



Utilization of Multiple Sclerosis Therapies in the Middle East Over a Decade: 2009–2018

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Abstract

Background The multiple sclerosis (MS) landscape has changed over the past two decades across the world and in the Middle East. The Middle East is an ethnically diverse region located between 12° and 42° of latitude and 35° and 54° of longitude and varying altitudes. The magnitude of the shifts observed in the epidemiology and management of MS differ in each region and from country to country.

Objectives The aim of this study was to provide a clinicodemographic overview of the cohorts of patients contributed to MSBase, a large international MS registry, in the Middle East and describe disease-modifying treatment (DMT) utilization in the different countries within the region. Understanding the differences between these cohorts is integral to interpretation of the studies conducted using registry data and provides insight into clinical practice in these cohorts.

Methods The MSBase registry was searched for patients with MS or clinically isolated syndrome from the Middle Eastern countries with data captured between 2009 and 2018. In 2-year epochs, and with special focus on the most recent epoch (2017–2018), we explored the demographic, clinical characteristics and treatment exposures of the studied cohorts and reported the results using standard descriptive statistics.

Results Over the 10-year study period, 13,356 patients from 17 centers in 8 Middle Eastern countries fulfilled the inclusion criteria. The represented countries were Egypt, Iran, Kuwait, Lebanon, Oman, Saudi Arabia, Turkey and the United Arab Emirates. Overall, the represented cohort was young (median 36 years, quartiles 29–45) and captured relatively early after the onset of MS (median disease duration < 10 years, quartiles 3–12). The relapsing-remitting phenotype was the most prevalent phenotype in all countries (73–97%) and the highest proportion of progressive MS was reported in Saudi Arabia (12%). Median Expanded Disability Status Scale (EDSS) ranged from 0 to 3, depicting a mildly disabled cohort, with the exception of Saudi Arabia where the median EDSS was 4 (quartiles 1.5–6.5). The median relapse frequency was highest in Lebanon (median 1.03, 95% CI 0.94–1.16) followed by Egypt (median 1.02, 95% CI 0.89–1.24) and lowest in Saudi Arabia (median 0.70, 95% CI 0.58–0.95) and Kuwait (median 0.75, 95% CI 0.71–0.80). The treatment landscape greatly varied between different countries. Platform injectable therapies were mostly utilized in Egypt, Iran and Turkey (86%, 79% and 53%, respectively), while oral therapies and monoclonal antibodies were more commonly used in Kuwait, Lebanon and the United Arab Emirates (87.2%, 67.3% and 58.7%, respectively).

Conclusion Patients in the Middle East enrolled in a large multinational registry are representative of the general MS population. The spectrum of therapies used in the individual countries, however, is highly variable. Further studies that include rural and non-academic practices are needed to enhance our understanding of the MS cohorts in the Middle East.

1 Introduction

The landscape of multiple sclerosis (MS) is evolving across the world. The changed facets include the prevalence of MS and its phenotypes, clinical presentations and availability of disease-modifying treatments (DMTs). The treatment landscape has evolved rapidly in the last 12 years with the introduction of high efficacy DMTs following the dominance

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Key Points

While the clinical MS landscape in many Middle Eastern countries is similar to Europe and Australia, the treatment landscapes differ, with a greater utilization of low-efficacy treatments.

It is also common in some countries within the Middle East that patients with secondary progressive MS continue to use disease-modifying treatments.

of platform injectable treatments. The Middle East is an ethnically diverse region located between 12° and 42° of latitude and 35° and 54° of longitude and varying altitudes [1–3]. While the epidemiology, risk factors and clinical characteristics of MS in the Middle East have previously been described, the treatment landscape is relatively less investigated [4–17]. By accessing the MSBase registry [18, 19], we examined the data recorded from Middle Eastern centers, and here we provide a descriptive overview of the clinical and treatment differences in the countries in this region. While registries such as MSBase enable researchers to aggregate data from all around the world, correct interpretation of the data depends on in-depth understanding of the structure of the individual cohorts. The aim of this study was to provide a clinicodemographic overview of the cohorts of patients contributing to MSBase in the Middle East and describe DMT utilization in the different countries within the region.

2 Methods and Materials

2.1 Patients and Eligibility

MSBase is an expanding large observational registry of MS patients with participating centers in 38 countries and > 76,000 patient records, which has been extensively discussed elsewhere [18]. All patients from MSBase centers within the Middle East (based on the definition used in the Global Burden of Disease report [3]) who fulfilled the eligibility criteria were included. The eligibility criteria consisted of diagnosis of MS or clinically isolated syndrome based on the 2005 or 2010 revised McDonald criteria [20–23], a minimum of one visit with recorded disability score, and availability of a minimum data set (consisting of demographic information, year of diagnosis and disease course).

2.2 Study Outcomes

Disability was quantified with the Expanded Disability Status Scale (EDSS), with Neurostatus certification at each MSBase site, embedded within the MSBase online platform [24, 25]. We excluded EDSS measurements performed within 30 days of a relapse from all analyses. Relapse was defined as occurrence of new or exacerbation of existing signs or symptoms lasting at least 24 h, occurring in the absence of febrile disease and at least 30 days from a previous relapse. Multiple sclerosis severity score (MSSS) was calculated for each patient using the method described by Roxburgh et al. [26, 27], with specific reference populations for relapsing-remitting/secondary progressive MS and for primary progressive MS. Treatment utilization was evaluated as recorded by treating neurologists and categorized as platform injectable DMTs (interferon β -1a and -1b, glatiramer acetate and peginterferon), broad immunosuppressive treatments (mitoxantrone and cladribine), monoclonal antibodies (mAbs) (natalizumab, alemtuzumab, rituximab and ocrelizumab) and oral DMTs (dimethyl fumarate, teriflunomide and fingolimod).

2.3 Analysis

In each country, we have described the cohort in five distinct epochs, each spanning 2 years: 01.01.2017–31.12.2018, 01.01.2015–31.12.2016, 01.01.2013–31.12.2014, 01.01.2011–31.12.2012 and 01.01.2009–31.12.2010. Patients could contribute information to multiple epochs. We have assessed demographic and clinical information from the cohorts represented in each country—both for each epoch and overall. EDSS categorization was carried out as follows: 0–3.5 as mild, 4–5.5 as moderate and 6–9.5 as severe disability. We calculated annualized relapse rate (ARR) by using the sum of relapses per country over the sum of the cumulative duration of follow-up within an epoch. We reported median and 95% confidence interval of ARR estimated using bias correction and accelerated bootstrapping with 100,000 replications [28]. Descriptive analysis was performed using R version 3.5.1 and the results were reported using mean, median, or percentage for point estimates and standard deviation or quartiles, as appropriate.

3 Results

Over 10 years, 13,356 patients from 17 centers in Middle Eastern countries were registered with MSBase, with 84,138 recorded visits, capturing a cumulative follow-up of 31,460 patient-years. The following countries had participating centers: three centers in Egypt, two in Iran, one in Kuwait,

one in Lebanon, one in Oman, one in Saudi Arabia, seven in Turkey and one in the United Arab Emirates (UAE). As presented in Table 1, the duration of follow-up with MSBase was limited for the UAE, Iran and Egypt. Overall, the cohort of patients in the Middle East was young (median 36 years, quartiles 29–45) and was captured relatively early after the onset of MS (median < 10 years, quartiles 3–12). Fifty-four percent of the cohort had longitudinal follow-up; however, contribution of countries to the longitudinal follow-up was different. Saudi Arabian patients had the highest (73%) proportion of longitudinal follow-up followed by Oman (70%). About 66% of the Turkish patients had longitudinal data followed by Lebanon and Kuwait at 63% and 61%, respectively. Patients in Iran had a lower percentage of longitudinal follow-up at 37%, while in Egypt it decreased to roughly 10%. In the UAE, the full cohort was represented cross-sectionally. The median follow-up duration varied from 1.5 to 4 years in different countries (Table 1).

Relapsing-remitting MS was the most prevalent disease course reported in all the countries with minor differences in the prevalence of the other phenotypes. No secondary progressive cases were recorded from Iran and Oman during the 2017–2018 and 2015–2016 epochs, respectively. More details on demographics, disability, relapse and treatment utilization of patients captured during each epoch can be viewed in the electronic supplementary material (ESM; Tables S1–S5).

3.1 Disease Outcomes

Generally, the cohorts had relatively mild disability in most epochs, except for Saudi Arabia, where the cohort was more disabled with a median EDSS of 4 (quartiles 1.5–6.4) and median MSSS of 3.8 (quartiles 2.2–6.4) for the non-progressive phenotype (Tables S1–S2, see ESM). Disability status during the 2017–2018 epoch is shown in Table 2. We did not observe any trends in the EDSS of enrolled patients over the five epochs.

ARR during the 2017–2018 epoch was highest in Lebanon (median 1.03, 95% CI 0.94–1.16) and Egypt (median 1.02, 95% CI 0.89–1.24) and lowest in Saudi Arabia (median 0.70, 95% CI 0.58–0.95) and Kuwait (0.75, 95% CI 0.71–0.80). An increasing trend of ARR over the study period can be seen in the cohorts from some of the represented countries (Table 3 and S3 [see ESM]).

3.2 Use of Disease-Modifying Therapies

The treatment utilization landscape has significantly changed over the studied epochs in all countries as oral DMTs were introduced and were gradually adopted. In the most recent epoch, more patients were on DMTs with a substantial increase in utilization of oral and mAb treatments in comparison with the oldest epoch (Fig. 1).

During the 2017–2018 epoch, in Egypt, Iran and Saudi Arabia the injectable DMTs were far more commonly prescribed, while fingolimod was only used by 12%, 16% and 26% of the patients, respectively. In Turkey, 53% of the patients utilized injectable DMTs and oral DMTs accounted for 39% of the DMTs prescribed. In Kuwait and Lebanon, however, oral DMTs surpassed injectable DMTs at 45% and 39% versus 17% and 33%, respectively. At 45%, Kuwait leads utilization of the oral DMTs, 27% of which was contributed by fingolimod. Turkey and Lebanon have the highest utilization of oral DMTs after Kuwait at 39%, with fingolimod as the most common oral therapy in both countries. Despite this similarity, these three countries are utilizing the other oral DMTs differently with dimethyl fumarate being the second most prescribed medication in Kuwait and Lebanon while in Turkey teriflunomide is recorded almost twice as commonly as dimethyl fumarate.

The most recent data from Oman and the UAE were from 2015 to 2017. In Oman, the injectable therapies accounted for 52% of the DMTs, while fingolimod and natalizumab were utilized at 37% and 11%, respectively. The UAE had the highest utilization of oral DMTs in the region from 2013 to 2016 (55% in total, fingolimod accounting for 39%), which surpassed the use of the injectables in this country. However, the UAE cohort was small and the follow-up duration was limited (Tables 4; S4 and S5, see ESM).

mAbs were most utilized in Kuwait followed by Lebanon. In the 2017–2018 epoch, 38% of patients recorded from Kuwait used mAbs (most commonly natalizumab, followed by ocrelizumab and rituximab) while the respective number for Lebanon was 29% (most commonly rituximab followed by natalizumab). Meanwhile, in Iran and Egypt, mAbs were used by 4.4% and 1.8% of the patients, with rituximab being the most utilized mAb at 2.8% and 1.2%, respectively. Throughout the study period, only Turkey, Kuwait and the UAE utilized alemtuzumab while other countries have no record of using this DMT (Table S4).

Broadly immunosuppressive treatments steadily declined with a sharp drop from the 2013–2014 epoch to the 2015–2016 epoch, and in the latest epoch < 1% of the patients used such treatments (Table 4 and Table S5, see ESM).

Patients from Turkey had access to the most diverse spectrum of DMTs over the study period and Turkey was the regional pioneer for participating in phase III investigational trials, which resulted in MSBase records of oral DMTs and ocrelizumab in this country before the other countries (Table S4 and S5, see ESM).

The majority of patients with secondary progressive multiple sclerosis (SPMS) were not receiving DMTs, with Kuwait and Egypt being the only exceptions where 76% and 57% of SPMS patients received a DMT, respectively—most commonly natalizumab followed by ocrelizumab and fingolimod in Kuwait and interferon β -1a in Egypt (Table 5).

Table 1 Pooled demographic information about the study cohorts

	Egypt	Iran	Kuwait	Lebanon	Oman	Saudi Arabia	Turkey	United Arab Emirates
Number of patients	1102	2358	1707	837	37	116	7021	178
Number of centers	3	2	1	1	1	1	7	1
Years with follow-up	2009–2018	2009–2018	2009–2018	2009–2018	2009–2017	2009–2018	2009–2018	2013–2016
Reported MS prevalence from literature (per 100,000)	13.74 [29]	5.34–115.94 [10, 30–34]	10.2, 85.05 [4, 35]	20.01–60 [36]	1.2, 4 [37, 37]	25 [38]	33.9–101.4 [7, 9, 39–41]	54.7, 57.09 [42, 43]
Proportion of the prevalent population captured by MSBase (%)	8.1	4.8	86.6	30.5	29.5	1.4	12.8	3.3
Female (%)	71	79	66	65	76	60	69	66
Age (y), median (quartiles)	31.4 (25.2–37.6)	33.9 (28.2–41.8)	34.2 (27.9–41.8)	37.2 (29.6–48.1)	29.1 (25.5–32.2)	33.8 (28.7–40)	38 (30.5–46.8)	34.1 (27.4–40.40.7)
Age, <i>n</i> (%)								
Under 18 y	46 (4)	45 (2)	50 (3)	20 (2)	0 (0)	1 (1)	79 (1)	6 (3)
18–35 y	718 (65)	1310 (56)	933 (55)	365 (44)	33 (89)	65 (56)	2950 (42)	99 (56)
36–53 y	319 (29)	896 (38)	624 (37)	327 (39)	4 (11)	45 (39)	3208 (46)	71 (40)
> 54 y	19 (2)	107 (4)	100 (6)	125 (15)	0 (0)	5 (4)	784 (11)	2 (1)
Cumulative MSBase follow-up (y)	305	2900	4310	1748	109	301	21,787	1
Patients with cross-sectional data only, <i>n</i> (%) ^b	996 (90)	1496 (63)	669 (39)	306 (37)	11 (30)	31 (27)	2421 (34)	178 (100)
MSBase follow-up duration (y), median (quartiles)	0 (0–0.2)	0 (0–2.1)	2 (0–4.4)	1.8 (0.4–3.3)	3 (1–5.6)	2.9 (0.9–4)	2.8 (0.6–6.6)	0
Follow-up duration (y) in patients with longitudinal data, median (quartiles)	1.5 (1.2–2.3)	3.0 (1.8–4.5)	3.9 (2.4–5.6)	3.0 (2–3.9)	4.4 (2.3–5.5)	3.4 (2.3–4.2)	4.3 (2.4–6.7)	0
Disease duration (y), median (quartiles)	4 (1.3–7.8)	5.1 (2–9.5)	6.4 (2.8–11.4)	7.1 (3.4–12.7)	3.7 (1.6–6)	7.3 (4.6–11.5)	7.2 (3.1–13.1)	7.5 (3.5–13.3)
EDSS ^a , median (quartiles), <i>n</i>	3 (1.5–5.5), 600	2.5 (1–5.5), 274	1.5 (1–2), 1014	1.5 (1–3), 754	1 (1–2.3), 32	4 (1.5–6.5), 58	1.5 (1–3.5), 4568	1.5 (1–3.8), 138
0–3.5, <i>n</i> (%)	360 (60)	181 (66)	866 (86)	614 (81)	30 (94)	27 (47)	3444 (75)	105 (76)
4–5.5, <i>n</i> (%)	98 (16)	29 (11)	64 (6)	24 (3)	1 (3)	10 (17)	615 (14)	21 (15)

Table 1 (continued)

	Egypt	Iran	Kuwait	Lebanon	Oman	Saudi Arabia	Turkey	United Arab Emirates
6–9.5, <i>n</i> (%)	142 (24)	64 (23)	84 (8)	116 (16)	1 (3)	21 (36)	509 (11)	12 (9)
MSSS in non-progressive cohort, median (quartiles), <i>n</i>	5.8 (2.9–8), 563	3.5 (1–5.8), 264	2.0 (1–3.7), 985	2.3 (0.8–4.8), 716	2.4 (2–3.9), 26	4.3 (2.6–7.8), 43	2.4 (0.7–4.8), 4402	2.3 (1–4.8), 135
MSSS in primary progressive and progressive relapsing cohort, median (quartiles), <i>n</i>	5.9 (3.7–7.4), 25	4.8 (2.7–6.6), 10	2.9 (2–6.4), 9	0.8 (0.3–6), 29		7.9 (7.4–9.2), 9	5.1 (2.4–7), 126	
MS phenotype	1077	2356	1687	826	32	109	6968	176
CIS, <i>n</i> (%)	145 (13)	4 (0.2)	128 (7)	21 (2.5)	0	6 (6)	699 (10)	6 (3)
Relapsing remitting, <i>n</i> (%)	803 (75)	2285 (97)	1347 (79.8)	633 (76.6)	31 (97)	80 (73)	5293 (76)	149 (85)
Primary progressive, <i>n</i> (%)	21 (2)	53 (2.2)	60 (3.6)	32 (3.9)	0	5 (5)	277 (4)	0
Progressive relapsing, <i>n</i> (%)	24 (2)	14 (0.6)	5 (0.3)	11 (1.3)	1 (3)	8 (7)	85 (1)	1 (1)
Secondary progressive, <i>n</i> (%)	84 (8)	0	147 (8.7)	129 (15.7)	0	10 (9)	614 (9)	20 (11)

CIS clinically isolated syndrome, EDSS Expanded Disability Status Scale, MS multiple sclerosis, MSSS Multiple Sclerosis Severity Score

^aThe most recent EDSS not recorded within 30 days of a relapse was included

^bLongitudinal follow-up was defined as > 1 year of follow-up

Table 2 Disability recorded during the 2017–2018 epoch

	Egypt (178)	Iran (75)	Kuwait (745)	Lebanon (588)	Saudi Arabia (38)	Turkey (2890)
EDSS ^a , median (quartiles)	2.5 (1.5–5.5)	3 (1.5–6)	1 (0–2)	1.5 (1–3)	4 (1.5–6.375)	1.5 (1–3)
0–3.5, <i>n</i> (%)	118 (66)	44 (59)	643 (86)	480 (82)	18 (47)	2245 (78)
4–5.5, <i>n</i> (%)	25 (14)	8 (11)	44 (6)	20 (3)	6 (16)	388 (13)
6–9.5, <i>n</i> (%)	35 (20)	23 (31)	58 (8)	88 (15)	14 (37)	257 (9)
MSSS in primary progressive and progressive relapsing cohort, median (quartiles), <i>n</i>	6.4 (4.7–7.2), 4	4.8 (3.4–6.4), 4	2.5 (2.1–5.2), 6	1.1 (0.3–5.9), 25	7.5 (6.1–9.1), 7	3.6 (2–5.9), 70
MSSS in non-progressive cohort, median (quartiles), <i>n</i>	5.0 (2.4–7.1), 174	3.7 (1.9–6.3), 71	1.8 (0.9–2.8), 731	2.1 (0.7–4.4), 555	3.8 (2.2–6.4), 26	2.0 (0.6–4.3), 2796

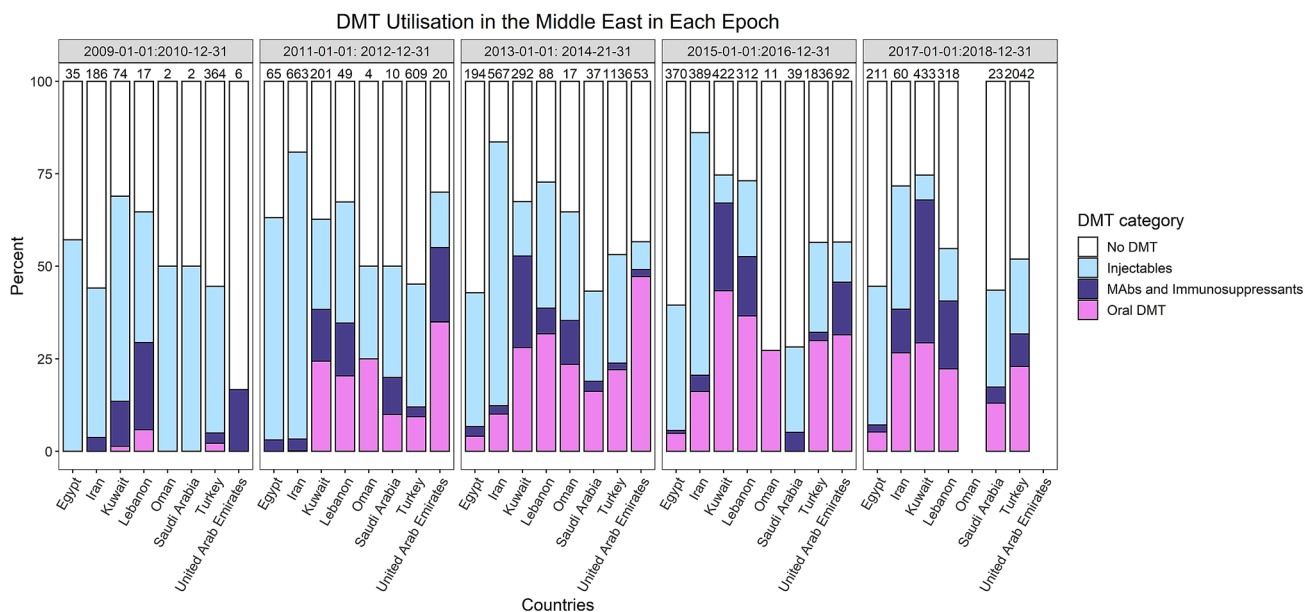
EDSS Expanded Disability Status Scale, MSSS Multiple Sclerosis Severity Score

^aThe latest EDSS recorded per patient within the epoch was utilized

Table 3 Annualized relapse rate in the 2017–2018 epoch

	Egypt (3)	Kuwait (206)	Lebanon (75)	Saudi Arabia (7)	Turkey (994)
Annualized relapse rate, median	1.02	0.75	1.03	0.70	0.94
95% CI ^a	0.89–1.24	0.71–0.80	0.94–1.16	0.58–0.95	0.92–0.97
Total number of relapses	40	235	100	8	1359
Total duration of follow-up (y)	39.23	313.71	97.27	11.37	1441.62

^aCrude, bias-corrected and accelerated bootstrapped 95% confidence interval

**Fig. 1** Treatment utilization in the Middle East over the study period (2009–2018). *DMT* disease-modifying treatment, *MAbs* monoclonal antibodies**Table 4** Treatment utilization in the Middle East in the 2017–2018 epoch by categories

Treatments ^a	Egypt (170)	Iran (250)	Kuwait (1071)	Lebanon (623)	Saudi Arabia (61)	Turkey (4057)
Broad immunosuppressants	1 (0.6)	1 (0.4)	0	0	0	14 (0.3)
Injectable DMTs	146 (85.9)	197 (78.8)	184 (17.2)	203 (32.6)	39 (63.9)	2164 (53.3)
Monoclonal antibodies	3 (1.8)	11 (4.4)	405 (37.8)	180 (28.9)	6 (9.8)	290 (7.1)
Oral DMTs	20 (11.8)	41 (16.4)	482 (45)	240 (38.5)	16 (26.2)	1579 (38.9)

DMTs disease-modifying therapies

^aData are presented as *n* (%)

4 Discussion

This study aimed to provide a descriptive overview of patients with MS in the Middle East using the data collected through the multinational MSBase registry between 2009 and 2018. Egypt, Iran, Kuwait, Lebanon, Oman, Saudi Arabia, Turkey and the UAE had participating centers in MSBase during the defined study period. We have shown

that, with the exception of Saudi Arabia, the studied cohorts from the Middle East follow the known global epidemiology of MS, with a typical representation of women (60–79%) and an overall tendency to be affected by a relatively mild disability. We have observed marked variability in prescription practices of MS therapies, with Kuwait assuming the most proactive approach.

The number of participating centers in different countries varied from one center (Kuwait, Lebanon, Oman, Saudi

Table 5 Treatment utilization in patients with SPMS in the 2017–2018 epoch

Treatments ^a	Egypt (21)	Kuwait (66)	Lebanon (88)	Saudi Arabia (5)	Turkey (260)
Interferon β -1a IM					1 (0.4)
Interferon β -1b	3 (14.3)		2 (2.3)		3 (1.2)
Interferon β -1a SC	4 (19)	2 (3)	4 (4.5)		3 (1.2)
Glatiramer acetate					13 (5)
Mitoxantrone					1 (0.4)
Teriflunomide			2 (2.3)		14 (5.4)
Dimethyl fumarate		2 (3)	3 (3.4)		6 (2.3)
Fingolimod	2 (9.5)	7 (10.6)	4 (4.5)	1 (20)	29 (11.2)
Natalizumab	1 (4.8)	18 (27.3)	4 (4.5)		5 (1.9)
Rituximab	2 (9.5)	8 (12.1)	18 (20.5)		5 (1.9)
Ocrelizumab		11 (16.7)			37 (14.2)
Alemtuzumab		2 (3)			
Investigational agents					3 (1.2)
Non-DMT medications	9 (42.9)	16 (24.2)	51 (58)	4 (80)	140 (53.8)

DMT disease-modifying therapy, IM intramuscular, SC subcutaneous

^aData are presented as *n* (%)

Arabia and the UAE) to seven (Turkey). Generally, in less populated countries, MSBase is capturing a higher percentage of the country's MS population, which can be due to fewer MS patients as well as provision of central MS care. For example, the participating center in Kuwait is capturing approximately 87% of the patients living with an MS diagnosis. In Lebanon and Oman, approximately 30% of the MS population is captured through the sole participating center. In contrast, the UAE has a medium prevalence of MS and a population of < 10 million; however, the MSBase cohort is representative of < 5% of the country's MS population. In countries with a greater population that is more widely dispersed, the MSBase coverage of the MS population is considerably lower. For example, in Turkey with a population of > 80 million in 2018 and seven participating centers, the captured cohort represents approximately 13% of the whole MS population. Similarly, Egypt and Iran are populous countries with three and two participating centers respectively, where MSBase is capturing approximately 8% and 5% of the prevalent MS.

The proportions of patients with longitudinal follow-up varied markedly among the represented countries, ranging from 73% in Saudi Arabia to 0% in the UAE. In five countries, at least 60% of the eligible patients had recorded longitudinal data. The scarcity of longitudinal follow-up and the differences in the duration of follow-up resulted in heterogeneous patterns in the cohort characteristics. As it has been noted previously, timely diagnosis of MS depends on the availability of diagnostic tools such as magnetic resonance imaging, and the access to these tools has improved in the Middle East over the last decade [10]. For example, while an increasing trend in disease duration can be seen

for most countries over the study epochs, the trend is not reflected in age or MSSS. This phenomenon may be related to the improved diagnostic standards over the last decade, which resulted in earlier detection of MS. The trends in ARR show differing patterns between countries and over time. This diversity may, in part, be due to the influence of newly registered patients, which is more accentuated in countries that lack longitudinal follow-up. In Saudi Arabia, Kuwait, Lebanon and Turkey, where relatively more longitudinal follow-up is captured, the median ARR ranges between 0.7 and 1. In Kuwait, ARR shows an unusual tendency to increase over time; this may be due to a shift in the cohort towards patients with more active disease being referred to the specialist MS center, or improved reporting of relapses due to implementation of clearer definitions of relapse. Contrary to this pattern, disability among the patients with relapsing MS from Kuwait shows a decreasing trend over time that is more accentuated in MSSS than the EDSS (Tables S1 and S3 in the ESM).

The cohort from Saudi Arabia showed the highest percentage of patients with progressive disease phenotypes across all the studied epochs. This was reflected in higher disability and, expectedly, not relapse rate. This most likely reflects differences in regional practices in enrolment of patients with progressive MS in registries. The treatment landscape in Saudi Arabia, however, shows continued utilization of platform injectables for most patients over the last decade. Similarly, in a recent report by Yamout and colleagues, it is shown that platform injectables are used in more than half of patients in the Middle East and North Africa region [44]. The rapid change in the population structure might impact the ability of healthcare systems to adjust

provision of medical services, as the World Bank report has shown that the population in the Middle East has grown by 50% during 2000–2020, with the highest growth in the age range of 25–65 years [45].

Globally, highly effective DMTs myParahave become more frequently prescribed over the last decade. We observed a similar shift in the Middle East, even though the magnitude of this shift has been slower than in Europe, Australia and North America, and it has varied substantially among the individual countries. We found that mAbs were more utilized in countries with a higher income, which could be driven by the out-of-pocket costs imposed on patients, which are higher in Egypt and Iran than in Turkey [45]. It must be noted that in countries with a lower gross domestic product per capita such as Egypt and Iran, this shift tends to occur at a slower rate. Separately, the influx of refugees fleeing from regional conflicts might contribute to the ability of host countries to provide reimbursement for more expensive DMTs and it might also affect provision of DMT to refugee patients who would benefit from treatment [46].

Engaging in interventional clinical research can be another marker of a proactive approach towards treatment and Turkey has been the regional leader in participating in phase III clinical trials and in adopting oral therapies over the past decade (Table S4, see ESM). Moreover, the difference in healthcare practices and policies is reflected in the variability of DMT utilization in patients with SPMS. In Kuwait, most patients with SPMS have retained access to DMTs (largely high efficacy treatments) in the latest epoch (Table 5).

5 Limitations

This study utilized the data registered by MSBase centers from 2009 until the end of 2018. We have used the data from these centers as samples of populations from the represented Middle Eastern countries. The MSBase centers, however, might not be representative of the populations with MS in the included countries and the broader geographical region (Table 1). This may contribute to selection bias when comparing the studied cohorts to the known epidemiology of MS (such as in Saudi Arabia). Moreover, some countries within the geographic Middle East were not represented in MSBase, such as Qatar, Bahrain, Iraq and Jordan. The prevalence of MS reported in these countries ranges from 39 per 100,000 in Jordan [47] to 65 per 100,000 in Qatar [15]. Gender ratio and clinical characteristics also differ between these countries with a relatively less pronounced gender gap in Qatar and more motor symptoms at presentation in Jordan.

The follow-up duration recorded in MSBase for most of the countries within the region was relatively short, limiting our ability to explore longitudinal changes in disability and

relapse rates. There might be differences in the assessment of EDSS and relapse reporting, although this issue has been mitigated by implementing Neurostatus accreditation at the participating centers—which has been shown to improve inter-rater agreement [24]—and by encouraging the use of a unified definition of relapse as per the MSBase Study Protocol. MRI and paraclinical data were recorded scarcely and inconsistently, which limits the ability to provide a complete description of the cohorts.

6 Conclusion

Clinical practices, including prescription of DMTs and inclusion of patients in MS registries, vary widely across the Middle East. There has been a consistent shift from injectable therapies to the more potent oral therapies and mAbs, at least at tertiary academic centers. Academic centers in some of the countries are likely to drive the more proactive approach to diagnostics and treatment of MS. Further epidemiological research of more inclusive cohorts is needed, especially with focus on the differences in care for MS patients in the regional and rural areas of the Middle Eastern countries.

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Declarations

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Conflicts of interest The MSBase Foundation acknowledges financial contributions to support the MSBase Registry from Biogen, Novartis, Merck, Roche and Sanofi Genzyme. NM has received compensation for consulting services from Actoverco Pharmaceuticals. RA received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme. MT received travel grants from Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis. CB received conference travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis. AA received personal fees and speaker honoraria from Teva, Merck, Biogen - Gen Pharma, Roche, Novartis, Bayer, Sanofi-Genzyme; received travel and registration grants from Merck, Biogen - Gen Pharma, Roche, Sanofi-Genzyme and Bayer. TK served on scientific advisory boards for BMS, Roche, Sanofi Genzyme, Novartis, Merck and Biogen, a steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck. SSH, CM, SO, VSH, BY, RT, RK, SH, AS, JI and TAH declare no conflicts of interest.

Ethics approval This research was conducted in accordance with the World Medical Association Declaration of Helsinki and was

approved by Melbourne Health Human Research Ethics Committee (2006.044) and local ethics committees in participating centers (unless exemption granted by the local regulations). MSBase is registered with WHO International Clinical Trials Registry Platform (ID ACTRN12605000455662). All participants have provided written or verbal consent to be registered in MSBase. Only pseudonymized non-identifiable data was utilized for the purpose of this study.

Availability of data and material The data analyzed in this study are the property of the individual contributing centers. They can be made available upon reasonable request for the purpose of replication of the analyses included in this study and at the discretion of the principal investigators.

Code availability Available upon request.

Consent for publication Not applicable.

Author contributions NM, SS, CM and TK designed, analyzed and drafted the manuscript. RA, SO, VS, MT, CB, BY, RT, RK, SH, AS, AA, JL, TAH revised the manuscript. All authors have read and approved the submitted manuscript.

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