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Time Delay to High-Efficacy Treatment Initiation in Demyelinating CNS Diseases Is Linked to Sociodemographic and Clinical Parameters

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Abstract

Background: Early initiation of high-efficacy treatment (HET) in patients with demyelinating central nervous system (CNS) diseases is associated with improved long-term prognosis. Identifying parameters linked to delayed HET initiation could facilitate strategies to optimize timely treatment. **Objective**: This study aims to identify clinical and sociodemographic parameters that influence the interval between recommendation and initiation of HET in patients with multiple sclerosis (MS) and related disorders. **Methods**: In this single-center retrospective cohort study, electronic health records of 136 patients who received a recommendation for HET between January 2016 and August 2023 at the Department of Neurology, Goethe University Frankfurt, were reviewed. Clinical and sociodemographic variables were tested for their relationship with time delay using parametric and non-parametric methods; independent predictors were identified by multivariable linear regression, with *p*-values corrected using the Benjamini–Hochberg false-discovery-rate procedure. **Results**: Mean time delay between HET recommendation and initiation was 144.3 days (±86.4). After correction for multiple comparisons, four variables remained independent predictors of time delay: a higher expanded disability status scale (EDSS) score at recommendation ($q = 0.034$) and a greater number of prior disease-modifying treatments (DMTs; $q = 0.009$) were associated with longer delays, whereas an explicit recommendation for HET initiation prior to completed immunization ($q < 0.001$) and an active relapse at recommendation predicted shorter delays ($q < 0.001$). In a model with reduced complexity, the predictors kept their significance with the exception of a number of prior DMTs. Here, the occurrence of temporary illness between HET recommendation and initiation gained significance. **Conclusion**: Patients with higher baseline disability appear prone to delayed HET initiation and may benefit from closer monitoring during transition to HET, whereas active relapses seem to prompt more timely treatment decisions. The number of prior DMTs and the occurrence of temporal illness between HET recommendation and initiation might be relevant for the time delay, too, although here future, better powered studies should replicate the effects.

Keywords: multiple sclerosis; high-efficacy treatments; immunosuppression; time delay; determinants

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1. Introduction

Early initiation of high-efficacy treatments (HET), particularly in patients with clinical or radiological predictors indicative of high inflammatory disease activity, has been recognized as a key strategy to achieve maximal disease control and yield more favorable long-term outcomes in people with multiple sclerosis (pwMSs) both with regard to progression independent of relapse activity (PIRA) and relapse-associated worsening (RAW) [1]. Large registry studies have demonstrated the better long-term prognosis of patients with MS (pwMSs) even if HET is started as the first line of treatment independently from baseline features of the respective MS case. The results of ongoing randomized trials are expected to provide further evidence for the hit-hard-and-early strategy, which is already the preferred treatment approach for many MS specialists [2]. Interestingly, the results of a recently published meta-analysis delivered evidence not only for the safety and efficacy, but also for the cost-effectiveness of the early HET strategy [3]. Since the early disease course of MS especially is characterized by predominant neuroinflammation whereas later stages are associated with a greater impact of neurodegenerative processes, timely HET initiation appears to be critical for early and sufficient suppression of the inflammatory disease component [4]. Similar advantages of aggressive initial immunosuppressive treatment for antibody-mediated demyelinating CNS diseases such as neuromyelitis optica spectrum disorder (NMOSD) and myelin-oligodendrocyte glycoprotein antibody-mediated disease (MOGAD) can be assumed [5]. Mamoei et al. report that longer delays in initiating immunosuppressive treatment are associated with increasing disability rates among Danish NMOSD patients. A key focus of the study pertains to the temporal interval between the initial relapsing episode and the initiation of treatment [6].

Existing data mainly focus on the comparison of the hit-hard-and-early strategy to treat-to-target cohorts [7]. However, in order to achieve timely suppression of disease activity, it seems reasonable not only to choose HET as first-line treatment, but also to keep the period of time without HET as short as possible. In support of this consideration, the time dependency of long-term disease outcomes has been reported for both low-efficacy treatment (LET) and HET initiation [8]. The Swiss Multiple Sclerosis Registry has provided data covering the time period from 1995 to 2024, suggesting a tendency for a decreasing time interval between MS diagnosis and treatment initiation [9]. A recent observational study from a large registry delivered robust evidence that longer delays between MS diagnosis and start of HET are associated with increased long-term disability [10]. Patient-reported outcome measures are affected in a similar manner with less physical and psychological symptom burden when treatment is commenced early in the disease course [11]. Importantly, the time delay in the above-mentioned studies referred to the time interval between MS diagnosis and HET initiation. However, the time period after the neurologist's recommendation for HET was not separately examined in these studies. This interval, however, might be affected by multiple factors, some of which might be modifiable and thus subject to strategic interventions aiming at reducing the time delay of HET initiation. In the context of the given time sensitivity for potentially irreversible CNS damage and concomitant disability accrual, this time delay appears to be of special interest. Identifying factors associated with a greater risk of time loss after the first treatment recommendation would allow clinicians to have this cohort under closer observation. The aim of this study was to assess the sociodemographic, biological and clinical parameters that contributed to the time delay between recommending and initiating HET.

2. Patients and Methods

This single-center retrospective cohort study was conducted at the Department of Neurology at the Goethe University in Frankfurt am Main, Germany. Approval for the study

was provided by the local ethics committee at the University Hospital Frankfurt (reference number: 2023-1433—approved on 17 August 2023). Reporting was carried out following the STROBE (Strengthening the reporting of observational studies in epidemiology) criteria [12].

Comprehensive data collection was performed on all patients who presented to the neuroimmunological outpatient clinic due to various demyelinating CNS diseases, received a recommendation for the initiation of HET and subsequently commenced treatment with one of the following DMTs between January 2016 and August 2023. The screening procedure was conducted exclusively on patients who finally initiated HET. In accordance with the available data on the comparative efficacy of the approved drugs, the following were considered to be HET (in alphabetical order): alemtuzumab, cladribine, fingolimod, natalizumab, ponesimod, ocrelizumab, ofatumumab, ozanimod, rituximab, and siponimod [13]. The latest approved anti-CD20 antibody ublituximab was not included in the analysis since the official authorization for use in Germany was provided shortly before the commencement of the study.

Clinical, sociodemographic and laboratory parameters were extracted from the electronic patient records for each individual: age, sex, occupation, disease entity and duration, EDSS, number of relapses during the last 12 months before as well as between HET recommendation and initiation, previous and newly acquired comorbidities, leucocyte and lymphocyte counts, number of previously used DMTs, currently used DMT, the presence of a recommendation for very early HET initiation (e.g., before full completion of the immunization status), pre-existing neurological care, number of required vaccinations and distance to vaccinating physician. The last parameter was assessed by using Google Maps (https://www.google.com/maps/, Google LLC, Mountain View, CA, USA; accessed on 30 August 2025). In order to ensure reliable calculations of time intervals, it was necessary to restrict the analysis to individuals for whom there was exact documentation of the timepoints of HET recommendations and treatment initiation in the healthcare records and for whom the clinical and epidemiological data were available. The immunization status was evaluated through comparing the vaccination recommendations issued by the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute, with the documented vaccination status recorded in the individual's vaccination book or with laboratory-confirmed present antibodies against the various diseases [14]. For instance, patients may not have received certain vaccinations (e.g., pneumococcal vaccine), which are typically considered essential prior to any immunocompromising therapy. In the context of vaccinations required prior to immunosuppressive therapy, full immunization was defined as documented vaccination or laboratory-confirmed immunity against diphtheria, tetanus, pertussis, measles, mumps, rubella, varicella zoster virus, hepatitis B, pneumococcus, meningococcus and influenza. Adequate SARS-CoV-2 immunity was only assessed in patients who received a HET recommendation after the onset of the COVID-19 pandemic. However, these vaccinations may be postponed after the treating physician determines that early treatment initiation is necessary. The vaccination recommendations put forth by ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) and EAN (European Academy of Neurology) largely align with the STIKO recommendations [15]. Final analysis was performed after removing outliers with a time delay > 1 year between HET recommendation and initiation.

To address the potential problem of overfitting in our multivariable linear regression analysis, we also performed an additional regression analysis with a reduced set of predictors selected a priori based on clinical relevance.

3. Statistics

Microsoft Excel Version 2312 (Redmond, WA, USA) was used for collection of raw data and statistical analysis was performed using IBM SPSS Statistics 29.0.2.0 (Armonk, NY, USA). Descriptive statistical measures were employed to calculate measures of central tendency and variation. Multivariable linear regression analysis was conducted to examine the impact of sociodemographic and clinical parameters on the dependent variable "time delay". Analysis also included the Mann–Whitney U, Kruskal–Wallis and Chi-Square tests as well as Spearman's rank for ordinal/ranked variables, while for parametric variables we employed analysis of variance (ANOVA) and *t*-tests. For the correction for multiple comparisons, we employed the false-discovery rate (FDR) and the Benjamini–Hochberg procedure. The significance level was set at $q < 0.05$. The *p*-values corresponding to the coefficients of interest in the multivariable linear regression were extracted and passed through the Benjamini–Hochberg procedure. The q-values represent FDR-adjusted *p*-values.

4. Results

4.1. Demographics and Clinical Characteristics

After review of all patient contacts in the study period, a total of $n = 412$ patients were considered potentially eligible for further analysis. In the first step, a number of patients had to be excluded due to either insufficient documentation of immunization status ($n = 210$) or to the fact that the HET recommendation/initiation was performed at a different center with no available data ($n = 38$). In four patients, the timepoints of HET recommendation and initiation could not be retraced (Figure 1). To control for potential bias, e.g., due to incompliance leading to excessive time delays, we restricted the final statistical analysis to 136 patients, who commenced HET in a time interval within 1 year after initial recommendation.

N = 136 individuals were included in the subsequent final analysis (Table 1). Of those, $n = 77$ were female (56.6%) and the mean age was 34.49 years (±12.9 SD). In total, $n = 69$ patients (50.7%) were diagnosed with relapsing–remitting MS (RRMS), while 52 (38.2%) presented with progressive MS phenotypes, including primary progressive MS (PPMS) and secondary progressive MS (SPMS). A minority of 15 patients (11%) had other different conditions: neuromyelitis optica spectrum disorder (NMOSD), myelin-oligodendrocyte glycoprotein antibody-associated disorder (MOGAD), and relapsing isolated optic neuritis (RION). The mean disease duration was 5.55 years (±7.31 SD), with an EDSS score of 3 (2–4.5 IQR) at the time of HET recommendation. The mean time delay between HET recommendation and initiation was 144.25 days (±86.4 SD). The prevalence of neurological and psychiatric comorbidities was 13.2% and 12.5%, respectively, while 14% of patients exhibited cardiovascular disease and 55.1% had other additional diagnoses beyond their neurological condition. In the interval between the recommendation of HET and its initiation, three individuals developed new chronic diseases, while 30 (22.1%) suffered from acute temporary diseases such as infectious diseases or injuries. The most prevalent were infections with genitourinary and respiratory origin while injuries and surgeries were less common (Table 2).

A total of 81 (59.6%) individuals did not utilize any DMT at the time of enrollment, and 48 (35.3%) experienced a clinical relapse at the timepoint of HET recommendation. The one-year annualized relapse rate preceding the recommendation for HET was 0.89 (±1.02 SD). The mean number of DMTs previously used was 1.11 (±1.29 SD).

Table 1. Clinical and demographic characteristics of the study cohort.

Patient Characteristics (*n* = 136)	
Female/Male	77/59
Age (years), mean (SD)	34.49 (12.9)
Time interval between HET recommendation and initiation (days), mean (SD)	144.25 (86.4)
Recommendation for HET initiation before full completion of immunization status, *n* (%)	30 (22.1)
EDSS at timepoint of treatment recommendation, median (IQR)	3 (2–4.5)
EDSS at timepoint of treatment initiation, median (IQR)	3 (2–4.5)
Disease entity	
RRMS, *n* (%)	69 (50.7)
PMS, *n* (%)	52 (38.2)
others, *n* (%)	15 (11)
Disease duration (years), mean (SD)	5.55 (7.31)
Comorbidities	
neurological (%)	18 (13.2)
psychiatric (%)	17 (12.5)
cardiovascular (%)	19 (14)
others (%)	75 (55.1)
Distance from place of residence to vaccinating physician (km), mean (SD)	7 (23.1)
Acute temporary disease between HET recommendation and initiation, *n* (%)	30 (22.1)
Newly diagnosed chronic disease between HET recommendation and initiation, *n* (%)	3 (2.2)
Number of prior DMTs, mean (SD)	1.11 (1.29)
DMT used at recommendation, *n* (%)	
none	81 (59.6)
beta interferons/glatiramer acetate	12 (8.8)
dimethyl-/diroximelfumarate, teriflunomide	13 (9.6)
cladribine, sphingosin-1-phosphate receptor modulators	12 (8.8)
natalizumab	11 (8.1)
anti-CD20 therapies	0 (0)
others (prednisolone, azathioprine)	7 (5.1)
Annualized relapse rate 12 months before HET recommendation, mean (SD)	0.89 (1.02)
Number of relapses between recommendation and initiation, mean (SD)	0.15 (0.5)
Relapse at timepoint of HET recommendation, *n* (%)	48 (35.3)
Leucocyte count at timepoint of treatment recommendation (/µL)	7.91 (3.67)
Lymphocyte count at timepoint of treatment recommendation (/µL)	1.75 (0.9)

EDSS, expanded disability status scale; HET, high-efficacy treatment; IQR, interquartile range; PMS, progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SD, standard deviation.

Table 2. Acute temporary diseases between HET recommendation and initiation.

Type of Temporary Disease	**N**
Infections (%)	17 (56.7)
Genitourinary (%)	7 (23.3)
Respiratory (%)	5 (16.7)
Shingles (%)	1 (3.3)
Conjunctivitis (%)	1 (3.3)
Bursitis (%)	1 (3.3)
Unknown focus (%)	2 (6.7)
Injuries (%)	1 (3.3)
Surgeries (%)	4 (13.3)
Others (%)	8 (26.7)

Table 2. *Cont.*

Type of Temporary Disease	N
Acute hepatopathy (%)	3 (10)
Rash of unknown origin (%)	1 (3.3)
Depression (%)	1 (3.3)
Pulmonary embolism (%)	1 (3.3)
Polyserositis (%)	1 (3.3)
Seizure (%)	1 (3.3)

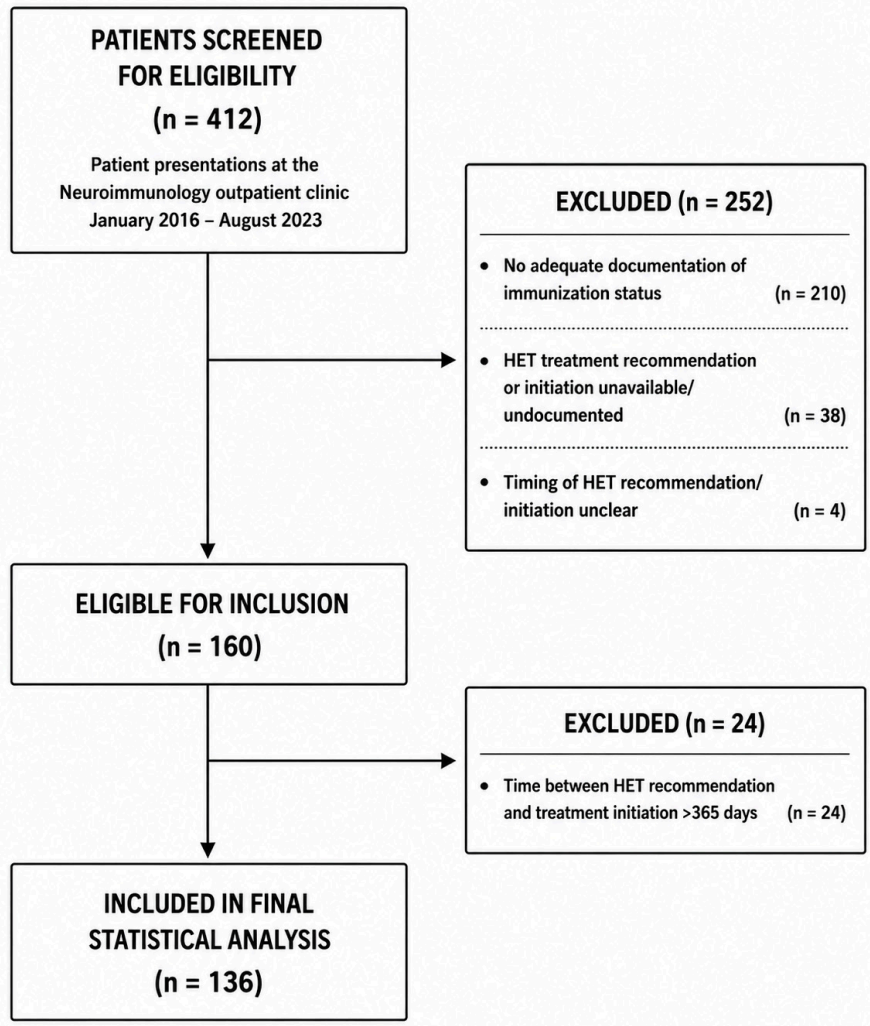


Figure 1. STROBE diagram illustrating the patient selection process. Following the initial screening of 412 patients, 160 patients remained after exclusion due to inadequate documentation of immunization status, irretraceable exact timepoints, and treatment recommendations and treatment initiations carried out externally. The data of 136 patients who commenced HET no later than 365 days after the recommendation was made were analyzed. HET: high-efficacy treatment.

4.2. Outcomes

Several patient characteristics showed significant correlations with time delay until HET start (see Table 3 for details). Higher disability at baseline ($p = 0.005$, r = 0.26) was associated with longer time periods until HET was commenced (Figure 2). The presence of a clinical relapse at the timepoint of HET recommendation ($p < 0.001$) was associated with less time delay (Figure 3). While higher ARR ($p = 0.041$) and acute temporary diseases such as infectious diseases and injuries ($p = 0.028$) resulted in longer time delays of therapy initiation after HET recommendation (Figures 4 and 5) in the initial analysis, those results

did not remain significant after correction for multiple comparison (Table 4). The observed numerical differences indicating a longer time delay with increasing age and progressive disease phenotypes did not reach significance ($p = 0.44$ and $p = 0.299$). No further variables were associated with time delay of HET initiation (Table 3).

Table 3. Results of multivariable linear regression analysis.

Examined Variable	Regression Coefficient (95% CI)	F Value	*p* Value
EDSS at baseline	**0.006 (0.002 to 0.010)**	**8.05**	**0.005**
Relapse at timepoint of HET recommendation	**−0.002 (−0.003 to −0.001)**	**18.01**	**<0.001**
One-year annualized relapse rate before HET recommendation	**−0.002 (−0.004 to −0.001)**	**4.26**	**0.041**
Number of prior DMTs	**0.003 (0.001 to 0.006)**	**7.06**	**0.009**
Temporary illness between recommendation and initiation	**0.001 (<0.001 to 0.002)**	**4.94**	**0.028**
Explicit recommendation for HET initiation before completion of immunization status	**−0.002 (−0.003 to −0.001)**	**23.19**	**<0.001**
Age	0.010 (−0.020 to 0.030)	0.60	0.441
Sex	<0.001 (−0.001 to 0.001)	0.55	0.458
Occupation	−0.003 (−0.006 to <0.001)	2.92	0.090
Disease entity	0.001 (−0.001 to 0.002)	1.09	0.299
Duration of disease	0.002 (−0.010 to 0.020)	0.05	0.819
Neurological comorbidities	<0.001 (<0.001 to 0.001)	0.94	0.334
Psychiatric comorbidities	<0.001 (−0.001 to <0.001)	0.91	0.343
Cardiovascular comorbidities	<0.001 (−0.001 to 0.001)	0.44	0.507
Pre-existing care from a neurologist	<0.001 (−0.001 to 0.001)	0.06	0.813
Distance from place of residence to vaccinating physician	−0.020 (−0.060 to 0.030)	0.51	0.478
DMT used at recommendation	0.002 (−0.001 to 0.006)	1.84	0.177
Leucocyte count at timepoint of treatment recommendation	<0.001 (−0.008 to 0.008)	<0.01	0.998
Lymphocyte count at timepoint of treatment recommendation	−0.001 (−0.003 to 0.001)	0.37	0.544

CI, confidence interval; DMT, disease-modifying therapy; EDSS, expanded disability status scale; HET, highly effective therapy. Bold rows indicate statistically significant associations ($p < 0.05$). Regression coefficients have been logarithmically transformed. Coefficients indicate the change in the clinical variable per one-day increase in time delay, e.g., for continuous variables, a 100-day longer delay was associated with an EDSS higher by approximately 0.55 points, approximately 0.33 more prior DMTs, and an annualized relapse rate in the preceding year lower by approximately 0.21 relapses. For binary variables (coded 0/1), coefficients represent the change in the proportion of patients with the respective characteristic (linear probability model): per 100 days of longer delay, the proportion of patients with an explicit recommendation for HET initiation before completion of immunization status was approximately 18 percentage points lower, the proportion with a relapse at the timepoint of HET recommendation approximately 19 percentage points lower, and the proportion with temporary illness between recommendation and initiation approximately 9 percentage points higher.

To evaluate the statistical sensitivity of our analyses, sensitivity power analyses were performed using G*Power 3.1 (linear multiple regression, fixed model, R^2 increase; $\alpha = 0.05$, power = 0.80), determining the minimum detectable effect size for a single predictor adjusted for 18 covariates. In the full sample (N = 160), the minimum detectable effect size was $f^2 = 0.050$ (partial $R^2 \approx 0.047$; partial $r \approx 0.22$); in the subsample (N = 136), it was $f^2 = 0.059$ (partial $R^2 \approx 0.055$; partial $r \approx 0.24$) (Table S1). Both analyses were therefore adequately powered to detect small-to-medium effects, whereas smaller effects may have remained undetected. The exclusion of 24 patients increased the minimum detectable effect size only marginally, indicating a negligible impact of the reduced sample size on statistical sensitivity.

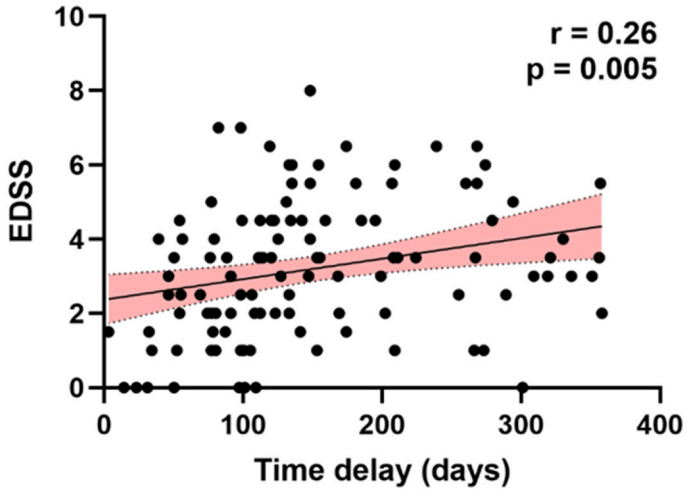


Figure 2. EDSS and time delay. Black dots represent individual patients; the solid line shows the linear regression fit, and the light red shaded area indicates the 95% confidence interval. Patients with higher grades of disability showed significantly longer time delays between HET recommendation and initiation (p = 0.005, Pearson's r = 0.26). EDSS: expanded disability status scale.

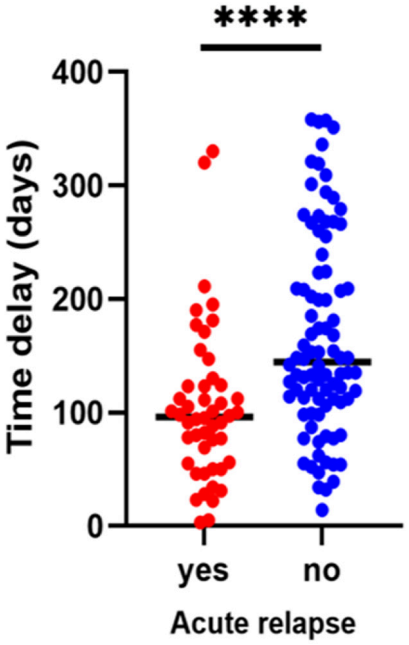


Figure 3. Relation of acute relapses at timepoint of HET recommendation with time delay. After stratification in two groups (with or without an acute relapse at the timepoint of HET recommendation) and post hoc analysis by means of independent-samples t-test, patients with acute relapses showed significantly less time lost between HET recommendation and initiation ($p < 0.001$). ****: significant.

To address the potential problem of overfitting in our multivariable linear regression analysis, we performed an additional regression analysis with a reduced set of predictors selected a priori based on clinical relevance. We now report the results of this additional analysis in the Supplementary Materials.

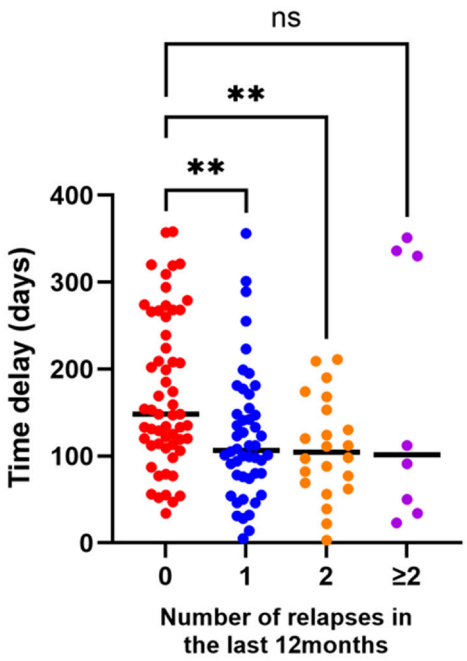


Figure 4. HET initiation time delay depending on the number of relapses 12 months before HET recommendation. After stratification into four groups based on the number of relapses experienced in the 12 months prior to the HET recommendation (no relapses, one relapse, two relapses, or more than two relapses), post hoc analysis using analysis of variance revealed significantly shorter time delays in patients with one or two relapses ($p = 0.002$ and $p = 0.003$, respectively), compared to those without any relapse. ns: not significant; **: significant.

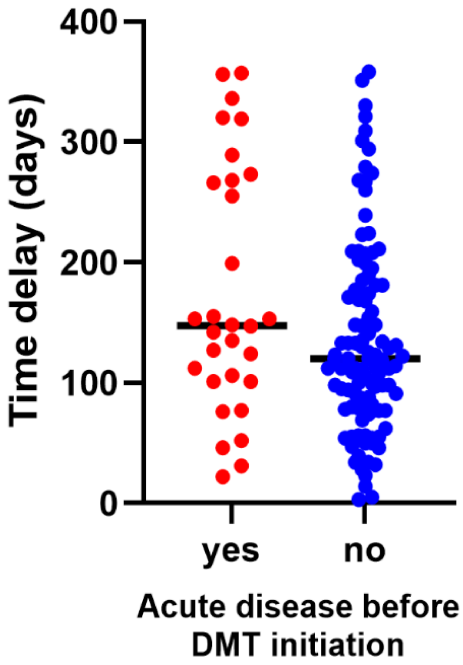


Figure 5. Effect of acute temporary illnesses in the interval between HET recommendation and initiation on the HET initiation time delay. The post hoc application of an independent-samples *t*-test revealed that the time delays were longer for patients with acute temporary diseases than for those suffering from no acute disease ($p < 0.001$). No significant correlation persisted after correction for multiple comparisons (Table 4). DMT, disease-modifying therapy.

Table 4. Analysis results after correction for multiple comparisons using the false-discovery rate with the Benjamini–Hochberg procedure.

	Benjamini–Hochberg q-Values
EDSS at baseline	**0.034**
Relapse at timepoint of HET recommendation	**<0.001**
Number of prior DMTs	**0.009**
Explicit recommendation for HET initiation before full completion of immunization status	**<0.001**
One-year annualized relapse rate before HET recommendation	0.13
Temporary illness between recommendation and initiation	0.106
Age	0.642
Sex	0.642
Occupation	0.244
Disease entity	0.593
Duration of disease	0.865
Neurological comorbidities	0.593
Psychiatric comorbidities	0.593
Cardiovascular comorbidities	0.642
Pre-existing care from a neurologist	0.865
Distance from place of residence to vaccinating physician	0.642
DMT used at recommendation	0.42
Leucocyte count at timepoint of treatment recommendation	0.998
Lymphocyte count at timepoint of treatment recommendation	0.646

DMT, disease-modifying therapy; EDSS, expanded disability status scale; HET, high-efficacy treatment. After applying the Benjamini–Hochberg procedure, significant correlations could only be observed for the following: EDSS at baseline; acute relapse at the time of HET recommendation; the number of prior DMTs; and an explicit recommendation for HET initiation before full immunization was achieved.

5. Discussion

Our study suggests that several clinical variables might put particular patients with MS and related disorders at a higher risk of a longer period of undertreatment. The knowledge of which key factors might contribute to a more expeditious HET initiation creates opportunities for optimizing patient care by specifically addressing these obstacles. Individuals with a higher burden of acquired disability were prone to experiencing greater time loss until appropriate treatment was started, which in turn might lead to further deterioration of their functional status. This was a rather unexpected finding, since these patients have an even narrower window of therapeutic opportunity due to their already accumulated disability. It also contrasts with previous findings that pwMSs with higher levels of disability are generally more likely to receive HET than those with less disability, whereas data on therapeutic delay after HET recommendation are lacking [16]. There are several possible reasons for this disparity: for example, those with advanced physical limitations are known to have less access to specialized neurological care, where recommendations for HET are often given [17]. Given the repeated appointments usually required to prepare for HET initiation (e.g., for blood sampling, vaccinations), reduced mobility may be a key factor in reduced accessibility to early HET. We conclude that increased attention in physically disabled patients is required for optimization of healthcare system access in pwMSs, i.e., involving the patient's social environment (family, friends, caregivers) into the holistic therapeutic strategy including HET initiation. Given the relatively modest effect of advanced disability on time delay, the clinical significance of this association must be weighed against potential risks arising from exposure to HET, particularly as more disabled individuals carry higher infection risks when treated with HET [18]. Thus, delaying HET

by 30 days might be less relevant for patients with higher EDSS (and perhaps a progressive course of disease). On the other hand, this delay might be relevant for an active course of disease since a new relapse can occur and result in more disability accumulation. This corresponds well with our findings that presence of a relapse at HET recommendation significantly affects the time delay, probably pushing both clinician and patient towards a quicker HET initiation.

Unsurprisingly, patients with an active disease, demonstrated by the recent number of relapses or the presence of a relapse when receiving the HET recommendation, appear to experience timely HET initiation and subsequent disease control. This likely reflects both the physician's and the patient's willingness to achieve stabilization and prevent further relapse-associated worsening: the acute deterioration in neurological function observed during relapses may lead to increased recognition of the apparent focal inflammatory disease activity, which in turn is the most modifiable pathophysiological component. Supporting the earliest possible DMT use in pwMSs and a high number of recent relapses, the association of a shorter therapeutic lag (i.e., the time between commencement and full therapeutic effect of DMTs) with higher ARR has been shown in two large registries.

The observed positive correlation between an increasing number of previously used DMTs and greater time loss until initiation of high-efficacy therapy—a relationship that may represent another potential target for clinical intervention—could be explained through several mechanisms. Necessary washout periods for specific substances (e.g., teriflunomide) and the need for normalization of relevant laboratory parameters before initiating the next therapy likely represent one such mechanism [19]. The lack of a statistically significant association between leucocyte or lymphocyte counts at the time of treatment recommendation and time delay in our study does not exclude this possibility due to potential underpowering. A further factor to consider is therapeutic inertia, defined as the failure to initiate or escalate treatment despite unmet therapeutic goals—a phenomenon that may become increasingly relevant in patients with a history of multiple unsuccessful treatment attempts [20]. Therapeutic inertia plausibly affects not only the general decision to escalate therapy, but also the urgency with which such a switch is ultimately performed.

Acute temporary diseases after HET recommendation showed an association with longer time delays in the initial analysis, but this association did not remain significant after correction for multiple comparisons ($q = 0.106$) and must therefore be interpreted with caution. Infections, which accounted for the largest share of temporary diseases in our cohort, are well documented to affect relapse rates, mortality, and healthcare costs [21], and acute illness may plausibly shift patients' treatment focus and perception of urgency. However, this variable occurs during the outcome period itself: patients with longer delays inherently have more time in which an illness can occur, so the analysis cannot distinguish whether illness caused the delay or whether a longer observation window simply increased the chance of recording one. Despite the lack of statistical significance, acute illness may still represent a clinically relevant, modifiable contributor to treatment delay. More regular outpatient visits and closer collaboration with other specialties (e.g., pneumology, urology for the most prevalent respiratory and urogenital infections in our cohort) may help ensure prompt HET initiation after recovery.

Surprisingly, we did not find an effect of the distance from the patients' homes to their neurologists or primary care physicians. This might be due to the well-established and interconnected means of transport in Western Europe and in particular in Germany but it could very much look different in other countries or continents where especially highly disabled patients might experience significant difficulties in gaining access to, e.g., public transport.

Several additional, potentially relevant determinants of treatment delay were not captured in our dataset and should be acknowledged as unmeasured confounders. These include the specific high-efficacy therapy prescribed, insurance- and authorization-related processes, the required washout period from previous treatment, laboratory screening prior to treatment initiation, infusion scheduling and appointment availability, individual patient preference, and pregnancy-related considerations. Each of these factors may independently influence the time to treatment initiation and could not be fully accounted for within the scope of the present analysis.

Our study is not without limitations. Several limitations warrant consideration, foremost among them the single-center, tertiary-care design of our study. While guidelines aim to harmonize procedures across tertiary-care centers, institutional practices may differ, which limits the generalizability of our results [22]. Moreover, patients treated at tertiary-care centers typically present with more complex disease courses than the general MS population, introducing a potential selection bias that may account for longer delays to treatment initiation than would be expected in an unselected cohort [23]. We had to exclude a rather large group of subjects due to missing data (especially with regard to the immunization status). However, comparing our remaining cohort with other cohorts in the literature, the main clinical and epidemiological parameters seem similar [24].

Furthermore, ethnicity and socioeconomic parameters have not been analyzed in particular in our trial due to missing information. The study population consisted of a patient cohort from a high-income country with sufficient accessibility to the healthcare system in an urban area. Since underrepresentation of ethnic minorities in medication trials and evidence for worse long-term outcomes among these patients are known problems, similar disparities could be expected for time delay of HET initiation [25,26]. For ethnic minorities, robust data investigating time delays until treatment in general and specifically HET are lacking. A multinational cohort study with inclusion of patients with various backgrounds would be appropriate in order to provide answers to this question.

A significant number of subjects were excluded from the study, primarily due to incomplete or inadequate documentation of their immunization status. It is evident that this circumstance gives rise to concerns regarding the potential for a selection bias. However, a more probable explanation for the observed phenomenon is the absence of digitalization of vaccination records and laboratory values, which poses a significant problem for this study, since all data incorporated into this study originate from electronic healthcare records. The occurrence of missing digitalized data is more likely to be random in nature, as opposed to being the result of a systematic error. This random absence has the potential to affect all patients equally, rather than selectively impacting specific populations.

Due to the small sample size, our study did not specifically examine the impact of particular treatment sequences or the potentially differential effects of vaccine type (e.g., live-attenuated versus inactivated vaccines) on therapeutic delay. Relevant effects of these factors can therefore not be ruled out. Given the mandatory safety interval required between vaccination and treatment initiation, unmeasured confounding by vaccine type appears likely [15]. Another limitation due to the small sample size is that the total number of predictors included in the linear regression was rather high as compared to the number of subjects. While this might lead to a higher risk of overfitting, the results gained by the statistical analysis make sense from a clinical point of view. In a model with reduced complexity, the predictors kept their significance, with the exception of number of prior DMTs. However, here the occurrence of temporary illness between HET recommendation and initiation gained significance. Thus, the number of prior DMTs and the occurrence of temporal illness between HET recommendation and initiation might be relevant for the time delay, too, although here future, better powered studies should replicate the effects.

Ideally, future studies should test prospectively if the identified factors are related to a time delay between recommending and initiating a HET.

Another influential factor worth considering with regard to the circumstances under which patients in this study received a treatment recommendation: The COVID-19 pandemic with its first public shutdown beginning in March 2020 in Germany led to significant impairments for patients as well as healthcare providers. As overall prescription rates for HET dropped and access to the healthcare system was restricted, a relevant effect on time delay until any HET was initiated after recommendation has to be assumed [27,28].

Furthermore, the inclusion of multiple demyelinating central nervous system (CNS) diseases within a single group could potentially introduce a confounding effect. The necessity for timely initiation of HET may vary according to the perceived risk of permanent neurological damage from relapses in NMOSD, which could result in earlier commencement of treatment [29]. Moreover, the paucity of approved treatments for NMOSD and MOGAD has the potential to result in protracted delays, as health insurance companies must first grant coverage for off-label therapies before these can be utilized [30]. These therapies are frequently the preferred treatment option for many physicians [31]. It is noteworthy that the disease phenotype (i.e., RRMS versus PMS) exhibited no substantial correlation with therapeutic delay. Given that patients diagnosed with PMS are generally likely to remain untreated, it could be hypothesized that there would be variances in the time periods preceding the initiation of HET among the cohorts. One possible explanation for this finding might lie in the number of relapses in both cohorts, where focal inflammatory activity in the progressive phenotype cohort could have resulted in more evenly distributed time intervals.

HET includes different treatment agents which differ in their administration requirements, monitoring protocols, and the logistical steps needed to initiate them. This might affect the time delay between recommendation and initiation of HET and can be viewed as a limitation. However, for most of those agents the requirements in Germany are not completely different—exclusion of chronic/acute infections, thorough lab work, up-to-date MRI and updating of the vaccination status and the variables investigated in our study, such as EDSS, age, occupation, etc., should vary similarly across different HET agents [32].

Several other methodological limitations should be considered. The relatively small sample size limits the statistical power of our analyses and increases the risk of overfitting within the multivariable model. Furthermore, patients with a treatment delay exceeding 1 year were excluded from the analysis—a decision that may have introduced selection bias and limits the generalizability of our findings to the full spectrum of treatment trajectories. Lastly, as a retrospective study, our analysis is inherently subject to limitations regarding data completeness and quality, since the underlying data were not originally collected for this specific research purpose.

6. Conclusions

The amount of time loss until HET are initiated after recommendation is significantly associated with pre-existing physical disability and disease activity. The acknowledgement of potentially modifiable risk factors for therapeutic delay in patients with MS (pwMSs) allows for the specific targeting of individual obstacles to the prompt initiation of HET. Subsequent studies will concentrate on larger and more heterogeneous patient cohorts, whilst also taking into account ethnic and socioeconomic factors.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diseases14110393/s1, Table S1: Sensitivity power analyses for a single predictor in multiple linear regression.

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Informed Consent Statement: Patient consent was not obtained as the study involved the secondary use of previously collected pseudonymized data and individual participants could not be directly identified.

Data Availability Statement: Data will be made available upon reasonable request to the corresponding author.

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