Manuscript ID: RJournal 2022-54

Title: Likelihood Ratio Test-Based Drug Safety Assessment Using R Package pvLRT

Responses to Reviewers' Comments

We thank the editorial team for the time spent on our paper and for the provided comments and feedback. In what follows, we address point-by-point all comments/questions made by the reviewers. To facilitate ease of communication we state in italic fond the questions/comments made by the reviewers and place our answers immediately below the statement.

Reviewer 1
Title: Likelihood Ratio Test-Based Drug Safety Assessment using the R Package pvLRT

This was a very interesting article! I appreciate the motivation of the problem at hand as well as the testing solutions. The package creates a nice solution for a niche but important testing framework.

Answer: We thank the reviewer for the comment, and for acknowledging the importance of the testing framework. Thank you, indeed, for the kind words.

My two biggest comments to address are page 3 (input data) and throughout the "Other" column in the data. Regarding page 3 input data, the user needs more guidance on how choices in preparing the data affect or do not affect the testing results. In addition, as row names are less commonly used features, the developers should provide guidance on how to appropriately format input data. Regarding "Other" therapies, the importance/implications/interpretation of this should be discussed.

Answer: We thank the reviewer for these comments. With respect to the preparation of input data, we refer the reader to the supplement of the paper by Ding, Markatou and Ball (2020, *Statistics in Medicine,* vol 39, issue 7, 845-874), pages 2 and 3 where we offer a complete description of how files were prepared.

With respect to providing guidance for data preparation, please see page 3 of the revised manuscript, line 5 of the third paragraph (line starting with "The package provides a convenience function…") presents the added functionality for data pre-processing.

Regarding the suggestion related to "Other" therapies, please see page 7 of the revised manuscript, line 9 counting from the beginning of the first paragraph under the heading "Adverse Event Data Analysis with pvLRT" where the implications of the "Other" column are discussed. This discussion starts with the paragraph "Second, one needs to identify which drugs….".

There are a few typos throughout? Please correct.

Answer: Thank you for your comment. We went very carefully, over the manuscript and made corrections as issues were identified. We hope that we have found and corrected all typos, please do let us know in the case of identification of new ones.

In general, the version of the package the manuscript is based needs to be the CRAN version. In addition, I encourage you to provide additional documentation on the github repository with examples in the readme, or even better, a pkgdown website with articles detailing some of these examples.

Answer: We thank the reviewer for these excellent suggestions, which we plan to implement in the near futureFurthermore, please see section entitled "**Discussion and Future Directions**" on page 19 of the revised manuscript where the sentence

"Include additional processed datasets, and expand the current documentations with examples on these additional datasets."

is added.

Page 2: Table 1; could be enhanced by 1) including a high level methods column (for example, PhViD implements methods such as PRR, ROR, and BCPNN, and (2) possibly reframing not as existing CRAN packages, but existing packages, and adding pvLRT to the table as well for easier comparison.

Answer: We thank the reviewer for these suggestions. Please notice that we added an additional column to Table 1 (on page 2) listing the methods the packages incorporate, and added our own package "pvLRT" as a new row. We have also updated the table caption to read "Table 1: Existing R packages on CRAN with functionalities for pharmacovigilance." We highlight the 'CRAN' aspect of these packages to make the scope of the table well-defined and to exclude under-development packages that may be available on the internet (e.g., via GitHub) but not yet published on CRAN.

Page 3: "the input data in pvLRT are always assumed to be pre-processed contingency tables (matrix like objects) enumerating adverse events report counts with AEs along the rows and Drugs (or other medical products) along the columns." I understand the motivation for this design choice. However, it would be helpful if there are guidelines or gotchas for the data preparation. For example, how are users expected to handle multiple AEs from the same subject. Should all AEs be included in the matrix? Or what is the impact (or non-impact) of this on your methodology? Or can you even typically identify that from this type of data? Are there any other data preparation considerations to mention?

Answer: We thank the reviewer for raising this point. In pvLRT v0.5 we have now included a new function that converts raw adverse event reporting data cataloging incidences of AE/drug pairs into a processed contingency table enumerating total counts per pair. This function also now helps distinguish raw adverse event data with processed count data (please also see our response to your next comment). The function can now optionally group AEs of less interest as "Other AE". We have also added discussion on these points on the revised manuscript (p. 8).

It is also an unusual choice to require rownames on the input matrix, as rownames are less commonly used recently. If you want the user to supply data of this format, a description of how to get your data in this format would be helpful.

Answer: Please note at the outset that the input data for pvlrt() is a pre-processed contingency table in a matrix-like form summarizing counts of Drug/AE pairs, and not the raw adverse event data (usually stored

in a data-frame like object). Unlike a data-frame that can contain data of different types as columns, numeric matrices in R cannot contain character columns, and hence the AE names has to be passed as row names. We do however recognize the potential confusion. In pvLRT v0.5 we have now included a new function convert_raw_to_contin_table() that summarizes and converts a raw adverse event reporting dataset into a processed contingency table in matrix form ready for use in pvlrt(). this In the revised manuscript we have also emphasized this point in the discussion on p. 8.

Page 4: Avoid making your reader feel inferior! Remove "Clearly the model reduces" in favor of "The model reduces" at the bottom of page 4.

Answer: We thank the reviewer for this suggestion. Please see page 5, the subsection entitled "Parametric hypothesis testing for signal in pharmacovigilance based on a Zero-Inflated Poisson (ZIP) model", where the suggested change is incorporated.

Page 7: Please add a description of what 7 is doing here "drug_class_idx=list(1:6, 7)". I am also curious if it is truly essential to require the user to specify both "test_drug_idx" and "drug_class_idx", or if 1:n-1 could be a default behavior, and the user is expected to only pass columns desired for analysis.

Answer: Thank you for these great suggestions. At the outset we note that up to version <= 0.4 of pvLRT all columns were required to be supplied in drug_class_idx to specify the class/group structure among the drugs required for simultaneous LRT. However, this comment led us to realize that this class structure is actually only necessary for drugs that are being tested (as supplied through test_drug_idx). Therefore, in version 0.5 we have relaxed the requirement so that the function now accepts partial specification of drug_class_idx: it now only requires class structures for the drugs present in test_drug_idx, and further, any drug that is present in test_drug_idx but absent in drug_class_idx now forms its own class. We also appreciate your suggestion on the default behaviors for these two parameters. Following your suggestion, test_drug_idx now defaults to 1:(ncol-1) and drug_class_idx now defaults to list(test_drug_idx) ensuring all drugs specified in test_drug_idx are now by default simultaneously tested in an extended LRT framework. With a view to this new default, we have now removed the specification of drug_class_idx from all pvlrt() calls (on p. 8, 12, 13, 15, and 17); however, we have kept the specification of test_drug_idx intact to highlight which drugs are being tested.

Page 8: "The likelihood ratio test statistics and p-values for all AE/drug pairs can be extracted using summary(). This will produce a data table, with each row providing the sample size, likelihood ratio, and p-value for each AE/drug pair present in the data."

It is worth describing that summary(obj) prints abbreviated output whereas storing this as y<-summary(obj) allows access to all results.

Answer: Thank you for your suggestion. We have added the following footnote while discussing summary(obj) on p. 9:

"The default printing specifications for a data.table object applies to the resulting summary, which abbreviates the output to show results for the top 5 and bottom 5 AE/drug pairs (arranged with respect to the computed LRT values) on the console for large summary tables. To print more pairs, use e.g.,

summary(test_statin46_poisson) %>% print(n) with a larger n. Storing the summary output to an object, e.g., summary_test <- summary(test_statin46_poisson) allows access to results from all pairs."

Page 8: Regarding plot figures, a useful option may be for the user to either show n or pct, where pct=percent of total AEs reported for that therapy. I am not 100% convinced the percent is meaningful in this context, and I welcome discussion.

Answer: We thank the reviewer for the suggestion and for raising the question of the importance of the percentage reporting in this context. We prefer to report the number n of AEs as opposed to the percentage, as we believe that reporting percentages is subject to confusion related to the denominator used to compute the percentage, and in certain cases may lead to misleading conclusions. Given these, we have elected to not report the percentages.

Lastly, the importance and interpretation of "Other" column in both the input data and the output test results is not clearly defined and needs to be more explicitly discussed.

Answer: We thank the reviewer for raising this important point. We have added a discussion on p. 7 (first paragraph) under "Adverse Event Data Analysis with pvLRT".

Reviewer 2

Review Comments for "Likelihood Ratio Test-Based Drug Safety Assessment using the R Package pvLRT"

This paper presented a new R package, "pvLRT" for drug safety assessment using likelihood ratio tests. The package implements a suite of LRT approaches and various post-processing and graphical summary functions.

I installed the "pvLRT" package and ran the example code files. All the functions can be smoothly implemented. The paper is also cleanly well-written. It seems that the R-package is an excellent contribution to the Drug Safety Assessment.

Answer: We thank the reviewer for the accurate and succinct description of our work and for the positive comment on our work. Thank you!

I have one specific comment.

The main statistical models in the package were Poisson regression and Zero-inflated Poisson for contingency tables. AIC can be used for model selection. In statistics, Logit models are also often used in this kind of data. Indeed, there is a close connection between the Logit model and the log-linear model. Could you implement the Logit model in your applications? How do you compare the Logit model and log-linear model in your setting?

Answer: Thank you for this note. Indeed, the reviewer is correct in both fronts – first, the analysis of the association between AE/drug pairs can indeed also be performed through a series of logistic regression models with the binary presence/absence of AEs in individual case reports as the response and the presence/absence of different drugs as predictors. Second, there indeed is a close connection between these logistic regression models and the log-linear model considered in our package/paper. Specifically, when the count data are generated from a Poisson model, identical maximum likelihood-based inferences are obtained on the AE/drug associations from both the log-linear and the logistic regression models (Agresti 2013). However, the log-linear model is more flexible than the logistic regression model in that by relaxing the Poisson model assumption it can handle a richer set of data (e.g., with zero-inflation), making it particularly useful for modeling adverse event data. We have included a comparative discussion of logistic vs. log-linear models on p. 4 (second paragraph) of the revised manuscript.

References

Agresti, Alan. 2013. *Categorical Data Analysis*. John Wiley & Sons.