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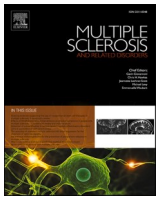

Original article

Disease modifying therapy after autologous haematopoietic stem cell transplantation in multiple sclerosis patients: 10-years follow-up data from Lithuania

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ABSTRACT

Background: There is limited information reported on the management of disease modifying treatment (DMT) in patients with multiple sclerosis (MS) who have been treated with autologous hematopoietic stem cell transplantation (AHSCT).
Methods: We conducted a single-centre prospective study of patients with highly active relapsing-remitting MS who underwent AHSCT in Lithuania from May 2014 till January 2025.
Results: Forty-two patients were selected and treated with AHSCT. 65.0 % of patients who underwent AHSCT achieved No Evidence of Disease Activity-3 (NEDA-3) over a 65-month median follow-up period. 35.6 % of patients experienced improvement in their Expanded Disability Status Scale (EDSS) scores by the third month post-transplant, and this improvement was maintained throughout the follow-up period. Twelve patients (28.5 %) who experienced disease activity after AHSCT were treated with DMT: eight patients (19.0 %) were treated with ocrelizumab, and in four patients (9.5 %), SPMS was diagnosed and patients were treated with siponimod. Five patients who were treated with ocrelizumab after AHSCT achieved NEDA-3, three of whom had been on DMT for >12 months.
Conclusion: The majority of patients maintained NEDA-3 up to five years after AHSCT. Patients who did not achieve NEDA-3 were successfully treated with high-efficacy DMT. No mortality was observed in our cohort. These findings support the efficacy and safety of AHSCT, as well as the use of DMT following AHSCT, in patients with highly active relapsing-remitting MS.

1. Introduction

Autologous hematopoietic stem cell transplantation (AHSCT) has emerged as a promising treatment for patients with multiple sclerosis (MS), particularly those with aggressive or treatment-resistant forms of the disease (Willison et al., 2022, Burt et al., 2022, Nawar et al., 2024). The treatment aims to reset the immune system and potentially reduces or eliminates the need for subsequent disease modifying treatment (DMT) in MS patients (Muraro et al., 2017, Cencioni et al., 2022, Massey et al., 2018). Phase II and phase III randomized controlled trials, also comparative treatment effectiveness studies have demonstrated AHSCT's superiority in reducing relapse rates and delaying disability progression compared to standard DMT for MS (Mancardi et al., 2015, Burt et al., 2019, Kalincik et al., 2023). Notably, ongoing clinical trials aim to address these uncertainties by evaluating the safety, efficacy, and long-term outcomes of AHSCT vs high efficacy DMTs in patients with active relapsing-remitting MS (RRMS) or aggressive MS who have previously been treated with DMTs (Inglese et al., 2024). There is increasing published evidence demonstrating robust clinical efficacy of AHSCT in patients with highly active MS, along with improved safety and significantly reduced mortality rates, supporting its incorporation into standard MS treatment algorithms (Sharrack et al., 2020, Ross et al.,

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2024, Stathopoulos et al., 2021).

AHSCT resets the immune system and immunological memory directed against autoantigens, however, the extent and duration of immune reconstitution varies in MS patients (Muraro et al., 2017, Massey et al., 2018, Burt et al., 2015). Formal guidelines exist for many aspects of care after AHSCT for autoimmune diseases, including MS, however, evidence-based recommendations for DMT reintroduction after AHSCT have not yet been provided (Sharrack et al., 2020, Muraro et al., 2025, Miller et al., 2021, Cohen et al., 2019), and questions remain regarding long-term disease suppression and patient management. There is limited information reported on the management of DMT in patients with MS who have been treated with AHSCT. In studies of AHSCT with follow-up periods of more than five years, DMTs were reintroduced in 11–35 % of patients, with retreatment initiated after a median of two years or later (Muraro et al., 2025, Silfverberg et al., 2024, Casanova et al., 2017). Reintroduction of DMTs followed MS relapses in the majority of cases and in some cases after evidence of MRI activity (Muraro et al., 2025, Burman et al., 2014). However, most of the studies had small sample sizes, and in some, patients were treated with different types of stem cell therapies (Manzano et al., 2022).

The aim of the study was to assess the long-term outcomes in MS patients treated with AHSCT and explore the treatment options for those who experienced disease activity after AHSCT.

2. Methods

A single-centre prospective study using real-world data was performed at Vilnius University Hospital Santaros Klinikos (VUHSK), Lithuania. The study was approved by Lithuanian Bioethics Committee in 2011 (2011–01–27 Nr: l-12–01/2), the permission to continue the study was granted in 2018 (2018–02–22 Nr: 6B-18–41). A total of 42 MS patient treated with AHSCT between May 2014 and January 2025 were enrolled in the study. All methods were performed in accordance with the relevant guidelines and regulations. All patients signed the informed consent form for the collection of data and its use for research purposes. Identified patients were required to meet the following study inclusion criteria: a confirmed MS diagnosis based on 2017 McDonald criteria (Thompson et al., 2018) and treatment with AHSCT for MS between 2014 and 2024.

The AHSCT was performed at our hospital as a routine clinical practice for patients with highly active RRMS who did not respond to second-line DMTs. Highly active MS patients in the case of AHSCT were defined the patients who experienced at least two relapses and had disability progression of at least 2.0 points according EDSS in the last year. Fingolimod, cladribine, natalizumab, ocrelizumab, ofatumumab and alemtuzumab are considered the second line therapy for MS in Lithuania based on the regulations of the Ministry of Health. The AHSCT procedure was carried out in Hematology, Oncology and Transfusion Medicine Center of Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania. The same protocol for AHSCT was used for all patients. Participants underwent peripheral blood stem cells mobilization: cyclophosphamide (2 g/m2 single dose with intravenous mesna prophylaxis) was administered, subcutaneous filgrastim 10 μg/kg was started on day +7 and peripheral blood stem cell (PBSC) apheresis procedure were targeted on day +12 after cyclophosphamide. A non-myeloablative conditioning was performed with cyclophosphamide (50 mg/kg on days −5, −4, −3, and −2), anti-thymocyte globulin (0.5 mg/kg on day −5 and 1.5 mg/kg on days −4,−3,−2, and −1), and high-dose methylprednisolone (1000 mg on days −5, −4, −3, −2, and −1.

DMT after AHSCT was considered on an individual basis for patients who experienced at least one relapse or demonstrated disease activity on brain MRI. MS relapses were determined by the same examining neurologist and were diagnosed when neurologic symptoms lasted >24 h, occurred at least 30 days after the onset of a preceding relapse, and were not associated with any other trigger. Neurological disability was assessed with Expanded Disability Status Scale (EDSS). Confirmed disability progression was defined as an increase in the EDSS score of at least one point if the baseline EDSS was ≤5.5 or an increase of ≥0.5 points if the baseline EDSS was >5.5. Confirmed disability regression was defined as a decrease of at least one point if the baseline EDSS was ≤5.5 or a decrease of ≥0.5 points if the baseline EDSS was >5.5. The primary outcome measure of the study was the proportion of patients who were treated with DMT after AHSCT. No Evidence of Disease Activity-3 (NEDA-3) in MS patients was defined as the absence of clinical relapses, disability progression, and magnetic resonance imaging (MRI) - detected disease activity (Giovannoni et al., 2015).

Brain MRI with Gadolinium was performed before AHSCT, at three months and every year after AHSCT. Cervical spine MRI was performed before AHSCT, one year after AHSCT, and subsequently whenever symptoms suggestive of spinal cord involvement occurred. MRI in all patients was performed using a 3.0 Tesla scanner Philips ACHIEVA 3TX. MRI assessment included the following sequences: T1 (repetition time 526 ms, echo time 14 ms), T2 (repetition time 4110 ms, echo time 105 ms) and fluid-attenuated inversion recovery (FLAIR) T2 (repetition time 9000 ms, echo time 122 ms). MRI was assessed by one and the same radiologist.

Statistical methods. The data were analysed via the statistical software package SPSS (version 23.0 for Windows). Continuous variables are reported as medians and ranges or means and standard deviations, whereas categorical variables are reported as absolute numbers and percentages of total patients.

3. Results

Forty-two patients were selected and treated with AHSCT. All patients had RRMS. The median follow-up was 65 months (range: 9 – 129). Demographic and clinical characteristics of the patients are provided in Table 1.

Twenty-six patients (65.0 %) who underwent AHSCT achieved No Evidence of Disease Activity-3 (NEDA-3) over a 10-years follow-up period. Twenty-seven patients (81.8 %) maintained NEDA-3 status at

Table 1
Demographic and clinical characteristics of patients treated with AHSCT.

Demographic and clinical variables	n or n (±)	%
Sex		
Female	28	70.0
Age (years)	38.1 ± 6.0	–
Disease duration (years)	9.6 ± 5.4	–
Education (years)	16.1 ± 3.0	–
Previous DMT*		
Fingolimod	11	27.5
Natalizumab	14	35.0
Cladribine	2	5.0
Ocrelizumab	8	20.0
Alemtuzumab	4	10.0
Interferon -beta**	1	2.5
Number of previously used DMT		
1	1	2.5
2	17	42.5
3	13	32.5
4	7	17.5
5	2	5.0
Relapses per one year before AHSCT	2.3 ± 0.8	–
range	1 - 4	
EDSS before AHSCT	5.7 ± 0.7	–
range	4.0 – 6.0	
MRI before AHSCT		
new lesions	11	27.5
active lesions	7	17.5

* the last disease modifying therapy is provided.
** special reimbursement was provided for the patient.
AHSCT - autologous haematopoietic stem cell transplantation, EDSS - Expanded Disability Status Scale, DMT – disease modifying therapy, MRI – magnetic resonance tomography.

two years, and sixteen patients (72.7 %) at five years. At two and five years after AHSCT, 17.1 % and 22.7 % of patients had experienced at least one relapse, 11.4 % and 18.2 % showed EDSS progression, and 2.9 % and 4.5 % had MRI activity, respectively.

Fourteen patients (35.0 %) experienced improvement in their EDSS scores by the third month post-transplant, and this improvement was maintained throughout the follow-up period. Fourteen patients (35.0 %) did not achieve NEDA-3 after AHSCT and in seven of these cases, secondary progressive MS was diagnosed. No mortality occurred in our cohort. Post-transplant patient outcomes are presented in Fig. 1.

Twelve patients (28.5 %) who experienced disease activity after AHSCT were treated with DMT. The median follow-up after AHSCT until DMT was 55 months (range: 22 – 107). Eight patients (19.0 %) were treated with ocrelizumab, and four patients (9.5 %) were diagnosed with SPMS and treated with siponimod. The median follow-up in patients treated with DMT was 19 months (range: 2 – 63). Five patients who were treated with ocrelizumab after AHSCT achieved NEDA-3, three of whom had been on DMT for >12 months. Three patients who were diagnosed with SPMS and treated with siponimod experienced disability progression, and one of them had a relapse. Two patients were treated with azatioprin, one of them had disability progression and in one patient treatment was just started (Table 2). Patients who received DMT after AHSCT had not been treated with the same therapy prior to AHSCT and did not experience any new or uncommon side effects while on DMT.

4. Discussion

In this study, we assessed the long-term outcomes of MS patients treated with AHSCT and explored subsequent treatment options for those who experienced disease activity after the treatment. Our study provided promising results, indicating that AHSCT is highly effective in achieving NEDA Fig. 2.

Previous studies have shown that patient selection is crucial in determining the outcomes of AHSCT for MS patients. Highly active RRMS, mild to moderate disability, shorter disease duration, and younger age have been identified as the primary criteria for recent investigations. In contrast, patients with progressive forms of MS without disease activity, higher disability (EDSS >6.0), older age (>50 years old), and longer disease duration are less likely to benefit from AHSCT (Burt et al., 2019, Muraro et al., 2017, Currò and Mancardi, 2016, Giedraitiene et al., 2020, Patti et al., 2022). Based on previous studies, we perform transplants only for highly active RRMS patients with clinical evidence of disease activity who have not responded to currently available MS therapies. In our study, 97.6 % of patients had failed second-line therapy for MS, indicating that the cohort represented highly active RRMS patients. Additionally, in line with the recommendations we included even relatively younger patients (median age 38.4 years) with less disability (EDSS ≤6.0).

During a 65-month median follow-up period in our study, the favorable treatment effect following AHSCT was sustained, with 65.0 % of patients achieving NEDA-3. These outcomes are highly promising, as compared to non-AHSCT treatments (Burt et al., 2019, Sormani et al., 2017), and consistent with those reported in other studies (Burt et al., 2022, Nash et al., 2017, Burman et al., 2014). The proportion of patients with NEDA-3 after AHSCT was comparable to what has been reported previously in the MIST trial, 93 % at 2 years and 79 % at 5 years (Burt et al., 2022), in the HALT-MS trial, 83 % at 2 years and 60 % at 5 years (Nash et al., 2017); and in a Swedish survey, 78 % at 2 years and 68 % at 5 years (Burman et al., 2014). While these studies provide valuable long-term data, differences in follow-up duration should be considered when comparing outcomes with our study.

AHSCT can be a highly effective treatment option for patients with active RRMS, offering the potential for both disability stabilization and improvement. Several studies have reported that AHSCT can result not only in stabilization of disease progression, also in improvement of disability (Burt et al., 2022, Muraro et al., 2017, Giedraitiene et al., 2020). In our study, 35.6 % of patients experienced improvement in their EDSS scores by the third month post-transplant, and this improvement was maintained in patients with available follow-up data for up to 10 years. Therefore, AHSCT has the potential not only to reduce disability levels but also to promote long-term disability improvement in MS.

Although patients were selected for AHSCT according to established criteria, 35 % of patients still had evidence of disease activity after the treatment during a 10-year follow-up period. Unfortunately, there are currently no formal guidelines on the use of DMTs following AHSCT -

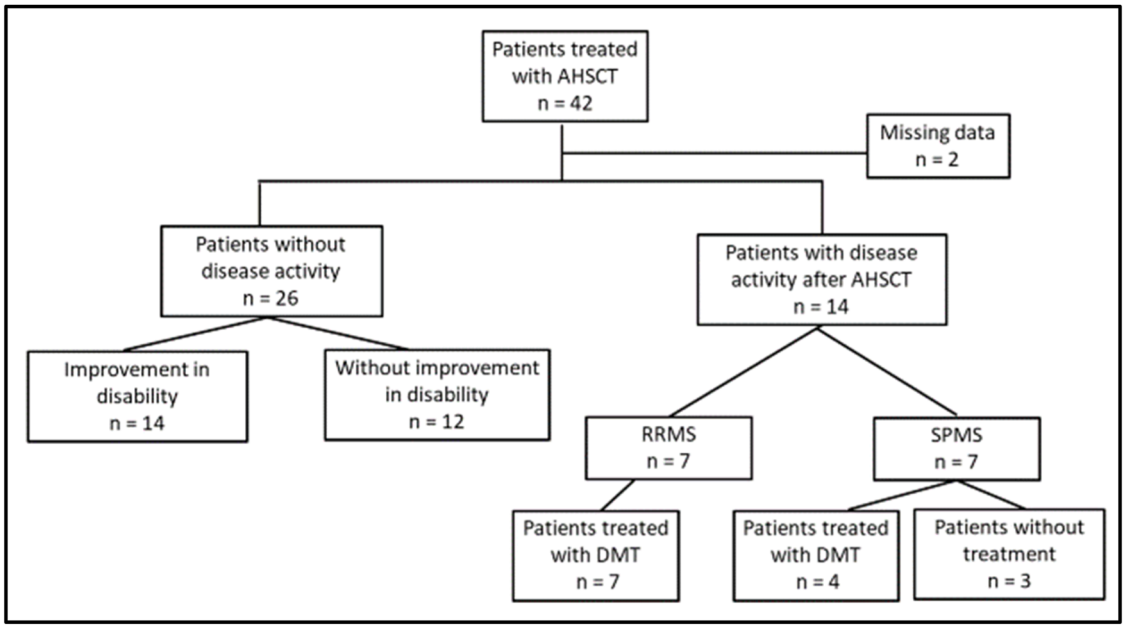


Fig. 1. Patient outcomes after AHSCT.
AHSCT - autologous haematopoietic stem cell transplantation, RRMS – relapsing-remitting multiple sclerosis, SPMS – secondary progressive multiple sclerosis, DMT – disease modifying therapy.

Table 2
DMT after AHSCT in patients with MS.

Patient No.	Age *	Gender	Disease duration, years*	Baseline EDSS	Follow-up after AHSCT, months	Disease activity after AHSCT	Clinical course**	DMT	Follow-up after DMT, months	Disease activity after DMT
1	34	F	4	5.5	129	Relapses, disability progression	RRMS	OCR	24	No relapses, no disability progression, no new/active lesions on MRI
2[1]	38	F	4	6.5	85	Relapses, disability progression	RRMS	OCR	63	Relapses, disability progression
3	44	M	18	6.0	79	Relapses, disability progression	RRMS	OCR	25	Disability progression
4	44	F	9	6.0	75	Relapses	RRMS	OCR	19	No relapses, no disability progression, no new/active lesions on MRI
5	28	F	4	4.5	73	Relapses	RRMS	OCR	39	Relapses, no disability progression, no new/active lesions on MRI
6	45	M	3	6.0	64	Relapses, disability progression	RRMS	OCR	41	No relapses, no disability progression, no new/active lesions on MRI
7	33	F	7	5.0	33	Relapses, active lesions on MRI	RRMS	OCR	9	No relapses, no disability progression, no new/active lesions on MRI
8	29	M	4	6.0	71	Relapses, disability progression	RRMS	OCR	6	No relapses, no disability progression, no new/active lesions on MRI
9	38	F	9	6.5	83	Relapses, disability progression	SPMS	SIP	19	Relapses, disability progression
10	34	M	3	6.0	117	Disability progression	SPMS	SIP	10	No relapses, no disability progression
11	40	M	9	6.5	45	Disability progression	SPMS	SIP	7	Disability progression
12[2]	41	F	9	6.0	84	Relapses, disability progression	SPMS	AZA	14	Disability progression
13[1]	38	F	4	6.5	85	Relapses, disability progression	SPMS	AZA	2	Treatment has started, patient is in the early follow-up
14[2]	41	F	9	6.0	84	Relapses, disability progression	SPMS	SIP	10	Disability progression

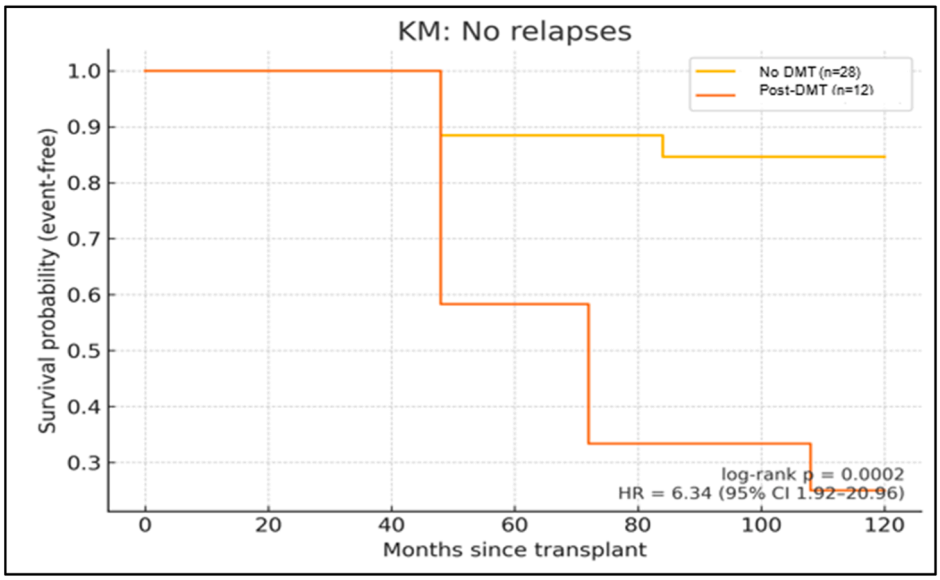
* at the time of AHSCT.
** disease course at the last follow-up
DMT – disease modifying therapy, AHSCT - autologous haematopoietic stem cell transplantation, MS – multiple sclerosis, F – female, M – male, RRMS – relapsing-remitting multiple sclerosis, SPMS – secondary progressive multiple sclerosis, OCR – ocrelizumab, SIP – siponimod, AZA – azatioprin, MRI – magnetic resonance tomography.
[1] - same patient, treated with Ocrelizumab and after that with Azatioprin.
[2] - same patient, treated with Azatioprin and after that with Siponimod.

only guidelines covering other aspects of post-AHSCT care for MS, but not DMT use specifically (Sharrack et al., 2020, Miller et al., 2021, Cohen et al., 2019). We identified twelve highly active RRMS patients who underwent AHSCT and restarted DMT during the post-transplant period. Five patients who were on anti-CD20 therapy after AHSCT displayed a stable disease course whereas three of whom had been on DMT for >12 months (longest 41 month). However, there is limited information available on the management of DMT in post-transplant patients. Several studies have reported that DMTs were administered after AHSCT in 11–35 % of patients after a median of two years or later (Silfverberg et al., 2024, Casanova et al., 2017, Manzano et al., 2022, Kvistad et al., 2024), most often using moderate- or high-efficacy DMTs. In our study, DMTs were reinitiated in 30 % of patients, which is consistent with the upper range reported in previous studies. This highlights that a substantial proportion of patients may require additional therapy after AHSCT, particularly those experiencing ongoing disease activity. In all RRMS patients who needed retreatment, high-efficacy DMTs were initiated due to their relatively high level of disability, highly active disease course, and the ineffectiveness of prior platform or moderate-efficacy DMTs.

Lack of control group and relatively low number of patients were the main limitations of our study. The key strength of our study lies in the fact that it is based on real-world clinical data collected by the same medical team at a single academic hospital centre, with consistent treatment criteria and goals maintained throughout the entire study period. The experiences from single centers and sustained long-term follow-up and treatment options after AHSCT remain important in providing valuable information about the efficacy and safety of AHSCT and DMT options after AHSCT.

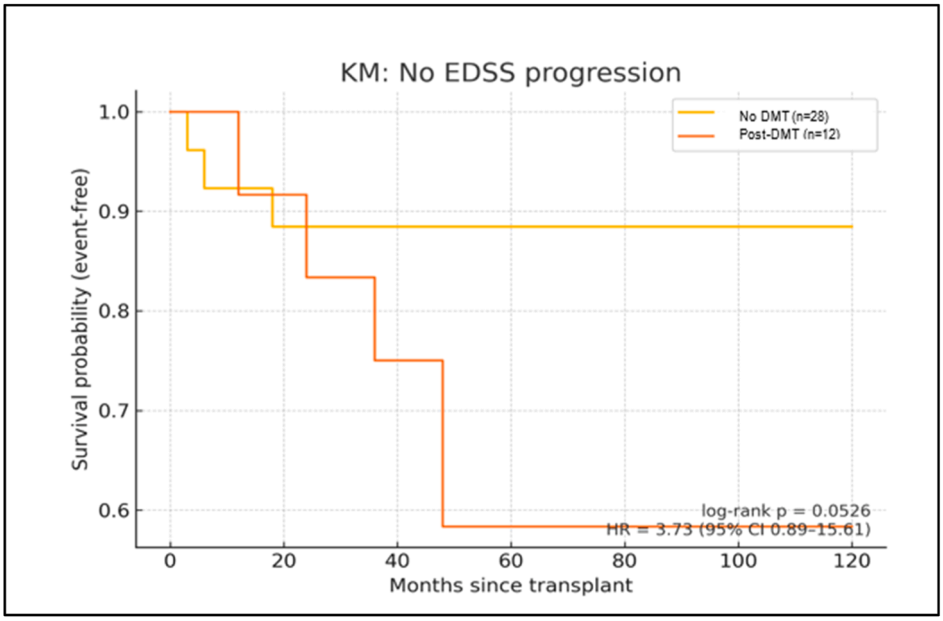
In conclusions, our study shows that AHSCT is highly effective long-term treatment in MS. The initial treatment response seems to persist in the majority, offering long-term disease-free survival. For patients in whom AHSCT was not fully effective, high-efficacy DMTs, particularly anti-CD20 therapies, may be considered. Since AHSCT is one of the most effective treatments for highly active MS, clinical trials investigating long-term monoclonal therapy following AHSCT therapy would be appropriate.

A. Relapse-free survival



KM - Kaplan–Meier, DMT - disease modifying therapy, HR – hazard ratio, CI – confidence interval.

B. Time to EDSS worsening



KM - Kaplan–Meier, EDSS - Expanded Disability Status Scale, DMT - disease modifying therapy, HR – hazard ratio, CI – confidence interval.

Fig. 2. Kaplan-Meier estimates of survival in patients with and without DMT.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

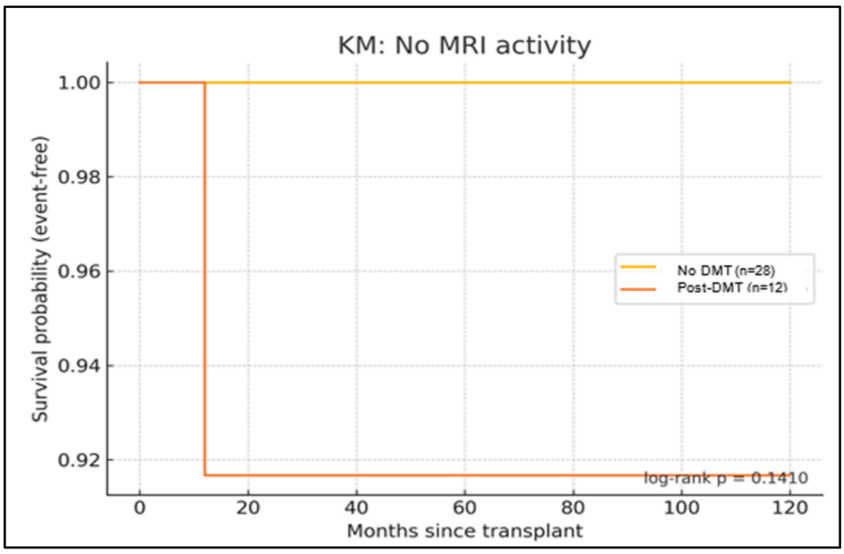
Role of funding source

The authors declare they have no financial interests.

CRediT authorship contribution statement

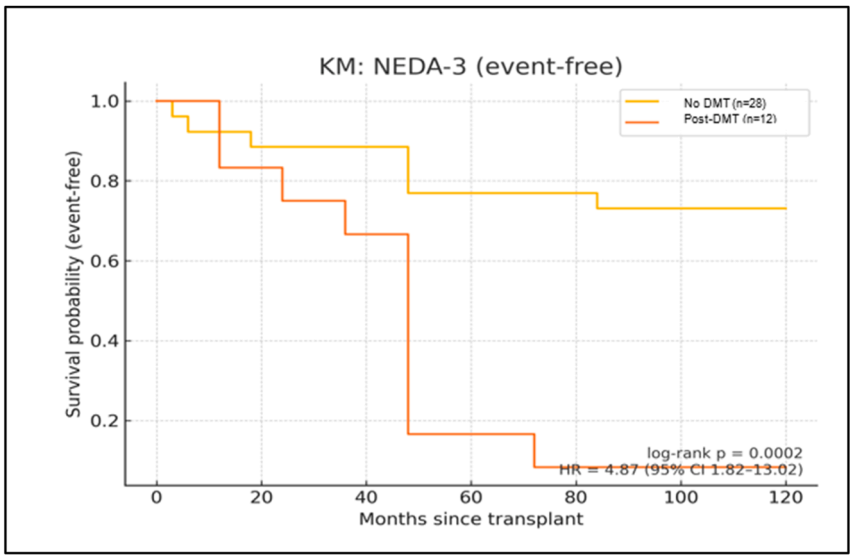
Nataša Giedraitienė: Writing – review & editing, Visualization, Supervision, Conceptualization. **Gintaras Kaubrys:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Rasa Kizlaitienė:** Writing – review & editing, Visualization, Conceptualization. **Valdas Pečeliūnas:** Writing – review & editing, Conceptualization. **Jūratė Dementavičienė:** Writing – review & editing,

C. Freedom from MRI activity



KM - Kaplan–Meier, MRI – magnetic resonance tomography, DMT - disease modifying therapy, HR – hazard ratio, CI – confidence interval.

D. Freedom from NEDA-3



KM - Kaplan–Meier, NEDA-3 - No Evidence of Disease Activity-3, DMT - disease modifying therapy, HR – hazard ratio, CI – confidence interval.

Fig. 2. (*continued*).

Conceptualization. **Andrius Žučenka:** Writing – review & editing, Conceptualization. **Laimonas Griškevičius:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare they have no financial interests.

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