Risk Stratified Analysis of Treatment Effect in Electronic Health Records

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Background

In evidence based medicine treatment decisions depend on globally derived treatment effect estimations (average treatment effects). However, individual treatment results may often vary substantially from the expected average outcome, leading to what is called heterogeneity of treatment effect [3].

Clinical trials assess this heterogeneity using subgroup analyses. Such analyses often lead to biased results, especially when treatment effects depend on coexistence of multiple patient characteristics, which are only assessed on a one-at-a-time basis. On the other hand, multivariable subgroup analyses quickly become under-powered.

Kent et al proposed risk stratified analysis of treatment effect as an alternative to subgroup analyses [1]. They applied their proposal on 32 large clinical trials [2], where they concluded that higher risk patients often account for most of treatment benefit. Contrarily, treatment with estimated overall benefit may even be harmful to low risk patients, in presence of positive probability of treatment-related harm.

In this work, the risk stratification method proposed will be transported from clinical trial data to the case of Electronic Health Records (EHR).

Methods

Cohort	Definition
Treatment	New users of celecoxib with rheumatoid arthritis or osteoarthritis and established cardiovascular disease.
Comparator	New users of naproxen with rheumatoid arthritis or osteoarthritis and established cardiovascular disease.
Outcome	Patients with clinically significant gastrointestinal events (CSGE).

Patients from the treatment cohort were matched to patients from the comparator using 1:1 propensity score matching. A Cox proportional hazards model was then fitted to the matched population to compare overall treatment effects.

A LASSO logistic regression model was developed based on the combined population of treatment and comparator cohorts to assign individual probabilities of the outcome.

Risk stratification was made on quartiles of predicted risk. Within each stratum patients were matched using the previous propensity score matching scheme. Cox proportional hazards model was used to produce stratum-specific comparisons.

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Results

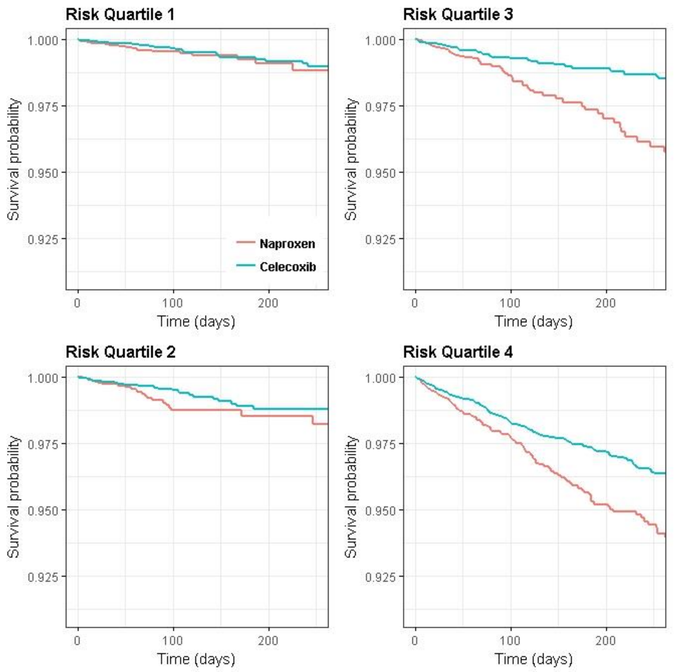

Figure 1: Kaplan-Meier survival curves within each quartile of predicted risk.

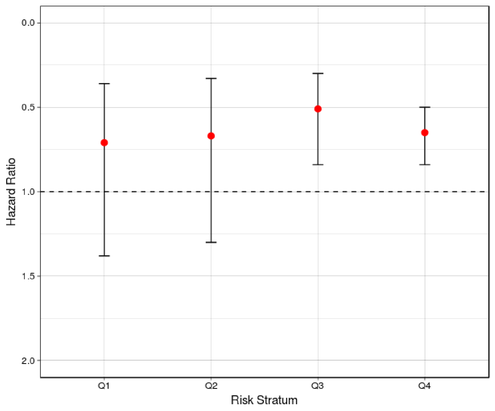

Figure 2: Estimated hazard ratios along with 95% confidence intervals, within each quartile of predicted risk.

In all risk quartiles there appeared to be no notable difference in risk of CSGE on the relative scale, which can be inferred by the very similar estimated hazard ratios within risk quartiles. This could be hint of presence of treatment effect heterogeneity on the absolute scale. Finally, differences in width of the confidence intervals can be partially attributed to non-constant number of patients being matched within risk strata.

Conclusions

An implementation of risk stratified analysis of treatment effect was carried out and will be made available to the OHDSI community. The proposed method gave promising results in detecting heterogeneity of treatment effect from EHR, even though work is still required to cope with their special characteristics. In the future, other propensity methods and different approaches to baseline risk assessment could be considered, while also extending to multiple databases and outcomes.

References

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