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RESEARCH ARTICLE

Global characteristics and outcomes of autologous hematopoietic stem cell transplantation for newly diagnosed multiple myeloma: A study of the worldwide network for blood and marrow transplantation (WBMT)

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Abstract

Autologous hematopoietic cell transplantation (AHCT) is a commonly used treatment in multiple myeloma (MM). However, real-world global demographic and outcome data are scarce. We collected data on baseline characteristics and outcomes from 61 725 patients with newly diagnosed MM who underwent upfront AHCT between 2013 and 2017 from nine national/international registries. The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS), relapse incidence (RI) and non-relapse mortality (NRM). Median OS amounted to 90.2 months (95% CI 88.2–93.6) and median PFS 36.5 months (95% CI 36.1–37.0). At 24 months, cumulative RI was 33% (95% CI 32.5%–33.4%) and NRM was 2.5% (95% CI 2.3%–2.6%). In the multivariate analysis, superior outcomes were associated with younger age, IgG subtype, complete hematological response at auto-

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HCT, Karnofsky score of 100%, international staging scoring (ISS) stage 1, HCT-comorbidity index (CI) 0, standard cytogenetic risk, auto-HCT in recent years, and use of lenalidomide maintenance. There were differences in the baseline characteristics and outcomes between registries. While the NRM was 1%–3% at 12 months worldwide, the OS at 36 months was 69%–84%, RI at 12 months was 12%–24% and PFS at 36 months was 43%–63%. The variability in these outcomes is attributable to differences in patient and disease characteristics as well as the use of maintenance and macroeconomic factors. In conclusion, worldwide data indicate that AHCT in MM is a safe and effective therapy with an NRM of 1%–3% with considerable regional differences in OS, PFS, RI, and patient characteristics. Maintenance treatment post-AHCT had a beneficial effect on OS.

1 | INTRODUCTION

Multiple myeloma (MM) is a plasma cell neoplasm characterized by uncontrolled proliferation of mutated plasma cells, leading to specific end-organ damage.[1] It was the third most common hematological malignancy after non-Hodgkin lymphoma and leukemia in 2020, contributing to 176 404 (14%) of the 1 278 362 blood cancers diagnosed worldwide.[2] Although the cause of MM remains largely unknown, the risk factors include male sex, Black race, older age, living in developed countries, family clusters, radiation exposure, and obesity.[1,3] Two additional studies confirmed a wide variation in the burden of MM, with a higher incidence and mortality observed in men and countries with a higher human development index.[4,5] Due to the introduction of newly developed targeted therapies and transplantation techniques, five-year overall survival (OS) has doubled over the past decade to approximately 54%.[4,5] The utilization of autologous hematopoietic cell transplantation (AHCT) plays an important role in the treatment of MM.[6–10]

The worldwide network for stem cell transplantation (WBMT) was founded as a federation of several societies working in the field of hematopoietic cell transplantation (HCT), with the aim of improving HCT, stem cell donation, cellular therapy, accreditation, and access to HCT worldwide, especially in countries with low or no activity. To this end, the WBMT has since 2006 regularly published worldwide transplant activity surveys.[11–13] Previous publications have revealed a variable incidence of MM between countries, which has increased uniformly since 1990, with the largest increase occurring in middle and low-middle sociodemographic index countries. Access to effective MM care is limited in many countries with low socioeconomic development, particularly in sub-Saharan Africa.[1] AHCT activity in plasma cell disorders, principally MM, has increased worldwide from 10 675 in 2002 to 23 701 in 2016.[2] Greater utilization has mostly been seen in high-income regions, and it remains poorly utilized in Africa and the Eastern Mediterranean Region (EMR). More work is needed to improve access to AHCT in MM patients, especially in low-income to middle-income countries.[14]

The overall objective of this study was to analyze the outcomes of AHCT in patients with MM from nine registries worldwide. The outcomes of patients with newly diagnosed MM (NDMM) were computed accounting for differences in patient and disease risk factors between countries and country-specific macroeconomic factors.

2 | PATIENTS AND METHODS

2.1 | Study design and data sources

This retrospective registry study was conducted through the WBMT, utilizing data from their member societies and international or regional registries on HCT for patients with NDMM aged ≥18 years between 2013 and 2017. As center-based activity reports do not contain patient-specific information, member societies were asked to provide patient, disease, AHCT characteristics, and outcome information. The need for additional informed consent from patients was waived because the study was performed by the secondary use of registry data, and no personal information was transferred. The primary endpoint was OS and the secondary endpoints were progression-free survival (PFS), cumulative relapse incidence (RI), and non-relapse mortality (NRM).

Outcome data were obtained through requests from the following regional registries:

1. The Center for International Blood and Marrow Transplantation (CIBMTR; www.cibmtr.org), the United States of America (USA),
2. The Canada registry using the Ottawa Blood Disease Center MM Database (OBDCMMD),
3. Latin American Blood and Marrow Transplantation group (LABMT).
4. The European Society for Blood and Marrow Transplantation (EBMT; www.ebmt.org)
5. Australia and New Zealand Transplant & Cellular Therapies Registry (ANZTCTR; www.anztct.org.au)
6. The Asian Pacific Blood and Marrow Transplant Group (APBMT; www.apbmt.org) with reporting registries
   a. Myeloma Transplant Registry, Ministry of Health, Malaysia (MTRMOHM)

b. Japan Society for Transplantation and Cellular Therapy/Japanese Data Center for Hematopoietic Cell Transplantation (JSTCT/JDCHCT)
c. Taiwan Society of Blood and Marrow Transplantation (TBMT)
d. Beijing Bone Marrow Transplant registry
7. Eastern Mediterranean Blood and Marrow Transplant Group (EMBMT).

2.2 | Regional contributions

In 2016, 1662 teams in 86 countries across six WHO regions delivered HCT services. These included the Americas (AMR/PAHO; WHO regions North, Middle, and South America, and Canada); Asia (SEAR/WPR; WHO regions Southeast Asia and the Western Pacific Region, which includes Australia and New Zealand); Europe (EUR, which includes Turkey and Israel); and AFR/EMR [WHO regions Africa (AFR) and Eastern Mediterranean Region (EMR)] (www.who.int/about/regions/en/). A detailed list of organizations providing activity data and the definitions used in the manuscript has been reported in previous publications.[4]

The registries reported all AHCTs without time interval restrictions between diagnosis and AHCT, except for CIBMTR, which provided information on patients who underwent transplantation within 12 months of diagnosis.

2.3 | Definitions

Deletion 17p and/or t(4:14) and/or t(14:16) were considered high-risk cytogenetic findings, with the remaining being standard risk.[15] Hematological responses were defined according to the IMWG criteria.[16] OS was defined as the time from AHCT to death from any cause and PFS was defined as survival without relapse or progression. RI was defined as the cumulative incidence of either relapse or progression post-AHCT, and NRM as death without evidence of relapse or progression. Transplant rate (TR) was defined as the number of AHCTs in a country per 10 million inhabitants.

2.4 | Economic factors

Gross National Income (GNI) is defined as gross domestic product, plus net receipts from abroad of compensation of employees, property income, and net taxes less subsidies on production (https://data.oecd.org/natincome/gross-national-income.htm). Current health expenditure (HCE) includes healthcare goods and services consumed each year without capital health expenditure. Both factors are expressed in current international dollars and converted into purchasing power parity (PPP) per capita. Factors were obtained from the World Bank (www.worldbank.org), WHO (www.who.int), and United Nations (http://hdr.undp.org) for 2013–2017.

2.5 | Statistical analysis

Clinical, demographic, and AHCT-related characteristics at baseline were tabulated by the year of AHCT, registry, and country. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as frequencies and proportions. Median follow-up after baseline and 95% confidence intervals (CIs) were calculated using the reverse Kaplan–Meier (KM) method. The probabilities of OS and PFS were estimated using the KM method, and the groups were compared using the log-rank test. The cumulative incidence of NRM together with RI was analyzed in a competing risk framework, and Gray's test was used to compare the differences between the groups.

Associations between patient characteristics and outcomes were evaluated by multivariate analysis (MVA) using Cox (cause-specific) proportional hazard models based on complete cases. All models included a random country effect (normally distributed) and the following variables: International staging scoring (ISS) at diagnosis, cytogenetic risk, age at AHCT, sex, year of AHCT, diagnosis and AHCT time interval, immunoglobulin subtype, Karnofsky score (100 and ≤90%), stage at diagnosis, preparative regimen (type and dose), HCT-comorbidity index (CI), and lenalidomide maintenance. As there was a high degree of missing information on ISS at diagnosis, cytogenetic risk, and HCT-CI, we analyzed the first model with all variables except ISS, cytogenetic risk, and HCT-CI. A second analysis was performed using a subset of patients with complete information on the three additional aforementioned variables. The association between maintenance therapy (lenalidomide, other, no maintenance) and OS, PFS, and relapse was analyzed using landmark Cox proportional hazards models at 3 months, including the subset of patients with available maintenance data and the same two sets of confounders as described above.

All outcomes in the MVA analyses were artificially censored at 36 months. All tests were two sided. To determine the factors associated with the time-to-event outcomes, the type 1 error rate was fixed at 0.05. No adjustments were made for the multiple comparisons. All analyses were performed in R version 4.2.2 using "survival," "cmprsk," and "prodlim" packages.[17]

The methods used for the analysis of country-specific macroeconomic factors are described in the Supplementary Material.

3 | RESULTS

3.1 | Patient characteristics

A total of 103 847 first AHCTs for MM were reported in the WBMT activity survey between 2013 and 2017.[3] Outcome information was available for 61 725 NDMM patients (59.5%) from 629 transplant centers in five WHO regions. AHCTs/year increased from 11 317 in 2013 (18.3%) to 13 498 in 2017 (21.9%). The mean number of transplantations per year increased in all regions except in EMR (Table S1). The transplant rate per 100 000 population in 2017 per region/country is shown in Table S4. The patient, disease, and AHCT

characteristics are shown in Tables 1A and 1B. The median age at diagnosis was 59.9 years with the lowest median age in the EMR (52.5 years) and Malaysia (54.3 years) and highest in Ottawa, Canada (61.5 years). The median year of diagnosis was 2014, and was well balanced between registries. IgG (54.0%), light chain (24.4%), and IgA (18.6%) were the predominant subtypes; however, there were significant differences between regions. Disease stage at diagnosis was reported in 54.5% of patients (ISS I in 38.0%, ISS II in 34.8%, and ISS III in 27.1%) and cytogenetics in 44.5% of patients (high risk 30.3%). Median age at AHCT was 60.8 (IQR: 54.6–65.8) years, lowest in EMR (53.6 years) and highest in Canada (62.2 years). Only 5.1% of patients were older than 70 years at AHCT, with the lowest proportions in Malaysia (0%) and EMR (0.6%), and the highest in the USA (9.8%). HCT-CI at AHCT (available in 71.8%) was low in 52%, intermediate in 25%, and high in 23%. USA and Latin America reported high-risk HCT-CI scores in 42.2% and 5.5%, respectively. Karnofsky score at AHCT was ≤90% in 72.0%, lowest in Latin America (44.3%) and highest in Ottawa (92.4%). Most patients underwent AHCT in very good partial remission (VGPR, 38.0%) and partial remission (PR, 36.2%). Complete remission (CR) was reported in 19.1% of patients, minimal remission/stable disease (MR/SD) in 4.7%, and relapse/progression in 1.8%. The percentage of patients with VGPR or better ranged from 76% in Latin America to 39% in Australia and New Zealand. The most frequently used conditioning regimen was melphalan at a dose of 200 mg/m^2 (70% of patients). However, only 60.4% of patients received this dose in Malaysia, as opposed to 89.6% in Ottawa, Canada. Only a minority of patients had tandem AHCTs (6.7%): 10.1% in Europe and 1.3% in the USA. Lenalidomide was used for posttransplant maintenance in 51% of 6801 patients for whom information was available (11.0% of all patients).

3.2 | Outcome in the entire population

After a median follow-up of 41 months (IQR 19–60), median OS was 90.2 months (95% CI 88.2–93.6) and OS at 24 months was 88.4% (95% CI 88.1–88.7) and 63.4% (95% CI 62.7%–64.0%) 72 months (Figure 1A). The median PFS was 36.5 months (95% CI 36.1–37.0), the PFS was 64.6% (95% CI 64.1%–65%) at 24 months, and 28.6% (95% CI 28.0%–29.2%) at 72 months (Figure 1B). The cumulative RI increased from 2.4% (95% CI 2.3–2.5) at 3 months to 33% (95% CI 32.5%–33.4%) at 24 months (Figure 1C) and 65.5% (95% CI 64.9%–66.1%) at 72 months. In contrast, NRM was 0.6% (95% CI 0.6%–0.7%), 2.5% (95% CI 2.3%–2.6%), and 5.9% (95% CI 5.6%–6.1%) at 3, 24, and 72 months, respectively (Figure 1D).

3.3 | Outcome according to regions

Three-year OS varied between regions, from 84.3% to 68.6% ($p < .001$; Figure 2A and Table S2a). The longest median OS was observed in the USA, and the shortest in Malaysia (Table S2a). The differences observed within 12 months became more pronounced with longer follow-up periods. PFS showed similar patterns (Figure 2B and Table S2a), with the highest PFS at 36 months in Japan (62.5%) and lowest in Malaysia (43.3%). This was reflected in the lowest cumulative 36-month RI observed in patients in Japan (31.7%) and the highest in those from the EMR (52.3%) (Figure 2C and Table S2b). The highest 36-months NRM of 5.8% was observed in patients from Japan and the lowest in patients from the EMR at 2.0% (Figure 2D).

3.4 | Outcome according to risk factors

Univariate analyses were performed using Karnofsky score, sex, MM subtype, ISS Staging, cytogenetic score, HCT-CI risk score, disease status, conditioning, graft source, age, and maintenance. All these factors were significantly associated with OS, while the interval from diagnosis to transplant, graft source, and tandem AHCT were not. Notably, the 36-month OS increased from 80% (95% CI 79%–81%) in 2013 to 84% (95% CI 83%–85%) in 2017.

3.5 | Multivariate analysis (MVA)

The MVA OS model (without ISS, cytogenetic risk, and HCT-CI) included 52 568 patients with complete data (Table S3). The most important risk factors for OS and PFS were relapse at AHCT (HR 5.23 for OS and HR 3.44 for PFS), SD/MR at AHCT (HR 1.99 and 1.84), no maintenance (HR 1.79 and 1.72), IgA subtype (HR 1.47 and 1.82), Karnofsky score ≤90% (HR 1.33 and 1.10), melphalan 140 mg/m^2 (HR 1.25 and 1.16), VGPR at AHCT (HR 1.21 and 1.28), light chain MM (1.14 and 1.08), older age (HR 1.1 and 1.03 per 10 years increase, respectively) as compared with baseline (CR at AHCT, maintenance, IgG subtype, Karnofsky score 100%, melphalan 200 mg/m^2 and younger age). A more recent calendar year of AHCT was associated with better OS, PFS, and RI (Table S3). The same factors, except for older age at AHCT (HR 0.95), were also associated with increased RI. Non-CR stage at AHCT (HR 2.5, 2.19, 1.47 for VGPR, PR, SD/MR, and relapse/progression, respectively), melphalan dose 140 mg/m^2 instead of 200 mg/m^2 (HR 1.64), Karnofsky score ≤90% (HR 1.40), and older age at AHCT (HR 1.36) were strongly associated with NRM. The time interval from diagnosis to AHCT was not significantly associated with OS, PFS, risk of relapse, or NRM.

An additional MVA was performed on a subset of 20 355 patients for whom data on cytogenetic risk, HCT-CI risk scores, and ISS at diagnosis were available (Tables 2A and 2B). A higher HCT-CI (HR 1.30 and 1.15 for high and intermediate) was significantly associated with worse OS but was not significantly associated with PFS or an increased risk of relapse. High-risk cytogenetics (HR 2.13) and a higher ISS (HR 2.13 and 1.51 for ISS III and II, respectively) were associated with worse OS, PFS, and RI. The point estimates of other variables in these analyses were similar to those presented in Table S3.

We then performed a three-month landmark analysis restricting the two data sets to patients with information on post-AHCT maintenance. The characteristics of the patients with and without maintenance information were similar, except for the year of HCT.

TABLE 1A Characteristics of patients and diseases of global population and by region.

Characteristics (information available)	Group All patients	Total 61 725	Europe 37 459	USA 16 217	Australia/New Zealand 3164	Japan 3122	EM region 543	Taiwan 524	Latin America 339	Ottawa, Canada 188	Malaysia 169	China 72
	% or median (range) [IQR]											
Age diagnosis ($n = 61\,663$)	Median years (IQR)	59.9 (17.0–82.7) [53.6–64.9]	59.6 (17–82.7) [53.5–64.4]	60.9 (19.7–82.5) [54.5–66.6]	60.7 (19.7–78.7) [54.6–65.4]	59 (24–76) [53–64]	52.5 (17.5–81.7) [46–58.1]	57.7 (27.6–74.3) [51.9–62.5]	55 (20–73) [48–60]	61.5 (34.2–72.6) [56.4–65.8]	54.3 (29.4–68.6) [48.3–58.9]	58. (34–73) [50–64]
Gender ($n = 61\,725$)	Male	58.0	58.1	57.3	62.7	55.4	61.3	53.2	57.2	59.6	60.9	52.8
Race ($n = 28\,023$)	Caucasian	73.1	93.4	79.9		0.2			98.3	87.9		
	Asian	15.7	3.1	2.1		99.7		100.0		5.3	100.0	100.0
	Black	10.7	3.2	17.4		0.1				6.1		
	Am. Indian/Alaska	0.1	0.1	0.2					1.7	0.8		
	Hawaiian/Other PI	0.3	0.1	0.5								
Ethnicity ($n = 27\,653$)	No Hispanic	91.8	91.3	92.1		100	100	100	0.3	100	100	100
Year of diagnosis ($n = 61\,663$)	Median year (range)	2014 (1976–2017)	2014 (1976–2017)	2015 (2012–2017)	2014 (1990–2017)	2014 (1999–2017)	2014 (1995–2017)	2015 (2006–2017)	2014 (2001–2017)	2015 (2010–2017)	2014 (2000–2017)	2016 (2011–2016)
	[IQR)]	[2013–2016]	[2013–2016]	[2013–2016]	[2013–2016]	[2013–2015]	[2013–2015]	[2013–2016]	[2013–2015]	]2013–2016)	[2013–2015]	[2013–2016]
MM classification ($n = 60\,429$)	IgG	54.0	52.1	56.2	61.6	56.7	46.0	51.4	61.7	59.6	73.6	52.4
	Light chain	24.4	27.2	20.7	16.5	19.3	37.8	21.3	16.4	14.4	4.3	17.5
	IgA	18.6	17.6	20.8	18.6	19.4	13.1	23.0	16.4	23.9	20.2	25.4
	Nonsecretory	1.7	1.9	11.2	1.9	1.6	1.1	0.4	3.0	1.1		
	Other Ig	1.3	1.1	1.1	1.4	3.0	1.9	3.9	2.4	1.1	1.8	3.2
ISS ($n = 33\,640$)	I	38.0	38.8	38.9	38.8	35.7	25.3	25.7	30.5	20.6	15.7	27.9
	II	34.8	34.0	34.6	37.5	38.7	36.0	36.4	24.1	47.5	41.3	41.2
	III	27.1	27.2	26.6	23.7	25.7	38.7	37.9	45.4	31.9	43.0	30.9
Cytogenetic risk ($n = 27\,468$)	High	30.3	31.3	34.8		9.9	5.2	11.8	22.3	61.9	27.4	41.4
Interval Dg—HCT ($n = 61\,663$)	Months	7.1 (0–476) [5.5–9.9]	7.4 (0–476) [5.6–10.9]	6.4 (0–12) [5.2–8.2]	6.9 (0–294) [5.5–9.9]	7.8 (0–173) [5.9–11.3]	8.6 (2.8–254) [6.3–13.2]	7.7 (1.8–101) [5.9–10.5]	13 (3–170) [8–20]	6.4 (3–35) [5.6–8.2]	10.8 (5–178) [8.3–15.9]	n.a.

Abbreviations: ANZTCT, Australia and New Zealand Transplant & Cellular Therapies Registry; BM, bone marrow; BM, bone marrow; CI, confidence interval; CR, complete response; EM, Eastern Mediterranean region; HCT, hematopoietic cell transplant; HCT-CI, hematopoietic cell transplant comorbidity index; HR, hazard ratio; IMID, immunomodulatory drug; IQR, inter quartile range; ISS, International staging scoring; NRM, non-relapse mortality; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; R/R, relapse/refractory; RI, relapse incidence; VGPR, very good partial response.
European data were provided by EBMT and included also patients from South Africa ($n = 142$), Colombia ($n = 12$), Singapore ($n = 48$), Iraq ($n = 1$), Iran ($n = 114$), India ($n = 3$), and Brazil ($n = 7$).

TABLE 1B AHCT characteristics of the global population and according to region.

Characteristics (information available)	Group All patients Transplant Rate (HCT/10 million population) % or median (range) [IQR]	Total 61 725 18.3/19.0/19.9	Europe 37 459 138.6 19/20/20	USA 16 217 213.7 17/18/19	Australia/ New Zealand 3164 226.9 19/18/20	Japan 3122 53.3 18/20.5/19.5	EM region 543 5.9 24/20/17	Taiwan 524 31.3 17/17/21	Latin America 339 22.8 11/16/17	Ottawa, Canada 188 37.2 15/18/21	Malaysia 169 17.4 16/21/22	China 72 3.6 18/8/8
Year of HCT ($n = 61\,725$)	2013/14/15											
	2016/17	21.0/21.9	20/21	22/23	22/21	20/21	16/23	23/23	24/32	27/19	18/22	21/44
Age at HCT ($n = 61\,725$)	Years	60.8 (18.1–83.2) [55–66]	60.7 (18.1–82.8) (54–65)	61.5 (20–83) (55–67)	61.6 (22.1–79.5) [55–66]	60 (25–77) [54–64]	53.6 (19–83) [47–59]	58.5 (28–75.7) [52–63]	56 (30.5–69) [50–61]	62 (36.5–73) [57–66]	56 (30.5–69) [49–60]	59(34–74) [51–65]
	<60/60–65/66–70	46/30/19	47/31/19	43/26.5/20	42/31/22	46/36/17	79/16/4	58/30/10.5	67/23/9	36/35/26	73/20/8	54/28/17
	>70	5.1	3.5	9.8	4.6	1.4	0.6	1.9	1.5	3.7		1
HCT-CI risk ($n = 44\,319$)	Low (0)	51.8	65.2	26.8		77.3	53.0	62.9	71.3	52.8	3.8	
	Intermediate (1–2)	25.0	21.6	31.1		16.9	31.7	28.3	23.2	28.9	63.8	
	High (≥3)	23.2	13.1	42.2		5.8	15.3	8.7	5.5	18.3	32.4	
Karnofsky at HCT ($n = 55\,799$)	≤90	72.2	66.9	88.1	78.2	52.5	57.9	50.6	44.3	92.4	82.6	
Disease at HCT ($n = 60\,367$)	CR	19.1	20.5	15.8	12.8	19.0	37.3	29.5	40.0	16.3	26.8	40.3
	VGPR	38.0	39.1	39.4	26.1	31.6	26.7	41.2	35.8	4.3	27.4	29.0
	PR	36.2	34.2	38.1	49.0	42.8	29.6	24.0	21.8	36.5	40.9	21.0
	SD/MR	4.7	3.4	6.7	10.1	4.0	4.3	1.8	1.5	12.9		6.5
	R/R	1.8	2.4	0.0	2.0	2.2	2.1	3.5	0.9		4.9	3.2
	Untreated	0.2	0.3		0.1	0.4						
Graft source ($n = 61\,725$)	PB/BM/PB + BM	99.8/0.1/0.0	99.7/0.2/0.1	100/0/0	99.9/0.1/0	99.9/0.0/0	99.6/0.2/0.2	99.8/0.2/0	100.0/0.0/0	100/0.0/0	100.0/0.0/0	100/0/0
Non cryopreserved ($n = 9567$)		0.7		1.2	0.0	0.0		0.0	13.6	0.0	0.0	0.0
Conditioning ($n = 61\,355$)	Mel200	70.1	62.2	81.8	88.5	81.7	71.0	77.8	83.7	88.6	60.4	90.3
	Mel140	12.0	9.8	18.2	10.2	8.4	4.6	20.7	7.7	5.9	29.0	9.7
	Unknown dosage/ others	14.8/3.1	23.5/4.5		0.1/1.2	8.0/1.8	11.3/13.1	0.6/1.0	0.0/8.6	1.1/4.3	0.0/10.7	
Tandem ($n = 61\,663$)	Yes	6.7	10.1	1.3	1.1	3.7	1.5	0.6	0.6	0.0	1.2	100.0
Maintenance ($n = 6789$)	Lenalidomide	50.8	58.4	57.9		46.2	61.7	1.2	24.7	44.6	4.2	15.7
	None	11.0		20.9		36.9			17.0	55.4	67.3	24.3
	Other(s)	10.6	19.2	2.9		1.9	10.0	0.2	1.1			
	Thalidomide	9.4	9.9	0.2			15.0	30.5	38.7		21.4	44.3
	Bortezomib	9.3	11.5	8.6		3.8	13.3		15.9		6.0	2.9
	IMiD/PI	7.9	0.1	7.9		11.2		67.7	2.6		1.2	
	Carfilzomib	1.0	0.9	1.6				0.4				

Abbreviations: ANZTCT, Australia and New Zealand Transplant & Cellular Therapies Registry; BM, bone marrow; BM, bone marrow; CI, confidence interval; CR, complete response; EM, Eastern Mediterranean region; HCT, hematopoietic cell transplant; HCT-CI, hematopoietic cell transplant comorbidity index; HR, hazard ratio; IMID, immunomodulatory drug; IQR, inter quartile range; ISS, International staging scoring; NRM, non-relapse mortality; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; R/R, relapse/refractory; RI, relapse incidence; VGPR, very good partial response.

European data were provided by EBMT and included also patients from South Africa ($n = 142$), Colombia ($n = 12$), Singapore ($n = 48$), Iraq ($n = 1$), Iran ($n = 114$), India ($n = 3$) and Brazil ($n = 7$).

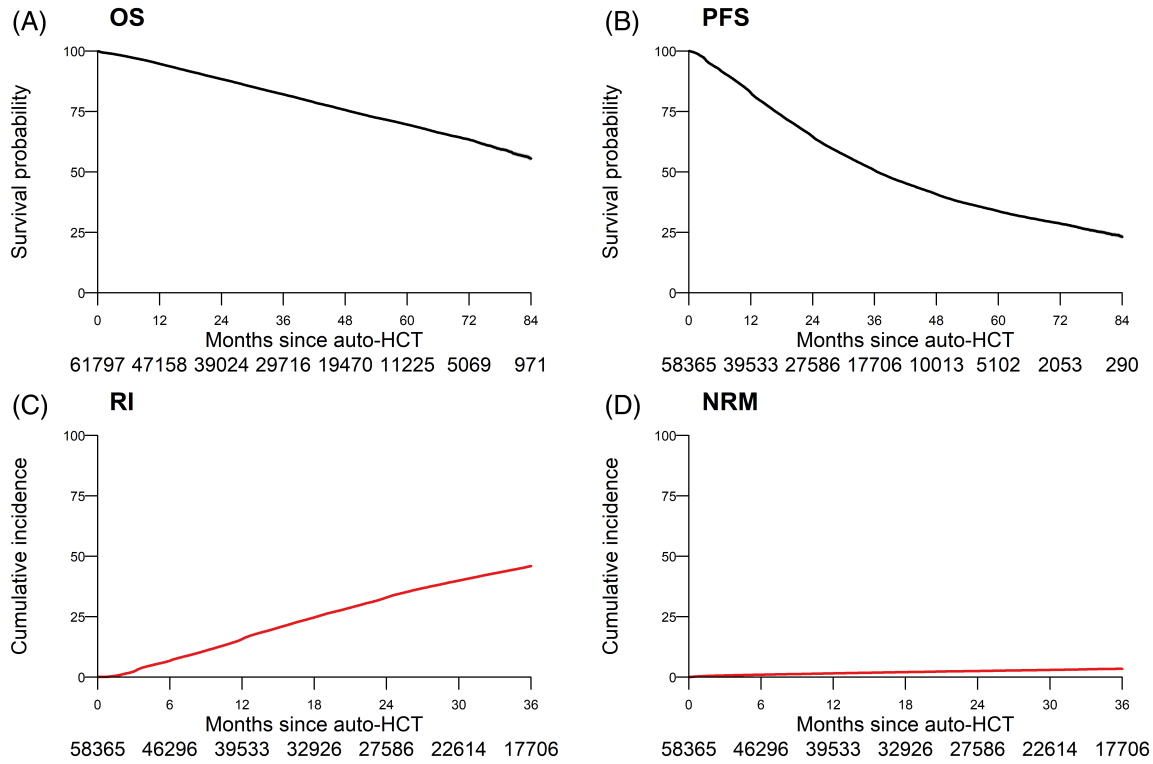

FIGURE 1 Outcome after auto-HCT: (A) probability of overall survival (OS), (B) progression-free survival (PFS), (C) cumulative relapse incidence (RI), and (D) cumulative incidence of non-relapse mortality (NRM). Due to the large number of patients, the 95% confidence intervals (CIs) are very narrow and cannot be distinguished from the point estimates. Numbers below the graphs show the number of patients at risk.

Lenalidomide maintenance was associated with improved OS, PFS, and lower RI, but not NRM (Figure S1). No treatment or treatment other than lenalidomide maintenance was associated with lower OS (HR 2.09 and 1.36), PFS (HR 1.61 and 1.39), and higher RI (HR 2.09 and 1.36) (Tables 2A, 2B, and S3).

3.6 | Transplant activity and outcomes by macroeconomic factors

Country HRs extracted from the model and country-specific health economic variables were correlated. TR correlated strongly with HCE, with higher AHCT activity in countries with higher HCE ($r = 0.67$, $p < .01$; Figure S2a). Furthermore, a lower risk of death after AHCT was observed in countries with higher HCE ($r = -0.49$, $p < .01$; Figure S2b) and in countries with higher HCE/GNI ($r = -0.45$, $p < .01$; Figure S2c). Similarly, the risks of death or relapse ($r = -0.39$, $p < .01$; Figure S2d) and relapse ($r = -0.37$, $p < .01$; Figure S2e) were lower in countries with higher HCE/GNI quotients. In contrast, only a trend was found between the HR for death without relapse and HCE/GNI ($r = -0.26$, $p = .06$; Figure S2f).

4 | DISCUSSION

Information on the outcomes of patients with MM undergoing upfront AHCT between 2013 and 2017 (inclusive) was collected from different regions worldwide. The median OS was 90.2 months and the median PFS 36.5 months. The cumulative RI was 15.7% at 12 months, and the NRM was 1.5% at 12 months and 3.4% at 36 months. This confirms the safety of AHCT worldwide, independent of the country's income. Notably, these were real-world data and were not derived from clinical trials with defined eligibility criteria.

In MVA, older age was associated with inferior OS, primarily due to a higher NRM. Females tended to have a slightly better OS than males as reported previously for other hematological diseases and solid tumors.[18–21] In recent years, outcomes have improved, most likely due to the availability of numerous novel therapies, such as immunomodulatory drugs (IMiDs), proteasome inhibitors, and CD38 monoclonal antibodies.[22] Interestingly, the stage of disease at AHCT was the most important prognostic factor. The risk of death was higher with more advanced disease at AHCT, underscoring the importance of utilizing a highly effective induction regimen at the outset to achieve the best response to AHCT. Achieving at least a complete remission (CR), and currently a minimal residual disease (MRD) negative status, has a clear positive impact on posttransplant outcomes.[23] With respect to the immunoglobulin subtype, our analysis confirms the detrimental outcomes seen with IgA compared with IgG paraproteins and, to a lesser extent, light chain myeloma compared with IgG subtype, as has also been previously reported.[24,25]

The association between lower Karnofsky scores and poorer outcomes was stronger for NRM and OS and weaker for RI. Higher HCT-CI was only associated with worse NRM and OS, whereas poor cytogenetic risk was associated with increased RI but had no impact

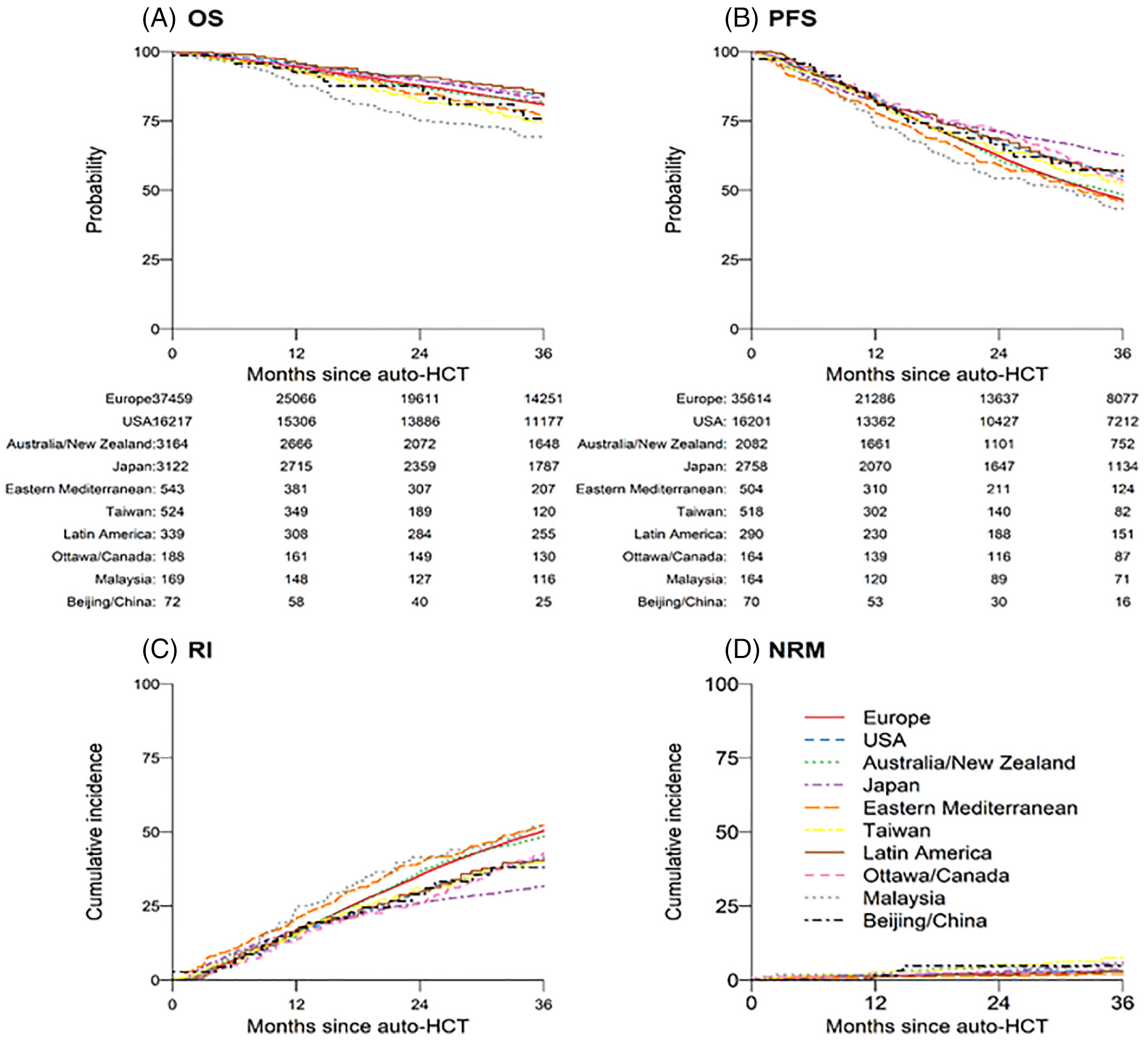

FIGURE 2 Outcome after auto-HCT by registry/region: (A) probability of overall survival (OS), (B) progression-free survival (PFS), (C) cumulative relapse incidence (RI), and (D) cumulative incidence of non-relapse mortality (NRM). Numbers below the graphs show the number of patients at risk.

on NRM. There was a strong association between the ISS stage and all outcomes.

The observation that patients conditioned with a melphalan dose of 140 mg/m^2 had poorer outcomes than those receiving 200 mg/m^2 was at odds with published data. Although we also found that the differences in the risk of adverse outcomes between lower and standard melphalan doses were substantially smaller in models adjusted for cytogenic risk, ISS at diagnosis, and number of comorbidities, a significantly higher risk of NRM remained in those who had received a lower melphalan dose. This finding may be due to selection bias, as patients receiving a lower dose of melphalan were older, had lower Karnofsky scores, and had more comorbidities. Despite adjusting for these factors, confounding by other factors that were not tested here may be possible. For example, we could not adjust for differences in renal function as the data were not readily available. In a previous study, outcomes were similar following melphalan 140 mg/m^2 and melphalan 200 mg/m^2, with remission status at the time of transplantation being the overriding determinant, that is, AHCT in less than PR favored melphalan 200 mg/m^2 over 140 mg/m^2 in terms of OS, PFS, and relapse risk.[26]

AHCT outcomes were significantly associated with macroeconomic factors. In general, a higher HCE/GNI ratio was associated with a lower risk of death and disease recurrence but not NRM. Unsurprisingly, this finding suggests that investment in healthcare services affects the outcomes. Further healthcare services and health economics research are required to elucidate the causes of this association, which may be due to a lack of access to maintenance therapy.

Our study has some important limitations. Reporting practices, data collection systems, and quality checks differ between registries, resulting in varying amounts of missing information. Despite a generally low NRM, significant differences in survival and relapse outcomes between registries were observed in univariate analyses. Different factors, including variations in the baseline characteristics, may be responsible for this effect. For example, lower-income regions tend to transplant younger patients and select patients who achieve a good hematological response, while in other registries, a higher percentage

TABLE 2A Multivariable analysis on outcome of patients according to characteristics at diagnosis.

Clinical characteristics		OS HR (95% CI)	p	PFS HR (95% CI)	p	Relapse HR (95% CI)	p	NRM HR (95% CI)	p
Gender	Male	1.00		1.00		1.00		1.00	
	Female	0.93 (0.87–1.01)	.08	0.94 (0.90–0.98)	.005	0.94 (0.90–0.99)	.01	0.94 (0.80–1.10)	.45
MM classification	IgG	1.00		1.00		1.00		1.00	
	IgA	1.42 (1.30–1.56)	<.0001	1.26 (1.19–1.34)	<.0001	1.24 (1.17–1.31)	<.0001	1.56 (1.28–1.90)	<.0001
	Light chain	1.10 (1.00–1.22)	.06	1.12 (1.05–1.19)	.0004	1.12 (1.05–1.19)	.0003	1.04 (0.84–1.31)	.61
Cytogenetic risk	Standard	1.00		1.00		1.00		1.00	
	High	2.13 (1.96–2.30)	<.0001	1.62 (1.55–1.70)	<.0001	1.65 (1.57–1.73)	<.0001	1.32 (1.11–1.58)	.002
ISS at diagnosis	I	1.00		1.00		1.00		1.00	
	II	1.51 (1.37–1.67)	<.0001	1.23 (1.16–1.30)	<.0001	1.22 (1.15–1.29)	<.0001	1.46 (1.19–1.79)	.0003
	III	2.16 (1.96–2.39)	<.0001	1.49 (1.41–1.58)	<.0001	1.46 (1.38–1.55)	<.0001	2.02 (1.64–2.49)	<.0001
Interval diagnosis-HCT	(per 6 months more)	1.02 (0.99–1.04)	.14	1.00 (0.99–1.01)	.99	1.00 (0.98–1.01)	.54	1.04 (1.00–1.08)	.04

Note: The OS model included 20 355, the PFS, relapse and NRM 19873 patients. HR > 1 is associated with an increased risk for the endpoint.
Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; MM, multiple myeloma; MR, minor response; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.
The association of lenalidomide was investigated in a separate landmark model including only patients without event at 3 months and with data on maintenance therapy available ($n = 2904$ for OS and 2753 for PFS and relapse) but including the variables listed in this table and a random country effect.

TABLE 2B Multivariable analysis on outcome of patients according to characteristics at HCT.

Clinical characteristics		OS HR (95% CI)	p	PFS HR (95% CI)	p	Relapse HR (95% CI)	p	NRM HR (95% CI)	p
Age at HCT	(per 10 year increase)	1.07 (1.02–1.12)	.005	0.98 (0.96–1.01)	.23	0.96 (0.94–0.99)	.01	1.29 (1.16–1.44)	.0004
Year of HCT	(per year later)	0.92 (0.89–0.95)	<.0001	0.92 (0.90–0.93)	<.0001	0.91 (0.90–0.93)	<.0001	0.95 (0.89–1.01)	.12
Karnofsky score at HCT	100	1.00		1.00		1.00		1.00	
	≤90	1.29 (1.17–1.44)	<.0001	1.10 (1.05–1.15)	<.0001	1.08 (1.01–1.15)	.02	1.31 (1.04–1.64)	.02
HCT-CI risk score	Low (0)	1.00		1.00		1.00		1.00	
	Intermediate (1–2)	1.15 (1.04–1.27)	.006	1.01 (0.96–1.08)	.65	0.99 (0.93–1.05)	.69	1.44 (1.15–1.80)	.001
	High (≥3)	1.30 (1.17–1.45)	<.0001	1.05 (0.98–1.12)	.15	1.00 (0.94–1.07)	.93	1.92 (1.52–2.43)	<.0001
Disease stage at HCT	CR	1.00		1.00		1.00		1.00	
	VGPR	1.17 (1.04–1.32)	.01	1.25 (1.16–1.34)	<.0001	1.26 (1.17–1.36)	<.0001	1.09 (0.84–1.40)	.53
	PR	1.44 (1.28–1.63)	<.0001	1.55 (1.44–1.67)	<.0001	1.54 (1.43–1.67)	<.0001	1.58 (1.22–2.03)	.0004
	SD/MR	2.20 (1.84–2.62)	<.0001	1.88 (1.68–2.11)	<.0001	1.81 (1.61–2.04)	<.0001	2.52 (1.77–3.59)	<.0001
	Relapse/progression	5.55 (4.36–7.06)	<.0001	3.07 (2.52–3.73)	<.0001	2.98 (2.42–3.67)	<.0001	3.83 (2.06–7.12)	<.0001
Conditioning	Melphalan 200	1.00		1.00		1.00		1.00	
	Melphalan 140	1.07 (0.96–1.19)	.21	1.09 (1.02–1.16)	.01	1.06 (0.99–1.14)	.09	1.36 (1.11–1.67)	.003
Maintenance[a]	Lenalidomide	1.00		1.00		1.00			
	Other	1.36 (1.04–1.78)	.03	1.39 (1.20–1.60)	<.0001	1.36 (1.04–1.78)	.03		
	None	2.09 (1.53–2.87)	<.0001	1.61 (1.33–1.96)	<.0001	2.09 (1.53–2.87)	<.0001		

Note: The OS model included 20 355, the PFS, relapse and NRM 19873 patients. HR > 1 is associated with an increased risk for the endpoint.
Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; MM, multiple myeloma; MR, minor response; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.
[a]The association of lenalidomide was investigated in a separate landmark model including only patients without event at 3 months and with data on maintenance therapy available ($n = 2904$ for OS and 2753 for PFS and relapse) but including the variables listed in this table and a random country effect.

of older patients (>70 years) were transplanted, and tandem HCT was used routinely. The percentage of patients with high HCT-CI scores also differed between regions, with the highest percentage among patients from the USA and Malaysia and a lower percentage of high-risk patients in Japan and Latin America. Importantly, there were limitations in data collection for post-HCT consolidation and maintenance

treatment. Maintenance therapy has been shown in prior studies to improve PFS and OS.[27] With the caveat that the data being limited, our analysis showed that patients with post-AHCT lenalidomide maintenance had a lower risk of relapse with improved OS and PFS. Access to lenalidomide varies globally, which may partially explain the different outcomes observed in Malaysia. We have tried to address the important issue of drug access, but we found it more difficult than expected. First, within the same region, country approval date varies considerably. Second, there may be an important gap between approval of a drug and its reimbursement. It depends very much on the type of medical coverage whether it is state driven ("social security system") or through private insurance. Sometimes, within the same country, both types of reimbursement exist, and in the end, it is difficult to capture for a single patient whether or not the patient actually has access to these new expensive myeloma drugs. Despite these limitations, this study provides important insights into the use of AHCT in NDMM and has generated useful data on its safety and efficacy at the global level.

In conclusion, this exceptionally large study provides a high-level overview of AHCT. Despite the reassuringly low early NRM rate, differences in patient selection, transplant procedures, and outcomes across geographic regions have been identified. To our knowledge, this is the first time that real-world outcome data encompassing almost 60% of the world's transplant activity have been reported in the field of MM. Patients with MM who underwent AHCT outside of clinical trials between 2013 and 2017 had a RI of 15.7% in the first year, a median PFS of 3 years, and a median OS of 7 years, and the treatment has been increasingly utilized.[28] However, the regional differences in relapse and survival outcomes warrant further investigation. Our new transplant registry collaboration provides a framework for evaluating and improving MM outcomes globally. In addition, the experience gained also paves the way for future analyses of novel non-transplant therapies and assessment of relative global access, utilization, and outcomes.

AUTHOR CONTRIBUTIONS

LGa, LGr, MA, YA, and DN designed the study; LK, LB, AD, NEM, PH, WS, AC, MI, SO, HT, SM, KK, YK, NH, BSK, CL, KWH, ASG, SKT, AME, AB, QNC, RA, MAB, MB, CAFO, ER, SG, FB, HM, AMcC, FRW, LM, MK, JS, SS, DMcL, PH, AS, and HG enrolled patients; LGa, LGr, DNe, NH, MA, YA, and DN analyzed the data; LGa, LGr, DNe, NH, MA, YA, and DN wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data can be obtained upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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