COVID-19 Machine Learning-Based Rapid Diagnosis From Laboratory Tests

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```r
library(png)
library(grid)
img <- readPNG("Project_Title.png")
 grid.raster(img)
```

```r
#Install Packages
#install.packages("ggthemes")
#install.packages("viridis")
#install.packages("e1071")
#install.packages("png")
#install.packages("grid")
```

COVID-19 Machine Learning-Based Rapid Diagnosis From Laboratory Tests

Objectives

This work has the objective to predict confirmed COVID-19 cases among suspected cases based on commonly collected laboratory exams.

We consider the following question:

Based on the results of laboratory tests commonly collected for a suspected COVID-19 case during an annual physical exam, would it be possible to predict the test result for SARS-Cov-2 (positive/negative)?

Data Set

The dataset contains anonymized data from patients seen at the Hospital Israelita Albert Einstein in São Paulo, Brazil, and who had samples collected to perform the SARS-CoV-2 RT-PCR and additional laboratory tests during a visit to the hospital.

```r
# load aux functions
source("00-Funcs.R")

#load input dataset
library("readxl");
data <- as.data.frame(read_excel("dataset.xlsx"), stringAsFactors=F)
```

The dataset contains 109 variables (predictors), a Patient ID and one target outcome variable, which indicates whether the patient tested positive/negative for SARS-Cov-2.

Data Preparation

Data cleaning procedures:

1. Make variable names syntactically valid by removing special characters, spaces and symbols
2. Convert strings that represent missing data to **NA**, namely the following values: 'Não Realizado' and 'not_done'
3. Convert string categorical values to factors
4. Convert the variable **Urine...pH** to numeric, as it contains a mix of string and numeric values in the input data

```r
# make variable names syntactically valid
names(data) <- make.names(names(data))
data$Patient.ID <- NULL

# Replace column values that should be empty for NA
data[data=='Não Realizado'] <- NA
data[data=='not_done'] <- NA
data[data=='<1000'] <- 500

data$Urine...Leukocytes <- as.integer(data$Urine...Leukocytes)
data$Urine...pH <- as.integer(data$Urine...pH)
```

```r
# convert string values to factors
ind <- sapply(data, is.character)
data[ind] <- lapply(data[ind], factor)

data$Lipase.dosage <- as.factor(data$Lipase.dosage)
```

Our outcome variable is given by the name **SARS.Cov.2.exam.result**, it is a binary variable which indicates whether the patient tested positive or negative for the virus SARS-COV2. We convert this variable such that $SARS.Cov.2.exam.result = 1$, if the patient tested positive and $SARS.Cov.2.exam.result = 0$, otherwise.

```r
outcome.var<-"SARS.Cov.2.exam.result"
data[, outcome.var] <- as.integer(data[, outcome.var]) - 1
```

We decide to remove variables that have too many missing data points (>= 95%). We also remove samples that are too sparse in laboratory data, we choose to keep negative samples that have at least 10 variables with data points available.

```r
data.deleted<-data
data.size<-nrow(data)
not.na.pct <- 0.05
data <- delete.na(data, n = data.size * not.na.pct, is.row = FALSE)


data.pos <- data[data$SARS.Cov.2.exam.result==1,]
data.neg <-  data[data$SARS.Cov.2.exam.result==0,]

### delete poor samples
min.non.na.vars <- 10
data.neg <- delete.na(data.neg, n = min.non.na.vars)

data <- rbind(data.pos, data.neg)
```

Hence, We have removed a lot of variables showing as below:

```r
print(setdiff(names(data.deleted), names(data)))
```

```
##  [1] "Serum.Glucose"
##  [2] "Mycoplasma.pneumoniae"
##  [3] "Alanine.transaminase"
##  [4] "Aspartate.transaminase"
##  [5] "Gamma.glutamyltransferase."
##  [6] "Total.Bilirubin"
##  [7] "Direct.Bilirubin"
##  [8] "Indirect.Bilirubin"
##  [9] "Alkaline.phosphatase"
## [10] "Ionized.calcium."
## [11] "Magnesium"
## [12] "pCO2..venous.blood.gas.analysis."
## [13] "Hb.saturation..venous.blood.gas.analysis."
## [14] "Base.excess..venous.blood.gas.analysis."
## [15] "pO2..venous.blood.gas.analysis."
## [16] "Fio2..venous.blood.gas.analysis."
## [17] "Total.CO2..venous.blood.gas.analysis."
## [18] "pH..venous.blood.gas.analysis."
## [19] "HCO3..venous.blood.gas.analysis."
## [20] "Rods.."
## [21] "Segmented"
## [22] "Promyelocytes"
## [23] "Metamyelocytes"
## [24] "Myelocytes"
## [25] "Myeloblasts"
## [26] "Urine...Esterase"
## [27] "Urine...Aspect"
## [28] "Urine...pH"
## [29] "Urine...Hemoglobin"
## [30] "Urine...Bile.pigments"
## [31] "Urine...Ketone.Bodies"
## [32] "Urine...Nitrite"
## [33] "Urine...Density"
## [34] "Urine...Urobilinogen"
## [35] "Urine...Protein"
## [36] "Urine...Sugar"
## [37] "Urine...Leukocytes"
## [38] "Urine...Crystals"
## [39] "Urine...Red.blood.cells"
## [40] "Urine...Hyaline.cylinders"
## [41] "Urine...Granular.cylinders"
## [42] "Urine...Yeasts"
## [43] "Urine...Color"
## [44] "Partial.thromboplastin.time..PTT.."
## [45] "Relationship..Patient.Normal."
## [46] "International.normalized.ratio..INR."
## [47] "Lactic.Dehydrogenase"
## [48] "Prothrombin.time..PT...Activity"
## [49] "Vitamin.B12"
## [50] "Creatine.phosphokinase..CPK.."
## [51] "Ferritin"
## [52] "Arterial.Lactic.Acid"
## [53] "Lipase.dosage"
## [54] "D.Dimer"
## [55] "Albumin"
## [56] "Hb.saturation..arterial.blood.gases."
## [57] "pCO2..arterial.blood.gas.analysis."
## [58] "Base.excess..arterial.blood.gas.analysis."
## [59] "pH..arterial.blood.gas.analysis."
## [60] "Total.CO2..arterial.blood.gas.analysis."
## [61] "HCO3..arterial.blood.gas.analysis."
## [62] "pO2..arterial.blood.gas.analysis."
## [63] "Arteiral.Fio2"
## [64] "Phosphor"
## [65] "ctO2..arterial.blood.gas.analysis."
```

And We keep the remaning variables for the prediction:

```r
print(names(data))
```

```
##  [1] "Patient.age.quantile"
##  [2] "SARS.Cov.2.exam.result"
##  [3] "Patient.addmited.to.regular.ward..1.yes..0.no."
##  [4] "Patient.addmited.to.semi.intensive.unit..1.yes..0.no."
##  [5] "Patient.addmited.to.intensive.care.unit..1.yes..0.no."
##  [6] "Hematocrit"
##  [7] "Hemoglobin"
##  [8] "Platelets"
##  [9] "Mean.platelet.volume"
## [10] "Red.blood.Cells"
## [11] "Lymphocytes"
## [12] "Mean.corpuscular.hemoglobin.concentration..MCHC."
## [13] "Leukocytes"
## [14] "Basophils"
## [15] "Mean.corpuscular.hemoglobin..MCH."
## [16] "Eosinophils"
## [17] "Mean.corpuscular.volume..MCV."
## [18] "Monocytes"
## [19] "Red.blood.cell.distribution.width..RDW."
## [20] "Respiratory.Syncytial.Virus"
## [21] "Influenza.A"
## [22] "Influenza.B"
## [23] "Parainfluenza.1"
## [24] "CoronavirusNL63"
## [25] "Rhinovirus.Enterovirus"
## [26] "Coronavirus.HKU1"
## [27] "Parainfluenza.3"
## [28] "Chlamydophila.pneumoniae"
## [29] "Adenovirus"
## [30] "Parainfluenza.4"
## [31] "Coronavirus229E"
## [32] "CoronavirusOC43"
## [33] "Inf.A.H1N1.2009"
## [34] "Bordetella.pertussis"
## [35] "Metapneumovirus"
## [36] "Parainfluenza.2"
## [37] "Neutrophils"
## [38] "Urea"
## [39] "Proteina.C.reativa.mg.dL"
## [40] "Creatinine"
## [41] "Potassium"
## [42] "Sodium"
## [43] "Influenza.B..rapid.test"
## [44] "Influenza.A..rapid.test"
## [45] "Strepto.A"
```

Predictive Analysis

Model Training

To predict the likelihood that a patient is infected with the SARS-Cov2 virus, we split the dataset randomly into training and testing tests in a train-to-test split ratio of 4/5. We decompose the dataset such that the outcome variable also follows the same split ratio between train and test sets.

```
library(caret)
```

```
## Loading required package: lattice
```

```
## Loading required package: ggplot2
```

```
set.seed(10^7)
SPLIT.RATIO <- 4/5
train.index <- createDataPartition(data$SARS.Cov.2.exam.result, p = SPLIT.RATIO , list = FALSE)
train <- data[train.index,]
test <- data[-train.index,]
```

We train a GBM-Gradient Boosting Machine- to produce a prediction model in the form of an ensemble of weak prediction models, typically decision treesmodel using the remaining dataset variables as predictors. We also define a relatively high bag fraction which defines the fraction of the training set observations randomly selected to propose the next tree in the expansion. This introduces randomnesses into the model fit and reduces overfitting.

```
train.features <- setdiff(names(train), c(outcome.var, "Patient.ID"))
myformula = as.formula(paste0(outcome.var," ~ ", paste0(train.features, collapse="+")))

BAG.FRACTION <- 0.8
library(gbm)
```

```
## Loaded gbm 2.1.8
```

```
gbm.model = gbm(myformula, data = train,
                n.trees = 500 ,
                bag.fraction = BAG.FRACTION,
                verbose=FALSE)
```

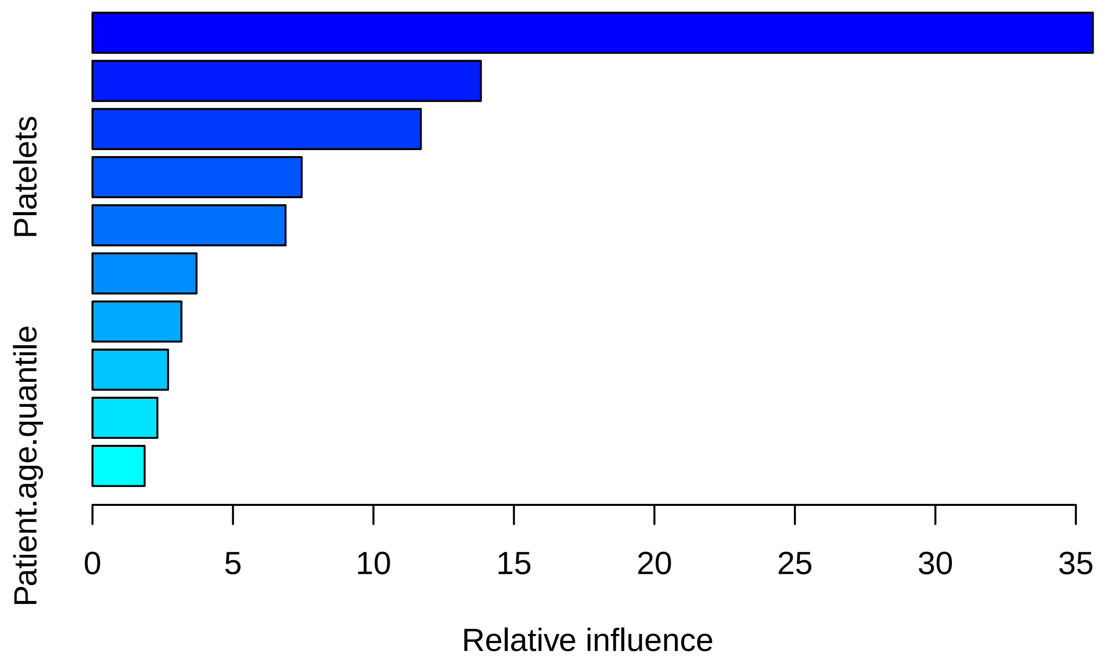
```
## Distribution not specified, assuming bernoulli ...
```

```
## Warning in gbm.fit(x = x, y = y, offset = offset, distribution = distribution, :
## variable 35: Parainfluenza.2 has no variation.
```

Model Interpretability

We evaluate model interpretability by looking at the relative influence of the top 10 most important variables. The importance measures are normalized and they are based on the number of times a variable is selected for tree splitting, weighted by the improvement to the model as a result of each split, and averaged over all trees.

```
model.summary<-summary(gbm.model, cBars=10)
```



```
print(model.summary[1:15,])
```

```
##                                                                                var
## Rhinovirus.Enterovirus                                          Rhinovirus.Enterovirus
## Respiratory.Syncytial.Virus                                Respiratory.Syncytial.Virus
## Leukocytes                                                                  Leukocytes
## Platelets                                                                    Platelets
## Inf.A.H1N1.2009                                                        Inf.A.H1N1.2009
## Monocytes                                                                    Monocytes
## Patient.addmited.to.regular.ward..1.yes..0.no. Patient.addmited.to.regular.ward..1.yes..0.no.
## Eosinophils                                                                Eosinophils
## Influenza.B                                                                Influenza.B
## Patient.age.quantile                                              Patient.age.quantile
## Red.blood.Cells                                                        Red.blood.Cells
## Proteina.C.reativa.mg.dL                                      Proteina.C.reativa.mg.dL
## Sodium                                                                          Sodium
## Urea                                                                              Urea
## Mean.corpuscular.volume..MCV.                            Mean.corpuscular.volume..MCV.
##                                                   rel.inf
## Rhinovirus.Enterovirus                         35.6047711
## Respiratory.Syncytial.Virus                    13.8232937
## Leukocytes                                     11.6870221
## Platelets                                       7.4455164
## Inf.A.H1N1.2009                               6.8708578
## Monocytes                                     3.7019542
## Patient.addmited.to.regular.ward..1.yes..0.no. 3.1646994
## Eosinophils                                   2.6903773
## Influenza.B                                   2.3094928
## Patient.age.quantile                          1.8545524
## Red.blood.Cells                               1.1346368
## Proteina.C.reativa.mg.dL                      1.0127916
## Sodium                                        0.9198511
## Urea                                          0.7646602
## Mean.corpuscular.volume..MCV.                 0.7561461
```

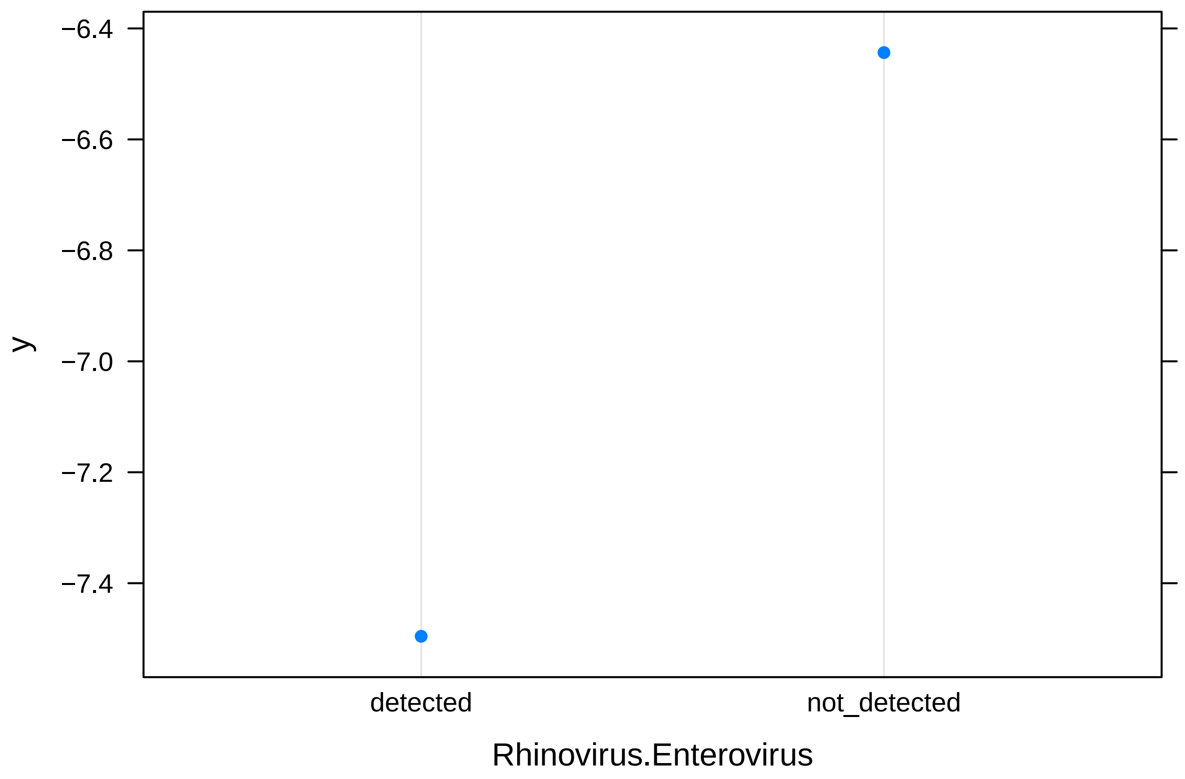
We also analyze the conditional probability plots of the top 5 most important variables below, where the x-axis represents the predictor and the y-axis represents the likelihood of infection .

```r
attach(mtcars)
```

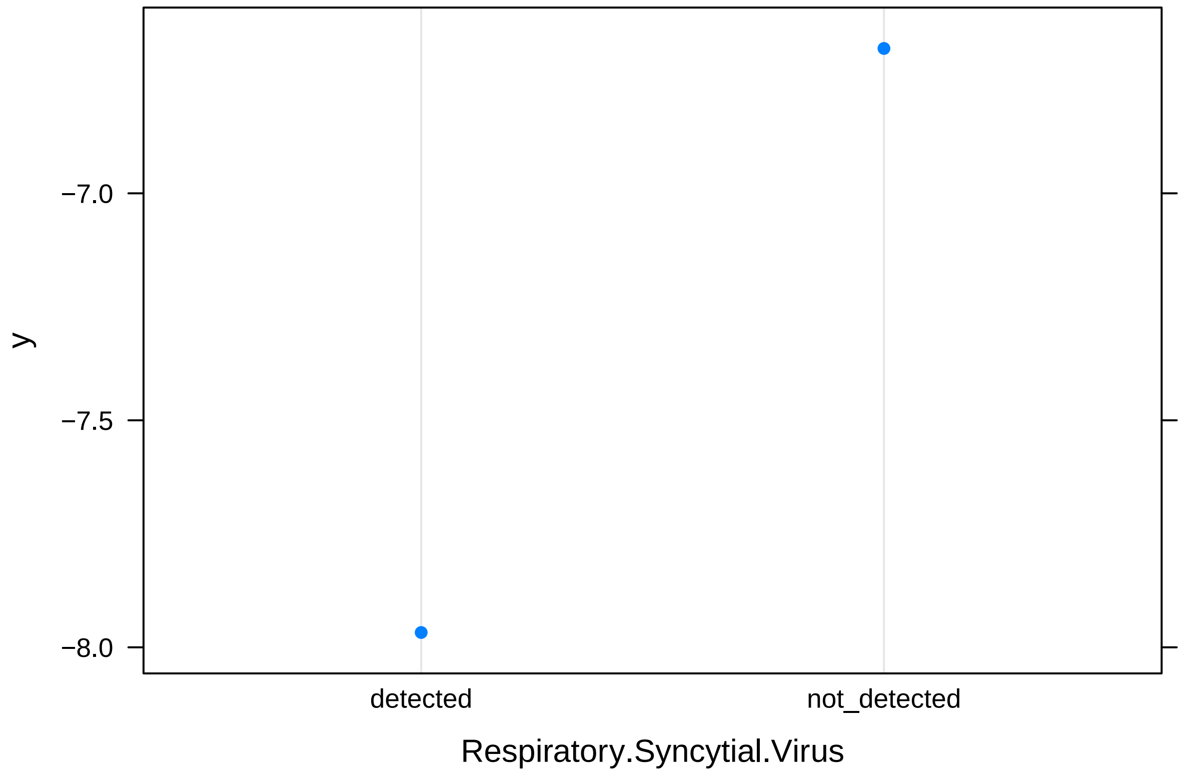
```
## The following object is masked from package:ggplot2:
##
##     mpg
```

```r
par(mfrow=c(2,2))
lapply(as.character(model.summary$var[1:5]), plot.gbm, x=gbm.model)
```

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

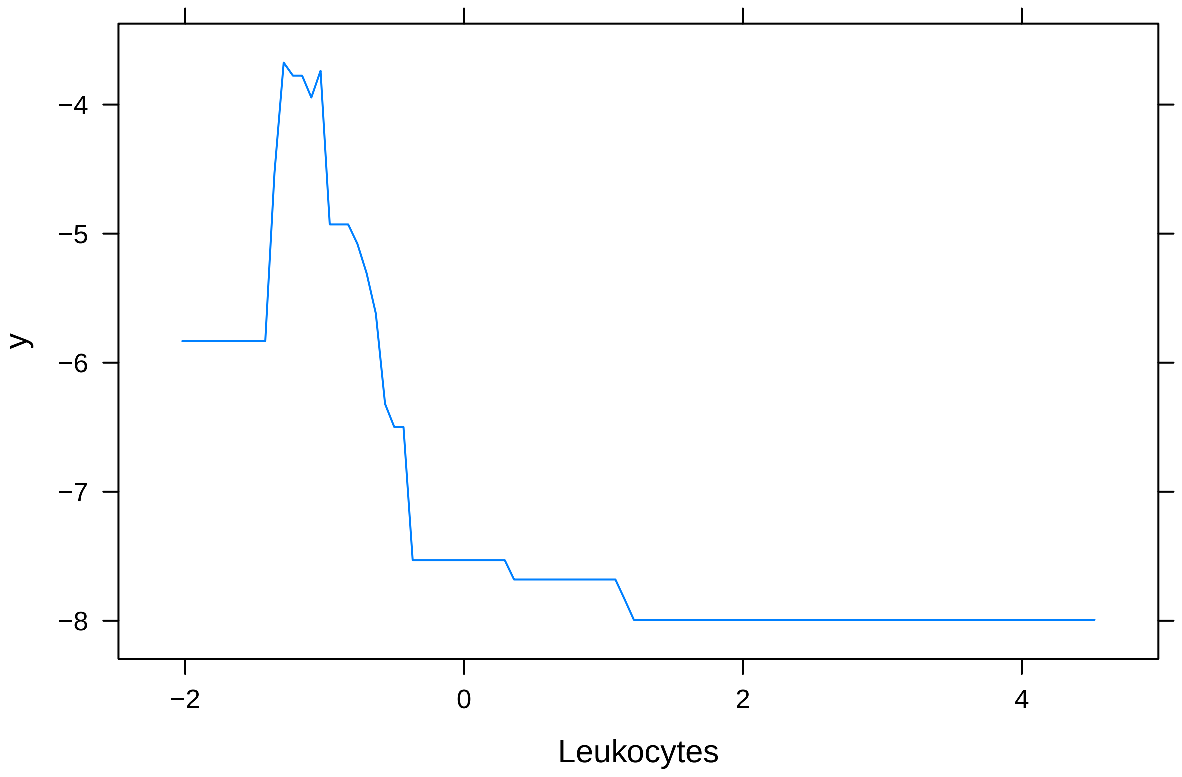


```
##
## [[2]]
```

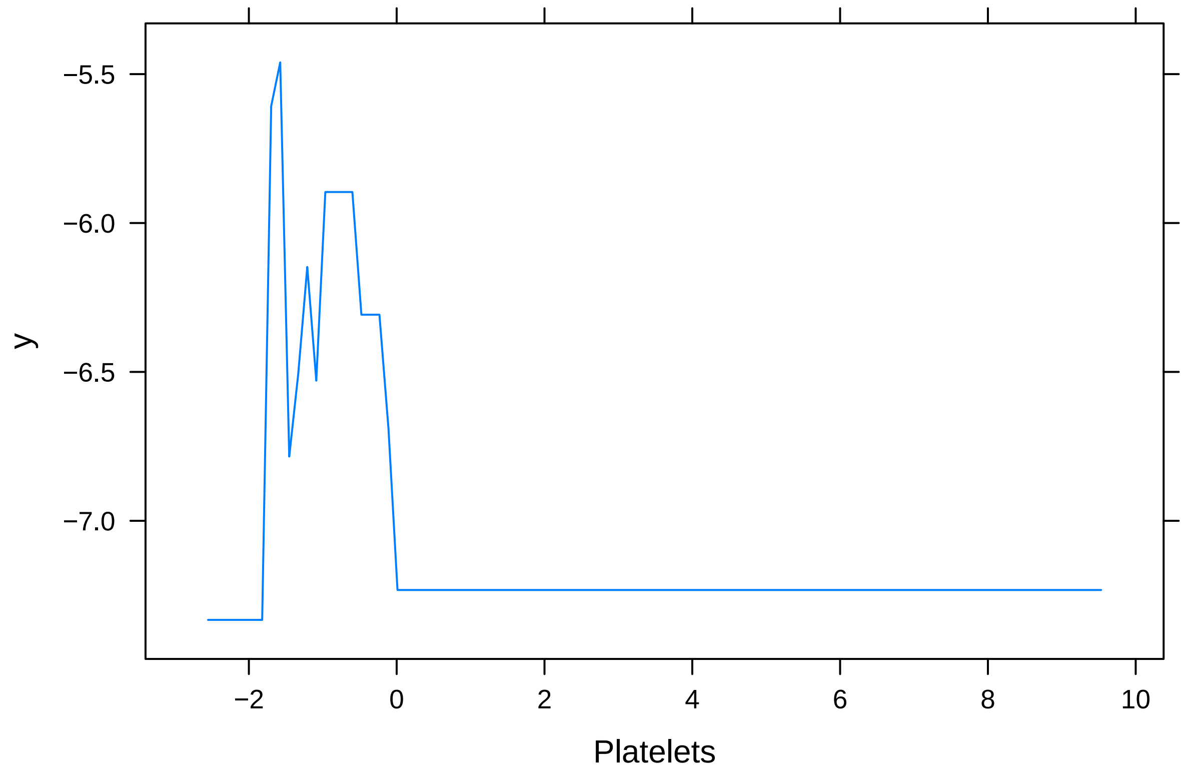


−7.0
−7.5
−8.0
y
detected
not_detected
Respiratory.Syncytial.Virus

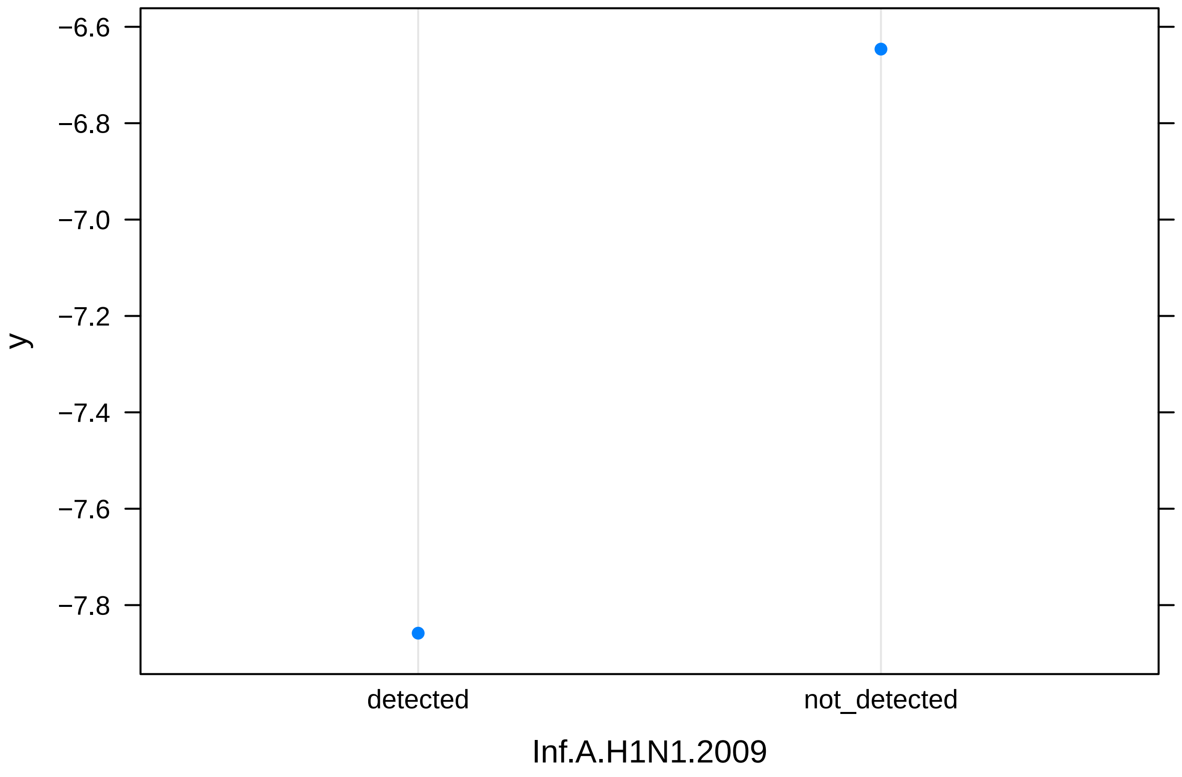
```
##
## [[3]]
```



```
##
## [[4]]
```



```
##
## [[5]]
```



We observe the following:

- When Rhinovirus.Enterovirus, Influenza.B or Inf.A.H1N1.2009 are not detected, patients are more likely to test positive for SARS-COV2
- Patients with low Leukocytes or Platelets are more likely to test positive for SARS-COV2

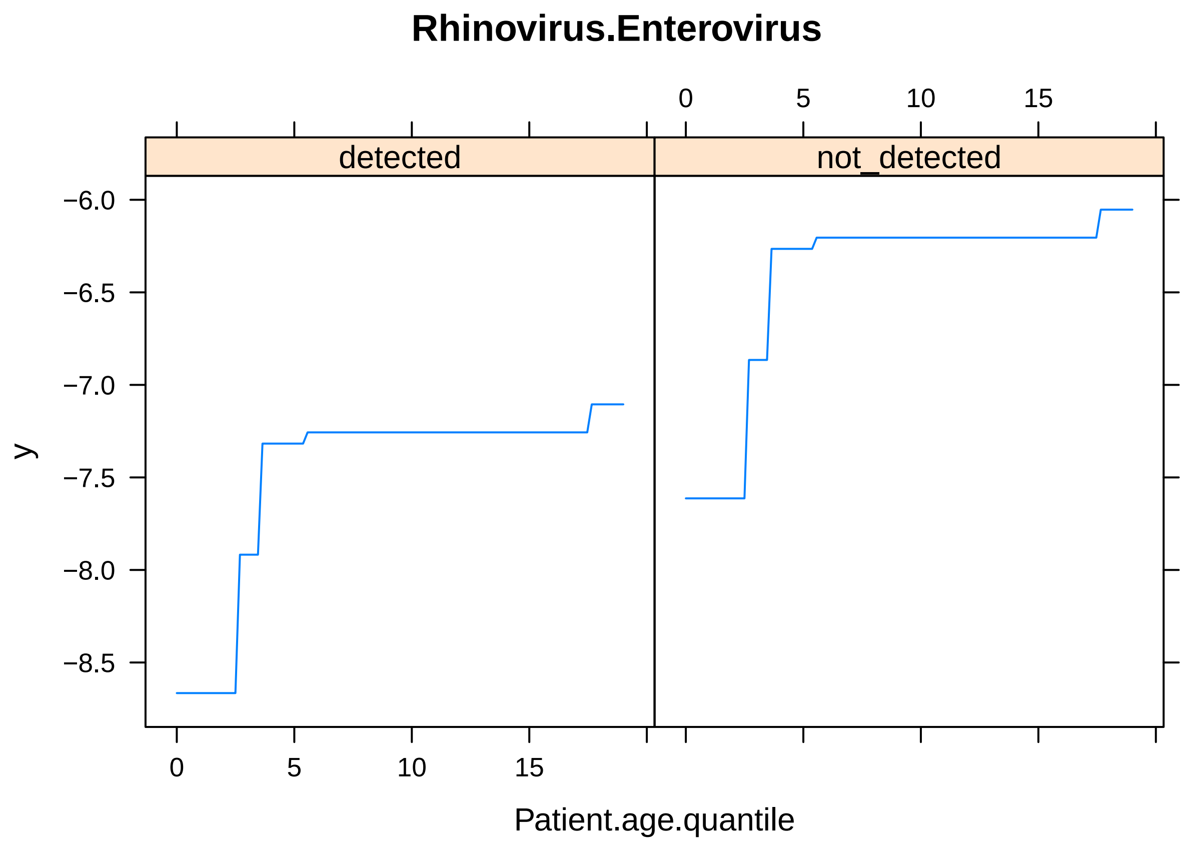
One variable that is widely discussed as a leading indicator of severe COVID-19 cases is age. Hence, we analyze the correlationship between the variable *age_quantile* and the top 5 most important variables discussed previously.

We observe that a patient's age quantile can increase the likelihood of SARS-COV2 infection regarding top 5 variables.

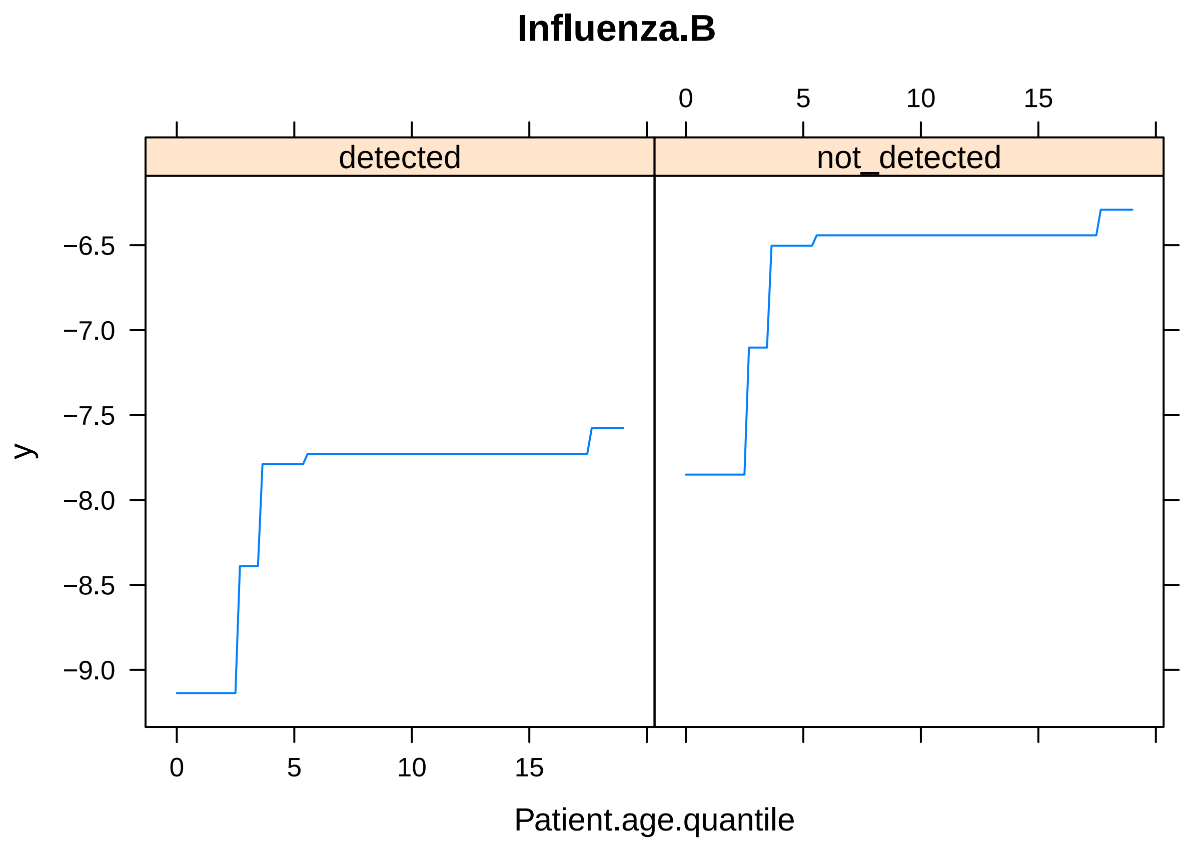
```
library(viridis)
```

```
## Loading required package: viridisLite
```

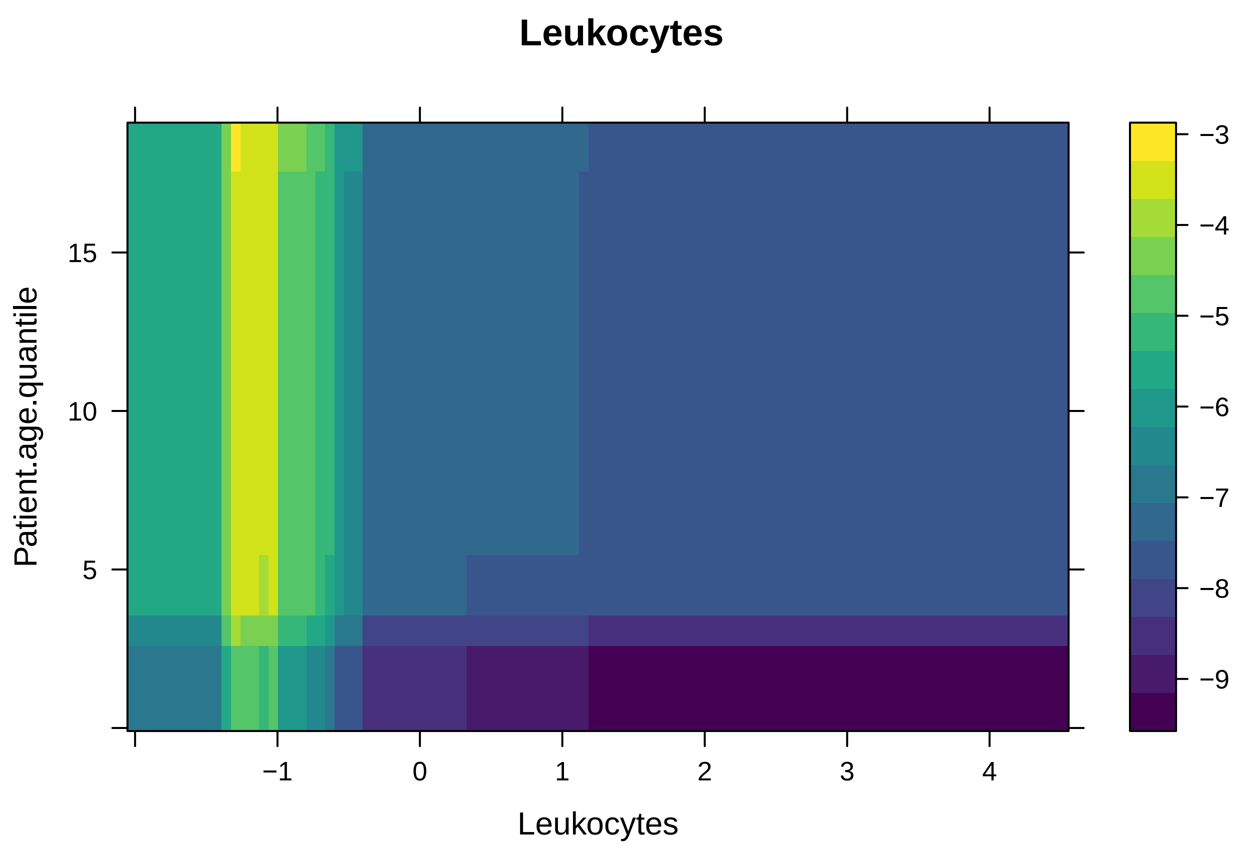
```
plot.gbm(gbm.model, i.var = c(as.character(model.summary$var[1]), 'Patient.age.quantile'),  main="Rhino
```



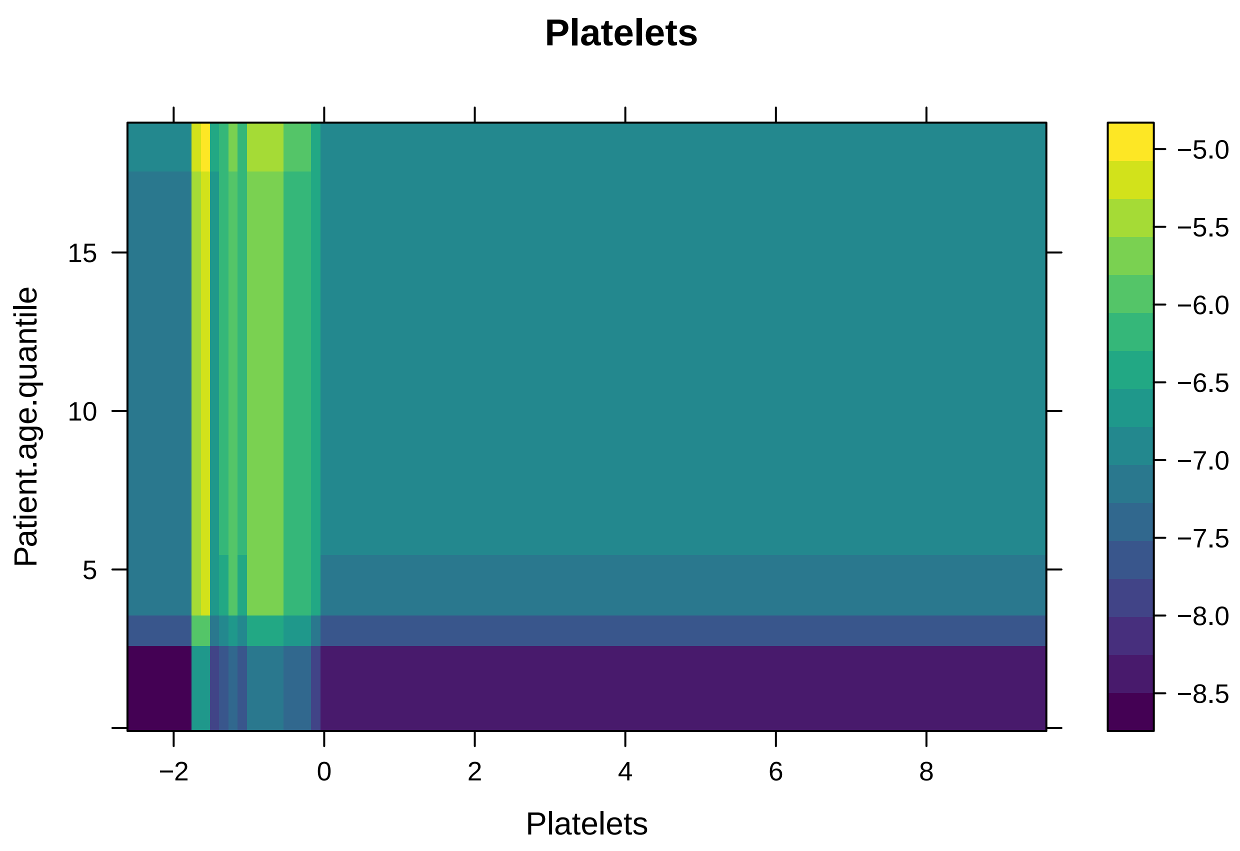
```
plot.gbm(gbm.model, i.var = c(as.character(model.summary$var[2]), 'Patient.age.quantile'),  main="Influ
```



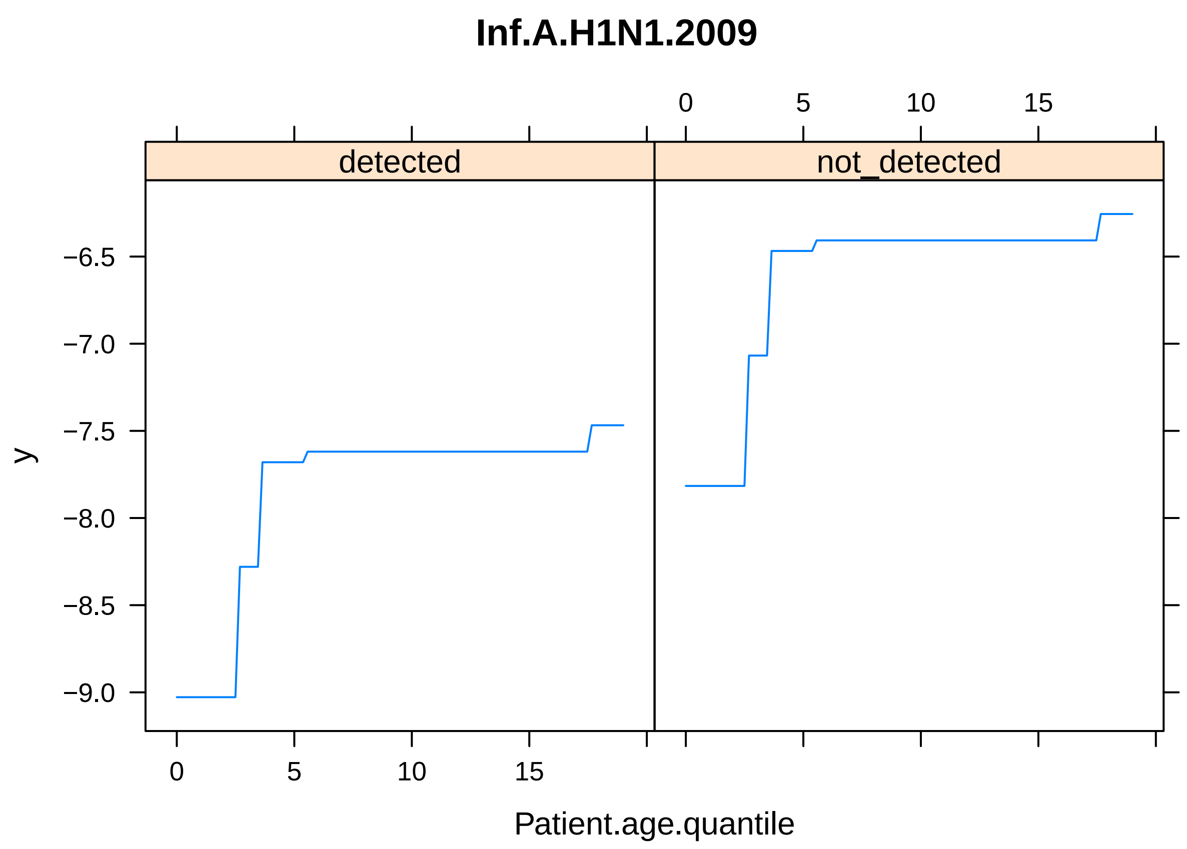
```
plot.gbm(gbm.model, i.var = c(as.character(model.summary$var[3]), 'Patient.age.quantile'),  main="Leuko
```



```
plot.gbm(gbm.model, i.var = c(as.character(model.summary$var[4]), 'Patient.age.quantile'),  main="Platel
```



```
plot.gbm(gbm.model, i.var = c(as.character(model.summary$var[5]), 'Patient.age.quantile'),  main="Inf.A
```



Prediction

We apply the trained model to the test dataset. We observe that the model performs very well with an AUC of 94%. However, the determination of model's specificity and sensitivity relies on the definition of a likelihood threshold to determine patients that will be considered as likely positive COVID-19 cases among suspected cases.

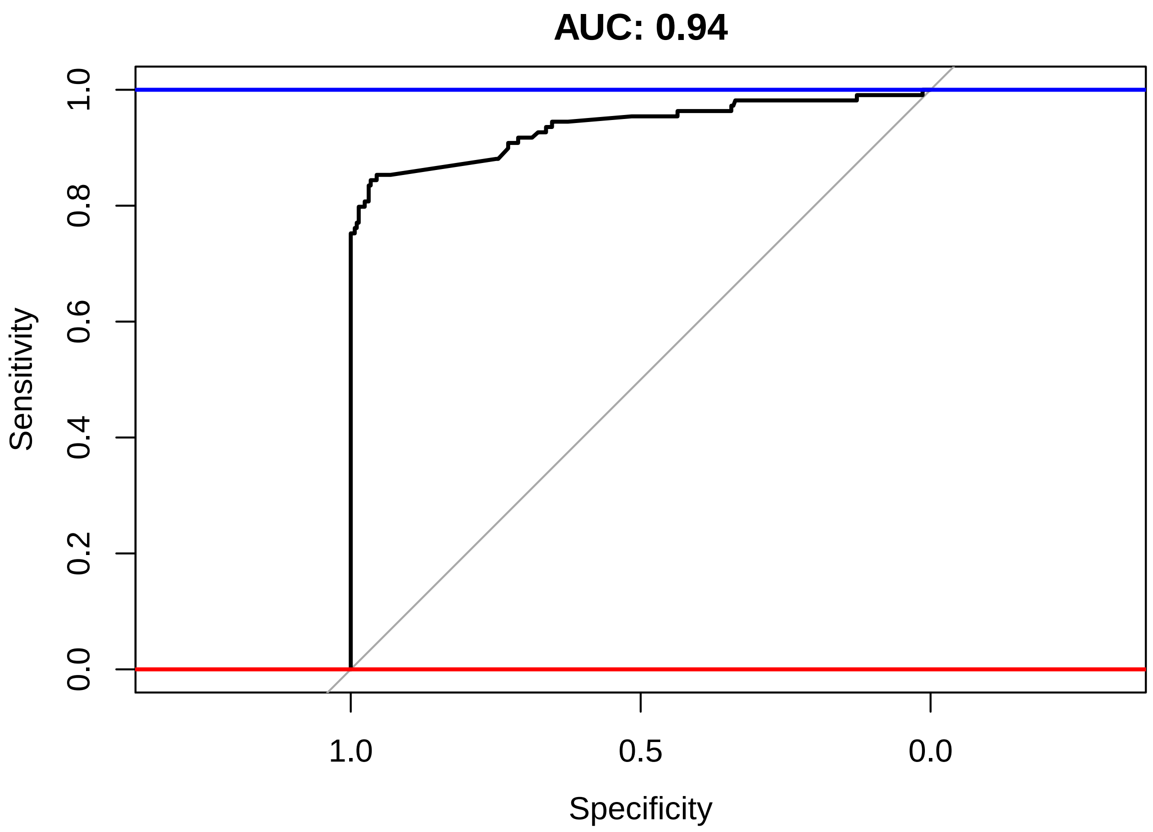
```
library(pROC)
```

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

##
## Attaching package: 'pROC'

## The following objects are masked from 'package:stats':
##
##     cov, smooth, var
```

```
test.current.prediction <-predict(gbm.model, newdata = test, n.trees = 500,
                                   type="response")

x.roc<-roc(response=test$SARS.Cov.2.exam.result, predictor=test.current.prediction)
```

```
## Setting levels: control = 0, case = 1
## Setting direction: controls < cases
```

```r
plot(x.roc, ylim=c(0,1),
     main=paste('AUC:',round(x.roc$auc[[1]],2)))
abline(h=1,col='blue',lwd=2)
abline(h=0,col='red',lwd=2)
```



A model with high sensitivity achieves good results in finding positive patients among those true positive patients. However, the number of patients predicted to be positive can be too high and impact the model's specificity.

Moreover, the hospital may not have enough resources to apply the necessary procedures for all patients assigned with a positive label if that number is too high. Hence, an ideal model is one that is well-balanced, i.e., one that has high sensitivity but it does not over-assign patients with positive labels.

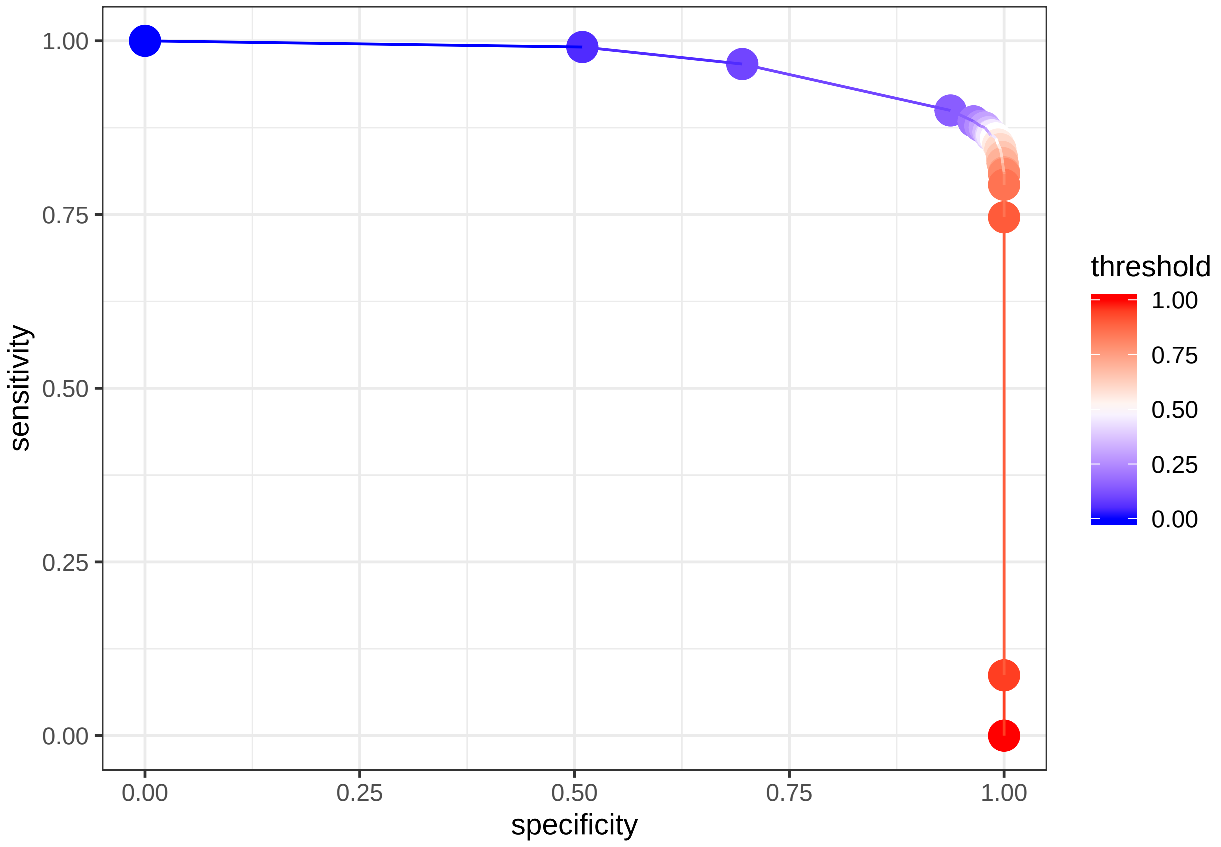
```r
train.current.prediction <-predict(gbm.model, newdata = train, n.trees = 500,
                                   type="response")
x.roc<-roc(response=train$SARS.Cov.2.exam.result, predictor=train.current.prediction)
```

```
## Setting levels: control = 0, case = 1
```

```
## Setting direction: controls < cases
```

```r
cc <- coords(x.roc, seq(from = 0, to = 1, by = 0.05), ret=c("sensitivity", "specificity", "threshold"),
library(ggplot2)
library(ggthemes)
mid<-median(cc$threshold)
```

```r
ggplot(cc, aes(x=specificity, y=sensitivity,
               color=threshold,
               fill=threshold)) + geom_point(size = 5) + geom_line() +
  theme_bw() +
  scale_color_gradient2(midpoint=mid, low="blue", mid="white", high="red", space ="Lab" ) +
  scale_fill_gradient2(midpoint=mid, low="blue", mid="white", high="red", space ="Lab" )
```



Scenario 1: High availability of resources

In Scenario 1, we assume that the hospital has high availability of resources. In that way, the model can be relaxed and over-estimate the number of positive cases. Hence, our objective function is one that maximizes sensitivity.

We use the train data to select the threshold that maximizes model's sensitivity. We then apply this threshold in the predicted probabilities in the test set. The procedure returns a probability threshold of 5.8% and the model presents a high sensitivity value of 98%, as intended.

However, the high recall comes at the cost of specificity, which presents a low value of 21%. Moreover, about 79% of the patients from the test set were labeled as positive, hence the model has limited usage as a prioritization tool.

```
library(pROC)
train.current.prediction <-predict(gbm.model, newdata = train, n.trees = 500,
                              type="response")


best.th<-coords(roc=x.roc, x=1, input="sensitivity", transpose = FALSE)$threshold
print(paste0("Optimal threshold = ", best.th))
```

```
## [1] "Optimal threshold = 0.00587137563843436"
```

```
oos.current.prediction <-predict(gbm.model, newdata = test, n.trees = 500,
                                 type="response")

print(paste0("Pct patients predicted as infected = ", sum(oos.current.prediction > best.th) / length(oos
```

```
## [1] "Pct patients predicted as infected = 0.8375"
```

```
oos.x.roc<-roc(test$SARS.Cov.2.exam.result, predictor=oos.current.prediction)
```

```
## Setting levels: control = 0, case = 1
```

```
## Setting direction: controls < cases
```

```
BinModelPerformance(oos.current.prediction, best.th, test$SARS.Cov.2.exam.result)
```

```
##           Reference
## Prediction positive negative
##   positive      107      228
##   negative        2       63
```

```
##       ROC      Sens      Spec
## 0.9358586 0.9816514 0.2164948
```

Scenario 2: Limited resources

In Scenario 2, we assume an environment with limited resources and hence a reduction in model's sensitivity is acceptable if we can obtain a well-balanced model, overall. For that purpose, we choose as objective function one that maximizes the Youden J's statistic defined as $max(sensitivity + specificy)$.

After making a prediction on the test set, we will then choose a threshold from the train set that maximizes the Youden J's statistic to achieve a well-balanced model. We observe that the model under Scenario 2 now delivers a Sensitivity of 82% compared to 98% from Scenario 1. However, it returns a Specificity of 97% while maintaining a high AUC of 94% (as the choice of threshold does not influence the AUC), hence delivering a more well-balanced model as expected. Moreover, now the model only assigns 28% of the test set with positive labels, showing to be useful as a potential patient prioritization tool.

```
oos.current.prediction <-predict(gbm.model, newdata = test, n.trees = 500,
                                 type="response")
```

```r
#obtain optimum threshold
best.th<-coords(x.roc, "best", ret="threshold", transpose = FALSE,
                best.method="youden")$threshold
print(paste0("Optimal threshold = ", best.th))
```

```
## [1] "Optimal threshold = 0.30444438520008"
```

```r
print(paste0("Pct patients predicted as infected = ",
             sum(oos.current.prediction > best.th) / length(oos.current.prediction)))
```

```
## [1] "Pct patients predicted as infected = 0.2475"
```

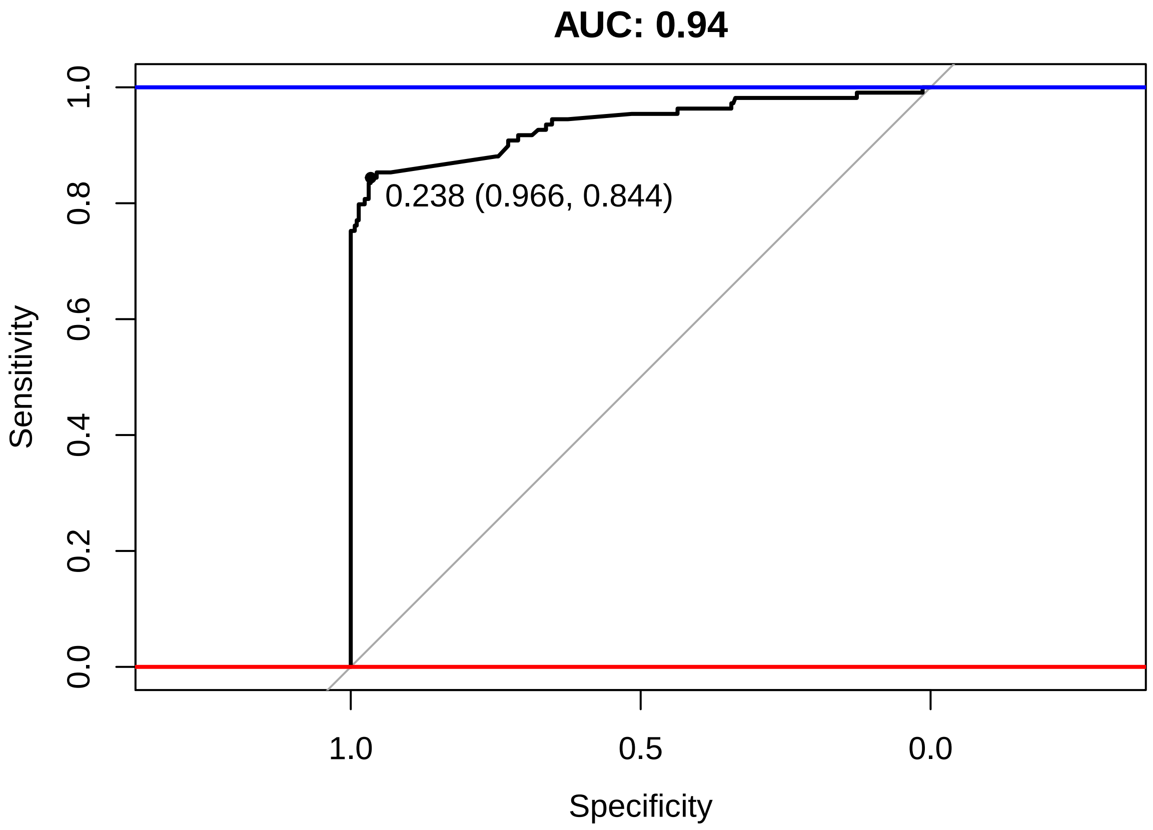
```r
BinModelPerformance(oos.current.prediction, best.th,  test$SARS.Cov.2.exam.result)
```

```
##           Reference
## Prediction positive negative
##   positive       90        9
##   negative       19      282

##       ROC      Sens      Spec
## 0.9358586 0.8256881 0.9690722
```

```r
oos.x.roc<-roc(test$SARS.Cov.2.exam.result, predictor=oos.current.prediction)
```

```
## Setting levels: control = 0, case = 1

## Setting direction: controls < cases
```

```r
# OUT-OF-SAMPLE ROC
plot(oos.x.roc, ylim=c(0,1), print.thres="best", print.thres.best.method="youden",
     main=paste('AUC:',round(oos.x.roc$auc[[1]],2)))
abline(h=1,col='blue',lwd=2)
abline(h=0,col='red',lwd=2)
```



Conclusion

The model's output can be used as a tool for prioritization and to support further medical decision making processes. On a periodic basis, input parameters and hospital's policy can be updated depending on health system conditions

The model has high interpretability further showing that patients admitted with COVID-19 symptoms who tested negative for Rhinovirus Enterovirus, Influenza B and Inf.A.H1N1.2009 and presented low levels of Leukocytes and Platelets were more likely to test positive for SARS-CoV-2.