Predicting Diagnostic Delays in Persons with Multiple Sclerosis

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Background

Diagnostic delays in multiple sclerosis (MS) negatively impacts long-term outcomes, as it delays the initiation of disease modifying therapies. In order to reduce treatment delays it is important to identify factors contributing to delays in the diagnosis of MS.

Objective: To identify predictors of diagnostic delays in MS

Materials & Methods

Study Population: 1,465 persons with MS (PwMS) from the Accelerated Cure Project (ACP; www.acceleratedcure.org) were included in this study. ACP is an open-access repository of detailed epidemiologic data and blood-derived biospecimen samples of PwMS, other demyelinating diseases, and unaffected controls, recruited from 10 US neurology centers.

Outcome Definition: Diagnostic delay what the difference between age of diagnosis and age of onset (first symptom).

Model Selection: Diagnostic delay was non-normally distributed, therefore we conducted data simulations to compare poisson, quasi-poisson, negative binomial, zero-inflated poisson, zero-inflated negative binomial, and zero-inflated geometric (ZIG) distribution (Figure 1). Based on goodness-of-fit statistics, the ZIG model was selected (Table 2).

ZIG Model: A zero-inflated model has two parts: the 1st part assesses probability of a delay; the 2nd part assesses the relationship between predictors and delay length. Backward stepwise selection was used to determine predictors relevant for each part of the ZIG regression model, with robust standard errors.

Predictors: Variables included key demographics (Table 1) and other relevant variables, including number of impaired functional domains (FDs: 1, 2-4, 5-8, ≥9; PwMS completed 30 questions on onset symptoms which were classified into 11 FDs: motor, cerebellar, brainstem/bulbar, etc), and era of onset (before 1983, 1983-2000, 2001-2004, ≥2005; to reflect landmark changes in diagnostic criteria). PwMS reported all comorbid conditions prior MS diagnosis. These conditions were grouped; e.g. hypercholesterolemia, hypertension, heat disease and Type 2 Diabetes were classified as vascular diseases (VD). We also grouped diseases into autoimmune diseases (AD), mental disorders (MD), neurological disorders (ND), cancers, and other physical diseases (OP).

Table 1: Study population demographics.

DEMOGRAPHICS		ONSET YEAR 1956-2012	1956-2000	2001-2012
N		1465	916	549
Mean diagnostic delay (range)		5 (0~35)	7 (0~35)	1 (0~9)
Age of onset (range)		34 (18~70)	32 (18~60)	37 (18~70)
Age of diagnosis (range)		39 (18~71)	39 (18~71)	38 (18~70)
Mean year of onset (range)		1995 (1956-2012)	1990 (1956-2000)	2005 (2001-2012)
Female		77.7%	78.8%	76%
MS subtype	RR	92.5%	92.4%	92.7%
	PP	7.5%	7.6%	7.3%
Race	White	90.2%	91%	88.7%
	Black	7.6%	7.3%	8.2%
	Other	2.2%	1.6%	3.1%
Smoker 5 years prior onset		33.1%	36.2%	27.3%
History of infectious mononucleosis		27.7%	26.5%	29.7%
Diagnosis of obesity at onset		8.4%	6.6%	11.5%
Years of education (range)		16 (4-30)	16 (4-30)	16 (9-26)
FDs	0	10.0%	10.8%)	8.6%)
	1	33%	33.5%)	32.1%)
	2-4	38.3%	38.3%)	38.3%)
	5-8	16%	14.7%)	18.0%)
	9-11	2.8%	2.6%)	3.1%)
VD comorbidity		18.4%	17.5%	19.9%
MD comorbidity		24.1%	22.5%	26.8%
ND comorbidity		28.1%	27%	30.1%
Cancer comorbidity		4.5%	4.3%	5.1%
OP comorbidity		29.4%	30.5%	27.2%
Era of onset	1956-1982	13%	20.9%	-
	1983-2000	49.5%	79.1%	-
	2001-2005	24%	-	63.9%
	2006-2012	13.5%	-	36.1%

Figure 1: Data simulations of the distribution of diagnostic delay.

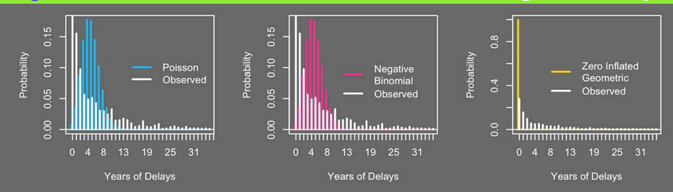


Table 2: Goodness-of-fit comparisons for Zero-Inflated models

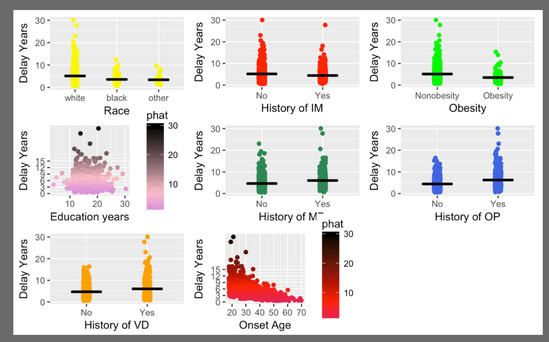
Model Comparison	ZINP	ZIG	ZINB
AIC		√	√
BIC		√	√
Prediction Plot	√	√	
Zero Count Prediction	√	√	

Table 3: Results for fully adjusted models for diagnostic delay, including stratified associations by era of onset.

PREDICTORS		ONSET YEAR 1956-2012		1956-2000		2001-2012	
N		1465		916		549	
		Coefficient	P-Value	Coefficient	P-Value	Coefficient	P-value
Zero Inflation Model							
Intercept		-1.93	0.087	21.31	**0.0047**	-3.91	0.43
Age of onset		-0.0016	0.92	0.23	**0.0040**	-0.0019	0.98
Male		-0.12	0.73	-0.91	0.54	5.28	**0.016**
Race	White	Ref	--	Ref	--	Ref	--
	Black	0.0084	0.99	-14.04	NA	-9.32	0.96
	Other	-1.097	0.28	-6.75	0.96	-13.00	0.99
MS subtype PP		-2.79	0.34	-10.39	0.93	-2.13	0.26
Smoker 5 years prior onset		0.15	0.63	-3.57	**0.023**	-8.70	**0.013**
History of infectious mononucleosis		-0.33	0.34	-3.55	0.17	6.63	**0.0082**
Diagnosis of obesity at onset		-0.57	0.27	-24.89	0.99	3.27	0.16
Years of education		0.035	0.52	-2.13	**0.0019**	-0.48	0.055
FDs	0	0.27	0.67	-6.27	0.063	-0.21	0.96
	1	Ref	--	Ref	--	Ref	--
	2-4	1.18	**0.0012**	-2.64	**0.026**	1.36	0.37
	5-8	1.014	**0.024**	-3.92	**0.024**	2.63	0.19
	9-11	2.10	**0.0017**	-0.77	0.77	12.67	**0.0022**
VD comorbidity		0.091	0.81	-4.25	**0.023**	5.42	**0.012**
MD comorbidity		-0.15	0.65	-2.02	0.28	-0.058	0.97
ND comorbidity		0.12	0.70	-4.56	**0.0073**	-6.75	**0.018**
Cancer comorbidity		-1.21	0.19	-18.96	0.99	-0.70	0.71
OP comorbidity		-0.64	0.069	3.01	**0.011**	-7.71	**0.011**
Era of onset	1956-1983	-2.26	**0.0021**	--	--	--	--
	1983-2000	-4.02	0.11	-1.36	0.28	--	--
	2001-2005	Ref	--	Ref	--	Ref	--
	2006-2012	0.58	**0.041**	--	--	3.4	0.057
Count Model							
Intercept		2.67	**$< 2*10^{-16}$**	2.99	**$< 2*10^{-16}$**	0.68	0.14
Age of onset		-0.049	**$< 2*10^{-16}$**	-0.037	**$< 2*10^{-16}$**	-0.017	**0.019**
Male		-0.0050	0.95	0.032	0.73	0.2	0.19
Race	White	Ref	--	Ref	--	Ref	--
	Black	-0.35	**0.0053**	-0.4	**0.0052**	-0.60	**0.013**
	Other	-0.52	**0.032**	-0.35	0.24	0.13	0.69
MS subtype PP		0.16	0.19	0.056	0.69	0.55	**0.018**
Smoker 5 years prior onset		0.12	0.089	0.053	0.49	0.00068	0.99
History of infectious mononucleosis		-0.27	**$3.1*10^{-4}$**	-2.89	**$5.7*10^{-4}$**	0.27	0.053
Diagnosis of obesity at onset		-0.42	**$9.4*10^{-4}$**	**-3.88**	**0.011**	0.051	0.8
Years of education		0.026	0.025	0.001	0.94	0.012	0.61
FDs	0	-0.0044	0.97	-0.098	0.45	-0.16	0.48
	1	Ref	--	Ref	--	Ref	--
	2-4	-0.085	0.27	-0.21	**0.02**	-0.29	**0.043**
	5-8	-0.18	0.071	-0.28	**0.016**	-0.12	0.50
	9-11	0.31	0.14	0.15	0.52	0.52	0.24
VD comorbidity		0.51	**$3.6*10^{-8}$**	0.42	**$2.6*10^{-5}$**	0.49	**0.0052**
MD comorbidity		1.23	**0.0072**	0.28	**0.0017**	0.033	0.82
ND comorbidity		0.21	0.11	0.12	0.17	-0.14	0.29
Cancer comorbidity		0.23	0.11	0.22	0.24	0.45	0.067
OP comorbidity		0.28	**$1.1*10^{-4}$**	0.34	**$5.2*10^{-5}$**	0.029	0.83

Table 4: Results for reduced models (after backward stepwise selection)

PREDICTORS		ONSET YEAR 1956-2012		2001-2012	
N		1465		549	
		Coefficients	P-Value	Coefficients	P-Value
Zero Inflation Model					
Intercept		-1.72	**$2.2*10^{-7}$**	-2.38	0.47
Male		--	--	3.83	**0.012**
Smoker 5 years prior onset		--	--	-7.72	**0.015**
History of infectious mononucleosis		--	--	5.81	**0.0016**
Diagnosis of obesity at onset		--	--	1.36	0.44
Years of education		--	--	-0.49	**0.032**
FDs	0	-0.032	0.96	-0.41	0.91
	1	Ref	--	Ref	--
	2-4	1.17	**0.0012**	2.07	0.24
	5-8	0.91	**0.035**	2.83	0.14
	9-11	2.12	**0.0013**	12.69	**0.0017**
VD comorbidity		--	--	3.71	**0.024**
ND comorbidity		--	--	-4.28	**0.02**
OP comorbidity		-0.58	0.074	-18.02	0.91
Era of onset	1956-1983	-2.28	**0.0082**	--	--
	1983-2000	-4.03	0.15	--	--
	2001-2005	Ref	--	Ref	--
	2006-2012	0.67	**0.013**	15.81	**0.049**
Count Model					
Intercept		2.66	**$< 2*10^{-16}$**	0.87	**$5*10^{-4}$**
Age of onset		-0.048	**$< 2*10^{-16}$**	-0.016	**0.017**
Race	White	Ref	--	Ref	--
	Black	-0.36	**0.0040**	-0.58	**0.015**
	Other	-0.46	**0.047**	0.19	0.55
Smoker 5 years prior onset		1.12	0.11	--	--
History of infectious mononucleosis		0.025	**$4.4*10^{-4}$**	0.26	**0.049**
Diagnosis of obesity at onset		-0.39	**0.0013**	--	--
Years of education		0.025	**0.027**	--	--
FDs	0	-0.0083	0.94	-0.16	0.46
	1	Ref	--	Ref	--
	2-4	-0.079	0.31	-0.28	**0.049**
	5-8	-0.18	0.074	-0.16	0.37
	9-11	0.33	0.12	0.54	0.25
VD comorbidity		0.50	**$3.2*10^{-8}$**	0.46	**0.0058**
MD comorbidity		0.22	**0.0044**	--	--
ND comorbidity		0.12	0.11	--	--
Cancer comorbidity		0.28	0.061	0.43	0.079
OP comorbidity		0.28	**$8.2*10^{-5}$**	--	--



Conclusions

- The number of impaired FDs and era of onset were the only significant predictors of probability of a delay. Polysymptomatic PwMS were significantly more likely to have no delay than monosymptomatics (odds ratio (OR)2-4 FDs=3.0, p<0.01; OR5-8 FDs=2.6, p<0.05, and OR≥9 FDs=6.0, p<0.01). As expected, PwMS with more recent onset were more likely to also have no delay compared to those with onset in 1983-2000 (OR2001-2004=17.9; OR≥2005=34.1; p<<0.001).
- Length of diagnostic delay was influenced by multiple predictors. Older age of onset (p<<0.001), history of IM (p<0.01), being black (p<0.01) or other race (p<0.05), experienced shorter delays. Primary progressives had a 31% increase in delay length compared to relapsing at onset PwMS. There was suggestive evidence for a 13% increase in delay length among smokers (p<0.1).

We identified multiple predictors of probability of a diagnostic delay, and predictors contributing to the length of delay in PwMS.