

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 28 February 2018 | doi:10.4414/smw.2018.14589

Cite this as: Swiss Med Wkly. 2018;148:w14589

Haematopoietic cell transplantation in Switzerland, changes and results over 20 years: a report from the Swiss Blood Stem Cell Transplantation Working Group for Blood and Marrow Transplantation registry 1997–2016

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Summary

In 1997, the Swiss Blood Stem Cell Transplantation Group (SBST) initiated a mandatory national registry for all haematopoietic stem cell transplants (HCTs) in Switzerland. As of 2016, after 20 years, information was available for 7899 patients who had received an HCT (2781 allogeneic [35%] and 5118 autologous [65%]). As some patients had more than one transplant the total number of transplants was 3067 allogeneic and 6448 autologous. We compared patient characteristics and outcome of the first decade (1997–2006) and second decade (2007–2016) of the registry. There were numerous changes over time. For allogeneic HCT, transplant rates, and therefore use of HCT technology, increased from 14 to 21.8 HCTs per 1 million inhabitants per year from the first to the second decade. Likewise autologous HCTs increased from 24.8 to 37.2 annually corrected for population growth. Allogeneic transplant recipients were older (38.4 vs 48.3 years) and more frequently had unrelated donors in the second decade. Similarly, age increased for recipients of autologous HCT (50.8 vs 56.4 years).

Analysis of outcome showed that the probabilities of overall and progression-free survival were stable over time, in spite of the treatment of older and higher risk patients. In multivariate analysis, nonrelapse mortality decreased in recipients of allogeneic HCT (relative risk 0.68, 95% confidence interval 0.52–0.87) over the two decades. Improvement in adjusted nonrelapse mortality compensated for the fact that higher risk patients were treated in more recent years, resulting in similar overall survival. Five-year survival probabilities were 56% (53–59%) in the first and 54% (51–57%) in the second decade for allogeneic HCT, and 59% (57–61%) in the first and 61% (59–63%) in the second decade for autologous HCT. Detailed analyses of changes over time are presented. This study included all HCTs performed in Switzerland during the period of observation and the data are useful for quality assurance programmes, healthcare cost estimation and healthcare planning. Between 50 and 60% of patients were long-term survivors after both types of HCT, indicating growing populations of surviving patients requiring long-term care and observation.

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Key words: Hematopoietic cell transplantation, Switzerland, demographics, outcome, overall survival, progression free survival, multivariate analyses

Introduction

Transplantation of haematopoietic stem cells (HCT) is today an established therapy and has expanded rapidly over recent decades. It is used for many severe acquired or congenital disorders of the haematopoietic system and for chemo, radio or immunosensitive malignancies. Stem cells from bone marrow, peripheral blood or cord blood are used, and may be derived from the patients themselves for autologous HCT or from siblings, other family members or unrelated donors for allogeneic HCT [1–6]. The goals of HCT are manifold. HCT can restore bone marrow function in patients with congenital deficiencies or acquired malfunction. Autologous transplants can be used to shorten the period of severe pancytopenia in the context of high-dose chemo-/radiotherapy. Allogeneic HCT provides a powerful targeted antitumour effect in the form of a graft-versus-host or graft-versus-tumour reaction in the treatment of haematological or nonhaematological malignancies. HCT can induce tolerance to donor tissue in solid organ transplantation and, last but not least, HCT can reset the ontogeny of the immune system in the treatment of autoimmune diseases [7]. HCT has a long history in Switzerland [8, 9]. HCT is a complex and cost-intensive therapeutic procedure. In Switzerland, costs of the procedure are covered by health insurance, based on the [guidance of the Federal Office for Social Insurance](#). In this guidance diseases are listed as “established”, “in evaluation with full payment”, “in evaluation without payment” or “not established”. On the occasion of a prior revision (2002), the Federal Office requested an analysis of this therapeutic instrument and asked for an evaluation registry. In anticipation of this requirement, in 1997 the Swiss Blood Stem Cell Transplantation Group (SBST) established a central registry for all HCTs in Switzerland. As reporting is mandatory, this report includes all patients receiving an autologous or allogeneic HCT in Switzerland over the past 20 years (1997–2016) and describes changes in patient characteristics and treatment outcomes over time.

Patients and methods

Data collection

In accordance with and in preparation for the Swiss transplant law, from 1997 data relating to all HCTs performed in Switzerland were collected. Data collection is based on the Minimal Essential Data sets (Med-A) of the [European Society for Blood and Marrow Transplantation](#) (EBMT). Patient data are updated annually. All patients receiving a transplant between 1 January 1997 and 31 December 2016 were included in this analysis. The data cut-off date was 31 July 2017, giving a minimum follow up of 6 months for all patients. Median follow-up for all allograft recipients was 4.4 years (quartiles 1.6–9.2) and for autografts was 3.7 years (1.1–7.4).

Definitions for haematopoietic stem cell transplantation

HCT was defined according to the criteria of the EBMT [10]. An HCT is the infusion of haematopoietic stem cells given with the intention to replace the pretransplant haematopoietic system of the recipient. Patient-related outcomes are reported. Some patients received more than one transplant and these are described for characteristics where the focus is on procedures.

A retransplant was defined as HCT given after a previous (either autologous or allogeneic) HCT, for the treatment of relapse or rejection. Multiple transplants are defined as subsequent infusions of stem cells in the context of planned double or triple transplant protocols.

Participating teams

HCT was performed during the defined observation period in Aarau (Kantonsspital), Basel (University Hospitals), Bellinzona (Kantonsspital), Berne (University Hospital), Geneva (University Hospital), Lausanne (University Hospital), St. Gallen (Kantonsspital) and Zurich (University Hospital, University Children’s Hospital and the Hirslanden Clinic). Allogeneic HCTs were restricted to Basel, Geneva, Zurich University Hospital and Zurich University Children’s Hospital; autologous transplants were performed at all centres. Since 1997, autologous HCTs in the French-speaking part of Switzerland were performed primarily in Lausanne, allogeneic HCTs primarily in Geneva. Paediatric transplants were performed in Basel (allogeneic and autologous), Berne (autologous), Geneva (allogeneic and autologous), Lausanne (autologous) and Zurich (allogeneic and autologous).

All teams were required to have ethics committee approval of data collection, and all patients or their legal representatives gave written informed consent before the transplant.

Statistical analysis

Descriptive statistics included median and range for continuous variables and frequencies for categorical variables. As the observation period covered 20 years, we used the first and second decade of the registry to compare changes in the use of technology, indications and outcomes over time. Comparison among groups was by use of the Kruskal-Wallis test for continuous variables and the chi-squared test for categorical variables. Transplant rates were calculated as number of allogeneic and autologous HCTs corrected per 1 million inhabitants per year for each of the decades, accounting for population growth in Switzerland. Outcomes measured were overall survival and progression-free survival, determined as the Kaplan-Meier estimates, and nonrelapse mortality and relapse incidence determined from cumulative incidence curves adjusted for competing risks as appropriate. For overall survival, death was the event, for progression-free survival it was time to relapse of the original disease or death measured from the time of transplant. Nonrelapse mortality was defined as death without relapse. Groups were compared using the log-rank test for the Kaplan-Meier estimates and Fine and Gray for cumulative incidence. A p-value of ≤ 0.05 was considered to be statistically significant.

Multivariate models were constructed using the Cox regression model or the competing risk model as appropriate [11]. All variables detailed in [tables 1 and 2](#) (see “Results”)

Table 1: a: Demographic characteristics and transplant technology for allogeneic haematopoietic cell transplants by decade for the years 1997–2016.

	1997–2006		2007–2016		Total		p-value
	n	%	n	%	n	%	
Patients (first allograft)							
No. 1st. allograft	997	88.8	1784	91.8	2781	90.7	
No. not 1st allograft	126	11.2	160	8.2	286	9.3	
Centre							0.01
1	427	42.8	654	36.7	1081	38.9	
2	233	23.4	456	25.6	689	24.8	
3	236	23.7	488	27.4	724	26	
4	101	10.1	186	10.4	287	10.3	
Disease							<0.0001
Acute myeloid leukaemia	314	31.5	651	36.5	965	34.7	
Acute lymphoid leukaemia	163	16.3	272	15.2	435	15.6	
Chronic lymphocytic leukaemia	23	2.3	54	3	77	2.8	
Chronic myeloid leukaemia	152	15.2	59	3.3	211	7.6	
Combined myelodysplastic/myeloproliferative	85	8.5	215	12.1	300	10.8	
Myeloproliferative neoplasms	22	2.2	93	5.2	115	4.1	
Hodgkin's lymphoma	21	2.1	35	2	56	2	
Non-Hodgkin's lymphoma	57	5.7	122	6.8	179	6.4	
Plasma cell disorder	54	5.4	113	6.3	167	6	
Solid tumours	8	0.8	2	0.1	10	0.4	
Bone marrow failure	51	5.1	59	3.3	110	4	
Inherited disorders of metabolism	6	0.6	17	1	23	0.8	
Primary immune disorders	29	2.9	57	3.2	86	3.1	
Haemoglobinopathy	9	0.9	18	1	27	1	
Histiocytic disorders	3	0.3	14	0.8	17	0.6	
Others	0	0	3	0.2	3	0.1	
Disease stage at transplant							<0.0001
Early	526	52.8	919	51.5	1445	52	
Intermediate	229	23	530	29.7	759	27.3	
Late	242	24.3	335	18.8	577	20.7	
Gender							0.30
Male	584	58.6	1081	60.6	1665	59.9	
Female	413	41.4	703	39.4	1116	40.1	
Age group							<0.0001
0–20 years	229	23	289	16.2	518	18.6	
20–40 years	300	30.1	344	19.3	644	23.2	
40–60 years	413	41.1	786	44.1	1199	43.1	
60–70 years	55	5.5	343	19.2	398	14.3	
>70 years	0	0	22	1.2	22	0.8	
Median age (years)	38.4		48.3		44.3		
Age range (years)	0.15–68.7		0.24–74.2		0.15–74.2		
Donor							<0.0001
HLA identical sibling	586	58.8	653	36.6	1239	44.6	
Twin	17	1.7	9	0.5	26	0.9	
Other relative	93	9.3	120	6.7	213	7.7	
Unrelated	301	30.2	1002	56.2	1303	46.9	
Stem cell source							<0.0001
Bone marrow	304	30.5	302	16.9	606	21.8	
Peripheral blood	679	68.1	1417	79.4	2096	75.4	
Cord blood	14	1.4	65	3.6	79	2.8	
Risk score							<0.0001
0–1	158	15.8	166	9.3	324	11.7	
2–3	471	47.2	810	45.4	1281	46.1	
4–5	326	32.7	676	37.9	1002	36	
6–7	42	4.2	132	7.4	174	6.3	
Comorbidities							
Yes	Data not collect-	–	631	35.4	631	35.4	
No	ed	–	601	33.7	601	33.7	
Missing		–	552	30.9	552	30.9	
Cytomegalovirus status (donor-recipient)							0.16
Neg-neg	201	34.4	555	32.4	756	32.9	

	1997–2006		2007–2016		Total		p-value
	n	%	n	%	n	%	
Pos-neg	87	14.9	215	12.5	302	13.1	
Pos-pos	195	33.4	588	34.3	783	34.1	
Neg-pos	101	17.3	357	20.8	458	19.9	
Sex match (donor-recipient)							0.74
Male-male	366	36.9	684	38.4	1050	37.8	
Female-male	217	21.9	396	64.6	613	22.1	
Male-female	212	21.3	352	19.7	564	20.3	
Female-female	198	19.9	351	19.7	549	19.8	
Conditioning							<0.0001
Non-myeloablative	214	26.1	704	39.6	918	35.3	
Myeloablative	607	73.9	1075	60.4	1682	64.7	
Total body irradiation							<0.0001
No	382	39.1	1151	64.7	1533	55.6	
Yes	595	60.9	629	35.3	1224	44.4	
T-cell depletion (<i>in vivo</i> or <i>in vitro</i>)							<0.0001
No	683	68.5	651	36.5	1334	48	
Yes	314	31.5	1133	63.5	1447	52	

were included in the model and removed by backward selection. Only variables with $p \leq 0.05$ were retained. Decade was the variable of interest and therefore forced into each of the models. A Cox regression model was used for overall and progression-free survival, whereas the model of Fine and Gray was used, because of competing risks, for nonrelapse mortality and relapse. Models of allogeneic HCT were stratified by centre because of a significant centre effect (not the objective of this analysis). Comorbid conditions were those conditions that are likely to affect the outcome of the transplant but may not be directly related to the indication for transplant. This information was not available for the majority of patients and is therefore not included in the models. None of the variables tested violated the proportionality assumption, and there were no first-order interactions.

Results

Numbers of HCTs

There were in total 9515 transplants over the 20-year period, 3067 (32%) allogeneic and 6448 (68%) autologous. As some patients received more than one transplant, the total numbers of allogeneic and autologous HCT recipients were 2781 and 5118, respectively. Of the allogeneic HCTs, 286 were repeated transplants, mostly due to relapse. Of the autologous HCTs, 1330 were repeated transplants, either due to relapse or as part of a planned sequential transplant protocol. Of the 3067 allogeneic HCTs, 1123 (37%) were performed in the first decade (1997–2006) and 1944 (63%) in the second decade (2007–2016). Corresponding numbers of autologous HCTs were 2689 (42%) in the first decade and 3759 (58%) in the second decade, showing an increase in transplant activity by 73% for allogeneic HCT and 40% for autologous HCT. Transplant rates, and therefore use of HCT technology, increased in allogeneic HCT from 14 to 21.8 HCTs per 1 million inhabitants per year from the first to the second decade. Likewise, autologous HCT increased from 24.8 to 37.2, annually corrected for population growth.

Indications and demographic data

Table 1 shows demographic characteristics and transplant technology separately for allogeneic (Table 1a) and autologous (Table 1b) HCT.

Table 1a shows that the number of patients receiving an allogeneic HCT increased from 997 to 1784 when comparing the first (1997–2006) and second (2007–2016) decades. The main indications for allogeneic HCT were acute and chronic leukaemia, with the most notable change in chronic myeloid leukaemia, which decreased from 15.2 to 3.3% during the period of observation owing to the development of potent kinase inhibitor drugs. Most other indications showed a proportional increase. The median age increased from 38 to 48 years from 1997 to 2016 and the proportion of unrelated donors increased dramatically. There were changes in the stem cell source (less bone marrow) and use of T-cell depletion (massive increase of *in vitro* or *in vivo* T-cell depletion strategies) and, more recently, patients had higher EBMT risk scores (the EBMT risk score includes variables associated with mortality after HCT and is referenced in [4] and [15]).

Table 1b shows autologous HCT over the two decades; the number of patients receiving an autologous HCT increased from 2042 to 3076. Indications were mainly lymphoid neoplasia, with the most impressive increases in plasma cell disorders (704 to 1486) and non-Hodgkin's lymphoma (577 to 963). Median age increased from 50.8 to 56.4 years. For autologous HCT, the stem cell source was almost exclusively peripheral blood.

Outcomes

Univariate analyses of overall and progression-free survival in the first and second decade are shown in table 2a and figure 1 for allogeneic HCT (without significant difference between decades) and for autologous HCT in table 2b and figure 2. Figure 1 also shows nonrelapse mortality and relapse incidence per decade; nonrelapse mortality was lower in more recent years, but the unadjusted difference is minor ($p = 0.08$ in univariate and $p = 0.002$ in multivariate analysis). Figures 1 and 2 (and tables 2a and 2b) show that OS at 5 years after allogeneic and autologous HCT is around 55 and 60%, respectively, for all patients transplanted in Switzerland. Figure 3 shows overall survival by

EBMT risk score; the score was not used for multivariate analysis as all the elements contributing to the score were analysed as separate variables. It is nevertheless of interest to see how risk score affected survival with little change between the decades. Univariate outcomes for autologous HCT are shown in [table 2b](#).

Results of multivariate analyses are shown in [table 3a](#) for allogeneic and [table 3b](#) for autologous HCT. Significant

factors impacting on outcome in allogeneic HCT were disease type, disease stage, patient age and donor type for all outcomes, and the use of T-cell depletion, conditioning intensity, stem cell source and donor-recipient cytomegalovirus status for some of the outcomes. The decade of transplantation was significant only in models of nonrelapse mortality where the risks of death not associated with relapse was 0.68 (95% confidence interval 0.52–0.87,) in

Table 1b: Demographic characteristics and transplant technology for autologous haematopoietic cell transplants by decade for the years 1997–2016.

	1997-2006		2007-2016		Total		p-value
	n	%	n	%	n	%	
Patients (first autograft)							
No. 1st autograft	2042	75.9	3076	81.8	5118	79.4	
No. not 1st autograft	647	24.1	683	18.2	1330	20.6	
Centre							<0.0001
1	170	8.3	251	8.2	421	8.2	
2	217	10.6	306	9.98	523	10.2	
3	124	6.1	142	4.6	266	5.2	
4	347	17	861	28	1208	23.6	
5	18	0.9	1	0	19	0.4	
6	575	28.2	592	19.2	1167	22.8	
7	135	6.6	206	6.7	341	6.7	
8	418	20.5	651	21.2	1069	20.9	
9	38	1.9	36	1.2	74	1.4	
10	0	0	30	1	30	0.6	
Disease							<0.0001
Acute myeloid leukaemia	145	7.1	182	5.9	327	6.4	
Acute lymphoid leukaemia	55	2.7	18	0.6	73	1.4	
Chronic lymphocytic leukaemia	18	0.9	4	0.1	22	0.4	
Chronic myeloid leukaemia	12	0.6	0	0	12	0.2	
Combined myelodysplastic/myeloproliferative	15	0.7	5	0.2	20	0.4	
Hodgkin's lymphoma	179	8.8	166	5.4	345	6.7	
Non-Hodgkin's lymphoma	577	28.3	963	31.3	1540	30.1	
Plasma cell disorder	704	34.5	1486	48.3	2190	42.8	
Solid tumours	328	16.1	237	7.7	565	11	
Autoimmune disorders	9	0.4	15	0.5	24	0.4	
Disease stage at transplant							<0.0001
Early	862	42.2	1433	46.6	2295	44.8	
Intermediate	448	21.9	1137	37	1585	31	
Late	732	35.8	506	16.4	1238	24.2	
Gender							0.25
Male	1254	61.4	1938	63	3192	62.4	
Female	788	38.6	1138	37	1926	37.9	
Age group							<0.0001
0–20 years	147	7.2	154	5	301	5.9	
20–40 years	427	20.9	356	11.6	783	15.3	
40–60 years	1083	53	1425	46.3	2508	49	
60–70 years	371	18.2	1052	34.2	1423	27.8	
>70 years	14	0.7	89	2.9	103	2	
Median age (years)	50.8		56.4		54.3		
Age range (years)	0.65–76.5		0.64–77.5		0.64–77.5		
Stem cell source							0.02
Bone marrow	14	0.7	8	0.3	22	0.4	
Peripheral blood	2028	99.3	3068	99.7	5096	99.6	
Cord blood	0	0	0	0	0	0	
Risk score							<0.0001
0–1	99	4.8	119	3.9	218	4.3	
2–3	1249	61.2	2295	74.6	3544	69.2	
4–5	694	34	662	21.5	1356	26.5	
Comorbidities							
Yes	Data not collected		209	6.8	209	6.8	
No			361	11.7	361	11.7	
Missing			2506	81.5	2506	81.5	

Table 2: a: Univariate analysis of overall and progression-free survival for allogeneic haematopoietic cell transplants by decade for the years 1997–2016.

	1997–2006				2007–2016			
	Overall survival at 5 years	p-value	Progression-free survival at 5 years	p-value	Overall survival at 5 years	p-value	Progression-free survival at 5 years	p-value
Patients receiving first allograft (n)	997		997		1784		1784	
	56% (53–59%)		47% (44–50%)		54% (51–57%)		46% (43–49%)	
Disease		<0.0001		<0.0001		<0.0001		<0.0001
Acute myeloid leukaemia	48% (42–54%)		46% (40–52%)		47% (42–52%)		45% (44–58%)	
Acute lymphoid leukaemia	47% (39–55%)		42% (34–50%)		64% (57–71%)		51% (34–50%)	
Chronic lymphocytic leukaemia	65% (45–85%)		57% (37–77%)		56% (40–72%)		42% (28–56%)	
Chronic myeloid leukaemia	76% (69–83%)		55% (47–63%)		61% (46–76%)		51% (35–67%)	
Combined myelodysplastic/myeloproliferative	41% (30–52%)		35% (25–45%)		50% (42–58%)		41% (33–49%)	
Myeloproliferative neoplasms	59% (38–80%)		46% (25–67%)		61% (48–74%)		49% (36–62%)	
Hodgkin's lymphoma	55% (33–77%)		21% (2–40%)		42% (22–62%)		33% (14–52%)	
Non-Hodgkin's lymphoma	63% (50–76%)		49% (36–62%)		56% (46–66%)		46% (35–57%)	
Plasma cell disorder	48% (34–62%)		28% (16–40%)		34% (24–44%)		19% (11–27%)	
Solid tumours	0%		0%		50% (0–100%)		0%	
Bone marrow failure	77% (65–89%)		77% (65–89%)		68% (54–82%)		69% (55–83%)	
Inherited disorders of metabolism	100%		50% (10–90%)		83% (63–100%)		75% (50–100%)	
Primary immune disorders	79% (64–94%)		70% (57–87%)		83% (70–96%)		71% (55–87%)	
Haemoglobinopathy	89% (69–100%)		89% (69–100%)		100%		94% (82–100%)	
Histiocytic disorders	67% (13–100%)		67% (13–100%)		91% (74–100%)		91% (74–100%)	
Others	–		–		100%		100%	
Disease stage at transplant		<0.0001		<0.0001		<0.0001		<0.0001
Early	70% (66–74%)		60% (56–64%)		65% (61–69%)		57% (53–61%)	
Intermediate	50% (43–57%)		41% (34–48%)		50% (45–55%)		41% (36–46%)	
Late	31% (25–37%)		23% (18–28%)		31% (25–37%)		24% (19–29%)	
Age group		<0.0001		<0.0001		<0.0001		<0.0001
0–20 years	63% (57–69%)		57% (50–64%)		73% (67–79%)		67% (60–74%)	
20–40 years	61% (55–67%)		51% (45–57%)		55% (49–61%)		45% (39–51%)	
40–60 years	52% (47–57%)		40% (35–45%)		51% (47–55%)		42% (38–46%)	
60–70 years	30% (18–42%)		27% (15–39%)		45% (38–42%)		40% (34–46%)	
>70 years	–		–		26% (0–55%)		15% (0–41%)	
Donor		<0.0001		<0.0001		<0.0001		0.001
HLA identical sibling	63% (59–67%)		52% (48–56%)		61% (57–65%)		51% (46–56%)	
Twin	59% (35–83%)		29% (7–51%)		76% (46–100%)		64% (29–98%)	
Other relative / haploidentical	44% (34–54%)		33% (23–43%)		35% (22–48%)		33% (20–46%)	
Unrelated	45% (39–51%)		41% (35–47%)		50% (46–54%)		43% (39–47%)	
Stem cell source		0.03		<0.0001		0.02		0.001
Bone marrow	63% (57–69%)		58% (52–64%)		66% (59–73%)		56% (49–63%)	
Peripheral blood	52% (48–56%)		41% (37–45%)		51% (48–55%)		44% (41–47%)	
Cord blood	57% (31–83%)		57% (31–83%)		56% (43–69%)		46% (33–59%)	
Risk score		<0.0001		<0.0001		<0.0001		<0.0001
0–1	78% (71–85%)		68% (61–75%)		83% (76–90%)		72% (64–80%)	
2–3	63% (59–67%)		54% (49–59%)		60% (56–64%)		52% (48–56%)	
4–5	39% (34–44%)		28% (23–33%)		45% (40–50%)		37% (33–41%)	
6–7	26% (12–40%)		24% (11–35%)		30% (20–40%)		25% (16–34%)	
Conditioning		0.002		<0.0001		0.03		0.03
Non-myeloablative	48% (41–55%)		36% (29–43%)		48% (43–53%)		42% (37–47%)	
Myeloablative	59% (55–63%)		50% (46–55%)		57% (53–61%)		48% (44–52%)	
T-cell depletion (<i>in vivo</i> or <i>in vitro</i>)		0.32		0.01		0.01		<0.0001
No	57% (53–61%)		51% (47–55%)		50% (45–55%)		40% (36–44%)	
Yes	53% (47–59%)		38% (33–43%)		57% (53–61%)		50% (46–54%)	

the later decade as compared with the earlier decade. In [table 3b](#), models of autologous HCT are shown; for none of the outcomes analysed was the decade of transplantation significantly associated with outcome.

Discussion

This report illustrates experience with haematopoietic cell transplantation in Switzerland over the 20 year period from 1997 to 2016 and it describes the current status. The report provides data on transplant activity and characteristics of treated patients, and technology used, and gives valuable information on outcome. Transplant activity generally increased over the observation period with an increase of

73% from the first to the second decade in allogeneic HCTs and 40% in autologous HCTs. This reflects trends seen in Europe, where corresponding increases were 52 and 47%. The increase in transplant activity in Switzerland was within the range of neighbouring European nations [12].

In the comparison of the two decades, some trends become evident. Patients receiving allogeneic HCT in the later decade were older, had higher risk scores, more often received stem cells from unrelated donors and, because of their higher risk status, probably also had more commonly received reduced intensity conditioning regimens and some form of T-cell depletion [13]. Outcome data were relatively stable, showing similar survival probabilities in the later decade but lower nonrelapse mortality. This lack of progress could be seen as a disappointment, but given that treated cohorts differed and that the later cohort included more high-risk patients, the outcome results appear encouraging and probably reflect therapeutic progress. Adjusted treatment-associated mortality risks were decreased by 32% in the later decade. The resulting message, therefore, is that currently older patients can be treated with use of more complex transplant technology and with results similar to those of younger patients treated in previous years; in multivariate analysis mortality related to the procedure was clearly less.

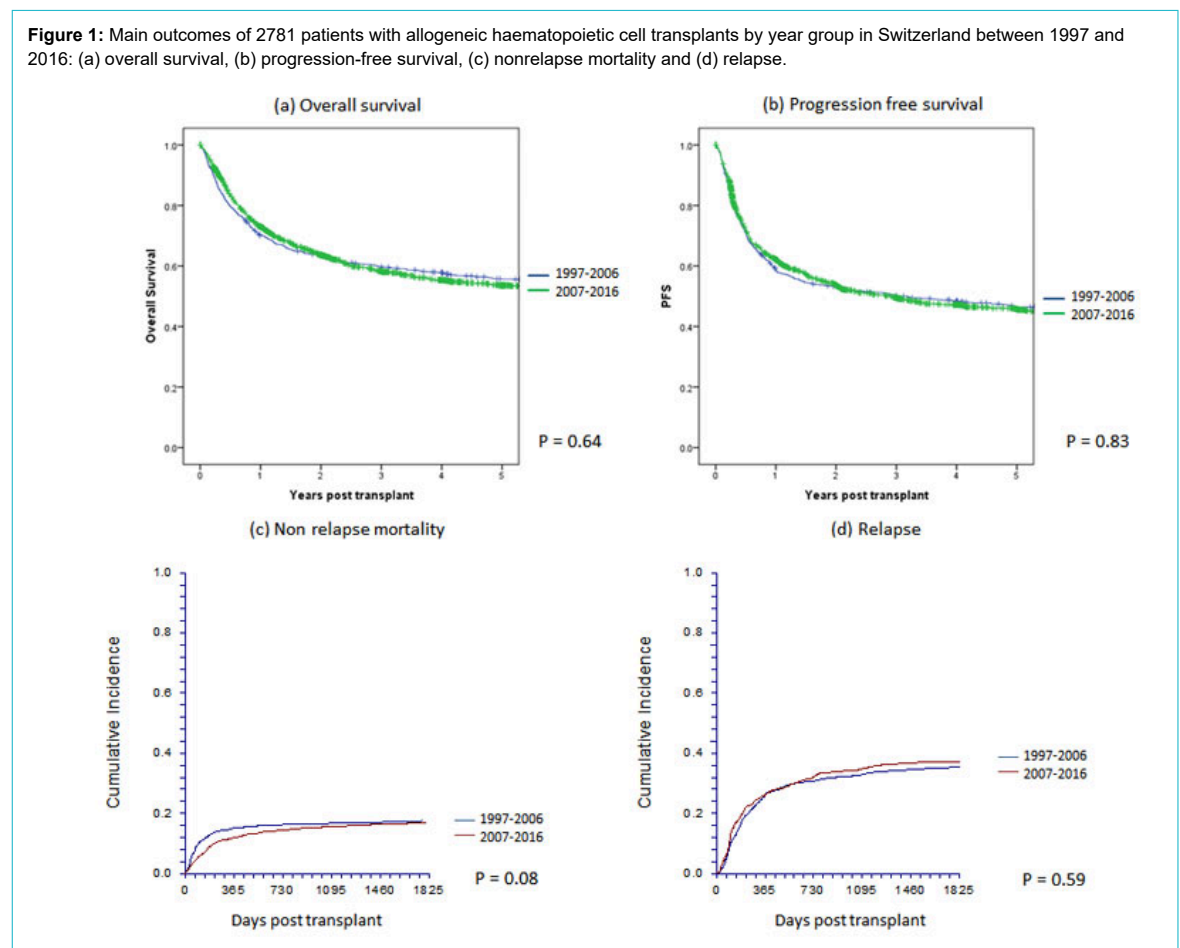
For autologous transplantation, effects were similar but less marked. The most important increase was in autologous HCT for myeloma, which doubled over the decades. This was related to confirmation of the use of high-dose chemotherapy as a first-line treatment in myeloma [14],

even now, in the era of modern drug treatment. As with allogeneic HCT, the age of treated patients increased by approximately 6 years. In spite of the treatment of older patients, outcome was not worse in later cohorts. Nonrelapse mortality with autologous HCT is consistently low, with little room for improvement (see fig. 2c).

Autologous and allogeneic HCT have different patterns of outcome. Nonrelapse mortality was lower with autologous HCT than with allogeneic HCT; on the other hand, the relapse rate was higher with autologous HCT and survival curves indicated an ongoing risk of relapse over time. Outcome of HCT is better when transplants are performed at an early stage of the disease. Nonrelapse mortality and risk of relapse increases in patients receiving transplants when their disease is at an advanced stage.

Total transplant rates, (the numbers of transplants in relation to number of inhabitants in Switzerland) were within the average of transplant rates in western Europe [12], but for allogeneic HCT, rates were lower than in, for example, Germany. These differences were possibly due to the particular situation in Switzerland, which puts allogeneic HCT under the regulation of the IVHSM (Interkantonale Vereinbarung über die hochspezialisierte Medizin). The data on outcome reflected the current situation. Outcome varies according to indication and clinical situation. It is dependent on disease, disease stage, donor type histocompatibility between donor and recipient in allogeneic HCT, and on main pretransplant risk factors, as previously described by the international transplant registries [15].

Figure 1: Main outcomes of 2781 patients with allogeneic haematopoietic cell transplants by year group in Switzerland between 1997 and 2016: (a) overall survival, (b) progression-free survival, (c) nonrelapse mortality and (d) relapse.



The age of treated patients continues to increase and large series of patients in their 70s receiving transplants from an allogeneic donor have been described [16]. As age continues to increase for both allogeneic and autologous HCT, proper evaluation of comorbidities [17] and geriatric assessment become ever more important [18]. The increasing age of treated patients is a reflection of improved technology that allows older patients to be treated; however, these improvements are difficult to pinpoint as they range from the use of cytotoxic drugs for conditioning, better choice of donor, including better tissue typing of unrelated donors, better technology to deal with mismatched donors and better graft-versus-host disease prophylaxis to improved management of infectious complications, transfusion support and other aspects of supportive care [19].

Advances in therapeutic drug development have led to a significant shift in the timing of allogeneic transplantation in some disease categories. In chronic myeloid leukaemia, recently most patients were transplanted after failed treatment with several kinase inhibitors [20], which was reflected in an increase in the interval from diagnosis to HCT from a median of 298 to 610 days. Similarly, in plasma cell myeloma, an important number of new drugs have become available and, as allogeneic HCT is used mainly as a salvage regimen, the interval from diagnosis to HCT in these patients increased from 538 to 823 days [21]. Therefore outcomes in some of the disease categories have become

worse over time. For example, for allogeneic HCT 5-year survival has dropped from 76 to 61% in chronic myeloid leukaemia, from 48 to 34% in plasma cell myeloma and from 53 to 42% in Hodgkin's lymphoma. It is important to note that since these are not entirely comparable patients this drop in 5-year survival probabilities does not reflect poorer technology.

As our registry does not have precise data on pretransplant treatment, we used interval from diagnosis to treatment as an indicator of prior therapy. It has been shown in many studies that intensive pretreatment decreases the success rate of allogeneic HCT. It has also been shown many times that the number of prior treatment lines and the interval from diagnosis to transplantation adversely impact nonrelapse mortality and relapse rates [15]. At the same time, we did not have information on patients who did not need an allogeneic HCT because of successful drug treatment. Therefore, comparison of outcome over time has to be interpreted cautiously and in the context of the global treatment landscape for specific diseases.

Limitations of these data are obviously the retrospective and observational nature of data collection and the fact that there is no information on outcomes of alternative treatments. It is among the strengths of this study that there is complete coverage of all transplanted patients over two decades, which is unique in Switzerland.

Table 2b: Univariate analysis of overall and progression-free survival for autologous haematopoietic cell transplants by decade for the years 1997–2016.

	1997–2006				2007–2016			
	Overall survival at 5 years	p-value	Progression-free survival at 5 years	p-value	Overall survival at 5 years	p-values	Progression-free survival at 5 years	p-values
Patients receiving first autograft (n)	2042		2042		3076		3076	
	59% (57–61%)		39% (37–41%)		61% (59–63%)		35% (33–37%)	
Disease		<0.0001		<0.0001		<0.0001		<0.0001
Acute myeloid leukaemia	44% (36–52%)		39% (31–47%)		51% (42–60%)		43% (35–51%)	
Acute lymphoid leukaemia	55% (41–69%)		44% (30–58%)		39% (12–66%)		44% (18–70%)	
Chronic lymphocytic leukaemia	82% (64–100%)		56% (33–79%)		33% (0–87%)		33% (0–87%)	
Chronic myeloid leukaemia	25% (0–50%)		25% (0–50%)		–		–	
Combined myelodysplastic/myeloproliferative	33% (9–57%)		29% (5–53%)		40% (0–100%)		40% (0–100%)	
Hodgkin's lymphoma	77% (70–84%)		62% (55–69%)		82% (75–89%)		63% (54–72%)	
Non-Hodgkin's lymphoma	62% (66–58%)		49% (45–53%)		61% (57–65%)		45% (41–49%)	
Plasma cell disorder	60% (56–64%)		23% (20–26%)		63% (59–67%)		22% (19–25%)	
Solid tumours	50% (44–56%)		41% (36–46%)		46% (38–54%)		41% (34–48%)	
Autoimmune disorders	78% (50–100%)		44% (11–77%)		80% (59–100%)		71% (47–95%)	
Disease stage at transplant		0.001		<0.0001		<0.0001		<0.0001
Early	60% (57–63%)		32% (29–35%)		64% (60–68%)		33% (29–37%)	
Intermediate	62% (57–67%)		50% (45–55%)		64% (60–68%)		37% (33–41%)	
Late	55% (51–59%)		39% (35–43%)		49% (44–53%)		36% (31–41%)	
Age group		<0.0001		<0.0001		<0.0001		<0.0001
0–20 years	58% (50–66%)		45% (37–53%)		51% (41–61%)		44% (35–53%)	
20–40 years	64% (59–69%)		55% (50–60%)		71% (65–77%)		57% (51–63%)	
40–60 years	60% (57–63%)		36% (33–39%)		64% (61–67%)		33% (30–36%)	
60–7 years0	51% (46–56%)		27% (22–32%)		56% (51–61%)		30% (26–34%)	
>70 years	33% (7–59%)		26% (1–51%)		40% (17–63%)		27% (10–44%)	
Stem cell source		0.31		0.4		0.01		0.48
Bone marrow	50% (23–77%)		36% (10–62%)		33% (0–69%)		33% (0–69%)	
Peripheral blood	59% (57–61%)		39% (37–41%)		61% (59–63%)		35% (33–37%)	
Risk score		0.001		0.002		<0.0001		<0.0001
0–1	67% (57–77%)		57% (67–67%)		75% (65–85%)		62% (50–74%)	
2–3	58% (54–62%)		36% (33–39%)		62% (59–65%)		34% (31–37%)	
4–5	58% (56–62%)		40% (36–44%)		55% (50–60%)		35% (30–40%)	

The current analysis looked at the results of evaluation of a registry and benefited from its 20 years of existence. It is comforting to see that progress continues, but this occurs in small steps and not in quantum leaps. Federal regulations in Switzerland have made it mandatory to maintain an evaluation registry, leading to a valuable database including all HCTs performed in Switzerland during the period of observation, which therefore constitutes a true obser-

vational registry with complete observation of all treated cases that will be useful for quality assurance programmes, healthcare cost estimation and healthcare planning. Between 50 and 60% of patients are expected to survive in the long-term after autologous and allogeneic HCT, indicating growing populations of surviving patients requiring long-term care and observation.

Figure 2: Main outcome of 5118 patients with autologous haematopoietic cell transplants by year group in Switzerland between 1997 and 2016: (a) overall survival, (b) progression-free survival, (c) nonrelapse mortality and (d) relapse.

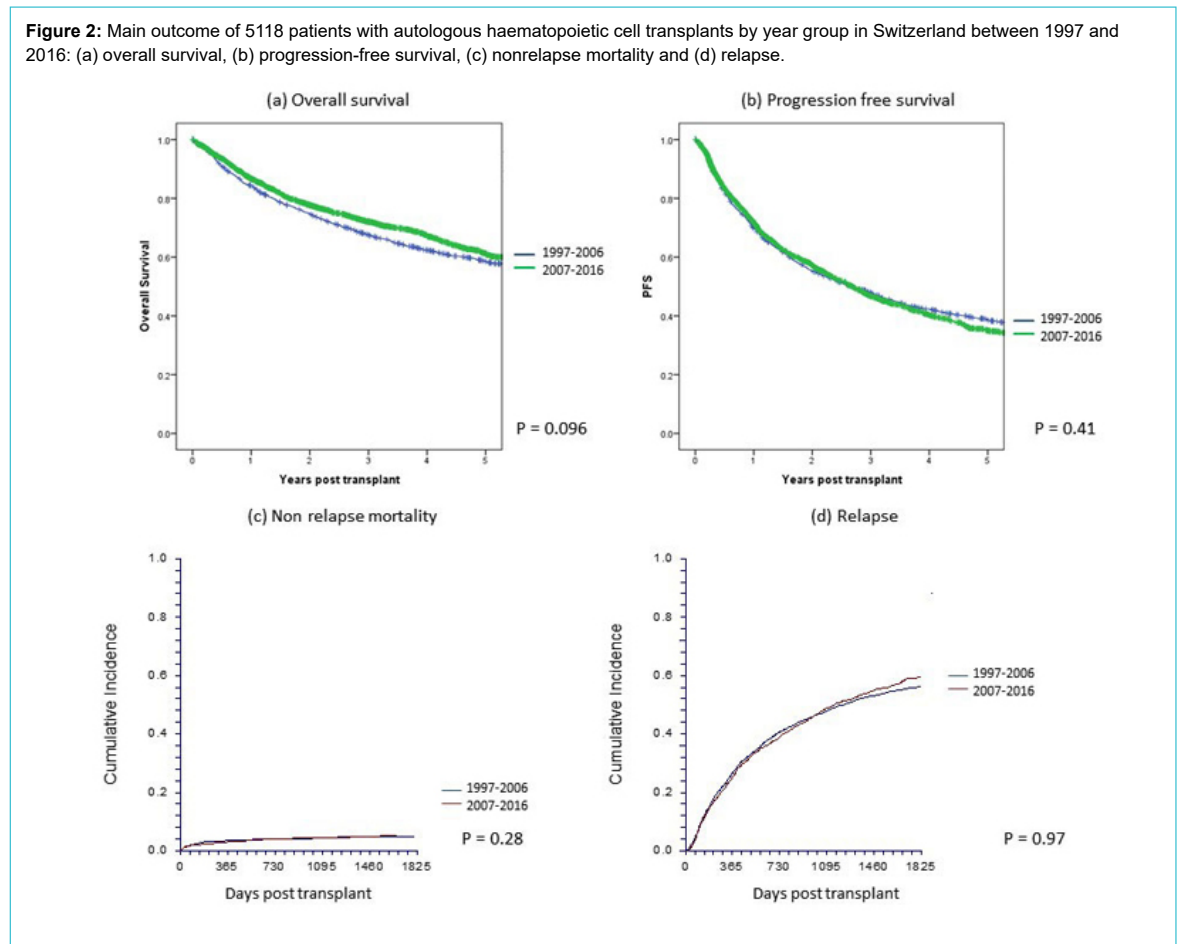
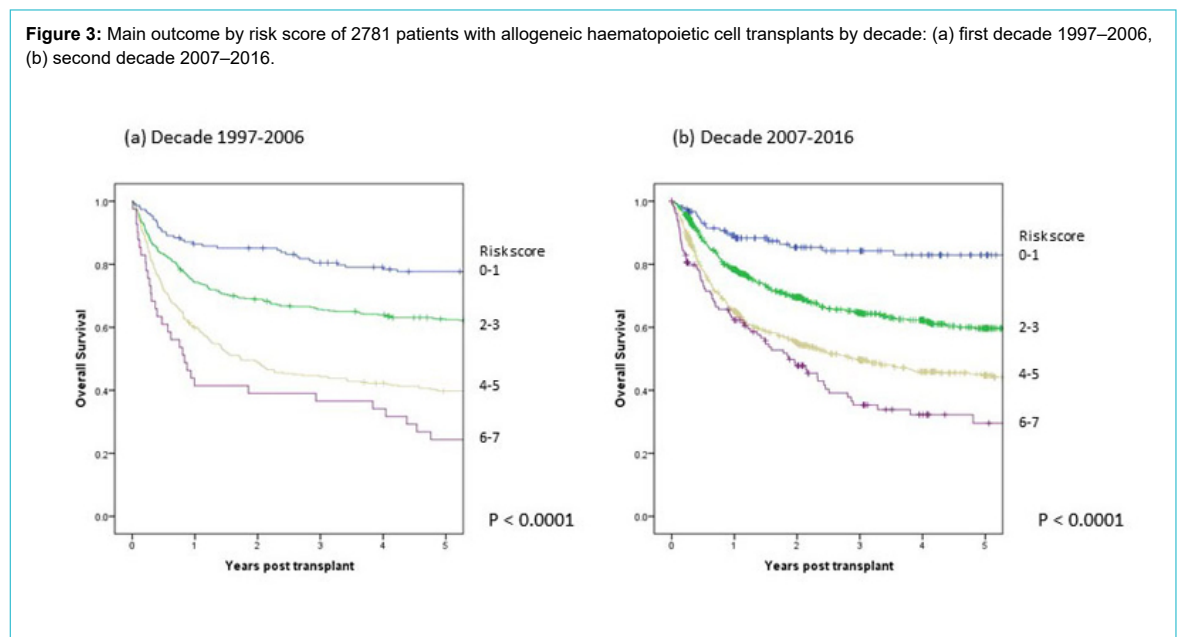


Figure 3: Main outcome by risk score of 2781 patients with allogeneic haematopoietic cell transplants by decade: (a) first decade 1997–2006, (b) second decade 2007–2016.



Acknowledgements:

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Table 3a:: Multivariate analysis of survival, progression free survival, nonrelapse mortality and relapse for allogeneic haematopoietic cell transplants for the years 1997–2016.

	Overall survival Relative risk (95% CI)	p-value	Progression-free survival Relative risk (95% CI)	p-value	Nonrelapse mor- tality Relative risk (95% CI)	p-value	Relapse Relative risk (95% CI)	p-value
Decade of Transplant		0.18		0.26				
1997–2006	1		1		1		1	
2007–2016	0.91 (0.80–1.05)		0.93 (0.82–1.06)		0.67 (0.52–0.86)	0.002	1.05 (0.90–1.22)	0.54
Disease		<0.0001		<0.0001				
Acute myeloid leukaemia	1		1		1		1	
Acute lymphoid leukaemia	0.88 (0.73–1.10)		1.12 (0.94–1.35)		1.09 (0.75–1.56)	0.66	1.09 (0.88–1.34)	0.44
Chronic lymphocytic leukaemia	0.50 (0.35–0.73)		0.65 (0.47–0.89)		1.29 (0.75–2.23)	0.35	0.63 (0.44–0.90)	0.01
Chronic myeloid leukaemia	0.47 (0.35–0.62)		0.85 (0.67–1.07)		0.87 (0.53–1.47)	0.62	0.92 (0.70–1.20)	0.54
Combined myelodysplastic/myeloproliferative	0.74 (0.61–0.90)		0.82 (0.68–0.99)		1.24 (0.85–1.79)	0.27	0.75 (0.59–0.95)	0.02
Myeloproliferative neoplasm	0.42 (0.30–0.59)		0.50 (0.37–0.67)		1.28 (0.77–2.11)	0.34	0.39 (0.26–0.59)	<0.0001
Hodgkin's lymphoma	0.58 (0.38–0.87)		0.75 (0.52–1.08)		2.18 (1.09–4.37)	0.03	0.51 (0.33–0.80)	0.004
Non-Hodgkin's lymphoma	0.58 (0.45–0.76)		0.66 (0.51–0.84)		1.93 (1.30–2.85)	0.001	0.43 (0.31–0.60)	0.0001
Plasma cell disorder	1.06 (0.85–1.33)		1.34 (1.08–1.65)		1.22 (0.74–2.01)	0.44	1.33 (1.05–1.68)	0.02
Solid tumours	1.23 (0.63–2.42)		1.76 (0.89–3.45)		–		2.31 (1.26–4.24)	0.01
Bone marrow failure	0.92 (0.62–1.38)		0.69 (0.45–1.04)		3.12 (1.77–5.49)	<0.0001	0.13 (0.05–0.37)	<0.0001
Inherited disorders of metabolism	0.61 (0.19–1.96)		1.31 (0.57–3.04)		3.16 (1.00–9.98)	0.05	0.67 (0.21–2.15)	0.50
Primary immune disorders	0.84 (0.45–1.56)		0.85 (0.47–1.51)		1.98 (0.79–4.95)	0.14	0.23 (0.93–0.58)	0.002
Haemoglobinopathy	0.19 (0.03–1.39)		0.32 (0.08–1.31)		–		0.15 (0.06–1.10)	0.06
Histiocytic disorders	0.83 (0.26–2.61)		0.69 (0.22–2.17)		1.07 (0.26–4.36)	0.92	–	–
Other	–		–		–		–	–
Disease stage at transplant		<0.0001		<0.0001				
Early	1		1		1		1	
Intermediate	1.76 (1.51–2.04)		1.69 (1.47–1.95)		1.39 (1.05–1.85)	0.021	1.57 (1.28–1.79)	<0.0001
Late	2.80 (2.40–3.27)		2.58 (2.22–3.0)		1.30 (0.97–1.77)	0.083	2.69 (2.25–3.23)	<0.0001
Age group		0.001		0.02				
0–20 years	1		1		1		1	
20–40 years	1.04 (0.82–1.33)		1.23 (0.97–1.57)		0.90 (0.58–1.39)	0.64	1.51 (1.16–1.96)	0.002
40–60 years	1.39 (1.10–1.75)		1.46 (1.14–1.86)		1.54 (1.01–2.37)	0.05	1.35 (1.04–1.75)	0.02
60–70 years	1.49 (1.14–1.95)		1.49 (1.12–1.98)		1.88 (1.14–3.09)	0.01	1.26 (0.92–1.73)	0.16
>70 years	1.79 (0.92–3.48)		1.67 (0.87–3.20)		2.86 (1.13–7.25)	0.03	1.40 (0.60–3.30)	0.44
Donor		<0.0001		<0.0001				
HLA identical sibling	1		1		1		1	
Twin	0.64 (0.35–1.17)		0.89 (0.49–1.64)		0.41 (0.05–3.18)	0.39	1.16 (0.58–2.32)	0.68
Other relative	2.01 (1.61–2.50)		1.76 (1.42–2.19)		3.27 (2.20–4.86)	<0.0001	1.11 (0.84–1.45)	0.468
Unrelated	1.52 (1.33–1.74)		1.24 (0.9–1.40)		2.65 (2.04–3.45)	<0.0001	0.79 (0.68–0.92)	0.002
Source				0.003				
Bone marrow	–		1		–		–	
Peripheral blood	–		0.98 (0.83–1.16)		–		–	
Cord blood	–		1.84 (1.27–2.66)		–		–	
Cytomegalovirus status (donor-recipient)								
Neg-neg	–		–		1		–	
Pos-neg	–		–		0.82 (0.55–1.23)	0.35	–	
Pos-pos	–		–		1.05 (0.80–1.37)	0.74	–	
Neg-pos	–		–		1.36 (1.03–1.78)	0.03	–	
Conditioning				0.011				
Non-myeloablative	–		1		1		1	
Myeloablative	–		0.83 (0.72–0.96)		1.50 (1.17–1.93)	0.001	0.66 (0.55–0.78)	<0.0001
T-cell depletion (<i>in vivo</i> or <i>in-vitro</i>)		0.02						
No	1		–		1		–	
Yes	0.85 (0.74–0.98)		–		0.75 (0.59–0.95)	0.02	–	

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Financial disclosure

The SBST registry is compulsory through an unfunded mandate by the Federal Office of Public Health. It is financed by contributions from the transplanting centres and the University of Basel.

Competing interests

The authors declare that they have no conflicts of interest.

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Table 3b: Multivariate analysis of overall survival, progression free survival, nonrelapse mortality and relapse for autologous haematopoietic cell transplants for the years 1997–2016.

	Overall survival	p-value	Progression-free survival	p-value	Nonrelapse mortality	p-value	Relapse	p-value
Decade of transplant		0.12		0.94				
1997–2006	1		1		1		1	
2007–2016	0.93 (0.84–1.02)		1.0 (0.92–1.08)		1.00 (0.77–1.31)	0.98	0.96 (0.88–1.04)	0.28
Disease		<0.0001		<0.0001				
Acute myeloid leukaemia	1		1		1		1	
Acute lymphoid leukaemia	0.86 (0.60–1.23)		0.92 (0.65–1.29)		0.47 (0.16–1.34)	0.16	1.0 (0.65–1.52)	0.99
Chronic lymphocytic leukaemia	0.38 (0.19–0.74)		0.56 (0.32–0.98)		0.65 (0.14–2.91)	0.57	0.61 (0.35–1.05)	0.07
Chronic myeloid leukaemia	1.46 (0.74–2.87)		1.57 (0.80–3.07)		2.33(0.64–8.40)	0.20	0.96 (0.38–2.41)	0.95
Combined myelodysplastic/myeloproliferative	1.04 (0.59–1.83)		0.93 (0.53–1.63)		1.79 (0.61–5.31)	0.29	0.68 (0.33–1.39)	0.29
Hodgkin's lymphoma	0.33 (0.25–0.44)		0.48 (0.37–0.61)		0.47 (0.26–0.87)	0.02	0.50 (0.37–0.67)	<0.0001
Non-Hodgkin's lymphoma	0.59 (0.49–0.71)		0.72 (0.61–0.85)		0.53 (0.33–0.86)	0.01	0.80 (0.65–0.98)	0.03
Plasma cell disorder	0.63 (0.53–0.75)		1.03 (0.88–1.21)		0.35 (0.23–0.55)	<0.0001	1.24 (1.03–1.51)	0.02
Solid tumours	0.75 (0.59–0.97)		0.76 (0.61–0.96)		0.27 (0.15–0.52)	<0.0001	0.91 (0.70–1.19)	0.51
Autoimmune disorders	0.30 (0.12–0.73)		0.50 (0.25–0.98)		0.54 (0.12–2.41)	0.42	0.49 (0.20–1.16)	0.11
Disease stage at transplant		<0.0001		<0.0001				
Early	1		1		1		1	
Intermediate	1.06 (0.93–1.20)		1.10 (0.99–1.21)		1.45 (1.03–2.05)	0.03	1.05 (0.95–1.16)	0.31
Late	1.47 (1.28–1.70)		1.55 (1.37–1.74)		2.07 (1.41–3.07)	<0.0001	1.37 (1.21–1.55)	<0.0001
Age group		<0.0001		<0.0001				
0–20 years	1		1		–		1	
20–40 years	0.90 (0.71–1.12)		0.84 (0.69–1.04)		–		0.81 (0.63–1.03)	0.08
40–60 years	1.26 (1.01–1.57)		1.19 (0.98–1.46)		–		1.11 (0.87–1.41)	0.39
60–70 years	1.60 (1.23–2.02)		1.40 (1.14–1.74)		–		1.19 (0.93–1.52)	0.17
>70 years	2.46 (1.69–3.59)		1.53 (1.10–2.15)		–		1.17 (0.80–1.70)	0.43
Patient gender		0.02		0.01				
Male	1		1		–		1	
Female	0.90 (0.82–0.98)		0.91 (0.84–0.98)		–		0.91 (0.84–0.98)	0.02

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