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Running head: Decreasing excess mortality after AHSCT for AL

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Data availability statement:

The raw data that support the findings of this study are available from DRST and PRSZT. The authors confirm that the data underlying the findings of this study are fully available within the article. Restrictions apply to the availability of these data which were used under license for this analysis.

Conflicts of interest:

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Author contributions:

CS, TS, IWB, MS, NK, KEH, ME, PD, JT, EWD, PB, MGS, BM, and KF read and approved the final manuscript. SF and AA analyzed data. JF and IH conceived and planned the analysis and wrote the manuscript.

Keywords:

Children, adolescents and young adults, CAYA, allogeneic hematopoietic stem cell transplantation, right to be forgotten (RTBF)

MAIN TEXT:

According to the European Society for Blood and Bone Marrow Transplantation (EMBT), the annual number of allogeneic hematopoietic stem cell transplantations (AHSCT) is increasing with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) being the main indications [1]. Survival following AHSCT for acute leukemia (AL, ALL and AML) has improved over recent decades: the overall probability of surviving five years has reached 53% for young adults (YA) aged 18-39 years [2].

Nevertheless, faced with a wide range of sequelae after surviving cancer, the absence of or the inability to detect malignant cells does not necessarily mean that children, adolescents and young adults (CAYA) feel healthy [3, 4]. Furthermore, according to the German Society for Haematologie and Medical Oncology (DGHO) and others, cancer survivors often face discrimination concerning, for example, insurance, occupation, loans, mortgages or adoption [5-9].

To illustrate, we present the case of Lisa, aged 36, who underwent AHSCT for AML at the age of 24. She vividly recounted the discrimination she faced when seeking employment and applying for disability insurance. She shared her experience of discrimination during consultations and gave us permission to publish her story.

> "*[…] I applied for various positions. […] At one job interview, there was a disabled employees' representative that I already knew from another job interview. I received the rejection from him. He spoke to me immediately and said that I didn't seem so pale that day. At the last conversation I was very pale. As they weren't sure whether it had to do with the leukemia, I did not receive the job, although they would have liked to hire me. […] Furthermore, I wanted to take out occupational disability insurance. Even after rehabilitation, I received only offers for policies with extremely high premiums because of the leukemia. Therefore, I do not have occupational disability insurance [today]."*

In 2016, France introduced a law which ensures the "right to be forgotten" (RTBF). This legislation prevents financial discrimination against cancer survivors by prohibiting insurers and lenders from considering an individual's medical history five years after the end of treatment, provided there has been no recurrence. Since then, several other European countries have

adopted the RTBF [5, 10]. Despite a broad and far-reaching political debate, there is still no such obligation in Germany, nor any harmonization at the European level [5].

Since robust medical data are necessary to draft legislation that reflects the latest scientific findings [11], the 11,257 participants in a recently published retrospective cohort study were additionally analyzed with regard to excess mortality compared to the general population in Germany [12]. The study examined the excess mortality of CAYA aged 0-39 years (2999, 26.6%) and the group of middle-aged and older adults aged 40-72 years (8258, 73.4%) with AL who were alive without relapse for one to five years after AHSCT. The patients' consent to perform analyses of their clinical data was obtained at the time of their registration in the EBMT or German Pediatric Registry for Stem Cell Transplants and Cell Therapies (PRSZT) database. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Jena University Hospital (2019-1499-Daten). Our analysis provides evidence substantiates both the need for structured after-care programs as well as the necessity and urgency of enshrining the RTBF in German law.

For the representation of the excess mortality, univariable Cox regressions were calculated for OS starting from AHSCT and one to five years after AHSCT for patients who survived without relapse. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were reported for patients with AL compared with the general population. These calculations were performed separately for patients aged <40 and ≥40 years. General population data were simulated using the survival data for the corresponding ages obtained from the Federal Statistical Office of Germany (GFSO, https://www.destatis.de/). All analyses were conducted using the statistical software R, version 4.3.2, including the package "survival" provided by the R Foundation.

Except where otherwise specified, AML and ALL were reported as AL. Depending on the underlying disease, descriptive statistics were presented for the patient- and transplantation-related variables, and were reported as absolute and relative numbers. Inclusion and exclusion criteria as well as definitions of relevant endpoints were used as described above [2, 12, 13].

As patients and AHSCT characteristics were recently published in detail [12], only a brief summary of important details related to content is presented here. Between 2011 and 2019, 573 children (C) aged 0-12, 268 adolescents (A) aged 13-17, 2158 YA aged 18-39, 4667 middle-aged adults (MAA) aged 40-59 and 3591 older adults (OA) aged 60-72 years who received a first AHSCT in one of 67 AHSCT centres in Germany were included in this analysis. Of these, 196 (2.2%) C, 100 (1.1%) A, 1,276 (14.4%) YA, 3,942 (44.6%) MAA, and 3,320 (37.6%) OA suffered from AML (8,834; 78.5%) and 377 (14.3%) C, 168 (6.9%) A, 882 (36.4%) YA, 725 (29.9%) MAA, and 271 (11.2%) OA from ALL (2,423; 21.5%). The predominant gender in the cohort was male (6,330; 56.2%).

The majority of the patients were transplanted with PBSCT (10,088; 89.6%) from an unrelated donor (8,066; 71.7%) while in complete remission (7734; 68.7%). Of the patients who died within 5 years of AHSCT, most of the patients died due to relapse or progression (472; 52.0%) or from AHSCT-related reasons (314; 34.6%).

From the time of AHSCT, the probabilities of surviving one / two / three / four / five years were 80% / 70% / 65% / 62% / 60% for the whole group of CAYA and 66% / 56% / 51% / 47% / 44% for the whole group of MAA and OA. For patients who survive one to five years after AHSCT, the corresponding probabilities increase annually (see **table 1**). Finally, after surviving AHSCT for five years without relapse, the chance of surviving for another year even increases to 99% for CAYA or 96% for elderly patients, respectively.

Direct comparison of reported survival rates with those described in contemporary literature is complicated by the fact the that latter are often given under certain conditions (**figure 1**). For instance, the 5-year OS after AHSCT between 2005-2012 ranged from 53 to 64% for patients with ALL under 25 years of age [14]. Sasaki and colleagues, however, reported on a 5-year OS after AHSCT between 2010-2017 of 59 to 93% for ALL and 63 to 70% for patients suffering from AML under the age of 39 years [15]. Against this backdrop, the 5-year survival rate for CAYA of almost 60% from the time of AHSCT aligns with expectations.

To illustrate the reduction in the excess mortality, the OS of CAYA and of MAA / OA with AL was conditioned on the status of being alive without relapse one to five years after AHSCT compared to the general population (**figure 1**). Expressed in HR, excess mortality steadily decreases with conditional recurrence-free survival of up to five years after transplantation. Therefore, the probability of survival approaches that of the corresponding age groups in the general population. At the time of AHSCT, the HR of surviving one year is 333.6 [312.1; 356.5] for CAYA and 27.4 [26.6; 28.4] for MAA / OA. However, if the patient survives one / three / five years after AHSCT without relapse, the HR decreases to 115.0 [99.5; 132.9], 35.6 [24.2; 52.3], and 31.1 [14.8; 65.3] as well as to 8.9 [8.3; 9.6], 4.7 [4.1; 5.5], and 4.0 [3.1; 5.3], respectively (**figure 2**). Interestingly, the percentage decrease in the HR compared with the previous value is greater for CAYA than for MAA/OA in the first three years following AHSCT, but similar in the fourth and fifth year following AHSCT (red bars).

By analyzing the time course of RFS of CAYA with AL as a function of an increasing time interval since the time of AHSCT, we demonstrate that OS converges with that of the respective age groups in the general population over the course of five years (**figure 2**). For this reason, CAYA who have survived for five or more years without relapse after AHSCT should be fully reintegrated into society, which requires the elimination of any stigma associated with their medical history [10].

Ultimately, the results support harmonizing a 5-year time frame between the completion of cancer treatment and the RTBF taking effect as a prerequisite for effective European legislation [5, 11].

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TABLE AND TABLE LEGEND

Table 1: Patient and transplant characteristics

Overall survival (OS) of CAYA / OA and MAA with AML / ALL…						
	at AHSCT	under the condition of having survived without relapse for…				
		1 year	2 years	3 years	4 years	5 years
n	2999 / 8258	1644 / 3627	1153 / 2396	870 / 1745	616 / 1240	412 / 848
one year(s) since AHSCT	80% / 66%	-	-	-	-	-
two year(s) since AHSCT	70% / 56%	94% / 90%				
three year(s) since AHSCT	65% / 51%	89% / 84%	97% / 95%			
four year(s) since AHSCT	62% / 47%	87% / 78%	95% / 89%	99% / 96%		
five year(s) since AHSCT	60% / 44%	85% / 74%	93% / 85%	98% / 91%	99% / 96%	
six year(s) since AHSCT	59% / 42%	83% / 70%	91% / 81%	96% / 87%	97% / 92%	99% / 96%

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; AHSCT: allogeneic hematopoietic stem cell transplantation; MAA: middle-aged adults; OA: older adults; OS: overall survival.

FIGURE LEGENDS

Figure 1: Overall survival of children, adolescents and young adults with acute leukemia compared to the general population

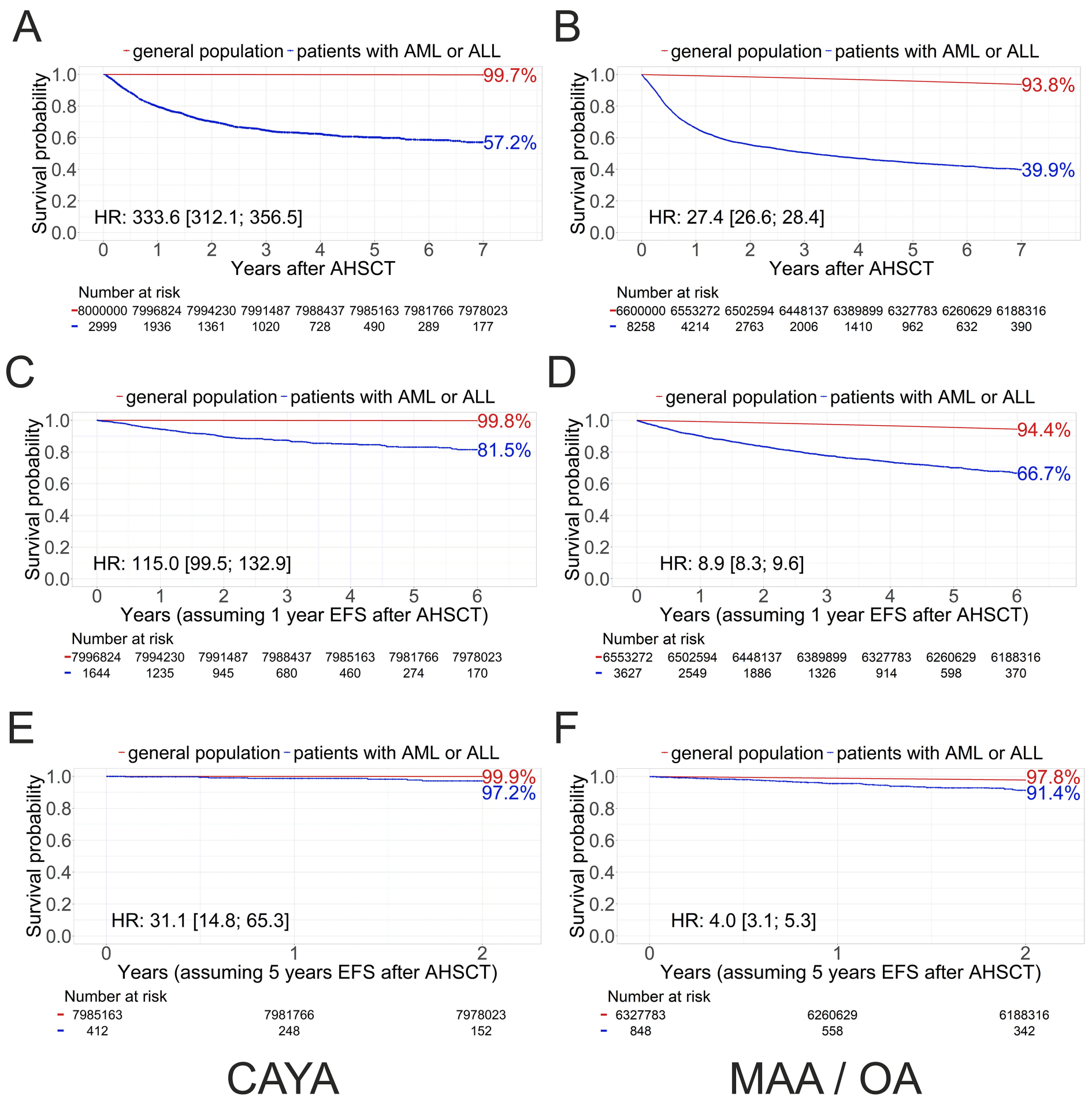
Overall survival (OS) of children, adolescents and young adults (CAYA; figures A, C, E) and middle-aged and older adults (MAA / OA; figures B, D, F) with acute leukemia following allogeneic hematopoietic cell transplantation (figures A+B) and depending on the condition of having survived one (figures C+D), and five (figures E+F) years without relapse.

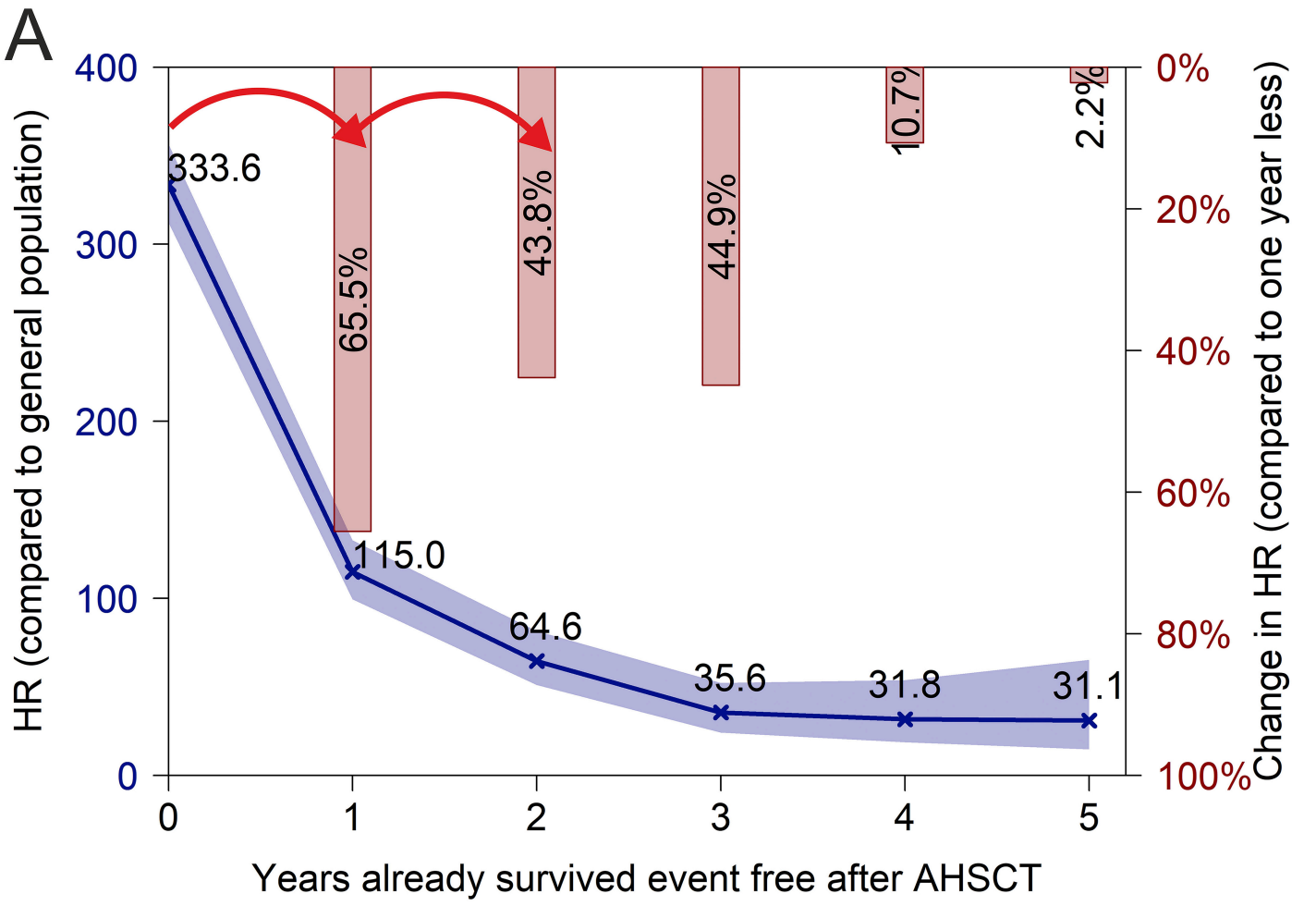
AHSCT: allogeneic hematopoietic stem cell transplantation; CAYA: children, adolescents and young adults; MMA: middle-aged adults; OA: older adults; OS: overall survival; HR: hazard ratio.

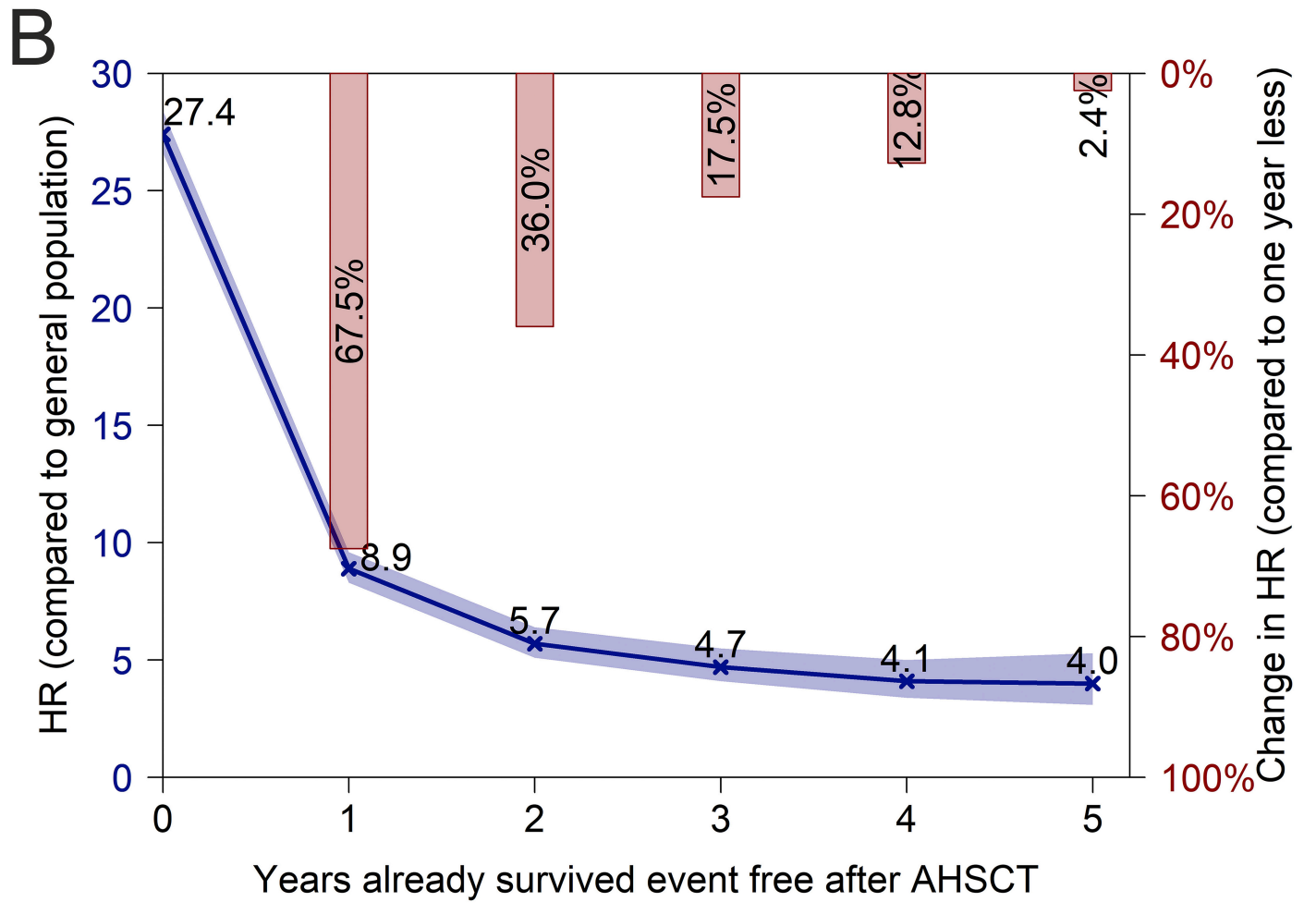
Figure 2: Excess mortality for the group of CAYA and the group of MAA and OA in comparison to the general population

Decreasing excess mortality (on the left, blue colored) expressed as HR of relapse-free children, adolescents and young adults (figure A; CAYA) and middle-aged and older adults (figure B; MAA/OA) with AML or ALL and increasing time to allogeneic hematopoietic stem cell transplantation (AHSCT). The percentage decrease in HR compared to the respective previous value is shown in red on the right.

AHSCT: allogeneic hematopoietic stem cell transplantation; HR: hazard ratio.


A
general population
patients with AML or ALL
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
99.7%
57.2%
HR: 333.6 [312.1; 356.5]
0
1
2
3
4
5
6
7
Years after AHSCT
Number at risk
8000000 7996824 7994230 7991487 7988437 7985163 7981766 7978023
2999 1936 1361 1020 728 490 289 177
B
general population
patients with AML or ALL
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
93.8%
39.9%
HR: 27.4 [26.6; 28.4]
0
1
2
3
4
5
6
7
Years after AHSCT
Number at risk
6600000 6553272 6502594 6448137 6389899 6327783 6260629 6188316
8258 4214 2763 2006 1410 962 632 390
C
general population
patients with AML or ALL
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
99.8%
81.5%
HR: 115.0 [99.5; 132.9]
0
1
2
3
4
5
6
Years (assuming 1 year EFS after AHSCT)
Number at risk
7996824 7994230 7991487 7988437 7985163 7981766 7978023
1644 1235 945 680 460 274 170
D
general population
patients with AML or ALL
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
94.4%
66.7%
HR: 8.9 [8.3; 9.6]
0
1
2
3
4
5
6
Years (assuming 1 year EFS after AHSCT)
Number at risk
6553272 6502594 6448137 6389899 6327783 6260629 6188316
3627 2549 1886 1326 914 598 370
E
general population
patients with AML or ALL
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
99.9%
97.2%
HR: 31.1 [14.8; 65.3]
0
1
2
Years (assuming 5 years EFS after AHSCT)
Number at risk
7985163 7981766 7978023
412 248 152
F
general population
patients with AML or ALL
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
97.8%
91.4%
HR: 4.0 [3.1; 5.3]
0
1
2
Years (assuming 5 years EFS after AHSCT)
Number at risk
6327783 6260629 6188316
848 558 342
CAYA
MAA / OA


A
400
300
200
100
0
HR (compared to general population)
0%
20%
40%
60%
80%
100%
Change in HR (compared to one year less)
333.6
115.0
64.6
35.6
31.8
31.1
65.5%
43.8%
44.9%
10.7%
2.2%
0
1
2
3
4
5
Years already survived event free after AHSCT


B
30
25
20
15
10
5
0
HR (compared to general population)
0%
20%
40%
60%
80%
100%
Change in HR (compared to one year less)
27.4
8.9
5.7
4.7
4.1
4.0
67.5%
36.0%
17.5%
12.8%
2.4%
0
1
2
3
4
5
Years already survived event free after AHSCT