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Use of upfront autologous stem cell transplantation in myeloma patients aged >65 years: a population-based study by the Nordic Myeloma Study Group

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KLFM participated in research design, acquisition, analysis and interpretation of data, wrote the original draft of the paper.

SR, AGS, VV, DL participated in research design, acquisition, analysis and interpretation of data, review of the paper.

AG, JT participated in research design, analysis and interpretation of data, review of the paper.

JNN, AK, KP, MP, AS participated in acquisition and interpretation of data, review of the paper.

VP participated in interpretation of data, review of the paper.

ST, DK-B, AL, FS, AJV, CHB participated in research design, interpretation of data, review of the paper.

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JT: Honoraria from AstraZeneca.

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ST: Honoraria from Abbvie, Thermo Fisher Scientific.

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CHB: Honoraria from Takeda, Amgen, Johnson & Johnson, Pfizer, Thermo Fisher, Sanofi.

Running head

Upfront ASCT in real-world MM patients 66-70 years

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Data sharing statement

The registry data that support the findings of this study are available from the Swedish Myeloma Registry, Danish Multiple Myeloma Registry, Cancer Registry of Norway and Icelandic Cancer

Registry. Restrictions apply to the availability of these data, which were used under license for this study. Data from the chart reviews are available from the authors on reasonable request, and in accordance with the ethical and data protection approvals of the study.

Acknowledgments

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Letter to the editor

An increasing number of newly diagnosed multiple myeloma (NDMM) patients aged above 65 years are treated with autologous stem cell transplantation (ASCT)[1]. Whether this reflects rising numbers of transplant eligible multiple myeloma (MM) patients due to an ageing population, or true changes in treatment patterns, is unknown. Three recent randomized clinical trials challenged the role of ASCT for patients ≤65 years in the era of modern MM treatment[2–4]. They all found improved progression-free survival[2–4], while one of the studies also demonstrated a survival benefit with ASCT[4]. Our study shows that an increasing proportion of NDMM patients aged 66-70 years were treated with upfront ASCT, reflecting a change in clinical practice. Upfront ASCT for selected patients aged 66-70 years was equally safe and effective as in younger patients.

The aims of the study were to investigate whether the proportion of NDMM patients >65 years treated with upfront ASCT was increasing. Additionally, we evaluated the response and survival of patients aged 66-70 and 71-75 years compared to those aged ≤65 years, to determine the safety and efficacy of expanding the use of ASCT to older MM patients.

We included NDMM patients aged 18-75 years in 6 countries in the Nordic and Baltic regions in the calendar period January 1st 2008 until December 31st 2020, with follow-up until December 31st 2021. Data were collected from the population-based nationwide Swedish Myeloma Registry, Danish Multiple Myeloma Registry, Cancer Registry of Norway and Icelandic Cancer Registry. Retrospective reviews of electronic health records of individual patients were conducted in Norway, Lithuania, Estonia, and Iceland. Icelandic data were available for the calendar period 2008-2018. Until 2015, ASCT was conducted at only one center in Lithuania, and patients treated at the second center were not included in this study. Induction treatment before ASCT was grouped, regardless of number of lines of therapy and reason for change of therapy. High-risk fluorescence in situ hybridization (FISH) was defined according to the International Myeloma Working Group (IMWG) criteria as deletion 17p and/or translocation (4;14) and/or translocation (14;16)[5], with cut-offs according to institutional standards.

To determine the proportion of NDMM patients undergoing ASCT, participants were excluded if there was no representative total NDMM population for comparison (Lithuania and a small proportion of Norwegian patients). For analyses of survival, we excluded patients diagnosed in 2020 due to incomplete reporting of survival in some of the datasets. Patients >75 years were excluded (n=2).

The annual proportion of NDMM patients undergoing ASCT, along with response rates and survival at 100 days, 1, 3, and 5 years, were calculated per country across three age groups (18–65, 66–70, 71–75 years). In Denmark and Sweden, outcomes were further stratified by high- vs. standard-risk FISH for 2015–2020. Response was assessed using IMWG criteria[6]. Data from all six countries were aggregated. Proportions were compared using Chi-squared tests, and trends in ASCT rates were analyzed via log-binomial regression. Due to robust mortality data in national registries and electronic health records, loss to follow-up was considered negligible, allowing overall survival (OS) estimation via empirical survival functions based on aggregated survival ratios. 95% confidence intervals (CI) were calculated using 1,000 bootstrap iterations.

To validate this approach, OS estimates were compared with Kaplan–Meier results in the Swedish cohort. A composite endpoint (survival at one year and very good partial response (VGPR) or better) was used as a surrogate for ASCT success. Analyses were conducted in R and STATA (versions 17 and 18).

The study was approved by national and institutional formally constituted ethical review boards and data protection agencies according to each country's national regulations. Due to the large study population, individual patients were not identifiable. Although the patients were fit at the time of their diagnosis and ASCT, many of them were frail or deceased at the time of the study. Only including patients well enough to consent would have introduced a significant bias, and the most vulnerable patients would have been underrepresented. All ethical review boards therefore considered that the patients were exempt from the requirement of informed consent. The study was conducted in accordance with the Helsinki Declaration of 1975, revised in 2013.

In total, 12,369 patients aged 18-75 years were diagnosed with MM in the 5 evaluable countries during the study period. The proportion of patients aged 18-65 treated with ASCT was 70% and remained stable during the study period. In contrast, the proportion of patients aged 66-70 years treated with ASCT increased 2.7-fold from 16% in 2008 to 37% during 2015-2020 (relative risk of ASCT=2.69; 95% CI 2.19-3.31; p<0.001) (Figure 1). Only 1.8% of patients (n=82) aged 71-75 received upfront ASCT, with a non-significant increasing trend (Figure 1). There was no difference between the proportion of women and men treated with upfront ASCT for the total population or any of the age groups (Supplemental Table S1).

5,753 patients were treated with upfront ASCT. Of these, 4,676 (81.4%) were 18-65 years, 993 (17.2%) were 66-70 years and 82 (1.4%) were 71-75 years at diagnosis. Distribution of sex and

baseline characteristics of MM were as expected and were consistent between the countries (Supplemental Table S2). More than 90% of patients received a proteasome inhibitor and/or an immunomodulatory agent as part of treatment before ASCT. Sixty-four (1%) patients were treated with daratumumab-based induction regimens (Supplemental Table S2).

There was no difference between the age groups regarding the proportion of patients achieving a response rate of VGPR or better (Table 1).

Patients of all age groups demonstrated an improving trend in 3- and 5-year OS with more recent transplant dates, while 1-year OS remained stable (Supplemental Figure S1). When stratifying survival by age, the 1-year, 3-year and 5-year OS were comparable for the youngest two age groups with 5-year OS 68.7% (95% CI 66.9-70.4) for the age group 18-65 years, 66.8% (95% CI 62.3-71.2) for the age group 66-70 years, and 57.1% (CI 95% 28.6-78.6) for the age group 71-75 years (overlapping CI with the other age groups) (Table 1 and Figure 2). Validation of the OS in the Swedish cohort confirmed the validity of the statistical method.

There was significantly longer 3-year OS for patients with standard-risk FISH compared to high-risk FISH in the Danish and Swedish cohorts. There was a trend towards the same within the three age groups, but the analysis was limited by small numbers and relatively short follow-up time.

Regarding the composite endpoint of achieving VGPR or better and being alive 1 year after ASCT, the proportion was similar for all patients (Table 1). Despite an increasing proportion of patients above the age of 65 years undergoing ASCT, 100-day mortality remained low at 0.9% for the total cohort, and there was no statistically significant difference between the age cohorts.

Our study shows that in a real-world setting, upfront ASCT for selected patients aged 66-70 years was equally safe and effective as in younger patients. This is in accordance with a systematic review and meta-analysis of ASCT in patients aged >65 years[7], and recent clinical trials[8–10].

Several studies have demonstrated the benefit of using quadruplet-based therapies including CD38-antibodies in first line treatment of both patients who are transplant-eligible[8] and either not eligible for transplant or with deferred transplant[11–14]. In the ongoing CARTITUDE-6 study, CAR-T is challenging the role of ASCT in first line (clinicaltrials.gov NCT05257083), and the optimal timing of treatment with bispecific antibodies has yet to be determined. Further studies are required to confirm these clinical trial findings in population-based real-world studies.

Our results suggest that the use of ASCT was lower in 2020. This was most likely due to both a change in practice and a lack of reporting during the Covid-19-pandemic. Future studies will reveal whether this was the start of a new trend, and whether it will affect the use of delayed transplants and OS for patients diagnosed during the pandemic years.

The strengths of this study include its large sample size, comprehensive reporting in the registries[15] and the unselected, multinational, population-based cohort derived from routine clinical practice. Patients had access to publicly funded healthcare systems, ensuring equal access to the treatment regimens that were reimbursed at the time. Limitations include lack of data on comorbidities, performance status, excess mortality due to myeloma and its treatment, a low proportion of patients treated with CD38-antibodies in first line, details of dosing and timing of treatments.

In this large, population-based multinational study reflecting real-world ASCT utilization and outcomes, we observed an increasing proportion of patients aged 66-70 with NDMM receiving ASCT, due to evolving clinical practice. Upfront ASCT was equally effective and safe in selected patients aged 66-70 as in younger patients. These findings have practical implications for healthcare planning, given the ageing and increasingly fit population in many countries. Our results support the current clinical trend towards an ambitious treatment approach including ASCT, for selected NDMM patients up to age 70 and potentially beyond, reinforcing its role as a standard of care. We recommend that future randomized trials on ASCT avoid excluding patients solely due to age.

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Table

Table 1: Overall survival and response rates of patients treated with autologous stem cell transplantation, by age groups

	Age group (years)	Total population (n)	Overall survival (95% CI)
1-year OS	18-65	4574	96.1% (95.6-96.6)
	66-70	956	97.5% (96.4-98.3)
	71-75	70	95.7 % (91.4-100.0)
3-year OS	18-65	3521	82.9% (81.5-84.1)
	66-70	645	83.9% (80.9-86.5)
	71-75	31	74.2% (58.1-87.1)
5-year OS	18-65	2790	68.7% (66.9-70.4)
	66-70	424	66.8% (62.3-71.2)
	71-75	14	57.1% (28.6-78.6)
Response ≥VGPR	18-65	4574	73.4% (72.1-74.6)
	66-70	956	74.9% (72.1-77.6)
	71-75	70	75.7% (65.7-85.7)
Response ≥VGPR and alive 1 year after ASCT	18-65	4574	70.8% (69.5-72.1)
	66-70	956	73.0% (70.2-75.6)
	71-75	70	72.9% (62.9-82.9)

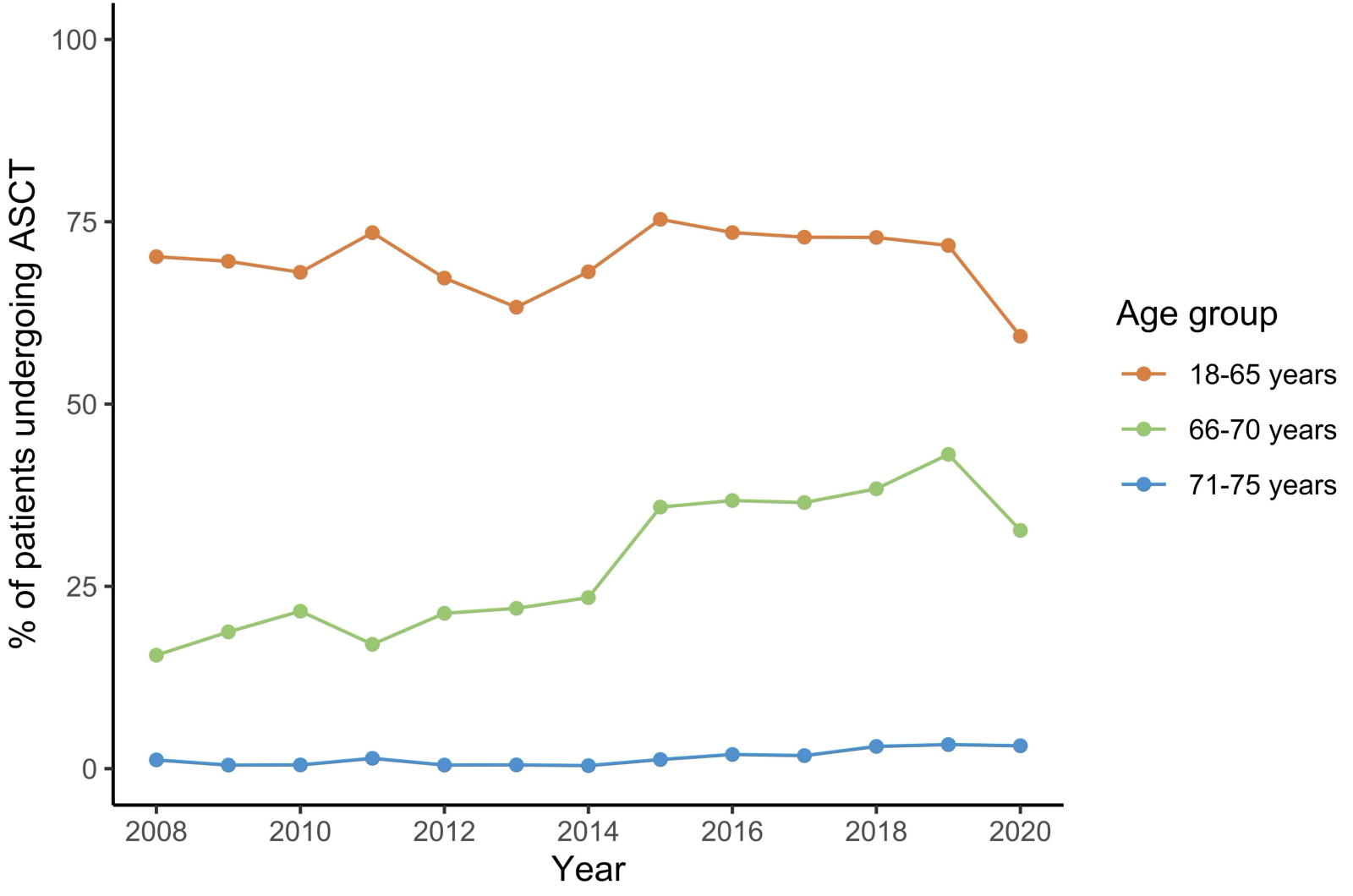
ASCT; Autologous stem cell transplantation. CI; Confidence interval. OS; Overall survival. VGPR; Very good partial response.

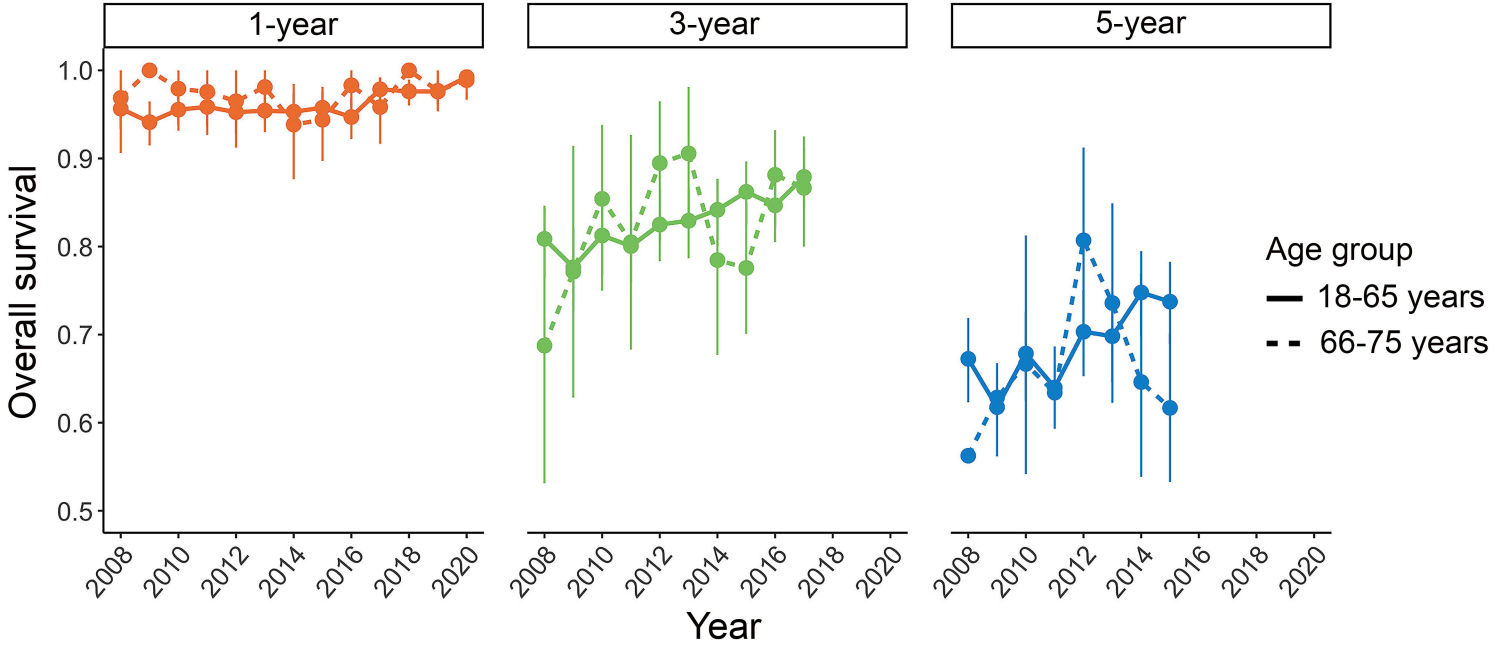
Figure legends

Figure 1: The proportion of newly diagnosed multiple myeloma patients treated with autologous stem cell transplantation. The proportion of newly diagnosed myeloma patients treated with autologous stem cell transplantation by age group for Sweden, Norway, Denmark, Estonia, Iceland.

ASCT; Autologous stem cell transplantation

Figure 2: Overall survival at 1 year, 3 years and 5 years of all patients treated with autologous stem cell transplantation, by age groups 18-65 years and 66-75 years. All transplanted patients from all 6 countries


100
75
50
25
0
% of patients undergoing ASCT
2008
2010
2012
2014
2016
2018
2020
Year
Age group
18-65 years
66-70 years
71-75 years


1-year
3-year
5-year
Overall survival
1.0
0.9
0.8
0.7
0.6
0.5
2008
2010
2012
2014
2016
2018
2020
Year
Age group
18-65 years
66-75 years

Supplemental Table S1: Proportion of patients treated with upfront autologous stem cell transplantation 2008-2020, by country, age group and sex

	Total population (n)				Denmark				Estonia			
	Not ASCT		ASCT		Not ASCT		ASCT		Not ASCT		ASCT	
Age group	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
18-65	1066	758	2494	1688	221	147	584	435	49	62	105	101
66-70	1242	961	526	366	307	198	143	119	50	56	19	23
71-75	1960	1349	40	19	460	355	5	4	63	72	5	5
Total	4268	3068	3060	2073	988	700	732	558	162	190	129	129

	Iceland				Lithuania				Norway				Sweden			
	Not ASCT		ASCT		Not ASCT		ASCT		Not ASCT		ASCT		Not ASCT		ASCT	
Age group	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
18-65	24	23	30	22	NA	NA	222	222	402	299	657	437	370	227	1118	693
66-70	15	13	6	7	NA	NA	40	41	385	282	96	64	485	412	262	153
71-75	0	0	5	1	NA	NA	5	10	570	344	7	2	867	578	23	8
Total	39	36	41	30	NA	NA	267	273	1357	925	760	503	1722	1217	1403	854

ASCT; Autologous stem cell transplantation. NA; Not available

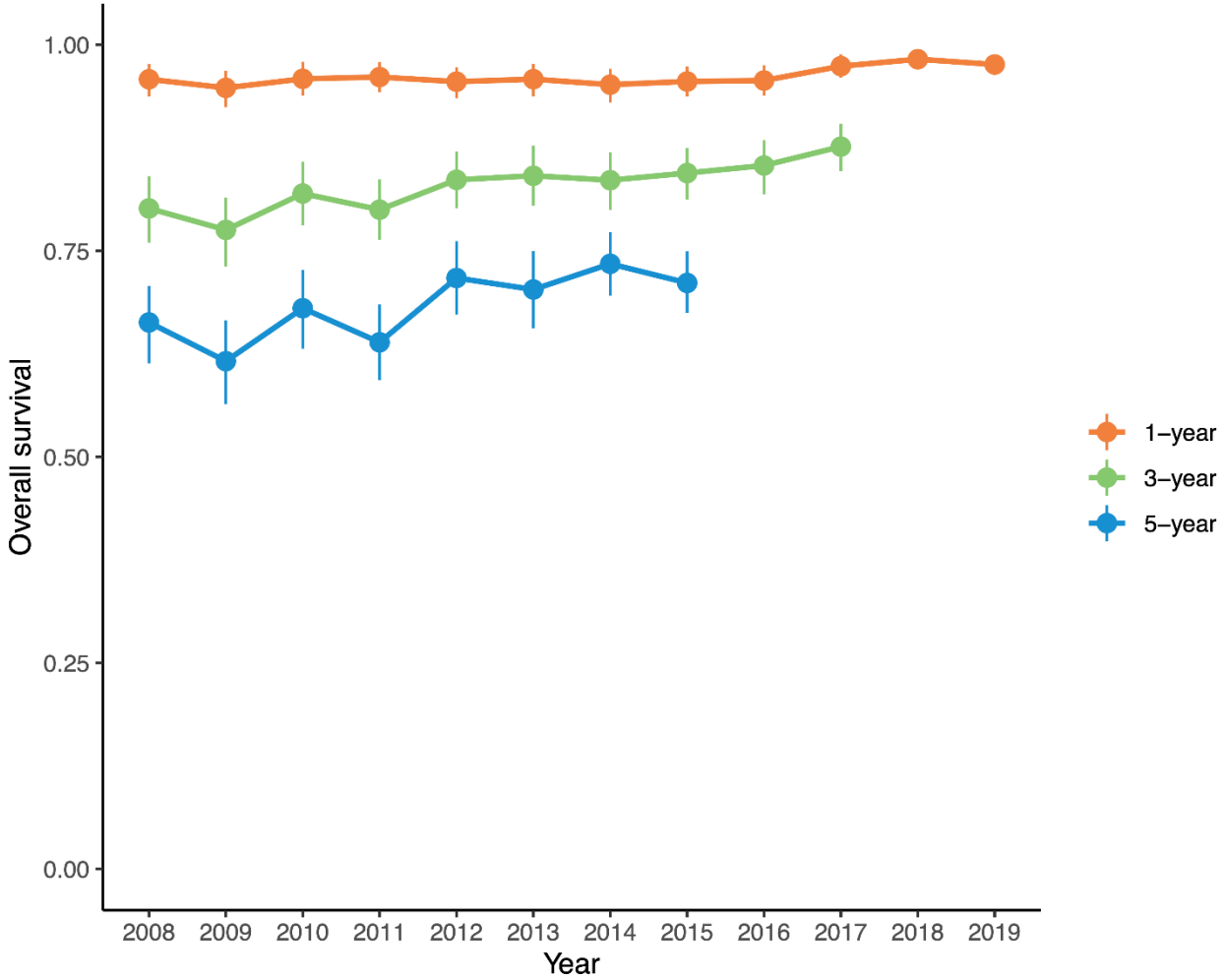
Statistical analysis by Chi-squared tests: There is no statistically significant difference between the proportion of men and women transplanted for the total population or any of the age subgroups.

Supplemental Table S2: Characteristics and induction regimen of population treated with upfront ASCT 2008-2020, by country

	Total	**Denmark**	**Estonia**	**Iceland**	**Lithuania**	**Norway**	**Sweden**
Total population treated with upfront ASCT	5753	1292	258	83	540	1323	2257
Female, n (%)	2383 (41%)	559 (43%)	129 (50%)	37 (45%)	273 (51%)	531 (40%)	854 (38%)
Mean age at diagnosis (years, standard deviation)	58.7 (7.7)	59.5 (7.7)	58.1 (8.3)	59.6 (9.17)	58 (8.2)	58 (7.3)	58.9 (7.8)
Median time to ASCT (days)	-	141	169	171	168	151	139
18-65 years, n (%)	4676 (81%)	1019 (79%)	206 (80%)	55 (66%)	444 (82%)	1141 (86%)	1811 (80%)
66-70 years, n (%)	993 (17%)	262 (20%)	42 (16%)	21 (25%)	81 (15%)	172 (13%)	415 (18%)
71-75 years, n (%)	82 (1.4%)	9 (0,7%)	10 (4%)	7 (8%)	15 (3%)	10 (0,8%)	31 (1,4%)
≥76 years, n (%)	2 (0.0%)	2 (0,2%)	0	0	0	0	0
Myeloma characteristics at diagnosis							
ISS available (n)	4839 (84%)	1152 (89%)	258 (100%)	46 (55%)	464 (86%)	1074 (81%)	1845 (82%)
ISS I (n)	1851 (38%)	541 (47%)	90 (35%)	29 (63%)	162 (35%)	455 (42%)	574 (31%)
ISS II (n)	1680 (35%)	287 (25%)	86 (33%)	13 (28%)	117 (25%)	350 (33%)	827 (45%)
ISS III (n)	1308 (27%)	324 (28%)	82 (32%)	4 (9%)	185 (40%)	269 (25%)	444 (24%)
Anemia* (n, %)	2000 (35%)	412 (32%)	112 (43%)	15 (18%)	173 (32%)	659 (50%)	629 (28%)
Hypercalcemia** (%)	1053 (18%)	272 (21%)	51 (20%)	51 (10%)	80 (15%)	187 (14%)	455 (20%)
Renal failure***	716 (12%)	122 (9%)	63 (24%)	8 (10%)	74 (14%)	163 (12%)	286 (13%)
Skeletal disease †	4312 (75%)	1009 (78%)	218 (84%)	48 (58%)	389 (72%)	1048 (79%)	1600 (71%)
FISH performed (%)	3123 (54%)	717 (55%)	184 (71%)	44 (53%)	311 (58%)	667 (50%)	1200 (53%)
High risk FISH (%)	565 (10%)	180 (14%)	39 (15%)	16 (19%)	56 (10%)	146 (20%)	128 (6%)
Induction regimens							
PI-based	3206 (56%)	879 (68%)	154 (60%)	69 (83%)	63 (12%)	736 (56%)	1305 (58%)
IMiD and PI-based	1589 (28%)	225 (17%)	80 (31%)	1 (1%)	227 (42%)	465 (35%)	591 (26%)
IMiD-based	347 (6%)	4 (0%)	3 (1%)	1 (1%)	231 (43%)	10 (1%)	98 (4%)
CD38-antibody-based	64 (1%)	7 (1%)	0 (0%)	0 (0%)	0 (0%)	4 (0%)	53 (2%)
Other (including chemotherapy-based)	529 (9%)	177 (14%)	21 (8%)	12 (14%)	19 (4%)	108 (8%)	192 (9%)
Missing	9 (0%)	0 (0%)	(0%)	0 (0%)	0 (0%)	0 (0%)	9 (0%)

*Anemia; Hemoglobin <100 g/l or Hemoglobin >20 g/l below lower limit of normal.
**Hypercalcemia; Ionized calcium >1.35 mmol/l or total calcium >2.75 mmol/l.
*** Renal failure; Creatinine >177 µmol/l or creatinine clearance <40 ml/min.
†Skeletal disease; ≥1 osteolytic lesion.
‡ High risk FISH; del17p and/or t(4;14) and/or t(14;16).
ASCT; Autologous stem cell transplantation. FISH; Fluorescence in situ hybridization. IMiD; Immunomodulatory drug. ISS; International Staging System. PI; proteasome inhibitor.

Supplemental Figure 1: Overall survival at 1 year, 3 years and 5 years of all patients treated with autologous stem cell transplantation.



All transplanted patients from all 6 countries.