Causal inference tools for estimating the effect of beta-interferon exposure in delaying disease progression in relapsing-remitting multiple sclerosis patients: an observational study

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1. Objective

Longitudinal observational data are required to assess the association between beta-interferon (β-IFN) drug exposure and disease progression in relapsing-remitting multiple sclerosis (MS) patients. Marginal Structural Cox Model (MSCM) represents a causal inference survival analysis tool for analyzing longitudinal observational study that allows adjustment for baseline characteristics as well as time-varying confounders through the use of inverse probability treatment and censoring (IPTC) weighting, a function of propensity scores in longitudinal settings (2). We investigated this association in 'real-world' settings using a novel MSCM approach (3).

2. Causal Diagram

According to the causal diagram (1) shown in Figure 1, in the first time period, cumulative relapse in the last two years (R_0) imposes confounding for the treatment exposure (E_0) and disease outcome (D) relationship, but cumulative relapse in the next time period (R_1) is the intermediate variable for the same relationship.

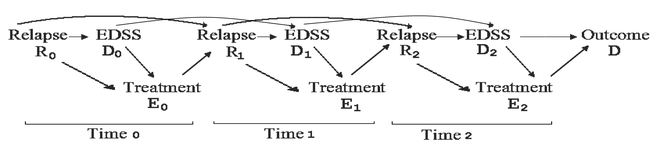

Figure 1: *Representation of the hypothesized causal relationships in the treatment of MS with three time points $j = 0, 1, 2$: here E_j denotes the binary β-IFN exposure variable that is measured immediately after the time-dependent confounder R_j, cumulative relapse and D_j, disability progression index, i.e., EDSS score of the j-th time period. The time-dependent confounder R_j at time j is affected by prior treatment E_{j-1}.*

Therefore, cumulative relapse in the last two years is a time-varying confounder. Simply incorporating such time-varying confounder as baseline or time-dependent covariate in a time-dependent Cox model may be inadequate to adjust for selection bias and confounding (2). Use of IPTC weights via the MSCM can be one way to adjust for this time-varying confounder.

3. Data and Methodology

- A retrospective study of prospectively collected data (1995-2008) in British Columbia (4).
- Baseline was considered as the first date a patient became eligible for β-IFN treatment between July 1995 and Dec 2004. The mean follow-up time was 4 years (IQR 4.3 years).
- In total, 1,697 patients with relapsing-onset MS were followed; 829 of which remained untreated.
- The survival outcome measure was time from β-IFN treatment eligibility to a sustained EDSS 6.
- Exposure to β-IFN was included as a time-dependent variable.
- 6,890 person-years of follow-up and 2,530 person-years of β-IFN exposure.

To fit a MSCM, we need to choose appropriate IPTC weights from the list below (3):

1. unstabilized weights w,
2. unstabilized normalized weights $w^{(n)}$,
3. stabilized weights sw or
4. stabilized normalized weights $sw^{(n)}$

4. Choosing Appropriate Weights

To find suitable weights for this chronic disease setting, we assess the statistical criteria of the weights (mean weight close to 1 and smaller variance) in Figure 2. $sw^{(n)}$ meets these criteria.

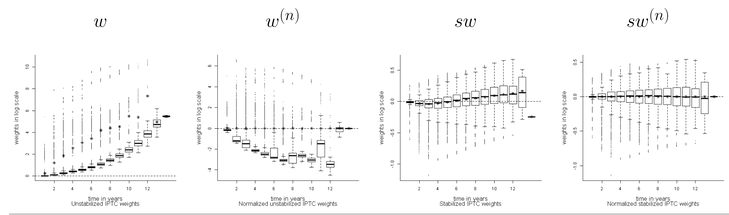

Figure 2: *Distribution of various IPTC weighting schemes for each year of follow-up. The means are indicated by $*$ in each boxplot.*

Also, in table 1, the consequence of choosing different weight schemes in MSCM are shown.

Table 1: *Different versions of the IPTC weights and the corresponding causal effect of β-IFN on the hazard of reaching sustained EDSS 6 for MS patients from BC (1995-2008).*

Scheme	Stabilized	Normalized	Estimated Weights		Causal Estimates	
			Mean (log-SD)	Min-Max	HR	95 % CI
w	No	No	28.17 (6.44)	1 - 43,985.38	1.54	0.09, 26.38
$w^{(n)}$	No	Yes	1 (2.45)	0.01 - 753.47	1.36	0.18, 10.40
sw	Yes	No	0.99 (-2.12)	0.30 - 1.95	1.36	0.95, 1.94
$sw^{(n)}$	Yes	Yes	1 (-2.18)	0.32 - 1.71	1.36	0.95, 1.94

Hazard ratio (HR) calculated using $sw^{(n)}$ is with smaller confidence interval (CI).

5. Main Results

Using MSCM (with $sw^{(n)}$) we adjust for potential baseline confounders, including age, sex, disease duration, EDSS score, and time-varying potential confounders (i.e., MS relapses). From this model, exposure to β-IFN was not associated with a statistically significant difference in the hazard of reaching EDSS 6 (hazard ratio: 1.36; 95% CI: 0.95 - 1.94 from Table 2).

Table 2: *The marginal structural Cox model (MSCM) fit with the normalized stabilized IPTC weights $sw^{(n)}$ for time to sustained EDSS 6 to estimate the causal effect of β-IFN treatment for multiple sclerosis (MS) patients from British Columbia, Canada (1995-2008). The model was also adjusted for the baseline covariates EDSS, age, disease duration and sex.*

Covariate	Estimate	HR	95% bootstrap CI
β-IFN	0.31	1.36	0.95 - 1.94
EDSS	0.54	1.72	1.54 - 1.92
Disease duration	-0.19	0.83	0.66 - 1.05
Age	0.28	1.32	1.08 - 1.62
Sex	-0.22	0.80	0.55 - 1.17

The findings were consistent based on IPTC weight adjusted survival curves (see Figure 3) and other sensitivity analyses conducted to check various MSCM assumptions.

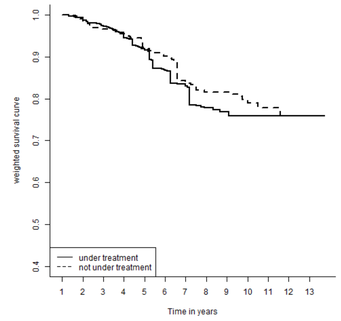

Figure 3: *5% truncated normalized unstabilized IPTC weights ($w^{(n)}$; truncated 5% extreme weights) adjusted Kaplan-Meier-type survival curves for the effect of β-IFN on time to reaching sustained EDSS 6 for multiple sclerosis (MS) patients from British Columbia, Canada (1995-2008).*

6. Conclusion

Using a novel statistical approach that allows adjustment for potential indication bias and related changes in patient characteristics which might influence subsequent treatment decisions, association between β-IFN exposure and the hazard of disability progression was not found to be significant among patients with relapsing-remitting MS in the 'real-world' clinical practice setting.

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