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Real-world Effectiveness of Autologous Haematopoietic Stem Cell Transplantation for MS in the UK

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Abstract

Background: Autologous haematopoietic stem cell transplantation (AHSCT) is increasingly used as a one-off disease-modifying therapy for aggressive forms of multiple sclerosis (MS). We report real-world effectiveness of AHSCT for MS in the United Kingdom (UK).

Methods: This retrospective open-label study included patients with (pw)MS treated with AHSCT between 2002 and 2023 in 14 UK centres. Outcomes included relapse-free survival (RFS), MRI activity-free survival (MFS), progression free survival (PFS) and no evidence of disease activity (NEDA-3). We assessed 6-month-confirmed Expanded Disability Status Scale (EDSS) score progression or improvement compared to pre-treatment. Treatment-related mortality (TRM) was defined as death from any cause within 100 days post autologous graft reinfusion.

Results: 364 pwMS were included (median age 40; 58% female). Of these, 271 pwMS had adequate neurological follow-up data: 168 (62%) had relapsing-remitting MS (pwRRMS) and 103 (38%) progressive MS (pwPMS). Median disease duration from symptom onset was 10 years (IQR 6-14), EDSS 6 (IQR 4.0-6.5) and follow-up from AHSCT 46 months. At 2 and 5 years from AHSCT, RFS was 94.6% and 88.6%; MFS 93.1% and 80.1%; PFS 83.5% and 62.4%; NEDA-3 72.3% and 46.2%. pwRRMS had significantly higher rates of PFS (p=0.007) and NEDA (p=0.001) than pwPMS. RRMS was a predictor of EDSS improvement, whose prevalence was 24.2% at 2 and 20.4% at 5 years. TRM was 1.4% (n=5/363).

Discussion: In this cohort with high EDSS at baseline and including pwPMS, AHSCT led to durable remission of inflammatory activity and stabilization or improvement of neurological disability, particularly in pwRRMS.

Keywords: Multiple sclerosis (MS), Autologous haematopoietic stem cell transplantation (AHSCT), disease modifying treatments (DMTs), real-world evidence, cohort study, No Evidence of Disease Activity (NEDA).

Key messages

What is already known on this topic

Autologous haematopoietic stem cell transplantation (AHSCT) is an acknowledged treatment option for aggressive forms of Multiple Sclerosis (MS). The treatment is currently recommended after the failure of highly effective disease modifying therapies (HE-DMTs). Given its potentially superior efficacy, AHSCT may also be a valid alternative to HE DMTs. While ongoing trials are comparing AHSCT with H-E DMTs, real-world data remain valuable for guiding AHSCT use as second- or further line DMT and identifying predictors of response to optimise patient selection and outcomes.

What this study adds

This study reports one of the largest real-world cohorts on long-term AHSCT outcomes and predictors of treatment response, reflecting a nationwide experience over 20 years.

How this study might affect research, practice or policy

Our findings demonstrate sustained suppression of inflammatory disease activity, low rates of disability progression, as well as opportunity for improvement following AHSCT. These results support AHSCT as an effective option for patients with aggressive MS who have failed standard DMTs, particularly when used early in the disease course before significant disability accrual.

Introduction

Several disease modifying treatments (DMTs) targeting inflammatory processes are available for treatment of patients with active relapsing-remitting MS (RRMS). Current high-efficacy (HE-)DMTs result in No Evidence of Disease Activity-3 (NEDA-3), defined by the absence of relapses, magnetic resonance imaging (MRI) activity and disability progression, in 34-48% of patients at 2 years[1].

Treatment options for progressive MS (PMS) are limited, and there is unmet need for treatment of patients with any aggressive forms of MS.

Autologous haematopoietic stem cell transplantation (AHSCT) is a treatment option for patients with aggressive autoimmune diseases. The rationale is to ablate mature lymphocytes through high-dose immunosuppressive conditioning and promote immune reconstitution from haematopoietic precursors, a process referred to as immune resetting[2]. Originally used as a rescue treatment in advanced MS, AHSCT has increasingly been applied in earlier stages, with improved outcomes[3]. The indication for AHSCT for the treatment of patients with (pw)RRMS following failure of conventional DMTs is endorsed by several national medical organisations[4-9]. The recently published consensus statement from the European Committee for Treatment and Research in MS (ECTRIMS) and the European Society for Blood and Marrow Transplantation (EBMT) has advanced the indication of AHSCT to second-line treatment for pwRRMS after failure of a single HE-DMT[10]. Given its potential greater efficacy[3 11]AHSCT is also evaluated as alternative to HE-DMT. Two randomised clinical trials (RCTs) have shown superior efficacy of AHSCT compared to mitoxantrone[12] or standard DMTs for RRMS (including natalizumab in a subset of patients)[13]. Currently, four RCTs are comparing AHSCT with HE-DMTs[10].

According to the EBMT database, 2,132 patients with MS underwent AHSCT in Europe until March 2023 and the largest cumulative number was in the United Kingdom (UK)[14]. To examine real-world neurological outcomes in patients who underwent AHSCT as clinical option for the treatment of MS in the UK we collected data from all centres participating in a BSBMTCT (British Society of Blood and Marrow Transplantation and Cellular Therapy) retrospective study.

Methods

Standard Protocol Approvals, Registrations, Ethics and Patient Consents

This retrospective, open-label study included patients who were consecutively treated with AHSCT at 14 centres in the UK between December 2002 and December 2023, excluding patients participating in any ongoing clinical trial. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[15]. All patients signed informed consent for AHSCT and data collection in accordance with the Declaration of Helsinki 1975. Consent was obtained locally by each centre for submission of non-identifiable pseudonymised data. The BSBMTCT committee IRB approved the study. All centres that had reported performing autologous AHSCT for MS to the BSBMTCT/EBMT databases during the stated treatment period were invited to participate in the study. To examine MS outcomes for our study, neurological and haematological data were collected with an encrypted password-protected Excel spreadsheet completed by the local clinicians. The spreadsheet template is shown in Supplementary material. Fully anonymised data returned from the centres were quality checked by the study team and acquired to the study database.

Patient selection and treatment

Inclusion criteria were diagnosis of MS according to the currently available McDonald criteria[16-18], and AHSCT performed for MS in the UK between December 2002 and December 2023. The MS disease course (RRMS, SPMS, PPMS) was based on clinical assessment by the treating neurologist according to the conventional Lublin-Reingold classification [19]. Eligibility for AHSCT as treatment in pwMS was assessed case-by-case by a local or regional multidisciplinary healthcare team that included Neurologists and Haematologists experienced in the treatment. According to the principles from the available EBMT guidelines[7 20 21], patients were selected for AHSCT if they had aggressive

forms of MS – either RRMS or PMS – characterised by clinical relapse, MRI inflammatory activity, and neurological worsening despite available HE-DMT. Patients deemed fit for AHSCT following haematological evaluation were offered to proceed with the treatment. Patients enrolled in an ongoing clinical trial on AHSCT[22] were excluded from the present study.

In our cohort, 9/359 patients - for whom conditioning data were available - received the myelo-ablative regimen consisting of a combination of BiCNU (carmustine), etoposide, Ara-C (cytarabine), melphalan (BEAM) and anti-thymocyte globulin (ATG), while 350/359 received the non-myeloablative Cy-cyclophosphamide and ATG (Cy-ATG) regimen. These conditioning schemes are both considered to be of intermediate intensity and were shown to be similarly effective in a Swedish cohort and in a preliminary report from the EBMT database[23].

Outcomes

The effectiveness of AHSCT was assessed through measures of MS inflammatory activity (relapses and MRI), and disability progression or improvement. Clinical data were recorded by local physicians, who assessed patients according to standard clinical practice at their centres. We used the accepted definition of relapse[16] and calculated the annualized relapse rate (ARR) as the mean number of relapses experienced in a year. Additionally, the relapse-free survival (RFS) was defined as the time free from clinical relapses from AHSCT up to the end of the follow-up. MRI activity was defined by the presence and number of new T2* and/or gadolinium enhancing lesions and/or enlargement of a pre-existing lesion based on the neuroradiology report of a brain MRI scan performed >6 months after the AHSCT (re-baseline scan). Lesion counts were considered in the definition of binary MRI activity. Patients with at least 1 lesion was considered active at the MRI during the follow-up. We did not consider the lesion count as an endpoint. We calculated the MRI-free-activity survival (MFS) as the cumulative probability to be free from any MRI activity from AHSCT up to the end of the follow-up. For both RFS and MFS, patients without events were censored at the last follow-up visit.

Confirmed disability progression (CDP) or improvement (CDI) were defined as a change (increase or decrease, respectively) of Extended Disability Status Scale (EDSS) score by 1.0 point if baseline EDSS <6.0 or by 0.5 point if baseline EDSS ≥6.0, confirmed 6 months after the reported change. We calculated progression-free survival (PFS), defined as absence of confirmed disability progression during the follow-up. We examined absence of progression independent of relapse activity (PIRA), and relapse-associated worsening (RAW)[24]. For a EDSS progression event to be considered PIRA, an absence of relapses was required during the 90 days before and 30 days after the event, as well as during the 90 days before and 30 days after the confirmation visit [25].

Lastly, we evaluated the composite outcome NEDA-3 over the follow-up. The effectiveness outcomes were reported for the entire subset of patients with adequate follow-up data and by disease subgroup – patients with relapsing-remitting multiple sclerosis (PwRRMS) and patients with progressive multiple sclerosis (PwPMS), examining jointly patients with secondary progressive (SPMS) and primary progressive (PPMS).

The present analysis focuses on the neurological outcomes, while details on AHSCT procedure and its safety and tolerability are reported elsewhere[26]. We only include here information on the transplant-related mortality (TRM) defined as any death occurred within 100 days from AHSCT in patients who started the conditioning regimen.

Statistical analyses

All patients were included in the baseline descriptive statistical evaluation and in the assessment of TRM. The neurological outcome analyses were performed on the subset of patients who had at least two follow-up assessments including EDSS rating and one MRI scan for the respective outcomes. Descriptive statistics were reported for demographics, disease history, and outcomes. Categorical data were reported as number and percentage, with 95% Confidence Interval (CI) provided for the

outcomes. Continuous data were reported as median and interquartile range (IQR) or mean and standard deviation (SD). Categorical and continuous data were compared across subgroups through the $\chi 2$ and Mann–Whitney U tests respectively.

Kaplan-Meier (KM) method was used to estimate cumulative probabilities of PFS, PIRA-free survival, RAW-free survival, RFS, MFS, NEDA-3 and cumulative incidence of EDSS improvement during the follow-up. PwRRMS and PwPMS were compared using the log-rank test. The prevalence of EDSS improvement, a measure that encompasses the rate of patients who maintained the improvement over time, was estimated trough the method previously published[27]. PwRRMS and PwPMS were compared by mean of a bootstrap approach with 500 replicates.

To identify predictors of PIRA, NEDA-3 failure and cumulative incidence of EDSS improvement, we conducted univariable and multivariable Cox regression analyses. Characteristics considered as potential predictors in the univariable analysis included age, sex, disease phenotype, disease duration, baseline EDSS, number of relapses in the previous 1 and 2 years, MRI activity at the last scan prior to baseline, number of previous DMTs, and number of prior high-efficacy DMTs. For multivariable analyses only characteristics significantly associated with each endpoint at the univariable analysis were considered. Variables with a p-value < 0.10 in the univariable analysis were retained for inclusion in the final model. Results were reported as Hazard-ratio (HR) together with the 95% confidence interval (CI). A level of significance of 5% was considered statistically significant. Stata (v.16; StataCorp) was used for the computation.

Results

Demographics and disease characteristics

Three hundred sixty-four patients were included in this study, 210 female (58.0%) and the overall median age was 40 years (IQR 5-14). Almost all patients (97.5%) received Cy-ATG conditioning

(Table 1). Two-hundred seventy-one (74.7%) patients had outcomes data fulfilling the criteria for evaluation of effectiveness (Figure 1). This subset showed similar baseline disease characteristics to the overall study cohort (Table 1). A comparison of the baseline characteristics between included and excluded patients is provided in the Supplementary material, Table S1, and reveals similar features in all variables and identical values for some key characteristics such as EDSS score, relapses prior to AHSCT and previous treatments. All disease subtypes were represented: RRMS (168/271, 62.0%) SPMS (64/271, 23.6%) and PPMS (39/271, 14.4%). The treated cohort was characterised by long disease duration from symptoms onset (median 10 years, IQR 6-14). The median ARR in the 2 years prior to AHSCT was 1 (IQR 0-2), suggesting moderate relapse activity and the median EDSS score was 6.0 (IQR 4-6.5), indicating an advancing level of disability. The median follow-up after AHSCT, with day 0 being the date of infusion of the autologous graft, was 46 months (IQR 25-65). Specifically, 100/271(36.9%) patients had a follow-up ≥5 years and 21/271 (7.7%) ≥10 years.

Effectiveness outcomes

AHSCT effectiveness on inflammatory activity

Relapses

There were 35 relapse events after AHSCT. In the evaluable subset, AHSCT significantly reduced the ARR observed pre-treatment, which dropped from a mean of 0.67 (SD 1.20) the year before the treatment to 0.044 (SD 0.23) the year after the treatment ($p<0.001$). RFS was 94.6% (95% CI 91.0-96.7) at 2 years and 88.6% (95% CI 83.6-92.2) at 5 years after the therapy (Figure 2A), without significant differences between PwRRMS (92.4%, with 95% CI 86.9-95.6 at 2 years and 87.2%, with 95% CI 80.2-91.8 at 5 years) and PwPMS (98.0%, with 95% CI 92.3-99.5 at 2 years and 91.0%, with 95% CI 82.7-95.4 at 5 years; $p=0.084$) (Figure 2B).

MRI outcomes

The median number of MRI scans analysed was 3 (IQR 2-5). For this outcome, 38 MRI activity events occurred after AHSCT. Similarly to RFS, a large proportion of the cohort was free from MRI activity during follow-up, with MFS 93.1% (95% CI 88.9-95.7) at 2 years and 80.1% (95% CI 72.6-85.8) at 5 years after the therapy (Figure 2C). However, PwRRMS had significantly higher rates of MFS (96.4%, with 95% CI 91.6-98.5 at 2 years and 82.5%, with 95% CI 72.8-89.0 at 5 years) compared with PwPMS (87.7%, with 95% CI 78.8-93.0 at 2 years and 76.9%, with 95% CI 63.5-85.9 at 5 years; p=0.033) (Figure 2D).

AHSCT effectiveness on disability progression

Progression free survival

The median number of EDSS visits was 5 (IQR 3-7). For this outcome, there were 78 EDSS progression events after AHSCT. In the evaluable subset, 83.5% (95% CI 78.1-87.6) had PFS at 2 years and 62.4% (95% CI 54.5-69.3) at 5 years after AHSCT (Figure 3A). PwRRMS had significantly higher rates of PFS (87.1%, 95% CI 80.5-91.6 at 2 years and 67.6%, 95% CI 57.4-75.9 at 5 years) compared with PwPMS (77.5%, 95% CI 67.5-84.7 at 2 years and 53.6%, 95% CI 40.8-64.8 at 5 years; p=0.007) (Figure 3B).

Absence of progression independent of relapse activity (PIRA) and relapse-associated worsening (RAW)

There were 75 PIRA and 3 RAW events after AHSCT. PIRA-free survival showed a near-complete overlap with PFS (Figure 3C). Almost all patients were free from RAW at 2 and 5 years after AHSCT (99.2%, 95% CI 96.9-100.0 and 98.4%, 95% CI 94.8-99.5, respectively). Similarly to PFS, PwRRMS were more frequently free from PIRA than PwPMS (p=0.006) (Figure 3D). Additionally, PMS, number of previous DMTs and 2+ previous highly active DMTs were confirmed as predictors of PIRA

at the univariable analysis (Supplemental material, Table S2). Results from multivariable analysis were not reported since PMS was the only factor that showed an adjusted p-value < 0.10.

No evidence of disease activity (NEDA)

NEDA-3 status was observed in 72.3% (95% CI 66.1-77.7) at 2 years and 46.2% (95% CI 38.2-53.7) at 5 years after AHSCT (Figure 4A). PwRRMS had significantly higher rates of NEDA-3 (77.4%, with 95% CI 69.6-83.4 at 2 years and 52.7%, with 95% CI 42.5-62.0 at 5 years) compared with PwPMS (63.9%, with 95% CI 52.7-73.1 at 2 years and 34.7%, with 95% CI 22.6-47.0 at 5 years; p=0.001) (Figure 4B). PMS, number of previous DMTs and 2+ previous HE-DMTs were significantly associated to the probability of NEDA-3 failure at the univariable analysis (Table S3 – Supplemental material). Also here, results from multivariable analysis are not reported since PMS was the only factor that showed an adjusted p-value < 0.10. When considering predictors of NEDA-3 failure by disease phenotype, the number of prior DMTs was associated with an increased risk of NEDA-3 failure among PwPMS (HR 1.23, 95% CI 1.02-1.49; p=0.034) but a reduced risk of NEDA-3 failure among PwRRMS (HR 0.77, 95% CI 0.63-0.94; p=0.012) (Table S4 - Supplemental material).

EDSS score improvement

In total, 24.9% (95% CI 20.1-30.8) patients showed EDSS score improvement at 2 years and 27.1% (95% CI 22.0-33.1) at 5 years after AHSCT (Figure 5A). The prevalence of EDSS score improvement — was 24.2% (95% CI 18.8-29.7) at 2 years and 20.4% (95% CI 15.6-25.7) at 5 years after the therapy (Figure 5B). Regarding disease phenotype, the prevalence of EDSS score improvement was significantly higher in PwRRMS (35.4%, with 95% CI 28.7-43.5 at 2 years and 29.1%, 95% CI 22.2-37.2 at 5 years) compared with PwPMS (6.2%, with 95% CI 1.9-10.7 at 2 years and 6.3%, with 95% CI 1.9-11.0 at 5 years; p<0.001) (Figure 5C). Additionally, RRMS was a predictor (HR 2.86, 95% CI 1.38-5.95, p=0.005) of EDSS score improvement, along with the number of HE DMTs (HR 1.52, 95% CI 1.22-1.89, p<0.001) (Table 2).

Safety outcomes

The safety outcomes for the entire study cohort (364 patients) are reported elsewhere[26]. We only report here the 5/364 (1.4%) TRM events, which all occurred in patients with EDSS score of 6 or 6.5 and with either RRMS (3 events) or PPMS (2 events). The TRM deaths occurred in 2017 (one), 2018 (two), 2019 (one), and 2021 (one).

Discussion

This real-world, nationwide UK study demonstrates high rates of suppression of inflammatory disease activity and modest rates of progression of disability after AHSCT in people with aggressive forms of MS who had previously failed standard DMT, suggesting effectiveness.

Treatment was mainly effective on the 'inflammatory' component of MS: not only suppressing relapses and MRI activity but also the worsening of disability driven by relapses (RAW). Improvements of EDSS were observed in >20% of the overall cohort and persisted in 30% of the RRMS patients 5 years post-therapy suggesting functional benefit especially in this subgroup. These results corroborate the indication for earlier treatment with AHSCT in pwRRMS who fail HE-DMT before their accumulation of disability and transition to SPMS[10].

When we compare our findings with the available evidence, it is important to consider that the published AHSCT cohorts are heterogeneous in respect of patient selection, treatment protocols and geographical distribution. The evidence has been recently reviewed and includes 26 publications published in the past 5 years (2019–2024), most of which were retrospective, single-centre or multi-

centre studies[10]. Amongst them we focus here on two nationwide studies[28 29] where differences in local practice resulted in the selection of different patient populations. An Italian observational retrospective multi-centre cohort study reported long-term outcomes after AHSCT in 210 pwMS of which 58% were pwRRMS, and 80% were treated with the BEAM conditioning regimen. [30] A more recent multicentre retrospective cohort from Sweden included 174 patients, all RRMS and predominantly treated with Cy-ATG (81%) or BEAM-ATG (19%) regimen[29]. The main differences we note in the results are in the PFS (65% at year 4 for the Italian cohort and 91% at year 5 for the Swedish) and TRM (1.4% and 0 for the Italian and Swedish cohorts, respectively). These differences may be related to differences in the patient population, comprising higher proportion of pwRRMS, shorter disease duration and lower EDSS levels at baseline in the Swedish cohort. In the present UK-wide study, where baseline MS type, age, disease duration and levels of disability are similar to the Italian cohort, we observe similar effectiveness and safety outcomes, in spite of the differences in geographical area and conditioning regimen, suggesting that disease stage strongly influences the outcomes. Accordingly, the stratification analyses in our study demonstrate significantly higher PFS and MFS in the pwRRMS subgroup. NEDA-3 rates were high at 2 years (72%) but reduced at 46% at 5 years after AHSCT, largely because of EDSS progression. The Swedish cohort[29], slightly smaller than ours (n=174 vs. 271 in the final analyses, respectively) but followed for longer (5.5 vs. 3.8 median years, respectively), had higher NEDA-3 results (73% at 5 years and 65% at 10 years, vs. 46% at 5 years in our cohort), a difference that is probably related to the selection of a more favourable patient profile: younger age (median 31 vs. 40 years in the Swedish and UK cohort, respectively), proportion of pwRRMS (100% vs. 62%), shorter disease duration (median 3.4 vs. 10 years) and lower EDSS (median score 3.5 vs. 6.0)[29].

Noteworthy in our study is a sustained EDSS score improvement detected in ~25% and maintained in 20% of the overall evaluable cohort at 5 years follow- up. The prevalence of EDSS improvement was higher in pwRRMS, approaching 30% at 5 years compared to 6% in the progressive MS

subgroup. Improvement was rarely evaluated as an outcome in previous large cohort studies. The same Swedish study reported 54% disability improvement at last follow-up (median duration 66 months)[29] and their higher improvement rate may again be explained by the inclusion of younger, early RRMS patients, features that are favourable to functional recovery after inflammatory MS disease is effectively stopped. Both these and our observed rates of improvements are greater than after standard DMT, which have been marginal even in pwRRMS. Additionally, we show that neurological function improves after AHSCT in a small subset of pwPMS.

We examined the factors associated with neurological outcomes following AHSCT. PIRA has recently been recognised as the main driver of worsening of disability in DMT-treated patient cohorts[24]. In our study, PIRA indeed appeared to be the main determinant of the overall disability accrual, showing a near-complete overlap with PFS, the main determinant of NEDA failure. Multivariable analysis showed that progressive disease phenotype was the only predictor of PIRA, and (univariable) analysis showed that the same factor was associated with NEDA failure. RRMS and the number of prior DMTs were identified by multivariable analysis as predictors of EDSS improvement. The Swedish group has identified gadolinium-enhancing lesions on baseline MRI and longer disease duration as factors associated with disease progression[31]. Prolonged disease duration may indicate a shift from neuroinflammatory to predominantly neurodegenerative processes, contributing to the transition from a relapsing to a progressive disease phenotype, which in our cohort was associated with poorer outcomes. Conversely, a recent consensus statement summarising the available evidence identified patient young age, short disease duration, presence of focal inflammation, lower EDSS score and RRMS as neurological variables predictive of better outcomes[10].

Although important in the evaluation of risk/benefit of any DMTs, an evaluation of safety and tolerability was not an aim of this paper. A detailed report of adverse events alongside their management and details of the haematological procedure is being published elsewhere[26]. The

observed TRM 1.4%, the same rate reported in the cited Italian cohort with similar baseline patient characteristics[28], is higher than in cohorts restricted to younger pwRRMS and was related to cardiac adverse events in patients with more advanced EDSS levels as well as undisclosed comorbidities and risk factors [30].

Limitations of our study include the observational and retrospective study design without a prospective analysis plan and prespecified outcomes. The inability to collect data for 25% of the cohort which may have introduced bias, though the baseline characteristics of the overall study cohort and of the subset with detailed MS data were similar suggesting that these features were not skewed by the subsequent follow-up data availability. Although 36.9% of patients had a follow-up of five years or longer, fewer than 10% reached a 10-year follow-up. The limited number of patients with prolonged follow-up prevented us from evaluating sustained treatment response. Also, the cohort was largely constituted by patients who had failed other DMTs with a median disease duration of 10 years, which limits the applicability of the findings to the entire MS population, particularly those with less disability or earlier-stage disease at transplantation. Further, the analysis of MRI outcomes was based on radiological reports and not on a centralised analysis. Lastly, the study lacks a comparator DMT arm, thereby preventing a direct comparative effectiveness analysis. Recent comparisons of statistically matched groups of treated pwMS suggest superior effectiveness of AHSCT over standard therapy, including HE-DMT [32-34]. The ongoing randomised controlled trials of AHSCT including STAR-MS for the UK[22] as well as RAM-MS, BEAT-MS and NET-MS internationally[10] will provide definitive comparative evidence for AHSCT and the current best standard treatment for pwRRMS. However, based on our retrospective data, new RCTs are also warranted to precisely define the place of AHSCT in progressive forms of MS, where treatment options are more limited. Limited data are available on the cost effectiveness of aHSCT compared with DMTs. However published cost analyses suggest that the one-off nature of aHSCT treatment and its potential long-term effects may offer cost savings[35-37]. The resource-intensive nature of AHSCT and the limited capacity in accredited transplant

centre, however, currently restricts the capacity of healthcare systems to make this treatment available to a large number of patients. These restrictions could be alleviated by dedicated resources enabling the necessary service development.

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Contributorship Statement

P. A. Muraro and M. Kazmi made equal contributions. P. A. Muraro, M. Kazmi, Basil Sharrack and J.A. Snowden designed the study. E. De Matteis, G. Brittain, A. Mariottini, and V. Mehra collected the data. R. Pearce, A. Signori and M.P. Sormani performed the statistical analyses. P. A. Muraro, M. Kazmi, E. De Matteis, G. Brittain and A. Signori drafted the manuscript. R. Nicholas, E. Silber, I. Gabriel, O. Ciccarelli and B. Sharrack contributed patient data and interpretation of clinical data. J. Lee, R. Paul, R. Malladi and V. Potter helped coordinate the study and critically revised the manuscript for relevant intellectual content. All authors reviewed and approved the manuscript. P.A. Muraro had access to all the data and is the guarantor of the integrity of this study.

Competing Interests

Paolo A. Muraro has received fees from consulting to Magenta Therapeutics, Jasper Therapeutics and Cellerys, all outside the submitted work. John A. Snowden declares advisory boards for Vertex, Jazz, Medac and BMS, not related to this study.

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Data availability statement

Anonymized data not published within this article will be made available by request from any qualified investigator.

Research Ethics Approval

This study was assessed using the online Ethics Decision Tool provided by the Health Research Authority (HRA) (https://www.hra-decisiontools.org.uk). Based on this assessment, the study was deemed exempt from review by a National Health Service (NHS) Research Ethics Committee (REC), in accordance with the requirements outlined in the Governance Arrangements for Research Ethics Committees (GAfREC), developed by the HRA in collaboration with the UK Devolved Administrations. Notwithstanding, the BSBMTCT committee IRB approved the study.

Tables

Table 1: Demographics and baseline disease characteristics of the study population

	Overall study cohort (N=364)		**Subset with detailed follow-up data (N=271)**	
	Evaluable number	**Value**	**Evaluable number**	**Value**
Age, median (range)	364	40 (19-66)	271	40.7 (19-66)
Female gender, N (%)	364	210 (58)	271	153 (56.5)
Disease phenotype, N (%)	364		271	
Relapsing remitting (RRMS)		209 (57.4)		168 (62.0)
Secondary progressive (SPMS)		83 (22.8)		64 (23.6)
Primary progressive (PPMS)		47 (12.9)		39 (14.4)
Unknown		25 (6.9)		0 (0)
Disease duration from symptoms onset, median years (IQR)	314	10 (5-14)	271	10 (6-14)
EDSS score, median (IQR)	323	6 (4-6.5)	271	6 (4-6.5)
Relapses 2 years prior AHSCT, median N (IQR)	250	1 (0-2)	206	1 (0-2)
Relapses 1 year prior AHSCT, median N (IQR)	250	0 (0-1)	206	0 (0-1)
Patients with baseline active scan, N (%)	323	293 (90.7)	268	243 (90.7)
New T2 lesions, n(%)	322	266 (82.6)	268	222 (82.8)
Enhancing lesions, n(%)	314	247 (78.6)	262	205 (78.2)
Previous treatments, median N (IQR)	294	2 (1-3)	271	2 (1-3)
Previous HE-DMT, median N (IQR)	294	1 (0-1)	271	1 (0-1)
Follow-up months, median (IQR)	364	41 (12-61)	271	46 (25-65)
Type of conditioning regimen N (%)	359		269	
BEAM/ATG		9 (3.0)		4 (1.5)
Cy/ATG		350 (97.0)		265 (98.5)

Abbreviations: ATG, anti-thymocyte globulin; BEAM, [BiCNU (carmustine), etoposide, Ara-C (cytarabine), melphalan]; Cy-cyclophosphamide; DMTs, disease modifying therapies; EDSS, Expanded Disability Status Scale; AHSCT, haematopoietic stem cell transplantation; IQR, interquartile range; MS, multiple sclerosis; N, number; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 2: Univariable and multivariable analyses on predictors of confirmed EDSS improvement

	Univariable (HR; 95% CI; p)	**Multivariable (HR; 95% CI; p)**
Age		
≥40	1.00 (ref)	1.00 (ref)
<40	2.03 (1.24-3.33); p=0.005	1.59 (0.97-2.62); p=0.067
Gender		
Female	1.00 (ref)	
Male	0.89 (0.55-1.44); p=0.64	
Baseline EDSS		
<6	1.00 (ref)	
≥6	0.85 (0.52-1.36); p=0.49	
Years from symptoms		
<10	1.00 (ref)	
≥10	0.67 (0.41-1.07); p=0.096	
ARR last year pre AHSCT	1.18 (0.88-1.58); p=0.28	
ARR last two years pre AHSCT	1.37 (1.02-1.83); p=0.035	
Type of MS		
RR	5.06 (2.51-10.20); p<0.001	2.86 (1.38-5.95); p=0.005
SP/PP	1.00 (ref)	1.00 (ref)
MRI active at last scan pre AHSCT	0.76 (0.10-5.63); p=0.79	
N. of previous DMTs	1.71 (1.31-2.10); p<0.001	1.52 (1.22-1.89); p<0.001
N. of previous HE-DMTs		
0	1.00 (ref)	
1	1.59 (0.67-3.80); p=0.29	
2+	4.84 (2.28-10.25); p<0.001	

Abbreviations: CI, confidence interval; DMTs, disease modifying therapy; EDSS, Expanded Disability Status Scale; AHSCT, haematopoietic stem cell transplantation; HR, hazard ratio; MS, multiple sclerosis; N, number; PPMS, primary progressive multiple sclerosis; ref, reference RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Figure captions

Figure 1: Consolidated Standards of Reporting Trials Diagram of Enrolment in the Study.

Abbreviations: EDSS, Expanded Disability Status Scale; FU, follow-up; MFS, magnetic resonance imaging-free activity survival; NEDA, no evidence of disease activity; RFS, relapse-free survival. * All patients were included in the safety assessment

Figure 2- AHSCT effectiveness on disease inflammatory activity. From left to right and from top to bottom, Kaplan Meier's curves of relapse-free survival in the entire study cohort (A) and by disease phenotype (B) and magnetic resonance imaging activity survival (C) in the entire study cohort and by disease phenotype (D).

Abbreviations: AHSCT, autologous hematopoietic stem cell transplantation; MRI, magnetic resonance imaging; PP, primary progressive multiple sclerosis; RR, relapsing remitting multiple sclerosis; SP, secondary progressive multiple sclerosis

Figure 3- AHSCT effectiveness on confirmed disease progression-free survival. From left to right and from top to bottom, Kaplan Meier's curves show: progression-free survival in the overall study cohort (A) and split by disease phenotype (B); progression independent from relapse (PIRA)-free survival activity compared with relapse associated worsening (RAW)-free survival (C); and PIRA-free survival by disease phenotype (D).

Abbreviations: AHSCT, autologous hematopoietic stem cell transplantation; PP, primary progressive multiple sclerosis; PIRA, progression independent of relapse activity; RAW, worsening associated with relapses; RR, relapsing remitting multiple sclerosis; SP, secondary progressive multiple sclerosis.

Figure 4: AHSCT effectiveness on no evidence of disease activity. From left to right, Kaplan Meier's curves no evidence of disease activity in the entire study cohort (A) and by disease phenotype (B).

Abbreviations: AHSCT, autologous hematopoietic stem cell transplantation; PP, primary progressive multiple sclerosis; RR, relapsing remitting multiple sclerosis; SP, secondary progressive multiple sclerosis

Figure 5: AHSCT-related disability improvement. From left to right, cumulative incidence of confirmed EDSS improvement in the entire study cohort (A), prevalence of confirmed EDSS improvement in the entire study cohort (B) and by disease phenotype (C).

Abbreviations: AHSCT, autologous hematopoietic stem cell transplantation; EDSS, Expanded Disability Status Scale; PP, primary progressive multiple sclerosis; RR, relapsing remitting multiple sclerosis; SP, secondary progressive multiple sclerosis.

Figure 1

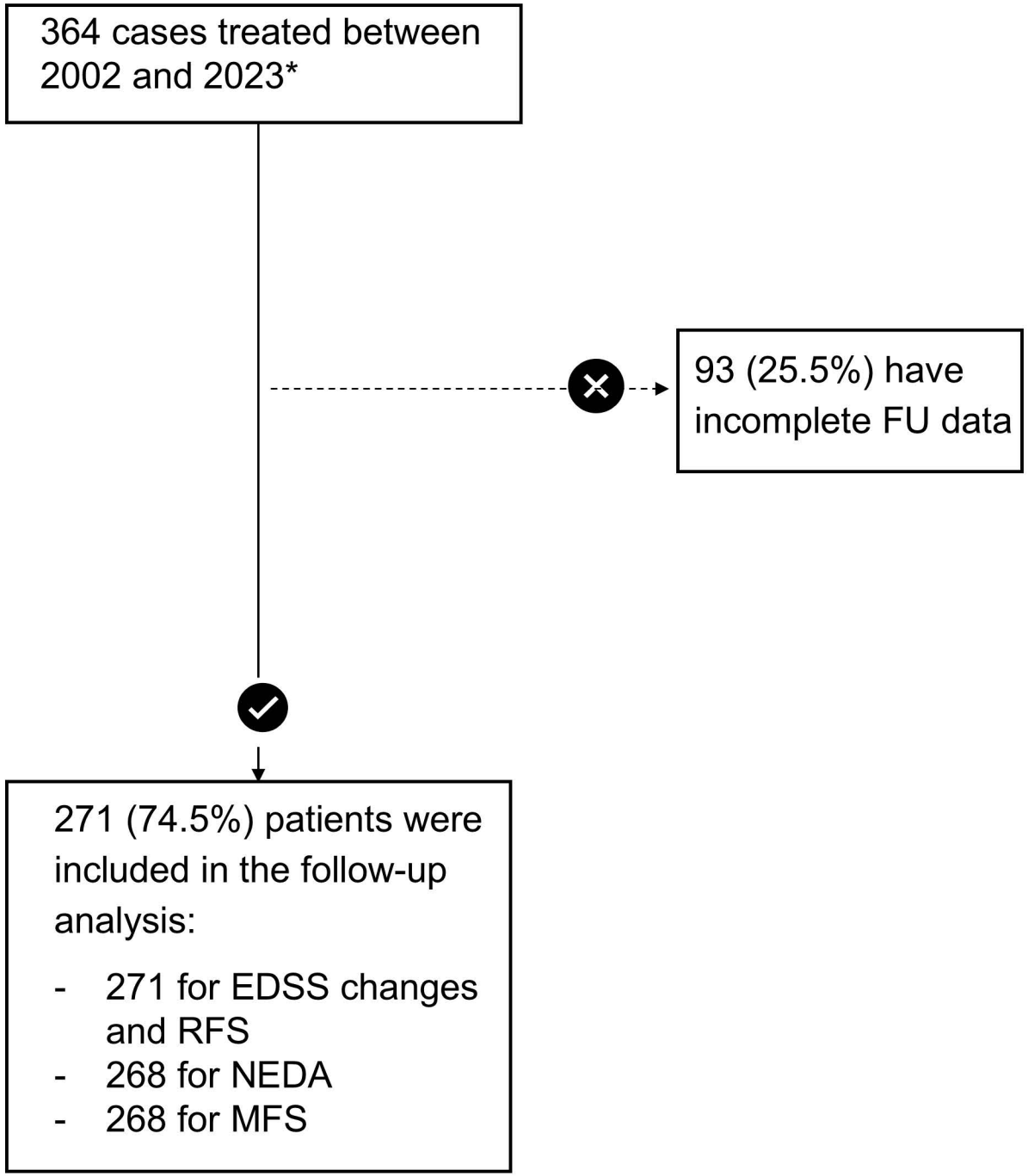
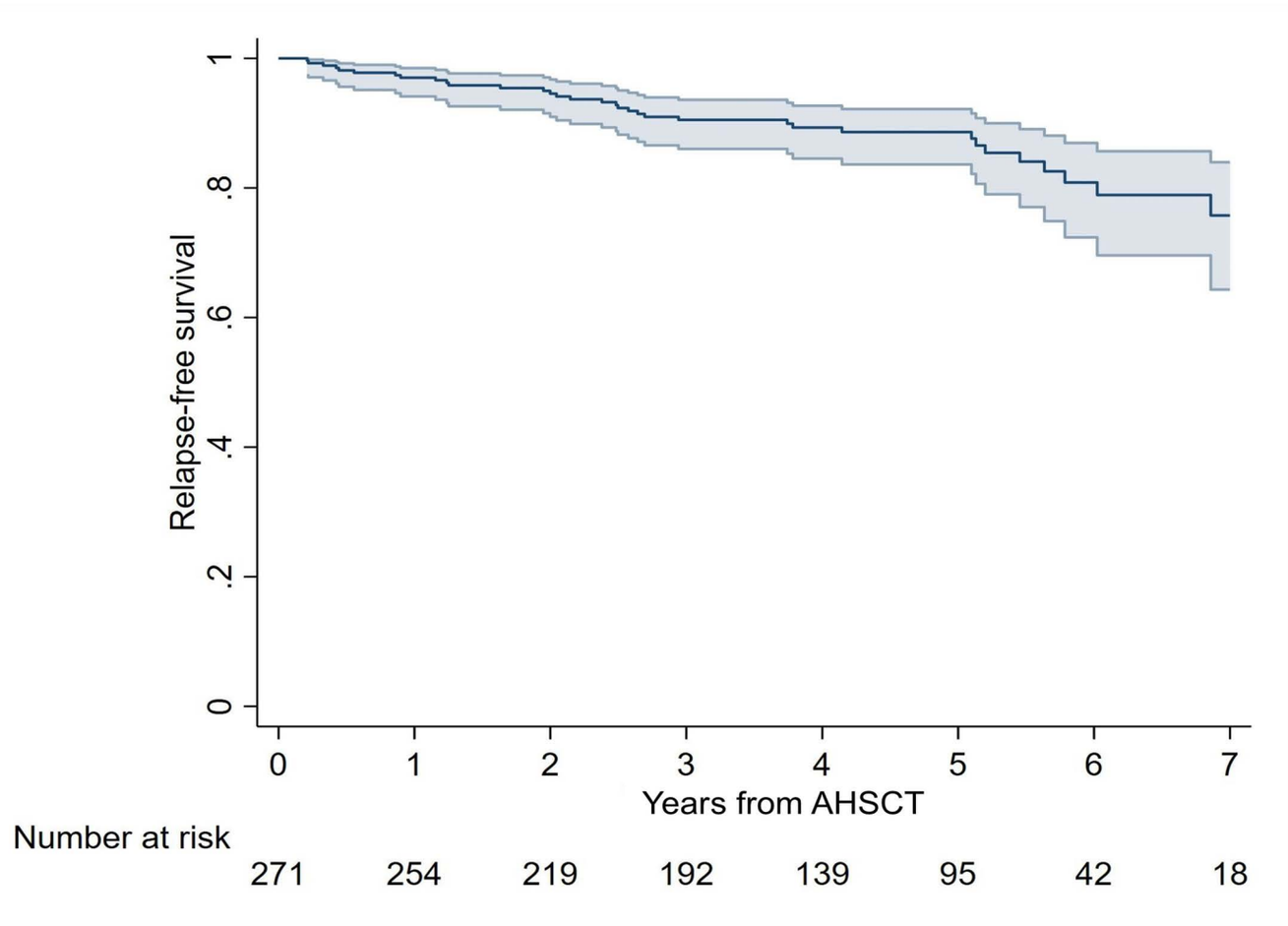
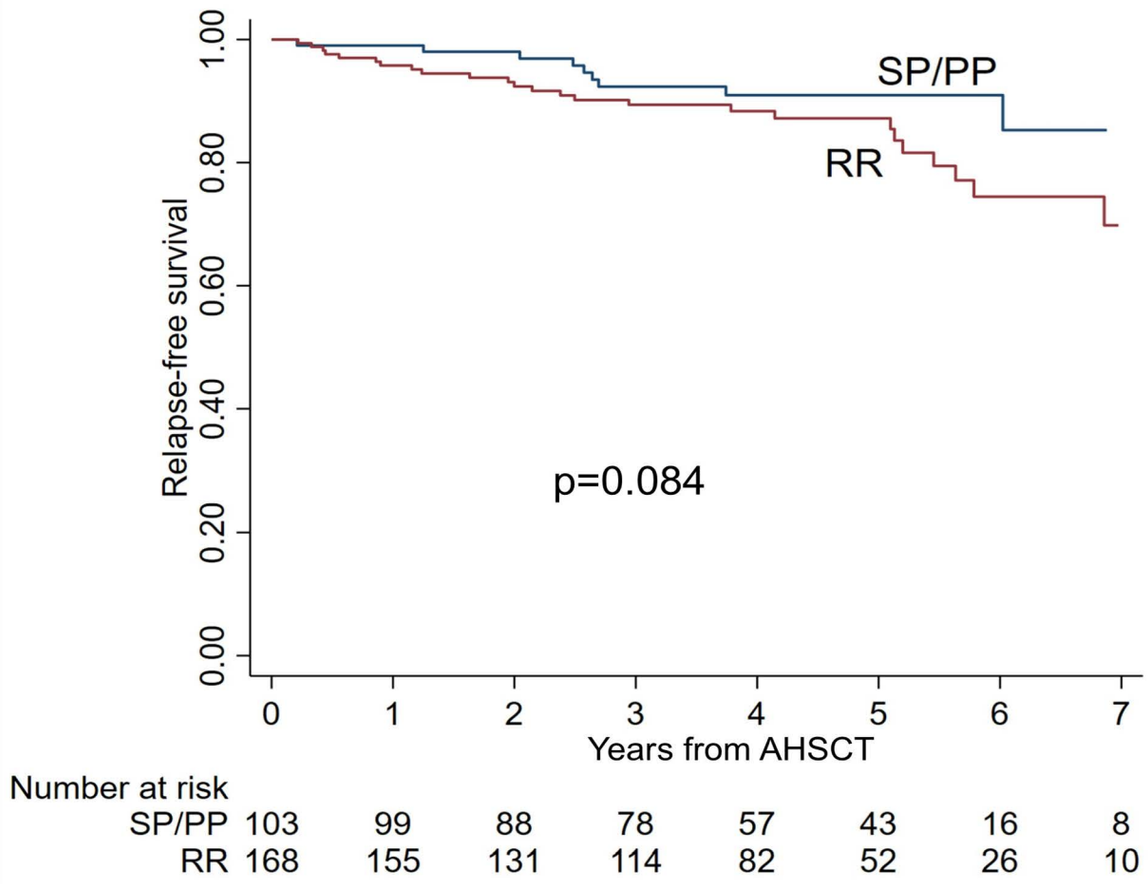

364 cases treated between 2002 and 2023*
93 (25.5%) have incomplete FU data
271 (74.5%) patients were included in the follow-up analysis:
- 271 for EDSS changes and RFS
- 268 for NEDA
- 268 for MFS

Figure 2

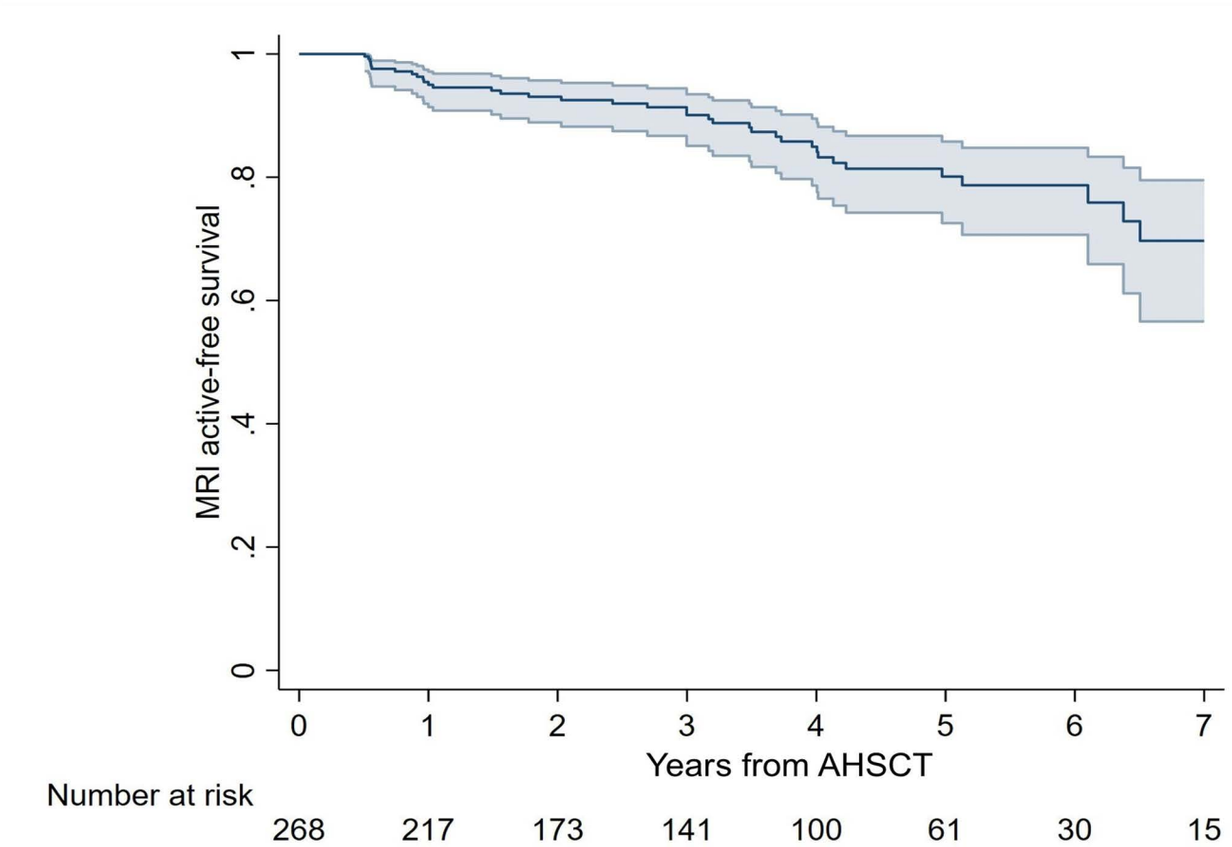
A. Relapse-free survival in the whole study cohort



B. Relapse-free survival by disease phenotype



C. MRI free-activity survival in the whole study cohort



D. MRI free-activity survival by disease phenotype

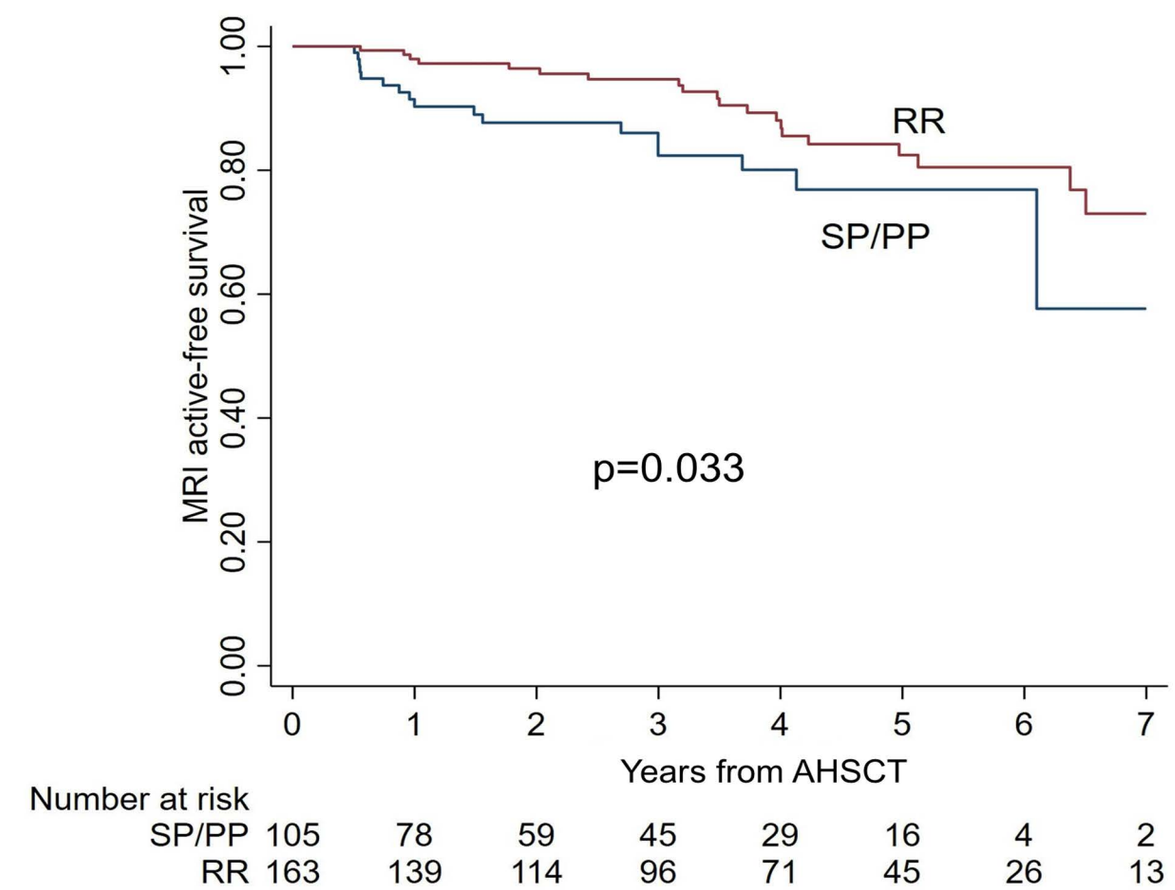
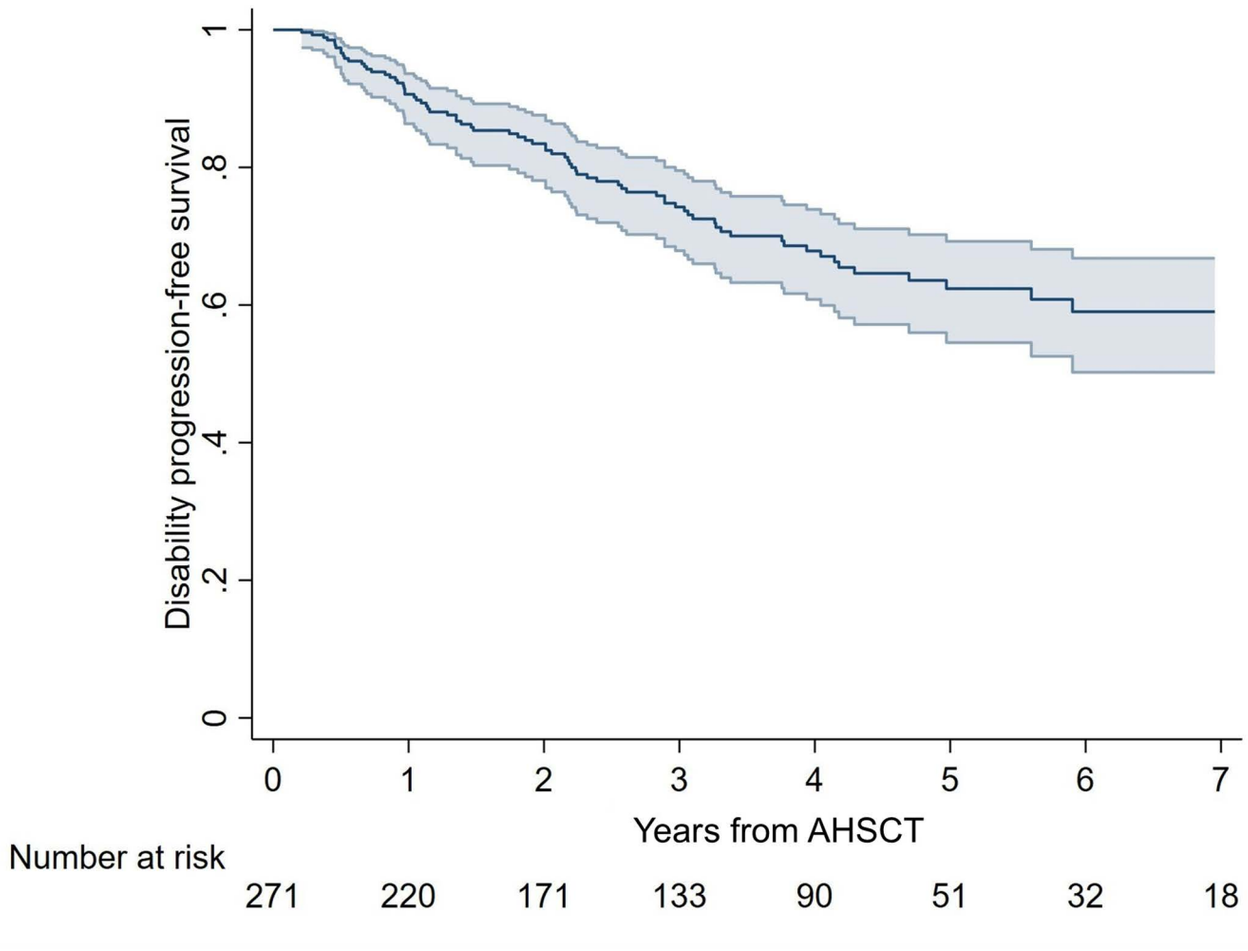
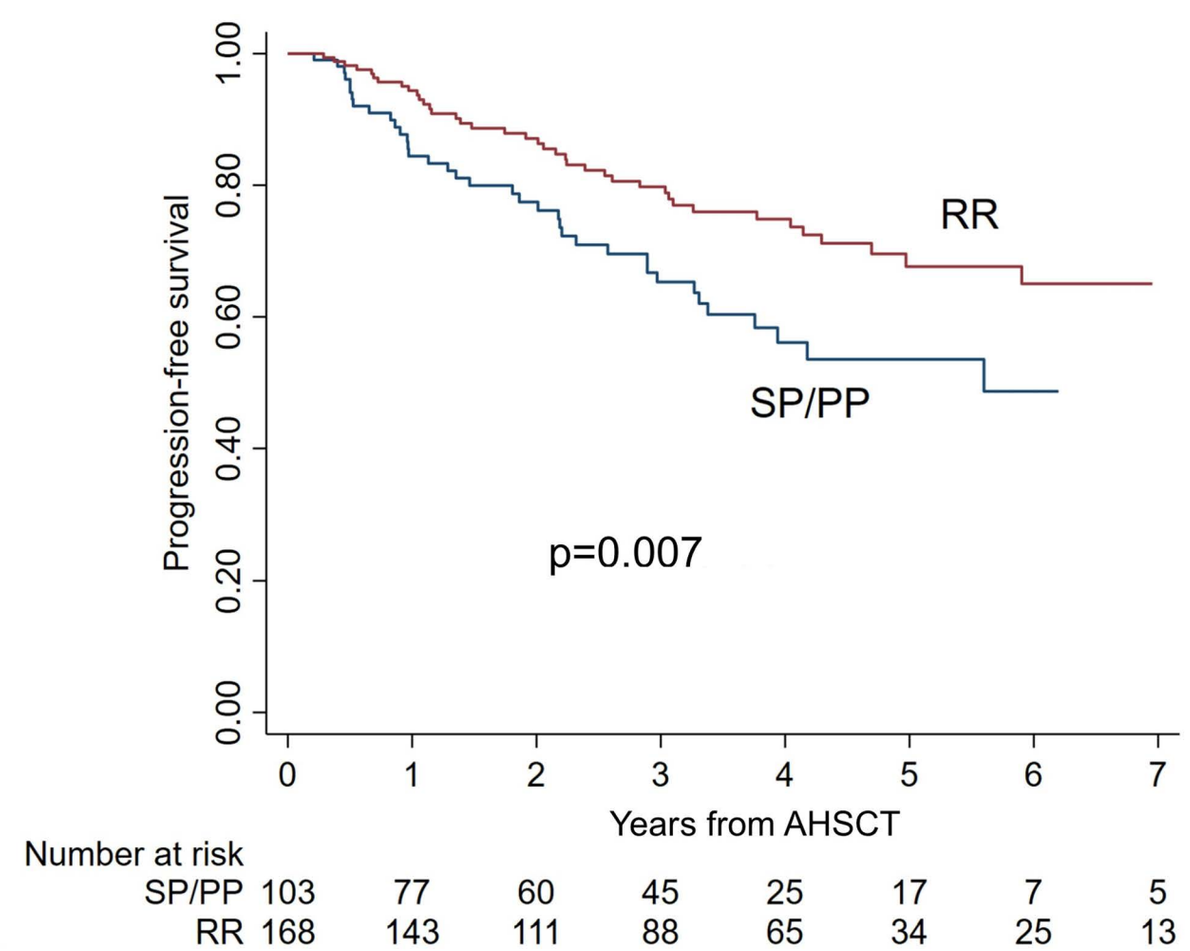


Figure 3

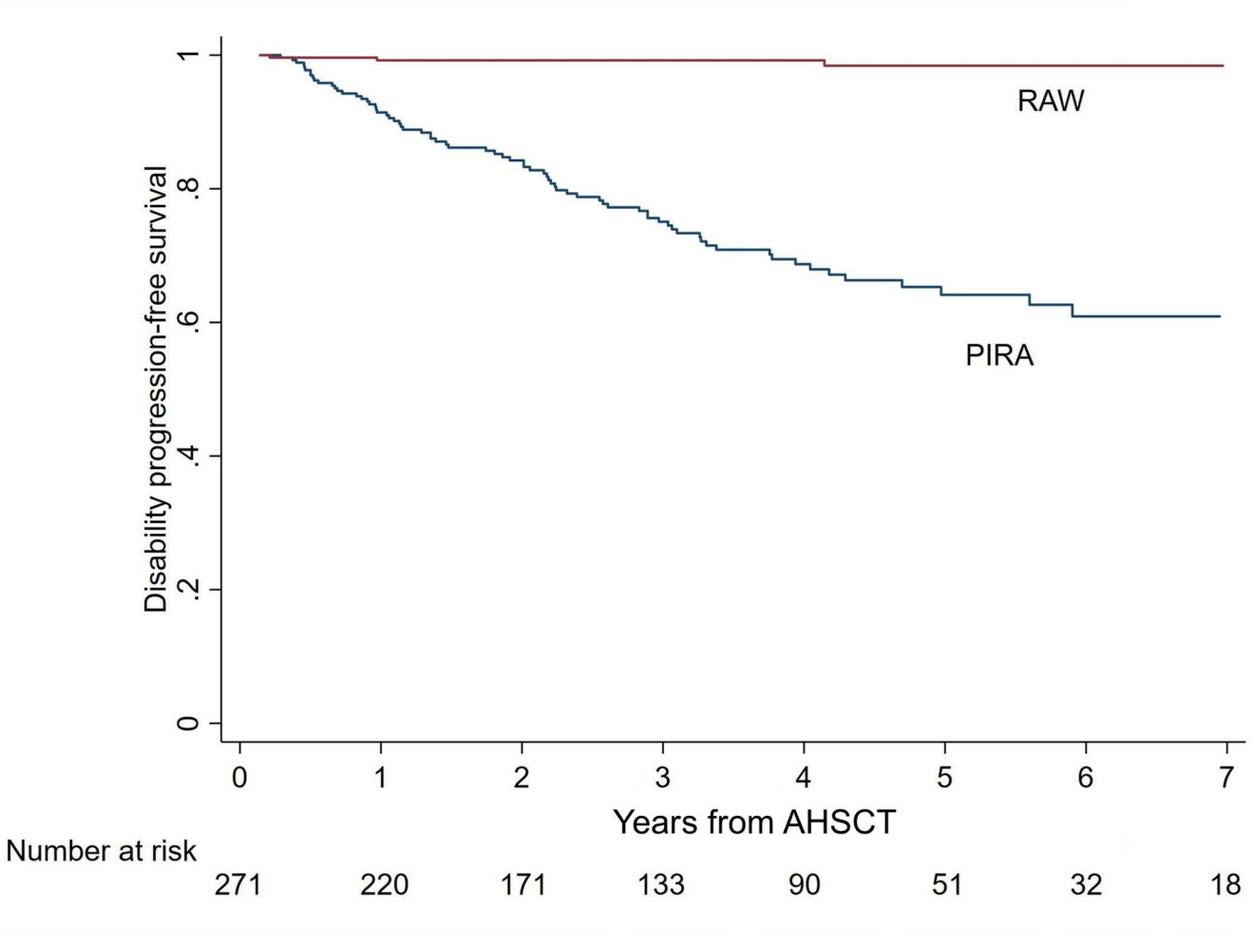
A. Progression-free survival



B. Progression-free survival by disease phenotype



C. Progression independent of relapse activity-free survival vs Relapse-associated worsening-free survival



D. Progression independent of relapse activity-free survival by disease phenotype

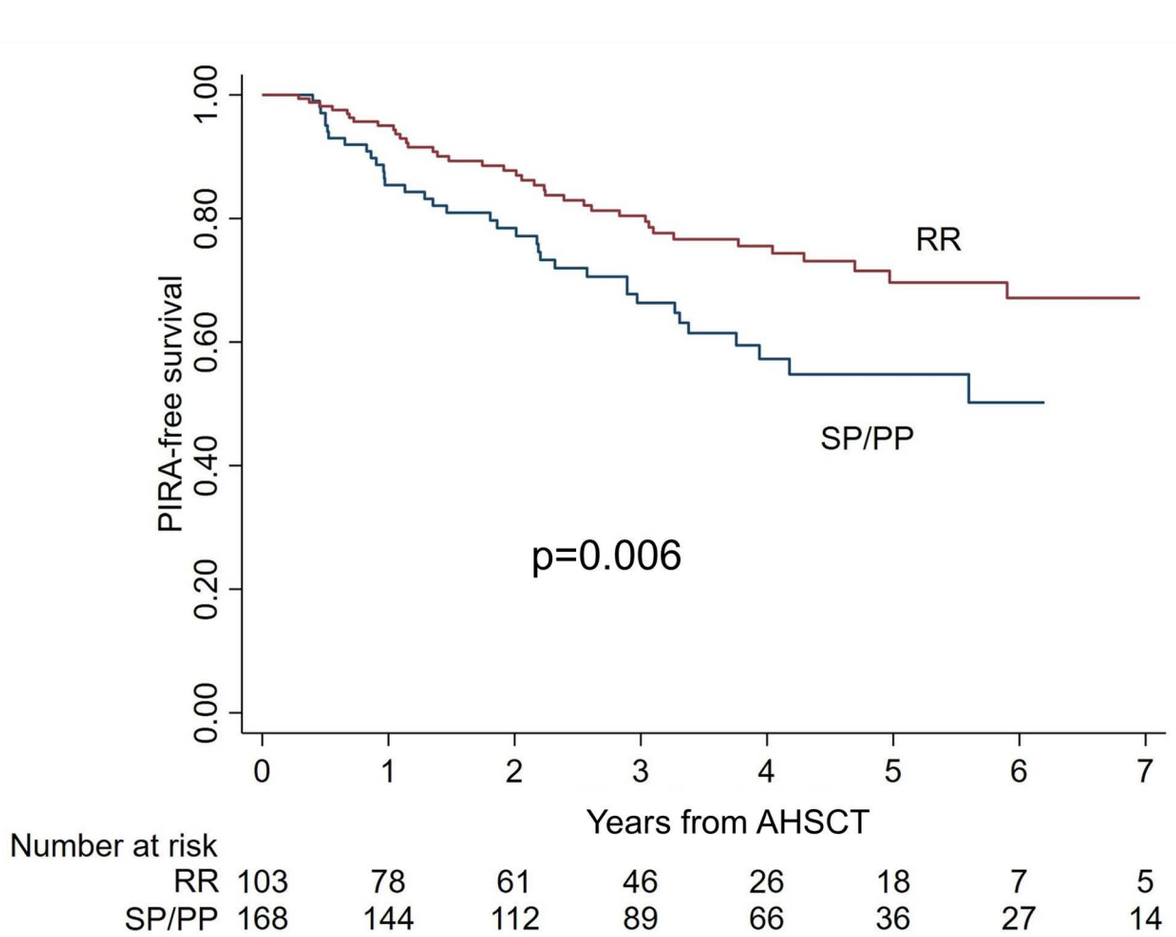
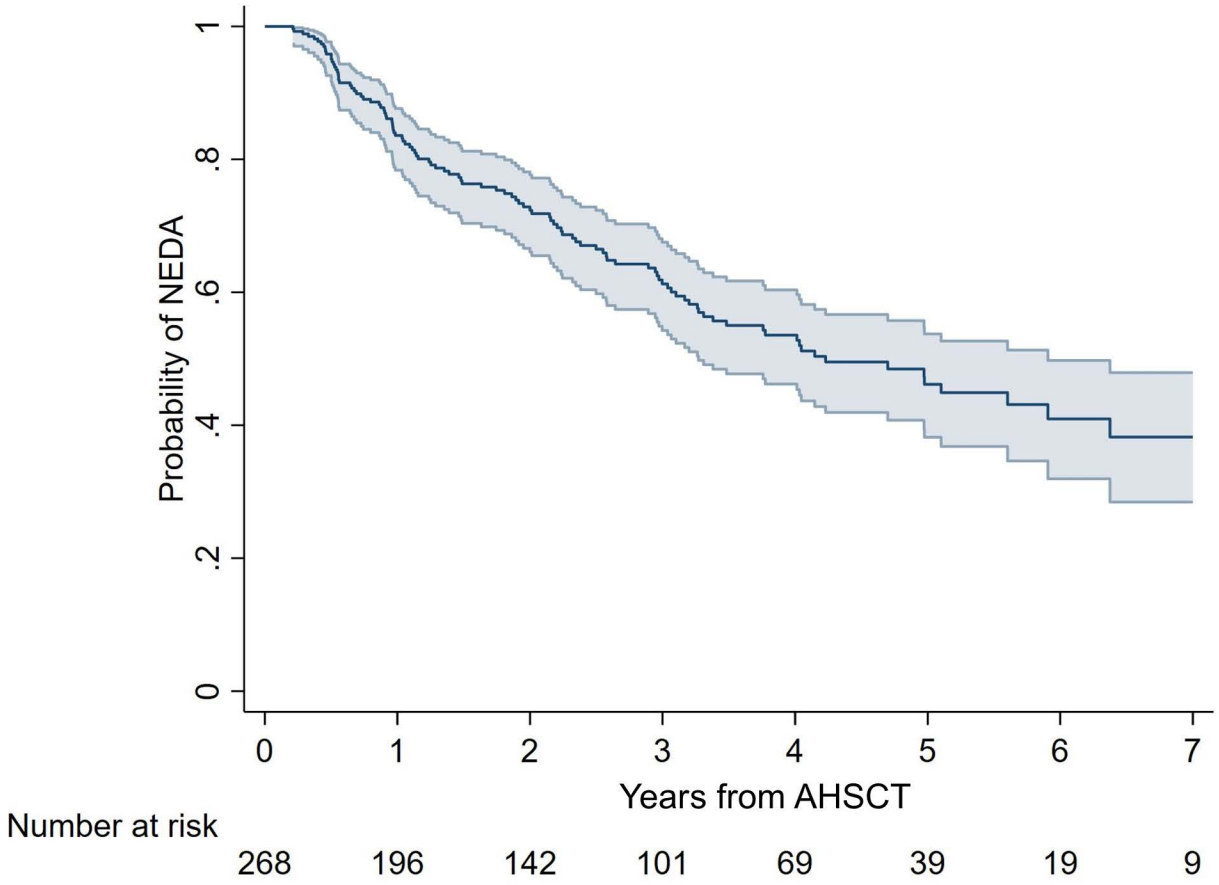


Figure 4

A. No evidence of disease activity in the whole study cohort



B. No evidence of disease activity by disease phenotype

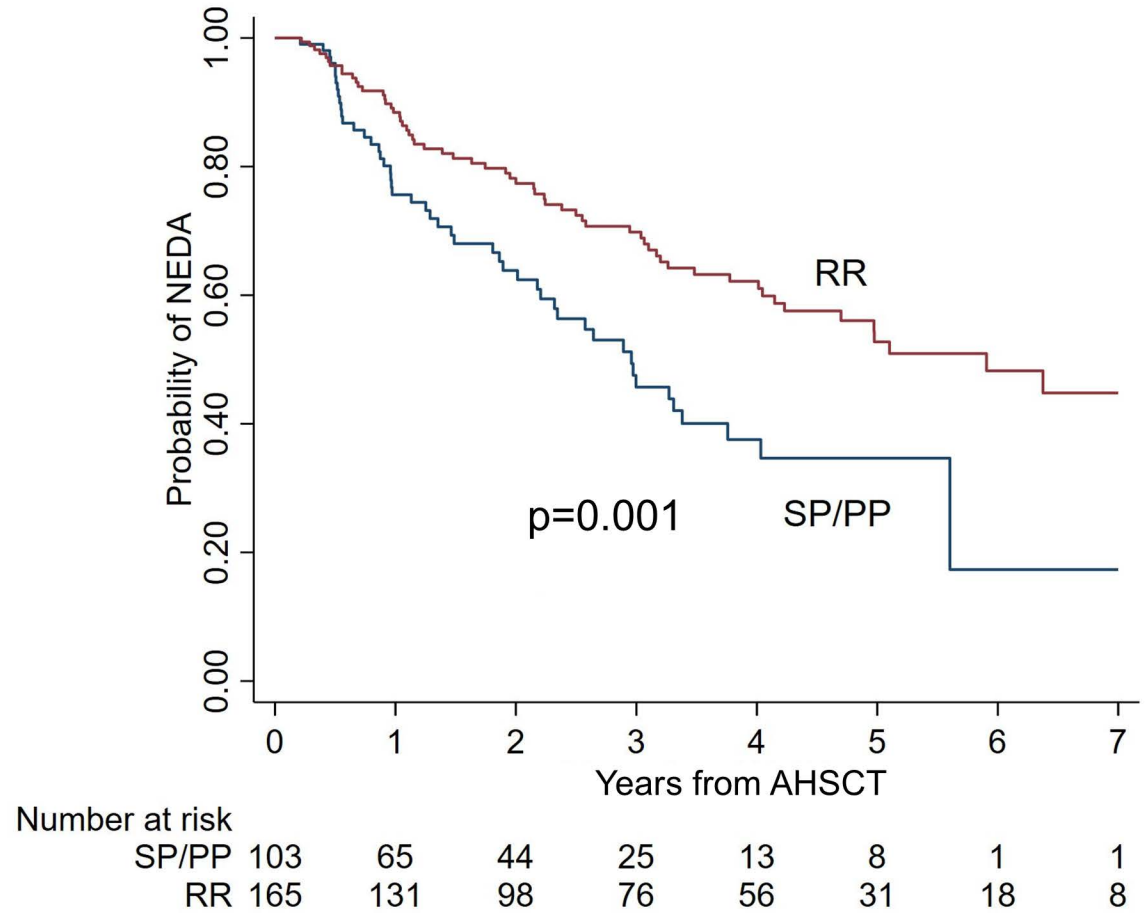
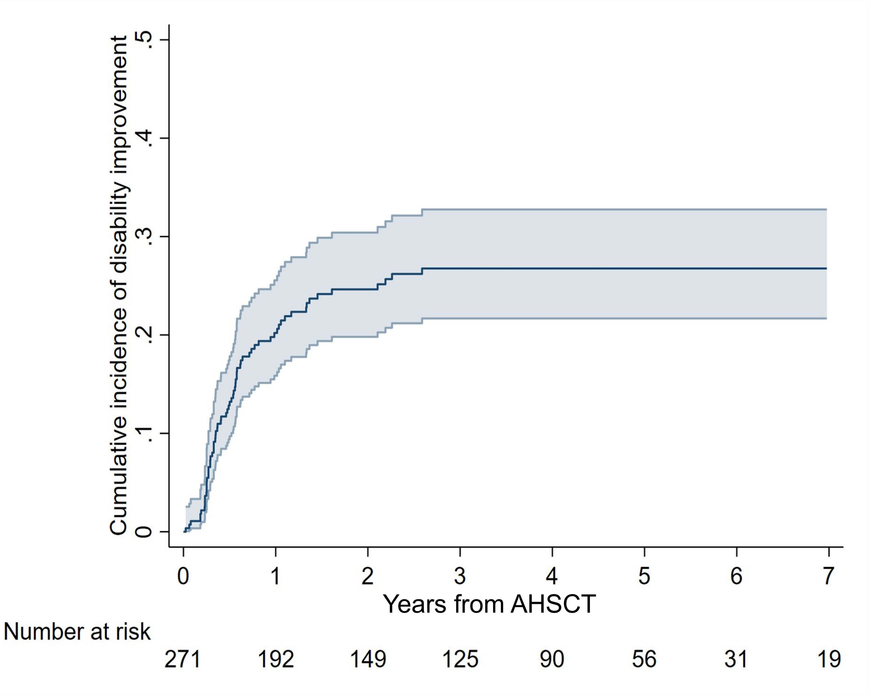


Figure 5

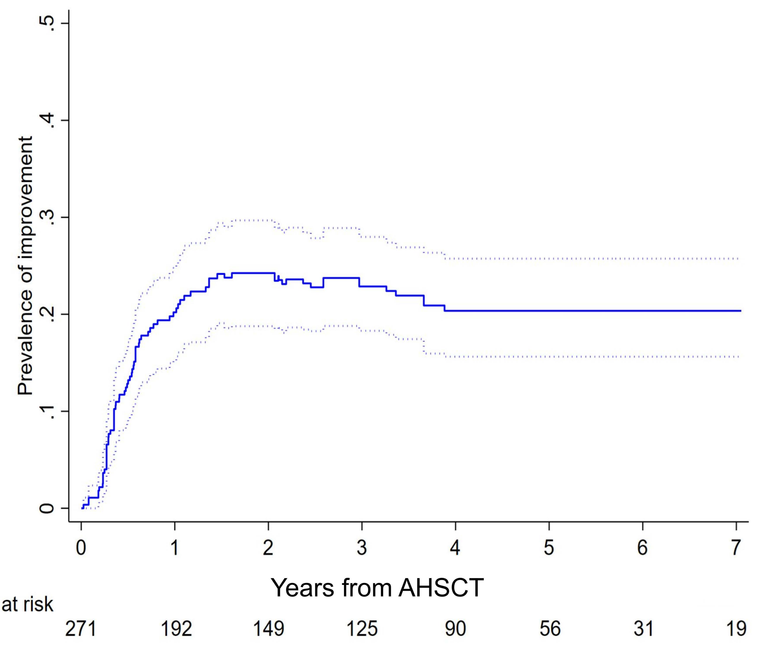
A. Cumulative incidence of confirmed EDSS improvement



Number at risk

271	192	149	125	90	56	31	19

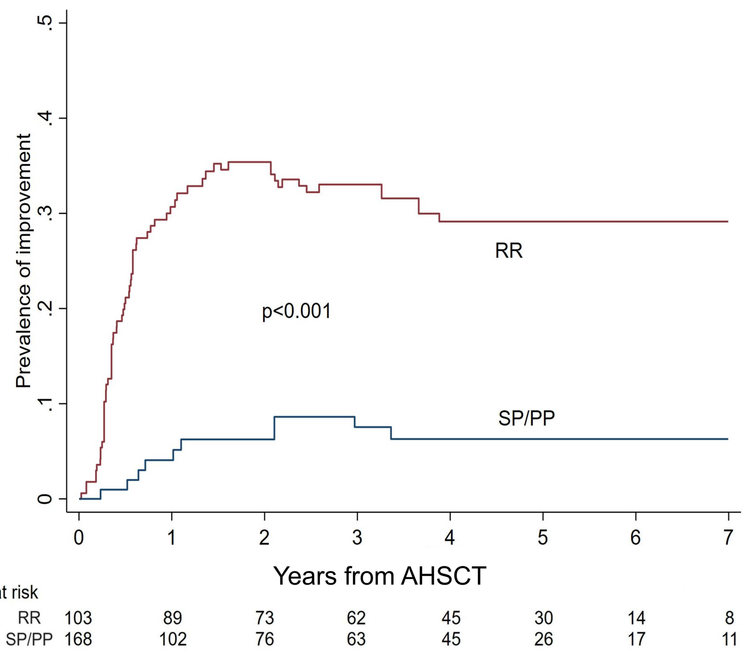
B. Prevalence of confirmed EDSS improvement



Number at risk

271	192	149	125	90	56	31	19

C. Prevalence of confirmed EDSS improvement by disease phenotype



Number at risk

RR	103	89	73	62	45	30	14	8
SP/PP	168	102	76	63	45	26	17	11

Supplementary materials

Table S1. Analysis comparing baseline characteristics between included and excluded patients.

Abbreviations: AHSCT, haematopoietic stem cell transplantation; CI, confidence interval; DMT, disease modifying

	Overall study cohort (N=364)		**Excluded patients (N=92)**		**Subset with detailed MS data (N=271)**	
	Evaluable number	**Value**	**Evaluable number**	**Value**	**Evaluable number**	**Value**
Age, median (range)	364	40 (19-66)	92	38 (23-67)	271	40.7 (19-66)
Female gender, N (%)	364	210 (58)	92	57 (62.0)	271	153 (56.5)
Disease phenotype, N (%)	338		67		271	
Relapsing remitting (RRMS)		209 (61.8)		41 (61.2)		168 (62.0)
Secondary progressive (SPMS)		83 (24.6)		19 (28.4)		64 (23.6)
Primary progressive (PPMS)		46 (13.6)		7 (10.4)		39 (14.4)
Disease duration from symptoms onset, median years (IQR)	313	10 (5-14)	48	11 (6-14)	271	10 (6-14)
EDSS score, median (IQR)	322	6 (4-6.5)	51	6 (4-6.5)	271	6 (4-6.5)
Relapses 2 years prior HSCT, median N (IQR)	249	1 (0-2)	43	1 (0-2)	206	1 (0-2)
Relapses 1 year prior HSCT, median N (IQR)	249	0 (0-1)	43	0 (0-1)	206	0 (0-1)
Patients with baseline active scan, N (%)	322	292 (90.7)	54	49 (90.7)	268	243 (90.7)
New T2 lesions, n(%)	321	265 (82.6)	53	43 (81.1)	268	222 (82.8)
Enhancing lesions, n(%)	313	246 (78.6)	51	41 (80.4)	262	205 (78.2)
Previous treatments, median N (IQR)	293	2 (1-3)	22	2 (1-3)	271	2 (1-3)
Previous high-efficacy treatments, median N (IQR)	293	1 (0-1)	22	1 (1-2)	271	1 (0-1)
Follow-up months, median (IQR)	364	41 (12-61)	52	0 (0-1)	271	46 (25-65)
Type of conditioning regimen N (%)	358		89		269	
BEAM/ATG		9 (3.0)		5 (5.6)		4 (1.5)
Cy/ATG		349 (97.0)		84 (94.4)		265 (98.5)

therapy; EDSS, Expanded Disability Status Scale; HE-DME, high-efficacy DMT; HR, hazard ratio; MS, multiple sclerosis; N, number; PPMS, primary progressive multiple sclerosis; ref, reference; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table S2: Univariable analyses on predictors of progression independent of relapse activity (PIRA)

	Univariable (HR; 95% CI; p)
Age	
<40	1.00 (ref)
≥40	1.70 (1.06-2.71); p=0.027
Gender	
Female	1.00 (ref)
Male	1.47 (0.94-2.32); p=0.095
Baseline EDSS	
<6	1.00 (ref)
≥6	1.20 (0.75-1.93); p=0.45
Years from symptoms	
<10	1.00 (ref)
≥10	1.09 (0.69-1.72); p=0.72
Relapses last year pre AHSCT	0.95 (0.75-1.19); p=0.64
Relapses last two years pre AHSCT	0.74 (0.45-1.22); p=0.24
Type of MS	
RRMS	1.00 (ref)
SPMS or PPMS	1.87 (1.18-2.94); p=0.007
MRI active at last scan pre AHSCT	0.75 (0.37-1.51); p=0.43
N. of previous DMTs	0.85 (0.73-0.98); p=0.028
N. of previous HE-DMTs	
0	1.00 (ref)
1	0.86 (0.50-1.50); p=0.60
2+	0.52 (0.30-0.92); p=0.024

Abbreviations: AHSCT, haematopoietic stem cell transplantation; CI, confidence interval; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; HE-DME, high-efficacy DMT; HR, hazard ratio; MS, multiple sclerosis; N, number; PPMS, primary progressive multiple sclerosis; ref, reference; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table S3 – Univariable analyses on predictors of no evidence of disease activity

	Univariate (HR; 95% CI; p)
Age	
<40	1.00 (ref)
≥40	1.30 (0.90-1.87); p=0.16
Gender	
Female	1.00 (ref)
Male	1.25 (0.87-1.80); p=0.22
Baseline EDSS	
<6	1.00 (ref)
≥6	1.13 (0.78-1.64); p=0.51
Years from symptoms	
<10	1.00 (ref)
≥10	1.04 (0.72-1.49); p=0.83
ARR last year pre AHSCT	1.11 (0.93-1.33); p=0.25
ARR last two years pre AHSCT	0.90 (0.75-1.07); p=0.24
Type of MS	
RRMS	1.00 (ref)
SPMS or PPMS	1.62 (1.13-2.33); p=0.009
MRI active at last scan pre AHSCT	1.80 (0.87-3.72); p=0.11
N. of previous DMTs	0.89 (0.79-0.99); p=0.042
N. of previous HE-DMTs	
0	1.00 (ref)
1	0.93 (0.59-1.47); p=0.76
2+	0.60 (0.38-0.93); p=0.024

Abbreviations: ARR, annual relapse rate; AHSCT, haematopoietic stem cell transplantation; CI, confidence interval; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; HE-DME, high-efficacy DMT; HR, hazard ratio; MS, multiple sclerosis; N, number; PPMS, primary progressive multiple sclerosis; ref, reference; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table S4 – Univariable analyses on predictors of no evidence of disease activity by disease phenotype

	RRMS	SPMS or PPMS
	Univariable (HR; 95% CI; p)	**Univariable (HR; 95% CI; p)**
Age		
<40	1.00 (ref)	1.00 (ref)
≥40	1.61 (0.98-2.67); p=0.062	1.10 (0.60-2.02); p=0.75
Gender		
Female	1.00 (ref)	1.00 (ref)
Male	1.27 (0.76-2.12); p=0.36	1.14 (0.64-2.03); p=0.65
Baseline EDSS		
<6	1.00 (ref)	1.00 (ref)
≥6	1.43 (0.86-2.38); p=0.17	0.66 (0.35-1.24); p=0.20
Years from symptoms		
<10	1.00 (ref)	1.00 (ref)
≥10	1.08 (0.65-1.79); p=0.77	1.18 (0.66-2.12); p=0.57
ARR last year pre AHSCT	1.02 (0.79-1.33); p=0.86	1.21 (0.91-1.62); p=0.18
ARR last two years pre AHSCT	0.96 (0.74-1.23); p=0.72	0.94 (0.66-1.33); p=0.72
MRI active at last scan pre AHSCT	0.60 (0.31-1.15); p=0.13	0.87 (0.21-3.63); p=0.85
N. of previous DMTs	0.77 (0.63-0.94); p=0.012	1.23 (1.02-1.49); p=0.034
N. of previous HE-DMTs	0.64 (0.43-0.97); p=0.033	1.22 (0.84-1.77); p=0.30

Abbreviations: ARR, annual relapse rate; AHSCT, haematopoietic stem cell transplantation; CI, confidence interval; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; HE-DME, high-efficacy DMT; HR, hazard ratio; MS, multiple sclerosis; N, number; PPMS, primary progressive multiple sclerosis; ref, reference; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.