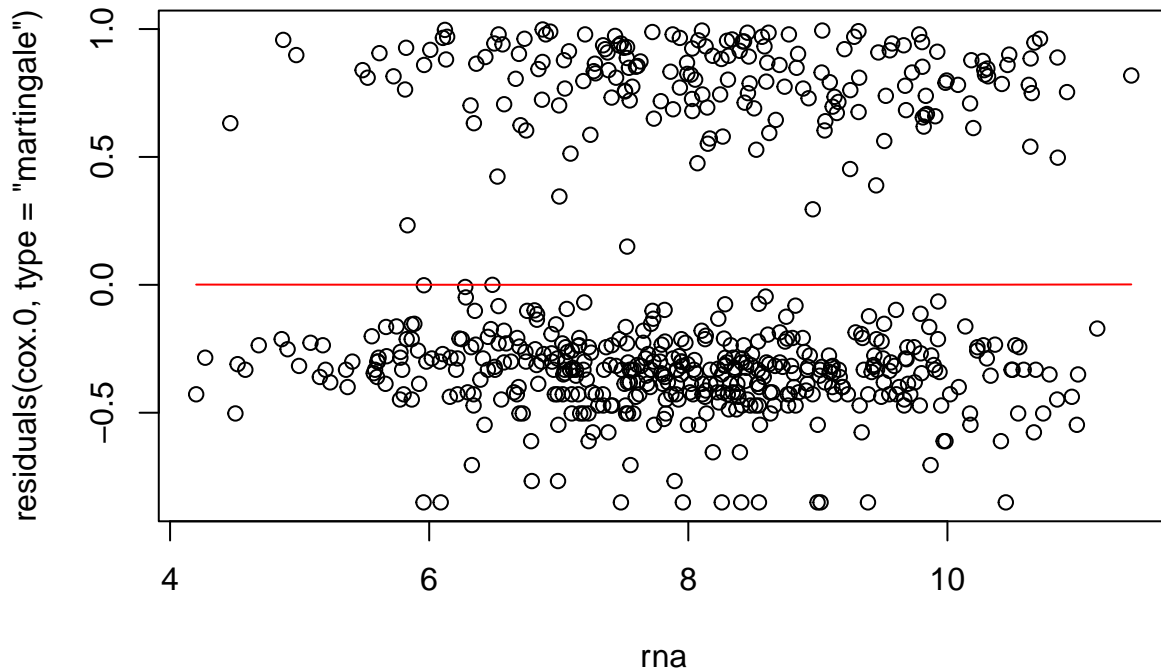
Pour avoir une idée de la fonction non paramétrique

```
#Regression smooth vis a vis de la censure si linéaire pas ok !
plot(rna,clinical.db$ensor)
```

```
lines(smooth.spline(rna,clinical.db$ensor),col='red')
```



```
#Residus martingales du modèle nul
cox.0<-coxph(survie ~1,data=clinical.db)
plot(rna,residuals(cox.0,type="martingale"))
lines(smooth.spline(rna,residuals(cox.gene,type="martingale")),col='red')
```



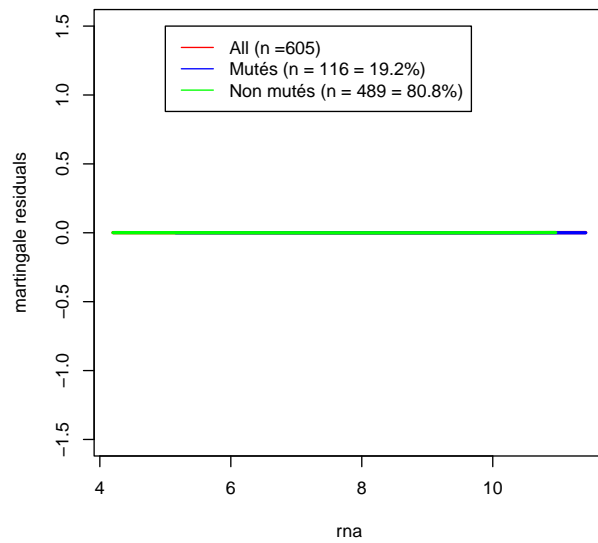
Comparaison mutés/non mutés/tous

```
par(mfrow=c(2,2))
for (gene.code in c('BCL2','BCL6','MYC','TP53')){
m.all<-linearCox.analyze(gene.code,graph=F)$m
m.mutes<-linearCox.analyze(gene.code,mutations = T,graph=F)$m
m.non.mutes<-linearCox.analyze(gene.code,mutations = F,graph=F)$m

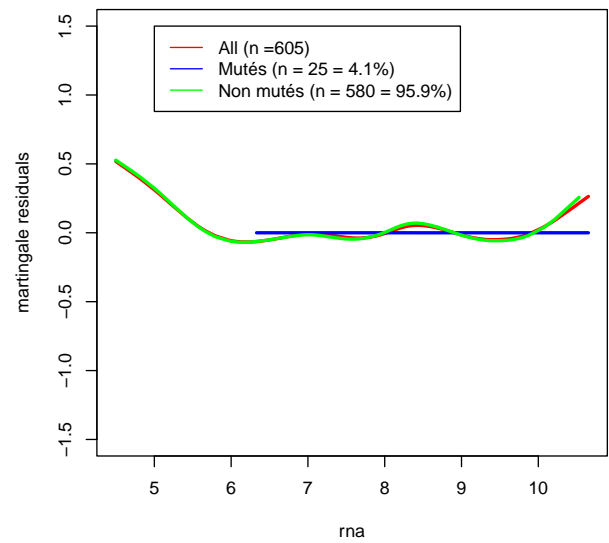
rna<-as.numeric(rna.db[,which(colnames(rna.db)==gene.code)])
idc.m<-which(mutations.db[,which(colnames(mutations.db)==gene.code)]==1)
rna.m<-rna[idc.m]
idc.nm<-which(mutations.db[,which(colnames(mutations.db)==gene.code)]==0)
rna.nonm<-rna[idc.nm]

#martingale residuals to RNA level
plot(rna,residuals(m.all,type="martingale"),main=paste0("Martingale residuals according to RNA level of ",gene.code))
lines(smooth.spline(rna,residuals(m.all,type="martingale")),col='red',lwd=2.5)
lines(smooth.spline(rna.m,residuals(m.mutes,type="martingale")),col='blue',lwd=2.5)
lines(smooth.spline(rna.nonm,residuals(m.non.mutes,type="martingale")),col='green',lwd=2.5)
legend(x=5,y=1.5,legend=c(paste0('All (n = ',length(rna),")"),paste0('Mutés (n = ',length(rna.m),")"),paste0('Non mutés (n = ',length(rna.nonm),")")),col=c('red','blue','green'),lty=1)
}
```

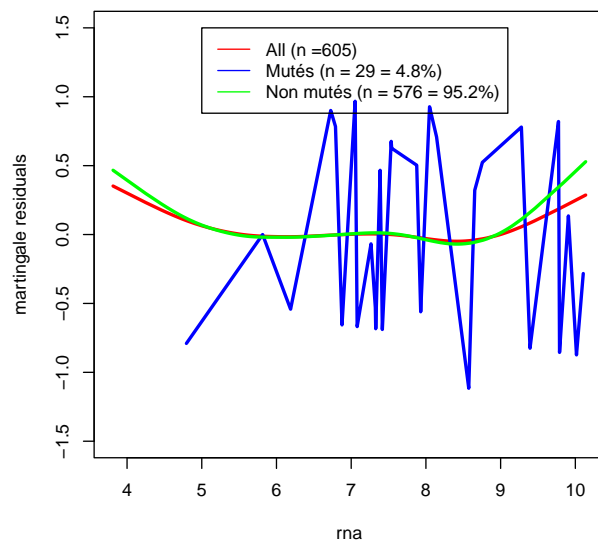
Martingale residuals according to RNA level of BCL2



Martingale residuals according to RNA level of BCL6



Martingale residuals according to RNA level of MYC



Martingale residuals according to RNA level of TP53

