Prediction of MS disability status in Japanese claims database using principal component analysis

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Disclosures

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- **Hiromichi Otaka** and **Kengo Ueda** are employees of Novartis Pharma K.K.
- **Kosuke Iwasaki** and **Tomomi Takeshima** are employees of Milliman inc.
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Background

- Before the emergence of siponimod, there has been no standardized treatment for SPMS and MS patients with higher disability status, and there have been limited reports on the healthcare situation of this population in Japan.
- Claims databases have been widely used in MS research to evaluate clinical practice and outcome of MS treatments in real-world settings taking advantage of their large sample size and long observational period.
- However, records of disability status as indicated by EDSS or MS subtype are not available in claim databases, which makes it difficult to understand current healthcare situation of MS patients with higher disability status like SPMS.
- This study aimed to develop a score to predict disability status by principal component analysis from claims database, and assess the healthcare situation in Japanese MS patients being predicted to have a higher disability status based on the score.

MS: Multiple Sclerosis, SPMS: Secondary Progressive Multiple Sclerosis, EDSS: Expanded Disability Status Scale

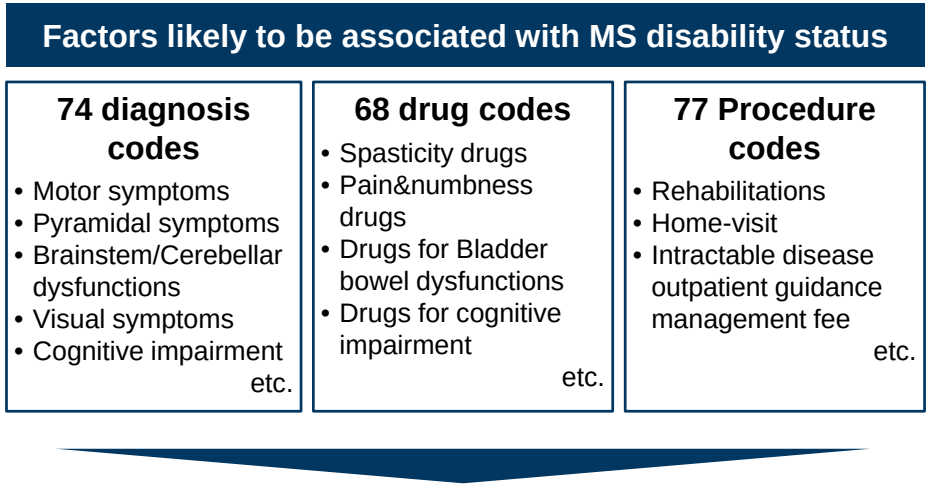
Methods: Data source, settings and patients

- **Data source**: Japanese claims database (April 2008 to August 2018) provided by MDV
  - Consisted of anonymized data from acute care hospitals including 20 million patients from 329 hospitals covering all diseases
- **Study period**: 2009—2018
  - **Observation period of each patient**: between the first and last record of any medical practice in the database
  - **First diagnosis of MS**: the earliest “FromDate” for MS. “FromDate” is recorded for the first diagnosis of each disease, and can be before the observation period.
- **Patients**: MS patients (meeting the following criteria)
  - With ≥1 claim of MS (coded as G35 by ICD-10),
  - Without claim of neuromyelitis optica (coded as G36 by ICD-10)
  - With any of (1) ≥1 hospitalization associated with MS, (2) ≥1 outpatient associated with MS and ≥1 claim of DMT prescription, (3) ≥1 outpatient associated with MS and a claim of first diagnosis of MS prior to the observation period, or (4) ≥3 claims associated with MS

MDV: Medical Data Vision Co., Ltd, ICD: International Classification of Diseases, DMT: Disease Modifying Therapy

Methods: Score development and assessment by the score

- **Score development**: principal component analysis was conducted on the factors that are likely associated with the disability status of MS. A score for each patient in each year from first diagnosis (excluding the year of the first diagnosis) was calculated based on the eigenvector coefficient for each factor of the first principal component.
  - **Factors**: diagnoses (defined by ICD-10), prescription of drugs (defined by generic name), and medical procedures (defined by the procedure code), which were selected from the database through discussion with a medical expert based on clinical experience or MS guideline.[1]
- **Assessing healthcare situation**: treatment pattern, healthcare resource utilization, and healthcare costs were analyzed based on the developed score
  - Each patient year (excluding the year of the first diagnosis) was classified into quartile groups using the score, and the frequency or costs (per patient per month) were calculated for each group. Patients with same score were classified into the group of lower score.
  - Relapse was defined based on relapse treatment (steroid pulse and plasma exchange).



Results: Score development and patient characteristics

- 7,067 MS patients were included from the database.
- The first principal component explained 3.2% of the total variance.
- The highest score group had fewer women, older age, and longer duration since first diagnosis compared with the lowest score group.

Level based on the score (Q1: lowest, Q4: highest)	Q1	Q2	Q3	Q4
No. of patients (patient year)	3,390	7,035	5,214	5,213
% of women	68.4 ± 0.8%	69.2 ± 0.6%	66.6 ± 0.7%	64.4 ± 0.7%
Age (years)	43.3 ± 0.2	48.1 ± 0.2	51.9 ± 0.2	55.4 ± 0.2
Years from the first diagnosis of MS	6.0 ± 0.1	5.9 ± 0.1	7.1 ± 0.1	8.1 ± 0.1

* ± Standard Error

- An increase in the score along with an increase in the years from the first diagnosis for each patient was confirmed by a random effect model below.

$$Score(i,t) \sim \beta_0 + \beta_1 \times t + \gamma_i + \varepsilon(i,t)$$

$$\varepsilon(i,t) \sim Normal(0, \sigma^2)$$

*Score(i, t) is the first principal component score for each patient (i) in the year from first diagnosis (t). γ_i represents the random effect, and β_0 is the intercept.

Results: Resource utilization and healthcare costs

- Frequency of hospitalizations and outpatient visits showed an increasing tendency with the rise in the score.
- The costs for MS treatment tended to be lower in the highest score group, while the total and other healthcare costs were higher.

Level based on the score		Q1	Q2	Q3	Q4
Number of patients (patient year)		3,390	7,035	5,214	5,213
Clinical tests (PPPM)	Magnetic resonance imaging	0.164 ± 0.007	0.097 ± 0.004	0.121 ± 0.005	0.155 ± 0.005
	Clinical psychological or neuropsychological test	0 ± 0	0.001 ± 0	0.001 ± 0.001	0.003 ± 0.001
	Neurological test	0.001 ± 0.001	0.002 ± 0	0.001 ± 0.001	0.002 ± 0.001
	Ophthalmic test	0.306 ± 0.009	0.294 ± 0.006	0.313 ± 0.008	0.416 ± 0.009
	Cerebrospinal fluid test	0 ± 0	0 ± 0	0.005 ± 0.001	0.011 ± 0.001
	Visual evoked potential test	0.001 ± 0	0 ± 0	0.001 ± 0	0.002 ± 0.001
	Somatosensory evoked potential test	0 ± 0	0 ± 0	0.001 ± 0	0.005 ± 0.001
Hospitalizations (PPPM)		0.004 ± 0.001	0.005 ± 0.001	0.016 ± 0.002	0.066 ± 0.004
Hospital visits (PPPM)		0.685 ± 0.014	0.601 ± 0.009	0.971 ± 0.014	1.292 ± 0.016
Healthcare costs (JPY, PPPM)	Total healthcare costs	102,053 ± 1,994	55,275 ± 1,156	84,403 ± 1,435	157,387 ± 2,895
	MS treatment costs	90,816 ± 1,938	43,216 ± 1,054	56,022 ± 1,248	47,740 ± 1,160
	Clinical test costs	2,071 ± 45	1,419 ± 28	1,671 ± 35	2,169 ± 45
	Other healthcare costs	9,165 ± 289	10,640 ± 400	26,711 ± 665	107,478 ± 2,704

* ± Standard Error

Results: Treatment status

- The higher score groups received oral steroids (prednisolone)* more frequently.
- Relapse rate was higher in the highest score group.

Level based on the score		Q1	Q2	Q3	Q4
Disease modifying therapy (PPPM)	Dimethyl fumarate	0.036 ± 0.003	0.011 ± 0.001	0.019 ± 0.002	0.038 ± 0.003
	Interferon (IFN)-ß1a	0.072 ± 0.005	0.048 ± 0.003	0.058 ± 0.003	0.052 ± 0.003
	IFN-ß1b	0.041 ± 0.003	0.042 ± 0.002	0.057 ± 0.003	0.067 ± 0.004
	Glatiramer acetate	0.015 ± 0.002	0.003 ± 0.001	0.007 ± 0.001	0.013 ± 0.002
	Fingolimod	0.128 ± 0.006	0.043 ± 0.002	0.081 ± 0.004	0.103 ± 0.004
	Natalizumab	0.009 ± 0.002	0.003 ± 0.001	0.007 ± 0.001	0.005 ± 0.001
Oral steroid (PPPM)	Prednisolone	0.075 ± 0.005	0.068 ± 0.003	0.154 ± 0.005	0.316 ± 0.008
Immunosuppressant (PPPM)	Azathioprine	0.003 ± 0.001	0.006 ± 0.001	0.021 ± 0.002	0.033 ± 0.003
	Tacrolimus	0.009 ± 0.002	0.006 ± 0.001	0.013 ± 0.002	0.028 ± 0.002
	Cyclosporine	0.002 ± 0.001	0.001 ± 0	0.006 ± 0.001	0.03 ± 0.002
	Mycophenolate mofetil	0 ± 0	0 ± 0	0.001 ± 0	0.006 ± 0.001
	Cyclophosphamide	0 ± 0	0 ± 0	0.001 ± 0	0.003 ± 0.001
	Methotrexate	0.002 ± 0.001	0.002 ± 0.001	0.008 ± 0.001	0.026 ± 0.002
	Mitoxantrone	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Relapses (PPPM)		0.011 ± 0.002	0.009 ± 0.001	0.019 ± 0.002	0.041 ± 0.003

* ± Standard Error

*Prednisolone coded after ≤ 3 months of prescription with the relapse treatment drugs (e.g. steroid pulse) was not counted to exclude the effect of follow-up treatment with oral steroid after pulse therapy.

Discussion

- Patient years with higher score had a longer disease duration since diagnosis and older age, which is in line with previously reported profile of patients with higher disability status.[1,2] We also confirmed that the score of each patient positively correlates with the duration since diagnosis under the random effect model. These results suggest that the score can be considered a reliable score predictive of disability status in MS.
- We observed an increase in the frequency of relapses with the increase in the score, which seems counterintuitive. This might be due to the specific definition of relapse that we applied.
- Healthcare costs (excluding MS treatment costs) and resource utilization (frequency of hospital visit and hospitalization) are higher among patients in the highest score group, which is in line with previous reports describing MS patients with higher disability status in other countries.[3-5]
- The observation that oral steroid (not for relapse treatment) was frequently used in patients within the higher score group may be related to the fact that, in the absence of any standardized treatment (DMT) for SPMS in the observational period of this study, some patients have likely been treated with oral steroids despite lack of clear evidence. (*It should be noted that higher score does not necessarily represent SPMS or higher EDSS as we did not conducted a validation study.)
- **Limitations**:
  - Relapse was defined based only on reported treatment. Thus, the defined relapse may not be always true relapse.
  - Disease duration was defined as the period from the first diagnosis, not from the true onset of MS.
  - The data source is limited to large acute care hospitals, and there are no data on diagnoses and treatments from other facilities.
  - Since the information is based on records of diagnoses and treatments, any lack of records or inaccuracy in recording may be reflected to the study results.

1. Confavreux, C. et al., *Brain*, 2006, 129, 595-605; 2. Weinshenker, B. G. et al., *Brain*, 1989, 112 (Pt 1), 133-46. ;3. Karampampa, K. et al., *J Med Econ*, 2019, 16, 939-50; 4. Palmer, A. et al., *Mult Scler*, 2013, 19, 1640-6; 5. Ruutiainen, J. et al., *J Med Econ*, 2016, 19, 21-33.

Conclusion

- We developed this novel score as an indicator of MS disability status with the information obtained from the Japanese claims database using principal component analysis.
- Patients who were considered to have higher disability status based on this score faced higher burden of cost, hospitalization and hospital visits while they were frequently treated with oral steroid which does not have definitive evidence for MS.
- Since the results are consistent with previous studies, we believe that the score is a well-defined indicator and provides a way to leverage the large sample size and long observational period of the claims databases when conducting a research to evaluate disability status of MS.
- Further study is necessary to validate the score with an actual disability measure such as the EDSS.