Empirical assessment of case-based methods for the identification of drug–related Acute Liver Injury (ALI) in the French nationwide healthcare database (SNDS)

Nicolas Thurin[1,2,3], Régis Lassalle[1], Patrick Blin[1], Marine Pénichon[1], Martijn Schuemie[4], Joshua J Gagne[5], Jeremy Rassen[6], Jacques Benichou[7,8], Alain Weill[9], Cécile Droz-Perroteau[1], Nicholas Moore[1,2,3]

[1]Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France; [2]INSERM U1219, Bordeaux, France; [3]CHU de Bordeaux, Bordeaux, France; [4]Observational Health Data Sciences and Informatics , New York, USA; [5]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, USA; [6]Aetion, Inc., New York, USA; [7]CHU de Rouen, Rouen, France; [8]INSERM U1219, Rouen, France; [9]Caisse Nationale de l'Assurance Maladie, Paris, France

Background

- **Acute liver injury (ALI)** is a common reason for withdrawing drugs from the market
- **SNDS** is the French Nationwide Healthcare System Database
  - covering 66.6 million persons (99% of the French population)
  - including individual pseudonymised information on
    - Sociodemographics
    - Hospital diagnoses
    - Procedures
    - Drug dispensings
    - Deaths
    - Costs, *etc.*
  - available for public health purposes, including drug-related risk identification
- Risk identification performances depends on
  - the method
  - the method settings
  - the environment = **the database**

➔ **Tools need to be tested and assessed in *real life* to ensure the generation of meaningful point estimates.**

Conflict of interest statement

The ALCAPONE project was funded by the French Ministry of Health (PREPS, 14-0635)

Objectives

- To compare case-based methods to measure an association between a suspected drug and Acute Liver Injury (ALI)

Methods

- **Construction of a drug reference set adapted to the French Market**
  - Composed of 81 drug controls supposed associated (positive) or not (negative) with the outcome
  - Restricted to the pairs with the minimum detectable relative risk <1.30
- **SNSD data extraction** based on all ALI cases between 2009 and 2014
- **Detection of drug-outcome pairs** *via* 2 designs and different settings
  - 96 self-controlled case series (SCCS) variants
  - 20 case control (CC) variants

  ➔ Generation of one point estimate by control by variant: 2 900 in total
- **Performance assessment** of the design variants based on
  - Discriminating power: area under the ROC curve (AUC)
  - Accuracy: mean square error (MSE) and coverage probability

Results

Self-controlled case series

Table 1. Results of the 10 best SCCS design variants for ALI

AUC	MSE	Coverage of 95% CI	Sensitivity	Specificity	Design
0,937	0,221	0,571	0,889	0,571	First occurrence of the outcome, risk window = period of dispensation
0,929	0,215	0,571	0,889	0,571	All occurrences of the outcome, risk window = period of dispensation, adjusted on age
0,929	0,215	0,571	0,889	0,571	All occurrences of the outcome, risk window = period of dispensation, adjusted on age and seasonality
0,929	0,216	0,571	0,889	0,571	All occurrences of the outcome, risk window = period of dispensation
0,929	0,216	0,571	0,889	0,571	All occurrences of the outcome, risk window = period of dispensation, adjusted on seasonality
0,929	0,221	0,571	0,889	0,571	First occurrence of the outcome, risk window = period of dispensation, adjusted on age and seasonality
0,929	0,221	0,571	0,889	0,571	First occurrence of the outcome, risk window = period of dispensation, adjusted on age
0,929	0,221	0,571	0,889	0,571	First occurrence of the outcome, risk window = period of dispensation, adjusted on seasonality
0,929	0,222	0,857	0,722	0,857	First occurrence of the outcome, risk window = period of dispensation, adjusted on age and multiple drugs
0,929	0,224	0,857	0,722	0,857	First occurrence of the outcome, risk window = period of dispensation, adjusted on multiple drugs

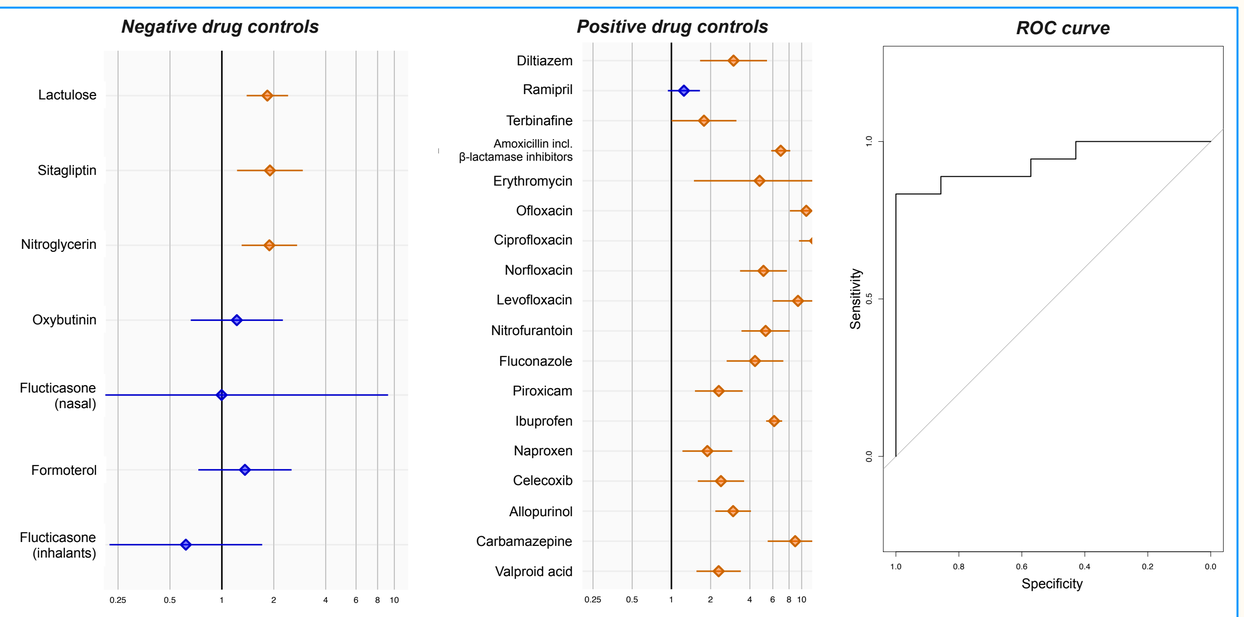

Figure 1. Positive and negative control plot, and ROC curve for the best SCCS variant

Case-control

Table 2. Results of the 10 best CC design variants for ALI

AUC	MSE	Coverage of 95% CI	Sensitivity	Specificity	Design
0,921	0,280	0,857	0,889	0,857	Up to 2 controls per case, all occurrences of the outcome, 7d risk window, matched on age and gender
0,899	0,322	0,857	0,833	0,857	Up to 2 controls per case, first occurrence of the outcome, 7d risk window, matched on age and gender
0,889	0,228	0,714	1,000	0,714	Up to 2 controls per case, first occurrence of the outcome, 30d risk window, matched on age and gender
0,873	0,250	0,571	1,000	0,571	Up to 10 controls per case, all occurrences of the outcome, 7d risk window, matched on age and gender
0,857	0,242	0,714	1,000	0,714	Up to 2 controls per case, first occurrence of the outcome, 60d risk window, matched on age and gender
0,857	0,380	0,571	1,000	0,571	Up to 10 controls per case, first occurrence of the outcome, 7d risk window, matched on age and gender
0,849	0,271	0,286	1,000	0,286	Up to 10 controls per case, all occurrences of the outcome, 30d risk window, matched on age and gender
0,841	0,246	0,286	1,000	0,286	Up to 10 controls per case, first occurrence of the outcome, 30d risk window, matched on age and gender
0,841	0,355	0,571	1,000	0,571	Up to 2 controls per case, all occurrences of the outcome, 30d risk window, matched on age and gender
0,833	0,257	0,286	1,000	0,286	Up to 10 controls per case, first occurrence of the outcome, 60d risk window, matched on age and gender

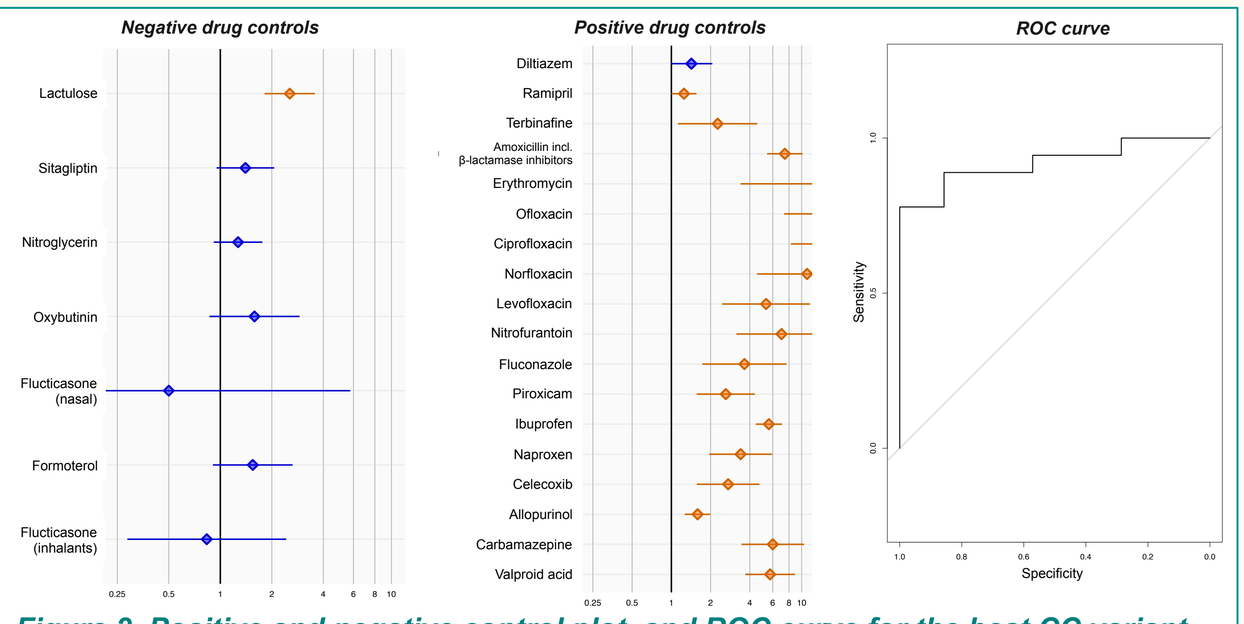

Figure 2. Positive and negative control plot, and ROC curve for the best CC variant

- 5 152 patients were extracted on 2009-2014, corresponding to 5 225 ALI
- 25 out of the 81 controls were considered as detectable (MDRR<1.30)
- The AUC>0.90 for 40/96 SCCS and 1/20 CC
- The AUC<0.80 for 8/96 SCCS and 6/20 CC
- The top 40 SCCS shared the same risk window (=period of dispensation)
- SCCS seem to be more discriminant and accurate than CC [Table 1 & 2]
  - 10 best SCCS variants
    - 0.93<AUC<0.94
    - MSE≈0.22
  - 10 best CC variants
    - 0.83<AUC<0.92
    - 0.23<MSE<0.38
- The best CC variant achieved a better specificity than the best SCCS variant (0.857 *vs.* 0.571) [Figure 1 & 2].
- The best AUC was however observed for the best SCCS variant (0.94)

Conclusion

- Performances of methods depend on parameter settings, which should be carefully selected according to the drug and outcome of interest
- SCCS globally achieves better results than CC for drug-related ALI evaluation
- Designs and settings tested can be used as reference methods for the identification of drug-related outcome in the SNDS

2019 ISPE Mid-Year Meeting
April 8-9, 2019, Rome, Italy
Poster #12

Scan me to download this poster !