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

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Received: April 17, 2025.
Accepted: July 23, 2025.
Early view: July 31, 2025.

https://doi.org/10.3324/haematol.2025.288041

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

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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

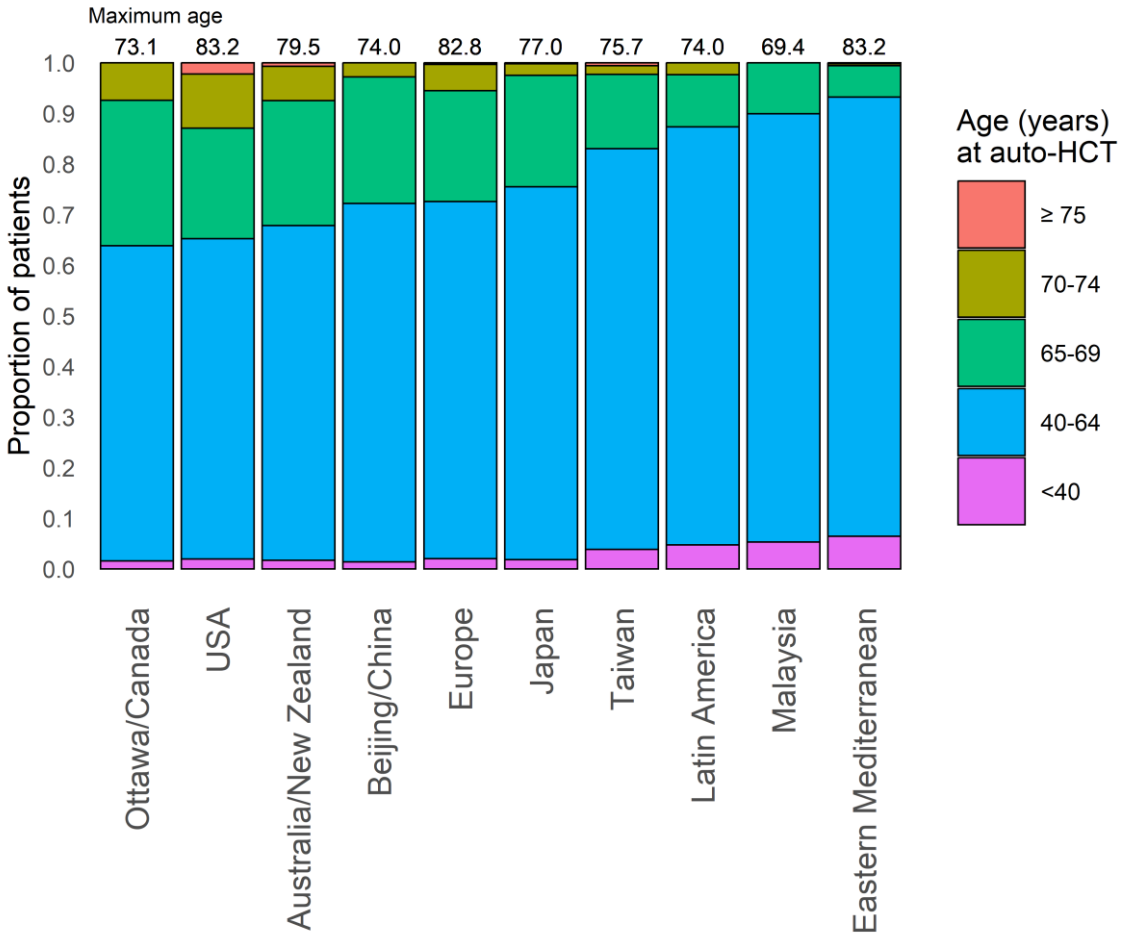

Figure S2. Adjusted hazard ratios (HR) by age at allo-HCT (with 65 years as reference, i.e., HR = 1) obtained using age at auto-HCT as a continuous linear variable and more flexibly using penalized splines: (a) Overall survival. (b) Progression-free survival. (c) Cumulative incidence of relapse. (d)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