Machine Learning Algorithms for Ischemic Heart Disease (IHD) Prediction

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Introduction

Ischemic heart disease (IHD) has been identified as a leading cause of death globally (1). Compelling evidence showed that lifestyle changes could be effective strategies for the secondary prevention of IHD (2). Therefore, to reduce the burden of IHD mortality, an efficient tool for IHD screening and early diagnosis is warranted. A machine learning algorithm that is developed with serum metabolites, cardiometabolic biomarkers, and self-reported phenotypic data is promising in simplifying the process and reducing the cost of IHD screening/diagnosis. IHD status could be accurately detected with a simple blood draw and metabolomic profiling. In this project, I aim to develop such an algorithm using data from a European population.

I will use data from the MetaCardis consortium that recruited participants aged 18-75 years from Denmark, France, and Germany (3). The data was published early this year as the supplementary material of an article on Nature Medicine (3). The original study included 372 individuals with IHD. These IHD cases were further classified into acute coronary syndrome (n = 112), chronic ischemic heart disease (n = 158), and heart failure (n = 102). With a case-control design, the study also included 3 groups of controls matched on various factors. The raw data includes 1,882 observations, including repeated records with the same participant ID but different case-control statuses.

For this project, I will use records from the 372 IHD cases and 372 controls matched on type 2 diabetes (T2D) status and body mass index (BMI). I will also extract data for age, gender, fasting plasma triglycerides, adiponectin, and CRP, systolic and diastolic blood pressure, left ventricular ejection fraction, physical activity level, and 1,513 log-transformed values of serum metabolites.

Exploratory data analysis

After reading in the data, I first filtered the observations to keep the IHD cases and their controls matched by T2D status and BMI. I then merged metabolites data with cardiometabolic biomarkers and self-reported phenotypic data to create a `main` dataset with 744 rows and 1522 columns. I noticed that several participants do not have any metabolites data and, therefore, need to be removed. Additionally, around 30% of participants had missing values for left ventricular ejection fraction and physical activity level. Many machine learning techniques could not be implemented with that many missing values, and it would also not be appropriate to replace the missing values with any arbitrarily selected value. So, I removed these two potential predictors from my analyses. Finally, for variables with less than 10% missing data, I replaced the missing values with the median of the non-missing data. The cleaned `main` dataset had 603 rows and 1522 columns. The first 6 rows of the cleaned `main` dataset were printed in the Appendix.

I then preprocessed the data to remove non-informative predictors with near-zero variances. Given that I planned to train at least one of my algorithms with regression, it would be better to have more predictors normally distributed so that model efficiencies could be improved. I tested the normality of each predictor with the Shapiro-Wilks Test and summarized the p-values. I found that only 101 predictors are normally distributed. It is also noteworthy that the metabolite values from the raw data were all log-transformed. Obviously, log transformation did not normalize the distributions successfully. So, I transformed all metabolite values back to the original scale and used rank-based inverse normal transformation (INT) to normalize

the distributions instead. As examples, histograms showing the distributions of oleoylcarnitine (C18:1) and S-methylcysteine sulfoxide before and after the transformation were shown (Figure 1-2). I ended up having 840 predictors normalized successfully.

Methodologies to use

The outcome that my algorithm aimed to predict is the binary IHD status (non-case = 0, case = 1). Considering that I had 1,422 predictors, I would use principal component analysis (PCA) to reduce dimensions. I would keep principal components that account for at least 70% of variability as new predictors and train an algorithm with logistic regression and an algorithm with K-nearest neighbor (KNN). Given that the principal components are hard to interpret, and algorithms developed based on PCA could be difficult to implement, I would train another KNN-based algorithm with all 1,422 predictors instead. Random forest would be the 4th training method I would use. Finally, I would use an ensemble to combine the results of all four algorithms. For all algorithms, I would evaluate the overall accuracy, sensitivity, specificity, F_1 score, and ROC curve. I would use a β of 2 to calculate the F_1 score because higher sensitivity is more important than high specificity when predicting disease. In other words, a false positive will be less costly than a false negative in this scenario. I would also use cross-validation and bootstrapping to tune the model parameters.

Results

For all the model training and fitting, I partitioned the `main` dataset, which includes IHD case status and all predictors, into a training (`train_set`) and a testing (`test_set`) dataset. Matrices for predictors and cases were also created. I then trained and assessed the models with the following 4 approaches: 1) Logistic regression with principal components as predictors (PCA + Logistic); 2) K-nearest neighbors with principal components as predictors (PCA + KNN); 3) K-nearest neighbors with serum metabolites, cardiometabolic biomarkers, and self-reported phenotypic data as predictors (KNN); and 4) Random forest with serum metabolites, cardiometabolic biomarkers, and self-reported phenotypic data as predictors (RF).

PCA + Logistic regression

The PCA in the training set generated 483 principal components (PCs) from 1,422 predictors, including age, gender, fasting plasma triglycerides, adiponectin, and CRP, systolic and diastolic blood pressure, and 1,415 inverse normal transformed serum metabolites. After evaluating the proportion of variance explained by each PC, I selected the first 69 PCs that accounted for 70% of the total variance as new predictors. The proportion of variance explained by each of the first 69 PCs was printed in the Appendix. I fitted a logistic regression with IHD cases as the dependent variable and the 69 PCs as the independent variables. For the logistic regression, there was no model parameter to tune. To make predictions in the testing set, I used the PC rotations to transform all 1,422 predictors in the testing set into 483 PCs and kept the first 69 PCs. The logistic regression estimates were then used to predict the probability of having IHD cases in the testing set. Participants with a predicted probability of having an IHD over 0.5 were defined as predicted IHD cases.

The overall accuracy of my predicted IHD cases from the logistic regression was 0.875 with a 95% confidence interval of (0.802, 0.928). This algorithm had a sensitivity of 0.892, a specificity of 0.854, and an F_1 score of 0.890. I also plotted the ROC and observed an area under the curve (AUC) of 0.946, which was very high (Figure 3).

PCA + KNN

I then used KNN to train the algorithm with the 69 PCs as predictors. To select the parameter K that maximizes the accuracy, I used 10-fold cross-validation with bootstrapping as the resampling scheme. Given that I have already reduced the dimension to 69 and we only have 603 observations, I did not worry much about the computation time of using 10-fold cross-validation. I fitted the model with K values from 2 to 100 with 20 as the increment. After plotting the accuracy under different K values, I was not able to identify a clearly optimized K, given that the curve of accuracy did not go down within the specified K range (Figure 4a). Therefore, I fitted the model with K values from 5 to 150 with 10 as the increment instead. I identified

75 as the K for the maximum accuracy and fitted the model again with this value (Figure 4b). The fitted KNN model was then used to predict the IHD cases in the testing set.

Using the combination of PCA and KNN, the overall accuracy of my predicted IHD cases was 0.842 with a 95% confidence interval of (0.764, 0.902). Compared to the algorithm developed with PCA and logistic regression, this algorithm had a higher sensitivity of 0.923, a lower specificity of 0.746, and a higher F_1 score of 0.898. I plotted the ROC and observed an AUC of 0.889 (Figure 5).

KNN

The previous two algorithms developed based on selected PCs already performed well in predicting IHD cases. However, people who want to implement these two algorithms have to use the PCA rotations to transform their data first. That could increase the burden of using these algorithms, particularly in clinical settings. Also, the PCs no longer have biological meaning and, therefore, could be difficult to interpret. With these concerns, I developed another KNN-based algorithm with 1,422 predictors, including 1,415 serum metabolites.

Given that the sample size of my study is not large, I used 10-fold cross-validation with bootstrapping as the resampling scheme to select the parameter K again. I found 65 as the K that maximized the model accuracy after fitting the model with K values from 5 to 150 with 10 as the increment (Figure 6). I then fitted the model in the training set and predicted the IHD cases in the testing set. The overall accuracy of my predicted IHD cases was 0.800 with a 95% confidence interval of (0.717, 0.868). Compared to the algorithm developed with PCA and KNN, this KNN algorithm had a slightly higher sensitivity of 0.939. But the specificity dropped to 0.636. The F_1 score was 0.894. I plotted the ROC and observed an AUC of 0.897 (Figure 7).

Random forest

The last approach I used to train my model was random forest. It was more computationally intensive because predictors had to be randomly selected using bootstrapping to predict a single tree. To stabilize accuracy, hundreds of trees might need to be predicted. Also, I had to change the number of predictors being sampled at each bootstrap iteration to find the one that maximized the accuracy. Therefore, I started training the model with 15 trees and tuning the number of predictors to be sampled between 10 and 1000 with 100 as the increment. I implemented a 5-fold cross-validation. The plot of error against the number of trees showed that the accuracy improved as I added more trees and stabilized at around 100 trees (Figure 8a & 9a). In my second attempt, I changed the number of trees to be predicted to be 100. The plot of accuracy by the number of randomly sampled predictors did show a maximum point. However, it seems that the range of 10 to 1000 predictors was too large (Figure 8b & 9b). So, I further tuned the number of predictors to be sampled from 10 to 500 with 20 as the increment. It turned out that randomly sampling 150 predictors and predicting 100 trees maximized and stabilized the accuracy of model prediction (Figure 8c & 9c).

The overall accuracy of my predicted IHD cases from the random forest model was 0.900 with a 95% confidence interval of (0.832, 0.947). This algorithm had a high sensitivity of 0.939, a high specificity of 0.855, a high F_1 score of 0.927, and a high AUC of 0.958 (Figure 10).

Conclusion

In this project, I aimed to develop an algorithm that uses serum metabolites, cardiometabolic biomarkers, and self-reported phenotypic data to predict ischemic heart disease (IHD) status in a European population. I obtained my data from a paper published early this year on Nature Medicine (3). For data preprocessing, I removed observations with missing metabolite measures and predictors with at least around 30% of missing data. For predictors with a small amount of missing data, I replaced the missing values with median values. Additionally, predictors with near-zero variance were also excluded. I used 4 approaches to train my model. The first two approaches used PCA to reduce dimension from 1,422 predictors. A logistic regression and a KNN-based algorithm were trained and fitted with the selected 69 PCs. The 3rd approach was also based on KNN but fitted the model with the 1,422 predictors. The last approach used random forest to develop the algorithm. I summarized the sensitivity, specificity, overall accuracy, F_1 score, and AUC of all models in a

table (Table 1). I also conducted an ensemble to combine results from the KNN model and random forest model and showed the performance at the end of the table. ROC curves were plotted on the same figure for comparison (Figure 11 & 12).

According to the table, the two algorithms developed with PCs had lower sensitivity than those trained with the original predictors. The KNN and random forest algorithms both had a very high sensitivity of 0.938. The two algorithms developed with KNN had lower specificity than the others. The random forest model also had a relatively high specificity of 0.855. The KNN-based algorithm with biologically meaningful predictors had the lowest overall accuracy, while the random forest model had the highest overall accuracy. The algorithms with PCs as predictors and used logistic regression for fitting had an overall accuracy of 0.875, while the one using PCs and KNN had an accuracy of 0.842. When evaluating with F_1 score, the random forest model performed the best while the rest three models performed similarly. Finally, the random forest model had the highest AUC, followed by the PCA + KNN model. It is interesting that the ensemble of KNN and random forest did not further improve the model performance. In conclusion, the algorithm developed with random forest performed the best in all measures (Table 1).

My analysis that used 4 different approaches to train the algorithm is successful. I identified the random forest algorithm as the best among the 4 according to all 5 measures. The sensitivity of predicting IHD is particularly high. It is particularly important because we don't want to miss any IHD cases if the patient really has IHD. Early detection could improve the prognosis and lower mortality. Moreover, the high sensitivity of my algorithm is not at the cost of low specificity. The specificity is also reasonably high. That could lower the probability of identifying healthy people as IHD cases and avoid overtreatment. It is also great that a random forest-based algorithm does not require extensive data transformation. Future implementation in clinical settings could be more efficient. If I had more time to spend on this project, I would look for metabolomics data in other populations and develop an algorithm that has higher generalizability.

Reference

1. Tsao, C.W., et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation 145, e153-e639 (2022).

2. Brinks, J., Fowler, A., Franklin, B.A. & Dulai, J. Lifestyle Modification in Secondary Prevention: Beyond Pharmacotherapy. Am J Lifestyle Med 11, 137-152 (2017).

3. Fromentin, S., et al. Microbiome and metabolome features of the cardiometabolic disease spectrum. Nat Med 28, 303-314 (2022).

Appendix

```
library(tidyverse)
library(readxl)
library(caret)
library(RNOmni)
library(pROC)
library(randomForest)
library(kableExtra)

#Read in
meta <- read_excel("/Users/xgu/Documents/Harvard/Fall 2022/BST260/bst260project/41591_2022_1688_MOESM3_
                           sheet = 13, skip = 1, na = "NA", col_types = "guess")
demo <- read_excel("/Users/xgu/Documents/Harvard/Fall 2022/BST260/bst260project/41591_2022_1688_MOESM3_
                   sheet = 10, skip = 1, na = "NA", col_types = c("text", "text", rep("numeric", 22), "

#Filter IHD cases and controls, keep phynotypic data and cardiometabolic biomarkers
demo_new <- demo %>%
```

```
  filter(Status %in% c("IHD372", "MMC372")) %>%
  mutate(case = case_when(Status == "MMC372" ~ 0, TRUE ~ 1),
         Gender = case_when(Gender == "Male" ~ 1, TRUE ~ 0)) %>%
  rename(age = "Age (years)", tag = "Fasting plasma triglycerides (mmol/L)",
         adiponectin = "Fasting plasma adiponectin (mg/L)", crp = "Fasting plasma CRP (mg/L)",
         sbp = "Systolic blood pressure (mmHg)", dbp = "Diastolic blood pressure (mmHg)",
         lvef = "Left ventricular ejection fraction (%)", act = "Physical activity (h/week)") %>%
  select(ID, case, age, tag, adiponectin, crp, sbp, dbp, Gender, lvef, act)

#Filter IHD cases and controls, keep metabolites
meta_new <- meta %>%
  filter(Status %in% c("IHD372", "MMC372")) %>%
  select(-c(Status))

#Merge
main <- demo_new %>%
  left_join(meta_new, by = "ID")

#Check missing
pctmiss <- function(x){
  pctmiss <- sum(is.na(x))/length(x)
  return(pctmiss)
}
miss <- as.data.frame(sapply(main, pctmiss))

#Further filtering and missing replacement
main <- main %>%
  select(-c("lvef", "act")) %>%
  filter(acetate != "NA", spermidine != "NA") %>%
  mutate(tag = case_when(is.na(tag) ~ median(tag, na.rm = TRUE), TRUE ~ tag),
         adiponectin = case_when(is.na(adiponectin) ~ median(adiponectin, na.rm = TRUE), TRUE ~ adipone
         crp = case_when(is.na(crp) ~ median(crp, na.rm = TRUE), TRUE ~ crp),
         sbp = case_when(is.na(sbp) ~ median(sbp, na.rm = TRUE), TRUE ~ sbp),
         dbp = case_when(is.na(dbp) ~ median(dbp, na.rm = TRUE), TRUE ~ dbp))
head(main)
```

```
## # A tibble: 6 x 1,522
##   ID          case   age   tag adipon~1   crp   sbp   dbp Gender acetate acetone
##   <chr>      <dbl> <dbl> <dbl>    <dbl> <dbl> <dbl> <dbl>  <dbl>   <dbl>   <dbl>
## 1 x14MCx1158     0    48 1.00      5.01 0.897  104   60.5      0   -3.91   -3.91
## 2 x14MCx2932     0    49 1.00      4.03 1.11   111   70        0   -3.91   -3.22
## 3 x14MCx2498     0    54 1.48      6.26 2.05   106.  68.5      1   -3.51   -3.51
## 4 x14MCx2237     0    47 0.787     3.44 0.67   138   78        1   -3.91   -4.95
## 5 x30MCx1828     0    66 0.59     11.0  0.427  110.  65.5      0   -3.91   -3.91
## 6 x30MCx1314     0    54 1.41      2.6  1.4    128.  75.5      1   -2.81   -3.91
## # ... with 1,511 more variables: artemisin <dbl>, `beta-sitosterol` <dbl>,
## #   betaine <dbl>, `betaine-aldehyde` <dbl>, butyrylcarnitine <dbl>,
## #   catechol <dbl>, cellotetraose <dbl>, choline <dbl>, `D-trehalose` <dbl>,
## #   `D-lyxose` <dbl>, `D-malate` <dbl>, `D-sorbitol` <dbl>, `D-threitol` <dbl>,
## #   decanoylcarnitine <dbl>, glyceraldehyde <dbl>, ethanol <dbl>,
## #   ethanolamine <dbl>, formate <dbl>, glucoheptonate <dbl>, glycolate <dbl>,
## #   halostachine <dbl>, hydroquinone <dbl>, isovalerylcarnitine <dbl>, ...
```

```r
#Keep the predictors
var <- main %>% select(-c("ID", "case"))

#Identify non-informative predictors with very low variance
nzv <- nearZeroVar(var)
col_index <- setdiff(1:ncol(var), nzv)
length(col_index)
```

```
## [1] 1422
```

```r
#Remove non-informative predictors
var_proc <- var[,col_index]

#Check normality
normality <- data.frame()
for (i in 1:length(colnames(var_proc))){
  normality[i, 1] <- colnames(var_proc)[i]
  normality[i, 2] <- shapiro.test(pull(var_proc[,i]))$p.value
  colnames(normality) <- c("metabolites", "shapiro.p")
}
table(ifelse(normality$shapiro.p >0.05, 1, 0)) #Only 101 normally distributed predictors
```

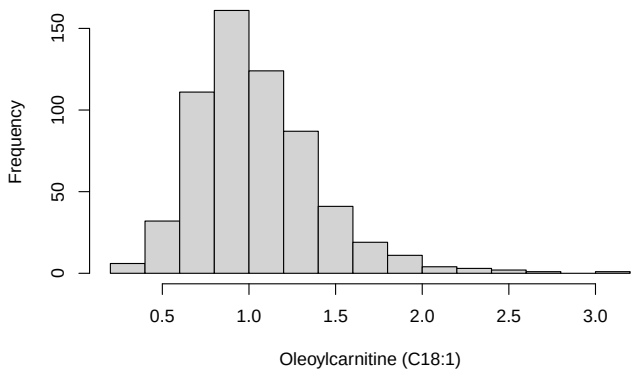
```
##
##    0    1
## 1321  101
```

```r
#which(normality$shapiro.p > 0.05)

#Exponentiate the log metabolites
m <- as.matrix(var_proc[,8:1422])
exp_m <- exp(m)
var_proc_exp <- cbind(var_proc[,1:7], as.data.frame(exp_m))

#Inverse-normal-transform the predictors
var_proc_int <- as.data.frame(sapply(var_proc_exp, RankNorm))

#Check normality again
normality_int <- data.frame()
for (i in 1:length(colnames(tibble(var_proc_int)))){
  normality_int[i, 1] <- colnames(tibble(var_proc_int))[i]
  normality_int[i, 2] <- shapiro.test(pull(tibble(var_proc_int)[,i]))$p.value
  colnames(normality_int) <- c("metabolites", "shapiro.p")
}
table(ifelse(normality_int$shapiro.p >0.05, 1, 0)) #Now have 840 normally distributed predictors
```

```
##
##   0   1
## 582 840
```

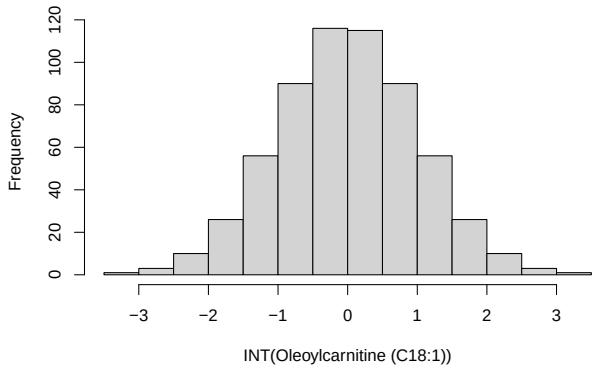
```r
#which(normality_int$shapiro.p > 0.05)

hist(var_proc_exp$`oleoylcarnitine (C18:1)`, main = "Fig 1a. Histogram of oleoylcarnitine", xlab = "Ole
```

Fig 1a. Histogram of oleoylcarnitine



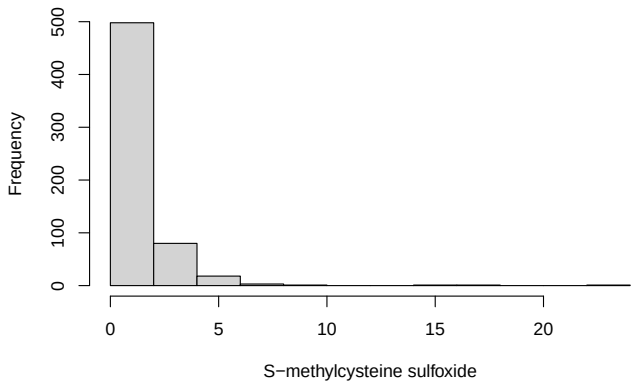

```
hist(var_proc_int$`oleoylcarnitine (C18:1)`, main = "Fig 1b. Histogram of INT-transformed oleoylcarnitin
```

Fig 1b. Histogram of INT−transformed oleoylcarnitine (C18:1))



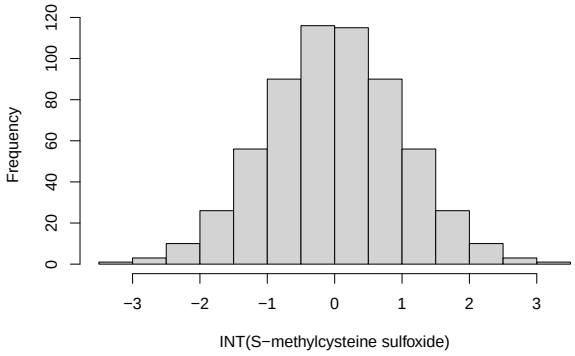

```
hist(var_proc_exp$`S-methylcysteine sulfoxide`, main = "Fig 2a. Histogram of S-methylcysteine sulfoxide
```

Fig 2a. Histogram of S−methylcysteine sulfoxide




```
hist(var_proc_int$`S-methylcysteine sulfoxide`, main = "Fig 2b. Histogram of INT-transformed S-methylcys
```

Fig 2b. Histogram of INT−transformed S−methylcysteine sulfoxide




```
#Split data
set.seed(34324)
main_new <- cbind(main[,1:2], var_proc_int)
train_index <- createDataPartition(main_new$case, times = 1, p = 0.8, list = FALSE)
train_set <- main_new[train_index,]
test_set <- main_new[-train_index,]

#X and Y matrix
x_train <- as.matrix(train_set[,3:1424])
y_train <- factor(train_set$case)
x_test <- as.matrix(test_set[,3:1424])
y_test <- factor(test_set$case)
```

```
#PCA
col_means <- colMeans(x_train)

pca <- prcomp(x_train)
s_pca_3 <- summary(pca)$importance[3,] ##69 pc
head(s_pca_3, 69)
```

```
##     PC1     PC2     PC3     PC4     PC5     PC6     PC7     PC8     PC9    PC10
## 0.09528 0.14187 0.17858 0.21450 0.24215 0.26855 0.29403 0.31393 0.33268 0.35060
##    PC11    PC12    PC13    PC14    PC15    PC16    PC17    PC18    PC19    PC20
## 0.36595 0.37976 0.39264 0.40522 0.41732 0.42849 0.43910 0.44940 0.45886 0.46815
##    PC21    PC22    PC23    PC24    PC25    PC26    PC27    PC28    PC29    PC30
## 0.47727 0.48587 0.49381 0.50149 0.50892 0.51619 0.52337 0.53013 0.53645 0.54261
##    PC31    PC32    PC33    PC34    PC35    PC36    PC37    PC38    PC39    PC40
## 0.54863 0.55446 0.56017 0.56585 0.57135 0.57666 0.58171 0.58672 0.59164 0.59644
##    PC41    PC42    PC43    PC44    PC45    PC46    PC47    PC48    PC49    PC50
## 0.60116 0.60573 0.61013 0.61444 0.61872 0.62298 0.62701 0.63098 0.63494 0.63877
##    PC51    PC52    PC53    PC54    PC55    PC56    PC57    PC58    PC59    PC60
## 0.64255 0.64624 0.64986 0.65345 0.65694 0.66041 0.66380 0.66717 0.67048 0.67372
##    PC61    PC62    PC63    PC64    PC65    PC66    PC67    PC68    PC69
## 0.67691 0.68005 0.68315 0.68620 0.68922 0.69224 0.69519 0.69808 0.70096
```

```
#New PC predictors
pc <- 69
x_train_pc <- pca$x[,1:pc]
```

```
#PCA + Logistic
glm_tmp <- as.data.frame(cbind(train_set$case, x_train_pc)) #Merge cases with PCs
glm_tmp <- glm_tmp %>% rename(case = V1)
fit_glm <- glm(case ~., data = glm_tmp, family = "binomial")
```

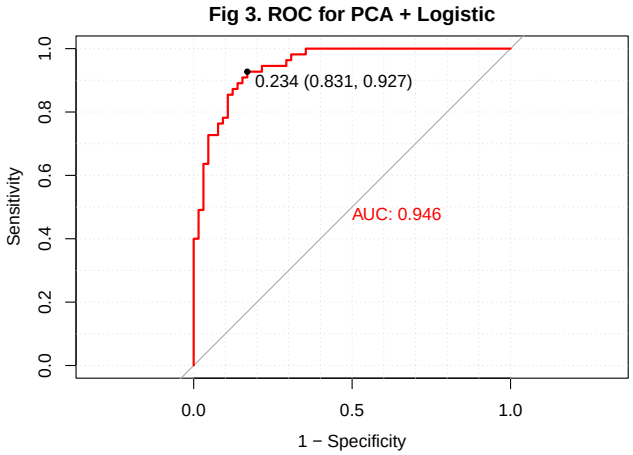
```
x_test_pc_pre <- sweep(x_test,2,col_means) %*% pca$rotation
x_test_pc <- x_test_pc_pre[,1:pc]
y_prob <- predict(fit_glm, as.data.frame(x_test_pc), type = "response")
y_pred_glm <- factor(ifelse(y_prob > 0.5, 1, 0))
confusionMatrix(y_pred_glm, y_test)
```

```
## Confusion Matrix and Statistics
##
##           Reference
## Prediction  0  1
##          0 58  8
##          1  7 47
##
##                Accuracy : 0.875
##                  95% CI : (0.8022, 0.9283)
##     No Information Rate : 0.5417
##     P-Value [Acc > NIR] : 5.161e-15
##
##                   Kappa : 0.7479
##
##  Mcnemar's Test P-Value : 1
##
##             Sensitivity : 0.8923
##             Specificity : 0.8545
##          Pos Pred Value : 0.8788
##          Neg Pred Value : 0.8704
##              Prevalence : 0.5417
##          Detection Rate : 0.4833
##    Detection Prevalence : 0.5500
##       Balanced Accuracy : 0.8734
##
##        'Positive' Class : 0
##
```

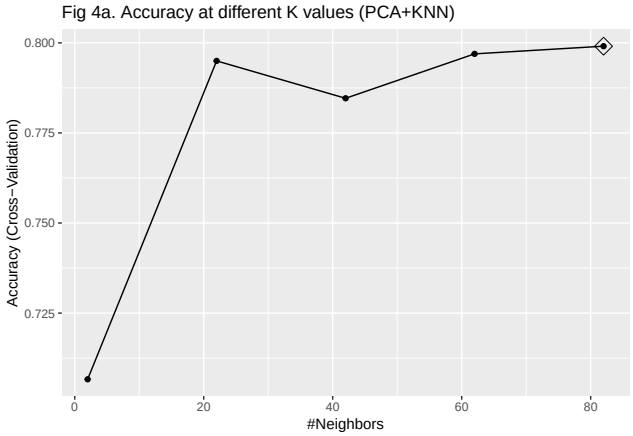
```
F_meas(y_pred_glm, y_test, beta = 2) #F_1 score with beta=2
```

```
## [1] 0.8895706
```

```
#ROC
roc_glm <- roc(as.factor(test_set$case), y_prob)
plot(roc_glm, print.thres="best", type = "line", print.auc = TRUE, legacy.axes = TRUE,
     grid = TRUE, ylim = c(0,1), xlim = c(1,0), col = "Red", main = "Fig 3. ROC for PCA + Logistic")
```

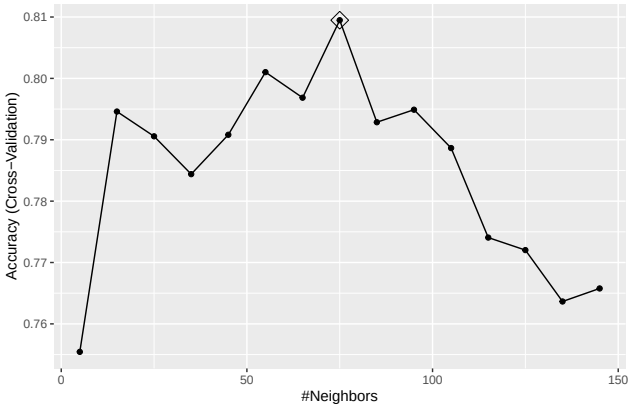



```
#PCA + KNN
set.seed(5436)
b <- 10
control_pca <- trainControl(method = "cv", number = b, p = .9)
train_pcaknn <- train(x_train_pc, y_train,
                      method = "knn",
                      tuneGrid = data.frame(k = seq(2,100,20)),
                      trControl = control_pca)
ggplot(train_pcaknn, highlight = TRUE) +
  ggtitle("Fig 4a. Accuracy at different K values (PCA+KNN)")
```




```
#Second attempt
set.seed(5432)
b <- 10
control_pca <- trainControl(method = "cv", number = b, p = .9)
train_pcaknn2 <- train(x_train_pc, y_train,
                      method = "knn",
                      tuneGrid = data.frame(k = seq(5,150,10)),
                      trControl = control_pca)
ggplot(train_pcaknn2, highlight = TRUE) +
  ggtitle("Fig 4b. Accuracy at different K values (PCA+KNN, 2nd attempt)")
```

Fig 4b. Accuracy at different K values (PCA+KNN, 2nd attempt)




```
train_pcaknn2$bestTune
```

```
##    k
## 8 75
```

```
train_pcaknn2$results$Accuracy
```

```
##  [1] 0.7554422 0.7946003 0.7905612 0.7843963 0.7908163 0.8010204 0.7968537
##  [8] 0.8094813 0.7928571 0.7948980 0.7886480 0.7740646 0.7720238 0.7636480
## [15] 0.7657738
```

```
fit_pcaknn <- knn3(x_train_pc, y_train, k = train_pcaknn2$bestTune$k)

y_pred_pcaknn <- predict(fit_pcaknn, x_test_pc, type = "class")
y_pred_pcaknn_p <- predict(fit_pcaknn, x_test_pc, type = "prob")
confusionMatrix(y_pred_pcaknn, y_test)
```

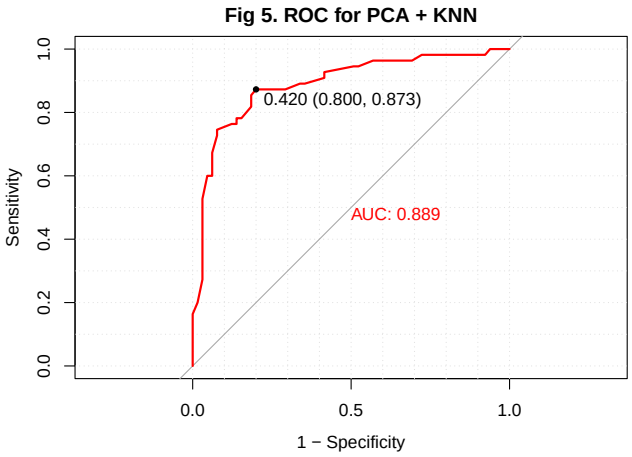
```
## Confusion Matrix and Statistics
##
##           Reference
## Prediction  0  1
##          0 60 15
##          1  5 40
##
##                Accuracy : 0.8333
##                  95% CI : (0.7544, 0.8951)
##     No Information Rate : 0.5417
##     P-Value [Acc > NIR] : 1.512e-11
##
##                   Kappa : 0.6596
##
##  Mcnemar's Test P-Value : 0.04417
##
##             Sensitivity : 0.9231
##             Specificity : 0.7273
##          Pos Pred Value : 0.8000
##          Neg Pred Value : 0.8889
##              Prevalence : 0.5417
##          Detection Rate : 0.5000
##    Detection Prevalence : 0.6250
##       Balanced Accuracy : 0.8252
##
```

```
##         'Positive' Class : 0
##
```

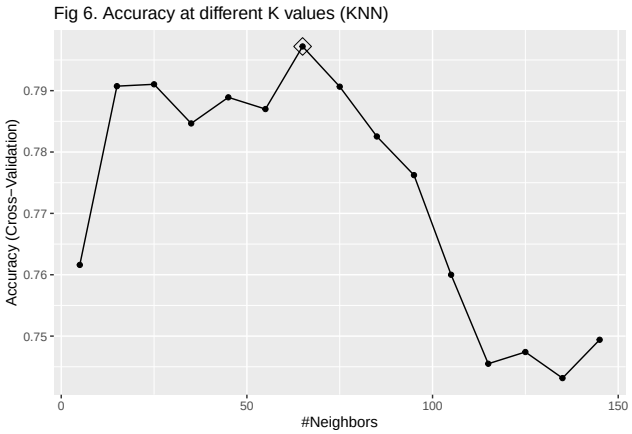
```
F_meas(y_pred_pcaknn, y_test, beta = 2)
```

```
## [1] 0.8955224
```

```
#ROC
roc_pcaknn <- roc(as.factor(test_set$case), y_pred_pcaknn_p[, 2])
plot(roc_pcaknn, print.thres="best", type = "line", print.auc = TRUE, legacy.axes = TRUE,
     grid = TRUE, ylim = c(0,1), col = "Red", main = "Fig 5. ROC for PCA + KNN")
```




```
#KNN
set.seed(3245)
b <- 10
control_knn <- trainControl(method = "cv", number = b, p = .9)
train_knn <- train(x_train, y_train,
                   method = "knn",
                   tuneGrid = data.frame(k = seq(5,150,10)),
                   trControl = control_knn)
ggplot(train_knn, highlight = TRUE) +
  ggtitle("Fig 6. Accuracy at different K values (KNN)")
```




```
train_knn$bestTune
```

```
##    k
## 7 65
```

```
train_knn$results$Accuracy
```

```
##  [1] 0.7616026 0.7907340 0.7910371 0.7846577 0.7889112 0.7870016 0.7972038
##  [8] 0.7906508 0.7825337 0.7762375 0.7599978 0.7454977 0.7474092 0.7431557
## [15] 0.7494057
```

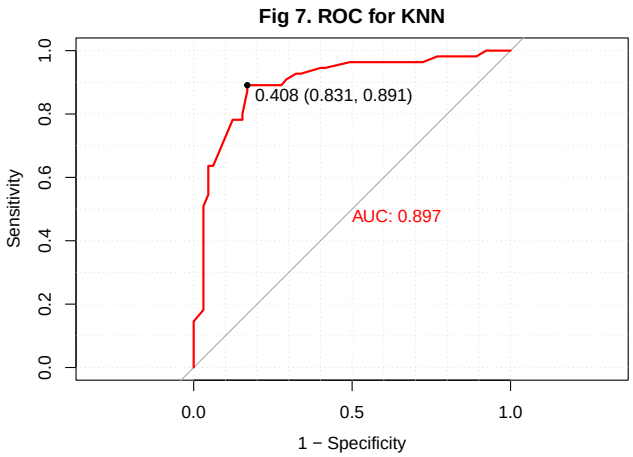
```
fit_knn <- knn3(x_train, y_train, k = train_knn$bestTune$k)

y_pred_knn <- predict(fit_knn, x_test, type = "class")
y_pred_knn_p <- predict(fit_knn, x_test, type = "prob")
confusionMatrix(y_pred_knn, y_test)
```

```
## Confusion Matrix and Statistics
##
##           Reference
## Prediction  0  1
##          0 61 20
##          1  4 35
##
##                Accuracy : 0.8
##                  95% CI : (0.7172, 0.8675)
##     No Information Rate : 0.5417
##     P-Value [Acc > NIR] : 3.087e-09
##
##                   Kappa : 0.588
##
##  Mcnemar's Test P-Value : 0.0022
##
##             Sensitivity : 0.9385
##             Specificity : 0.6364
##          Pos Pred Value : 0.7531
##          Neg Pred Value : 0.8974
##              Prevalence : 0.5417
##          Detection Rate : 0.5083
##    Detection Prevalence : 0.6750
##       Balanced Accuracy : 0.7874
##
##        'Positive' Class : 0
##
```

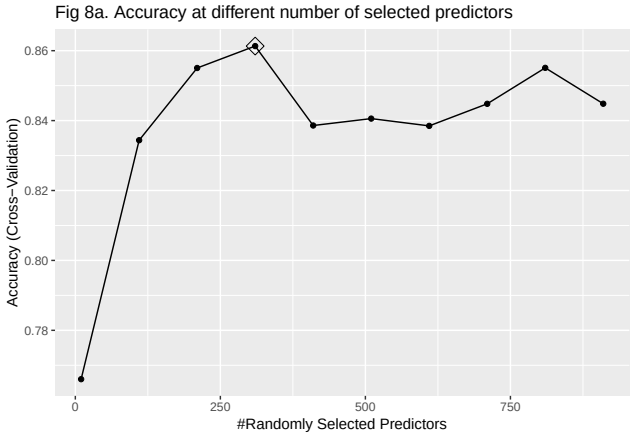
```
F_meas(y_pred_knn, y_test, beta = 2)
```

```
## [1] 0.8944282
```

```
#ROC
roc_knn <- roc(as.factor(test_set$case), y_pred_knn_p[, 2])
plot(roc_knn, print.thres="best", type = "line", print.auc = TRUE, grid = TRUE, legacy.axes = TRUE,
     ylim = c(0,1), col = "Red", main = "Fig 7. ROC for KNN")
```




```
#Random forest
set.seed(4536)
b <- 5
control_rf <- trainControl(method="cv", number = b, p = .9)
train_rf <-  train(x_train, y_train,
                   method = "rf",
                   ntree = 15,
                   trControl = control_rf,
                   tuneGrid = data.frame(mtry = seq(10, 1000, 100)))
ggplot(train_rf, highlight = TRUE) +
  ggtitle("Fig 8a. Accuracy at different number of selected predictors")
```




```
train_rf$bestTune
```

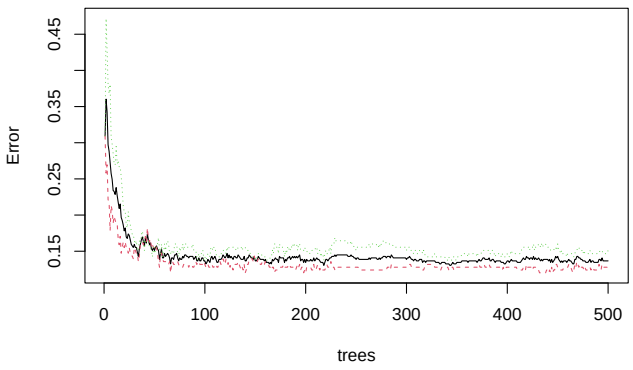
```
##   mtry
## 4  310
```

```
train_rf$results$Accuracy
```

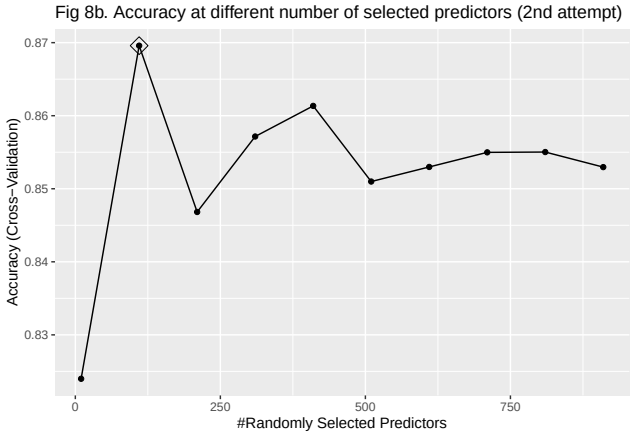
```
##  [1] 0.7660223 0.8343857 0.8550473 0.8613187 0.8385954 0.8405713 0.8384880
##  [8] 0.8448024 0.8550902 0.8448239
```

```
fit_rf <- randomForest(x_train, y_train,
                       mtry = train_rf$bestTune$mtry,
                       minNode = 10)
plot(fit_rf, main = "Fig 9a. Error by number of trees")
```

Fig 9a. Error by number of trees




```
set.seed(6543)
b <- 5
control_rf <- trainControl(method="cv", number = b, p = .9)
train_rf2 <-  train(x_train, y_train,
                    method = "rf",
                    ntree = 100,
                    trControl = control_rf,
                    tuneGrid = data.frame(mtry = seq(10, 1000, 100)))
ggplot(train_rf2, highlight = TRUE) +
  ggtitle("Fig 8b. Accuracy at different number of selected predictors (2nd attempt)")
```




```
train_rf2$bestTune
```

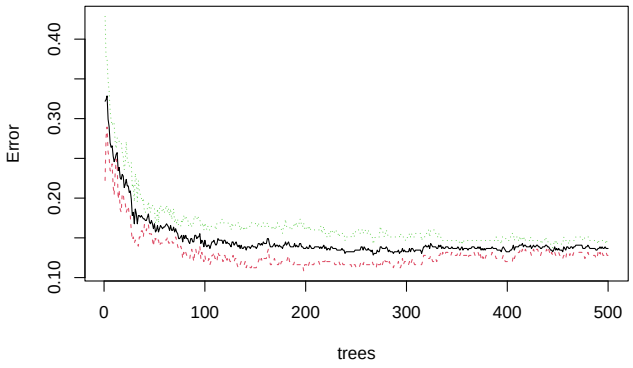
```
##   mtry
## 2  110
```

```
train_rf2$results$Accuracy
```

```
##  [1] 0.8239905 0.8695876 0.8468213 0.8571521 0.8613402 0.8509880 0.8529854
##  [8] 0.8549828 0.8550258 0.8529639
```

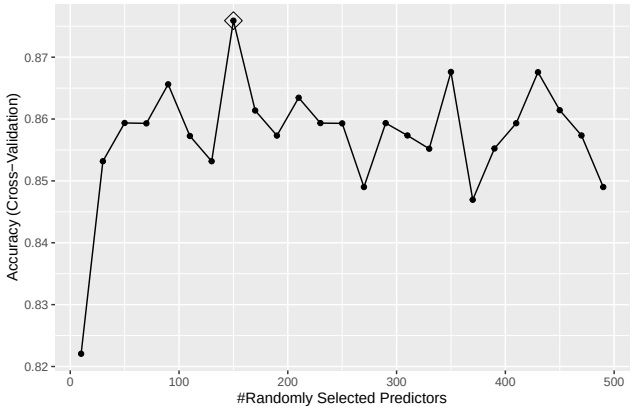
```
fit_rf2 <- randomForest(x_train, y_train,
                        mtry = train_rf2$bestTune$mtry,
                        minNode = 10)
plot(fit_rf2, main = "Fig 9b. Error by number of trees (2nd attempt)")
```

Fig 9b. Error by number of trees (2nd attempt)




```
set.seed(232)
b <- 5
control_rf <- trainControl(method="cv", number = b, p = .9)
train_rf3 <-  train(x_train, y_train,
                    method = "rf",
                    ntree = 100,
                    trControl = control_rf,
                    tuneGrid = data.frame(mtry = seq(10, 500, 20)))
ggplot(train_rf3, highlight = TRUE) +
  ggtitle("Fig 8c. Accuracy at different number of selected predictors (3rd attempt)")
```

Fig 8c. Accuracy at different number of selected predictors (3rd attempt)




```
train_rf3$bestTune
```

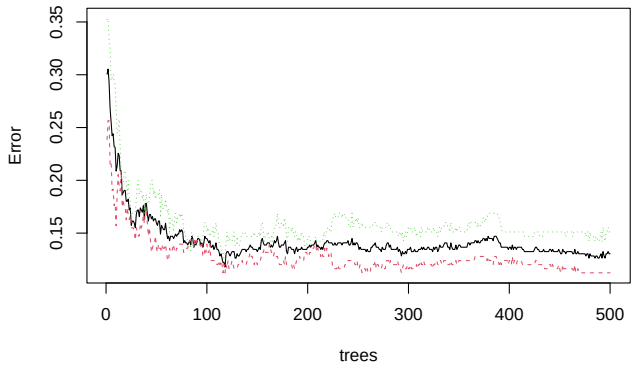
```
##   mtry
## 8  150
```

```
train_rf3$results$Accuracy
```

```
##  [1] 0.8220576 0.8531787 0.8593643 0.8592998 0.8656143 0.8572595 0.8531787
##  [8] 0.8759021 0.8613832 0.8573239 0.8634450 0.8593428 0.8592998 0.8490120
## [15] 0.8593428 0.8573454 0.8551976 0.8676117 0.8469502 0.8552405 0.8593213
## [22] 0.8675687 0.8614261 0.8573454 0.8490120
```

```
fit_rf3 <- randomForest(x_train, y_train,
                        mtry = train_rf3$bestTune$mtry,
                        minNode = 10)
plot(fit_rf3, main = "Fig 9c. Error by number of trees (3rd attempt)")
```

Fig 9c. Error by number of trees (3rd attempt)




```
y_pred_rf <- predict(fit_rf3, x_test, type = "class")
y_pred_rf_p <- predict(fit_rf3, x_test, type = "prob")
confusionMatrix(y_pred_rf, y_test)
```

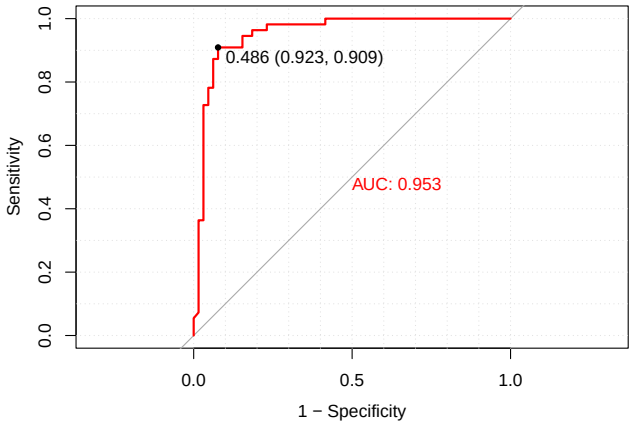
```
## Confusion Matrix and Statistics
##
##           Reference
## Prediction  0  1
##          0 60  6
##          1  5 49
##
##                Accuracy : 0.9083
##                  95% CI : (0.8419, 0.9533)
##     No Information Rate : 0.5417
##     P-Value [Acc > NIR] : <2e-16
##
##                   Kappa : 0.8151
##
##  Mcnemar's Test P-Value : 1
##
##             Sensitivity : 0.9231
##             Specificity : 0.8909
##          Pos Pred Value : 0.9091
##          Neg Pred Value : 0.9074
##              Prevalence : 0.5417
##          Detection Rate : 0.5000
##    Detection Prevalence : 0.5500
##       Balanced Accuracy : 0.9070
##
##        'Positive' Class : 0
##
```

```
F_meas(y_pred_rf, y_test, beta = 2)
```

```
## [1] 0.9202454
```

```
roc_rf <- roc(as.factor(test_set$case), y_pred_rf_p[, 2])
plot(roc_rf, print.thres="best", type = "line", print.auc = TRUE, grid = TRUE, legacy.axes = TRUE,
     ylim = c(0,1), col = "Red", main = "Fig 10. ROC for RF")
```

Fig 10. ROC for RF



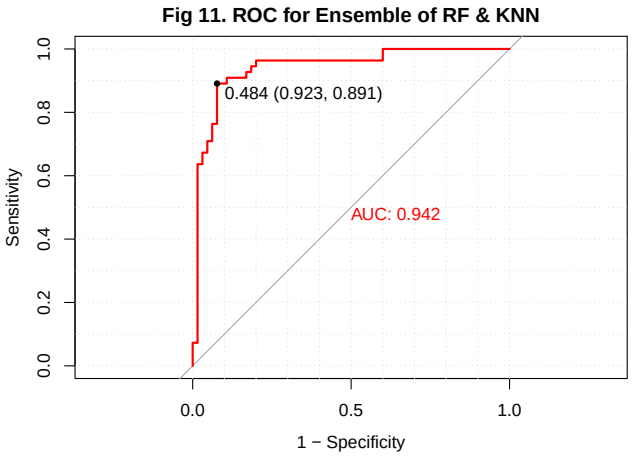

```
#Ensemble
p_knn <- y_pred_knn_p
p_rf <- y_pred_rf_p / rowSums(y_pred_rf_p)
p_pcaknn <- y_pred_pcaknn_p
p_glm <- as.matrix(cbind(1-y_prob, y_prob))
colnames(p_glm) <- c(0, 1)
p <- (p_rf + p_knn)/2
y_pred <- factor(apply(p, 1, which.max)-1)
confusionMatrix(y_pred, y_test)
```

```
## Confusion Matrix and Statistics
##
##           Reference
## Prediction  0  1
##          0 60  9
##          1  5 46
##
##                Accuracy : 0.8833
##                  95% CI : (0.812, 0.9347)
##     No Information Rate : 0.5417
##     P-Value [Acc > NIR] : 8.505e-16
##
##                   Kappa : 0.7637
##
##  Mcnemar's Test P-Value : 0.4227
##
##             Sensitivity : 0.9231
##             Specificity : 0.8364
##          Pos Pred Value : 0.8696
##          Neg Pred Value : 0.9020
##              Prevalence : 0.5417
##          Detection Rate : 0.5000
##    Detection Prevalence : 0.5750
##       Balanced Accuracy : 0.8797
##
##        'Positive' Class : 0
##
```

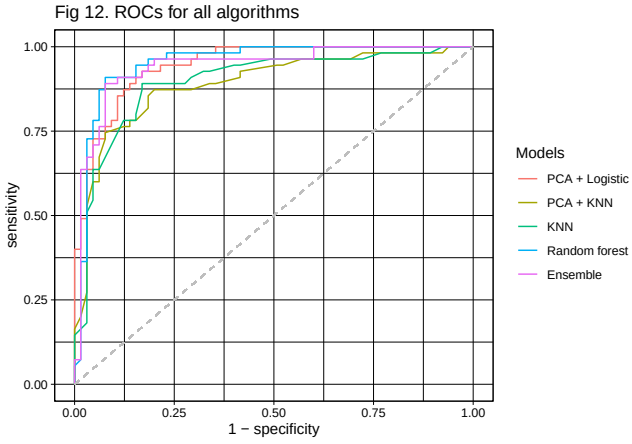
```
F_meas(y_pred, y_test, beta = 2)
```

```
## [1] 0.9118541
```

```
roc_es <- roc(as.factor(test_set$case), p[, 2])
plot(roc_es, print.thres="best", type = "line", print.auc = TRUE, grid = TRUE, legacy.axes = TRUE,
     ylim = c(0,1), col = "Red", main = "Fig 11. ROC for Ensemble of RF & KNN")
```




```
#Combine ROCs
ggroc(list(roc_glm, roc_pcaknn, roc_knn, roc_rf, roc_es), legacy.axes = TRUE) +
  theme_linedraw() +
  ggtitle("Fig 12. ROCs for all algorithms") +
  geom_segment(aes(x = 0, xend = 1, y = 0, yend = 1), color="grey", linetype="dashed") +
  scale_colour_discrete(labels = c("PCA + Logistic", "PCA + KNN", "KNN", "Random forest", "Ensemble")) +
  labs(color = "Models")
```




```
#Create a summary table
summary <- data.frame()
summary[1,1] <- round(confusionMatrix(y_pred_glm, y_test)$byClass[1], 3)
summary[1,2] <- round(confusionMatrix(y_pred_glm, y_test)$byClass[2], 3)
summary[1,3] <- round(confusionMatrix(y_pred_glm, y_test)$overall["Accuracy"], 3)
summary[1,4] <- round(F_meas(y_pred_glm, y_test, beta = 2), 3)
summary[1,5] <- round(roc_glm$auc, 3)

summary[2,1] <- round(confusionMatrix(y_pred_pcaknn, y_test)$byClass[1], 3)
summary[2,2] <- round(confusionMatrix(y_pred_pcaknn, y_test)$byClass[2], 3)
```

Table 1: Table 1. Summary of performance measures for all algorithms

	Sensitivity	Specificity	Overall accuracy	F_1 score	AUC
PCA + Logistic	0.892	0.855	0.875	0.890	0.946
PCA + KNN	0.923	0.727	0.833	0.896	0.889
KNN	0.938	0.636	0.800	0.894	0.897
Random forest	0.923	0.891	0.908	0.920	0.953
Ensemble of KNN & RF	0.923	0.836	0.883	0.912	0.942

```
summary[2,3] <- round(confusionMatrix(y_pred_pcaknn, y_test)$overall["Accuracy"], 3)
summary[2,4] <- round(F_meas(y_pred_pcaknn, y_test, beta = 2), 3)
summary[2,5] <- round(roc_pcaknn$auc, 3)

summary[3,1] <- round(confusionMatrix(y_pred_knn, y_test)$byClass[1], 3)
summary[3,2] <- round(confusionMatrix(y_pred_knn, y_test)$byClass[2], 3)
summary[3,3] <- round(confusionMatrix(y_pred_knn, y_test)$overall["Accuracy"], 3)
summary[3,4] <- round(F_meas(y_pred_knn, y_test, beta = 2), 3)
summary[3,5] <- round(roc_knn$auc, 3)

summary[4,1] <- round(confusionMatrix(y_pred_rf, y_test)$byClass[1], 3)
summary[4,2] <- round(confusionMatrix(y_pred_rf, y_test)$byClass[2], 3)
summary[4,3] <- round(confusionMatrix(y_pred_rf, y_test)$overall["Accuracy"], 3)
summary[4,4] <- round(F_meas(y_pred_rf, y_test, beta = 2), 3)
summary[4,5] <- round(roc_rf$auc, 3)

summary[5,1] <- round(confusionMatrix(y_pred, y_test)$byClass[1], 3)
summary[5,2] <- round(confusionMatrix(y_pred, y_test)$byClass[2], 3)
summary[5,3] <- round(confusionMatrix(y_pred, y_test)$overall["Accuracy"], 3)
summary[5,4] <- round(F_meas(y_pred, y_test, beta = 2), 3)
summary[5,5] <- round(roc_es$auc, 3)

rownames(summary) <- c("PCA + Logistic", "PCA + KNN", "KNN", "Random forest", "Ensemble of KNN & RF")
colnames(summary) <- c("Sensitivity", "Specificity", "Overall accuracy", "F_1 score", "AUC")

summary %>%
  kbl(caption = "Table 1. Summary of performance measures for all algorithms") %>%
  kable_material(c("striped"))
```