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The impact of age on survival and excess mortality after autologous hematopoietic cell transplantation in newly diagnosed multiple myeloma patients

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The impact of age on survival and excess mortality after autologous hematopoietic cell transplantation in newly diagnosed multiple myeloma patients

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Author contributions

SM, 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, MK, JS, SS, DMcL, PH, AS, and HG enrolled patients; SM, LGa, LGr, DNe, NH, MA, YA, DR, and DN analyzed the data; SM, LGa, LGr, DNe, NH, MA, EV, YA, DR, and DN wrote the manuscript.

Conflict of interest statement

Shohei Mizuno received research funding from Hayashikane Sangyo and lecture fee from Johnson & Johnson. Anita D'Souza reports clinical trial funding to institution; Abbvie, Alexion, Prothena, Janssen, Novartis, and Regeneron; IRC, DMC, or Steering Committee role with Abbvie, BMS, Janssen, and Prothena; Advisory Board role with Abbvie, BMS, Janssen, Prothena, and Pfizer. Minako Iida received research funding from AIR WATER Inc., Hiroyuki Takamatsu received honorarium from Janssen, Ono, Sanofi, and Bristol-Myers Squibb and consultancy fee from Adaptive Biotechnologies. Koji Kawamura declares honorarium from Sanofi. John A. Snowden declares consulting fees from Medac, Jazz, MSD and Vertex. Yoshiko Atsuta received lecture fee/honorarium from Otsuka Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Novartis Pharma K.K., Meiji Seika Pharma Co., Ltd, and Janssen Pharmaceutical K.K., and consultant fee from JCR Pharmaceuticals Co., Ltd. Laurent Garderet received consultancy fee from Janssen, Bristol-Myers Squibb, Sanofi, Pfizer and GSK. All other authors declare no conflicts of interest.

Data availability statement

Datasets from the Worldwide Network for Blood and Marrow Transplantation are not publicly available outside of working groups. Access to these datasets requires permission from the WBMT executive committee. The corresponding author can be contacted at shohei@aichi-med-u.ac.jp, if the details of the datasets are required.

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Abstract

Despite the availability of novel agents, autologous hematopoietic cell transplantation (auto-HCT) remains the standard of care in newly diagnosed multiple myeloma (MM) patients. The impact of age on overall survival (OS), progression-free survival (PFS), relapse incidence, non-relapse mortality (NRM), and excess mortality (taking account of general population mortality) was investigated using information on 61,797 MM patients transplanted between 2013 and 2017. The median age at auto-HCT was 60.8 (range: 18.1–83.2) years of whom 2.0% were 18–39 years, 68.9% 40–64 years, 21.8% 65–69 years, 6.5% 70–74 years, and 0.8% ≥75 years of age, respectively. The corresponding OS probabilities at three years were 85.9%, 82.8%, 81.1%, 78.4%, and 74.8%, respectively ($p<0.001$). Excess mortality cumulative incidences were 13.1%, 15.0%, 14.6%, 15.0%, and 14.1% at three years, respectively ($p=0.67$). In multivariable analyses, older age was a significant risk factor for OS, PFS, and NRM but not for excess mortality or relapse risk. Our results indicate that advanced age alone should not preclude the use of auto-HCT in patients with MM.

Introduction：

Multiple myeloma (MM) has a worldwide prevalence that continues to increase, with over 175,000 new cases reported in 2020 [1]. The median age at diagnosis is approximately 70 years; MM is rare (<1% of all cases) in those less than 40 years of age according to the limited available information [2-5], but has a higher incidence in older individuals [6-8]. For newly diagnosed, transplant-eligible MM patients, induction therapy with proteasome inhibitors and immunomodulatory drugs followed by autologous hematopoietic cell transplantation (auto-HCT) is considered the standard of care [9-12]. Due to improvements in supportive care, auto-HCT activities in MM have gradually been extended to older patients [13] and outcomes have continued to improve. These results are expected to improve further with the addition of anti-CD38 antibodies to induction therapy leading to improved response rates and progression-free survival (PFS) [3, 14, 15]. Age is considered to be an important factor when choosing therapeutic strategies in general and especially in MM, but no age effect (<65 and ≥65 years of age) has been reported in studies to date [18]. The impact of age on outcomes in the context of known risk factors and global differences in disease management remains largely unexplored, especially in large population cohorts and in the context of excess mortality.

Using a large worldwide database, we have for the first time analyzed the associations between age at auto-HCT and both known and currently unknown (including conditioning regimens) risk factors on outcome after auto-HCT.

Methods:

The retrospective study was conducted by the Worldwide Network for Blood and Marrow Transplantation, utilizing data from its member societies and international or regional HCT registries. The study included patients with MM who underwent upfront auto-HCT between 2013 and 2017, were ≥18 years of age at auto-HCT. The supplementary material provides an overview of the reg-

istries that contributed data. The primary endpoint was overall survival (OS) and secondary endpoints were PFS, relapse incidence (RI, either progression or relapse), non-relapse mortality (NRM), and excess mortality. The study was approved by the Institutional Review Board of Aichi Medical University.

Statistical methods:

Baseline clinical, demographic, and transplantation-related characteristics were grouped according to the following age cohorts: 18–39, 40–64, 65–69, 70–74, and ≥75 years old (measured at auto-HCT), and were reported as median, range, and interquartile ranges for continuous variables. Differences between age groups were assessed using p-values obtained with the $\chi 2$ test for categorical variables and the Mann-Whitney U-test for continuous data. Median follow-up after auto-HCT and 95% confidence intervals (CI) were calculated using the reverse Kaplan-Meier method. OS was calculated as the time from auto-HCT to death from any cause, PFS as the time from auto-HCT to death, relapse or progression, RI as time to relapse (progression or relapse) after auto-HCT, and NRM as death without evidence of relapse. In analyses of OS, PFS, RI, and NRM, events occurring more than three years post auto-HCT were artificially censored. The probability of OS and PFS was estimated based on the Kaplan-Meier method and differences were analyzed using the log-rank test. Cumulative RI and NRM were modeled using the crude cumulative incidence estimator and compared between groups with Gray's test. Multivariable analyses were performed using Cox (cause-specific) proportional hazards models. Details on variables included in the models can be found in the supplementary material. A relative survival model was used to estimate the proportion of deaths in our cohort that could be attributed to general population causes (population mortality) versus the proportion related to MM, including auto-HCT and other treatment (excess mortality) [16-18]. Patients from countries with population mortality tables available in the Human Mortality Database (http://www.mortality.org/) were matched to the general

population cohort by age, sex, country, and year of auto-HCT. The excess mortality hazard was defined as the difference between the observed hazard in the patient with MM and in the matched general population cohort, assuming that the life expectancy of the patients with MM is similar to that of the general population apart from their disease and its treatment. These hazards were used to calculate the cumulative incidences of population mortality and excess mortality, which add up to all observed mortality. To estimate the association between age groups and excess mortality adjusted for measured confounders, we used Cox proportional hazards model for the excess hazard of death. All statistical tests were 2-sided, and significance was defined as $p < 0.05$. All analyses were performed in R version 4.4.2 [19] using 'survival', 'cmprsk,', 'prodlim', 'relsurv' and 'pspline' packages. No adjustment for multiple comparisons were made.

Results:

Patient characteristics

A total of 61,797 patients from 61 countries of whom 60.6% were from Europe, 26.2% from United States of America (USA), 5.1% each from Australia/New Zealand and Japan, 0.9% from the Eastern Mediterranean Region (EMRO), 0.8% from Taiwan, 0.5% from Latin America, 0.3% each from Ottawa and Malaysia, and 0.1% from Beijing were included in this analysis (Table 1). Overall, the median age at auto-HCT was 60.8 (range: 18.1–83.2) years. A total of 2.0% were patients aged 18–39 years, 68.9% 40–64 years, 21.8% 65–69 years, 6.5% 70–74 years, and 0.8% ≥75 years (Table 1). The median age varied considerably between regions and countries and was lowest in the EMRO (53.6 years) and highest in Ottawa (62.2 years; Figure 1). EMRO, Latin America, and Malaysia had the higher percentage of younger (<40 years) patients (6.4%, 4.7%, and 5.3%, respectively) as compared with Europe, USA, Australia/New Zealand, Japan, Ottawa, and Beijing (2.0%, 2.0%, 1.7%, 1.8%, 1.6%, and 1.4%, respectively) (Table 1, Figure 1 and S1). Accordingly, the percentage of patients aged ≥65 years was lower in the former group of regions

(6.9%, 12.7%, and 10.1%, respectively) as compared to the latter group of regions (27.4%, 34.8%, 32.2%, 24.5%, 36.1%, and 27.8%, respectively). The highest patient age in each region ranged from 69.4 years (Malaysia) to 83.2 years (USA and EMRO) and most of the patients aged ≥75 years (69.2%) were reported from the USA (Figure 1). Auto-HCT activity increased annually from 11,330 in 2013 to 13,530 in 2017 mainly due to more patients ≥65 years who constituted 25.0% of the total in 2013 and 32.7% in 2017 (Figure 2). As expected, IgG was the most frequent isotype (54.0%), followed by light chain (24.4%) and IgA (18.6%). A higher percentage of patients with IgG and IgA and a lower percentage with light chain isotypes were observed in the older age groups (Table 1). Younger patients were more likely to have International Staging System (ISS) stage I disease (43.9%, 39.0%, 35.8%, 34.6%, and 33.0% for age groups 18–39, 40–64, 65–69, 70–74, and ≥75, respectively) and standard-risk cytogenetic profiles (74.6%, 70.2%, 69.2%, 65.6%, and 64.5%, respectively). Auto-HCT was performed at a median of 7.1 (interquartile range: 5.5–9.9) months after diagnosis without significant differences according to age. The percentage of patients with high risk HCT-specific comorbidity index (HCT-CI) scores was 14.4% in the youngest cohort and 49.6% in the oldest age cohort. Similarly, the percentage of patients with Karnofsky performance status (KPS) ≤90 ranged from 63.4% in the youngest to 85.5% in the oldest age group. In addition, the percentage of patients in Complete response (CR) was higher in the youngest (21.9%) when compared to the oldest (14.3%) cohort. Melphalan 200 mg/m^2 was the most commonly used conditioning regimen across all ages (70.2%) but was replaced by melphalan 140 mg/m^2 in the older groups (78.4%, 75.4%, 63.2%, 40.6%, and 28.3% for 200 mg/m^2, respectively). Tandem auto-HCT was given in 6.9% of patients and information on maintenance therapy was only available in 11.1% of patients. The most commonly used maintenance regimens in the available information were lenalidomide in Europe (58.4%), in USA (57.9%), in Japan (46.2%), and in the EMRO (61.7%), imides and proteasome inhibitors (67.7%) in Taiwan, thalidomide in Latin America (38.7%) and in Beijing (44.3%) and no maintenance in

Ottawa (55.4%) and in Malaysia (67.3%). Maintenance therapy was not included in the multivariable analysis.

Transplant outcome

The median OS was 90.2 (95% CI: 88.2–93.6) months with a median follow-up of 41 (interquartile range: 19–60) months (Table S1). OS three years post-transplant declined with increasing age at auto-HCT and ranged from 85.9% (95% CI: 83.6%–88.2%) in the age group 18–39 years to 74.8% (95% CI: 70.8%–78.8%) in those ≥75 years (Figure 3a; p<0.001). Similarly, older age was associated with shorter PFS at three years (p<0.001): 55.8% (95% CI: 52.5%–59.1%), 51.3% (95% CI: 50.7%–51.8%), 49.6% (95% CI: 48.5%–50.6%), 47.3% (95% CI: 45.5%–49.1%), and 44.9% (95% CI: 40.3%–49.6%) in each age group, respectively (Figure 3b; p<0.001). The cumulative RI at three years was not significantly associated (p=0.18) with older age and was 41.8% (95% CI: 38.5%–45.0%), 45.8% (95% CI: 45.3%–46.4%), 46.2% (95% CI: 45.2%–47.2%), 47.4% (95% CI: 45.6%–49.2%), and 47.4% (95% CI: 42.7%–52.1%), respectively (Figure 3c). The cumulative incidence of NRM increased with age (p<0.001) being 0.5%, 1.3%, 2.1%, 2.2%, 3.8% at one year and 2.4%, 2.9%, 4.3%, 5.3%, 7.6% at three years, respectively (Figure 3d; Table S1).

Multivariable analysis

In multivariable analysis, age older than 64 years was significantly associated with reduced OS and PFS (p<0.001 and p=0.001, respectively; Table 2). This was due to increased NRM (p<0.001) and not to a higher risk of relapse (p=0.19). In patients younger than 40 years, borderline superior OS (p=0.05), but not PFS (p=0.24), relapse (p=0.25) or NRM (p=0.34) compared to patients aged 40–64 years was detected. Female gender was also associated with improved OS (p<0.001), PFS (p<0.001) and a lower risk of both relapse (p<0.001) and NRM (p=0.04). A more recent year of

auto-HCT was significantly associated with improved OS (hazard ratio [HR] 0.94 [95% CI 0.92–0.96]), PFS (HR 0.95, [95% CI 0.94–0.96]) and RI (HR 0.95 [95% CI 0.94–0.96]) per year later though there was no such association with NRM (p=0.45). Variables associated with worse OS, PFS and a higher risk of relapse included an isotype other than IgG, a high-risk cytogenetic profile, a higher ISS, a poorer disease status at auto-HCT, a KPS ≤90 and a lower melphalan dose of 140 mg/m^2 compared to 200 mg/m^2. The most adverse association with OS and PFS was seen in patients with relapse/progression at auto-HCT (HR compared to CR 4.84 and 3.49, respectively) and, in descending order, ISS III (HR compared to ISS I 2.23 and 1.59), a high-risk cytogenetic profile (HR compared to standard-risk 2.09 and 1.59), minor response/stable disease at auto-HCT (HR compared to CR 1.85 and 2.30), ISS II (HR compared to ISS I 1.51 and 1.25), age at auto-HCT ≥75 years (HR compared to 40–64 years 1.45 and 1.20) and other Ig isotypes (HR compared to IgG 1.49 and 1.20; Table 2). The highest risk factors for RI were relapse/progression (HR compared to CR 3.61), a high-risk cytogenetic profile (HR compared to standard-risk 1.61), ISS III (HR compared to ISS I 1.56), and IgA subtype (HR compared to IgG 1.23). Variables affecting NRM included age ≥75 years (HR compared to 40–64 years 2.11), being in relapse/progression at auto-HCT (HR compared to CR 2.05), ISS III (HR compared to ISS I 2.03), high HCT-CI risk (HR compared to low HCT-CI risk 1.84) and non-secretory isotype (HR compared to IgG 1.54).

Age was next modeled both as a continuous variable with a linear effect and, in a more flexible manner, using splines adjusted for the variables listed in Table 2. In the spline model, hazard of death increased significantly in patients aged ≥70 years, but, because of limited patient numbers, CIs were wide and were not significantly different from the linear model (p=0.17; Figure S2a). Hazards of events in PFS and relapse increased more strongly in patients aged ≥70 years and decreased more strongly in patients aged <40 years in the spline model as compared to the linear model (difference from linear model p=0.05 and p=0.06, respectively; Figure S2b-c). For NRM, the spline model was not significantly different from the linear age model (p=0.62), but

both were more strongly associated with age as compared to OS, PFS, and relapse (Figure S2d). In the linear model, the association between age and OS, PFS, relapse, and NRM was 1.10 (95% CI: 1.07–1.14), 1.03 (95% CI: 1.01–1.05), 1.01 (95% CI: 0.99–1.03), and 1.37 (95% CI: 1.28–1.47) for each ten-year increment, respectively.

Association between melphalan dose and outcome for different age at auto-HCT

We examined whether the beneficial association between high dose melphalan (200 mg/m^2 vs. 140 mg/m^2) and outcomes (Table 2) was similar across all age groups by including an interaction term between melphalan dose and age. We found a significant interaction in the analysis of OS (p=0.004), PFS (p=0.02), and relapse (p=0.04), but no significant interaction in the NRM analysis (p=0.78; Table 3). In the analyses of OS, PFS, and relapse, the beneficial association between 200 mg/m^2 melphalan and outcome after auto-HCT decreased with lower age at auto-HCT, resulting in no significant differences in OS, PFS, and relapse for patients aged 37 years at auto-HCT (median age in the group of patients <40 years of age at auto-HCT). In older patients, the beneficial association between 200 mg/m^2 melphalan and OS, PFS, relapse was stronger compared to the results obtained from the model without interaction.

Excess mortality

Population mortality tables were available for 58,620 patients from 34 countries (out of 61,797 patients from 61 countries). The excess mortality rates at one and three years attributable to MM and its treatment in this subset were 4.2% (95% CI: 4.0%–4.4%) and 14.9% (95% CI: 14.5%–15.3%), respectively, while population mortality rates at one and three years were 0.9% and 2.8%, respectively (Figure 4a and Supplementary Table S2). Excess mortality was not significantly different according to age at auto-HCT (p=0.67) and was 13.1% (95% CI: 10.7%–15.5%), 15.0% (95% CI: 14.6%–15.5%), 14.6% (95% CI: 13.8%–15.3%), 15.0% (95% CI: 13.5%–16.5%), and

14.1% (95% CI: 9.8%–18.3%) at three years in the age groups 18–39, 40–64, 65–69, 70–74, and ≥75, respectively (Figure 4b and Supplementary Table S2). Excess mortality was not significantly different between male and female patients (p=0.43) and was 15.0% (95% CI: 14.5%–15.5%) and 14.7% (95% CI: 14.2%–15.3%) at three years, respectively (Figure 4c and Supplementary Table S2). Finally, in the multivariable analyses, age was not a significant risk factor for excess mortality (p=0.30), and neither was sex (p=0.40; Table 4). As in the multivariable analysis for OS, a more recent year of auto-HCT, a higher KPS, M-protein isotype IgG, standard-risk cytogenetic, lower ISS, lower HCT-CI status and melphalan 200 mg/m^2 were associated with lower excess mortality.

Discussion:

This study was based on a comprehensive dataset of 61,797 patients with newly diagnosed MM who underwent auto-HCT worldwide between 2013 and 2017. We observed a clear age-related trend in OS and PFS, with patients aged 65–69, 70–74, and ≥75 years at the time of auto-HCT having poorer survival rates compared to those aged 40–64 years in uni- and multivariable analyses adjusted for differences in the distribution of ISS stage, high-risk cytogenetics, low KPS, HCT-CI, melphalan dose and disease stage before auto-HCT. However, in uni- and multi-variable analyses taking mortality in the general population into account, we found excess mortality to be similar in those aged 40–64, 65–69, 70–74, and ≥75 years. The NRM at one year was 0.5% in patients aged <40 years, 1.3% in patients aged 40–64 years, and 3.8% in patients aged ≥75 years. Other reports in older patients found that NRM at 100 days and one year to be approximately 1%–3% [20, 21]. One centre reported that patients aged ≤40 years transplanted after 2010 had a significantly improved median PFS (84.9 months vs. 28.2 months, p<0.001) and OS (not reached vs. 91.8 months, p<0.001) compared to those transplanted prior to 2010 [3]. Age has traditionally been used as a variable to determine eligibility for auto-HCT, with some guidelines suggesting arbitrary

cut-offs of 65 or 70 years [22, 23]. Advances in supportive care have reduced NRM [15], making auto-HCT a feasible option for older patients. Whereas in the past, a higher NRM and poorer OS [24] may have prevented older patients from being considered for this option, auto-HCT rates increased by approximately 20% between 2013 and 2017 and mostly in patients aged ≥65 years. There are relatively few reports of auto-HCT in patients aged ≥75 years. Patients are often excluded because of age, frailty or comorbidities (high-risk score for HCT-CI in our study) and global clinical practice varies considerably. Overall, the percentage of patients aged ≥75 years was less than 1% of all patients and they were predominantly treated in the USA, Europe, and Australia/New Zealand. Health insurance, age distribution in the general population, and local practice guidelines may influence this variation. Interestingly, the risk of relapse did not differ significantly in these older groups despite higher ISS stages and higher cytogenetic risk profiles. Belotti et al. reported that in patients aged 70–75 years classified as unfit according to the International Myeloma Working Group frailty score, no significant PFS difference was observed between auto-HCT and no auto-HCT [25]. However, the Center for International Blood and Marrow Transplantation Research reported that even frail patients aged 65–83 years, as classified by the simplified frailty index, have an expected 100-day NRM of <2% after auto-HCT [26]. These earlier reports, as well as our own, support the view that age alone should not be used to determine eligibility for auto-HCT.

The melphalan dose used for conditioning plays a significant role in patient outcomes. The dose is selected at the physician's discretion or based on local practice guidelines, generally according to factors such as renal function or performance status. Melphalan 140 mg/m^2 was commonly used in patients aged ≥70 years in this real-world study as well as in other reports [20, 21, 27, 28]. However, a French study reported the safety and efficacy of a melphalan dose of 200 mg/m^2 for older patients in a prospective multicentre study [29]. Another report found that OS, PFS, and NRM, but not RI, were superior in patients who received melphalan 200 mg/m^2 than in those who received melphalan 140 mg/m^2, suggesting that patient selection based on perceived frailty may

result in lower OS and PFS, and higher NRM in the melphalan 140 mg/m^2 group [28]. Our study identified a melphalan dose of 140 mg/m^2 to be a risk factor for NRM at all ages suggesting that physicians likely selected the lower melphalan dose for less fit patients, as indicated by the similar findings in these two studies. Meanwhile, Auner et al. reported similar outcomes of melphalan 140 mg/m^2 compared with 200 mg/m^2 in patients aged ≥65 years according to the remission status in a retrospective analysis [30]. Although we attempted to adjust for different variables in the multivariate analysis, there remains the potential for additional confounding by uninvestigated factors such as renal function and other factors related to frailty not fully captured by the KPS.

Shah et al. reported that auto-HCT was cost-effective compared with non-transplant approaches and should be considered in patients aged >65 years in the era of novel agents [31]. Recently, results of triplet or quadruplet therapies with anti-CD38 antibodies were published. For patients receiving daratumumab plus 1enalidomide and dexamethasone in the MAIA trial, the estimated 5-year OS and PFS rates were 66.6% and 52.1%, respectively [32]. With the quadruplet therapy in the IMROZ trial using isatuximab, lenalidomide, bortezomib and dexamethasone, the 5-year OS and PFS were 72.3% and 63.2%, respectively [33-36]. In our real-world multicenter and multiregional study, the 5-year OS and PFS were 69.6% (95% CI 69.1–70.1) and 33.8% (95% CI 33.2–34.3), respectively. However, cross trial comparisons should be interpreted with caution due to differences in patient populations (HCT ineligible, HCT-deferred. age). Whether these new drugs, either alone or in combination, further improve the results of auto-HCT in newly diagnosed MM patients should be studied prospectively. Chimeric antigen receptor T-cells and T-cell redirecting bispecific antibodies directly harness T-cell activity and have shown substantial efficacy in heavily pretreated MM patients. In the CARTITUDE-4 and KarMMA-3 trials, chimeric antigen receptor T-cells showed improved PFS compared to standard of care therapies after 1–3 prior lines of therapy in lenalidomide-refractory MM or after 2–4 prior lines of therapy in daratumumab-refractory MM patients.[37, 38] Bispecific antibodies such as teclistamab, elranatamab,

and talquetamab showed impressive single agent response rates (63% [39], 61% [40], and 60%-70% [41], respectively) in heavily pretreated patients with triple-class refractory MM..

Older age at auto-HCT and male sex were identified as prognostic factors for poorer OS; however, these factors are also associated with reduced life expectancy in the general population. Consequently, we analyzed excess mortality and found that neither age nor sex were significant prognostic factors. The small proportion of transplant recipients aged ≥75 years likely represent a highly selected group of fit patients. As a consequence, population mortality might have been overestimated and the excess mortality underestimated. Although age should be considered when assessing risk, it should not be used as the sole reason to exclude older patients from auto-HCT. The results of this study do not imply that auto-HCT is safe for all older patients. Therefore, auto-HCT has been shown to be a safe and effective treatment for older patients who have undergone thorough eligibility screening by their hematologist or oncologist. Previous studies in patients with MM have documented a short-term deterioration in health-related quality of life after auto-HCT and a recovery within 3–6 months [42, 43]. A very small proportion of patients continue to report moderate to severe symptoms that persist at one year and beyond [44]. But also, no difference in both physical and mental health scores were reported in long-term survivors of auto-HCT [45]. In addition to the presence or absence of complications, consideration of post-transplant quality of life is important.

Our study has important limitations. Reporting practices, data collection systems, and quality control measures vary between registries, leading to differences in the amount of missing information. Unfortunately, causes of death and detailed comorbidities were not reported, which prevented further analyses. Maintenance therapy policies might vary depending on regional insurance coverage and guidelines. Additionally, due to limited data on maintenance therapy, we were not able to include it as a variable in the analysis. Since maintenance therapy was reported in 84% to 90% of patients with available information across all age groups, the bias of not including

maintenance in the model may be neglectable. The rate of maintenance therapy following auto-HCT was reported to be approximately 30% in 2013, which significantly increased to approximately 80% in 2017 [46]. In the current study, the year of auto-HCT also emerged as a favorable prognostic factor for OS, PFS, and relapse. This increase in uptake of maintenance therapy over time may partly explain our observation of improved outcomes over time.

In conclusion, this large study demonstrated the age differences in patients undergoing auto-HCT in different geographical regions. Furthermore, increasing age was shown to be a risk factor for OS, PFS, and NRM in patients with MM aged ≥65 years, but not for relapse and excess mortality. In other words, auto-HCT should be considered in the treatment plan for patients deemed eligible, regardless of their age. The patients aged ≥70 years with MM undergoing auto-HCT outside of clinical trials can expect 1-year NRM of 2%–4%, 3-year PFS of 45%–48%, 3-year OS of 74%–79%, and 3-year excess mortality of 14%–15%. Auto-HCT is increasingly used [13] worldwide as a safe procedure for transplant eligible patients based on the physician's decision, especially due to the increased auto-HCT rate of patients aged ≥ 65 years. Our data provides a useful perspective as the number of older patients for whom auto-HCT may be the standard of care increases worldwide.

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Table 1: Patient characteristics at diagnosis and at autologous hematopoietic cell transplantation

Age at auto-HCT (years)	**Total**	**18–39**	**40–64**	**65–69**	**70–74**	**≥75**
All Patients, n (%)	61797 (100)	1252 (2.0)	42570 (68.9)	13452 (21.8)	4003 (6.5)	520 (0.8)
	%					
Sex						
Male	58.0	59.7	57.5	57.4	62.7	66.0
Region						
Europe	60.6	59.2	62.1	61.0	48.7	24.6
USA	26.2	25.3	24.1	26.4	43.3	69.2
Australia/New Zealand	5.1	4.2	4.9	5.8	5.4	4.2
Japan	5.1	4.6	5.4	5.1	1.8	1.2
Eastern Mediterranean	0.9	2.8	1.1	0.3	0.0	0.2
Taiwan	0.8	1.6	1.0	0.6	0.2	0.6
Latin America	0.5	1.3	0.7	0.3	0.2	
Ottawa, Canada	0.3	0.2	0.3	0.4	0.3	
Malaysia	0.3	0.7	0.3	0.1		
Beijing, China	0.1	0.1	0.1	0.1	0.0	
M-protein isotype						
IgG	54.0	50.4	53.5	55.5	56.1	55.4
IgA	18.6	13.1	18.4	19.6	19.7	20.4
Light chain	24.4	31.9	25.0	22.6	21.7	20.8
Other Ig	1.3	1.9	1.3	1.1	1.1	1.8
Non-secretory	1.7	2.8	1.8	1.2	1.4	1.6
Missing (n=1332)	*2.2*	*2.5*	*2.2*	*2.2*	*1.5*	*1.2*
ISS						
I	38.0	43.9	39.0	35.8	34.6	33.0
II	34.9	31.3	34.1	36.9	36.5	38.4
III	27.1	24.8	27.0	27.3	28.9	28.7
Missing (n=28111)	*45.5*	*43.1*	*46.2*	*45.1*	*41.4*	*32.3*
Cytogenetic risk						
Standard	69.7	74.6	70.2	69.2	65.6	64.5
High	30.3	25.4	29.8	30.8	34.4	35.5
Missing (n=34292)	*55.5*	*54.2*	*56.6*	*55.2*	*48.2*	*34.4*
At auto-HCT						
Interval diagnosis-HCT median (IQR) months	7.1 (5.5–9.9)	6.7 (5.2–9.2)	7.0 (5.5–9.9)	7.2 (5.6–10.1)	7.0 (5.5–9.6)	6.9 (5.3–9)
Year of auto-HCT						
2013	18.3	21.5	19.3	16.1	15.1	12.9
2014	18.9	18.7	19.5	18.1	16.3	15.6
2015	19.9	18.8	20.1	19.4	19.1	21.5
2016	21.0	20.0	20.3	22.6	22.8	20.6
2017	21.9	21.1	20.8	23.9	26.7	29.4
HCT-CI risk group						
Low risk (0)	51.8	62.0	54.2	48.8	39.0	25.7
Intermediate risk (1–2)	25.0	23.6	25.0	24.7	26.4	24.8
High risk (≥3)	23.2	14.4	20.8	26.5	34.6	49.6
Missing (n=17486)	*28.3*	*30.0*	*29.8*	*26.4*	*20.8*	*12.3*
KPS						
100	27.8	36.6	29.6	25.2	17.6	14.5
≤90	72.2	63.4	70.4	74.8	82.4	85.5
Missing (n=6012)	*9.7*	*9.1*	*9.9*	*10.2*	*7.7*	*4.8*

Disease status						
CR	19.2	21.9	19.8	18.0	15.7	14.3
VGPR	38.0	36.1	37.8	38.7	39.0	38.0
PR	36.2	34.6	35.8	37.0	37.9	36.6
MR/SD	4.7	5.1	4.6	4.6	5.5	7.6
Refractory/progression	1.8	2.0	1.8	1.6	1.6	2.9
Untreated	0.2	0.2	0.2	0.2	0.2	0.6
Missing (n=1379)	*2.2*	*3.4*	*2.2*	*2.4*	*2.0*	*0.8*
Conditioning regimen						
Mel 200 mg/m^2	70.2	78.4	75.4	63.2	40.6	28.3
Mel 140 mg/m^2	12.0	5.5	6.8	17.8	43.6	60.7
Mel unknown dose	14.7	12.2	14.6	16.3	12.8	8.5
Other conditioning	3.1	3.9	3.2	2.7	3.0	2.5
Missing (n=386)	*0.6*	*0.6*	*0.7*	*0.5*	*0.5*	*0.2*
Tandem auto-HCT						
No	93.1	91.2	92.4	94.8	96.1	97.3
Yes	6.9	8.8	7.6	5.2	3.9	2.7
Missing (n=75)	*0.1*	*0.2*	*0.1*	*0.1*	*0.0*	
Maintenance therapy						
Yes	88.8	84.1	89.0	89.7	87.2	83.9
None	11.2	15.9	11.0	10.3	12.8	16.1
Missing (n=54926)	*88.9*	*84.5*	*88.6*	*89.8*	*90.2*	*89.2*

Abbreviations: USA, United States; ISS, international scoring system; Auto-HCT, autologous hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; KPS, Karnofsky performance status; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; SD, stable disease; Mel, melphalan.

High cytogenetic risk was defined as: deletion 17p, and/or t(4;14), and/or t(14;16); in Europe deletion 17p, and/or t(4;14), and/or t(14;16) and/or t(14;20) and/or hypodiploid and/or 1q gain and/or deletion 1p.

Percentages for each variable are calculated excluding missing values.

Table 2: Risk estimates of the association between age at autologous hematopoietic cell transplantation and other baseline characteristics, and outcome after autologous hematopoietic cell transplantation obtained using multivariable Cox (cause-specific) proportional hazards models.

	Overall survival		Progression-free survival		Relapse		Non-relapse mortality	
Variables	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age at auto-HCT (years)		(<0.001)		(0.001)		(0.19)		(<0.001)
18–39	0.84 (0.70–1.00)	0.05	0.94 (0.85–1.04)	0.24	0.94 (0.85–1.04)	0.25	0.80 (0.52–1.25)	0.34
40–64	1.00		1.00		1.00		1.00	
65–69	1.10 (1.05–1.17)	<0.001	1.03 (1.00–1.07)	0.05	1.01 (0.98–1.04)	0.61	1.43 (1.27–1.60)	<0.001
70–74	1.23 (1.13–1.34)	<0.001	1.09 (1.03–1.15)	0.003	1.05 (0.99–1.11)	0.10	1.62 (1.36–1.94)	<0.001
≥ 75	1.45 (1.19–1.76)	<0.001	1.20 (1.05–1.36)	0.006	1.12 (0.98–1.29)	0.09	2.11 (1.48–3.02)	<0.001
Sex								
Male	1.00		1.00		1.00		1.00	
Female	0.92 (0.88–0.96)	<0.001	0.93 (0.90–0.95)	<0.001	0.93 (0.90–0.96)	<0.001	0.90 (0.81–1.00)	0.04
M-protein isotype		(<0.001)		(<0.001)		(<0.001)		(0.001)
IgG	1.00		1.00		1.00		1.00	
IgA	1.41 (1.33–1.49)	<0.001	1.23 (1.19–1.28)	<0.001	1.23 (1.19–1.28)	<0.001	1.34 (1.17–1.53)	<0.001
Light chain	1.11 (1.05–1.18)	<0.001	1.06 (1.02–1.10)	<0.001	1.06 (1.02–1.09)	0.002	1.11 (0.98–1.27)	0.10
Other Ig	1.49 (1.26–1.77)	<0.001	1.20 (1.07–1.35)	0.002	1.18 (1.04–1.32)	0.008	1.35 (0.91–2.00)	0.13
Non-secretory	1.44 (1.21–1.71)	<0.001	1.08 (0.97–1.21)	0.16	1.05 (0.93–1.18)	0.42	1.54 (1.06–2.22)	0.02
Cytogenetic risk		(<0.001)		(<0.001)		(<0.001)		(<0.001)
Standard	1.00		1.00		1.00		1.00	
High	2.09 (1.95–2.23)	<0.001	1.59 (1.53–1.66)	<0.001	1.61 (1.54–1.68)	<0.001	1.34 (1.15–1.57)	<0.001
International Staging System		(<0.001)		(<0.001)		(<0.001)		(<0.001)
I	1.00		1.00		1.00		1.00	
II	1.51 (1.40–1.64)	<0.001	1.25 (1.19–1.30)	<0.001	1.24 (1.19–1.30)	<0.001	1.45 (1.22–1.72)	<0.001
III	2.23 (2.07–2.42)	<0.001	1.59 (1.52–1.66)	<0.001	1.56 (1.49–1.64)	<0.001	2.03 (1.71–2.40)	<0.001
Time from diagnosis to HCT (per 6 months more)	1.00 (0.99–1.01)	0.68	1.00 (0.99–1.00)	0.70	1.00 (0.99–1.00)	0.54	1.00 (0.98–1.02)	0.82
Disease status at auto-HCT		(<0.001)		(<0.001)		(<0.001)		(<0.001)
CR	1.00		1.00		1.00		1.00	
VGPR	1.20 (1.12–1.28)	<0.001	1.26 (1.21–1.31)	<0.001	1.28 (1.22–1.33)	<0.001	0.99 (0.85–1.15)	0.89
PR	1.48 (1.38–1.59)	<0.001	1.58 (1.52–1.65)	<0.001	1.59 (1.52–1.67)	<0.001	1.42 (1.22–1.65)	<0.001
MR/SD	2.07 (1.85–2.30)	<0.001	1.94 (1.81–2.08)	<0.001	1.93 (1.80–2.07)	<0.001	2.01 (1.59–2.53)	<0.001
Relapse/progression	4.84 (4.29–5.47)	<0.001	3.49 (3.20–3.81)	<0.001	3.61 (3.30–3.95)	<0.001	2.05 (1.39–3.01)	<0.001

Untreated	1.08 (0.59–1.95)	0.81	1.25 (0.90–1.74)	0.18	1.26 (0.90–1.77)	0.18	0.89 (0.22–3.60)	0.87
KPS at auto-HCT								
100	1.00		1.00		1.00		1.00	
≤90	1.25 (1.18–1.33)	<0.001	1.09 (1.05–1.13)	<0.001	1.07 (1.04–1.11)	<0.001	1.33 (1.16–1.52)	<0.001
HCT-CI risk		(<0.001)		(0.05)		(0.98)		(<0.001)
Low (0)	1.00		1.00		1.00		1.00	
Intermediate risk (1–2)	1.14 (1.06–1.21)	<0.001	1.02 (0.98–1.06)	0.35	1.00 (0.96–1.04)	0.92	1.34 (1.16–1.56)	<0.001
High (≥3)	1.36 (1.26–1.45)	<0.001	1.06 (1.02–1.11)	0.004	1.02 (0.97–1.07)	0.42	1.84 (1.57–2.15)	<0.001
Year of auto-HCT (per year later)	0.94 (0.92–0.96)	<0.001	0.95 (0.94–0.96)	<0.001	0.95 (0.94–0.96)	<0.001	0.98 (0.94–1.03)	0.45
Conditioning regimen								
Melphalan 140 mg/m^2	1.00		1.00		1.00		1.00	
Melphalan 200 mg/m^2	0.89 (0.83–0.95)	<0.001	0.91 (0.87–0.95)	<0.001	0.93 (0.89–0.97)	0.002	0.71 (0.62–0.82)	<0.001
Other conditioning	0.96 (0.83–1.11)	0.59	0.91 (0.84–1.00)	0.05	0.93 (0.85–1.02)	0.14	0.78 (0.56–1.10)	0.15

Models included a country specific random effect. Overall p-values were obtained using the likelihood ratio test and test whether in multicategorical variables associations between categories and the outcome in question are all the same. Missing values were modeled using a missing category (not shown in this table).

Abbreviations: Auto-HCT, autologous hematopoietic cell transplantation; HR, hazard ratio; KPS, Karnofsky performance status; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; SD, stable disease. High cytogenetic risk was defined as: deletion 17p, and/or t(4;14), and/or t(14;16); in Europe deletion 17p, and/or t(4;14), and/or t(14;16) and/or t(14;20) and/or hypodiploid and/or 1q gain and/or deletion 1p.

Table 3: Association between melphalan dose and outcome for different ages at autologous hematopoietic cell transplantation.

	Overall survival (risk of death)		Progression-free survival (risk of relapse/ death)		Relapse		Non-relapse mortality (death without relapse)	
Age at auto-HCT	HR (95% CI) Mel 200 vs. Mel 140	p value	HR (95% CI) Mel 200 vs. Mel 140	p value	HR (95% CI) Mel 200 vs. Mel 140	p value	HR (95% CI) Mel 200 vs. Mel 140	p value
37 years	1.21 (0.95–1.53)	0.12	1.06 (0.92–1.22)	0.43	1.06 (0.92–1.23)	0.41	0.67 (0.40–1.11)	0.12
57 years	0.95 (0.87–1.04)	0.28	0.94 (0.89–0.99)	0.02	0.95 (0.90–1.01)	0.11	0.70 (0.57–0.85)	<0.001
67 years	0.84 (0.79–0.99)	<0.001	0.88 (0.84–0.92)	<0.001	0.90 (0.86–0.95)	<0.001	0.72 (0.62–0.83)	<0.001
72 years	0.79 (0.73–0.87)	<0.001	0.85 (0.81–0.90)	<0.001	0.88 (0.83–0.93)	<0.001	0.73 (0.61–0.87)	<0.001
77 years	0.75 (0.66–0.85)	<0.001	0.83 (0.77–0.89)	<0.001	0.85 (0.79–0.92)	<0.001	0.74 (0.57–0.94)	0.02
Interaction		0.004		0.02		0.04		0.78
Model without age interaction*	0.89 (0.83–0.95)	0.001	0.91 (0.87–0.95)	<0.001	0.93 (0.89–0.97)	0.002	0.71 (0.62–0.82)	<0.001

Abbreviations: Auto-HCT, autologous hematopoietic cell transplantation; HR, hazard ratio; Mel 200, melphalan 200 mg/m^2; Mel 140, melphalan 140 mg/m^2.

Mel 140 is the reference (HR = 1). Estimates of the HR of Mel 200 vs. Mel 140 are shown for example ages (37, 57, 67, 72, and 77 years; median ages of the age groups <40, 40-65, 65-70, 70-75, ≥75 respectively. Age at auto-HCT-was included in the Cox PH models as a continuous variable (covering all ages) with a linear effect on the (log) hazard. Models included, melphalan dose, interaction term age × melphalan dose, variables presented in Table 2 and a country specific random effect.

* As presented in table 2.

Table 4. Multivariable analysis of excess mortality.

	Excess mortality	
	HR (95% CI)	p
Age at auto-HCT (years)		(0.30)
18–39	0.90 (0.74-1.10)	0.29
40–64	1.00	
65–69	0.97 (0.91–1.04)	0.36
70–74	0.94 (0.84–1.06)	0.32
≥75	0.89 (0.65–1.23)	0.49
Sex		
Male	1.00	
Female	0.98 (0.93–1.03)	0.40
Year of auto-HCT (per year later)	0.93 (0.91–0.95)	<0.001
KPS at auto-HCT		
100	1.00	
≤90	1.21 (1.13–1.30)	<0.001
M-protein isotype		(<0.001)
IgG	1.00	
IgA	1.50 (1.40–1.61)	<0.001
Light chain	1.12 (1.04–1.20)	<0.001
Other Ig	1.70 (1.39–2.06)	<0.001
Non-secretory	1.55 (1.27–1.90)	<0.001
Cytogenetic risk		(<0.001)
Standard	1.00	
High	2.25 (2.07–2.44)	<0.001
International Staging System		(<0.001)
I	1.00	
II	1.66 (1.50–1.84)	<0.001
III	2.64 (2.40–2.92)	<0.001
Time diagnosis auto-HCT (per 6 months more)	1.00 (0.99–1.01)	0.41
Disease status at auto-HCT		(<0.001)
CR	1.00	
VGPR	1.24 (1.13–1.35)	<0.001
PR	1.57 (1.44–1.72)	<0.001
MR/SD	2.21 (1.95–2.51)	<0.001
Relapse/progression	5.95 (5.20–6.82)	<0.001
Untreated	0.77 (0.31–1.93)	0.58
HCT-CI risk		(<0.001)
Low (0)	1.00	
Intermediate risk (1–2)	1.05 (0.97–1.14)	0.19
High (≥3)	1.18 (1.09–1.28)	<0.001
Conditioning regimen		(<0.001)
Melphalan 140 mg/m^2	1.00	
Melphalan 200 mg/m^2	0.87 (0.80–0.95)	0.001
Other conditioning	0.97 (0.81–1.16)	0.75

Auto-HCT, autologous hematopoietic cell transplantation; HR, hazard ratio; KPS, Karnofsky performance status; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; SD, stable disease

Legend to the figure:

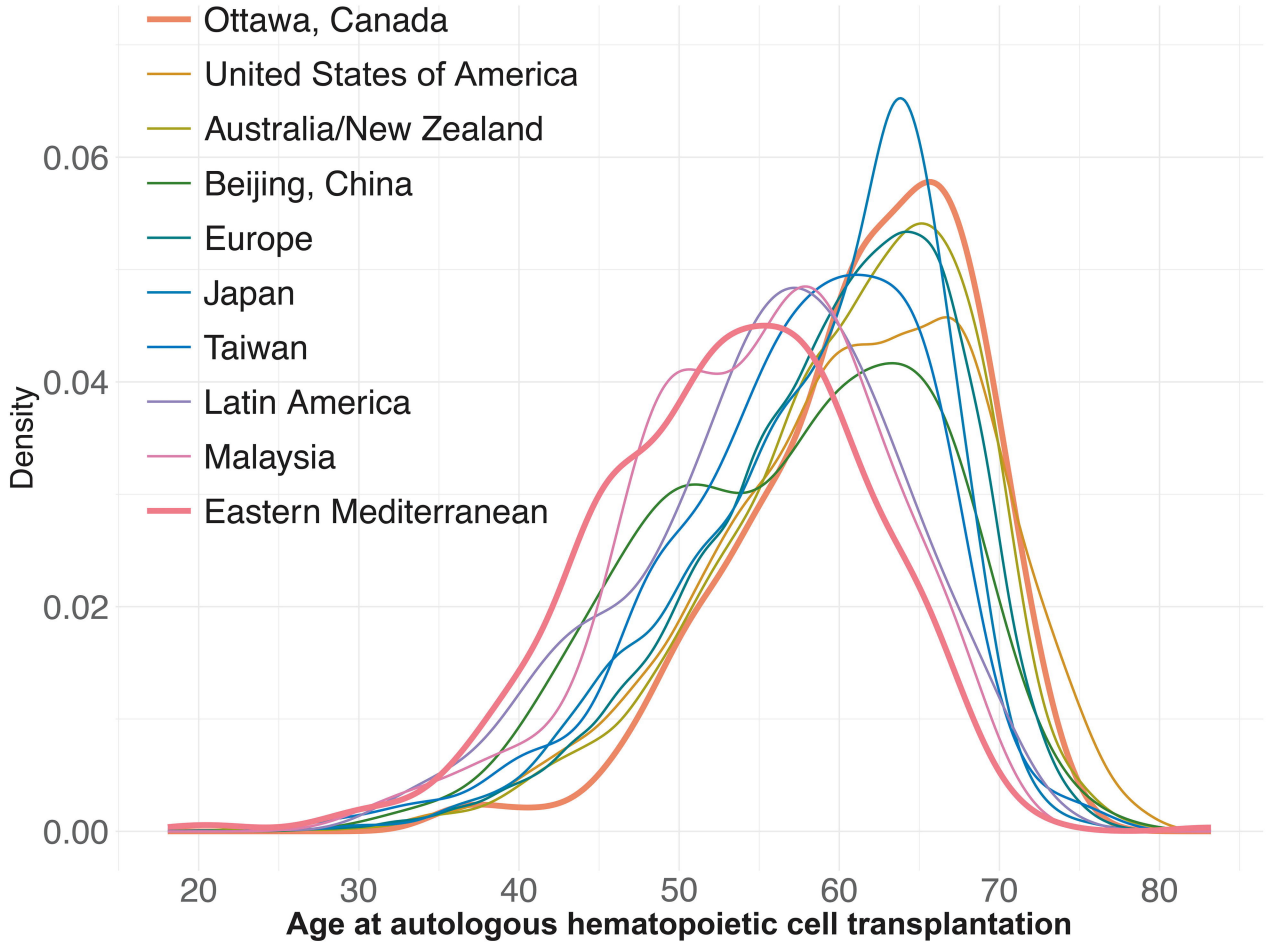
Figure 1. Age distribution at autologous hematopoietic cell transplantation according to region. Abbreviation; y, years

Figure 2. Annual number of autologous hematopoietic cell transplantation by categories of age at autologous hematopoietic cell transplantation.

Figure 3. Transplant outcomes in multiple myeloma by age group: (a) Overall survival. (b) Progression-free survival. (c) Cumulative incidence of relapse. (d) Cumulative incidence of non-relapse mortality.

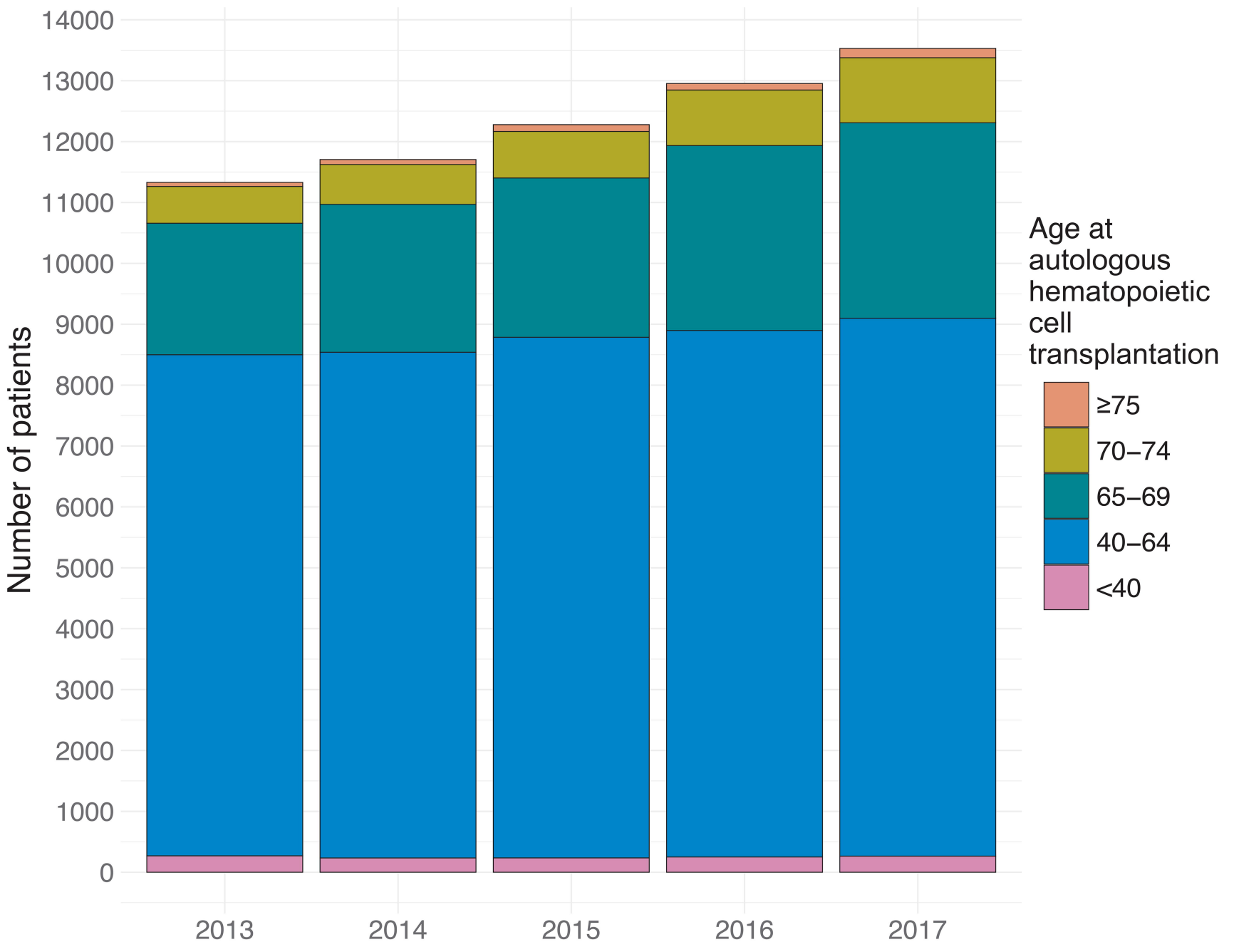
Figure 4. Population mortality and excess mortality on 58,620 patients from 34 countries: (a) all patients. (b) by age at autologous hematopoietic cell transplantation. (c) by sex.

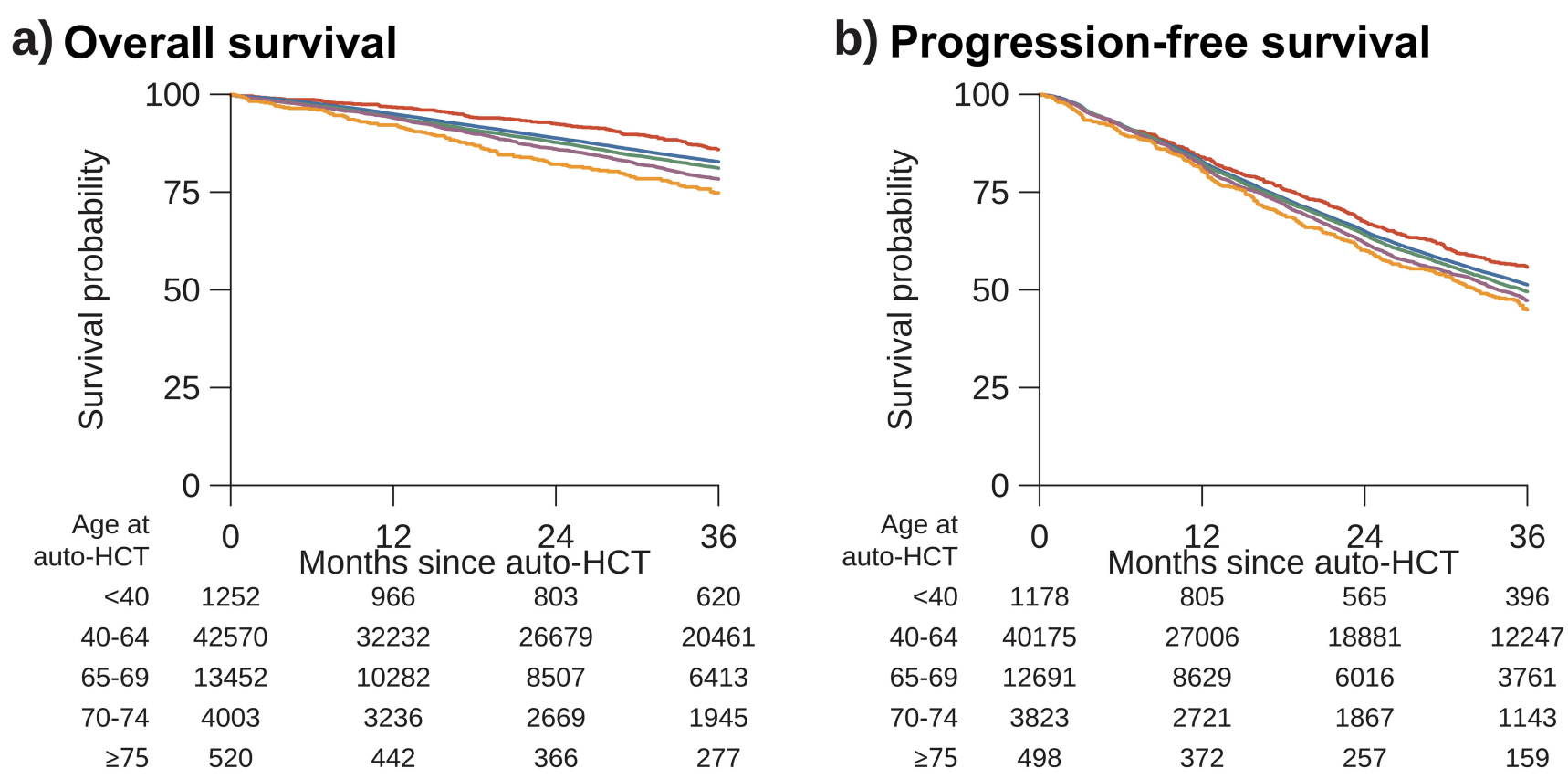
A



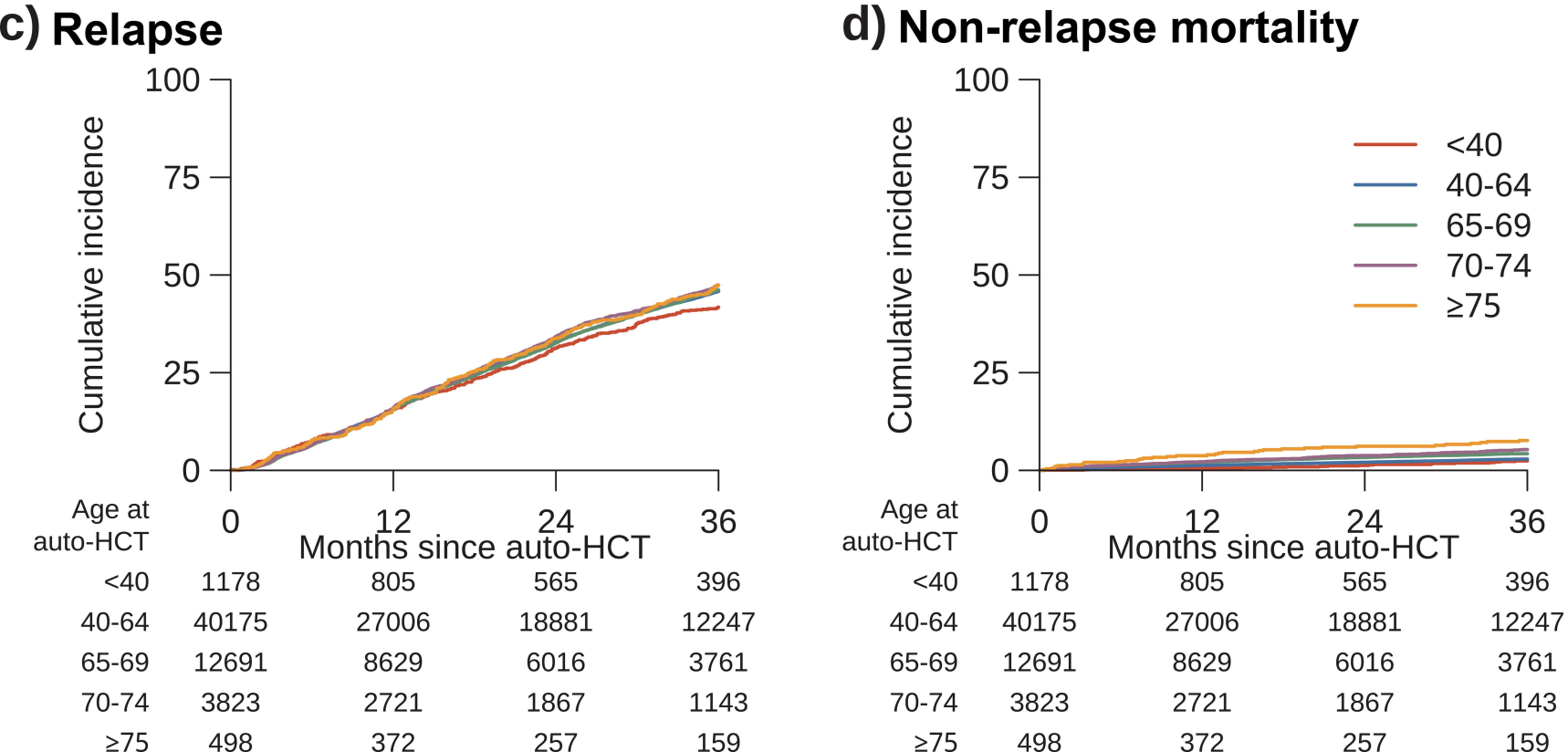
B

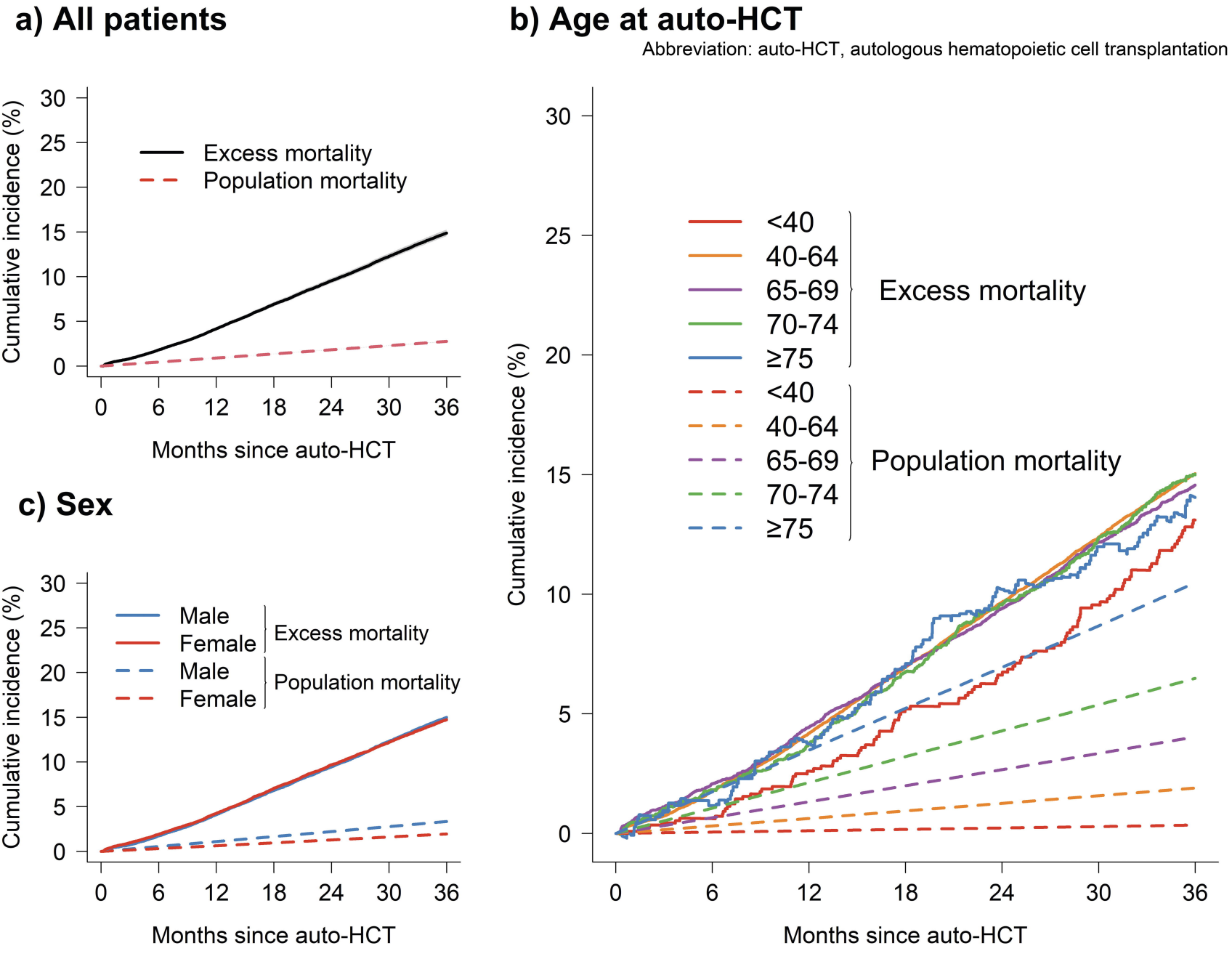
Region	Total n	18–39 n (%)	40–64 n (%)	65–69 n (%)	70–74 n (%)	≥75 n (%)	Age (years) Median	Age (years) Range
Total	61797	1252 (2.0)	42570 (68.9)	13452 (21.8)	4003 (6.5)	520 (0.8)	60.8	18.1–83.2
Europe	37459	741 (2.0)	26439 (70.6)	8203 (21.9)	1948 (5.2)	128 (0.3)	60.7	18.1–82.8
United States of America	16217	317 (2.0)	10260 (63.3)	3546 (21.9)	1734 (10.7)	360 (2.2)	61.5	20.2–83.2
Australia/ New Zealand	3164	53 (1.7)	2094 (66.2)	780 (24.7)	215 (6.8)	22 (0.7)	61.6	22.1–79.5
Japan	3122	57 (1.8)	2300 (73.7)	688 (22.0)	71 (2.3)	6 (0.2)	60.0	25.0–77.0
Eastern Mediterranean	543	35 (6.4)	471 (86.7)	34 (6.3)	2 (0.4)	1 (0.2)	53.6	19.1–83.2
Taiwan	524	20 (3.8)	415 (79.2)	77 (14.7)	9 (1.7)	3 (0.6)	58.5	28.2–75.7
Latin America	339	16 (4.7)	280 (82.6)	35 (10.3)	8 (2.4)		56.0	21.0–74.0
Ottawa, Canada	188	3 (1.6)	117 (62.2)	54 (28.7)	14 (7.4)		62.2	36.5–73.1
Malaysia	169	9 (5.3)	143 (84.6)	17 (10.1)			56.0	30.5–69.4
Beijing, China	72	1 (1.4)	51 (70.8)	18 (25.0)	2 (2.8)		59.0	34.0–79.5


14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Number of patients
2013
2014
2015
2016
2017
Age at autologous hematopoietic cell transplantation
≥75
70–74
65–69
40–64
<40



Abbreviation: auto-HCT, autologous hematopoietic cell transplantation




a) All patients
Cumulative incidence (%)
Excess mortality
Population mortality
Months since auto-HCT
b) Age at auto-HCT
Abbreviation: auto-HCT, autologous hematopoietic cell transplantation
Cumulative incidence (%)
<40
40-64
65-69
70-74
≥75
Excess mortality
<40
40-64
65-69
70-74
≥75
Population mortality
Months since auto-HCT
c) Sex
Cumulative incidence (%)
Male
Female
Excess mortality
Male
Female
Population mortality
Months since auto-HCT

Supplementary material

Data source

This study included patients with multiple myeloma (MM) who underwent upfront autologous hematopoietic cell transplantation (auto-HCT) between 2013 and 2017, were ≥18 years of age at auto-HCT and were from the following regional registries:

1) Asian-Pacific Blood and Marrow Transplantation Group (APBMT; www.apbmt.org) with its reporting registries

a. Australia and New Zealand Transplant & Cellular Therapies (ANZTCT; www.anztct.org.au)

b. Myeloma Transplant Registry, Ministry of Health, Malaysia (MTRMOHM)

c. Japanese Society for Transplantation and Cellular Therapy/The Japanese Data Center for Hematopoietic Cell Transplantation (JSTCT/JDCHCT)

d. Taiwan Society of Blood and Marrow Transplantation (TBMT)

e. Beijing Bone Marrow Transplant registry

2) Canadian registry using the Ottawa Blood Disease Center MM Database (OBDCMMD)

3) Center for International Blood and Marrow Transplantation Research (CIBMTR; www.cibmtr.org) for the United States of America

4) European Society for Blood and Marrow Transplantation (EBMT; www.ebmt.org)

5) Eastern Mediterranean Blood and Marrow Transplant Group (EMBMT) for the Eastern Mediterranean Region (EMRO)

6) Latin American Blood and Marrow Transplantation Group (LABMT) for Latin America

Registries reported all auto-HCTs without restrictions on diagnosis and auto-HCT interval, except CIBMTR, which provided information on patients with intervals of ≤12 months. No additional informed consent from patients was required, since anonymized data were used and no personal information shared. The study was approved by the Institutional Review Board of Aichi Medical University.

Statistical analysis

Multivariable analyses were performed using Cox (cause-specific) proportional hazards models including a random effect for country. Age at auto-HCT was used in the multivariable analyses as a categorical and as a continuous variable (assuming a linear association between age and the log-hazard of outcome) and, in a more flexible manner, using penalized splines [1]. Models further included patient sex, year of auto-HCT, disease stage at auto-HCT, Karnofsky performance status (KPS), myeloma sub-classification, melphalan conditioning dosage, time from diagnosis to auto-HCT, HCT-specific comorbidity index (HCT-CI), International Staging System (ISS) at diagnosis, and cytogenetic risk. High cytogenetic risk was defined as: deletion 17p, and/or t(4;14), and/or t(14;16); in Europe deletion 17p, and/or t(4;14), and/or t(14;16) and/or t(14;20) and/or hypodiploid and/or 1q gain and/or deletion 1p. Complete response, very good partial response, partial response, minor response/stable disease, and relapse/progression were defined according to the International Myeloma Working Group criteria [2]. Conditioning was split between melphalan 140 mg/m^2 and 200 mg/m^2 and named others in combination with additional drugs for conditioning. We analyzed whether the association between the melphalan dose and outcome after auto-HCT was similar across ages by including an interaction term age

at auto-HCT (included as a continuous variable, as described above) × conditioning in the models. Maintenance therapy was reported in 11% and not included in the multivariable analysis. Missing values were modeled using a separate missing category.

References

1. Therneau T. Splines Terms in a Cox Model. https://cran.r-project.org/web/packages/survival/vignettes/splines.pdf. 2024.
2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17(8):e328-e346.

Supplementary Table S1. Outcome after auto-HCT for multiple myeloma according to age

Supplementary Table S2. Estimates of excess mortality after auto-HCT due to disease/auto-HCT procedure and population mortality according to sex and age, obtained using relative survival models.

Supplementary Figure S1. Distribution of age at auto-HCT by region

Supplementary Figure S2. Multivariable analysis using age at auto-HCT as a continuous linear variable and more flexibly using restricted cubic splines: (a) Overall survival. (b) Progression-free survival. (c) Cumulative incidence of relapse. (d) Cumulative incidence of non-relapse mortality. Shaded areas show the 95% confidence intervals.

Table S1. Outcome after auto-HCT for MM according to age

Age at auto-HCT (years)	Total	18–39	40–64	65–69	70–74	≥75
OS % at 3 years (95%CI %)	82.1 (81.7–82.4)	85.9 (83.6–88.2)	82.8 (82.3–83.2)	81.1 (80.4–81.9)	78.4 (76.9–79.8)	74.8 (70.8–78.8)
PFS % at 3 years (95%CI %)	50.6 (50.2–51.1)	55.8 (52.5–59.1)	51.3 (50.7–51.8)	49.6 (48.5–50.6)	47.3 (45.5–49.1)	44.9 (40.3–49.6)
RI % at 3 years (95%CI %)	46.0 (45.5–46.4)	41.8 (38.5–45.0)	45.8 (45.3–46.4)	46.2 (45.2–47.2)	47.4 (45.6–49.2)	47.4 (42.7–52.1)
NRM % at 1 year (95%CI %)	1.5 (1.4–1.6)	0.5 (0.1–0.9)	1.3 (1.1–1.4)	2.1 (1.9–2.4)	2.2 (1.7–2.7)	3.8 (2.1–5.5)
NRM% at 3 years (95%CI %)	3.4 (3.2–3.6)	2.4 (1.4–3.4)	2.9 (2.7–3.1)	4.3 (3.9–4.7)	5.3 (4.5–6.1)	7.6 (5.2–10.1)
Median OS months	90.2	not reached	93.9	85.1	79.3	72.9

Table S2. Probabilities of excess mortality after auto-HCT (NRM, relapse incidence) and mortality in the general population according to sex and age obtained using relative survival models. It is assumed that the life expectation of the MM patients is similar to that of the general population apart from their disease and treatment.

	Excess mortality after auto-HCT % (95% CI)			Population mortality %		
at months	12	24	36	12	24	36
All	4.2 (4.0–4.4)	9.5 (9.3–9.8)	14.9 (14.5–15.3)	0.9	1.8	2.8
Age at auto-HCT (years)						
18–39	2.6 (1.7–3.6)	6.7 (5.1–8.4)	13.1 (10.7–15.5)	0.1	0.2	0.3
40–64	4. 2 (4.0–4.4)	9.7 (9.3–10.0)	15.0 (14.6–15.5)	0.6	1.3	1.9
65–69	4.4 (4.0–4.9)	9.4 (8.8–10.1)	14.6 (13.8–15.3)	1.3	2.7	4.0
70–74	3.7 (3.0–4.6)	9.6 (8.4–10.8)	15.0 (13.5–16.5)	2.1	4.3	6.5
≥75	3.7 (1.3–6.0)	10.2 (6.6–13.6)	14.1 (9.8–18.3)	3.5	6.9	10.5
Sex						
Male	4.1 (3.9–4.4)	9.4 (9.1–9.9)	15.0 (14.5–15.5)	1.1	2.2	3.3
Female	4.3 (4.0–4.6)	9.7 (9.3–10.1)	14.7 (14.2–15.3)	0.6	1.3	1.9

Figure S1. Distribution of age at auto-HCT by region

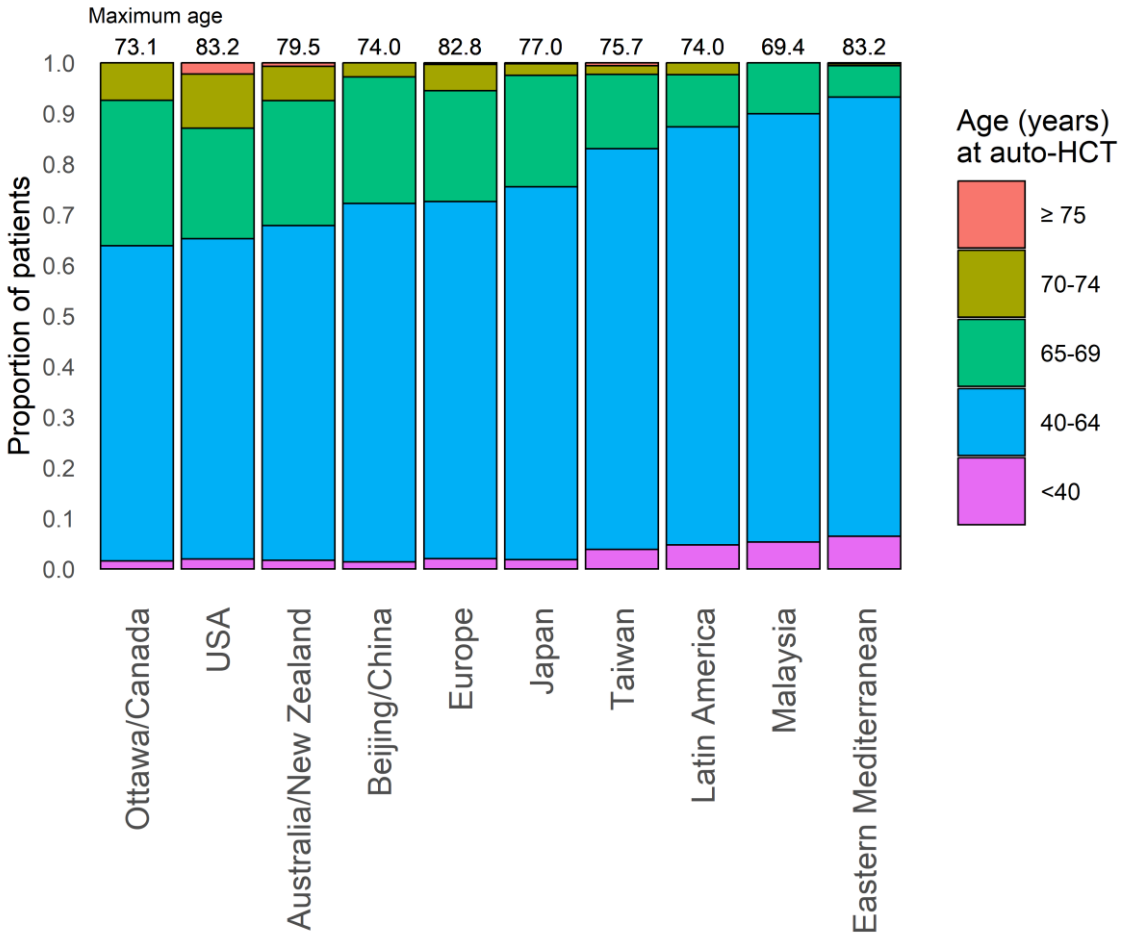


Figure S2. Adjusted hazard ratios (HR) by age at allo-HCT (with 65 years as reference, i.e., HR = 1) obtained using age at auto-HCT as a continuous linear variable and more flexibly using penalized splines: (a) Overall survival. (b) Progression-free survival. (c) Cumulative incidence of relapse. (d) Cumulative incidence of non-relapse mortality. Shaded areas show the 95% confidence intervals.