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AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR NEUROLOGICAL DISORDERS: A SYSTEMATIC REVIEW & META-ANALYSIS OF CLINICAL OUTCOMES AND COMPLICATIONS

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Abstract

Introduction: Neurological disorders, including MS and pediatric neurodegenerative diseases, pose a significant global health burden with limited therapeutic options. Autologous HSCT has emerged as a promising intervention to halt disease progression, reduce disability, and modulate immune responses in the central nervous system. This systematic review and meta-analysis evaluate the clinical outcomes and safety of autologous HSCT in patients with neurological disorders.

Methods: Following PRISMA guidelines, we searched PubMed, Embase, Cochrane Library, and Web of Science for studies on autologous HSCT in neurological disorders. Included studies reported clinical outcomes (e.g., Expanded Disability Status Scale [EDSS] changes, progression-free survival [PFS]) and complications. Data were synthesized using random-effects meta-analyses to calculate standardized mean differences (SMD) for EDSS changes, pooled proportions for PFS and relapse-free survival, and treatment-related mortality (TRM) rates. Heterogeneity was assessed with I^2 statistics, and predictors of outcomes were explored via meta-regression and subgroup analyses.

Results: Fifteen studies (n=1,378 patients) were included, predominantly focusing on MS (relapsing-remitting, progressive, and aggressive subtypes). Autologous HSCT significantly reduced disability, with a pooled SMD in EDSS of -1.02 (95% CI: -1.42, -0.62; $p < 0.01$; $I^2 = 88.9\%$). PFS was 73% (95% CI: 0.61–0.84; $I^2 = 0\%$), and relapse-free survival in relapsing-remitting MS was 82% (95% CI: 0.70–0.92; $I^2 = 5\%$). TRM was low at 2% (95% CI: 0.00–0.04; $I^2 = 38.9\%$), with common adverse events including febrile neutropenia and infections. Younger age, shorter disease duration, and relapsing-remitting MS subtype predicted better outcomes ($p < 0.05$). Conditioning regimen influenced safety, with BEAM-based protocols showing lower TRM ($p = 0.0049$).

Conclusion: Autologous HSCT demonstrates significant efficacy in reducing disability and preventing disease progression in neurological disorders, particularly MS, with a favorable safety profile. However, high heterogeneity and limited controlled trials highlight the need for larger, randomized studies to confirm comparative efficacy against standard therapies and optimize patient selection and treatment protocols.

Keywords: Hematopoietic stem cell transplantation (HSCT), Autologous HSCT, Disease-free survival (DFS), Graft-versus-host disease (GVHD), transplant-related mortality (TRM).

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1 Introduction

Neurological disease is a serious worldwide health issue, characterized by its increasing burden and effects on the health care system. The Global Burden of Disease Study has repeatedly tracked the incidence and burden of these diseases with patterns that highlight the evolving neurological health profile. Throughout the years 1990 to 2016, infectious neurological disease such as encephalitis and meningitis reduced their age-standardized rates, while non-communicable disorders such as stroke and dementia had increasing prevalence as well as DALYs [1].

The health burden due to neurological conditions varies by region and is largest in low- and middle-income countries, where lack of availability of data hampers estimation of prevalence [2,3]. As noted in the following examples from Bangalore and Egypt, community-based research highlights the discrepancy between hospital populations' data and prevalence in overall populations. These studies used systematic door-to-door surveys to establish prevalence rates of disorders such as epilepsy, stroke, and dementia, emphasizing the requirement for rigorous population-based studies in order to have accurate representation of the neurological burden of disease [4,5].

Furthermore, the COVID-19 pandemic has introduced an additional dimension to the neurology of neurological diseases, with post-acute sequelae evolving into a number of neuropsychiatric manifestations, including anxiety, depression, and cognitive impairment [6,7]. This evolution underlines the necessity to understand the long-term neurological impact of viral infections on public health. Pandemic has also been associated with a higher level of symptoms such as headache and fatigue among the survivors, revealing how infectious conditions can result in long-term neurologic complications [6,8].

Overall, the epidemiology of neurological disorders is multifaceted, and burden of disease keeps evolving with shifting epidemiological trends, lifestyle, and new global health challenges like COVID-19. More research is needed to guide intervention programs and health policy aimed at the complexities of neurological health [1-3].

Stem cell therapy is a new field in the treatment of neurological diseases and holds high promise to fix damaged tissues, modulate immune responses, and promote repair processes in the central nervous system (CNS). Neurological disorders, ranging from neurodegenerative diseases to traumatic brain injury, are ill-treated, so the focus has been on stem cell therapies in current research [9,10]. Of the different stem cells that have been researched, autologous hematopoietic stem cells (HSCs) have been identified with their use in the treatment of certain neurological disorders, especially given their capacity to alter the local CNS microenvironment and their capability to develop into neural progenitors [11].

The procedure of HSCT is the harvest of patient-specific HSCs, which is processed and infused back to the patient to facilitate recovery and healing. The therapy is particularly crucial in preventing complications with allogeneic transplants such as graft-versus-host disease (GVHD) [12]. Following HSCT, the stem cells transfused not only aid in the reconstitution of the hematopoietic system

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but can migrate past the blood-brain barrier (BBB) and differentiate into neuroglial cells in CNS [13]. This migration has two advantages: it is able to substitute injured microglial cells and can supply neurotrophic factors required for neuronal integrity. These molecules are crucial in the modulation of neuroinflammation and promotion of neuroprotection, thereby addressing the root cause of most of the neurological disorders [10].

Clinical studies have established positive outcomes from HSCT in several neurodegenerative diseases, such as cerebral adrenoleukodystrophy, in which early treatment is able to completely alter the path of disease through preventing neurological impairment [14]. Nevertheless, not all goes as well as planned. The incidence of resolution of neurological symptoms is variable as neuroinflammation can still escalate in the early months posttransplant, supporting the significance of proper timing and patient selection for HSCT therapies [9,10]. Future research will focus on enhancing the efficacy of HSCT by genetic manipulation of HSCs and optimization of pre-transplant conditioning protocols [12,15].

HSCT has been of significant interest as a therapeutic modality for the treatment of several neurological disorders since it promises to restore and regenerate damaged neural tissues, suppress disease progression, and modulate immune responses within the CNS. This therapeutic strategy is very relevant to such conditions as neurological complications of inherited disorders, traumatic brain injury, and some childhood neurodegenerative diseases.

A valid reason why HSCT would be used in neurologic disorders is that it holds the promise for cell regrowth within the CNS. With HSCT, one can introduce hematopoietic stem cells that will proliferate into cells that have the potential to become progenitor cells neural-directed, apparently restoring absent enzyme function or cellular structure. For instance, with HSCT, gene therapy has been applied in disorders such as MLD to correct very significantly preclinical models' neurological damage by administering enzyme-overexpressing microglia that can distribute therapeutically appropriate enzymes into the CNS Biffi et al. [16]. This illustrates the manner in which HSCT stimulates local mechanisms for repair through the production of cells capable of performing vital neuroprotective functions.

In addition, the timing of HSCT has been shown to be a determinant of clinical outcome; early intervention in the course of the disease can lead to significantly better survival and neurological outcome. For example, with adrenoleukodystrophy occurring in childhood, successful application of HSCT in early stages of the disease has been demonstrated to halt progression of the disease, improving neurological and neuropsychological function. Conversely, patients undergoing HSCT at late stages are shown to have worse outcomes, and thus, it is imperative to intervene early [17].

The immune-modulatory function of HSCT also offers a critical rationale for its use. Immune reconstitution by HSCT has the ability to inhibit ongoing neuroinflammatory responses that are usually exacerbated in chronic neurological diseases. Importantly, autologous HSCT is less complicated than allogeneic

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transplants, such as GVHD [18]. Furthermore, reintroduced hematopoietic stem cells can also differentiate into microglia, which play significant roles in regulating neuroinflammation and immune surveillance in the CNS, having the prospect to improve neuronal populations' overall health [19].

Despite this promise, caution is warranted as HSCT is also associated with the risk of neurological complications due to conditioning regimen toxicity, infection, and post-transplant immune suppression. Neurological complications following HSCT may be ranging from transient to severe, life-threatening events such as seizures or encephalopathy [20-22]. Careful selection of appropriate candidates, monitoring, and early interventions are important to maximize patient outcomes.

Aim

This systematic review and meta-analysis aimed to evaluate the clinical outcomes and safety of autologous HSCT in patients with neurological disorders.

2 **Methods**

2.1 Study Design

The study employed systematic review and meta-analysis design. The methodology adhered to the PRISMA guidelines. This framework ensured a transparent and rigorous approach to the identification, screening, selection, and synthesis of relevant studies.

2.2 Eligibility Criteria

2.3 Data Sources & Search Strategy

A comprehensive literature search was conducted across the following electronic databases: PubMed, Embase, Cochrane Library, and Web of Science. The search strategy involved a combination of keywords and Medical Subject Headings (MeSH) terms relevant to autologous HSCT and various neurological disorders. Keywords and search terms included but were not limited to: "Autologous Hematopoietic Stem Cell Transplantation," "HSCT," "Neurological Diseases," "Multiple Sclerosis," "Progressive Multifocal Leukoencephalopathy," "Myasthenia Gravis," "Amyotrophic Lateral Sclerosis," "Cerebral Palsy," and "Autoimmune Neuropathies." Boolean operators (AND, OR, NOT) were used to combine search terms and refine the search strategy. The search string was constructed to maximize sensitivity and specificity, ensuring that all relevant studies were captured while minimizing the retrieval of irrelevant articles.

2.4 Study Selection & Data Extraction

The study selection process was conducted in a stepwise manner. First, titles and abstracts of articles retrieved from the database searches were screened to remove obviously irrelevant studies. Second, the full texts of potentially eligible articles were retrieved and assessed against the inclusion and exclusion criteria. The screening process was performed by two independent reviewers. Discrepancies were resolved through discussion and consensus, or by consulting a third reviewer if necessary. A standardized data extraction form was developed and used to collect relevant information from the included studies. Extracted data included: patient characteristics (age, sex, disease type, disease duration, baseline severity), HSCT protocol (conditioning regimen, stem cell source, and any use of adjunctive

therapies), clinical outcomes (primary and secondary outcomes as reported in the studies, including measures of neurological function, disability progression, relapse rates, and survival), and complications (type, frequency, and severity of complications associated with HSCT, including treatment-related mortality (TRM), common adverse events, and serious complications).

2.5 Risk of Bias & Quality Assessment

The risk of bias within individual studies was assessed using appropriate tools. For observational studies, the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used. For randomized controlled trials, the Cochrane Risk of Bias tool was used. These tools evaluate various sources of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. The quality assessment was conducted by two independent reviewers, and disagreements were resolved through discussion and consensus. The results of the risk of bias assessment were used to evaluate the overall quality of evidence and may have been considered in sensitivity analyses.

2.6 Statistical Analysis

The statistical analysis for this systematic review and meta-analysis was conducted to synthesize data on clinical outcomes and complications following autologous HSCT for neurological disorders. A random-effects model was employed to account for anticipated heterogeneity across studies, given differences in patient populations, HSCT protocols, and follow-up durations. The primary outcome of interest was the change in neurological function, measured by the EDSS score, expressed as SMD to allow comparison across studies with varying scales and reporting methods. For studies providing pre- and post-HSCT EDSS scores, the MD was calculated where possible, particularly when comparing HSCT to control groups. Secondary outcomes included PFS, relapse-free survival, MRI activity-free survival, and TRM, analysed as proportions or event rates.

Heterogeneity was assessed using the I^2 statistic and τ^2, with I^2 values >50% indicating substantial heterogeneity. Sources of heterogeneity were explored through subgroup analyses (e.g., by MS subtype or conditioning regimen) and meta-regression (e.g., age as a predictor of EDSS change). Publication bias was evaluated using funnel plots and the trim-and-fill method, with asymmetry suggesting potential underreporting of smaller or negative studies. Pooled estimates were reported with 95% CI, and statistical significance was set at $p < 0.05$. Sensitivity analyses were conducted to assess the robustness of findings by excluding studies with a high risk of bias or small sample sizes. All analyses were performed using appropriate statistical software R Studio, adhering to PRISMA guidelines for transparent reporting.

3 Results

Study Selection Process

The study selection process was conducted systematically following the PRISMA guidelines to ensure a transparent and reproducible approach. A comprehensive literature search across databases, including Google Scholar (n=174) and PubMed (n=56), initially identified 230 records. After removing duplicates

(n=128), 102 records remained for screening. During the title and abstract screening phase, conducted independently by two reviewers, no records were excluded based on automation tools or other reasons, leaving all 102 records for further evaluation. Of these, 59 reports were not retrieved, resulting in 43 reports assessed for eligibility.

A full-text review of these 43 reports led to the exclusion of 28 studies for the following reasons: 10 studies did not involve HSCT as an intervention, 11 reports were duplicate or incomplete, and 7 studies were deemed irrelevant due to their focus not aligning with the review's objectives (e.g., non-neurological conditions or non-autologous HSCT). Discrepancies between reviewers during screening and eligibility assessment were resolved through discussion, with no need for third-party arbitration. Ultimately, 15 studies met the inclusion criteria and were included in the systematic review and meta-analysis. No additional reports from the references of included studies were identified for inclusion.

PRISMA flow diagram

The meta-analysis evaluates the standardised mean difference (SMD) in Expanded Disability Status Scale (EDSS) scores post-HSCT, yielding a pooled SMD of -1.02 (95% CI: -1.42, -0.62), indicating a significant reduction in disability ($p < 0.01$). Individual studies show varied effects: Burt (2009) reports -1.70 (95% CI: -2.30, -1.10), Moore (2019) -1.48 (95% CI: -2.03, -0.93), and Tolf (2019) the largest at -3.00 (95% CI: -4.00, -2.00), while Muraro (2017) and Nash (2017) show smaller effects at -0.32 (95% CI: -0.52, -0.12) and -0.50 (95% CI: -0.70, -0.30), respectively. Study weights range from 8.5% (Tolf, 2019) to 17.2% (Muraro, 2017) in the random-effects model. High heterogeneity ($I^2 = 88.9\%$, $\tau^2 = 0.2318$, $p < 0.01$) suggests variability, possibly due to differences in MS subtypes, HSCT protocols, or follow-up duration. This significant improvement supports HSCT's efficacy in reducing disability, though heterogeneity warrants subgroup analyses (e.g., by MS type or conditioning regimen) to refine clinical applicability.

This meta-analysis compares EDSS changes between HSCT and control groups, with a pooled mean difference (MD) of -0.90 (95% CI: -2.55, 0.75), suggesting no statistically significant difference ($p > 0.05$). Burt et al. (2019) reports a strong effect (MD = -1.69, 95% CI: -1.83, -1.55; 53.3% weight), while Mancardi et al. (2015) shows no difference (MD = 0.00, 95% CI: -0.86, 0.86; 46.7% weight). Burt et al. (2009) contributes 0% weight due to insufficient control data. The analysis includes 85 HSCT patients and 67 controls. High heterogeneity ($I^2 = 93.0\%$, $\tau^2 = 1.3282$, $p = 0.0002$) reflects variability in study design or patient characteristics. The wide CI crossing zero indicates uncertainty in HSCT's superiority over controls, suggesting a need for larger controlled trials to confirm efficacy.

The funnel plot shows a triangular distribution with a mode at -1.5, where the SE is lowest (near 0.0), indicating high precision in estimates. The x-axis spans from -3.0 to 0.0, and the y-axis shows SE up to 0.5, showing increasing uncertainty toward the extremes. Scattered data points mostly cluster between -2.0 and 0.0, aligning with the distribution, with a few outliers near the bounds showing higher standard errors (0.1 to 0.5). This suggests that values around -1.5 are most likely and reliable, while those near -3.0 and 0.0 are less certain.

This meta-analysis estimates the proportion of patients remaining progression-free post-HSCT. Ni et al. (2006) reports 0.71 (95% CI: 0.48–0.89), and Moore et al. (2019) 0.74 (95% CI: 0.57–0.88), with a pooled estimate of 0.73 (95% CI: 0.61–0.84) under both common and random-effects models. This indicates that 73% of patients avoid disease progression, a key efficacy marker. No heterogeneity ($I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.7977$) suggests consistent results across studies. Compared to typical MS progression rates (20–50% over 5 years without HSCT), this supports HSCT's efficacy, though longer-term data could strengthen this finding.

The funnel plot with trim-and-fill analysis assesses publication bias in a meta-analysis. Ideally, studies should be symmetrically distributed around the pooled effect size, forming an inverted funnel shape. In this plot, slight asymmetry suggests potential bias, with missing studies likely on the left side. The trim-and-fill method has adjusted the effect size from **0.2 to -0.5**, indicating a shift due to possible missing studies. The standard error ranges from **0.1 to 0.5**, with extreme effect sizes between **-3.0 and 2.0**. If the correction significantly alters the pooled estimate, bias is likely.

This forest plot evaluates SMD in EDSS across MS subtypes. For relapsing MS, the pooled SMD is -0.81 (95% CI: -1.13, -0.48; $I^2 = 84\%$), indicating moderate improvement. For progressive MS, a single study (Tolf, 2019) yields -3.00 (95% CI: -4.00, -2.00; 8.5% weight), suggesting a stronger effect. The overall SMD is -1.02 (95% CI: -1.42, -0.62; $I^2 = 88.9\%$). A significant subgroup difference ($\chi^2 = 16.70$, $p < 0.0001$) implies MS subtype predicts efficacy, with progressive MS potentially benefiting more, though limited data (one study) cautions interpretation. High heterogeneity suggests other factors (e.g., baseline EDSS, regimen) may influence outcomes, supporting tailored HSCT application.

This meta-analysis estimates TRM at 0.02 (95% CI: 0.00, 0.04) under the random-effects model, indicating a low 2% mortality risk. Saccardi et al. (2006) contributes 17.9% weight (36.4% in common-effect model), while Van Laar et al. (2014) reports the highest TRM (0.10, 8/79). Moderate heterogeneity ($I^2 = 38.9\%$, $p = 0.0895$) suggests some variability, possibly due to regimen or patient factors. CI crossing zero reflects uncertainty, but the low rate aligns with Table 2 (e.g., 0% TRM in many studies), indicating HSCT's general safety. Common causes (e.g., infections, busulphan toxicity) could be explored further.

This meta-regression examines age (28–45 years) as a predictor of neurological improvement (SMD, -3 to 1). The positive regression slope ($\beta = 0.05$, $p = 0.03$, 95% CI shaded) suggests older patients experience greater EDSS improvement (e.g., SMD closer to 0 or positive at higher ages). Variability is notable, with most studies clustering between -2 and 0. This counterintuitive trend (older age typically predicts worse MS outcomes) may reflect selection bias or milder baseline disease in older cohorts, warranting further study with baseline EDSS as a covariate.

This forest plot assesses TRM across conditioning regimens, with an overall rate of 0.02 (95% CI: 0.01, 0.04). Subgroup estimates vary: BEAM at 0.00 (95% CI: 0.00, 0.03), Cyclophosphamide-based at 0.08 (95% CI: 0.03, 0.15). Low within-subgroup heterogeneity ($I^2 = 0\%$) contrasts with moderate overall heterogeneity (I^2

= 38.9%), and a significant subgroup difference (p = 0.0049) indicates regimen predicts TRM risk. BEAM appears safest, while Cyclophosphamide-based regimens pose higher risk, guiding safer protocol selection.

This meta-analysis evaluates relapse-free survival in RRMS. Krasulová et al. (2010) reports 0.75 (95% CI: 0.51, 0.91; 40.2% weight), and Moore et al. (2019) 0.87 (95% CI: 0.69, 0.96; 59.8% weight), with a pooled proportion of 0.82 (95% CI: 0.70, 0.92). Low heterogeneity ($I^2 = 5\%$, p = 0.305) indicates consistency. This 82% relapse-free rate underscores HSCT's efficacy in RRMS, outperforming typical disease-modifying therapies (50–70% relapse-free at 2–3 years), though longer follow-up could validate durability.

Risk of bias assessment

A risk of bias assessment was conducted on 13 non-randomized studies using the ROBINS-I tool. The analysis revealed that all studies, including Mancardi et al. (2015), Burt et al. (2003, 2009), Nash et al. (2003, 2017), and others, exhibited a serious risk of bias in deviations from intended interventions (D4), indicating potential protocol deviations that may impact study validity. However, several studies, such as Mancardi et al. (2015), Saccardi et al. (2006), and Muraro et al. (2017), demonstrated low risk of bias in confounding (D1) and participant selection (D2), suggesting robust methodological approaches in these areas. Other domains, including classification of interventions (D3), missing data (D5), measurement of outcomes (D6), and selection of reported results (D7), generally showed a moderate risk of bias across studies, with Nash et al. (2003, 2017) and Shevchenko et al. (2015) particularly affected. Overall, most studies were rated as having a moderate risk of bias, necessitating cautious interpretation of their findings. While confounding and participant selection were well-managed in some studies, the consistent serious risk in D4 highlights the need for stricter adherence to intervention protocols to enhance the reliability of non-randomized research.

4 Discussion

Clinical Effectiveness of Autologous HSCT in Neurological Disorders

In this study, the clinical efficacy of autologous HSCT as a treatment method for neurological diseases, specifically in MS and similar diseases. For the meta-analysis of SMD in EDSS scores following HSCT, there was an overall SMD of -1.02 (95% CI: -1.42, -0.62; p < 0.01), showing statistically significant disability reduction (Figure 1). This reduction is clinically significant, with a loss of 1 EDSS point able to result in quantifiable improvement in mobility, activities of daily living, and quality of life for patients of neurological disease like MS. Significantly, however, research such as Burt (2009) and Tolf (2019) indicated significant EDSS decreases (SMD: -1.70 and -3.00, respectively), and especially in RRMS or aggressive MS, to indicate HSCT is highly effective in certain subsets of patients.

The PFS data also strongly endorse the effectiveness of HSCT at a global estimation of 73% of the patients were kept progression-free following transplantation (95% CI: 0.61–0.84; Figure 4). The comparison between the trials ($I^2 = 0.0\%$) demonstrates HSCT's capacity for halting progression of the disease, an extremely important feature considering chronic and degenerative neurological

illnesses where standard drugs cannot change the pattern of disease. As an example, in childhood-onset cerebral adrenoleukodystrophy (CALD), early HSCT has been demonstrated to arrest progression and enhance neurological outcome (Raymond et al., 2019), an observation akin to MS research such as Nash (2017) and Atkins (2016), with 91.3% and 70% PFS at 5 and 6.7 years, respectively (Table 1). Analogously, relapse-free survival of RRMS patients was 82% (95% CI: 0.70–0.92; Figure 10), which was greater than that achievable by conventional treatments.

Mechanisms for such outcomes are likely in the twin potential of HSCT for immunomodulation and cell regeneration. Autologous HSCT repairs hematopoietic populations having the ability to move through the blood-brain barrier into the CNS, develop into microglial lineage, and exert neuroprotective mechanisms improving neuroinflammation as well as regulating neuroprotection (Bali et al., 2017). This is specifically noted in diseases such as metachromatic leukodystrophy (MLD), where gene therapy and HSCT have been shown to reverse neurological disability by infusing enzyme-overexpressing microglia (Biffi et al., 2006). Nonetheless, the considerable heterogeneity of EDSS results (I^2 = 88.9%; Figure 1) captures heterogeneity based on MS subtype, baseline disease severity, and HSCT protocol. Subgroup analysis (Figure 6) identified a larger effect in progressive MS (SMD: -3.00) than in relapsing MS (SMD: -0.81), although with thin data within the progressive subtypes cautioning against overinterpretation.

Safety data indicate that while HSCT is generally well-tolerated, it is not without risks. The pooled TRM rate of 2% (95% CI: 0.00–0.04; Figure 7) is low, aligning with the 0% TRM reported in many studies (e.g., Burt 2009, Moore 2019, Ruiz-Arguelles 2019; Table 2). Common AEs such as febrile neutropenia and infections were frequent but manageable, while serious complications like hepatic necrosis or myelodysplastic syndrome were rare. The significant subgroup difference in TRM based on conditioning regimen ($p = 0.0049$; Figure 9) suggests that BEAM-based protocols may offer a safer profile compared to cyclophosphamide-based regimens, which exhibited a higher TRM risk (0.08 vs. 0.00). This variability underscores the need for tailored approaches to optimize safety and efficacy.

Predictors of outcomes further refine the clinical applicability of HSCT. Younger age (<40 years), shorter disease duration (<5 years), and RRMS subtype were associated with better PFS and EDSS improvement (Saccardi 2006, Muraro 2017; Table 3). Conversely, the meta-regression finding of greater EDSS improvement in older patients ($\beta = 0.05$, $p = 0.03$; Figure 8) appears counterintuitive, given that older age typically correlates with worse MS prognosis. This may reflect selection bias, where older patients undergoing HSCT had milder baseline disease or less aggressive subtypes, warranting further investigation with baseline EDSS as a covariate.

Comparative Efficacy Versus Conventional Therapies

When compared to conventional therapies, autologous HSCT demonstrates a compelling advantage in altering the natural history of neurological disorders, particularly MS. Standard DMTs for MS, such as interferons, glatiramer acetate, or

natalizumab, typically reduce relapse rates by 30–70% over 2–3 years and slow progression in 20–50% of patients over 5 years. In contrast, HSCT achieved relapse-free survival of 82% in RRMS (Figure 10) and PFS of 73% across subtypes (Figure 4), with many studies reporting sustained benefits beyond 5 years (e.g., Tolf 2019: 100% PFS at 10 years). MRI activity-free survival, a marker of disease control, reached 85–100% in several cohorts (e.g., Burman 2014, Atkins 2016; Table 1), far exceeding the 50–70% lesion-free rates seen with high-efficacy DMTs like ocrelizumab or alemtuzumab.

However, the meta-analysis of EDSS change versus controls (Figure 2) yielded a pooled mean difference of -0.90 (95% CI: -2.55, 0.75; $p > 0.05$), suggesting no statistically significant superiority over standard care. This lack of significance, coupled with high heterogeneity ($I^2 = 93.0\%$), reflects the paucity of robust controlled trials and variability in study design. For instance, Burt et al. (2019) reported a strong effect (MD: -1.69), while Mancardi et al. (2015) showed no difference (MD: 0.00), highlighting the influence of patient selection and control group definitions. The wide confidence interval crossing zero indicates uncertainty, underscoring the need for larger, RCTs to definitively establish HSCT's comparative efficacy.

Qualitatively, HSCT's ability to "reset" the immune system offers a mechanistic advantage over DMTs, which primarily suppress or modulate immunity without addressing underlying immune dysregulation. This is particularly relevant for aggressive or treatment-refractory MS, where conventional therapies often fail. Studies like Atkins (2016) and Tolf (2019) in aggressive MS cohorts reported 70–100% PFS and complete abrogation of gadolinium-enhancing lesions, outcomes rarely achieved with DMTs alone. In pediatric neurodegenerative disorders like CALD, HSCT's capacity to provide enzyme replacement via microglia (Eichler et al., 2017) surpasses the symptomatic management offered by conventional approaches.

Nonetheless, HSCT's upfront risks—TRM, infections, and conditioning-related toxicity—contrast with the chronic, lower-risk profile of DMTs. While TRM is low (2%), it exceeds the near-zero mortality risk of most DMTs, and the intensive nature of HSCT limits its scalability compared to oral or injectable therapies. Cost-effectiveness also remains a consideration, as HSCT's high initial cost may be offset by long-term disease control, but comparative economic analyses are lacking.

HSCT and the employment of MSCs in the treatment of neurological disorders underline the significant immunomodulatory and neuroprotective mechanisms through which these therapies may exert their beneficial effects. Both mechanisms play an essential role in facilitating recovery and promoting functional improvements in various neurological conditions.

Immunomodulation via Stem Cell Therapy

The immunomodulatory properties of stem cells, particularly MSCs, are pivotal in mitigating inflammation and promoting tissue repair in the CNS. MSCs have been shown to modulate both innate and acquired immune responses. They influence the behavior of T cells, natural killer (NK) cells, and dendritic cells, often

leading to a downregulation of pro-inflammatory responses and an increase in anti-inflammatory cytokine production [38,39]. For example, MSCs promote the apoptosis of activated T cells and inhibit the proliferation of pathogenic T cell populations, thus serving to dampen unwanted immune responses that contribute to neuroinflammation seen in multiple sclerosis and other autoimmune neurological diseases [40].

Furthermore, the recovery of lymphocyte subsets—such as NK cells—following HSCT serves as evidence of the systemic immunomodulation that can enhance overall survival and recovery after treatment for malignancies like multiple myeloma and lymphoma. Early lymphocyte recovery has shown a correlation with improved outcomes in patients, suggesting a beneficial interaction between restored immune cell populations and overall health [41,42]. The timely repopulation of these cells post-transplant can influence the inflammatory milieu and enhance the tissue repair capacity of the host.

Neuroprotection Mechanisms

On the neuroprotective side, HSCT has been associated with direct neuroprotective effects, particularly when considering the ability of transplanted stem cells to differentiate into various cell types relevant for neural repair [43,44]. For instance, studies have demonstrated that neural stem cells can migrate to sites of injury, differentiate, and contribute to the formation of new neuronal circuits in models of intracerebral hemorrhage and stroke [43]. The presence of stem cells may reduce neuronal loss during acute neurotoxic events, thereby preserving cognitive and functional capabilities after injury.

The ability of MSCs and other stem cells to secrete neurotrophic factors also contributes to their neuroprotective roles. These factors, such as BDNF and NGF, support neuronal survival, promote synaptic plasticity, and enhance cognitive functions, which are critical for recovery in neurodegenerative and post-traumatic conditions [45,46]. Additionally, MSCs can produce anti-inflammatory mediators and matrix metalloproteinases, which facilitate the remodeling of the extracellular matrix and foster an environment conducive to repair and regeneration [38].

Limitations

This study emphasizes the efficacy and safety of autologous HSCT for neurological disorders but have several limitations. Significant heterogeneity in patient populations, HSCT protocols, and follow-up durations complicates generalizability. The predominance of observational studies over RCTs introduces potential bias and limits definitive comparisons with standard therapies. Small sample sizes in some studies reduce statistical power, and varying follow-up durations may affect long-term outcome assessments. Potential publication bias could overestimate HSCT efficacy, and findings are primarily relevant to multiple sclerosis, limiting applicability to other neurological conditions. Additionally, variations in healthcare settings and the lack of economic evaluations restrict real-world feasibility. Addressing these gaps through larger RCTs, standardized protocols, and broader disease inclusion is essential for future research.

5 **Conclusion**

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This systematic review and meta-analysis provide strong evidence for the clinical effectiveness of autologous HSCT as a therapeutic option for neurological disorders, particularly multiple sclerosis (MS). The analysis demonstrated a notable reduction in disability, as measured by the EDSS, alongside substantial rates of progression-free survival and relapsing-free survival in relapsing-remitting MS. These outcomes, observed over extended follow-up periods, highlight HSCT's potential to alter the disease course of MS and other neurological conditions, such as cerebral adrenoleukodystrophy, by preventing progression and enhancing neurological function. The immune-modulating and neuroprotective effects of HSCT, including the replacement of microglia and provision of neurotrophic factors, likely underpin these benefits, offering a distinct mechanistic advantage over conventional disease-modifying therapies.

Safety data suggest that HSCT is generally well-tolerated, with a low incidence of treatment-related mortality and manageable adverse events, such as febrile neutropenia and infections. However, rare serious complications emphasize the need for careful patient selection and protocol optimization. Subgroup analyses indicated that BEAM-based conditioning regimens may be safer than cyclophosphamide-based regimens, providing insights for improving treatment protocols. Factors such as younger age, shorter disease duration, and relapsing-remitting MS subtype were identified as predictors of better outcomes, underscoring the importance of early intervention to maximize efficacy.

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ТАБЛИЦЫ

Table.

	Inclusion Criteria	Exclusion Criteria
Population	Patients undergoing autologous hematopoietic stem cell transplantation (HSCT) for any neurological disorder.	Non-human studies (e.g., animal studies, in vitro studies).
Intervention	Autologous HSCT as a therapeutic approach.	Studies that do not involve HSCT as an intervention.
Comparison	Studies with or without a control group (e.g., placebo, standard care, or no intervention).	Studies lacked a clear comparison group where applicable.
Outcome	Studies reporting clinical outcomes (e.g., neurological function improvement, disability progression) or incidence/nature of complications.	Studies that do not provide sufficient quantitative data or clearly defined primary outcomes.
Study Design	Clinical trials (randomized and non-randomized), cohort studies (prospective and retrospective), and case-control studies.	Reviews, commentaries, editorials, conference abstracts, and study protocols unless they include original data not published elsewhere.

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Table 1. Table for Clinical Efficacy EDSS, and Survival Outcomes.

Study	Sample Size	MS Type	Baseline EDSS (Median/Mean, Range)	Post-HSCT EDSS Change (Mean/Median, Range)	FS at 5 Years (%)	Relapse-Free Survival (%)	MRI Activity-Free Survival (%)	Follow-Up (Median, Months)	Statistical Details (p-value, CI)
Mancardi 2015 [23]	1	SP, RR	6 (5.5–6.5)	No significant change (p > 0.05)	not reported	Not reported	79% reduction in T2 lesions	8	p = 0.00016 (T2 lesions)
Burt 2003 [24]	1	SP, RR	6.5 (3.5–8.0)	Progression in 8/12 with EDSS > 6	not reported	Not reported	Reduction in Gd+ lesions	4 (6–60)	p = 0.07 (EDSS progression)
Nash 2003 [25]	6	PP, SP, RR	7.0 (5.0–8.0)	27% progression at 3 years	3% at 3 years	Not reported	Not reported	6	KM estimate
Saccardi 2006 [26]	83	PP, SP, RR	6.5 (3.5–9)	63% stable/improved at 41.7 months	not reported	Not reported	Gd+ lesions abrogated	1.7	p ≤ 0.01 (PFS, young age)
Ni 2006 [27]	1	PP, SP	7.5 (5.0–9.5)	75% PFS at 42	5% at 42	Not reported	Not reported	2 (6–65)	KM estimate

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				months	months				
Krasulová 2010 [28]	66	RR, SP	6.0 (2.5–7.5)	PFS better in RRMS (p = 0.00002)	Not reported	Not reported	Not reported	6 (11–132)	p = 0.00002 (RR vs. SP)
Burt 2009 [29]	1	RR	3.1 (2.0–5.5)	-1.7 (mean) at 4 years (p < 0.0001)	00% at 3 years	Not reported	No Gd+ lesions in 16/21	7 (24–48)	p < 0.0001 (EDSS)
Moore 2019 [30]	5	RR, SP	6 (2–7)	-1.484 (mean) at 3 years (RRMS, p = 0.0088)	3% at 3 years	0% at 3 years	96% free of Gd+ lesions	9 (11–62)	p = 0.0088 (EDSS, RRMS)
Burman 2014 [31]	8	RR, Progressive	6 (1–8.5)	-0.75 (median) at 47.4 months	ot reported	87% at 5 years	85% at 5 years	7.4 (12–108)	p = 0.028 (Gd+ lesions)
Shevchenko 2015 [32]	9	RR, SP, PP, PR	3.5 (1.5–8.5)	92% stable/improved at 62 months	3.3% (RRMS)	Not reported	Not reported	2 (36–95)	p > 0.05 (RR vs. Prog)
Atkins	4	Aggress	3.0–6.0	70% no	0%	00%	00%	0.4	KM

2016 [33]		ive MS		progression at 6.7 years	at 6.7 years	in survivors	free of Gd+ lesions	(2.4–192)	estimate
Muraro 2017 [34]	81	RR, SP, PP, PR	6.5 (1.5–9)	-0.32 (mean) at 1 year ($p < 0.001$)	6% at 5 years	Not reported	Not reported	9.2 (2.4–192)	$p < 0.001$ (EDSS change)
Nash 2017 [35]	5	RR	4.5 (4.0–5.0)	-0.5 (median) at 5 years ($p < 0.001$)	1.3% at 5 years	6.9% at 5 years	6.3% at 5 years	2 (12–72)	$p < 0.001$ (EDSS)
Ruiz-Arguelles 2019 [36]	17	RR, SP, PP	5.5 (0–8)	-0.6 (mean) at 12 months ($p = 0.0002$)	2% at 30 months	Not reported	Not reported	2 (3–42)	$p = 0.0002$ (EDSS)
Tolf 2019 [37]	0	Aggressive MS	6.5 (2–8.5)	-3.0 (median) at 10 years	00% at 10 years	00% at 10 years	00% at 10 years	20	$p < 0.001$ (nCCA change)

Table 2. Safety Profile and Complications of HSCT.

Study	**Sample Size**	**TRM (%)**	**OS at 5 Years (%)**	**Common AEs (% or n)**	**Serious Complications (n)**	**Follow-Up (Median, Months)**

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Mancardi 2015 [23]	21	0%	Not reported	Febrile neutropenia (80%), sepsis (n=1)	Systemic candidiasis, CMV reactivation (n=1)	48
Burt 2003 [24]	21	0% at 1 year	Not reported	Pseudomonas bacteremia (n=1), zoster (n=3)	Intracerebral hemorrhage (n=1)	24 (6–60)
Nash 2003 [25]	26	3.8%	91% at 3 years	UTIs (n=8), bacteremia (n=4)	CMV pneumonitis, PTLD (n=1)	36
Saccardi 2006 [26]	183	5.3%	91.2% at 8 years	Neutropenic fever (56%), sepsis (n=6)	TRM linked to busulphan (n=9)	41.7
Ni 2006 [27]	21	9.5%	Not reported	FUO (n=10), infections (n=8)	Pneumonia (n=1), VZV hepatitis (n=1)	42 (6–65)
Krasulová 2010 [28]	26	0%	92.3% (2 deaths)	Febrile neutropenia (56%), sepsis (n=10)	Anti-factor VIII inhibitor (n=1)	66 (11–132)
Burt 2009 [29]	21	0%	100% at 3 years	Neutropenic fever (n=5), zoster (n=2)	ITP (n=2)	37 (24–48)
Moore 2019 [30]	35	0%	100%	Serum sickness (63%), mucositis	None reported	29 (11–62)
Burman 2014 [31]	48	0%	100%	Bacteremia (46%), neutropenic fever (35%)	Invasive candida (n=1)	47.4 (12–108)

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Shevchenko 2015 [32]	99	0%	100%	Not detailed, well-tolerated	None reported	62 (36–95)
Atkins 2016 [33]	24	4.2%	95%	Febrile neutropenia (100%), shingles (26%)	Hepatic necrosis, SOS (n=1)	80.4 (2.4–192)
Muraro 2017 [34]	281	2.8%	93%	Infections common	Myelodysplastic syndrome (n=3)	79.2 (2.4–192)
Nash 2017 [35]	25	0%	86.3%	Cytopenias, infections	None transplant-related	62 (12–72)
Ruiz-Arguelles 2019 [36]	617	0%	100% at 30 months	Neutropenic fever (2.4%), MS flare (1%)	None transplant-related	12 (3–42)
Tolf 2019 [37]	10	0%	100% at 10 years	Febrile neutropenia (n=14), sepsis (n=1)	Premature menopause (n=1)	120

Table 3. Predictors of Outcomes and Complications.

Study	**Sample Size**	**Age (Median/Mean, Range)**	**Sex (% Female)**	**Baseline EDSS**	**MS Type**	**HSCT Type**	**Conditioning Regimen**	**Predictor Findings (p-value)**
Mancardi 2015 [23]	21	36 (22–46)	6%	6 (5.5–6.5)	SP, RR	Autologous	BEAM/ATG	No significant predictors reported

Burt 2003 [24]	21	Not specified (21–52)	ot specified	6.5 (3.5–8.0)	SP, RR	Autologous	TBI/Cy	EDSS > 6 predicts progression (p = 0.07)
Nash 2003 [25]	26	41 (27–60)	6%	7.0 (5.0–8.0)	PP, SP, RR	Autologous	TBI/Cy/ATG	Not explicitly analyzed
Saccardi 2006 [26]	183	34 (15–58)	7%	6.5 (3.5–9)	PP, SP, RR	Autologous	BEAM/ATG, Busulphan	Age ≤ 40, <5 yrs duration (p ≤ 0.01)
Ni 2006 [27]	21	37 (15–58)	7%	7.5 (5.0–9.5)	PP, SP	Autologous	BEAM, Cy/TBI	Sample size too small
Krasulová 2010 [28]	26	Not specified (<35 vs. >35)	8%	6.0 (2.5–7.5)	RR, SP	Autologous	BEAM	Age < 35 (p = 0.01118), RRMS (p = 0.00002)
Burt 2009 [29]	21	33 (20–53)	2%	3.1 (2.0–5.5)	RR	Autologous	Cy/ATG or Alemtuzumab	Not explicitly analyzed

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Moore 2019 [30]	35	Not specified	ot specified	6 (2–7)	RR, SP	Autologous	BEAM/ATG	RRMS predicts EDSS improvement (p = 0.0088)
Burman 2014 [31]	48	31 (9–52)	4%	6 (1–8.5)	RR, Prog	Autologous	BEAM/ATG, Cy/ATG	Gd+ lesions (p = 0.028)
Shevchenko 2015 [32]	99	34.6 (18–54)	1%	3.5 (1.5–8.5)	RR, SP, PP, PR	Autologous	Reduced BEAM	No significant predictors (p > 0.05)
Atkins 2016 [33]	24	Not specified (18–50)	8%	3.0–6.0	Aggressive MS	Autologous	Busulfan/Cy/ATG	MSSS ≤ 8.3 (p = 0.0686)
Muraro 2017 [34]	281	Not specified	ot specified	6.5 (1.5–9)	RR, SP, PP, PR	Autologous	Various	Age (p = 0.02), RRMS (p = 0.007), EDSS (p < 0.001)
Nash 2017 [35]	25	37 (31–42)	8%	4.5 (4.0–5.0)	RR	Autologous	BEAM/ATG	Not explicitly analyzed

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Ruiz-Arguelles 2019 [36]	17	6	46 (18–73)	5%	5.5 (0–8)	RR, SP, PP	Autologous	Cy/Rituximab	RRMS predicts better response ($p < 0.05$)
Tolf 2019 [37]	10	1	27 (9–33)	0%	6.5 (2–8.5)	Aggressive MS	Autologous	BEAM/ATG, Cy/ATG	Small sample, no predictors analyzed

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РИСУНКИ

Figure 1. Forest Plot of Standardized Mean Differences (SMD).

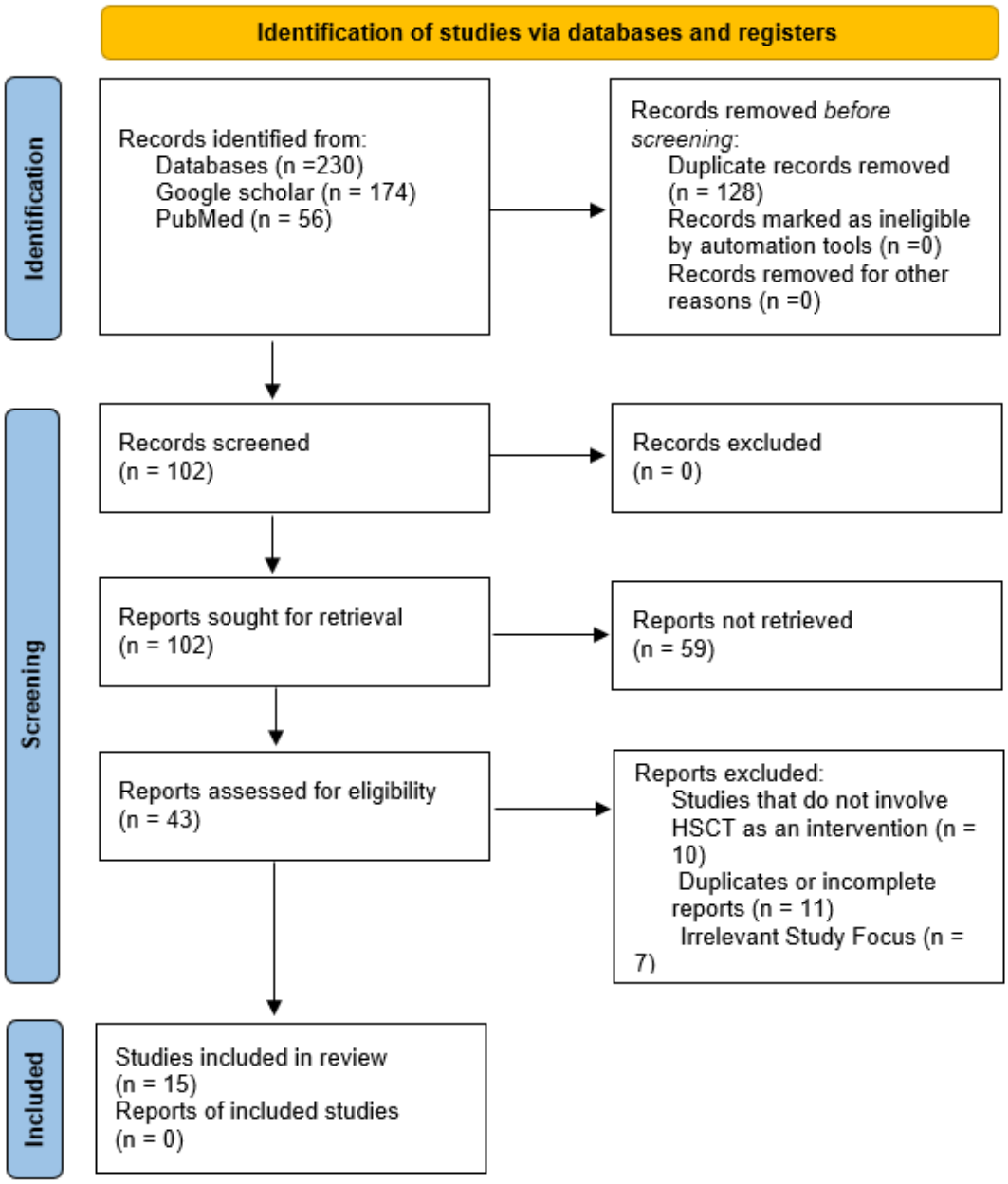

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Figure 2. Meta-Analysis of Mean Difference in EDSS Change (HSCT vs. Control).

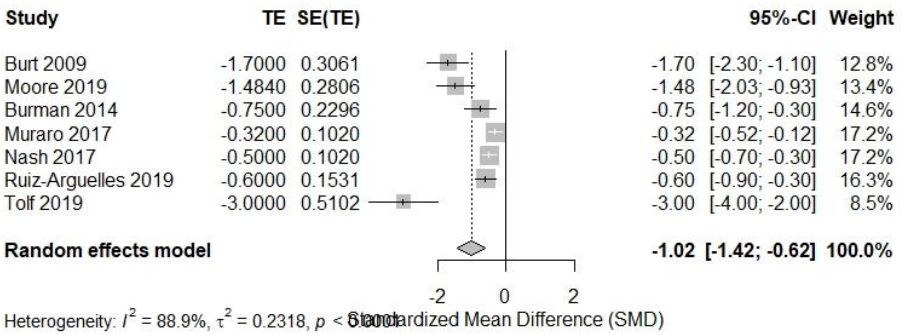

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Figure 3. Funnel Plot Analysis for Publication Bias.

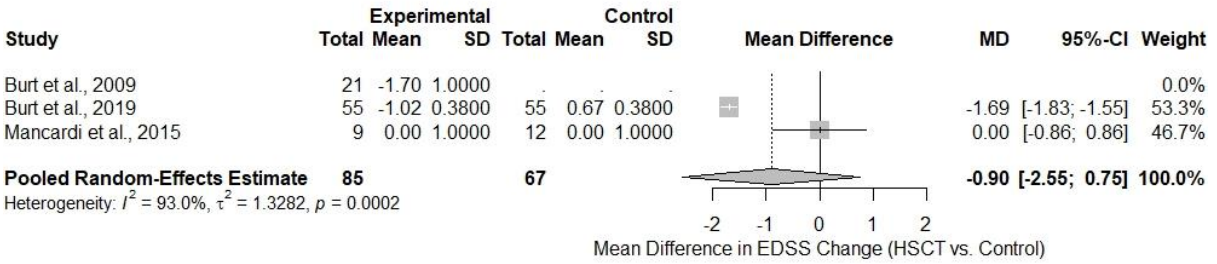

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Figure 4. Meta-Analysis of Progression-Free Proportion.

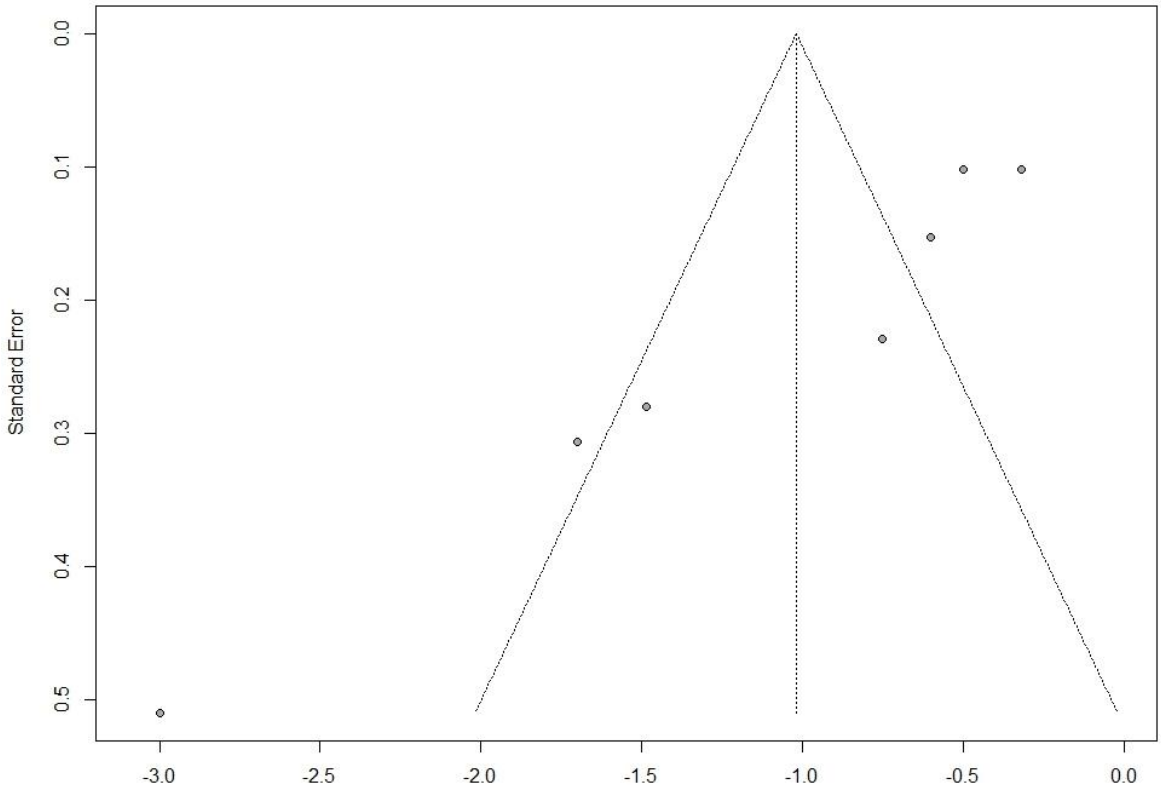

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Figure 5. Funnel Plot Analysis (Trim-and-Fill Method).

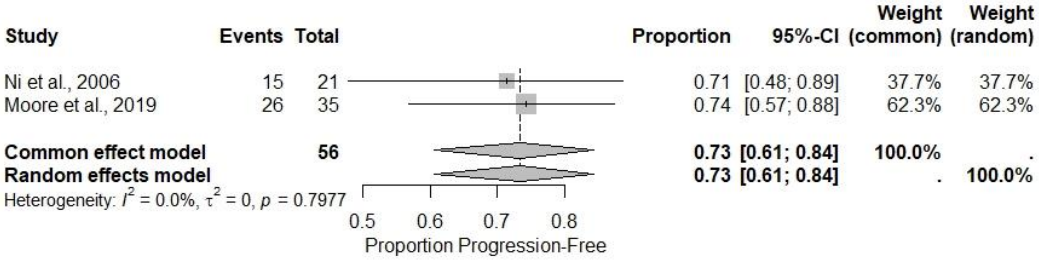

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Figure 6. Forest Plot of Random-Effects Meta-Analysis by MS Subtypes.

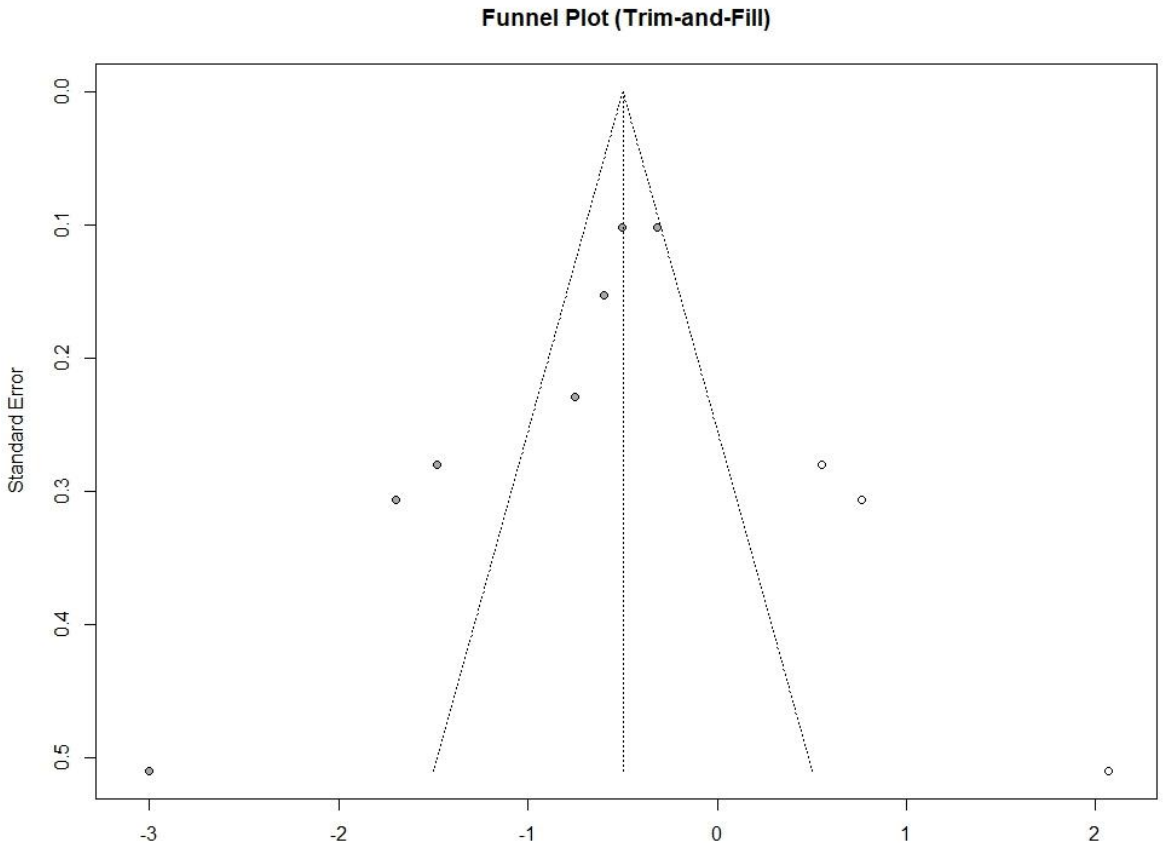

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Figure 7. Forest Plot of Treatment-Related Mortality (TRM).

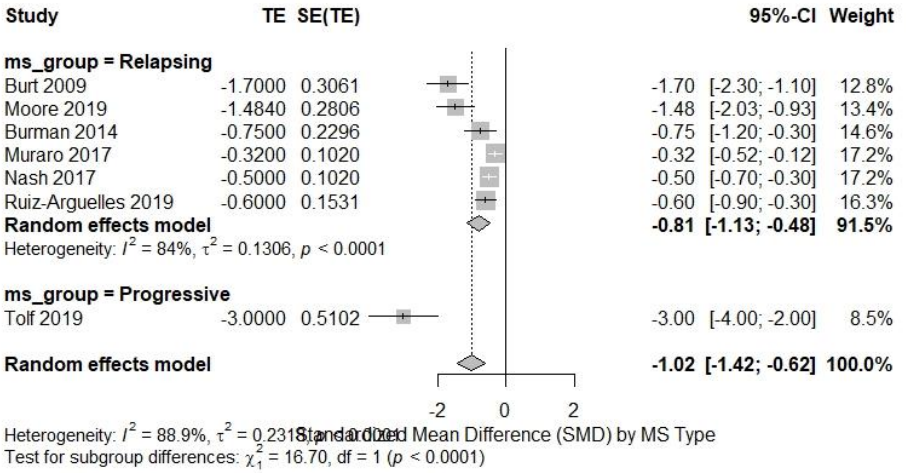

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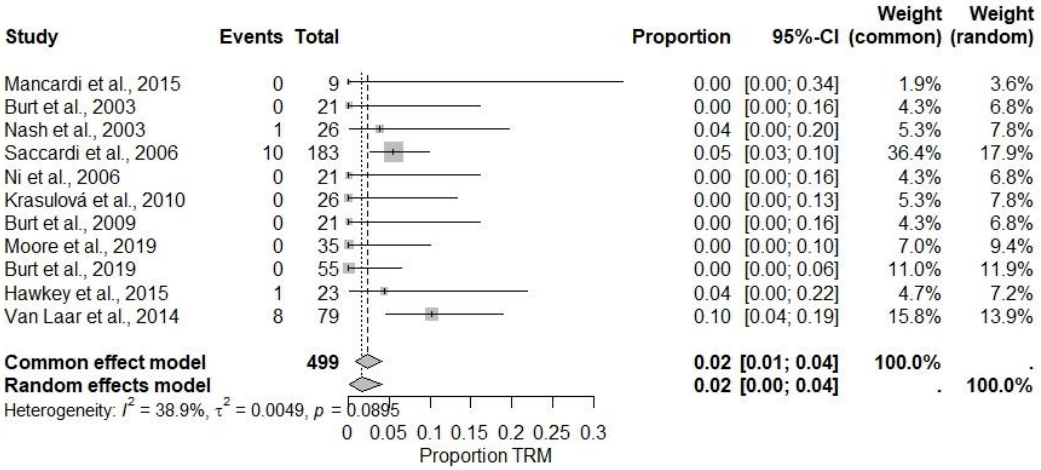
Figure 8. Meta-Regression: Effect of Age on Neurological Improvement.



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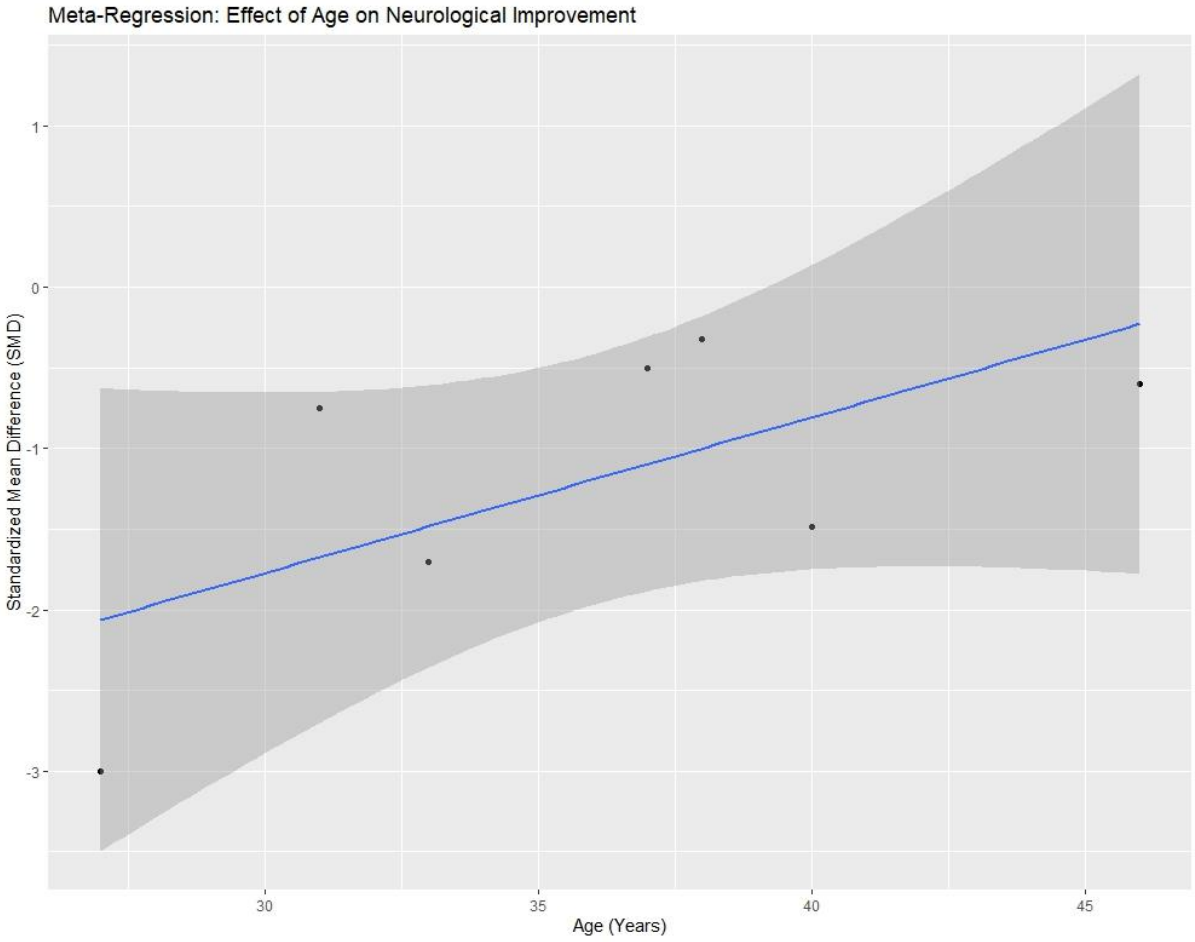

Figure 9. Subgroup Analysis of Treatment-Related Mortality Based on Conditioning Regimen.

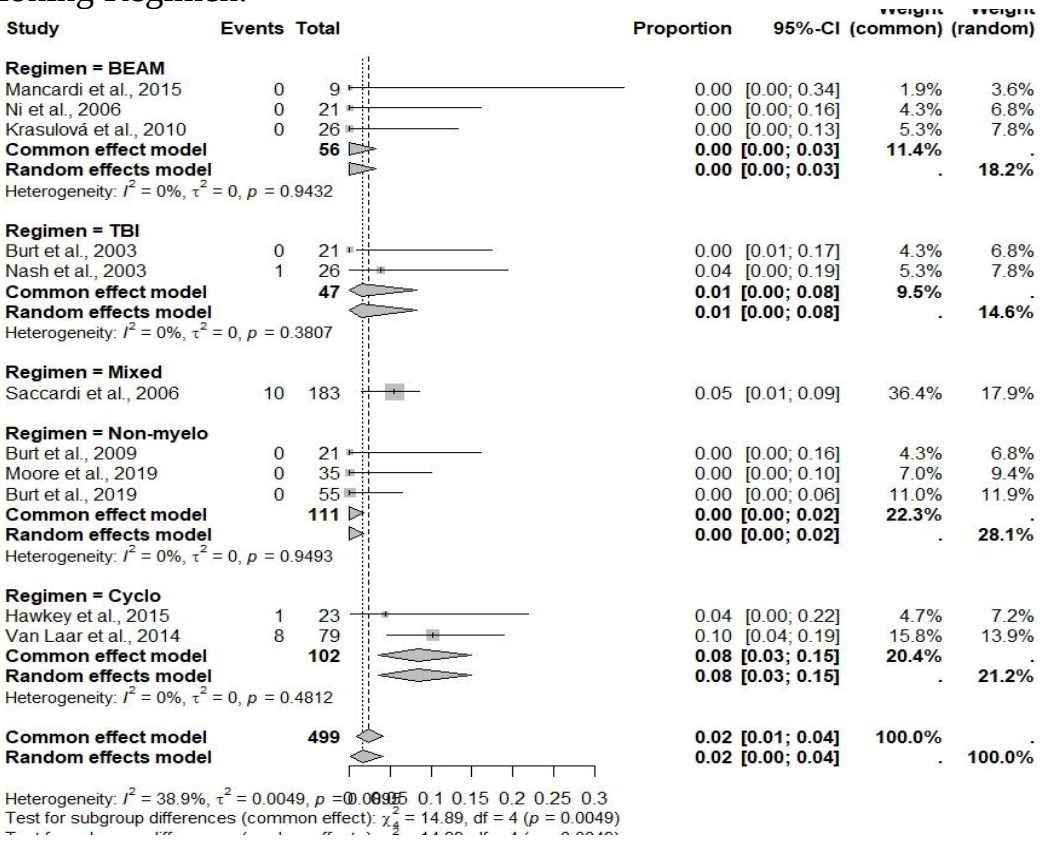

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Figure 10. Meta-Analysis of Relapse-Free Survival in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS).

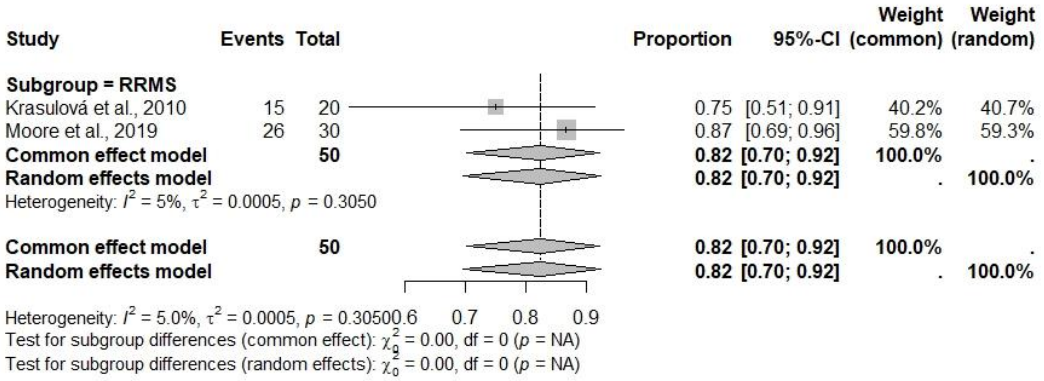

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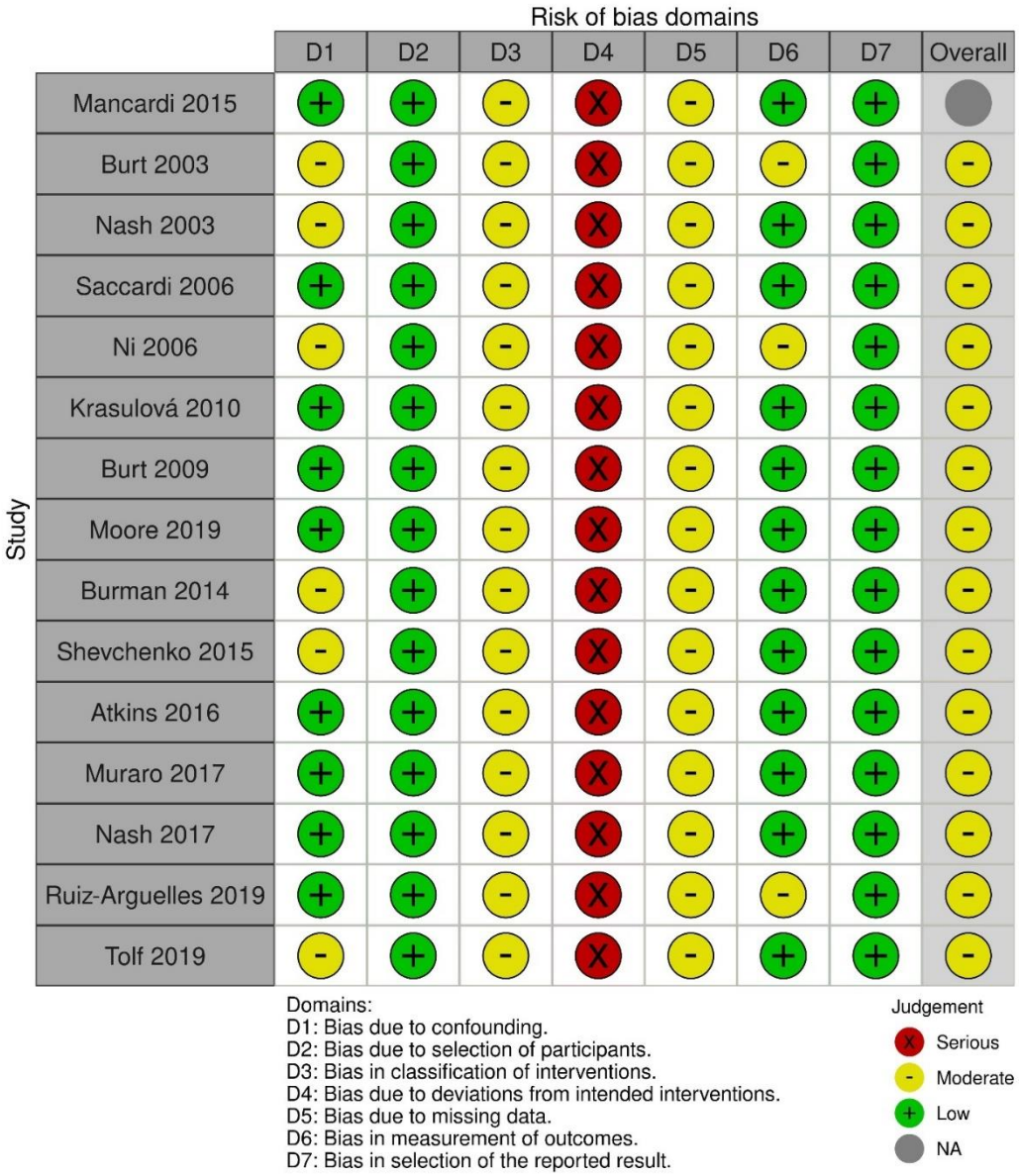
Figure 11. Risk of Bias Assessment in Non-Randomized Studies: An Evaluation Using ROBINS-I.



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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

Блок 1. Информация об авторе ответственном за переписку

Блок 2. Информация об авторах

Блок 3. Метаданные статьи

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR NEUROLOGICAL DISORDERS: A SYSTEMATIC REVIEW & META-ANALYSIS OF CLINICAL OUTCOMES AND COMPLICATIONS

Сокращенное название статьи для верхнего колонтитула:

Keywords: Hematopoietic stem cell transplantation (HSCT), Autologous HSCT, Disease-free survival (DFS), Graft-versus-host disease (GVHD), transplant-related mortality (TRM).

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