# Predictive assessments of pharmacokinetic alterations in subjects with renal disease

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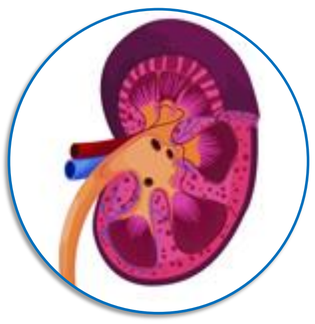
## BACKGROUND.



The kidneys are one of the most important organs responsible for the elimination of xenobiotics; for this reason, regulatory authorities are often requesting pharmacokinetic studies in subjects with renal impairment to identify the dose level that is able to realize a similar drug systemic exposure in these subjects compared to healthy subjects.
The **objective** of this work is to find a model capable of predicting, relying on a minimum amount of PK information in normal subjects, the effect of renal impairment on the exposure of a drug. Three categories of renal impairment (mild, moderate and severe) were considered according to the KDIQO (Kidney Disease - Improving Global Outcome) guideline.

## MATERIALS AND METHODS.

### *Data collection and preprocessing*

For a list of **64 marketed medications**, PK descriptors and recommended dosage adjustments for subjects with renal impairment were obtained from drug labels via the Daily Med website [1] and from other literature sources.

$$AUC\ ratio = \frac{AUC_{disease}}{AUC_{normal}}$$

*PK parameters*

| Generic | CL/F (L/h) | F (%) | CL (L/h) | Ae (%) | ppb (%) | EH | AUC ratio mild/normal | AUC ratio moderate/normal | AUC ratio severe/normal |
|---|---|---|---|---|---|---|---|---|---|
| Abiraterone acetate | 1550 | 5 | NA | 0 | 99 | 0.94 | 1 | 1 | 1 |
| Alvimopan | NA | 6 | 24.12 | 35 | 80 | 0.16 | 1 | 1 | 1 |
| Aripiprazole | 3.6 | 87 | NA | 0 | 99 | 0.03 | 1.33 | 1.16 | 0.76 |
| Meropenem | NA | NA | 15.4 | 73.70 | 2 | 0.04 | 2.49 | 4.33 | 10.91 |

### *Two different analyses*

**1)** Exploring the potential correlations between the **AUC ratios** and the PK variables for each level of renal impairment.

AUC ratio $\overset{?}{=} f($ PK parameters $)$

- Multiple linear regression (MLR)
- PLS-NIPALS regression

**2)** Classifying the drugs in different **levels of risk** of administering wrong dosage to renal impaired patients basing on their PK parameters.

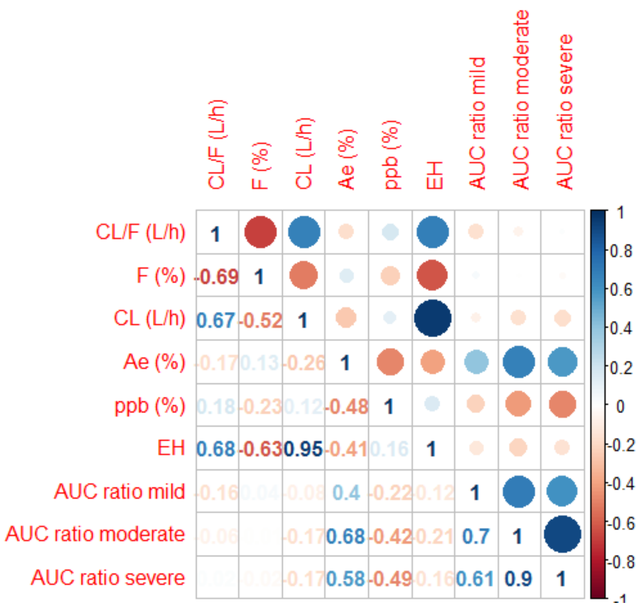
Level of risk $\overset{?}{=} f($ PK parameters $)$

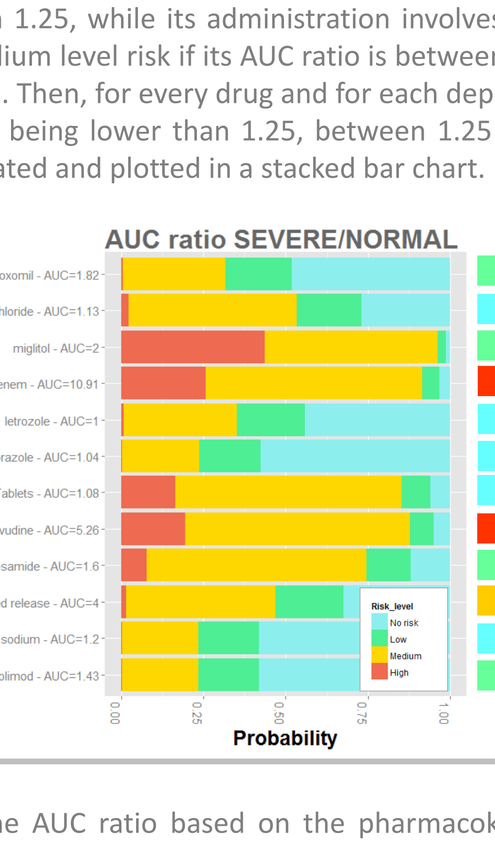
- CN2 rules
- *k*-Nearest Neighbours (*k*-NN)
- Naïve Bayes (NB)
- Self-Organizing Maps (SOM)
- Classification Tree
- Support Vector Machine (SVM)

## RESULTS.

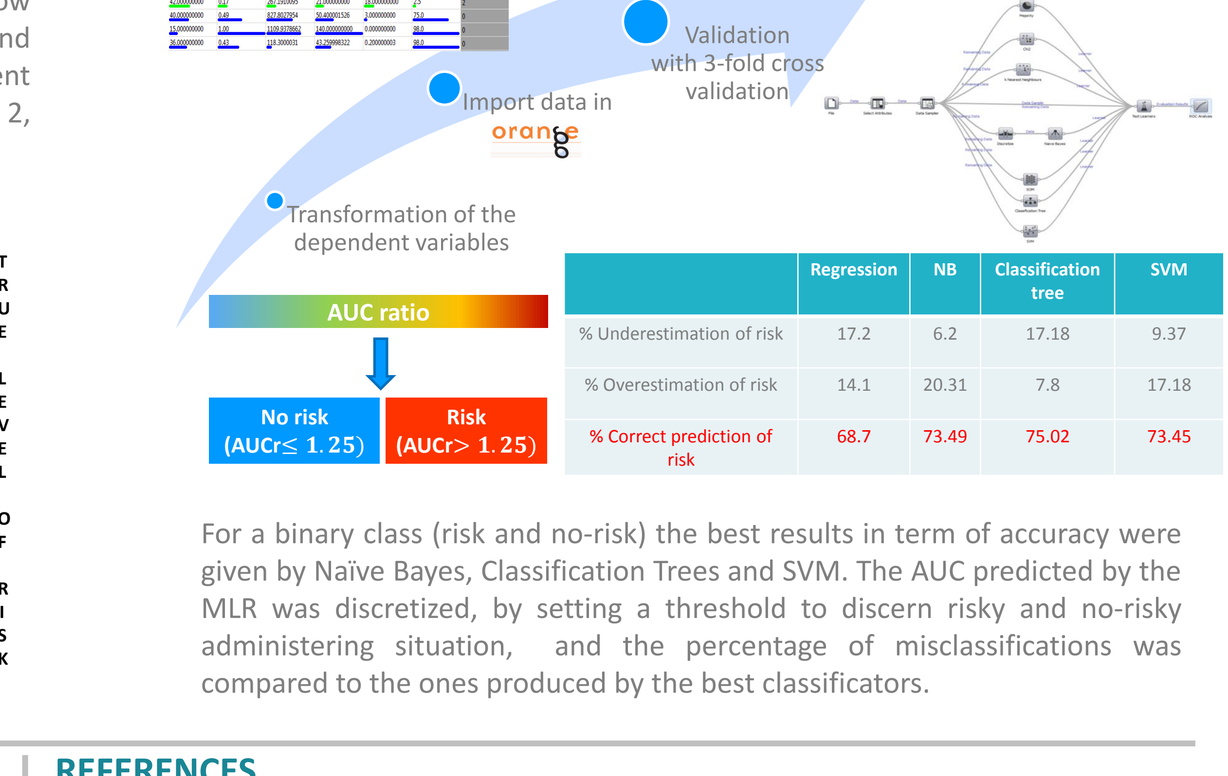
### 1) *Univariate analysis*

Only amount excreted unchanged in urine (**Ae**) and binding to plasma protein (**ppb**) show a correlation with the AUC ratios.




### *Multiple linear regression (MLR) with stepwise selected regressors*




$$AUCratio_{mild} = \hat{\beta}_0 + \hat{\beta}_1 Ae$$

$$AUCratio_{moderate} = \hat{\beta}_0 + \hat{\beta}_1 Ae$$

$$AUCratio_{severe} = \hat{\beta}_0 + \hat{\beta}_1 Ae + \hat{\beta}_2 ppb$$

### *Post-processing of regression predictions*

For each severity level, all the drugs have been classified in four levels of risk of overexposure: no risk, low, medium and high, according to their real AUC ratios and three defined threshold values. A drug is considered safe if its AUC ratio is lower than 1.25, while its administration involves a low level risk if its AUC ratio is between 1.25 and 2, a medium level risk if its AUC ratio is between 2 and 5, and a high level risk if its AUC ratio is greater than 5. Then, for every drug and for each dependent variable, the probabilities of the MLR predictions of being lower than 1.25, between 1.25 and 2, between 2 and 5 and greater than 5 have been calculated and plotted in a stacked bar chart.

- AUC ratio>5 • High risk of overexposure
- 2<AUC ratio<5 • Medium risk of overexposure
- 1.25<AUC ratio<2 • Low risk of overexposure
- AUC ratio<1.25 • Safe administration




### 2) *Classification problem*




| | Regression | NB | Classification tree | SVM |
|---|---|---|---|---|
| % Underestimation of risk | 17.2 | 6.2 | 17.18 | 9.37 |
| % Overestimation of risk | 14.1 | 20.31 | 7.8 | 17.18 |
| % Correct prediction of risk | 68.7 | 73.49 | 75.02 | 73.45 |

For a binary class (risk and no-risk) the best results in term of accuracy were given by Naïve Bayes, Classification Trees and SVM. The AUC predicted by the MLR was discretized, by setting a threshold to discern risky and no-risky administering situation, and the percentage of misclassifications was compared to the ones produced by the best classificators.

## CONCLUSIONS.

A quantitative prediction of the increase of the AUC ratio based on the pharmacokinetic characteristics can be done with a reasonable degree of accuracy. The proposed approaches may provide a useful guidance for designing the studies of new compounds and for highlighting the specific physiological aspects that need additional investigations.

## REFERENCES.

[1] http://dailymed.nlm.nih.gov/dailymed/index.cfm
[2] http://orange.biolab.si/