Allogeneic hematopoietic stem cell transplantation in patients aged 60-79 years in Germany (1998-2018): a registry study

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Abstract

Incidences of diseases treated with transplantation frequently peak at higher age. The contribution of age to total risk of transplantation has not been estimated amidst an aging society. We compare outcomes of 1,547 patients aged 70-79 years and 9,422 patients aged 60-69 years transplanted 1998-2018 for myeloid, lymphoid and further neoplasia in Germany. To quantify the contribution of population mortality to survival, we derive excess mortality based on a sex-, year- and age-matched German population in a multistate model that incorporates relapse and graft-*versus*-host-disease (GvHD). Overall survival, relapse-free survival (RFS) and GvHD-free-relapse-free survival (GRFS) is inferior in patients aged 70-79 years, compared to patients aged 60-69 years, with 36% (95% Confidence Interval [CI]: 34-39%) *versus* 43% (41-44%), 32% (30-35%) *versus* 36% (35-37%) and 23% (21-26%) *versus* 27% (26-28%) three years post-transplant (P<0.001). Cumulative incidences of relapse at three years are 27% (25-30%) for patients aged 70-79 *versus* 29% (29-30%) (60-69 years) (P=0.71), yet the difference in non-relapse mortality (NRM) (40% [38-43%] *vs*. 35% [34-36%] in patients aged 70-79 *vs*. 60-69 years) (P<0.001) translates into survival differences. Median OS of patients surviving >1 year relapse-free is 6.7 (median, 95% CI: 4.5-9.4, 70-79 years) *versus* 9 (8.4-10.1, 60-69 years) years since landmark. Three years after RFS of one year, excess NRM is

14% (95% CI: 12-18%) in patients aged 70-79 *versus* 12% [11-13%] in patients aged 60-69, while population NRM is 7% (6-7%) *versus* 3% (3-3%). Mortality for reasons other than relapse, GvHD, or age is as high as 27% (24-29%) and 22% (22-23%) four years after transplantation. In conclusion, survival amongst older patients is adequate after allogeneic stem cell transplantation.

Introduction

Cancer is intrinsically tied to age.[1,2] Age has long been viewed as one prominent risk factor for survival after cancer.[3] Incidences of most diseases treated with allogeneic hematopoietic stem cell transplantation peak beyond the 6th decade of life. In contrast, transplantation had long been restricted to younger individuals since older persons were considered too frail to transplant. With the ongoing demographic changes, this resulted in an offer-demand shortage.[4] Consecutively, huge efforts were made to facilitate transplantation in older persons. While in the year 2000 patients undergoing transplantation were rarely ≥60 years, nowadays this intervention is offered to patients up to 80 years of age.[5-7] Transplantation in patients ≥70 years results in 2-year-overall survival (OS) of around 40%, with non-relapse mortality (NRM) exceeding 30%.[6-12] However, mortality can be considered as a combination of population mortality and excess mortality. Population mortality reflects the baseline mortality that also occurs in the age- and sex-matched general population. Excess mortality is a disease- or treatment-related component.[13] Analyses investigating procedures in older patients need to give special consideration to the age-dependent contribution of population mortality to mortality after a particular procedure.[8,11,14]

Recently, relative survival has been integrated into multistate modeling.[13-18] Here, we apply this modeling to the largest set of real-world data reported so far. Data in this analysis span two decades (1998-2018) of treatment in Germany and include 9,422 patients aged 60-69 years and 1,547 patients aged 70-79 years. In this way, we analyze population mortality and excess mortality with and without GvHD and relapse. To our knowledge, we here present the largest analysis of this kind. We report OS, relapse-free survival (RFS), graft-*versus*-host-disease-free-relapse-free survival (GRFS), non-relapse-mortality (NRM), relapse, and the risk factors thereof for patients in their 7th and 8th decades of life. We conclude that transplantation can efficiently treat diseases in both age groups. Excess mortality is particularly high during the first year after transplantation.

Methods

Study population

The patient cohort consisted of patients transplanted between 1998-2018 in 55 German centers and reported to the German registry for stem cell transplantation (Deutsches Register für Stammzelltransplantation). Inclusion criteria were: 1) transplantation of bone marrow or peripheral blood stem cells from a mismatched or matched related or unrelated allogeneic donor for any malignant disease between 1998-2018; 2) age at transplantation ≥60 years; 3) consent to reporting data to DRST. Exclusion criteria were: i) cord blood transplantation; ii) partial/ full duplicates using the reported co-variates UPN, center and patient-ID; iii) missing OS data; and, iv) beyond first allogeneic transplantation. Of 11,031 patients, 62 (0.56%) were excluded. Information was extracted from the DRST database on May 1, 2021. Informed consent had been retrieved prior to reporting. The study was approved by the data access committees of the DRST and by the institutional review board of the Medical Faculty/ University Hospital Tübingen (N. 291/2021BO2) (*Online Supplementary Figure S1*).

Definitions

Myeloablative[5] and reduced intensity conditioning (RIC) as well as total conditioning intensity (TCI) were defined as published (*Online Supplementary Table S1*).[19-21] OS was defined as time to event (death) after transplantation with patients censored if still alive at last follow-up. Similarly, RFS was defined as the time to either relapse or confirmed progression or death, whichever came first. GRFS was defined as the time to the first of RFS-events or severe GvHD (acute [aGvHD]: grade III or IV; chronic [cGvHD] extensive). Missing data for relapse, aGvHD and cGvHD were treated as “no relapse”, “no aGvHD”, and “no cGvHD”, and were censored at last follow-up regarding these events (*Online Supplementary Appendix Chapter 3*). Cumulative incidences of relapse / progression and NRM were calculated regarding the two as competing risks. Cumulative incidences of severe aGvHD and cGvHD were analyzed with death as a competing risk. Median follow-up was calculated using the reverse Kaplan-Meier method.[22] Multistate models (see below) allowed information to be obtained about patients dying after relapse, after GvHD, or after both, as well as patients alive with these complications at different time-points during follow-up.

Statistical analysis

We performed univariable and multivariable analysis for OS, RFS and GRFS using Kaplan-Meier estimations, logrank testing and Cox regression with period-dependent effects. In an environment regarding relapse and death as competing risks, cumulative incidence of relapse and NRM were estimated.[23] Likewise, this was repeated for severe GvHD incidence and death without GvHD. To identify risks beyond

the first year we chose a landmarking approach to examine OS for the patients alive at one year after transplantation (OS landmark [LM] population), alive and relapse-free at that timepoint (RFS LM population), and alive without previous relapse or GvHD at that timepoint (GRFS population). We split all mortality into population (the mortality that the patients would have faced in the absence of their disease and treatment) and excess mortality (all additional mortality associated with the disease, and with previous and current treatment) using techniques from relative survival. To apply this method, we had to assume that the population mortality risk of the transplanted patients is equal to that of the German population matched by sex, age, and year of transplant. While this approach still ignores other covariates that are considered important to create appropriate population hazards (socioeconomic status, comorbidities) (see Discussion), this already offers a promising approach to obtain increasingly precise estimates.[13] Data for the general population were derived from population tables as available from the Human Mortality Database (accessed Nov 21, 2021).[24] We created time-inhomogeneous Markov Multistate models for relapse / progression, GvHD, and death that integrate population mortality to discover differences in excess mortality between age groups, and before and after post-transplantation events. These models allow an in-depth evaluation of complex outcomes. In addition to Kaplan-Meier analysis, this provided information about the probability of reaching different states of death (death after relapse, death after GvHD, non-relapse-death) and about different states of being alive (alive with or after relapse or GvHD). We split all death states into a population and excess part.[13] The use of the suffix ".e" denotes excess, while ".p" denotes population contribution.

Relevant comorbidities are defined as pre-existing medical conditions that have previously been associated with increased risk of mortality after transplantation. These comorbidities include conditions such as pulmonary, cardiovascular, hepatic, and renal disease, as well as diabetes, malignancies, and infections, and were decided by the treating physician.

Excess mortality could be analyzed in an additive model (relsurv package, rsadd), (*Online Supplementary Appendix Chapter 1)*. Because of their reported impact on transplantation outcomes, for all multivariable regression models, we selected the covariates sex, diagnosis, period of transplantation, HLA-match, related / unrelated donors, donor age, stem cell source, conditioning intensity, Karnofsky performance status, known comorbidities prior to transplantation, relationship of cytomegalovirus (CMV) status between donor and patient, and remission status at transplantation. Where applicable, models allowing the effect of baseline covariates to differ between the first year and later years were applied.[25] Statistical analysis was carried out in R (v.4.0.5, 2021-03-31, Shake and Throw) using the packages dplyr, survival, survminer, prodlim, mstate, mice, and relsurv.[13,15-17,25-27] All *P* values are two-sided. $P<0.05$ is considered significant.

To handle missing predictor values in this registry analysis, we chose multiple imputation by chained equations and result-pooling by Rubin's rules as the main strategy (*Online Supplementary Appendix Chapter 3*).[27] Finally, we included only patients from centers that completed ≥50% of follow-up into outcomes and risk factor analyses to avoid too heavy a reliance on the assumption of non-informative censoring for assessing long-term outcomes (50 centers, N=8,560 aged 60-69, N=1,427 aged 70-79) (*Online Supplementary Appendix*). When we compared these results to centers with a follow-up of >80%, no difference in outcomes with respect to age as the main covariate of interest were observed. Age was tested via Schoenfeld Residuals in different follow-up approaches (*Online Supplementary Figure 7.1, 7.2*).

Prior to analysis, the study was approved by the Institutional Review Board of the Medical Faculty of Tübingen University (N. 291/2021BO2).

Results

Patients' characteristics

We present epidemiological data from 10,969 patients (9,422 aged 60-69 years and 1,547 aged 70-79 years) from 55 German transplantation centers (Table 1). In both age groups, acute leukemia, myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) are the most frequent indications for transplantation. The percentage of unrelated donors increased to >50% after 2002 and is higher in older patients (60-69 years: 75%; 70-79 years: 86%; $P<0.001$). Donors of older patients are significantly younger than donors of younger patients (37 years for patients aged 60-69 years *vs*. 35 years for patients aged 70-79 years; $P<0.001$). Bone marrow as a graft source has decreased from around 10% to just below 5% in recent years. Higher age is associated with less myeloablative conditioning (MAC) (60-69 years: 37%; 70-79 years: 24%; $P<0.001$). TCI is significantly lower in older patients. In both age groups, approximately 20% of patient-donor-pairs are CMV IgG seropositive patient and seronegative donor (Table 1).

The number of annual transplantations in patients aged 60 years or older rose from a minimum of 13 (1998) to a maximum of 1,140 (2018). The number of patients aged 70 years or older increased from 1 (1999) to 201 (2018) (Figure 1).

Changes over time

We compared the two decades analyzed in the cohort described. Changes in patients aged 60-69 years and >70 years are significant in parts: median age increased from 63.69 (1998-2008: 61.79-65.81) to 64.37 (2009-2018: 62.24-66.90) in patients aged 60-69 years, and from 71.25 (70.50-73.11) to 72.09 (70.91-73.64) in patients aged 70-79 years (Wilcoxon rank

sum *P*=0.001). Again, comparing the two periods studied, 1998-2008 and 2009-2018, we observe a decrease in allogeneic stem cell transplantation to treat chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML), likely due to the introduction of novel therapies. We observe an increase in the use of a combination of calcineurin inhibitors (CNI) and mycophenolic acid (MPA), while TCI is lower in patients aged >70 years. Patients with a Karnofsky score <80 are less frequently transplanted while patients with a score of 90-100 undergo transplant more frequently. Furthermore, we find an increase in the number of patients with a complete response (1st or other CR) status before

Table 1. Demographic and clinical characteristics of the patients at transplantation.

Characteristic	DRST data							
	Age group 60-69, N=9,422				Age group 70-79, N=1,547			
	N	1998-2008 N=2,217[1]	2009-2018 N=7,205[1]	*P*[2]	N[1]	1998-2008 N=112[1]	2009-2018 N=1,435[1]	*P*[2]
Patient sex	9,420			0.8	1,545			0.6
Female		881 (40)	2,839 (39)			37 (33)	508 (35)	
Male		1,336 (60)	4,364 (61)			75 (67)	925 (65)	
Patient age in years	9,422	63.69 (61.79-65.81)	64.37 (62.24-66.90)	<0.001	1,547	71.25 (70.50-73.11)	72.09 (70.91-73.64)	0.001
Diagnosis	9,422			<0.001	1,547			0.3
Acute leukemia		1,197 (54)	3,789 (53)			80 (71)	934 (65)	
CLL		115 (5.2)	240 (3.3)			0 (0)	37 (2.6)	
CML		99 (4.5)	76 (1.1)			2 (1.8)	10 (0.7)	
Lymphoma		141 (6.4)	646 (9.0)			3 (2.7)	60 (4.2)	
MDS/MPN		431 (19)	1,867 (26)			25 (22)	343 (24)	
Others		77 (3.5)	213 (3.0)			2 (1.8)	37 (2.6)	
Plasma cell disorders		157 (7.1)	374 (5.2)			0 (0)	14 (1.0)	
Donor age in years	4,310	42 (32-58)	36 (27-49)	<0.001	790	40 (31-65)	34 (27-44)	0.001
Stem cell source	9,409			>0.9	1,541			0.014
Bone marrow		119 (5.4)	383 (5.3)			0 (0)	74 (5.2)	
PBSC		2,095 (95)	6,812 (95)			112 (100)	1,355 (95)	
GvHD-prophylaxis	8,655			<0.001	1,517			<0.001
CNI+MPA		701 (46)	4,337 (61)			46 (49)	948 (67)	
CsA+MTX		389 (25)	1,878 (26)			10 (11)	266 (19)	
Other		442 (29)	908 (13)			37 (40)	210 (15)	
TCI-category	7,309			0.002	1,307			0.005
High		41 (3.3)	126 (2.1)			1 (1.2)	9 (0.7)	
Int		654 (53)	3,489 (57)			56 (67)	614 (50)	
Low		532 (43)	2,467 (41)			26 (31)	601 (49)	
Karnofsky Performance Index	7,970			0.002	1,415			0.041
<80		127 (11)	535 (7.9)			13 (17)	122 (9.1)	
80		334 (28)	1,814 (27)			27 (35)	410 (31)	
90-100		727 (61)	4,433 (65)			38 (49)	805 (60)	
Relevant comorbidities	4,897	301 (62)	2,804 (64)	0.6	980	35 (78)	645 (69)	0.2
CMV status relationship	8,483			<0.001	1,494			0.015
Both negative		375 (26)	1,862 (26)			25 (27)	385 (27)	
Both positive		549 (38)	3,042 (43)			28 (30)	615 (44)	
Negative patient, positive donor		156 (11)	581 (8.2)			12 (13)	104 (7.4)	
Positive patient, negative donor		350 (24)	1,568 (22)			28 (30)	297 (21)	
Disease status at HSCT - only CR	8,954	644 (31)	2,534 (37)	<0.001	1,489	32 (29)	528 (38)	0.040

[1]N (%); median (IQR); [2]Pearson's X^2 test; Wilcoxon rank sum test; Fisher's exact test. Values per decade of transplant. IQR: interquartile range; DRST: German registry for stem cell transplantation; PBSC: peripheral blood stem cell; CsA: cyclosporine A; MPA: mycophenolic acid; CMV: cytomegalovirus; GvHD: graft-*versus*-host disease; CNI: calcineurin inhibitors; MTX: methotrexate; TCI: total conditioning intensity; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; MDS/MPN: myelodysplastic syndromes/myeloproliferative neoplasms; CR: complete remission. Full table in the *Online Supplementary Appendix*.

SCT (Table 1, *Online Supplementary Table S2*).

Completed follow-up

Follow-up estimated by reverse Kaplan-Meier is 3.9 [95% CI: 3.8-4] years in the whole cohort.[22] After exclusion of 5 centers for a completeness of follow-up <50%, data from 8,560 patients (aged 60-69 years, 91%) and 1,427 patients (aged 70-79 years, 92%) (total 9,987 patients) were included

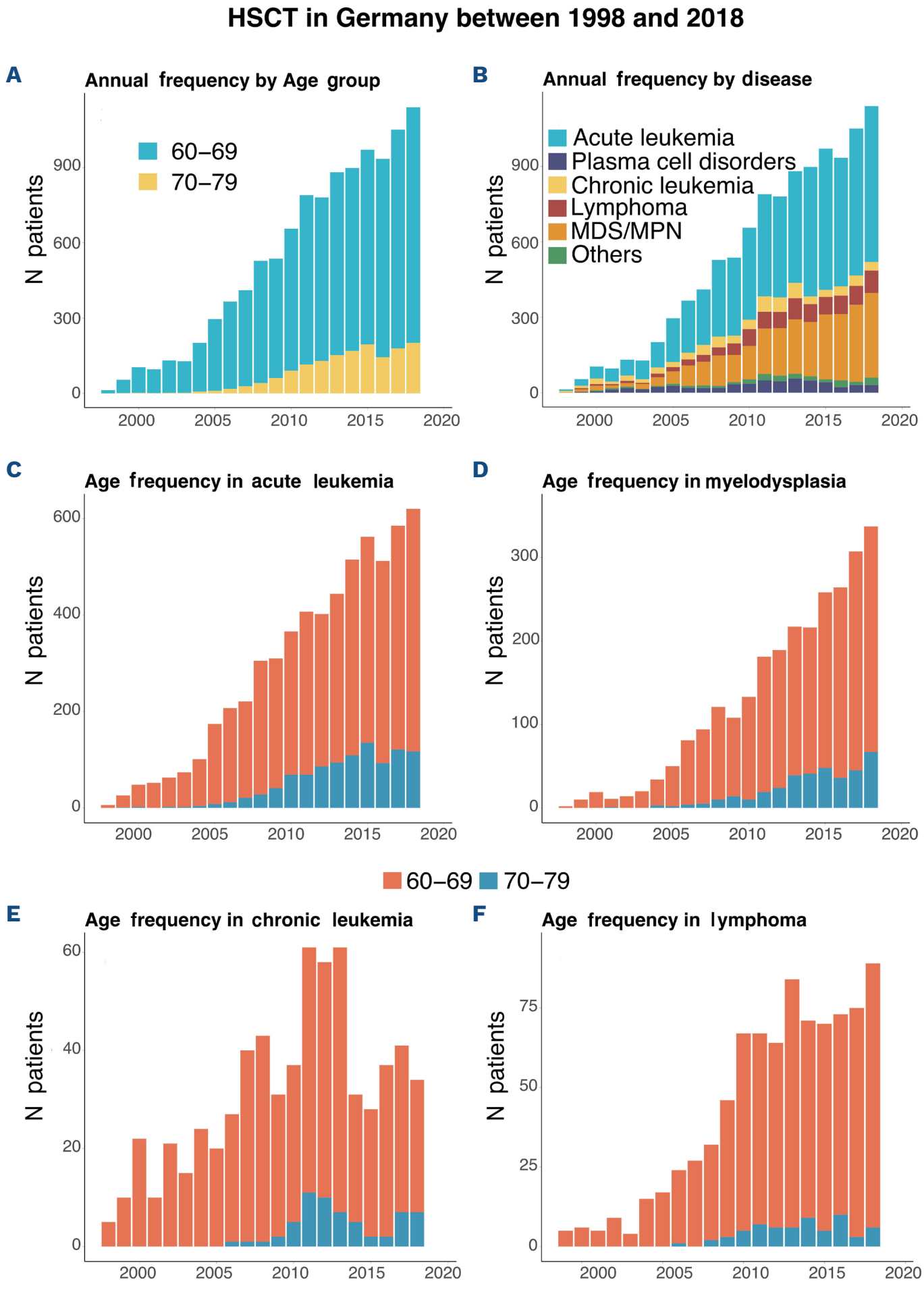

Figure 1. Epidemiology of reported population. (A) Frequency of age groups among all patients. (B) Frequency of disease among all patients. (C) Frequency of age groups in patients with acute leukemia. (D) Frequency of age groups in patients with myelodysplasia. (E) Frequency of age groups in patients with chronic leukemia. (F) Frequency of age groups in patients with lymphoma. (G) Frequency of age groups in patients with other diseases than those described above (bone marrow failure, solid tumors, hemoglobinopathies, etc.). HSCT: hematopoietic stem cell transplantation.

in further analysis. In this analysis cohort, follow-up is 4.2 [95%CI 4.1-4.4] years (*Online Supplementary Chapter 2*).

Survival estimates and cumulative incidences

Overall survival, RFS, and GRFS of the entire cohort are 1.6 (median, 95% CI: 1.5-1.7), 1 (95% CI: 0.9-1) and 0.6 (95% CI: 0.5-0.6) years (Figure 2A). Median OS is 1.7 (95% CI: 1.6-1.9) years in patients aged 60-69 years *versus* 1.1 (95%CI 1-1.3; logrank *P*<0.001) years in patients aged 70-79 years. Median RFS is 1.0 (95% CI: 0.9-1.1) years *versus* 0.8 (95% CI: 0.7-0.9 years; *P*<0.001). Median GRFS is 0.6 (95% CI: 0.5-0.6) years *versus* 0.5 (95% CI: 0.4-0.5 years; *P*<0.001). (See Table 2 for detailed survival probabilities.)

Overall survival improved in patients treated more recently exclusively in the group 60-69 (median OS, 1998-2008 1.15 [95% CI: 1.03-1.38] years, and 2009-2018 1.94 [95% CI: 1.76-2.13] years; logrank *P*<0.001). We observe no significant difference in the group 70-79 (median OS for 1998-2008: 1.18 [95% CI: 0.82-3.39] years; for 2009-2018: 1.08 [95% CI: 0.94-1.31] years; logrank *P*=0.44) (Figure 2E).

To examine long-term survivorship, we performed landmark analyses for the 1-year OS, RFS, and GRFS LM populations. Outcome after LM is 7.4 (median, 95% CI: 6.8-8.2) *versus* 4.8 (95% CI: 4.1-7.1) years regarding the OS-LM population, 9 (95% CI: 8.4-10.1) *versus* 6.7 (95% CI: 4.5-9.4) years regarding the RFS-LM population, and 10.1 (95% CI: 9.1-11.1) *versus* 6.7 (95% CI: 4.8-NA) years regarding the GRFS-LM population, when patients aged 60-69 years are compared to those aged 70-79 years, respectively (Figure 2B).

Multivariable analysis for 1-year and subsequent survival

We performed multivariable analyses in the entire cohort (60-79 years old) including age, diagnosis, remission status, sex, comorbidities, conditioning intensity, use of TBI, Karnofsky performance status, CMV status, donor type (family or unrelated, HLA-match, age), stem cell source (bone marrow or peripheral blood), treatment period (1998-2008, 2009-2018) (Table 3, *Online Supplementary Table S5*). To estimate different risk factor effects early and later after transplantation, alongside multivariable analysis addressing OS in total, we also performed an analysis split into first and subsequent years of follow-up.

Probability of OS is lower in the age group 70-79 years *versus* 60-69 years, with similar effect sizes during follow-up (overall: Hazard Ratio [HR] 1.19 [95% CI: 1.1-1.28], *P*<0.001; first year after transplantation: HR 1.18 [1.08-1.29], *P*<0.001; subsequent years of follow-up: HR 1.22 [1.07-1.4], *P*=0.004). Transplantation for CLL (HR 0.58 [0.49-0.68], *P*<0.001), CML (HR 0.73 [0.59-0.9], *P*=0.003) and MDS/ MPN (HR 0.76 [0.71-0.81], *P*<0.001) is associated with longer OS. Transplantation in complete remission is protective both in the first year after transplantation and thereafter (HR 0.71 [0.66-0.75], *P*<0.001). Transplantation from unrelated *versus* family donors adversely influences OS during the first year of follow-up but not thereafter, and donor age below median age of all donors (HR 0.86 [0.79-0.93], *P*<0.001) positively affects OS. Male patient sex correlates with reduced OS in total (HR 1.08 [1.03-1.14], *P*=0.004) with insignificant differences during the first year but significant impact during subsequent years of follow-up (HR 1.16 [1.05-1.27], *P*=0.003). Additional adverse factors for OS are the presence of relevant comorbidities as defined by the treating physician (HR 1.16 [1.07-1.25], *P*<0.001), a low Karnofsky performance status prior to transplantation (<80 *vs*. 90-100, HR 1.84 [1.68-2.02], *P*<0.001), and a mismatched HLA-donor (HR 1.33 [1.19-1.49], *P*<0.001). Low or intermediate TCI do not impact OS significantly, *versus* high intensity (HR 0.91 [0.75-1.1], *P*=0.32, HR 0.93 [0.77-1.12], *P*=0.44). In multivariable analysis, transplantation before 2009 shows poorer survival when compared to transplantation between 2009-2018 (HR 0.9 [0.84-0.97], *P*=0.009) only during the first year. Table 3 and Online Supplementary Table S5 show the entire regression analysis.

Multistate model calculation of survival: quantification of excess mortality

Relapse-free survival environment - Recently, the integration of relative survival into multistate modeling offered a new method to estimate excess and population survival with and without intermediate events in an age-dependent fashion (*Online Supplementary Figure S2.1*).[13]

We built such an RFS multistate model to quantify the dependence of excess mortality on age (Figure 3, *Online Supplementary Figures S5.1-S5.4, S6*). The model was set for all patients as well as only for patients with RFS of at least one year (60-69 years: 49.91% [95% CI: 49.32-50.51]; 70-79 years: 45.59% [95% CI: 43.26-48.05%], LM).

Among patients aged 70-79 years, 35.44% [95% CI: 33.61-37.36%] and 38.14% [95% CI: 35.57-40.91%] died from excess NRM (NRM.e) two and four years after transplantation. Among patients aged 60-69 years, this excess mortality is lower: 31.28% (95% CI: 30.16-32.44%) and 33.81% (95%CI 32.51-35.16%). The proportion of population deaths without relapse (population mortality, NRM.p) steadily increases from 1.42% (95% CI: 1.39-1.45%) to 2.48% (95% CI: 2.41-2.55%) (60-69 years) and 2.58% (95% CI: 2.47-2.7%) to 4.54% (95% CI: 4.33-4.76%) (70-79 years). One and three years after 1-year LM, NRM.p is 1.18% (95% CI: 1.15-1.21%) and 3.3% (95% CI: 3.21-3.4%) (60-69 years) *versus* 2.28% (95% CI: 2.18-2.39%) and 6.57% (95% CI: 6.35-6.8%) (70-79 years) (Figure 3A, B).

Graft-*versus*-host-relapse-free survival environment

The referenced RFS-multistate model allows the addition of further possible states.[13] These, such as living with severe GvHD, can more precisely specify the estimation of non-disease-non-treatment-related death as non-relapse-non-GvHD-mortality (*Online Supplementary Figure S2.2*).

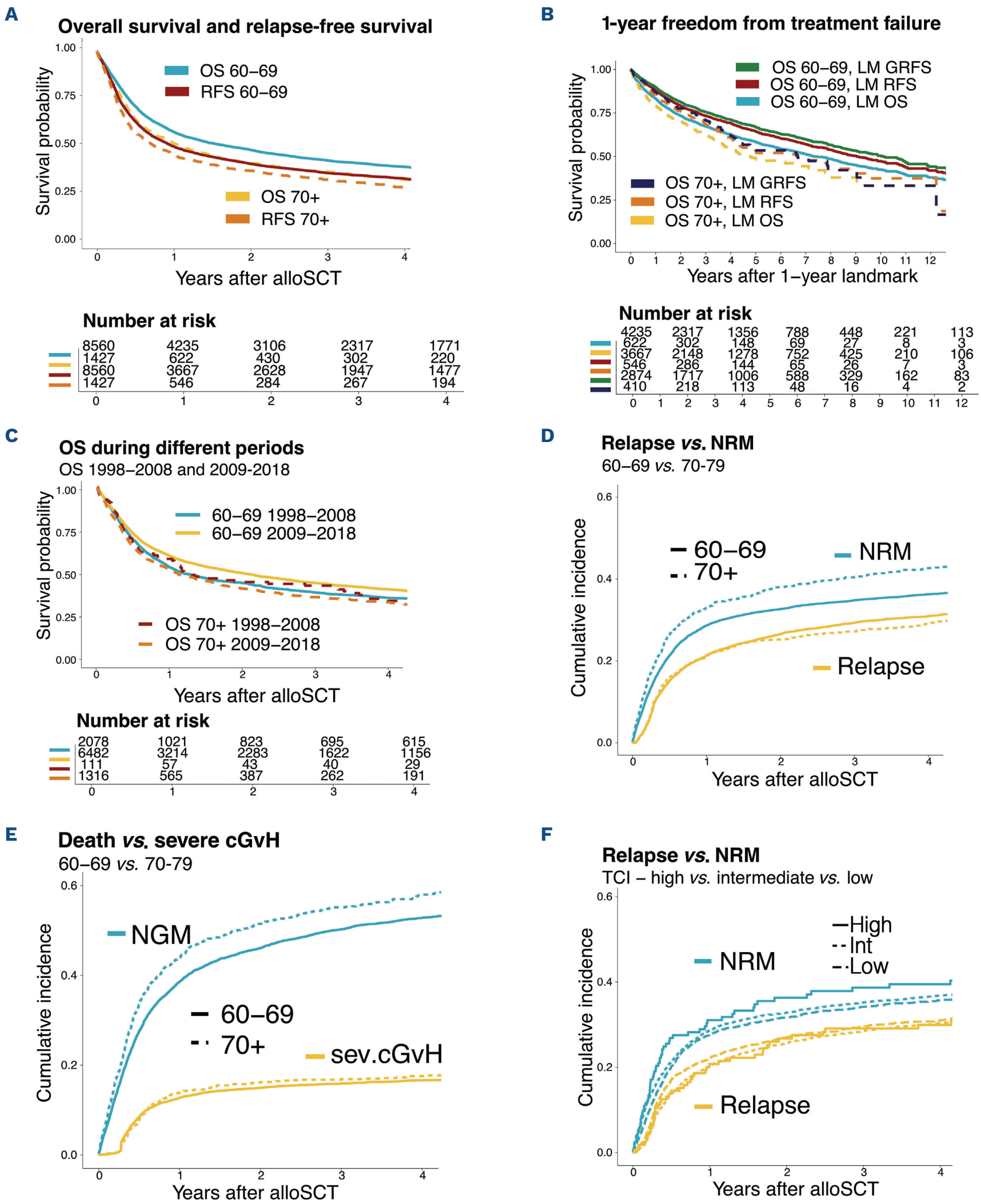

Figure 2. Survival analysis. (A) Kaplan-Meier estimations of overall survival (OS) and relapse-free survival (RFS) by age group. (B) Kaplan-Meier estimations of OS after having reached 1-year failure-free survival of different definitions: death (OS), death + relapse (RFS), death + relapse + severe graft-versus-host disease (GvHD) (graft-*versus*-host-relapse-free-survival; GRFS). All patients with respective events before 1-year landmark (LM) were excluded. (C) Kaplan-Meier estimations of age-group-specific OS during 1998-2008 and 2009-2018. (D) Competing risk analysis of relapse and non-relapse mortality (NRM). (E) Competing risk analysis of severe GvHD and non-GvHD-mortality (NGM). (F) Competing risk analysis of relapse and NRM with regards to low versus intermediate versus high TCI. alloSCT: allogeneic stem cell transplantation; TCI: total conditioning intensity.

Table 2. Detailed outcome data.

	Overall survival *P*<0.001+		Relapse-free survival *P*<0.001+		Graft-*versus*-host-relapse-free survival *P*<0.001+		NRM *P*<0.001*		Relapse *P*=0.71*		Sev. cGvHD *P*=0.58*		Sev. aGvHD *P*=0.74*	
	Age group 60-69	Age group 70-79	Age group 60-69	Age group 70-79	Age group 60-69	Age group 70-79	Age group 60-69	Age group 70-79	Age group 60-69	Age group 70-79	Age group 60-69	Age group 70-79	Age group 60-69	Age group 70-79
Median in years (95% CI)	1.7 (1.6-1.9)	1.1 (1-1.3)	1 (0.9-1.1)	0.8 (0.7-0.9)	0.6 (0.5-0.6)	0.5 (0.4-0.5)	-	-	-	-	-	-	-	-
Day 100, % (95% CI)	-	-	-	-	-	-	-	-	-	-	-	-	11.8 (11.1-12.5)	11.3 (9.7-13.0)
1 year, % (95% CI)	57.8 (56.7-58.9)	51.9 (49.2-54.7)	49.9 (48.8-51)	45.6 (42.9-48.4)	39.4 (38.3-40.4)	34.1 (31.6-36.8)	28.7 (27.7-29.7)	33.1 (30.6-35.7)	21.4 (20.5-22.3)	21.3 (19.1-23.5)	12.7 (12.0-13.5)	14.0 (12.1-16.0)	-	-
2 years, % (95% CI)	48.1 (47-49.3)	41.0 (38.4-43.9)	40.7 (39.6-41.8)	36.8 (34.2-39.5)	30.9 [29.8-31.9]	26.7 (24.3-29.3)	32.7 (31.7-33.7)	38.0 (35.4-40.7)	26.6 (25.6-27.6)	25.2 (22.9-27.6)	15.0 (14.2-15.8)	16.2 (14.2-18.3)	-	-
3 years, % (95% CI)	42.5 (41.4-43.7)	36.4 (33.7-39.3)	35.8 (34.7-37.0)	32.4 (29.8-35.2)	26.9 (25.9-27.9)	23.3 (21-25.9)	34.8 (33.8-35.9)	40.4 (37.7-43.1)	29.3 (28.3-30.4)	27.2 (24.7-29.7)	16.0 (15.1-16.8)	16.8 (14.8-19.0)	-	-
4 years, % (95% CI)	39.0 (37.8-40.2)	32.4 (29.7-35.3)	32.7% (31.6-33.9)	28.3 (25.7-31.1)	24.2 (23.2-25.3)	20.1 (17.9-22.7)	36.3 (35.2-37.4)	42.7 (39.8-45.5)	31.0 (29.9-32.1)	29.1 (26.5-31.7)	16.7 (15.9-17.6)	17.6 (15.5-19.9)	-	-

NRM: non-relapse mortality; Sev. cGvHD: severe chronic GvHD and Sev. aGvHD: severe acute GvHD. +Logrank. *Gray's test; CI: confidence interval.

To refine the analysis of NRM as non-relapse-non-GvHD-mortality (NRNGM), multistate analysis was repeated in a GRFS-environment (1-year-GRFS, 60-69 years: 39.37% [95% CI: 38.41-40.34%]; 70-79 years: 34.08% [95% CI: 32.27-36%]). At two and four years, NRNGM.e is 21% (95% CI: 20.36-21.66%], 22.22% (95% CI: 21.61-22.84%] and NRNGM.p 1.17% (95% CI: 1.13-1.2%), 1.97% (95% CI: 1.9-2.04%) for patients aged 60-69 years *versus* 25.02% (95% CI: 23.13-27.07%), 26.58% (95% CI: 24.42-28.93%) and 2.06% (95% CI: 1.98-2.15%), 3.48% (95% CI: 3.28-3.69%) for patients aged 70-79 years, respectively. In patients GvHD- and relapse-free after one year, 4.84% (95% CI: 4.25-5.51%) and 7.93% (95% CI: 7.26-8.66%) (60-69 years) *versus* 6.08% (95% CI: 5.39-6.86%) and 10.64% (95% CI: 7.27-15.59%) (70-79 years) still suffer NRNGM.e at one and three years after LM. NRNGM.p increases to 1.15% (95% CI: 1.14-1.17%] and 3.2% (95% CI: 3.13-3.27%] (60-69) *versus* 2.23% (95% CI: 2.12-2.34%] and 6.38% (95% CI: 5.95-6.85%] (70-79 years) (Figure 3C, D). Full data and state proportions can be found in the *Online Supplementary Appendix* and *Online Supplementary Table S3.1.-S3.4*.

Risk factors for excess mortality

The integration of relative survival into regression models can enable the impact of risk factors on excess mortality to be estimated. (See *Online Supplementary Chapter 1* for additive modeling.)

Age influences excess mortality during the entire, and especially the first year, of follow-up (HR 1.14 [1.05-1.24], *P*=0.001, 70-79 years *vs*. 60-69 years, first year: HR 1.16 [1.06-1.27], *P*=0.001). However, significance is lost after 1-year of OS (HR 1.09 [0.91-1.3], *P*=0.35) despite similar effect size.

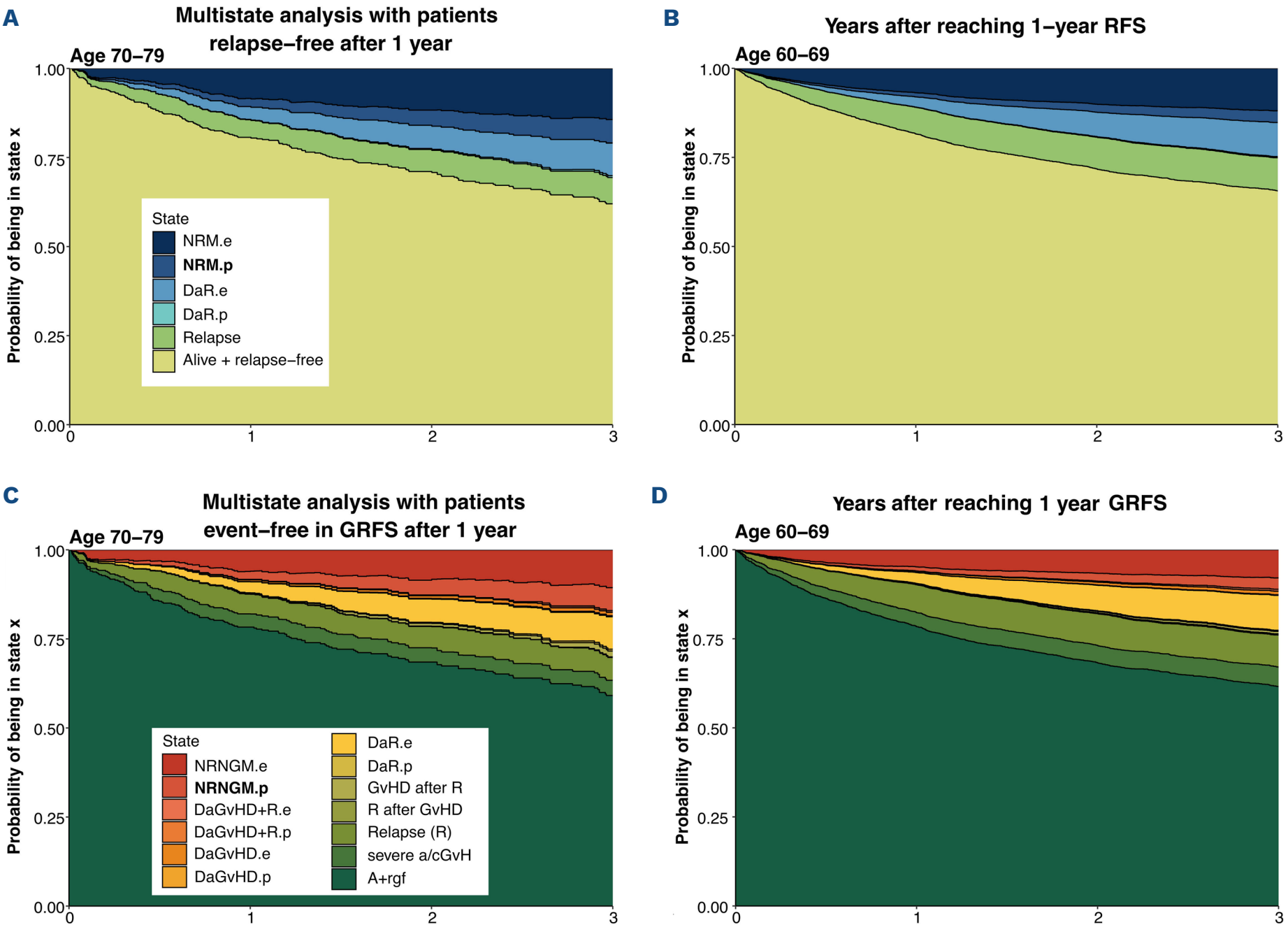

Figure 3. Multistate modeling of relapse-free survival and graft-*versus*-host-relapse-free-survival. (A) Multistate progress of follow-up after one year without failure (death / relapse) in patients aged 70-79 years. (B) Multistate progress of follow-up after one year without failure (death / relapse) in patients aged 60-69 years. (C) Multistate progress of follow-up after one year without failure (death / relapse / severe graft-*versus*-host disease [GvHD]) in patients aged 70-79 years. (D) Multistate progress of follow-up after one year without failure (death / relapse / severe GvHD) in patients aged 60-69 years. NRM: non-relapse-mortality; DAR: death after relapse; NRNGM: non-relapse-non-GvHD-mortality; DaGvHD+R: death after GvHD and relapse; DaGvHD: death after GvHD; R: Relapse; p: due to population mortality (NRM and NRNGM in bold); e: due to excess mortality.

Table 3. Regression analyses.

Co-variate	Cox regression regarding overall survival			Additive proportional hazards model regarding excess mortality+		
	Total FU* HR (95% CI)	First year of FU* HR (95% CI)	Years 1+ of FU* HR (95% CI)	Total FU* HR (95% CI)	First year of FU* HR (95% CI)	First year of FU* HR (95% CI)
Age group ref. 60-69 70-79	1 1.19 (1.1-1.28), *P*<0.001	1 1.18 (1.08-1.29), *P*<0.001	1 1.22 (1.07-1.4), *P*=0.004	1 1.14 (1.05-1.24), *P*=0.001	1 1.16 (1.06-1.27), *P*=0.001	1 1.09 (0.91-1.3), *P*=0.35
Disease, ref. acute leukemia CLL CML Lymphoma MDS/MPN Plasma cell disorders Others *P* value after Cox Anova	1 0.58 (0.49-0.68), *P*<0.001 0.73 (0.59-0.9), *P*=0.003 1.08 (0.97-1.19), *P*=0.16 0.76 (0.71-0.81), *P*<0.001 0.97 (0.86-1.09), *P*=0.56 1.06 (0.92-1.22), *P*=0.42 *P*<0.001	1 0.53 (0.43-0.65), *P*<0.001 0.78 (0.6-1), *P*=0.048 1.19 (1.06-1.33), *P*=0.004 0.75 (0.69-0.81), *P*<0.001 0.81 (0.7-0.94), *P*=0.007 1.02 (0.86-1.22), *P*=0.78 *P*<0.001	1 0.68 (0.53-0.88), *P*=0.003 0.65 (0.45-0.94), *P*=0.021 0.83 (0.68-1.02), *P*=0.08 0.78 (0.69-0.89), *P*<0.001 1.29 (1.07-1.55), *P*=0.007 1.15 (0.89-1.49), *P*=0.28 *P*<0.001	1 0.53 (0.44-0.63), *P*<0.001 0.72 (0.56-0.91), *P*=0.006 1.1 (0.99-1.23), *P*=0.09 0.74 (0.68-0.8), *P*<0.001 0.87 (0.76-0.99), *P*=0.036 1.06 (0.91-1.23), *P*=0.47 -	1 0.5 (0.41-0.62), *P*<0.001 0.77 (0.59-1), *P*=0.05 1.19 (1.06-1.34), *P*=0.004 0.73 (0.67-0.8), *P*<0.001 0.8 (0.69-0.94), *P*=0.006 1.03 (0.86-1.22), *P*=0.77 -	1 0.62 (0.44-0.87), *P*=0.006 0.54 (0.31-0.94), *P*=0.028 0.79 (0.61-1.04), *P*=0.09 0.76 (0.65-0.9), *P*=0.001 1.07 (0.84-1.37), *P*=0.59 1.18 (0.87-1.61), *P*=0.3 -
Sex ref. female Male	1 1.08 (1.03-1.14), *P*=0.004	1 1.05 (0.98-1.12), *P*=0.17	1 1.16 (1.05-1.27), *P*=0.003	1 1.06 (1-1.12), *P*=0.06	1 1.04 (0.97-1.11), *P*=0.23	1 1.11 (0.98-1.25), *P*=0.1
Comorbidity ref. No Yes	1 1.16 (1.07-1.25), *P*<0.001	1 1.18 (1.07-1.29), *P*<0.001	1 1.12 (0.99-1.26), *P*=0.07	1 1.16 (1.07-1.26), *P*<0.001	1 1.2 (1.1-1.31), *P*<0.001	1 1.05 (0.89-1.24), *P*=0.54
Karnofsky Perf. Index, ref. 90-100 80 <80 *P* value after Cox Anova	1 1.27 (1.19-1.35), *P*<0.001 1.84 (1.68-2.02), *P*<0.001 *P*<0.001	1 1.31 (1.22-1.42), *P*<0.001 1.96 (1.75-2.18), *P*<0.001 *P*<0.001	1 1.17 (1.04-1.32), *P*=0.008 1.53 (1.27-1.85), *P*<0.001 *P*<0.001	1 1.3 (1.21-1.39), *P*<0.001 1.95 (1.77-2.15), *P*<0.001 -	1 1.33 (1.23-1.44), *P*<0.001 2.04 (1.82-2.3), *P*<0.001 -	1 1.2 (1.01-1.42), *P*=0.035 1.56 (1.24-1.97), *P*<0.001 -
Period, ref. 1998-2008 2009-2018	1 0.95 (0.89-1.01), *P*=0.09	1 0.9 (0.84-0.97), *P*=0.009	1 1.04 (0.93-1.16), *P*=0.51	1 0.92 (0.85-0.99), *P*=0.021	1 0.9 (0.83-0.97), *P*=0.008	1 1 (0.86-1.15), *P*=0.96
Remission state at HSCT, ref. No CR Complete remission	1 0.71 (0.66-0.75), *P*<0.001	1 0.66 (0.61-0.72), *P*<0.001	1 0.82 (0.73-0.92), *P*<0.001	1 0.67 (0.63-0.72), *P*<0.001	1 0.65 (0.6-0.7), *P*<0.001	1 0.76 (0.66-0.88), *P*<0.001
Likelihood Ratio Test	*P*<0.001	*P*<0.001	*P*<0.001	NA	NA	NA

*See *Online Supplementary Appendix* for model: added total conditioning intensity (TCI), type of allograft (peripheral blood [PB] *vs.* bone marrow [BM]), donor age, cytomegalovirus (CMV) status relation, donor type, total body irradiation (TBI) part of conditioning and follow-up (FU) hazards; *Online Supplementary Table S5*). Values obtained from a multivariable Cox regression model are depicted overall and separately for the first year and subsequent years of (FU). Likewise, a Cox model was fitted for excess hazard only. An overall *P* value of a likelihood ratio test was added. CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; MDS/MPN: myelodysplastic syndromes/myeloproliferative neoplasms; CR: complete remission; HSCT: hematopoietic stem cell transplantation; HR: hazard ratio; CI: confidence interval; NA: not available; ref.: reference.

Interestingly, the negative impact of male sex is lost when only excess mortality (HR 1.06 [1-1.12], *P*=0.06) is considered. Table 3 shows the regression analysis.

Discussion

This study on 1,547 patients aged 70-79 years and 9,422 patients aged 60-69 years, transplanted during two decades (1998-2018), is the largest real-world data analysis investigating the influence of age on survival after transplantation for myeloid neoplasia, but also chronic leukemia, lymphoma, MDS/ MPN, plasma cell disorders, and other types of neoplasia. Notably, no patient over the age of 79 years is documented in the database. This real-world dataset is a picture of the heterogeneous landscape (e.g., disease, conditioning, GvHD-prophylaxis) of stem cell transplantation. We preserve this heterogeneity on purpose.[6] The design of the study with a long inclusion period enabled us to capture time trends in numbers of transplanted older patients and outcomes.

Absolute hazards for excess mortality are known to increase with age.[14,28] Here we aim to dissect mortality in older cohorts into the naturally occurring, age-dynamic, population-based mortality and excess (disease- and treatment-related) mortality in order to better define the impact of age as risk factor for transplantation. In general, our study confirms older age as a risk factor for poor survival in patients receiving transplantation. OS of patients aged 60-69 years exceeds that of their older peers (70-79 years) by 7.5 months (Table 2).[6-8,28] Death rates in older patients (70-79 years) are markedly increased during the first year of follow-up. Importantly, overall survivors after 1-year are expected to survive a median of 7.4 years (60-69 years) and 4.8 years (70-79 years), respectively, consistent with other studies.[6,7]

The contribution of population mortality to NRM has been shown in long-term survivors of transplantation for MDS.[14] Furthermore, over the age of 55, the risk of death roughly doubles in every age decade within the general population, which would give a hazard ratio of 2.0 for age decade (*Online Supplementary Figure S3*).[29] To separate the contribution of age, GvHD and relapse to post-transplantation mortality, we performed multistate analysis in an RFS- and GRFS-environment for all patients (*Online Supplementary Figure S5.1-S5.4*) and exclusively for 1-year event-free survivors (Figure 3). Two main messages stand out clearly. First, NRM and NRNGM seem to gradually outweigh “death after GvHD” and “death after relapse” in older patients. Strikingly, up to 25% of older patients will have died for reasons other than GvHD, relapse or age up to four years after transplantation (*Online Supplementary Table S3.3, Online Supplementary Figure S4.1, S4.2*). However, in one-year survivors followed up to four years after transplantation (i.e., LM plus three years), population mortality contributes roughly from a fifth to a third to NRM: NRM.p divided by NRM.p+.e for 70-79 years equals 31.4%, for 60-69 years 21.6%. The quotient of NRNGM.p and NRNGM.p+.e for the group 70-79 years is 37.3%, and for 60-69 years 29.2%. Thus, the contribution of population mortality is more pronounced with higher age. Hence, differences in excess survival are less pronounced (Table 3), especially at longer follow-up. Thus, we add the most accurate estimation of the increased hazard for excess mortality for higher age and this is revealed to be, indeed, moderate (HR 1.2-1.3 per decade).[8,14,28] As a first conclusion, whereas excess mortality drives mortality the year after transplantation, the contribution of population mortality increases with distance to transplantation but excess mortality remains dominant. Defining and addressing the remaining causes of death should be a matter of further research.

It remains speculative as to why OS of patients aged 60-69 years improves over time whereas it does not change for patients aged 70-79 years. Patient selection is one possible explanation.

Furthermore, our comprehensive analysis confirms previous results on the impact of donor characteristics (related *vs.* unrelated, young donor age[30-34]), disease (CLL, CML, MDS, MPN), disease state at transplant (complete remission or not) on outcome. One reason for the dominance of the male sex within the dataset is probably the tendency towards curative treatment options and against palliative regimen for men.[35] Regression analysis suggests that worse outcome in male patients is largely due to higher population mortality. There is no significant difference in excess mortality between male and female patients during all follow-up periods. Sex differences, both as to whether frequencies and outcome are concerned, must remain a matter of future research.

Limitations of our analysis are the degree of missing data any registry analysis must face. It remains debatable if an adequate follow-up might have differed to any great extent. We are sure that a maximum error of 5% must be anticipated for registry analysis; however, this should be tackled within the registries. With regards to our regression analysis, it needs to be mentioned that MICE would not generally accept missing not-at-random values. This is an issue of the model assumption that is described in the literature.[36] In addition, our data span two decades, contributing to the heterogeneity in this work. To account for medical progress during that time, we considered outcomes from patients transplanted between 2006-2018 in a separate analysis (*Online Supplementary Tables S5, S6, S7, Online Supplementary Figure S8.1, 8.2*). It is important to be aware that relative survival analysis models rely on the assumption that the patients’ state of health before transplantation does not differ from that of the general population. This assumption might not be met in the context of a treatment-based registry; it is likely that patients who have severe comorbidities or a disadvantaged socioeconomic

background will not be offered transplantation. This would imply that the background mortality is somewhat smaller in our patient cohort than in the general population and the excess mortality thus larger than estimated. This would not change our main messages though. Next to an improved completeness of follow-up, future registry documentation might boost coverage of frailty and comorbidity indices. We, therefore, further encourage the community to focus on raw data for variables like the HCT-CI comborbidity index and the Disease Risk Index.

In conclusion, transplantation is particularly challenging for older adults due to comorbidities, impaired functional status, and cognitive impairment. These factors may negatively affect recovery after transplantation and increase the risk of complications. Therefore, thorough screening and careful planning are critical for older adults considering transplantation. Practical clinical implications on whom to choose and how to prepare for transplantation cannot be concluded from this registry analysis and have been reviewed elsewhere.[37-40] Although it is evident that older patients generally have worse outcomes, the difference between patients aged 70 to 79 years compared with patients aged 60 to 69 years is not so high as to justify exclusion from transplantation on the basis of age alone.

Disclosures

HN is an employee of the German Registry for Stem Cell Transplantation (DRST). SF is, in part, financed through the German Registry for Stem Cell Transplantation (DRST). In an honorary capacity, NK, KF, PD, JS and MS are on the board of the German Registry for Stem Cell Transplantation (DRST). The other authors have no conflicts of interest to disclose.

Contributions

JFW and MC are responsible for the conception of the analysis, data retrieval, statistical analysis and interpretation, and writing of the manuscript. LdW is responsible for the discussion of results, statistical analysis, and writing of the manuscript. CL contributed to the discussion of results. JF, JS, UP, HE, TS, CF, MS, PD, IWB, GW, JT, CS, AE, MB, WB, KF and NK are responsible for the contribution of patient data and discussion of results. HN and SF curated primary data. All authors read the final version of the manuscript and agreed to its content.

Data-sharing statement

The code used for the analyses is available upon request from the corresponding author. Data of the individual participants will not be shared.

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