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Disease-modifying therapy usage in patients with multiple sclerosis in France: a 6-year population-based study

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Abstract

Background: Most data regarding the use of disease-modifying therapies (DMTs) in multiple sclerosis (MS) comes from clinical series or regional databases that have a risk of recruitment bias. French health administrative data offers the significant advantage of being extensive in regards to both MS population coverage and DMT prescriptions.

Objectives: To describe patterns of DMTs usage at the level of the entire French population of MS patients from 2010 to 2015.

Methods: MS patients were identified during a 6-year study period via the French national health data system (covering 97% of the general population) and characteristics of patients who received at least one treatment were compared to those that never received treatment over the indicated period. A state sequence analysis was performed to study in a longitudinal way MS patients who started DMTs in 2010 and then to classify them into groups of similar therapeutic patterns. DMTs were categorized into first-line, second-line and off-label use, and included untreated periods for at least six months. Groups that were obtained were described and compared using a multinomial logistic regression.

Results: A total of 112,415 patients with MS were identified, of whom 54.0% received at least one DMT over the 6 years. The probability of being treated significantly decreased with age. Comorbidities and physical limitations appeared to be more frequent in not treated patients than in treated patients. Significant differences were also found between the two groups regarding the use of healthcare services (hospitalizations and visits to general practitioner, neurologist and nurse). Based on the 6-year therapeutic sequences, a four-cluster typology was obtained on the 4,474 patients who started a DMT in 2010. The first group which consisted of more than half of the patients (57.0%) mainly used first-line DMTs. The second group (13.1%) represented patients with second-line DMTs whereas the third group (7.3%) was comprised of off-label users and the last group (22.6%) was composed of MS patients who received no or minimal treatments. Classification into one of these groups was associated with patient's age, long-term disease status, pregnancy occurrence, estimated level of disability, levels of care (visits to a neurologist, nurse and/or physiotherapist and hospital/rehabilitation stays) and occurrence of death.

Conclusions: The exhaustive population-based dataset from the French national health data system gave the opportunity to provide a detailed description regarding the use of DMTs for MS at national level.

The innovative method of state sequence analysis allowed obtaining four homogeneous groups of patients among thousands of longitudinal therapeutic sequences. The predominant place of first-line treatments was confirmed even if the type of first-line treatments has probably changed since 2015.

Keywords:

Multiple sclerosis, disease-modifying therapies, health administrative database, neurologists, state sequence analysis

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which affects 2.8 million people worldwide¹. There is currently no cure for MS, however, around 15 disease-modifying therapies (DMTs) which are only prescribed by neurologists in France are now available² with the purpose of reducing the occurrence of relapse and delaying disability progression. DMTs can be classified according to their order in the therapeutic strategy (first-line, second-line and off-label use) or by their mode of administration (subcutaneous injections, intravenous infusions and oral pills)³. As first-line treatments, beta-interferon or glatiramer acetate are administered by injection and delivered via pharmacy, and two oral treatments (dimethyl fumarate and teriflunomide) have been marketed in 2014. Other treatments, even if not MS-specific, may be prescribed with an off-label use such as azathioprine, methotrexate, and mycophenolate mofetil. For active MS with many relapses or for when a first-line treatment is not effective, a second-line treatment can be proposed. Administered orally, fingolimod is the only second-line treatment distributed at pharmacies. Natalizumab, alemtuzumab, cyclophosphamide and mitoxantrone are administered intravenously or orally in hospitals.

Increasing numbers and varieties of DMTs have led neurologists to modify treatments when needed for cases such as safety concerns or therapeutic failure. Discontinuation of a treatment may also be related to a patient's choice for convenience or for family planning. Regardless, these recent therapeutic advances have led to major changes in the attitude of patients and neurologists toward drug prescriptions⁴.

Previous studies about DMTs in France were mainly effectiveness studies and came from clinical regional or national data with a lack of descriptive data about use of DMTs over time. In that context, the French health insurance database offers the opportunity to get a national population-based overview, on a large number of patients without any risk of recruitment bias but with a lack of clinical data. The primary objective of this study was to describe therapeutic sequences in MS patients from the treatment initiation in 2010 to the end of follow-up in 2015. The secondary objective was to describe characteristics of treated and never-treated MS patients over the 6-year period.

2. Materials and methods

2.1 Data source

Data from the French national health data system (*Système National des Données de Santé*; SNDS)⁵ was used which is an administrative database and covers about 97% of the general French population. It contains exhaustive individual data regarding the reimbursement of ambulatory healthcare procedures such as doctor consultations, biological tests and drug prescriptions. It also includes patient hospital activity (inpatient/outpatient visits), demographics data, general insurance coverage, universal health insurance plans (*Couverture Maladie Universelle* (CMU) which applies to specific low-income people) and medical characteristics such as long-term disease (LTD) which entitles a patient to 100% reimbursement for all medical costs. Individuals on the system are identified by a unique anonymized personal identifier. Ethical and data access approvals for the present study were obtained in accordance with applicable French legislation.

2.2 Study population

People with MS were identified from 2010 to 2015 using a three-criterion algorithm proposed by the French health insurance system⁶. Subjects were considered as having MS if they met at least one of the following criteria: (i) having at least one reimbursement for an MS-specific DMT (including beta-interferon, glatiramer acetate, fingolimod, natalizumab, teriflunomide or dimethyl fumarate); (ii) having an active LTD status for MS, or (iii) having at least one hospital admission with a diagnosis of MS based on the International Classification of Diseases, 10th version (ICD-10) G35 diagnosis code⁷. The date of MS identification was defined as the earliest date between the date of admission into LTD status for MS (potentially before 2010), the first date of hospitalization for MS or the first date of DMT prescription from 2010 to 2015⁸. To estimate some study inclusion parameters, data was extracted for the years from 2007 to 2015.

Firstly, the overall MS population was considered before focusing on MS patients who started a DMT in 2010 and had no DMT prescription over the period from 2007 to 2009. This was done to ensure a six-year follow up for each patient over the period from 2010 to 2015 and to get the opportunity to explore their therapeutic patterns in a longitudinal way.

2.3 Data

Patients were considered as treated if they had at least one delivery of beta-interferon, glatiramer acetate, fingolimod, natalizumab, teriflunomide, dimethyl fumarate, azathioprine, methotrexate or mycophenolate mofetil over the study period. Neither mitoxantrone, nor cyclophosphamide and alemtuzumab were considered since they were not available in the hospital data. DMTs were grouped according to their level in therapeutic strategy: first-line (glatiramer acetate, beta-interferon, teriflunomide and dimethyl fumarate), second-line (natalizumab and fingolimod) and off-label use (mycophenolate mofetil, methotrexate and azathioprine). Only DMT treatment cessation of at least six months was considered.

The following patient characteristics were identified: gender, age at the start of the study (2010), region of residence, occurrence of death, insurance coverage (including CMU), LTD status and pregnancy occurrence. Pregnancies were identified through their outcome based on the last hospital stay for birth or abortion (diagnosis and/or medical procedures) which were derived from hospital databases or the last reimbursement transaction for a non-hospital medical abortion⁹. The Charlson Comorbidity Index, adapted for French administrative databases¹⁰, was calculated based on data from the 12 months preceding the date of MS identification and categorized as a four-level score (0, 1-2, 3-4, ≥ 5). This score was found to predict the 1-year mortality¹¹ and was used here to approximate the general health status. Patients were classified as missing if 12 months of data were not available.

In terms use of healthcare services, visits with general practitioners (GPs), neurologists, nurses and physiotherapists were considered. Hospitalizations in medicine, surgery and obstetrics wards (MSO) and rehabilitation wards (REHAB) were also analyzed. Hospitalizations corresponding to DMT injections were excluded from these analyses. Outpatient consultations performed in hospitals were also included and assigned by default to the GP category when the medical specialty was missing.

An approximated level of disability was computed based on prescriptions of technical aids at inclusion and categorized as follows: mild if the patient never had a technical aid, moderate if the patient had at least one prescription for a walking stick, walker or wheelchair, and severe if the patient had at least one prescription of a medical bed, a patient lift or an anti-pressure ulcer mattress.

2.4 Statistical analysis

Patients in the overall population who took at least one DMT over the study period were compared to patients who never received DMT using the Wilcoxon or Pearson chi-square tests when applicable. A multivariate logistic regression including parameters related to demographics and use of healthcare services was also performed. After that, a state sequence analysis^{12, 13, 14}(SSA) was performed among the subgroup of patients who initiated a DMT in 2010 (without DMT from 2007 to 2009) to identify groups of similar patterns regarding the use of DMTs over the six- year time frame.

The general principle of SSA is to compare sequences regarding to the succession of their states. The term “sequence” referred to the entire individual therapeutic pathway and states were defined as the level in the therapeutic strategy of the DMTs prescribed. The four following states were considered: first-line, second-line, off-label use and no treatment. The time unit in the sequence was chosen as monthly, therefore, data was managed to assign one of these four states for each patient and each month. When different states could be assigned to the same month, the first occurring state was considered. For periods without treatment of less than six months, the preceding state was assigned. An additional fifth state which was coded non-attributed (NA) was used for the states following the occurrence of death. This procedure created right-truncated sequences and avoided the creation of a specific cluster dedicated to patients who died. All patients had the same sequence length of 72 months, except for right-truncated sequences.

After creating individual therapeutic sequences, a two-by-two comparison of sequences was performed using the optimal matching (OM) method to measure dissimilarity between each couple of sequences^{15, 16}. The matrix of substitution costs was estimated empirically using the transition rates observed in the dataset^{17, 18}. The dissimilarity matrix was used to cluster sequences and to create a typology of homogeneous patterns of DMT use with an agglomerative hierarchical clustering method using the Ward criterion¹⁹. The optimal number of clusters was chosen using the fall in inertia. All grouped sequences were visually presented on an index plot¹⁹.

Once the clusters were obtained, they were described and compared using a Kruskal-Wallis test, a Pearson chi-square test, or a Fisher exact test, where appropriate. A multinomial logistic regression²⁰ was also performed.

All computational and statistical analyses were performed with R v3.4.3 software²¹. The sequence analysis and the clustering used the *TraMineR* library 2.2-0.1¹⁸ and the *WeightedCluster* library v1.4²².

3. Results

3.1 Comparison of treated to untreated patients

Among the 112,415 patients identified as having MS in France, 54.0% received at least one DMT over the period. The most prescribed DMT was beta-interferon for more than half of treated patients, followed by glatiramer acetate which was prescribed for one quarter of these patients. The evolution in the use of DMTs from 2010 to 2015 is presented in Figure 1. The impact of the arrival of new oral treatments on the market is observable from 2012 for fingolimod, and from 2014 for dimethyl fumarate and teriflunomide. Use of DMTs over the study period differed somewhat between various French regions (Figure 2).

Figure 1 and 2 here

Number of women among treated patients (72.0%) was slightly higher than untreated patients (69.6%). Treated patients were significantly younger with a median age in 2010 of 41 years versus 53 years for untreated patients. Accordingly, there was less occurrence of death over the study period in the treated group (1.6%) than in the untreated group (7.8%). The difference in the number of admissions for LTD for MS between the two groups (92.8% for treated patients versus 76.1% for untreated patients) most likely reflected the need for LTD status due to the high costs of DMT treatment. Additional characteristics are presented and compared between the two groups in Table 1 and differences between the two groups from the multivariate logistic regression model are summarized in Figure 3. DMT use was associated with lower age groups because the probability of being treated over the study period decreased significantly with age. Moreover, the Charlson Comorbidity Index and the approximated level

of disability showed that health and physical limitations of untreated patients were worse than those of treated patients.

Figure 3 here

In addition, the use of healthcare services over the period was found to be different between the two groups (Table 1). There were more patients with at least one visit to a GP, neurologist or nurse among patients who received at least one DMT, while the number of patients with at least one visit to a physiotherapist was similar in the two groups. Moreover, the number of patients with at least one MS-related hospitalization in MSO was significantly higher for treated patients (47.2%) versus 29.9% for untreated patients. The same was noted for MS-related hospitalizations in REHAB. However, the length of stay of MS-related hospitalizations per patient in MSO were similar for the two groups but the length of stay of MS-related hospitalizations in REHAB were slightly higher for untreated patients (5.8 days versus 7.2 days per patient-year, in median).

Table 1 here

3.2 Identification of homogeneous patterns of DMT use over time

Among treated patients, 4,474 initiated DMTs in 2010 after being untreated from 2007 to 2009. These patients had approximately the same characteristics as the 60,693 treated patients described previously (Table 2). Among these 4,474 patients, 2,481 different 72-monthly therapeutic sequences were identified and compared. Their partitioning led to a four-cluster typology (Figure 4) which was helpful understanding therapeutic practices. Clearly, Cluster 1 predominantly contained more than half the patients and corresponded to patients who spent most of their follow-up under first-line DMTs with a median of 86.1% of the follow-up. Cluster 2 comprised almost one quarter of the patients who were mostly not treated (83.3% of the follow-up, in median) after a short period with either a first-line DMT or an off-label treatment (median of 12.5 and 13.9% of the follow-up, respectively). Patients in Cluster 3, which represented 7.3% of all the patients, had mainly prescriptions for off-label use treatments with a median of 81.9% of the follow-up. Finally, Cluster 4 represented 13.1% of the patients and most of them were treated by second-line DMTs (65.3% of the follow-up, in median). This period of second-

line DMT treatment was preceded, for half of them, by a short first-line DMT treatment period that lasted, in median, only one quarter of the time.

Figure 4 and Table 2 here

3.3 Comparison of clusters

Patient characteristics, use of healthcare and DMTs are summarized for each cluster in Table 1. Cluster 1 was chosen as the reference group in the multinomial logistic regression since it comprised the largest part of the study population. Results are presented on Figure 5.

Compared to Cluster 1, patients in Cluster 2 (mainly not receiving DMTs) were older with a median age in 2010 of 44 years versus 38 years old. The approximated level of disability was higher and there were more occurrences of death over the study period in this cluster (4.0% versus 0.4%). There were fewer patients with at least one visit to a neurologist (91.5% versus 96.9%), while the number of patients with at least one visit to a physiotherapist was higher (57.1% versus 49.8%). In accordance, the probability of being in Cluster 2 in comparison to Cluster 1 was associated with higher age and estimated level of disability.

Patients in Cluster 3 (mainly treated using off-label treatments) were significantly older than patients in Cluster 1 (median age of 51 years old versus 38 years old in 2010). The number of patients with a moderate or severe level of estimated disability was also higher (36.9% versus 5.5%) and there were more occurrences of death in this cluster (4.9% versus 0.4%). The number of patients with at least one visit to a neurologist was similar in Clusters 3 and 1, while there were more patients with at least one visit to a physiotherapist in Cluster 3 (79.1% versus 49.8%). The probability of being in Cluster 3 compared to Cluster 1 was thus associated with higher age and estimated level of disability.

Patients in Cluster 4 (mainly on second-line DMTs) were slightly younger than patients in Cluster 1 with a median age of 35 years old. The number of patients who had visited a neurologist was very high (99.5%) and Cluster 4 had the highest rate of MS-related hospitalizations in MSO (80.5%). The probability of being in Cluster 4 compared to Cluster 1 was associated with younger age. Moreover, this probability was higher for patients who had visited a neurologist at least once.

Figure 5 here

4. Discussion

This study allowed a comparison to be made between patients with MS who were treated and untreated patients from 2010 to 2015 and was based upon the entire population of MS patients in France. Our study showed that patients who had not received DMT were older, used less healthcare services, and had a higher estimated level of disability. Some differences were found between French regions in the choice of DMTs over time, but interpretation should be cautious since no adjustment was done and these are crude results.

The primary objective of the study was to describe therapeutic practices among patients who initiated a treatment in 2010 and identify specific patterns of DMT usage. From the 2,481 different 6-year sequences identified among the 4,474 patients, a four-cluster typology was obtained from the state sequence analysis and indicated a correspondence with actual therapeutic practices according to MS phenotypes. Half the patients (Cluster 1) were treated with first-line DMTs that may reflect the most common form of MS, i.e. relapsing remitting MS (RRMS). A proportion of these patients needed to be treated with second-line DMTs due to an aggressive or active MS and/or first-line DMT failure. They were classified into Cluster 4 (13.1%). Cluster 4 also showed patients who directly started with a highly effective DMT, which was probably due to early negative prognostic factors. A small percentage of patients (7.3%), shown in Cluster 3, used off-label treatments which are not approved for MS and most likely corresponded to patients with a progressive form of MS. Lastly, a quarter of patients were not treated (Cluster 2) which was probably due to either the benign form of the disease or the evolved form of their disease which could be the most plausible hypothesis because patients appeared to be older and with higher disability than in the other groups. Moreover, although these patients were not treated during the six year study period, they may have received treatment earlier in the course of the disease, however data was unavailable before 2007.

To our knowledge, there are very few studies conducted on the entire population of MS patients in France that provide such a detailed description of DMT usage. A recent study was conducted in France

using the same administrative database to assess real-world use of first-line DMTs in naïve patients with RRMS. Between September 1, 2014 and August 31, 2016, 10,240 patients starting a first-line DMT for RRMS were identified. Two-thirds of patients were mainly treated with oral forms (teriflunomide and dimethyl fumarate) and the other third with interferon and glatiramer acetate²³. Another study was carried out between 2013 and 2015 dedicated to self-employed workers (Régime Social des Indépendants, RSI) that represents 6% of the French population²⁴. They found a DMT utilization rate increased due to recently developed DMTs (teriflunomide and dimethyl fumarate) while first-generation DMT (beta-interferon) utilization rate decreased. As in our study, they showed that DMT utilization significantly decreased with age and that there were significant variations according to French geographic regions.

In our study, the population came from a nearly exhaustive database of the French general population (97% coverage) with systematic data collection provided by the national health insurance system. It should be noted that neither mitoxantrone, nor cyclophosphamide were available in the database which may lead to misclassification of some patients who started DMT in 2010, however, this should not strongly impact the results since they are rarely prescribed. This population-based data allowed avoiding any recruitment bias and the opportunity to get complete follow-up over the six-year period. This may represent a significant advantage over clinical series or regional databases that may not be population-based and recruitment through MS expert centers may lead to more severe MS patients²⁵. However, the main limitation of the present study was the lack of clinical data, especially MS-related data such as EDSS (Expanded Disability Status Scale) scores, laboratory data or MRI results because the database was principally designed for administrative functions.

Due to the absence of neurologist-based data collection, several assumptions were required to be made. The date of MS onset was approximated by the date of MS identification in the database. This approximation did not allow the whole therapeutic sequence from MS onset to be analyzed. This is the reason why therapeutic sequences started to be studied from the first initiation of treatment in 2010. Since the date of DMT administration was not available (except for natalizumab), the date of delivery from pharmacists was used even if there may have been several days or weeks lag time between delivery

and real intake. Moreover, the assumption that patients initiated their first treatment in 2010 was based on the absence of any DMT prescriptions over the period from 2007 to 2009. However, data were not available for some specific insurance plans during this period that indicates that around 10% of patients may have been classified as newly treated in 2010 when in fact they had been previously treated before. This may have created a limited misclassification bias. Finally, the level of disability was approximated using prescription records for technical aids without knowing the precise applications of such materials. This approximation, however, was mainly based on the purchases of such equipment rather than short-term rentals that may be caused by limited traumatic events instead of MS. In the same way, the Charlson Comorbidity Index was used to approximate the general health status as it identifies comorbid conditions that alter the risk of 1-year mortality^{10,11}. This score is based on a list of 17 defined comorbidities and did not take into account all the patient's conditions.

A strength of this study was the use of SSA that is an innovative and flexible method that allows the whole therapeutic sequence to be considered in contrast to conventional approaches that analyze each state independently. Because MS onset dates were not available, the decision was made to start the therapeutic pathway analysis from January 2010 that allowed for the same length and left-aligned sequences except for deceased patients, hence, clustering may not have been driven by the length of the sequences. Furthermore, this work was based on calendar months and, periodically, different states could have been assigned to the same month that probably corresponded to a switch between DMTs. In this case, only the first DMT was considered and the second was considered in the next state. Moreover, the choice was made to consider only treatment cessations lasting at least six months. When precisely considering the months without treatment as a sensitivity analysis, similar clusters were obtained and showed only an 11% discrepancy. This may be explained by the larger number of distinct individual therapeutic sequences; 4,208 different sequences compared to 2,481 initially among the 4,474 patients. Such significant variability highlights the need for appropriate methods of partitioning to determine a relevant typology of therapeutic practices based on thousands of sequences summarized into only four comprehensive homogeneous clusters.

In conclusion, a clustering method on therapeutic sequences on a nationwide level to describe DMT prescriptions over a six year period was applied and four main clusters were found. Overall, more than half the patients (57%) were treated with first-line DMTs, 13% with second-line DMTs (either moving from first-line or starting directly with such highly effective therapies), 7% with off-label treatments and 23% who rapidly stopped treatment. Unfortunately, the dataset used was outdated due to the quickly evolving therapeutic progress in MS treatment. The present analysis is planned to be updated to include data up to 2019 that may offer an opportunity to better characterize current therapeutic practices and may show a potential increasing place of new drugs, such as anti-CD20 and S1P drugs.

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Contributors

EL and SL conceived and designed the study. SL performed the data analysis. SL wrote the first draft of the manuscript. EL, ELP, JR and HT provided revisions.

All authors participated in the interpretation of the results, and writing of the manuscript, and approved the decision to submit the final version of the paper for publication

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Table 1. Characteristics of the 112,415 patients with multiple sclerosis (MS) over the study period from 2010 to 2015

	Overall N= 112,415 (100.0%)	At least one DMT n= 60,693 (54.0%)	Untreated n= 51,722 (46.0%)	p-value ^a
Women, n (%)	79,735 (70.9%)	43,714 (72.0%)	36,021 (69.6%)	<0.001
Age in 2010 ^b (years)	46 (36 – 57)	41 (32 – 50)	53 (42 – 63)	<0.001
≤ 30	17,122 (15.2%)	12,732 (21.0%)	4,390 (8.5%)	
]30-40]	22,761 (20.2%)	16,019 (26.4%)	6,742 (13.0%)	
]40-50]	28,454 (25.3%)	17,206 (28.3%)	11,248 (21.7%)	
>50	44,078 (39.2%)	14,736 (24.3%)	29,342 (56.7%)	
Deaths over the study period, n (%)	5,005 (4.5%)	961 (1.6%)	4,044 (7.8%)	<0.001
Long-term disease for MS at inclusion, n (%)	95,709 (85.1%)	56,334 (92.8%)	39,375 (76.1%)	<0.001
Health insurance coverage, n (%)				<0.001
General (excluding CMU beneficiaries)	98,359 (87.5%)	53,275 (87.8%)	45,084 (87.2%)	
Agricultural workers	4,148 (3.7%)	2,039 (3.4%)	2,109 (4.1%)	
Self-employed workers	4,242 (3.8%)	2,090 (3.4%)	2,150 (4.2%)	
CMU beneficiaries	4,258 (3.8%)	2,571 (4.2%)	1,687 (3.3%)	
Other plans	1,408 (1.3%)	718 (1.2%)	690 (1.3%)	
At least one occurrence of pregnancy, n (%) ^c	8,564 (10.7%)	6,028 (13.8%)	2,536 (7.0%)	<0.001
Approximated level of disability at inclusion, n (%) ^d				<0.001
Mild	89,001 (79.2%)	51,166 (84.3%)	37,835 (73.2%)	
Moderate	11,830 (10.5%)	5,952 (9.8%)	5,878 (11.4%)	
Severe	11,584 (10.3%)	3,575 (5.9%)	8,009 (15.5%)	
Charlson Comorbidity Index ^e , n (%)				<0.001
Missing	8,960 (8.0%)	4,753 (7.8%)	4,207 (8.1%)	
0	83,637 (74.4%)	48,025 (79.1%)	35,612 (68.9%)	
1-2	17,159 (15.3%)	7,168 (11.8%)	9,991 (19.3%)	
3-4	2,156 (1.9%)	608 (1.0%)	1,548 (3.0%)	
≥5	503 (0.4%)	139 (0.2%)	364 (0.7%)	
Health services use over the study period				
At least one visit to, n (%)				
General practitioner	109,963 (97.8%)	60,044 (98.9%)	49,919 (96.5%)	<0.001
Neurologist	99,856 (88.8%)	57,834 (95.3%)	42,022 (81.2%)	<0.001
Nurse	94,664 (84.2%)	53,607 (88.3%)	41,057 (79.4%)	<0.001

Physiotherapist	61,332 (54.6%)	32,965 (54.3%)	28,367 (54.8%)	0.076
At least one hospitalization in MSO, n (%)				
All diagnoses	92,007 (81.8%)	49,483 (81.5%)	42,524 (82.2%)	0.003
MS-related ^f	44,125 (39.3%)	28,643 (47.2%)	15,482 (29.9%)	<0.001
At least one hospitalization in REHAB, n (%)				
All diagnoses	27,236 (24.2%)	13,172 (21.7%)	14,064 (27.2%)	<0.001
MS-related	20,117 (17.9%)	11,235 (18.5%)	8,882 (17.2%)	<0.001
At least one DMT prescription of, n (%)				-
Beta-interferon	- -	31,871 (52.5%)	- -	
Glatiramer acetate	- -	15,329 (25.3%)	- -	
Dimethyl fumarate	- -	9,573 (15.8%)	- -	
Fingolimod	- -	8,941 (14.7%)	- -	
Natalizumab	- -	8,248 (13.6%)	- -	
Teriflunomide	- -	7,203 (11.9%)	- -	
Mycophenolate mofetil	- -	3,883 (6.4%)	- -	
Azathioprine	- -	3,713 (6.1%)	- -	
Methotrexate	- -	2,698 (4.4%)	- -	
At least one prescription among, n (%)				-
First-line	- -	48,483 (79.9%)	- -	
Second-line	- -	14,154 (23.3%)	- -	
Off-label use	- -	9,506 (15.7%)	- -	
Year of treatment start, n (%)				-
Before 2010	- -	32,952 (54.3%)	- -	
2010	- -	4,474 (7.4%)	- -	
2011	- -	4,477 (7.4%)	- -	
2012	- -	4,850 (8.0%)	- -	
2013	- -	4,209 (6.9%)	- -	
2014	- -	4,401 (7.3%)	- -	
2015	- -	5,330 (8.8%)	- -	

^a p-value comparing the two groups treated with at least one DMT vs. untreated by the Wilcoxon or Pearson's chi-square tests; ^b Median (q1 - q3); ^c percentage calculated only for women;

^d approximated level of disability based on prescription of technical aids; ^e based on data from the 12 months preceding study entry (if available); ^f hospitalizations corresponding to DMT injections were excluded.

MS = multiple sclerosis; CMU = universal health insurance (*Couverture Maladie Universelle*); MSO = medicine, surgery or obstetrics; REHAB = rehabilitation; DMT = disease-modifying therapy.

Table 2. Characteristics of the four groups of naïve multiple sclerosis (MS) patients obtained by the clustering procedure over the period from 2010 to 2015 (n= 4,474)

	Overall	Cluster 1 “First-line DMTs”	Cluster 2 “Not treated”	Cluster 3 “Off-label use”	Cluster 4 “Second-line DMTs”	p-value ^a
	4,474 (100.0%)	2,552 (57.0%)	1,011 (22.6%)	325 (7.3%)	586 (13.1%)	
Women, n (%)	3,199 (71.5%)	1,863 (73.0%)	695 (68.7%)	209 (64.3%)	432 (73.7%)	0.001
Age in 2010 (years) ^b , n (%)	40 (31 – 49)	38 (30 – 47)	44 (34 – 54)	51 (43 – 59)	35 (26 – 43)	<0.001
≤ 30	1,082 (24.2%)	652 (25.5%)	192 (19.0%)	22 (6.8%)	216 (36.9%)	
]30-40]	1,283 (28.7%)	816 (32.0%)	234 (23.1%)	43 (13.2%)	190 (32.4%)	
]40-50]	1,149 (25.7%)	683 (26.8%)	253 (25.0%)	86 (26.5%)	127 (21.7%)	
>50	960 (21.5%)	401 (15.7%)	332 (32.8%)	174 (53.5%)	53 (9.0%)	
Deaths, n (%)	69 (1.5%)	10 (0.4%)	40 (4.0%)	16 (4.9%)	3 (0.5%)	<0.001
Long-term disease for MS in 2010, n (%)	2,312 (51.7%)	1,216 (47.6%)	553 (54.7%)	234 (72.0%)	309 (52.7%)	<0.001
Health insurance coverage, n (%)						<0.001
General scheme (excluding CMU beneficiaries)	3,868 (86.5%)	2,234 (87.5%)	862 (85.3%)	277 (85.2%)	495 (84.5%)	
Agricultural workers	152 (3.4%)	86 (3.4%)	30 (3.0%)	20 (6.2%)	16 (2.7%)	
Self-employed workers	205 (4.6%)	99 (3.9%)	64 (6.3%)	16 (4.9%)	26 (4.4%)	
CMU beneficiaries	216 (4.8%)	123 (4.8%)	46 (4.5%)	12 (3.7%)	35 (6.0%)	
Other schemes	33 (0.7%)	10 (0.4%)	9 (0.9%)	0 (0.0%)	14 (2.4%)	
At least one occurrence of pregnancy, n (%) ^c	496 (15.5%)	290 (15.6%)	120 (17.3%)	10 (4.8%)	76 (17.6%)	<0.001
Estimated disability scale at inclusion, n (%) ^d						<0.001
Mild	3,987 (89.1%)	2,411 (94.5%)	834 (82.5%)	205 (63.1%)	537 (91.6%)	
Moderate	318 (7.1%)	116 (4.5%)	101 (10.0%)	65 (20.0%)	36 (6.1%)	
Severe	169 (3.8%)	25 (1.0%)	76 (7.5%)	55 (16.9%)	13 (2.2%)	
Charlson Comorbidity Index, n (%) ^e						<0.001
Missing	549 (12.3%)	328 (12.9%)	107 (10.6%)	18 (5.5%)	96 (16.4%)	
0	3,255 (72.8%)	1,923 (75.4%)	699 (69.1%)	220 (67.7%)	413 (70.5%)	
1-2	607 (13.6%)	288 (11.3%)	173 (17.1%)	73 (22.5%)	73 (12.5%)	
3-4	53 (1.2%)	11 (0.4%)	26 (2.6%)	13 (4.0%)	3 (0.5%)	
≥ 5	10 (0.2%)	2 (0.1%)	6 (0.6%)	1 (0.3%)	1 (0.2%)	
Health services use over the study period						
At least one visit to, n (%)						
General practitioner	4,436 (99.2%)	2,535 (99.3%)	996 (98.5%)	322 (99.1%)	583 (99.5%)	0.084
Neurologist	4,296 (96.0%)	2,474 (96.9%)	925 (91.5%)	314 (96.6%)	583 (99.5%)	<0.001

Nurse	4,065 (90.9%)	2,329 (91.3%)	888 (87.8%)	310 (95.4%)	538 (91.8%)	<0.001
Physiotherapist	2,477 (55.4%)	1,270 (49.8%)	577 (57.1%)	257 (79.1%)	373 (63.7%)	<0.001
At least one hospitalization in MSO, n (%)						
All diagnoses	3,800 (84.9%)	2,120 (83.1%)	852 (84.3%)	284 (87.4%)	544 (92.8%)	<0.001
MS-related ^f	2,464 (55.1%)	1,370 (53.7%)	457 (45.2%)	165 (50.8%)	472 (80.5%)	<0.001
At least one hospitalization in REHAB, n (%)						
All diagnoses	960 (21.5%)	359 (14.1%)	304 (30.1%)	166 (51.1%)	131 (22.4%)	<0.001
MS-related	817 (18.3%)	312 (12.2%)	249 (24.6%)	137 (42.2%)	119 (20.3%)	<0.001
At least one DMT prescription of, n (%)						NA
Beta-interferon	2,897 (64.8%)	2,005 (78.6%)	495 (49.0%)	37 (11.4%)	360 (61.4%)	
Glatiramer acetate	1,458 (32.6%)	994 (38.9%)	284 (28.1%)	21 (6.5%)	159 (27.1%)	
Dimethyl fumarate	616 (13.8%)	507 (19.9%)	70 (6.9%)	7 (2.2%)	32 (5.5%)	
Teriflunomide	388 (8.7%)	320 (12.5%)	48 (4.7%)	9 (2.8%)	11 (1.9%)	
Fingolimod	758 (16.9%)	322 (12.6%)	52 (5.1%)	9 (2.8%)	375 (64.0%)	
Natalizumab	648 (14.5%)	139 (5.4%)	90 (8.9%)	12 (3.7%)	407 (69.5%)	
Mycophenolate mofetil	311 (7.0%)	17 (0.7%)	115 (11.4%)	173 (53.2%)	6 (1.0%)	
Azathioprine	290 (6.5%)	35 (1.4%)	151 (14.9%)	98 (30.2%)	6 (1.0%)	
Methotrexate	235 (5.3%)	11 (0.4%)	126 (12.5%)	96 (29.5%)	2 (0.3%)	
At least one prescription among, n (%)						NA
First-line	3,743 (83.7%)	2,552 (100.0%)	680 (67.3%)	59 (18.2%)	452 (77.1%)	
Second-line	1,152 (25.7%)	417 (16.3%)	129 (12.8%)	20 (6.2%)	586 (100.0%)	
Off-label use	740 (16.5%)	59 (2.3%)	343 (33.9%)	325 (100.0%)	13 (2.2%)	
Proportion of the follow-up under treatment (%) ^b						
First-line	65.3 (29.2 - 88.9)	86.1 (62.5 - 93.1)	12.5 (4.2 - 22.2)	17.4 (11.5 - 31.2)	23.6 (13.9 - 31.9)	<0.001
Second-line	45.8 (22.2 - 66.7)	27.8 (15.3 - 37.5)	12.5 (2.8 - 25.0)	10.4 (6.2 - 22.6)	65.3 (55.6 - 80.6)	<0.001
Off-label use	33.3 (11.1 - 76.4)	9.7 (5.6 - 19.4)	13.9 (4.2 - 26.4)	81.9 (61.1 - 88.9)	9.0 (4.2 - 14.6)	<0.001
No treatment	18.1 (8.3 - 56.9)	12.5 (6.9 - 26.4)	83.3 (72.2 - 94.4)	15.3 (8.3 - 27.8)	12.5 (6.9 - 22.2)	<0.001

^a p-value comparing the four groups by the Kruskal-Wallis, Pearson's chi-square test, or Fisher's exact test; ^b Median (q1 - q3); ^c percentage calculated only for women; ^d approximated level of disability based on prescription of technical aids; ^e based on data from the 12 months preceding study entry (if available); ^f hospitalizations corresponding to DMT injections were excluded.

MS= multiple sclerosis; CMU= universal health insurance (*Couverture Maladie Universelle*); MSO= medicine, surgery or obstetrics; REHAB= rehabilitation; DMT= disease-modifying therapy.

Figure 2. Use of multiple sclerosis-specific disease modifying therapies (DMTs) over the period from 2010 to 2015 (n= 60,693)

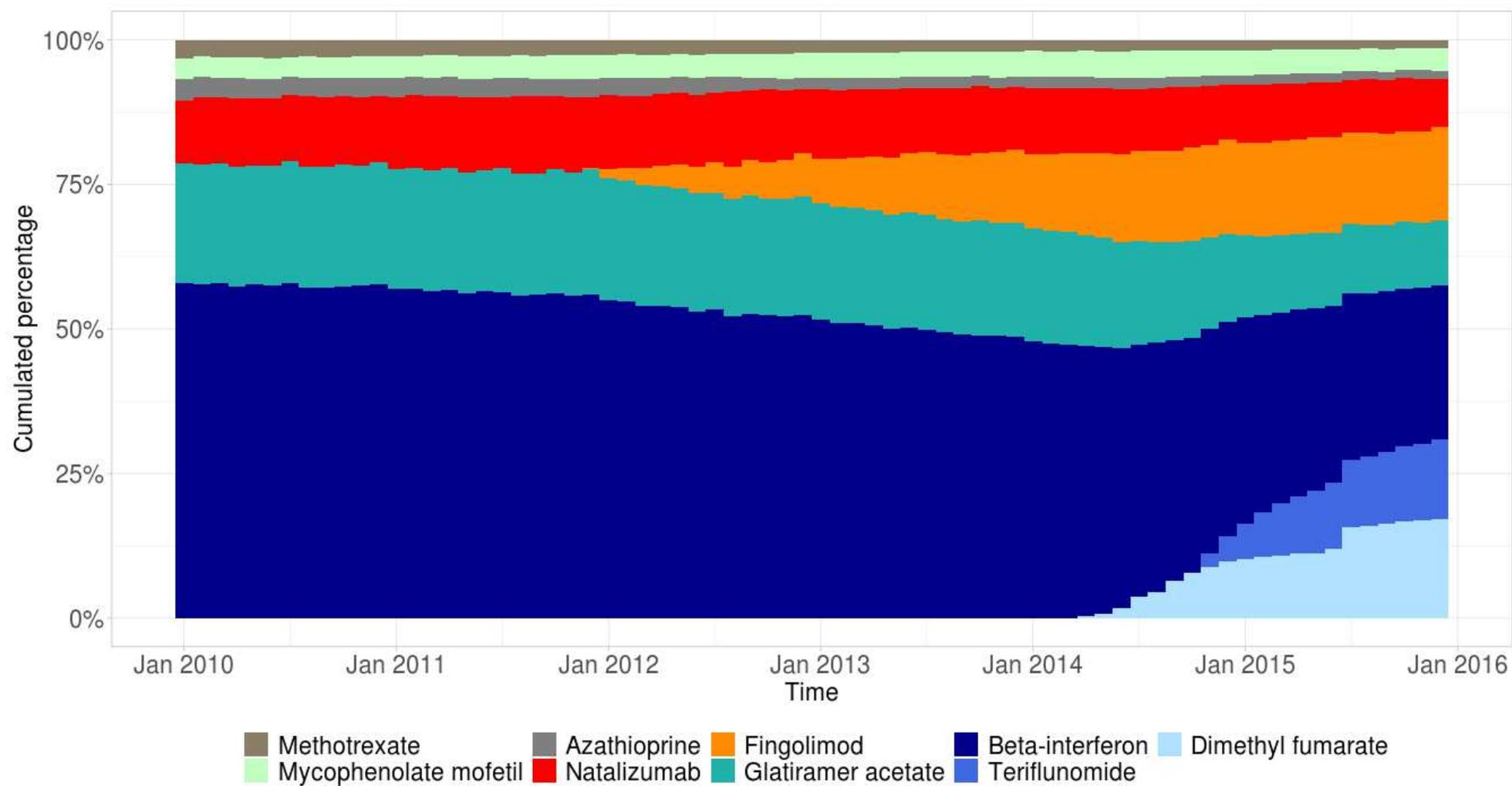


Figure 3. Use of multiple sclerosis-specific disease modifying therapies (DMTs) per French region over the period from 2010 to 2015 (n= 60,693; region of residence missing for 516 patients)

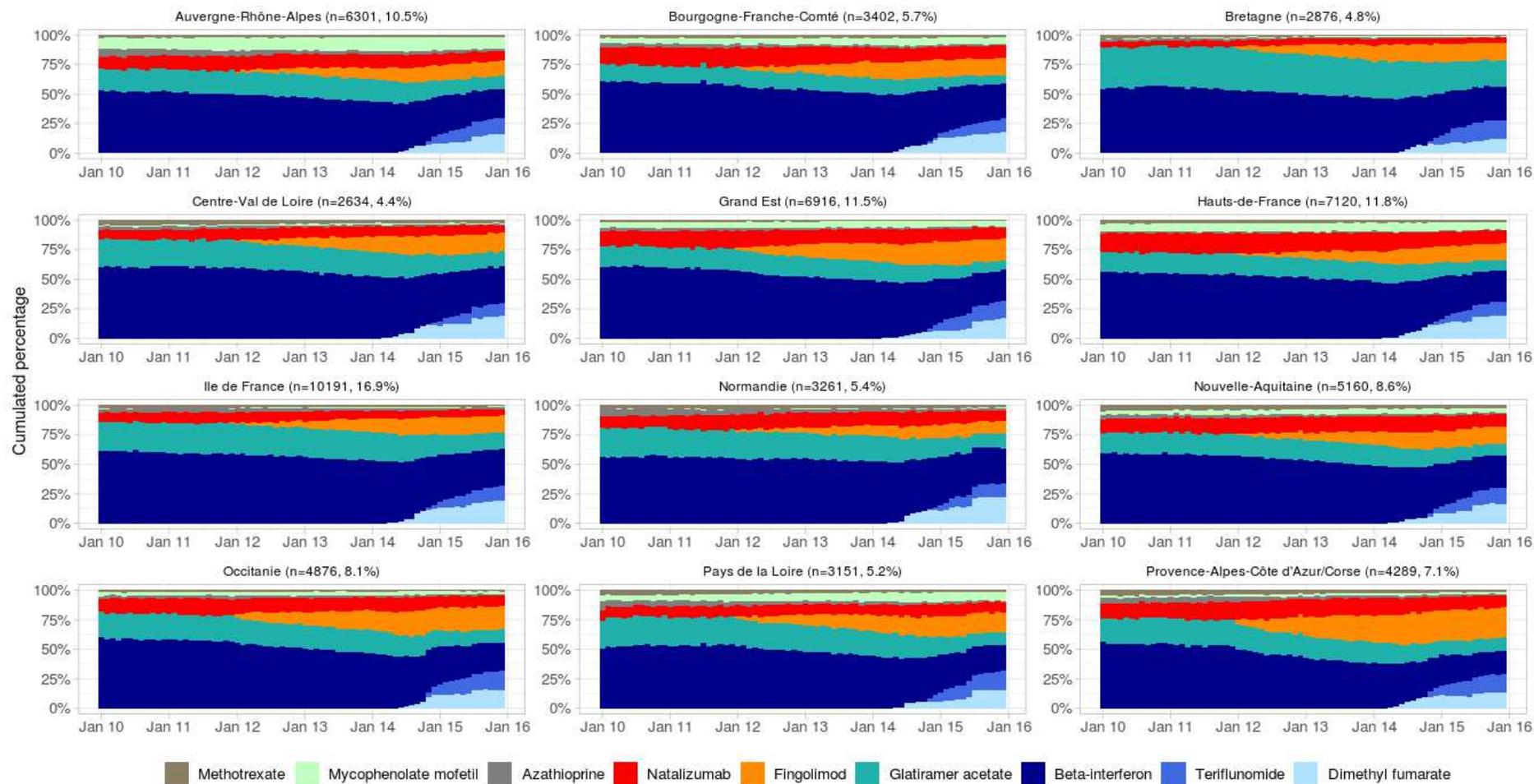


Figure 4. Index plot of therapeutic sequences of naïve multiple sclerosis patients over the period from 2010 to 2015 (n= 4,474)

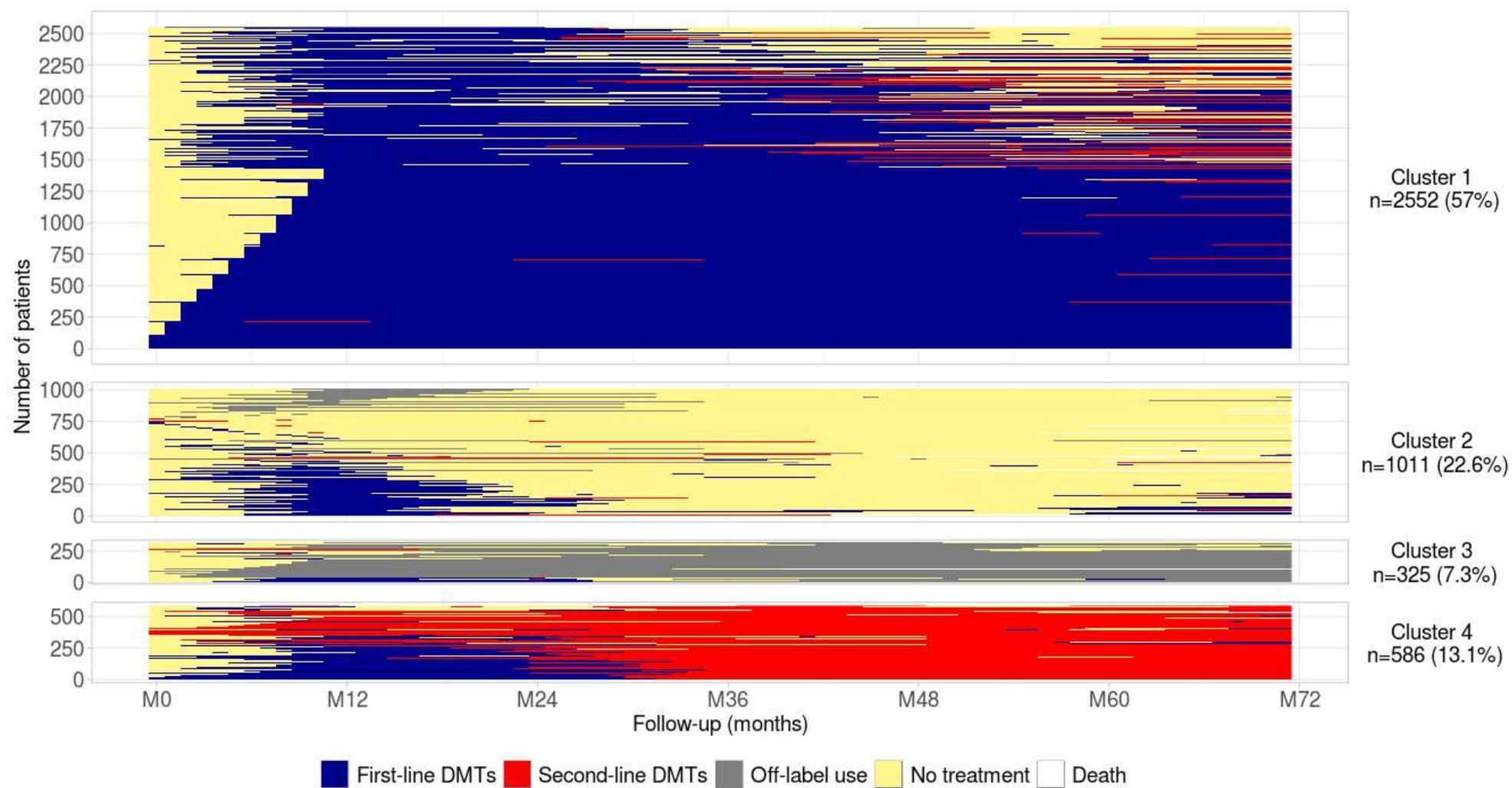
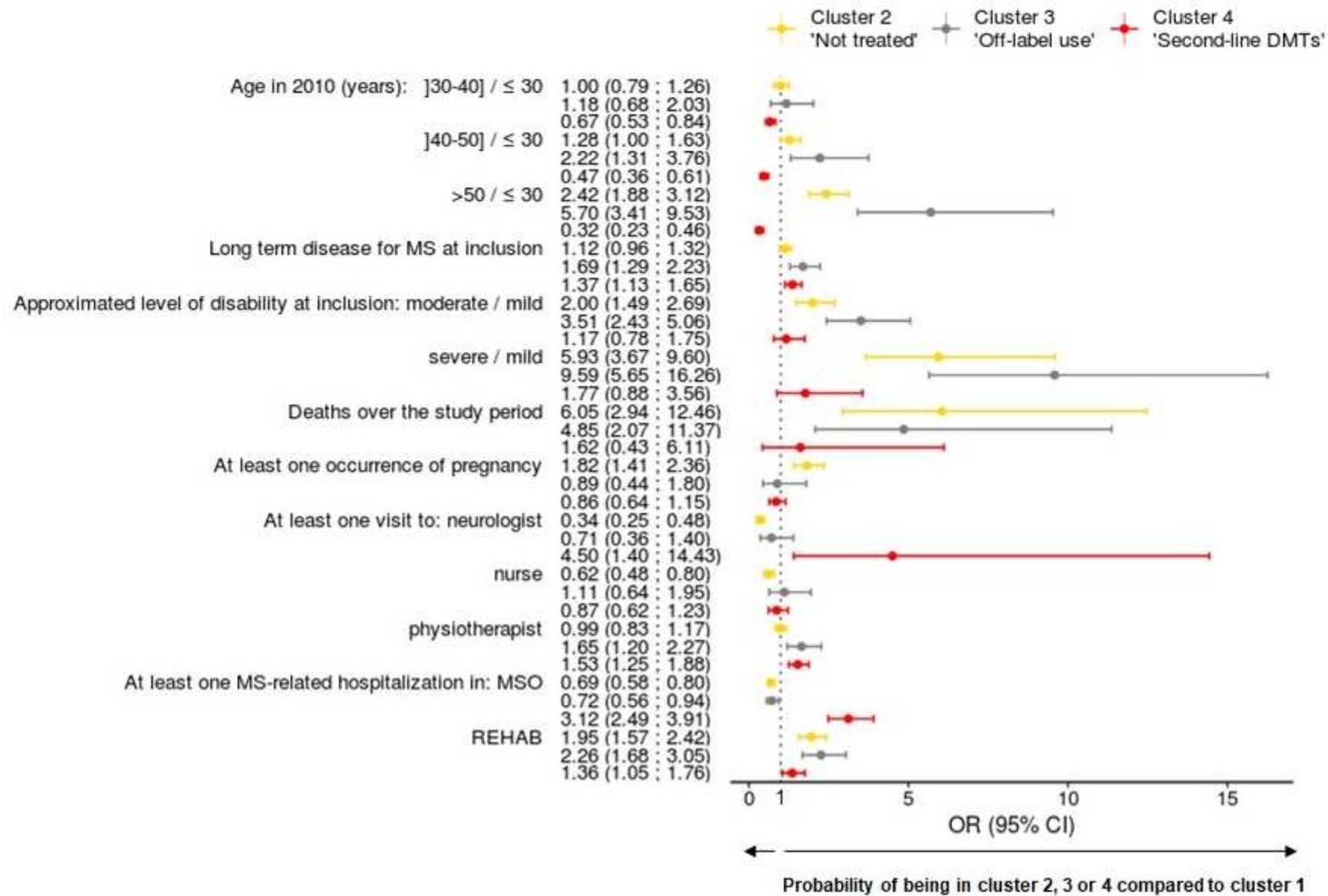


Figure 5. Characteristics associated with clusters in naïve multiple sclerosis patients over the period from 2010 to 2015 (n= 4,474)
 Forest plot of adjusted odds ratios (with 95% confidence intervals) from a multivariate multinomial logistic regression analysis (reference: Cluster 1 ‘First line DMTs’)



DMT=disease-modifying therapy, MS= multiple sclerosis; MSO= medicine, surgery or obstetrics; REHAB= rehabilitation