A two-stage prediction model for heterogeneous effects for many treatment options

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Motivation: Effectiveness of drugs in Relapsing-Remitting Multiple Sclerosis (MS)

• Several drugs, compared in Network Meta-Analyses (NMA)
• We focus on Dimethyl fumarate, Glatiramer acetate, and Natalizumab

Outcome: Relapse MS in 2 years (Yes/No)
• We want to find the drug that minimizes the risk of relapse, subject to patient characteristics
  • Previous evidence suggests that patients at different age groups and at different stages of the disease might respond differently to the same treatment ⇒ Heterogeneous Treatment Effects

- Tramacere I. et al., 2015
Aim

To develop a *two-stage* evidence synthesis *prediction model* to predict the most likely outcome under several possible treatment options while accounting for patients’ characteristics using *individual participant data network meta-regression* with *risk scores*.
Treatments

- Dimethyl Fumarate
- Glatiramer acetate
- Natalizumab
- Placebo

Predicted Effect

A

B

C

D

Predicted Effect

Prognostic Factors

Effect modifiers

Risk score

Prognostic model

\[ h(y_i) = \beta_0 + \sum_{j=1}^{n} \beta_j \times PF_{ij} \]

Prediction model with IPD Network meta-regression using only the risk score

Prediction model using IPD Network meta-regression with PF and EM
**Prognostic model**

\[ h(y_i) = \beta_0 + \sum_{j=1}^{n} \beta_j \times PF_{ij} \]

**#STAGE1**

**Risk score**

**Prediction model using IPD Network meta-regression using only the risk score**

**#STAGE2**

### Treatments

- **Dimethyl Fumarate**
  - Predicted Effect A

- **Glatiramer acetate**
  - Predicted Effect B

- **Natalizumab**
  - Predicted Effect C

- **Placebo**
  - Predicted Effect D
Data

DEFINE
- 1234 observations

CONFIRM
- 1417 observations

AFFIRM
- 939 observations

Total: 2990 observations

70 potential prognostic factors
- previous treatment,
- years since onset of symptoms, etc.

33 potential prognostic factors
Two-stage model

1. Build the *prognostic score model*
2. Use the risk score in the *Individual Participant Data Network meta-regression*
Step 1: Build the prognostic score model (in R using packages glmnet, pentrace)
**Selection of factors included in the model**

<table>
<thead>
<tr>
<th>Model 1</th>
<th>LASSO variable selection technique through the <strong>whole dataset</strong> – 10-fold cross validation to choose the optimal $\lambda$ that minimizes the Binomial deviance of the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 2</td>
<td>Exactly the same variables as in Model 1 &amp; restricted cubic splines for non-linearity</td>
</tr>
<tr>
<td>Model 3</td>
<td>Exactly the same variables as in Model 1 &amp; LASSO selection technique for all possible interactions</td>
</tr>
</tbody>
</table>
| Model 4 | 1. Creation of 100 randomly half-datasets  
2. LASSO technique for variable selections to each one of them  
3. We selected the variables that were included in the model more than 40 times (40%)                                                                 |
| Model 5 | The variables indicated as prognostic factors in the literature (Fabio Pellegrini et al., 2019).                                                                                               |
Build the prognostic score model
Fit various models using 2 shrinkage approaches

**Shrinkage of coefficients**

**Uniform shrinkage**

- Uses a heuristic shrinkage factor \( s \)
  \[
  s = \frac{\text{model} \chi^2 - df}{\text{model} \chi^2},
  \]
  \( \text{model} \chi^2 \): the likelihood of the fitted model and \( df \): the degrees of freedom of the model

**Penalized shrinkage**

- Maximizes a penalized version of the log-likelihood in which a penalty factor is used. The optimal value of penalty \( \lambda \) is the one that maximizes a modified Akaike’s Information Criterion (AIC)
Select the best model with response to **predictive ability and calibration** *(500 bootstraps & correction for optimism)*

<table>
<thead>
<tr>
<th>Model &amp; Shrinkage method</th>
<th>c-index</th>
<th>Calibration slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model1 uniform shrinkage</td>
<td>0.6458</td>
<td>0.888</td>
</tr>
<tr>
<td>Model1 penalized shrinkage</td>
<td>0.6480</td>
<td>1.004</td>
</tr>
<tr>
<td>Model2 uniform shrinkage</td>
<td>0.6485</td>
<td>0.887</td>
</tr>
<tr>
<td><strong>Model2 penalized shrinkage</strong></td>
<td><strong>0.6497</strong></td>
<td><strong>1.004</strong></td>
</tr>
<tr>
<td>Model3 uniform shrinkage</td>
<td>0.6397</td>
<td>0.758</td>
</tr>
<tr>
<td>Model3 penalized shrinkage</td>
<td>0.6425</td>
<td>0.912</td>
</tr>
<tr>
<td>Model4 uniform shrinkage</td>
<td>0.6277</td>
<td>0.935</td>
</tr>
<tr>
<td>Model4 penalized shrinkage</td>
<td>0.6281</td>
<td>1.004</td>
</tr>
<tr>
<td>Model5 uniform shrinkage</td>
<td>0.6254</td>
<td>0.882</td>
</tr>
<tr>
<td>Model5 penalized shrinkage</td>
<td>0.6263</td>
<td>0.988</td>
</tr>
</tbody>
</table>
### Build the prognostic score model

#### Results: Model selection

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Expanded disability status scale</td>
<td></td>
</tr>
<tr>
<td>Splines (No. of relapses 3 years prior to study)</td>
<td></td>
</tr>
<tr>
<td>Months since recent Pre-Study relapse</td>
<td></td>
</tr>
<tr>
<td>Prior MS treatment group</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
</tr>
<tr>
<td>Baseline 9 Hole Peg Test Average score</td>
<td></td>
</tr>
<tr>
<td>Baseline Gadolinium Lesions</td>
<td></td>
</tr>
<tr>
<td>Baseline Short Form (SF) 36 Health Survey Physical Component Summary (PCS)</td>
<td></td>
</tr>
<tr>
<td>Baseline Sensory Functional Systems Scores (FSS)</td>
<td></td>
</tr>
<tr>
<td>Baseline Actual Distance Walked</td>
<td></td>
</tr>
</tbody>
</table>

**Events per variable:**

- 39
Build the prognostic score model

Results: Distribution of Risk

The distribution of the Risk in the whole dataset

<table>
<thead>
<tr>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>35%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Risk per relapse or non-relapse (Risk as a prognostic factor)

C-index = 0.65
Build the prognostic score model

Results: Distribution of Risk
The Risk per arm and relapse non-relapse (risk as effect modifier)
Build the prognostic score model

Results: Distribution of Risk

The Risk per arm and relapse non-relapse (risk as effect modifier)

<table>
<thead>
<tr>
<th>Treatment &amp; Outcome</th>
<th>Median pre-treatment Risk</th>
<th>95% CI of mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab/ NO relapse</td>
<td>35%</td>
<td>(35%, 38%)</td>
</tr>
<tr>
<td>Natalizumab/ YES relapse</td>
<td>42%</td>
<td>(42%, 46%)</td>
</tr>
<tr>
<td>Placebo/ NO relapse</td>
<td>31%</td>
<td>(30%, 33%)</td>
</tr>
<tr>
<td>Placebo/ YES relapse</td>
<td>40%</td>
<td>(39%, 43%)</td>
</tr>
</tbody>
</table>
Step 2: Use the risk score in the IPD Network meta-regression (In JAGS using self-programmed routines)
IPD Network meta-regression

**Notation**

- $i$: Individuals
- $j$: study
- $k$: treatment
- $b_j$: baseline treatment in study $j$

**Likelihood**

$Y_{ijk} \sim Bernoulli(p_{ijk})$

**B**: Individual level covariate regression term for Risk / the impact of Risk as prognostic factor

**$D_{bjk}$**: the treatment effect of treatment $k$ versus placebo / **fixed effect**

**$G_{bjk}$**: The interaction of treatment and risk. Different for each treatment vs study's control / the impact of Risk as effect modifier

$logit(p_{ijk}) = \begin{cases} 
    u_j + B \times (\text{logit}R_{ij} - \overline{\text{logit}R_j}) & \text{if } k = b_j \\
    u_j + D_{bjk} + B \times (\text{logit}R_{ij} - \overline{\text{logit}R_j}) + G_{bjk} \times (\text{logit}R_{ij} - \overline{\text{logit}R_j}) & \text{if } k \neq b_j 
\end{cases}$

Saramago et al., 2012
IPD Network meta-regression

Results: Estimation of model parameters

OR for relapse for one unit increase in logit-risk in untreated patients (placebo) - $\exp(B) = 3.38$

<table>
<thead>
<tr>
<th>Drug</th>
<th>OR for relapse versus placebo at the study mean risk ($\exp(D)$)</th>
<th>OR versus placebo for one unit of increase in the logit risk ($\exp(G)$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>0.27</td>
<td>0.68</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>0.50</td>
<td>0.92</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>0.40</td>
<td>1.14</td>
</tr>
</tbody>
</table>

\[
\text{logit}(p_{i,j,k}) = \begin{cases} 
  u_j + B \times (\text{logit}R_{ij} - \text{logit}R_j) & \text{if } k = b_j \\
  u_j + D_{b,j,k} + B \times (\text{logit}R_{ij} - \text{logit}R_j) + G_{b,j,k} \times (\text{logit}R_{ij} - \text{logit}R_j) & \text{if } k \neq b_j 
\end{cases}
\]
Predicted relapse rate by baseline risk score

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>Less than 25% Risk</th>
<th>More than 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>29%</td>
<td>12%</td>
<td>48%</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>41%</td>
<td>10%</td>
<td>60%</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>39%</td>
<td>9%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Best treatment
- Dimethyl fumarate - 3% Absolute benefit compared to Natalizumab
- Natalizumab - 14% Absolute benefit compared to Dimethyl Fumarate
Github repository - https://github.com/htx-r
Conclusions and further research

Future research
• Comparison with effect modification method
• Use of Swiss MS cohort to build the risk score
• External validation of prediction model
• R-shiny app

Conclusions
• This is the first prediction model that uses risk score from a nested prognostic model within a IPD Network meta-regression framework
• The risk of relapse at baseline is important for the optimal treatment choice and moderates the absolute benefit
  • Dimethyl fumarate seems to be the optimal choice for low-risk patients, whereas Natalizumab seems to be the optimal choice for high-risk patients