Predicting disease activity for patients with Relapsing Remitting Multiple Sclerosis using Electronic Medical Records | P1.395

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CONCLUSIONS

- **This study demonstrated that real world Electronic Medical Record (EMR) data could be used to successfully stratify Relapsing Remitting Multiple-Sclerosis (RRMS) patients according to the probability of experiencing a relapse. This confirms the feasibility of using routinely collected EMR data to develop risk stratification tools to support clinical decision-making**
- **Moderate to good predictive accuracy was obtained for predicting relapse for a composite cohort on BRACE therapy. However, the accuracy of predicting relapse was poor to moderate for most subcohorts involving treatment switch / escalation from BRACE therapy. This suggests that risk stratification may be effective based on predictions of disease activity, but that 'prescriptive' predictions (counterfactual predictions for 'what if' patient treatement transitions) remain as yet unproven as an effective basis for risk stratification. Research is on-going to improve model accuracy for all algorithms, especially for treatment switch / escalation cohorts**

INTRODUCTION

- Relapse Remitting Multiple Sclerosis (RRMS) is a chronic demyelinating, immune-mediated disease of the central nervous system characterised by inflammation and destruction of the myelin sheath covering of nerve fibres in the brain and spinal cord. RRMS is the most common type of MS and is characterised by unpredictable acute attacks (relapses) accompanied by worsening of symptoms
- There is no cure for MS, however there exists a number of disease modifying therapies (DMTs) aimed at preventing and treating relapses, preventing new attacks, managing symptoms, slowing disease progression and preventing or postponing long-term disability. Interferons (Betaferon®, Avonex®, Rebif®, Extavia®) and glatiramer acetate (Copaxone®) have been available since mid-1990s and are widely used DMTs for the treatment of MS and are known jointly as the BRACE therapies. Since 2005 a number of new DMTs with different mechanisms of action, efficacy and safety profiles have been approved. These therapies may be grouped into three broad categories according to common clinical practice: first-line BRACE therapies, first-line oral therapies (Aubagio® and Tecfidera®) and second-line therapies (Gilenya® and Tysabri®)
- The increased availability of disease modifying therapies for RRMS is placing a greater focus on clinicians to better understand likely disease activity in order to optimize treatment choice. It is important to understand whether routinely collected EMR data can be used to predict disease activity for RRMS patients since these predictions could potentially be used by clinicians to help improve treatment allocation and patient outcomes
- An assessment of available MS clinical decision-support tools and focus groups with clinicians were carried as an initial part of this study to provide context, motivation and direction to the analysis. Amongst other things, this research confirmed unmet need for a tool to support treatment optimization based on predictions of disease activity using real-world data and helped identify candidate covariates for modeling

OBJECTIVE

- To predict patient disease activity for a cohort of RRMS patients in Germany, both for a composite cohort and separate subcohorts grouped by treatment switch from initial BRACE therapy
- The long-term aspiration is to use results of the algorithm to develop a clinical decision-support tool to aid physicians in treatment choice and patient engagement

DESIGN/ METHODS

Study Design:

- This was a retrospective cohort study using Electronic Medical Records (EMR) data from the Neuro Trans Data (NTD) group of neurology practices in Germany for RRMS patients receiving BRACE therapy. Analysis was carried out for all RRMS patients (a composite cohort) as well as separately for four subgroups grouped by treatment pattern, creating a total of five cohorts for analysis:
  1. BRACE continuation – patients continuing on the same initial BRACE treatment;
  2. BRACE switch - patients switching from the initial BRACE therapy to a new BRACE therapy;
  3. First-line oral switch - patients switching from BRACE therapy to a first-line oral therapy (Aubagio and Tecfidera);
  4. Second-line escalation - patients switching from BRACE therapy to a second-line therapy (Gilenya and Tysabri);
  5. Composite – Patients on BRACE therapy, irrespective of subsequent treatment pattern

Patients were allowed to appear in more than one cohort, representing different treatment patterns at different points in time. However, patients were only permitted to appear within any given cohort once, with the record chosen for analysis selected at random. For example, a patient was allowed to enter both BRACE switch and first-line oral switch cohorts across different points in time, but only one of these records was selected at random for inclusion in the composite cohort.

PATIENTS

- Patient records were historically extracted from the NTD database covering the period 1st January 2010 through 30th June 2015. A 360 day follow-up period was used to measure disease activity (defined below). The index date was cohort specific and defined as follows:
  - The date of switch in the BRACE switch, first-line oral switch and second-line escalation cohorts
  - A random date at least three months after the last prescription of BRACE therapy for the BRACE continuation cohort

Table 1. General and cohort specific inclusion criteria

General Inclusion Criteria	Cohort Specific Inclusion Criteria
Confirmed diagnosis of RRMS	Prescription of BRACE therapy between 1st January 2010 and 30th June 2014
At least 12 months of follow-up data post index-date	Patients in the BRACE switch, oral switch and escalation cohorts must meet the following criteria
Non-missing baseline EDSS score	Prescription of BRACE therapy in 360 days prior to index date

STUDY ASSESSMENTS

- Disease activity, the outcome measure, was proxied by a binary outcome indicating whether a patient experienced a relapse over the twelve-month follow-up period. A relapse is defined as "Patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS [central nervous system], current or historical, with duration of at least 24 hours, in the absence of fever or infection"3
- Covariates included demographics, diagnostic history, treatment, disability status, disability history and cranial and spinal lesion counts

STATISTICAL ANALYSIS

- Continuous and count covariates were dichotomized following clinical guidelines and / or inspection of the data, to capture non-linear associations whilst facilitating transparency on model parameters
- Logistic regression with elastic-net penalty was used to model relapse for each of the five cohorts
- The Area Under the Curve (AUC) was used as the key performance metric, computed from left-out folds using cross-validation
- Patients were assigned to risk bands based on quintiles of predicted probability of relapse, with the gradient of actual relapse by risk group used as a secondary performance metric
- Variables retained by the elastic-net regression were entered into a standard (unconstrained) logistic regression to compute odds ratios with associated p-values

RESULTS

- The table below shows the number of patients in each cohort, along with the proportion experiencing a relapse. Relapse rates varied from 12.4% to 25.0%; the relapse rate for the Composite cohort was 18.2%. These are unconditional means and take no account of differences in attributes by treatment group (confounding by indication)

For instance, patients switching to second-line treatment would be expected to be further advanced on average in their disease course than other patients and hence may experience higher relapse rates, even if second-line treatment is more effective.

Table 2. Patients counts and relapse rates by cohort

Cohort	Number of Patients	Relapse Rate (%)	95%CI
BRACE Continuation	3794	20.2%	[18.9%, 21.5%]
BRACE to BRACE	396	25.0%	[20.7%, 29.3%]
BRACE to first line	443	12.4%	[9.3%, 15.5%]
BRACE to second line	634	24.3%	[21.0%, 27.6%]
Composite	4129	18.2%	[17.0%, 19.4%]

These are relapse rates intended simply to report raw outcomes by cohort and not intended to make any claims about treatment effectiveness

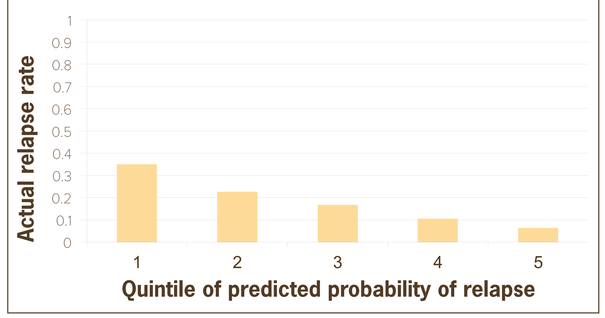
- The table below shows the AUCs for each cohort. The AUCs were 0.69 and 0.70 for the Composite and BRACE continuation cohorts respectively, indicating moderate to good predictive discrimination. AUCs for the BRACE-to-BRACE and BRACE to second-line cohorts were <0.60, indicating poor predictive accuracy

Table 3. AUCs for relapse prediction by cohort

Cohort	Area Under the Curve (AUC)	95% CI
Composite Cohort	0.69	[0.67, 0.71]
BRACE Continuation	0.70	[0.68, 0.72]
BRACE to BRACE	0.54	[0.47, 0.60]
BRACE to first-line	0.65	[0.57, 0.72]
BRACE to second-line	0.55	[0.50, 0.60]

- The graph below depicts the gradient of actual relapse by quintile of predicted relapse. The actual relapse rate for the highest risk group was 5.6 times higher than the lowest risk group (35.1% vs. 6.3%)

Graph 1: Actual relapse by quintile of predicted relapse for the composite cohort



- The table below reports odds ratios from the logistic regression. The odds ratio was significantly greater than unity (at the 0.05% level) for recent relapses, younger ages, being born in Central Europe and significantly lower than unity for pre-index Expanded Disability Status Scale of zero. Amongst other factors, counts of cranial and spinal lesions were not significant

Table 4. Odds ratios from logistic regression for predictions of relapse

Variable	Odds Ratio	2.5% CI	97.5% CI	p-value
Whether the patient experienced at least 1 relapse in the 180-360 days prior to index date	2.24	1.76	2.85	<0.001
Whether the patient was aged <30 years at index date	1.70	1.34	2.16	<0.001
Whether the patient experienced at least 1 relapse in the 360-720 days prior to index date	1.58	1.30	1.91	<0.001
Whether the patient was aged >=30 and <40 years at index date	1.41	1.14	1.75	0.001
Whether the patient was born in Central Europe	1.40	1.13	1.76	0.003
Whether Gilenya was available at the index date	0.75	0.60	0.93	0.008
Whether Aubagio was available at the index date	0.64	0.53	0.79	<0.001
Whether the patient has an EDSS score of 0 earlier than 360 days prior to index date	0.48	0.35	0.66	<0.001

References

1. Halpern et al, 2011
2. Polman, Reingold and Banwell, 2010
3. Zou and Hastie, 2005

Acknowledgement

The authors would like to thank the physicians of the NTD network for their participation in clinician focus groups conducted during the initial phases of the study.

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This study was funded by Novartis Pharma AG, Basel, Switzerland | Poster presented at American Academy of Neurology Annual Meeting, April 15 – April 21, 2016, Vancouver