The Kurtzke EDSS rank stability increases 4 years after the onset of multiple sclerosis: results from the MSBase Registry

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RESEARCH PAPER

The Kurtzke EDSS rank stability increases 4 years after the onset of multiple sclerosis: results from the MSBase Registry

Stella Hughes,[1,2,3] Timothy Spelman,[1] Maria Trojano,[4] Alessandra Lugaresi,[5] Guillermo Izquierdo,[6] Francois Grand'Maison,[7] Pierre Duquette,[8] Marc Girard,[8] Pierre Grammond,[9] Celia Oreja-Guevara,[10] Raymond Hupperts,[11] Cavit Boz,[12] Roberto Bergamaschi,[13] Giorgio Giuliani,[14] Maria Edite Rio,[15] Jeannette Lechner-Scott,[16] Vincent van Pesch,[17] Gerardo Iuliano,[18] Marcela Fiol,[19] Freek Verheul,[20] Michael Barnett,[21] Mark Slee,[22] Joseph Herbert,[23] Ilya Kister,[23] Norbert Vella,[24] Fraser Moore,[25] Tatjana Petkovska-Boskova,[26] Vahid Shaygannejad,[27] Vilija Jokubaitis,[1] Gavin McDonnell,[2] Stanley Hawkins,[2,3] Frank Kee,[3] Orla Gray,[28] Helmut Butzkueven,[1,29,30] on behalf of the MSBase Study Group

For numbered affiliations see end of article.

Correspondence to
Professor Helmut Butzkueven, MS Clinical and Research Unit, Department of Medicine, Royal Melbourne Hospital and University of Melbourne, Grattan St, Parkville, Victoria 3050, Australia; butz@unimelb.edu.au

To see the members of the MSBase Study group see end of article.
OG and HB contributed equally to this work.

ABSTRACT

Background The Expanded Disability Status Scale (EDSS) is widely used to rate multiple sclerosis (MS) disability, but lack of disease duration information limits utility in assessing severity. EDSS ranking at specific disease durations was used to devise the MS Severity Score, which is gaining popularity for predicting outcomes. As this requires validation in longitudinal cohorts, we aimed to assess the utility of EDSS ranking as a predictor of 5-year outcome in the MSBase Registry.

Methods Rank stability of EDSS over time was examined in the MSBase Registry, a large multicentre MS cohort. Scores were ranked for 5-year intervals, and correlation of rank across intervals was assessed using Spearman's rank correlation. EDSS progression outcomes at 10 years were disaggregated by 5-year EDSS scores.

Results Correlation coefficients for EDSS rank over 5-year intervals increased with MS duration: years 1−6=0.55, years 4−9=0.74, years 7−12=0.80 and years 10−15=0.83. EDSS progression risk at 10 years after onset was highly dependent on EDSS at 5 years; one-point progression risk was greater for EDSS score of >2 than ≤2. Two-point progression was uncommon for EDSS score of <2 and more common at EDSS score of 4.

Conclusions EDSS rank stability increases with disease duration, probably due to reduced relapses and less random variation in later disease. After 4 years duration, EDSS rank was highly predictive of EDSS rank 5 years later. Risk of progression by 10 years was highly dependent on EDSS score at 5 years duration. We confirm the utility of EDSS ranking to predict 5-year outcome in individuals 4 years after disease onset.

INTRODUCTION

Multiple sclerosis (MS) is the most common cause of neurological disability in young adults in the developed world. However, there is marked variability in the degree of disability in MS among people who have the same disease duration. The most widely used validated measure of disability is the Kurtzke Expanded Disability Status Scale (EDSS).[1] This is a non-linear scale with 19 numbered half-steps ranging from 0, indicating no disability, to a score of 10, denoting death due to MS. An EDSS score between 4.0 and 9.5 is determined largely by the degree to which an individual's ambulation is impaired. A score from 0 to 3.5 is applied to fully ambulatory patients and calculated by scoring maximal impairment in each of the Kurtzke Functional Systems, consisting of pyramidal, cerebellar, brainstem, sensory, bowel/bladder, cerebral/mental, visual and 'other' categories.

The EDSS is commonly used in both clinical and research settings to delineate an individual's disease progression. However, in order to assess the disease severity, some measure of disease duration should ideally be incorporated into this score. The global Multiple Sclerosis Severity Score (MSSS), proposed by Roxburgh and colleagues, has provided researchers with a tool to quantify the degree of neurological disability for a given duration of MS. The MSSS was devised using a database containing 9892 European and Australian MS cases from 11 countries.[2] For most patients, a single EDSS score was recorded. EDSS scores were stratified according to the time since the onset of MS and ranked for years 1−30. The MSSS simply represents this rank of EDSS for a cohort of a given disease duration expressed as a decile.

In order to validate the predictive value of the MSSS, the authors assessed the stability of the MSSS over time in two French longitudinal cohorts in which serial EDSS scores had been recorded. A mean change of zero was observed in the MSSS for each group, despite significant variation in an individual's scores at different time points.[2] They

concluded that the MSSS could be used to measure and compare disease severity in groups of MS patients but that it had not yet been shown to be suitable for tracking an individual's progress over time. Consequently, the MSSS has been used in a number of research studies,[3–9] including two genome-wide association scans of MS severity[8][9] and has also recently been used to compare the disease severity among white and African American US patients[10] and to investigate the changing disease severity in temporally separated cohorts in the New York State Multiple Sclerosis Consortium Database.[11] In light of its increasing popularity, we decided to assess the performance of EDSS ranks as a predictor of 5-year outcome in the MSBase cohort, using cohorts with different baseline disease durations, all assessed prospectively for 5 years. We also aimed to disaggregate the probability of disability progression by EDSS scores at a disease duration of 5 years, in order to provide neurologists with a clinically meaningful risk stratification for the subsequent 5 years.

METHODS
MSBase Registry

The MSBase Registry prospectively collects outcomes data in MS from participating neurology centres worldwide using an internet-based system (https://www.msbase.org). Each centre records patient details in an offline local electronic database using iMed© software and intermittently uploads anonymised datasets to the MSBase server. A minimum required dataset must be fulfilled before a record is deemed complete and eligible for inclusion. Data include the date of onset of MS, diagnostic criteria met and results of investigations such as MRI, evoked potentials and cerebrospinal fluid examination. During a patient's routine clinic visit, the clinician adds information on relapses and treatments and records an EDSS score at least annually. Informed consent is obtained from all patients for inclusion of their anonymised data in MSBase, and each centre has obtained Human Research Ethics Committee approval or exemption. Data were extracted for this study on 17 May 2010. All participating neurologists have obtained Neurostatus certification for EDSS competency (http://www.neurostatus.net).

Inclusion and exclusion criteria

All analysed cases met Poser criteria for definite MS[12] or McDonald criteria for MS[13] and were within 15 years of onset of MS. Disease onset was defined as the date of first symptom attributable to MS. EDSS scores which were known to be recorded at a clinic visit during a relapse were excluded. Cases who had at least two recorded EDSS scores 5 years apart were included. For each cohort, an EDSS score was only included if there was also a score recorded for that patient 5 years later. Cases did not necessarily have an EDSS score recorded in more than one time interval. Cases excluded from the analysis were those who had only a single EDSS score recorded (2545 patients) and those who had no EDSS scores recorded (697 patients). There were also 6348 patients excluded for whom at least two EDSS scores were recorded but whose EDSS scores were less than 5 years apart. Following these exclusions, a total of 13 676 EDSS scores from 4219 patients were analysed. The number of EDSS scores included for each time interval is shown in table 2.

Cohort

In May 2010, the MSBase Registry had 14 062 cases enrolled from 67 centres in 27 countries. Data extracted for this study were taken from 42 centres in 19 countries with 91 730 complete

EDSS calculations from 13 809 patients. Centres of origin were European in 65.3% of cases, 21.3% were from North America, 5.5% from Australia, 5.2% were from Central and South America and 2.9% from Near-East Asia. The number of patients by country is shown in table 1. The female to male ratio was 2.3:1. Relapsing remitting MS comprised 74.3% of cases, 16.7% had secondary progressive or progressive relapsing MS, 4.5% had primary progressive MS and MS type was unknown in 4.5%.

Statistical analysis

For each eligible patient, an EDSS score was determined for each year from the onset of MS up to 15 years. A median EDSS score was calculated over a 2-year period if more than one score was recorded within this time. For example, a 'year 4 score' was the median of EDSS scores recorded between 3 and 5 years since the onset of MS. Year 0 scores were omitted from analysis as EDSS scores at onset of MS have previously been shown to have poor correlation with scores later in the disease course.[2]

Patients who had at least two EDSS scores recorded 5 years apart were divided into subsets according to the time intervals in which these scores fell. Time intervals were as follows: 1–6, 2–7, 3–8, 4–9, 5–10, 6–11, 7–12, 8–13, 9–14 and 10–15 years. EDSS scores were ranked for both the year at the beginning and the year at the end of the interval. The rank of EDSS for patients across each 5-year time interval was charted with jittered scatterplots. Spearman's rank correlation (with 95% CIs) was used to assess the correlation of EDSS rank at the beginning and end of the 5-year time intervals. The change in EDSS score, as a function of baseline score for the 5–10 year subgroup, was analysed further, and rates of progression were compared between groups using χ^2 test. All statistical analyses were performed using Stata® software, V.11.

RESULTS
Disability and treatment

The median age at onset of MS in this cohort was 30.4 years (IQR 24.1–38.3 years), and median duration of disease was 10.9 years (IQR 7.9–14.4 years). Table 2 shows the median EDSS at the beginning of each time interval. Disease progression has been compared in this study with the original cohort used

Table 1 Country of origin for patients included in the analysis of this study

Country	Patients, n (%)
Italy	1452 (34.4)
Canada	898 (21.3)
Spain	503 (11.9)
Netherlands	442 (10.5)
Australia	233 (5.5)
Argentina	143 (3.4)
Portugal	129 (3.1)
Denmark	108 (2.6)
Belgium	87 (2.1)
Turkey	70 (1.7)
Cuba	68 (1.6)
Israel	52 (1.2)
Malta	20 (0.5)
Brazil	8 (0.2)
France	4 (0.1)
Macedonia	2 (0.05)
Total patients	4219

Table 2 Number of EDSS scores examined, median EDSS scores at start of interval and correlation coefficients for rank of EDSS at start and end of intervals

5-year time interval (years)	No. of EDSS scores analysed	Median EDSS score (IQR) at start of interval	Spearman's rank correlation coefficients (95% CI) for EDSS rank across interval
1–6	1664	1.75 (1.0–2.5)	0.55 (0.52 to 0.59)
2–7	1601	2.0 (1.0–2.5)	0.63 (0.60 to 0.66)
3–8	1567	2.0 (1.0–3.0)	0.63 (0.61 to 0.66)
4–9	1507	2.0 (1.25–3.5)	0.74 (0.72 to 0.76)
5–10	1426	2.0 (1.5–3.5)	0.77 (0.75 to 0.79)
6–11	1391	2.0 (1.5–4.0)	0.77 (0.74 to 0.79)
7–12	1264	2.5 (1.5–4.0)	0.80 (0.77 to 0.81)
8–13	1199	2.5 (1.5–4.0)	0.79 (0.77 to 0.81)
9–14	1065	2.5 (1.5–4.5)	0.83 (0.81 to 0.84)
10–15	992	2.75 (1.5–4.75)	0.83 (0.81 to 0.85)

CI, confidence intervals; EDSS, Expanded Disability Status Scale; IQR, interquartile range.

by Roxburgh to develop the MSSS, as shown in table 3. It appears that our cohort has less severe disease than that reported in a similar sized dataset by Roxburgh and colleagues[2] in 2005, which was collected as part of the GAMES genetics study in the late 1990s. One possible explanation for this discrepancy could be increased exposure to disease-modifying treatments. In our cohort, 81.3% of patients had been exposed at some time to an immunomodulatory drug for MS (excluding corticosteroids), with a median duration of exposure of 2.3 years (IQR 1.0–5.1 years). In 78.4% of cases, there was exposure to interferon or glatiramer acetate, with a median duration of treatment 2.6 years (IQR 1.0–5.4 years). Exposure to other immunomodulatory drugs, including natalizumab, azathioprine, cyclophosphamide, methotrexate and mitoxantrone, was observed in 16.4% of cases for a median duration of 1.7 years (IQR 0.7–2.7 years).

Rank stability

Spearman's rank correlation coefficients were calculated for each of the time intervals analysed to determine the stability of the EDSS rank over time. Results revealed that EDSS rank stability increases with disease duration as correlation coefficients increased from 0.55 for years 1–6 to 0.74 for years 4–9, 0.77 for years 5–10, 0.80 for years 7–12 to 0.83 for years 10–15.

Table 3 Comparison of patients reaching EDSS milestone scores in the current study (for those whose scores were analysed for the disease durations below) with the cohort used to devise the MSSS[2]

Disease duration (years)	EDSS score greater than or equal to	Patients in this study, n (%)	Patients in original MSSS cohort (%)
5	3	530 (37.2)	48
	6	94 (6.6)	14
	8	9 (0.6)	4
10	3	495 (49.9)	67
	6	168 (16.9)	30
	8	14 (1.4)	5
15	3	607 (61.2)	75
	6	273 (27.5)	38
	8	33 (3.3)	11

EDSS, Expanded Disability Status Scale; MSSS, Multiple Sclerosis Severity Score.

Scatterplots for four of the time intervals examined are displayed in figure 1, showing rank of EDSS for two time points 5 years apart with jittering to visually represent tied values. The additional axes show the EDSS scores at the beginning and end of each of the intervals shown. On visual inspection of the graphs, cases increasingly lie around the leading diagonal as disease duration increases. The correlation coefficients for the remaining intervals are shown in table 2. These results suggest that the within-cohort rank of a person's EDSS is increasingly consistent or 'stable' over 5 years, with strong correlation observed from 4 years after the onset of MS.

As expected, the majority of cases in the cohorts with shorter disease durations have EDSS scores in the lower ranges, as is evident on inspection of figure 1. Although constituting a small proportion of patients in this study, those with higher EDSS scores earlier in their disease course are more likely to maintain a high EDSS ranking over time. We therefore examined the rank stability further in those with EDSS scores in the lower range, where variability over time is more likely to occur. Spearman's rank correlation was used to assess correlation of EDSS rank over 5 years for cases who had an EDSS score between 0 and 3.5 at the beginning of the 5-year time intervals. Again, increasing correlation was observed as disease duration increased with coefficients of 0.46 for years 1–6, 0.60 for years 4–9, 0.61 for years 7–12 and 0.62 for years 10–15.

Change in EDSS scores

As EDSS ranks are difficult to interpret in clinical practice, we explored the predictive risks of disability progression from 5-year EDSS scores for the subsequent 5 years. The change in EDSS scores over time was explored further for the 5–10-year disease duration interval, due to its utility in previous studies examining the predictive value of early disease course in MS outcomes.[2 14 15] In order to explore the probability of EDSS worsening over the subsequent 5 years as a function of EDSS at 5 years of disease duration, we tabulated the percentage of MS patients with an increase in the EDSS score of either 1 or 2 points over the 5–10-year interval, disaggregated by EDSS score at 5 years duration. The proportion of patients with one- and two-point progressions was dependent on EDSS scores at 5 years. The probability of a one-point progression for patients with 5-year EDSS scores of 1, 1.5 or 2 was around 30% but rose sharply to over 50% for patients with a 5-year EDSS score of 2.5 or greater ($p < 0.001$) (see table 4). The probability of a two-point progression for patients with 5-year EDSS scores of 1 or 1.5 was only around 10%, for 5-year scores between 2 and 3.5, it was around 20%, but for patients with a 5-year EDSS score of 4, it rose sharply to almost 40% (see table 4) ($p < 0.001$).

DISCUSSION

In this study, we aimed to validate the longitudinal stability of EDSS ranking in clinical practice using the MSBase Registry, a large longitudinal dataset of MS patients. We observed strong correlation between a patient's rank of EDSS score at one time point and the rank of their EDSS score 5 years later, in cohorts with disease duration of 4 years and longer. Our results suggest the utility of EDSS ranking as a tool to assess disease severity in individual patients of at least 4 years of disease duration. This type of ranking tool could ultimately provide a basis on which to test outcomes of different treatment choices, allowing the potential validation of proposed treatment algorithms.

Although 5-year prospective EDSS ranks stabilised after a disease duration of 4 years, examination of progression
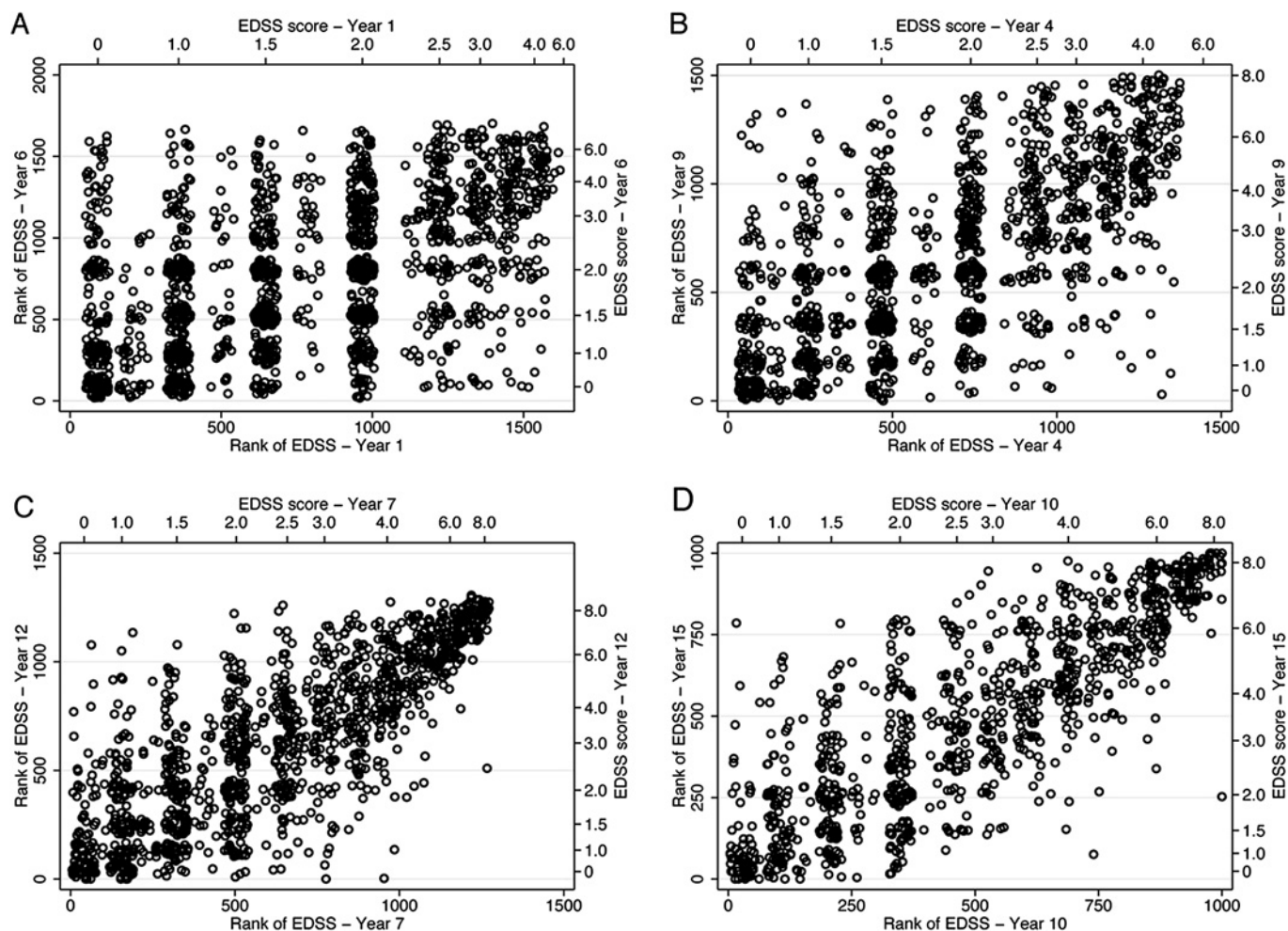
Figure 1 (A—D) Rank of Expanded Disability Status Scale (EDSS) for cases analysed for the following 5-year time intervals: (A) years 1—6, (B) years 4—9, (C) years 7—12 and (D) years 10—15. The additional axes show EDSS scores at the start and end of the interval for each cohort.

probabilities from different EDSS scores in the year 5—10 cohort may suggest critical EDSS values determining the risk of subsequent one or two-point EDSS increases over the next 5 years. The ability to identify patients with high progression rates at 5 years of disease duration would be of use clinically and in future observational studies to examine the effect of treatment escalation in this population. From this exploratory analysis, we propose that cases with a 5-year EDSS score of 0—1.5 are at low risk, 2.0—3.5 at intermediate risk and a score of 4.0 or 4.5 are at high risk of two-point (ie, severe) EDSS progression by 10 years after disease onset.

Our findings add to those of previous observational studies, in which early disease course was found to predict later outcomes, validating this concept in a very large clinical practice cohort. Originally, Kurtzke investigated factors that predicted disability at later stages of disease in a cohort of 527 patients with MS,[14] using the Disability Status Scale (DSS), which he later refined as the EDSS.[1] The best predictor of DSS at disease durations of 10 and 15 years was found to be the DSS score at 5 years after onset, with a correlation coefficient exceeding 0.7. The scores for both the pyramidal and cerebellar components of the DSS at 5 years were also predictive of later disability, although less so than the overall DSS score at 5 years. In the London Ontario natural history studies, it was also observed that the DSS at both 2 and 5 years was predictive of disability later in the disease course.[15] Using the MSBase Registry, further study will include

analysis of lead components of the EDSS, or Kurtzke Functional System scores, to determine which of these contribute to the stability of EDSS rank over time.

Table 4 Increase in EDSS scores for cohort of patients examined across the 5—10-year interval

EDSS score at 5 years after the onset of MS*	EDSS score ≥1.0-point increase at 10 years, n (%)	EDSS score ≥2.0-point increase at 10 years, n (%)
0	63 (54.3)	19 (16.4)
1.0	66 (35.3)	18 (9.6)
1.5	65 (27.6)	22 (9.1)
2.0	80 (32.7)	44 (18.0)
2.5	63 (54.3)	24 (20.7)
3.0	54 (46.9)	27 (23.5)
3.5	61 (52.2)	27 (23.1)
4.0	56 (54.8)	40 (39.2)
4.5	24 (64.9)	13 (35.1)
5.0	25 (73.5)	9 (26.5)
5.5	15 (48.4)	3 (9.7)
6.0	18 (42.9)	3 (7.1)
≥6.5	16 (31.4)	1 (2.0)

*'EDSS score at 5 years' represents the median of all scores recorded for an individual between 4 and 6 years after the onset of MS.
EDSS, Expanded Disability Status Scale.

Lastly, the MSSS was found to be stable over time when initially validated by Roxburgh et al[2] using a subset of 3605 patients from the Lyons and Rennes cohorts. Strong correlation in disability ranking was observed in individuals from 3 years after the onset of MS at time points 5, 10 and 15 years later. However, there was evidence that the MSSS fluctuated for patients over time and so caution was advised in interpreting the MSSS for individuals rather than groups.

Our cohort has similar characteristics to the combined groups used to devise the MSSS, with respect to the age at onset and disease duration.[2] Centres from Europe, North, Central and South America, Australia and Near-East Asia contributed patients to the present study, in which 34.9% of the cohort were from non-European centres. This encompasses a more geographically diverse sample than Roxburgh's cohort, in which 99% of cases were from Europe. The cohorts also differ drastically with respect to treatment exposure. Roxburgh's original cohort was a largely untreated group (27% treated), whereas 81.3% of patients in our cohort had been treated with an immunomodulatory drug for MS, other than corticosteroids.

The difference in rates of treatment exposure may account for the smaller proportion of patients in this cohort reaching disability milestones compared with Roxburgh's cohort, as shown in table 3. There is supportive evidence that disease-modifying treatments can delay or attenuate disability in MS, as observed in a number of studies involving interferon-β and glatiramer acetate.[16–21] A recent study using the New York State MS Consortium compared the distribution of the MSSS for patients enrolled between 1996 and 2007.[11] It was observed that the more recent enrollees had lower MSSSs than earlier enrollees, and this appeared to be independent of age, gender, ethnicity and time of diagnosis. The authors hypothesised that this apparent reduction in disease severity may be due to long-term efficacy of disease-modifying treatment, given that exposure to disease-modifying treatments rose from 51% to 71% over the course of the time period examined. The effect of treatment on rank stability of the EDSS will be explored further in a future study using the MSBase Registry.

This study is of course limited by the drawbacks of the EDSS itself, which includes the non-linearity of the scale and potential for variability in its grading. However, this is the gold standard disability grading tool in MS, and it is therefore widely used. Inter-rater variability on assessment of EDSS in patients with MS has been observed.[22] This effect is most important at the lower end of the scale where symptoms and subtle signs can determine scores giving rise to subjective rating by patients and clinicians. We anticipated fluctuations and 'regression to the mean' effects for EDSS scores in our cohort and attempted to minimise this by using a median EDSS score, taken over a 2-year interval to define the disease-duration-specific EDSS. We also considered the possibility of 'apparent' rank stability, as those with higher EDSS ranks early in the disease course may maintain a high rank due to severe irreversible disability. However, on assessment of those with EDSS scores below 4.0 at the beginning of 5-year intervals, correlation of EDSS rank over 5-year intervals also became strong after 4 years of disease duration.

CONCLUSIONS

This study has confirmed increasing stability of EDSS ranks over 5-year intervals in individuals from a disease duration of 4 years using a large global database of MS patients in the MSBase Registry. It also suggests that certain EDSS score cut-off points for risk of 5-year EDSS progression could be defined to identify cohorts at high risk of progression in both clinical and research

settings. Although EDSS ranking was originally used in the MSSS to allow comparison of severity between groups, we propose that EDSS ranks at specific disease durations can be used to assess and monitor disease severity in individuals.

Author affiliations
[1]Department of Neurology, Royal Melbourne Hospital, Victoria, Australia
[2]Royal Victoria Hospital, Belfast, UK
[3]UKCRC Centre of Excellence for Public Health Research, Queen's University Belfast, Belfast, UK
[4]University of Bari, Bari, Italy
[5]MS Center, Department of Neuroscience and Imaging, University of 'G. d'Annunzio', Chieti, Italy
[6]Hospital Universitario, Sevilla, Spain
[7]Neuro Rive-Sud, Quebec, Canada
[8]Hopital Notre Dame, Montreal, Canada
[9]Hotel-Dieu de Levis, Quebec, Canada
[10]Hospital Universitario La Paz, IdiPAZ, Madrid, Spain
[11]Maaslandziekenhuis, Sittard, The Netherlands
[12]Karadeniz Technical University, Trabzon, Turkey
[13]Neurological Institute IRCCS Mondino, Pavia, Italy
[14]Ospedale di Macerata, Macerata, Italy
[15]Hospital S. Joao, Porto, Portugal
[16]John Hunter Hospital, New South Wales, Australia
[17]Cliniques Universitaires Saint Luc, Brussels, Belgium
[18]Ospedali Riuniti di Salerno, Salerno, Italy
[19]FLENI, Buenos Aires, Argentina
[20]Groen Hart Ziekenhuis, Gouda, The Netherlands
[21]Brain and Mind Research Institute, New South Wales, Australia
[22]Flinders Medical Centre, South Australia, Australia
[23]New York University Hospital for Joint Diseases, New York, USA
[24]Mater Dei Hospital, Msida, Malta
[25]Jewish General Hospital, Montreal, Canada
[26]Clinic of Neurology Clinical Center, Skopje, Macedonia
[27]Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
[28]Craigavon Area Hospital, Portadown, UK
[29]Department of Medicine, The University of Melbourne, Victoria, Australia
[30]Department of Neurology, Box Hill Hospital, Monash University, Victoria, Australia

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REFERENCES

1. **Kurtzke JF.** Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**:1444–52.
2. **Roxburgh RH,** Seaman SR, Masterman T, *et al.* Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. *Neurology* 2005;**64**:1144–51.
3. **Daumer M,** Neuhaus A, Herbert J, *et al.* Prognosis of the individual course of disease: the elements of time, heterogeneity and precision. *J Neurol Sci* 2009;**287** (Suppl 1):S50–5.
4. **Karussis D,** Teitelbaum D, Sicsic C, *et al.* Long-term treatment of multiple sclerosis with glatiramer acetate: natural history of the subtypes of anti-glatiramer acetate antibodies and their correlation with clinical efficacy. *J Neuroimmunol* 2010;**220**:125–30.
5. **Van der Walt A,** Stankovich J, Bahlo M, *et al.* Heterogeneity at the HLA-DRB1 allelic variation locus does not influence multiple sclerosis disease severity, brain atrophy or cognition. *Mult Scler* 2010;**17**:344–52.
6. **Rejdak K,** Eikelenboom MJ, Petzold A, *et al.* CSF nitric oxide metabolites are associated with activity and progression of multiple sclerosis. *Neurology* 2004;**63**:1439–45.
7. **Brynedal B,** Wojcik J, Esposito F, *et al.* MGAT5 alters the severity of multiple sclerosis. *J Neuroimmunol* 2010;**220**:120–4.
8. **Baranzini SE,** Wang J, Gibson RA, *et al.* Genome-wide association analysis of susceptibility and clinical phenotype in multiple sclerosis. *Hum Mol Genet* 2009;**18**:767–78.
9. **Briggs FB,** Shao X, Goldstein BA, *et al*; International Multiple Sclerosis Genetics Consortium. Genome-wide association study of severity in multiple sclerosis. *Genes Immun* 2011;**12**:615–25.
10. **Kister I,** Chamot E, Bacon J, *et al.* Rapid disease course in African Americans with multiple sclerosis. *Neurology* 2010;**75**:217–23.
11. **Kister I,** Chamot E, Bacon JH, *et al.* Trend for decreasing Multiple Sclerosis Severity Scores (MSSS) with increasing calendar year of enrollment into the New York State Multiple Sclerosis Consortium. *Mult Scler* 2011;**17**:725–33.
12. **Poser CM,** Paty DW, Scheinberg L, *et al.* New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;**13**:227–31.
13. **Polman CH,** Reingold SC, Edan G, *et al.* Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005;**58**:840–6.
14. **Kurtzke JF,** Beebe GW, Nagler B, *et al.* Studies on the natural history of multiple sclerosis—8. Early prognostic features of the later course of the illness. *J Chronic Dis* 1977;**30**:819–30.
15. **Weinshenker BG,** Rice GP, Noseworthy JH, *et al.* The natural history of multiple sclerosis: a geographically based study. 3. Multivariate analysis of predictive factors and models of outcome. *Brain* 1991;**114**:1045–56.
16. **Ebers GC,** Traboulsee A, Li D, *et al.* Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. *J Neurol Neurosurg Psychiatry* 2010;**81**:907–12.
17. **Ford C,** Goodman AD, Johnson K, *et al.* Continuous long-term immunomodulatory therapy in relapsing multiple sclerosis: results from the 15-year analysis of the US prospective open-label study of glatiramer acetate. *Mult Scler* 2010;**16**: 342–50.
18. **Kappos L,** Traboulsee A, Constantinescu C, *et al.* Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. *Neurology* 2006;**67**:944–53.
19. **Trojano M,** Pellegrini F, Fuiani A, *et al.* New natural history of interferon-beta-treated relapsing multiple sclerosis. *Ann Neurol* 2007;**61**:300–6.
20. **Trojano M,** Pellegrini F, Paolicelli D, *et al.* Real-life impact of early interferon beta therapy in relapsing multiple sclerosis. *Ann Neurol* 2009;**66**:513–20.
21. **Veugelers PJ,** Fisk JD, Brown MG, *et al.* Disease progression among multiple sclerosis patients before and during a disease-modifying drug program: a longitudinal population-based evaluation. *Mult Scler* 2009;**15**:1286–94.
22. **Noseworthy JH,** Vandervoort MK, Wong CJ, *et al.* Interrater variability with the Expanded Disability Status Scale (EDSS) and Functional Systems (FS) in a multiple sclerosis clinical trial. The Canadian Cooperation MS Study Group. *Neurology* 1990;**40**:971–5.

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