Reviewer's report

Title: Adverse drug events with hyperkalemia during hospitalization: Evaluation of an automated method for retrospective detection in hospital databases

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Reviewer: Vassilis Koutkias

Reviewer's report:

This study elaborated on the evaluation of an automated method for retrospective detection of adverse drug events concerning hyperkalemia. For this evaluation the authors employed data obtained from a general hospital in a continuous 9-month period. The automated method relies on what the authors call "complex detection rules", which have been extracted by exploiting observational electronic data to identify drug safety risks. Observational data are gaining wide interest lately (as a secondary use / repurposing) for detecting drug safety issues (e.g. within EU-ADR, Mini-Sentinel and OMOP projects).

While several methods have been proposed to analyze observational data for drug safety risk detection, a series of empirical assessments that have been conducted recently [cf. Ryan PB, et al. A Comparison of the Empirical Performance of Methods for a Risk Identification System. Drug Saf (2013) 36 (Suppl 1):S143–S158], revealed that high false-positive rates are still a major limitation of all methods. While trying to eliminate this shortcoming, the trade-off between sensitivity and specificity is another concern towards the optimal detection.

The present study demonstrates significant results along the above perspectives. Still, the authors discuss the weakness in generalizing the outcomes, given the employed dataset and the specific focus on hyperkalemia-related ADEs. These two aspects have been recognized as important limitations on reproducibility of the outcomes in other studies as well [cf. Schuemie MJ, et al. Replication of the OMOP Experiment in Europe: Evaluating Methods for Risk Identification in Electronic Health Record Databases. Drug Saf (2013) 36 (Suppl 1):S159–S169.]

Thus, it is important that the authors compare in the paper their outcomes with those obtained from three other studies coping with hyperkalemia-related ADEs.

Overall, the study is sound and the methodology is appropriate. However, there are various issues that have to be tackled and clarified before considering the paper for publication.

- Major Compulsory Revisions

1) Definitions of ADRs and ADEs are provided as background information. It is not clear, however, what exactly the underlying method is capable of detecting. Is it rules for detecting preventable ADEs (i.e. not ADRs), is it ADEs in general? How can this be specified in rule-induced methods? If it is only on type of ADEs,
it is suggested to shorten the relevant paragraphs, because they may be quite confusing for the reader. Citations to widely accepted definitions of these concepts shall be sufficient. Likewise, please, clarify and potentially revise appropriately the respective text (lines 70-72).

2) It is considered essential to explicitly state what the novelty of the proposed detection rules is. For example, can the 18 rules presented in the study be found in commercial pharmacovigilance databases?

3) Please clarify whether there is any relation between the data used for evaluation and the data used to extract the detection rules.

4) The structure of the employed rules (presented in line 100) has to be explained. What is a Cause in the general case? Why only AND is foreseen as an operator linking Causes?

5) The selection of the “5 days” threshold in the “chronology of the rules” is not self-evident. A justification has to be provided.

6) It is important to refer to recent studies presenting and evaluating methods for drug safety risk detection exploiting observational healthcare data. Also, as the authors concentrate on the "strength" of laboratory examination results for detecting ADEs, reference to relevant studies could be provided as well (e.g. [Liu M, et al. Comparative analysis of pharmacovigilance methods in the detection of adverse drug reactions using electronic medical records. JAMIA (2013) 20(3):420-426]). Overall, the bibliography of the paper shall be updated with more recent works.

- Minor Essential Revisions

1) There are various typos as well as syntax and grammar issues. An indicative list follows:

- "ADEs with hyperkalemia" or "ADEs related with hyperkalemia"? This is phrase is used throughout the paper and its title as well.
- Abstract: replace "rules" taking into" with "rules", which take into"
- Abstract, replace "the data used are" with "the data used concern"
- Abstract, "quality of the set...": the term "quality" is vague. Please revise.
- Abstract: It is suggested to rephrase the Results paragraph to be more communicative.
- "In post-marketing (phase IV trials), pharmacovigilance studies..." sentence requires revision.
- "The quality of these tools depends on the quality of the detection rules they implement.": Since it is not necessary that detection tools employ rules, it is suggested to refer at "detection logic" which is more general.
- replace "Recall and precision are defined in the following method" with "Recall and precision are defined in Methods section".
- replace "the “drug - lab alerts” describes" with "the “drug - lab alerts” describe"
- replace "details in the method" with "details in the Methods section"
- replace "...‘expert judgment’, and “algorithm”’ with "... “expert judgment”, and "algorithmic approaches”".
- replace "the average review delay" with "the average review time/duration"
- "small effective of serious ADEs": phrase not favorable, please revise.
- replace "These results presented" with "The results presented"
- Conclusions, replace "rules were evaluated retrospectively on a French general hospital during the first nine months of 2010" with "rules were evaluated retrospectively using data from a French general hospital obtained during the first nine months of 2010".

2) Some acronyms like ATC, C-NPU etc. are not defined in the text. Overall, please define acronyms in their first occurrence in the manuscript and use them thereon (cf. ADE proper use).

3) In some cases, redundant information is provided in the paper (e.g. "This work is performed in ignoring the results obtained by an automated analysis of inpatient stays.", "The expert review has highlighted 57 ADEs with hyperkalemia"). Please check the entire manuscript and omit such redundant parts.

4) In table 5, last column label: shouldn’t be "AD and ER" instead of "HD and ER"?

- Discretionary Revisions
1) It is suggested to describe the Kramer algorithm via a flowchart, instead of using plaintext.
2) "Tools for ADE detection": Given the content of this section, it is suggested that the title explicitly refers to "Computerized" Tools.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.