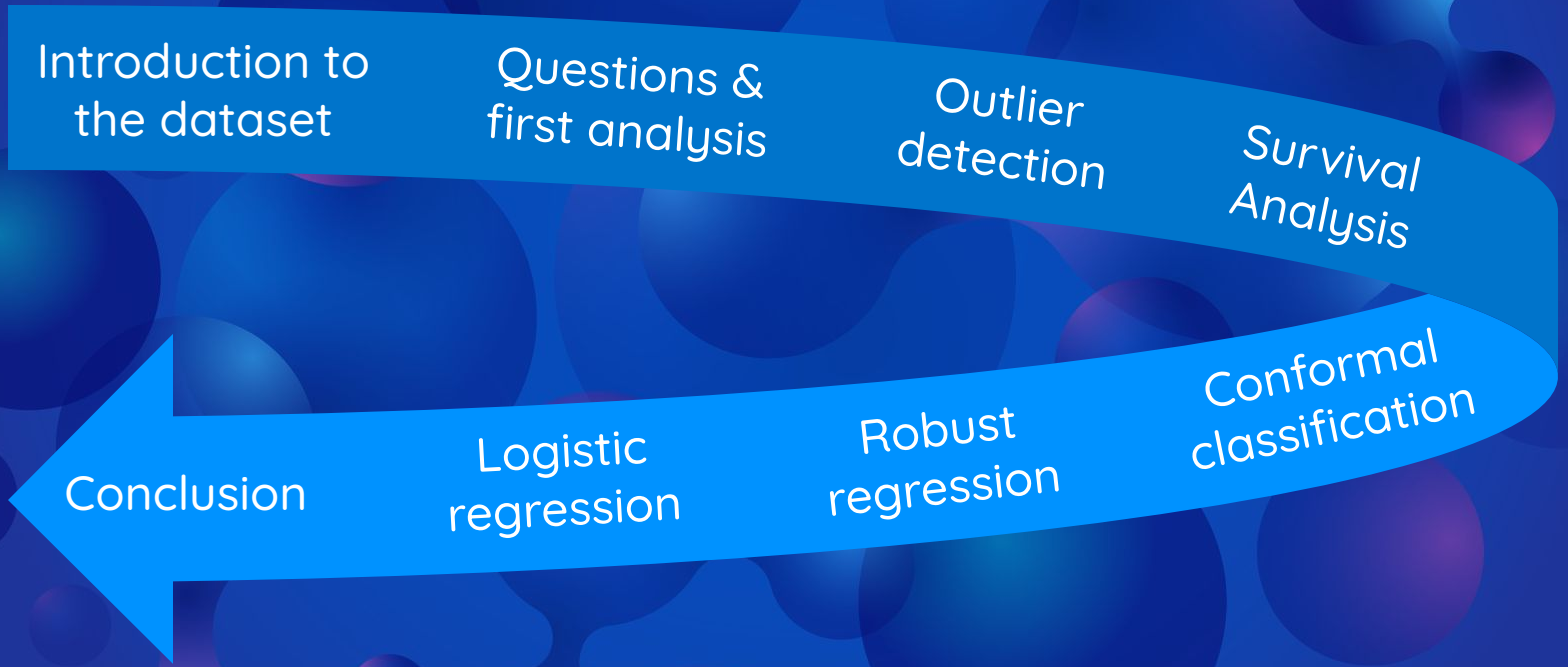
Dementia Disease: Nonparametric Models for prediction and Survival Analysis

Francesca Di Filippo, Erica Manfrin,
Elena Musiari, Edoardo Palli

Nonparametric Statistics
2021-2022

PROJECT DEVELOPMENT



DATASET

- ID: the identification number for each patient
- M.F: the gender
- Hand: the dominant hand
- Age
- EDUC: the educational level, with values ranging from 1 to 25
- SES: the socio-economic status, with values ranging from 1 to 5
- MMSE: the Mini Mental State Examination, with values ranging from 1 to 30
- CDR: the Clinical Dementia Rating, ranging between 0 and 3
- eTIV: the Estimated Total Intracranial Volume
- nWBV: the Normalize Whole Brain Volume
- ASF: the Atlas Scaling Factor
- Delay: the days passed from the first visit
- Group: the label pointing to the type of patient

DATASET

- ID: the identification number for each patient
- M.F: the gender
- Hand: the dominant hand
- Age
- EDUC: the educational level, with values ranging from 1 to 25
- SES: the socio-economic status, with values ranging from 1 to 5
- MMSE: the Mini Mental State Examination, with values ranging from 1 to 30
- CDR: the Clinical Dementia Rating, ranging between 0 and 3
- eTIV: the Estimated Total Intracranial Volume
- nWBV: the Normalize Whole Brain Volume
- ASF: the Atlas Scaling Factor
- Delay: the days passed from the first visit
- Group: the label pointing to the type of patient

DATASET

- ID: the identification number for each patient
- M.F: the gender
- Hand: the dominant hand
- Age
- EDUC: the educational level, with values ranging from 1 to 25
- SES: the socio-economic status, with values ranging from 1 to 5
- MMSE: the Mini Mental State Examination, with values ranging from 1 to 30
- CDR: the Clinical Dementia Rating, ranging between 0 and 3
- eTIV: the Estimated Total Intracranial Volume
- nWBV: the Normalize Whole Brain Volume
- ASF: the Atlas Scaling Factor
- Delay: the days passed from the first visit
- Group: the label pointing to the type of patient

RESEARCH QUESTIONS

Is there statistical difference between demented and non demented patients?

The Dementia diagnosis can be predicted using non-specific medical tests?

Which type of patients are more likeable to become demented?

EXPLORATORY ANALYSIS

USING ANOVA AND PERMUTATION TESTS

PERMUTATION TEST

Study the statistical difference between the two groups using Tukey median

$$H_0 : X_{Demented} \overset{\mathrm{d}}{=} X_{Nondemented} \quad vs \quad H_1 : X_{Demented} \overset{\mathrm{d}}{\neq} X_{Nondemented}$$

p-value = 0.002

SIGNIFICANCE TESTS

- ANOVA TEST:

Study the importance of M.F variable in the grouping, using permutational ANOVA

p-value = 0.011

- PERMUTATION TEST:

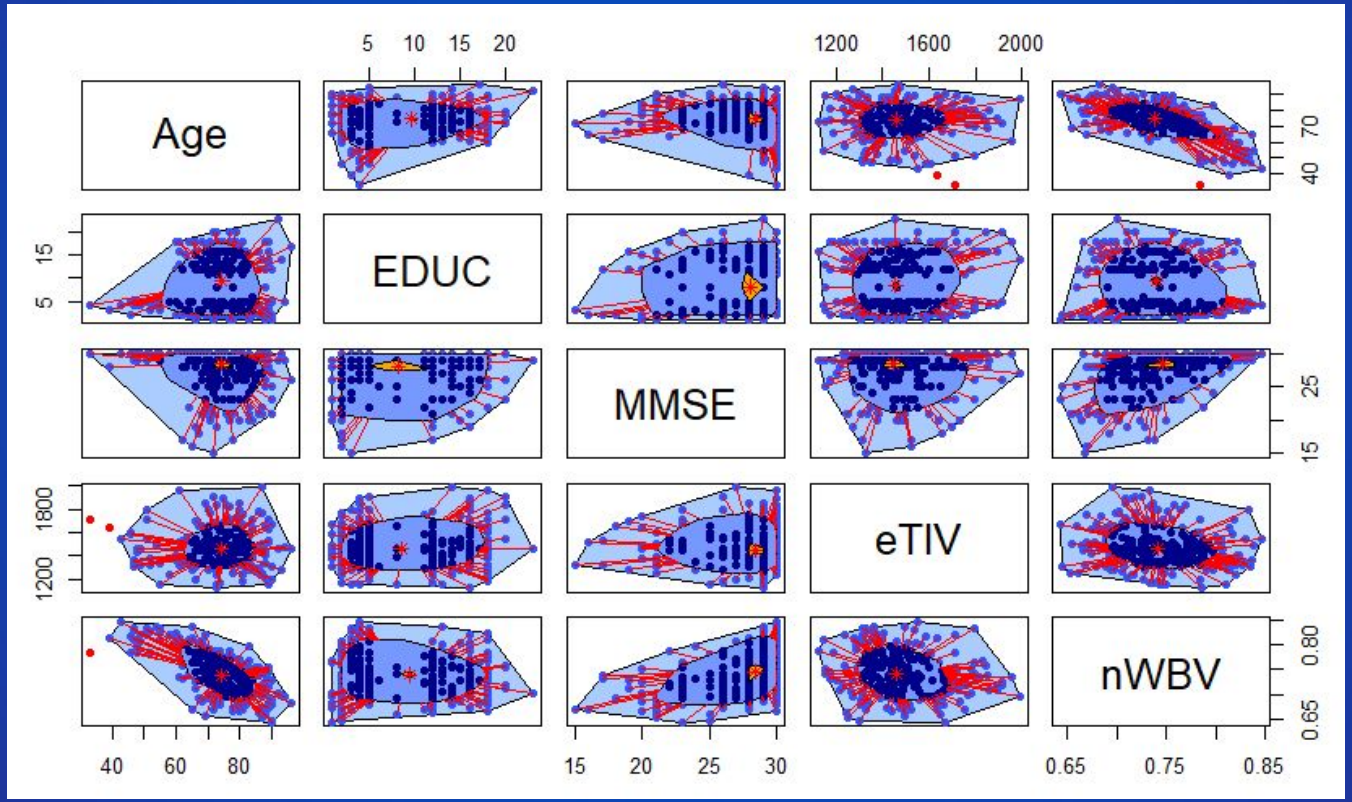
Study the importance of Age variable in the grouping

p-value = 0

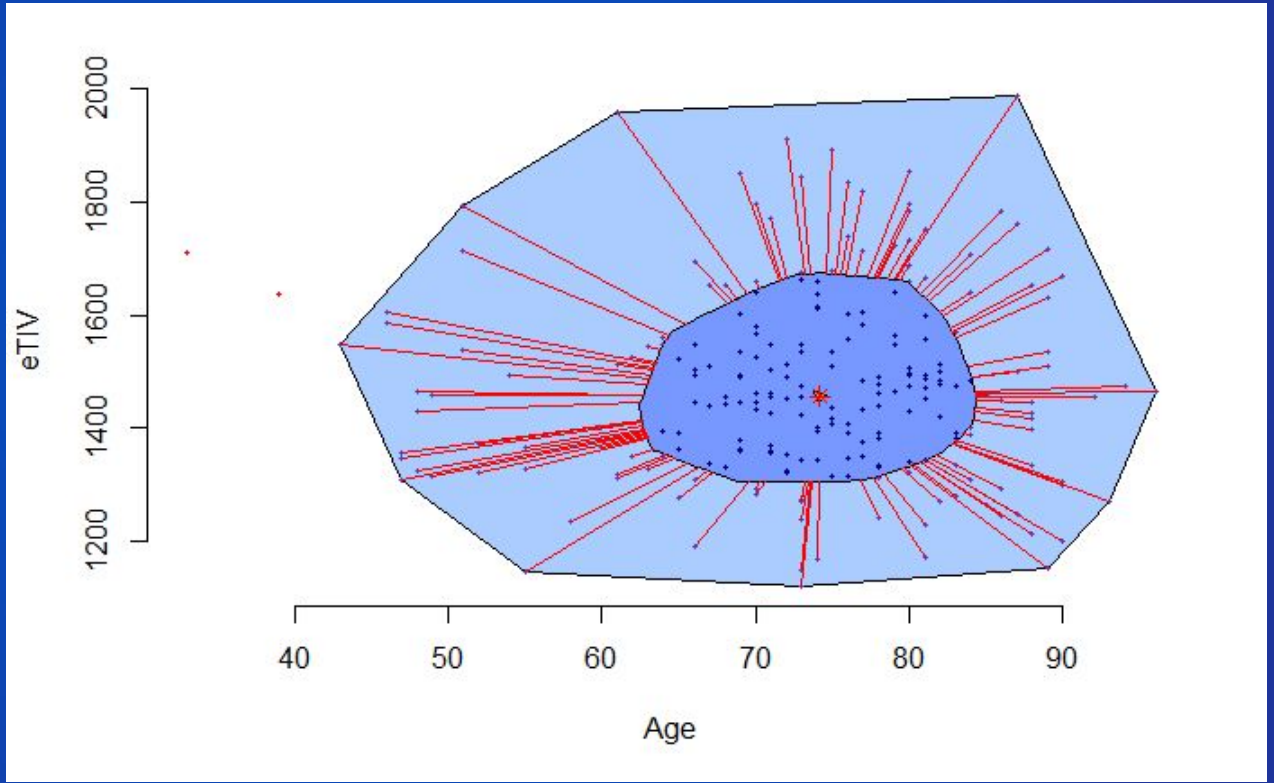
OUTLIER DETECTION

USING DEPTH MEASURES

BAGPLOT MATRIX TRAINING DATASET

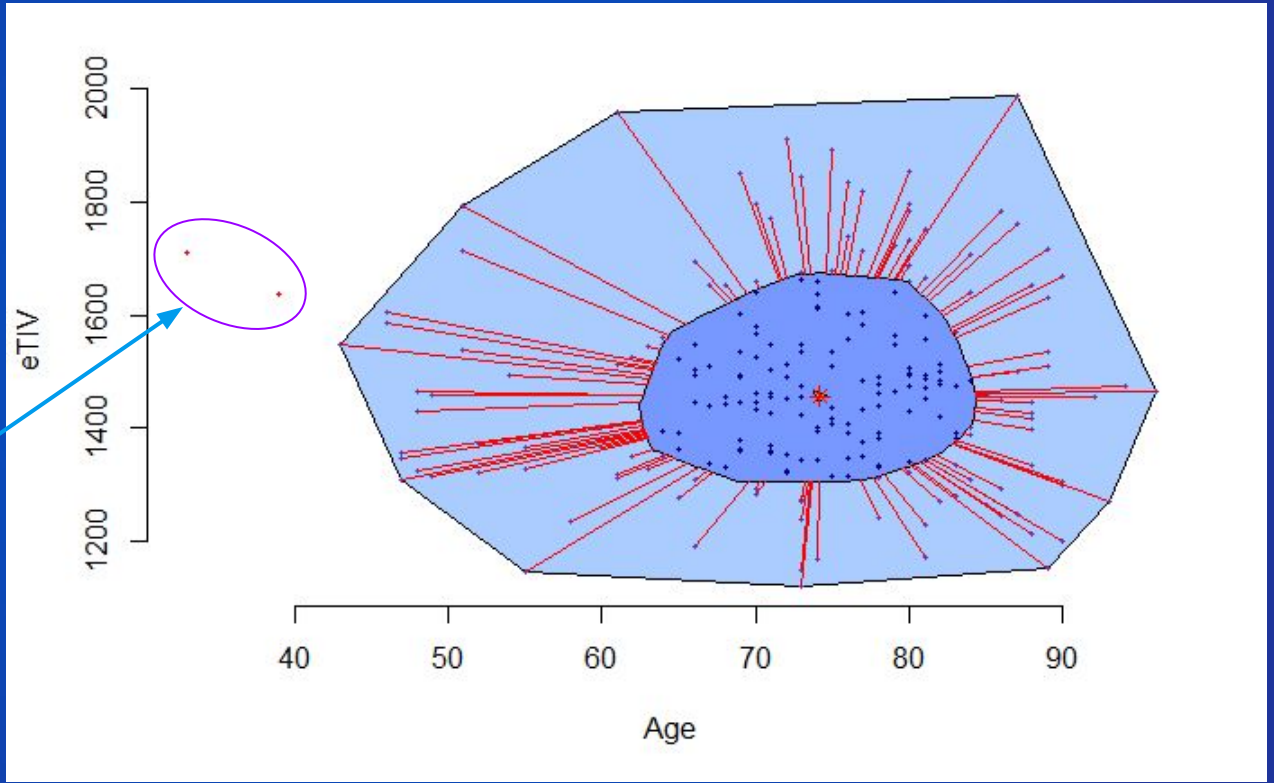


BAGPLOT MATRIX TRAINING DATASET

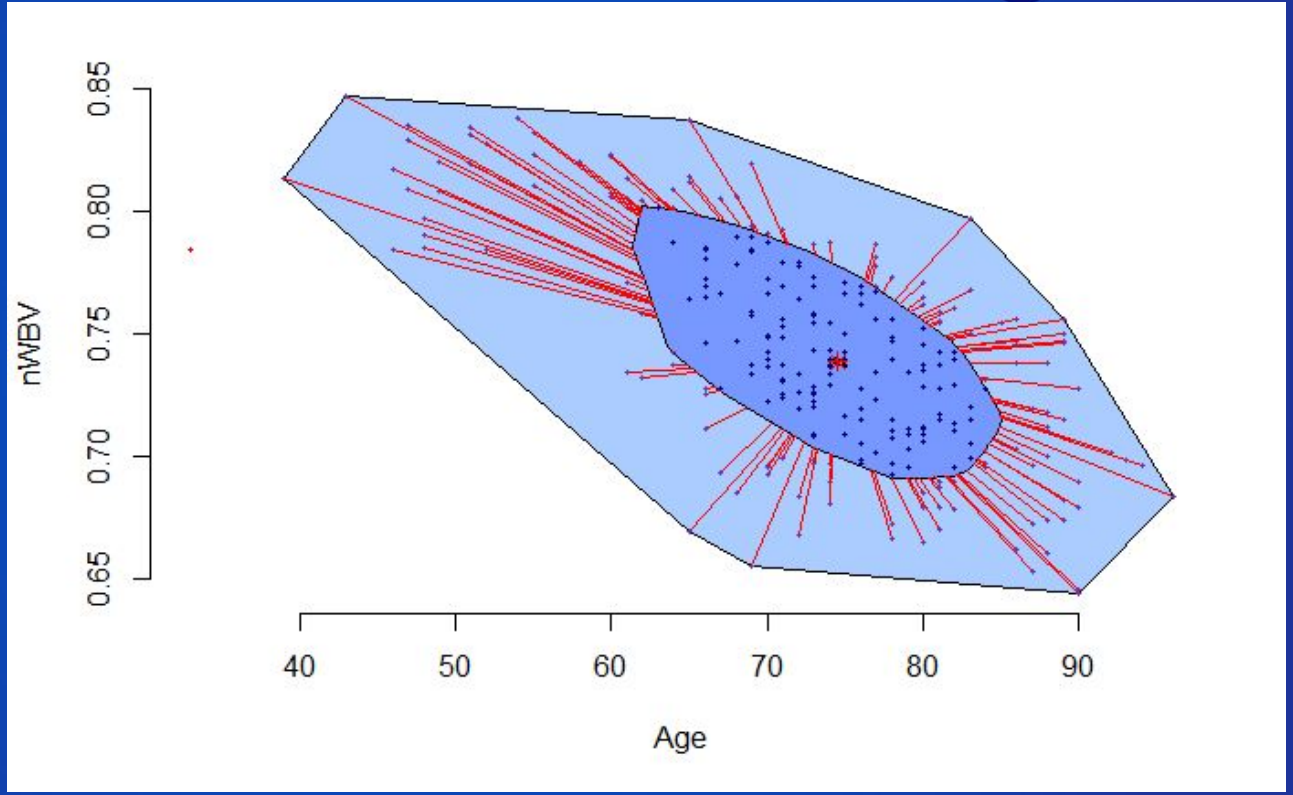


BAGPLOT MATRIX TRAINING DATASET

patients at lines 145 and 175

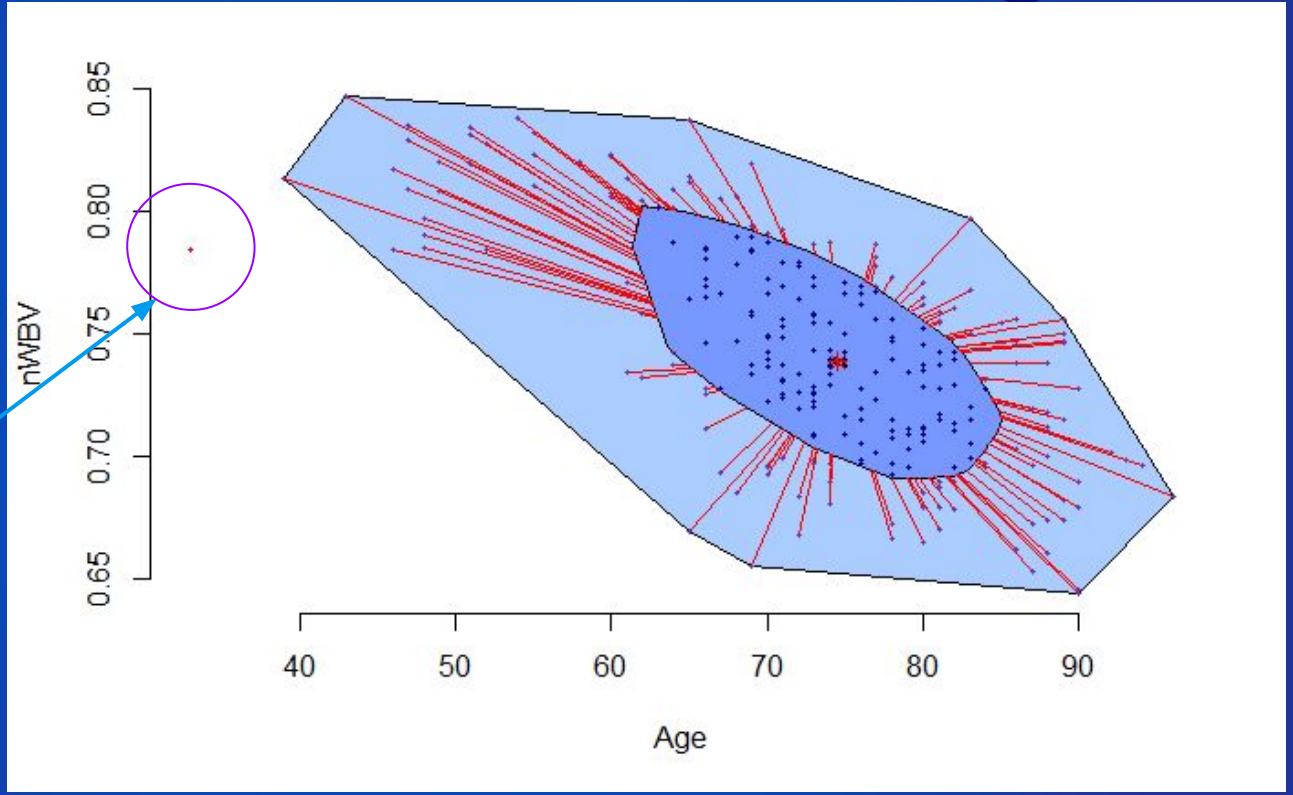


BAGPLOT MATRIX TRAINING DATASET

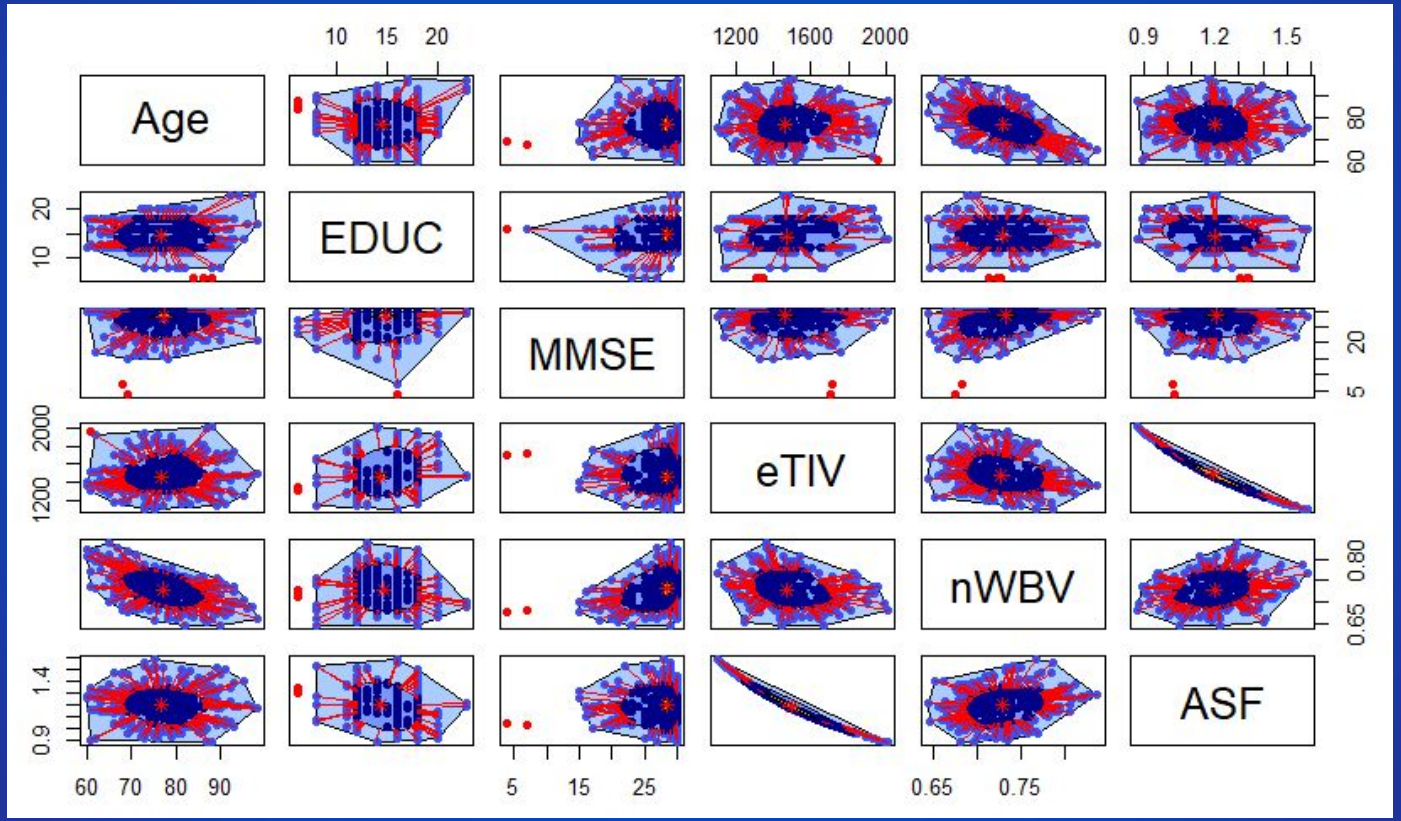


BAGPLOT MATRIX TRAINING DATASET

patient at line 175

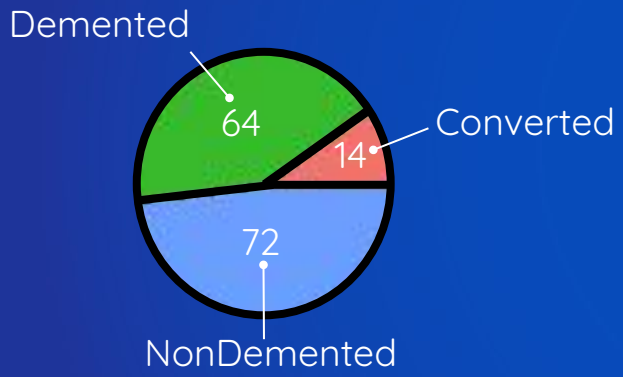


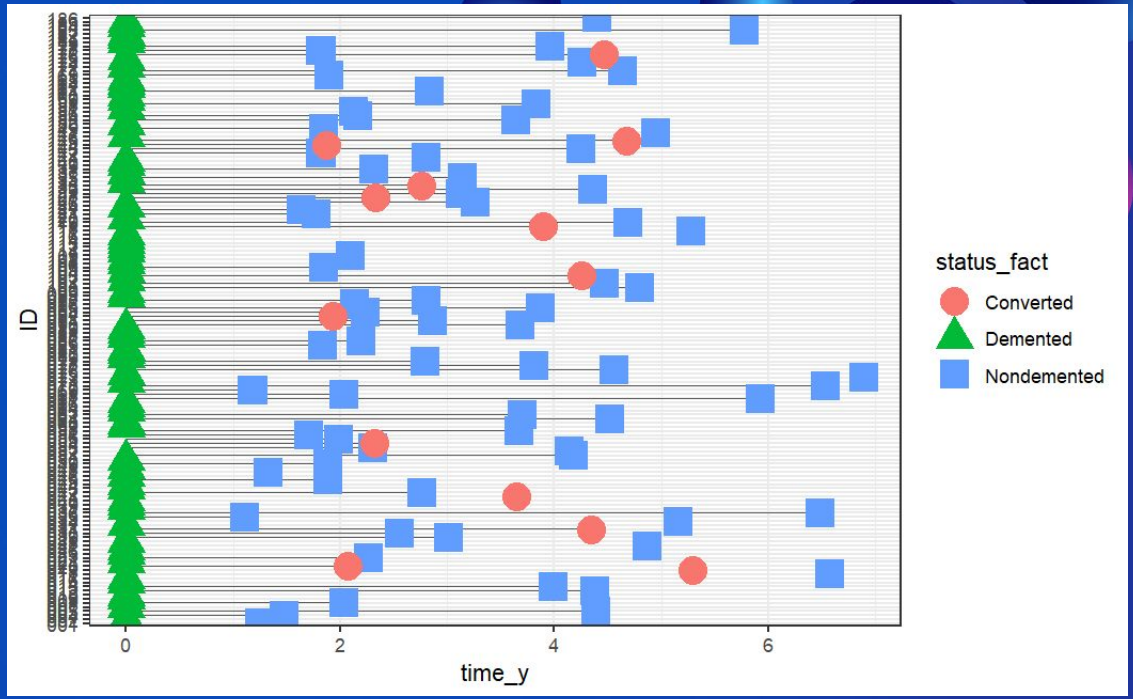
BAGPLOT MATRIX LONGITUDINAL DATASET



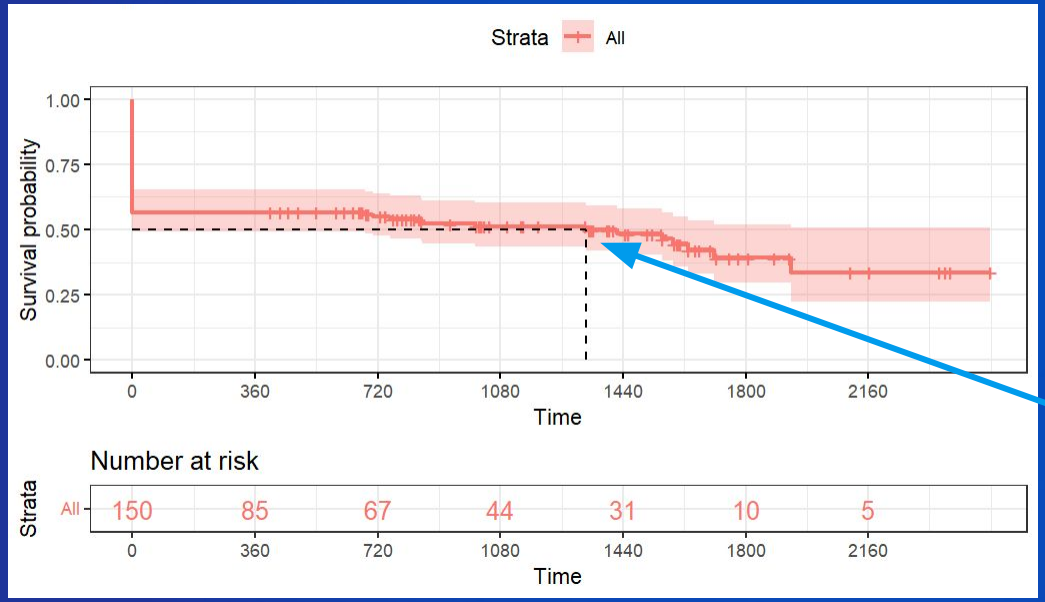
SURVIVAL ANALYSIS

TIME TO EVENT DATASET





KAPLAN MEIER ESTIMATOR OF SURVIVAL PROBABILITY



$$S(t) = P(T < t)$$

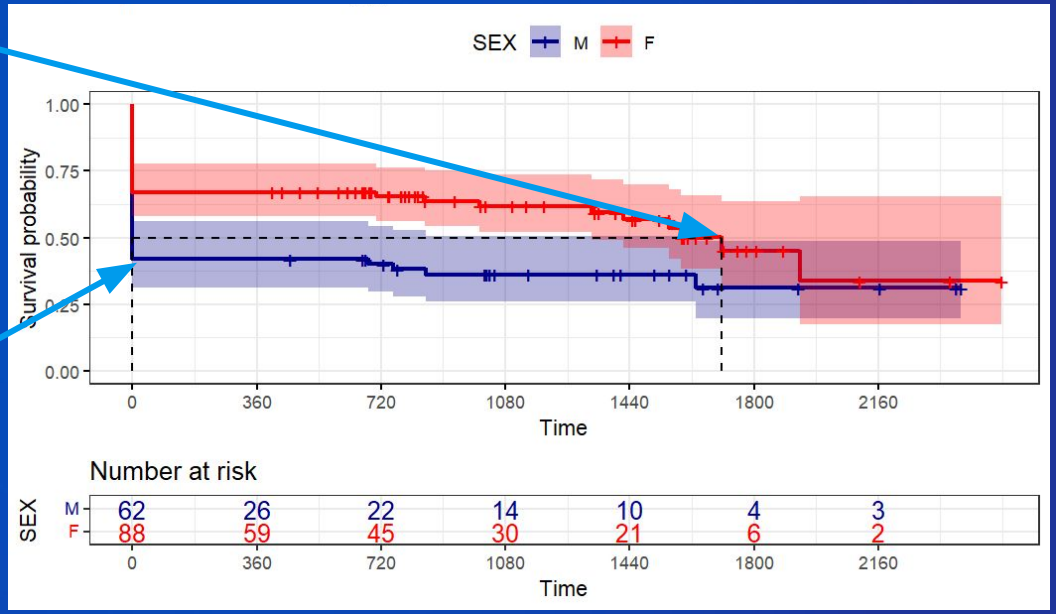
median survival time:
3 and a half years

KAPLAN MEIER ESTIMATOR WITH GENDER CLASSIFICATION

$$S(t) \sim Gender$$

Female median survival time:
almost 5 years

Male median survival time:
at the first visit the Survival probability is already below 50%



LOG-RANK TEST

$$H_0: \ S_{male}(\cdot) = S_{female}(\cdot) \ \ vs \ \ H_1: \ S_{male}(\cdot) \neq S_{female}(\cdot)$$

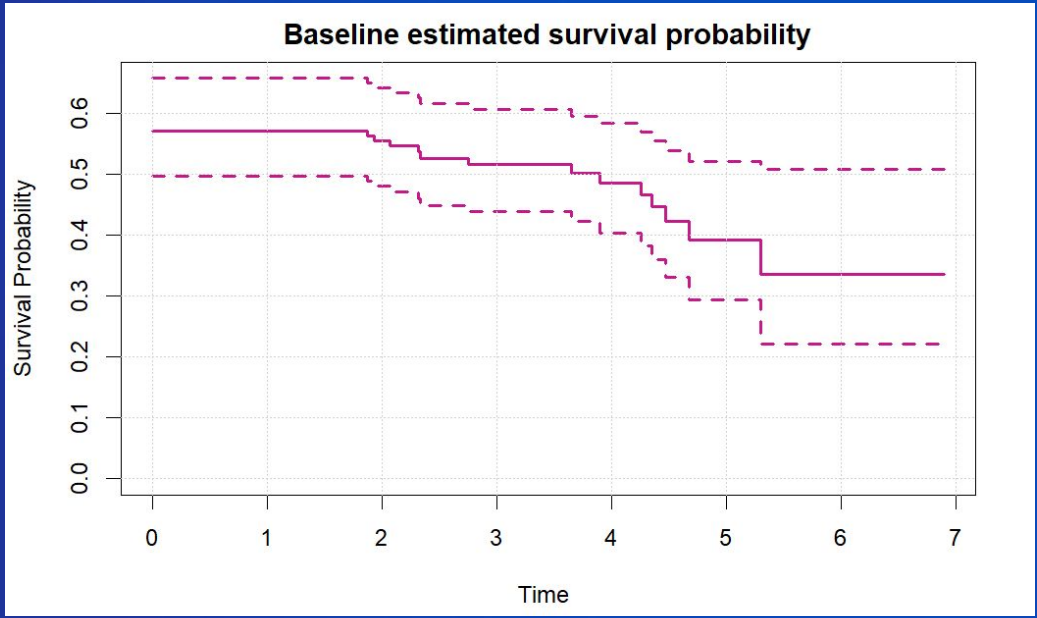
p-value=0.01

$$HR_{MF} = \frac{O_{Male}/E_{Male}}{O_{Female}/E_{Female}} = 1,57$$

Male
risk factor

COX MODEL WITH VARIABLE AGE

$$h(t) = h_0(t)\exp(\beta_{Age} Age)$$



AGE

coefficient = -0.0377

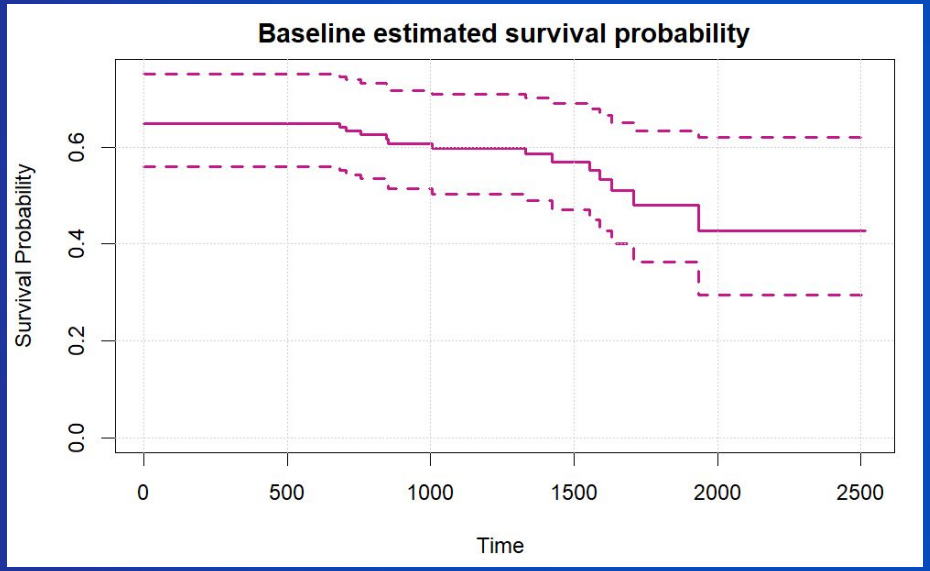
Wald test p-value = 0.0116

Hazard ratio and CI at 95%

lw	*fit*	*up*
0.9351	0.9629	0.9916

COX MODEL WITH AGE AND GENDER

$$h(t) = h_0(t)\exp(\beta_{Age}Age + \beta_{Gender}Gender)$$



AGE

coefficient = -0.03664

Wald test p-value = 0.0155

Hazard ratio and CI at 95%

lw	*fit*	*up*
0.9358	0.9640	0.9931

GENDER

coefficient = -0.58

Wald test p-value = 0.0106

Hazard ratio and CI at 95%

lw	*fit*	*up*
0.3583	0.5595	0.8737

GLOBAL TEST:

likelihood ratio test, Wald test, Score (log-rank) test

p-values =0.002

CONFORMAL CLASSIFICATION

INDUCTIVE CONFORMAL PREDICTION (ICP)

TRANSDUCTIVE CONFORMITY PREDICTION (TCP)

RANDOM FOREST

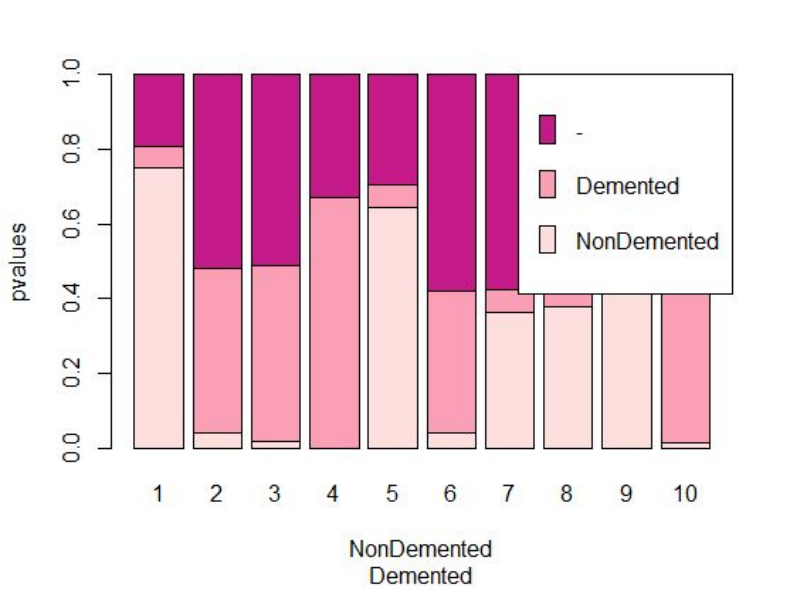
CONFORMITY SCORE: $\alpha_i(y) = \frac{\sharp\ trees\ voting\ for\ class\ y}{\sharp\ of\ trees}$

INDUCTIVE CONFORMAL PREDICTION (ICP)

- Proper Training set: $Z_p = z_1, \ldots, z_q$ of size q=216 (80% of Training Set)
- Calibration set: $Z_c = z_{q+1}, \ldots, z_n$ of size n-q= 271- 216
- Test set: $Z_t = z_1, \ldots, z_m$ of size m=100

ICP- PVALUES

$$p_y = \frac{|z_i \in Z_c:\ y_i = y, \alpha_i(y) < \alpha_{new}(y)| + u_i * |z_i \in Z_c:\ y_i = y, \alpha_i(y) = \alpha_{new}(y)|}{n_y + 1}$$



$$u_i \sim U[0, 1]$$

$$n_{Demented} = 45$$

$$n_{NonDemented} = 55$$

EVALUATION OF PERFORMANCES

ERROR RATE: $\frac{1}{m}\sum_{i=1}^{m} I_{y_i \notin \Gamma_i^\epsilon} = 0.1$

EFFICIENCY: $\frac{1}{m}\sum_{i=1}^{m} I_{|\Gamma_i^\epsilon|>1} = 0.5$

OBSERVED FUZZYNESS: $\frac{1}{m}\sum_{i=1}^{m}\sum_{y_i \neq y} p_i^y = 0.155$

$\epsilon = 0.05$

LOGISTIC REGRESSION

FOR ALZHEIMER PREDICTION

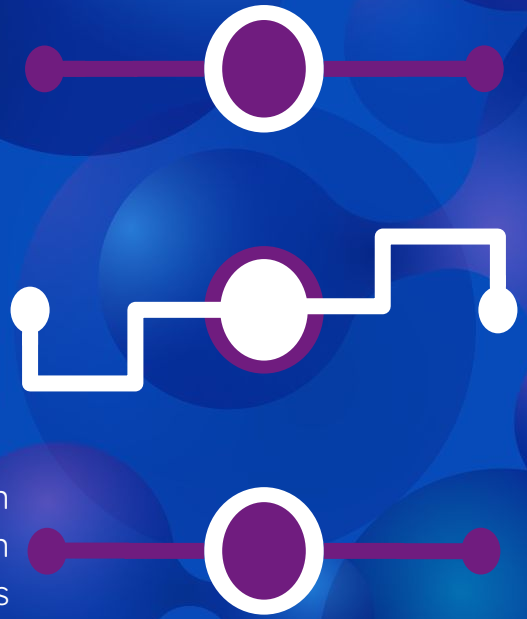
TWO DIFFERENT APPROACHES

MMSE as unique covariate

very informative for disease classification

we want to exploit all the information in it

- Global Polynomial Regression
- Local Likelihood Regression
- Regression Splines



GAM without MMSE

Develop a model to be used in addition to MMSE test

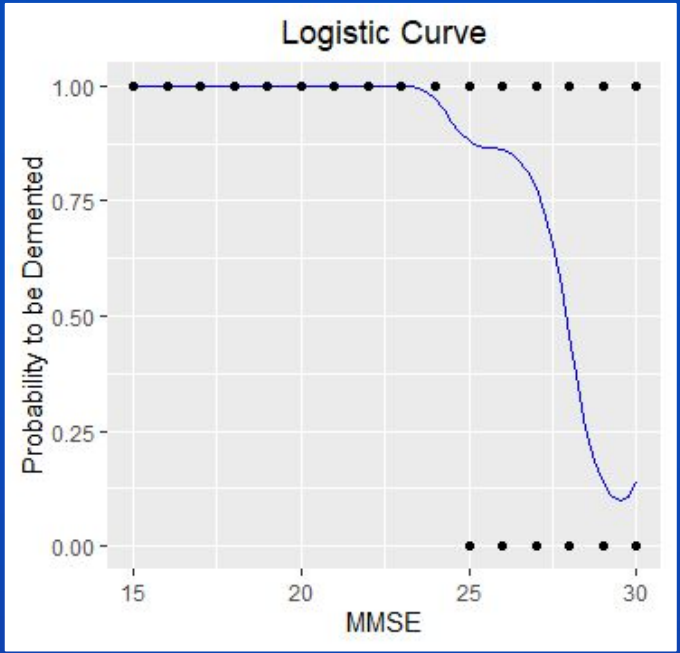
Generalized Additive Model

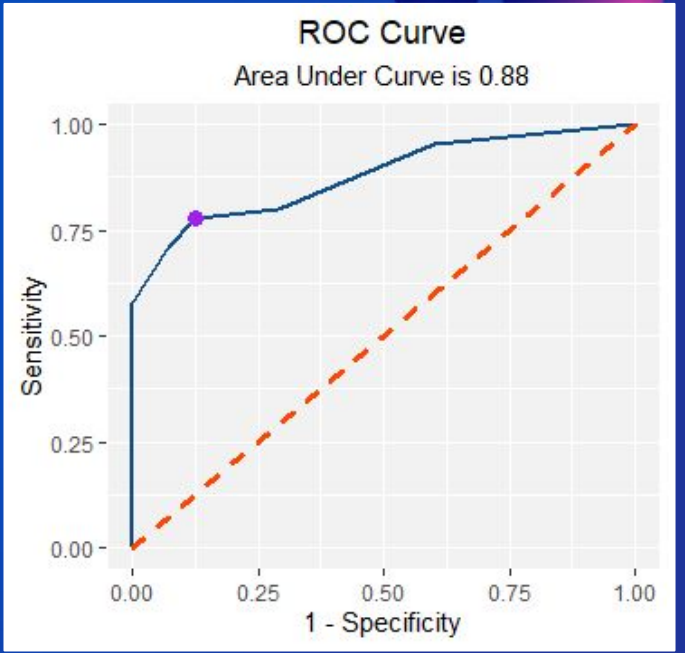
GLOBAL POLYNOMIALS

$$log\frac{p}{1-p} = \beta_0 + \beta_1 * MMSE + \beta_2 * MMSE^2 + \beta_3 * MMSE^3 + \beta_4 * MMSE^4$$

- R^2 = 0.4463
- Sensitivity = 0.78
- Specificity = 0.87
- accuracy = 0.83
- precision = 0.83
- F1 score = 0.80

No monotonic behaviour



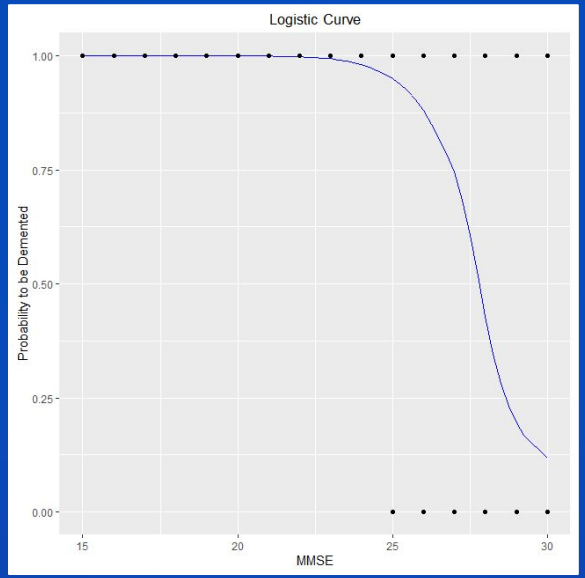


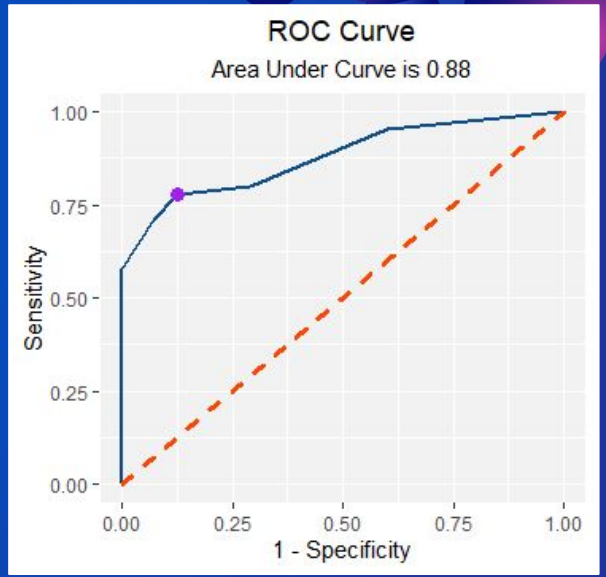
LOCAL LIKELIHOOD

$$\ell_{x,h}(\boldsymbol{\beta}) := \sum_{i=1}^{n} \ell(Y_i, \eta(MMSE_i - x)) K_h(x - MMSE_i) \; \eta(x) := \beta_0 + \beta_1 x.$$

$K_h(x)$: gaussian kernel

- Sensitivity = 0.78
- Specificity = 0.87
- accuracy = 0.83
- precision = 0.83
- F1 score = 0.80



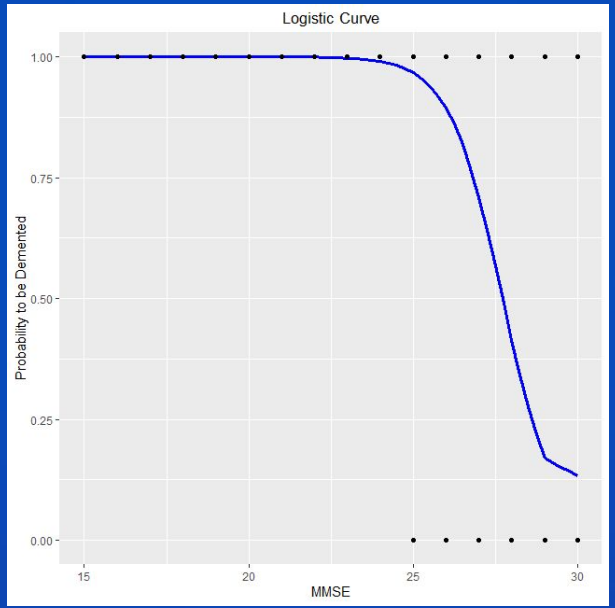


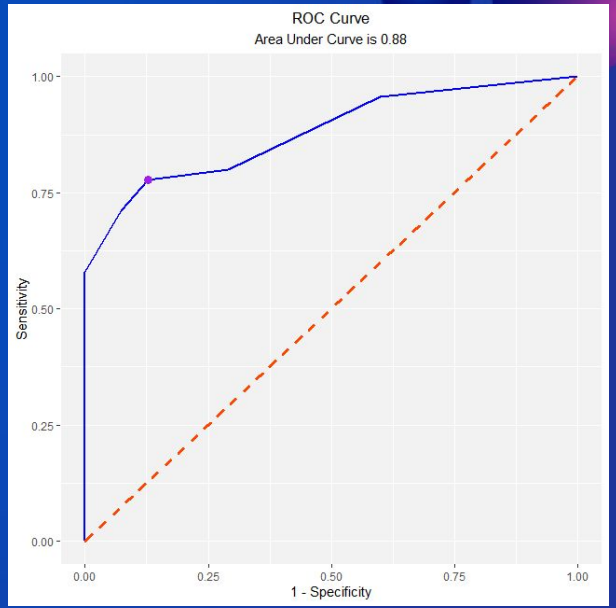
REGRESSION SPLINE

$$log\frac{p}{1-p} = \beta_0 + \sum_{j=1}^{k+1} \beta_j g_j\,(MMSE)$$

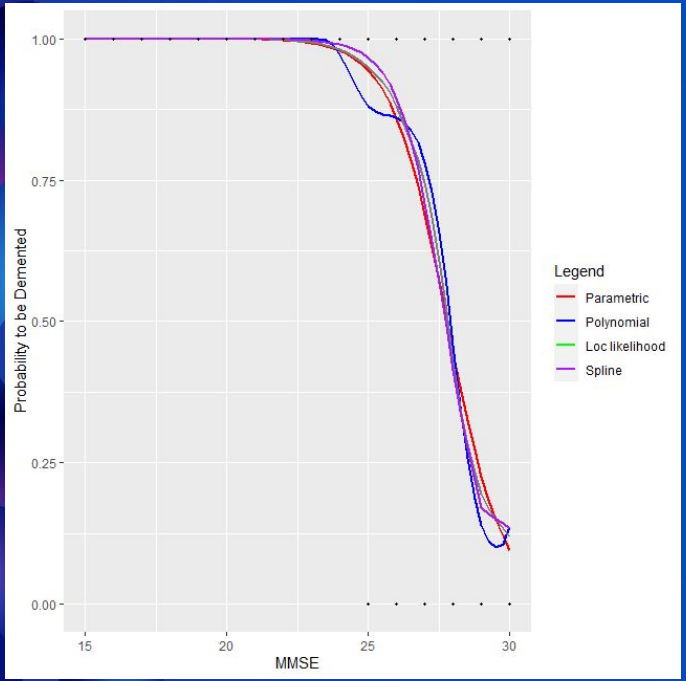
K = 1 knot at the median

- R^2 = 0.4377
- Sensitivity = 0.78
- Specificity = 0.87
- accuracy = 0.83
- precision = 0.83
- F1 score = 0.80





COMPARISON BETWEEN MODELS

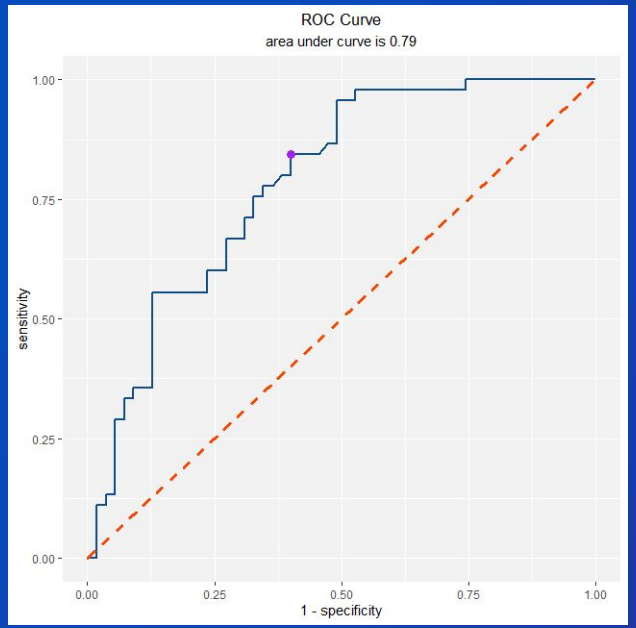


	R^2	AIC	AUC
PARAMETRIC GLM	0.429	216.0	**0.879**
GLOBAL POLYNOMIALS	**0.446**	215.8	**0.879**
LOCAL LIKELIHOOD	–	–	**0.879**
CUBIC SPLINE	0.4377	**213.03**	0.854

GENERALIZED ADDITIVE MODEL

$$ln\frac{p}{1-p} = \beta_0 + \beta_1 Sex + f_2(EDUC) + f_3(nWBV) + f_4(nWBV * Sex) + f_5(Age) + f_6(eTIV) + f_7(eTIV * Sex)$$

- R^2 = 0.3608
- Sensitivity = 0.84
- Specificity = 0.6
- Accuracy = 0.71
- Precision = 0.63
- F1 score = 0.72



ROBUST REGRESSION

THEORY ABOUT *GLMROB*

We find the robust estimator for beta from the estimating equations:

$$\sum_{i=1}^{n} \psi(y_i, \mu_i) = 0$$

It is an M-estimator characterized by the score function:

$$\psi(y, \mu) = \nu(y, \mu) \cdot w(x) \cdot \mu' - a(\beta)$$

with $a(\beta) = \frac{1}{n} \sum_{i=1}^{n} E[\nu(y_i, \mu_i)]$

For binomial models we have: $\nu(y_i, \mu_i) = \psi_c(r_i) \frac{1}{V^{1/2}(\mu_i)}$ $r_i = \frac{y_i - \mu_i}{V^{1/2}(\mu_i)}$

$\psi_c(r)$ is the Huber function defined by r if |r|< c and by c*sign(r) if |r|>c

THREE MODELS

Robust Regression Model with all the covariates:

-with B-splines
-without B-splines

Robust Regression Model with only MMSE:

-with B-splines
-without B-splines

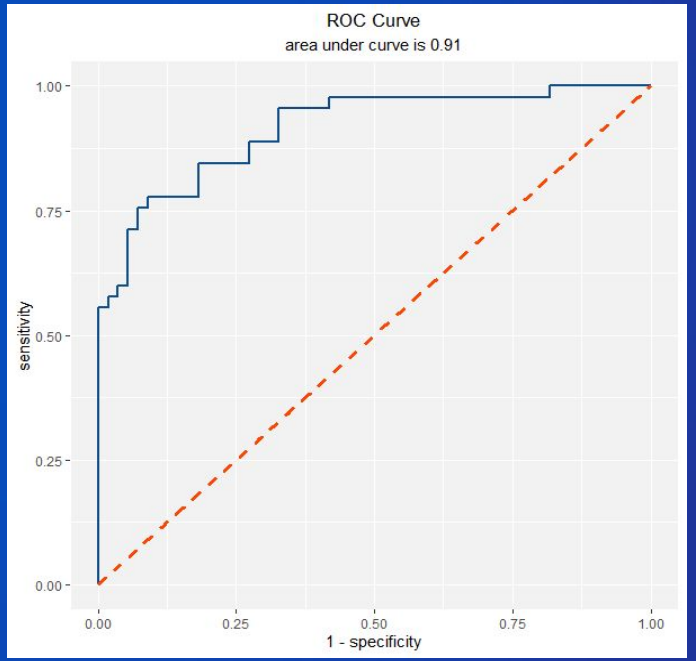
Robust Regression Model without MMSE:

-all the covariates with and without B-splines

COMPLETE MODEL

$$log(\frac{p}{1-p}) = \beta_1 \cdot M.F + \beta_2 \cdot EDUC + \beta_3 \cdot nWBV + \beta_4 \cdot Age + \beta_5 \cdot MMSE + \beta_6 \cdot eTIV$$

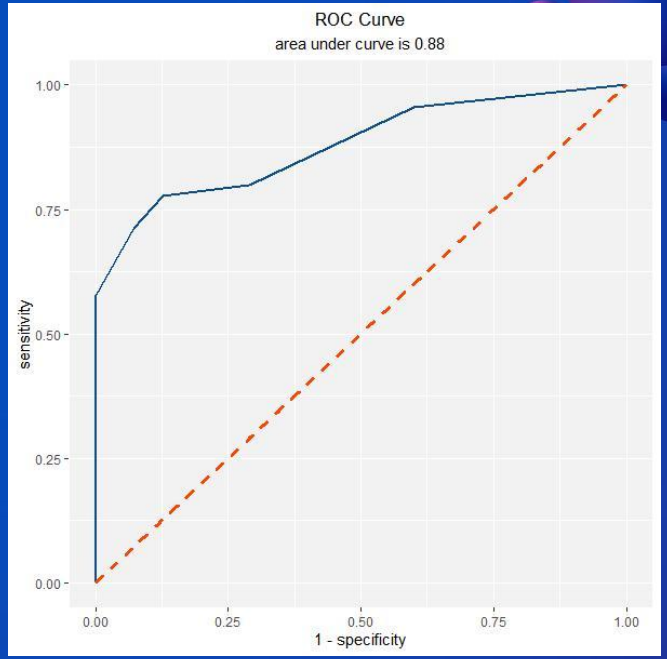
- F1-score=0.7916667
- accuracy= 0.8
- precision=0.745098
- sensitivity=0.875
- specificity=0.733333



MODEL WITH ONLY MMSE

$$log(\frac{p}{1-p}) = \beta \cdot MMSE$$

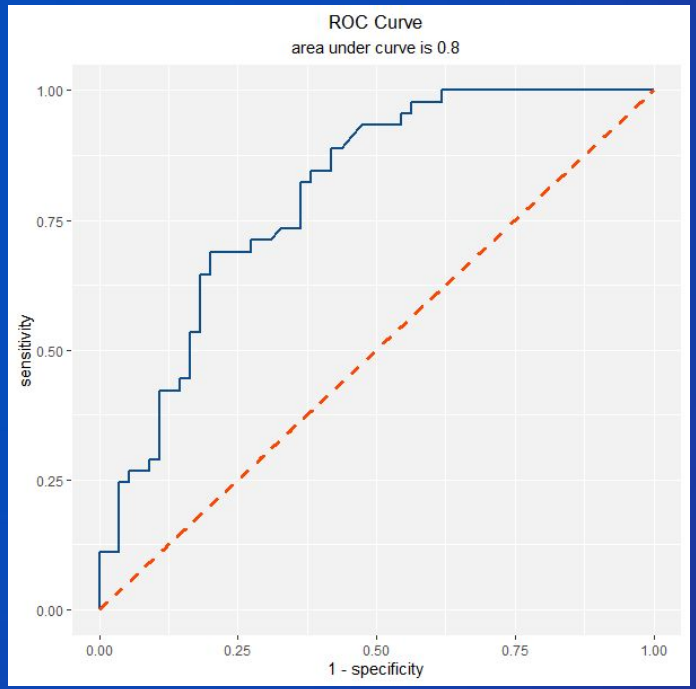
- F1-score=0.80
- accuracy= 0.83
- precision=0.83
- sensitivity=0.78
- specificity=0.87



MODEL WITH ALL PARAMETERS WITHOUT MMSE

$$log(\frac{p}{1-p}) = \beta_1 \cdot M + \beta_2 \cdot bs(Age) + \beta_3 \cdot bs(nWBV) + \beta_4 \cdot bs(eTIV)$$

- F1-score=0.73
- accuracy= 0.71
- precision=0.63
- sensitivity=0.73
- specificity=0.71



CONCLUSIONS

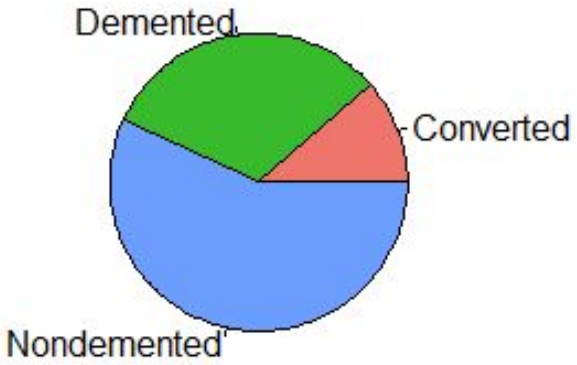
We can say that there are significative differences between demented and nondemented

We can predict Dementia with the use of information that are not the Mini Mental State Examination, and so with less medical information

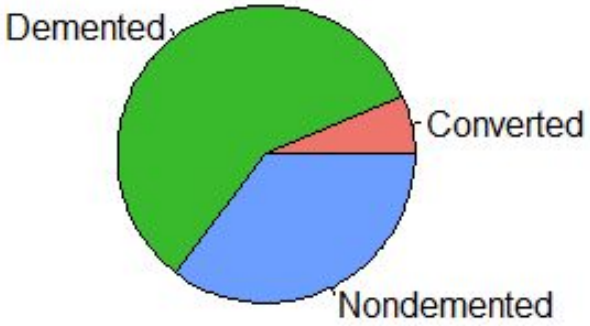
For our analysis the risk to contract dementia is higher in men and it decreases when people get older


THANK YOU

Female pie plot

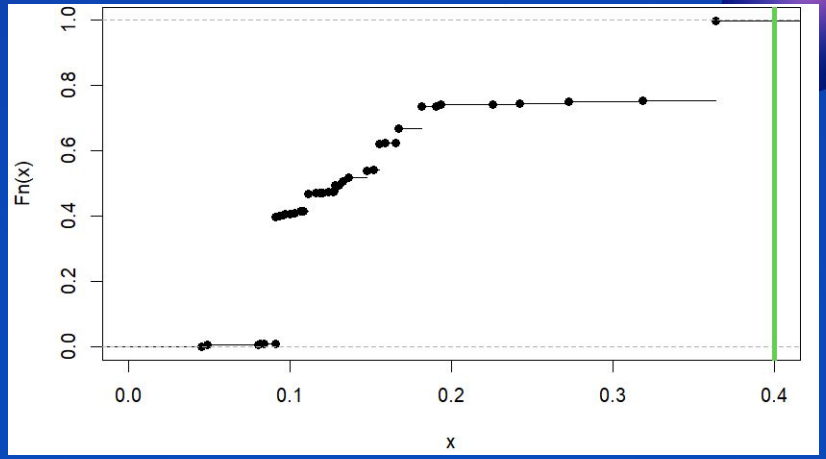


Male pie plot

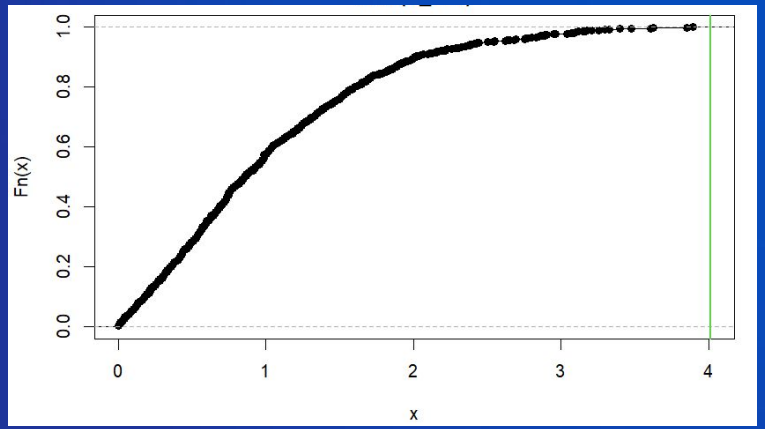


PLOTS TESTS

Permutation test on grouping



Permutation test on Age importance



Permutational ANOVA test on Sex importance