Cognitive Screening: Simulation (A2)

Hans-Aloys Wischmann and Marco Piccininni

Edited: 2024-03-14 / Executed: 2024-03-14

## [1] "Raw MoCA scores are rounded and clipped: FALSE"

| Parameter | Value |
| --- | --- |
| cutoff\_sens | 0.841 |
| cutoff\_spec\_high | 0.977 |
| cutoff\_spec\_low | 0.841 |
| edu\_age\_max | 64 |
| edu\_age\_min | 30 |
| n\_sample\_development | 5000 |
| n\_sample\_validation | 50000 |
| n\_simulation\_runs | 10000 |
| pop\_age\_max | 89 |
| pop\_age\_min | 55 |
| pop\_census | 2022 |
| pop\_yob\_max | 1967 |
| pop\_yob\_min | 1933 |
| score\_individual\_SD | 2.9 |
| score\_offset\_dem | -10.7 |
| score\_offset\_mci | -5.1 |

eTable e1: Published Regressions

| model\_name | intercept | age\_coeff | age\_offset | edu\_coeff | edu\_offset |
| --- | --- | --- | --- | --- | --- |
| Santangelo | 21.98 | 4.228000 | 1.58 | 3.201000 | 3.250000 |
| Conti | 23.28 | -0.175000 | 70.08 | -24.300000 | 0.126000 |
| Aiello | 24.17 | -0.000008 | 297,697.18 | 3.331407 | 2.325648 |

##   
## If you use pROC in published research, please cite the following paper:  
##   
## Xavier Robin, Natacha Turck, Alexandre Hainard, Natalia Tiberti,  
## Frédérique Lisacek, Jean-Charles Sanchez and Markus Müller (2011).  
## pROC: an open-source package for R and S+ to analyze and compare ROC  
## curves. BMC Bioinformatics, 12, p. 77. DOI: 10.1186/1471-2105-12-77  
## <http://www.biomedcentral.com/1471-2105/12/77/>  
##   
## A BibTeX entry for LaTeX users is  
##   
## @Article{,  
## title = {pROC: an open-source package for R and S+ to analyze and compare ROC curves},  
## author = {Xavier Robin and Natacha Turck and Alexandre Hainard and Natalia Tiberti and Frédérique Lisacek and Jean-Charles Sanchez and Markus Müller},  
## year = {2011},  
## journal = {BMC Bioinformatics},  
## volume = {12},  
## pages = {77},  
## }

## Prerequisites: Target Population

The target population distribution needs to be provided in a file “Italy\_Pop\_Age\_Sex\_Disease\_Prob.csv” with columns separated by “;”, including the variables sex (character “m” or “f”), edu (integer >= 1 [years]), age\_group (character = “age\_from-age\_to”), age\_from (integer >= 0, <= 99 [years]), age\_to (integer >= 0, <= 99 [years]), healthy (double >= 0.0, <= 100.0), mci (double >= 0.0, <= 100.0), dementia (double >= 0.0, <= 100.0). For each disease status, i.e., the columns healthy, mci, and dementia, the value indicates the proportion of the population that falls into the bucket defined by sex, age\_group, edu, and the disease status. The total sum across all observation rows for these disease status columns should be equal to 100.0 (up to rounding errors).

## Simulation Setup: Infinite Target Population

The infinite target population mimics the resident population in Italy, per January 1st, 2023, in the range from 55 to 89 years of age, as defined by realistic proportions by sex, age, education, and health status, the latter defined as exactly one of healthy, MCI, or dementia.

## Simulation Setup: Modeling MoCA Scores

We model the raw MoCA test score of healthy indivitualss using three different regressions that were published in recent normative studies in Italy [Aiello, 2021], [Conti, 2015], and [Santangelo, 2015]. Within each simulation run, each of these regression functions is used to compute one score for every indivituals in the development sample and in the validation sample.

For patients with MCI or dementia, these “healthy” MoCA scores are shifted by -5.1 and -10.7 points, respectively, where the offset values are the averages of a) the differences -5.333 ± 0.531 and -12.278 ± 0.592 between mean MoCA raw scores in a study in Portugal whose sub-groups were matched on age and education [Freitas, 2013], b) coefficients of -4.07 ± 0.63 and -9.66 ± 0.84 from a US study [Hong, 2022], and c) coefficients of -5.769 ± 0.696 and -10.147 ± 0.688 from a study in Hong Kong [Yeung, 2014], where the combined regression models in b) and c) included age and education in addition to status and other independent variables. For every indivituals, a normally distributed offset is added, with a mean of 0 and a standard deviation of 2.9, consistent with the standard deviation of the residuals in (2). If enable\_round\_clip is set to TRUE, the resulting raw MoCA scores are rounded to the nearest integer and clipped to the possible range of test scores, i.e., [0,30] points.

## Function to Correct Scores for Age and Education

Each published regression model function is fitted to the healthy subset of each development sample, and the coefficients are used to correct the scores of the development sample (for determining cutoffs) and of the validation sample (for evaluating auc as well as sensitivity and specificity for the cutoffs).

## Simulations

Perform 10000 simulation runs, where each run consists of the following steps:

* Selection of a development sample of 5000 persons and of a separate validation sample of 50000 persons, each as random samples from the infinite target population;
* Regression fit (for each regression model) of the raw scores of healthy indivitualss in the development sample, and correction of the raw scores for all indivitualss in the validation sample using the fitted coefficients, without any discretization nor clipping;
* Evaluation of overall discrimination power of the test using the area under the curve (AUC), separately for raw scores and for corrected scores, in the separate validation sample, for each regression model;
* Evaluation of sensitivity and specificity in the validation sample, separately for raw and for corrected scores, using cutoffs determined in the traditional manner from normative scores, i.e., pre-selected specificity among healthy indivitualss in the development sample, and then using cutoffs determined from the scores of the mci patients, i.e., pre-selected sensitivity among mci patients in the development sample.

AUC values are calculated for distinguishing:

* Patients with cognitive impairment (MCI or dementia) from healthy indivitualss, across the total validation sample;
* Patients with MCI from healthy indivitualss, in the absence of patients with dementia;
* Patients with dementia from healthy indivitualss, in the absence of patients with MCI.

Sensitivity and specificity are calculated (both in total and separately for each age/education box) for distinguishing patients with MCI from healthy indivitualss, in the absence of patients with dementia, as this reflects most closely the clinical setting of screening an asymptomatic population for (new onset) mild cognitive impairment, where the dementia patients will have already been identified and separated.

# Results

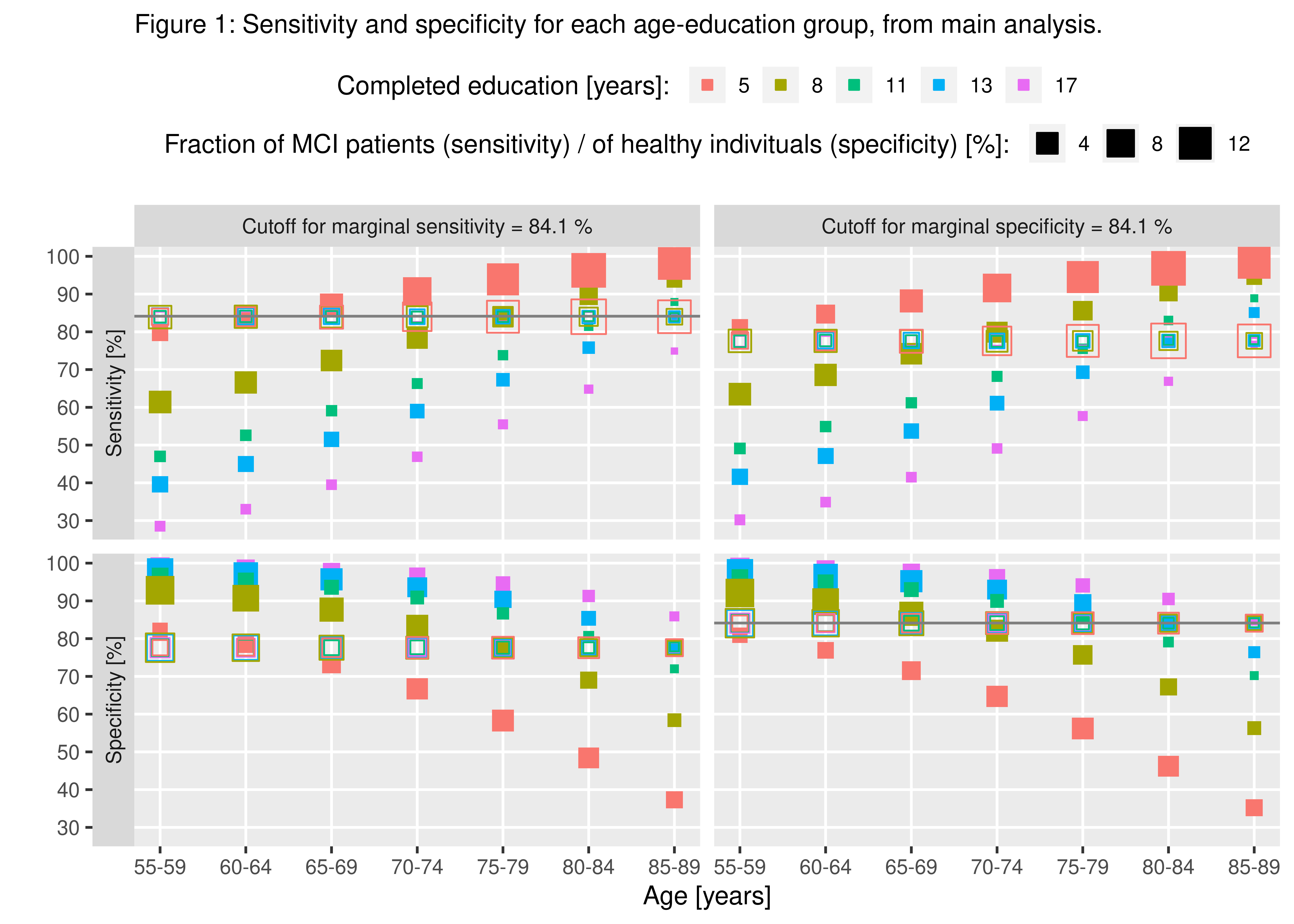


Table X: AUC (Model = Aiello, Validation Samples, 10000 Simulations)

| Scores | (MCI or Dem.) vs. Healthy | MCI vs. Healthy | Dementia vs. Healthy |
| --- | --- | --- | --- |
| Analytic (Corrected) | 0.9232 | 0.8932 | 0.9955 |
| Corrected | 0.9232 [0.918,0.928] | 0.8931 [0.887,0.899] | 0.9954 [0.994,0.996] |
| Raw | 0.9465 [0.944,0.949] | 0.9251 [0.921,0.929] | 0.9977 [0.997,0.998] |

Table X: AUC (Model = Conti, Validation Samples, 10000 Simulations)

| Scores | (MCI or Dem.) vs. Healthy | MCI vs. Healthy | Dementia vs. Healthy |
| --- | --- | --- | --- |
| Analytic (Corrected) | 0.9232 | 0.8932 | 0.9955 |
| Corrected | 0.9232 [0.918,0.928] | 0.8931 [0.887,0.899] | 0.9954 [0.994,0.996] |
| Raw | 0.9422 [0.939,0.945] | 0.9192 [0.915,0.923] | 0.9975 [0.997,0.998] |

Table X: AUC (Model = Santangelo, Validation Samples, 10000 Simulations)

| Scores | (MCI or Dem.) vs. Healthy | MCI vs. Healthy | Dementia vs. Healthy |
| --- | --- | --- | --- |
| Analytic (Corrected) | 0.9232 | 0.8932 | 0.9955 |
| Corrected | 0.9232 [0.918,0.928] | 0.8931 [0.887,0.899] | 0.9954 [0.994,0.996] |
| Raw | 0.9462 [0.943,0.949] | 0.9250 [0.921,0.929] | 0.9970 [0.996,0.998] |

Table X: Sens/Spec, Total and Range by Age/Edu (Aiello, Validation, 10000 Simulations)

|  |  | Raw | | Corrected | |  |
| --- | --- | --- | --- | --- | --- | --- |
| Age | Edu | Sensitivity [%] | Specificity [%] | Sensitivity [%] | Specificity [%] | cutoff |
| \* | \* | 51.6 [48.0,55.1] | 97.7 [97.2,98.1] | 40.6 [36.9,44.3] | 97.7 [97.2,98.1] | Spec = 97.7 % |
| 85.1 [83.6,86.5] | 84.1 [83.0,85.2] | 77.6 [75.5,79.6] | 84.1 [82.9,85.2] | Spec = 84.1 % |
| 84.0 [80.4,87.4] | 85.1 [81.6,88.1] | 84.0 [80.4,87.3] | 77.6 [73.2,81.6] | Sens = 84.1 % |
| (54,59] | 17 | 4.1 [0.0,16.7] | 100.0 [99.9,100.0] | 40.6 [15.4,66.7] | 97.7 [96.7,98.6] | Spec = 97.7 % |
| (84,89] | 5 | 81.7 [77.6,85.6] | 80.3 [76.4,84.1] | 40.6 [34.9,46.4] | 97.7 [96.4,98.8] |
| (54,59] | 17 | 30.2 [7.7,55.6] | 98.9 [98.2,99.4] | 77.5 [53.8,100.0] | 84.1 [81.5,86.6] | Spec = 84.1 % |
| (84,89] | 5 | 98.4 [97.3,99.3] | 35.2 [31.5,39.0] | 77.6 [73.3,81.6] | 84.1 [80.7,87.2] |
| (54,59] | 17 | 28.5 [6.7,53.8] | 99.0 [98.2,99.6] | 83.9 [62.5,100.0] | 77.6 [72.1,82.6] | Sens = 84.1 % |
| (84,89] | 5 | 98.1 [96.7,99.2] | 37.3 [30.3,44.5] | 84.0 [79.4,88.4] | 77.6 [72.2,82.6] |

Table X: Sens/Spec, Total and Range by Age/Edu (Conti, Validation, 10000 Simulations)

|  |  | Raw | | Corrected | |  |
| --- | --- | --- | --- | --- | --- | --- |
| Age | Edu | Sensitivity [%] | Specificity [%] | Sensitivity [%] | Specificity [%] | cutoff |
| \* | \* | 50.0 [46.5,53.4] | 97.7 [97.2,98.1] | 40.6 [36.9,44.3] | 97.7 [97.2,98.1] | Spec = 97.7 % |
| 83.6 [82.0,85.0] | 84.1 [83.0,85.2] | 77.6 [75.5,79.6] | 84.1 [82.9,85.2] | Spec = 84.1 % |
| 84.0 [80.4,87.4] | 83.6 [79.9,86.8] | 84.0 [80.4,87.3] | 77.6 [73.2,81.7] | Sens = 84.1 % |
| (54,59] | 17 | 2.5 [0.0,13.3] | 100.0 [99.9,100.0] | 40.6 [15.4,66.7] | 97.7 [96.7,98.6] | Spec = 97.7 % |
| (84,89] | 5 | 84.5 [80.6,88.1] | 77.1 [72.7,81.2] | 40.6 [35.1,46.2] | 97.7 [96.5,98.8] |
| (54,59] | 17 | 25.8 [5.6,50.0] | 99.2 [98.7,99.7] | 77.5 [53.8,100.0] | 84.1 [81.6,86.5] | Spec = 84.1 % |
| (84,89] | 5 | 99.0 [98.2,99.7] | 28.0 [24.4,31.7] | 77.6 [73.4,81.6] | 84.1 [80.8,87.2] |
| (54,59] | 17 | 26.7 [5.6,52.4] | 99.1 [98.3,99.7] | 83.9 [62.5,100.0] | 77.6 [72.2,82.6] | Sens = 84.1 % |
| (84,89] | 5 | 99.1 [98.1,99.8] | 27.3 [20.6,34.2] | 84.0 [79.4,88.4] | 77.6 [72.3,82.5] |

Table X: Sens/Spec, Total and Range by Age/Edu (Santangelo, Validation, 10000 Simulations)

|  |  | Raw | | Corrected | |  |
| --- | --- | --- | --- | --- | --- | --- |
| Age | Edu | Sensitivity [%] | Specificity [%] | Sensitivity [%] | Specificity [%] | cutoff |
| \* | \* | 51.9 [48.2,55.4] | 97.7 [97.2,98.2] | 40.6 [36.9,44.3] | 97.7 [97.2,98.1] | Spec = 97.7 % |
| 85.1 [83.6,86.5] | 84.1 [83.0,85.2] | 77.6 [75.5,79.6] | 84.1 [82.9,85.2] | Spec = 84.1 % |
| 84.0 [80.4,87.3] | 85.1 [81.6,88.1] | 84.0 [80.4,87.3] | 77.6 [73.2,81.6] | Sens = 84.1 % |
| (54,59] | 17 | 2.0 [0.0,12.5] | 100.0 [99.9,100.0] | 40.6 [15.4,66.7] | 97.7 [96.7,98.6] | Spec = 97.7 % |
| (84,89] | 5 | 76.6 [72.0,80.9] | 84.9 [81.5,88.1] | 40.6 [34.9,46.4] | 97.7 [96.4,98.8] |
| (54,59] | 17 | 19.9 [0.0,42.9] | 99.5 [99.1,99.9] | 77.5 [53.8,100.0] | 84.1 [81.5,86.6] | Spec = 84.1 % |
| (84,89] | 5 | 97.4 [96.1,98.6] | 42.5 [38.5,46.4] | 77.6 [73.2,81.7] | 84.1 [80.7,87.3] |
| (54,59] | 17 | 18.5 [0.0,41.7] | 99.6 [99.1,99.9] | 83.9 [62.5,100.0] | 77.6 [72.1,82.6] | Sens = 84.1 % |
| (84,89] | 5 | 97.0 [95.1,98.6] | 44.7 [37.0,52.2] | 84.0 [79.4,88.4] | 77.6 [72.1,82.6] |