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Autologous haematopoietic stem cell transplantation in patients with multiple sclerosis: Experience from South Africa

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Background. Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease that remains a major cause of neurological disability in young adults. While disease-modifying therapies (DMTs) can delay progression, many patients with highly active relapsing-remitting MS (RRMS) continue to experience breakthrough disease. Autologous haematopoietic stem cell transplantation (ASCT) offers durable immune reconstitution and remission but remains underutilised in upper-middle-income settings such as South Africa (SA).
Objective. To evaluate the safety, feasibility and clinical outcomes of ASCT for MS in a real-world SA cohort.
Methods. We conducted a retrospective record review of all MS patients who underwent ASCT between 1 January 2009 and 31 December 2024 at two JACIE-accredited tertiary centres (Wits Donald Gordon Medical Centre and Netcare Pretoria East Hospital). Data were extracted from institutional transplant records and analysed using descriptive statistics and Kaplan-Meier survival estimates. The primary outcome was the safety of ASCT for MS, and the secondary outcomes were the clinical outcomes of patients who underwent ASCT for MS.
Results. Thirty-two patients were included (median age 42 years; 53% female; 94% RRMS). Median disease duration prior to ASCT was 7.4 years, and 97% had received prior DMTs. Conditioning included cyclophosphamide (97%), anti-thymocyte globulin (69%) and fludarabine (34%). The median neutrophil and platelet engraftment occurred at 10 and 14 days, respectively. Relapse-free survival was 100% at 1 year and 91% (95% confidence interval 68 - 98) at 5 years. Approximately 90% of evaluable patients demonstrated neurological improvement or stabilisation at 1 year. Treatment-related adverse events occurred in 63% of cases, and 95% of these side-effects were grade 3 or less: most commonly neutropenic fever (50%) and mucositis (16%). Only 5% of adverse reactions were grade 4, with no transplant-related mortality.
Conclusion. ASCT is safe, feasible and highly effective in aggressive, treatment-refractory RRMS in SA. Its earlier use in selected patients may offer durable remission and substantial cost savings compared with long-term DMTs. The expansion of accredited national ASCT programmes and registry-based outcome monitoring is warranted.

Keywords: multiple sclerosis, autologous stem cell transplantation, relapsing-remitting MS, South Africa, disease-modifying therapy, cost-effectiveness, hematopoietic stem cell transplantation

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Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system characterised by inflammation, demyelination, gliosis and neuro-axonal degeneration.[1,2] Although the precise cause remains unclear, it is widely considered autoimmune in nature, initiated by autoreactive T lymphocytes crossing the blood-brain barrier and triggering local inflammatory cascades that lead to progressive neurological dysfunction.[2,3]

In South Africa (SA), epidemiological data on MS remain limited, but the prevalence is estimated to be between 5 and 29 per 100 000 persons, placing the country in a medium-frequency category.[4] MS predominantly affects adults between 20 and 40 years of age, with a female predominance of ~2 - 3 to 1.[5] It represents one of the leading causes of non-traumatic neurological disability in young adults.[6]

Diagnosis is based on the McDonald criteria, which integrate clinical, radiological and laboratory findings.[1] MS manifests as four main phenotypes: clinically isolated syndrome, relapsing-remitting MS (RRMS), primary progressive MS and secondary progressive MS.[7] Approximately 70 - 80% of patients initially present with RRMS, while 15 - 20% exhibit a progressive form from the onset.[8] It is important to note that the aforementioned subtypes are largely artificial and do not account for individual patient disease course.[7]

Treatment is multidisciplinary, encompassing symptomatic care such as analgesia, physiotherapy and occupational therapy together

with emotional and social support. Lifestyle modifications include exercise, diet and smoking cessation. Disease-modifying therapies (DMTs) target the immune system to reduce the frequency and severity of attacks. Finally, there are immune-reconstitution strategies such as autologous haematopoietic stem cell transplantation (ASCT).[9-11]

DMTs are effective in reducing relapse rates and delaying progression, particularly when initiated early in the disease course.[12,13] However, patients with highly active or treatment-refractory MS may continue to experience inflammatory disease activity despite optimal therapy.[14] This has prompted the exploration of ASCT as a means to achieve durable remission by 'resetting' immune tolerance.[15]

ASCT involves the mobilisation of autologous haematopoietic stem cells, lympho-ablative conditioning and reinfusion to reconstitute a naive immune repertoire.[16]

Randomised and observational studies, including the MIST trial,[17] have demonstrated that ASCT significantly reduces disability progression compared with continued DMTs in RRMS, with prolonged relapse-free survival and improved magnetic resonance imaging (MRI) outcomes.[17,18] Updated guidelines from the European Society for Blood and Marrow Transplantation (EBMT) endorse ASCT for patients with aggressive RRMS refractory to standard DMTs.[19]

Recent systematic reviews confirm its efficacy and safety, reporting extremely low transplant-related mortality at ~0.3% in patients who received ASCT for MS after 2005.[18,20,21] It is critical to consider and categorise the adverse events associated with ASCT for MS. The CTCAE (common terminology criteria for adverse events) is a widely accepted tool used to grade adverse events.[22] The criteria comprise 5 grades of adverse events: grade 1 – mild; grade 2 – moderate; grade 3 – severe; grade 4 – life-threatening; and grade 5 – death. A Swedish study on ASCT for RRMS showed that 70% of patients had a grade 3 adverse event, of which febrile neutropenia was the most common at 58%, and only 3% of patients experienced a grade 4 adverse event.[23]

Although ASCT remains underutilised in low- and middle-income settings, economic analyses suggest that it may offer long-term cost-effectiveness compared with ongoing high-efficacy DMTs.[24] This study presents the SA experience of ASCT in MS, evaluating its feasibility, early safety and outcomes in our setting.

Methods

Study design and setting

This was a retrospective record review of patients with MS who underwent ASCT between 1 January 2009 and 31 December 2024. The study was conducted at two private tertiary centres in SA with Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation (JACIE)-accredited transplant programmes: Wits Donald Gordon Cellular and Immunotherapy Centre in Johannesburg, and Netcare Pretoria East Hospital in Pretoria.

Study population

All transplant files at the designated centres were reviewed and all eligible patients who received ASCT for MS during the study period were included. In each case, the diagnosis of MS was made by a neurologist using the applicable version of the McDonald diagnostic criteria at the time of diagnosis. The cohort size was 32 patients.

Data collection

Data were extracted from institutional transplant records and medical files and entered into a REDCap-based data collection tool developed for the study. Each patient was assigned a unique identifier to ensure de-identification. Collected variables included age at ASCT, sex, duration of MS, comorbidities, indications for ASCT, previous disease-modifying treatment (with details), method of stem cell mobilisation (and associated details), stem cell conditioning regimen (and associated details), number of days to neutrophil and platelet recovery, adverse reactions, date of death (all-cause mortality)/date last seen, date of relapse/date last seen and expanded disability status scale (EDSS) at 30 days, 100 days, 1 year and 5 years, with a breakdown of how many patients were seen at each of the defined time intervals post transplant.

Statistical analysis

Descriptive statistics were used to summarise the patient demographics and clinical characteristics. Overall survival (OS) was defined as the time to death from all causes, and relapse-free survival (RFS) as the time to death or relapse/progression, whichever came first. A relapse was defined by a clear neurological decline lasting at least 24 hours and not attributable to an external cause.[23] OS and RFS were estimated using Kaplan-Meier survival curves.

Platelet engraftment was defined as day 1 of a sustained platelet count of $>20 \times 10^9$/L for 3 consecutive days without platelet transfusions in the 7 days prior, and neutrophil engraftment was defined as day 1 of 3 consecutive days of a sustained peripheral blood neutrophil count of $>0.5 \times 10^9$/L.[25] Delayed engraftment was defined as engraftment of platelets and/or neutrophils after day 28, with day 0 defined as the day of transfusion.[25] Cumulative incidence functions were used to estimate engraftment. Data analysis was performed using SAS version 9.4 for Windows (SAS Institute, USA). $P<0.05$ significance level was used.

Ethical considerations

Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (HREC ref. no. M2502116). All data were anonymised and handled in compliance with the institutional and national confidentiality standards.

Results

Thirty-two patients underwent ASCT between 2009 and 2024. The baseline demographics, disease and transplant characteristics are depicted in Table 1. Their median age was 42 years (range 14 - 60), and 53% were female. The median disease duration was 7.4 years. Most patients had RRMS (94%). Corticosteroids were used in 87% of patients and 97% received prior DMTs, namely interferon-β1a (65%), glatiramer acetate (23%), fingolimod (19%) and teriflunomide (16%). Ninety percent had received combinations of DMTs; however, the combinations used were variable and no standard combination therapy was implemented. In all instances, DMTs were stopped post ASCT. Baseline disability before transplantation was substantial (Table 2): the median EDSS was ~6, with 53% (17/32) at EDSS ≥6 and 31% (10/32) at EDSS ≤4, indicating a cohort enriched for advanced functional impairment at the time of AHSCT, as a patient with an EDSS of 6 requires a walking aid to walk 100 m with or without breaks.[26]

Mobilisation, the process whereby stem cells are moved from the bone marrow into peripheral blood using medication,[20] was achieved using granulocyte-colony stimulating factor (G-CSF) + cyclophosphamide in 62% of cases, and G-CSF alone in 38% of cases. Conditioning, the preparative lymphodepleting regimen given prior to receiving stem cells[20] included cyclophosphamide (97%), rabbit anti-thymocyte globulin (ATG) (69%) and fludarabine (34%).

Adverse events occurred in 62% of patients, mainly neutropenic fever (50%), mucositis (16%) and urinary tract infections (13%), while 38% of patients did not experience any adverse reactions.

Table 1. Baseline demographic, disease, and transplant characteristics (*N*=32)

Variable	*n* (%)*
Age, years, median (IQR), range	42 (30 - 49), 14 - 60
Sex	
Male	15 (47)
Female	17 (53)
Duration of MS, years, median (IQR), range	7.4 (2.0 - 11.3), 0.3 - 24.3
Comorbidities	
Hypertension	8 (25)
Thyroid disease	4 (13)
Diabetes mellitus	4 (13)
Depression	4 (13)
Epilepsy	1 (3)
None	11 (34)
Other	5 (16)
Indication for transplant	
RRMS	30 (94)
PPMS	1 (3)
Paediatric MS	1 (3)
Previous DMT	
Yes	31 (97)
Unknown	1 (3)
Previous treatment (*n*=31)	
Corticosteroids	27 (87)
Inteferon beta-1a	20 (65)
Glatiramer acetate	7 (23)
Fingolimod	6 (19)
Teriflunomide	5 (16)
Ocrelizumab	3 (10)
Natalizumab	2 (6)
Mitoxantrone	2 (6)
Methotrexate	2 (6)
Alamtuzumab	2 (6)
Cyclophosphamide	1 (3)
Rituximab	1 (3)
Ozanimod	1 (3)
Inteferon beta-1b	0
Azathioprine	0
Combination of the above	28 (90)
Method of SC mobilisation	
GCSF + CY	20 (62)
GCSF only	12 (38)
SC conditioning regimen	
CY	31 (97)
ATG	22 (69)
FLU	11 (34)
MEL	1 (3)
Post-transplant adverse reactions	
Total	20 (62)
Neutropenic fever (grade 3)	16 (50)
Mucositis (grade 1 - 3)	5 (16)
Urinary tract infection (grade 2 - 3)	4 (13)
Haemorrhagic cystitis (grade 3)	3 (9)
Bacteremia (grade 2)	2 (6)
Pneumonia (grade 2 - 3)	1 (3)
Diarrhoea (grade 2 - 3)	1 (3)
Renal dysfunction – dialysis (grade 4)	1 (3)
Renal failure (grade 4)	1 (3)
Secondary malignancy (grade 3)	1 (3)
No reaction	12 (38)

IQR = interquartile range; MS = multiple sclerosis; RRMS = relapsing-remitting MS; PPMS = primary progressive MS; DMT = disease-modifying therapy; SC = stem cell; GCSF = granulocyte-colony stimulating factor; CY = cyclophosphamide; ATG = anti-thymocyte globulin; FLU = fludarabine; MEL = melphalan.
*Unless otherwise specified.

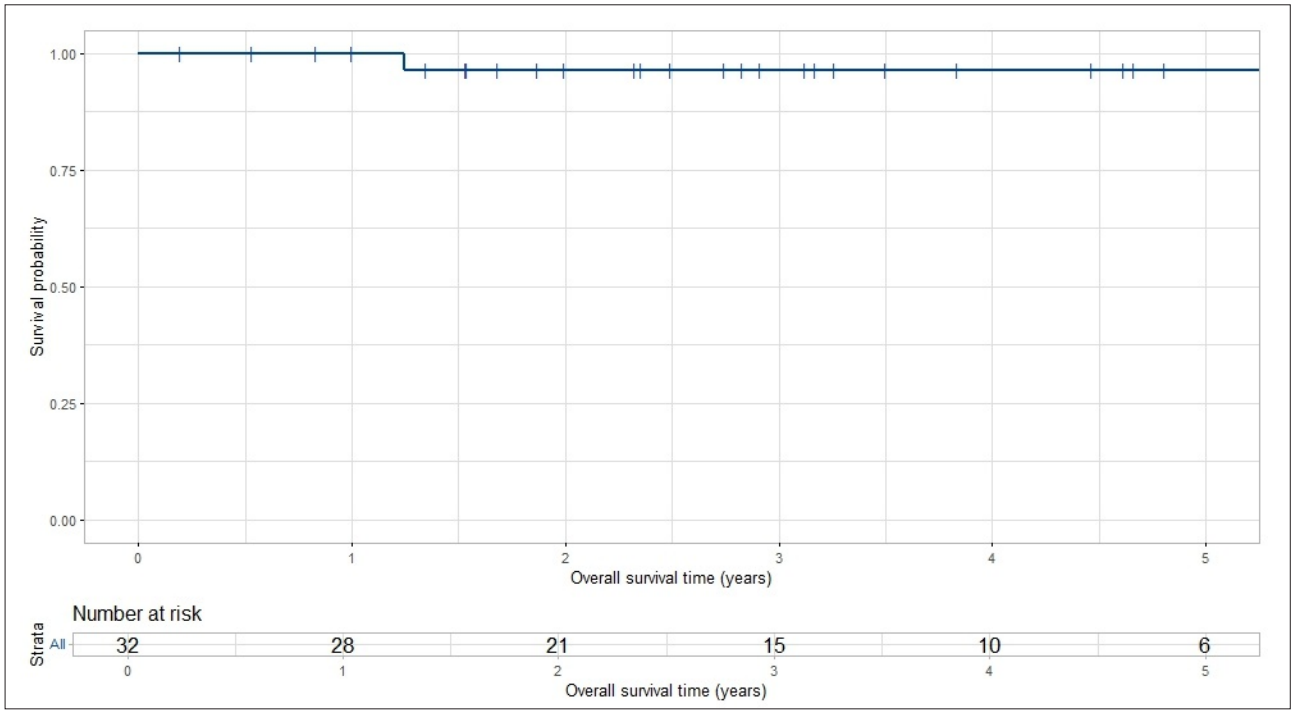


Fig. 1. Overall survival of entire autologous stem cell transplant cohort (N=*32).*

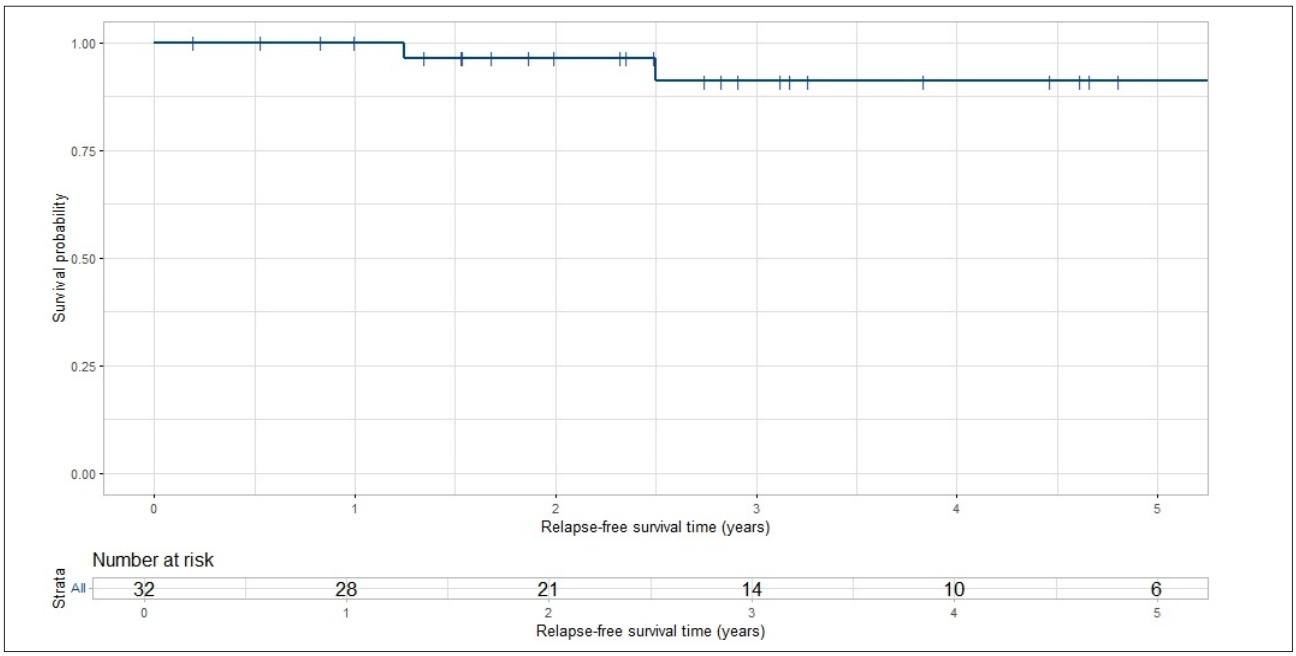


Fig. 2. Relapse-free survival of whole autologous stem cell transplant cohort (N=*32).*

The median follow-up time was 2.9 years. No transplant-related deaths occurred during the follow-up period.

Patient demographics

Overall survival of cohort

The Kaplan-Meier analysis demonstrates excellent overall survival following ASCT (Fig. 1). Only one of 32 patients died during the follow-up period, from a non-transplant, non-MS-related cause (motor vehicle accident). Estimated overall survival was 100% at 1 year and 96% (95% confidence interval (CI) 77 - 99%) at both 3 and 5 years. When excluding the non-disease-related death, overall survival remained 100% throughout the study period.

Relapse-free survival

The Kaplan-Meier curve demonstrates excellent relapse-free survival following ASCT (Fig. 2) Only 1 of 32 patients experienced relapse during the follow-up period. Estimated relapse-free survival was 100% at 1 year and 91% (95% CI 68 - 98) at both 3 and 5 years. When excluding the single non-transplant, non-MS-related death, disease-free survival increased to 96% (95% CI 77 - 99) at both 3 and 5 years.

Engraftment of neutrophils and platelets

The left panel in Fig. 3 depicts neutrophil engraftment, and the right panel shows platelet engraftment in the study cohort. Median time to neutrophil recovery (absolute neutrophil count >0.5 × 10^9/L) was 10 days (range 7 - 13

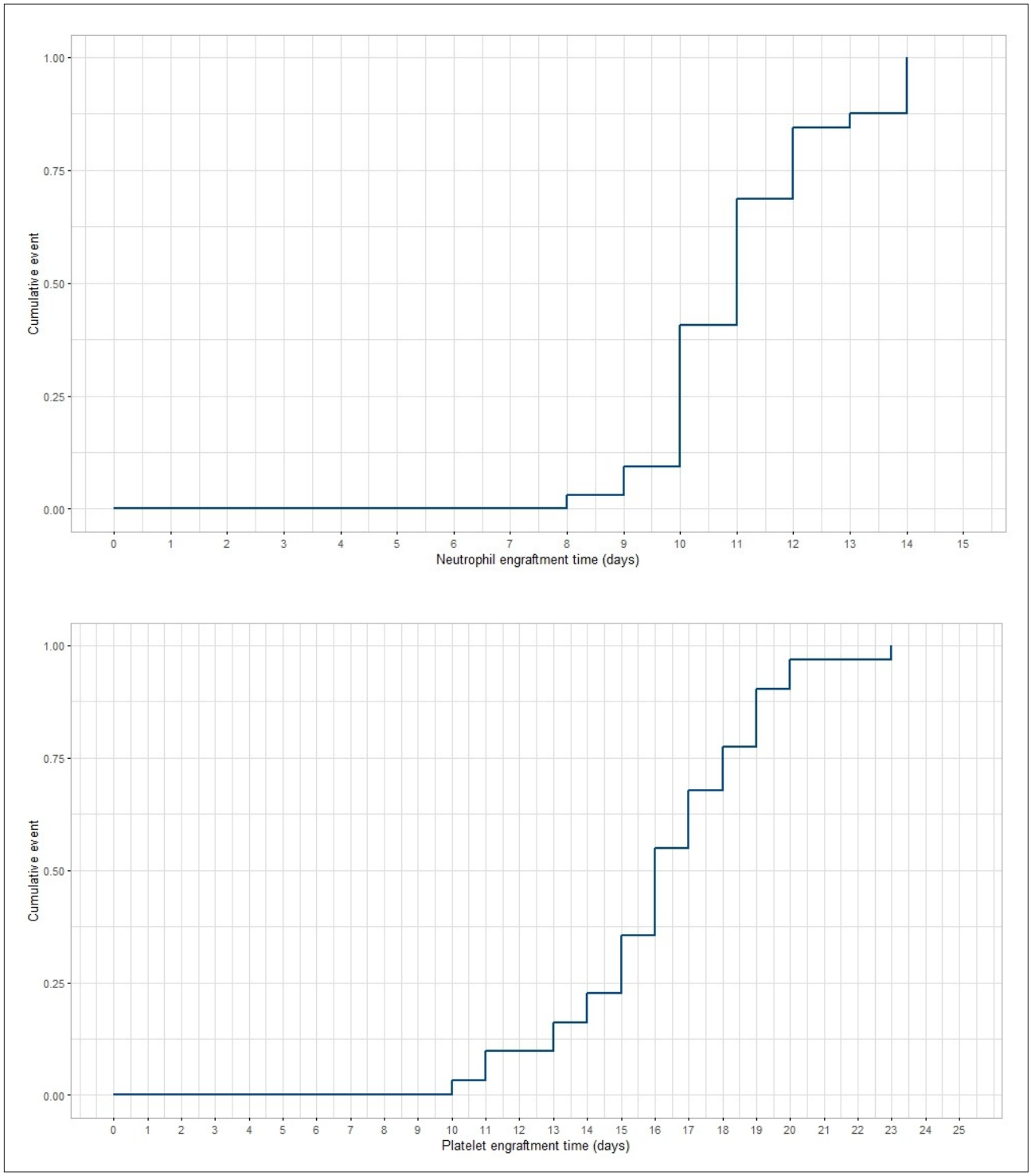


Fig. 3. Cumulative incidence of neutrophil (top) and platelet (bottom) engraftment.

days), while median time to platelet recovery (>20 × 10^9/L) was 14 days (range 10 - 23 days). These findings indicate prompt and consistent haematopoietic reconstitution post-ASCT, with no cases of delayed engraftment or primary graft failure observed.

Disease status post autologous stem cell transplant

Fig. 4 illustrates the clinical outcomes based on disease status, which was measured through the use of the EDSS scores at 30 days (*n*=32), 100 days (*n*=31) and 1 year (*n*=29) post transplant. An increase in the EDSS score implied a worsening of symptoms, while a reduction in EDSS was deemed an improvement in symptoms and a static EDSS indicated disease stabilisation. By 100 days, the majority of patients demonstrated neurological improvement or stabilisation, with sustained benefit at 1 year. Specifically, ~90% of evaluable patients showed improvement or no further progression at 12 months. Too few patients had complete 5-year follow-up for long-term EDSS data to be analysed. Of note, at all the above end points, no cases of deterioration in EDSS were noted. These findings indicate durable neurological stabilisation and early functional recovery after ASCT in this cohort.

Table 2. Expanded disability status scale (EDSS) prior to transplant

EDSS score	Patients, *n* (%)
2	3 (9)
2.5	1 (3)
3	2 (6)
3.5	1 (3)
4	3 (9)
4.5	1 (3)
5	1 (3)
5.5	3 (9)
6	11 (34)
7	4 (13)
7.5	2 (6)

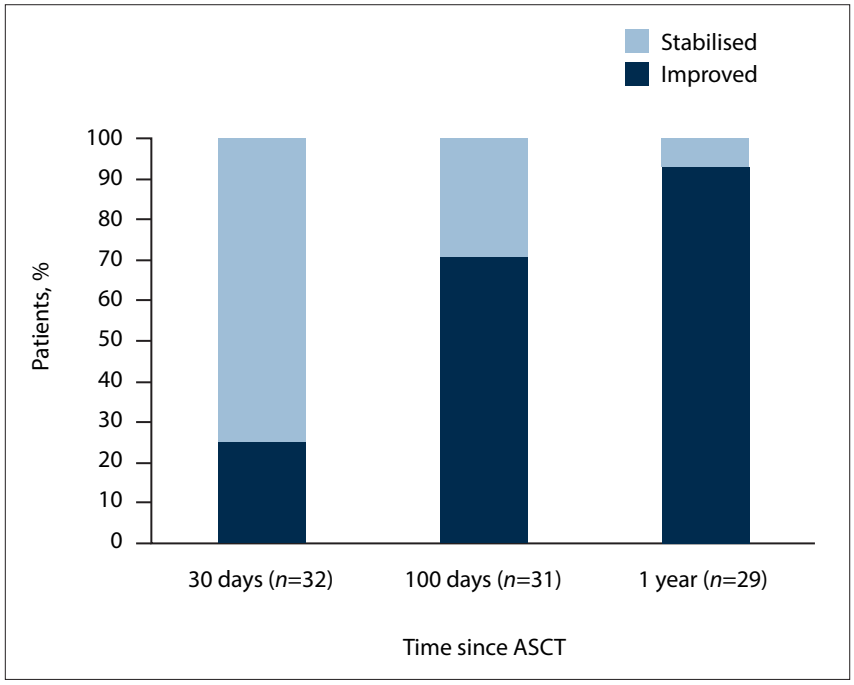


Fig. 4. Disease status following autologous haematopoietic stem cell transplantation (ASCT).

Discussion

This study presents the first and only published SA experience with ASCT for MS. Our findings show that ASCT is safe, feasible and provisionally highly effective in our real-world, resource-limited setting. Only one relapse occurred during follow-up, and no transplant-related mortality was observed. These results align with international evidence confirming ASCT as one of the most potent disease-modifying therapies for RRMS refractory to conventional DMTs.[21,27,28]

Large international studies and meta-analyses have reinforced the superior efficacy of ASCTs for RRMS. Kalincik *et al.*[27] reported a 2.7-fold higher probability of confirmed disability improvement with ASCT compared with high-efficacy DMTs such as ocrelizumab and natalizumab, with a durable benefit over 5 years. A 2024 meta-analysis including 422 patients found significant reductions in relapse rate and MRI activity, with no transplant-related deaths.[21] Our outcomes are in keeping with these results.

Neurological stabilisation or improvement was seen in nearly all evaluable patients (≈90% at 1 year), consistent with the MIST randomised trial, which demonstrated a 79% reduction in disability progression with ASCT compared with continued DMTs.[17] These findings support the immune reconstitution hypothesis, in which ASCT restores immune tolerance and halts ongoing neuroinflammation. In our study cohort the median duration of MS was 7.4 years, and the mean EDSS was 5 at the time of transplant. This means that owing to the natural progression of MS, one would have expected a deterioration without ASCT at 1 year.[29]

Treatment-related toxicity was manageable, predominantly comprising grade 3 (or lower) adverse reactions, which were mostly transient cytopenias such as neutropenic fever (50%) and mucositis (16%), with no graft failure or transplant-related mortality. This is consistent with modern EBMT registry data reporting <0.3% mortality.[19] Only one patient experienced a grade 4 reaction in the form of renal failure requiring dialysis. All patients engrafted neutrophils and platelets timeously. Platelet and neutrophils engraftment kinetics in our cohort were comparable to those described internationally.[30]

While ASCT is generally reserved for highly active RRMS refractory to high-efficacy DMTs, emerging data suggest superior outcomes when performed earlier in the disease course.[19,28] The 2024 - 2025 EBMT/International Society for Cellular Therapy guidelines acknowledge that first-line ASCT may be appropriate for rapidly evolving, poor-prognosis RRMS, particularly where access to costly DMTs is limited.[28] Evidence increasingly supports earlier intervention to prevent irreversible neurological decline.[21,27,28]

In SA's upper-middle-income but resource-limited setting, these findings have important implications. Access to high-efficacy DMTs is sometimes restricted, and chronic therapy costs remain prohibitive. Introducing ASCT earlier for aggressive RRMS could prevent disability progression and reduce long-term healthcare expenditure.[19,20] Economic analyses demonstrate that ASCT is cost-effective within 5 years, being approximately fivefold less costly than ongoing DMTs and associated with better quality-adjusted outcomes.[24,28] These data highlight ASCT's potential as a durable, cost-effective option when implemented in accredited centres adhering to international standards.

With constrained budgets and relatively limited DMT access, earlier ASCT for carefully selected, highly active RRMS could be both clinically superior and cost-saving. A national framework could specify: (*i*) high-efficacy DMTs as first-line for most; (*ii*) early ASCT for rapidly evolving RRMS; (*iii*) close collaboration between neurology and haematology services for early referral for ASCT in select MS cases; and (*iv*) registry participation for outcomes and cost tracking. Such structured implementation would optimise outcomes, support equitable access and align SA with global standards while addressing local constraints.

Limitations of this study include its retrospective design, modest sample size and incomplete long-term follow-up, because many patients opted only to follow up with their neurologist post ASCT, and many patients were not yet 5 years post ASCT, so that meaningful analysis was not yet possible. The lack of uniform MRI and biomarker data limits direct international comparisons. Nonetheless, this study provides important real-world evidence that ASCT is feasible, safe and potentially cost-effective in the SA population.

In conclusion, ASCT is a safe, powerful and durable therapeutic option for aggressive, treatment-refractory MS. Earlier use in appropriately selected patients could achieve lasting remission, improved quality of life and substantial cost savings. Expanding national ASCT programmes and registry-based evaluations will be essential for ensuring equitable access to this transformative therapy in SA.

Data availability. The data used for this study are available on request from the first author.

Declaration. This study was conducted for the purposes of AS's MMed (Internal Medicine) degree at the University of the Witwatersrand.

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Author contributions. AS conceptualised the study in discussion with JRdT and SD. AS obtained ethics approval, conducted data collection, wrote up the manuscript and co-ordinated the research under the supervision of JRdT, SD and AM. AP, JD, DM, DB and JT critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript and accept responsibility for its content.

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Conflicts of interest. None.

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